Alex Lam

Diabetes in young people

The search for genetic links

Juvenile diabetes is a genetic disease, but the causes are still not entirely known because of its complexity. This article describes what is being done to improve our understanding of the genetics behind this disease, and the range of activities in medical research.

Going to work with diabetes?

Jason Cooper has been diabetic since he was a teenager. Each morning after breakfast, he injects himself with a dose of insulin, kisses his wife Irene and daughter Maddi goodbye, then hops on his bicycle to Addenbrooke's Hospital in Cambridge. But he is not about to see a doctor regarding his diabetes. He works there everyday at the medical genetics department in the University of Cambridge, and his work is about understanding the genetics of juvenile diabetes.

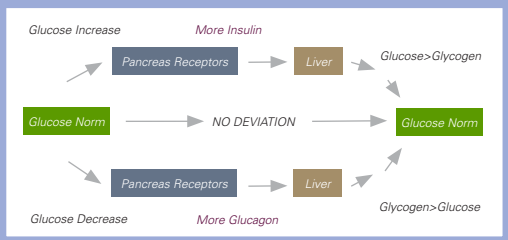
Jason Cooper

What is juvenile diabetes?

Juvenile diabetes, also known as Type 1 diabetes, affects over 200 000 people in the UK. People who suffer from this disease have an inadequate supply of insulin, a hormone that is essential for maintaining blood glucose at a constant level – see Box 1. In diabetics, the insulin-producing cells in their pancreas are destroyed by their body's own immune system (which normally defends against infections). As the disease develops, less and less insulin is produced, blood glucose levels rise and, without treatment, the patient may suffer from a hyperglycaemic (high blood sugar) reaction which can be life-threatening. This can be for a whole host of reasons, including damage, over a long time, to the heart, kidneys and blood vessels. In the short term, a condition known as Diabetic Ketoacidosis may develop; this causes the blood pH to become too low for the proper functioning of enzymes. Finally, there may be osmotic problems which lead to the production of a lot of urine, which can lead to dehydration and, eventually, coma.

Box 1
How insulin helps to control blood sugar?

At some time after a meal (after some digestion has happened), the level of sugar in the blood starts to rise. This is detected by cells in the pancreas, which respond by secreting the hormone insulin. This is carried all over the body in the blood (as are all hormones) but it has its main effect on cells in the liver. These are stimulated to take up glucose from the blood and make it into the polysaccharide glycogen, and so blood sugar falls back to normal. Later, when blood sugar starts to fall, the pancreas is stimulated to secrete another hormone, glucagon, which has more or less the reverse effect of insulin, raising the blood sugar.

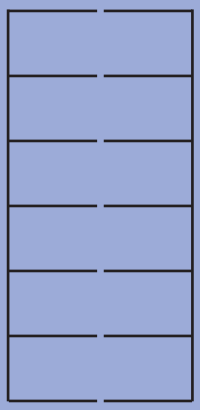


Key words
Genetic disease
Diabetes
Allele
Gene therapy

After diagnosis, insulin replacement is usually given by injection. Good control of blood glucose levels is critical in minimising long term complications and improving long term survival. Although most patients do not have relatives in their immediate families who also suffer from the disease, juvenile diabetes is a genetic disease as scientists have identified that certain DNA sequence variations (variations in the sequence of bases along the DNA molecule) increase the risk of developing juvenile diabetes.

Box 2
DNA Base Sequences

A DNA molecule consists of two strands (the Double Helix), each one is made up of many molecules called nucleotides joined together in a chain, like half a ladder. With the other (matching or complementary) chain the whole structure resembles a ladder which is then twisted into a spiral (helix).



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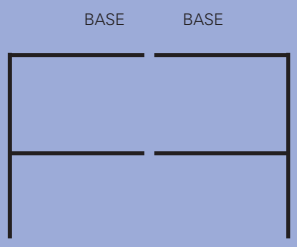
Each half ladder, as mentioned, is made of nucleotides joined together. The important bit of the nucleotide is the BASE sticking out from it. These bases join with those on the other half ladder, to make the rung:



In addition, one of the half ladders carries a sequence of bases (the base sequence) which carries the genetic information. It is these sequnc3es which make us who or what we are, and which vary to cause differences, including diseases, such as juvenile diabetes.

