Causes of Type 1 and Type 2 Diabetes

About 382 million people worldwide have diabetes; 90-95% of these have Type 2 diabetes. A further 316 million have impaired glucose tolerance and are at high risk of progressing to ‘full-blown’ diabetes. By the year 2035 the global prevalence figure is predicted to have risen to 471 million. Type 1 diabetes accounts for only 5-10% of cases of diabetes.

Those at high risk of developing Type 2 diabetes include:

- **People over forty**: Type 2 diabetes, which accounts for the majority of diabetes, is most common in middle and old age (although younger people are increasingly developing Type 2 diabetes)
- **People who are overweight**: Over 80% of people with Type 2 diabetes are obese
- **People with diabetic relatives**: Both Type 1 and Type 2 diabetes are associated with an inherited tendency (see below). The genetic component of the disease is different for Type 1 and Type 2. Many scientists believe that the risk of passing on Type 2 diabetes to offspring is greater if the diabetic parent is the mother.

Diabetes is rare in some populations and racial groups, but occurs more frequently in others. The annual incidence of Type 1 diabetes in Finland, for example, is 64 per 100,000; in China it is only about 0.1 per 100,000. Maori males are 3 times, and females 5 times, more likely to develop Type 2 diabetes, compared to their New Zealand European counterparts. In the United States, African Americans appear to be twice as likely to develop Type 2 diabetes than white Americans.

So what do we know about the causes of diabetes?

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Part 1: What Causes Diabetes?

Here, we consider potential causes of the two most prevalent forms of diabetes – Type 1 and Type 2 diabetes. The precise mechanisms underlying the conditions are still not fully understood and it will be a while yet before scientists and researchers have all the answers. In the mean time, however, we do have a number of clues that we can piece together to give us at least some idea of what might be going on.

Both Type 1 and Type 2 diabetes are thought to have a genetic basis, but this alone is not sufficient to give rise to the condition. The genetics are complex. There are many genes involved; some may contribute towards diabetes, others may protect us from diabetes. In addition, there are other factors that appear to influence our risk of developing either Type 1 or Type 2 diabetes. These are known as environmental factors and they often tend to be associated with the way in which we live our lives.

Together, genetic and environmental influences combine to determine our destiny.
The Genetic Element

What are Genes?

Embedded in our cells are series of instructions which control how our cells function and define us as human beings. These instructions are coded by strings of molecules which make up DNA. Genes are lined up along our chromosomes, each gene being a segment of DNA which tells the cell to make a specific protein. A gene can be thought of as a unit of inheritance.

Inheriting genes

We inherit TWO copies of every gene. One comes from our mother and one from our father. The ‘outcome’ will depend on the combination of genes that we have. How genes are expressed usually depends on their interaction with other genes, and also their interaction with the environment. Often one ‘trait’ will depend on many genes. And one gene may affect many traits.

Learning from twins

Identical twins come from the same fertilised egg and therefore both have the same combination of genes. Yet if one of a pair of identical twins develops Type 1 diabetes, the chance of the other twin becoming diabetic is probably less than 50%. If diabetes was purely down to our genes, we would expect all identical twins to be equally affected. This means that something other than genes is involved in the development of the disease - the environment. Twin studies in Type 2 diabetes have shown that the genetic contribution in this type of diabetes is far greater than it is in Type 1 diabetes.

Genes for Type 1 diabetes

Whilst genes obviously play a role in diabetes, the majority of people with Type 1 diabetes (up to 90%) are thought to have no family history of the disease. Why? This is partly because so many genes are involved, and partly due to the environmental input. So, even if you do inherit a set of genes ‘for diabetes’, you only really inherit a susceptibility towards diabetes.

Two major gene regions have been shown to be associated with Type 1 diabetes. The most important (known as HLA) is involved in the immune process of identifying a persons own cells as ‘self’. Failure to recognise the body’s own cells may result in an autoimmune response - destruction of our own cells (beta cells in the case of Type 1 diabetes). There may be two or more genes in this region involved in giving an individual a susceptibility towards diabetes. The second region identified as being involved in Type 1 diabetes is the insulin gene region. It is thought that these two gene regions only account for, at most, about 50% of the genetics. Several other gene regions are involved in Type 1 diabetes (possibly more than twelve, may be up to twenty or more) and researchers are now trying to clarify these.
Genetic markers conferring *increased risk for Type 1 diabetes*

HLA DR3 - DQA1*0501 - DQB1*0201

and

HLA DR4 - DQA1*0301 - DQB1*0302

Genetic markers conferring *protection from Type 1 diabetes*

HLA DR2 - DQA1*0102 - DQB1*0602

**Genes for Type 2 diabetes**

Whilst it is clear that Type 2 diabetes has a strong genetic element, few specific genes have yet been identified for the later-onset type of diabetes, although many genes have been identified as likely candidates. Little is known either, about the number of genes that are involved. A few research groups have now proposed possible gene regions which may contribute to the genetics of Type 2 diabetes in various populations.

