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Review

The genetic side of type 2 diabetes – A review

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ABSTRACT

Aim: Type 2 diabetes (T2DM) is a complex disease. Interactions between genetic susceptible variants and environmental cues results in the development of this heterogenous disease. Having an understanding of the genetics of T2DM may lead to a better perspective and management of the pathogenesis contributing to T2DM.
Materials and methods: Published primary and secondary sources were reviewed covering the keywords "genetics + type 2 diabetes" using PubMed and Google Scholar as the main databases. Full articles were considered when the title and the abstract was found to be sufficiently related to the review's aim.
Results: Various genetic aspects of T2DM were summarised including a general understanding of the heritability and heterogeneity of T2DM. Furthermore, an explanation of the different genetic modalities that can be used to identify T2DM susceptible genes was provided.
Conclusion: In this day and era, researchers and healthcare professionals working in the field of metabolic disorders should have an understanding of T2DM genetics. The future lies in preventive and management action plans targeting the combination of genetics and environmental risk factors for a better health outcome.

1. Diabetes genetics – an introduction

Type 2 diabetes (T2DM) is a heterogenous disease caused by an interaction between genetics (non-modifiable) and environmental (modifiable) factors, as seen in Fig. 1 [1]. These interactions increase the risk for insulin resistance, beta cell dysfunction, obesity and ultimately lead to the development of diabetes mellitus [2–5].

T2DM is a polygenic disease, not obeying the Mendelian mode of inheritance and therefore classified as a complex disease [6]. The T2DM genetic linkage is further reinforced in comparative studies between mono and dizygotic twins (as discussed below). However, individuals inheriting the genetic risk do not necessarily develop the disease phenotype, unless exposed to particular environmental cues. Both genetic and environmental (alone and in combination) factors influence different traits that contribute to the diabetic phenotype (beta cell mass, insulin action, insulin secretion, fat distribution and obesity) [7–9]. This genetic susceptibility is further enhanced by environmental factors driven by sedentary lifestyles and unhealthy dietary change [1]. In fact, physical activity was reported to reduce insulin resistance, while high carbohydrate and fat diets with poor fibre content aggravate insulin resistance [10]. An association between obesity and type 2 diabetes has long been reported. It was suggested that both conditions share susceptibility genes [11].

This review provides a simplified summary of T2DM genetics and the methods of genetic analysis aimed at researchers and healthcare professionals. Understanding the genetics of T2DM may lead to a better perspective of the pathogenesis contributing to T2DM. This may provide new information that will aid clinical diagnosis. It will also help public health specialists in burden prevention as well as developing predictive screening. Such understanding may also contribute to new drug therapy, particularly targeted pharmacotherapy with possible individual optimized treatment.

2. Heritability of T2DM – an interaction between genes and environment

Heritability plays an important role in the development of T2DM, with an estimated 20–80% of T2DM being acquired in such manner [12,13]. A poor nutritional prenatal environment and subsequently low birth weight has been associated with insulin resistance and T2DM in adulthood [14,15]. It was further proposed that such poor foetal nutrition results in metabolic adaptation and "programming" leading to the development of metabolic syndrome

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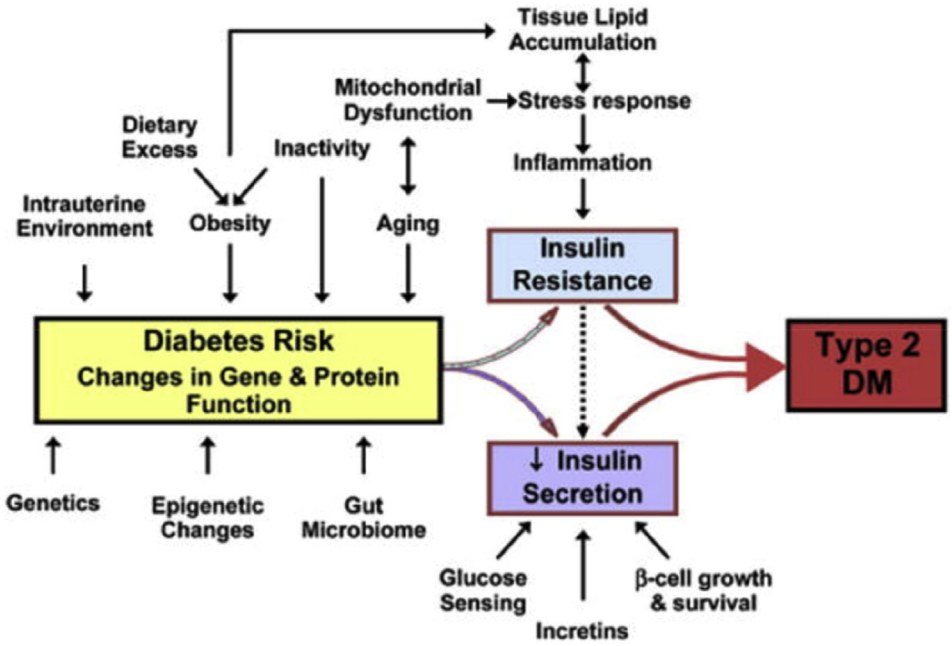

Fig. 1. Complex pathogenesis of T2DM [1].

and cardiovascular disease apart from T2DM [16–18].

