3. Genetic Factors in Type 2 Diabetes

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Type 2 diabetes has been loosely defined as "adult onset" diabetes, although as diabetes becomes more common throughout the world, cases of type 2 diabetes are being observed in younger people. It is increasingly common in children.

In determining the risk of developing diabetes, environmental factors such as food intake and exercise play an important role. The majority of individuals with type 2 diabetes are either overweight or obese. Inherited factors are also important, but the genes involved remain poorly defined.

In rare forms of diabetes, mutations of one gene can result in disease. However, in type 2 diabetes, many genes are thought to be involved. "Diabetes genes" may show only a subtle variation in the gene sequence, and these variations may be extremely common. The difficulty lies in linking such common gene variations, known as single nucleotide polymorphisms (SNPs), with an increased risk of developing diabetes.

One method of finding the diabetes susceptibility genes is by whole-genome linkage studies. The entire genome of affected family members is scanned, and the families are followed over several generations and/or large numbers of affected sibling-pairs are studied. Associations between parts of the genome and the risk of developing diabetes are looked for. To date only two genes, calpain 10 (CAPN10) and hepatocyte nuclear factor 4 alpha (HNF4A), have been identified by this method.

The Sulfonylurea Receptor (ABCC8)

Summary

Sulfonylureas are a class of drugs used to lower blood glucose in the treatment of type 2 diabetes. These drugs interact with the sulfonylurea receptor of pancreatic beta cells and stimulate insulin release. The sulfonylurea receptor is encoded by the ABCC8 gene, and genetic variation of ABCC8 may impair the release of insulin.

Nomenclature

Official name: ATP-binding cassette, sub-family C, member 8
Official gene symbol: ABCC8
Alias: sulfonylurea receptor, SUR, SUR1

Background

The protein encoded by the ABCC8 gene is a member of the ATP-binding cassette transporters. These proteins use energy in the form of ATP to drive the transport of various molecules across cell membranes. ABCC8 belongs to a subfamily of transporters that contains the chloride channel that is mutated in cystic fibrosis (CFTR) and also the proteins that are involved in multi-drug resistance.

Read more: The Human ATP-Binding Cassette (ABC) Transporter Superfamily [www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowTOC&rid=mono_001.TOC&depth=2]

The ABCC8 protein is also known as the sulfonylurea urea receptor (SUR). SUR is one of the proteins that composes the ATP-sensitive potassium channel (KATP channel) found in the pancreas (1). The other protein, called Kir6.2, forms the core of the channel and is encoded by the KCNJ11 gene. KATP channels play a central role in glucose-induced insulin secretion by linking signals derived from glucose metabolism (a rise in ATP) to membrane depolarization (due to KATP channels closing) and the secretion of insulin.

The activity of the KATP channel regulates the release of insulin. The sulfonylureas are drugs that can modulate KATP channel activity and are used in the treatment of type 2 diabetes. By binding to SUR, they inhibit the channel and stimulate the release of insulin. This leads to a lowering of blood glucose levels.

Further information on sulfonylureas from MEDLINEplus [www.nlm.nih.gov/medlineplus/druginfo/uspdi/202742.html]

The activity of the KATP channel is also modulated by the subtype of SUR (SUR, also known as SUR1, is encoded by ABCC8; or SUR2A and SUR2B, which are encoded by ABCC9). In the pancreas, most KATP channels are thought to be a complex of four SUR1 proteins and four Kir6.2 proteins.

Mutations in either ABCC8 or KCNJ11 can result in up-regulated insulin secretion, a condition termed familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (2-4). Genetic variation in ABCC8 has also been implicated in the impaired release of insulin that is seen in type 2 diabetes.

Molecular Information

ABC genes are found in many different eukaryotic species and are highly conserved between species, indicating that many of these genes existed early in eukaryotic evolution. A BLAST search [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507317&cut=100&org=1] using human ABCC8 as a query finds proteins in 30 different species, which include multicellular organisms (metazoans), fungi, and plants. Potential true homologous genes have been identified in the mouse and rat.

By fluorescence in situ hybridization, it was found that the ABBC8 gene maps to the short arm of chromosome 11 (Figure 1) (5). It has 41 exons (coding regions) that span over 84,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009237.16&gene=ABCC8&graphiconly=TRUE]).

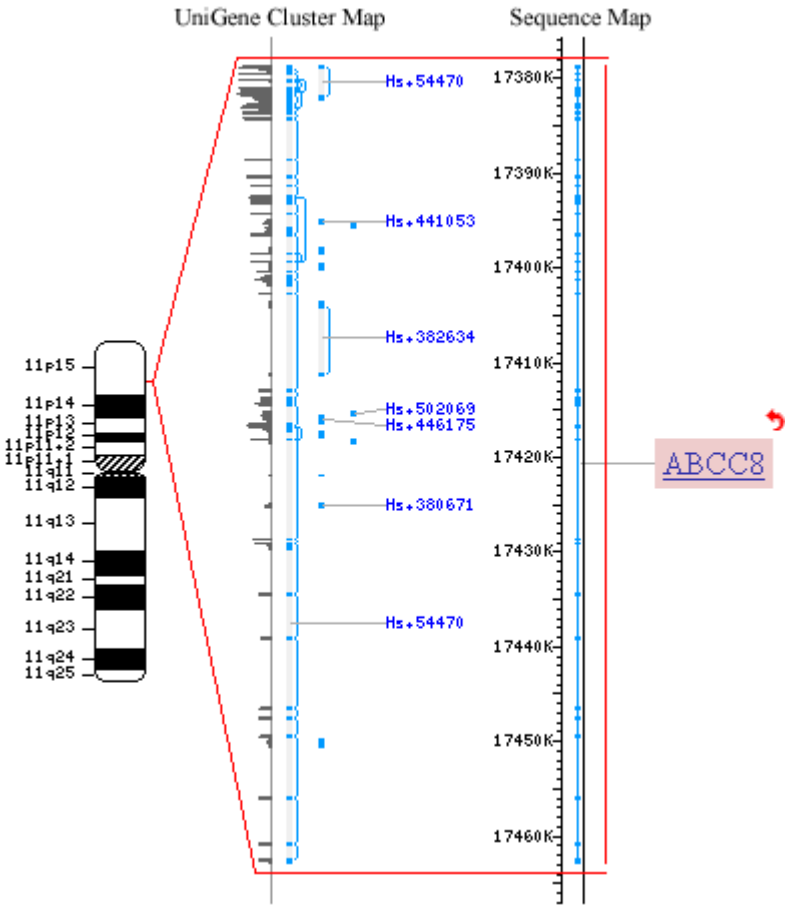

Figure 1: Location of ABCC8 on the human genome.

ABCC8 maps to chromosome 11, between approximately 17,370–17,470 kilobases (kb). Click or here for a current and interactive view of the location of ABCC8 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 ABCC8 may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

The ABC transporter proteins, such as ABCC8, typically contain two ATP-binding domains and two transmembrane domains (view domains [www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4507317]).

The ATP-binding domains are also known as nucleotide binding folds (NBFs), and mutations in either NBF1 or NBF2 can lead to PHHI (6). This suggests that both NBF regions of the SUR are needed for the normal regulation of KATP channel activity.

As found in all proteins that bind ATP, the nucleotide binding domains of the ABC family of proteins contain characteristic motifs called Walker A and B. The Walker A motif contains a lysine residue that is critical for activating the KATP channel. When this lysine residue is mutated in NBF1, but not NBF2, the KATP channel can no longer be activated (7). In addition, ABC genes also contain a signature C motif.

The transmembrane domains contain 6–11 membrane spanning helices, and the ABCC protein contains 6. These helices provide the protein with specificity for the molecule they transport across the membrane.

Several single nucleotide polymorphisms (SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6833&view=view&chooseRs=coding&.cgifields=chooseRs]) have been found within the ABCC8 gene. Usually SNPs linked with disease occur within the coding regions (exons) of the genes, and they result in a non-synonymous amino acid change. In ABCC8, there are seven such SNPs (at the time of writing) that cause a switch of amino acids in the mature protein (Figure 2). However, one of the SNPs of the ABCC8 gene that has been linked with diabetes (R1273R) does not cause an amino acid change (see below).

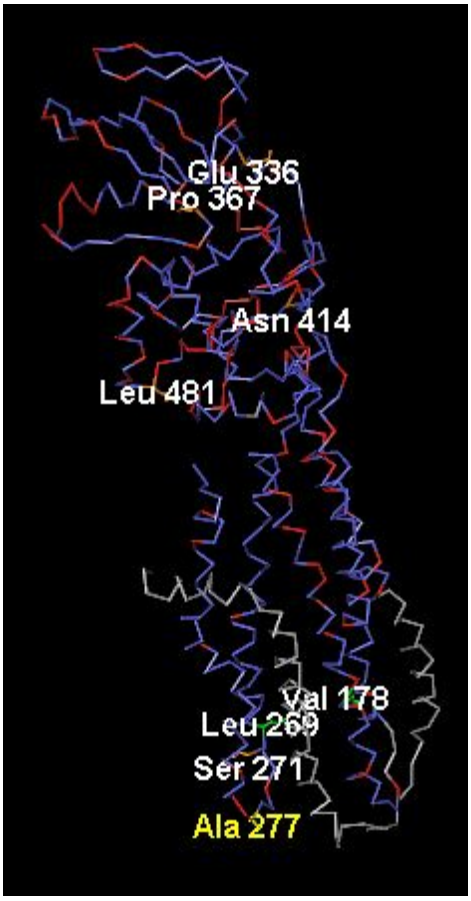

Figure 2: SNP positions of ABCC8 mapped to the 3D structure of a multidrug resistance ABC transporter homolog in Vibrio *cholera*.

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)

ABCC8 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on ABCC8 and diabetes, search PubMed.

The two genes that encode the KATP channel, ABBC8 and KCNJ11, reside adjacent to one another on chromosome 11. A variant of ABCC8, called A1369S, is in almost complete linkage disequilibrium with a variant of KCNJ11 called E23K. This means that from the genetic evidence, it is difficult to determine whether it is the A1369S variant or the E23K variant that predisposes to type 2 diabetes (8).

A mutation in ABCC8 was observed to cause an extremely rare form of diabetes, autosomal dominant diabetes, in a Finnish family (9). The switch of glutamate to lysine at residue 1506 (E1506K) in the SUR1 protein caused a congenital hyperinsulinemia. The mutation reduced the activity of KATP channels, increasing insulin secretion. By early adulthood, the ability of the beta cells to secrete adequate amounts of insulin was exhausted, leading to diabetes (10).

A silent variant in exon 31 of the ABCC8 gene has been associated with high concentrations of insulin in non-diabetic Mexican Americans. The codon AGG is mutated to AGA, but this still codes for the residue arginine (R1273R). The normal and mutant alleles were called G and A, respectively. Among non-diabetics, those who were homozygous for the mutant allele (AA genotype) had higher levels of insulin when fasting, compared with heterozygotes (AG) and normal wild-type (GG). Because type 2 diabetes is more common in Mexican Americans than in the general US population, it has been proposed that individuals with the AA genotype are at a higher risk of diabetes because of an over-secretion of insulin (11).

Two common polymorphisms of the ABCC8 gene (exon 16-3t/c and exon 18 T/C) have been variably associated with type 2 diabetes. However, a recent large case control study in Britain revealed that these ABCC8 variants did not appear to be associated with diabetes (12).

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Background Information

ABCC8 in OMIM

The Human ATP-Binding Cassette (ABC) Transporter Superfamily [www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mono_001.TOC&depth=2] on the Bookshelf

Molecular Biology

ABCC8 in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009237.16&gene=ABCC8&graphiconly=TRUE] | Map Viewer | Domains [www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4507317]: Transmembrane region 1, ATPase 1, Transmembrane domain 2, ATPase 2 | SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6833&view=view&chooseRs=coding&.cgifields=chooseRs] | BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507317&cut=100&org=1] | HomoloGene

The Calpain 10 Enzyme (CAPN10)

Summary

Calpain 10 is a calcium-activated enzyme that breaks down proteins. Variation in the non-coding region of the CAPN10 gene is associated with a threefold increased risk of type 2 diabetes in Mexican Americans. A genetic variant of CAPN10 may alter insulin secretion, insulin action, and the production of glucose by the liver.

Nomenclature

Official gene name: calpain 10
Official gene symbol: CAPN10
Alias: calcium-activated neutral protease

Background

The discovery of CAPN10 marks the first time that screening the entire genome led to the identification of a gene linked to a common and genetically complex disease such as type 2 diabetes.

In 1996, a link was made between a region of chromosome 2 and an increased risk of diabetes in Mexican Americans in Texas, USA (1). The region on the chromosome, located near the end of the long arm of chromosome 2, was named NIDDM1 (Non-Insulin-Dependent Diabetes Mellitus 1). To pinpoint a gene that conferred risk, new statistical techniques were used, and the region was sequenced in greater and greater detail. Four years later, a new diabetes susceptibility gene, CAPN10, was discovered (2).

The new gene encoded the enzyme calpain 10, a member of the calpain family of cysteine proteases. These enzymes are activated by calcium and regulate the functions of other proteins by cleaving pieces off, leaving the altered protein either more or less active. In this way, they regulate biochemical pathways and are involved in intracellular signaling pathways, cell proliferation, and differentiation.