How are the risk sequence variations identified?

It is now known that over 99% of the approximately three billion bases of the human genome are identical amongst individuals. Interestingly, a small proportion of the remaining DNA could be important for explaining what makes people different - for example, why people are different in height and why some people may be more susceptible to certain genetic diseases than others. Scientists such as Jason and his colleagues survey DNA sequence variations on every chromosome from thousands of people with and without the disease. This provides clues to scientists in identifying which DNA sequence variations are involved in the disease process. The basic idea of the strategy is that if there is a version of a sequence (called an allele) that contributes to increasing risk of the disease, this risk-allele should be observed more frequently in patients than in the unaffected subjects – see Figure 1.

See Box 3 on page 21 if you are uncertain of some of the genetics terms used in this article.

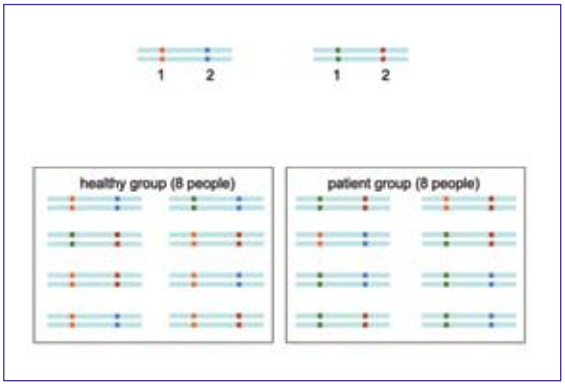


Figure 1 *Consider two sites with sequence variations (1 and 2) in the genome. There are two alleles (red or green) for site 1, and two alleles (blue or brown) for site 2.*

When we inspect the genomes of healthy people and patients, it appears that the green allele in site 1 is more frequently found amongst the patients. The blue and brown alleles of site 2 appear evenly spread across the healthy and disease groups. This suggests that the green allele of site 1 is more likely to be a risk-allele than the other alleles observed.

By contrast, observing the different alleles of a disease-neutral sequence variation would be equally likely in patients and in unaffected subjects. "The huge challenge in detecting the DNA sequence variations with an increased risk of juvenile diabetes and many other complex diseases is that, unlike single gene disorders (such as Cystic Fibrosis), the disease is driven by multiple sequence variations located throughout the human genome, as well as by the environment," Jason explained.

"As the majority of disease-associated sequence variations are expected to make only a small contribution towards the risk of the disease, to detect them we need to conduct big studies with large numbers of patients and unaffected subjects."

	Single Gene Disorders	Multi-factorial Complex Diseases
Examples	Cystic Fibrosis, Huntington's Disease, Haemophilia	Juvenile Diabetes, Rheumatoid Arthritis, Multiple Sclerosis
Incidence	Tend to be rare	More common, incidence often varies between populations / ethnic backgrounds
Disease inheritance	An individual who inherits a disease-allele either develops the disease or becomes a carrier (if the disease is a recessive trait)	Inheriting one or more risk-alleles could increase the risk of the individual developing the disease
Genetic location	Disease-allele(s) are usually found within a single gene (for example: the CFTR gene for Cystic Fibrosis)	Risk-alleles can spread over multiple locations in the genome and are sometimes found on a stretch of DNA outside genes
Environmental influence	Generally not influenced by external factors	Genetic risk of disease is greatly modified by the environment, for example: smoking, diet and infections
Disease mechanism	Disease-allele introduces changes in gene sequence which leads to disruption of the protein's or enzyme's normal functions	It is not entirely clear but the changes introduced by risk-alleles are likely to be very subtle and complicated

