2. Genetic Factors in Type 1 Diabetes

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Type 1 diabetes is an autoimmune disorder in which the body attacks its pancreatic beta cells. The onset of type 1 diabetes is attributed to both an inherited risk and external triggers, such as diet or an infection. The hunt for these genetic and enviromental risk factors is on-going.

About 18 regions of the genome have been linked with influencing type 1 diabetes risk. These regions, each of which may contain several genes, have been labeled IDDM1 to IDDM18.

The most well studied is IDDM1, which contains the HLA genes that encode immune response proteins. Variations in HLA genes are an important genetic risk factor, but they alone do not account for the disease and other genes are involved.

There are two other non-HLA genes which have been identified thus far. One of these non-HLA genes, IDDM2, is the insulin gene, and the other non-HLA gene maps close to CTLA4, which has a regulatory role in the immune response.

IDDM1 Contains the HLA Genes

Summary

HLA genes encode molecules that are crucial to the immune system. These molecules hold small chains of amino acids on the cell surface so that immune cells can analyze these chains. When the immune cells find an inappropriate chain, they begin attacking. Without HLA genes, immune cells would not find the chains of viruses, bacteria, or tumor cells. On the other hand, inheriting certain versions (alleles) of the HLA genes increases the probability that immune cells will attack the body's healthy cells. This is how IDDM1 contributes to the immune attack of the beta cells and thus type 1 diabetes.

Background

The HLA region is a cluster of genes on chromosome 6. The genes encode glycoproteins that are found on the surfaces of most cells and help the immune system to distinguish between self (its own cells, e.g., beta cells of the pancreas) and non-self (e.g., bacteria, viruses).

Autoimmune disease results when the immune system launches an attack against the body's tissues. The risk of developing autoimmune disease is sometimes related to the alleles of HLA genes in the body. Type 1 diabetes is unique among these diseases in that HLA alleles may increase the risk of diabetes, have no effect, or even be protective.

The HLA genes encode proteins called major histocompatibility complex (MHC), and there are two main classes of MHC proteins, both of which display chains of amino acids. The chains are called antigens, and immune cells (called T cells) analyze them. Class I MHC present chains from inside cells, whereas MHC class 2 present chains from outside the cells. If T cells bind to the chain presented on an MHC, the T cell immediately orchestrates powerful attacks by the body's other immune cells. Ideally, the body only contains T cells that bind to chains from infectious organisms (viruses, bacteria, etc.) and tumor cells. Healthy development largely achieves this ideal. The alternative is found in autoimmune diseases such as diabetes: T cells bind to chains from the body's healthy cells.

There are many different alleles of the HLA genes, leading to many different variants of MHC proteins and allowing a variety of chains to be presented to cells. The inheritance of particular HLA alleles can account for over half of the genetic risk of developing type 1 diabetes (1). The genes encoding class II MHC proteins are most strongly linked with diabetes, and these genes are called HLA-DR, HLA-DQ, and HLA-DP.

In the general population, only half of the people inherit a copy (allele) of DR gene called DR3 and DR4, and less than 3% of the people have two alleles. However, in type 1 diabetes at least one allele of DR3 or DR4 is found in 95% of Caucasians, and individuals with both DR3 and DR4 are particularly susceptible to type 1 diabetes (2). Conversely, the DR2 allele is protective (3).

Similar to the DR gene, certain alleles of the DQ gene are risk factors for developing the disease, whereas other alleles of DQ are protective. There is also a tendency for people who inherit DR3 or DR4 to inherit DQ, which adds to their genetic risk of developing diabetes. Conversely, the protective alleles of DR and DQ tend to be inherited together. These tendencies have complicated the study of the effects of individual HLA-DR or HLA-DQ genes.

IDDM1 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on IDDM1 and diabetes, search PubMed.

Associations between HLA alleles and diabetes began to be documented in the 1970s when serological markers were used. This association was later confirmed with genome-wide scans.