For a detailed description of the action of cysteine proteases, visit Stryer's Biochemistry [www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.section.1170#1192]

Calpains are found in all human cells, and 14 members of the calpain family are now known, many of which are associated with human disease (3). Calpains 1 and 2 are implicated in causing injury to the brain after a stroke and also have been linked to the pathology seen in Alzheimer's disease. Calpain 3 is mainly found in the muscle, and mutations cause limb-girdle muscular dystrophy . Mutations of calpains in the worm *Caenorhabditis elegans* affect sexual development (4), and mutations of a calpain-like gene in the fly cause a degeneration of parts of the nervous system (5).

Calpain 10 was an unexpected find in the search for a putative diabetes susceptibility gene. Its link with diabetes is complex; susceptibility is not attributable to a single variation but to several variations of DNA that interact to either increase, decrease, or have no effect on the risk of developing diabetes. In Mexican Americans, it is thought that the highest risk combination of

these variations (termed 112/121, see below) results in a population-attributable risk of 14%, i.e., 14% of Mexican Americans who have diabetes would not have diabetes if they did not have the high-risk genetic variant CAPN10.

Calpain 10 is an atypical member of the calpain family, and its biological role is unknown. Because CAPN10 mRNA is expressed in the pancreas, muscle, and liver, its role in diabetes may involve insulin secretion, insulin action, and the production of glucose by the liver (2).

Molecular Information

Calpains are found in all human cells and are found throughout the animal kingdom. A BLAST search [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=13186302&cut=100&org=1] using human CAPN10 as a query finds proteins in 18 different species, all of which are multicellular organisms (metazoans). However, potential true homologous genes have been identified only in the mouse.

The calpains consist of a large catalytic subunit and a small regulatory subunit. The large subunit contains four domains (I–IV), and the catalytic center of the cysteine protease is located in domain II. Domain I is the N-terminal domain that is processed when the enzyme is activated, domain III is a linker domain, and the C-terminal domain IV binds calcium and resembles the calcium-binding protein, calmodulin. Domain IV also has characteristic EF-hand motifs (6).

Calpain 10 is an atypical calpain in that it lacks the calmodulin-like domain IV and instead has a divergent C-terminal domain, domain T. Calpains 5 and 6 also have a domain T, and together they form a subfamily of calpains (6).

The CAPN10 gene maps to chromosome 2 (Figure 1). It has 13 exons (coding regions) that span about 30,000 bases (see evidence [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_005416.11&gene=CAPN10&graphiconly=TRUE]) (2). Alternate splicing of the gene creates at least eight transcripts (named isoform a through isoform h), which in turn encode proteins ranging from 138 to 672 amino acids in length.

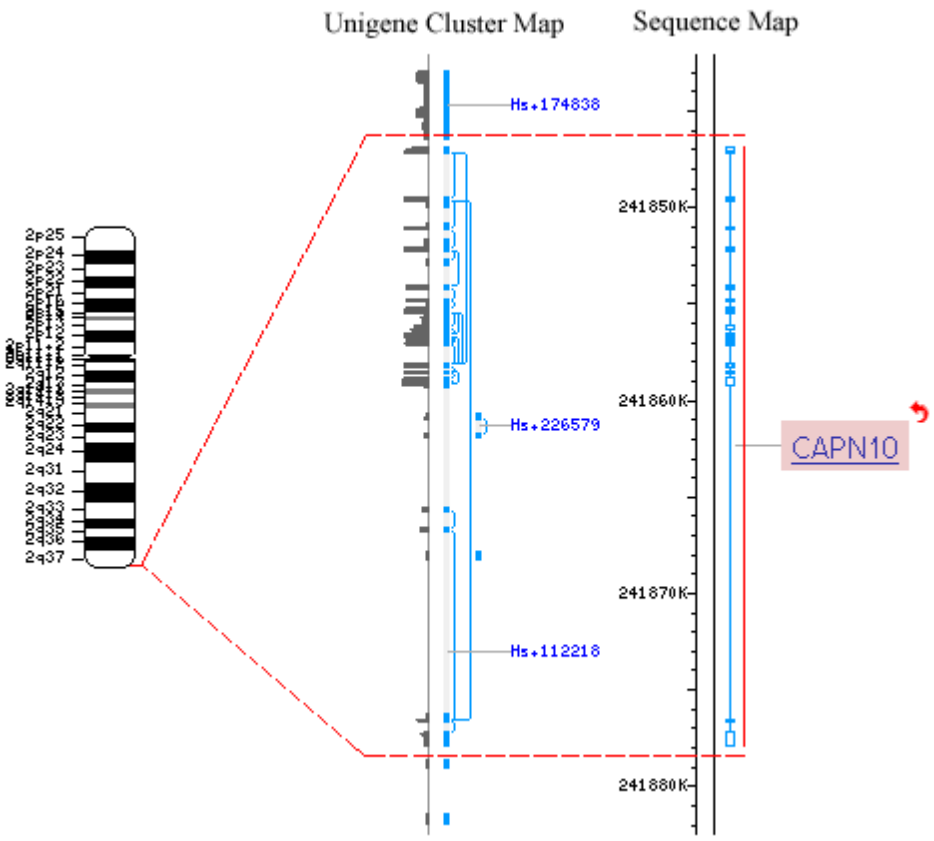

Figure 1: Location of CAPN10 on the human genome.

CAPN10 maps to chromosome 2, between approximately 241,840–241,880 kilobases (kb). Click or here for a current and interactive view of the location of CAPN10 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 CAPN10 may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

Calpain isoform a is the most abdundant isoform. It lacks exons 8, 14, and 15 but remains the longest transcript and encodes a protein of 672 amino acids that is found in all tissues, with the highest levels being found in the heart.

Although the structure of CAPN10 has not yet been solved, mapping the CAPN10 sequence to the crystal structure of human m-caplain (also known as calpain 2 or CAPN2) gives a good estimate of structure. The domains span from residues 1–672 (see domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=13186302]).

Many single nucleotide polymorphisms (SNPs) have been found within the CAPN10 gene. A surprise finding was that the SNPs linked with type 2 diabetes in the Mexican Americans were located in the non-coding regions (introns) of the gene. Usually, SNPs linked with disease occur within the coding regions (exons) of the genes, and they result in a non-synonymous amino acid change. In calpain isoform a, there are four such SNPs (at the time of writing) that cause a switch of amino acids in the mature protein (Figure 2). However, the SNPs of the CAPN10 gene that

have been linked with diabetes are located in introns (introns 3, 6, and 19), and because introns are not transcribed, they do not directly cause an amino acid change. Instead, it is proposed that SNPs in CAPN10 introns may alter risk by affecting the transciptional regulation of calpain 10 (2).

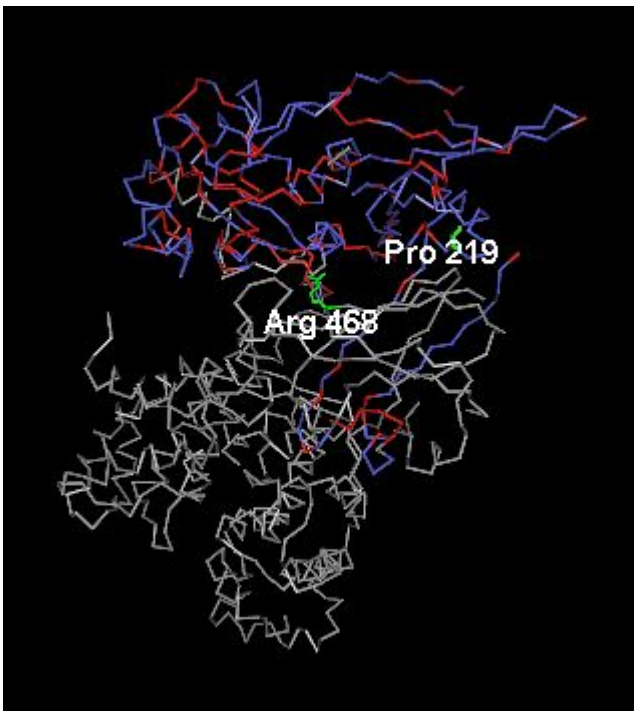

Figure 2: SNP positions of CAPN10 mapped to the 3D structure of human m-calpain.
The figure shows the positions of two of the non-synonymous amino acid changes (green residues) caused by SNPs in the coding sequence.

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)

CAPN10 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on CAPN10 and diabetes, search PubMed.

Over 10% of Mexican Americans are affected by type 2 diabetes. By studying generations of Mexican Americans in Star County, Texas, it was found that SNPs in introns of the calpain 10 gene were associated with an increased susceptibility to diabetes.

Intron 3 of the CAPN10 gene contained SNP-43 (also called UCSNP-43 for University of Chicago SNP-43) in which adenine had been switched to guanine. The high-risk genotype is SNP-43 G/G. SNPs were also found in intron 6 (SNP-19) and intron 13 (SNP-63). Together, these three SNPs interact to affect the risk of diabetes.

With two different versions of the gene at three distinct sites, there are eight possible combinations, but only four combinations of alleles are commonly found. At each SNP site, the allele was labeled "1" and "2". The most common combination in Mexican Americans was 112 on one chromosome and 121 on the other. This 112/121 comination was associated with a three-fold increased risk of diabetes. The high-risk combination also increased the risk of developing dia-

betes in Northern Europeans, but because the at-risk genotype is less common, it has less of a role in determining susceptibility in Europeans. The genotype 112/111 had no effect on the risk of developing diabetes, and the 112/221 combination actually decreased the risk (2).

Similar to the Mexican Americans, the Pima Indians of Arizona have a high prevalence of type 2 diabetes. However, in a study among the Pima Indians, no association was found between the high-risk genotype SNP-43 G/G and an increased prevalence of diabetes, although G/G individuals did have reduced expression of CAPN10 mRNA and showed signs of insulin resistance, which may increase susceptibility to diabetes (7).

In Europe, CAPN10 appears to contribute less to type 2 diabetes. In Britain, there was no association between SNP-43, SNP-19, and SNP-63 and diabetes, but it is possible that SNPs at other sites in the calpain gene may increase the type 2 diabetes risk (8). In a large study in Scandinavians, no association was found between these three SNPs and diabetes (9). In Asia, genetic variation in CAPN10 did not contribute to diabetes in Japan (10) or in the Samoans of Polynesia (11), although variations of CAPN10 may play a role in the risk of diabetes in the Chinese (12, 13).

The biological function of calpain 10 has remained unknown for several years; however, a recent study suggests that calpain 10 may have a critical role in beta cell survival. There are several intracellular stores of calcium; one of these stores contains calcium channels that are sensitive to ryanodine (RyR2). In the beta cell, blocking RyR2 initiates a newly discovered pathway that activates CAPN10 and triggers cell death (14).

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The Glucagon Receptor (GCGR)

Summary

Glucagon is a key hormone in the regulation of glucose levels. As such, the GCGR gene which encodes its receptor is a candidate diabetes susceptibility gene. A mutant glucagon receptor has been associated with diabetes.

Background

Glucagon, like insulin, is a peptide hormone that is secreted by the pancreas. Unlike insulin, glucagon acts to promote the mobilization of fuels, particularly glucose. See Figure 1 for a summary of the actions of insulin and glucagon on their three main target tissues, the liver, muscle, and adipose tissue.

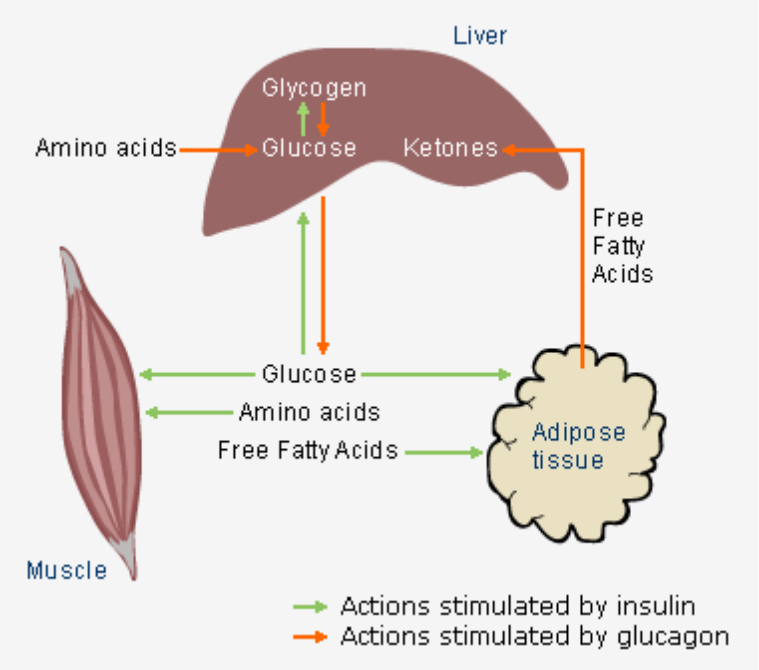

Figure 1: Action of glucagon and insulin on the liver, muscle, and adipose tissue.
Glucagon and insulin have opposing effects on their three main target organs.

Glucagon acts on the liver to stimulate glucose production, either from the breakdown of glycogen (glycogenolysis) or by the fresh production of glucose from the carbon skeletons of amino acids (glucogenogenesis).

In addition to raising blood glucose levels, glucagon also stimulates the formation of ketone bodies. Glucagon does this by stimulating the release of free fatty acids (FFAs) from adipose tissue, and when these enter the liver, glucagon directs their metabolic fate. Instead of being used to make triglycerides (a storage form of lipid), the FFAs are shunted toward beta-oxidation and the formation of ketoacids, which can be used by several organs as an alternative fuel to glucose.

