This fact sheet describes the different forms of diabetes and includes a discussion of the symptoms, causes and available testing.

In summary

- There are three types of diabetes
  - ◊ Type 1 (insulin dependent diabetes mellitus: IDDM)
  - ◊ Type 2 (non-insulin dependent diabetes mellitus: NIDDM)
  - ◊ Mature onset diabetes of the young (MODY).
- All forms of diabetes result in high levels of glucose in the blood
- Both type 1 and type 2 diabetes are due to an interaction between genetic and environmental factors
- MODY is a rare form of diabetes, generally caused by a dominant mutation in one of six known genes.

## WHAT IS DIABETES?

**Diabetes mellitus** (commonly known as diabetes) refers to a group of conditions which cause high levels of *glucose* (a form of sugar) in the blood. Glucose provides the energy that 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:

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

There is also another rarer type of diabetes called **mature onset diabetes of the young** (MODY).

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

### Type 1 diabetes (IDDM)

Type 1 diabetes is a chronic autoimmune disease, where the immune system destroys the insulin-producing cells of the pancreas. About 10% to 15% of people with diabetes in Australia have type 1 diabetes.

The general population risk for developing type 1 diabetes is around 1 in 1000. The condition is usually first seen in childhood or adolescence and so is sometimes called juvenile diabetes. The risk of type 1 diabetes in 0-14 year olds around 1 in 750. It can, however, occur at any age and onset after the age of 20 years occurs in 50% of cases.

Symptoms include:

- thirst
- frequent urination
- weight loss
- fatigue
- blurred vision
- sugar in the 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 (IDDM). In about 90% of cases, individuals are insulin dependent from the onset of symptoms.

*What causes type 1 diabetes?*

Type 1 diabetes is thought to be due to the interaction of both genetic and environmental factors, however the exact cause is still unknown. When both genetics and external factors combine to cause a disease, this is called *multifactorial inheritance*. (See figure 48.1)

Our bodies are made up of millions of cells. Each cell contains a complete copy of our genetic information or DNA. Our DNA contains the instructions for growth and development and is packaged into chromosomes that contain all our genes. A variation in a gene that creates a fault is called a **pathogenic variant** or **mutation**. Genes are sections of DNA that code for the proteins our body needs to function. A mutation in a gene will affect the body differently depending on how much it changes the resulting protein, how critical that protein is to the body and how much of that protein is needed in the body.

There are several genes in which mutations can lead to a 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.

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. Genetic testing is still in the research phase.

**Type 2 diabetes (NIDDM)**

Type 2 diabetes is also called non-insulin dependent diabetes mellitus: NIDDM). It affects around 5% of the general population and accounts for more than 85% of people with diabetes in Australia.

Type 2 diabetes is a progressive disease where either the pancreas does not make enough insulin or the body has become resistance to insulin's action. It most often occurs after the age of 45, but can also occur in younger people. Symptoms of type 2 diabetes include:

- Being thirsty
- Passing more urine
- Fatigue
- Blurred vision
- High blood sugar levels (hyperglycaemia)
- Poor wound healing

*What causes type 2 diabetes?*

Type 2 diabetes, like type 1, is thought to be due to the interaction of both genetic and environmental factors and the exact cause is still unknown.

When both genetics and external factors combine to cause a disease, this is called *multifactorial inheritance*. (See figure 48.1)

There are, however, known lifestyle factors that increase the risk of type 2 diabetes, such as:

- A history of a cardiovascular event (stroke, angina, myocardial infarction, peripheral vascular disease)
- Being over 40 years of age and overweight (BMI $\geq$ 30kg/m$^2$) or having high blood pressure
- Being from Aboriginal or Torres Strait Islander background
- Being over 35 years and from Pacific Island, Indian subcontinent or Chinese cultural background
- Being a woman who has given birth to a child over 4.5kg (9lbs) or have a history of gestational diabetes
- Being a woman with polycystic ovary syndrome (PCOS) who is obese
- Taking antipsychotic medication.

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

As the genetic factors involved in type 2 diabetes are not well understood, 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.

**Maturity-onset diabetes of the young (MODY)**

Maturity-onset diabetes of the young is a rare form of diabetes that affects 2% - 5% of people with diabetes.

This form of diabetes is caused by impaired insulin production or release by the beta cells of the pancreas. Features of the condition include:

- Being diagnosed with diabetes under the age of 25
- Not necessarily needing insulin
- There is no association with obesity, as occurs with the common form of type 2 diabetes.