The IDDM1 locus contains many diabetes susceptibility genes, and it remains difficult to identify the specific risk alleles because of linkage disequilibrium; certain alleles tend to be co-inherited with other alleles, making it difficult to distinguish between the effects of either on diabetes susceptibility.

Fine mapping of these regions suggests that the two alleles DQB1 and DRB1 are the most important (4). Alleles in the DQB1 gene are often tightly associated with alleles in the DRB1 gene, and variants of both or either allele may confer an increased risk of diabetes.

Sequences in the DQB1 gene that code for an amino acid other than aspartic acid at position 57 (non-ASP57) are highly associated with type 1 diabetes (5). Crystal structures suggest that loss of aspartic acid at this position creates an "oxyanion hole". This may be occupied by the T cell during the interaction between HLA and the T-cell receptor (6). The diabetes risk of non-ASP57 is further increased when the haplotype also contains the DRB1*0401 allele, suggesting the possible existence of at least two separate loci of susceptibility (7).

One of the protective HLA haplotypes is DQA1*0102, DQB1*0602. Aproximately 20% of Americans and Europeans have this haplotype, whereas less than 1% of children with type 1 diabetes do (8).

A well-known marker for type 1 diabetes is the presence of islet cell autoantibodies. However, even in the presence of islet cell autoantibodies, the haplotype DQA1*0102, DQB1*0602 has a protective effect. But once the diabetes disease process begins, the mechanism that protected these individuals from diabetes is lost, suggesting that inheriting these alleles does not prevent diabetes but may somehow delay or arrest the progression of the disease (9).

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Background Information

IDDM1 in OMIM

Type 1 diabetes in Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.137]

Molecular Biology

IDDM1 in Entrez Gene | Map Viewer

IDDM2 Contains the Insulin Gene (INS)

Summary

The IDDM2 locus contains the insulin gene (INS). Mutations of INS cause a rare form of diabetes that is similar to MODY (Maturity Onset Diabetes in the Young). Other variations of the insulin gene (variable number tandem repeats and SNPs) may play a role in susceptibility to type 1 and type 2 diabetes.

Background

Insulin is a hormone that has a wide range of effects on metabolism. Its overall action is to encourage the body to store energy rather than use it, e.g., insulin favors the storage of glucose as glycogen or fat as opposed to breaking down glucose to release ATP. For a summary of the actions of insulin, see the Physiology and Biochemistry of Sugar Regulation.

Insulin is composed of two distinct polypeptide chains, chain A and chain B, which are linked by disulfide bonds. Many proteins that contain subunits, such as hemoglobin, are the products of several genes. However, insulin is the product of one gene, INS.

INS actually encodes an inactive precursor called preproinsulin. Preproinsulin is processed into proinsulin by removal of a signaling peptide; however, proinsulin is also inactive. The final processing step involves removal of a C-peptide (a connecting peptide that links chain A to chain B), and this process produces the mature and active form of insulin. For further information, see The Story of Insulin.

Molecular Information

Several species, including the rat, mouse, and some species of fish, have two insulin genes. In contrast, in humans there is a single insulin gene that is located on chromosome 11 (Figure 1). It has three exons (coding regions) that span about 2,200 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009237.16&gene=INS&graphiconly=TRUE]). Exon 2 encodes the B chain, along with the signal peptide and part of the C-peptide found in the precursors of insulin. Exon 3 encodes the A chain and the remainder of the C-peptide.

C-peptide is secreted in equal amounts to insulin, but it has long been thought that it has no biological role. However, in diabetic rats C-peptide has been shown to reduce the dysfunction of blood vessels and the nervous system that is common in diabetes (1). C-peptide contains the greatest variation among species, whereas regions of insulin that bind to the insulin receptor are highly conserved.

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3630&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the INS gene, none (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein (see the allelic variants that are known to be associated with disease).

