DIABETES TYPES 1 AND 2 AND INHERITED PREDISPOSITION

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Important points

- Diabetes mellitus (diabetes) is a condition resulting in high levels of sugar (glucose) in the blood
- There are several types of diabetes: type 1 (insulin dependent diabetes), type 2 (non-insulin dependent diabetes) and Maturity-onset diabetes of the young (MODY)

Type 1 diabetes can occur at any age:

- Onset after the age of 20 years occurs in 50% of cases
- It is likely to be due to an inherited predisposition triggered by exposure to other 'environmental factors'
- Several genes in which changes lead to predisposition have been identified, including certain genes that control the immune system.
- Currently, it is only possible to give general risks for other family members when one member is diagnosed with type 1 diabetes based on data observed in many families
- Genetic testing is still in the research phase

Type 2 diabetes is more common and makes up 85% of all Australians affected with diabetes.

- The frequency, and the most common age of onset is different in different populations. The condition is epidemic in some countries
- Both a genetic and environmental contribution is likely
- For example, changes in the *HNF-4α* gene are associated with about a 30% increased susceptibility to type 2 diabetes
- Currently, it is only possible to give general risks for other family members being affected when one member is diagnosed with type 1 diabetes based on data observed in many families
- Genetic testing is still in the research phase

Maturity-onset diabetes of the young (MODY) is a rare form of type 2 diabetes that onsets generally before 25 years of age.

- 2%-5% of the diabetic population has MODY
- The function of specific cells in the pancreas is impaired, causing reduced insulin secretion
- Most people with MODY carry a change in one of six known susceptibility genes
- Genetic testing is available on a research basis in Australia

Diabetes mellitus (commonly known as diabetes) is a group of conditions, all resulting in high levels of *glucose* (a form of sugar) in the blood. Glucose plays an essential role in maintaining the metabolism of the body's cells: it provides the energy cells need to function. The level of glucose in an individual's blood is carefully regulated by the hormone *insulin.* Insulin is produced in the pancreas and its role is to keep the levels of glucose balanced - not too high and not too low - as both extremes are dangerous and can disrupt the body's chemical processes.

There are two major forms of diabetes mellitus:

- Type 1 (insulin dependent: IDDM)
- Type 2 (non-insulin dependent: NIDDM)

There is also another rarer type of diabetes called Mature Onset Diabetes of the Young (MODY).

All of these forms of diabetes have a different clinical picture and genetic basis.

Type 1 diabetes

About 10% to 15% of people with diabetes in Australia have type 1 diabetes (also called insulin dependent diabetes mellitus or IDDM). The general population risk for developing type 1 diabetes is around 1 in 300.

The condition is usually first seen in childhood or adolescence and so is often called juvenile diabetes but this term can be misleading. Type 1 diabetes can occur at any age and onset after the age of 20 years occurs in 50% of cases.

What are the characteristics of type 1 diabetes?

Symptoms include thirst, frequent urination and sugar in the urine. The symptoms in these individuals are due to their pancreas producing little or no insulin, leading to the high levels of glucose in their blood and urine.

Insulin medication (usually by injection) is necessary to provide the body with insulin, and thus type 1 diabetes is described as insulin-dependent diabetes.

In about 90% of cases, individuals are absolutely insulin dependent from the onset of symptoms. Their insulin producing cells in the pancreas (*beta cells*) become damaged by their body's own immune system acting against itself. This is why diabetes is referred to as an **auto-immune disease.**

What causes type 1 diabetes?

Type 1 diabetes is thought to be due to an inherited predisposition to develop the condition as well as an interaction with other 'environmental factors' that trigger the onset of symptoms.

Without these triggers, the condition does not develop. See Genetics Fact Sheet 11 for more information about conditions due to environmental and genetic interactions.

The cells of the body contain the genes or set of instructions for the cell to make all the necessary proteins (chemicals) for our bodies to grow and work normally (see Genetics Fact Sheet 1).