The glucagon receptor is a member of the 7-transmembrane receptor (7TM) family. These receptors have also been called the Serpentine receptors because of the way the single polypeptide chain of the receptor "snakes" back and forth across the cell membrane. This diverse family of receptors not only responds to hormones such as glucagon but also transmits many other signals including light, smell, and neurotransmitters.

Read more about 7TM receptors in Stryer's Biochemistry [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.section.2055]

When glucagon outside of the cell binds to the glucagon receptor, it induces a conformational change in the receptor that can be detected inside the cell. The activated receptor stimulates intracellular cAMP production, which in turn stimulates protein kinase A (PKA) to phosphorylate many target proteins, including two enzymes that lead to the breakdown of glycogen and inhibit further glycogen synthesis.

Molecular Information

The GCGR gene maps to chromosome 17 (Map Viewer). It has 14 exons (coding regions) that span around 10,700 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_079568.1&gene=GCGR&graphiconly=TRUE]). The 7TM receptor encoded by this gene is also known as a G protein coupled receptor because a G protein (guanyl nucleotide-binding protein) conveys an intermediate step in signal transduction.

In the unactivated state, the G protein coupled to the glucagon receptor exists as a heterotrimer consisting of α, β, and γ subunits. The α subunit (Gα) binds GDP. Many different G proteins exist, and for the glucagon receptor, because the activated Gα subunit stimulates adenylate cyclase, the receptor is classified as a Gαs receptor ("s" for stimulatory effect of the subunit).

Binding of glucagon initiates the exchange of Gαs-bound GDP for GTP. The G protein then dissociates into Gα and a Gβγ dimer; the latter transmits the signal that the receptor has bound its ligand. A single glucagon receptor can activate many G proteins, leading to a greatly amplified signal.

The signal from an occupied glucagon receptor is "switched off" when the Gα hydrolyzes the bound GTP back to GDP, and the GDP-bound Gα can now reassociate with Gβγ to reform the heterotrimeric protein.

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503947&cut=100&org=1] using human GCGR as a query finds proteins in 35 different species, which are all metazoans (multicellular organisms). However, potential true homologous genes have thus far been identified only in the mouse, rat, and fruit fly.

GCGR and Diabetes: Digest of Recent Articles

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

A missense mutation in the glucagon receptor gene has been associated with decreased tissue sensitivity to glucagon and type 2 diabetes (1, 2).

A Gly40Ser mutation of the receptor gene was linked with type 2 diabetes in French and Sardinian patients. The mutation occurs in exon 2 and disrupts an extracellular region of the receptor (1).

When the signaling properties of the Gly40Ser mutant receptor were examined, it was found that the mutant receptor bound glucagon with a threefold lower affinity compared with the wild-type receptor. In addition, the production of cAMP in response to glucagon was decreased, and glucagon-stimulated insulin secretion was also decreased (2). Decreased insulin secretion was observed in Gly40Ser carriers in a Brazilian population, but the mutant receptor was not associated with type 2 diabetes (3).

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The glucagon receptor in OMIM

Molecular Biology

Gene name in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_079568.1&gene=GCGR&graphiconly=TRUE] | Map Viewer | Domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4503947]: Hormone receptor, 7 Transmembrane domain | SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=2642&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503947&cut=100&org=1] | HomoloGene

The Enzyme Glucokinase (GCK)

Summary

Glucokinase, encoded by the GCK gene speeds up glucose metabolism and acts as a "glucose sensor" in the beta cell. Mutant glucokinase causes a rare form of diabetes and may also play a role in type 2 diabetes.

Nomenclature

Official gene name: Glucokinase
Official gene symbol: GCK
Alias: GK, hexokinase IV, HK4, Maturity Onset Diabetes in the Young type 2, MODY2

Background

The enzyme glucokinase catalyzes glucose metabolism in the liver and in the pancreatic beta cell. Glucokinase traps glucose inside the cell by catalyzing its phosphorylation to produce glucose-6-phosphate. This is the first and rate-limiting step in glycosis, a pathway that produces energy in the form of ATP from glucose.

Glucokinase (also called hexokinase IV) differs from the other hexokinases that are found in other tissues. First, glucokinase has a lower affinity for glucose. This allows other organs such as the brain and muscles to have first call on glucose when their supply is limited. A second feature is that glucokinase is not inhibited by its product, glucose-6-phosphate. This lack of negative feedback inhibition enables hepatic glucokinase to remain active while glucose is abundant, ensuring that the liver can continue removing glucose from the blood ensuring that no glucose goes to waste.

Glucokinase is proposed to be an important "glucose sensor" in the following way. The rate of glucose metabolism is determined by the rate of glucose phosphorylation, which is catalyzed by glucokinase in the liver and pancreas. The liver and pancreas also express glucose transporter-2 (GLUT2), an insulin-independent cellular protein that mediates the transport of glucose into cells. The capacity of GLUT2 to transport glucose is very high, facilitating rapid equilibrium between extracellular and intracellular glucose. Thus, in effect, the extracellular glucose concentrations are sensed by glucokinase.

By catalyzing the rate-limiting step of glucose metabolism in the liver, glucokinase enables the liver to buffer the rise in glucose that takes place after a meal. In the pancreas, glucokinase is the glucose sensor for insulin release. The threshold for glucose-stimulated insulin release is about 5 mmol/l (1). Mutations of GCK that alter this threshold manifest as three different syndromes and highlight the importance of GCK in glucose homeostasis and diabetes:

1. Activating mutations lower the beta cell threshold for insulin release to as low as 1.5 mmol/l of glucose, leading to an increase in insulin release. This manifests as persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (2).

2. Inactivating mutations raise the beta cell threshold for insulin release. If two alleles altered by inactivating mutations are inherited, the level of glucose needed to stimulate insulin release from the pancreas is extremely high. Affected individuals present with diabetes at birth (permanent neonatal diabetes) (3, 4).

3. Maturity onset diabetes in the young, type 2 (MODY2) is caused by inheriting one allele that has been altered by an inactivating mutation. This partial inactivation leads to an increase in glucose-stimulated insulin release to about 7 mmol/l. This causes a mild hyperglycemia that is present at birth but often is only detected in later life (5).

Because of its role as a glucose sensor, GCK is a candidate susceptibility gene for type 2 diabetes.

Molecular Information

The hexokinase family consists of several enzymes that are all evolutionarily related. In vertebrates, there are four hexokinases named I to IV. Glucokinase is a distinct member of this family.

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503951&cut=100&org=1] using human GCK as a query finds proteins in 46 different species, which range from metazoa (multicellular organisms), fungi, plants, and other eukaryotes. Potential true homologous genes have thus far been identified in the mouse, rat, fly, mosquito, nematode worm, and the plant, mouse-ear cress.

The GCK gene maps to chromosome 7 (Figure 1). It has 12 exons (coding regions) that span around 46,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_007819.14&gene=GCK&graphiconly=TRUE]). There are three GCK transcript variants that differ in their first exon, and their expression is tissue specific. One isoform predominates in the pancreatic beta cells; the other two isoforms are found in the liver. The glucokinase enzyme is found in the outer membrane compartment of mitochondria in these tissues.

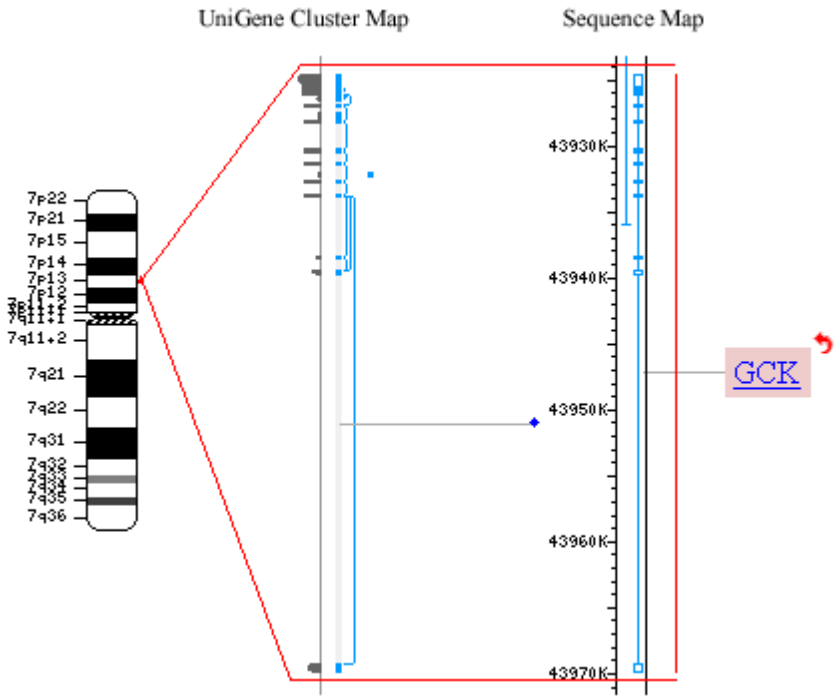

Figure 1: Location of GCK on the human genome.

GCK maps to chromosome 7, between approximately 43,000–44,000 kilobases (kb). Click or here for a current and interactive view of the location of GCK 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 GCK may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

GCK and Diabetes: Digest of Recent Articles

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

Mutations known to activate glucokinase include a switch of amino acids at position 455 (Val to Met) (6) and position 456 (Ala to Val) (7). These mutations are all clustered in one area of the glucokinase structure that is remote from the substrate binding site, and this region has been termed the allosteric activator site. Because naturally occurring mutations at this site are associated with an increase in insulin release, the search began for pharmacological allosteric activators that could increase GCK activity, increase the release of insulin, and be used in the treatment of diabetes.

The metabolic changes that take place in type 2 diabetes include impaired insulin secretion from the pancreas and increased glucose production by the liver. In turn, studies of gluckokinase activators (GKAs) appear to show a dual mechanism of action: they increase the release of insulin from the pancreas and stimulate the use of glucose in the liver, thus making GKAs ideal candidates for diabetes therapy (8, 9).

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Link Roundup

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Gene name in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_007819.14&gene=GCK&graphiconly=TRUE] | Map Viewer | Domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=15967159] | SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=2645&view+rs+=view+rs+&chooseRs=all&.cgifields=chooseRs] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503951&cut=100&org=1] | HomoloGene

The Glucose Transporter GLUT2

Summary

The GLUT2 gene encodes a glucose transporter which regulates the entry of glucose into pancreatic beta cells and is thought to be a "glucose sensor". Mutations of GLUT2 cause a rare genetic syndrome that disrupts blood glucose regulation. Common variants of GLUT2 may be linked with type 2 diabetes.

Nomenclature

Official gene name: solute carrier family 2 (facilitated glucose transporter), member 2
Official gene symbol: SLC2A2
Alias: glucose transporter 2, GLUT2

Background

The family of glucose transporter proteins transports glucose across plasma membranes. The proteins are facilitative transporters carrying glucose across membranes without requiring energy. Each member of the family has its own specialized function and tissue distribution.

For a summary of the family of glucose transporters, named GLUT1 to GLUT5, read Stryer's Biochemistry [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.section.2245#2255].

Beta cells in the pancreas express GLUT2. The transporter has a low affinity for glucose, requiring a high concentration of glucose to achieve half its maximal rate of transport (high K_m). This enables the beta cell to only begin the insulin secretion cascade during times of plenty. By regulating the entry of glucose into the beta cell, it has been proposed that GLUT2 is an important "glucose sensor" (1, 2).

GLUT2 is also found in the liver and transports glucose both into and out of liver cells. It allows the liver to buffer changes in glucose concentration after a meal. GLUT2 has a high capacity for glucose, so once the glucose levels have risen, the liver can quickly remove large amounts of glucose from the blood into the liver cells.

Mutations in the gene that encodes GLUT2, called SLC2A2, cause an extremely rare genetic syndrome called Fanconi-Bickel syndrome (FBS) (3). FBS was named for the scientists who first described the condition in 1949, and since then over 100 cases have been observed. Affected individuals may exhibit hyperglycemia in the fed state and/or hypoglycemia during fasting.

Hyperglycemia in FBS may involve inappropriate glucose uptake into the liver and this hyperglycemia could be further enhanced by inappropriate insulin secretion by the pancreas. The rise in liver intracellular glucose may inhibit the breakdown of glycogen, leading to low levels of glucose in the blood and increased levels of glycogen stored in the liver. A transport defect of the kidneys also leads to the loss of glucose in the urine which further worsens the hypoglycemia.

Whereas mutations of SLC2A2 cause a rare genetic syndrome that disrupts glucose regulation, it it possible that variations of this gene may also be involved in type 2 diabetes, a common form of diabetes.

Molecular Information

The GLUT2 gene maps to chromosome 3 (Figure 1). It has 11 exons (coding regions) that span about 31,400 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_005612.14&gene=SLC2A2&graphiconly=TRUE]).

Members of the glucose transporter family each consist of a single polypeptide of about 500 residues long. This peptide crosses the membrane several times, and there are typically 12 transmembrane segments. The translocation of glucose across the membrane is thought to involve inward-facing and outward-facing glucose binding sites that are located in transmembrane segments 9, 10, and 11 of the GLUT protein. Mutations of these regions severely impair glucose transport (4-6).

A highly conservered motif, (R)XGRR, is found not only in the facilitative glucose transporters but also in the sugar transport superfamily (7). Mutations that disrupt this conserved sequence result in the Fanconi-Bickel syndrome (3).