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557671&cut=100&org=1] using human proinsulin precursor as a query finds proteins in 107 different species, which are all metazoans apart from three plants and one bacterium. However, potential true homologous genes have thus far been identified only in the mouse and rat.

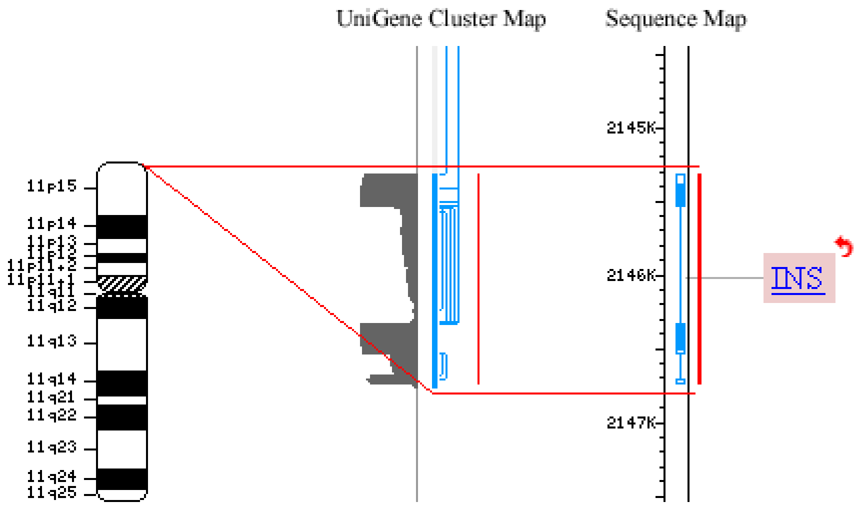

Figure 1: Location of INS on the human genome.

INS maps to chromosome 11, approximately between 2144–2148 kilobases (kb). Click on the figure or here for a current and interactive view of the location of INS in the human genome.

Note: this figure was created from Build 34 of the human genome. Because the data are recomputed between genome builds, the exact location of INS may fluctuate; therefore, the live Web site may not appear exactly as in this figure.

IDDM2 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on INS and diabetes, search PubMed.

The IDDM2 locus contributes about 10% toward type 1 diabetes susceptibility (2). The "risk area" of this locus is localized to a region flanking the insulin gene that contains a short sequence of DNA that is repeated many times (3, 4). The repeats are found 0.5 kb upstream from the site where transcription of INS begins. Because the repeated sequences follow one behind the other (in tandem) and because the number of repeats varies between individuals, this phenomenon is called variable number tandem repeats (VNTRs).

There are three classes of VNTR in the insulin gene (5):

- Class I has alleles that range from 26 to 63 repeat units.
- Class II has alleles that average around 80 repeat units.
- Class III has alleles ranging from 141 to 209 repeat units.

The class I VNTRs are most common in Caucasians, with around 70% of alleles being in the range of 30-44 repeats, and nearly all other alleles are longer than 110 repeats (class III). The intermediate lengths (class II) are rare.

The class of VNTR is associated with susceptibility to type 1 diabetes. Short class I alleles are associated with a higher risk of developing type 1 diabetes, whereas the longer class III alleles are protective. The presence of at least one class III allele is associated with a 3-fold reduction in the risk of type 1 diabetes, compared with common I/I homozygote genotype (6).

Because the VNTR occurs in a non-coding region, its influence on diabetes risk cannot be attributed to an alteration of the protein sequence. Instead, the VNTR probably affects the transcription of the insulin gene in some way. Indeed in the pancreas, the class III alleles are associated with 15-30% lower INS mRNA.

In contrast, class III alleles are associated with higher levels of INS mRNA in the thymus. This gland has an important role in training the immune system in the developing embryo. Immature T cells are presented with chains of amino acids, such as insulin, and T cells that form a response to them (and thus are autoreactive) are deleted. Because the longer VNTRs cause more insulin to be produced in the thymus, the detection and deletion of autoreactive T cells may be more efficient. This improved immune tolerance to insulin would lessen the risk of a future onset of type 1 diabetes caused by anti-insulin antibodies.

