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Nucleotide Pattern Matching on the Intel iPSC/860 Hypercube

by

John L. Houle, B.Sc., Hons. B.Sc.

A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of
the requirements for the degree of

Master of Computer Science

Ottawa-Carleton Institute for Computer Science
School of Computer Science
Carleton University
Ottawa, Ontario
December 1, 1994

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Nucleotide Pattern Matching on the Intel iPSC/860 Hypercube

submitted by

John L. Houle, B.Sc., Hons. B.Sc.

in partial fulfillment of the requirements for
the degree of Master of Computer Science

Chairman, School of Computer Science

Thesis Supervisor

Carleton University

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Abstract

Numerous sequence analysis problems in computational molecular biology can be expressed as string search problems. We consider the multiple keyword search problem and develop a parallel solution for the hypercube architecture. The thesis reports a multiple keyword search algorithm for the Intel iPSC/860 Hypercube. The data-parallel algorithm is specialized to searching for class 1 nucleotide motifs within DNA sequences. The human interferon-alpha multigene family within the 9p13 - 9p22 chromosomal bands was characterized using restriction analysis and transcription analysis. Using this algorithm we have produced a series of human interferon-alpha restriction maps and transcription maps. Transcription analysis revealed five families of potential promoter elements: 1. tata boxes, 2. virus-response elements, 3. distal interferon regulatory factor sites, 4. proximal interferon regulatory factor sites and 5. TG sequences. On the basis of computational evidence, a theoretical model for the transcriptional control of human interferon-alpha gene expression is proposed. Future directions for human interferon-alpha transcriptional regulation research are identified.

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The author acknowledges the contributions of several individuals and institutions. The systematic characterization of the human interferon-alpha promoters was a problem originally posed to us by Dr. Mark Hayes of the Division of Cytokine Biology at the Center for Biologics Evaluation and Research, Food and Drug Administration.

Theoretical aspects of algorithm design were developed in collaboration with Dr. Elena Lodi and Dr. Nicola Santoro. Dr. Elena Lodi was a visiting researcher from the Department of Mathematics at the University of Siena. Dr. Nicola Santoro is a professor with the School of Computer Science at Carleton University. Dr. Nicola Santoro was my thesis advisor. I am particularly indebted to Dr. Santoro for his academic and financial support throughout the duration of my masters candidacy. Together we experimented with several strategies for solving the multiple keyword search problem in nucleotide sequences. These brainstorming sessions formed an integral component of graduate education.

The mechanics of hypercube operation were assisted by Anton Saarimaki and Peter Choynowski. Masters candidate Anton Saarimaki provided a wealth of experience in the correct use of hypercube parallel library routines. Software engineer Peter Choynowski maintained the operation of the Intel iPSC/860 Hypercube.

Sequence data was generously provided by Dana Macelis and the National Center for Biotechnology Information. Dana Macelis of New England BioLabs sent several copies of REBASE, the restriction endonuclease database. The National Center for Biotechnology Information at the National Library of Medicine, National Institutes of Health sent a copy of TFD, the transcription factors database. The Genbank molecular sequence database of the National Center for Biotechnology Information sent further copies of the human retinoblastoma susceptibility gene and the human interferon-alpha genes.

Scientific visualization of molecular biology data was made possible through the efforts of Dr. Paul Adler, Dr. Manual Diaz, Dr. Nicholas Murgolo, Nancy Manning, Govindachari Raghunath, Blair Griezic and Stacy Fietz. Dr. Paul Adler of the Department of Pathology at the University of Washington generated the human chromosome 9 ideogram. Dr. Manual Diaz of the Oncology Institute at the Loyola University Medical Center conveyed a preliminary copy of the human type-I interferon gene cluster map. Dr. Nicholas Murgolo of Schering-Plough Pharmaceuticals released x-ray crystallographic coordinates of the human interferon-alpha 2 protein which were modeled by Nancy Manning of the Protein Data Bank at the Brookhaven National Laboratory. Doctoral candidate Govindachari Raghunath provided instruction in the use of both the CricketGraph graph plotter and the Hewlett-Packard ScanJet IICx image scanner. Graphic artists Blair Griezic and Stacy Fietz drew all the genetic maps.

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Chapter 1

Introduction

Open research problems in computational molecular biology are described. Precedent research in nucleotide motif analysis is reported. The nucleotide motif search problem is formally defined. Research findings and thesis organization are summarized.

1.1 Genome Informatics

The Human Genome Project is a concerted effort to systemically delineate genetic and physical maps of the total DNA complement of *Homo sapiens*, ultimately yielding the total nucleotide sequence of this DNA. The Human Genome Project has five objectives: 1. construction of a high resolution genetic map of the human genome, 2. production of a variety of physical maps of all human chromosomes and the chromosomes of selected model organisms, 3. determination of the complete sequence of human DNA and of the DNA of selected model organisms, 4. development of informatics capabilities to collect, store, analyze and distribute the data produced and 5. creation of the DNA sequencing and computing technologies necessary to achieve these objectives (Pearson and Soll, 1991).

Genome projects will generate enormous amounts of information. Genbank 84.0, the August 1994 version of the U.S. national depository of nucleic acid sequences contains approximately 201 million nucleotides (Genbank, 1994). A major objective of the Human Genome Project is the development of more advanced DNA sequencing technologies. Concerted genome sequencing using these advanced technologies will result in further increases in the rate at which DNA sequences are obtained. DNA sequence growth rates are already creating significant bottlenecks in user accessibility and usage. The Genbank DNA sequence data exponential growth rate is presented (Table 1.1.1.) (Figure 1.1.1.).

Release	Date	Nucleotides	Entries
3	Dec 82	680338	606
14	Nov 83	2274029	2427
20	May 84	3002088	3665
24	Sep 84	3323270	4135
25	Oct 84	3368765	4175
26	Nov 84	3689752	4393
32	May 85	4211931	4954
36	Sep 85	5204420	5700
40	Feb 86	5925429	6642
42	May 86	6765476	7416
44	Aug 86	8442357	8823
46	Nov 86	9615371	9978
48	Feb 87	10961380	10913
50	May 87	13048473	12534
52	Aug 87	14855145	14020
53	Sep 87	15514776	14584
54	Dec 87	16752872	15465
55	Mar 88	19156002	17047
56	Jun 88	20795279	18226
57	Sep 88	22019698	19044
57.1	Oct 88	23800000	20579
58	Dec 88	24690876	21248
59	Mar 89	26382491	22479
60	Jun 89	31808784	26317
61	Sep 89	34762585	28791
62	Dec 89	37183950	31229
63	Mar 90	40127752	33377
64	Jun 90	42495893	35100
65	Sep 90	49179285	39533
66	Dec 90	51306092	41057
67	Mar 91	55169276	43903
68	Jun 91	65868799	51418
69	Sep 91	71947426	55627
70	Dec 91	77337678	58952
71	Mar 92	83894652	65100
72	Jun 92	92160761	71280
73	Sep 92	101008486	78608
74	Dec 92	120242234	97084
75	Feb 93	126212259	106684
76	Apr 93	129968355	111911
77	Jun 93	138904393	120134
78	Aug 93	147215633	131328
79	Oct 93	157152442	143492
80	Dec 93	163802597	150744
81	Feb 94	173261500	162946
82	Apr 94	180589455	169396
83	Jun 94	191393939	182753
84	Aug 94	201815802	196703

Table 1.1.1. Genbank DNA sequence data (Genbank, 1994).

Figure 1.1.1. Genbank DNA sequence growth curve (December, 1982 - August, 1994).

Computational biology refers to the study of biological phenomena through computational experiments. Computational molecular biology focuses on the computational interpretation of biological phenomena that involve nucleic acid and protein sequences. Genome informatics refers to the computational molecular biology aspects of genome projects. Genome informatics has identified five theoretical and computational problems amenable to solution by parallel computing: 1. database representations of genetic and physical maps, 2. combinatorial and statistical problems in map and sequence assembly, 3. prediction of protein structures from amino acid sequences, 4. sequence similarity comparisons and 5. recognition of functionally-significant patterns in sequences.

1. Database representations of genetic and physical maps. Chromosome genetic linkage maps represent distances between markers based on meiotic recombination frequencies. Chromosome physical maps represent distances between markers based on

numbers of nucleotides. Genomic databases should define four data types: 1. genetic, 2. physical, 3. sequence and 4. bibliographic. Genetic data should include: 1. locus name, 2. location, 3. recombination distance, 4. polymorphisms, 5. breakpoints, 6. rearrangements and 7. disease association. Physical data should include: 1. restriction sites, 2. probe locations and 3. contigs. Sequence data should include: 1. sequence-tagged sites, 2. noncoding regions, 3. coding regions, 4. control regions, 5. telomeres, 6. centromeres, 7. repeats and 8. metaphase chromosome bands. Bibliographic references should cite primary scientific and medical literature.

Genomic databases are classified into four categories based on their contents: 1. bibliographic, 2. molecular, 3. genetic and 4. organism. Bibliographic databases include: 1. Medline, 2. Biological Abstracts (Biosis), 3. Chemical Abstracts Service (CAS) and 4. Agricola. Molecular databases include: 1. European Molecular Biology Laboratory Nucleotide Sequence Data Library (EMBL), 2. Genbank, 3. Geninfo, 4. DNA Database of Japan (DDBJ), 5. Protein Identification Resource (PIR), 6. GenPept, 7. Swissprot, 8. Carbank, 9. BioMagRes (BMR) and 10. Protein Data Base (PDB). Genetic databases include: 1. Genome Data Base (GDB), 2. Online Mendelian Inheritance in Man (OMIM), 3. DRHPL and 4. Gbase. Organism databases include: 1. *E. coli* Genetic Stock Center and 2. American Type Culture Collection. Genomic databases have been reviewed (Pearson and Soll, 1991).

2. Combinatorial and statistical problems in map and sequence assembly. Genetic maps are constructed by assembling random DNA fragments into composite DNA sequences. The assembly procedure seeks to maximize the probable order and spacing of markers within a map.

The construction of a physical map typically requires the overlap and ordering of 1000 to 10000 partially-characterized clones to be established. First, the pairwise probability of clone overlap is estimated. Second, for those clones deduced to overlap with high probability a greedy algorithm is used to assemble the overlapping clones into contigs.

During the process of contig construction, the characterization of a new clone may confirm or contradict an assigned overlap. Several weak though consistent overlaps may be necessary to acquire confidence in a contig. Therefore, a more systematic method for treating multiple overlapping clones for the entire contig would be preferable to simple pairwise overlaps. Interval graph theory may be useful in developing such an algorithm (Bell, 1990).

3. Prediction of protein structures from amino acid sequences. Protein folding refers to the mechanism by which the amino acid sequence of a protein adopts its functional three-dimensional conformation. The *protein folding problem* is the determination of the set of rules for predicting the native three-dimensional structure of a protein based entirely upon its amino acid sequence. The protein folding problem has been made more urgent by advances in DNA sequencing technology which have generated DNA sequences at a greater rate than the ability to isolate and characterize the protein products. The development of a folding code to complement the genetic code would complete the information transfer in the central dogma of molecular biology: DNA → RNA → protein → functional conformation.

Three methods have been developed to predict protein structure: 1. substructure condensation, 2. homology modeling and 3. energetic methods. In substructure condensation, secondary structures are predicted and these secondary structure units are then packed together to construct an approximate tertiary structure. Homology modeling exploits a recognizable sequence relationship between the protein under question and another protein of known structure to model a tertiary structure. Energetic methods construct a potential energy function and follow the thermodynamic gradient to the optimal structure (energy minimization) or simulate the time-dependent motions of the polypeptide during the conformational transitions to a more thermodynamically-stable state (molecular dynamics). None of these prediction methods have been entirely successful (Ponder and Richards, 1987). Thus, the protein folding problem remains an open research question in

structural molecular biology. The protein folding problem has been reviewed (Murphy and Freire, 1992) (Matthews, 1993).

4. Sequence similarity comparisons. Nucleic acid and protein sequence comparison is an important tool in genome informatics. Initial clues to understanding the structure or function of a macromolecular sequence arise from homologies to other macromolecules that have been previously studied. Genomic database searches reveal biologically-significant sequence relationships and suggest future investigation strategies.

Molecular sequence database homology searching is affected by five factors: 1. algorithms, 2. scoring systems, 3. alignment statistics, 4. database updates and 5. database sequence bias. 1. Algorithms. Database search algorithms are based upon measures of local sequence similarity. Algorithms must balance the competing factors of speed, hardware requirements and sensitivity to biological relationships. 2. Scoring systems. Alignments are ranked by scores whose calculations are dependent upon the particular scoring systems used. The appropriate scoring system to use is largely dependant upon the problem under consideration. 3. Alignment statistics. Given a specific query, database search algorithms produce an ordered list of imperfectly-matched database similarities. An important question is defining the critical point of statistical significance. 4. Database updates. The use of an up-to-date sequence database is essential to any similarity search. 5. Database sequence bias. There are biases in the molecules chosen to be included in nucleic acid and protein sequence databases. Issues in searching molecular sequence databases have been reviewed (Altschul et. al., 1994).

5. Recognition of functionally-significant patterns in sequences. Functional sites in DNA have been studied and partially characterized. DNA functional sites are sequences recognized and bound to by specific proteins, e.g. promoter elements. DNA recognition sequences are difficult to characterize computationally. Recognition sequence algorithms exhibit performance tradeoffs between increasing sensitivity (ability to detect true positives) and decreasing selectivity (ability to exclude false positives).

The identification of intron-exon boundaries and splice sites where RNA is transcribed from genomic DNA is of further importance. The ability to accurately predict introns would greatly facilitate the translation of genomic DNA into the amino acid sequence of the gene product.

Comparative analysis of DNA sequences is an important technique in detecting biologically-significant relationships. Multiple sequence alignment is a useful technique in analyzing sequence-structure relationships. The DNA sequence of an unknown gene often exhibits structural homology with a known gene. Thus, homology relationships frequently permit biological and functional insights to be made regarding the mechanism of action of the unknown gene. Multiple sequence alignment is important for the recognition of patterns or motifs common to a set of functionally-related DNA sequences and is of assistance in structure prediction and molecular modeling. Multiple sequence alignment algorithms use variations of the dynamic programming method. Dynamic programming methods use an explicit measure of alignment quality, consisting of defined costs for aligned pairs of residues or residues with gaps and use an algorithm for finding an alignment with minimum total cost. Multiple sequence alignment algorithms have been reviewed (Chan et. al., 1992).

Genome analysis has been identified as a *Grand Challenge* problem in computational science. Genome informatics has been reviewed (Smith, 1994).

1.2 Nucleotide Motifs

Nucleotide motifs are conserved patterns of nucleotides that are common to a group of functionally-related sequences and often encode a discrete function, e.g. the tata box is a nucleotide sequence required for accurate transcription initiation. Nucleotide motifs are frequently compiled into machine-readable collections for the purposes of database searching and automated motif detection (Ghosh, 1993). Motifs are usually derived from the multiple alignment of a group of related sequences. Motifs are usually presented as consensus sequences. Consensus sequences are useful for computational searches along DNA sequences.

Consider the nucleotide motif search problem. The nucleotide motif search input consists of two items: 1. a finite set of nucleotide motifs and 2. a DNA sequence. The sum of the lengths of the nucleotide motifs is defined as m . The length of the DNA sequence is defined as n . Precendent solutions have been proposed for the nucleotide motif search problem. The GCG Map program finds restriction endonuclease recognition sites using a brute force algorithm in $O(nm)$ time (Devereux et. al., 1984). The Signal Scan 3.0 program determines transcription factor binding sites using an indexed brute force algorithm of undetermined time complexity (Prestridge and Stormo, 1993). Restriction endonuclease recognition sites are identified using a nondeterministic finite automaton algorithm of undetermined time complexity (Mount and Conrad, 1986). Nondeterministic finite automaton algorithms are superior to brute force algorithms but have the disadvantage of a stack requirement for execution. The stack requirement can be eliminated using a deterministic finite automaton. Restriction endonuclease recognition sites are identified using a deterministic finite automaton algorithm in $O(n + m)$ time (Smith, 1988). The Intelligenetics PC Gene Restri program finds restriction endonuclease recognition sites using an unidentified algorithm.

Motifs have varying specificity. Because of the problem of false positives, the discovery of a particular motif in a sequence should be interpreted cautiously. Motifs are nevertheless useful for making functional inferences concerning a novel DNA sequence (Boguski, 1992).

1.3 Notation and Problem Statement

Numerous sequence analysis problems in computational molecular biology can be expressed as nucleotide motif search problems, e.g. restriction analysis and transcription analysis. Nucleotide motif search is a specialized instance of the multiple keyword search problem. A multiple keyword search algorithm was developed for searching for class 1 nucleotide motifs within DNA sequences.

Consider the keyword k and the text t to be two strings defined over an arbitrary alphabet Σ . The keyword length is defined as m , $|k| = m$. The text length is defined as n , $|t| = n$. The keyword length m is typically much shorter than the text length n , $m \leq n$. The keyword search problem is to find all occurrences of the keyword as a substring within the text. The output is the set of positions in the text where the keyword occurs.

The multiple keyword search problem is a generalization of the keyword search problem. Consider a finite set of y keywords $k_1, k_2, \dots, k_y$ and a text t defined as strings over an arbitrary alphabet Σ . The multiple keyword search problem is to find all occurrences of each keyword as a substring within the text. The output is the set of positions in the text where any of the keywords occur.

A motif is defined as a continuous segment of a macromolecular sequence. The class 1 nucleotide motif involves an exact match to a short defined sequence (Staden, 1990). Class 1 nucleotide motifs occur within DNA as transcription factor binding sites and restriction endonuclease recognition sites.

The nucleotide motif search problem may be stated as follows. Consider a finite set of y class 1 nucleotide motifs $k_1, k_2, \dots, k_y$ and a DNA sequence t defined as sequences over the alphabet $\Sigma_{\text{DNA}} = \{A, C, G, T\}$. The nucleotide motif search problem is to find all occurrences of each nucleotide motif as a subsequence within the DNA sequence. The output is the set of positions in the DNA where any of the nucleotide motifs occur.

In DNA sequence analysis, nucleotide motif search is a specialized instance of the multiple keyword search problem. Two DNA sequence analysis problems can be expressed as nucleotide motif search problems: 1. restriction analysis and 2. transcription analysis. Thus, the identification of transcription factor binding sites and restriction endonuclease recognition sites within an arbitrary DNA sequence are specialized cases of the multiple keyword search problem.

1.4 Thesis Contributions

A multiple keyword search algorithm was developed for the Intel iPSC/860 Hypercube. The algorithm is specialized to searching for class 1 nucleotide motifs within DNA sequences (Staden, 1990). Consider a hypercube composed of p processors, a DNA sequence of length n nucleotides and a list of nucleotide motifs of total m nucleotides. Under such conditions, the parallel class 1 nucleotide motif search algorithm would require $O(m + (n/p))$ time and occupy $O(n + mp)$ space.

The nucleotide motif search algorithm was used to characterize the human interferon-alpha multigene family. Eleven human interferon-alpha genes were subjected to restriction analysis and transcription analysis: IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA13, IFNA14, IFNA16 and IFNA17. Nucleotide motif analysis of the human interferon-alpha genes yielded six types of genetic markers: 1. restriction endonuclease sites, 2. virus response elements, 3. distal interferon regulatory factor sites, 4. proximal interferon regulatory factor sites, 5. TG sequences and 6. polyadenylation signals. The nucleotide motif sites were visualized to produce human interferon-alpha restriction maps and transcription maps. On the basis of computational evidence, a theoretical model for the transcriptional control of human interferon-alpha gene expression was proposed. The distribution of original research findings among the human interferon-alpha genes is summarized (Table 1.4.1.).

Data	Human Interferon-Alpha Genes
nucleotide motif analysis algorithm	1, 2, 4, 5, 6, 7, 8, 13, 14, 16, 17
restriction endonuclease sites	1, 2, 4, 5, 6, 7, 8, 13, 14, 16, 17
restriction maps	1, 2, 4, 5, 6, 7, 8, 13, 14, 16, 17
virus response elements	6, 16, 17
distal interferon regulatory factor sites	2, 4, 5, 6, 7, 13, 14, 16, 17
proximal interferon regulatory factor sites	2, 4, 5, 6, 7, 13, 14, 16, 17
TG sequences	2, 4, 5, 6, 7, 13, 14, 16, 17
polyadenylation signals	1, 2, 17
transcription maps	1, 2, 4, 5, 6, 7, 13, 14, 16, 17
transcription regulatory mechanism	1, 2, 4, 5, 6, 7, 13, 14, 16, 17

Table 1.4.1. Thesis contributions.

1.5 Thesis Outline

The remainder of the thesis is organized as follows. Chapter 2 describes seven topics in molecular biology: 1. nucleic acids, 2. protein, 3. restriction endonucleases, 4. transcription factors, 5. interferon, 6. retinoblastoma and 7. Human Genome Project. Chapter 3 defines the nucleotide motif search algorithm. Chapter 4 defines the nucleotide motif search algorithm implementation on the Intel iPSC/860 Hypercube. Chapter 5 presents the human interferon-alpha nucleotide motif search results for restriction endonuclease recognition sites and transcription factor binding sites. Chapter 6 presents a genetic analysis of the human interferon-alpha multigene family. Chapter 7 presents a performance analysis of the parallel nucleotide motif search algorithm using restriction endonucleases and transcription factors. Chapter 8 concludes with a summary of the nucleotide motif search algorithm and the human interferon-alpha genetic analysis. Future directions for parallel nucleotide motif search algorithm research and human interferon-alpha transcriptional regulation research are proposed.

Chapter 2

Molecular Biology

Molecular biology is a modern branch of science concerned with the study of biological phenomena at the molecular level. Molecular genetics is a subject focusing on the properties of deoxyribonucleic acid. Molecular genetics uses biochemical and biophysical techniques to investigate genetic problems. Seven topics in molecular biology are presented: 1. nucleic acids, 2. protein, 3. restriction endonucleases, 4. transcription factors, 5. interferon, 6. retinoblastoma and 7. Human Genome Project.

1. Nucleic acids. DNA and RNA are nucleic acids responsible for the storage and transmission of genetic information. Nucleic acid biochemistry is discussed.

2. Protein. Proteins are polypeptides responsible for cellular structure and metabolism. Protein biochemistry and the genetic code are discussed.

3. Restriction endonucleases. Type II restriction endonucleases recognize and cleave double-stranded DNA at specific sequences. Restriction endonucleases are used as analytical tools in recombinant DNA technology. Restriction maps of the human interferon-alpha multigene family were determined.

4. Transcription factors. Transcription factors are a class of DNA-binding proteins that bind to specific DNA sequences in gene regulatory regions and control gene expression. Transcription maps of the human interferon-alpha multigene family were determined.

5. Interferon. The interferons are a class of potent multifunctional cytokines that form a primary defense mechanism against viral infections and neoplasms. The human interferon-alpha multigene family was subjected to nucleotide motif analysis.

6. Retinoblastoma. The retinoblastoma gene is a tumor suppressor gene that negatively regulates cell proliferation. The retinoblastoma gene spans 180,388 nucleotides

of genomic DNA and forms the longest known contiguous human DNA sequence. Thus, retinoblastoma DNA was used as the experimental subject in nucleotide motif search algorithm parallel performance experiments.

7. Human Genome Project. The Human Genome Project is an international research initiative with the goal of producing detailed genetic and physical maps of the 24 different human chromosomes. The significance of genetic mapping and sequencing is rationalized.

2.1 Nucleic Acids

Nucleic acids are macromolecules that function to store and transmit genetic information. Nucleic acids are polynucleotides, i.e. polymers composed of a sequence of nucleotide monomers. There are two kinds of nucleic acids: 1. deoxyribonucleic acid (DNA) and 2. ribonucleic acid (RNA).

DNA stores genetic information. A DNA nucleotide sequence is converted to a corresponding RNA nucleotide sequence in a process referred to as *transcription*. The RNA nucleotide sequence is subsequently converted to a corresponding protein amino acid sequence in a process referred to as *translation*. The DNA sequence containing the genetic information required for the synthesis of a functional biological product (RNA or protein) is referred to as a *gene*. A cell typically contains thousands of genes. Thus, DNA molecules are very large.

RNA transmits genetic information from DNA to protein. There are three classes of RNA molecules: 1. ribosomal RNA, 2. messenger RNA and 3. transfer RNA. Ribosomal RNAs (rRNA) are structural components of ribosomes, the large complexes that synthesize proteins. Messenger RNAs (mRNA) act as intermediate molecules moving the information specifying a gene from the DNA of the nucleus to the ribosome, where the corresponding proteins are synthesized. Transfer RNAs (tRNA) are adapter molecules that translate the

genetic information in an mRNA molecule into the corresponding sequence of amino acids that comprise a protein.

A nucleotide has three components: 1. a nitrogenous base, 2. a pentose and 3. a phosphate. A nucleoside has two components: 1. a nitrogenous base and 2. a pentose. Thus, a nucleotide can be considered the 5' monophosphorylated derivative of a nucleoside. The nitrogenous bases and pentoses are heterocyclic compounds in which the carbon and nitrogen atoms are numbered.

1. **Nitrogenous base.** Nitrogenous bases are derivatives of two parent compounds: 1. purine and 2. pyrimidine. Nucleic acids possess two major purine derivatives: 1. adenine (A) and 2. guanine (G). Adenine and guanine are found in both DNA and RNA. Nucleic acids possess three major pyrimidine derivatives: 1. cytosine (C), 2. thymine (T) and 3. uracil (U). Cytosine and thymine are found in DNA while cytosine and uracil are found in RNA. Thymine residues in DNA correspond to uracil residues in RNA. Nitrogenous base structural formulas are presented (Figure 2.1.1.).

2. **Pentose.** A pentose is a 5-carbon cyclic sugar. Nucleic acids possess two kinds of pentoses: 1. 2-deoxyribose and 2. ribose. 2-deoxyribose is found in DNA while ribose is found in RNA. The difference between a 2-deoxyribose and a ribose lies solely on the 2' hydroxyl group on ribose. Thus, the major structural distinction between DNA and RNA is based on the sugar residues: DNA contains only 2-deoxyribose while RNA contains only ribose. Pentose structural formulas are presented (Figure 2.1.1.).

3. **Phosphate.** The pyrophosphate group PO_4 is linked to the hydroxyl group on the pentose 5' carbon.

Deoxyribonucleotides (deoxyribonucleoside 5'-monophosphates) are the structural units of DNAs while ribonucleotides (ribonucleoside 5'-monophosphates) are the structural units of RNAs. The nucleotide sequence is termed the *primary structure* of a nucleic acid. The primary structure stores the genetic information of a DNA molecule. Nucleotide

structural formulas are presented (Figure 2.1.2.). Nucleic acid nomenclature is presented (Table 2.1.1.).

Figure 2.1.1. Nitrogenous bases and ribose sugars (Lehninger, 1982).

Figure 2.1.2. Deoxyadenosine monophosphate conformational model, generic nucleotide structure and deoxynucleotide structural formulas (Kornberg and Baker, 1992).

Category	Base	Nucleoside	Nucleotide	Nucleic Acid
Purines	adenine	adenosine	adenylate	RNA
		deoxyadenosine	deoxyadenylate	DNA
	guanine	guanosine	guanylate	RNA
		deoxyguanosine	deoxyguanylate	DNA
Pyrimidines	cytosine	cytidine	cytidylate	RNA
		deoxycytidine	deoxycytidylate	DNA
	thymine	thymidine	thymidylate	DNA
	uracil	uridine	uridylate	RNA

Table 2.1.1. Nucleic acid nomenclature (Kornberg and Baker, 1992).

Polynucleotide chains are long unbranched polymers formed by phosphodiester bonds between the 5'-hydroxyl group of one nucleotide and the 3'-hydroxyl group of the next nucleotide. Thus, the covalent backbones of nucleic acids consist of alternating phosphate and pentose residues. The nitrogenous bases are side groups that are joined to the sugar-phosphate backbone at regular intervals.

The nucleotide sequences of nucleic acids can be represented schematically. Nitrogenous bases are summarized by four letters: A, C, G and T. 2-deoxyriboses are represented as either vertical or horizontal lines. 2-deoxyribose carbon atoms are represented from 1' at the top to 5' at the bottom of the vertical line. Phosphodiester bonds are symbolized by the letter P within a diagonal line. The connecting lines between nucleotides are drawn diagonally from the middle (3') of the 2-deoxyribose of one nucleotide to the bottom (5') of the 2-deoxyribose of the next nucleotide.

DNA chains exhibit polarity. One end of the chain has a 5'-OH group and the other end has a 3'-OH group that is not linked to another nucleotide. By convention, an oligonucleotide is written with the unreacted 5'-OH group on the left end and the unreacted 3'-OH group on the right end. Thus, the nucleotide sequence is written in the 5' → 3' direction.

Polynucleotides can be written in abbreviated formats. An oligonucleotide with an unreacted 3'-OH would be represented: pApCpGpT. An oligonucleotide with an unreacted 5'-OH would be represented: ApCpGpTp. The most compact nomenclature for the nucleotide sequence would be: ACGT. Polynucleotide structural and schematic formulas are presented (Figure 2.1.3.).

Figure 2.1.3. Polydeoxynucleotide segment (Kornberg and Baker, 1992).

Two polynucleotide strands align themselves to form a double helix. Nucleotides from opposite strands use hydrogen bonds to form complementary polynucleotide strands. Two interacting nucleotides from opposite polynucleotide strands are referred to as a *base pair*. There are two types of base pairs: 1. adenine-thymine and 2. cytosine-guanine. The adenine-thymine (AT) base pair forms two hydrogen bonds. The cytosine-guanine (CG) base pair forms three hydrogen bonds. The two types of base pairs occupy the same amount of space, permitting the DNA double helix to be of uniform diameter. Base-pair interaction between two complementary polynucleotide strands is presented (Figure 2.1.4.).

Figure 2.1.4. DNA double helix unrolled to illustrate the sugar-phosphate backbones and base-pair rungs (Suzuki et. al., 1989).

The two polynucleotide chains of a DNA double helix are antiparallel. The 5' → 3' phosphodiester bonds run in opposite directions. The antiparallel polarity of the two complementary polynucleotide strands is presented (Figure 2.1.5.).

Figure 2.1.5. DNA duplex demonstrating the antiparallel polarity of the complementary strands (Kornberg and Baker, 1992).

Base-pairing between nucleotides is responsible for the alignment of two polynucleotide strands to form a stabilized double helix. The base-pairing complementary of the two strands accounts for the accurate replication of DNA and the accurate transcription of RNA. The three-dimensional topology is referred to as the *secondary structure* of a nucleic acid.

DNA can occur in five conformations: A, B, C, D and Z. The B conformation is the most stable structural form under physiological conditions and is therefore the standard reference point for DNA architecture. B-conformation DNA helix parameters were elucidated using x-ray crystallography.

The sugar-phosphate backbones of the two chains form a right-handed double helix with a 20 Å diameter. The double helix has a wide major groove and a narrow minor groove. The sugar-phosphate backbones of the two chains are on the exterior of the molecule and are connected as a ladder, with the ladder rungs being the nitrogenous bases

connected by hydrogen bonds. The nitrogenous base surface planes are perpendicular to the helical axis. Neighboring bases are spaced 3.4 Å apart. There are ten base pairs per helix turn. Thus, each base pair is rotated 36° relative to its neighbor. Each full turn has a length of 34 Å. The standard B-conformation double-helical model of DNA is presented (Figure 2.1.6.) (Figure 2.1.7.).

The three-dimensional structure of DNA has been reviewed (Zimmerman, 1982) (Dickerson, 1992).

Figure 2.1.6. Double-helical model of DNA. Sticks represent base pairs and the ribbons represent the sugar-phosphate backbones of the two antiparallel strands (Suzuki et. al., 1989).

Figure 2.1.7. B-DNA helix of the dodecamer CGCGAATTCGCG (Suzuki et. al., 1989).

2.2 Protein

Proteins are macromolecules that are responsible for cellular structure and metabolism. Proteins catalyze biochemical reactions which perform numerous functions, e.g. gene regulation. Proteins are polypeptides, i.e. polymers composed of a sequence of amino acid monomers.

The generic amino acid formula is $\text{H}_2\text{N}-\text{CHR}-\text{COOH}$, where R is an amino acid-specific side group which varies from a hydrogen atom in the case of the amino acid glycine, to a complex ring in the case of the amino acid tryptophan. There are 20 common amino acids found in living organisms. The generic amino acid structural formula is presented (Figure 2.2.1.).

Figure 2.2.1. Generic amino acid structural formula, R is an amino acid-specific side group.

The amino acid structural formulas are presented (Figure 2.2.2.).

Amino acids can be covalently linked through a substituted amide linkage termed a *peptide bond* to form a peptide. Such a linkage is formed by the removal of a water molecule (*dehydration*) from the carboxyl group of one amino acid and the amino group of the other amino acid. Thus, peptide-bond formation is an example of a *condensation reaction*. A peptide bond is presented (Figure 2.2.3.).

Figure 2.2.2. Common amino acids found in proteins (Lehninger, 1982).

Figure 2.2.3. Portion of a protein molecule. Three amino acids are linked together by peptide bonds (Watson et. al., 1987).

Several amino acids linked together by peptide bonds form a molecule referred to as a *polypeptide*. The amino acid units in a peptide are often referred to as *residues*. The amino acid residue at the end of a peptide having a free amino group is referred to as the *amino-terminal (N-terminal)* residue. The residue at the opposite end of the peptide having a free carboxyl group is referred to as the *carboxyl-terminal (C-terminal)* residue. Oligopeptide names are derived from the sequence of their constituent amino acids, beginning with the amino terminus on the left and proceeding towards the carboxyl terminus on the right. The tripeptide composed from the three amino acids alanine, valine and aspartic acid is presented (Figure 2.2.4.).

Figure 2.2.4. Tripeptide composed of three amino acids: alanine, valine and aspartic acid (Watson et. al., 1987).

The sequence of amino acids which constitutes a protein can be represented as a sequence of characters from a twenty-character alphabet. This structure is encoded in DNA by the *genetic code* in which each amino acid is represented by a triplet of DNA nucleotides. DNA is a sequence of nucleotides which can be represented as a sequence of characters from a four-character alphabet. Protein synthesis is called *translation* because the information contained in the four-character nucleotide alphabet is translated into the twenty-character amino acid alphabet.

The linear arrangement of amino acids in a polypeptide chain is referred to as the *primary structure* of the protein. The side groups of amino acids attract or repel one

another resulting in different types of *secondary structure* of the protein. Two examples of secondary structures include: 1. the α -helix and 2. the β -pleated sheet. Proteins can be further folded to form a *tertiary structure*. Several folded structures can associate to form a *quarternary structure*, e.g. the oxygen-transporting protein hemoglobin is composed of four protein subunits.

Human interferon-alpha 2 (iFNA2) is a cytokine with broad-spectrum antiviral, antiproliferative and immunomodulatory properties. Human interferon-alpha 2 inhibits viral replication, inhibits malignant cell growth, regulates oncogene expression and activates natural killer cells. Human interferon alpha 2 is effective against eight human diseases: 1. hairy cell leukemia, 2. Kaposi's sarcoma, 3. chronic myelogenous leukemia, 4. non-Hodgkin's lymphoma, 5. chronic granulomatous disease, 6. condyloma acuminatum, 7. juvenile laryngeal papillomatosis and 8. chronic infection with hepatitis B and C viruses (Sen and Lengyel, 1992).

Human interferon-alpha 2 codes for a protein having a signal peptide of 23 amino acids and a mature peptide of 165 amino acids with a calculated molecular weight of 19,390 daltons (Goeddel et. al., 1980) (Maeda et. al., 1980) (Streuli et. al., 1980) (Goeddel et. al., 1981) (Lawn et. al., 1981b) (Bowden et. al., 1984). The three-dimensional structure of the human interferon-alpha 2 protein has been recently determined based on a homology model with the murine interferon-beta protein (Murgolo et. al., 1993). The human interferon-alpha 2 protein backbone trace diagram is presented (Figure 2.2.5.).

Figure 2.2.5. Human interferon-alpha 2 protein, backbone trace diagram (Murgolo et. al., 1993)

The genetic code is the relationship between the sequence of nucleotides in DNA (or mRNA transcript) and the sequence of amino acids in the corresponding protein. The genetic code uses genetic information in the sequence of nucleotides in a DNA molecule to specify the sequence of amino acids in a protein. During protein synthesis, the coded information in DNA is initially transmitted to mRNA, i.e. the deoxyribonucleotide sequence is *transcribed* into a complementary sequence of ribonucleotides. The mRNA is then *translated* into one or more polypeptides, with each amino acid of a polypeptide being encoded for by a particular sequence of three nucleotides (*codon*) in the mRNA. An mRNA molecule contains a series of nonoverlapping nucleotide triplets (codons) which specify the amino acid sequence of a polypeptide. Polypeptide synthesis begins at a specific AUG (*initiator codon*) in the mRNA and the translating machinery reads the triplets sequentially from this point. Thus, although triplets in a sequence of nucleotides could be read in three different ways (*reading frames*), in practice the correct reading frame is determined by the fixed starting point.

A codon does not interact directly with its corresponding amino acid. The amino acid must be linked to a tRNA adaptor molecule which contains a triplet of nucleotides (*anticodon*) complementary to the codon for that amino acid. For example, codon ACG is recognized by a tRNA containing the anticodon CGU. Codons and anticodons are written in the 5'-to-3' direction. The first nucleotide in a codon pairs with the third nucleotide in its corresponding anticodon.

The four nucleotides (A,C,G and U) when grouped into triplets in an mRNA molecule can generate $4^3 = 64$ possible triplet combinations. 61 codons encode for 20 amino acids. In most cases an amino acid is encoded by multiple (*synonymous*) codons. This phenomenon is referred to as *degeneracy*. The remaining three codons, UAA (*ochre codon*), UAG (*amber codon*) and UGA (*opal or umber codon*), are called *nonsense codons* (*stop codons*) (*termination codons*) which specify the termination of polypeptide chain synthesis.

The three bases of a codon do not contribute equally to the specificity of the codon. The second base contributes maximally and the third base contributes minimally. Thus, certain codons which specify the same amino acid differ from each other only in the third base. This phenomenon is referred to as the *wobble hypothesis*.

The genetic code is nearly universal, i.e. applicable to all living systems. This phenomenon is referred to as the *universal code theory*. There are exceptions, e.g. in mammalian mitochondria AUA specifies methionine, while AGA and AGG function as stop codons. Mitochondria have a different genetic code because mitochondrial DNA uses a distinct set of tRNAs. Thus, the genetic code is nearly but not absolutely universal. It is believed that distinct genetic codes evolved from a common primordial genetic code (Singleton and Sainsbury, 1987). The genetic code is presented (Table 2.2.1.).

Codon	Amino Acid
AAA	lysine
AAC	asparagine
AAG	lysine
AAU	asparagine
ACA	threonine
ACC	threonine
ACG	threonine
ACU	threonine
AGA	arginine
AGC	serine
AGG	arginine
AGU	serine
AUA	isoleucine
AUC	isoleucine
AUG	methionine
AUU	isoleucine
CAA	glutamine
CAC	histidine
CAG	glutamine
CAU	histidine
CCA	proline
CCC	proline
CCG	proline
CCU	proline
CGA	arginine
CGC	arginine
CGG	arginine
CGU	arginine
CUA	leucine

CUC	leucine
CUG	leucine
CUU	leucine
GAA	glutamic acid
GAC	aspartic acid
GAG	glutamic acid
GAU	aspartic acid
GCA	alanine
GCC	alanine
GCG	alanine
GCU	alanine
GGA	glycine
GGC	glycine
GGG	glycine
GGU	glycine
GUA	valine
GUC	valine
GUG	valine
GUU	valine
UAA	stop
UAC	tyrosine
UAG	stop
UAU	tyrosine
UCA	serine
UCC	serine
UCG	serine
UCU	serine
UGA	stop
UGC	cysteine
UGG	tryptophan
UGU	cysteine
UUA	leucine
UUC	phenylalanine
UUG	leucine
UUU	phenylalanine

Table 2.2.1. Genetic code (Suzuki et. al., 1989).