Table 1 *compares single gene disorders and complex genetic diseases*

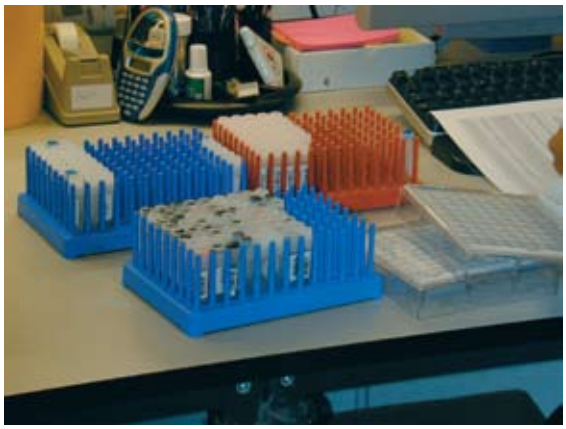
Researchers in action

A statistician uses software to look for patterns in the data. He or she is also involved in designing research projects to ensure that the data produced is useful.

Jason works as a statistician at the Diabetes and Inflammation Laboratory (DIL) in the University of Cambridge with over 50 colleagues. "We have many people from a wide range of disciplines working here in the DIL," said Jason. The laboratory has connections with many hospital doctors and nurses for recruiting patients and healthy volunteers from all over the UK and many parts of Europe. Once the blood or mouth swab samples have arrived at the laboratory, there are molecular biologists who extract and process the DNA. They do so to ensure the high quality and continual supply of DNA for experiments.

DNA samples are stored in liquid nitrogen at -196°C for future use.

Robotic machines are run by the geneticists to record hundreds of thousands of DNA sequence variations simultaneously. This technology has only been available in recent years and has revolutionised the research by empowering the scientists to survey more than 500,000 sequence variations very rapidly. The geneticists also work with the statisticians because many detection methods are based on mathematical models. As the data which the DIL is dealing with are large and complex, sophisticated computer systems are necessary to manage the records carefully and perform the analyses efficiently. Vincent Everett is the computer systems manager of the laboratory. "There are about ten I.T. professionals working here and we do a lot of computer related tasks such as designing a barcode catalogue system for the DNA samples and creating database software for integrating the information we generate at different stages of our research. Besides biology, skills in mathematics and computer science can also be readily applicable in medical research."



Each plastic tube contains an individual DNA sample.

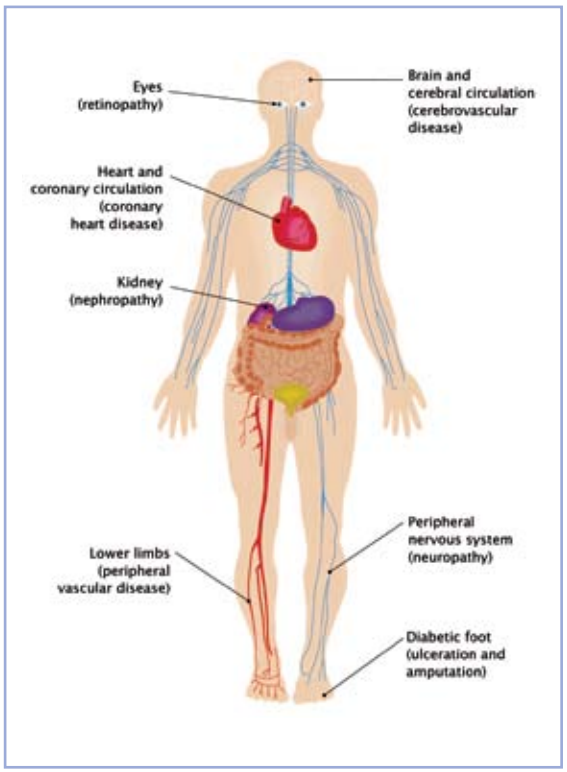
What benefits will this work bring?

Laboratories such as the DIL hope to understand how the disease develops and, ultimately, to help prevent the disease. Since 2000, when the DIL was first established, they have found several DNA sequence variations, identifying regions of the human genome that influence juvenile diabetes susceptibility in Western European populations. Once a sequence variation has been identified, there are still many additional experiments required for scientists to understand how the sequence variation would lead to the destruction of the insulin-producing cells. For example, the changes caused by the DNA sequence variation to protein (e.g. enzyme) function and abundance, and subsequently to the immune system, are studied using biochemistry and cell biology techniques in the DIL.

