# 4. Other Types of Diabetes

Created: July 7, 2004

The vast majority of diabetes cases fall into the categories of type 1 and type 2 diabetes. However, up to 5% of cases have other specific causes and include diabetes that results from the mutation of a single gene.

# Genetic Defects of Beta Cell Function (MODY and Others)

## MODY

Maturity onset diabetes in the young (MODY) is an uncommon cause of diabetes that may be mistaken for type 2 diabetes because treatment of both conditions does not require insulin, at least in the early stages of the disease.

However, many differences exist between MODY and type 2 diabetes (Table 1). Whereas the nature of the genetic predispostion of type 2 diabetes is unclear with many susceptibility genes being implicated, MODY is a monogenic condition (caused by a mutation of a single gene) that is inherited as an autosomal dominant trait. The onset of diabetes usually occurs in childhood or adolescence, usually before 25 years of age, although the hyperglycemia is mild in some cases and may be missed, as with type 2 diabetes. When hyperglycemia is detected in children, MODY may be misdiagnosed as type 1 diabetes.

Genetic studies have defined a number of subtypes of MODY. Mutations in the genes encoding hepatic nuclear factor 4 (HNF4), glucokinase (GCK), hepatic nuclear factor 1 alpha and 1 beta (commonly known as HNF1A and HNF1B, but official symbols are TCF1 and TCF2, respectively), insulin promoter factor 1 (IPF-1), and NEUROD1 are the cause of the six known forms of MODY (MODY1-6). See Table 2 for a comparison of the MODY-related genes.

MODY2 is caused by a mutant glucokinase enzyme that fails to accurately sense the circulating concentrations of glucose. All of the remaining MODY genes encode transcription factors. HNF4A, TCF1, TCF2, and IPF-1 form crucial links in the cascade of transcription factors that control the appropriate expression of beta cell genes, such as insulin and the glucose transporter GLUT2. Mutations of these genes may disrupt the development of beta cells in the embryo and result in dysfunctioning beta cells in the adult. However, the precise role of these proteins in adult pancreatic islets is only beginning to be unraveled.

MODY3 and MODY2 are the most common causes of MODY but remain relatively uncommon causes of diabetes.

**Table 1. Comparison between type 2 diabetes and MODY**

| Characteristic | Type 2 diabetes | MODY |
|---|---|---|
| Inheritance | Polygenic | Monogenic, autosomal dominant |
| Age of onset | Usually >40 years of age | Usually <25 years of age |
| Pedigree | Rarely seen across generations | Usually seen across generations |
| Penetrance | Variable (10-40%) | 80-90% |
| Obesity | Usually obese | Non-obese |
| Metabolic syndome[1] | Usually present | Absent |

1 Metabolic syndrome: diabetes, insulin resistance, hypertension, and hypertriglyceridemia.

**Table 2. Comparison of MODY-related genes**

| Type of MODY[1] | Gene | Molecular basis |
|---|---|---|
| MODY1 | HNF4A | Abnormal regulation of gene transcription in beta cells causes a defect in the metabolic signaling of insulin secretion, beta cell mass, or both. |
| MODY2 | Glucokinase | Reduced phosphorylation of glucose results in a defect in sensitivity of beta cells to glucose and a defect in the storage of glucose as glycogen in the liver. |
| MODY3 | TCF1 (HNF1A) | Abnormal regulation of gene transcription in beta cells causes a defect in the metabolic signaling of insulin secretion, beta cell mass, or both. |
| MODY4 | IPF1 | Abnormal transcriptional regulation of beta cell development and function. |
| MODY5 | TCF2 (HNF1B) | Abnormal regulation of gene transcription in beta cells causes a defect in the metabolic signaling of insulin secretion, beta cell mass, or both. |
| MODY6 | NeuroD1 (BETA2) | Abnormal transcriptional regulation of beta cell development and function. |

1 MODY, maturity onset diabetes in the young; HNF4A, hepatocyte nuclear factor 4α; TCF1, Transcription Factor 1; HNF1A, Hepatocyte Nuclear Factor 1α; IPF1, Insulin Promoter Factor; TCF2, Transcription Factor 2; HNF1B, Hepatocyte Nuclear Factor 1β; NeuroD1, Neurogenic differentiation factor; BETA2, Beta cell E-box transactivator 2.

## Other Mutations That Cause Diabetes by Impairing Beta Cell Function

Mutations in mitochondrial DNA are a rare cause of diabetes. Mitochondrial DNA is a circular molecule that contains 37 genes that are passed on from the mother to her offspring. Paternal transmission of mitochondrial DNA is thought not to occur, because after fertilization, the fertilized egg destroys mitochondria derived from the sperm.

Diabetes and hearing loss are associated with a point mutation of mitochondrial DNA. The mutation occurs in the gene that encodes tRNA leucine, leading to the substitution of guanine for adenine (A→G) at position 3243.

The tRNA Leu 3243 mutation was originally identified in patients with the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome); however, diabetes is not part of this syndrome, suggesting that this mitochondrial mutation may be expressed as different phenotypes (1).

## References

1. Kadowaki T, Kadowaki H, Mori A *et al*. A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. N Engl J Med 330:962–968; 1994. (PubMed)

# MODY1: Caused by a Mutation in Transcription Factor HNF4A

## Summary

The HNF4A gene encodes a transcription factor that is found in the liver and pancreas. HNF4A is found in a region of chromosome 20 that is linked with type 2 diabetes, and mutations of this gene cause a rare form of autosomal dominant diabetes (MODY1).

## Nomenclature

Official gene name: hepatocyte nuclear factor 4 alpha
Official gene symbol: HNF4A
Alias: transcription factor 14, TCF14, Maturity Onset Diabetes in the Young type 1, MODY1

## Background

The expression of a wide range of genes in the liver is regulated by the transcription factor hepatocyte nuclear factor 4 alpha (HNF4A). 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, including HNF4A.

As the name suggests, HNF4A is found in abundance in the liver, but it is also found in the beta cells of the pancreas, 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 functions 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 (GLUT2) and glucose and mitochondrial metabolism (1, 2).

The HNF4A gene is suspected to play a role in type 2 diabetes; inheriting particular HNF4A variants may alter insulin secretion and predispose toward hyperglycemia. Mutations of HNF4A can cause an extremely rare form of diabetes, maturity onset diabetes in the young type 1 (MODY1). Whereas type 2 diabetes is a disorder usually of late onset with significant polygenetic basis, MODY by definition occurs in the young (onset at age less than 25 years) and is a monogenetic disorder inherited in an autosomal dominant fashion.

## 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 (3).

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 only three species: the mouse, rat, and the nematode *Caenorhabditis elegans*.

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.

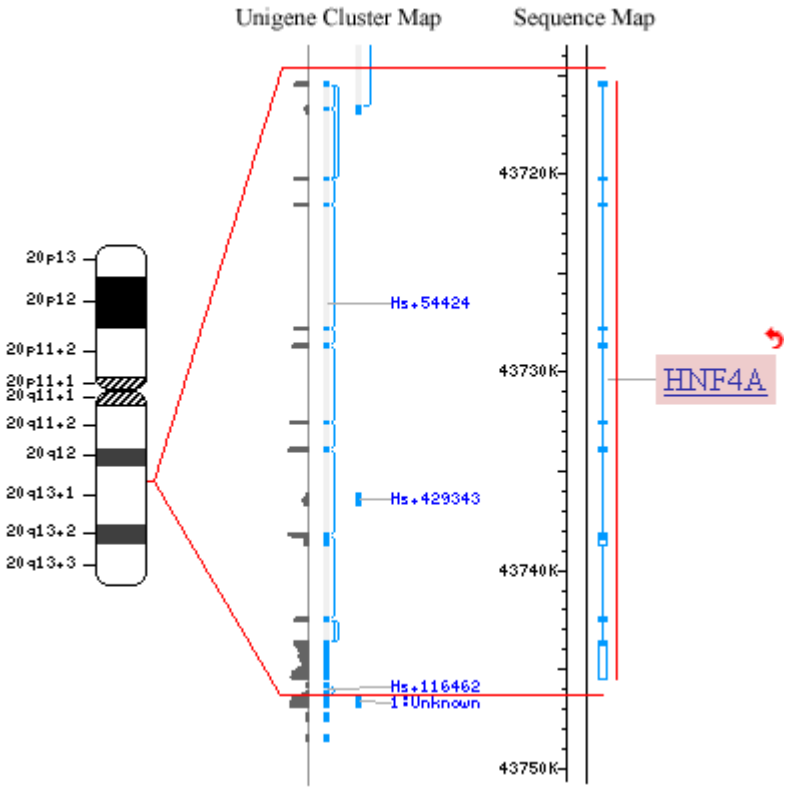


**Figure 1: Location of HNF4A on the human genome.**

HNF4A maps to chromosome 20, approximately between 43,700–43,750 kilobases (kb). Click on the figure 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).