The three-dimensional structure of proteins has been reviewed (Richardson and Richardson, 1989) (Rizo and Gierasch, 1992).

2.3 Restriction Endonucleases

Restriction endonucleases are strain-specific enzymes which enable bacteria to recognize and rapidly destroy foreign DNA. Restriction endonucleases are endodeoxyribonucleases that recognize specific double-stranded DNA sequences and cleave both strands. A restriction-modification system is a pair of enzymes consisting of a restriction endonuclease (restriction enzyme) and a methylase (modification enzyme). A methylase recognizes and modifies the same DNA sequence recognized by its corresponding restriction endonuclease. Methylases transfer methyl groups from S-adenosyl-methionine (AdoMet) to specific adenine or cytosine residues in the DNA. Modification enzymes protect host DNA against their own restriction endonucleases. Restriction-modification systems are found throughout bacteria and function to eliminate foreign DNA that gains entrance to the cell.

The restriction endonuclease nomenclature system consists of three components: 1. an italicized three-letter acronym identifies the genus and species of the parent organism, 2. an additional letter, if necessary, identifies the strain or serotype and 3. a Roman numeral reflects the chronological order of identification or characterization. For example, *EcoRI* designates the first restriction endonuclease that was isolated from *Escherichia coli* strain R (Smith and Nathans, 1973).

Three categories of restriction-modification systems have been defined on the basis of DNA cleavage. In type I systems, DNA cleavage occurs at nonspecific sites 400-7000 nucleotides from the recognition site. In type II systems, DNA cleavage occurs at specific sites within or adjacent to the recognition site. In type III systems, DNA cleavage occurs 25-27 nucleotides from the recognition site. Because of their specific recognition sites and the proximity of their cleavage sites, type II restriction endonucleases have been exploited as analytical tools in molecular biology. Therefore, the remainder of this section will focus on type II restriction endonucleases.

Restriction endonuclease recognition sequences are usually composed of uniquely-specified nucleotides. Degenerate recognition sequences also occur in which restriction endonucleases can accept several alternative nucleotides at a given position while rigorously excluding others. For example, the restriction endonuclease *AccI* has the recognition sequence *gmkac*. The degenerate nucleotide *m* indicates that the enzyme can cleave the DNA sequence if either *a* or *c* nucleotides are present at the third residue. The restriction enzyme cannot cleave if *g* or *t* nucleotides are present. The degenerate nucleotide *k* indicates that the enzyme can cleave the DNA sequence if either *g* or *t* nucleotides are present at the fourth residue. The restriction enzyme cannot cleave if *a* or *c* nucleotides are present. Thus, at both central positions *AccI* is recognizing two specific base pairs in a specific orientation. The basis for this is unknown.

Restriction endonuclease recognition sequences are usually 4-8 nucleotides long. Most recognition sites contain a dyad axis of symmetry. A symmetrical recognition sequence is termed a *palindrome*. A restriction endonuclease makes two single-stranded breaks, one on each DNA strand at the recognition site. If the two breaks occur at the center of symmetry, the resulting termini are referred to as *flush* or *blunt* ends. If the two breaks are staggered, i.e. equidistant from and on opposite sides of the center of symmetry, the resulting termini are known as *cohesive* or *sticky* ends.

Restriction endonuclease cleavage usually occurs symmetrically within the recognition sequence. Some endonucleases cleave on the 5' side of the dyad axis producing overhanging 5' single-stranded termini, e.g. *EcoRI* (Hedgpeth et. al., 1972). Other endonucleases cleave in the center producing flush termini, e.g. *PvuII* (Gingeras et. al., 1981). Yet other endonucleases cleave on the 3' side producing overhanging 3' single-stranded termini, e.g. *SacI* (Arrand et. al., 1994). Restriction endonuclease cleavage patterns are presented (Table 2.3.1.).

Endonuclease	Recognition Sequence	Cleavage Products		Classification
SacI	GAGCTC CTCGAG	GAGCT C	C TCGAG	sticky ends
PvuII	CAGCTG GTCGAC	CAG GTC	CTG GAC	blunt ends
EcoRI	GAATTC CTTAAG	G CTTAA	AATTC G	sticky ends

Table 2.3.1. Restriction endonuclease cleavage patterns.

The property of staggered cleavage generates DNA fragments with protruding termini. Protruding termini are referred to as cohesive or sticky because such ends will form hydrogen bonds with complementary ends. DNA fragments produced by restriction endonuclease staggered cleavage readily anneal with other fragments produced by the same restriction enzyme.

Consider DNA fragments that were generated by restriction endonuclease cleavage. DNA fragments originating from different sources can be joined together at their common restriction sites using the enzyme T4 DNA ligase. Protruding termini are readily ligated together. Blunt ends are more difficult to ligate than either type of protruding extension. The efficient joining of blunt-ended DNA fragments requires higher DNA fragment and T4 DNA ligase concentrations (Sgaramella, 1972).

The ability of restriction endonucleases to cleave DNA at specific nucleotide sequences combined with the ability of T4 DNA ligase to rejoin phosphodiester backbone nicks in DNA permits the formation of recombinant DNA molecules. This ability to restructure DNA forms the basis of *recombinant DNA technology*.

In addition to the creation and manipulation of recombinant DNA molecules, restriction endonucleases are further used for the initial characterization of DNA molecules. Using restriction endonucleases, it is possible to form a diagrammatic representation of the linear arrangement at which the restriction endonuclease cleavage sites occur within a DNA molecule. Such a diagram is referred to as a *restriction map*. Restriction endonuclease

cleavage sites serve as useful reference points for allowing investigators to identify areas between unknown fragments and to target specific regions for nucleotide sequencing reactions.

Restriction endonucleases are used to identify potential genes in unmapped DNA. Nucleotide sequences in the promoter regions of numerous genes contain CG-rich regions that are identifiable by restriction endonucleases such as HpaII.

A total of 2558 restriction endonucleases are now known including 21 type I enzymes, 2532 type II enzymes and 5 type III enzymes (Macelis, 1994). There are 199 type II enzymes with prototype recognition sequences (Macelis, 1994). Numerous restriction endonucleases share common specificities. Restriction endonucleases with identical recognition sequences are termed *isoschizomers*. Restriction endonucleases with identical recognition sequences but different cleavage sites represent a restricted class of isoschizomers termed *neoschizomers*. For example, the SmaI and XmaI recognition sequences are *ccc*ggg* and *c*ccggg* respectively, where the asterisk represents the cleavage site. Thus, the restriction endonucleases SmaI and XmaI are neoschizomers.

A comprehensive list of restriction endonucleases is compiled and broadcast monthly (Roberts and Macelis, 1994). Restriction endonucleases have been reviewed (Yuan, 1981) (Brooks, 1987) (Anderson, 1990) (Wilson and Murray, 1991) (Kant, 1992) (Roberts and Halford, 1993).

2.4 Transcription Factors

Eukaryotic transcription is the synthesis of a messenger RNA (mRNA) molecule in which ribonucleotide 5'-triphosphates base-pair with complementary deoxyribonucleotides on a DNA template and are polymerized in the the 5'-to-3' direction. The transcription reaction is mediated by the enzyme RNA polymerase (transcriptase). Transcription has been reviewed (Weinmann, 1992) (Buratowski, 1994).

Gene expression is a multistage process which yields the formation of functional proteins. Transcription is the first stage of the gene expression process and results in the production of a primary mRNA transcript from genomic DNA. This is followed by the post-transcriptional processes of RNA splicing and translation. Thus, transcription represents a primary target for gene regulation.

Transcription factors are a diverse class of DNA-binding proteins that bind to specific DNA sequences in gene regulatory regions and control gene transcription. DNA-binding proteins are classified into families on the basis of the protein structures used to mediate DNA binding or the dimerization that is often essential for DNA binding. Transcription factors are grouped into seven classes of related structural motifs: 1. helix-turn-helix, 2. homeodomain, 3. zinc finger, 4. steroid receptor, 5. leucine zipper, 6. helix-loop-helix and 7. β -sheet (Pabo and Sauer, 1992).

Transcription factors bind to specific DNA recognition sites and exert two possible effects on gene expression: 1. transcriptional activation and 2. transcriptional repression.

1. **Transcriptional activation.** Activation domains are specific regions of the transcription factor protein which activate transcription (Ptashne, 1988). Activation domains are distinct from the DNA binding regions of a transcription factor. Activation domains either interact with RNA polymerase directly or interact with other transcription factors in order to facilitate transcription. Transcription factors form a basal transcriptional complex that subsequently interacts with RNA polymerase. For example, transcription

factor TFIID specifically binds to a DNA sequence referred to as a TATA box. The mammalian transcription factor ATF then binds to and changes the conformation of the transcription factor TFIID. This altered conformation facilitates the subsequent binding of transcription factors TFIIC, TFIIIE and RNA polymerase to form a stable transcriptional complex (Horikoshi et. al., 1988). In summary, transcription factor DNA-binding domains attach to DNA. Transcription factor activation domains alter the conformation of other transcription factors that have previously bound to DNA. This facilitates the assembly of a stable transcriptional complex.

2. Transcriptional repression. Transcription factors exert inhibitory effects on transcription by four mechanisms: 1. competition for binding, 2. sequestration in solution, 3. quenching of activity and 4. direct repression.

1. Competition for binding. A negatively-acting transcription factor could act by binding to a DNA site and preventing the binding of a positively-acting transcription factor. For example, the β -interferon promoter has two transcriptional activators which are necessary for gene activation. A transcriptional repressor competes with the two activators for the same binding site. During viral infection the repressor is inactivated, allowing the two activators to bind thereby activating transcription (Goodbourn et. al., 1986).

2. Sequestration in solution. A negatively-acting transcription factor can interfere with DNA binding by interacting with a positively-acting transcription factor in solution and forming a complex which cannot bind to DNA. For example, the negatively-acting I-POU transcription factor interacts with the positively-acting CF1a-POU transcription factor and prevents it from binding to DNA (Treacey et. al., 1991).

3. Quenching of activity. An inhibitory transcription factor can interfere with the activation of transcription mediated by a bound factor. For example, yeast mating type $\alpha 2$ protein binds to a site adjacent to the MCM1 transcriptional activator site. The activation domain is masked thereby preventing the MCM1 from activating the α -specific genes (Keleher et. al., 1986).

4. **Direct repression.** It is possible that transcription factors directly inhibit transcription using an inhibitory domain analogous to the activation domain. The inhibitory domain would interfere with the formation or stability of the basal transcriptional complex.

Gene expression is regulated in response to a particular signal or a particular cell type. Transcription factors are modulated by two mechanisms: 1. regulation of synthesis and 2. regulation of activity.

1. **Regulation of synthesis.** Regulated synthesis results in a particular transcription factor being present in only a specific cell type. For example, the expression of the Oct-2 transcription factor gene results in the specific activation of immunoglobulin gene expression in B cells (Scheidereit et. al., 1987).

2. **Regulation of activity.** A transcription factor may be synthesized in all tissues but is converted into an active form only in a specific cell type or in response to a specific stimulus. Transcription factors may be activated by three mechanisms: 1. ligand binding, 2. dissociation of an inhibitory protein and 3. protein modification.

1. **Ligand binding.** A transcription factor when bound with a ligand undergoes conformational change resulting in activation. For example, yeast transcription factor ACE1 activates transcription of the metallothionein gene in response to copper. The yeast transcription factor undergoes a conformational change in the presence of copper. This allows ACE1 to bind regulatory sites in the metallothionein gene and activate transcription (Furst et. al., 1988).

2. **Dissociation of an inhibitory protein.** A transcription factor may be activated by the disruption of an inhibitory protein-protein interaction. For example, the phorbol ester treatment of T cells or HeLa cells disrupts the interaction of an inhibitory protein with the NF- κ B protein. Thus, phorbol ester treatment activates the NF- κ B transcription factor (Baeurele and Baltimore, 1988).

3. **Protein modification.** Protein modification is a direct means of activating a transcription factor in response to a specific signal. For example, cyclic AMP stimulates

the enzyme protein kinase A. Protein kinase A then phosphorylates the CREB transcription factor. CREB subsequently mediates the activation of several genes (Yamamoto et. al., 1990).

Transcription factors have been reviewed (Morimoto, 1992) (Pabo and Sauer, 1992) (Latchman, 1993).

2.5 Interferon

The cytokines are a broad heterogeneous group of proteins that regulate intercellular communication. The cytokines are endogenous mediators of inflammatory and immunological host defense reactions. The cytokines have multiple regulatory roles: 1. cell proliferation, 2. cell differentiation, 3. hematopoiesis, 4. immune response, 5. fever, 6. inflammatory response, 7. cytotoxic cells, 8. phagocytic cells, 9. tissue remodelling, 10. bone formation, 11. antiparasitic host defense and 12. antiviral host defense. Cytokine classes include: 1. growth factors, 2. lymphokines, 3. colony stimulating factors, 4. transforming growth factors, 5. tumor necrosis factors and 6. interferons. Cytokine research will generate insight into the basic principles of cell biology and immunology. The cytokines are of further clinical significance. Thus, the cytokines have been the subject of intense investigation. Cytokine biochemistry has been reviewed (Evans and Whicher, 1993).

The interferons are a class of potent multifunctional cytokines that form a primary defense mechanism against viral infections and neoplasms. The interferons were originally identified on the basis of their ability to inhibit viral replication. The interferons exhibit additional regulatory effects: 1. cell proliferation, 2. cell differentiation, 3. immune system, 4. macrophage activation, 5. enhancement of lymphocyte-mediated toxicity and 6. hormonal interactions. The interferons exert their multiple effects primarily by inducing protein synthesis. The interferons are present in numerous vertebrate species including: 1. man, 2. mouse, 3. rat, 4. pig and 5. cattle. Interferon biochemistry has been reviewed (Sen and Lengyel, 1992).

Interferon classification is based on three parameters: 1. sensitivity to acid treatment, 2. antigenicity and 3. cellular origin. Sensitivity to acid treatment: type I and type II interferons are acid-stable and acid-labile respectively. Antigenicity: α , β , ω and γ interferons designate four serologically-distinct families. Cellular origin: leukocyte.

fibroblast and immune interferons correspond to the α , β and γ serotypes respectively. The paper adopts the systematic interferon nomenclature of Diaz et. al. (1993) (Table 2.5.1.).

Type	Family	Gene	Symbol
I	alpha	interferon-alpha 1 gene	IFNA1
		interferon-alpha 2 gene	IFNA2
		interferon-alpha 4 gene	IFNA4
		interferon-alpha 5 gene	IFNA5
		interferon-alpha 6 gene	IFNA6
		interferon-alpha 7 gene	IFNA7
		interferon-alpha 8 gene	IFNA8
		interferon-alpha 10 pseudogene	IFNA10
		interferon-alpha 13 gene	IFNA13
		interferon-alpha 14 gene	IFNA14
		interferon-alpha 16 gene	IFNA16
		interferon-alpha 17 gene	IFNA17
		interferon-alpha 21 gene	IFNA21
		interferon-alpha 22 pseudogene	IFNAP22
	beta	interferon-beta 1 gene	IFNB1
	omega	interferon-omega 1 gene	IFNW1
		interferon-omega 2 pseudogene	IFNWP2
		interferon-omega 4 pseudogene	IFNWP4
		interferon-omega 5 pseudogene	IFNWP5
		interferon-omega 9 pseudogene	IFNWP9
		interferon-omega 15 pseudogene	IFNWP15
		interferon-omega 18 pseudogene	IFNWP18
		interferon-omega 19 pseudogene	IFNWP19
	non-alpha, non-omega	interferon-alpha 11 pseudogene (type y)	IFNP11
		interferon-alpha 12 pseudogene (type x)	IFNP12
		interferon-alpha 20 pseudogene	IFNP20
		interferon-alpha ? pseudogene	IFNP23
II	gamma	interferon-gamma gene	IFNG

Table 2.5.1. Nomenclature of the human interferon genes (Diaz et. al., 1993).

Human interferon-alpha corresponds to an acid-stable, serologically-distinct family of cytokines produced by leukocytes. The human interferon-alpha family consists of twelve proteins: 1. IFNA1, 2. IFNA2, 3. IFNA4, 4. IFNA5, 5. IFNA6, 6. IFNA7, 7. IFNA8, 8. IFNA13, 9. IFNA14, 10. IFNA16, 11. IFNA17 and 12. IFNA21 (Diaz et. al.,

1993). Human inteferon-alpha protein molecular weights range from 16,000 to 27,000 (Zoon et. al., 1987). Disulfide bonds are formed between the residues cys 1 - cys 98 and cys 29 - cys 138 in human inteferon-alpha 2 (Wetzel, 1981). Several human interferon-alpha proteins are glycosylated (Labdon et. al., 1984). Human interferon-alpha has demonstrated significant activity in the treatment of several viral and oncological diseases: 1. hairy cell leukemia, 2. condyloma acuminata, 3. AIDS-related Kaposi's sarcoma, 4. hepatitis B and 5. chronic hepatitis C (Dorr, 1993). Human interferon-alpha has been reviewed (Gutterman, 1994).

The human interferon-alpha multigene family consists of twelve genes and two pseudogenes. The twelve genes include: 1. IFNA1, 2. IFNA2, 3. IFNA4, 4. IFNA5, 5. IFNA6, 6. IFNA7, 7. IFNA8, 8. IFNA13, 9. IFNA14, 10. IFNA16, 11. IFNA17 and 12. IFNA21. The two pseudogenes include: 1. IFNA10 and 2. IFNAP22 (Diaz et. al., 1993). The human interferon-alpha genes and pseudogenes have been localized by *in situ* chromosomal hybridization to the 9p13 - 9p22 chromosomal bands (Figure 2.5.1.) (Trent et. al., 1982). A physical map of the human type-I interferon gene cluster has been constructed from YAC clones. The physical map demonstrates the location and relative orientation of the human interferon-alpha genes and pseudogenes (Figure 2.5.2.) (Diaz et. al., 1994).

Figure 2.5.1. Human chromosome 9 cytogenetic map featuring type-I interferon gene cluster locus (Trent et. al., 1982) (Adler, 1994).

Figure 2.5.2. Human type-I interferon gene cluster (Diaz et al., 1994).

The human interferon-alpha genes lack introns (Henco et. al., 1985). A human interferon-alpha gene encodes a preinterferon protein that consists of a signal (leader) peptide and a mature peptide. The signal peptide facilitates interferon transport through the cellular membrane during secretion. During maturation the leader peptide is proteolytically cleaved from the preinterferon protein leaving the mature interferon protein. The signal peptide is composed of 23 amino acids. The mature interferon peptide is composed of 165 - 166 amino acids (Weissmann and Weber, 1986).

Human interferon-alpha genes are normally not expressed in uninduced cells. Human interferon-alpha induction occurs in response to three stimuli: 1. viruses, 2. double-stranded RNA in the form of poly (I)-poly (C) or 3. bacterial lipopolysaccharides (DeMaeyer and DeMaeyer-Guignard, 1988). Double-stranded RNA is the intermediate product responsible for viral-induced interferon synthesis (Lai and Joklik, 1973).

Current knowledge of human interferon-alpha transcriptional regulation is limited primarily to the human interferon-alpha 1 gene. The human interferon-alpha 1 gene is transcriptionally regulated (Weidle and Weissmann, 1983). Viral-induced transcription is mediated by the 5'-promoter region of the human interferon-alpha 1 gene. The 5' flanking regions of the human interferon-alpha genes display a 75% degree of homology (Sehgal, 1982). The virus-response element is the minimal promoter requirement for conferring transient viral-induced transcription on heterologous promoter elements. The virus-response element is the promoter sequence extending between positions -109 to -64 in the 5' direction relative to the cap site of the human interferon-alpha 1 gene. The virus-response element is composed of two imperfect repeats: 1. RepA and 2. RepB. RepA contains two multiple-sequence alignment regions termed R1 and R2. RepB similarly contains two multiple-sequence alignment regions termed R1' and R2' (Ryals et. al., 1985).

The TG factor is a transcriptional activator of human interferon-alpha. The TG factor recognition site is referred to as the TG sequence. One TG sequence has been identified in the human interferon-alpha 1 promoter (MacDonald et. al., 1990).

The interferon regulatory factors are transcriptional regulators of human interferon-alpha and human interferon-beta. Two interferon regulatory factors have been identified: interferon regulatory factor 1 (IRF-1) and interferon regulatory factor 2 (IRF-2). Interferon regulatory factor 1 recognizes sequences in both human interferon-alpha and human interferon-beta promoters (Fujita et. al., 1988) (Miyamoto et. al., 1988). Interferon regulatory factors 1 and 2 are structurally related and recognize the same binding sequences. However, these factors have opposite effects: interferon regulatory factor 1 is a transcriptional activator whereas interferon regulatory factor 2 is a transcriptional repressor (Harada et. al., 1989). Two interferon regulatory factor-like sites were identified in the human interferon-alpha 1 promoter (MacDonald et. al., 1990).

In summary, current knowledge of human interferon-alpha transcriptional regulation is limited primarily to the human interferon-alpha 1 gene. The promoters of the remaining human interferon-alpha genes are less well characterized than the human interferon-alpha 1 promoter. The current research objective is the characterization of the human interferon-alpha promoters. Identification of promoter transcription factor binding sites will facilitate elucidation of the transcriptional mechanism by which the human interferon-alpha genes are expressed. Human interferon-alpha molecular genetics has been reviewed (Henco et. al., 1985) (Weissmann and Weber, 1986) (Hayes and Zoon, 1994).

2.6 Retinoblastoma

Retinoblastoma (Rb) is a malignant intraocular tumor of the developing retina that occurs in early childhood (Shields, 1983). The term *retinoblastoma* originated from the resemblance of tumor cells to undifferentiated retinoblasts (Gallie et. al., 1982). Retinoblastoma is correlated with the inactivation of both alleles of the retinoblastoma (Rb1) gene. The retinoblastoma gene is usually inactivated by somatic mutation. Retinoblastoma gene failure renders cells incapable of negative regulation of cell proliferation and ultimately leads to neoplastic transformation.

Retinoblastoma gene dysfunction predisposes primarily to retinoblastoma. Retinoblastoma mutations have been extended to numerous malignancies: 1. bladder carcinomas (Horowitz et. al., 1989), 2. small cell lung carcinomas (Harbour et. al., 1988), 3. prostate carcinomas (Bookstein et. al., 1990), 4. breast carcinomas (Lee et. al., 1988) and 5. primary leukemia (Furukawa et. al., 1991). These findings provided the first evidence that the loss of a gene is correlated with tumorigenesis. This gave rise to the concept of a *tumor suppressor gene* which has a negative influence on the regulation of cell growth. Thus, the retinoblastoma gene is the prototype model for a tumor suppressor gene (Friend et. al., 1986).

The retinoblastoma gene has been mapped by detailed karyotypic analysis to the 13q14.2 chromosomal band (Bowcock et. al., 1991). The retinoblastoma gene spans 180,388 nucleotides of genomic DNA and consists of 27 exons (Toguchida et. al., 1993). The retinoblastoma promoter is highly rich in GC residues that constitute a CG island (Ford et. al., 1990). CCAAT and TATA motifs have not been located. Several potential binding sites for the transcription factors Sp1, ATF and E2/DRTF1 have been found (Zacksenhaus et. al., 1993). Endogenous retinoblastoma mRNA expression was observed in nearly all tissues examined. Ubiquitous expression of retinoblastoma mRNA is consistent with the promoter being a *housekeeping* promoter (Goodrich and Lee, 1993). The retinoblastoma

mRNA (Rb1 mRNA) is 4.7 kb long and consists of three regions: 1. short 5' untranslated sequence, 2. 2.7 kb coding region and 3. 2 kb 3' untranslated sequence (Lee et. al., 1987a).

The retinoblastoma protein (p110^{Rb1}) is a 110-kD nuclear phosphoprotein. The retinoblastoma protein consists of 928 amino acids and exhibits DNA-binding activity (Lee et. al., 1987b). The retinoblastoma protein is a transcription factor that regulates cell proliferation by modulating the activity of other transcriptional activators such as Sp1, ATF2 and E2F/DRTF1 (Zacksenhaus et. al., 1993).

Retinoblastoma oncogenic mutations have been classified into four categories: 1. deletion, 2. frameshift, 3. chain termination and 4. point (Zhang et. al., 1993). Chromosomal deletion mutations lead to a complete loss of function. Frameshift mutations and chain termination mutations lead to premature termination of translation leading to truncated or unstable retinoblastoma proteins (Dunn et. al., 1989). Point mutations produce missense mutant retinoblastoma proteins (Gallie et. al., 1990). Point mutations affect RNA splicing donor or acceptor sequences and cause entire exons to be deleted from the processed retinoblastoma mRNA (Dunn et. al., 1989). Point mutations have been found in the potential Sp1 and ATF recognition sites in the retinoblastoma promoter (Sakai et. al., 1991). This suggests that these transcription factors are required for activating retinoblastoma transcription. Mutation analysis indicates that two conserved regions of the retinoblastoma protein, termed A and B, between amino acid residues 393 - 572 and 646 - 772 form a binding site for viral oncoprotein interactions (Hu et. al., 1990).

Retinoblastoma molecular genetics has been further reviewed (Weinberg, 1992) (Goodrich and Lee, 1993) (Levine, 1993) (Zacksenhaus et. al., 1993) (Zhang et. al., 1993).

2.7 Human Genome Project

The human genome is the complete DNA sequence of *Homo sapiens* containing its entire genetic information. The diploid human genome is organized linearly into 23 pairs of chromosomes. A eukaryotic chromosome is a cytological structure located in the nucleus of a eukaryotic cell. Chromosomes are large double-helical DNA molecules that are associated with RNA and histone proteins. The DNA component is comprised of genes which function in the storage and transmission of genetic information. A genome is divided into a number of chromosomes that is characteristic for each species.

The diploid human genome contains 6 - 7 billion base pairs of DNA which specify an estimated 100,000 genes (Guyer and Collins, 1993). A gene is a DNA protein-encoding sequence and its associated regulatory sequences. The coding nucleotides are transcribed to a messenger RNA (mRNA) molecule which is then translated to a protein molecule. A gene occupies a specific locus along a chromosome.

The 100,000 human genes encode an equal number of proteins. The proteins control all aspects that comprise a functional organism, i.e. reproduction, development and metabolism. Currently, the function of only a small number of genes is known. The systematic characterization of all the genes comprising the human genome will have an enormous impact on medicine. Human genome structure has been reviewed (Wagner et. al., 1993).

The Human Genome Project (HGP) is an international research initiative with the goal of producing detailed genetic and physical maps for each of the 24 different human chromosomes. DNA sequence determination of the human genome will proceed when sequencing technology advances to the point at which it is economically feasible. Several nonhuman model organism genomes will be further analyzed. The model organism genomes will provide comparative information essential for understanding how the human genome functions.

A genetic map depicts the linear arrangement of genes or genetic marker sites along a chromosome. Two types of genetic maps are identified: 1. genetic linkage maps and 2. physical maps. Genetic linkage maps are based on the frequency with which genetic markers are coinherited. The centimorgan (cM) is the distance unit in genetic linkage maps. 1 cM is equivalent to approximately 1 million base pairs or 1 megabase (Mb). Physical maps determine actual distances between genes on a chromosome. Physical maps are based on collections of overlapping DNA fragments referred to as *contigs*. The base pair is the distance unit in physical maps. Either kilobase (kb) or megabase (Mb) units are used. A DNA sequence map in which the genetic code is specified by individual nucleotides, is the highest resolution physical map. Genetic maps serve as resources in the search for genes responsible for genetically-mediated diseases as well as for the further study of gene structure, function and expression.

The Human Genome Project has six scientific objectives: 1. genetic map, 2. physical map, 3. DNA sequence, 4. model organisms, 5. technology development and 6. computational tools.

1. Genetic map. The creation of a dense (2 cM resolution) genetic linkage map of the human genome. This map will require approximately 1650 evenly spaced and polymorphic markers to be characterized within the genome (Donis-Keller et. al., 1987). Such a map will facilitate the localization of genes exhibiting mendelian inheritance to within a tolerance of 1 Mb (McKusick, 1994).

2. Physical map. The creation of a physical map of the human genome. This map will be formed by assembling contigs of at least 2 Mb in length with sequence-tagged sites spaced every 100 kb. The sequence-tagged site (STS) has been adopted as a genetic map definition language. A sequence-tagged site is a 100 - 1000 nucleotide sequence with three characteristics: 1. unique in the genome, 2. identifies a mapped element and 3. amplifiable by the polymerase chain reaction. Sequence-tagged sites can be used to identify clones to

generate overlapping inserts for a physical map. Sequence-tagged sites can also be used as correspondence points between genetic and physical maps (Olson et. al., 1989).

3. DNA sequence. Current genome analysis strategy is a two-tier approach in which maps are created first and wholesale sequencing will be delayed until technological improvements are made. Sequencing technology is being improved by two approaches: 1. optimization of existing technologies and 2. development of novel technologies. Existing sequencing technology optimizations include: 1. improved experimental planning, 2. automation and 3. increased data throughput. Novel sequencing technologies undergoing development include: 1. time-of-flight mass spectrometry (Jacobson et. al., 1991), 2. atomic force and scanning tunneling microscopies (Lindsay et. al., 1991), 3. single molecule sequencing (Soper et. al., 1991) and 4. hybridization (Drmanac et. al., 1990). Innovative sequencing technologies will offer order-of-magnitude improvements.

4. Model organisms. Parallel analysis of the genomes of a small number of well-characterized nonhuman model organisms offers two advantages: 1. model genomes are smaller and more tractable to analysis and 2. elucidation of model genomes will facilitate interpretation of the human genome. Nine organisms have been designated for genome analysis: 1. *Mus musculus* (mouse), 2. *Caenorhabditis elegans* (nematode), 3. *Drosophila melanogaster* (fruit fly), 4. *Arabidopsis thaliana* (plant), 5. *Saccharomyces cerevisiae* (yeast), 6. *Escherichia coli* (bacterium), 7. *Bacillus subtilis* (bacterium), 8. *Mycobacterium tuberculosis* (bacterium) and 9. *Mycobacterium leprae* (bacterium).

5. Technology development. Methods for genetic mapping, physical mapping and DNA sequencing will have to be substantially improved before the complete analysis of large genomes is feasible. Instrumentation technologies to automate mapping and sequencing procedures are vital to the success of the genome project. Automation and robotics cut across numerous areas of genome research and require particular attention.

6. Computational tools. The collection, organization, interpretation and dissemination of large amounts of complex mapping and sequencing data generated by the

Human Genome Project will require algorithms, software, databases and operational infrastructure development. Genome informatics consists of three areas: 1. laboratory data management, 2. databases and 3. analytical tools. The Genome Data Base (GDB) is emerging as a major resource for genome research. The Genome Data Base stores human gene mapping data including DNA markers, map locations, genetic disease loci and bibliographic reference citations (Cuttichia et. al., 1993). Computational genome tools have three analytical roles: 1. analyze the complex signals generated by data-acquisition devices, 2. extract meaningful information from molecular sequences and 3. visualize scientific data. Genome informatics has been reviewed (Smith, 1994).

The impact of genomic maps on locating disease genes is already evident. New disease genes are being found and reported at the rate of several per month (Guyer and Collins, 1993). Positional cloning is a technique that makes it possible to isolate genes from defined chromosomal locations (Collins, 1992). For example, the Kallmann syndrome is an X-linked disorder of the gonadal and olfactory functions. Genetic linkage mapping localized the Kallmann syndrome gene to the Xp22.3 chromosomal band (Meitinger et. al., 1990). The Kallmann syndrome gene has been isolated (Franco et. al., 1991) (Legouis et. al., 1991).

The Human Genome Project has been further reviewed (Yager et. al., 1991) (Collins and Galas, 1993) (Engel, 1993) (Guyer and Collins, 1993) (Olson, 1993) (Hoffman, 1994).

Chapter 3

Nucleotide Motif Search Algorithm

Numerous sequence analysis problems in computational molecular biology can be expressed as nucleotide motif search problems, e.g. restriction analysis and transcription analysis. Nucleotide motif search is a specialized instance of the multiple keyword search problem. A multiple keyword search algorithm was developed for searching for class 1 nucleotide motifs within DNA sequences.

3.1 Keyword Search Problem

Consider the keyword k and the text t to be two strings defined over an arbitrary alphabet Σ . The keyword length is defined as m , $|k| = m$. The text length is defined as n , $|t| = n$. The keyword length m is typically much shorter than the text length n , $m \leq n$. The keyword search problem is to find all occurrences of the keyword as a substring within the text. The output is the set of positions in the text where the keyword occurs.

The multiple keyword search problem is a generalization of the keyword search problem. Consider a finite set of y keywords $k_1, k_2, \dots, k_y$ and a text t defined as strings over an arbitrary alphabet Σ . The multiple keyword search problem is to find all occurrences of each keyword as a substring within the text. The output is the set of positions in the text where any of the keywords occur. The multiple keyword search problem has been solved using deterministic finite automata (Aho and Corasick, 1975). String processing algorithms have been reviewed (Aho, 1990).

3.2 Nucleotide Motif Search Problem

A motif is defined as a continuous segment of a macromolecular sequence. Several motif classes have been defined including: 1. exact match, 2. percentage match, 3. weighted matrix match, 4. inverted repeat or stem-loop, 5. direct repeat or 6. set membership (Table 3.2.1.). The simplest category is the class 1 motif which involves an exact match to a short defined sequence (Staden, 1990). Class 1 nucleotide motifs occur within DNA as transcription factor binding sites and restriction endonuclease recognition sites.

Class	Description
1	Exact match to a short defined sequence. The IUB symbols can be used for DNA sequences (FEBS, 1985).
2	Percentage match to a defined short sequence. In nucleic acids, the IUB symbols can be used.
3	Match to a defined sequence, using a score matrix and a cutoff score. The DNA matrix gives scores to IUB symbols depending on the amount of overlap between them (Staden, 1988). MDM78 is used for proteins (Dayhoff et. al., 1978).
4	Match to a weight matrix. Scores can be added or multiplied (by adding their algorithms).
5	As in class 4 but on the complementary strand.
6	Inverted repeat or stem-loop. Fixed stem length, range of loop sizes and cutoff score using A-T, G-C = 2; G-T = 1.
7	Exact match to short sequence but with a defined step size.
8	Direct repeat. Fixed repeat length, range of gap sizes and cutoff score. For protein sequences scores are calculated using MDM78, but an identity matrix is used for nucleic acids.
9	Members of a set. A list of sets of allowed amino acids for each position in the motif. When they are first entered into the computer they can be typed in with the sets separated by commas. For example IVL,,,DEKR,FYWILVM defines a motif of length 5 residue positions in which one of I,V or L must be found in the first position, then anything in the next three; D,E,K or R in the fourth position and F,Y,W,I,L,V or M in the fifth. Alternatively the sets can be written in the form of a weight matrix, which is how the program will store them. This class only applies to protein sequences because for nucleic acids "membership of a set" can be achieved using IUB symbols.

Table 3.2.1. Current list of motif classes (Staden, 1990).

The nucleotide motif search problem may be stated as follows. Consider a finite set of y class 1 nucleotide motifs $k_1, k_2, \dots, k_y$ and a DNA sequence t defined as sequences over the alphabet $\Sigma_{\text{DNA}} = \{A, C, G, T\}$. The nucleotide motif search problem is to find all occurrences of each nucleotide motif as a subsequence within the DNA sequence. The output is the set of positions in the DNA where any of the nucleotide motifs occur.

In DNA sequence analysis, nucleotide motif search is a specialized instance of the multiple keyword search problem. Two DNA sequence analysis problems can be expressed as nucleotide motif search problems: 1. restriction analysis and 2. transcription analysis. Thus, the identification of transcription factor binding sites and restriction endonuclease recognition sites within an arbitrary DNA sequence are specialized cases of the multiple keyword search problem.

3.3 Nucleotide Motif Search Algorithm

A multiple keyword search algorithm was developed for searching for class 1 nucleotide motifs within DNA sequences. The serial class 1 nucleotide motif search algorithm is an adaptation of the Aho and Corasick (1975) algorithm.

The serial class 1 nucleotide motif search algorithm input consists of: 1. a finite set of y class 1 nucleotide motifs $k_1, k_2, \dots, k_y$ defined as strings over the extended DNA alphabet $\Sigma_{\text{extended}} = \{A, C, G, T, K, M, R, S, W, Y, B, D, H, V, N\}$ (Table 3.3.1.) and 2. a DNA sequence t defined as a string over the basic DNA alphabet $\Sigma_{\text{basic}} = \{A, C, G, T\}$. The sum of the lengths of the y nucleotide motifs is defined as m , $\sum_{i=1}^y |k_i| = m$. The length of the DNA sequence is defined as n , $|t| = n$.

Symbol	Nucleotides
A	A
C	C
G	G
T	T
K	G or T
M	A or C
R	A or G
S	C or G
W	A or T
Y	C or T
B	C or G or T
D	A or G or T
H	A or C or T
V	A or C or G
N	A or C or G or T

Table 3.3.1. Summary of single-letter code nucleotide designations (FEBS, 1985).

The serial class 1 nucleotide motif search algorithm consists of two steps: 1. automaton construction and 2. DNA sequence processing.

1. Automaton construction. The set of nucleotide motifs is used to construct a deterministic finite automaton. The deterministic finite automaton consists of a finite set of

states S and a state-transition function s . Each state $s \in \Sigma_{\text{extended}}$. The finite states are constructed into a 15-ary tree graph with each state represented as a separate graph node. Each tree node has a maximum possible fanout of fifteen descendant nodes. A descendant pointer represents a state transition corresponding to one of the fifteen characters in the extended DNA alphabet.

For each state $s_1 \in S$ and input symbol $n \in \Sigma_{\text{basic}}$, the state-transition function $\sigma(s_1, n)$ produces another state $s_2 \in S$. The state-transition function σ has two possible outcomes: 1. a forward state transition and 2. a failure state transition. In a forward state transition, the input symbol n matches an automaton node descendant. This causes the deterministic finite automaton to descend one level down the 15-ary tree. In a failure state transition, the input symbol does not match any of the automaton node descendants. In this case, the deterministic finite automaton is reassigned to the root node. Thus, the deterministic finite automaton makes a state transition on each input symbol.

2. DNA sequence processing. The 15-ary tree root node is designated as the deterministic finite automaton start state. The DNA sequence is applied as input to the deterministic finite automaton. The deterministic finite automaton processes the DNA text by successively reading the DNA sequence nucleotides. The deterministic finite automaton makes a state transition on each DNA sequence nucleotide. When the deterministic finite automaton makes a transition to any of the designated accept states, a nucleotide motif has been traversed and the nucleotide motif position is output.

The serial class 1 nucleotide motif search algorithm output consists of a set of nucleotide motif positions. Each position indicates the leftmost boundary of a nucleotide motif that occurs as a subsequence within the DNA sequence.

Chapter 4

Intel iPSC/860 Hypercube Implementation

The hypercube interconnection topology is introduced. The data-parallel programming model is further presented. These concepts are combined in the parallel adaptation of the serial class 1 nucleotide motif search algorithm for the hypercube architecture. The parallel class 1 nucleotide motif search algorithm is based on the Single Program Multiple Data programming paradigm.

4.1 Hypercube Network

A multiprocessor computer system is a parallel computer with two or more processors. Numerous topologies have been proposed for interconnecting the processors of a distributed multiprocessor computer system. A message-passing multiprocessor computer system based on the binary k -dimensional hypercube interconnection topology was first proposed by Squire and Palais (1963). A binary k -dimensional hypercube interconnection network consists of 2^k vertices. The hypercube vertices each represent a processing node while the hypercube edges represent communication links between the processing nodes.

The processors communicate by passing messages along these links. A message sent from one processor to another may be routed through intermediate processors. The ordered list of processors visited by the message is a path. The length of a path is the number of links in the path.