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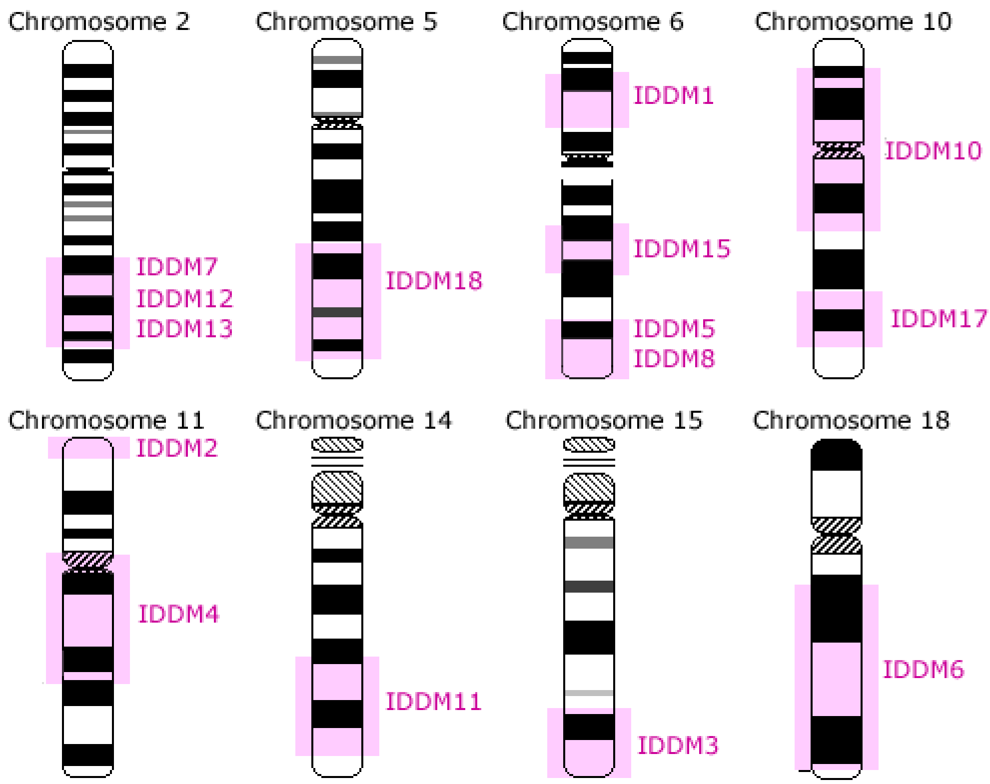
Other Type 1 Diabetes Susceptibility Loci: IDDM3–IDDM18

IDDM1 (containing the HLA system) and IDDM2 (containing the insulin gene) were both originally identified by investigating the suspected genes, HLA genes and INS, respectively, using case-control studies. The remaining type 1 diabetes susceptibility loci, IDDM3–IDDM18, were mainly discovered by genome scan linkage studies, e.g., looking for linkage between regions of the genome and disease in affected sib-pairs.

The IDDM loci are found on several different chromosomes and contain many genes, many of which have now been identified. Some of these genes are suspected to play a role in susceptibility to type 1 diabetes, and they are discussed below.



IDDM3

No diabetes susceptibility genes have been identified in the IDDM3 locus, which is found on chromosome 15.

IDDM4

Several potential candidate genes lie near the IDDM4 locus on chromosome 11. These include ZFM1 (zinc finger protein 162), which encodes a transcription factor found in the pancreas, and FADD (Fas-associated death protein). The transmission of the "cell death" signal involves the interaction between FAS and FADD, and in type 1 diabetes, the apoptosis of pancreatic beta cells may involve the FADD. Apoptosis of the beta cell may be triggered by the binding of Fas (expressed on the beta cell) with Fas ligand (expressed on the cytotoxic T cell) (1).