If a gene is changed so that it does not work properly, the gene is described as being faulty (ie. there is a gene *mutation* present). The information contained in the product of the faulty gene is impaired, or is not produced in the right amounts (see Genetics Fact Sheets 4 & 5).

There are several genes in which changes lead to predisposition to type 1 diabetes, including certain genes that control the immune system. This association is not surprising since diabetes is an auto-immune disease, as described above.

These immune system genes code for the proteins in the **HLA (human leukocyte antigen) system**.

The immune system (HLA system)

The HLA system is primarily responsible for the body being able to distinguish between cells that belong to the person ('self') and those from foreign or invading organisms ('non-self' cells). When a foreign cell or body is recognised as 'non-self', the body rejects it by marshalling the proteins of the HLA system. That is why it is important, for example, in organ transplantation for the cells of the donated organ to be HLA 'compatible' (have the same or similar HLA genetic make-up) with the cells of the person receiving the transplant so that the body does not reject it as something foreign.

The genes of the HLA system contain the information for the body to make certain proteins (called *antigens)* that 'mark' the white blood cells so that the body can recognise them as part of 'self'. The *HLA* genes have been localised to the short ('p') arm of chromosome 6 (6p) - see Genetics Fact Sheet 1. Cells that do not have the same 'antigen' would be considered 'non-self'.

The HLA system is made up of a large number of different genes including *HLA-A HLA-B, HLA-C, HLA-D, HLA-DR* and *HLA-DQ*. Each of these *HLA* genes contains the information for particular antigens that mark the cells, so a person can be classified according to their white blood cell antigens or HLA make-up. Similarly red blood cells are marked with antigens so that they can be distinguished as belonging to any of blood groups A, B, O or AB.

The HLA system however, is very complex and each of the different *HLA* genes can also have a number of different forms (designated as *HLA-A1, HLA-A2* etc), due to variations in their information: for example, *HLA-A1, HLA-A2*. So there are many possible combinations of the *HLA* gene types, which is why it can be so difficult to find another person who is a match for their HLA system, when donors are needed for transplants.

Everyone has two copies of each gene, one inherited from their mother and one from their father. So the *HLA* genes for the white blood cell antigens are passed from parent to child: each parent contributes one set of *HLA* genes to the child.

HLA genes and inherited predisposition to type 1 diabetes

The contribution of changes in the *HLA* genes to predisposition to type 1 diabetes however is complex. The *HLA-DR* and *HLA-DQ* genes contribute to both genetic susceptibility and protection.

Figure 57.1 shows the possible combinations of the *HLA-DR* genes in a family. The father's *HLA-DR* genes are of type *DR3* and *DR7*; the mother's are of type *DR4* and *DR5*.

- One of the children has inherited the *HLA-DR3* gene copy from their father and the *HLA-DR4* gene copy from their mother and has developed type 1 diabetes
- On the other hand, one of the other children also has the *HLA-DR3/DR4* combination and they do not have diabetes – but they are at risk for developing the condition. Yet that risk for developing type 1 diabetes is only about 19% (or 1 chance in 5-6) over their lifetime. Type 1 diabetes is more likely to develop at a younger age: the older the person gets, the lower this chance becomes for them to develop the condition
- The chances for the other children of these parents to develop diabetes when they have different combinations of the *HLA-DR* group ie. *DR3/DR5*, *DR7/DR4* and *DR7/DR5*, is about 4% (or 4 chances in 100) over their lifetime

So, it appears that:

- If a individual inherits the *HLA-DR3* type from one parent and the *HLA-DR4* type from the other parent, they have a high chance of developing type 1 diabetes
- BUT, there are many people with this HLA make-up (*HLA-DR3/DR4*) who never develop type 1 diabetes, even within the same family

To add to the complexity, it appears that a person with the genetic make-up *HLA-DR2, DR5* has almost no chance of developing type 1 diabetes.