The term *hypercube* refers to a binary k -dimensional hypercube interconnection topology. Hypercubes are synonymously known as *boolean hypercubes*, *boolean n -cubes*, *binary cubes* or Q_n . A hypercube with n nodes is constructed by numbering the

nodes from 0 to $n - 1$ and linking each pair of nodes whose binary representations differ by exactly one bit. Thus, a k -dimensional hypercube has a set of 2^k functional nodes and links. Hypercube networks are illustrated (Figure 4.1.1):

Figure 4.1.1. One-, two-, three- and four-dimensional hypercubes (Hatcher and Quinn, 1991).

The hypercube interconnection network has been the subject of significant research and commercial efforts. The hypercube has become a dominant topology because of its strong connectivity, regularity, symmetry and ability to embed other topologies (Saad and Schultz, 1988). The hypercube interconnection topology has formed the basis for viable multiprocessor computer systems, e.g. Intel iPSC/860 Hypercube (Intel Scientific Computers, 1990). The hypercube interconnection network and its associated algorithmic techniques have been further reviewed (Ranka and Sahni, 1990).

4.2 Data-Parallel Programming Model

Parallel computation may be classified according to computational partitioning strategy. There are two computational partitioning methods: 1. data-parallelism and 2. control-parallelism (King et. al., 1990).

Data-parallelism refers to the use of multiple functional units to apply the same operation simultaneously to elements of a dataset. A data-parallel computation divides data among the processors. Processors execute the same program but work on different data subsets. Data-parallel algorithms are appropriate for applications which perform the same set of operations repeatedly and independently on a large set of data. If there is no overhead associated with an increase in parallelism, then an n -fold increase in the number of functional units should lead to an n -fold increase in system throughput. Applications that feature nested loops to handle static and regular data structures are suitable candidates for data-parallel decomposition, e.g. linear algebra operations (King et. al., 1990) (Quinn, 1994).

Control-parallelism is achieved through the simultaneous application of different operations to different data elements. A control-parallel computation decomposes an algorithm into modules of different functionality, which can be executed in parallel on multiple processors. Data flow between the processors can be arbitrarily complex. Control-parallelism is suitable for applications that use numerous independent subroutines, e.g. computer graphics simulations (King et. al., 1990) (Quinn, 1994).

Single Instruction Multiple Data (SIMD) computers are capable only of data parallelism. Multiple Instruction Multiple Data (MIMD) computers are capable of both data-parallelism and control-parallelism. Data-parallelism has two advantages over control-parallelism: 1. scalability and 2. simplicity. Data-parallel algorithms are better able to scale to large numbers of processors. Data-parallel algorithms have a single control flow which

makes them easier to write and debug. Therefore, data-parallel implementations should be sought before control-parallel implementations are attempted (Quinn, 1994).

The Single Program Multiple Data (SPMD) paradigm refers to data-parallel implementations on MIMD architectures. SPMD parallelism arises from simultaneous operations across large datasets rather than from multiple threads of control. Thus, SPMD programs are easier to write and debug than arbitrary MIMD programs (Quinn, 1994).

Asynchronous algorithms have greater potential for errors such as deadlocks than synchronous algorithms. Hence the popularity of the SPMD programming style. SPMD programs characteristically resolve blocks of code by calls to message-passing routines. Processors execute identical blocks of code asynchronously using data stored in local memory. Data is then exchanged with other processors. Communication points further serve a synchronization function (Quinn and Hatcher, 1990).

4.3 Intel iPSC/860 Hypercube Implementation

The serial class 1 nucleotide motif search algorithm has been converted into a parallel version. The parallel class 1 nucleotide motif search algorithm is an adaptation for the hypercube architecture (Saad and Schultz, 1988). The number of hypercube nodes present is p . Load balancing is achieved by partitioning the text string into the subtext strings $s_1, s_2, \dots, s_q$. The number of subtext strings q is the same as the number of hypercube processors p , $p = q$. The subtext length is defined as r , $n \bmod p = r$.

The parallel class 1 nucleotide motif search algorithm consists of three steps: 1. host-to-node communication, 2. computation and 3. node-to-host communication. 1. Host-to-node communication. The host broadcasts the entire set of y class 1 nucleotide motifs to all hypercube nodes and routes one unique subtext to each hypercube node. 2. Computation. Within each hypercube node, the motif set and subtext are subjected to the serial class 1 nucleotide motif search algorithm to independently compute a set of nucleotide motif occurrences. 3. Node-to-host communication. All hypercube nodes route their individual nucleotide motif occurrence sets back to the host.

The parallel class 1 nucleotide motif search algorithm uses a single thread of control and is written in Single Program Multiple Data (SPMD) programming style. The program uses a single thread of control and is loosely synchronous. Between the communication synchronization points, the processors asynchronously execute the same program but manipulate individual datasets. Thus, the parallel class 1 nucleotide motif search algorithm is an example of a data parallel algorithm. Data parallelism is defined as the simultaneous application of the same operation to elements of a dataset using multiple processors (Quinn, 1994).

The parallel class 1 nucleotide motif search algorithm operates in $O(m + (n / p))$ time and occupies $O(n + mp)$ space.

The parallel class 1 nucleotide motif search algorithm was implemented on the Intel iPSC/860 Hypercube (Intel Scientific Computers, 1990). The algorithm was programmed in C language. The 15-ary tree data structure was programmed using recursion.

Chapter 5

Experimental Results

Using the Intel iPSC/860 Hypercube implementation, twelve human genes were characterized by nucleotide motif search analysis. The genes are tabulated (Table 5.1.).

Gene	Location
interferon-alpha 1	appendix D
interferon-alpha 2	appendix E
interferon-alpha 4	appendix F
interferon-alpha 5	appendix G
interferon-alpha 6	appendix H
interferon-alpha 7	appendix I
interferon-alpha 8	appendix J
interferon-alpha 13	appendix K
interferon-alpha 14	appendix L
interferon-alpha 16	appendix M
interferon-alpha 17	appendix N
retinoblastoma	-

Table 5.1. Human genes analyzed by nucleotide motif search.

Nucleotide motif search analysis was performed using restriction endonuclease and transcription factor patterns. The restriction endonuclease and transcription factor patterns are tabulated (Table 5.2.).

Patterns	Location
restriction endonucleases	appendix A
transcription factors	appendix B
human interferon transcription factors	appendix C

Table 5.2. Restriction endonuclease and transcription factor patterns.

Twelve types of genetic markers have been delineated on the human interferon-alpha genes: 1. preinterferon peptide-encoding sequence, 2. signal peptide-encoding sequence, 3. mature interferon peptide-encoding sequence, 4. tata box, 5. virus-response

element, 6. distal interferon regulatory factor site, 7. proximal interferon regulatory factor site, 8. TG sequence, 9. polyadenylation signal, 10. transcription initiation site, 11. transcription termination site and 12. restriction endonuclease cleavage sites.

A human interferon-alpha gene encodes a preinterferon protein that consists of a signal (leader) peptide and a mature peptide. The signal peptide facilitates interferon transport through the cellular membrane during secretion. During maturation the leader peptide is proteolytically cleaved from the preinterferon protein leaving the mature interferon protein. The preinterferon peptide-encoding sequence is translated into the preinterferon peptide which is made up of 188 - 189 amino acids. The signal peptide-encoding sequence encodes the leader peptide which is comprised of 23 amino acids. The mature interferon peptide-encoding sequence directs the synthesis of the mature interferon peptide which is composed of 165 - 166 amino acids (Weissmann and Weber, 1986).

The tata box (TB) is a conserved AT-rich sequence commonly found in eukaryotic promoters. The tata box is the binding sequence recognized by transcription factor TFIID. Transcription factor TFIID is responsible for positioning RNA polymerase II at the transcription initiation site. The tata box is usually located -35 to -19 nucleotides 5' relative to the transcription initiation site. The most common sequence is *tataaaa*. The tata box is otherwise known as the Hogness box after its discoverer D. Hogness.

The virus-response element (VRE) is the minimal promoter requirement for conferring transient viral-induced transcription on heterologous promoter elements. The virus-response element 5' boundary commences at -111 nucleotides 5' relative to the transcription initiation site of the human interferon-alpha 1 gene. The human interferon-alpha 1 virus-response element is 46 nucleotides long. The virus-response element sequence was determined to be *gagtgcattgaaggaaagcaaaaacagaaatggaaagtggcccagaa*. The virus-response element is composed of two imperfect repeats: 1. RepA and 2. RepB. RepA contains two multiple-sequence alignment regions termed R1 and R2. RepB

similarly contains two multiple-sequence alignment regions termed R1' and R2' (Ryals et. al., 1985).

Interferon regulatory factors are transcriptional regulators of human interferon-alpha and human interferon-beta. Two interferon regulatory factors have been identified: interferon regulatory factor 1 (IRF-1) and interferon regulatory factor 2 (IRF-2). Interferon regulatory factors 1 and 2 are structurally related. However, these factors have opposite effects: interferon regulatory factor 1 is a transcriptional activator whereas interferon regulatory factor 2 is a transcriptional repressor (Harada et. al., 1989). Interferon regulatory factor 1 recognizes sequences in both human interferon-alpha and human interferon-beta promoters (Fujita et. al., 1988) (Miyamoto et. al., 1988).

Harada et. al. (1989) claim that the distinct transcription factors interferon regulatory factor 1 and interferon regulatory factor 2 bind to identical regulatory sequences. In binding site selection experiments, the interferon regulatory factor 1 and interferon regulatory factor 2 recognition sites were determined to be *b(a)awa(n)y(r)amavn* and *s(a)waa(s)ygaaasb* respectively (Tanaka et. al., 1993).

The presence of two interferon regulatory factor binding sites within the human interferon-alpha 1 promoter was first proposed by MacDonald et. al. (1990). On the basis of their relative 5' distances from the transcription initiation site, the two sites are designated: 1. distal interferon regulatory factor site (DIRF) and 2. proximal interferon regulatory factor site (PIRF).

Within human interferon-alpha 1, the distal interferon regulatory factor site 5' boundary occurs at position -99 nucleotides relative to the cap site. The distal interferon regulatory factor site is 12 nucleotides long. The distal interferon regulatory factor site sequence is *gaaagcauaaac*. The proximal interferon regulatory factor site 5' boundary occurs at position -58 nucleotides relative to the cap site. The proximal interferon regulatory factor site is 13 nucleotides long. The proximal interferon regulatory factor site sequence is *gaangtggaatc* (MacDonald et. al., 1990).

The TG factor (TG) is a transcription factor active in the transcriptional activation of the human interferon-alpha 1 gene. The TG sequence is located within the virus-response element and is 12 nucleotides long. The TG sequence 5' boundary occurs at position -85 nucleotides 5' relative to the transcription initiation site. The TG sequence was determined to be *gaaatggaaagt* (MacDonald et. al., 1990).

Polyadenylation is the enzymatic addition of adenine nucleotides to the 3' end of eukaryotic mRNA molecules. Polyadenylation is part of the processing that primary mRNA transcripts undergo subsequent to transcription and prior to transport from the nucleus to the cytoplasm. The polyadenylation tail refers to the segment of approximately 200 adenosine residues that is appended to the 3' end of the mRNA molecule. The polyadenylation tail has two possible functions: 1. mRNA stability and 2. mRNA transport out of the nucleus. The polyadenylation signal is the hexanucleotide *aataaa* which plays an unknown role in polyadenylation. The polyadenylation signal occurs within the 3'-untranslated region of a eukaryotic gene and is located -20 to -18 nucleotides 5' relative to the polyadenylation tail.

Transcription refers to the synthesis of single-stranded mRNA from a double-stranded DNA template catalyzed by RNA polymerase. The mRNA is formed by complementary base pairing to the DNA template. The transcription initiation site refers to the first DNA nucleotide to be transcribed to mRNA. Thus, the transcription initiation site corresponds to the 5' end of the mRNA molecule. The transcription initiation site is otherwise known as the cap site. The transcription termination site refers to the last DNA nucleotide to be transcribed to mRNA. Thus, the transcription initiation site corresponds to the 3' end of the mRNA molecule.

A restriction endonuclease cleavage site is the specific nucleotide sequence in a double-stranded DNA recognized by a type II restriction endonuclease at which the enzyme cleaves the molecule. Restriction endonuclease recognition sites are usually 4 - 6 nucleotides long and exhibit bilateral symmetry, i.e. the recognition sites are palindromes.

The DNA strands may be cleaved opposite to one another to create blunt ends, e.g. PvuII. Alternately, the DNA strands may be cut in a staggered pattern to create sticky ends, e.g. EcoRI (Table 2.3.1.).

5.1 Human Interferon-Alpha 1 Gene

The human interferon-alpha 1 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box, virus response element, distal interferon regulatory factor site, proximal interferon regulatory factor site, TG sequence, transcription initiation site and transcription termination site (Mantei et. al., 1980) (Nagata et. al., 1980) (Goeddel et. al., 1981) (Bowden et. al., 1984) (Ryals et. al., 1985) (MacDonald et. al., 1990). Human interferon-alpha 1 restriction analysis and transcription analysis data is presented (Tables 5.1.1. - 5.1.3.).

Data	Location
nucleotide sequence	appendix D.1
restriction endonuclease sites	appendix D.2
transcription factor sites	table 5.1.2.

Table 5.1.1. Human interferon-alpha 1 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaagg	120
VRE	gagtgcatgaaggaaagcaaaaacagaaatggaaagtggcccagaa	43
DIRF	gaaagcaaaaac	55
PIRF	gaaagtggaaatc	96
TG	gaaatggaaagt	68

Table 5.1.2. Human interferon-alpha 1 transcription control elements.

Parameter	Data
nucleotides	1179
restriction endonuclease sites	187
transcription factor sites	157
interferon transcription factor sites	173

Table 5.1.3. Human interferon-alpha 1 restriction and transcription analysis summary.

5.2 Human Interferon-Alpha 2 Gene

The human interferon-alpha 2 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box, virus response element, transcription initiation site and transcription termination site (Goeddel et. al., 1980) (Maeda et. al., 1980) (Streuli et. al., 1980) (Goeddel et. al., 1981) (Lawn, et. al., 1981b) (Bowden et. al., 1984) (Ryals et. al., 1985). Human interferon-alpha 2 restriction analysis and transcription analysis data is presented (Tables 5.2.1. - 5.2.3.).

Data	Location
nucleotide sequence	appendix E.1
restriction endonuclease sites	appendix E.2
transcription factor sites	table 5.2.2.

Table 5.2.1. Human interferon-alpha 2 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaagg	411
VRE	gagtgataaagaaaagcaaaaagagaagtagaaagtaacacaggg	335
DIRF	gaaagcaaaaag	346
PIRF	gaaaatgtaaagc	387
TG	gaagtagaaagt	359

Table 5.2.2. Human interferon-alpha 2 transcription control elements.

Parameter	Data
nucleotides	1733
restriction endonuclease sites	225
transcription factor sites	182
interferon transcription factor sites	195

Table 5.2.3. Human interferon-alpha 2 restriction and transcription analysis summary.

5.3 Human Interferon-Alpha 4 Gene

The human interferon-alpha 4 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box, virus response element and transcription initiation site (Hienco et. al., 1985) (Ryals et. al., 1985). Human interferon-alpha 4 restriction analysis and transcription analysis data is presented (Tables 5.3.1. - 5.3.3.).

Data	Location
nucleotide sequence	appendix F.1
restriction endonuclease sites	appendix F.2
transcription factor sites	table 5.3.2.

Table 5.3.1. Human interferon-alpha 4 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaaga	697
VRE	gagtgcgtaaagaaagcaaaaacagagatagaaagtacaactagg	621
DIRF	gaaagcaaaaac	632
PIRF	gaaaatggaaatt	673
TG	gagatagaaagt	645

Table 5.3.2. Human interferon-alpha 4 transcription control elements.

Parameter	Data
nucleotides	2022
restriction endonuclease sites	265
transcription factor sites	231
interferon transcription factor sites	208

Table 5.3.3. Human interferon-alpha 4 restriction and transcription analysis summary.

5.4 Human Interferon-Alpha 5 Gene

The human interferon-alpha 5 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box, virus response element and transcription initiation site (Henco et. al., 1985) (Ryals et. al., 1985). Human interferon-alpha 5 restriction analysis and transcription analysis data is presented (Tables 5.4.1. - 5.4.3.).

Data	Location
nucleotide sequence	appendix G.1
restriction endonuclease sites	appendix G.2
transcription factor sites	table 5.4.2.

Table 5.4.1. Human interferon-alpha 5 restriction and transcription analysis data.

Element	Sequence	Site
TB	ttttaaga	337
VRE	aagagcataaaagaaagcaaaaagagaagtagaaagtaacacaagg	261
DIRF	gaaagcaaaaag	273
PIRF	gaaaatggaaact	313
TG	gaagtagaaagt	286

Table 5.4.2. Human interferon-alpha 5 transcription control elements.

Parameter	Data
nucleotides	1475
restriction endonuclease sites	183
transcription factor sites	166
interferon transcription factor sites	179

Table 5.4.3. Human interferon-alpha 5 restriction and transcription analysis summary.

5.5 Human Interferon-Alpha 6 Gene

The human interferon-alpha 6 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box and transcription initiation site (Henco et. al., 1985). Human interferon-alpha 6 restriction analysis and transcription analysis data is presented (Tables 5.5.1. - 5.5.3.).

Data	Location
nucleotide sequence	appendix H.1
restriction endonuclease sites	appendix H.2
transcription factor sites	table 5.5.2.

Table 5.5.1. Human interferon-alpha 6 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaaga	391
VRE	gagtaaataaatgaaagcaaaatcagacgtagaaagtaaattctgaa	323
DIRF	gaaagcaaaatc	335
PIRF	gaaaatggaaact	367
TG	gacgtagaaagt	348

Table 5.5.2. Human interferon-alpha 6 transcription control elements.

Parameter	Data
nucleotides	1544
restriction endonuclease sites	212
transcription factor sites	152
interferon transcription factor sites	183

Table 5.5.3. Human interferon-alpha 6 restriction and transcription analysis summary.

5.6 Human Interferon-Alpha 7 Gene

The human interferon-alpha 7 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box, virus response element and transcription initiation site (Henco et. al., 1985) (Ryals et. al., 1985). Human interferon-alpha 7 restriction analysis and transcription analysis data is presented (Tables 5.6.1. - 5.6.3.).

Data	Location
nucleotide sequence	appendix I.1
restriction endonuclease sites	appendix I.2
transcription factor sites	table 5.6.2.

Table 5.6.1. Human interferon-alpha 7 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaaga	652
VRE	gagtgcataaagaaagcaaaaacagagatagaaagtaaaactagg	576
DIRF	gaaagcaaaaac	587
PIRF	gaaaatggaaatt	628
TG	gagatagaaagt	600

Table 5.6.2. Human interferon-alpha 7 transcription control elements.

Parameter	Data
nucleotides	1983
restriction endonuclease sites	237
transcription factor sites	220
interferon transcription factor sites	205

Table 5.6.3. Human interferon-alpha 7 restriction and transcription analysis summary.

5.7 Human Interferon-Alpha 8 Gene

The human interferon-alpha 8 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide and mature peptide (Henco et. al., 1985). The human interferon-alpha 8 promoter region has not been sequenced. Therefore, it was not possible to determine the human interferon-alpha 8 transcription control elements. Human interferon-alpha 8 restriction analysis and transcription analysis data is presented (Tables 5.7.1. - 5.7.2.).

Data	Location
nucleotide sequence	appendix J.1
restriction endonuclease sites	appendix J.2

Table 5.7.1. Human interferon-alpha 8 restriction analysis data.

Parameter	Data
nucleotides	633
restriction endonuclease sites	120
transcription factor sites	73
interferon transcription factor sites	78

Table 5.7.2. Human interferon-alpha 8 restriction and transcription analysis summary.

5.8 Human Interferon-Alpha 13 Gene

The human interferon-alpha 13 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: peptide, tata box, virus response element and transcription initiation site (Mantei et. al., 1980) (Todokoro, et. al., 1984) (Ryals et. al., 1985). Human interferon-alpha 13 restriction analysis and transcription analysis data is presented (Tables 5.8.1. - 5.8.3.).

Data	Location
nucleotide sequence	appendix K.1
restriction endonuclease sites	appendix K.2
transcription factor sites	table 5.8.2.

Table 5.8.1. Human interferon-alpha 13 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaagg	119
VRE	gagttcaagaaggaaagcaaaaacagaaatggaaagtgggtccagaa	42
DIRF	gaaagcaaaaac	54
PIRF	gaaaggggaaatc	95
TG	gaaatggaaagt	67

Table 5.8.2. Human interferon-alpha 13 transcription control elements.

Parameter	Data
nucleotides	1108
restriction endonuclease sites	184
transcription factor sites	140
interferon transcription factor sites	162

Table 5.8.3. Human interferon-alpha 13 restriction and transcription analysis summary.

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5.9 Human Interferon-Alpha 14 Gene

The human interferon-alpha 14 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box, virus response element and transcription initiation site (Henco et. al., 1985) (Ryals et. al., 1985). Human interferon-alpha 14 restriction analysis and transcription analysis data is presented (Tables 5.9.1. - 5.9.3.).

Data	Location
nucleotide sequence	appendix L.1
restriction endonuclease sites	appendix L.2
transcription factor sites	table 5.9.2.

Table 5.9.1. Human interferon-alpha 14 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaaga	176
VRE	caggacataaaggaaagccaaaagagaagtagaaaaaacatga	99
DIRF	gaaagccaaaag	111
PIRF	gaaaatggaagct	152
TG	gaagtagaaa	124

Table 5.9.2. Human interferon-alpha 14 transcription control elements.

Parameter	Data
nucleotides	1126
restriction endonuclease sites	160
transcription factor sites	133
interferon transcription factor sites	157

Table 5.9.3. Human interferon-alpha 14 restriction and transcription analysis summary.

5.10 Human Interferon-Alpha 16 Gene

The human interferon-alpha 16 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: signal peptide, mature peptide, tata box and transcription initiation site (Henco et. al., 1985). Human interferon-alpha 16 restriction analysis and transcription analysis data is presented (Tables 5.10.1 - 5.10.3.).

Data	Location
nucleotide sequence	appendix M.1
restriction endonuclease sites	appendix M.2
transcription factor sites	table 5.10.2.

Table 5.10.1 Human interferon-alpha 16 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaaga	385
VRE	gagtgcataaagaaagcaaaaacagagatagaaagtaaaaccaggg	309
DIRF	gaaagcaaaaac	320
PIRF	gaaaatggaaatt	361
TG	gagatagaaagt	333

Table 5.10.2. Human interferon-alpha 16 transcription control elements.

Parameter	Data
nucleotides	1133
restriction endonuclease sites	148
transcription factor sites	123
interferon transcription factor sites	143

Table 5.10.3. Human interferon-alpha 16 restriction and transcription analysis summary.

5.11 Human Interferon-Alpha 17 Gene

The human interferon-alpha 17 genomic DNA nucleotide sequence has been determined. Biologically-significant subsequences have been further elucidated: peptide, tata box, transcription initiation site and transcription termination site (Lawn et. al., 1981a). Human interferon-alpha 17 restriction analysis and transcription analysis data is presented (Tables 5.11.1 - 5.11.3.).

Data	Location
nucleotide sequence	appendix N.1
restriction endonuclease sites	appendix N.2
transcription factor sites	table 5.11.2.

Table 5.11.1 Human interferon-alpha 17 restriction and transcription analysis data.

Element	Sequence	Site
TB	tatttaagg	539
VRE	gagtgcaaaaagaaagcaaaaacagacatagaaagtaaaactagg	463
DIRF	gaaagcaaaaac	474
PIRF	gaaaatggaaatt	515
TG	gacatagaaagt	487

Table 5.11.2. Human interferon-alpha 17 transcription control elements.

Parameter	Data
nucleotides	1873
restriction endonuclease sites	236
transcription factor sites	211
interferon transcription factor sites	182

Table 5.11.3. Human interferon-alpha 17 restriction and transcription analysis summary.

5.12 Human Retinoblastoma Susceptibility Gene

The human retinoblastoma genomic DNA nucleotide sequence has been determined. The retinoblastoma susceptibility gene is composed of 180,388 nucleotides making it the longest known continuous human DNA sequence (Toguchida et. al., 1993). Thus, the retinoblastoma susceptibility gene was used as an experimental subject in the nucleotide motif search parallel performance experiments. Human retinoblastoma restriction analysis and transcription analysis data is presented (Table 5.12.1.).

Parameter	Data
nucleotides	180388
restriction endonuclease sites	24699
transcription factor sites	20174
interferon transcription factor sites	16662

Table 5.12.1. Human retinoblastoma restriction and transcription analysis summary.

Chapter 6

Genetic Analysis

The nucleotide motif analysis is presented as four series of computational results: 1. human interferon-alpha genetic maps, 2. human interferon-alpha promoter transcription maps, 3. human interferon-alpha promoter elements and 4. human interferon-alpha transcription regulatory mechanism.

6.1 Human Interferon-Alpha Genetic Maps

Human interferon-alpha genetic maps comprise the entire genes. The diagrams include the complete protein-encoding region as well as the nontranslated 5' and 3' flanking regions. The human interferon-alpha genetic maps indicate twelve types of genetic marker sites: 1. preinterferon peptide-encoding sequence (Peptide), 2. signal peptide-encoding sequence (Signal), 3. mature interferon peptide-encoding sequence (Mature Peptide), 4. tata box (Tata), 5. virus-response element (VRE), 6. distal interferon regulatory factor site (DIRF), 7. proximal interferon regulatory factor site (PIRF), 8. TG sequence (TG), 9. polyadenylation signal (PolyA), 10. transcription initiation site (mRNA>), 11. transcription termination site (mRNA<) and 12. restriction endonuclease cleavage sites (BsrI, EcoKI, MaeI, etc.). The human interferon-alpha genetic maps are presented (Figures 6.1.1. - 6.1.11.).

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA	Transcription Initiation Site
mRNA	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.1. Human interferon-alpha 1 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA ►	Transcription Initiation Site
mRNA ◄	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.2. Human interferon-alpha 2 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA▶	Transcription Initiation Site
mRNA◀	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.3. Human interferon-alpha 4 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA	Transcription Initiation Site
mRNA	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.4. Human interferon-alpha 5 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA ►	Transcription Initiation Site
mRNA ◄	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.5. Human interferon-alpha 6 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA▶	Transcription Initiation Site
mRNA◀	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.6. Human interferon-alpha 7 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA▶	Transcription Initiation Site
mRNA◀	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.7. Human interferon-alpha 8 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA	Transcription Initiation Site
mRNA	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.8. Human interferon-alpha 13 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA ▶	Transcription Initiation Site
mRNA ◀	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.9. Human interferon-alpha 14 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA▶	Transcription Initiation Site
mRNA◀	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.10. Human interferon-alpha 16 genetic map.

100bp

DIRF	Distal Interferon Regulatory Factor Site
mRNA ►	Transcription Initiation Site
mRNA ◄	Transcription Termination Site
PIRF	Proximal Interferon Regulatory Factor Site
PolyA	Polyadenylation Signal
Tata	Tata Box
TG	TG Sequence
VRE	Virus Response Element

Figure 6.1.11. Human interferon-alpha 17 genetic map.

6.2 Human Interferon-Alpha Promoter Transcription Maps

Human interferon-alpha promoter transcription maps are restricted to the promoter regions. The human interferon-alpha promoter transcription maps indicate six types of promoter elements: 1. distal interferon regulatory factor site (DIRF), 2. proximal interferon regulatory factor site (PIRF), 3. tata box (Tata), 4. TG sequence (TG), 5. virus-response element (VRE) and 6. transcription initiation site (Cap). The diagrams further denote six multiple-sequence alignment regions: 1. RepA, 2. RepB, 3. R1, 4. R2, 5. R1' and 6. R2' (Ryals et. al., 1985). The human interferon-alpha promoter transcription maps are presented (Figures 6.2.1. - 6.2.10.).

Figure 6.2.1. Human interferon-alpha 1 promoter transcription map.

Figure 6.2.2. Human interferon-alpha 2 promoter transcription map.

Figure 6.2.3. Human interferon-alpha 4 promoter transcription map.

Figure 6.2.4. Human interferon-alpha 5 promoter transcription map.

Figure 6.2.5. Human interferon-alpha 6 promoter transcription map.

Figure 6.2.6. Human interferon-alpha 7 promoter transcription map.

Figure 6.2.7. Human interferon-alpha 13 promoter transcription map.

Figure 6.2.8. Human interferon-alpha 14 promoter transcription map.

Figure 6.2.9. Human interferon-alpha 16 promoter transcription map.

6.3 Human Interferon-Alpha Promoter Elements

Transcription analysis of the human interferon-alpha genes indicates a series of transcription control elements that occur within all human interferon-alpha promoters. Five potential human interferon-alpha promoter elements have been identified: 1. tata boxes (Tata), 2. virus-response elements (VRE), 3. distal interferon regulatory factor (DIRF) sites, 4. proximal interferon regulatory factor (PIRF) sites and 5. TG sequences (TG). The human interferon-alpha promoter elements are presented (Figures 6.3.1. - 6.3.5.).

The tata box consensus sequence is *twtttaagr*. The tata boxes are 9 nucleotides long. The tata box 5' boundaries occur at positions -34 to -32 nucleotides relative to the cap site. The human interferon-alpha tata boxes have been previously discovered. Thus, the current tata box results are strictly confirmatory. The tata boxes are presented (Figure 6.3.1.).

Gene	Sequence
	Tata
	+-----+
IFNA1	tattttaagg
IFNA2	tattttaagg
IFNA4	tattttaaga
IFNA5	ttttttaaga
IFNA6	tattttaaga
IFNA7	tattttaaga
IFNA13	tattttaagg
IFNA14	tattttaaga
IFNA16	tattttaaga
IFNA17	tattttaagg
IFNA-Cons	twttttaagr

Figure 6.3.1. Tata boxes.

Ryals et. al. (1985) performed a multiple-sequence alignment on the virus-response elements. The virus-response elements of seven human interferon-alpha genes were aligned: IFNA1, IFNA2, IFNA4, IFNA5, IFNA7, IFNA13 and IFNA14. Six multiple-

Interferon regulatory factor recognition sequences have been investigated. Harada et. al. (1989) claim that the distinct transcription factors interferon regulatory factor 1 and interferon regulatory factor 2 bind to identical regulatory sequences. In binding site selection experiments, the interferon regulatory factor 1 and interferon regulatory factor 2 recognition sites were determined to be *b(a)awa(n)y(r)am:avn* and *s(a)waa(s)ygaasb* respectively (Tanaka et. al., 1993).

The presence of two interferon regulatory factor binding sites within the human interferon-alpha 1 promoter was first proposed by MacDonald et. al. (1990). Two potential interferon regulatory factor binding sites were identified in all human interferon-alpha promoters. On the basis of their relative 5' distances from the transcription initiation site, the two sites are designated: 1. distal interferon regulatory factor site and 2. proximal interferon regulatory factor site.

The distal interferon regulatory factor site consensus sequence is *gaaagcmaaaws*. The distal interferon regulatory factor sites are 12 nucleotides long. The distal interferon regulatory factor site 5' boundaries occur at positions -99 to -85 nucleotides relative to the cap site. The proximal interferon regulatory factor site consensus sequence is *gaaatgkaaryb*. The proximal interferon regulatory factor sites are 13 nucleotides long. The proximal interferon regulatory factor site 5' boundaries occur at positions -58 to -56 nucleotides relative to the cap site. The distal interferon regulatory factor sites and proximal interferon regulatory factor sites are presented (Figures 6.3.3. - 6.3.4.).

Gene	Sequence
	DIRF
	+-----+
IFNA1	gaaagcaaaaac
IFNA2	gaaagcaaaaag
IFNA4	gaaagcaaaaac
IFNA5	gaaagcaaaaag
IFNA6	gaaagcaaaaac
IFNA7	gaaagcaaaaac
IFNA13	gaaagcaaaaac
IFNA14	gaaagccaaaag
IFNA16	gaaagcaaaaac
IFNA17	gaaagcaaaaac
IFNA-Cons	gaaagcmaaaws

Figure 6.3.3. Distal interferon regulatory factor sites.

Gene	Sequence
	PIRF
	+-----+
IFNA1	gaaagtggaaatc
IFNA2	gaaaatgtaaagc
IFNA4	gaaaatggaaatt
IFNA5	gaaaatggaaact
IFNA6	gaaaatggaaact
IFNA7	gaaaatggaaatt
IFNA13	gaaagtggaaatc
IFNA14	gaaaatggaaact
IFNA16	gaaaatggaaatt
IFNA17	gaaaatggaaatt
IFNA-Cons	gaaartgkaaryb

Figure 6.3.4. Proximal interferon regulatory factor sites.

The TG factor is a transcription factor active in the transcriptional activation of the human interferon-alpha 1 gene. The human interferon-alpha 1 TG sequence was determined to be *gaaatggaaagt* (MacDonald et. al., 1990). Potential TG sequences were identified in the remaining human interferon-alpha promoters. The TG sequences are located within the virus-response elements. Observe that the human interferon-alpha 13 TG sequence *gaaatggaaagt* is identical to the human interferon-alpha 1 TG sequence. These findings suggest the existence of a potential family of TG sequences. The TG consensus sequence is *gavtrrgaaa(g)(t)*. The TG sequences are 10 - 12 nucleotides long. The TG

sequence 5' boundaries occur at positions -86 to -75 nucleotides relative to the cap site. The TG sequences are presented (Figure 6.3.5.).

Gene	Sequence	Differences Relative to IFNA1
	TG	
	+-----+	
IFNA1	gaaatggaaagt	0
IFNA2	gaagtagaaagt	2
IFNA4	gagatagaaagt	2
IFNA5	gaagtagaaagt	2
IFNA6	gacgtagaaagt	3
IFNA7	gagatagaaagt	2
IFNA13	gaaatggaaagt	0
IFNA14	gaagtagaaa	4
IFNA16	gagatagaaagt	2
IFNA17	gacatagaaagt	2
IFNA-Cons	gavrttgaaagt	3
	--	

Figure 6.3.5. TG sequences.

The promoter element consensus sequences are summarized (Table 6.3.1.).

Name	Sequence
Tata	twtttaagr
VRE	vagddhrwraa(d)gaaagcmaaawsagavrttgaaa(g)(t)rvhh(y)cwdr
DIRF	gaaagcmaaaws
PIRF	gaaartgkaaryb
TG	gavrttgaaa(g)(t)

Table 6.3.1. Promoter element consensus sequences.

6.4 Human Interferon-Alpha Transcription Regulatory Mechanism

The human interferon-alpha genes are activated by viral infection. The human interferon-alpha gene regulatory region extends -111 to -100 nucleotides 5' relative to the transcription initiation site. The human interferon-alpha gene regulatory region contains four promoter elements responsible for the transcriptional regulation of viral induction: 1. tata box (Tata), 2. regulatory domain 1 (RD1), 3. regulatory domain 2 (RD2) and 4. regulatory domain 3 (RD3).

The tata box is the binding sequence recognized by transcription factor TFIID. Transcription factor TFIID is responsible for positioning RNA polymerase II at the transcription initiation site. The tata box consensus sequence is *twtttaagr*. Tata boxes are 9 nucleotides long. Tata box 5' boundaries occur at positions -34 to -32 nucleotides relative to the transcription initiation site.

Regulatory domain 1 corresponds to the proximal interferon regulatory factor site. Regulatory domain 1 could be recognized by either interferon regulatory factor 1 or interferon regulatory factor 2. Interferon regulatory factor 1 is a transcriptional activator whereas interferon regulatory factor 2 is a transcriptional repressor (Harada et. al., 1989). The regulatory domain 1 consensus sequence is *gaaartgkaaryb*. Regulatory domain 1 sequences are 13 nucleotides long. Regulatory domain 1 sequence 5' boundaries occur at positions -58 to -56 relative to the cap site.

Regulatory domain 2 corresponds to the TG sequence. Regulatory domain 2 is recognized by the TG factor. The TG factor is a transcriptional activator of human interferon-alpha 1 (MacDonald et. al., 1990). The regulatory domain 2 consensus sequence is *gavrtrgaaa(g)(t)*. Regulatory domain 2 sequences are 10 - 12 nucleotides long. Regulatory domain 2 sequence 5' boundaries occur at positions -86 to -75 relative to the cap site.

Regulatory domain 3 corresponds to the distal interferon regulatory factor site. Regulatory domain 3 could be recognized by either interferon regulatory factor 1 or interferon regulatory factor 2. Interferon regulatory factor 1 is a transcriptional activator whereas interferon regulatory factor 2 is a transcriptional repressor (Harada et. al., 1989). The regulatory domain 3 consensus sequence is *gaaagcmaaaws*. Regulatory domain 3 sequences are 12 nucleotides long. Regulatory domain 3 sequence 5' boundaries occur at positions -99 to -85 relative to the cap site.

The human interferon-alpha transcription regulatory sequences are summarized (Table 6.4.1.) (Figure 6.4.1.).

Regulatory Sequence	Transcription Factor	Function
tata box	TFIID	RNA polymerase II orientation
regulatory domain 1	interferon regulatory factor 1	transcriptional activation
	interferon regulatory factor 2	transcriptional repression
regulatory domain 2	TG factor	transcriptional activation
regulatory domain 3	interferon regulatory factor 1	transcriptional activation
	interferon regulatory factor 2	transcriptional repression

Table 6.4.1. Human interferon-alpha transcription regulatory sequences.

10bp

Cap ▲	Transcription Initiation Site
RD1	Regulatory Domain 1
RD2	Regulatory Domain 2
RD3	Regulatory Domain 3
Tata	Tata Box
VRE	Virus Response Element

Figure 6.4.1. Human interferon- α transcription regulatory sequence organization.

A theoretical model for the transcriptional regulation of human interferon-alpha is hypothesized. The virus-response element is critical to viral-induced transcription and is involved in transcriptional activation. Three functional components have been defined: regulatory domain 1, regulatory domain 2 and regulatory domain 3.

Regulatory domain 1 is located 3' relative to the virus-response element. Regulatory domain 1 is recognized by interferon regulatory factor 2. Regulatory domain 1 is responsible for transcriptional repression and is renamed negative regulatory domain 1 (NRD1).

Regulatory domain 2 is located within the virus-response element. Regulatory domain 2 is recognized by the TG factor (MacDonald et. al., 1990). Regulatory domain 2 is responsible for transcriptional activation and is renamed positive regulatory domain 1 (PRD1).

Regulatory domain 3 is located within the virus-response element. Regulatory domain 3 is recognized by interferon regulatory factor 1 (MacDonald et. al., 1990). Regulatory domain 3 is responsible for transcriptional activation and is renamed positive regulatory domain 2 (PRD2).

The theoretical model of human interferon-alpha transcriptional regulation operates as follows. Interferon regulatory factor 2 normally binds to negative regulatory domain 1. The repressor blocks transcription factor binding to positive regulatory domains 1 and 2. Induction involves repressor inactivation. Interferon regulatory factor 1 and TG factor could then bind to positive regulatory domains 1 and 2 respectively. Transcription is then activated. This model is supported solely by computational evidence and requires experimental verification. The prototype model will require modification as additional transcription factor binding sites are discovered.

Chapter 7

Parallel Performance Analysis

Three metrics for parallel performance analysis are defined: 1. scaled speedup, 2. cost and 3. scaled efficiency. Parallel performance of the nucleotide motif search algorithm was evaluated by nucleotide motif searches of the retinoblastoma gene. Parallel performance experiments used three sets of nucleotide motifs: 1. Restriction Enzyme Database (REBASE) release 405, 2. Transcription Factors Database (TFD) and 3. Human Interferon Transcription Factors Database (HuIFNTFD). All three parallel performance experiments demonstrated near-linear speedup curves. Parallel algorithm performance properties are further discussed.

7.1 Performance Measures

The term *metric* refers to a criterion used to measure the performance of a system. Parallel algorithms have two performance goals: 1. minimize the execution time and 2. equalize workload distribution across the processors. Parallel algorithm performance can be evaluated using three metrics: 1. scaled speedup, 2. cost and 3. scaled efficiency.

The scaled speedup of a parallel algorithm is the ratio between the parallel algorithm execution time requirements using a single processor on the parallel computer to the parallel algorithm execution time requirements using multiple processors on the parallel computer (Gustafson et. al., 1988). This ratio can exaggerate the actual speedup because it masks the parallel algorithm overhead. Therefore, the alternate term *parallelizability* is introduced to refer to the ratio between the time taken by a parallel algorithm executing on one processor to the time taken by the parallel algorithm executing on multiple processors.