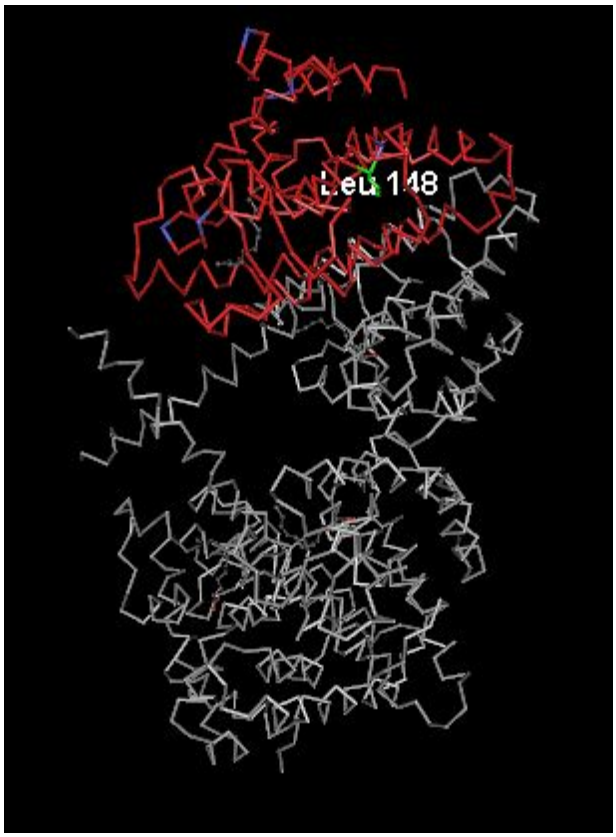


**Figure 2: SNP positions of HNF4A mapped to the 3D structure of the ligand-binding domain of rat HNF4A.** The figure shows the positions of a non-synonymous amino acid change (Leu-148) caused by a SNP in the coding sequence.

**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 MODY1: Digest of Recent Articles

For a more complete list of research articles on HNF4A and MODY1, search PubMed.

Mutations in the HNF4A gene resulting in MODY1 are rare; to date, only 13 families world-wide have been identified as having this form of MODY. Because HNF4A regulates the expression of HNF1A (the cause of MODY3), the mechanisms that underly these forms of MODY are thought to be similar (4).

Patients with MODY1 or MODY3 primarily have impaired beta cell function (shown by a defect in glucose-induced insulin secretion), as opposed to a primary defect in insulin activity. Patients with these forms of MODY present with a mild form of diabetes with a worsening of hyperglycemia over time, leading to up to 40% of patients requiring insulin. These patients have the full spectrum of complications of diabetes that is seen in type 1 and type 2 diabetes (4).

In addition to its effects on beta cell function, a deficiency of HNF4A affects the liver. In the developing embryo, HNF4A is needed for normal liver architecture (5). In the adult, a deficiency of HNF4A affects lipid synthesis and is associated with reduced serum levels of triglycerides and lipoproteins (6).

## References

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## Link Roundup

### Live Searches

Diabetes and HNF4A in PubMed | PubMed Central | Books

### Background Information

HNFA4 in OMIM

MODY1 in OMIM

### Molecular Biology

HNF4A in Entrez Gene | Evidence Viewer [www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_011362.8&gene=HNF4A&graphiconly=TRUE] | Map Viewer | Domains [www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=31077205]: Zinc Finger, Ligand-binding Domain | SNPs [www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3172&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=31077205&cut=100&org=1] | HomoloGene

# MODY2: Caused by a Mutation in the Enzyme Glucokinase (GCK)

## Summary

Glucokinase, encoded by the GCK gene, catalyzes the first step of glucose metabolism in the liver. It may also be an important "glucose sensor" in the pancreas. Mutant glucokinase causes a rare autosomal dominant form of diabetes (MODY2) and may also play a role in type 2 diabetes.

## Nomenclature

Official gene name: Glucokinase
Official gene symbol: GCK
Alias: GK, hexokinase 4, 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).

## 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 with a different kinetic profile.

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 "mouseear cress".

The GCK gene maps to chromosome 7 (Figure 1). It has 12 exons (coding regions) that span about 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 exons 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.

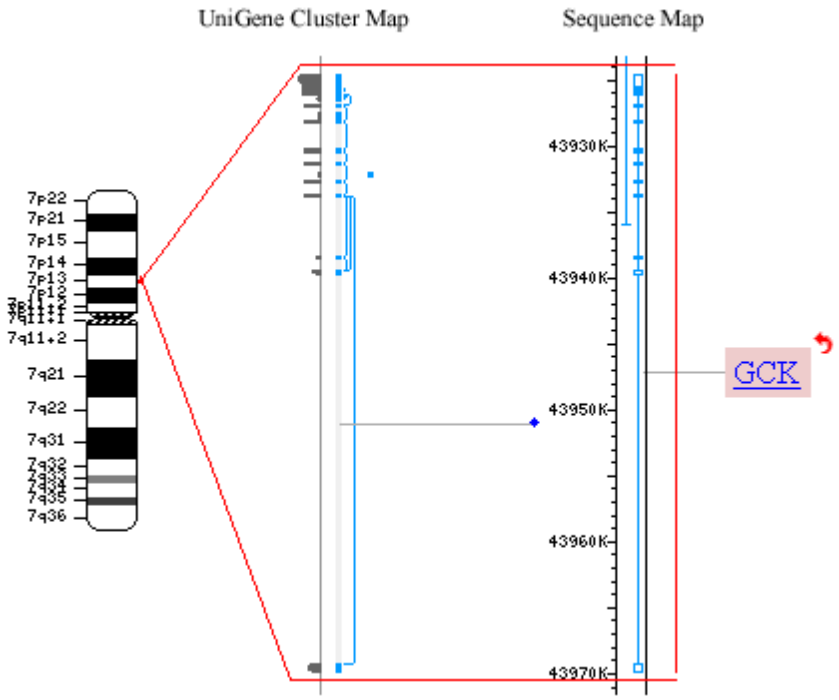


**Figure 1: Location of GCK on the human genome.**

GCK maps to chromosome 7, between approximately 43000–44000 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 MODY2: Digest of Recent Articles

For a more complete list of research articles on GCK and MODY2, search PubMed.

Around 200 mutations have been identifed in the GCK gene. No one mutation appears to be a common cause of MODY2, and the mutations are found throughout the gene (4).

Although MODY is a uncommon cause of diabetes, MODY2 is a common form of this disorder, especially in children with mild hyperglycemia and in women with gestational diabetes and a family history of diabetes (5). MODY2 has been described in many different populations (6, 7).

Unlike the other forms of diabetes, MODY2 causes a hyperglycemia that is both mild and nonprogressive. Although present from an early age, hyperglycemia is usually only picked up in adulthood during screening for other conditions and may be misdiagnosed as type 2 diabetes. MODY2 can often be treated with diet alone. Only 2% of patients require insulin therapy, and complications of diabetes are rare (4).