Other candidate genes in this region include LRP5, which encodes a novel transmembrane protein that is similar to receptors belonging to the low-density lipoprotein family (2).

IDDM5

The region of chromosome 6 that contains the IDDM5 locus includes the SOD2 gene, which encodes mitochondrial superoxide dismutase. SOD2 metabolizes harmful oxygen free radicals, which are intermediates in many biological reactions, and converts them into less reactive and less harmful molecules. There is some evidence that free oxygen radicals may play a role in the destruction of beta cells. Enzymes such as SOD2 may therefore offer protection against type 1 diabetes, and genetic variants of SOD2 may increase susceptibility to disease (1).

IDDM6

Several candidate diabetes susceptibility genes have been identified in the IDDM6 locus. They include a gene associated with colorectal cancer (DCC) that may be linked with autoimmune disease, a gene that encodes a zinc finger DNA binding domain (ZNF236) that may be linked with diabetic kidney disease, and a molecule that opposes apoptosis (bcl-2) (1).

IDDM7

Within the IDDM7 locus on chromosome 2 are several candidate diabetes risk genes. One is NEUROD1 (3), a transcription factor that is expressed widely in the developing brain and pancreas. NEUROD1 regulates the transcription of the insulin gene, and in addition to its association with type 1 diabetes, variants of this gene have been implicated in susceptibility to type 2 diabetes; a mutation of this gene causes MODY6.

Other genes located within the IDDM7 locus include IGRP (islet-specific glucose-6-phosphatase catalytic subunit-related protein), which encodes the beta cell-specific version of the enzyme glucose-6-phosphatase. IGRP has emerged as a major target of cell-mediated autoimmunity in type 1 diabetes (4).

Many other candidate genes (interleukin-1 gene cluster, HOXD8, GAD1, GALNT3) in this region have been investigated but none of these genes have been shown to be associated with type 1 diabetes (1).

IDDM8

No diabetes susceptibility genes have been identified in the IDDM8 locus, which is found on chromosome 6.

IDDM9

The symbol IDDM9 has not yet been approved.

IDDM10

The gene GAD2 is closely linked to the region of chromosome 10 designated as IDDM10. Glutamic acid decarboxylase (GAD) catalyzes formation of the neurotransmitter GABA. Targeting of this enzyme by autoantibodies has been implicated in the pathogenesis of stiff-man syndrome and type 1 diabetes (5, 6). Both diseases feature insulin deficiency, but stiff-man syndrome also bears the features of an autoimmune attack against the central nervous system, characterized by painful muscle spasms and increasing stiffness of axial muscles. The difference between stiff-man syndrome and type 1 diabetes may be because GAD is expressed in two different isoforms: one is expressed in the central nervous system, and the other is in the beta cells (7). The nature of the immune attack against these two isoforms also appears to be different (8).

The GAD2 gene encodes GAD65, and this protein contains a 24-amino acid segment that is similar to an amino acid sequence found in the Coxsackie virus, a suspected environmental trigger for the onset of type 1 diabetes. Autoimmunity in IDDM may thus arise by "molecular mimicry" between GAD and a viral polypeptide (9). However, evidence of cross-reactivity has not been demonstrated in immune cells from patients with diabetes.

Autoantibodies against GAD have been found in patients who have had preclinical type 1 diabetes (10). In the type 1 diabetes mouse, the expression of GAD by beta cells is required for the development of autoimmune diabetes. Complete suppression of beta-cell GAD expression blocks the generation of diabetogenic T cells, leading to the theory that modulation of GAD might have therapeutic value in type I diabetes (11).

IDDM11

One candidate gene in the IDDM11 locus is the ENSA gene, which encodes alpha-endosulphine. This protein is thought to be an endogenous regulator of the beta cell potassium channel (KATP channel).