The cost of a parallel algorithm is a measure of the total number of operations performed. The cost of a parallel algorithm is defined as the product of the time elapsed and the number of processors used.

The scaled efficiency of a parallel algorithm is the scaled speedup divided by the number of processors used.

The parallel performance analysis involved nucleotide motif searches of the retinoblastoma gene. Three sets of nucleotide motifs were used: 1. Restriction Enzyme Database (REBASE) release 405, 2. Transcription Factors Database (TFD) and 3. Human Interferon Transcription Factors Database (HuIFNTFD). The retinoblastoma gene spans 180,388 nucleotides of genomic DNA (Toguchida et. al., 1993). In the current parallel performance analysis, the problem size (i.e. the number of retinoblastoma nucleotides) remained fixed as the number of processors was increased.

The parallel performance experiments are summarized (Table 7.1.1.). Parallel performance results are plotted as three types of graphs: 1. speedup curves, 2. cost curves and 3. efficiency curves. The parallel performance graphs are summarized (Table 7.1.2.).

Patterns	Table
restriction endonucleases	7.2.1.
transcription factors	7.3.1.
human interferon transcription factors	7.4.1.

Table 7.1.1. Parallel performance analysis experiments.

Patterns	Curve	Figure
restriction endonucleases	speedup	7.2.1.
restriction endonucleases	cost	7.2.2.
restriction endonucleases	efficiency	7.2.3.
transcription factors	speedup	7.3.1.
transcription factors	cost	7.3.2.
transcription factors	efficiency	7.3.3.
human interferon transcription factors	speedup	7.4.1.
human interferon transcription factors	cost	7.4.2.
human interferon transcription factors	efficiency	7.4.3.

Table 7.1.2. Parallel performance analysis graphs.

7.2 Restriction Endonucleases

The Restriction Enzyme Database (REBASE) is a comprehensive list of known restriction endonucleases (Roberts and Macelis, 1994). REBASE release 405 represents all known type II restriction endonucleases reported as of May 1, 1994. The retinoblastoma gene spans 180,388 nucleotides of genomic DNA (Toguchida et. al., 1993). The first parallel performance experiment involved a restriction analysis of the retinoblastoma gene using the REBASE release 405 type II restriction endonucleases. The retinoblastoma gene contained 24,699 type II restriction endonuclease recognition sites. The parallel performance results are presented (Table 7.2.1.). The speedup curve (Figure 7.2.1.), cost curve (Figure 7.2.2.) and efficiency curve (Figure 7.2.3.) are further presented.

processors	time (seconds)	speedup	cost	efficiency
1	25.576360	1.000000	25.576360	1.000000
2	12.789119	1.999853	25.578238	0.999927
4	6.395067	3.999389	25.580268	0.999847
8	3.198284	7.996901	25.586272	0.999613

Table 7.2.1. Parallel performance analysis of restriction endonuclease patterns.

Figure 7.2.1. Speedup curve of restriction endonuclease patterns. The ideal speedup curve $s = p$ is plotted as a dashed line for comparison.

Figure 7.2.2. Cost curve of restriction endonuclease patterns.

Figure 7.2.3. Efficiency curve of restriction endonuclease patterns.

7.3 Transcription Factors

The Transcription Factors Database (TFD) is the largest compiled list of transcription factor recognition sequences (Ghosh, 1993). TFD represents transcription factors reported as of September 1, 1993. The retinoblastoma gene spans 180,388 nucleotides of genomic DNA (Toguchida et. al., 1993). The second parallel performance experiment involved a transcription analysis of the retinoblastoma gene using the TFD transcription factors. The retinoblastoma gene contained 20,174 transcription factor recognition sites. The parallel performance results are presented (Table 7.3.1.). The speedup curve (Figure 7.3.1.), cost curve (Figure 7.3.2.) and efficiency curve (Figure 7.3.3.) are further presented.

processors	time (seconds)	speedup	cost	efficiency
1	103.097774	1.000000	103.097774	1.000000
2	51.561620	1.999506	103.123240	0.999753
4	25.788495	3.997821	103.153980	0.999455
8	12.906601	7.987988	103.252808	0.998499

Table 7.3.1. Parallel performance analysis of transcription factor patterns.

Figure 7.3.1. Speedup curve of transcription factor patterns. The ideal speedup curve $s = p$ is plotted as a dashed line for comparison.

Figure 7.3.2. Cost curve of transcription factor patterns.

Figure 7.3.3. Efficiency curve of transcription factor patterns.

7.4 Human Interferon Transcription Factors

The Human Interferon Transcription Factors Database (HuIFNTFD) is a comprehensive list of known human interferon transcription factor and promoter element recognition sequences. The retinoblastoma gene spans 180,388 nucleotides of genomic DNA (Toguchida et. al., 1993). The third parallel performance experiment involved a transcription analysis of the retinoblastoma gene using the HuIFNTFD transcription factors. The retinoblastoma gene contained 16,662 human interferon transcription factor recognition sites. The parallel performance results are presented (Table 7.4.1.). The speedup curve (Figure 7.4.1.), cost curve (Figure 7.4.2.) and efficiency curve (Figure 7.4.3.) are further presented.

processors	time (seconds)	speedup	cost	efficiency
1	13.588732	1.000000	13.588732	1.000000
2	6.795848	1.999564	13.591696	0.999782
4	3.399615	3.997138	13.598460	0.999285
8	1.701392	7.986832	13.611136	0.998354

Table 7.4.1. Parallel performance analysis of human interferon transcription factor patterns.

Figure 7.4.1. Speedup curve of human interferon transcription factor patterns. The ideal speedup curve $s = p$ is plotted as a dashed line for comparison.

Figure 7.4.2. Cost curve of human interferon transcription factor patterns.

Figure 7.4.3. Efficiency curve of human interferon transcription factor patterns.

7.5 Performance Analysis

The parallel performance experiments did not include I/O requirements within the elapsed times. Thus, the parallel algorithm performance was evaluated on a dedicated Intel iPSC/860 Hypercube. The dedicated machine strategy avoids the reduced performance that results when a program must contend for system resources with unrelated programs. Competition between unrelated programs for limited machine resources commonly occurs in time-sharing systems. Competition for network queueing resources to perform I/O is referred to as the *I/O bottleneck*. Parallelism eliminates the CPU bottleneck only to expose a secondary I/O bottleneck. This points out the need for high I/O rates to match the high computation rates of parallel computers. Thus, I/O should be performed in parallel as well.

Examination of the restriction endonuclease patterns speedup curve (Figure 7.2.1.), transcription factor patterns speedup curve (Figure 7.3.1.) and human interferon transcription factor patterns speedup curve (Figure 7.4.1.) reveals near-linear speedups in all three parallel performance experiments using a small number of processors.

Properties of the parallel performance metrics have been studied. For example, given a parallel architecture and a problem instance of fixed size, the parallel algorithm speedup does not indefinitely increase with an increasing number of processors. Speedup curves eventually exhibit saturation kinetics. For a fixed problem size, the speedup achieved by a parallel algorithm is limited by two factors: 1. parallel algorithm overhead grows with an increasing number of processors and 2. number of processors eventually exceeds the degree of concurrency inherent in the algorithm. 1. Parallel algorithm overhead. Certain parallel algorithm overheads are independent of the problem size, e.g. process creation. Other parallel algorithm overheads increase with the problem size but at a slower rate than the grain size, e.g. input/output and process synchronization. 2. Problem size. If there is not enough work to be done by the number of processors

available, then the parallel algorithm demonstrates constrained speedup. This factor gives rise to a phenomenon referred to as the *Amdahl effect* (Goodman and Hedetniemi, 1977). The Amdahl effect explains why speedup is a nondecreasing function of input problem size.

Given a parallel algorithm and an arbitrary number of processors p , speedup arbitrarily close to p can be obtained by executing the parallel algorithm on problem instances of sufficiently large size. The *isoefficiency function* is a scalability metric that relates problem size to the number of processors necessary for a proportional increase in speedup. In *scalable* parallel algorithms, efficiency levels can be maintained at some fixed value (between 0 and 1) for an increasing number of processors by increasing the corresponding problem size.

The *scalability* of a parallel algorithm on a parallel architecture is a measure of its capacity to effectively utilize an increasing number of processors. Scalability analysis is useful for three purposes. 1. Selection of the best parallel algorithm and parallel architecture combination for a problem under different problem size and processor number growth constraints. 2. Performance prediction of a parallel algorithm and parallel architecture combination from known performance on fewer processors. 3. Given a fixed problem size, determination of the optimal number of processors to be used and the maximum possible speedup to be obtained. Scalability analysis of parallel algorithms has been reviewed (Kumar and Gupta, 1994).

Chapter 8

Conclusions

The parallel nucleotide motif search algorithm and human interferon-alpha genetic analysis are summarized. Future directions for parallel nucleotide motif search algorithm research and human interferon-alpha transcriptional regulation research are proposed.

8.1 Summary

In summary, a multiple keyword search algorithm was developed for searching for class 1 nucleotide motifs within DNA sequences. The serial class 1 nucleotide motif search algorithm uses a deterministic finite automaton and is an adaptation of the Aho and Corasick (1975) algorithm. The serial class 1 nucleotide motif search algorithm was further modified for the hypercube architecture to form the parallel class 1 nucleotide motif search algorithm. The parallel class 1 nucleotide motif search algorithm was developed under the Single Program Multiple Data programming paradigm. The data parallel algorithm operates in $O(m + (n / p))$ time and occupies $O(n + mp)$ space, where n is the number of nucleotides in the DNA sequence, m is the total number of nucleotides in the finite set of class 1 nucleotide motifs and p is the number of processors forming the hypercube.

Numerous sequence analysis problems in computational molecular biology can be expressed as nucleotide motif search problems, e.g. restriction analysis and transcription analysis. Restriction analysis using nucleotide motif search leads to the unambiguous identification of restriction endonuclease recognition sites. Transcription analysis using nucleotide motif search suffers from the problem of low selectivity, i.e. the inability to

exclude false positives. Problems in the prediction of transcription factor recognition sites have been reviewed (Wingender et. al., 1990).

The parallel class 1 nucleotide motif search algorithm was implemented on the Intel iPSC/860 Hypercube. Using the Intel iPSC/860 Hypercube implementation, the human interferon-alpha multigene family was characterized by nucleotide motif search analysis. Nucleotide motif search analysis was performed using restriction endonuclease and transcription factor patterns. Nucleotide motif search analysis of the human interferon-alpha genes yielded restriction endonuclease recognition sites and transcription factor binding sites.

The human interferon-alpha promoters are defined as the regions immediately upstream from the transcription initiation site. The human interferon-alpha promoter 5' boundaries occur at positions -111 to -100 nucleotides 5' relative to the cap site. The human interferon-alpha promoter 3' boundaries occur at position -1 nucleotide 5' relative to the cap site. Nucleotide motif search analysis localized nucleotide sequences of transcriptional significance to within the human interferon-alpha promoters. The human interferon-alpha promoters underwent comparative analysis using multiple sequence alignment. Multiple sequence alignment recognized several series of homologous motifs. The homologous motifs were conserved regions of potential significance as transcription factor recognition sequences. Within each human interferon-alpha promoter five potential transcription control elements were identified: 1. tata box (TB), 2. virus-response element (VRE), 3. distal interferon regulatory factor site (DIRF), 4. proximal interferon regulatory factor site (PIRF) and 5. TG sequence (TG).

On the basis of computational evidence, a theoretical model for the transcriptional regulation of human interferon-alpha gene expression was proposed. The theoretical model is composed of three transcriptional control elements: 1. negative regulatory domain 1 (NRD1), 2. positive regulatory domain 1 (PRD1) and 3. positive regulatory domain 2 (PRD2). The theoretical model of human interferon-alpha transcriptional regulation

operates as follows. Human interferon-alpha genes operate under negative regulation. Interferon regulatory factor 2 (IRF-2) normally binds to negative regulatory domain 1. The repressor blocks transcription factor binding to positive regulatory domains 1 and 2. Induction involves repressor inactivation. TG and interferon regulatory factor 1 (IRF-1) can then bind to positive regulatory domains 1 and 2 respectively. Transcription is then activated. The hypothesis is supported solely by computational evidence and requires experimental verification. The prototype model will require modification as additional transcription factor binding sites are discovered.

8.2 Future Research

Future directions for parallel nucleotide motif search algorithm research and human interferon-alpha transcriptional regulation research are advanced: 1. improved multiple keyword search algorithms, 2. identification of additional transcription factor binding sites, 3. verification of regulatory domain function and boundaries, 4. isolation of regulatory proteins, 5. viral activation rates and 6. endogenous human interferon-alpha induction.

1. Improved multiple keyword search algorithms. The multiple keyword search problem was solved using a deterministic finite automaton (Aho and Corasick, 1975). Multiple keyword search algorithms with improved time complexities have been proposed. The Boyer and Moore (1977) technique was incorporated into the Commentz-Walter (1979) algorithm. The Horspool (1980) technique was used in the Baeza-Yates and Regnier (1990) algorithm. The n-gram technique was introduced to the Kim and Shawe-Taylor (1992) algorithm. Future parallel nucleotide motif search algorithms should be based on these more efficient multiple keyword search algorithms.

2. Identification of additional transcription factor binding sites. The human interferon-beta promoter has been well characterized. The human interferon-beta promoter regulatory region extends -200 nucleotides 5' relative to the transcription initiation site. The promoter region contains six regulatory elements which are classified as either positive or negative according to their transcriptional effects. There are four positive regulatory elements involved in the transcriptional activation of the human interferon-beta gene: positive regulatory domains 1 to 4 (PRDI - PRDIV). There are two negative regulatory elements involved in the stable transcriptional repression of the human interferon-beta gene prior to induction: negative regulatory domains 1 and 2 (NRDI - NRDII). Human interferon-beta transcriptional regulation has been reviewed (Maniatis et. al., 1992).

The human type-I interferon category includes the interferon-alpha, interferon-beta and interferon-omega genes. The interferon-alpha, interferon-beta and interferon-omega

genes are thought to have evolved from a single ancestral gene (Weissmann and Weber, 1986). Because the human interferon-beta and human interferon-alpha genes are related, the search for additional transcription factor binding sites within the human interferon-alpha genes should focus on the promoter region within -200 nucleotides 5' relative to the transcription initiation site.

3. Verification of regulatory domain function and boundaries. The negative regulatory domain should repress transcription when placed upstream of a heterologous promoter. All regulatory domain boundaries should be resolved using deletion and mutation analysis.

4. Isolation of regulatory proteins. Several strategies are possible for identifying proteins that bind to the human interferon-alpha promoter including gel shift and footprinting experiments. Genes encoding for the regulatory proteins could be cloned by screening cDNA expression libraries. Screening a cDNA expression library using regulatory sequences would yield a large group of proteins that recognize the regulatory domains. Additional experiments would be necessary to resolve the proteins directly involved in the human interferon-alpha regulation. The TG factor has not yet been isolated or cloned (MacDonald et. al., 1990). An alternate strategy for the identification of human interferon-alpha regulatory proteins would be the selective inactivation of the genes that encode for the regulatory proteins (Maniatis et. al., 1992).

5. Viral activation rates. The viral activation rates of human interferon genes should be established. Correlations between differential activation rates and regulatory sequence nucleotide differences should be further investigated.

6. Endogenous human interferon-alpha induction. The pharmaceutical use of human interferon-alpha is limited by pharmacokinetic factors. Human interferon-alpha produced by recombinant DNA technology has a short plasma elimination half-life, ranging from 4 to 5 hours. Clearance of human interferon-alpha is mediated by renal tubule catabolism. The biological half life of human interferon-alpha extends for 2 to 3 days

following administration. To compensate for rapid renal clearance, human interferon-alpha is administered every 1 to 2 days at elevated nonphysiological doses (Dorr, 1993). A better understanding of the human interferon-alpha transcription regulatory mechanism could yield alternate pharmacological strategies involving endogenous human interferon-alpha induction (Hayes and Zoon, 1994).

In conclusion, the design of more efficient parallel nucleotide motif search algorithms and the elucidation of the human interferon-alpha transcription regulatory mechanism remain open research problems.

Appendix A

Restriction Endonucleases

The Restriction Enzyme Database (REBASE) is a comprehensive list of known restriction endonucleases (Roberts and Macelis, 1994). REBASE release 405 type II restriction endonuclease nucleotide recognition sequences are presented.

enzyme	recognition sequence
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AatII	gacgtc
AccI	gtmkac
AciI	ccgc
AclI	aacgtt
AcyI	grcgyc
AflII	cttaag
AflIII	acrygt
AgeI	accggt
AhaIII	ttaaa
AluI	agct
AlwNI	cagnnnctg
ApaI	gggccc
ApaBI	gcannnnntgc
ApaLI	gtgcac
ApoI	raatty
AscI	ggcgcgcc
AsuI	ggncc
AsuII	ttcgaa
AvaI	cycgrg
AvaII	ggwcc
AvaIII	atgcat
AvrII	cctagg
BaeI	acnnnngtayc
BalI	tggcca
BamHI	ggatcc
BbvI	gcagc
BbvII	gaagac
BccI	ccatc
Bce83I	cttgag
BceII	acggc
BcgI	gcannnnnnntcg
BclI	tgatca
BetI	wccggw
BglI	gccnnnnnggc

BglII	agatct
BlnI	ggatc
Bpu10I	cctnagc
BsaAI	yacgr
BsaBI	gatnnnnatc
Bsbl	caacac
BscGI	cccgt
BsePI	gcgcgc
BseRI	gaggag
BsgI	gtgcag
Bsil	ctcgtg
BsiYI	ccnnnnnnngg
Bsrl	gaatgc
BsmAI	gtctc
Bsp24I	gacnnnnnntgg
Bsp1407I	tgata
BspGI	ctggac
BspHI	tcatga
BspLI'11I	acatgt
BspMI	acctgc
BspMII	tccgga
BsrI	actgg
BsrBI	gagcgg
BsrDI	gcaatg
BstEII	ggtnacc
BstXI	ccannnnnntgg
Cac8I	gcnnge
CauII	ccsgg
CfrI	yggccr
Cfr10I	rccggy
CjeI	ccannnnnngt
CjePI	ccannnnnnntc
Clal	atcgat
CviJI	rgcy
CviRI	tgca
Ddel	ctnag
DpnI/MboI	gatc
DraII	rggnccy
DraIII	cacnnngtg
DrdI	gacnnnnnngtc
DrdII	gaacca
DsaI	ccrygg
Eam1105I	gacnnnnnngtc
EciI	tccgcc
Eco31I	ggctctc
Eco47III	agcgct
Eco57I	ctgaag
EcoNI	cctnnnnnagg
EcoRI	gaattc
EcoRII	ccwgg
EcoRV	gatac
EspI	gctnagc
Esp3I	cgctc
FauI	cccgc

FinI	gggac
FnuDII	cgcg
Fnu4HI	gcngc
FokI	ggatg
FseI	ggccggcc
GdiII	yggccg
GsuI	ctggag
HaeI	wggccw
HaeII	rgcgcy
HaeIII	ggcc
HgaI	gacgc
HgiAI	gwgwcw
HgiCI	ggyrcc
HgiEII	accnnnnnnggt
HgiJII	grgcyc
HhaI	gcgc
HindII	gtyrac
HindIII	aagctt
HinfI	ganc
HpaI	gttaac
HpaII	ccgg
HphI	ggtga
KpnI	ggtacc
Ksp632I	ctcttc
MaeI	ctag
MaeII	acgt
MaeIII	gtnac
MboII	gaaga
McrI	cgrycg
MfeI	caatg
MluI	acgcgt
MmeI	tccrac
MnlI	cctc
MseI	ttaa
MslI	caynnnnrtg
MstI	tgcgca
MwoI	gcnnnnnnngc
NaeI	gccggc
NarI	ggcgcc
NcoI	ccatgg
NdeI	catatg
NheI	gctagc
NlaIII	catg
NlaIV	ggrrcc
NotI	gcggccgc
NruI	tcgcca
NspI	rcatgy
NspBII	cmgckg
PacI	ttaattaa
Pfl1108I	tcgtag
PflMI	ccannnnntgg
PleI	gagtc
PmaCI	cacgtg
PmeI	gttaaac

PpuMI	rggwccy
PshAI	gacnnnngtc
PstI	ctgcag
PvuI	cgatcg
PvuII	cagctg
RleAI	ccaca
RsaI	gtac
RsrII	cggwccg
SacI	gagctc
SacII	ccgctg
Sall	gtcgac
SapI	gctcttc
SauI	cctnagg
Scal	agtact
ScrFI	ccngg
SduI	gdgchc
SecI	ccnngg
SexAI	accwggg
SfaNI	gcatc
SfeI	ctryag
SfiI	ggccnnnnnggcc
Sgfi	gcgatcgc
SgrAI	crccggyg
SmaI	cccggg
SnaI	gtatac
SnaBI	tacgta
SpeI	actagt
SphI	gcatgc
SpII	cgtacg
SrfI	gcccgggc
Sse8387I	cctgcagg
SspI	aatatt
StuI	aggcct
StyI	ccwwgg
Swal	atttaa
TaqI	tcga
TaqIIa	caccca
TaqIIb	gaccga
TfiI	gawtc
TseI	gcwgc
Tsp45I	gtsac
TspEI	aatt
Tth111I	gacnnngtc
Tth111II	caarca
VspI	attaat
XbaI	tctaga
XcmI	ccannnnnnnnntgg
XhoI	ctcgag
XhoII	rgatcy
XmaIII	cggccg
XmnI	gaannnttc

Appendix B

Transcription Factors

The Transcription Factors Database (TFD) is the largest compiled list of known transcription factors (Ghosh, 1993). TFD transcription factor nucleotide recognition sequences are presented.

Enzyme	Recognition Sequence
S00001	cggagtactgtcctccg
S00002	tggatgggag
S00003	ctngaannttcnag
S00004	gcgtgtgca
S00005	atgactcat
S00006	aggaagtgaaa
S00007	gggcgtaacgagtaagattggccatttc
S00008	accgnnnncggt
S00009	gatttggtaatgg
S00010	ttttggcaaagat
S00011	gcaagggaattagtt
S00012	tggtaatgacracagt
S00013	accnnnnnnnggt
S00014	cacacacaca
S00015	tsatttgcatt
S00016	agaaatagatgagtaaacag
S00017	tgactc
S00018	wtatycat
S00019	agaacagatg
S00020	ggtgtggaaagt
S00021	gctgtggaatgt
S00022	tggggattcccca
S00023	ctgggtccg
S00024	ccccattgacgtcaatggg
S00025	tgacgttgttt
S00026	gggactttcc
S00027	taatgarat
S00028	gyatgntaatgarattcyttgnggg
S00029	gtgcatgctaatgatattctttgggg
S00030	gccaatgacaagacg
S00031	gtcaagatggccgatcag
S00032	aggtcatgtggcaag
S00033	atgcaaatna
S00034	gccaggtggc

S00035 tgatttgcac
 S00036 tgcagctgtgncnan
 S00037 ggggactttcc
 S00038 gaacag
 S00039 caggata
 S00040 cctgc
 S00041 ctctgcactccgccc
 S00042 tggmnnnnngccaa
 S00043 tgggmnnnnngcca
 S00044 tggnnnnnnngcca
 S00045 cagaggggactttccgagagg
 S00046 gggaaattcc
 S00047 gicccatgtggttac
 S00048 atttgcac
 S00049 atttgcagna
 S00050 atttgcacnt
 S00051 cagggtggc
 S00052 atgcaaat
 S00053 gaccgc
 S00054 gaagtgaactaactg
 S00055 gaccgca
 S00056 tctcttttaattagttgctaggcaactgccctccagagggcagt
 S00057 cctgawwa
 S00058 gctgtaattaatcaaaa
 S00059 tcttctcttctg
 S00060 acggtaaattggccc
 S00061 tcaattagtca
 S00062 aagtatgcaaag
 S00063 gtggwwwggtcccca
 S00064 kggggcgrry
 S00065 atcyyattwtctgkttgta
 S00066 taatgarat
 S00067 accgcctg
 S00068 ytggcannntgccar
 S00069 taatgarat
 S00070 ccacaccc
 S00071 aawaangaaaggr
 S00072 tgacgtca
 S00073 agcttctaaattatecat
 S00074 tggatcaaatgttct
 S00075 tagcatatgcta
 S00076 ccatgcataaatgtacacag
 S00077 atcraawtagwaakagcaat
 S00078 aracttagataaawww
 S00079 tgcrcnc
 S00080 ttitgcacacggcac
 S00081 gggrhtyyhc
 S00082 gttgcyngrcaac
 S00083 tcttatgcaatactcttcta
 S00084 accgtgcatgccgattggtg
 S00085 gatgtcc
 S00086 gatgtccatataggacac
 S00087 tataaa
 S00088 ggycaatct

S00089	canyyy
S00090	gagagga
S00091	actcagaggaana
S00092	ggccacgtgacc
S00093	gggwtggtcakg
S00094	tccccangcg
S00095	ccccaggc
S00096	gggtgtggaaagtc
S00097	ycagctgygg
S00098	aaccaat
S00099	agccact
S00100	agccaat
S00101	gttaatnattaac
S00102	yggtwcamwtgtyct
S00103	cacgaaaa
S00104	gkacgw
S00105	tctccaactataagttggaga
S00106	caattaaa
S00107	tttttgctggaacggttcag
S00108	caactgataaggat
S00109	atgcaaag
S00110	atgcact
S00111	gggcgg
S00112	rgttamtntynncm
S00113	tcaattaaatga
S00114	aaarrggaaryg
S00115	tcctatca
S00116	gtcatcatagacg
S00117	sggtwcaanntgtyct
S00118	yrgttcrytтын
S00119	atgctctaataaattt
S00120	ttcctaattaggaa
S00121	tknngyaak
S00122	tgttcccattatgttct
S00123	gagattccac
S00124	tcaggta
S00125	ggtcannntgacc
S00126	ccaggggtcaggggggggtgctt
S00127	gtgtcagtca
S00128	aanccaaa
S00129	tataat
S00130	atccaaacaatcrattttaccaatc
S00131	s. : gtgkgtt
S00132	accgaccg
S00133	tctgtctg
S00134	accgactg
S00135	ctcgagtacgaaccgaccgtcggtagg
S00136	ttatccaaaacctcggtttacaggaaac
S00137	aaaactacgtcatctcca
S00138	tcgcgccctttct
S00139	gtinwayattnatnng
S00140	tataaa
S00141	gagtgatgactcacgtcaag
S00142	agaaccaatgggcac

S00143 stgactma
 S00144 kwcgtca
 S00145 ttggctnnnagccaa
 S00146 gggcgg
 S00147 tticgcgc
 S00148 aggtgaaatcc
 S00149 cgggggtgattgggcaattggactg
 S00150 ctgtggaatg
 S00151 gtgtcnnggcaac
 S00152 tgggaatt
 S00153 rtgacgt
 S00154 gtcctaagagtca
 S00155 wdcnynnnnnacgad
 S00156 hcwathaaa
 S00157 tcagcaccg
 S00158 tgacgtca
 S00159 grgrttycay
 S00160 tatggtgtcaaagggtcaaact
 S00161 cagcccccggcgcagc
 S00162 cccagcgagtgatg
 S00163 cccattggtt
 S00164 gsgggscgkgtgca
 S00165 ctntgcrencggccc
 S00166 taatatgtaaaacattt
 S00167 ctgattggttc
 S00168 tkctgattgtytmm
 S00169 cctagcaacagatg
 S00170 ggacctg
 S00171 yagttcwytttycc
 S00172 wtttayrttwb
 S00173 tnatttgcatt
 S00174 ctcaggccct
 S00175 ggtgaccr
 S00176 gagttgggaaatccct
 S00177 cccactgaggaacc
 S00178 mctaacgggactttccaa
 S00179 ccccatgacgtcaatggg
 S00180 ccscrggc
 S00181 gagaagtgaaagtg
 S00182 gtgggaaattcc
 S00183 ggaaattcctctgaatagagagaggac
 S00184 gtgacgtmr
 S00185 agtgayrtca
 S00186 gttagtcat
 S00187 attagtcag
 S00188 atgagtcag
 S00189 aagagtcatt
 S00190 aagcgtcat
 S00191 taaatta
 S00192 aataaat
 S00193 aaaggcgg
 S00194 ctaatagcgataatagcgaggg
 S00195 ttaccgatctttcc
 S00196 ctaatagcgataatagcgaggg

S00197 tcatcgtccg'aaaccccgcca
 S00198 aaagtcctcggatgatgcaaccctccaagaa
 S00199 ctgcaattgcacaagg
 S00200 ccttgctgcaattgcacaagg
 S00201 cacaaggggaaact
 S00202 ctcaagattttaatctaa
 S00203 ttgtggttgccccag
 S00204 cctgcttatgiaattatct
 S00205 caattcctcctcctgc
 S00206 ctccaccaatcggc
 S00207 ggcagtcag
 S00208 cctctaagagacag
 S00209 actggccagcagccaac
 S00210 gacagtcac
 S00211 atcacgtg
 S00212 tgwtwtgnnttccgaannnnnaaa
 S00213 agtttttgcttccgaagatgtaa
 S00214 ccagaagccccacctaccaaggacgc
 S00215 gccccacc
 S00216 gccccgcc
 S00217 gccccacc
 S00218 gttagacgtttcagcttccaaaacagaagaatgtg
 S00219 aagccctctccc
 S00220 ctgcaggaa
 S00221 ggccatcttg
 S00222 tgccagctgc
 S00223 tgccacatga
 S00224 cgccatctgc
 S00225 mgagagagc
 S00226 ygagyc
 S00227 tattttaggaagcaaa
 S00228 ggggaatctccc
 S00229 gggtcgaccag
 S00230 ccwwwwwwgg
 S00231 gcaggatcatgtggcaagg
 S00232 actaggtaaacttgtagctgtgg
 S00233 tgaaacact
 S00234 aaagtccag
 S00235 tgggtaatttgcatttcta
 S00236 gcaggatcatgtggcaagg
 S00237 ggggaagggaataaaacc
 S00238 actaggtaaacttgtagctgtggttg
 S00239 gaaagtccaggc
 S00240 tgggtaatttgcatttctaaataagtt
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 S00242 ttgaaca
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 S00245 ccgaaac
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 S00247 ggtgggttggttccagg
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 S00249 ttattcaact
 S00250 tgrmcc

S00251 tggttaat
 S00252 ctgatta
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 S00254 aacctccgttatctccatt
 S00255 acattctccttgccaag
 S00256 ccckcccwect
 S00257 cctctccagattacattcatc
 S00258 scccaccic
 S00259 sccccagnntc
 S00260 ctcccyctgycc
 S00261 ctaaatac
 S00262 tcntactc
 S00263 taatactc
 S00264 tcttactc
 S00265 acctactc
 S00266 taagactc
 S00267 tcttaagc
 S00268 ttccacac
 S00269 tcctaccc
 S00270 tcatacca
 S00271 gtlagggtgtggaaagtccc
 S00272 aggatatctgtgtaagca
 S00273 agtgtggttttgcaaggaggaa
 S00274 gccatctg
 S00275 rgggrmtyycc
 S00276 ggggactttcc
 S00277 agggactttcc
 S00278 gggggactttcc
 S00279 ggggaatcccc
 S00280 ggggaatctcc
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 S00284 tggctttgggccaa
 S00285 tggatttgtgccaa
 S00286 tggaaaggcagccaa
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 S00301 gccaatga
 S00302 accccgccca
 S00303 tggattgaagccaata
 S00304 tgacgtca

S00305 actggaticccaactttg
 S00306 asaaasgaggaaaaactg
 S00307 cagagaacacagg
 S00308 ttatgtacaggg
 S00309 agaagactttccattctggccaca
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 S00313 cagatcccagccagtggacttagccccctgtttgct
 S00314 ctccgataactg
 S00315 accttggttaataatcaccagca
 S00316 gggtagaccttggttaatatt
 S00317 tggccctctggatccactgcttaa
 S00318 ctctctgg
 S00319 gggactttcc
 S00320 ataacgtttttgggtagttggaac
 S00321 accggcccacct
 S00322 ggggcggggc
 S00323 tgggcggggc
 S00324 tgggcggagt
 S00325 ggggcggagc
 S00326 ggggcggggg
 S00327 ggggcgggggt
 S00328 tgggcgggggt
 S00329 tgggcgggaac
 S00330 ggggcgggat
 S00331 ggggcgggac
 S00332 ggggcggaga
 S00333 ggggcggcgc
 S00334 cgttacgtca
 S00335 cgttacgtca
 S00336 cggcacgtca
 S00337 aactacgtca
 S00338 attcacgtca
 S00339 aattacgtca
 S00340 ggtcacgtga
 S00341 ccttacgtca
 S00342 yyacgtca
 S00343 tgacgtrr
 S00344 cagcccccggcgcag
 S00345 cccccggc
 S00346 ycccmnsss
 S00347 cgggaggtcaaagattgcgc
 S00348 gggcgattgggcaacccggc
 S00349 tcttgacctgagcccagct
 S00350 gtgctggactccctccactcgcgg
 S00351 gtggccgcgtccatctggtcagaaaagaca
 S00352 aaaagaacatcttt
 S00353 ccatgtaattacctaataagggaatttacacgct
 S00354 tcgagcgtgtaaatctcc
 S00355 catgtaattacctaataagggaatttacacgc
 S00356 aattaccgaaaaaggaaatt
 S00357 acttaccgaattaggaaatt
 S00358 aattaccgaaaaaggaaatt

S00359 attacctattcgggaaatt
 S00360 aattaccnaataaggaaatt
 S00361 aattgcagagctgggaatcggggggggggggggggggcgggtgggtgg
 S00362 tttaacctctggcgggtgataat
 S00363 gccacaccc
 S00364 ctgtgaaatattaactaaa
 S00365 tggtaggtaatt
 S00366 gtttacacaacct
 S00367 ctgataacagt
 S00368 gtccccagagctc
 S00369 ccggcccgaggcc
 S00370 ttgcctggagc
 S00371 gtccccgaggcg
 S00372 tgccctctggcc
 S00373 tgccccctggct
 S00374 ccggccaccggcc
 S00375 acccccgagctgt
 S00376 ctccccaaggagac
 S00377 agccccaacatat
 S00378 atccccagccct
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 S00385 ggataagataaggccg
 S00386 caaggagataagggtc
 S00387 ggccgtgataagagcc
 S00388 gtggctgataaagagc
 S00389 gcagcagatagcctcg
 S00390 tgactaa
 S00391 gaccgca
 S00392 aggaag
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 S01739 agtgcact
 S01740 aagcaattaag
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 S01802 tgttagaataactaaca
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 S01807 atgcatcrw
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 S01809 aaccgaaacgttttgggt
 S01810 gttcgaacgtttcggat
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 S01812 gtcattgaacgaatttttc
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 S01827 tattaaaa
 S01828 agatcttgatttcacaagactcca
 S01829 aaatctgatgcgtaa
 S01830 tcattagtgataattacctccaaa
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 S01835 ggaagggtcacgtccaa
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 S01837 taaggagcagtgactaagagaggc
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 S01840 ccaaatatggcgacgg
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 S01842 ctctctgctccgcccttaagt
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 S01908 gacccaaccaagttatcatg
 S01909 gaggtc
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 S01912 aaaagggtca
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S01985	ggttctttccgcc
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S01987	tgcrcrc
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S01989	ytawaaatar
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S01999	tcagrt
S02000	tknngnaak
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S02002	gccaratgacc
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S02006	ygcgcaygcgr
S02007	ggaacctcccc
S02008	atgcaaay
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S02010	agaaagggaagga
S02011	aggaar
S02012	agaacannntgttct
S02013	aagtgaagt
S02014	tcagagtataaatact
S02015	agaggaact
S02016	gggtggg
S02017	aggtcatgacct
S02018	cccctagcaacagatg
S02019	aagataaaacc
S02020	gttggttaa
S02021	ccgctc
S02022	krggckrrk
S02023	mamag
S02024	saggaagy
S02025	aagtgtttgc
S02026	aggaagtcc
S02027	aggtcaaggtea
S02028	gnncaactcaag
S02029	ggscacrtgac
S02030	gtttacataaac
S02031	ctttctcacgcaact
S02032	cacctgtcttttccc

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 S02037 cacgaaa
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S02151	cttctgcgtcagcgccagtat
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Appendix C

Human Interferon Transcription Factors

The Human Interferon Transcription Factors Database (HuIFNTFD) is a comprehensive list of known human interferon transcription factor and promoter element nucleotide recognition sequences. HuIFNTFD human interferon transcription factor and promoter element nucleotide recognition sequences are presented.