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6514&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the GLUT2 gene, four (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein. One of these variants (T110I) may be associated with type 2 diabetes status (8), and different variants have been associated with the Fanconi-Bickel syndrome (view known allelic variants).

The problem of fuel transport appears to have been solved early in evolutionary terms. A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557851&cut=100&org=1] using human SLC2A2 as a query finds proteins in 55 different species that include sugar transporters in organisms as diverse as bacteria, fungi, plants, and multicellular species (metazoa). However, potential true homologous genes have thus far been identified only in the mouse and rat.

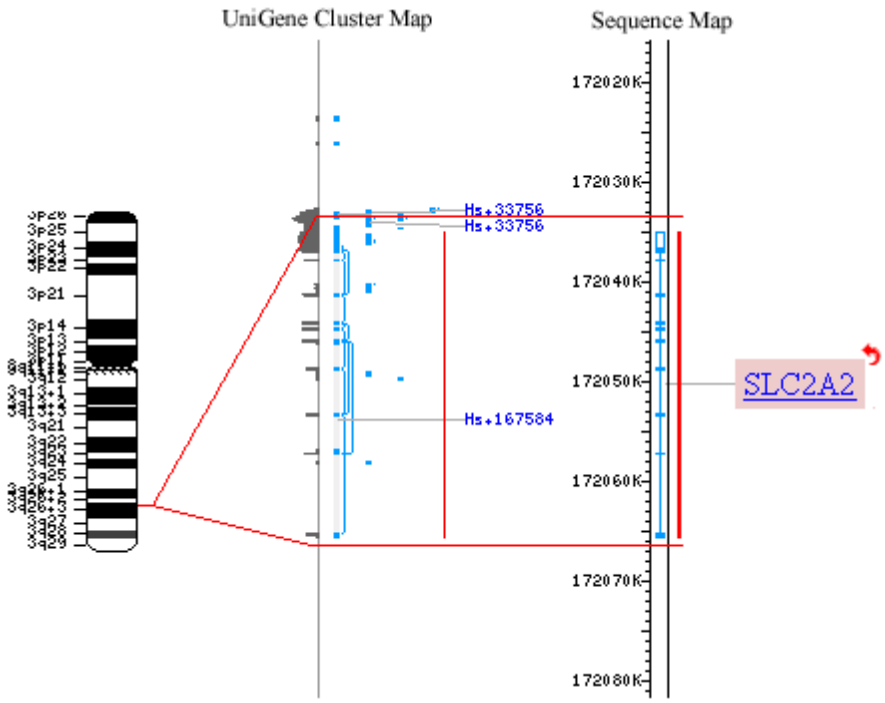

Figure 1: Location of SLC2A2 on the human genome.

SLC2A2 maps to chromosome 3, between approximately 172,030–172,070 kilobases (kb). Click or here for a current and interactive view of the location of SLC2A2 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 SLC2A2 may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

SLC2A2 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on SLC2A2 and diabetes, search PubMed.

SLC2A2 is a likely candidate gene for type 2 diabetes because it is a high K_m transporter that regulates entry of glucose in the pancreatic beta cell and triggers insulin secretion.

In one diabetic patient, a mutation that disrupts a highly conserved valine in the 5th membrane spanning domain of GLUT2 was found (3, 9). The valine at position 197 was switched to an isoleucine residue (V197I). Expression of this mutant protein in Xenopus oocytes abolished the transporter activity of GLUT2, suggesting that defects in GLUT2 may have a causative role in the development of diabetes (10).

Many studies have been unsuccessful in finding evidence of association between SNPs in the SLC2A2 gene and type 2 diabetes (11-13). One SNP that may be significant is a threonine to isoleucine switch at residue 110 (T110I), which occurs in the second membrane spanning domain of GLUT2. This SNP is present equally in diabetics and non-diabetics (9), but in one additional study a modest association between the T110I variant and type 2 diabetes was observed (8). The functional role of this polymorphism remains unclear as the variant protein appears to have similar levels of expression and does not seem to disrupt glucose transporter activity (10).

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The Transcription Factor HNF4A

Summary

The HNF4A gene encodes a transcription factor that is found in the liver and pancreas. Because HNF4A maps to a region of chromosome 20 that is linked with type 2 diabetes and because mutations of this gene cause a rare form of autosomal dominant diabetes, the HNF4A gene is considered to be a strong candidate for involvement in type 2 diabetes.

Nomenclature

Official gene name: hepatocyte nuclear factor 4 alpha
Official gene symbol: HNF4A
Alias: transcription factor 14, TCF14

Background

The expression of a wide range of genes in the liver is regulated by the transcription factor HNF4A (hepatocyte nuclear factor 4 alpha). Many functions that the liver carries out may appear and disappear, depending on whether HNF4A is expressed. In addition, HNF4A controls the expression of another transcription factor; hepatocyte nuclear factor 1α (HNF1A), which in turn regulates the expression of several important genes in the liver.

As the name suggests, hepatocyte nuclear factor 4 is found in abundance in the liver, but it is also found in the beta cells of the pancreas, the kidneys, and intestines. Together with other transcription factors such as HNF1A and HNF1B (encoded by TCF1 and TCF2, respectively), they make up part of a network of transcription factors that function together to control gene expression in the developing embryo. In particular, HNF4A is thought to play an important role in the development of the liver, kidney, and intestines.

In pancreatic beta cells, this network of transcription factors regulates the expression of the insulin gene. In addition, HNF4 and HNF1 regulate the expression of several other genes linked with insulin secretion, e.g., genes that encode proteins involved in glucose transport and glucose metabolism (1, 2).

Mutations of HNF4A can cause an extremely rare form of diabetes, maturity onset diabetes in the young (MODY). Whereas type 2 diabetes is a disorder usually of late onset with significant genetic basis, MODY by definition occurs in the young (onset at age less than 25 years) and is inherited in an autosomal dominant fashion.

Patients with MODY caused by HNF4A mutations exhibit a normal response to insulin (they are not insulin resistant) but do show an impaired response to secreting insulin in the presence of glucose. Over time, the amount of insulin secreted decreases, leading to diabetes. Affected individuals are usually treated with oral hypoglycemic agents, but up to 40% of patients may require insulin. This form of diabetes is extremely rare and has only been identified in 13 families (3).

The HNF4A gene is suspected to play a role in type 2 diabetes. Because a mutation of this gene causes a rare form of diabetes and because the gene maps to an area of chromosome 20 that has been linked with type 2 diabetes, it is speculated that particular HNF4A haplotypes may be associated with altered insulin secretion.

Molecular Information

Hepatocyte nuclear factors (HNFs) are a heterogeneous class of evolutionarily conserved transcription factors that are required for cellular differentiation and metabolism. HNF4A is an orphan receptor; the ligand(s) that binds to this receptor is unknown (4).

A BLAST search [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=31077205&cut=100&org=1] using human HNF4A as a query finds proteins in 47 different species, which are all multicellular species (metazoans). However, potential true homologous genes have thus far been identified in the mouse, rat, and nematode worm.

The HNF4A gene maps to chromosome 20 (Figure 1). It has 11 exons (coding regions) that span over 30,000 bases (see evidence [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_011362.8&gene=HNF4A&graphiconly=TRUE]). There are at least three different transcript variants of this gene, which encode three different protein isoforms (a, b, and c). The longest mRNA transcript, NM_000457, encodes the longest HNF4A protein (isoform b), containing over 450 amino acids.

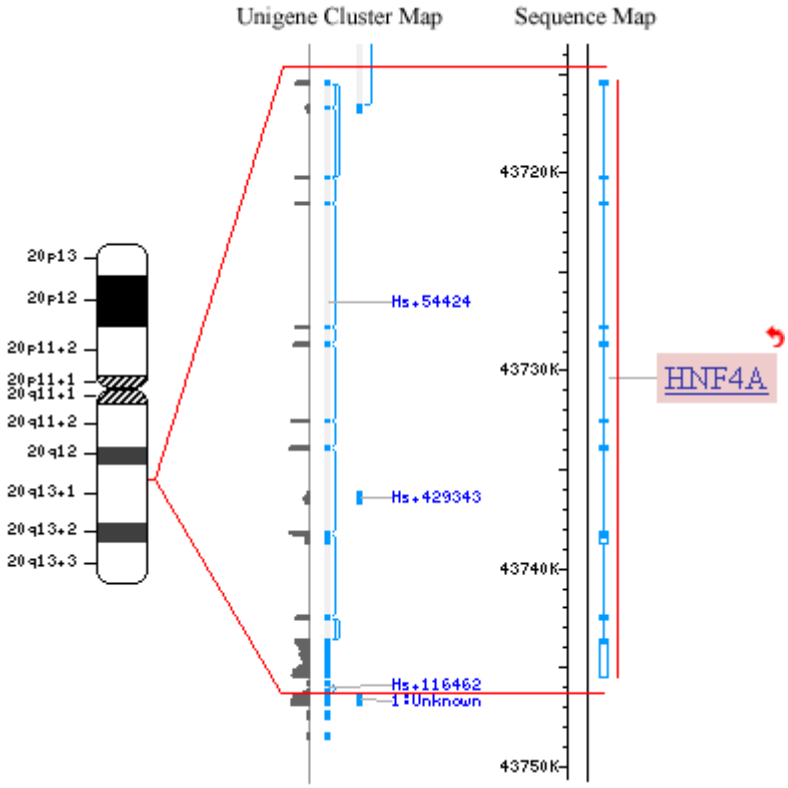

Figure 1: Location of HNF4A on the human genome.

HNF4A maps to chromosome 20, between approximately 43,700–43,750 kilobases (kb). Click or here for a current and interactive view of the location of HNF4A 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 HNF4A may fluctuate. Therefore, the live Web site may not appear exactly as in this figure.

Several single nucleotide polymorphisms (SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3172&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the HNF4A gene (Figure 2). At the time of writing, three non-synonymous amino acid changes caused by SNPs have been observed in the longest protein isoform (isoform b). At present, none of these SNPs have been associated with either type 2 diabetes or MODY (see known allelic variants). However, several SNPs upstream of the coding region have been associated with both MODY and type 2 diabetes (see below).

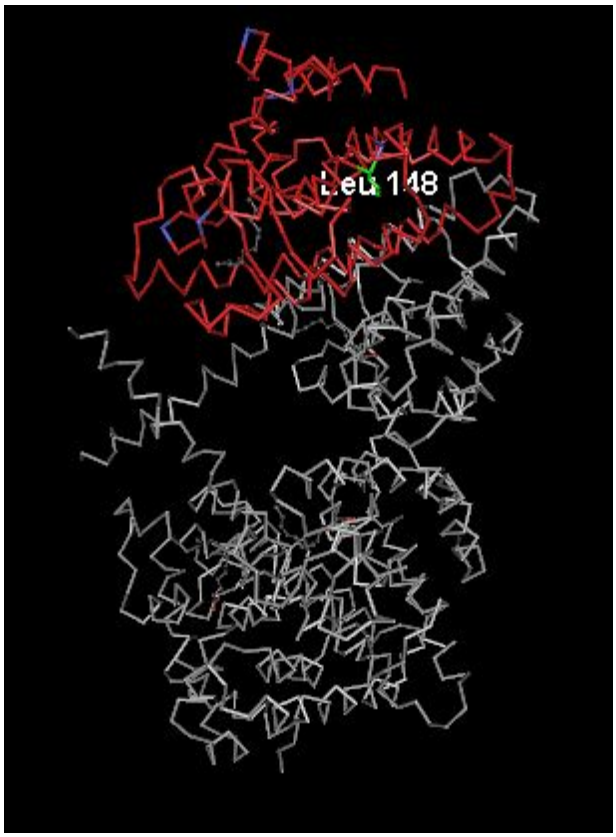

Figure 2: SNP positions of HNF4A mapped to the 3D structure of the ligand-binding domain of rat HNF4A. The figure shows the positions of a non-synonymous amino acid change (Leu148) caused by a SNP in the coding sequence.

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)

HNF4A and Diabetes: Digest of Recent Articles

For a more complete list of research articles on HNF4A and diabetes, search PubMed.

It has been proposed that the pancreatic beta cell is sensitive to the amount of HNF4A present (5). A variety of nonsense and missense mutations in HNF4A cause MODY, where a decline in insulin secretion occurs. Similarly, SNPs of the gene may have an impact on the beta cell function, increasing or decreasing insulin secretion.

In one British study, a haplotype that was linked with reduced disease risk was identified (5). Individuals with the "reduced risk" haplotype were significantly associated with increased insulin secretion. These individuals also showed a trend toward lower fasting glucose levels and 2-hour plasma glucose levels. This finding led to the speculation that a particular HNF4A haplotype might be associated with increased insulin secretion capacity and protection against diabetes.

Genetic variants associated with increased diabetes risk have been identified upstream of the HNF4A coding region, in a recently discovered alternative promoter called P2. P2 lies 46 kb upstream of the P1 promoter, and while both promoters are involved in the transcription of HNF4A, they seem to have different roles in different cells. Transcripts from both P1 and P2 have been found in the pancreas, but the P2 promoter is thought to be the primary transcription site in the beta cells and a mutation of P2 is a cause of MODY (6).

In the search for genetic variation near the HNF4A gene, two studies, one of the Ashkenazi Jew population (7), and the other of the Finnish population (8), identified four SNPs that were associated with type 2 diabetes. These SNPs (named rs4810424, rs1884613, rs1884614, and rs2144908) flanked the P2 promoter and were associated with type 2 diabetes risk in both study populations, and the risk of diabetes attributed to each SNP was very similar between the two populations.