## References

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## Link Roundup

### Live Searches

Diabetes and GCK in PubMed | PubMed Central | Books

### Background Information

Glucokinase in OMIM

MODY2 in OMIM

### Molecular Biology

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

# MODY3: Caused by a Mutation in Transcription Factor TCF1

## Summary

The TCF1 gene encodes a transcription factor that is found in the liver and pancreas and is important in the development of these and other organs. A mutation of TCF1 causes a rare form of autosomal dominant diabetes (MODY3).

## Nomenclature

Official gene name: Transcription factor 1

Official gene symbol: TCF1

Alias: Hepatic nuclear factor 1 Alpha, HNF1A, Hepatic nuclear factor 1, HNF1, Albumin proximal factor, LFB1, Maturity Onset Diabetes in the Young type 3, MODY3

## Background

TCF1 belongs to a network of transcription factors that co-ordinates the expression of a wide range of genes in the liver. In the embryo, this network of nuclear proteins guides the development of the liver and continues to be important in the adult. Many functions of the liver appear and disappear, depending on the expression of these transcription factors.

Although found in highest amounts in the liver, this network of transcription factors is found in other organs, such as the pancreas and kidney. The transcription factor HNF4A regulates the expression of TCF1 and may also regulate TCF2.

In pancreatic beta cells, HNF4 and TCF1 regulate the expression of the insulin gene along with several other genes linked with insulin secretion, e.g., genes that encode proteins involved in glucose transport (GLUT2) and glucose metabolism (1, 2). Because TCF2 has been found to be expressed in pancreatic islets, it has been suggested that TCF2 functions with TCF1 to regulate gene expression in beta cells.

TCF1 and TCF2 share similar domains; they have a similar DNA binding region and dimerization domain. The TCF2 protein is believed to form heterodimers with TCF1, and depending on the TCF2 isoform, the result may be to activate or inhibit transcription of target genes.

Mutations of HNF4A, TCF1, and TCF2 each cause a distinct form of maturity onset diabetes in the young (MODY). Mutations of HNF4A cause MODY1, mutations of TCF1 cause MODY3, and mutations of TCF2 cause MODY5.

## Molecular Information

The TCF1 gene is a member of the homeobox family of genes.

In the early 1980s, important developmental genes were identified in the fruit fly. These master control genes lay out the body plan, and if they are mutated, the development of the fly is disrupted. These genes were called homeobox genes after "homeotic", the description for a shift in structual development.

Homeobox genes contain a conserved DNA motif of 180 base pairs that encodes a domain (a homeodomain) of about 60 amino acids. Homeodomains bind to certain regions of DNA and regulate the transcription of many other genes, several of which in turn play a key role in the control of embryogenesis.

Read more about homeodomains in Gilbert's Developmental Biology [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.box.2019]

The TCF1 gene maps to chromosome 12 (Figure 1). It has nine exons (coding regions) that span about 25,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009775.14&gene=TCF1&graphiconly=TRUE]). The gene encodes a protein of 631 amino acids in length.

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6928&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the TCF1 gene, four (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein (Figure 2). One of these SNPs (rs1169288) has been associated with observed cases of MODY3 (allelic variant .0011).

A BLAST [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=38016909&cut=100&org=1] search using human TCF1 as a query finds proteins in 31 different species, which are all metazoans apart from two fungi, one plant, and one bacterium. However, potential true homologous genes have thus far been identified only in the mouse and rat.

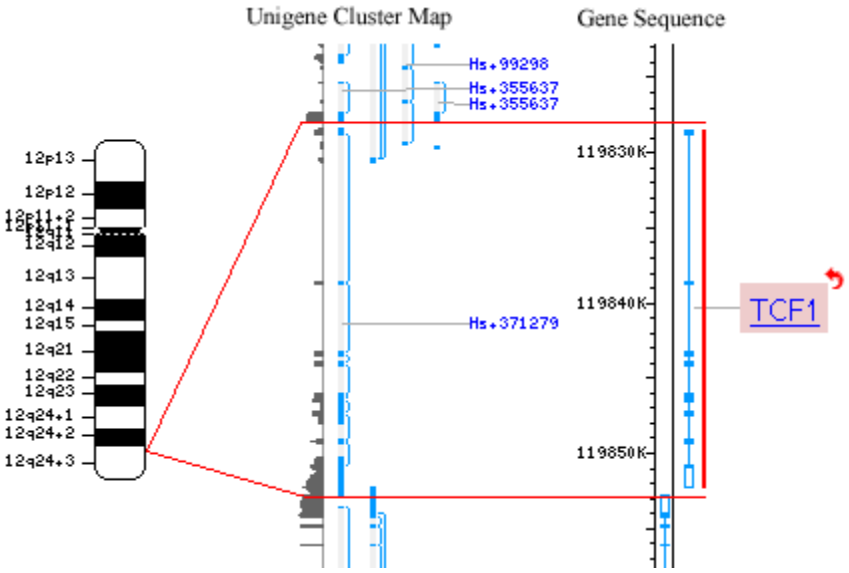


**Figure 1: Location of TCF1 on the human genome.**

TCF1 maps to chromosome 12, approximately between 119,800–119,880 kilobases (kb). Click on the figure or here for a current and interactive view of the location of TCF1 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 TCF1 may fluctuate. Therefore, the live Web site may not appear exactly as in this figure.


**Figure 2: SNP positions of TCF1 mapped to the 3D structure of chain A of human HNF1A (TCF1) bound to DNA.** The figure shows the position of a non-synonymous amino acid change (Ala 14, the 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)**

## TCF1 and MODY3: Digest of Recent Articles

For a more complete list of research articles on TCF1 and MODY3, search PubMed.

In many populations, mutations in the TCF1 gene resulting in MODY3 are the most common cause of MODY. Because the expression of TCF1 is regulated by HNF4A (the cause of MODY1), the mechanisms that underly these forms of MODY are thought to be similar (3).

Patients with MODY1 or MODY3 primarily have impaired beta cell function (shown by a defect in glucose-induced insulin secretion), as opposed to a primary defect in insulin activity (3). Patients with these forms of MODY present with a mild form of diabetes with a worsening of hyperglycemia over time. Up to 40% of patients require insulin, and the full spectrum of diabetes complications that are seen in type 1 and type 2 diabetes may develop.

In animal models, a deficiency of the TCF1 gene causes hyperglycemia because of defective beta cell signaling, leading to defective insulin secretion (4). The beta cell dysfunction in MODY3 may be caused by loss-of-function mechanisms, such as reduced DNA binding and impaired transcriptional activation (5).

In addition to its effects on beta cell function, a deficiency of TCF1 affects the kidneys and genital system. Patients with TCF1 mutations have decreased renal reabsorption of glucose and excrete glucose in the urine (glycosuria) (6).

Several of the mRNA transcripts encoded by the mutant HNF1A genes are unstable, suggesting that haploinsufficiency (deficient amounts of gene product) of HNF1A is responsible for the pathogenesis of MODY3 (7, 8). Haploinsufficiency for HNF1A may also cause diabetes that may be misdiagnosed as type 1 diabetes but is not caused by an autoimmune attack (idiopathic type 1 diabetes) (9).

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### Background Information

TCF1 in OMIM

MODY3 in OMIM

### Molecular Biology

TCF1 in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_009775.14&gene=TCF1&graphiconly=TRUE] | Map Viewer | Domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=38016909]: N terminus domain, Homeodomain, C terminus domain (beta isoform), C terminus domain (alpha isoform) | SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6927&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=38016909&cut=100&org=1] | HomoloGene

# MODY4: Caused by a Mutation in Transcription Factor IPF1

## Summary

Insulin promotor factor-1 (IPF1) is responsible for the development of the pancreas in the embryo and is also a key regulator of insulin gene expression. Mutations of IPF1 cause a rare form of autosomal dominant diabetes (MODY4) and may play a role in susceptibility to type 2 diabetes.