Enzyme	Recognition Sequence	Reference
IFN001	aaaaaactgtgaaaatacgtaatcc	Penix et. al. (1993)
IFN002	aaaactgaaa	Goodbourn et. al. (1986)
IFN003	aaaatgtaaa	Goodbourn et. al. (1986)
IFN004	aaagaaag	Ryals et. al. (1985)
IFN005	aaagga	Harada et. al. (1989)
IFN006	aaatga	Harada et. al. (1989)
IFN007	aaatga	Miyamoto et. al. (1988)
IFN008	aaatgactgaatatcgacttgct	Hardy et. al. (1985)
IFN009	aaatgg	Miyamoto et. al. (1988)
IFN010	aaatgt	Miyamoto et. al. (1988)
IFN011	aaattcctctgcatagagagaggac	Hiscott et. al. (1989)
IFN012	aacaga	Maniatis (1988)
IFN013	aactga	Miyamoto et. al. (1988)
IFN014	aagaaag	Ryals et. al. (1985)
IFN015	aagaaag	Ryals et. al. (1985)
IFN016	aagaaag	Ryals et. al. (1985)
IFN017	aagga	Maniatis (1988)
IFN018	aaggaaag	Ryals et. al. (1985)
IFN019	aaggaaag	Ryals et. al. (1985)
IFN020	aaggaaag	Ryals et. al. (1985)
IFN021	aaggaaagcaaaaacagaa	Ryals et. al. (1985)
IFN022	aaggga	Harada et. al. (1989)
IFN023	aaggga	Miyamoto et. al. (1988)
IFN024	aagtga	Harada et. al. (1989)
IFN025	aagtga	Miyamoto et. al. (1988)
IFN026	aagtgaattttgagttcttt	Hardy et. al. (1985)
IFN027	aagtgg	Miyamoto et. al. (1988)
IFN028	aagtgg	Miyamoto et. al. (1988)
IFN029	aartgraa	Taniguchi (1989)
IFN030	aatgaaaa	Ryals et. al. (1985)
IFN031	aatgtt	Maniatis (1988)
IFN032	aattcctctga	Nourbakhsh et. al. (1993)

IFN033	aattcctctgaatagagagaggac	Hiscott et. al. (1989)
IFN034	actaaaagtataatgacataggaaaactgaaagggagaagtga	Dinter et. al. (1983)
IFN035	actgaaag	Ryals et. al. (1985)
IFN036	agaa	Ryals et. al. (1985)
IFN037	agaagtgaagt	Du et. al. (1992)
IFN038	agaagtgaagtgggaaa	Maniatis (1988)
IFN039	agagtca	Schwarz et. al. (1993)
IFN040	aggaaactcta	Fraser et. al. (1991)
IFN041	agtttctttt	Hardy et. al. (1987)
IFN042	anggaaagy	Kuhl et. al. (1987)
IFN043	atagaaag	Ryals et. al. (1985)
IFN044	atagaaag	Ryals et. al. (1985)
IFN045	atagga	Miyamoto et. al. (1988)
IFN046	atgacatag	Du et. al. (1992)
IFN047	atgcaaag	Garcia-Blanco et. al. (1989)
IFN048	atgcaaat	Garcia-Blanco et. al. (1989)
IFN049	atgctaagtatat	Garcia-Blanco et. al. (1989)
IFN050	atggaaag	Ryals et. al. (1985)
IFN051	atggaaag	Ryals et. al. (1985)
IFN052	atggaaagt	Kuhl et. al. (1987)
IFN053	atggaaagtggcccagaa	Ryals et. al. (1985)
IFN054	atgtaaatga	Tanaka et. al. (1992)
IFN055	atgtacttacc	Garcia-Blanco et. al. (1989)
IFN056	attcctct	Wang et. al. (1990)
IFN057	attcctctgaatagagagaggac	Hiscott et. al. (1989)
IFN058	caaaaacgaaacc	Tanaka et. al. (1993)
IFN059	caaaaccgaaacg	Tanaka et. al. (1993)
IFN060	caaaaccgaaacc	Tanaka et. al. (1993)
IFN061	caaaacgaaaca	Tanaka et. al. (1993)
IFN062	caaaagtgaacac	Tanaka et. al. (1993)
IFN063	caaaagtgaacct	Tanaka et. al. (1993)
IFN064	caaaagtgaagc	Tanaka et. al. (1993)
IFN065	caaagcgaaagt	Tanaka et. al. (1993)
IFN066	caaatcgacaac	Tanaka et. al. (1993)
IFN067	caagg	Ryals et. al. (1985)
IFN068	cagaa	Ryals et. al. (1985)
IFN069	cagaa	Ryals et. al. (1985)
IFN070	cagaa	Ryals et. al. (1985)
IFN071	cagaa	Ryals et. al. (1985)
IFN072	cagag	Ryals et. al. (1985)
IFN073	cagag	Ryals et. al. (1985)
IFN074	caggg	Ryals et. al. (1985)
IFN075	catga	Ryals et. al. (1985)
IFN076	ccattgttct	Giese et. al. (1992)
IFN077	cctatctgtcaccatct	Penix et. al. (1993)
IFN078	cctctgaatagagagaggac	Hiscott et. al. (1989)
IFN079	cccttgaa	Giese et. al. (1992)
IFN080	ctaatga	Garcia-Blanco et. al. (1989)
IFN081	ctagg	Ryals et. al. (1985)
IFN082	ctagg	Ryals et. al. (1985)
IFN083	ctcatga	Garcia-Blanco et. al. (1989)
IFN084	ctctgaatagagagaggac	Hiscott et. al. (1989)

3

PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

PRECISIONSM RESOLUTION TARGETS

IFN085	ga	Ryals et. al. (1985)
IFN086	gaaa	Harada et. al. (1989)
IFN087	gaaaacgaaacc	Tanaka et. al. (1993)
IFN088	gaaaacgaaagt	Tanaka et. al. (1993)
IFN089	gaaaactgaaagg	Tanaka et. al. (1993)
IFN090	gaaaactgaaagg	Du et. al. (1992)
IFN091	gaaaagcgaaagc	Tanaka et. al. (1993)
IFN092	gaaaagcgaaagc	Tanaka et. al. (1993)
IFN093	gaaacc	MacDonald et. al. (1990)
IFN094	gaaacg	MacDonald et. al. (1990)
IFN095	gaaact	MacDonald et. al. (1990)
IFN096	gaaactgaaacc	Tanaka et. al. (1993)
IFN097	gaaactgaaacc	Tanaka et. al. (1993)
IFN098	gaaagc	MacDonald et. al. (1990)
IFN099	gaaagcaaaagt	Tanaka et. al. (1993)
IFN100	gaaagcgaaacc	Tanaka et. al. (1993)
IFN101	gaaagcgaaacc	Tanaka et. al. (1993)
IFN102	gaaagcgaaagt	Tanaka et. al. (1993)
IFN103	gaaagcgaaagt	Tanaka et. al. (1993)
IFN104	gaaagt	MacDonald et. al. (1990)
IFN105	gaaagtgaaacc	Tanaka et. al. (1993)
IFN106	gaaagtgaaacc	Tanaka et. al. (1993)
IFN107	gaaagtgaaacc	Tanaka et. al. (1993)
IFN108	gaaagtgaaacc	Tanaka et. al. (1993)
IFN109	gaaagtgaaacc	Tanaka et. al. (1993)
IFN110	gaaagtgaaacc	Tanaka et. al. (1993)
IFN111	gaaagtgaaacc	Tanaka et. al. (1993)
IFN112	gaaagtgaaacg	Tanaka et. al. (1993)
IFN113	gaaagtgaaact	Tanaka et. al. (1993)
IFN114	gaaagtgaaact	Tanaka et. al. (1993)
IFN115	gaaagtgaaagt	Tanaka et. al. (1993)
IFN116	gaaagtgaaagt	Tanaka et. al. (1993)
IFN117	gaaann	MacDonald et. al. (1990)
IFN118	gaaatg	MacDonald et. al. (1990)
IFN119	gaaatgaaagt	Tanaka et. al. (1993)
IFN120	gaaatggaaa	MacDonald et. al. (1990)
IFN121	gaaatggaaag	Tanaka et. al. (1992)
IFN122	gaaatggaaagt	MacDonald et. al. (1990)
IFN123	gaaattcctctgaatagagagaggac	Hiscott et. al. (1989)
IFN124	gaagtgaaag	Tanaka et. al. (1992)
IFN125	gaartgraa	Taniguchi (1989)
IFN126	gagaa	Ryals et. al. (1985)
IFN127	gagaa	Ryals et. al. (1985)
IFN128	gagaa	Ryals et. al. (1985)
IFN129	gagaa	Ryals et. al. (1985)
IFN130	gagaagtgaaagt	Tanaka et. al. (1993)
IFN131	gagaagtgaaagt	Tanaka et. al. (1992)
IFN132	gagaagtgaaagt	Maniatis et. al. (1992)
IFN133	gagaagtgaaagtgggaaatt	Kuhl et. al. (1987)
IFN134	gagaagtgaaagtgggaaattcctctgaatagagagaggac	Goodbourn et. al. (1985)
IFN135	gagtgcataaggaagcaaaaacagaaatggaaagtggcccgagaa	Ryals et. al. (1985)
IFN136	gataacgaaagg	Tanaka et. al. (1993)
IFN137	gatagtgaaacc	Tanaka et. al. (1993)
IFN138	gctttgt	Giese et. al. (1992)

IFN139 ggaaaactgaaagggagaagtgaaagtggg
 IFN140 ggaaattcctctgaatagagagaggac
 IFN141 gggaaattcc
 IFN142 ggggaattccc
 IFN143 ggggaattccc
 IFN144 gggactttcc
 IFN145 ggggattttccc
 IFN146 gggggaatcccc
 IFN147 ggggactttccac
 IFN148 ggggattttccc
 IFN149 gggrhwyymy
 IFN150 gtagaaaa
 IFN151 gtagaaag
 IFN152 gtagaaag
 IFN153 gtgaaag
 IFN154 gtgacgtmr
 IFN155 gtgagtma
 IFN156 gtgggaaattcc
 IFN157 taaaaccgaaagc
 IFN158 taataggtgtaata
 IFN159 taggaaa
 IFN160 tatgataatga
 IFN161 tcaattaaatga
 IFN162 tcctctgaatagagagaggac
 IFN163 tctgaatagagagaggac
 IFN164 tgaaagtgaagt
 IFN165 tgacgtmr
 IFN166 tgtaaatgacatag
 IFN167 ttctctgaatagagagaggac
 IFN168 ttctttgtty
 IFN169 ttcttttaaaatt
 IFN170 tttatgaattttccaaaa
 IFN171 yyattgtctc

Dron et. al. (1992)
 Hiscott et. al. (1989)
 Baeuerle (1991)
 Ballard et. al. (1990)
 Ballard et. al. (1990)
 Baeuerle (1991)
 Nakayama et. al. (1992)
 Fan et. al. (1990)
 Nakayama et. al. (1992)
 Nakayama et. al. (1992)
 Lenardo et. al. (1989)
 Ryals et. al. (1985)
 Ryals et. al. (1985)
 Ryals et. al. (1985)
 Ryals et. al. (1985)
 Hai et. al. (1989)
 Hai et. al. (1989)
 Maniatis et. al. (1992)
 Tanaka et. al. (1993)
 Garcia-Blanco et. al. (1989)
 Ryals et. al. (1985)
 Garcia-Blanco et. al. (1989)
 Garcia-Blanco et. al. (1989)
 Hiscott et. al. (1989)
 Hiscott et. al. (1989)
 Naf et. al. (1991)
 Du et. al. (1992)
 Maniatis et. al. (1992)
 Hiscott et. al. (1989)
 Giese et. al. (1992)
 Hardy et. al. (1985)
 Sica et. al. (1992)
 Giese et. al. (1992)

Appendix D

Human Interferon Alpha-1 Gene

D.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 1 gene was retrieved from the Genbank sequence file *humifnad* (Mantei et. al., 1980) (Nagata et. al., 1980) (Goeddel et. al., 1981) (Bowden et. al., 1984) (Benson et. al., 1993).

```

1 aaaacaaaac attgagaaa cacggctcta aactcatgta aagagtgcac gaaggaaagc
61 aaaaacagaa atggaaagtg gccagaagc attaagaaag tggaaatcac tatgttcctt
121 atttaaggca ttgcaggc ca gcaaggcctt cagagaacct agagcccaag gticagagtc
181 acccatctca gcaagcccag aagtaictgc aataictacg atggcctcgc ccttgcctt
241 actgatggtc ctggtgggtc tcagctgcaa gtcaagctgc tcctctgggt gtgatctccc
301 tgagaccac agcctggata acaggaggac ctgatgctc ctggcacaaa tgagcagaat
361 ctctcttcc tcctgtctga tggacagaca tgacttggga tttcccagg aggagtttga
421 tggcaaccag ttccagaagg ctccagccat ctctgtcctc catgagctga tccagcagat
481 ctccaacctc ttaccacaa aagattcatc tgctgcttgg gatgaggacc tctagacaa
541 attctgcacc gaactctacc agcagctgaa tgacttggaa gcctgtgtga tgcaggagga
601 gaggggtgga gaaactcccc tgatgaatgc ggactccatc ttggctgtga agaaatactt
661 ccgaagaatc actctctatc tgacagagaa gaaatacagc ccttgtgcct gggaggttgt
721 cagagcagaa atcatgagat cctctcttt atcaacaaac ttgcaagaaa gattaaggag
781 gaaggaataa catctgttcc aacatgaaaa caattcttat tgactcatc accaggtcac
841 gctttcatga attctgtcat ttcaaagact ctacccctg ctataactat gaccatgctg
901 ataaactgat ttatctattt aaatatttat ttaactattc ataagattta aattattttt
961 gttcatataa cgtcatgtgc acctttacac tgtggtagt gtaataaaac atgttccta
1021 tatttactca atccattatt ttgtgtgtt cattaaactt ttactatagg aacttcctgt
1081 atgtgttcat tcttaatat gaaattccta gcctgactgt gcaacctgat tagagaataa
1141 aggggtatatt ttatttgcct atcattatta tatgtaaga

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D.2 Restriction Endonuclease Sites

The human interferon-alpha 1 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
BcefI	22
CviJI	24
NlaIII	35
CviRI	46
NlaIII	48
HaeIII	80
AsuI	80
CviJI	80
MseI	92
EcoNI	118
BsiYI	118
MseI	123
CviRI	133
StuI	144
HaeI	144
HaeIII	145
CviJI	145
MaeI	159
HgiJII	162
SduI	162
CviJI	163
StyI	166
SecI	166
PleI	176
HinfI	176
Tsp45I	178
MaeIII	178
TaqIIa	180
BccI	183
DdeI	187
Cac8I	191
CviJI	194
CviRI	208
HaeI	222
HaeIII	223
CviJI	223
MnlI	225
AvaII	247
AsuI	247
EcoRII	250
ScrFI	250
HgiAI	257

SduI	257
EspI	259
DdeI	260
PvuII	262
NspBII	262
AluI	263
CviJI	263
TseI	264
Fnu4HI	264
CviRI	266
MwoI	267
AluI	275
CviJI	275
TseI	276
Fnu4HI	276
MwoI	279
CviJI	287
DpnI/MboI	293
DdeI	300
RleAI	306
PflMI	307
BsiYI	307
CviJI	311
EcoRII	313
ScrFI	313
PpuMI	326
DraII	326
AvaII	327
AsuI	327
EcoRII	340
ScrFI	340
TfiI	357
HinfI	357
MnlI	369
NlaIII	389
SecI	405
CjeI	406
EcoRII	406
ScrFI	406
BseRI	410
NlaIV	439
CviJI	439
CviJI	445
BccI	447
MnlI	457
NlaIII	461
AluI	465
CviJI	465
MwoI	466
DpnI/MboI	469
EglII	477
XhoII	477
DpnI/MboI	478
MnlI	487

TfiI	503
HinfI	503
TseI	512
Fnu4HI	512
FokI	520
PpuMI	525
DraII	525
AvaII	526
AsuI	526
MnlI	529
MaeI	533
ApoI	539
TspEI	540
CviRI	545
AlwNI	560
BbvI	562
TseI	562
Fnu4HI	562
PvuII	563
NspBII	563
AluI	564
CviJI	564
CviJI	580
CviRI	591
BseRI	596
BsmI	625
HinfI	632
BccI	636
CviJI	643
MboII	649
XmnI	652
MboII	663
TfiI	666
HinfI	666
MboII	688
CviJI	698
EcoRII	708
ScrFI	708
SecI	708
BspHI	732
NlaIII	733
XhoII	737
DpnI/MboI	738
MnlI	742
CviRI	762
MseI	773
AvaII	796
AsuI	796
MmeI	798
NlaIII	803
TspEI	812
HinfI	822
SexAI	831
EcoRII	832

ScrFI	832
Tsp45I	836
MaeIII	836
BspHI	845
NlaIII	846
EcoRI	849
ApoI	849
TspEI	850
HinfI	867
NlaIII	894
SwaI	917
AhaIII	918
MseI	919
SspI	922
MseI	931
SwaI	946
AhaIII	947
MseI	948
TspEI	951
MaeII	970
NlaIII	974
ApaLI	977
HgiAI	977
SduI	977
CviRI	978
BspLU11I	1009
AflIII	1009
NspI	1009
NlaIII	1010
MseI	1053
SfeI	1064
MseI	1094
ApoI	1102
TspEI	1103
MaeI	1108
CviJI	1110
CviRI	1120

The human interferon-alpha 1 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AflIII	1009
AhaIII	918
AhaIII	947
AluI	263
AluI	275
AluI	465
AluI	564

AlwNI	560
ApaLI	977
ApoI	539
ApoI	849
ApoI	1102
AsuI	80
AsuI	247
AsuI	327
AsuI	526
AsuI	796
AvaII	247
AvaII	327
AvaII	526
AvaII	796
BbvI	562
BccI	183
BccI	447
BccI	636
BceI	22
BglII	477
BseRI	410
BseRI	596
BsiYI	118
BsiYI	307
BsmI	625
BspHI	732
BspHI	845
BspLU11I	1009
Cac8I	191
CjeI	406
CviJI	24
CviJI	80
CviJI	145
CviJI	163
CviJI	194
CviJI	223
CviJI	263
CviJI	275
CviJI	287
CviJI	311
CviJI	439
CviJI	445
CviJI	465
CviJI	564
CviJI	580
CviJI	643
CviJI	698
CviJI	1110
CviRI	46
CviRI	133
CviRI	208
CviRI	266
CviRI	545
CviRI	591

CviRI	762
CviRI	978
CviRI	1120
DdeI	187
DdeI	260
DdeI	300
DpnI/MboI	293
DpnI/MboI	469
DpnI/MboI	478
DpnI/MboI	738
DraII	326
DraII	525
EcoNI	118
EcoRI	849
EcoRII	250
EcoRII	313
EcoRII	340
EcoRII	406
EcoRII	708
EcoRII?	832
EspI	259
Fnu4HI	264
Fnu4HI	276
Fnu4HI	512
Fnu4HI	562
FokI	520
HaeI	144
HaeI	222
HaeIII	80
HaeIII	145
HaeIII	223
HgiAI	257
HgiAI	977
HgiJII	162
HinfI	176
HinfI	357
HinfI	503
HinfI	632
HinfI	666
HinfI	822
HinfI	867
MaeI	159
MaeI	533
MaeI	1108
MaeII	970
MaeIII	178
MaeIII	836
MboII	649
MboII	663
MboII	688
MmeI	798
MnlI	225
MnlI	369
MnlI	457

MnlI	487
MnlI	529
MnlI	742
MseI	92
MseI	123
MseI	773
MseI	919
MseI	931
MseI	948
MseI	1053
MseI	1094
MwoI	267
MwoI	279
MwoI	466
NlaIII	35
NlaIII	48
NlaIII	389
NlaIII	461
NlaIII	733
NlaIII	803
NlaIII	846
NlaIII	894
NlaIII	974
NlaIII	1010
NlaIV	439
NspI	1009
NspBII	262
NspBII	563
PflMI	307
PleI	176
PpuMI	326
PpuMI	525
PvuII	262
PvuII	563
RleAI	306
ScrFI	250
ScrFI	313
ScrFI	340
ScrFI	406
ScrFI	708
ScrFI	832
SduI	162
SduI	257
SduI	977
SecI	166
SecI	405
SecI	708
SexAI	831
SfeI	1064
SspI	922
StuI	144
StyI	166
SwaI	917
SwaI	946

TaqIIa	180
TfiI	357
TfiI	503
TfiI	666
TseI	264
TseI	276
TseI	512
TseI	562
Tsp45I	178
Tsp45I	836
TspEI	540
TspEI	812
TspEI	850
TspEI	951
TspEI	1103
XhoII	477
XhoII	737
XmnI	652

The human interferon-alpha 1 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	0
AciI	ccgc	0
AclI	aacggt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	1
AgeI	accggt	0
AhaIII	tttaaa	2
AluI	agct	4
AlwNI	cagnnnctg	1
ApaI	gggccc	0
ApaBI	gcannnnntgc	0
ApaLI	gtgcac	1
ApoI	raatty	3
AscI	ggcgcgcc	0
AsuI	ggncc	5
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	4
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnnagtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	1

BbvII	gaagac	0
BccI	ccatc	3
Bce83I	cttgag	0
Bcefi	acggc	1
BcgI	gcannnnnntcg	0
BclI	tgatca	0
BetI	wccggw	0
BglI	gccnnnnnggc	0
BglII	agatct	1
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnatc	0
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	2
BsgI	gtgcag	0
BsiI	ctcgtg	0
BsiYI	ccnnnnnnngg	2
BsmI	gaatgc	1
BsmAI	gtctc	0
Bsp24I	gacnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	2
BspLU11I	acatgt	1
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	0
BsrBI	gagcgg	0
BsrDI	gcaatg	0
BstEII	ggtnacc	0
BstXI	ccannnnnntgg	0
Cac8I	gcnngc	1
CauII	ccsgg	0
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnngt	1
CjePI	ccannnnnnntc	0
ClaI	atcgat	0
CviJI	rgcy	18
CviRI	tgca	9
DdeI	ctnag	3
DpnI/MboI	gatc	4
DraII	rggnccy	2
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0

Eco57I	ctgaag	0
EcoNI	cctnnnnnnagg	1
EcoRI	gaattc	1
EcoRII	ccwgg	6
EcoRV	gatatc	0
EspI	gctnagc	1
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	4
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	0
HaeI	wggccw	2
HaeII	rgcgcy	0
HaeIII	ggcc	3
HgaI	gacgc	0
HgiAI	gwgcwc	2
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	1
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	0
HinfI	gante	7
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	0
KpnI	ggtacc	0
Ksp632I	ctcttc	0
MaeI	ctag	3
MaeII	acgt	1
MaeIII	gtnac	2
MboII	gaaga	3
McrI	cgrycq	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	1
MnlI	cctc	6
MseI	ttaa	8
MslI	caynnnnnrtg	0
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	3
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	0
NheI	gctagc	0
NlaIII	catg	10
NlaIV	ggnncc	1
NotI	gcggccgc	0
NruI	tcgcga	0

NspI	rcatgy	1
NspBII	cmgckg	2
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	1
PleI	gagtc	1
PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	2
PshAI	gacnnnngtc	0
PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	2
RleAI	cccaca	1
RsaI	gtac	0
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0
ScaI	agtact	0
ScrFI	ccngg	6
SduI	gdgchc	3
SecI	ccnngg	3
SexAI	accwggg	1
SfaNI	gcate	0
SfeI	ctryag	1
SfiI	ggccnnnnnggcc	0
Sgfi	gcgategc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	0
SnaBI	tacgta	0
SpeI	actagt	0
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gccggggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	1
StuI	aggcct	1
StyI	ccwwgg	1
SwaI	atttaaatt	2
TaqI	toga	0
TaqIIa	caccca	1
TaqIIb	gaccga	0
TfiI	gawtc	3
TseI	gcwgc	4
Tsp45I	gtsac	2
TspEI	aatt	5
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	0
XbaI	tctaga	0

XcmI	ccannnnnnnnntgg	0
XhoI	ctcgag	0
XhoII	rgatcy	2
XmaIII	cggccg	0
XmnI	gaanrnttc	1
Total		187

Appendix E

Human Interferon Alpha-2 Gene

E.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 2 gene was retrieved from the Genbank sequence file *humifnaa* (Goeddel et. al., 1980) (Maeda et. al., 1980) (Streuli et. al., 1980) (Goeddel et. al., 1981) (Lawn et. al., 1981b) (Bowden et. al., 1984) (Benson et. al., 1993).

```

1  ggcctctta tgtaccaca aaaatctatt tcaaaaaag ttgctctaag aatatagtta
61 tcaagttaag taaatgtca atagcctttt aatttaattt ttaattgttt tatcattctt
121 tgcaataata aaacattaac ttatacttt ttaattaat gtatagaata gagatataca
181 taggatattt aaatagatac acagtgtata tgtgattaaa atataatggg agattcaatc
241 agaaaaaagt ttctaaaaag gcctctggggg aaaagaggaa ggaaacaata atgaaaaaaa
301 tgtggtgaga aaaacagctg aaaacccatg taaagagtgt ataaagaaag caaaaagaga
361 agtagaaagt aacacagggg catttggaat atgtaaacga gtatgtccc tatttaaggc
421 taggcacaaa gcaaggctt cagagaacct ggagcctaag gtttaggctc acccattca
481 accagtctag cagcatctgc aacatctaca atggccttga ccttgcctt actggtggcc
541 ctctgtgtgc tcagctgcaa gtcaagctgc tctgtgggt gtgatctgc tcaaaccac
601 agcctgggta gcaggaggac ctgatgtct ctggcacaga tgaggagaat ctctctttc
661 tctgtctga aggacagaca tgacttggga ttccccagg aggagtgtg caaccagttc
721 caaaaggtg aaaccatccc tgctctccat gagatgatcc agcagatct caatctctc
781 agcacaagg actcatctgc tgcctgggat gagaccctcc tagacaaat ctacactgaa
841 ctctaccagc agctgaatga cctggaagcc tgtgtgatac aggggggtggg ggtgacagag
901 actccctga tgaaggagga ctccattctg gctgtgagga aatcttcca aagaatcact
961 ctctatctga aagagaagaa atacagccct tgtgcctggg aggtgtcag agcagaaatc
1021 atgagatctt ttctttgtc aacaaacttg caagaaagt taagaagtaa ggaatgaaaa
1081 ctggttcaac atggaaatga tticattga tctgtatgc agctcaccct ttatgatct
1141 gccatttcaa agactcatgt ttctgtatg accatgacac gatttaaatc ttccaatg
1201 ttttaggag tattaatcaa cattgtattc agctcttaag gcactagtc ctacagagg
1261 accatgctga ctgaccatt atctatttaa atattttaa aatattatt atttaactat
1321 ttataaaaca actattttt gtcatatta tgcattgtc accttgcac agtgggtaat
1381 gtaataaaat gtgtctttg tatttggtaa attattttg tctgttcat tgaactttg
1441 ctatggaact ttgtacttg ttattcttt aaaatgaaat tccaagccta attgtgcaac
1501 ctgattacag aataactggt acacttcatt tgcctatcaa tatttatct aagatataag
1561 taaaaataaa cttctgtaa accaagtgt atgtgtact caagataaca ggggtgaacct
1621 aacaaataca attctgtct cttgtgtatt tgattttgt atgaaaaaaa ctaaaaatgg
1681 taatcatact taattatcag ttatggtaaa tggatatga agagaagga acg

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E.2 Restriction Endonuclease Sites

The human interferon-alpha 2 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
HhaI	1
MnlI	4
RsaI	12
RleAI	15
DdeI	46
MseI	66
CviJI	83
MseI	89
TspEI	91
MseI	94
TspEI	96
MseI	101
TspEI	103
CviRI	121
MseI	136
MseI	151
TspEI	153
MseI	156
MseI	216
TfiI	232
HinfI	232
CviJI	260
HphI	304
PvuII	315
NspBII	315
AluI	316
CviJI	316
NlaIII	327
MaeIII	369
EcoNI	409
BsiYI	409
MseI	414
CviJI	418
MaeI	420
EcoRII	448
ScrFI	448
GsuI	449
NlaIV	451
CviJI	453
SauI	455
DdeI	456
CviJI	466

TaqIIa	470
MaeI	487
BbvI	490
ApaBI	490
TseI	490
Fnu4HI	490
MwoI	490
AlwNI	491
SfaNI	493
CviRI	498
HaeI	512
HaeIII	513
CviJI	513
BsrI	531
HaeIII	537
AsuI	537
CviJI	537
MnlI	540
EcoRII	543
ScrFI	543
HgiAI	547
SduI	547
EspI	549
DdeI	550
PvuII	552
NspBII	552
AluI	553
CviJI	553
TseI	554
Fnu4HI	554
CviRI	556
MwoI	557
AluI	565
CviJI	565
TseI	566
Fnu4HI	566
MwoI	569
CviJI	577
DpnI/MboI	583
Mn-I	589
*RleAI	596
PflMI	597
BsiYI	597
CviJI	601
MwoI	602
EcoRII	603
ScrFI	603
SecI	603
PpuMI	616
DraII	616
AvaII	617
AsuI	617
EcoRII	630
ScrFI	630

BseRI	642
TfiI	647
HinfI	647
NlaIII	679
SecI	695
CjeI	696
XcmI	696
EcoRII	696
ScrFI	696
BseRI	700
CviJI	726
BccI	734
MnlI	744
NlaIII	748
DpnI/MboI	756
BglII	764
XhoII	764
DpnI/MboI	765
Ksp632I	775
HinfI	790
TseI	799
Fnu4HI	799
FokI	807
MnlI	816
MaeI	820
ApoI	826
TspEI	827
AlwNI	847
BbvI	849
TseI	849
Fnu4HI	849
PvuII	850
NspBII	850
AluI	851
CviJI	851
EcoRII	861
ScrFI	861
CviJI	867
HphI	891
Tsp45I	892
MaeIII	892
HinfI	900
EcoNI	906
BsiYI	906
HinfI	919
CviJI	930
XmnI	939
TfiI	953
HinfI	953
MboII	975
CviJI	985
EcoRII	995
ScrFI	995
SecI	995

BspHI	1019
NlaIII	1020
BglII	1024
XhoII	1024
DpnI/MboI	1025
HindII	1038
CviRI	1049
MseI	1060
BsrI	1080
NlaIII	1090
MslI	1090
TfiI	1109
HinfI	1109
Cac8I	1118
AluI	1121
CviJI	1121
DpnI/MboI	1136
HinfI	1152
NlaIII	1156
NlaIII	1173
BsaBI	1181
SwaI	1182
AhaIII	1183
MseI	1184
VspI	1212
MseI	1213
AluI	1231
CviJI	1231
MwoI	1232
AflII	1235
MseI	1236
SpeI	1243
MaeI	1244
EcoNI	1250
BsiYI	1250
AvaII	1259
AsuI	1259
NlaIII	1263
DpnI/MboI	1273
SwaI	1285
AhaIII	1286
MseI	1287
SspI	1290
AhaIII	1296
MseI	1297
SspI	1301
MseI	1313
NlaIII	1354
ApaLI	1357
HgiAI	1357
SduI	1357
CviRI	1358
CviRI	1366
MseI	1376

ApoI	1409
TspEI	1410
RsaI	1454
AhaIII	1468
MseI	1469
ApoI	1477
TspEI	1478
CviJI	1485
TspEI	1490
CviRI	1495
BsrI	1515
RsaI	1519
BccI	1534
SspI	1539
RsaI	1596
HphI	1612
TspEI	1630
MseI	1690
TspEI	1692
MboII	1717
MboII	1722

The human interferon-alpha 2 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AflII	1235
AhaIII	1183
AhaIII	1286
AhaIII	1296
AhaIII	1468
AluI	316
AluI	553
AluI	565
AluI	851
AluI	1121
AluI	1231
AlwNI	491
AlwNI	847
ApaBI	490
ApaLI	1357
ApoI	826
ApoI	1409
ApoI	1477
AsuI	537
AsuI	617
AsuI	1259
AvaII	617
AvaII	1259

BbvI	490
BbvI	849
BccI	734
BccI	1534
BglII	764
BglII	1024
BsaBI	1181
BseRI	642
BseRI	700
BsiYI	409
BsiYI	597
BsiYI	906
BsiYI	1250
BspHI	1019
BsrI	531
BsrI	1080
BsrI	1515
Cac8I	1118
CjeI	696
CviJI	83
CviJI	260
CviJI	316
CviJI	418
CviJI	453
CviJI	466
CviJI	513
CviJI	537
CviJI	553
CviJI	565
CviJI	577
CviJI	601
CviJI	726
CviJI	851
CviJI	867
CviJI	930
CviJI	985
CviJI	1121
CviJI	1231
CviJI	1485
CviRI	121
CviRI	498
CviRI	556
CviRI	1049
CviRI	1358
CviRI	1366
CviRI	1495
DdeI	46
DdeI	456
DdeI	550
DpnI/MboI	583
DpnI/MboI	756
DpnI/MboI	765
DpnI/MboI	1025
DpnI/MboI	1136

DpnI/MboI	1273
DraII	616
EcoNI	409
EcoNI	906
EcoNI	1250
EcoRII	448
EcoRII	543
EcoRII	603
EcoRII	630
EcoRII	696
EcoRII	861
EcoRII	995
EspI	549
Fnu4HI	490
Fnu4HI	554
Fnu4HI	566
Fnu4HI	799
Fnu4HI	849
FokI	807
GsuI	449
HaeI	512
HaeIII	513
HaeIII	537
HgiAI	547
HgiAI	1357
HhaI	1
HindII	1038
HinfI	232
HinfI	647
HinfI	790
HinfI	900
HinfI	919
HinfI	953
HinfI	1109
HinfI	1152
HphI	304
HphI	891
HphI	1612
Ksp632I	775
MaeI	420
MaeI	487
MaeI	820
MaeI	1244
MaeIII	369
MaeIII	892
MboII	975
MboII	1717
MboII	1722
MnlI	4
MnlI	540
MnlI	589
MnlI	744
MnlI	816
MseI	66

MseI	89
MseI	94
MseI	101
MseI	136
MseI	151
MseI	156
MseI	216
MseI	414
MseI	1060
MseI	1184
MseI	1213
MseI	1236
MseI	1287
MseI	1297
MseI	1313
MseI	1376
MseI	1469
MseI	1690
MslI	1090
MwoI	490
MwoI	557
MwoI	569
MwoI	602
MwoI	1232
NlaIII	327
NlaIII	679
NlaIII	748
NlaIII	1020
NlaIII	1090
NlaIII	1156
NlaIII	1173
NlaIII	1263
NlaIII	1354
NlaIV	451
NspBII	315
NspBII	552
NspBII	850
PflMI	597
PpuMI	616
PvuII	315
PvuII	552
PvuII	850
RleAI	15
RleAI	596
RsaI	12
RsaI	1454
RsaI	1519
RsaI	1596
SauI	455
ScrFI	448
ScrFI	543
ScrFI	603
ScrFI	630
ScrFI	696

ScrFI	861
ScrFI	995
SduI	547
SduI	1357
SecI	603
SecI	695
SecI	995
SfaNI	493
SpeI	1243
SspI	1290
SspI	1301
SspI	1539
SwaI	1182
SwaI	1265
TaqIIa	470
TfiI	232
TfiI	647
TfiI	953
TfiI	1109
TseI	490
TseI	554
TseI	566
TseI	799
TseI	849
Tsp45I	892
TspEI	91
TspEI	96
TspEI	103
TspEI	153
TspEI	827
TspEI	1410
TspEI	1478
TspEI	1490
TspEI	1630
TspEI	1692
VspI	1212
XcmI	696
XhoII	764
XhoII	1024
XmnI	939

The human interferon-alpha 2 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	0
AciI	ccgc	0
AclI	aacggt	0

AcyI	grcgyc	0
AflII	cttaag	1
AflIII	acrygt	0
AgeI	accggt	0
AhaIII	tttaaa	4
AluI	agct	6
AlwNI	cagnnnctg	2
ApaI	gggcc	0
ApaBI	gcannnnntgc	1
ApaLI	gtgcac	1
ApoI	raatty	3
AscI	ggcgccgc	0
AsuI	ggncc	3
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	2
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	2
BbvII	gaagac	0
BccI	ccatc	2
Bce83I	cttgag	0
Bcefi	acggc	0
BcgI	gcannnnnnntcg	0
BclI	tgatca	0
BetI	wccggw	0
BglI	gccnnnnnnggc	0
BglII	agatct	2
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnnatac	1
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	2
BsgI	gtgcag	0
BsiI	ctcgtg	0
BsiYI	ccnnnnnnnngg	4
BsmI	gaatgc	0
BsmAI	gtctc	0
Bsp24I	gacnnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	1
BspLU11I	acatgt	0
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	3
BsrBI	gagcgg	0
BsrDI	gcaatg	0

BstEII	ggtnacc	0
BstXI	ccannnnnnntgg	0
Cac8I	gcnnge	1
CauII	ccsgg	0
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	1
CjePI	ccannnnnnntc	0
ClaI	atcgat	0
CviJI	rgcy	20
CviRI	tgca	7
DdeI	ctnag	3
DpnI/MboI	gatc	6
DraII	rggnccy	1
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	0
EcoNI	cctnnnnnnnagg	3
EcoRI	gaattc	0
EcoRII	ccwgg	7
EcoRV	gatatc	0
EspI	gctnagc	1
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	5
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	1
HaeI	wggccw	1
HaeII	rgcgcy	0
HaeIII	ggcc	2
HgaI	gacgc	0
HgiAI	gwgcwc	2
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	1
HindII	gtyrac	1
HindIII	aagctt	0
HinfI	gantc	8
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	3
KpnI	ggtacc	0
Ksp632I	ctcttc	1

MaeI	ctag	4
MaeII	acgt	0
MaeIII	gtnac	2
MboII	gaaga	3
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	5
MseI	ttaa	19
MslI	caynnnnrtg	1
MstI	tgcgca	0
MwoI	gcnnnnnnngc	5
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	0
NheI	gctagc	0
NlaIII	catg	9
NlaIV	ggnncc	1
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	0
NspBII	cmgckg	3
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	1
PleI	gagtc	0
PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	1
PshAI	gacnnnngtc	0
PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	3
RleAI	cccaca	2
RsaI	gtac	4
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	1
ScaI	agtact	0
ScrFI	ccngg	7
SduI	gdgchc	2
SecI	ccnngg	3
SexAI	acwgggt	0
SfaNI	gcate	1
SfeI	ctryag	0
SfiI	ggccnnnnnggcc	0
SgfI	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0

SnaI	gtatac	0
SnaBI	tacgta	0
SpeI	actagt	1
SphI	gcattg	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	3
StuI	aggcct	0
StyI	ccwwgg	0
SwaI	atttaaatt	2
TaqI	tcga	0
TaqIIa	caccca	1
TaqIIb	gaccga	0
TfiI	gawtc	4
TseI	gcwgc	5
Tsp45I	gtsac	1
TspEI	aatt	10
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	1
XbaI	tctaga	0
XcmI	ccannnnnnnnntgg	1
XhoI	ctcgag	0
XhoII	rgatcy	2
XmaIII	cggccg	0
XmnI	gaannnttc	1
Total		225

Appendix F

Human Interferon-Alpha 4 Gene

F.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 4 gene was retrieved from the Genbank sequence file *hsifna4b* (Henco et. al., 1985) (Benson et. al., 1993).