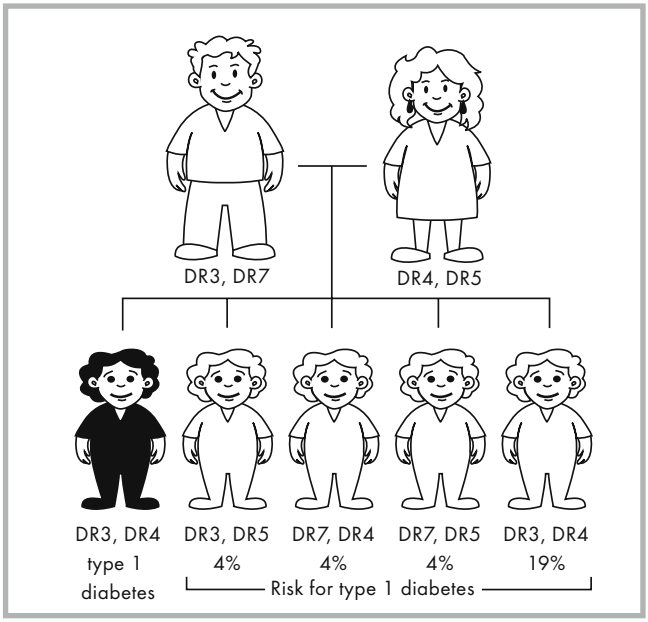

Figure 57.1: *A person's HLA genetic make-up may contribute to their risk for developing type 1 diabetes. Source: S. Serjeantson (1994). The Genetics of diabetes. Diabetes and You: an Owners Manual. Diabetes Australia, Canberra.*

DR2 and *DR5* are referred to as 'diabetes resistance' genes.

In a family where one or more members have type1 diabetes, knowing the HLA-DR antigen make-up can enable doctors to estimate the chance that other members may also develop the condition.

If one of the parents has diabetes, the chance for diabetes in his or her children, also depends on the child's HLA. Each family needs to be studied very carefully and the risk figures provided to the parents will relate to their *HLA* genetic make-up.

Other work has suggested that different HLA-DR and HLA-DQ combinations can impact on the age of onset of the type 1 diabetes and the degree of severity of the condition. These findings again illustrate the complexity of the HLA and diabetes relationship.

Research is continuing to identify other HLA genes as well as genes associated with the insulin gene in conferring susceptibility to develop type 1 diabetes.

Currently, it is only possible to give general risks for other family members developing type 1 diabetes when one member is diagnosed with the condition (*Table 57.1*). Genetic testing is still in the research phase.

What are the environmental triggers that lead to the onset of type 1 diabetes?

Regardless of a person's HLA genetic make-up, the condition will only develop if additional factors are present. These include viruses, interactions with the information in other genes or other unknown environmental factors.

One possible explanation for the onset of symptoms is that an unidentified virus stimulates an autoimmune attack against the cells of the pancreas that produce insulin in some genetically predisposed people.

Research is continuing to identify the factors that may be important in prevention.

Table 57.1. *Approximate risks for developing type 1 diabetes (European data)*

Family situation	Risk for developing type 1 diabetes
In the general population	1 in 300
When a brother or sister is affected and they do not have the same HLA combination	1 in 100
When a parent is affected	1 in 25
When a brother or sister is affected	1 in 14
When a brother or sister is affected and they have the same combinations for 2 or more of the HLA genes	1 in 6
When a brother or sister and a parent or child is affected	1 in 6
When an identical twin is affected	1 in 3

Type 2 diabetes

Type 2 diabetes (also called non-insulin dependent diabetes mellitus: NIDDM).

- Affects between 1% and 5% of the general population and accounts for more than 85% of people with diabetes in Australia
- Overall, about 7.5% of the Australian population aged 25 years and older has diabetes
- Over 23.6% of people 75 years and older have diabetes

The frequency of the condition, and the most common age of onset, is different in different populations. The condition is epidemic in some countries.