The life-time risk for Type 2 diabetes in the Western world is around 10%, first-degree relatives of patients have a 20-40% risk for the disease, and concordance rates for identical twins have been estimated to be 57% or higher (up to 90%) for type 2 diabetes in male twins.

Advances in genotyping techniques and the availability of large patient cohorts have made it possible to identify common genetic variants associated with Type 2 diabetes through genome-wide association studies (GWAS). So far, genetic variants on 19 loci have been identified.

In addition, some clues are to be found from studying other more specific types of diabetes, such as 'MODY' or 'Monogenic Diabetes' (see box below).

**Genes relating to other types of diabetes**

**MODY (Mature Onset Diabetes of the Young) or Monogenic Diabetes** - Eight different genes have now been identified as being separate causes of this rarer type of diabetes which develops in young people and runs in families. Identifying these genes has helped scientists to understand in finer detail how insulin and glucose normally interact at cell level to control blood glucose (see box).

**MIDD (Maternally Inherited Diabetes and Deafness)** - A different type of gene may cause this diabetes which comes hand in hand with a form of deafness. *Mitochondrial*
genes are passed on only by women and, instead of having only two copies of mitochondrial genes, we have many. The severity of the disease may therefore depend on how many copies of the gene are defective and how many are not.

**TNDM (Transient Neonatal Diabetes) and PNDM (Permanent Neonatal Diabetes)**

**Transient neonatal diabetes mellitus**

TNDM is, as its name suggests, not permanent. It develops within days and can disappear in weeks or months. Usually insulin need only be given for around the first 3 months of life. There is a chance that Type 2 diabetes may subsequently develop during adolescence.

Exactly what causes TNDM is not yet known. It has been suggested that it is simply that the infant has immature beta-cells. Some studies have shown abnormalities of chromosome 6 in infants with TNDM which may be responsible for slowing down the maturation of the beta-cells. However that does not show up in all cases.

**Permanent neonatal diabetes mellitus**

PNDM can also develop within days of birth, but may take months to appear and it remains for life. So if the diabetes persists beyond the first year of life it will usually be permanent i.e. PNDM.

When these infants are tested for c-peptide levels they are non-existent, which indicates total failure of the beta-cells. It is very possible that the destruction occurred in utero.

Like MODY, PNDM is thought to be caused by a mutation in a gene, and each case is not always the same gene.

Around half the cases of PNDM have a mutation in the gene KCNJ11. This form of PNDM tends to develop later than other forms and can also be responsible for such complications as epilepsy or delayed motor development. It does respond well to treatment by sulfonylurea drugs, which means there is still some form of pancreatic activity.

When the gene involved is the transcription factor insulin promoter factor (IPF)-1 or GCK there may be no beta-cell activity at all and therefore no insulin production - so insulin replacement therapy will be necessary. This may be likened to Type 1 or insulin-dependent diabetes.

In 2004 scientists from the Institute of Cancer Research in Sutton, UK found yet another gene that was responsible for PNDM in two UK families - PTF1A (sourced from Affymetrix)
Genetic testing can differentiate between PNDM / TNDM in newborns. If identification of the gene responsible for PNDM is possible, then the most appropriate treatment will be more apparent.

Learning from MODY genes

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2570381/

The Environmental Element

Type 1 diabetes

That there is an environmental input in the development of diabetes cannot be questioned. But what exactly this is, and how it acts or interacts with certain gene combinations to lead to diabetes at some time in a person’s life, is a much debated question. It is most likely that diabetes results from a combination of environmental events (a kind of ‘lethal cocktail’) which may arise at the same time, or at different times, and their effect is additive.

There are several environmental factors which may play a part in the development of Type 1 diabetes. These include cows milk, some viruses, and cold weather (see below).