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1  aatgcaaata gcttatatta tatgatttat ttctagtaaa gttattcaac acatcagtac
61  itatgtcaag tgctgaaaag aaaaaagtgt tggcaacatc tggatgaata ctgcagctga
121 tgaagtttac aaattatttt gtcataataa gcaaaattca aagcttcata cactaagaga
181 aaaaatttaa aaaattattc attcatattt ttaggagttt tgaatgattg gatatgtaat
241 tataticata ttattaatgt gtatctatat agatttttat ttgcatatg tacttgata
301 caaaatttac atgaacaaat tacactaaaa gttaticcac aaatatactt atcaaattaa
361 gttaaatgtc aatagctttt aaacttaaat tttagtttaa cttttctgtc attctttact
421 ttgaataaaa agagcaaaact ttgtagtttt tatctgtgaa gtagagggtat acgtaataata
481 cataaataga tatgccaaat ctgtgttatt aaaatttcac gaagatttca attagaaaaa
541 aataccataa aaggccttga gtgcagggtga aaaataggca atgatgaaaa aaaatgaaaa
601 acittttaaa cacatgtaga gagtgcgtaa agaaagcaaa aacagagata gaaagtacaa
661 ctagggaatt tagaaaatgg aaattagtat gttcactatt taagacctat gcacagagca
721 aagtcctcag aaaacctaga ggccgaagtt caaggttatc catctcaagt agcctagcaa
781 tatttgaac atcccaatgg cctgtcctt ttcttactg atggccgtgc tgggtctcag
841 ctacaaa:cc atctgtctc tgggctgtga tctgcctcag acccacagcc tgggtaatag
901 gagggccttg atactcctgg cacaatggg aagaatctct catttctctt gcctgaagga
961 cagacatgat ttggaticc ccgaggagga gttgatggc caccagtcc agaagactca
1021 agccatctct gtctccatg agatgatcca gcagaccttc aatctcttca gcacagagga
1081 ctatctgctt gcttgggaac agagcctcct agaaaaattt tccactgaac ttaccagca
1141 actgaatgac ctggaagcat gtgtgataca ggagggttggg gtggaagaga ctccccctgat
1201 gaatgtggac tccatcctgg ctgtgaggaa atacttccaa agaatcactc ttatctaac
1261 agagaagaaa tacagccctt gtgcctggga ggttgtc:ga gcagaaatca tgagatccct
1321 ctctgttcca acaaaactgc aaaaaagatt aaggaggaag gattgaaacc tgggtcaaca
1381 tggaaatgat cctgactgac taatacatta tctcacac.. tcatgagtic ttccattca
1441 aagactcact tctataacca ccacgagttg aatcaaaaatt tcaaatgtt ttacgcagtg
1501 tgaagaagct tgggtgtatc ctgtgcaggc actagtctt tacagatgac aatgctgatg
1561 tctctgnea tctatttatt taaatattta ttattttta aaatttaaat tatttttat
1621 gtgatatcat gactaccttt acattgtggt gaatgtaaca atatatgttc ttcatattta
1681 gccaatatat taatttctt ttcaaaaaa ttitttactt acaaaatttt tgtgtttgtt
1741 tattctttaa gataa:aatgc caaggetgac ttacaacct gacttaaaaa tagatgattt
1801 aattaaagta cctatcataa ttatttcaa gttataaaaa aacatatttt tctgtacctg
1861 gttatatgtt gccttcagga tataaatgtg aacataaaat atacagtcce tcttctctg
1921 taicttttat ttgttcagg aaagaaatct aaaaacaata ataatgetga attaatatca
1981 gtgatgctaa ctgctataat gtgaggaagt aaaaaacaa tg

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F.2 Restriction Endonuclease Sites

The human interferon-alpha 4 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
CviRI	3
AluI	10
CviJI	10
MaeI	33
BsbI	47
ScaI	56
RsaI	57
MslI	97
FokI	102
PstI	111
SfeI	111
CviRI	112
BbvI	113
TseI	113
Fnu4HI	113
PvuII	114
NspBII	114
AluI	115
CviJI	115
TspEI	132
ApoI	154
TspEI	155
HindIII	161
AluI	162
CviJI	162
DdeI	173
ApoI	182
TspEI	183
AhaIII	186
MseI	187
TspEI	193
TspEI	238
VspI	253
MseI	254
CviRI	283
NdeI	285
RsaI	290
ApoI	303
TspEI	304
NlaIII	310
TspEI	318
TspEI	355

MseI	357
MseI	362
AluI	374
CviJI	374
AnaIII	378
MseI	379
MseI	385
ApoI	387
TspEI	388
MseI	397
SnaI	467
AccI	467
SnaBI	470
BsaAI	470
MaeII	471
MseI	509
ApoI	512
TspEI	513
BspHI	517
NlaIII	518
MboII	521
TspEI	530
CviJI	553
MwoI	554
BsgI	561
CviRI	562
HphI	566
BsrDI	578
AhaIII	605
MseI	606
BspLU11I	612
AflIII	612
NspI	612
NlaIII	613
RsaI	655
MaeI	661
ApoI	666
TspEI	667
TspEI	682
MseI	700
CviRI	710
MaeI	736
HaeIII	741
CviJI	741
BccI	760
CjeI	760
CviJI	771
MaeI	774
ApaBI	777
MwoI	777
SspI	779
CviRI	785
MslI	790
HaeIII	799

AsuI	799
CviJI	799
GdiII	822
CfrI	822
HaeIII	823
CviJI	823
HgiAI	833
SduI	833
EspI	835
DdeI	836
AluI	839
CviJI	839
BccI	849
CjePI	849
XcmI	849
CviJI	863
DpnI/MboI	869
MnlI	875
DdeI	876
RleAI	882
PflMI	883
BsiYI	883
CviJI	887
EcoRII	889
ScrFI	889
SecI	889
DraII	902
AsuI	903
HaeIII	904
CviJI	904
EcoRII	916
ScrFI	916
MboII	930
TfiI	933
HinfI	933
Eco57I	953
NlaIII	965
TfiI	975
HinfI	975
BsiYI	979
AvaI	980
SecI	981
BseRI	983
BseRI	986
BalI	997
CfrI	997
HaeI	997
HaeIII	998
CviJI	998
MboII	1012
BbvII	1012
HinfI	1015
CviJI	1021
BccI	1023

MnlI	1033
NlaIII	1037
DpnI/MboI	1045
Ksp632I	1064
HinfI	1079
TseI	1088
Fnu4HI	1088
CviJI	1103
MnlI	1105
MaeI	1109
ApoI	1115
TspEI	1116
AlwNI	1136
EcoRII	1150
ScrFI	1150
NspI	1157
NlaIII	1158
MboII	1184
HinfI	1189
HinfI	1208
BccI	1212
EcoRII	1216
ScrFI	1216
CviJI	1219
XmnI	1228
TfiI	1242
HinfI	1242
MboII	1264
CviJI	1274
EcoRII	1284
ScrFI	1284
SecI	1284
BspHI	1308
NlaIII	1309
XhoII	1313
DpnI/MboI	1314
MnlI	1318
CviRI	1338
MseI	1349
SexAI	1368
EcoRII	1369
ScrFI	1369
NlaIII	1379
MslI	1379
DpnI/MboI	1388
MslI	1416
BspHI	1421
NlaIII	1422
HinfI	1443
CjeI	1458
TfiI	1470
HinfI	1470
ApoI	1476
TspEI	1477

MboII	1502
HindIII	1506
AluI	1507
CviJI	1507
SnaI	1515
AccI	1515
BsgI	1523
CviRI	1524
Cac8I	1525
SpeI	1531
MaeI	1532
BsmAI	1560
SwaI	1578
AhaIII	1579
MseI	1580
SspI	1583
AhaIII	1597
MseI	1598
ApoI	1601
TspEI	1602
SwaI	1603
AhaIII	1604
MseI	1605
TspEI	1608
EcoRV	1623
BspHI	1627
NlaIII	1628
RsaI	1633
MslI	1642
HphI	1648
MaeIII	1655
CviJI	1680
VspI	1689
MseI	1690
TspEI	1692
MseI	1706
ApoI	1708
TspEI	1709
ApoI	1724
TspEI	1725
AflII	1746
MseI	1747
StyI	1760
SecI	1760
CviJI	1764
MseI	1784
MseI	1799
PacI	1799
TspEI	1801
MseI	1803
MaeIII	1807
TspEI	1819
RsaI	1854
SexAI	1856

EcoRII	1857
ScrFI	1857
MnlI	1909
Ksp632I	1910
TspEI	1970
VspI	1971
MseI	1972

The human interferon-alpha 4 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AccI	467
AccI	1515
AflII	1746
AflIII	612
AhaIII	186
AhaIII	378
AhaIII	605
AhaIII	1579
AhaIII	1597
AhaIII	1604
AluI	10
AluI	115
AluI	162
AluI	374
AluI	839
AluI	1507
AlwNI	1136
ApaBI	777
ApoI	154
ApoI	182
ApoI	303
ApoI	387
ApoI	512
ApoI	666
ApoI	1115
ApoI	1476
ApoI	1601
ApoI	1708
ApoI	1724
AsuI	799
AsuI	903
AvaI	980
BclI	997
BbvI	113
BbvII	1012
BccI	760
BccI	849

BccI	1023
BccI	1212
BsaAI	470
BsbI	47
BseRI	983
BseRI	986
BsgI	561
BsgI	1523
BsiYI	883
BsiYI	979
BsmAI	1560
BspHI	517
BspHI	1308
BspHI	1421
BspHI	1627
BspLU11I	612
BsrDI	578
Cac8I	1525
CfrI	822
CfrI	997
CjeI	760
CjeI	1458
CjePI	840
CviJI	10
CviJI	115
CviJI	162
CviJI	274
CviJI	553
CviJI	741
CviJI	771
CviJI	799
CviJI	823
CviJI	839
CviJI	863
CviJI	887
CviJI	904
CviJI	998
CviJI	1021
CviJI	1103
CviJI	1219
CviJI	1274
CviJI	1507
CviJI	1680
CviJI	1764
CviRI	3
CviRI	112
CviRI	283
CviRI	562
CviRI	710
CviRI	785
CviRI	1338
CviRI	1524
DdeI	173
DdeI	836

DdeI	876
DpnI/MboI	869
DpnI/MboI	1045
DpnI/MboI	1314
DpnI/MboI	1388
DraII	902
Eco57I	953
EcoRII	889
EcoRII	916
EcoRII	1150
EcoRII	1216
EcoRII	1284
EcoRII	1369
EcoRII	1857
EcoRV	1623
EspI	835
Fnu4HI	113
Fnu4HI	1088
FokI	102
GdiII	822
HaeI	997
HaeIII	741
HaeIII	799
HaeIII	823
HaeIII	904
HaeIII	998
HgiAI	833
HindIII	161
HindIII	1506
HinfI	933
HinfI	975
HinfI	1015
HinfI	1079
HinfI	1189
HinfI	1208
HinfI	1242
HinfI	1443
HinfI	1470
HphI	566
HphI	1648
Ksp632I	1064
Ksp632I	1910
MaeI	33
MaeI	661
MaeI	736
MaeI	774
MaeI	1109
MaeI	1532
MaeII	471
MaeIII	1655
MaeIII	1807
MboII	521
MboII	930
MboII	1012

MboII	1184
MboII	1264
MboII	1502
MnlI	875
MnlI	1033
MnlI	1105
MnlI	1318
MnlI	1909
MseI	187
MseI	254
MseI	357
MseI	362
MseI	379
MseI	385
MseI	397
MseI	509
MseI	606
MseI	700
MseI	1349
MseI	1580
MseI	1598
MseI	1605
MseI	1690
MseI	1706
MseI	1747
MseI	1784
MseI	1799
MseI	1803
MseI	1972
MslI	97
MslI	790
MslI	1379
MslI	1416
MslI	1642
MwoI	554
MwoI	777
NdeI	285
NlaIII	310
NlaIII	518
NlaIII	613
NlaIII	965
NlaIII	1037
NlaIII	1158
NlaIII	1309
NlaIII	1379
NlaIII	1422
NlaIII	1628
NspI	612
NspI	1157
NspBII	114
PacI	1799
PflMI	883
PstI	111
PvuII	114

RleAI	882
RsaI	57
RsaI	290
RsaI	655
RsaI	1633
RsaI	1854
ScaI	56
ScrFI	889
ScrFI	916
ScrFI	1150
ScrFI	1216
ScrFI	1284
ScrFI	1369
ScrFI	1857
SduI	833
SecI	889
SecI	981
SecI	1284
SecI	1760
SexAI	1368
SexAI	1856
SfeI	111
SnaI	467
SnaI	1515
SnaBI	470
SpeI	1531
SspI	779
SspI	1583
StyI	1760
SwaI	1578
SwaI	1603
TfiI	933
TfiI	975
TfiI	1242
TfiI	1470
TseI	113
TseI	1088
TspEI	132
TspEI	155
TspEI	183
TspEI	193
TspEI	238
TspEI	304
TspEI	318
TspEI	355
TspEI	388
TspEI	513
TspEI	530
TspEI	667
TspEI	682
TspEI	1116
TspEI	1477
TspEI	1602
TspEI	1608

TspEI	1692
TspEI	1709
TspEI	1725
TspEI	1801
TspEI	1819
TspEI	1970
VspI	253
VspI	1689
VspI	1371
XcmI	849
XhoII	1313
XmnI	1228

The human interferon-alpha 4 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	2
AccI	ccgc	0
AccI	aacgtt	0
AcyI	grogyc	0
AflII	cttaag	1
AflIII	acrygt	1
AgeI	accggt	0
AhaIII	tttaaa	6
AluI	agct	6
AlwNI	cagnnnctg	1
ApaI	gggccc	0
ApaBI	gcannnnntgc	1
ApaLI	gtgcac	0
ApoI	raatty	11
AscI	ggcgcgcc	0
AsuI	ggncc	2
AsuII	ttcgaa	0
AvaI	cycgrg	1
AvaII	ggwcc	0
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	1
BamHI	ggatcc	0
BbvI	gcagc	1
BbvII	gaagac	1
BccI	ccatc	4
Bce83I	cttgag	0
Bcefi	acggc	0
BcgI	gcannnnnntcg	0
BclI	tgatca	0

BetI	wccggw	0
BglI	gccnnnnnnggc	0
BglII	agatct	0
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	1
BsaBI	gatnnnnnatc	0
BsbI	caacac	1
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	2
BsgI	gtgcag	2
BsiI	ctcgtg	0
BsiYI	ccnnnnnnnngg	2
BsmI	gaatgc	0
BsmAI	gtctc	1
Bsp24I	gacnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	4
BspLU11I	acatgt	1
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	0
BsrBI	gagcgg	0
BsrDI	gcaatg	1
BstEII	ggtnacc	0
BstXI	ccannnnnntgg	0
Cac8I	gcnngc	1
CauII	ccsgg	0
CfrI	yggccr	2
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	2
CjePI	ccannnnnnntc	1
ClaI	atcgat	0
CviJI	rgcy	21
CviRI	tgca	8
DdeI	ctnag	3
DpnI/MboI	gatc	4
DraII	rggnccy	1
DraIII	cacnnrgtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	1
EcoNI	cctnnnnnnnagg	0
EcoRI	gaattc	0
EcoRII	ccwgg	7
EcoRV	gatatc	1
EspI	gctnagc	1

Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	2
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	1
GsuI	ctggag	0
HaeI	wggccw	1
HaeII	rgcgcy	0
HaeIII	ggcc	5
HgaI	gacgc	0
HgiAI	gwgcwc	1
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	2
HinfI	ganc	9
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	2
KpnI	ggtacc	0
Ksp632I	ctcttc	2
MaeI	ctag	6
MaeII	acgt	1
MaeIII	gtnac	2
MboII	gaaga	6
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	5
MseI	ttaa	21
MslI	caynnnnnrtg	5
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	2
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	1
NheI	gctagc	0
NlaIII	catg	10
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	2
NspBII	cmgckg	1
PacI	ttaattaa	1
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	1
PleI	gagtc	0

PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	0
PshAI	gacnnnngtc	0
PstI	ctgcag	1
PvuI	cgatcg	0
PvuII	cagctg	1
RleAI	cccaca	1
RsaI	gtac	5
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0
ScaI	agtact	1
ScrFI	ccngg	7
SduI	gdgchc	1
SecI	ccnngg	4
SexAI	accwgt	2
SfaNI	gcatc	0
SfeI	ctryag	1
SfiI	ggccnnnnnnggcc	0
Sgfi	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	2
SnaBI	tacgta	1
SpeI	actagt	1
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	2
StuI	aggcct	0
StyI	ccwwgg	1
Swal	atttaaatt	2
TaqI	tcga	0
TaqIIa	caccca	0
TaqIIb	gaccga	0
TfiI	gawtc	4
TseI	gcwgc	2
Tsp45I	gtsac	0
TspEI	aatt	23
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	3
XbaI	tctaga	0
XcmI	ccannnnnnnnntgg	1
XhoI	ctcgag	0
XhoII	rgatcy	1
XmaIII	cggccg	0
XmnI	gaannnttc	1

Total

265

Appendix G

Human Interferon-Alpha 5 Gene

G.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 5 gene was retrieved from the Genbank sequence file *hsifna5* (Henco et. al., 1985) (Bowden et. al., 1993).

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1  cttaatccgg gactgaattta attctatatt acattctatt acgctgcttt taaagcatta
61  aagaagtaca atattctctc tcgataatgg gtactgtaat gtatatacat cagccaacac
121  atagtataat tgtgttatta aaatttaatt ggatttttag ttagaaaaaa aatttctaaa
181  aagcatatgt ggcagagtga agatgaggta ataatgtaa aataaataaa ctgagaaaca
241  ctctgtaca tctatgtaga aagagcataa aagaaagcaa aangagaagt agaaagtaac
301  acaaggcatt cagaaaatgg aaactcgtat gtgacctttt taagatctgt gcacaaaaca
361  aggtcttcag agaagagccc aaggttcagg gtcactcaat ctcaacagcc cagaagcate
421  tgcaacctcc ccaatggcct tggcctttgt ttactgatg gccctgggtg tgctcaactg
481  caagtcaatc tgttctctgg gctgtgatct gcctcagacc cacagcctga gtaacaggag
541  gactttgatg ataatggcac aaatgggaag aatctctcct ttctcctgcc tgaaggacag
601  acatgacttt ggatttcctc aggaggagtt tgatggcaac cagtccaga aggetcaagc
661  catctctgtc ctccatgaga tgatccagca gaccttcaat ctcttcagca caaaggactc
721  atctgctact tgggatgaga cacttctaga caaattctac actgaacttt accagcagct
781  gaatgacctg gaagccigta tgatgcagga ggttggagtg gaagacactc ctctgatgaa
841  tgtggactct atcctgactg tgagaaaata ctccaaga atcacctct atctgacaga
901  gaagaaatac agcccttggt catgggaggt tgcagagca gaaatcatga gatcctctc
961  ttatcagca aacttgcaag aaagattaag gaggaaggaa tgaaaactgg ttcaacatcg
1021  aaatgattct cattgactag tacaccattt cacacttctt gattctgccc gttcaata
1081  ttaatttctg ctatatccat gacttgagtt gaatcaaaat ttcaaacgt ttacacgtg
1141  ttaagcaaca ctcttttagc tccacaggga caaaatcttt acagatgac atgccaatct
1201  atctattcta tctatttate tatctgtctg tcttctatct aatctatta aatatttatt
1261  tatttataag atttaataa tttaataa tgtttgtica ggtaataa catccacctt
1321  tacttttggt ctaataaat aaaatatgtt ctttatgttt tgtaactga ttatttget
1381  ttgtcatta gatttttact attaatgtt tgtttattct ttaaaatgaa actccaagcc
1441  tgattgtata acttgattaa aaacagatgg tacag

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G.2 Restriction Endonuclease Sites

The human interferon-alpha 5 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
MseI	2
HpaII	7
CauII	7
ScrFI	7
FinI	9
XmnI	15
ApoI	19
TspEI	20
TseI	43
Fnu4HI	43
MwoI	46
AhaIII	49
MseI	50
MseI	58
RsaI	66
SspI	70
TaqI	81
RsaI	91
CviJI	112
BsbI	115
MseI	138
ApoI	141
TspEI	142
MseI	145
ApoI	170
TspEI	171
MwoI	183
NdeI	184
MboII	199
DdeI	231
Bsp1407I	245
RsaI	246
MaeIII	296
Tsp45I	331
MaeIII	331
MseI	340
BglII	343
XhoII	343
DpnI/MboI	344
ApaLI	349
HgiAI	349
SduI	349

CviRI	350
MboII	372
HgiJII	375
SduI	375
CviJI	376
StyI	379
SecI	379
Tsp45I	391
MaeIII	391
CviJI	407
SfaNI	416
CviRI	421
MnlI	426
HaeI	435
HaeIII	436
CviJI	436
HaeIII	460
AsuI	460
CviJI	460
SecI	462
EcoRII	463
ScrFI	463
HgiAI	470
SduI	470
CviRI	479
CviJI	500
DpnI/MboI	506
MnlI	512
DdeI	513
RleAI	519
CviJI	524
DdeI	527
MaeIII	531
MboII	567
TfiI	570
HinfI	570
Eco57I	590
NlaIII	602
MnlI	617
SauI	617
DdeI	618
BseRI	623
CviJI	652
CviJI	658
BccI	660
MnlI	670
NlaIII	674
DpnI/MboI	682
Ksp632I	701
HinfI	716
FokI	733
XbaI	745
MaeI	746
ApoI	752

TspEI	753
AlwNI	773
BbvI	775
TseI	775
Fnu4HI	775
PvuII	776
NspBII	776
AluI	777
CviJI	777
EcoRII	787
ScrFI	787
CviJI	793
CviRI	804
MboII	821
BbvII	821
MnlI	830
HinfI	845
TfiI	879
HinfI	879
MnlI	886
MboII	901
CviJI	911
CviRI	919
NlaIII	921
BspHI	945
NlaIII	946
XhoII	950
DpnI/MboI	951
CviRI	975
MseI	986
BsrI	1006
AslI	1016
TaqI	1018
XmnI	1020
TfiI	1025
HinfI	1025
SpeI	1036
MaeI	1037
RsaI	1040
Bce83I	1058
SspI	1077
VspI	1080
MseI	1081
TspEI	1083
NlaIII	1098
Bce83I	1103
TfiI	1111
HinfI	1111
ApoI	1117
TspEI	1118
AclI	1126
MaeII	1127
AflIII	1134
PmaCI	1135

BsaAI	1135
MaeII	1136
AflIII	1136
MseI	1141
BsbI	1146
AluI	1158
CviJI	1158
FinI	1167
BclI	1186
DpnI/MboI	1187
NlaIII	1190
SwaI	1246
AhaIII	1247
MseI	1248
SspI	1251
SwaI	1271
AhaIII	1272
MseI	1273
TspEI	1276
AhaIII	1282
MseI	1283
TspEI	1286
SspI	1304
CviJI	1329
HindII	1362
VspI	1401
MseI	1402
TspEI	1404
AhaIII	1420
MseI	1421
CviJI	1437
MseI	1457
RsaI	1470

The human interferon-alpha 5 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AccI	1126
AflIII	1134
AflIII	1136
AhaIII	49
AhaIII	1247
AhaIII	1272
AhaIII	1282
AhaIII	1420
AluI	777
AluI	1158
AluNI	773

ApaLI	349
ApoI	19
ApoI	141
ApoI	170
ApoI	752
ApoI	1117
AsuI	460
BbvI	775
BbvII	821
BccI	660
Bce83I	1058
Bce83I	1103
BclI	1186
BglII	343
BsaAI	1135
BsbI	115
BsbI	1146
BseRI	623
Bsp1407I	245
BspHI	945
BsrI	1006
CauII	7
CviJI	112
CviJI	376
CviJI	407
CviJI	436
CviJI	460
CviJI	500
CviJI	524
CviJI	652
CviJI	658
CviJI	777
CviJI	793
CviJI	911
CviJI	1158
CviJI	1329
CviJI	1437
CviRI	350
CviRI	421
CviRI	479
CviRI	804
CviRI	919
CviRI	975
DdeI	231
DdeI	513
DdeI	527
DdeI	618
DpnI/MboI	344
DpnI/MboI	506
DpnI/MboI	682
DpnI/MboI	951
DpnI/MboI	1187
Eco57I	590
EcoRII	463

EcoRII	787
FinI	9
FinI	1167
Fnu4HI	43
Fnu4HI	775
FokI	733
HaeI	435
HaeIII	436
HaeIII	460
HgiAI	349
HgiAI	470
HgiJII	375
HindII	1362
HinfI	570
HinfI	716
HinfI	845
HinfI	879
HinfI	1025
HinfI	1111
HpaII	7
Ksp632I	701
MaeI	746
MaeI	1037
MaeII	1127
MaeII	1136
MaeIII	296
MaeIII	331
MaeIII	391
MaeIII	531
MboII	199
MboII	372
MboII	567
MboII	821
MboII	901
MnlI	426
MnlI	512
MnlI	617
MnlI	670
MnlI	830
MnlI	886
MseI	2
MseI	50
MseI	58
MseI	138
MseI	145
MseI	340
MseI	986
MseI	1081
MseI	1141
MseI	1248
MseI	1273
MseI	1283
MseI	1402
MseI	1421

MseI	1457
MslI	1016
MwoI	46
MwoI	183
NdeI	184
NlaIII	602
NlaIII	674
NlaIII	921
NlaIII	946
NlaIII	1098
NlaIII	1190
NspBII	776
PmaCI	1135
PvuII	776
RleAI	519
RsaI	66
RsaI	91
RsaI	246
RsaI	1040
RsaI	1470
SauI	617
ScrFI	7
ScrFI	463
ScrFI	787
SduI	349
SduI	375
SduI	470
SecI	379
SecI	462
SfaNI	416
SpeI	1036
SspI	70
SspI	1077
SspI	1251
SspI	1304
StyI	379
SwaI	1246
SwaI	1271
TaqI	81
TaqI	1018
TfiI	570
TfiI	879
TfiI	1025
TfiI	1111
TseI	43
TseI	775
Tsp45I	331
Tsp45I	391
TspEI	20
TspEI	142
TspEI	171
TspEI	753
TspEI	1083
TspEI	1118

TspEI	1276
TspEI	1286
TspEI	1404
VspI	1080
VspI	1401
XbaI	745
XhoII	343
XhoII	950
XmnI	15
XmnI	1020

The human interferon-alpha 5 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	0
AciI	ccgc	0
AclI	aacgtt	1
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	2
AgeI	accggt	0
AhaIII	tttaaa	5
AluI	agct	2
AlwNI	cagnnnctg	1
ApaI	gggccc	0
ApaBI	gcannnnntgc	0
ApaLI	gtgcac	1
ApoI	raatty	5
AscI	ggcgcgcc	0
AsuI	ggncc	1
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	0
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	1
BbvII	gaagac	1
BccI	ccatc	1
Bce83I	cttgag	2
Bcefi	acggc	0
BcgI	gcannnnnnntcg	0
BclI	tgatca	1
BetI	wccggw	0
BglI	gccnnnnnggc	0

BglII	agatct	1
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	1
BsaBI	gatnnnnatc	0
BsbI	caacac	2
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	1
BsgI	gtgcag	0
BsiI	ctcgtg	0
BsiYI	ccnnnnnnnngg	0
BsmI	gaatgc	0
BsmAI	gtctc	0
Bsp24I	gacnnnnnnntgg	0
Bsp1407I	tgtaca	1
BspGI	ctggac	0
BspHI	tcatga	1
BspLU11I	acatgt	0
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	1
BsrBI	gagcgg	0
BsrDI	gcaatg	0
BstEII	ggtnacc	0
BstXI	ccannnnnnntgg	0
Cac8I	gcnngc	0
CauII	ccsgg	1
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	0
CjePI	ccannnnnnntc	0
ClaI	atcgat	0
CviJI	rgcy	15
CviRI	tgca	6
DdeI	ctnag	4
DpnI/MboI	yatc	5
DraII	rggnccy	0
DraIII	cacnnngta	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	1
EcoNI	cctnnnnnnagg	0
EcoRI	gaattc	0
EcoRII	ccwgg	2
EcoRV	gatatc	0
EspI	gctnagc	0
Esp3I	cgtctc	0
FauI	cccgc	0

FinI	gggac	2
FnuDII	cgcg	0
Fnu4HI	gongc	2
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	0
HaeI	wggccw	1
HaeII	rgcgcy	0
HaeIII	ggcc	2
HgaI	gacgc	0
HgiAI	gwgwcw	2
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyr	1
HhaI	gcgc	0
HindII	gtyrac	1
HindIII	aagctt	0
HinfI	ganc	6
HpaI	gttaac	0
HpaII	ccgg	1
HphI	ggtga	0
KpnI	ggtacc	0
Ksp632I	ctcttc	1
MaeI	ctag	2
MaeII	acgt	2
MaeIII	gtnac	4
MboII	gaaga	5
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	6
MseI	ttaa	15
MslI	caynnnnnrtg	1
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	2
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	1
NheI	gctagc	0
NlaIII	catg	6
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	0
NspBII	cmgckg	1
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	0
PleI	gagtc	0
PmaCI	cacgtg	1
PmeI	gtttaaac	0

PpuMI	rggwccy	0
PshAI	gacnnnngtc	0
PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	1
RleAI	cccaca	1
RsaI	gtac	5
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gtctcttc	0
SauI	cctnagg	1
ScaI	agtact	0
ScrFI	ccngg	3
SduI	gdgchc	3
SecI	ccnngg	2
SexAI	accwgg	0
SfaNI	gcac	1
SfeI	ctryag	0
SfiI	ggccnnnnnggcc	0
Sgfi	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	0
SnaBI	tacgta	0
SpeI	actagt	1
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	4
StuI	aggcct	0
StyI	ccwwgg	1
SwaI	atttaa	2
TaqI	tcga	2
TaqIIa	caccca	0
TaqIIb	gaccga	0
TfiI	gawtc	4
TseI	gcwgc	2
Tsp45I	gtsac	2
TspEI	aatt	9
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	2
XbaI	tctaga	1
XcmI	ccannnnnnnnntgg	0
XhoI	ctcgag	0
XhoII	rgatcy	2
XmaIII	cggccg	0
XmnI	gaannnttc	2
Total		133

Appendix H

Human Interferon-Alpha 6 Gene

H.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 6 gene was retrieved from the Genbank sequence file *hsifna6* (Henco et. al., 1985) (Benson et. al., 1993).

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1 atgtcagag ttaagttaa tgctaaatt taaaaaatt aacttttagt taaattactt.
61 tgcattcct aacagatcaa gaaataataa aagtaaactt tagtctttt ctttagtgt
121 gcaagtagac atacatacag tacataagga gatatacaat atatttgta ttaaattta
181 ataaaaattt aatttcaatt aagaaaaaaa ttcttataaa gactctggag gcaggcaaga
241 gaagggagtg tcaataatga ccacatacac acacaaacac acacacaaaa ctgggtgaaa
301 aactactcta tacccatgta gagagtaaat aaatgaaagc aaaatcagac gtagaaagta
361 aattctgaaa atggaaacta gtatgttccc tatttaagac ctacacataa agcaaggctt
421 tcagagaacc tagagctgaa ggttcagagt caccatctc aacaagtcca acagcatctg
481 caacatctac aatggctttg ccttttgctt tactgatggc cctgggtggg ctacagctga
541 agtcaagctg ctctctggac tgtgatctgc ctacagacca cagcctgggt cacaggagga
601 ccatgatget cctggcacia atgaggagaa tctctcttt ctctgtctg aaggacagac
661 atgacttcag attccccag gaggagtgtg atggcaacca gtccagaag gctgaagcca
721 tctctgctt ccatgaggtg attcagcaga ccttcaatct ctacagcaca aaggactcat
781 ctgttgctt ggatgagagg ctctagaca aactctatac tgaactttac cagcagctga
841 atgacctgga agcctgtgtg atgcaggagg tgtgggtggg agggactccc ctgatgaatg
901 aggactccat cctggctgtg agaaaatct tccaaagaat cactctctac ctgacagaga
961 aaa .gtacag ccttgtgccc tgggaggttg tcagagcaga aatcatgaga tcttctctt
1021 catcaagaaa ctgcaagaa aggttaagga ggaaggaata agacctgac caacacagaa
1081 acgactccca ttgacgacta caccagcttg cacttcatg atctgccatt ttaaagactc
1141 ttgtttctgc tataaccata ccatgagttg aatcaaacgc gtcaagtatt tcaagtggtg
1201 ttaagcaaca tcgtgttcag ttgcacagga actagtcctt tacagatgac taagctgatg
1261 gatctatita tctatitatt aaatgtatat ttattgaca ataatttta atttttgcc
1321 catataagtg cataaaatgt ataccittat attgttgata acataacaaa atatatttc
1381 tatgttagt cgatgtatta ttgttttag ttattaaat atttactata gaaaacttct
1441 tggatttgtt tattctctaa ggagaaacac caagccgatt ctccaacatg atttaaaat
1501 gtatggtica attcatgat tcattgttat tatactcaag ttat

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H.2 Restriction Endonuclease Sites

The human interferon-alpha 6 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
DdeI	4
MseI	11
MseI	16
ApoI	25
TspEI	26
AhaIII	30
MseI	31
ApoI	35
TspEI	36
MseI	39
MseI	50
TspEI	53
DpnI/MboI	75
CviRI	120
AccI	125
RsaI	140
MseI	171
ApoI	174
TspEI	175
MseI	178
ApoI	185
TspEI	186
MseI	189
TspEI	191
TspEI	197
MseI	199
ApoI	208
TspEI	209
MseI	215
HinfI	221
GsuI	225
Cac8I	231
Tth111II	274
BsrI	290
NlaIII	315
MaeII	349
ApoI	360
TspEI	361
SpeI	377
MaeI	378
MseI	394
MaeI	430

AluI	434
CviJI	434
Eco57I	436
PleI	447
HinfI	447
Tsp45I	449
MaeIII	449
TaqIIa	451
BccI	454
MmeI	467
AlwNI	472
SfaNI	474
CviRI	479
CviJI	494
HaeIII	518
AsuI	518
CviJI	518
SecI	520
EcoRII	521
ScrFI	521
HgiAI	528
SduI	528
EspI	530
DdeI	531
PvuII	533
NspBII	533
AluI	534
CviJI	534
TseI	535
Fnu4HI	535
CviRI	537
MwoI	538
AluI	546
CviJI	546
TseI	547
Fnu4HI	547
BspGI	555
DpnI/MboI	564
MnlI	570
DdeI	571
RleAI	577
PflMI	578
BsiYI	578
CviJI	582
EcoRII	584
ScrFI	584
SecI	584
Tsp45I	589
MaeIII	589
AvaII	598
AsuI	598
XcmI	601
NlaIII	602
EcoRII	611

ScrFI	611
BseRI	623
TfiI	628
HinfI	628
Eco57I	648
NlaIII	660
SecI	676
CjeI	677
EcoRII	677
ScrFI	677
BseRI	681
CviJI	710
Eco57I	712
CviJI	716
BccI	718
MnlI	728
EcoNI	728
BsiYI	728
NlaIII	732
XphI	737
TfiI	740
HinfI	740
Ksp632I	759
HinfI	774
FokI	791
CviJI	799
XbaI	803
MaeI	804
AlwNI	831
BbvI	833
TseI	833
Fnu4HI	833
PvuII	834
NspBII	834
AluI	835
CviJI	835
EcoRII	845
ScrFI	845
CviJI	851
CviRI	862
FinI	882
HinfI	884
HinfI	903
BccI	907
EcoRII	911
ScrFI	911
CviJI	914
TfiI	937
HinfI	937
RsaI	965
CviJI	969
EcoRII	979
ScrFI	979
SecI	979

BspHI	1003
NlaIII	1004
XhoII	1008
DpnI/MboI	1009
Ksp632I	1016
CviRI	1033
MseI	1044
DpnI/MboI	1067
MmeI	1069
BsbI	1071
HinfI	1083
AluI	1105
CviJI	1105
Cac8I	1106
CviRI	1109
MslI	1111
BspHI	1116
NlaIII	1117
DpnI/MboI	1120
AhaIII	1130
MseI	1131
HinfI	1136
NlaIII	1162
TfiI	1170
HinfI	1170
MluI	1177
AflIII	1177
FnuDII	1178
MseI	1201
CviRI	1222
SpeI	1231
MaeI	1232
DdeI	1250
AluI	1253
CviJI	1253
BinI	1260
XhoII	1260
DpnI/MboI	1261
MseI	1279
SspI	1303
MseI	1308
TspEI	1310
MslI	1321
CviRI	1329
SnaI	1339
AccI	1339
TaqI	1390
MseI	1415
SspI	1418
SfeI	1426
DdeI	1457
CjePI	1470
CviJI	1473
TfiI	1477

HinfI	1477
MmeI	1482
NlaIII	1487
AhaIII	1492
MseI	1493
TspEI	1510
TfiI	1518
HinfI	1518

The human interferon-alpha 6 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AccI	125
AccI	1339
AflIII	1177
AhaIII	30
AhaIII	1130
AhaIII	1492
AluI	434
AluI	534
AluI	546
AluI	835
AluI	1105
AluI	1253
AlwNI	472
AlwNI	831
ApoI	25
ApoI	35
ApoI	174
ApoI	185
ApoI	208
ApoI	360
AsuI	518
AsuI	598
AvaII	598
BbvI	833
BccI	454
BccI	718
BccI	907
BinI	1260
BsbI	1071
BseRI	623
BseRI	681
BsiYI	578
BsiYI	728
BspGI	555
BspHI	1003
BspHI	1116

BsrI	290
Cac8I	231
Cac8I	1106
CjeI	677
CjePI	1470
CviJI	434
CviJI	494
CviJI	518
CviJI	534
CviJI	546
CviJI	582
CviJI	710
CviJI	716
CviJI	799
CviJI	835
CviJI	851
CviJI	914
CviJI	969
CviJI	1105
CviJI	1253
CviJI	1473
CviRI	120
CviRI	479
CviRI	537
CviRI	862
CviRI	1033
CviRI	1109
CviRI	1222
CviRI	1329
DdeI	4
DdeI	531
DdeI	571
DdeI	1250
DdeI	1457
DpnI/MboI	75
DpnI/MboI	564
DpnI/MboI	1009
DpnI/MboI	1067
DpnI/MboI	1120
DpnI/MboI	1261
Eco57I	436
Eco57I	648
Eco57I	712
EcoNI	728
EcoRII	521
EcoRII	584
EcoRII	611
EcoRII	677
EcoRII	845
EcoRII	911
EcoRII	979
EspI	530
FinI	882
FnuDII	1178

Fnu4HI	535
Fnu4HI	547
Fnu4HI	833
FokI	791
GsuI	225
HaeIII	518
HgiAI	528
HinfI	221
HinfI	447
HinfI	628
HinfI	740
HinfI	774
HinfI	884
HinfI	903
HinfI	937
HinfI	1083
HinfI	1136
HinfI	1170
HinfI	1477
HinfI	1518
HphI	737
Ksp632I	759
Ksp632I	1016
MaeI	378
MaeI	430
MaeI	804
MaeI	1232
MaeII	349
MaeIII	449
MaeIII	589
MluI	1177
MmeI	467
MmeI	1069
MmeI	1482
MnlI	570
MnlI	728
MseI	11
MseI	16
MseI	31
MseI	39
MseI	50
MseI	171
MseI	178
MseI	189
MseI	199
MseI	215
MseI	394
MseI	1044
MseI	1131
MseI	1201
MseI	1279
MseI	1308
MseI	1415
MseI	1493

MslI	1111
MslI	1321
MwoI	538
NlaIII	315
NlaIII	602
NlaIII	660
NlaIII	732
NlaIII	1004
NlaIII	1117
NlaIII	1162
NlaIII	1487
NspBII	533
NspBII	834
PflMI	578
PleI	447
PvuII	533
PvuII	834
RleAI	577
RsaI	140
RsaI	965
ScrFI	521
ScrFI	584
ScrFI	611
ScrFI	677
ScrFI	845
ScrFI	911
ScrFI	979
SduI	528
SecI	520
SecI	584
SecI	676
SecI	979
SfaNI	474
SfeI	1426
SnaI	1339
SpeI	377
SpeI	1231
SspI	1303
SspI	1418
TaqI	1390
TaqIIa	451
TfiI	628
TfiI	740
TfiI	937
TfiI	1170
TfiI	1477
TfiI	1518
TseI	535
TseI	547
TseI	833
Tsp45I	449
Tsp45I	589
TspEI	26
TspEI	36

TspEI	53
TspEI	175
TspEI	186
TspEI	191
TspEI	197
TspEI	209
TspEI	361
TspEI	1310
TspEI	1510
Tth111II	274
XbaI	803
XcmI	601
XhoII	1008
XhoII	1260

The human interferon-alpha 6 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	2
AciI	ccgc	0
AclI	aacggt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	1
AgeI	accggt	0
AhaIII	tttaaa	3
AluI	agct	6
AlwNI	cagnnnctg	2
ApaI	gggccc	0
ApaBI	gcannnnntgc	0
ApaLI	gtgcac	0
ApoI	raatty	6
AscI	ggcgcgcc	0
AsuI	ggncc	2
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	1
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	1
BbvII	gaagac	0
BccI	ccatc	3
Bce83I	cttgag	0
Bcefi	acggc	0

BcgI	gcannnnnnntcg	0
BclI	tgatca	0
BetI	wccggw	0
BglI	gccnnnnnnggc	0
BglII	agatct	0
BinI	ggatc	1
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnnatac	0
BsbI	caacac	1
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	2
BsgI	gtgcag	0
BsiI	ctcgtg	0
BsiYI	ccnannnnnngg	2
BsmI	gaatgc	0
BsmAI	gtctc	0
Bsp24I	gacnnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	1
BspHI	tcatga	2
BspLU11I	acatgt	0
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	1
BsrBI	gagcgg	0
BsrDI	gcaatg	0
BstEII	ggtnacc	0
BstXI	ccannnnnnntgg	0
Cac8I	gcnnge	2
CauII	ccsgg	0
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	1
CjePI	ccannnnnnntc	1
ClaI	atcgat	0
CviJI	rgcy	16
CviRI	tgca	8
DdeI	ctnag	5
DpnI/MboI	gata	6
DraII	rggnccy	0
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	3
EcoNI	cctnnnnnnagg	1
EcoRI	gaattc	0
EcoRII	ccwgg	7

EcoRV	gatatc	0
EspI	gctnagc	1
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	1
FnuDII	cgcg	1
Fnu4HI	gcngc	3
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	1
HaeI	wggccw	0
HaeII	rgcgcy	0
HaeIII	ggcc	1
HgaI	gacgc	0
HgiAI	gwgcwc	1
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	0
HinfI	gante	13
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	1
KpnI	ggtacc	0
Ksp632I	ctcttc	2
MaeI	ctag	4
MaeII	acgt	1
MaeIII	ctnac	2
MboII	gaaga	0
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	1
MmeI	tccrac	3
MnlI	cctc	2
MseI	ttaa	18
MslI	caynnnnrtg	2
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	1
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	0
NheI	gctagc	0
NlaIII	catg	8
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgaga	0
NspI	rcatgy	0
NspBII	cmgckg	2
PacI	ttaattaa	0
Pfl1108I	tcgtag	0

PflMI	ccannnnntgg	1
PleI	gagtc	1
PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	0
PshAI	gacnnnngtc	0
PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	2
RleAI	cccaca	1
RsaI	gtac	2
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0
ScaI	agtact	0
ScrFI	ccngg	7
SduI	gdgchc	1
SecI	ccnngg	4
SexAI	accwgg	0
SfaNI	gcac	1
SfeI	ctryag	1
SfiI	ggccnnnnnggcc	0
SgfI	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	1
SnaBI	tacgta	0
SpeI	actagt	2
SphI	gcacgc	0
SpI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	2
StuI	aggcct	0
StyI	ccwggg	0
SwaI	atttaa	0
TaqI	tcga	1
TaqIIa	cacca	1
TaqIIb	gaccga	0
TfiI	gawtc	6
TseI	gcwgc	3
Tsp45I	gtsac	2
TspEI	aatt	11
Tth111I	gacnnngtc	0
Tth111II	caarca	1
VspI	attaat	0
XbaI	tctaga	1
XcmI	ccannnnnnnnntgg	1
XhoI	ctcgag	0
XhoII	rgatcy	2