The KATP channels co-ordinate a rise in blood glucose with insulin secretion. As glucose levels rise, the corresponding rise in ATP shuts the channel, leading to a change in membrane polarity. Voltage-sensitive calcium channels flip open, allowing Ca^{2+} ions to enter into the beta cells, triggering exocytosis of insulin. The KATP channel pore is encoded by the KIR gene, and the channel is regulated by the sulfonylurea receptor encoded by the ABCC8 gene.

Recombinant alpha-endosulphine has been shown to inhibit the binding of the diabetes drug sulfonylurea to its receptor, to reduce the flow of K^+ through the KATP channel, and to stimulate insulin secretion (12).

Another candidate gene in this region is the SEL1L gene. It is a negative regulator of the Notch signalling pathway which controls the differentiation of pancreatic endocrine cells (13).

IDDM12

Several candidate genes have been located in the IDDM12 locus, and the strongest candidates encode co-stimulatory receptors on the T cell. When the T cell is presented with a chain of amino acids, its T-cell receptor binds to the HLA molecules that are presenting the chains. For the T cell to become fully activated, there is additional signaling between co-stimulatory receptors and corresponding ligands on the antigen-presenting cell. These co-stimulatory receptors are encoded by the candidate genes for type 1 diabetes susceptibility CTLA4, CD28, and ICOS.

Read more about the role of CTLA4 in type 1 diabetes.

IDDM13

Several IDDM13 candidate genes have been investigated, but variants of these genes have yet to be associated with type 1 diabetes.

IDDM14

The symbol IDDM14 has not yet been approved.

IDDM15

The IDDM15 locus has been linked with type 1 diabetes, and mutations near this region are associated with a rare form of diabetes called transient neonatal diabetes (14).

IDDM16

One of the candidate genes in the IDDM16 locus is the immunoglobulin heavy chain. Immunoglobulins (antibodies) have a central role in the immune response against foreign antigens and in error can also attack self antigens, resulting in autoimmune disease. Immunoglobulins are known to interact with HLA molecules, variants of which are associated with diabetes protection or susceptibility (IDDM1 contains the HLA genes). Immunoglobulins are composed of two heavy chains and two light chains, and the IDDM16 locus contains the gene that encodes the heavy chain. Genetically controlled differences in the immunoglobulin heavy chain may affect an individual's immune response to self antigens and thus alter the risk of developing autoimmune diseases such as type 1 diabetes (1).

IDDM17

The IDDM17 locus was discovered to be linked to type 1 diabetes, but the candidate gene(s) is not yet known. The FAS gene maps to this genomic area, but it has been excluded as a possible diabetes susceptibility gene.

IDDM18

A candidate diabetes susceptibility gene in the IDDM18 locus is ILB12. This gene encodes a subunit of IL-12p40, a signaling molecule secreted by white blood cells. In animal models, IL-12 plays an important role in the induction of diabetes. In humans, variation in IL-12p40 production may influence the reactivity of T cells and initiate or protect against autoimmune diseases such as type 1 diabetes (15, 6).

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Link Roundup

Background information in Entrez Gene

IDDM3 IDDM4 IDDM5 IDDM6

IDDM7 IDDM8 IDDM9 IDDM10

IDDM11 IDDM12 IDDM13 IDDM14

IDDM15 IDDM16 IDDM17 IDDM18

Background information in OMIM

IDDM3 IDDM4 IDDM5 IDDM6

IDDM7 IDDM8 [IDDM9] [IDDM10]

IDDM11 IDDM12 IDDM13 [IDDM14]

IDDM15 [IDDM16] IDDM17 IDDM18

An Inhibitor of the Immune Response (CTLA4)

Summary

Immune cells are continually analyzing small chains of amino acids to detect infectious agents or tumor cells. When a foreign chain is found, the immune cells become activated and begin to attack. The CTLA4 gene encodes a molecule that hinders the activation of immune cells. The region of the chromosome that contains CTLA4 has been linked with susceptibility to many autoimmune diseases including type 1 diabetes.