Type 2 diabetes

Genetics are thought to play a much larger part in Type 2 diabetes than in Type 1 diabetes and therefore the environment may play a smaller part. Nevertheless, age, obesity and lifestyle factors may influence or accelerate the development of Type 2 diabetes in genetically susceptible people.

Also of note, an association between low birth weight and insulin resistance has received attention.
Part 2: What Happens in the Body?

Having introduced the concept of genetic susceptibility and environmental influence, we now turn to see how these factors might interact, and take a look at the events occurring in the body which may ultimately give rise to diabetes.

Type 1 Diabetes

Type 1 diabetes is usually caused by the destruction of the cells in the pancreas which normally manufacture and secrete insulin. These beta cells are attacked by the body’s own immune system, a phenomenon known as an autoimmune response. Why does this happen?

Autoantibodies and the Immune Response

Our immune system normally protects us from disease via two basic types of cell:-

- **B cells** - B cells are programmed to make proteins called antibodies that recognise certain parts of invaders as foreign, then initiate their destruction. Sometimes B cells make antibodies which recognise certain parts of our own cells. These self-recognising antibodies are called autoantibodies. (NOTE: Try not to confuse B cells of the immune system with beta cells of the pancreas!)

- **T cells** - T cells can be primed to attack foreign invaders directly. Two subgroups of T cells (Th1 and Th2) usually maintain a balance between destructive and protective immune responses.

The autoimmune response against the insulin-producing beta cells is thought to be caused by a series of events involving both of these types of immune cell. The final destruction of beta cells leading to clinical onset of the disease is possibly a result of an imbalance in Th1/Th2 T cell activity.

Autoantibodies directed against different entities have been detected in people with Type 1 diabetes. These include:

- Islet cells
- Insulin
- A protein known as GAD
- A protein known as IA-2

These autoantibodies associated with Type 1 diabetes may be manufactured up to 8 years before the disease is evident in terms of a high blood glucose level and accompanying symptoms. This means that the disease process is actually a long drawn out one, probably consisting of several stages. The autoantibodies probably contribute to the disease process early on by selectively identifying the beta cells as those that will be destroyed.
What role does the environment play in an autoimmune response?

The development of diabetes seems to be the result of a series of events which ultimately give rise to autoimmune destruction of the pancreatic beta cells.

- Firstly, the autoimmune process needs to be **initiated** and this may happen very early on in life - either in childhood, or perhaps even before birth, during fetal development.
- Further environmental factors may **accelerate** the process.
- Finally, some events may act to **precipitate** the onset of clinical diabetes, the stage at which diagnosis occurs and insulin replacement becomes essential.

*NOTE: There are many people who appear to experience some kind of immune attack on beta cells (indicated by autoantibodies, detected in their blood), but do not go on to develop diabetes.*

Cow’s milk proteins

The introduction of cow’s milk too early in a baby’s life (before 4 months old) may trigger an autoimmune response. It is thought that antibodies are made in response to a protein in cow’s milk called **bovine serum albumin** or **BSA**. By chance, these antibodies also bind to a protein on pancreas cells, which are then mistakenly identified as foreign.

Viruses

Viruses may act in the early initiation of the autoimmune process, or may add to an already started destruction of beta cells. Fetal exposure during pregnancy to viral agents may be important. The viruses that cause mumps and German measles have been proposed as possible candidates.

**Coxsackie B4** is a virus which has been associated with Type 1 diabetes. This virus has a slight structural similarity to the protein GAD - this may be significant, since many people have high levels of autoantibodies directed against GAD before the clinical onset of their diabetes. Reasoning along the same lines as the cow’s milk theory, it is possible that, after infection with Coxsackie B4, antibodies are made which also cross-react with the GAD protein (effectively therefore, these are autoantibodies).

*Once the damage process has begun, Type 1 diabetes may begin to evolve. Some environmental factors may worsen the situation by putting extra stress on the pancreatic beta cells to produce insulin...*

Cold Weather

Type 1 diabetes is much more common in the colder Scandinavian countries than it is in Asia. It has also been noted that diagnosis seems to increase during the winter months. Cold weather alters the body’s metabolism and may increase the load on beta cells; if the autoimmune process is already underway then this may precipitate diabetes.
Growth

The most common age for developing Type 1 diabetes is in early puberty. This is a time when growth increases rapidly and levels are high. Growth hormone hinders insulin action, so the beta cells are put under stress to produce more insulin. Again, if the beta cells are already partially damaged this extra stress may precipitate the onset of diabetes.