## Nomenclature

Official gene name: Insulin promoter factor 1
Official gene symbol: IPF1
Alias: Homeodomain transcription factor, Islet/Duodenum homeobox-1, IDX-1, Somatostatin transcription factor 1, STF-1, Pancreas duodenum homeobox-1, PDX-1, Maturity Onset Diabetes in the Young type 4, MODY4

## Background

In the developing embryo, the pancreas is formed from two buds of the primitive gut that eventually fuse together to form the pancreas gland. The exocrine part of the pancreas consists of cells that produce digestive enzymes, such as proteases and lipases, that are delivered to the gut via pancreatic ducts. The endocrine pancreas is much smaller and mainly consists of three cell types—alpha, beta, and delta—that produce glucagon, insulin, and somatostatin, respectively.

The development of the pancreas has been well studied, and many transcription factors can be used to identify pancreatic cells at different stages of development. Insulin promoter factor-1 (IPF1) is one such transcription factor and is an early pancreatic marker that is also found in adult beta cells. At a slightly later stage in pancreas development, TCF1 is expressed and is also found in adult beta cells.

In the embryo, the presence of IPF1 is vital to ensure the correct development of the pancreas. Loss of both copies of the gene can cause the pancreas not to form (pancreas agenesis). Without IPF1, the proliferation and differentiation of precursor cells into the endocrine and exocrine parts of the pancreas are blocked (1, 2).

IPF1 continues to be essential for normal pancreatic function in the adult. IPF1 regulates the expression of several pancreatic genes, most notably insulin (INS), glucose transporter type 2 (GLUT2), glucokinase (GCK), and somatostatin. Loss of one copy of IPF1 has been linked to MODY4 and may play a role in susceptibility to type 2 diabetes.

The dual role of IPF1 during the development of the pancreas in the embryo and as a regulator of pancreatic genes in the adult underscores the importance of IPF1 in glucose homeostasis.

## Molecular Information

The IPF1 gene is a member of the homeobox family of genes.

In the early 1980s, important developmental genes were identified in the fruit fly. These master control genes lay out the body plan, and if they are mutated, the development of the fly is disrupted. These genes were called homeobox genes after "homeotic", the description for a shift

in structural development. Homeobox genes such as IPF1 are important in determining cell fates; in the embryo, the presence of IPF1 ensures that pancreatic precursor cells develop into their destined mature pancreatic cells.

Homeobox genes contain a conserved DNA motif of 180 base pairs that encodes a domain (a homeodomain) of about 60 amino acids. Homeodomains bind to certain regions of DNA and regulate the transcription of many other genes, several of which in turn play a key role in the control of embryogenesis.

Read more about homeodomains in Gilbert's Developmental Biology [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.box.2019]

The IPF1 gene maps to chromosome 13 (Figure 1). It has two exons (coding regions) that span about 6,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_024524.13&gene=IPF1&graphiconly=TRUE]). The gene encodes a protein of 283 amino acids in length.

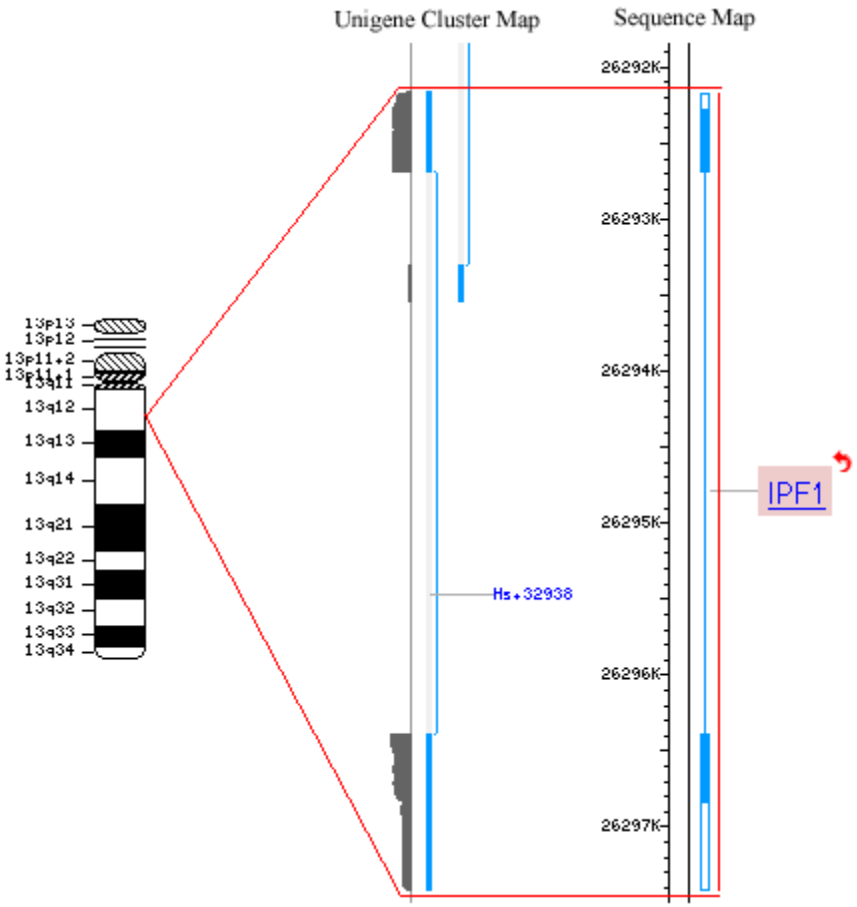


**Figure 1: Location of IPF1 on the human genome.** The IPF1 gene maps to chromosome 13, approximately between 26,285–26,300 kilobases (kb). Click on the figure or here for a current and interactive view of the location of IPF1 in the human genome.

Note: this figure was created from Build 34 of the human genome. Because the data are recomputed between genome builds, the exact location of IPF1 may fluctuate. Therefore, the live Web site may not appear exactly as in this figure.

The IPF1 gene sequence is highly conserved throughout evolution. Even a species that is distant in evolution from humans, such as the zebrafish, has a homeodomain that shares 95% homology with animal IPF1 homeodomains (3). A BLAST search [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557673&cut=100&org=1] using human IPF1 as a query finds proteins in 47 different species, which are all metazoans (multicellular organisms). However, potential true homologous genes have thus far been identified only in the mouse and the plant *Arabidopsis thaliana* (the first plant for which the complete genome has been sequenced).

## IPF1 and Diabetes: Digest of Recent Articles

For a more complete list of research articles on IPF1 and diabetes, search PubMed.

Mutations in the gene that encodes IPF1 are a rare cause of MODY; in fact, the current understanding of MODY 4 is based on studies of a single family (4).

In this family, an infant was born with agenesis of the pancreas that resulted in permanent neonatal diabetes and lack of pancreatic digestive enzymes. The infant was found to be homozygous for a deletion mutation in IPF1 that caused a frameshift. The resulting truncated protein did not contain the homeodomain that is essential for DNA binding (5).

Family members who were heterozygous for the same mutation had a mild form of diabetes (now called MODY4) that was being treated with either diet alone or oral hypoglycemic agents. Being heterozygous carriers for the IPF1 mutation was linked with severely impaired insulin secretion. Affected family members could be traced back to six generations. Compared with other forms of MODY, the expression of this form of diabetes may occur at later ages (2).

Further investigations into the role of IPF1 in the developing pancreas and in the functioning of the adult pancreas will improve our understanding of how beta cell dysfunction arises and leads to diabetes. The nature of IPF1 is also important when considering how to produce functional beta cells that can be transplanted in the hope that such cells can continue secreting insulin, thus providing a cure for diabetes (6).

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## Link Roundup

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### Background Information

IPF1 in OMIM

MODY4 in OMIM

### Molecular Biology

IPF1 in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_024524.13&gene=IPF1&graphiconly=TRUE] | MapViewer | Homeobox domain [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4557673] | SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3651] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557673&cut=100&org=1] | Homologene

# MODY5: Caused by a Mutation in Transcription Factor TCF2

## Summary

TCF2 encodes a transcription factor that is found in the liver and pancreas and is important in the development of these and other organs. A mutation of TCF2 causes a rare form of autosomal dominant diabetes (MODY5).