- The lowest frequency is seen in less developed countries (up to 2% in China and Africa)
- The highest frequency can be found in certain ethnic groups around the world:
  - Australian Aboriginal people - about 50% are affected
  Pima Indians in USA
  South Sea Islanders and Pacific Islanders, all of whom develop type 2 diabetes early in their lives and quite severely

What are the characteristics of type 2 diabetes?

The pancreas produces some insulin in people with type 2 diabetes, but their bodies become resistant to the insulin's action. This leads to high blood sugar levels.

Type 2 diabetes most often occurs after the age of 40 so it is sometimes referred to as maturity-onset diabetes.

- Several rare forms of type 2 diabetes occur in childhood, adolescence or young adulthood under 25 years. These are therefore referred to as maturity-onset diabetes of the young (MODY; see below)
- Increasing incidence of diabetes parallels the increase in incidence of obesity in the community

What causes type 2 diabetes?

The involvement of genetics in predisposition for type 2 diabetes is stronger than for type 1. It is still, however, unknown how much of the contribution to the condition is genetic, and it is likely that there are a number of genes involved.

It is clear that type 1 and type 2 diabetes 'cluster' in the same families. These findings support a possible common genetic interaction between type 1 and type 2 diabetes involving the HLA genes, although to date no other clear association with the HLA complex genes has been shown.

Since type 2 diabetes involves the development of resistance to the action of insulin, changes in the genes associated with insulin production and action were thought to be possible causes of the condition. Research is ongoing in this area and more work is needed to understand the genetic basis of the condition.

Further work is concentrating on the genes containing information that governs the transport of glucose in and out of cells. For example, having one of several different changes in the hepatocyte nuclear factor 4 alpha (HNF-4α) gene is associated

Table 57.2. *Approximate risks for developing type 2 diabetes (European data)*

Family situation	Risk for developing type 2 diabetes
General population	Variable
When a brother or sister is affected	1 in 10
When a parent is affected	1 in 10
When a brother or sister and a parent or child is affected	1 in 5
When an identical twin is affected	1 in 2

with about 30% increased susceptibility to type 2 diabetes over the general risk in that particular population.

Currently, it is only possible to give general risks for other family members for developing type 2 diabetes when one member is diagnosed with the condition. (*Table 57.2*). Genetic testing is still in the research phase.

What are the environmental triggers that lead to the onset of type 2 diabetes?

One of the known triggers for the condition is obesity.

Importantly, even though a person may have an inherited susceptibility to develop diabetes, diet and exercise may delay the onset of the condition, or it may not develop at all.

Nevertheless, prevention by the manipulation or avoidance of other unknown environmental triggers is still subject to much research.

Maturity-onset diabetes of the young (MODY)

Maturity-onset diabetes of the young is a rare form of type 2 diabetes. 2%-5% of the diabetic population has MODY.

What are the characteristics of MODY?

This form of diabetes is also associated with abnormality of the function of the beta cells of the pancreas, so affected individuals have impaired insulin secretion with minimal or no defect in insulin action. Features of the condition include:

- Mild increases in glucose levels at an early age (generally before age 25 years)
- There is variable severity and age of onset but symptoms usually are present before 25 years of age
- There is no association with obesity, as occurs with the common form of type 2 diabetes

What causes MODY?

Unlike the common form of type 2 diabetes, MODY does have a clear-cut pattern of inheritance in families. There are a number of different forms of the condition associated with changes in different genes. Around 87% of the different forms of MODY are a result of changes in one of six different genes. All play a crucial role in insulin production and insulin secretion (*Table 57.3*)

What is the pattern of inheritance of MODY in families?

Two factors influence the pattern of inheritance of the faulty genes identified in the different forms of MODY.