Psychological Stress

Stress hormones (such as cortisol) oppose insulin in a similar fashion to growth hormone. So during particularly stressful periods the beta cells need to work harder and this may add to an already worsening situation.

Another possibility is that an environmental factor directly damages the beta cells. If proteins from the beta-cell are released or become exposed when the cell is damaged then these proteins (which are normally kept ‘hidden’ inside the cell) may be considered foreign. The immune system may then mount an attack on the beta cells which is actually secondary to the damage caused by the environment. Coxsackie B4 virus, which causes inflammation of the pancreas, has been proposed to act in this way.

Type 2 Diabetes

Type 2 diabetes is, in many respects, more complex than Type 1 diabetes. The precise sequence of events which occur over many years has not yet been confirmed. There are a number of factors thought to be involved, but exactly what their individual roles are in causing, or contributing to, Type 2 diabetes is still under much investigation.

In the non-diabetic person, when food is eaten, the blood glucose starts to rise. The pancreatic beta cells are prompted to release insulin so that the body’s cells can take the glucose from the blood and use it. Beta cells are ‘sensitive’ to glucose. Body cells, such as fat and muscle cells, are ‘sensitive’ to insulin. ‘Being sensitive’ involves a multitude of reactions between molecules and therefore there are a great number of potential places in these chemical pathways where something may be going wrong.

Insulin secretion

Glucose enters beta cells by way of a transporter (a kind of molecular gate). The glucose is then modified by enzymes and this produces electrical changes within the cell. In response to these electrical changes, insulin secretion is triggered.

In type 2 diabetics, the beta-cell doesn’t respond properly to the blood glucose level, and insulin secretion is not sufficient to keep blood glucose levels within ‘normal’ limits.

The first enzyme to react with the glucose as it enters the cell is called glucokinase and a genetic defect in this molecule has already been verified as being responsible for many cases of MODY (Mature Onset Diabetes of the Young).
Insulin resistance

Normally, body cells such as fat and muscle cells respond to insulin by taking glucose from the blood. Insulin reacts with a surface protein on the cell (insulin receptor) and this triggers a number of enzyme reactions in the cell. Glucose transporters appear on the cell surfaces and let the glucose in.

In people with Type 2 diabetes (and in obese people that do not have diabetes) the fat and muscle cells do not seem to react properly to the insulin; this is called insulin resistance. The problem possibly lies with the glucose transporter, which is called GLUT-4. Alternatively, the insulin receptor has been proposed to be at fault. It is also possible that there is a problem in between insulin docking at the cell and glucose being taken in.

Additional glucose from the liver

To further complicate matters, when stimulated the liver releases glucose into the blood. Normally after a meal glucose is taken up and stored as glycogen. The glycogen is then later converted back to glucose and released when needed. This process is partly under the control of insulin - insulin binds to receptors on the liver cell and, through a series of signals, reduces the release of glucose.

The liver is another site of insulin resistance in people with Type 2 diabetes. If the liver cells do not respond to insulin they may release more glucose into the blood, compounding the problem of a high blood glucose level.

How does it all fit together?

Clearly there are different factors and these may all be related to one another, either directly or indirectly. It is apparent that Type 2 diabetes takes a long time to develop, but exactly what causes what in the first place is still unclear.

It is interesting that in the early stages of Type 2 diabetes, it has been noted that insulin levels in the blood are high. This has led scientists to believe that initially, the beta cells do respond to high blood glucose, but that they can’t keep it up and eventually suffer from ‘exhaustion’. Indeed, many believe that insulin resistance is the primary defect in Type 2 diabetes and that this puts extra strain on the pancreas to produce more and more insulin; if the beta cells can’t cope then diabetes results.

It does now seem evident that, whether insulin resistance or a defect in insulin secretion comes first, (if they do not develop in parallel), one is ultimately followed by the other.

Additionally, it is important to note that high blood glucose levels can further damage beta cells and reduce their sensitivity to the level of glucose in the blood; this conceivably adds to an already worsening situation.
What role does obesity play?

At least 80% of people with Type 2 diabetes are overweight. **Obesity causes insulin resistance** in its own right. The need for extra insulin to overcome this may just be too great in those who already have weak or weakening beta-cell function.

Whilst **genetics** play a role in obesity, today's sedentary and westernised **lifestyle** also add to the problem of insulin resistance in many populations.