## Nomenclature

Official gene name: Transcription factor 2

Official gene symbol: TCF2

Alias: Hepatic nuclear factor 1 Beta, HNF1B, Hepatic nuclear factor 2, HNF2, Transcription factor, liver-specific; Variant hepatic nuclear factor, VHNF1, LFb3, Maturity Onset Diabetes in the Young type 5, MODY5

## Background

TCF2 belongs to a network of transcription factors that co-ordinates the expression of a wide range of genes in the liver. In the embryo, this network of nuclear proteins guides the development of the liver and continues to be important in the adult. Many functions of the liver appear and disappear, depending on the expression of these transcription factors.

Although found in highest amounts in the liver, this network of transcription factors is found in other organs, such as the pancreas and kidney. The transcription factor HNF4A regulates the expression of TCF1 and may also regulate TCF2.

In pancreatic beta cells, HNF4 and TCF1 regulate the expression of the insulin gene along with several other genes linked with insulin secretion, e.g., genes that encode proteins involved in glucose transport and glucose metabolism (1, 2). Because TCF2 has been found to be expressed in pancreatic islets, it has been suggested that TCF2 functions with TCF1 to regulate gene expression in the beta cells.

TCF1 and TCF2 share similar domains; they have a similar DNA binding region and dimerization domain. The TCF2 protein is believed to form heterodimers with TCF1, and depending on the TCF2 isoform, the result may be to activate or inhibit transcription of target genes.

Mutations of HNF4A, TCF1, and TCF2 each cause a distinct form of maturity onset diabetes in the young (MODY). Mutations of HNF4A cause MODY1, mutations of TCF1 cause MODY3, and mutations of TCF2 cause MODY5.

## Molecular Information

The TCF2 gene is a member of the homeobox family of genes.

In the early 1980s, important developmental genes were identified in the fruit fly. These master control genes lay out the body plan, and if they are mutated, the development of the fly is disrupted. These genes were called homeobox genes after "homeotic", the description for a shift in structural development. In the embryo, the presence of TCF2 is needed for the correct development of the kidneys and genital system.

Homeobox genes contain a conserved DNA motif of 180 base pairs that encodes a domain (a homeodomain) of about 60 amino acids. Homeodomains bind to certain regions of DNA and regulate the transcription of many other genes, several of which in turn play a key role in the control of embryogenesis.

Read more about homeodomains in Gilbert's Developmental Biology [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.box.2019]

The TCF2 gene maps to chromosome 17 (Figure 1). It has nine exons (coding regions) that span about 60,000 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_078100.1&gene=TCF2&graphiconly=TRUE]). The gene encodes a protein of 557 amino acids in length.

There are at least two transcript variants of TCF2; a third variant has been identified in the rat but not yet in man. Transcript variant a encodes protein isoform a, which predominates in the liver and stimulates transcription. Transcript variant b contains an intron that is spliced out of other variants, and as a result the encoded protein, isoform b, has a distinct C terminus. Isoform b appears to be unable to stimulate transcription and instead inhibits the transactivation activity of TCF1 (3).

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6928&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the TCF2 gene, two (at the time of writing) of which cause non-synonymous amino acid changes in the mature protein (Figure 2). One of these SNPs (rs1800575) has been associated with observed cases of MODY5 (allelic variant .0001).

A BLAST [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507397&cut=100&org=1] search using human TCF2 isoform a as a query finds proteins in 23 different species, which are all metazoans apart from two fungi and one bacterium. However, potential true homologous genes have thus far been identified only in the mouse and rat.

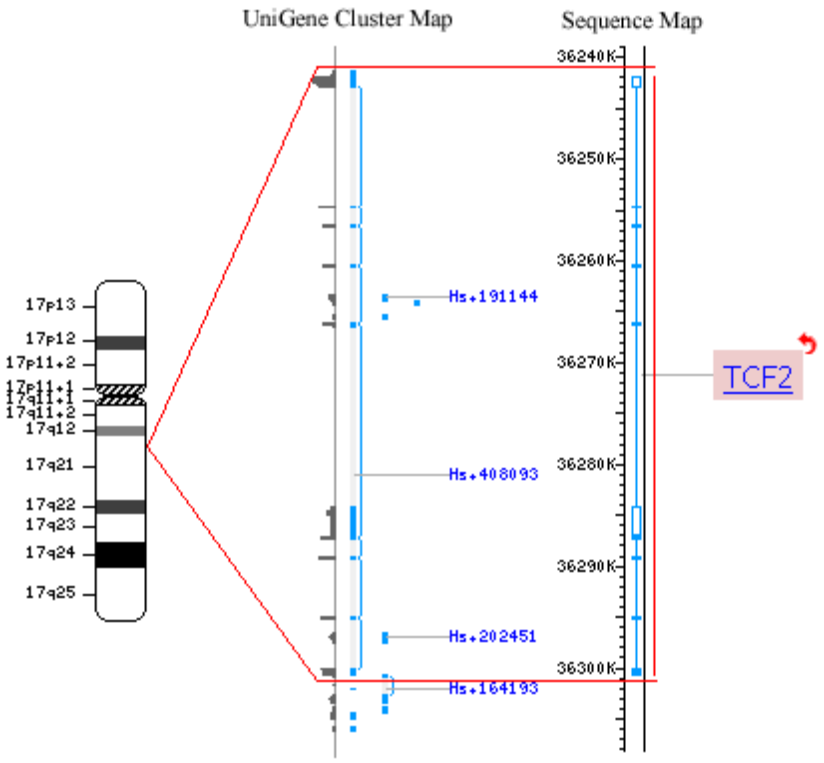


**Figure 1: Location of TCF2 on the human genome.**

TCF2 maps to chromosome 17, approximately between 36,220–36,320 kilobases (kb). Click on the figure or here for a current and interactive view of the location of TCF2 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 TCF2 may fluctuate. Therefore, the live Web site may not appear exactly as in this figure.

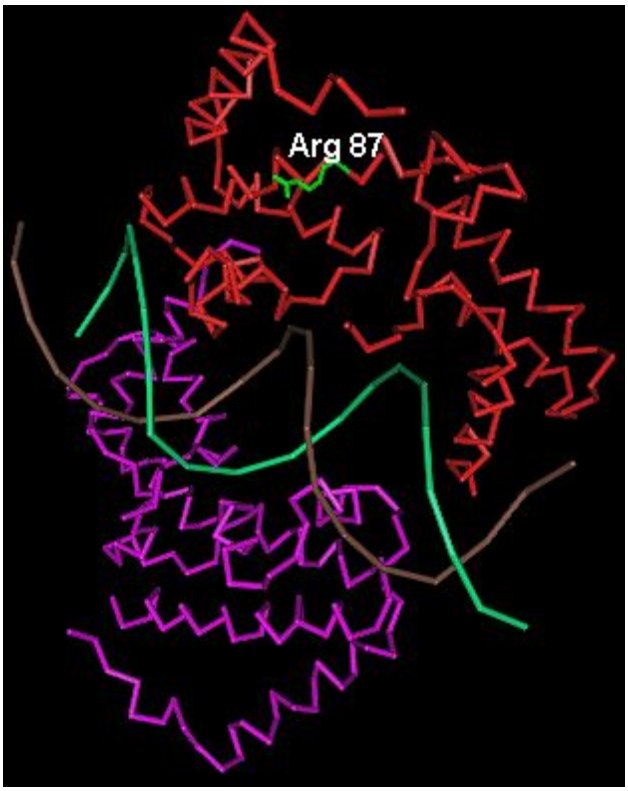


**Figure 2: SNP positions of TCF2 mapped to the 3D structure of human TCF1 bound to DNA.**
The figure shows the position of a non-synonymous amino acid change (Arg87, green residue) caused by a SNP in the coding sequence.

**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)**

## TCF2 and MODY5: Digest of Recent Articles

For a more complete list of research articles on TCF2 and MODY5, search PubMed.

Mutations in TCF2 are associated with MODY5, severe renal defects, and genital malformations (4).

