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# The genomic contribution to diabetes

**Diabetes mellitus is a major public health concern estimated to affect over 7% of the population in England<sup>1</sup>. Risk factors related to lifestyle - e.g. obesity and lack of exercise - are well documented and are the focus for public health interventions.**

However, results from twin studies have established a genetic basis for susceptibility to diabetes, although the genetic markers remained elusive until recently. With the new ability to rapidly sequence DNA and conduct genome wide association studies (GWAS) – the genetic contributors to the development and progression of diabetes are now being revealed. Below we assess the consequences for preventing, diagnosing and managing diabetes based on the latest knowledge of the genomic contribution to the disease.

## Recommendations

- **Genetic susceptibility to type 1 diabetes:** At present there is no evidence to suggest that identification of individuals with high risk genetic alleles for developing T1D will lead to beneficial preventative strategies.
- **Genetic susceptibility to type 2 diabetes:** There is no evidence at present to suggest the addition of genetic risk profiling of individuals in screening programmes to identify those at high risk of developing T2D. Family history of T2D is an important factor that should be included in all risk profiling calculators for T2D. Population based prevention of diabetes remains primarily with the promotion of healthy lifestyle choices.
- **Monogenic neonatal diabetes:** Genetic testing should be considered for all patients presenting with diabetes in the first six months of life. Approximately 50% of permanent neonatal diabetes cases will be identified with variant monogenic forms. (*KCNJ11* and *ABCC8*) amenable to specific medical management using sulphonylurea drugs rather than insulin therapy.
- **Monogenic MODY diabetes:** For all people under the age of 25 diagnosed with diabetes, MODY should be considered and differentiated from T1D and T2D. The MODY calculator - [www.diabetesgenes.org](http://www.diabetesgenes.org) (Shields et al 2012) should be used to determine risk of MODY. Genetic diagnosis should be offered for individuals meeting threshold levels for testing. A positive result for variants in *HNF1A* or *HNF4A* will help inform clinicians on treatment options where the use of sulphonylureas is preferred.

At a population level, promotion of healthy lifestyle choices should remain the focus of public health interventions combined with, at the individual level, consideration of family history to identify those at higher risk of developing the disease.

### Lifestyle v. genes in the development of diabetes

Diabetes mellitus is a major public health concern estimated to affect over 7% of the population in England<sup>1</sup>. Lifestyle factors such as obesity and lack of exercise are well documented risk factors and consequently provide the focus for interventions to prevent diabetes in the population. Analysis of twin data recognised a genetic contribution and susceptibility to diabetes several decades ago<sup>2</sup> but until recently, genetic markers for diabetes remained largely elusive. The revolution in genomics - the ability to rapidly sequence DNA and conduct GWAS - has uncovered many genetic contributors to the development and progression of diabetes.

### Genetic susceptibility to type 1 (T1D) diabetes

T1D is characterised by the failure of the pancreatic beta-cells to produce insulin and the reliance upon external sources of insulin to compensate for this failure. T1D affects around 1/300 and represents about 10% of diabetes cases. T1D is caused by a combination of genetic and non-genetic factors. This is highlighted in monozygotic (MZ) - *i.e.* genetically identical - twin studies that show, where one twin is T1D-affected around 50% of co-twins go on to develop the disease<sup>2,3</sup>.

The genetic susceptibility to T1D is associated with factors affecting autoimmunity to insulin producing pancreatic beta cells<sup>4</sup>. There is a strong association between developing T1D and the MHC (Major Histocompatibility Complex) region located on chromosome 6 (6p21.3)<sup>4</sup>. It is estimated that 50% of the genetic risk for T1D lies in this region. Within the MHC region two haplotypes together (*DR3-DQ2/ DR4-DQ8*) are identified in 30-40% of children with T1D and present in 2.4% of the general population. The absolute risk for developing T1D is 1/15 for those haplotypes compared with 1/300 for general population<sup>5,6</sup>.

Outside the MHC region, over 50 loci of interest as susceptibility genes for developing T1D have now been identified through GWAS. Fifteen loci have been confirmed in robust studies across multiple ethnicities<sup>7,8</sup> three of which (*PTPN22*, *CTLA4* and *IL2RA/CD25*) are associated with immune responses by altering T-cell regulation or function<sup>9,10,11</sup>. Individually, many of the associated mutations confer little additional risk of disease. However, there is compelling evidence of cumulative risk of developing T1D associated with combinations of risk alleles<sup>12</sup>. Despite this, no practical application in the identification of these risk alleles for primary prevention of T1D has been reported<sup>13</sup>.

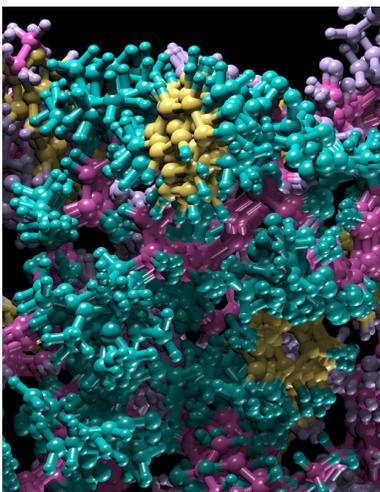
### Genetic susceptibility to type 2 (T2D) diabetes

T2D accounts for approximately 90% of diabetes cases and is characterised by insulin resistance or insensitivity. T2D is normally associated with obesity and older age.

