Milestone 16

Genetics of T2D

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Type 2 diabetes (T2D) is a complex and multifactorial disease. Notable risk factors include poor diet, obesity, low physical activity levels and older age. However, twin studies published in the 1980s suggested that genetic factors can contribute to T2D risk, as monozygotic twins showed greater concordance for T2D than dizygotic twins.

Genetic risk factors for diseases are typically assessed by genome-wide association studies (GWAS), which analyse the genomes of many people for the presence of genetic markers that can predict disease. Of note, many factors can cause variable results in GWAS, including multiple hypothesis testing and publication bias, among others. For example, prior to 2000, many genetic associations were reported for T2D but none was confirmed in multiple populations, using comprehensive controls.

In 2000, a ground-breaking paper was published that evaluated 16 previously identified genetic associations to T2D. A multi-layered, family-based study design was used to control for population stratification. Associations were first tested in 333 Scandinavian parent–offspring trios. Alleles that showed a nominal association were tested for replication in three additional study populations of European ancestry. Notably, only one association was confirmed: the common Pro12Ala polymorphism in peroxisome proliferator-activated receptor-γ (PPARγ).

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The researchers found a small (1.25-fold) but significant ($P = 0.002$) increase in T2D risk associated with the more common proline allele (occurring at ~85% frequency). Although the effect size is modest, the high frequency of the risk allele translates into a large risk at the population level. As much as 25% of T2D in the general population might be influenced by this allele. However, the study did not confirm whether PPARγ-Pro12Ala or a variant in linkage disequilibrium was the causal variant.

In further association studies, chromosome 10q was reported to have linkage with T2D in Icelandic and Mexican American populations. To further investigate this association, a 2006 study used genotyping of microsatellite markers. The probable gene associated with T2D risk was identified as *TCF7L2*, which encodes a transcription factor implicated in blood glucose homeostasis.

Encouragingly, in 2007, three independent GWAS of different European populations were published in a single issue of *Science*, with overlapping findings. All three studies identified T2D susceptibility loci in or near *CDKAL1*, *CDKN2A* and *CDKN2B*, *IGF2BP2*, *HHEX* and *SLC30A8*. Later work identified protein-truncating mutations in *SLC30A8* as the first loss-of-function mutations that are protective against T2D. This gene encodes ZnT8, which is highly expressed in insulin granules, and loss of its function increases insulin secretion. These important studies provided in vivo validation of ZnT8 as a drug target in T2D.

As the field advanced, findings from GWAS were further interrogated to elucidate the mechanistic basis for observed associations. For example, 2014 and 2015 studies on obesity and T2D-associated variants in *FTO* found that this gene forms long-range functional connections with the transcription factor *IRX3* and could be involved in a pathway for adipocyte thermogenesis regulation.

In 2019, a GWAS was published of T2D in sub-Saharan African individuals, an understudied group. This paper identified a new T2D risk locus specific for African populations at *ZRANB3*. Also of note, a 2020 meta-analysis of GWAS T2D risk in East Asian populations analysed data from 77,418 individuals with T2D and 356,122 control individuals. The analysis identified 61 loci that are newly implicated in T2D risk. It is important that further investigations are carried out in understudied populations in order to realize the true breadth of genetic risk of T2D.

To date, GWAS have identified >550 signals associated with the risk of T2D. The knowledge gleaned from these genetic factors has been used to inform our understanding of mechanisms of disease. In the future, precision medicine approaches might also use genetic information to predict which people will respond best to different therapies.

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Milestone study

Altshuler, D. et al. The common PPARγ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat. Genet.* **26**, 76–80 (2000)

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