Although renal disease is a common complication of diabetes, the renal disease that is associated with TCF2 mutations and MODY5 appears to be a direct result of the TCF2 mutation rather than a complication of hyperglycemia (5, 6).

Several mutations of TCF2 have been identified, many of which involve a deletion that disrupts the DNA binding domain (7). One such mutation was found in a Norwegian family in which a deletion in exon 2 resulted in a protein that lacked amino acids Arg-137 to Lys-161. Affected members had mild diabetes and non-diabetic renal disease that was worsening; both are features of MODY5. In addition, two affected female carriers of this mutation had an undeveloped vagina and uterus (8).

This mutant TCF2 protein was unable to bind to TCF1 and could not stimulate transcription of a target gene, indicating that this was a loss-of-function mutation.

A deletion mutation of TCF2 that spared the DNA binding domain was found to encode a protein with increased transactivation potential, suggesting that this was a gain-of-function mutation (9).

When both types of human mutant TCF2 were overexpressed in the embryo of the developing frog, they both interrupted the proper development of the kidney. This reflects the different types of renal disease that are seen in individuals with different types of TCF2 mutations. These findings imply that TCF2 has a central role in normal kidney development (9, 10).

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Diabetes and TCF2 in PubMed | PubMed Central | Books

### Background Information

TCF2 in OMIM

MODY5 in OMIM

### Molecular Biology

TCF2 name in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_078100.1&gene=TCF2&graphiconly=TRUE] | Map Viewer | Domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=6031205]: N terminus domain, Homeodomain | SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6928&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507397&cut=100&org=1] | HomoloGene

# MODY6: Caused by a Mutation in Transcription Factor NEUROD1

## Summary

The transcription factor NEUROD1 can directly activate the transcription of the insulin gene. It is also needed in the development of the pancreas beta cells and the nervous system. Mutations of this gene cause MODY6, the most recently discovered form of autosomal dominant diabetes, and may also play a role in type 1 and type 2 diabetes.

## Nomenclature

Official gene name: Neurogenic differentiation 1
Official gene symbol: NEUROD1
Alias: NEUROD, NeuroD, BETA2, BHF-1, Maturity Onset Diabetes in the Young type 6, MODY6

## Background

The development and the normal functioning of the endocrine pancreas are dependent on a network of transcription factors. These proteins influence the transcription of genes in a negative or positive way. The NEUROD1 gene encodes a transcription factor that is a positive regulator for the transcription of the insulin gene.

NEUROD1 (for "neurogenic differentiation") is a protein that was first discovered to be important in the development of the embyronic nervous system. The expression of NEUROD1 stimulates neurons to mature, or differentiate, and it has the potential to convert undifferentiated cells into neurones.

In animal models, mutations of the NEUROD1 gene disrupts the normal development of the pancreas, leading to diabetes (1). Certain structures in the brain, such as the cerebellum and hippocampus, also fail to develop properly, resulting in seizures (2, 3).

The link between NEUROD1 and diabetes was first suggested when it was discovered that the NEUROD1 gene is located in the same region of a chromosome that is linked with type 1 diabetes susceptibility (4). This region is called IDDM7 and is found on the short arm of chromosome 2.

In addition to the link with type 1 diabetes, variants of NEUROD1 have also been linked with susceptibility to type 2 diabetes (5), and a mutation of NEUROD1 causes the most recently discovered form of autosomal dominant diabetes, maturity onset diabetes in the young type 6 (MODY6) (5, 6).

## Molecular Information

NEUROD1 belongs to a group of transcription factors called basic helix-loop-helix (bHLH) proteins. The bHLH proteins contain a conserved sequence of amino acids that binds to DNA. This sequence is also known as a DNA-binding motif, and the HLH motif consists of a short alpha helix connected by a flexible loop to a second, longer alpha helix (see the HLH domain [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4505377]).

bHLH proteins are classified into two groups based on how they bind to DNA and in what tissues they are found. Class A members tend to be expressed in all tissues, whereas class B members, such as NEUROD1, are found only in specific tissues, mainly in the nervous system and the pancreas.

bHLH proteins can function as transcription factors only when two bHLH monomers complex to form a dimer. The two-helix structure of HLH binds both to DNA and to the HLH motif of a second HLH protein. The second HLH protein can be the same (resulting in a homodimer) or different (resulting in a heterodimer), and alpha helices extending from the dimerization interface make specific contacts with DNA.

The NEUROD1 gene maps to chromosome 2 (Figure 1). It has two exons (coding regions) that span about 4,860 bases (see evidence [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_005403.14&gene=NEUROD1&graphiconly=TRUE]); only exon 2 is translated (7). The gene encodes a protein of 356 amino acids.

Several single nucleotide polymorphisms (SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4760&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs]) have been found within the NEUROD1 gene, three (at the time of writing) of which cause non-synonymous amino acid changes in the mature proteins.

A BLAST [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4505377&cut=100&org=1] search using human NEUROD1 as a query finds proteins in 24 different species, which are all metazoans (multicellular). However, potential true homologous genes have thus far been identified only in the mouse, rat, and roundworm.

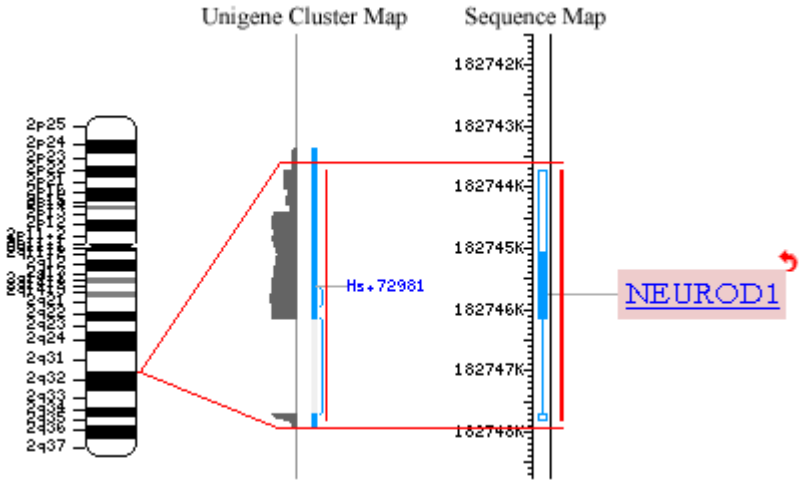


**Figure 1: Location of NEUROD1 on the human genome.**

NEUROD1 maps to chromosome 2, approximately between 18,2730–18,2760 kilobases (kb). Click on the figure or here for a current and interactive view of the location of NEUROD1 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 NEUROD1 may fluctuate. Therefore, the live Web site may not appear exactly as in this figure.

## NEUROD1 and MODY6: Digest of Recent Articles

For a more complete list of research articles on NEUROD1 and MODY6, search PubMed.

NEUROD1, after its heterodimerization with the HLH protein E37, regulates transcription of the insulin gene. NEUROD1 binds to the E-box motif of the insulin gene promoter. It is proposed that deficient binding of NEUROD1 or binding of transcriptionally inactive NEUROD1 to target promoters in pancreatic islets leads to the development of diabetes (5).

Mutations in NEUROD1 have been found in three families to date, and these mutations are associated with type 2 diabetes and MODY (8).

In one family, a G → T substitution in codon 111 caused a switch in amino acids at this position from arginine to leucine (Arg111Leu). The Arg-111 residue is found in the DNA-binding domain of NEUROD1 and has been evolutionarily conserved from the fruit fly to mammals and is found in all members of the HLH family of transcription factors (1). In this family, the Arg111Leu mutation was associated with type 2 diabetes; of the six carriers of the mutation, four were diagnosed with diabetes in their mid-40s, and two had impaired glucose tolerance.