The mechanism by which SNPs near and in the HNF4A gene increases the risk of diabetes is not yet known. Perhaps because many HNF transcription factors can bind directly to the P2 promoter, any alteration of the binding sites for these factors could disrupt the regulation of HNF4A expression. Whereas both P1 and P2 promoters are used in liver cells, mainly P2 is used in pancreas cells, leading to SNPs affecting the P2 promoter disproportionately affecting HNF4A expression in the pancreas, in turn leading to beta cell malfunction and diabetes (9).

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The Insulin Hormone (INS)

Summary

The INS gene gene encodes the precursor to the hormone insulin. Genetic 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 insulin precursors. 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 the 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.

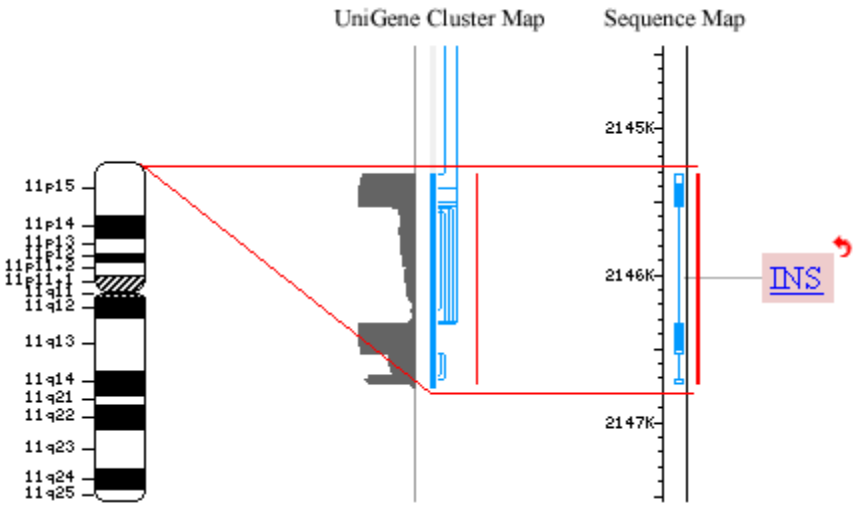

Figure 1: Location of INS on the human genome.

INS maps to chromosome 11, approximately between 2,144–2,148 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.

INS and Diabetes: Digest of Recent Articles

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

There is conflicting evidence for the role of the insulin gene in type 2 diabetes predisposition. The gene contains a variable number of tandem repeats, and it has been proposed that the number of repeats may have an impact on birth weight and diabetes susceptibility (2).

In one study, a DNA variant in the 3' untranslated region of the INS gene was associated with type 2 diabetes risk (3).

Certain mutations of the insulin gene can result in a rare form of diabetes. One form of mutant insulin, called Chicago insulin, has been found in individuals who have diabetes that resembles MODY. This form of diabetes is rare; it is caused by a single gene (is monogenic) and is inherited in an autosomal dominant fashion.

Mutations of insulin affecting the phenylalanine amino acid at position 24 or 25 of the B chain (B24 or B25) are associated with diabetes. In Chicago insulin, B25 is mutated to leucine (4-6), or B24 is mutated to serine (7). The phenylalanine at position 24 is highly conserved, and in crystal structures of insulin, the aromatic ring of this amino acid is important in anchoring the region of the insulin that binds to the insulin receptor (8).

Point mutations of INS can also result in increased levels of proinsulin (proinsulinemia) (9). A switch from arginine to histidine at amino acid position 65 results in proinsulinemia, when it is probable that the mutation of arginine 65 disrupts the site at which the C-peptide is cleaved by beta cell proteases to produce insulin from proinsulin. This mutation does not appear to impair glucose tolerance in heterozygous carriers (10, 11).

Other point mutations of arginine 65 have been found in individuals with type 2 diabetes and a raised level of insulin and/or proinsulin (12, 13). However, one of the individuals had a Arg65Pro mutation that was not thought to be linked to their diabetes, because the mutation was present in a non-diabetic daughter and absent in a daughter who had had gestational diabetes (13).

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The Insulin Receptor (INSR)

Summary

The INSR gene encodes the receptor for insulin. Mutations of the insulin receptor can cause rare forms of diabetes and may play a role in susceptibility to type 2 diabetes.

Background

Some receptors found on the surfaces of cells are directly linked to enzymes located inside the cell. The insulin receptor belongs to the largest family of such enzyme-linked receptors, known as the receptor protein-tyrosine kinase (RTK) family.

More than 50 RTKs have been identified, and they share a common structure: an N-terminal extracellular domain containing a ligand-binding site, a single transmembrane α helix, and a C-terminal cytosolic domain with protein-tyrosine kinase activity.

Receptor tyrosine kinases in Molecular Cell Biology [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=mcb.section.5803]

Most of the RTKs consist of single polypeptides, and in response to ligand binding, they dimerize. An exception is the insulin receptor that exists as a dimer in the absence of its ligand. After the ligand has bound to and activated its receptor, the tyrosine kinase activity of the cystolic domain of the RTK is activated. Each kinase phosphorylates specific tyrosine residues in the cytosolic domain of its dimer partner, a process termed autophosphorylation.

Autophosphorylation occurs in two stages. First, tyrosine residues near the catalytic site are phosphorylated. In the insulin receptor, this results in a conformational change that permits ATP binding, and it may also increase the receptor protein kinase activity. The receptor kinase then phosphorylates other tyrosine residues outside the catalytic domain, creating phosphotyrosine residues that serve as docking ports for additional proteins that transmit intracellular signals downstream of the activated receptors.

Read more on the signal pathways initiated by insulin binding in Molecular Cell Biology [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=mcb.section.5890#5898]

One important docking protein in the insulin receptor is IRS1 (insulin receptor substrate 1). IRS1 binds to the phosphotyrosine residues in activated receptors via its Src homology 2 (SH2) domains. Binding of insulin to its receptor can initiate two distinct signaling pathways: one that includes Ras, and one that does not. The initiation of both pathways appears to involve IRS1.

Molecular Information

The insulin receptor is a dimer, consisting of two polypeptide chains that are linked by disulfide bonds. Each polypeptide contains an alpha subunit (extracellular) and a beta subunit (transmembrane and intracellular). The alpha and beta subunits are encoded by a single gene, INSR, which maps to chromosome 19 (Figure 1). It has 23 exons (coding regions) that span about 180,000

bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_011255.14&gene=INSR&graphiconly=TRUE]). The INSR gene encodes a precursor that starts with an 27-amino acid signal sequence, followed by the receptor alpha subunit, the cleavage site of the processing enzyme, and the receptor beta subunit (1).

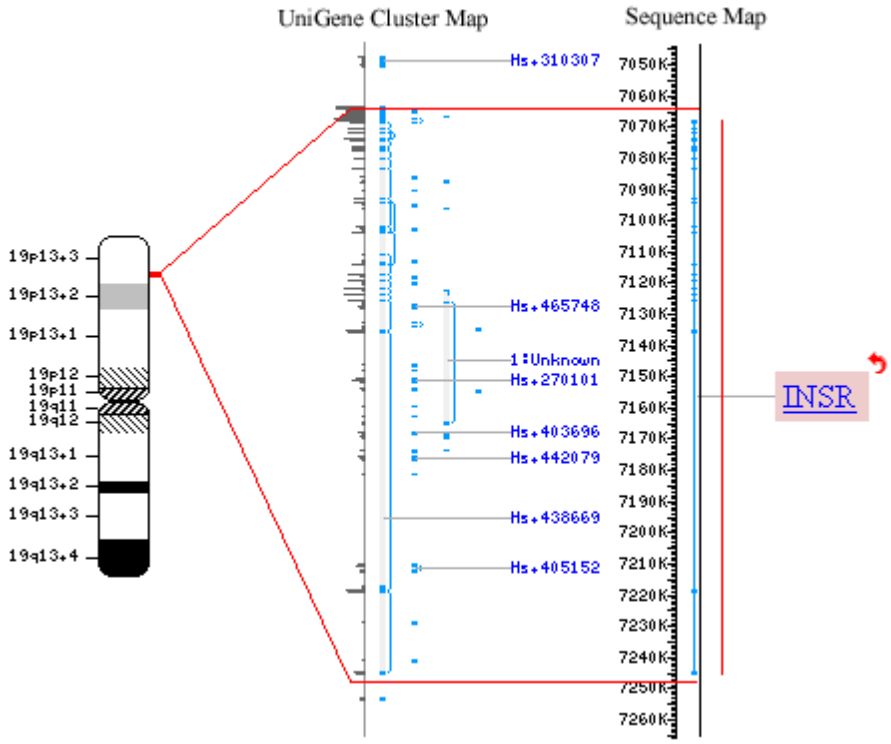

Figure 1: Location of INSR on the human genome.

INSR maps to chromosome 19, between approximately 6,700–7,500 kilobases (kb). Click or here for a current and interactive view of the location of INSR 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 INSR may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

Depending upon where the insulin receptor is expressed, there are differences in its composition. The alpha subunit found in INSR in the liver differs from its form in muscle and adipose tissue in terms of molecular weight, carbohydrate composition, and antigenicity (2). The level of activity of its tyrosine kinase may also differ, depending on the tissue in which the receptor is expressed. The mechanism underlying receptor heterogeneity is unknown.

Alternative splicing of exon 11 of the INSR gene generates two insulin receptor isoforms, INSR type a (without exon 11) and INSR type b (with exon 11). These two transcripts are expressed in a highly regulated fashion and predominate in different tissues (3). There is evidence that selectivity in the action of insulin may be brought about by the two INSR isoforms (4).

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3643&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the INSR gene, one (at the time of writing) of which causes non-synonymous amino acid changes in the mature protein (Figure 2). This protein variant has not been associated with observed cases of disease (see known allelic variants).

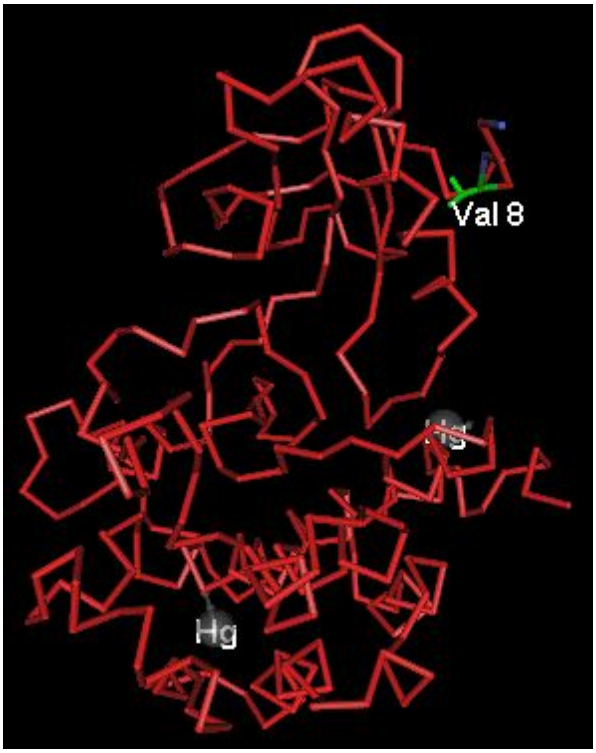

Figure 2: SNP positions of INSR mapped to the 3D structure of a mutant human insulin receptor.
The figure shows the position of a non-synonymous amino acid changes (green residue) caused by a SNP in the coding sequence.

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)

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557884&cut=100&org=1] using human INSR as a query finds proteins in 42 different species, which are all metazoans apart from two viruses. However, potential true homologous genes have thus far been identified only in the mouse, rat, and mosquito.

INSR and Diabetes: Digest of Recent Articles

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

Mutations in INSR lead to a variety of rare clinical syndromes ranging in severity from Leprechaunism (usually fatal within the first 2 years of life), Rabson-Mendenhall syndrome (survival into the second decade), and type A insulin resistance (survival into middle age and beyond).

Resistance to insulin is one of the characteristics of type 2 diabetes. However, most diabetics have a normal sequence of the insulin receptor, indicating that if insulin receptor mutations contribute to the development of type 2 diabetes, they will be present only in a minor fraction of the diabetic population.

Several variants of the insulin receptor have been associated with hyperglycemia and type 2 diabetes (5, 6). A heterozygous mutation changing Val-985 into methionine has been found to be more common in type 2 diabetics than in controls; the relative risk for diabetes was over 4% for Met-985 carriers. The prevalence of the mutation increased with increasing serum glucose levels, suggesting a role for this receptor variant in hyperglycemia.

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The Potassium Channel KCNJ11

Summary

Closure of potassium channels in the beta cells of the pancreas triggers the release of insulin. Drugs that close the channel are used in the treatment of diabetes. Variation of the KCNJ11 gene which encodes this channel has been linked to both increased and decreased insulin release.

Nomenclature

Official gene name: potassium inwardly-rectifying channel, subfamily J, member 11
Official gene symbol: KCNJ11
Alias: inwardly rectifying potassium channel, KIR6.2; beta-cell inward rectifier subunit, BIR; ATP-sensitive inward rectifier potassium channel 11, IKATP

Background

Similar to all cells, pancreatic beta cells maintain a concentration gradient of electolytes (e.g., potassium, sodium, and calcium) across their membranes. Ion pumps create the gradient by pushing sodium (Na^+) out of cells and potassium (K^+) into cells. This produces a membrane polarity; the inner side of the membrane has a negative charge of around -70 mV. To maintain the membrane potential and to be able to alter it, specific proteins called ion channels span the membrane and regulate the passage of ions.