XmaIII	cggccg	0
XmnI	gaannnttc	0
Total		212

Appendix I

Human Interferon-Alpha 7 Gene

I.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 7 gene was retrieved from the Genbank file *hsifna7* (Henco et. al., 1985) (Benson et. al., 1993).

```

1 cacatcagta cttatgtcaa gtgctgaaaa gaaaaaagtg ttggcaatat ctggatgaat
61 actgcagcta gtgaagttaa caaattattt tctcatataa agcaaaattc aaagcttcat
121 atactatgag aaaatttttt taaaattgat tcatatttct agcagittg aatgattagg
181 tatgtaatta cattcatatt aatgtgtatt atacagattt ttattttgca tatgtaatt
241 gaaacaccaa aatttacatg aacaaattac attaaaagtt attccacaaa tatacttate
301 taattaaact tagattttta tagcttttaa acttagattt tagtttaact ttctgtcat
361 tcttaactta ctttgaataa aaagagcaaa ctccatactt ttatctgtg aagtagaggt
421 atatgtagaa tacctaaata gatatgccaa atctgtgtta ttaaaatttc atgaacattt
481 caattagaaa aaaataccat aaaaggcttt gagtgcaggg gaaaaacagg caatgatgaa
541 aaaaaaaatg aaaaacgtat ttaaacacat ggagagagtg cataaagaaa gcaaaaacag
601 agatagaaaag taaaactagg gcatttagaa aatggaaatt agtatgttca ctatttaaga
661 cctatgcaca gagcaaagtc tccagaaaac ctaggaggcca cggttcaagt taccacctc
721 aggtagccta gtgatatttg caaaatccca atggcccggg cctttcttt actgatggtc
781 gtgtcggtag tcagctacaa atccatctgc tctctgggct gtgatctgcc tcagaccac
841 agcctgcgta ataggagggc cttgatactc ctggcacaaa tgggaagaat ctctccttc
901 tctgtcttga aggacagaca tgaattcaga ttcccagagg aggagtttga tggccaccag
961 ttccagaaga ctcaagccat ctctgtcttc catgagatga tccagcagac ctccaatctc
1021 ttcagcacag aggactcacc tctgtcttgg gaacagagcc tcttagaaaa attttccat
1081 gaactttacc agcaactgaa tgacctggaa gcattgttga tacaggaggt tgggggtgaa
1141 gagactcccc tgatgaatga ggacttcac ctggctgtga ggaaatactt ccaaagaatc
1201 actctttatc taatggagaa gaaatacagc ccttgtgcct gggagggttg cagagcagaa
1261 atcatgagat ccttctcttt ttaacaaaac ttgaaaaaag gattaaggag gaaggattga
1321 aaactgggtc atcatggaaa tgattctcat tgactaatgc atcatctac actttcatga
1381 gtcttccat ttaagaact cactctata accaccacaa gtgaatcaa aatttccaaa
1441 tgtttcagg agtgtaaga agcatcgtgt ttacctgtgc aggcactagt cctttacaga
1501 tgaccattct gatgtctct tcatctatt tatttaataa ttattttatt taactatttt
1561 tatttttaa attattttt atgtaatac atatgtacct ttacattgtg gttaatgtaa
1621 caaatagttt ctcatattt agccaatata ttaatttct ttacattaa attttacta
1681 tacaaaattt ctgtgtttg ttatttttt aagattaaat gccaaacctg actgtataac
1741 ctgacttaaa aatagatgat taaagtaagt taccatcat aattttatc aagttataga
1801 aaaaatatatt ttctatacc aggttatctg ttgcctcat gatataaacg tgaactataa
1861 aaatacagtt ctgttctct tgtatctttg attttgtca ggaaagaant ctaaaacaaa
1921 taataatgct gaattaatat cgtttatact aactgtctga atgtgaggaa gtaaaaaaaa
1981 atg

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I.2 Restriction Endonuclease Sites

The human interferon-alpha 7 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
ScaI	7
RsaI	8
FokI	53
PstI	62
SfeI	62
CviRI	63
BbvI	64
TseI	64
Fnu4HI	64
AluI	66
CviJI	66
MaeI	68
TspEI	83
ApoI	105
TspEI	106
HindIII	112
AluI	113
CviJI	113
ApoI	132
TspEI	133
AhaIII	139
MseI	140
TspEI	144
TfiI	148
HinfI	148
MaeI	159
TspEI	186
MslI	195
VspI	198
MseI	199
CviRI	227
NdeI	229
TspEI	236
ApoI	250
TspEI	251
NlaIII	257
TspEI	265
MseI	272
TspEI	302
MseI	304
DdeI	309
MseI	317

AluI	322
CviJI	322
AhaIII	326
MseI	327
DdeI	332
MseI	345
MseI	363
MseI	461
ApoI	464
TspEI	465
BspHI	469
NlaIII	470
TspEI	482
CviJI	505
MwoI	506
BsgI	513
CviRI	514
BsrDI	530
MaeII	555
AhaIII	560
MseI	561
NlaIII	568
CviRI	579
MaeI	616
TspEI	637
MseI	655
CviRI	665
BsmAI	678
MaeI	691
HaeI	695
HaeIII	696
CviJI	696
DsaI	698
SecI	698
MaeIII	709
BsiYI	713
CjeI	714
MnlI	717
SauI	717
DdeI	718
CviJI	725
MaeI	728
CviRI	739
HaeIII	753
AsuI	753
CviJI	753
CauII	755
ScrFI	755
HpaII	756
AvaII	758
AsuI	758
RsaI	787
DdeI	790
AluI	793

CviJI	793
BccI	803
CjePI	803
XcmI	803
MwoI	809
CviJI	817
DpnI/MboI	823
MnlI	829
DdeI	830
RleAI	836
CviJI	841
Cac8I	842
DraII	856
AsuI	857
HaeIII	858
CviJI	858
EcoRII	870
ScrFI	870
MboII	884
TfiI	887
HinfI	887
NlaIII	919
EcoRI	922
ApoI	922
TspEI	923
TfiI	929
HinfI	929
BsiYI	933
BseRI	937
BseRI	940
BalI	951
CfrI	951
HaeI	951
HaeIII	952
CviJI	952
MboII	966
BbvII	966
HinfI	969
CviJI	975
BccI	977
MnlI	987
NlaIII	991
DpnI/MboI	999
Ksp632I	1018
HinfI	1033
TseI	1042
Fnu4HI	1042
CviJI	1057
MnlI	1059
MaeI	1063
ApoI	1069
TspEI	1070
AlwNI	1090
EcoRII	1104

ScrFI	1104
NspI	1111
NlaIII	1112
MboII	1138
HinfI	1143
EcoRII	1170
ScrFI	1170
CviJI	1173
XmnI	1182
TfiI	1196
HinfI	1196
MboII	1218
CviJI	1228
EcoRII	1238
ScrFI	1238
SecI	1238
BspHI	1262
NlaIII	1263
XhoII	1267
DpnI/MboI	1268
MseI	1303
BsrI	1323
NlaIII	1333
MslI	1333
XmnI	1337
TfiI	1342
HinfI	1342
AvaIII	1357
CviRI	1358
SfaNI	1359
MslI	1370
BspHI	1375
NlaIII	1376
HinfI	1397
CjeI	1412
TfiI	1424
HinfI	1424
ApoI	1430
TspEI	1431
CjePI	1436
MseI	1455
SfaNI	1462
BsgI	1477
CviRI	1478
Cac8I	1479
SpeI	1485
MaeI	1486
MslI	1505
BsmAI	1514
SwaI	1532
AhaIII	1533
MseI	1534
SspI	1537
MseI	1550

SwaI	1565
AhaIII	1566
MseI	1567
TspEI	1570
NdeI	1590
RsaI	1595
MseI	1612
MaeIII	1617
CviJI	1641
VspI	1650
MseI	1651
TspEI	1653
MseI	1667
ApoI	1669
TspEI	1670
ApoI	1685
TspEI	1686
MseI	1709
MseI	1715
CviJI	1725
MseI	1746
MseI	1761
MaeIII	1769
TspEI	1781
SexAI	1818
EcoRII	1819
ScrFI	1819
BspHI	1837
NlaIII	1838
MaeII	1848
TspEI	1932
VspI	1933
MseI	1934

The human interferon-alpha 7 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AhaIII	139
AhaIII	326
AhaIII	560
AhaIII	1533
AhaIII	1566
AluI	66
AluI	113
AluI	322
AluI	793
AlwNI	1090
ApoI	105

ApoI	132
ApoI	250
ApoI	464
ApoI	922
ApoI	1069
ApoI	1430
ApoI	1669
ApoI	1685
AsuI	753
AsuI	758
AsuI	857
AvaII	758
AvaIII	1357
BalI	951
BbvI	64
BbvII	966
BccI	803
BccI	977
BseRI	937
BseRI	940
BsgI	513
BsgI	1477
BsiYI	713
BsiYI	933
BsmAI	678
BsmAI	1514
BspHI	469
BspHI	1262
BspHI	1375
BspHI	1837
BsrI	1323
BsrDI	530
Cac8I	842
Cac8I	1479
CauII	755
CfrI	951
CjeI	714
CjeI	1412
CjePI	803
CjePI	1436
CviJI	66
CviJI	113
CviJI	322
CviJI	505
CviJI	696
CviJI	725
CviJI	753
CviJI	793
CviJI	817
CviJI	841
CviJI	858
CviJI	952
CviJI	975
CviJI	1057

CviJI	1173
CviJI	1228
CviJI	1641
CviJI	1725
CviRI	63
CviRI	227
CviRI	514
CviRI	579
CviRI	665
CviRI	739
CviRI	1358
CviRI	1478
DdeI	309
DdeI	332
DdeI	718
DdeI	790
DdeI	830
DpnI/MboI	823
DpnI/MboI	999
DpnI/MboI	1268
DraII	856
DsaI	698
EcoRI	922
EcoRII	870
EcoRII	1104
EcoRII	1170
EcoRII	1238
EcoRII	1819
Fnu4HI	64
Fnu4HI	1042
FokI	53
HaeI	695
HaeI	951
HaeIII	696
HaeIII	753
HaeIII	858
HaeIII	952
HindIII	112
HinfI	148
HinfI	887
HinfI	929
HinfI	969
HinfI	1033
HinfI	1143
HinfI	1196
HinfI	1342
HinfI	1397
HinfI	1424
HpaII	756
Ksp632I	1018
MaeI	68
MaeI	159
MaeI	616
MaeI	691

MaeI	728
MaeI	1063
MaeI	1486
MaeII	555
MaeII	1848
MaeIII	709
MaeIII	1617
MaeIII	1769
MboII	884
MboII	966
MboII	1138
MboII	1218
MnlI	717
MnlI	829
MnlI	987
MnlI	1059
MseI	140
MseI	199
MseI	272
MseI	304
MseI	317
MseI	327
MseI	345
MseI	363
MseI	461
MseI	561
MseI	655
MseI	1303
MseI	1455
MseI	1534
MseI	1550
MseI	1567
MseI	1612
MseI	1651
MseI	1667
MseI	1709
MseI	1715
MseI	1746
MseI	1761
MseI	1934
MslI	195
MslI	1333
MslI	1370
MslI	1505
MwoI	506
MwoI	809
NdeI	229
NdeI	1590
NlaIII	257
NlaIII	470
NlaIII	568
NlaIII	919
NlaIII	991
NlaIII	1112

NlaIII	1263
NlaIII	1333
NlaIII	1376
NlaIII	1838
NspI	1111
PstI	62
RleAI	836
RsaI	8
RsaI	787
RsaI	1595
SauI	717
ScaI	7
ScrFI	755
ScrFI	870
ScrFI	1104
ScrFI	1170
ScrFI	1238
ScrFI	1819
SecI	698
SecI	1238
SexAI	1818
SfaNI	1359
SfaNI	1462
SfeI	62
SpeI	1485
SspI	1537
SwaI	1532
SwaI	1565
TfiI	148
TfiI	887
TfiI	929
TfiI	1196
TfiI	1342
TfiI	1424
TseI	64
TseI	1042
TspEI	83
TspEI	106
TspEI	133
TspEI	144
TspEI	186
TspEI	236
TspEI	251
TspEI	265
TspEI	302
TspEI	465
TspEI	482
TspEI	637
TspEI	923
TspEI	1070
TspEI	1431
TspEI	1570
TspEI	1653
TspEI	1670

TspEI	1686
TspEI	1781
TspEI	1932
VspI	198
VspI	1650
VspI	1933
XcmI	803
XhoII	1267
XmnI	1182
XmnI	1337

The human interferon-alpha 7 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	0
AciI	ccgc	0
AclI	aacggt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	0
AgeI	accggt	0
AhaIII	tttaaa	5
AluI	agct	4
AlwNI	cagnnnctg	1
ApaI	gggccc	0
ApaBI	gcannnnntgc	0
ApaLI	gtgcac	0
ApoI	raatty	9
AscI	ggcgcgcc	0
AsuI	gggcc	3
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	1
AvaIII	atgcat	1
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	1
BamHI	ggatcc	0
BbvI	gcagc	1
BbvII	gaagac	1
BccI	ccatc	2
Bce83I	cttgag	0
Bcefi	acggc	0
BcgI	gcannnnnnntcg	0
BclI	tgatca	0
BetI	wccggw	0
BglI	gccnnnnnnggc	0

BglII	agatct	0
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnatc	0
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	2
BsgI	gtgcag	2
BsiI	ctcgtg	0
BsiYI	ccnnnnnnngg	2
BsmI	gaatgc	0
BsmAI	gtctc	2
Bsp24I	gacnnnnnntgg	0
Bsp1407	tgtaca	0
BspGI	ctggac	0
BspHI	tcctga	4
BspLU11I	acatgt	0
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	1
BsrBI	gagcgg	0
BsrDI	gcaatg	1
BstEII	ggtnacc	0
BstXI	ccannnnnntgg	0
Cac8I	gcnnge	2
CauII	ccsgg	1
CfrI	yggccr	1
Cfr10I	rccggy	0
CjeI	ccannnnnngt	2
CjePI	ccannnnnnntc	2
ClaI	atcgat	0
CviJI	rgcy	18
CviRI	tgca	8
DdeI	ctnag	5
DpnI/MboI	gac	3
DraII	rggnccy	1
DraIII	cacnnngtg	0
DrdI	gacnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	1
Eam1105I	gacnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	0
EcoNI	cctnnnnnagg	0
EcoRI	gaattc	1
EcoRII	ccwgg	5
EcoRV	gatatc	0
EspI	gctnagc	0
Esp3I	cgtctc	0
FauI	cccgc	0

FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	2
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	0
HaeI	wggccw	2
HaeII	rgcgcy	0
HaeIII	ggcc	4
HgaI	gacgc	0
HgiAI	gwgcwc	0
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	1
HinfI	ganc	10
HpaI	gttaac	0
HpaII	ccgg	1
HphI	ggtga	0
KpnI	ggtacc	0
Ksp632I	ctcttc	1
MaeI	ctag	7
MaeII	acgt	2
MaeIII	gtnac	3
MboII	gaaga	4
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	4
MseI	ttaa	24
MslI	caynnnnnrtg	4
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	2
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	2
NheI	gctagc	0
NlaIII	catg	10
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	1
NspBII	cmgckg	0
PacI	ttaattaa	0
Pfl1108r	tcgtag	0
PflMI	ccannnnntgg	0
PleI	gagtc	0
PmaCI	cacgtg	0
PmeI	gtttaaac	0

PpuMI	rggwccy	0
PshAI	gacnnnngtc	0
PstI	ctgcag	1
PvuI	cgatcg	0
PvuII	cagctg	0
RleAI	cccaca	1
RsaI	gtac	3
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	ccnagg	1
ScaI	agtact	1
ScrFI	ccngg	6
SduI	gdgchc	0
SecI	ccnngg	2
SexAI	accwgg	1
SfaNI	gcac	2
SfeI	ctryag	1
SfiI	ggccnnnnnggcc	0
Sgfi	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	0
SnaBI	tacgta	0
SpeI	actagt	1
SphI	gcatgc	0
SpII	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	1
StuI	aggcct	0
StyI	ccwwgg	0
SwaI	atttaaat	2
TaqI	tcga	0
TaqIIa	caccca	0
TaqIIb	gaccga	0
TfiI	gawtc	6
TseI	gcwgc	2
Tsp45I	gtsac	0
TspEI	aatt	21
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	3
XbaI	tctaga	0
XcmI	ccannnnnnnnntgg	1
XhoI	ctcgag	0
XhoII	rgatcy	1
XmaIII	cggccg	0
XmnI	gaannnnnttc	2
Total		237

Appendix J

Human Interferon-Alpha 8 Gene

J.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 8 gene was retrieved from the Genbank sequence file *hsifna8* (Henco et. al., 1985) (Benson et. al., 1993).

```

1 aggggtcatc catctgaacc agctcagcag catccacaac atctacaatg gccttgactt
61 ttattttact ggtggcccta gtggtgctca gctacaagtc attcagctct ctgggctgtg
121 atctgccica gactcacagc ctgggtaaca ggagggcctt gatactcctg gcacaaatgc
181 gaagaatctc tcctttctcc tgcctgaagg acagacatga ctttgaattc ccccaggagg
241 agtttgatga taaacagtc cagaaggctc aagccatctc tgcctccat gagatgatcc
301 agcagaccit caacctcttc agcacaagg actcatctgc tgccttgat gagacccttc
361 tagatgaatt ctacatgaa ctgaccagc agctgaatga cctggagtcc tgtgtgatgc
421 aggaagtggg ggtgatagag tctccctga tgtacgagga cccatcctg gctgtgagga
481 aatacttcca aagaatcact ctatatctga cagagaagaa atacagctct tgtgctggg
541 aggtgtcag agcagaaatc atgagatcct tctcttate aatcaactg caaaaaagat
601 tgaagagtaa ggaaagagac ctggtacaac acg

```

J.2 Restriction Endonuclease Sites

The human interferon-alpha 8 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
BccI	10
DrdII	16
AluI	21
CviJI	21
EspI	22
DdeI	23
BbvI	27
TseI	27
Fnu4HI	27
SfaNI	30
HaeI	49
HaeIII	50
CviJI	50
BsrI	68
HaeIII	74
AsuI	74
CviJI	74
MaeI	78
HgiAI	84
SduI	84
EspI	86
DdeI	87
AluI	90
CviJI	90
AluI	105
CviJI	105
MwoI	106
CviJI	114
DpnI/MboI	120
MnlI	126
DdeI	127
HinfI	131
CviJI	138
EcoRII	140
ScrFI	140
SecI	140
MaeIII	145
DraII	153
AsuI	154
HaeIII	155
CviJI	155
EcoRII	167

ScrFI	167
MboII	181
TfiI	184
HinfI	184
Eco57I	204
NlaIII	216
EcoRI	225
ApoI	225
TspEI	226
BsiYI	230
SecI	232
CjeI	233
EcoRII	233
ScrFI	233
BseRI	237
CviJI	266
CviJI	272
BccI	274
MnlI	284
NlaIII	288
DpnI/MboI	296
MnlI	314
Ksp632I	315
HinfI	330
TseI	339
Fnu4HI	339
FokI	347
XbaI	359
MaeI	360
EcoRI	366
ApoI	366
TspEI	367
TaqI	376
AlwNI	387
BbvI	389
TseI	389
Fnu4HI	389
PvuII	390
NspBII	390
AluI	391
CviJI	391
Eam1105I	399
EcoRII	401
ScrFI	401
GsuI	402
PleI	405
HinfI	405
CviRI	418
HphI	431
PleI	438
HinfI	438
BsmAI	440
RsaI	452
HinfI	459

BccI	463
EcoRII	467
ScrFI	467
CviJI	470
XmnI	479
TfiI	493
HinfI	493
MboII	515
AluI	525
CviJI	525
EcoRII	535
ScrFI	535
SecI	535
BspHI	559
NlaIII	560
XhoII	564
DpnI/MboI	565
CviRI	589
MboII	602
SexAI	619
EcoRII	620
ScrFI	620
RsaI	624
BsbI	627

The human interferon-alpha 8 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AluI	21
AluI	90
AluI	105
AluI	391
AluI	525
AlwNI	387
ApoI	225
ApoI	366
AsuI	74
AsuI	154
BbvI	27
BbvI	389
BccI	10
BccI	274
BccI	463
BsbI	627
BseRI	237
BsiYI	230
BsmAI	440
BspHI	559

BsrI	68
CjeI	233
CviJI	21
CviJI	50
CviJI	74
CviJI	90
CviJI	105
CviJI	114
CviJI	138
CviJI	155
CviJI	266
CviJI	272
CviJI	391
CviJI	470
CviJI	525
CviRI	418
CviRI	589
DdeI	23
DdeI	87
DdeI	127
DpnI/MboI	120
DpnI/MboI	296
DpnI/MboI	565
DraII	153
DrdII	16
Eam1105I	399
Fco57I	204
EcoRI	225
EcoRI	366
EcoRII	140
EcoRII	167
EcoRII	233
EcoRII	401
EcoRII	467
EcoRII	535
EcoRII	620
EspI	22
EspI	86
Fnu4HI	27
Fnu4HI	339
Fnu4HI	389
FokI	347
GsuI	402
HaeI	49
HaeIII	50
HaeIII	74
HaeIII	155
HgiAI	84
HinfI	131
HinfI	184
HinfI	330
HinfI	405
HinfI	438
HinfI	459

HinfI	493
HphI	431
Ksp632I	315
MaeI	78
MaeI	360
MaeIII	145
MboII	181
MboII	515
MboII	602
MnlI	126
MnlI	284
MnlI	314
MwoI	106
NlaIII	216
NlaIII	288
NlaIII	560
NspBII	390
PleI	405
PleI	438
PvuII	390
RsaI	452
RsaI	624
ScrFI	140
ScrFI	167
ScrFI	233
ScrFI	401
ScrFI	467
ScrFI	535
ScrFI	620
SduI	84
SecI	140
SecI	232
SecI	535
SexAI	619
SfaNI	30
TaqI	376
TfiI	184
TfiI	493
TseI	27
TseI	330
TseI	389
TspEI	226
TspEI	367
XbaI	359
XhoII	564
XmnI	479

The human interferon-alpha 8 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	0
AciI	ccgc	0
AclI	aacgtt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	0
AgeI	accggt	0
AhaIII	tttaaa	0
AluI	agct	5
AlwNI	cagnnnctg	1
ApaI	gggccc	0
ApaBI	gcannnnntgc	0
ApaLI	g ^u gcac	0
ApoI	raatty	2
AscI	ggcgcgcc	0
AsuI	ggncc	2
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	0
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	2
BbvII	gaagac	0
BccI	ccatc	3
Bce83I	cttgag	0
Bcefi	acggc	0
BcgI	gcannnnnnntcg	0
BclI	tgatca	0
BetI	wccggw	0
BglI	gcnnnnnnnggc	0
Bgl ⁺ I	agatct	0
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnatc	0
BsbI	caacac	1
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	1
BsgI	gtgcag	0
BsiI	ctcgtg	0
BsiYI	ccnnnnnnnngg	1
BsmI	gaatgc	0

BsmAI	gtctc	1
Bsp24I	gacnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	1
BspLU11I	acatgt	0
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	1
BsrBI	gagcgg	0
BsrDI	gcaatg	0
BstEII	ggtnacc	0
BstXI	ccannnnnntgg	0
Cac8I	gcnngc	0
CauII	ccsgg	0
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	1
CjePI	ccannnnnnntc	0
ClaI	atcgat	0
CviJI	rgcy	13
CviRI	tgca	2
DdeI	ctnag	3
DpnI/MboI	gatc	3
DraII	rggnccy	1
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	1
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	1
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	1
EcoNI	cctnnnnnnagg	0
EcoRI	gaattc	2
EcoRII	ccwgg	7
EcoRV	gatatc	0
EspI	gctnagc	2
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	3
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	1
HaeI	wggccw	1
HaeII	rgcgcy	0
HaeIII	ggcc	3
HgaI	gacgc	0
HgiAI	gwgcwc	1
HgiCI	ggyrcc	0

HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	0
HinfI	ganc	7
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggatga	1
KpnI	ggatcc	0
Ksp632I	ctcttc	1
MaeI	ctag	2
MaeII	acgt	0
MaeIII	gtnac	1
MboII	gaaga	3
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	3
MseI	ttaa	0
MslI	caynnnnrtg	0
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	1
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	0
NheI	gctagc	0
NlaIII	catg	3
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	0
NspBII	cmgckj	1
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	0
PleI	gagtc	2
PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	0
PshAI	gacnnnngtc	0
PstI	ctgcag	0
PvuI	cgatec	0
PvuII	cagctg	1
RleAI	cccaca	0
RsaI	gtac	2
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0

ScaI	agtact	0
ScrFI	ccngg	7
SduI	gdgchc	1
SecI	ccnngg	3
SexAI	accwgg	1
SfaNI	gcatc	1
SfeI	ctryag	0
SfiI	ggccnnnnnnggcc	0
SgfI	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	0
SnaBI	tacgta	0
SpeI	actagt	0
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	0
StuI	aggcct	0
StyI	ccwwgg	0
SwaI	atttaa	0
TaqI	tcga	1
TaqIIa	cacca	0
TaqIIb	gaccga	0
TfiI	gawtc	2
TseI	gcwgc	3
Tsp45I	gtsac	0
TspEI	aatt	2
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	0
XbaI	tctaga	1
XcmI	ccannnnnnnnntgg	0
XhoI	ctcgag	0
XhoII	rgatcy	1
XmaIII	cggccg	0
XmnI	gaannnttc	1
Total		120

Appendix K

Human Interferon-Alpha 13 Gene

K.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 13 gene was retrieved from the Genbank sequence file *hsifr18* (Mantei et. al., 1980) (Todokoro et. al., 1984) (Benson et. al., 1993).

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1 aaacaaaatg gttgagaaac acggctctaa actcatgtaa agagttcaag aaggaaagca
61 aaaacagaaa tggaaagtgg tccagaagca ttaagaaagt ggaaatcagt atgttccta
121 ttaaggcat ctgcaggaag caaagccttc agagaaccta gagcccaagg tcagagtca
181 cccatctcag caagcccaga agcatctgca atatctatga tggcctcgcc cttgcctta
241 ctgatggtec tggtggtgct cagctgcaag tcaagctgct cctgggctg tgatctccct
301 gagacccaca gccctggataa caggaggacc ttgatgctcc tggcacaaat gaggcagaatc
361 tctcttctct cctgtctgat ggacagacat gacttggat ttccccagga ggaattgat
421 ggcaaccagt tccagaagge tccagccatc tctgtctccc atgagctgat ccagcagatc
481 ttaacctctt ttaccacaaa agattcatct gctgcttggg atgaggacct cctagacaaa
541 ttctgcaccg aactctacca gcagctgaat gacttgggaag cctgtgtgat gcaggaggag
601 aggggtgggag aaactccctt gatgaatgag gactccatct tggctgtgaa gaaatacttc
661 cgaagaatca ctctctatct gacagagaag aaatacagcc ctgtgcctg ggaggttgc
721 agagcagaaa tcatgagatc cctctcttta tcaacaaact tgcaagaaag attaaggagg
781 aaggaataac acctgggtcca acatgaaaac aattctatt gactcatata ccaggtcacg
841 cticcatgaa ttctgtcatt tcaaagactc tcacctctgc tataactatg accatgctga
901 taaactgatt tatctatta aatatattt tagctattca taagatttaa attatttg
961 tcatataaac atcatgtgca tcttacact gtggttagtg taataaaaca tgttccat
1021 actactcaa ttattattt tatgtgttc attaaacttt tactatagga acttccgtga
1081 tgtgttcatt cttaataca taaattcc

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K.2 Restriction Endonuclease Sites

The human interferon-alpha 13 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
BcefI	21
CviJI	23
NlaIII	34
AvaII	79
AsuI	79
MseI	91
EcoNI	117
BsiYI	117
MseI	122
SfaNI	127
PstI	131
SfeI	131
CviRI	132
CviJI	144
MaeI	158
HgiJII	161
SduI	161
CviJI	162
StyI	165
SecI	165
PleI	175
HinfI	175
Tsp45I	177
MaeIII	177
TaqIIa	179
BccI	182
DdeI	186
Cac8I	190
CviJI	193
SfaNI	202
CviRI	207
HaeI	221
HaeIII	222
CviJI	222
MnlI	224
AvaII	246
AsuI	246
EcoRII	249
ScrFI	249
HgiAI	256
SduI	256
EspI	258

4 of/de 4

PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

PRECISIONSM RESOLUTION TARGETS

DdeI	259
PvuII	261
NspBII	261
AluI	262
CviJI	262
TseI	263
Fnu4HI	263
CviRI	265
MwoI	266
AluI	274
CviJI	274
TseI	275
Fnu4HI	275
MwoI	278
CviJI	286
DpnI/MboI	292
DdeI	299
RleAI	305
PflMI	306
BsiYI	306
CviJI	310
EcoRII	312
ScrFI	312
PpuMI	325
DraII	325
AvaII	326
AsuI	326
EcoRII	339
ScrFI	339
TfiI	356
HinfI	356
MnlI	368
NlaIII	388
SecI	404
CjeI	405
EcoRII	405
ScrFI	405
BseRI	409
NlaIV	438
CviJI	438
CviJI	444
BccI	446
MnlI	456
NlaIII	460
AluI	464
CviJI	464
MwoI	465
DpnI/MboI	468
BglII	476
XhoII	476
DpnI/MboI	477
MnlI	486
TfiI	502
HinfI	502

TseI	511
Fnu4HI	511
FokI	519
PpuMI	524
DraII	524
AvaII	525
AsuI	525
MnlI	528
MaeI	532
ApoI	538
TspEI	539
CviRI	544
AlwNI	559
BbvI	561
TseI	561
Fnu4HI	561
PvuII	562
NspBII	562
AluI	563
CviJI	563
CviJI	579
CviRI	590
BseRI	595
BsmI	624
HinfI	631
BccI	635
CviJI	642
MboII	648
XmnI	651
MboII	662
TfiI	665
HinfI	665
MboII	687
CviJI	697
EcoRII	707
ScrFI	707
SecI	707
BspHI	731
NlaIII	732
XhoII	736
DpnI/MboI	737
MnlI	741
CviRI	761
MseI	772
SexAI	791
EcoRII	792
ScrFI	792
AvaII	795
AsuI	795
MmeI	797
NlaIII	802
TspEI	811
HinfI	821
SexAI	830

EcoRII	831
ScrFI	831
Tsp45I	835
MaeIII	835
BspHI	844
NlaIII	845
EcoRI	848
ApoI	848
TspEI	849
HinfI	866
NlaIII	893
SwaI	916
AhaIII	917
MseI	918
SspI	921
AluI	932
CviJI	932
SwaI	945
AhaIII	946
MseI	947
TspEI	950
NlaIII	973
CviRI	977
SfaNI	978
BspLU11I	1008
AflIII	1008
NspI	1008
NlaIII	1009
TspEI	1029
MseI	1052
SfeI	1063
MseI	1093
ApoI	1102
TspEI	1103

The human interferon-alpha 13 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AflIII	1008
AhaIII	917
AhaIII	946
AluI	262
AluI	274
AluI	464
AluI	563
AluI	932
AlwNI	559
ApoI	538

ApoI	848
ApoI	1102
AsuI	79
AsuI	246
AsuI	326
AsuI	525
AsuI	795
AvaII	79
AvaII	246
AvaII	326
AvaII	525
AvaII	795
BbvI	561
BccI	182
BccI	446
BccI	635
BceI	21
BglII	476
BseRI	409
BseRI	595
BsiYI	117
BsiYI	306
BsmI	624
BspHI	731
BspHI	844
BspLU11I	1008
Cac8I	190
CjeI	405
CviJI	23
CviJI	144
CviJI	162
CviJI	193
CviJI	222
CviJI	262
CviJI	274
CviJI	286
CviJI	310
CviJI	438
CviJI	444
CviJI	464
CviJI	563
CviJI	579
CviJI	642
CviJI	697
CviJI	932
CviRI	132
CviRI	207
CviRI	265
CviRI	544
CviRI	590
CviRI	761
CviRI	977
DdeI	186
DdeI	259

DdeI	299
DpnI/MboI	292
DpnI/MboI	468
DpnI/MboI	477
DpnI/MboI	737
DraII	325
DraII	524
EcoNI	117
EcoRI	848
EcoRII	249
EcoRII	312
EcoRII	339
EcoRII	405
EcoRII	707
EcoRII	792
EcoRII	831
EspI	258
Fnu4HI	263
Fnu4HI	275
Fnu4HI	511
Fnu4HI	561
FokI	519
HaeI	221
HaeIII	222
HgiAI	256
HgiJII	161
HinfI	175
HinfI	356
HinfI	502
HinfI	631
HinfI	665
HinfI	821
HinfI	866
MaeI	158
MaeI	532
MaeIII	177
MaeIII	835
MboII	648
MboII	662
MboII	687
MmeI	797
MnlI	224
MnlI	368
MnlI	456
MnlI	486
MnlI	528
MnlI	741
MseI	91
MseI	122
MseI	772
MseI	918
MseI	947
MseI	1052
MseI	1093

MwoI	266
MwoI	278
MwoI	465
NlaIII	34
NlaIII	388
NlaIII	460
NlaIII	732
NlaIII	802
NlaIII	845
NlaIII	893
NlaIII	973
NlaIII	1009
NlaIV	438
NspI	1008
NspBII	261
NspBII	562
PflMI	306
PleI	175
PpuMI	325
PpuMI	524
PstI	131
PvuII	261
PvuII	562
RleAI	305
ScrFI	249
ScrFI	312
ScrFI	339
ScrFI	405
ScrFI	707
ScrFI	792
ScrFI	831
SduI	161
SduI	256
SecI	165
SecI	404
SecI	707
SexAI	791
SexAI	830
SfaNI	127
SfaNI	202
SfaNI	978
SfeI	131
SfeI	1063
SspI	921
StyI	165
SwaI	916
SwaI	945
TaqIIa	179
TfiI	356
TfiI	502
TfiI	665
TseI	263
TseI	275
TseI	511

TseI	561
Tsp45I	177
Tsp45I	835
TspEI	539
TspEI	811
TspEI	849
TspEI	950
TspEI	1029
TspEI	1103
XhoII	476
XhoII	736
XmnI	651

The human interferon-alpha 13 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	0
AccI	ccgc	0
AccI	aacgtt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	1
AgeI	accggt	0
AhaIII	tttaaa	2
AluI	agct	5
AlwNI	cagnnctg	1
ApaI	gggcc	0
ApaBI	gcannnnntgc	0
ApaLI	gtgcac	0
ApoI	raatty	3
AscI	ggcgcgcc	0
AsuI	ggncc	5
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	5
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	1
BbvII	gaagac	0
BccI	ccatc	3
Bce83I	cttgag	0
BceI	acggc	1
BcgI	gcannnnnnntcg	0
BclI	tgatca	0

BetI	wccggw	0
BglI	gccnnnnnggc	0
BglII	agatct	1
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnnadc	0
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	2
BsgI	gtgcag	0
BsiI	ctcgtg	0
BsiYI	ccnnnnnnngg	2
BsmI	gaatgc	1
BsmAI	gtctc	0
Bsp24I	gacnnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	2
BspLU11I	acatgt	1
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	0
BsrBI	gagcgg	0
BsrDI	gcaatg	0
BstEII	ggtnacc	0
BstXI	ccannnnnnntgg	0
Cac8I	gcnngc	1
CauII	ccsgg	0
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	1
CjePI	ccannnnnnntc	0
ClaI	atcgat	0
CviJI	rgcy	17
CviRI	tgca	7
DdeI	ctnag	3
DpnI/MboI	gatc	4
DraII	rggnccy	2
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	0
EcoNI	cctnnnnnnnagg	1
EcoRI	gaattc	1
EcoRII	ccwgg	7
EcoRV	gatatc	0
EspI	gctnagc	1

Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	4
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	0
GsuI	ctggag	0
HaeI	wggccw	1
HaeII	rgcgcy	0
HaeIII	ggcc	1
HgaI	gacgc	0
HgiAI	gwgcwc	1
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	1
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	0
HinfI	γantc	7
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	0
KpnI	ggtacc	0
Ksp632I	ctcttc	0
MaeI	ctag	2
MaeII	acgt	0
MaeIII	gtnac	2
MboII	gaaga	3
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	1
MnlI	cctc	6
MseI	ttaa	7
MslI	caynnnnnrtg	0
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	3
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	0
NheI	gctagc	0
NlaIII	catg	9
NlaIV	ggnncc	1
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	1
NspBII	cmgckg	2
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	1
PleI	gagtc	1

PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	2
PshAI	gacnnnngtc	0
PstI	ctgcag	1
PvuI	cgatcg	0
PvuII	cagctg	2
RleAI	cccaca	1
RsaI	gtac	0
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0
ScaI	agtact	0
ScrFI	ccngg	7
SduI	gdgchc	2
SecI	ccnngg	3
SexAI	accwgg	2
SfaNI	gcac	3
SfeI	ctryag	2
SfiI	ggccnnnnnggcc	0
Sgfi	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	0
SnaBI	tacgta	0
SpeI	actagt	0
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	1
StuI	aggcct	0
StyI	ccwggg	1
SwaI	atttaa	2
TaqI	tcga	0
TaqIIa	caccca	1
TaqIIb	gaccga	0
TfiI	gawtc	3
TseI	gcwgc	4
Tsp45I	gtsac	2
TspEI	aatt	6
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	0
XbaI	tctaga	0
XcmI	ccannnnnnnnntgg	0
XhoI	ctcgag	0
XhoII	rgatcy	2
XmaIII	cggccg	0
XmnI	gaannnttc	1

Total

184

Appendix L

Human Interferon-Alpha 14 Gene

L.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 14 gene was retrieved from the Genbank sequence file *hsifna14* (Henco et. al., 1985) (Benson et. al., 1993).

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1 gaatttgaaa gaaatttcta aaaagcccat ggggcaggga aagatgaggt aatactgaaa
61 ataaaagtgg ttgagaaact gctctacacc catgtagaca ggacataaag gaaagccaaa
121 agagaagtag aaaaaaacat gaagacgttc agaaaatgga agctagtatg ttctttattt
181 aagacctatg cacagagcaa ggtcttcaga aaacctacaa cccaagggtc agtggtaccc
241 ctcatcaacc agcccagcag catcttcggg attcccaatg gcattgccct ttgctttaat
301 gatggccctg gtgggtgctca gctgcaagtc aagctgctct ctgggctgta atctgtctca
361 aaccacagc ctgaataaca ggaggacttt gatgctcatg gcacaaatga ggagaatctc
421 tctttctcc tgccgaagg acagacatga ctttgaattt ccccaggagg aatttgatgg
481 caaccagttc cagaaagctc aagccatctc tgcctccat gagatgatgc agcagacctt
541 caatctctc agcacaaga actcatctgc tgcctgggat gagacctcc tagaaaaatt
601 ctacattgaa cttttccagc aaatgaatga cctggaagcc tgrtgatag aggaggttgg
661 ggtggaagag actccctcga tgaatgagga ctccatcctg gctgtgaa ga aafacttcca
721 aagaatcact ctttatctga tggagaagaa atacagccct tctgctggg aggttgtcag
781 agcagaaatc atgagatccc tctcttttc aacaaacttg ccaaaaagat taaggaggaa
841 ggattgaaaa ctgggtcacc atggaaaiga ttctattga caataacac atctcacact
901 tcatgagtt ctccattc aaagactcac ttctctata accaccacaa gtggaatcaa
961 aatttcaaa tgtttcagg agtgtaaaga agcatcatgt atacctgtgc aggcactagt
1021 cctttacaga tgacctgct gatgtctct tcatctatt tatttaata ttatttatt
1081 taactattt tattattaa attattttt atgtaatt atgtgt

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L.2 Restriction Endonuclease Sites

The human interferon-alpha 14 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
ApoI	1
TspEI	2
ApoI	12
TspEI	13
CviJI	24
BglI	25
MwoI	25
NcoI	27
DsaI	27
StyI	27
SecI	27
NlaIII	28
TaqIIa	87
NlaIII	91
AccI	94
CviJI	114
NlaIII	138
MboII	141
BbvII	141
XmnI	141
MaeII	145
AluI	161
CviJI	161
MaeI	163
MseI	179
CviRI	189
StyI	222
SecI	222
MaeIII	234
MnlI	240
CviJI	251
BbvI	257
BcgI	257
TseI	257
Fnu4HI	257
SfaNI	260
TfiI	270
HinfI	270
MseI	296
HaeIII	304
AsuI	304
CviJI	304

SecI	306
EcoRII	307
ScrFI	307
HgiAI	314
SduI	314
EspI	316
DdeI	317
PvuII	319
NspBII	319
AluI	320
CviJI	320
TseI	321
Fnu4HI	321
CviRI	323
MwoI	324
AluI	332
CviJI	332
TseI	333
Fnu4HI	333
MwoI	336
CviJI	344
BsmAI	355
RleAI	363
CviJI	368
NlaIII	397
BseRI	409
TfiI	414
HinfI	414
Eco57I	434
NlaIII	446
ApoI	455
TspEI	456
SecI	462
EcoRII	463
ScrFI	463
ApoI	470
TspEI	471
AluI	496
CviJI	496
CviJI	502
BccI	504
MnlI	514
NlaIII	518
CviRI	528
BbvI	529
TseI	529
Fnu4HI	529
Ksp632I	545
TseI	569
Fnu4HI	569
FokI	577
MnlI	586
MaeI	590
ApoI	596

TspEI	597
EcoRII	631
ScrFI	631
CviJI	637
MboII	665
HinfI	670
HinfI	689
BccI	693
EcoRII	697
ScrFI	697
CviJI	700
MboII	706
XmnI	709
TfiI	723
HinfI	723
MboII	745
CviJI	755
EcoRII	765
ScrFI	765
SecI	765
BspHI	789
NlaIII	790
XhoII	794
DpnI/MboI	795
MnlI	799
CviRI	819
MseI	830
BsrI	850
NlaIII	860
MslI	860
XmnI	864
TfiI	869
HinfI	869
MslI	897
BspHI	902
NlaIII	903
HinfI	924
CjeI	942
TfiI	954
HinfI	954
ApoI	960
TspEI	961
SfaNI	992
NlaIII	996
SnaI	999
AccI	999
BsgI	1007
CviRI	1008
Cac8I	1009
SpeI	1015
MaeI	1016
NlaIII	1035
MslI	1035
BsmAI	1044

SwaI	1062
AhaIII	1063
MseI	1064
SspI	1067
MseI	1080
SwaI	1095
AhaIII	1096
MseI	1097
TspEI	1100
NlaIII	1120

The human interferon-alpha 14 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AccI	94
AccI	999
AhaIII	1063
AhaIII	1096
AluI	161
AluI	320
AluI	332
AluI	496
ApoI	1
ApoI	12
ApoI	455
ApoI	470
ApoI	596
ApoI	960
AsuI	304
BbvI	257
BbvI	529
BbvII	141
BccI	504
BccI	693
BcgI	257
BglI	25
BseRI	409
BsgI	1007
BsmAI	355
BsmAI	1044
BspHI	789
BspHI	902
BsrI	850
Cac8I	1009
CjeI	942
CviJI	24
CviJI	114
CviJI	161

CviJI	251
CviJI	304
CviJI	320
CviJI	332
CviJI	344
CviJI	368
CviJI	496
CviJI	502
CviJI	637
CviJI	700
CviJI	755
CviRI	189
CviRI	323
CviRI	528
CviRI	819
CviRI	1008
DdeI	317
DpnI/MboI	795
DsaI	27
Eco57I	434
EcoRII	307
EcoRII	463
EcoRII	631
EcoRII	597
EcoRII	765
EspI	316
Fnu4HI	257
Fnu4HI	321
Fnu4HI	333
Fnu4HI	529
Fnu4HI	569
FokI	577
HaeIII	304
HgiAI	314
HinfI	270
HinfI	414
HinfI	670
HinfI	689
HinfI	723
HinfI	869
HinfI	924
HinfI	954
Ksp632I	545
MaeI	163
MaeI	590
MaeI	1016
MaeII	145
MaeIII	234
MboII	141
MboII	665
MboII	706
MboII	745
MnlI	240
MnlI	514

MnlI	586
MnlI	799
MseI	179
MseI	296
MseI	830
MseI	1064
MseI	1080
MseI	1097
MslI	860
MslI	897
MslI	1035
MwoI	25
MwoI	324
MwoI	336
NcoI	27
NlaIII	28
NlaIII	91
NlaIII	138
NlaIII	397
NlaIII	446
NlaIII	518
NlaIII	790
NlaIII	860
NlaIII	903
NlaIII	996
NlaIII	1035
NlaIII	1120
NspBII	319
PvuII	319
RleAI	363
ScrFI	307
ScrFI	463
ScrFI	631
ScrFI	697
ScrFI	765
SduI	314
SecI	27
SecI	222
SecI	306
SecI	462
SecI	765
SfaNI	260
SfaNI	992
SnaI	999
SpeI	1015
SspI	1067
StyI	27
StyI	222
SwaI	1062
SwaI	1095
TaqIIa	87
TfiI	270
TfiI	414
TfiI	723

TfiI	869
TfiI	954
TseI	257
TseI	321
TseI	333
TseI	529
TseI	569
TspEI	2
TspEI	13
TspEI	456
TspEI	471
TspEI	597
TspEI	961
TspEI	1100
XhoII	794
XmnI	141
XmnI	709
XmnI	864

The human interferon-alpha 14 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	2
AciI	ccgc	0
AclI	aacggt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	0
AgeI	accggt	0
AhaIII	tttaaa	2
AluI	agct	4
AlwNI	cagnnnctg	0
ApaI	gggccc	0
ApaBI	gcannnnntgc	0
ApaLI	gtgcac	0
ApoI	raatty	6
AscI	ggcgcgcc	0
AsuI	ggncc	1
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	0
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	2

BbvII	gaagac	1
BccI	ccatc	2
Bce83I	cttgag	0
BcefiI	acggc	0
BcgI	gcannnnnnntcg	1
BclI	tgatca	0
BetI	wccggw	0
BglI	gccnnnnnnggc	1
BglII	agatct	0
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnnatc	0
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	1
BsgI	gtgcag	1
BsiI	ctcgtg	0
BsiYI	ccnnnnnnnngg	0
BsmI	gaatgc	0
BsmAI	gtctc	2
Bsp24I	gacnnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	2
BspLU11I	acatgt	0
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	1
BsrBI	gagcgg	0
BsrDI	gcaatg	0
BstEII	ggtnacc	0
BstXI	ccannnnnnntgg	0
Cac8I	gcnnge	1
CauII	ccsgg	0
CfrI	yggccr	0
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	1
CjePI	ccannnnnnntc	0
ClaI	atcgat	0
CviJI	rgcy	14
CviRI	tgca	5
DdeI	ctnag	1
DpnI/MboI	gatc	1
DraII	rggnccy	0
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	1
Eam1105I	gacnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0

Eco57I	ctgaag	1
EcoNI	cctnnnnnagg	0
EcoRI	gaattc	0
EcoRII	ccwgg	5
EcoRV	gatatc	0
EspI	gctnagc	1
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	5
FokI	ggatg	1
FseI	ggcgggcc	0
GdiII	yggcgc	0
GsuI	ctggag	0
HaeI	wggccw	0
HaeII	rgcgcy	0
HaeIII	ggcc	1
HgaI	gacgc	0
HgiAI	gwgcwc	1
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	0
HinfI	gantc	8
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	0
KpnI	ggtacc	0
Ksp632I	ctcttc	1
MaeI	ctag	3
MaeII	acgt	1
MaeIII	gtnac	1
MboII	gaaga	4
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	4
MseI	ttaa	6
MslI	caynnnnnrtg	3
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	3
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	1
NdeI	catatg	0
NheI	gctagc	0
NlaIII	catg	12
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0

NspI	rcatgy	0
NspBII	cmgckg	1
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	0
PleI	gagtc	0
PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	0
PshAI	gacnnnngtc	0
PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	1
RleAI	cccaca	1
RsaI	gtac	0
RsrII	cggwccg	0
SacI	gagtc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0
ScaI	agtact	0
ScrFI	ccngg	5
SduI	gdgchc	1
SecI	ccnngg	5
SexAI	accwgg	0
SfaNI	gcac	2
SfeI	ctryag	0
SfiI	ggccnnnnnggcc	0
SgfI	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	1
SnaBI	tacgta	0
SpeI	actagt	1
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	1
StuI	aggcct	0
StyI	ccwggg	2
SwaI	atttaa	2
TaqI	tcga	0
TaqIIa	caccca	1
TaqIIb	gaccga	0
TfiI	gawtc	5
TseI	gcwgc	5
Tsp45I	gtsac	0
TspEI	aatt	7
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	0
XbaI	tctaga	0

XcmI	ccannnnnnnnntgg	0
XhoI	ctcgag	0
XhoII	rgatcy	1
XmaIII	cggccg	0
XmnI	gaannnttc	3
Total		160

Appendix M

Human Interferon-Alpha 16 Gene

M.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 16 gene was retrieved from the Genbank sequence file *hsifn16* (Henco et. al., 1985) (Benson et. al., 1993).