Nomenclature

Official gene name: cytotoxic T-lymphocyte-associated protein 4
Official gene symbol: CTLA4
Alias: CD152

Background

One of the steps in mounting an immune response involves an interaction between two cells. The first cell, called the antigen-presenting cell (APC), displays small chains of amino acids (antigens) on its surface, and they present these antigens to the second type of cell, T cells. Once the T cell has analyzed the antigen, it can either become activated and launch an immune attack or be deactivated. In a healthy immune system, T cells become activated only to foreign antigens, such as fragments from bacteria or viruses. If the T cells become activated in response to self antigens, autoimmune diseases such as diabetes results.

Optimal activation of the T cell requires a two-way interaction between the T-cell receptor and the antigen (the first signal) and between co-stimulatory receptors on the surface of the T cell with co-stimulatory ligands expressed by APCs (the second signal). Failure of the T cell to receive a second signal can lead to its deactivation.

One of the co-stimulatory molecules on the T cell is called cytotoxic T lymphocyte-associated antigen 4 (CTLA4). CTLA4 has a negative regulatory effect on the immune system because it down-regulates T-cell activation by interfering with the second signal. Mice with a targeted disruption of the CTLA4 gene develop a fatal disorder characterized by massive lymphocyte proliferation (1).

Unlike other co-stimulator receptors on the T cell, CTLA4 is only expressed when the T cell has been activated after antigen presentation. Because it is only expressed in activated T cells, and because it down regulates the function of T cells, it is likely that CTLA4 has a role in guarding against autoimmunity (2). Loss of this gene may result in activated T cells attacking self antigens. Indeed, genetic variants of CTLA4 have been linked with autoimmune disorders such as autoimmune hypothyroid disease, Graves' disease (3), systemic lupus erythematosus (SLE) (4), celiac disease (5), and type 1 diabetes (6-8).

Molecular Information

CTL4A maps to IDDM12 on chromosome 2 (Figure 1), and the equivalent area of the mouse genome has been linked to type 1 diabetes in the non-obese diabetic (NOD) mouse (9). It has four exons (coding regions) that span around 7,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_005403.14&gene=CTLA4&graphiconly=TRUE]). The gene encodes a protein of 223 amino acids.

The CTLA4 protein contains an immunoglobulin V-like domain (view domain [http://www.ncbi.nlm.nih.gov:80/Structure/cdd/cddsrv.cgi?uid=3897]), a transmembrane region, and a putative cytoplasmic region that is identical to the mouse CTLA4 protein. This conservation of the cytoplasmic region between species suggests that it has an important role in the functioning of CTLA4 (10).

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=1493&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the CTLA4 gene, two (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein (Figure 2). None of these variants have yet to be associated with disease (see known allelic variants).

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=21361212&cut=100&org=1] using human CTLA4 as a query finds proteins in 19 different species, which are all metazoans (multicellular). However, potential true homologous genes have thus far been identified only in the mouse and rat.