The release of insulin is controlled by ion channels that conduct K^+ and are sensitive to ATP (KATP channels). A rise in glucose and the corresponding rise in ATP shuts the KATP channels, which increases the membrane potential to -40 mV. This state, known as depolarization, opens calcium channels, and the entry of Ca^{2+} into the cell triggers the secretion of insulin (Figure 1).

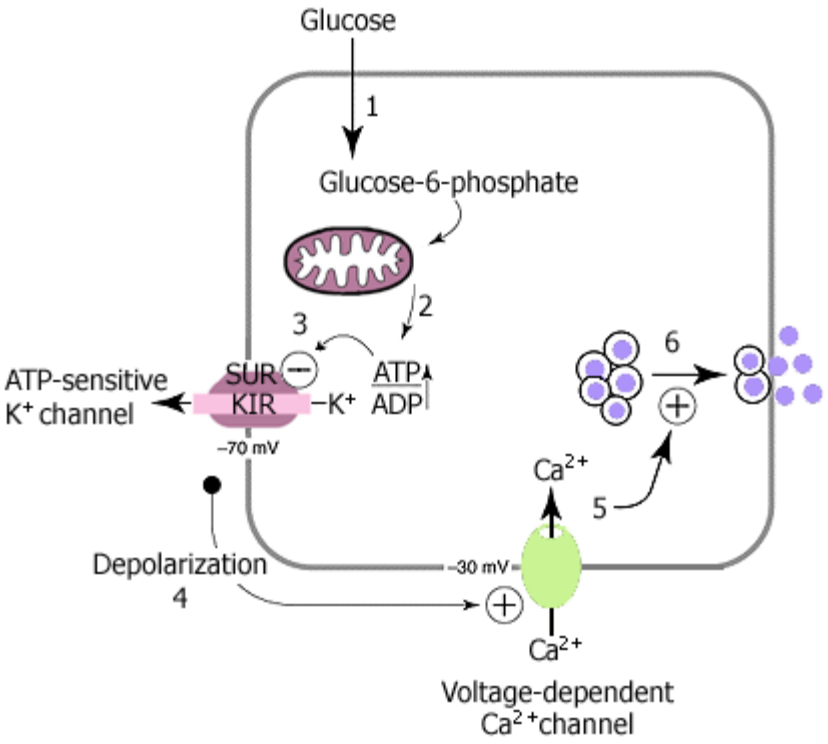

Figure 1: Insulin secretion.

1. Glucose is transported into the beta cell by type 2 glucose transporters (GLUT2). Once inside, the first step in glucose metabolism is the phosphorylation of glucose to produce glucose-6-phosphate. This step is catalyzed by hexokinase; it is the rate-limiting step in glycolysis, and it effectively traps glucose inside the cell.

2. As glucose metabolism proceeds, ATP is produced in the mitochondria.

3. The increase in the ATP:ADP ratio closes ATP-gated potassium channels in the beta cell membrane. Positively charged potassium ions (K^+) are now prevented from leaving the beta cell.

4. The rise in positive charge inside the beta cell causes depolarization.

5. Voltage-gated calcium channels open allowing calcium ions (Ca^{2+}) to flood into the cell.

6. The increase in intracellular calcium concentration triggers the secretion of insulin via exocytosis.

Drugs (e.g., sulfonylureas) that close beta cell KATP channels are used to treat type 2 diabetes. They are referred to as "oral hypoglycemic agents" because they are taken by mouth and stimulate the release of insulin, which lowers blood sugar levels.

The KATP channel consists of two types of subunit: a K^+-channel subunit (termed Kir6.2), and a sulfonylurea receptor subunit (SUR), which is a member of the family of ATP-binding cassette (ABC) transporter proteins. The potassium channel is made from four Kir6.2 subunits and four SUR subunits (1).

The Kir6.2 subunit is encoded by the KCNJ11 gene. The four Kir6.2 subunits form the pore of the channel through which K^+ passes and also contains the ATP-binding sites. The ABCC8 gene encodes the SUR subunit. The four SUR subunits modulate the activity of the channel and contain the binding site of the sulfonylurea drugs.

Mutations in either KCNJ11 or ABBC8 can reduce KATP channel activity, leading to increased insulin release and low blood sugar levels, a rare disorder called persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (2-4). In contrast, mice that have targeted overactivity of the KATP channel have severe diabetes (5), and in humans, activating mutations of KCNJ11 cause permanent neonatal diabetes (6).

Molecular Information

The KCNJ11 gene maps to chromosome 11 (Figure 2). It has only one exon (coding region) that spans about 2000 bases (2 kilobases, or 2 kb) and does not contain introns (non-coding regions) (see evidence) [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009237.16&gene=KCNJ11&graphiconly=TRUE]. The gene encodes a protein of 390 amino acids and two transmembrane segments.

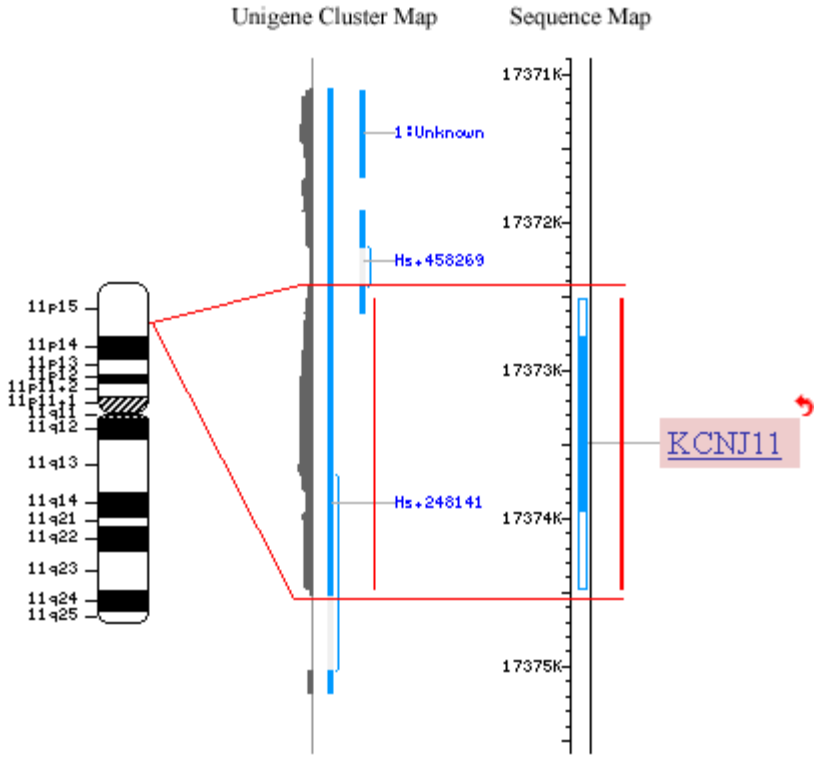

Figure 2: Location of KCNJ11 on the human genome.

KCNJ11 maps to chromosome 11, between approximately 17,372–17,375 kilobases (kb). Click or here for a current and interactive view of the location of KCNJ11 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 KCNJ11 may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

Each Kir6.2 subunit is associated with a much larger SUR subunit and also contains a binding site for ATP. The binding of one molecule of ATP causes a conformational change in the channel protein that closes the channel (7-9).

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=25777632&cut=100&org=1] using human KCNJ11 as a query finds proteins in 30 different species, which are all metazoans. However, potential true homologous genes have thus far been identified only in the mouse, rat, and nematode.

Several single nucleotide polymorphisms (SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3767&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the KCNJ11 gene, four (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein (Figure 3). At least two of these, rs5219 which encodes the E23K polymorphism and rs5215 which encodes the I337V polymorphism, have been associated with impaired insulin response and increased risk of type 2 diabetes (see below).

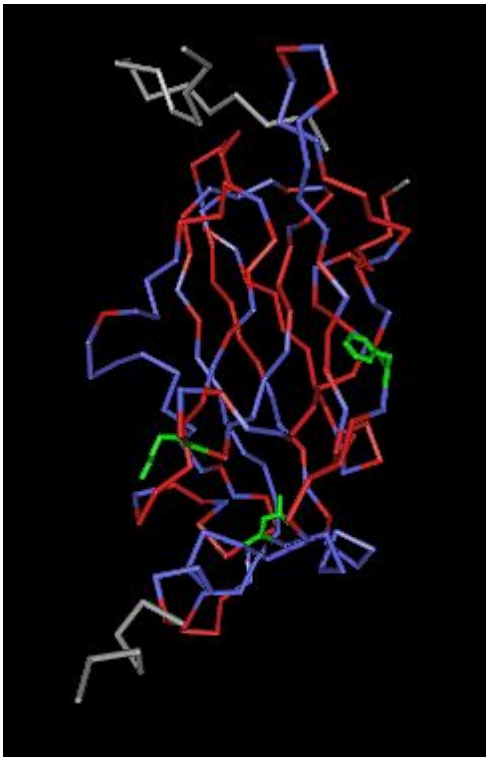

Figure 3: SNP positions of KCNJ11 mapped to the 3D structure of inward rectifier potassium channel 1.
The figure shows the positions of some of the non-synonymous amino acid changes (green residues) caused by SNPs in the coding sequence.

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)

KCNJ11 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on KCNJ11 and diabetes, search PubMed.

Three common SNPs (E23K, L270V, and I337V) have been found in the KCNJ11 gene in Caucasians (10-13).

The E23K variant is caused by a switch of guanine to adenine, resulting in a glutamic acid (E) to lysine (K) substitution at codon 23. Analysis of the E23K variant in various Caucasian populations shows that KK homozygosity has a stronger association with diabetes compared with heterozygous EK or the wild-type EE (11). However, this risk has not been observed in other Caucasian populations (12).

To investigate the effect of E23K, L270V, and I337V on the functioning of the KATP channel, human potassium channels containing these SNPs were made. Only one variant, E23K, altered channel function; it made the channel less sensitive to ATP. Therefore, the E23K channels were more excitable; they needed greater amounts of ATP before they closed and so were more likely to remain open. Because the release of insulin is inhibited when the KATP channel is open, E23K is thought to contribute to the development of diabetes by impairing insulin release (14-16).

The two genes that encode the KATP channel, ABBC8 and KCNJ11, reside adjacent to one another on chromosome 11. A variant of ABCC8, called A1369S, is in almost complete linkage disequilibrium with the E23K variant of KCNJ11. This means that from the genetic evidence, it is difficult to determine whether it is the A1369S variant or the E23K variant that predisposes to type 2 diabetes (17).

In individuals who are obese or have type 2 diabetes, a chronic elevation of free fatty acids is seen. This leads to the accumulation of long-chain acyl-CoAs in pancreatic beta cells that stimulate KATP channels and inhibit insulin release. The diabetogenic effect of possessing both the E23K and I337V variants may involve an enhanced stimulatory effect of long-chain acyl-CoAs in polymorphic KATP channels (18).

The theory that variations in the KCNJ11 gene may inhibit insulin secretion is supported by a study of adults who did not have diabetes but did have the E23K SNP. It was found that E23K was associated with a impaired insulin release in response to glucose and also an increased body mass index (BMI) (19).

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Link Roundup

Live Searches

Diabetes and KCNJ11 in PubMed | PubMed Central | Books

Background Information

OMIM [http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600937]

Molecular Biology

KCNJ11 in Entrez Gene | Evidence Viewer [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009237.16&gene=KCNJ11&graphiconly=TRUE] | Map Viewer | Domain [www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=25777632] | SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3767&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=25777632&cut=100&org=1] | HomoloGene

The Enzyme Lipoprotein Lipase (LPL)

Summary

Lipoprotein lipase (LPL) is an enzyme that breaks down triglycerides. LPL is functionally impaired or present at low levels in many type 2 diabetics. Some evidence suggests that insulin plays a role in regulating LPL synthesis.

Background

Cholesterol and triglycerides circulate in the blood as a complex with proteins, called lipoproteins. There are several different types of lipoprotein: high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL).

VLDL and LDL are sometimes referred to as “bad cholesterol” because they deposit cholesterol in arteries, which over time contributes to the lipid core of atherosclerotic plaques. LDL makes up 60–70% of the total cholesterol in blood, whereas VLDL makes up 10–15%.

IDL is an intermediate between VLDL and LDL. It is richer in cholesterol than VLDL and in clinical tests gets collected with the LDL fraction.

HDL, sometimes referred to as “good cholesterol”, makes up about 30% of blood cholesterol. The level of HDL is inversely correlated with the risk of coronary heart disease, and it seems to play a protective role. HDL might carry cholesterol away from the arteries to the liver, where it is broken down.

For more information about blood cholesterol levels, visit the National Heart, Blood, and Lung Institute [www.nhlbi.nih.gov/health/public/heart/chol/wyntk.htm].

The breakdown and reformation of lipoproteins are interlinked via several steps that often require the action of enzymes, one of which is lipoprotein lipase (LPL). It is found in heart, muscle, and adipose tissue, where it breaks down triglycerides in VLDL and chylomicrons by hydrolysis into IDL (intermediate-density lipoprotein), fatty acids, and glycerol. Although the fatty acids can be used as fuel, the IDL, which is richer in cholesterol than VLDL, is taken up by the liver or is formed into LDL (low-density lipoprotein). LPL activity also indirectly raises HDL levels because LPL-mediated hydrolysis of VLDL provides surface components that merge with HDL3 to form HDL2 particles.