Monozygous twin studies show that for T2D concordance ranges between 30% and 80% and family studies estimate heritability at 30-70%<sup>14,15,16</sup> highlighting the importance of genetic factors in determining disease outcome. In addition, there is considerable ethnic variation in prevalence of diabetes, underpinning the argument that diabetes has a strong genetic component<sup>17,18</sup>. However, T2D is increasing in prevalence indicating genetic susceptibility factors may be modified by environmental influences for diabetes to become overt.

#### What is diabetes?

Diabetes is an inability to regulate raised levels of blood glucose and is a failure of either insulin production or response to insulin by cells within the body. The disease is classified according to how it presents and the underlying cause of the failure to regulate raised blood glucose.



Candidate gene and linkage-based studies identified a small set of genes, including variants in the gene *PPARG*, and *KCNJ11* as implicated in T2D susceptibility with an odds ratio of 1.25 and 1.15 respectively<sup>19,20,21,22</sup>.

The advent of GWAS has led to the identification of over 60 genetic susceptibility loci associated with risk for T2D multiple genes, including several that were not known to play any role in T2D<sup>23, 24, 25, 26, 27</sup>. All variants have only been shown to add a small risk of developing T2D (odds ratios mostly between 1.0 and 1.2) and in sum account for approximately 10% of the genetic component attributable to T2D<sup>25, 28</sup>. Despite the large number of genes now identified as associated with susceptibility to T2D, there is no evidence at present to suggest the addition of genetic risk profiling of individuals in screening programmes to identify those at high risk of developing T2D<sup>28, 29, 30</sup>. It therefore remains a public health priority to promote healthy lifestyle choices in preventing the onset of diabetes at the population level. Consideration of family history should continue to be included at the individual level to identify those at higher risk of developing the disease.



### The genetic contribution to monogenic forms diabetes

Monogenic forms of diabetes, including neonatal diabetes and Maturity Onset Diabetes of the Young (MODY) are highly penetrant genetic conditions and extremely predictive of outcome in terms of developing diabetes. Monogenic neonatal diabetes is extremely rare (around 1 in 200,000 births) and diagnosed within the first six months of life. MODY affects between 0.3% and 2.4% of diabetes cases<sup>31,32,33</sup> and usually presents in people under the age of 25 years old. Monogenic forms of diabetes are often misdiagnosed as T1D or T2D diabetes in neonates and young people.

#### Monogenic neonatal diabetes

Monogenic neonatal diabetes can be transient or permanent and is characterised by known defects in a number of genes some of which also contribute to complex developmental conditions and genetic syndromes. Forms of neonatal diabetes that are not strongly associated with complex genetic syndromes include *PLAG1*, *KCNJ11*, *ABCC8*, *INS* and *GCK* genetic variants. Some of these variants require specific treatments - sulphonylurea therapy is effective over insulin treatment in patients identified with *KCNJ11* and *ABCC8* variants<sup>34,35,36</sup>, whereas insulin therapy is essential in patients with *INS* mutations - a condition that leads to irreversible beta cell destruction<sup>37</sup>. As specific therapies are recommended for particular forms of neonatal diabetes, it follows that genetic testing has clinical utility for patients presenting with diabetes in the first six months of life.

#### Monogenic causes of MODY

Genetic variants of *HNF1A*, Glucokinase (*GCK*), *HNF1B*, *HNF4A*, *IPF1* and *NEUROD1* have been identified as causative agents in MODY cases of diabetes, accounting for 87% of UK MODY prevalence ([www.diabetesgenes.org](http://www.diabetesgenes.org)).

People with *HNF1A* diabetes - approximately 52% of MODY cases<sup>38</sup> - and *HNF4A* diabetes are particularly sensitive to the blood glucose lowering effects of sulphonylureas and can often stop insulin treatment<sup>38,39</sup>. Mutations in the *GCK* gene account for approximately 32% of all MODY cases<sup>38</sup> and result in a mild rise in blood glucose that usually does not need treatment.

- Monogenic forms of diabetes are often misdiagnosed as T1D or T2D diabetes in neonates and young people
- As specific therapies are recommended for particular forms of neonatal diabetes, it follows that genetic testing has clinical utility for patients presenting with diabetes in the first six months of life
- It is worth considering MODY as a differential diagnosis in those under 25 diagnosed with diabetes to ensure they are offered the most appropriate treatment

As the prevalence of MODY is estimated between 0.3 and 2.4% of diabetes cases, it is worth considering MODY as a differential diagnosis in under-25s diagnosed with diabetes to ensure they are offered the most appropriate treatment options. Shields and colleagues have developed an online calculator for predicting whether patients have monogenic MODY as differentiated from type 1 or type 2 diabetes, available at [www.diabetesgenes.org](http://www.diabetesgenes.org)<sup>40,41</sup>.

Genetic diagnosis should be offered for individuals meeting threshold levels for testing. A positive result for variants in *HNF1A* or *HNF4A* will help inform treatment. As monogenic forms of diabetes are highly penetrant, it would be worth considering genetic testing of close family members (siblings and offspring) of probands to identify individuals with the same genetic variant if research were to determine a benefit to those individuals in terms of monitoring for the signs of early development of diabetes and /or interventions to prevent or limit disease.

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