A second family had an insertion of a cytosine residue in codon 206 (206+C), resulting in a frameshift mutation. The truncated protein that was synthesized lacked the C-terminal third of the protein, which includes the transactivation domain (9). Of the nine carriers of the 206+C mutation, seven had diabetes. The nature of the diabetes observed in the second family was different in several ways: the diabetes was diagnosed at an earlier age and was more severe (2 of the 206 +C carriers required treatment with insulin), and the affected individuals were not obese and had low insulin levels. The early onset and severity of diabetes resemble MODY rather than type 2 diabetes. Thus, mutations in NEUROD1 are proposed to be the cause of a new subtype of MODY, designated MODY6.

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NEUROD1 in OMIM

MODY6 in OMIM

### Molecular Biology

NEUROD1 name in Entrez Gene | Evidence Viewer [http://www.ncbi.nlm.nih.gov/sutils/evv.cgi?taxid=9606&contig=NT_005403.14&gene=NEUROD1&graphiconly=TRUE] | Map Viewer | Domains [http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi?INPUT_TYPE=precalc&SEQUENCE=4505377]: Helix-Loop-Helix (HLH) Domain | SNPs [http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4760&view+rs+=view+rs+&chooseRs=coding&.cgifields=chooseRs] | Allelic Variants | BLink [http://www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4505377&cut=100&org=1] | HomoloGene

# Genetic Defects in Insulin Action

A defect in the action of insulin, or the body being resistant to insulin, occurs when a given amount of insulin produces a subnormal biological response. Obesity is by far the most common cause of insulin resistance; however, genetic defects that disrupt the action of insulin may also cause insulin resistance (Table 1).

One symptom of severe insulin resistance is a skin disorder called acanthosis nigricans. Areas of the skin have abnormally increased coloration (hyperpigmentation) and "velvety" thickening (hyperkeratosis). This is particularly noticable in skin fold regions, such as of the neck and groin and under the arms. Acanthosis nigricans is commonly seen in inherited syndromes of severe insulin resistance.

## Type A Insulin Resistance

A previous classification of severe insulin resistance recognized two syndromes, type A and type B. Type A insulin resistance is inherited in a dominant manner (1), and in a minority of cases, a mutation in the insulin receptor gene can be isolated (2). Type B insulin resistance is not inherited; instead, it is caused by anti-insulin receptor antibodies and is often seen in older females with signs of autoimmune disease.

Type A Insulin Resistance in OMIM

Individuals with type A insulin resistance often have signs of polycystic ovarian syndrome: increased virilization caused by high levels of androgen hormones (hyperandrogenemia), a disruption of the menstrual cycle (oligomenorrhea), and an increase in body hair (hirsutism).

## Leprechaunism

Leprechaunism is an autosomal recessive disorder attributable to a defect in the insulin receptor (INSR). In 1954, the first cases were described by Donohue and Uchida, hence the alternative name for this condition, Donahue's syndrome (2).

The clinical features of Leprechaunism include an "elfin-like" facial appearance with protuberant ears and relatively large hands and feet. A decreased amount of subcutaneous fat and muscle mass is seen, and the skin is abnormal with increased hair growth. Acanthosis nigricans is also often present. This condition is usually fatal within the first couple of years of life.

Leprechaunism in OMIM

A number of mutations of the INSR have been found to cause leprechaunism. Among these are mutations that: cause a premature chain termination in the alpha subunit, thereby deleting the transmembrane and tyrosine kinase domains of the receptor (4); impair INSR dimerization and transport to the cell surface (5); and impair autophosphorylation of INSR (6).

## Rabson-Mendenhall Syndrome

In 1956, a pathologist, Dr. Rabson, and a family physician, Dr. Mendenhall, described the case of three young siblings who initially presented with skin and teeth abnormalities. The children, two girls and one boy, had a distinct appearance with coarse skin, acanthosis nigricans, and a senile facies. It was later discovered that the pineal gland, a gland at the base of the brain that secretes melatonin, was increased in size (pineal hyperplasia).

The constellation of pineal hyperplasia, insulin resistance, and other somatic abnormalities is called Rabson-Mendenhall syndrome. This rare syndrome is caused by a mutation of the insulin receptor gene, which leads to severe insulin resistance.

Rabson-Mendenhall syndrome in OMIM

Additional symptoms that appear from the first year of life include abdominal swelling and abnormal enlargement of the clitoris in females and penis in boys. Deficiency or absence of adipose tissue may also be present.

## Lipoatrophic Diabetes

Lipoatrophy is the wasting away (atrophy) of fat tissue. In the syndrome Berardinelli-Seip, lipoatrophy is so severe that from birth adipose tissue is almost absent. From early infancy severe insulin resistance causes diabetes. Other features include acanthosis nigricans, increased production of androgen hormones, an enlarged liver, and increased muscle mass.

Berardinelli-Seip Congenital Lipodystrophy syndrome in OMIM

At least two mutations on different chromosomes have been identified as a cause of Berardinelli syndrome, mutations in AGPAT2 on chromosome 9 (7) and mutations in BSCL2 mutation on chromosome 11 (8, 9). In many cases, disruption of the structure and the function of the insulin receptor cannot be found. For this reason, it is assumed that the problem lies at the post-receptor level, involving signal transduction.

**Table 1. Syndromes of severe insulin resistance**

| Syndrome | Cause | Mode of inheritance |
|---|---|---|
| **Disruption of insulin receptor** | | |
| Type A insulin resistance | Mutation of insulin receptor in up to 10% of cases | Usually dominant |
| Leprechaunism | Mutation of insulin receptor | Recessive |
| Rabson-Mendenhall syndrome | Mutation of insulin receptor | Recessive |
| **Lipoatrophic syndromes** | | |
| e.g., Berardinelli-Seip (congenital generalized lipodystrophy) | Involves at least two loci | Recessive |
| **Acquired syndromes** | | |
| Type B insulin resistance | Anti-insulin receptor antibodies | N/A |

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## Diseases in the Exocrine Pancreas

The pancreas gland lies across the posterior abdominal wall, behind the stomach. It has two main portions, the endocrine portion that secretes hormones and the exocrine portion that secretes enzymes.

The exocrine portion of the pancreas makes up more than 95% of its total cell mass. Here, powerful digestive enzymes are produced and are delivered to the duodenum (a part of the small intestine) via the pancreatic duct. These enzymes break down carbohydrates, proteins, and fats into smaller molecules that can be absorbed across the gut wall.

Any processes that diffusely injure the pancreas can result in diabetes and include:

- pancreatitis
- trauma or surgical removal of the pancreas
- cancer of the pancreas
- cystic fibrosis
- fibrocalculous pancreatopathy
- the iron storage disease hemochromatosis

# Diseases of the Endocrine System

Most cases of diabetes are caused by a combination of loss of beta cell function and insulin resistance. However, diabetes may also be caused by endocrine disorders that produce excess hormones that antagonize the action and secretion of insulin e.g., cortisol, growth hormone, and glucagon.

Patients with these endocrine diseases frequently develop diabetes secondary to a hormone-induced hyperglycemia that causes either insulin loss or an increase in insulin resistance. Treatment of the underlying disorder often leads to the normalization of blood glucose levels.

## Cushing's Syndrome

Cortisol increases blood sugar by increasing the liver's production of glucose while at the same time increasing insulin resistance in peripheral tissues. Cushing's syndrome is caused by an excess of cortisol, and hyperglycemia or diabetes is commonly observed in affected individuals.

## Acromegaly

Growth hormone is synthesized in the pituitary gland in the brain. A tumor in this gland is the main cause of acromegaly, an endocrine disorder characterized by excess growth hormone. Growth hormone increases insulin resistance, resulting in over half the patients showing signs of glucose intolerance and hyperinsulinemia.

## Pheochromocytoma

Epinephrine, as part of the "fight or flight" response, mobilizes glucose to ensure a readily accessible source of fuel in an emergency. By acting on alpha adrenoreceptors, epinephrine inhibits insulin secretion, increases the breakdown of glycogen to glucose in the liver and muscle, and also stimulates the breakdown of fat. By acting on beta adrenoreceptors, epinephrine increases peripheral insulin resistance.