For a detailed description of lipoprotein interconversions, visit The University of Manitoba [www.umanitoba.ca/faculties/medicine/units/biochem/coursenotes/blanchaer_tutorials/LipTutWeb/pages/page1.htm].

As well as the well-established role of LPL in lipid metabolism, it can also bind specific cell-surface proteins, often via heparan sulfate proteoglycans attached to epithelial cells. This action is independent of any catalytic activity, which means that LPL can "bridge" lipoproteins and the surface of cells, leading to an increase in the cellular uptake of lipoproteins (1). In the blood vessel wall, this action is thought to be proatherogenic.

Severe mutations in LPL cause a deficiency that results in type I hyperlipoproteinemia (OMIM; emedicine [www.emedicine.com/oph/topic505.htm]), a disorder characterized by high levels of lipoprotein and triglycerides in the blood.

Molecular Information

Lipoprotein lipase was so difficult to purify that the protein sequence had to be determined from the nucleotide sequence of its cDNA. The LPL gene maps to chromosome 8 (Figure 1). It has 10 exons (coding regions) that span about 28,800 bases (see evidence [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_030737.8&gene=LPL&graphiconly=TRUE]) (2-5). The gene encodes a preprotein of 475 amino acids that contains a signal peptide. Cleavage of the signal results in a mature protein of 448 amino acids.

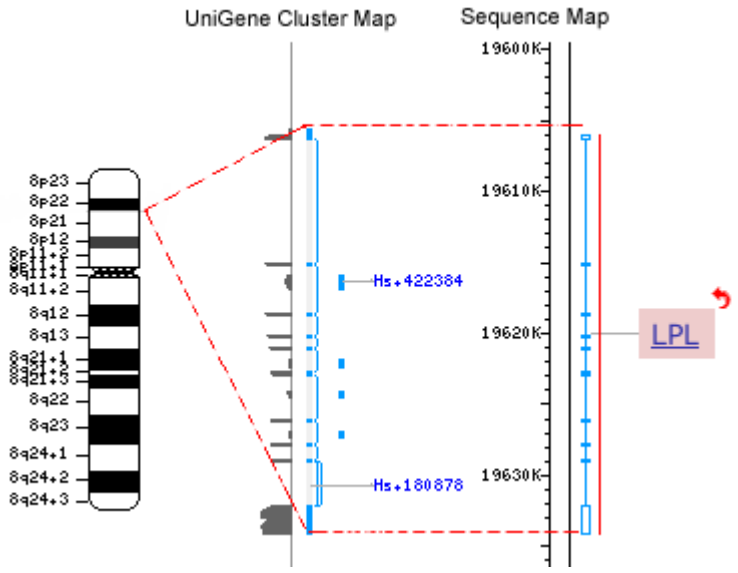

Figure 1: Location of LPL on the human genome.

LPL maps to chromosome 8, between approximately 19,600–19,830 kilobases (kb). Click or here for a current and interactive view of the location of LPL in the human genome.

Note: this figure was created from Build 33 of the human genome. Because the data are recomputed between genome builds, the exact location of LPL may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

Lipoprotein lipase, along with hepatic lipase and pancreatic lipase, makes up a lipase superfamily (6); that is, based on a comparison of the amino acid sequence, all three proteins appear to have evolved from a common ancestor.

All lipases, including evolutionarily unrelated prokaryotic lipases, share a serine protease-like catalytic triad of amino acids (Ser-His-Asp). Another class of enzyme, serine proteases, hydrolyzes peptide bonds in many biological settings, for example, within the blood-clotting cascade. The similar catalytic triad seen in the lipase superfamily suggests that a similar mechanism of hydrolysis [www.ncbi.nlm.nih.gov/books/bv.fcgi?tool=bookshelf&call=bv.View..

ShowSection&searchterm=serine&rid=stryer.section.1170#1178] is used, this time to hydrolyze fats rather than peptides. Site-directed mutagenesis experiments on LPL support this hypothesis (7).

Although the structure of LPL has not yet been solved, mapping the LPL sequence to the crystal structure of pancreatic lipase [www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi?form=6&db=t&Dopt=s&uid=21535] (8) gives a good estimate of the structure of LPL [www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4557727]. Although the enzymatic activity involving the catalytic triad is in the large amino-terminal lipase domain (residues 1–312), the smaller carboxy-terminal domain (the PLAT/LH2 domain; residues 313–448) binds the lipoprotein substrate. In nature, LPL occurs as a homodimer and, when in this form, binds to cell-surface molecules via several heparin-binding sites, a function that is thought to increase the cellular uptake of lipoproteins.

Several single nucleotide polymorphisms (SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4023&view=view&chooseRs=coding&.cgifields=chooseRs]) have been found within the LPL gene, seven (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein (Figure 2). At least three of these (rs268, rs328, and rs1801177) have been associated with observed cases of type I hyperlipoproteinemia (allelic variants [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=238600&a=238600_AllelicVariant] .0033, .0014, and .0035, respectively).

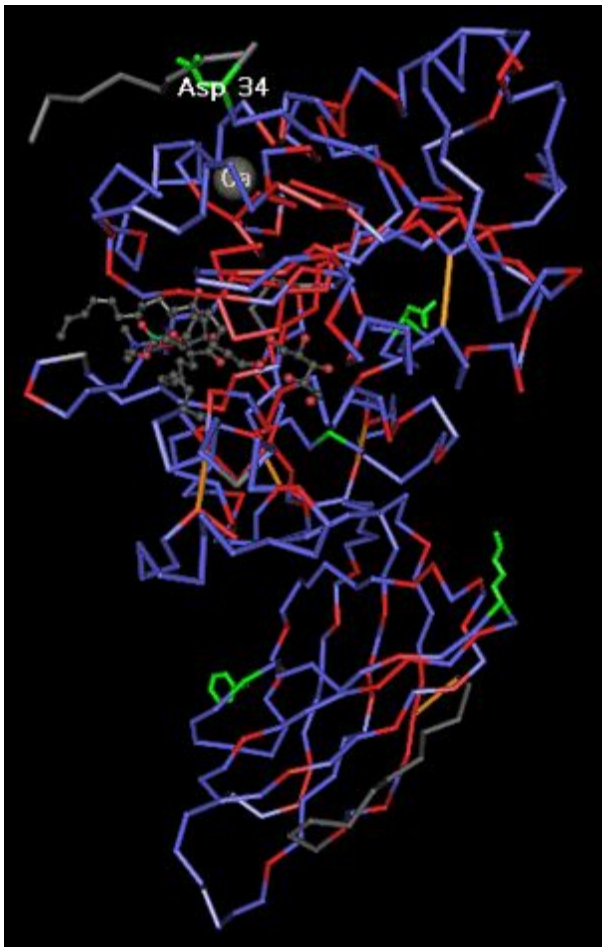

Figure 2: SNP positions of LPL mapped to the 3D structure of lipase.
The figure shows the positions of non-synonymous amino acid changes (green residues) caused by SNPs in the coding sequence. Disulfide bridges between cysteine residues are shown in orange.

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)

A BLAST search [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557727&cut=100&org=1] using human LPL as a query finds proteins in 38 different species, which are all metazoans apart from one bacterium, *Trichodesmium erythraeum*, an oceanic nitrogen producer. However, potential true homologous genes have thus far been identified only in the mouse and rat.

LPL and Diabetes: Digest of Recent Articles

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

A common complication of type 2 diabetes is microalbuminuria, that is, protein being excreted in the urine because of kidney damage through chronic inflammation. In a study of 386 type 2 diabetic patients, a correlation was found between the presence/severity of microalbuminuria and genetic variants of LPL (9). Higher concentrations of LDL constituents have been linked previously to progression of microalbuminuria. Furthermore, foam cells (white blood cells that have "mopped up" excess LDL or VLDL) are observed in many chronic inflammatory diseases, includ-

ing atherosclerosis and kidney disease. These observations point to a possible role for altered LPL in the progression of inflammatory kidney disease, and therefore the microalbuminuria often seen in diabetes type 2 patients (9). [More articles like this]

Another study compared the levels of LPL in the blood of 40 type 2 diabetes patients and a group of healthy individuals prior to heparin injection (10). Because functional LPL is usually anchored to heparan sulfate proteoglycans on the surface of cells, heparin injection releases the enzyme into the blood. The amount of LPL in the type 2 diabetes patients was significantly lower than that of healthy individuals. However, after a course of insulin, the levels of LPL were increased in the diabetic patients. Because this increase cannot be attributed to released LPL because no heparin injection was given, it must be caused by the administered insulin (10). This finding supports previous work showing that insulin plays a role in regulating LPL synthesis (11, 12). [More articles like this]

The H+ allele of the T495G HindIII polymorphism of LPL is associated with coronary heart disease. This polymorphism was further investigated in 785 Chinese subjects, of which about 60% had been diagnosed with early-onset type 2 diabetes (<40 years old). Within this subset, the polymorphism was associated with higher plasma triglyceride and lower HDL-cholesterol levels (13). [More articles like this].

Most recently, SNPs in the 3' end of the LPL gene were found to be associated with insulin resistance in Mexican Americans (14). The SNPs were analyzed as groups inherited together on the same chromosome (haplotypes). One haplotype was associated with insulin sensitivity, another with insulin resistance. Insulin resistance is a pathophysiological determinant of type 2 diabetes. Of note, these same haplotypes were also associated with coronary artery disease, suggesting that LPL may be a genetic link between diabetes and atherosclerosis (15).

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Link Roundup

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Diabetes and LPL in PubMed | PubMed Central | Books

Background Information

Cholesterol levels at the National Heart, Blood, and Lung Institute [www.nhlbi.nih.gov/health/public/heart/chol/wyntk.htm]

Lipoprotein interconversions at the The University of Manitoba [www.umanitoba.ca/faculties/medicine/units/biochem/coursenotes/blanchaer_tutorials/LipTutWeb/pages/page1.htm]

Type I hyperlipoproteinemia in: OMIM | emedicine [www.emedicine.com/oph/topic505.htm]

Mechanism of hydrolysis [www.ncbi.nlm.nih.gov/books/bv.fcgi?tool=bookshelf&call=bv.View..ShowSection&rid=stryer.section.1170#1178], foam cells on the Bookshelf

Molecular Biology

Lipoprotein lipase in Entrez Gene | Evidence Viewer [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_030737.8&gene=LPL&graphiconly=TRUE] | Map Viewer | Domains [www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4557727]: Lipase, PLAT/LH2 | SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4023&view=view&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=238600&a=238600_AllelicVariant] | BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557727&cut=100&org=1] | HomoloGene

Hepatic lipase in Entrez Gene

Pancreatic lipase in Entrez Gene | Structure [www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi?form=6&db=t&Dopt=s&uid=21535]

The Transcription Factor PPARG

Summary

An important diabetes risk factor and drug target is peroxisome proliferator activated receptor gamma (PPARγ). This protein is a member of the nuclear hormone receptor super-family of transcription factors. PPARγ is a key regulator of fat cell differentiation. Drugs that activate PPARγ increase sensitivity to insulin and lower blood sugar levels in diabetics. Variants of PPARγ influence the risk of developing obesity and type 2 diabetes.

Nomenclature

Official gene name: peroxisome proliferator activated receptor gamma
Official gene symbol: PPARG
Alias: PPARG1, PPARG2

Background

Small can be powerful. Some genetic risk factors may increase the risk of developing a particular disease by only a small amount. But when the genetic risk factor is common, its effects can tip the balance toward millions of people developing disease. For type 2 diabetes, one such genetic risk is the gene that encodes PPARγ (peroxisome proliferator activated receptor gamma). Variants of this gene are among the first to be identified as causing a broad impact on the risk of developing type 2 diabetes (1).

There are three known subtypes of PPAR—alpha (α), delta (δ), and gamma (γ). The latter subtype, PPARγ, is abundant in adipose tissue and plays a key role in fat cell differentiation. PPARγ is also the target of the type 2 diabetes drugs called thiazolidinediones (TZDs).

Found in the nucleus of many cells, PPARs are both hormone receptors and transcription factors. PPARs therefore have two binding sites, one site for ligands (such as fatty acids, hormones, and specific diabetic drugs) and one site for DNA.

To act as a transcription factor, PPARγ must first form a complex with another transcription factor called retinoid X receptor (RXR). When a ligand such as the drug TZD binds to the receptor PPARγ, it activates the PPARγ–RXR complex. The activated complex binds to the promoter region of specific genes and activates transcription.

To date, several genes have been identified as being direct targets for PPARγ, including lipoprotein lipase (LPL), fatty acid transport protein (FATP), and acetyl CoA-synthase (ACS) (2). Transcription of these genes influences the metabolism of fatty acids. TZDs such as rosiglitazone [www.nlm.nih.gov/medlineplus/druginfo/medmaster/a699023.html] can increase insulin-stimulated glucose disposal by activating the PPARγ–RXR complex primarily in fat cells. In doing so, such drugs improve sensitivity to insulin and lower blood glucose levels in type 2 diabetes patients.

Molecular Information

Nuclear receptors such as PPAR are one of the largest groups of transcription factors known today. The members of this family are conserved functionally and structurally and are expressed in a wide range of multicellular (metazoan) species. A BLAST [http://www.ncbi.nlm.nih.gov/sutils/

blink.cgi?pid=20336231&cut=100&org=1] search using human PPARG as a query finds proteins in 48 different species. However, potential true homologous genes have thus far been identified only in the mouse and rat.