```

1 aattacacta aaagttattc cagaaatata cttatcaaat taagttatat gtcaacagct
61 tttaaactta gattttagtt taacttttct gtcattctta actttacatt gaataaaaag
121 agcaaacttt atagtttita tctgtgaagt agaggtatac gtagtatata taaatagata
181 tgccaaactct gtgttattaa aatttcattga agattccaat tagtaaaaaa taccataaaa
241 gtctttgagt gcagggggaaa aataggcaat gatgaacaaa atgaaaaaca tatgtaaaca
301 catgtagaga gtgcataaag aaagcaaaaa cagagataga aagtaaaacc agggcattta
361 gaaaatggaa attagtatgt tcactattta agaactatgc acagagcaaa gtcttcagaa
421 aacctagagg ccaagggtca agtttaccce tcctcagtag cctagcaata ttgcaacat
481 cccaatggcc ctgtcctttt ctttactgat ggccgtgctg gtgctcagct acaaatccat
541 ctgttctctg ggctgtgatc tgcctcagac tcacagcctg ggtaatagga gggccttgat
601 actcctggca caaatgggaa gaatctctca ttctcctgc ctgaaggaca gatattgatt
661 cggattcccc caggaggtgt ttgatggcaa ccagttccag aaggctcaag ccattctctg
721 ctccatgag atgatccagc agacctcaa tctcttcagc acaaaggatt catctgctgc
781 ttgggatgag accctcctag acaaattcta cattgaactt ttccagcaac tgaatgacct
841 agaagccctg gtgacacagg aggttggggg ggaagagatt gccctgatga atgaggactc
901 catcctggct gtgaggaaat actttcaaag aatcactctt tatctgatgg ggaagaaata
961 cagcccttgt gccctgggagg ttgtcagagc agaaatcatg agatccttct cttttcaac
1021 aaacttgcaa aaaggattaa gaaggaaagga ttgaaaactc attcaacatg gaaatgatcc
1081 tcattgatta atacatc atc tcacacttcc atgagttctt ccatttcaaa gac

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M.2 Restriction Endonuclease Sites

The human interferon-alpha 16 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
TspEI	1
TspEI	38
MseI	40
HindII	51
AluI	57
CviJI	57
AhaIII	61
MseI	62
DdeI	67
MseI	80
MseI	98
SnaI	155
AccI	155
SnaBI	158
BsaAI	158
MaeII	159
SnaI	164
AccI	164
MseI	197
ApoI	200
TspEI	201
BspHI	205
NlaIII	206
MboII	209
TfiI	212
HinfI	212
TspEI	218
BsgI	249
CviRI	250
BsrDI	266
NdeI	289
BspLU11I	300
AflIII	300
NspI	300
NlaIII	301
CviRI	312
EcoRII	349
ScrFI	349
SecI	349
TspEI	370
MseI	388
CviRI	398

MaeI	424
HaeI	428
HaeIII	429
CviJI	429
StyI	431
SecI	431
BccI	448
CjeI	448
CviJI	459
MaeI	462
ApaBI	465
MwoI	465
SspI	467
CviRI	473
MslI	478
HaeIII	487
AsuI	487
CviJI	487
GdiII	510
CfrI	510
HaeIII	511
CviJI	511
HgiAI	521
SduI	521
EspI	523
DdeI	524
AluI	527
CviJI	527
BccI	537
CjePI	537
XcmI	537
CviJI	551
DpnI/MboI	557
MnlI	563
DdeI	564
HinfI	568
CviJI	575
EcoRII	577
ScrFI	577
SecI	577
DraII	590
AsuI	591
HaeIII	592
CviJI	592
EcoRII	604
ScrFI	604
MboII	618
TfiI	621
HinfI	621
Eco57I	641
TfiI	663
HinfI	663
BsiYI	667
SecI	669

CjeI	670
EcoRII	670
ScrFI	670
CviJI	703
CviJI	709
MwoI	710
BccI	711
NlaIII	725
DpnI/MboI	733
Ksp632I	752
TfiI	767
HinfI	767
TseI	776
Fnu4HI	776
FokI	784
MnlI	793
MaeI	797
ApoI	803
TspEI	804
AlwNI	824
MaeI	839
CviJI	844
Tsp45I	851
MaeIII	851
MboII	872
HinfI	896
BccI	900
EcoRII	904
ScrFI	904
CviJI	907
TfiI	930
HinfI	930
MboII	952
CviJI	962
EcoRII	972
ScrFI	972
SecI	972
BspHI	996
NlaIII	997
XhoII	1001
DpnI/MboI	1002
CviRI	1026
MseI	1037
NlaIII	1067
MslI	1067
DpnI/MboI	1076
MnlI	1079
VspI	1087
MseI	1088
MslI	1104
BspHI	1109
NlaIII	1110

The human interferon-alpha 16 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AccI	155
AccI	164
AflIII	300
AhaIII	61
AluI	57
AluI	527
AlwNI	824
ApaBI	465
ApoI	200
ApoI	803
AsuI	487
AsuI	591
BccI	448
BccI	537
BccI	711
BccI	900
BsaAI	158
BsgI	249
BsiYI	667
BspHI	205
BspHI	996
BspHI	1109
BspLU11I	300
BsrDI	266
CfrI	510
CjeI	448
CjeI	670
CjePI	537
CviJI	57
CviJI	429
CviJI	459
CviJI	487
CviJI	511
CviJI	527
CviJI	551
CviJI	575
CviJI	592
CviJI	703
CviJI	709
CviJI	844
CviJI	907
CviJI	962
CviRI	250
CviRI	312
CviRI	398
CviRI	473
CviRI	1026

DdeI	67
DdeI	524
DdeI	564
DpnI/MboI	557
DpnI/MboI	733
DpnI/MboI	1002
DpnI/MboI	1076
DraII	590
Eco57I	641
EcoRII	349
EcoRII	577
EcoRII	604
EcoRII	670
EcoRII	904
EcoRII	972
EspI	523
Fnu4HI	776
FokI	784
GdiII	510
HaeI	428
HaeIII	429
HaeIII	487
HaeIII	511
HaeIII	592
HgiAI	521
HindII	51
HinfI	212
HinfI	568
HinfI	621
HinfI	663
HinfI	767
HinfI	896
HinfI	930
Ksp632I	752
MaeI	424
MaeI	462
MaeI	797
MaeI	839
MaeII	159
MaeIII	851
MboII	209
MboII	618
MboII	872
MboII	952
MnlI	563
MnlI	793
MnlI	1079
MseI	40
MseI	62
MseI	80
MseI	98
MseI	197
MseI	388
MseI	1037

MseI	1088
MslI	478
MslI	1067
MslI	1104
MwoI	465
MwoI	710
NdeI	289
NlaIII	206
NlaIII	301
NlaIII	725
NlaIII	997
NlaIII	1067
NlaIII	1110
NspI	300
ScrFI	349
ScrFI	577
ScrFI	604
ScrFI	670
ScrFI	904
ScrFI	972
SduI	521
SecI	349
SecI	431
SecI	577
SecI	669
SecI	972
SnaI	155
SnaI	164
SnaBI	158
SspI	467
StyI	431
TfiI	212
TfiI	621
TfiI	663
TfiI	767
TfiI	930
TseI	776
Tsp45I	851
TspEI	1
TspEI	38
TspEI	201
TspEI	218
TspEI	370
TspEI	804
VspI	1087
XcmI	537
XhoII	1001

The human interferon-alpha 16 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	2
AciI	ccgc	0
AclI	aacgtt	0
AcyI	grcgyc	0
AflII	cttaag	0
AflIII	acrygt	1
AgeI	accggt	0
AhaIII	tttaaa	1
AluI	agct	2
AlwNI	cagnnnctg	1
ApaI	gggcc	0
ApaBI	gcannnnntgc	1
ApaLI	gtgcac	0
ApoI	raatty	2
AscI	ggcgcgcc	0
AsuI	ggncc	2
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	0
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	0
BbvII	gaagac	0
BccI	ccatc	4
Bce83I	cttgag	0
Bcefi	acggc	0
BcgI	gcannnnnnntcg	0
BclI	tgatca	0
BetI	wccggw	0
BglI	gccnnnnnggc	0
BglII	agatct	0
BinI	ggatc	0
Bpu10I	cctnagc	0
BsaAI	yacgtr	1
BsaBI	gatnnnnatc	0
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	0
BsgI	gtgcag	1
BsiI	ctcgtg	0
BsiYI	ccnnnnnnnagg	1

BsmI	gaatgc	0
BsmAI	gtctc	0
Bsp24I	gacnnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcatga	3
BspLU11I	acatgt	1
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	0
BsrBI	gagcgg	0
BsrDI	gcaatg	1
BstEII	ggtnacc	0
BstXI	ccannnnnnntgg	0
Cac8I	gcnngc	0
CauII	ccsgg	0
CfrI	yggccr	1
Cfr10I	rccggy	0
CjeI	ccannnnnnngt	2
CjePI	ccannnnnnntc	1
ClaI	atcgat	0
CviJI	rgcy	14
CviRI	tgca	5
DdeI	ctnag	3
DpnI/MboI	gatc	4
DraII	rggnccy	1
DraIII	cacnnngtg	0
DrdI	gacnnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggctctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	1
EcoNI	cctnnnnnnnagg	0
EcoRI	gaattc	0
EcoRII	ccwgg	6
EcoRV	gatatc	0
EspI	gctnagc	1
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0
Fnu4HI	gcngc	1
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	1
GsuI	ctggag	0
HaeI	wggccw	1
HaeII	rgcgcy	0
HaeIII	ggcc	4
HgaI	gacgc	0
HgiAI	gwgwcw	1

HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	1
HindIII	aagctt	0
HinfI	ganc	7
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	0
KpnI	ggtacc	0
Ksp632I	ctcttc	1
MaeI	ctag	4
MaeII	acgt	1
MaeIII	gtnac	1
MboII	gaaga	4
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	3
MseI	ttaa	8
MslI	caynnnnnrtg	3
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	2
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	1
NheI	gctagc	0
NlaIII	catg	6
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	1
NspBII	cmgckg	0
PacI	ttaattaa	0
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	0
PleI	gagtc	0
PmaCI	cacgtg	0
PmeI	gtttaaac	0
PpuMI	rggwccy	0
PshAI	gacnnnnngtc	0
PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	0
RleAI	cccaca	0
RsaI	gtac	0
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0

SauI	cctnagg	0
ScaI	agtact	0
ScrFI	ccngg	6
SduI	gdgchc	1
SecI	ccnngg	5
SexAI	accwgg	0
SfaNI	gcatc	0
SfeI	ctryag	0
SfiI	ggccnnnnnnggcc	0
SgfI	gcgatcgc	0
SgrAI	crecgggyg	0
SmaI	cccggg	0
SnaI	gtatac	2
SnaBI	tacgta	1
SpeI	actagt	0
SphI	gcatgc	0
SpI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	1
StuI	aggcct	0
StyI	ccwgg	1
SwaI	atttaa	0
TaqI	tcga	0
TaqIIa	caccca	0
TaqIIb	gaccga	0
TfiI	gawtc	5
TseI	gcwgc	1
Tsp45I	gtsac	1
TspEI	aatt	6
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	1
XbaI	tctaga	0
XcmI	ccannnnnnnnntgg	1
XhoI	ctcgag	0
XhoII	rgatcy	1
XmaIII	cggccg	0
XmnI	gaannnttc	0
Total		148

Appendix N

Human Interferon-Alpha 17 Gene

N.1 Nucleotide Sequence

The genomic DNA sequence of the human interferon-alpha 17 gene was retrieved from the Genbank sequence file *hsifd2* (Lawn et. al., 1981a) (Benson et. al., 1993).

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1 agcttcatac actaagagaa aaattttaaa aaattattga ttctatttt caggagttt
61 gaatgatcag gtatgtaatt atattcatat tattaatgtg tatttatata gattttatt
121 ttgcacaggt actttgatac aaaatttaca tgaacaaatt acactaaaag ttatttcaca
181 aatatactta tcaagttaag ttaaatgcaa tagctttaaa cttagatttt aatttaactt
241 ttctatcat cattctttac attaaataaa aaaagcaaac ttatagttt ttatctataa
301 agtagaggta tacatagtat acataaatac atatgccaaa tctgtgttat taaaacttca
361 tgaagatttc gattacaaaa aaataccgta aaagactttg agtgcagaag aaaaatgggc
421 aatgatgaaa aacaatgaaa aacattctta aacacatgta gagagtgcga aaagaaagca
481 aaaacagaca tagaaagtaa aactagggca tttagaaaaa ggaaattagt atgttacta
541 ttaaggcct atgcacagag caaagcttc agaaaaccta gaggccaaag ticaaggtta
601 cccatctcaa gtagectagc aacatttgc acatcccaat ggccctgtcc ttctcttac
661 tgatggccgt gctgggtgct agctacaaat ccctctgttc tctaggctgt gatctgcctc
721 agaccacag cctgggtaat aggagggcct tgatactctt ggcacaaatg ggaagaatct
781 ctccttctc ctgectgaag gacagacctg actttggact tccccaggag gagtttgatg
841 gcaaccagtt ccagaagact caagccatct ctgtctctca tgagatgac cagcagacct
901 tcaatctct cagcacagag gactcatctg ctgcttgga acagagcctc ctagaaaaat
961 ttccactga actttaccag caactgaata acctggaagc atgtgtgata caggagggtg
1021 ggatggaaga gactccccctg atgaatgagg acitccatctt ggctgtgagg aaatacttcc
1081 aaagaatcac tctttatcta acagagaaga aatacagccc ttgtgcctgg gaggttgta
1141 gagcagaaat catgagatct ctctctttt caacaaactt gcaaaaaata ttaaggagga
1201 aggattgaaa actgggtcaa catggcaatg atcctgattg actaatatcat tatctcacac
1261 ttcatgagt tcttccattt caaagactca ctctataac caccacagat tgaatcaaaa
1321 ttcaaaatg ttacagcag tgaagaag cgtcgtgtat acctgtgcag gcactagtag
1381 ttacagatg acctgcctga tctctctgt catctattta ttiaaataat tatttaatta
1441 ttttaagat ttaaaattat ttttatgta atatcatgtg tacccttaca ttgtggtgaa
1501 tgaacaata tatgttcttc atatttagcc aataatataa ttctctttt cattaaattt
1561 ttactataca aaatttcttg ttttggtta ttcttaaga taaaatgtcg aggcctgactt
1621 tacaacctga cttaaaaaata tatgatttaa ttaagttate tatcataatt ttattcaagt
1681 tattaataaa acattttctt gttactgggt atatgttgc ttaagatat aaactgtaac
1741 ataaatata caatccctgt tctctgtat cttgatttt tgcaggaaa gaaatctaaa
1801 aacaataata atgtgaatt aatatcagtg atgctaactg ctataatgtg aggaagtaaa
1861 atacaatgaa ttc

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N.2 Restriction Endonuclease Sites

The human interferon-alpha 17 gene restriction endonuclease recognition sites are arranged by ascending sequence location.

Name	Site
AluI	1
CviJI	1
DdeI	12
ApoI	21
TspEI	22
AhaIII	25
MseI	26
TspEI	32
TfiI	39
HinfI	39
BclI	64
DpnI/MboI	65
TspEI	77
VspI	92
MseI	93
CviRI	122
RsaI	129
ApoI	142
TspEI	143
NlaIII	149
TspEI	157
MseI	196
MseI	201
CviRI	206
AluI	212
CviJI	212
AhaIII	215
MseI	216
DdeI	221
MseI	229
TspEI	231
MseI	234
MseI	262
SnaI	308
AccI	308
SnaI	317
AccI	317
NdeI	330
MseI	350
BspHI	358
NlaIII	359
MboII	362

TaqI	369
BsgI	402
CviRI	403
MboII	407
BsrDI	419
MseI	448
BspLU11I	454
AflIII	454
NspI	454
NlaIII	455
CviRI	466
MaeI	503
TspEI	524
MseI	542
StuI	545
HaeI	545
HaeIII	546
CviJI	546
CviRI	552
MaeI	578
HaeI	582
HaeIII	583
CviJI	583
BstEII	596
MaeIII	597
BccI	602
CjeI	602
CviJI	613
MaeI	616
ApaBI	619
MwoI	619
CviRI	627
MslI	632
HaeIII	641
AsuI	641
CviJI	641
GdiII	664
CfrI	664
HaeIII	665
CviJI	665
HgiAI	675
SduI	675
EspI	677
DdeI	678
AluI	681
CviJI	681
BccI	691
CjePI	691
MaeI	702
CviJI	705
DpnI/MboI	711
MnlI	717
DdeI	718
RleAI	724

PflMI	725
BsiYI	725
CviJI	729
EcoRII	731
ScrFI	731
SecI	731
DraII	744
AsuI	745
HaeIII	746
CviJI	746
EcoRII	758
ScrFI	758
MboII	772
TfiI	775
HinfI	775
Eco57I	795
BsiYI	807
SecI	823
CjeI	824
EcoRII	824
ScrFI	824
BseRI	828
MboII	854
BbvII	854
HinfI	857
CviJI	863
BccI	865
MnlI	875
NlaIII	879
DpnI/MboI	887
Ksp632I	906
HinfI	921
TseI	930
Fnu4HI	930
CviJI	945
MnlI	947
MaeI	951
ApoI	957
TspEI	958
AlwNI	978
EcoRII	992
ScrFI	992
NspI	999
NlaIII	1000
FokI	1021
MboII	1026
HinfI	1031
HinfI	1050
BccI	1054
EcoRII	1058
ScrFI	1058
CviJI	1061
XmnI	1070
TfiI	1084

HinfI	1084
MboII	1106
CviJI	1116
EcoRII	1126
ScrFI	1126
SecI	1126
BspHI	1150
NlaIII	1151
BglII	1155
XhoII	1155
DpnI/MboI	1156
CviRI	1180
SspI	1187
MseI	1191
BsrI	1211
NlaIII	1221
MslI	1221
BsrDI	1225
DpnI/MboI	1230
MslI	1258
BspHI	1263
NlaIII	1264
MnlI	1272
HinfI	1285
CjeI	1300
TfiI	1312
HinfI	1312
ApoI	1318
TspEI	1319
SnaI	1357
AccI	1357
BsgI	1365
CviRI	1366
Cac8I	1367
SpeI	1373
MaeI	1374
ScaI	1376
RsaI	1377
NlaIII	1393
MslI	1393
BsmAI	1402
SwaI	1420
AhaIII	1421
MseI	1422
SspI	1425
MseI	1434
TspEI	1436
MseI	1444
SwaI	1449
AhaIII	1450
MseI	1451
TspEI	1454
NlaIII	1475
RsaI	1480

MslI	1489
HphI	1495
MaeIII	1502
CviJI	1527
VspI	1536
MseI	1537
TspEI	1539
MseI	1553
ApoI	1555
TspEI	1556
ApoI	1571
TspEI	1572
MseI	1595
TaqI	1608
CviJI	1612
MseI	1632
MseI	1647
PacI	1647
TspEI	1649
MseI	1651
TspEI	1667
MseI	1683
MaeIII	1701
BsrI	1704
MaeII	1733
AlwNI	1751
TspEI	1817
VspI	1818
MseI	1819
EcoRI	1868
ApoI	1868
TspEI	1869

The human interferon-alpha 17 gene restriction endonuclease recognition sites are arranged by enzyme.

Name	Site
AccI	308
AccI	317
AccI	1357
AflIII	454
AhaIII	25
AhaIII	215
AhaIII	1421
AhaIII	1450
AluI	1
AluI	212
AluI	681
AlwNI	978

AlwNI	1751
ApaBI	619
ApoI	21
ApoI	142
ApoI	957
ApoI	1318
ApoI	1555
ApoI	1571
ApoI	1868
AsuI	641
AsuI	745
BbvII	854
BccI	602
BccI	691
BccI	865
BccI	1054
BclI	64
BglII	1155
BseRI	828
BsgI	402
BsgI	1365
BsiYI	725
BsiYI	807
BsmAI	1402
BspHI	358
BspHI	1150
BspHI	1263
BspLU11I	454
BsrI	1211
BsrI	1704
BsrDI	419
BsrDI	1225
BstEII	596
Cac8I	1367
CfrI	664
CjeI	602
CjeI	824
CjeI	1300
CjePI	691
CviJI	1
CviJI	212
CviJI	546
CviJI	583
CviJI	613
CviJI	641
CviJI	665
CviJI	681
CviJI	705
CviJI	729
CviJI	746
CviJI	863
CviJI	945
CviJI	1061
CviJI	1116

CviJI	1527
CviJI	1612
CviRI	122
CviRI	206
CviRI	403
CviRI	466
CviRI	552
CviRI	627
CviRI	1180
CviRI	1366
DdeI	12
DdeI	221
DdeI	678
DdeI	718
DpnI/MboI	65
DpnI/MboI	711
DpnI/MboI	887
DpnI/MboI	1156
DpnI/MboI	1230
DraII	744
Eco57I	795
EcoRI	1868
EcoRII	731
EcoRII	758
EcoRII	824
EcoRII	992
EcoRII	1058
EcoRII	1126
EspI	677
Fnu4HI	930
FokI	1021
GdiII	664
HaeI	545
HaeI	582
HaeIII	546
HaeIII	583
HaeIII	641
HaeIII	665
HaeIII	746
HgiAI	675
HinfI	39
HinfI	775
HinfI	857
HinfI	921
HinfI	1031
HinfI	1050
HinfI	1084
HinfI	1285
HinfI	1312
HphI	1495
Ksp632I	906
MaeI	503
MaeI	578
MaeI	616

MaeI	702
MaeI	951
MaeI	1374
MaeII	1733
MaeIII	597
MaeIII	1502
MaeIII	1701
MboII	362
MboII	407
MboII	772
MboII	854
MboII	1026
MboII	1106
MnlI	717
MnlI	875
MnlI	947
MnlI	1272
MseI	26
MseI	93
MseI	196
MseI	201
MseI	216
MseI	229
MseI	234
MseI	262
MseI	350
MseI	448
MseI	542
MseI	1191
MseI	1422
MseI	1434
MseI	1444
MseI	1451
MseI	1537
MseI	1553
MseI	1595
MseI	1632
MseI	1647
MseI	1651
MseI	1683
MseI	1819
MslI	632
MslI	1221
MslI	1258
MslI	1393
MslI	1489
MwoI	619
NdeI	330
NlaIII	149
NlaIII	359
NlaIII	455
NlaIII	879
NlaIII	1000
NlaIII	1151

NlaIII	1221
NlaIII	1264
NlaIII	1393
NlaIII	1475
NspI	454
NspI	999
PacI	1647
PflMI	725
RleAI	724
RsaI	129
RsaI	1377
RsaI	1480
ScaI	1376
ScrFI	731
ScrFI	758
ScrFI	824
ScrFI	992
ScrFI	1058
ScrFI	1126
SduI	675
SecI	731
SecI	823
SecI	1126
SnaI	308
SnaI	317
SnaI	1357
SpeI	1373
SspI	1187
SspI	1425
StuI	545
SwaI	1420
SwaI	1449
TaqI	369
TaqI	1608
TfiI	39
TfiI	775
TfiI	1084
TfiI	1312
TseI	930
TspEI	22
TspEI	32
TspEI	77
TspEI	143
TspEI	157
TspEI	231
TspEI	524
TspEI	958
TspEI	1319
TspEI	1436
TspEI	1454
TspEI	1539
TspEI	1556
TspEI	1572
TspEI	1649

TspEI	1667
TspEI	1817
TspEI	1869
VspI	92
VspI	1536
VspI	1818
XhoII	1155
XmnI	1070

The human interferon-alpha 17 gene restriction endonuclease recognition sites are summarized by enzyme.

Name	Pattern	Sites
AatII	gacgtc	0
AccI	gtmkac	3
AciI	ccgc	0
AclI	aacggt	0
AcyI	grcgyc	0
AflIII	cttaag	0
AflIII	acrygt	1
AgeI	accggt	0
AhaIII	tttaaa	4
AluI	agct	3
AlwNI	cagnnnctg	2
ApaI	gggccc	0
ApaBI	gcannnnntgc	1
ApaLI	gtgcac	0
ApoI	raatty	7
AscI	ggcgcgcc	0
AsuI	ggncc	2
AsuII	ttcgaa	0
AvaI	cycgrg	0
AvaII	ggwcc	0
AvaIII	atgcat	0
AvrII	cctagg	0
BaeI	acnnnngtayc	0
BalI	tggcca	0
BamHI	ggatcc	0
BbvI	gcagc	0
BbvII	gaagac	1
BccI	ccatc	4
Bce83I	cttgag	0
Bcefi	acggc	0
BcgI	gcannnnnnntcg	0
BclI	tgatca	1
BetI	wccggw	0
BglI	gccnnrnnnggc	0
BglII	agatct	1
BinI	ggatc	0

Bpu10I	cctnagc	0
BsaAI	yacgtr	0
BsaBI	gatnnnnnatc	0
BsbI	caacac	0
BscGI	cccgt	0
BsePI	gcgcgc	0
BseRI	gaggag	1
BsgI	gtgcag	2
BsiI	ctcgtg	0
BsiYI	ccnnnnnnngg	2
BsmI	gaatgc	0
BsmAI	gtctc	1
Bsp24I	gacnnnnnntgg	0
Bsp1407I	tgtaca	0
BspGI	ctggac	0
BspHI	tcata	3
BspLU11I	acata	1
BspMI	acctgc	0
BspMII	tccgga	0
BsrI	actgg	2
BsrBI	gagcgg	0
BsrDI	gcaatg	2
BstEII	ggtnacc	1
BstXI	ccannnnnntgg	0
Cac8I	gcnngc	1
CauII	ccsgg	0
CfrI	yggccr	1
Cfr10I	rccggy	0
CjeI	ccannnnnngt	3
CjePI	ccannnnnnntc	1
ClaI	atcgat	0
CviJI	rgcy	17
CviRI	tgca	8
DdeI	ctnag	4
DpnI/MboI	gata	5
DraII	rggnccy	1
DraIII	cacnnngtg	0
DrdI	gacnnnnnngtc	0
DrdII	gaacca	0
DsaI	ccrygg	0
Eam1105I	gacnnnnnngtc	0
EciI	tccgcc	0
Eco31I	ggtctc	0
Eco47III	agcgct	0
Eco57I	ctgaag	1
EcoNI	cctnnnnnagg	0
EcoRI	gaattc	1
EcoRII	ccwgg	6
EcoRV	gatata	0
EspI	gctnagc	1
Esp3I	cgtctc	0
FauI	cccgc	0
FinI	gggac	0
FnuDII	cgcg	0

Fnu4HI	gcngc	1
FokI	ggatg	1
FseI	ggccggcc	0
GdiII	yggccg	1
GsuI	ctggag	0
HaeI	wggccw	2
HaeII	rgcgcy	0
HaeIII	ggcc	5
HgaI	gacgc	0
HgiAI	gwgwc	1
HgiCI	ggyrcc	0
HgiEII	accnnnnnnnggt	0
HgiJII	grgcyc	0
HhaI	gcgc	0
HindII	gtyrac	0
HindIII	aagctt	0
HinfI	ganc	9
HpaI	gttaac	0
HpaII	ccgg	0
HphI	ggtga	1
KpnI	ggtacc	0
Ksp632I	ctcttc	1
MaeI	ctag	6
MaeII	acgt	1
MaeIII	gtnac	3
MboII	gaaga	6
McrI	cgrycg	0
MfeI	caattg	0
MluI	acgcgt	0
MmeI	tccrac	0
MnlI	cctc	4
MseI	ttaa	24
MslI	caynnnnrntg	5
MstI	tgcgca	0
MwoI	gcnnnnnnnngc	1
NaeI	gccggc	0
NarI	ggcgcc	0
NcoI	ccatgg	0
NdeI	catatg	1
NheI	gctagc	0
NlaIII	catg	10
NlaIV	ggnncc	0
NotI	gcggccgc	0
NruI	tcgcga	0
NspI	rcatgy	2
NspBII	cmgckg	0
PacI	ttaattaa	1
Pfl1108I	tcgtag	0
PflMI	ccannnnntgg	1
PleI	gagtc	0
PmaCI	cacgtg	0
PmeI	gtttaa	0
PpuMI	rggwccy	0
PshAI	gacnnnngtc	0

PstI	ctgcag	0
PvuI	cgatcg	0
PvuII	cagctg	0
RleAI	cccaca	1
RsaI	gtac	3
RsrII	cggwccg	0
SacI	gagctc	0
SacII	ccgcgg	0
SalI	gtcgac	0
SapI	gctcttc	0
SauI	cctnagg	0
ScaI	agtact	1
ScrFI	ccngg	6
SduI	gdgchc	1
SecI	ccnngg	3
SexAI	accwgg	0
SfaNI	gcatc	0
SfeI	ctryag	0
SfiI	ggccnnnnnnggcc	0
SgfI	gcgatcgc	0
SgrAI	crccggyg	0
SmaI	cccggg	0
SnaI	gtatac	3
SnaBI	tacgta	0
SpeI	actagt	1
SphI	gcatgc	0
SplI	cgtacg	0
SrfI	gcccgggc	0
Sse8387I	cctgcagg	0
SspI	aatatt	2
StuI	aggcct	1
StyI	ccwwgg	0
SwaI	atttaaat	2
TaqI	toga	2
TaqIIa	caccca	0
TaqIIb	gaccga	0
TfiI	gawtc	4
TseI	gcwgc	1
Tsp45I	gtsac	0
TspEI	aatt	18
Tth111I	gacnnngtc	0
Tth111II	caarca	0
VspI	attaat	3
XbaI	tctaga	0
XcmI	ccannnnnnnnntgg	0
XhoI	ctcgag	0
XhoII	rgatcy	1
XmaIII	cggccg	0
XmnI	gaannnttc	1
Total		236

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MaeI	532
ApoI	538
TspEI	539
CviRI	544
AlwNI	559
BbvI	561
TseI	561
Fnu4HI	561
PvuII	562
NspBII	562
AluI	563
CviJI	563
CviJI	579
CviRI	590
BseRI	595
BsmI	624
HinfI	631
BccI	635
CviJI	642
MboII	648
XmnI	651
MboII	662
TfiI	665
HinfI	665
MboII	687
CviJI	697
EcoRII	707
ScrFI	707
SecI	707
BspHI	731
NlaIII	732
XhoII	736
DpnI/MboI	737
MnlI	741
CviRI	761
MseI	772
SexAI	791
EcoRII	792
ScrFI	792
AvaII	795
AsuI	795
MmeI	797
NlaIII	802
TspEI	811
HinfI	821
SexAI	830