Excess epinephrine can be the result of a pheochromocytoma, a tumor originating from the adrenal gland. The tumor increases epinephrine synthesis, and the resulting increased circulating levels of epinephrine can lead to diabetes.

## Glucagonoma

Glucagon opposes many of insulin's actions. Tumors of the pancreatic alpha cells are rare, but they may cause an increase in glucagon levels, resulting in impaired glucose regulation.

## Somatostatinoma

Somatostatin is secreted by a range of tissues, including the delta cells of the pancreas, and somatostatin inhibits the secretion of growth hormone. Diabetes is associated with somatostatinoma, a rare endocrine pancreatic tumor that secretes excess somatostatin, which inhibits insulin secretion.

# Drug- or Chemical-induced Diabetes

Many medications can impair insulin secretion. Such drugs may not directly cause diabetes but rather precipitate diabetes in individuals with pre-exisitng insulin resistance and deficiency. In addition, certain hormones, when in excess or when given as a therapy, can impair the action of insulin, e.g., glucocorticoids, thyroid hormone.

Although rare, particular toxins such as rat poison and specific drugs can permanently destroy the beta cells of the pancreas. This results in the abrupt onset of diabetes that requires insulin treatment, e.g., Vacor, Pentamidine.

## Beta-Adrenergic Agonists

Beta-Adrenergic agonists such as salbutamol are most commonly used in the treatment of asthma. One of the possible side effects of beta agonists is hyperglycemia, which is caused by a decrease in insulin sensitivity.

## Diazoxide

Diazoxide is used to treat hypoglycemia, and it works by preventing the pancreas from releasing insulin. Diazoxide is a potassium channel opener; it activates the pancreatic beta cell ATP-sensitive K+ (KATP) channel, hyperpolarizes the beta cell, and prevents insulin release. It is used in the treatment of insulinomas (insulin-secreting tumors), persistant hyperinsulimic hypoglycemia of infancy, and because diazoxide also dilates blood vessels, it can be used to lower high blood pressure.

## Glucocorticoids

Glucocorticoid drugs are synthetic copies of the body's steroid hormones. Steroids raise blood glucose levels by counteracting many of the actions of insulin, favoring the break down of carbohydrates, fat, and even protein, releasing raw materials from which glucose can be made. Excess steroid hormone (e.g., in Cushing's disease) or prolonged use of steroid drugs (e.g., prednisolone) can lead to glucose intolerance or diabetes.

## Interferon-alpha Therapy

The body makes interferon alpha (IFNα) as part of the immune response. It is produced in particular types of white blood cells in response to infection or cancer. IFNα can be given as a treatment for certain types of cancer and long-standing infections and inflammatory conditions.

When IFNα therapy is used to treat chronic hepatitis C, a rare side effect is that some patients develop diabetes. IFNα appears to trigger an autoimmune attack against several endocrine organs, including the pancreas islet cells. Similar to type 1 diabetes, this new-onset diabetes requires treatment with insulin.

## Nicotinic Acid

Nicotinic acid is a B vitamin that is found in meat, poultry, fish, wholemeal cereals, pulses, and coffee. It is also taken as a drug to lower lipid levels (serum cholesterol and triglycerides). There are several side effects of taking nicotinic acid, including liver toxicity and deranged blood glucose levels.

## Pentamidine

Pentamidine is an antiprotozoal agent used to treat trypanosomiasis, leishmaniasis, and some fungal infections. A more common use of this drug in the United States is in the treatment of pneumocystis pneumoniae, which can cause pneumonia in immunocomprised patients. Pentamidine can cause irreversible beta cell damage, leading to loss of insulin and resulting in diabetes. It is also toxic to the central nervous system.

## Phenytoin

Phenytoin is an anticonvulsant drug that is effective in controlling a wide variety of seizure disorders. It is thought to suppress seizures by blocking sodium ion channels in neurons, preventing overexcitation. One side effect of phenytoin use is hyperglycemia. This may be because phenytoin blocks calcium ion channels in the pancreatic beta cells, inhibiting insulin release.

## Thiazides

High doses of thiazides (a type of diuretic) can worsen hyperglycemia in type 2 diabetes. Thiazides appear to impair insulin secretion as a consequence of causing K+ depletion (a known side effect of thiazides). Thiazides may also increase insulin resistance. The effect on glucose intolerance is less when the dose of thiazide is decreased.

## Vacor

Accidental ingestion of the rat poison Vacor can be fatal. Vacor is toxic to pancreatic beta cells, rapidly depleting insulin production and causing acute diabetic ketoacidosis.

## Link Roundup

### MedlinePlus Drug Information

Pentamidine [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202449.html] | Nicotinic acid [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202405.html] | Glucocorticoids [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202018.html] | Diazoxide [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202191.html] | Beta adrenergic agonists: inhaled [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202095.html], oral [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202096.html] | Thiazides [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202208.html] | Phenytoin [http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682022.html] | Interferon-alpha therapy [http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202299.html]

# Infections

A genetic predisposition to type 1 diabetes has been well established. However, many lines of evidence also point to the existence of environmental risk factors that may act as the trigger for the autoimmune attack on the pancreas (1).

Viruses have been suspected to contribute to the onset of type 1 diabetes because new cases of diabetes occur more frequently at certain times of the year (2). More recently, virus-specific IgM antibodies have been isolated from patients with new-onset diabetes (3), and pancreatic extracts from patients who died from new-onset diabetes cause diabetes in animals by the destruction of beta cells (4).

Several viruses have been associated with inducing certain cases of diabetes and include the following:

- rubella virus
- Coxsackie B virus
- mumps virus
- cytomegalovirus
- Epstein-Barr virus
- adenovirus
- rotavirus

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# Uncommon Forms of Immune-mediated Diabetes

Type 1 diabetes is caused by an autoimmune attack of the pancreatic islets. Immune-mediated attacks are also responsible for rarer syndromes of which diabetes is a feature, including those discussed below.

## Antibodies to Insulin

Rarely, the formation of insulin autoantibodies can deplete levels of insulin to such an extent that diabetes develops.

## Antibodies to the Insulin Receptor

Autoantibodies directed against the insulin receptor are occasionally found in patients who have co-existing autoimmune diseases, such as systemic lupus erythematosus (SLE). As in other states of severe insulin resistance, the skin disorder acanthosis nigricans is often found. The syndrome of severe insulin resistance with circulating antibodies to the insulin receptor is known as type B insulin resistance.

Anti-insulin receptor antibodies can cause hyperglycemia by binding to the insulin receptor and blocking the binding of insulin to its receptor in target tissues. In rare cases, these autoantibodies can have the opposite effect, causing hypoglycemia by mimicking the action of insulin.

## "Stiff Man" Syndrome

The Stiff Man syndrome is a rare autoimmune disorder of the central nervous system that is characterized by stiffness of the axial muscles. Individuals have painful muscle spasms that may be precipitated by unexpected events or physical contact. As the disease progresses, there is increasing stiffness of the muscles supporting the spine and in the arms and legs.

Stiff Man Syndrome in OMIM

The autoantibody anti-glutamic acid decarboxylase (GAD) is found in high levels in classical Stiff Man syndrome (1). The antibody is directed against an enzyme found in the nerve tissue and may play a role in the abnormal muscle activity of these patients (electrical studies show that the muscle is unable to relax). In addition, anti-GAD antibodies may attack the pancreas, which also contains the enzyme. This may be the cause of one in three patients with Stiff Man syndrome developing a form of insulin-dependent diabetes.

## References

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# Other Genetic Syndromes Sometimes Associated with Diabetes

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus and include syndromes caused by a single gene mutation and syndromes caused by a chromosomal abnormality.

## Gene Mutations

- Friedreich ataxia [Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.205]]
- Huntington's chorea [Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.207]]
- Lawrence-Moon-Biedel syndrome
- Myotonic dystrophy [Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.164]]
- Porphyria [Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.267]]
- Prader-Willi syndrome [Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.182]]
- Wolfram's syndrome

## Chromosomal Abnormalities

- Down's syndrome
- Klinefelter's syndrome
- Turner's syndrome