When scientists have a better understanding of which DNA sequence variations are involved and how they are involved in juvenile diabetes, there will be more opportunities for finding new treatments, such as new drugs. Another future possibility is

gene therapy whereby the genes containing risk alleles are replaced by protective alleles. For this purpose, the identification of the genetic factors involved in the disease is essential.

A further prospect comes from the observation that some patients can respond to different drugs with varying degrees of success. In the future doctors might be able to prescribe treatments to individuals according to their genetic background and environmental exposure. The successes of the possibilities mentioned above will depend on the advances in science and the dedication of the scientists for many more years. Indeed, defeating a disease like juvenile diabetes is a very long battle. Nevertheless, a great deal of progress has been achieved by the DIL and other international efforts in recent years. It is hoped that having a cure for the juvenile diabetes sufferers like Jason will one day be a reality.



Diabetes Atlas, International Diabetes Federation

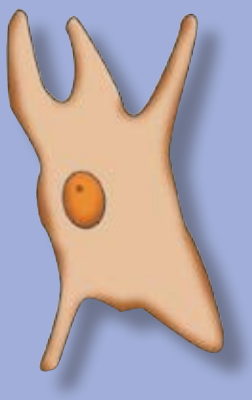
The major diabetic complictions

Alex Lam is currently studying a PhD degree in genetics at the University of Edinburgh. He worked in the DIL at the University of Cambridge as a computer associate from 2001 to 2005.

Look here!

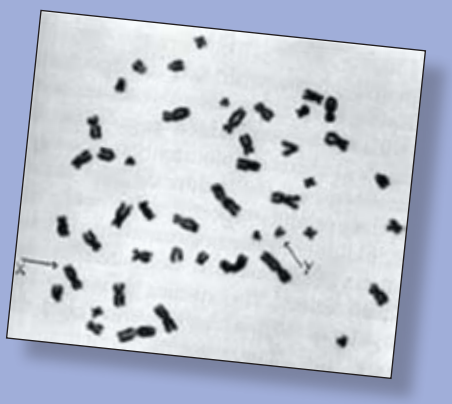
The DIL is supported by the charities Juvenile Diabetes Research Foundation (JDRF) and the Wellcome Trust. Information on juvenile diabetes can be found on the webpage of JDRF and Diabetes UK.
www.jdrf.org
www.diabetes.org.uk
www-gene.cimr.cam.ac.uk/todd/

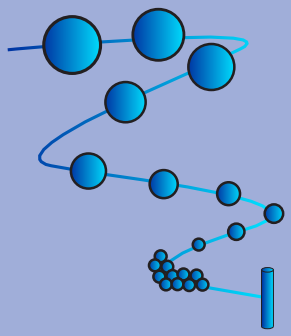
Box 3 Basic genetics



The cell nucleus contains all the genes of that organism. In a human, all the genes of that person, the GENOME

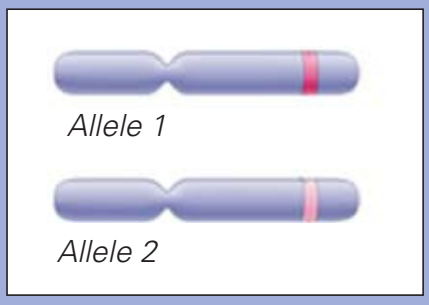
These genes are packaged on structures called chromosomes, 46 in humans. Like a string of beads on a wire, they are coiled up into the chromasome.





Each gene may exist in many forms, each one is called an allete, and this variation in which allele of each gene we have is at the heart of what makes us all different.

Genes (and therefore alleles) are made of DNA, and the information they carry is stored in the sequence of bases.



Diabetes Atlas, International Diabetes Federation

Published incidence rates of type 1 diabetes in children (0-14 age range) (cases per 100,000 population per year)