1. All of the MODY genes are located on autosomes (one of the numbered chromosomes)
2. The effect of a change in the MODY gene copy is 'dominant' over the information in the working copy of the gene on the partner chromosomes (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance of the faulty gene copy predisposing to MODY in families, is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In *Figure 57.2*, the autosomal dominant faulty gene copy causing MODY is represented by 'D'; the working copy by 'd'.

Table 57.3. *Faulty genes identified in the different forms of MODY. Table reproduced from Chan J Searching for diabetes genes – A clinician scientist's perspective. Department of Medicine & Therapeutics The Chinese University of Hong Kong http://www.apdec.diabetes.net.au/ Accessed May 2007*

	MODY 1	MODY2	MODY3	MODY4	MODY5	MODY6
Chromosomal location	20	7	12	13	17	2
Gene name	HNF-4α	glucokinase (GCK)	HNF-1α	IPF-1	HNF-1β	NEUROD-1
Distribution (% of families)	Rare	10-65	20-75	Rare	Rare	10-20
Age at diagnosis	Post-pubertal	Childhood	Post-pubertal	Early adulthood	Early adulthood	Variable
Severity of diabetes	Severe	Mild	Severe	Mild-severe	Severe	Mild-severe

Where one of the parents has MODY due to having a faulty MODY gene copy, **in every pregnancy**, each child has:

- A 1 chance in 2 (50% chance) of having inherited the particular faulty copy from the affected parent
- A 50% chance of not having inherited it. Children who have not inherited the faulty gene copy are not at risk of developing MODY Importantly, these children cannot pass the faulty gene copy on to their own children

While the father is shown as the parent carrying the faulty MODY gene copy in *Figure 57.2*, the same situation would arise if it was the mother. MODY usually affects men and women equally.

What does understanding the faulty genes involved in MODY mean for people with a family history of the condition?

Knowing the genetic variation and its impact on the gene product may facilitate the design of targeted treatments for the specific type of diabetes.

In some cases, the management of the symptoms of diabetes may be changed if the causative faulty gene is identified.

Genetic testing to determine if a family member has inherited the faulty gene copy predisposing to MODY may be available if the specific change in the faulty copy of the gene has been identified in an affected family member. Such testing should only be considered after genetic counselling (see Genetics Fact Sheet 3).

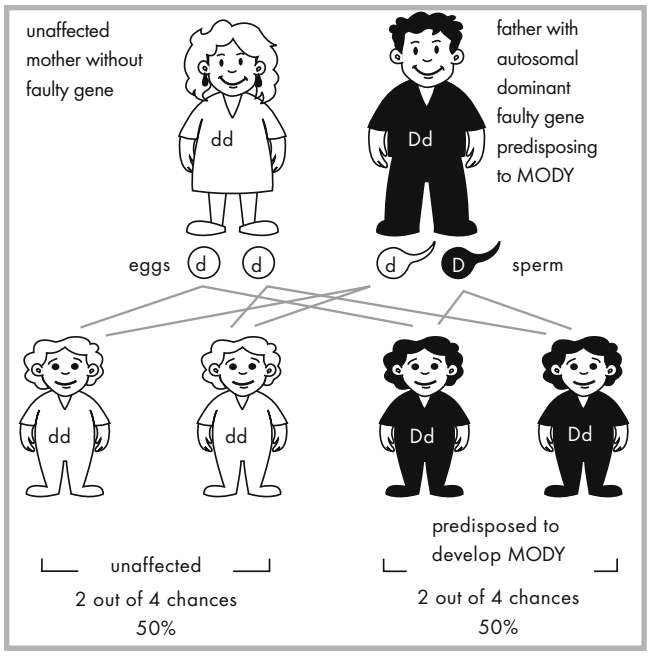

Figure 57.2: *Autosomal dominant pattern of inheritance where one parent has the faulty MODY gene copy. The faulty MODY gene copy is represented by 'D'; the working copy by 'd'.*

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 11

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