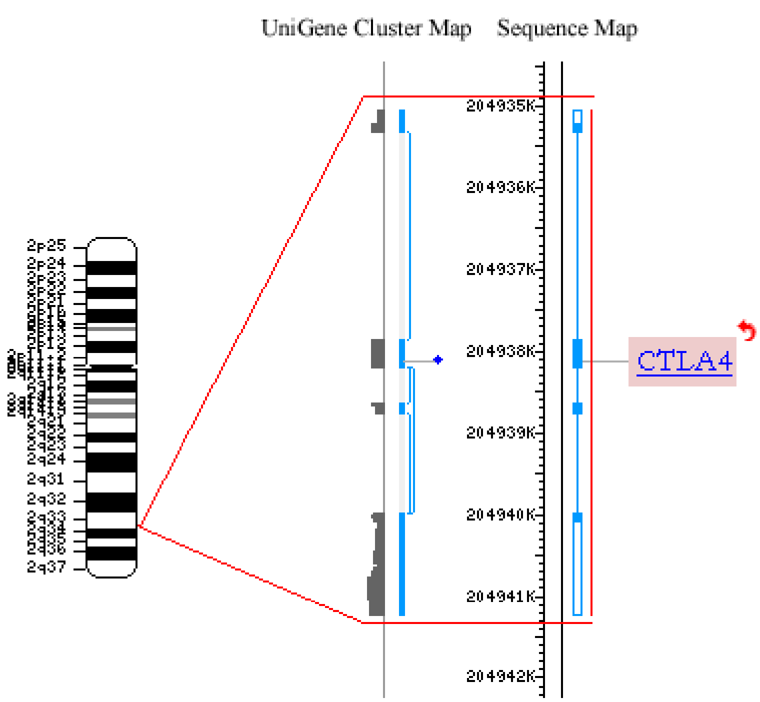

Figure 1: Location of CTLA4 on the human genome.

CTLA4 maps to chromosome 2, between approximately 204,930–204,945 kilobases (kb). Click on the image or here for a current and interactive view of the location of CTLA4 in the human genome.

Note: this figure was created from Build 34 of the human genome. Because the data are recomputed between genome builds, the exact location of CTLA4 may fluctuate. Therefore, the live Web site may not appear exactly as in this figure.

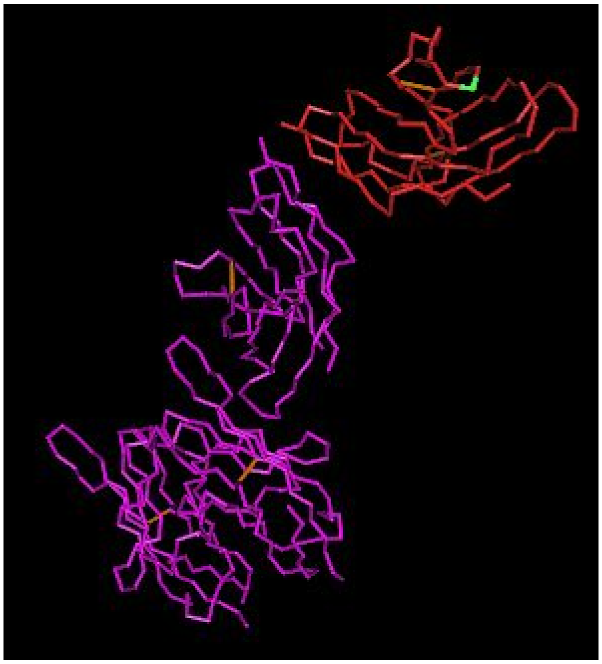

Figure 2: SNP positions of CTLA4 mapped to the 3D structure of human Ctla-4B7-2 complex.
The figure shows the positions of non-synonymous amino acid changes (green residues) caused by SNPs in the coding sequence.

Click on the figure or this Cn3D icon for a dynamic view (you will need to download the Cn3D viewer [www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml] to do this)

CTLA4 and Diabetes: Digest of Recent Articles

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There are several SNPs in the 3' untranslated region of the CTLA4 sequence that have been implicated in determining the risk for several common autoimmune disorders, including type 1 diabetes.

One of the SNPs, termed CT60, encodes a genotype that is either protective (A/A) or predisposes (G/G) toward autoimmune disease. The disease susceptibility G allele is common, being found in 50% of individuals without autoimmune disorders, and is more common in individuals with Graves' disease (63%). The G/G haplotype correlated with lower production of the soluble alternative splice from of CTLA4 (sCTLA4) compared with the protective A/A haplotype. This reduction of sCTLA4 levels could lead to reduced blocking of signals between T cells and APCs, leading to increased activation of T cells. This allele was also associated with type 1 diabetes but the effect was small (11).

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