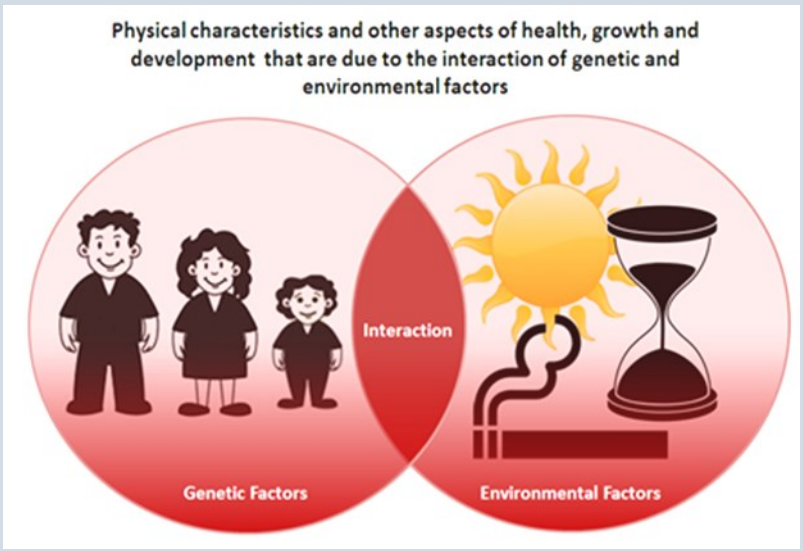


***Figure 48.1:*** *A diagrammatic representation of the interaction between genetic and environmental factors*

*What causes MODY?*

MODY, unlike other types of diabetes, is not a multifactorial condition. MODY is caused by a single mutation in a specific gene. Around 87% of the different forms of MODY are the result of changes in one of six different genes. All play a crucial role in insulin production and insulin secretion *(see Table 481).*

*How is MODY inherited?*

MODY follows a pattern called *autosomal dominant inheritance* in a family.

MODY is due to a mutation in a specific autosomal gene. An **autosomal** gene is a gene located on a numbered chromosome and usually affects males and females in the same way.

There are two copies of the gene in each cell and both copies of the gene normally send a message to the cells to produce a protein. A person with MODY will have one working copy of the gene and one faulty copy in their cells, so there will be less than the usual amount of the protein produced. This means that certain processes in the body will not work as efficiently as they should. The faulty gene copy is therefore described as being "dominant" since a person only needs one faulty copy to develop symptoms.

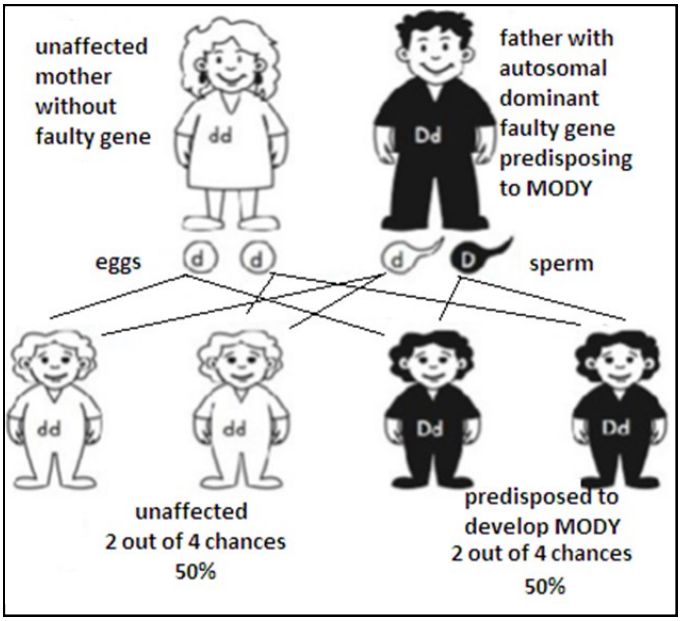


***Figure 48.2:*** *Autosomal dominant pattern of inheritance where one parent has the faulty MODY gene copy. The faulty MODY gene copy is represented by 'D'; the working copy by 'd'*

| | 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 |

***Table 48.1.*** *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*

In *Figure 48.2*, the faulty gene copy causing MODY is represented by 'D' and the working copy by 'd'. When one of the parents has MODY due to a faulty gene copy, there are four possible combinations of the genetic information that is passed on by the parents.

This means that, **in every pregnancy**, there is

- A 1 chance in 2 (i.e. 2 chances in 4) or 50% chance that their child will inherit a copy of the faulty gene and will therefore be affected by MODY at some time in their life
- An equal chance (i.e. 1 chance in 2) or 50% that their child will inherit the working copy of the gene from his/her affected parent as well as a working copy from his/her unaffected parent. In this case, the child will not develop MODY and cannot pass on the faulty gene copy to any of his/her children.

While the father is shown as the parent carrying the faulty MODY gene copy in *Figure 48.2,* the same situation would arise if it was the mother. MODY usually affects men and women equally.

Knowing the genetic variation and its impact on the gene product can be important for targeted treatments for the specific type of diabetes.

In some cases, the management of the symptoms of diabetes may be changed if a mutation is identified.

Once the mutation is identified, family members who are at up to 50% chance of having inherited the faulty gene, but who do not have any symptoms of the condition, can have 'presymptomatic' genetic testing.

## IS THERE ANY TESTING AVAILABLE FOR DIABETES?

The chance that a person in the general population will develop type I diabetes is around 1 in 1000. This risk increases to 1 in 16 if a first degree relative (parent, child, brother or sister) has been diagnosed with type I diabetes.

The chance of developing type II diabetes if a first degree relative has the condition is approximately 1 in 10.

To diagnose diabetes, a blood test that measures the amount of glucose in the blood is needed. Genetic testing for type I and type II diabetes is not available at this stage.

Genetic testing may be available for MODY if there is a significant family history and a diagnosis of diabetes has already been made. For family members who are at up to 50% chance of having inherited a MODY gene mutation, but do not have any symptoms of the condition, 'presymptomatic' genetic testing may be available following genetic counselling.

Genetic counselling in conjunction with your diabetes care team may be useful in providing the most up-to-date information and advice about the availability and implications of genetic testing.