The PPARγ gene maps to chromosome 3 (Figure 1). It has 11 exons (coding regions) that span more than 140,000 bases (see evidence) [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_022517.16&gene=PPARG&graphiconly=TRUE] (3). There are three isoforms that differ at their 5′ ends (4). The isoform type 2 (PPARγ2) has an additional 84 nucleotides at its 5′ end compared with the isoform type 1 (5) and is also much less abundant than isoform 1, its highest levels being found in adipose tissue and the colon (4).

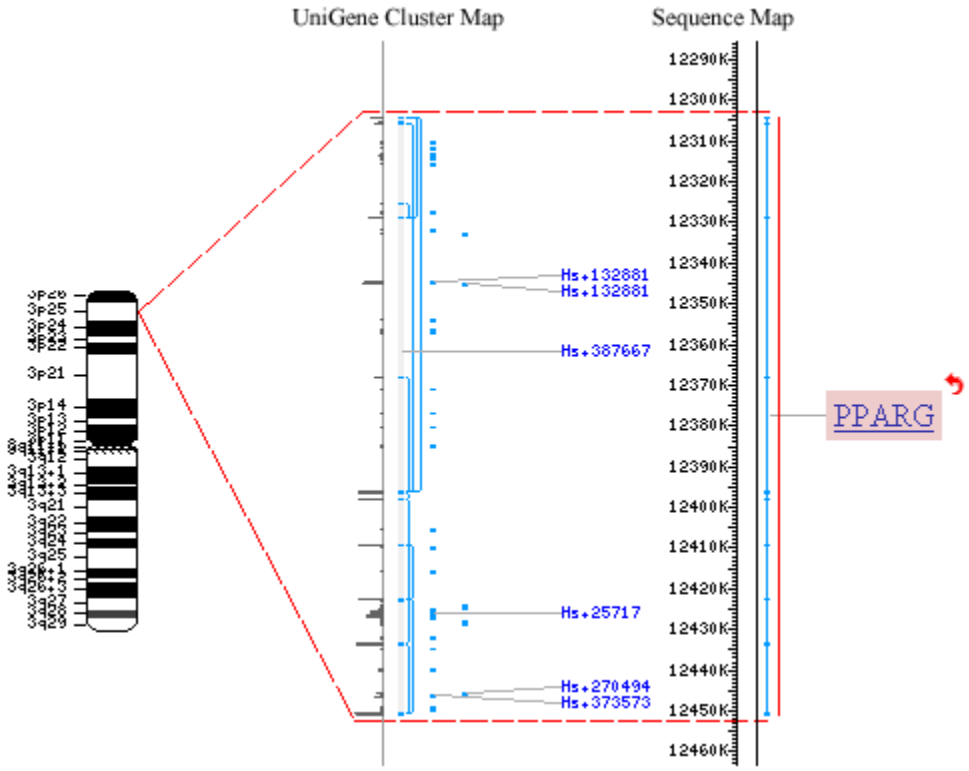

Figure 1: Location of PPARG on the human genome.

PPARG maps to chromosome 3, between approximately 12,300–12,450 kilobases (kb). Click or here for a current and interactive view of the location of PPARG 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 PPARG may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

The crystal structure of the ligand-binding domain of PPARγ has been solved (6, 7) and shares many structural features with other nuclear receptors, including a central DNA binding domain and a ligand-binding domain (LBD) in the C-terminal half of the receptor. The LBD contains 11-13 alpha helices that fold to form a hydrophobic pocket where ligands can bind. The AF2 (activating function-2) helix of PPARγ is found here and interacts with RXR and is thought to aid dimerization and transactivation of the two receptors and also initiates transcription (8).

Crystal structures of the heterodimer of PPARγ and RXR in complex with their ligands (such as rosglitazone and 9-*cis*-retinoic acid, respectively) have also been solved (8, 9). Such structures give us a molecular understanding of how PPARγ is able to bind a variety of ligands and aid the design of drugs that specifically target the gamma receptor.

Several single nucleotide polymorphisms (SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=5468&view=view&chooseRs=coding&.cgifields=chooseRs]) have been found within the PPARG gene, three (at the time of writing) of which cause non-synonymous amino acid changes in isoform type 2 of the protein NP_056953. At least one of these (rs1801282) has been associated with obesity (allelic variant .002 [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601487&a=601487_AllelicVariant0002]).

PPARG and Diabetes: Digest of Recent Articles

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

The variant of the PPAR receptor inherited may affect the risk of obesity or developing type 2 diabetes. Of particular interest is position 12 of the coding region. Most people have the amino acid proline here; this confers a small risk of developing obesity, about 1.3% (1). For the individual, this 1.3% increase in risk is a small risk, but because 75% of the population have the proline allele, this translates into a tremendous impact on the number of people developing diabetes (10).

A common variant of the PPARγ2 is a single nucleotide polymorphism (SNP) that has alanine in the place of proline at position 12 (Pro12Ala). Individuals who inherit this variant have a degree of protection against insulin resistance and obesity (11).

One study screened Pima Indians of Arizona for variations in PPARγ2. Type 2 diabetes is particularly common among this population. Affected individuals are obese and resistant to the insulin they produce in inadequate amounts. Several new SNPs were identified, many in the promoter region of the gene (12). It is not yet clear which SNPs are the most important in contributing to diabetes in this and in other populations.

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Link Roundup

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Background Information

PPARG in OMIM

Molecular Biology

PPARG in Entrez Gene | Evidence Viewer [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_022517.16&gene=PPARG&graphiconly=TRUE] | Map Viewer | Domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=20336231]: Ligand-binding domain, Zinc finger | SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=5468&view=view&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=20336231&cut=100&org=1] | HomoloGene

The Regulatory Subunit of a Phosphorylating Enzyme (PIK3R1)

Summary

The PIK3R1 gene encodes the regulatory subunit of a lipid kinase that has a key role in insulin signaling. A variant of this regulatory subunit may interfere with the cascade of events that occurs after insulin binds to its receptor.

Nomenclature

Official gene name: phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)
Official gene symbol: PIK3R1
Alias: GRB1, p85-ALPHA

Background

Binding of insulin to its receptor triggers a cascade of phosphorylation and dephosphorylation reactions beginning at the receptor itself (autophosphorylation) and specific target proteins of the receptor called insulin receptor substrates (IRSs). The cascade of phosphorylation reactions spreads to various cellular proteins and is finally terminated when the insulin receptor is dephosphorylated.

Enzymes that catalyze the phosphorylation of proteins are called kinases, and one particular kinase, phosphatidylinositol 3-kinase (PI3-K), is a major pathway for the metabolic effects of insulin. It plays a key role in the stimulation of glucose transport, glycogen synthesis, and fat breakdown.

PI3-K is made up of a catalytic subunit and a regulatory subunit. The regulatory subunit is encoded by the p85alpha gene, which generates three protein products of 85, 55, and 50 kDa. Each of the three proteins (p85alpha, p55alpha, and p50alpha) are found in different tissues and may have specific roles in various tissues (1). The p85alpha protein is the most common protein isoform in all tissues.

Insulin can initiate multiple signaling pathways, and the PI3-K enzyme is important in the "RAS-independent pathway". After insulin binding and autophosphorylation of the receptor, IRS-1 binds to a phosphorylated tyrosine residue on the receptor. The regulatory subunit of the PI3-K enzyme then binds via its Src homology 2 (SH2) domains to the receptor-bound IRS-1. The catalytic subunit phosphorylates specific lipids to produce a second messenger, PIP3 (phosphatidylinositol 3,4,5-phosphate). PIP3 binds to and leads to the activation of protein kinase B, which in turn promotes the metabolic effects of insulin, promoting glucose uptake (by moving GLUT4 from intracellular stores to the plasma membrane) and glycogen synthesis (by activating glycogen kinase 3).

The p85alpha gene is a candidate gene for the development of diabetes because of its role in insulin signaling. The most predominant protein this gene encodes is the p85alpha protein, but the p50alpha and p55alpha proteins may also have an important role.

Molecular Information

The PIK3R1 gene maps to chromosome 5 (Figure 1). It has 17 exons (coding regions) that span over 75,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_006431.13&gene=PIK3R1&graphiconly=TRUE]).

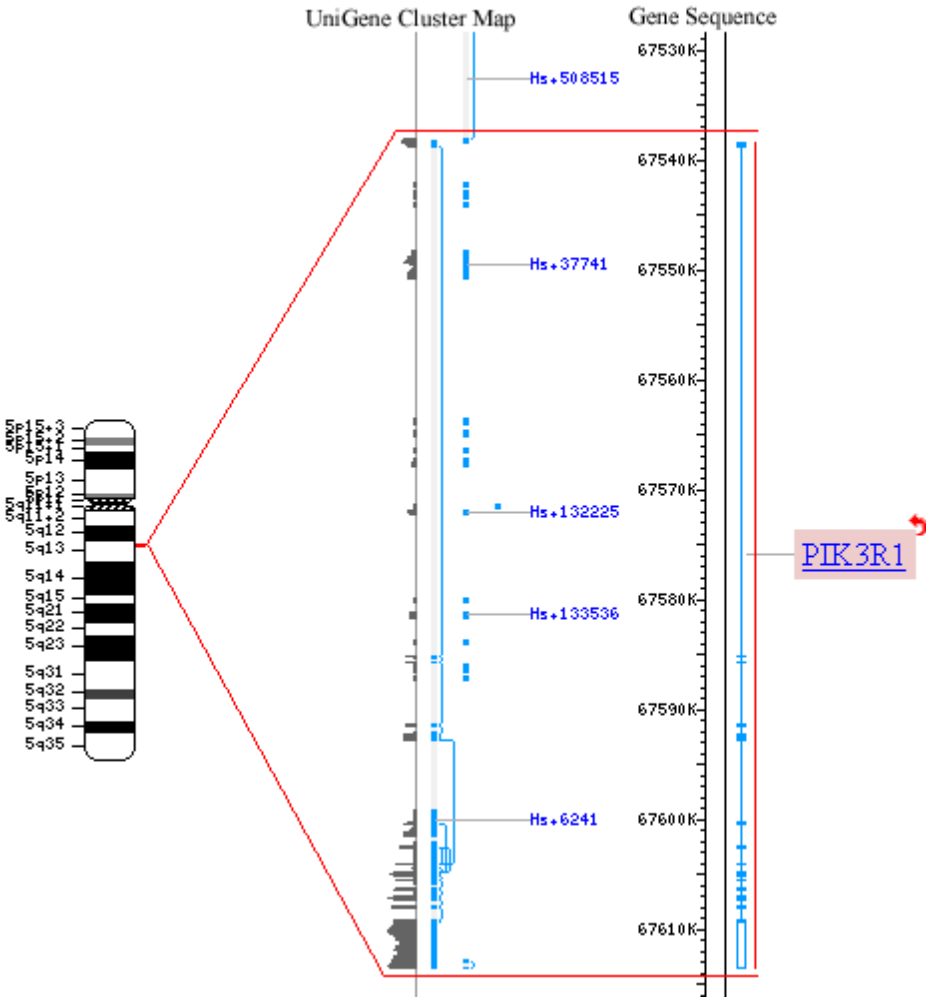

Figure 1: Location of PIK3R1 on the human genome.

PIK3R1 maps to chromosome 5, between approximately 67,530–67,620 kilobases (kb). Click or here for a current and interactive view of the location of PIK3R1 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 PIK3R1 may fluctuate. The live Web site may, therefore, not appear exactly as in this figure.

Alternative splicing of the p85alpha gene results in three transcript variants that encode three different protein isoforms. The longest isoform (NP_852664) is 744 amino acids long.

The regulatory subunit of PI3-K contains two SH2 domains that bind to specific phosphorylated tyrosine residues present in motifs possessing the sequence YXXM or YMXM. These motifs are present on the insulin receptor and in all four of the insulin receptor substrates (IRS-1, -2, -3,

and -4). For full activation of the kinase, both SH2 domains of the regulatory subunit need to bind to the motif present on IRS-1. The resulting conformational change of the regulatory subunit activates the catalytic subunit (2, 3).

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=5295&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the PIK3R1 gene, and these variants may be involved in the development of diabetes (4). Each of the three protein variants encoded by this gene exhibit two (at the time of writing) amino acid changes caused by SNPs in the coding region of PIK3R1.

A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=32455248&cut=100&org=1] using human PIK3R1 as a query finds proteins in 20 different species, which are all metazoans apart from five proteins found in fungi and one protein found in Archaea (single-cell organisms that are distinct from bacteria). However, potential true homologous genes have thus far been identified only in the mouse and rat.

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A methionine to isoleucine switch at residue 326 (M326I) has been observed in Europeans and Japanese (5-7). This change occurs just six amino acids from the N-terminal SH2 domain and appears to affect glucose homeostasis. In the Danish population, the variant was common in both diabetics and healthy subjects, with homozygous carriers being less effective at glucose regulation (5). In the Pima Indians, diabetes was less common in homozygous carriers compared with individuals who were heterozygous or wild type (8).

The M326I variant may lead to a reduced level of protein being expressed (but this may be offset by an observed increased interaction of the enzyme with IRS-1). The enzyme variant may also be less efficient in suporting the development of fat cells and in supporting insulin-stimulated glucose uptake into certain cells (3).

Overall, the M326I variant may only have a minor impact on the signaling events initiated by the insulin. But if combined with gene variants encoding other signaling proteins or acquired alterations in protein levels, this enzyme variant may contribute to a functional impact on insulin signaling and thus contribute to the events that lead to type 2 diabetes.

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