Heritability can present in clusters within families and first-degree relatives when compared to the general population, with a 3.5 fold increased risk of developing diabetes [19,20]. Individuals born to a single diabetic parent, have a 40% lifetime risk of developing T2DM, while having both parents suffering from T2DM increases the risk to 70% [21]. The diabetic genetic link is further reinforced by twin studies that show a higher concordance for the disease in monozygotic twins (70%) when compared to dizygotic twins (10%) [22,23].

Despite the importance of the genetic element for the development of T2DM, environmental factors must play a role in accelerating the disease in those having a genetic predisposition. In fact, a number of observations have been reported where an increase in diabetes prevalence was evident when ethnic groups migrate from a less developed regions to a more urbanized regions and gradually adopt the Westernized lifestyle and dietary habits [24].

Furthermore, epigenetics plays a role in the development of T2DM. This involves the hereditary ability to alter gene functions without a change in the nucleotide sequences. A number of mechanisms may occur such as DNA-methylation, histone acetylation and non-coding RNA, which are responsible for the regulation of gene expression and may be altered following environmental cues [25]. Maternal environment may influence the infant metabolic risk due to epigenetic changes rather than due to inherited variation in the DNA sequence [26]. The *Pedersen hypothesis* covers this phenomenon, where maternal hyperglycaemia contributes to foetal hyperglycaemia and hypertrophy of the pancreas islet cells of the foetus due to insulin-hypersecretion. This contributes to macrosomia and increased risk of development of T2DM later on in life [27].

3. Single nucleotide polymorphisms (SNPs)

Single nucleotide polymorphisms (SNPs) are variations found at single bases within the DNA sequence of a genome. The exchange of single base pairs is the most common sequence variation in the human genome accounting for 90% of variations [28].

SNPs are the basis of complex diseases' genetic variations. The genetics of common complex diseases are elucidated by means of SNPs by using genome-wide association studies, candidate gene case-control association studies as well as genome-wide linkage analyses [29]. Identifying the SNPs responsible for the development of these complex diseases leads to earlier diagnosis, prevention and treatment of the disease [30,31].

4. Identification of T2DM susceptible genes

There are two main approaches for identifying susceptibility genes in T2DM, namely: (1) the use of candidate gene studies and (2) the genome wide scan approach.

5. Candidate gene studies

Candidate gene studies are based on known or presumed biological function of selective putative genes that are related to the disease under study [20]. This requires prior knowledge of the disease being investigated including the role of the gene within the disease pathophysiology (*priori hypothesis*) [32]. Candidate gene association studies consider the statistical efficiency of the biological understanding of the phenotype and the association analysis of the complex disease under study [33]. One can compare this gene study to a traditional epidemiological approach in order to identify the cause of the disease. The association between the gene and the disease is investigated by means of case-control studies. This kind of study has been found to be clinically relevant apart from acting as a potential disease diagnostic tool for genetic disorders [34]. In diabetes studies, the genes encoding for insulin signalling proteins and glucose homeostasis are excellent candidates for such candidate gene studies. Candidate gene studies usually comprise of a random unrelated T2DM cohort with a matched control cohort. Such an approach enables the identification of possible polymorphic alleles that occur at a significantly higher frequency within the T2DM cohort than in the control cohort, leading to the establishment of an association between T2DM and the allelic marker [24]. These associations can be

influenced by selection bias, recall bias, misclassification and confounding factors [33].

6. Genome-wide association studies

Genome-wide association studies (GWAS) have enabled the identification of a number of variants that are contributing to common diseases that were previously unrecognized in candidate gene studies [35]. The GWAS have been characterized as "hypothesis-free" as this method offers the opportunity to overcome all hurdles of incomplete understanding of the pathophysiology of the disease while scanning large chunks of the genome [36,37]. GWAS are mainly used for the discovery of common variants conferring low to moderate risks of the disease [38]. The most common type of variants identified by GWAS are the gains and losses of DNA (copy number variants) that are known to have phenotypic effects on gene expression as well as function [39]. However, a number of variants are not picked up by GWAS, namely structural variants, noncoding RNAs and epigenetic changes [40]. Furthermore, GWAS tests associations between each individual variant and a specific phenotype while assuming independent effects. This is despite the fact that complex diseases are caused by the interplay of multiple genetic and environmental functions [41]. It has been reported that many SNPs have small individual size effects and it is only in combination that their genetic effect is enhanced [42]. Therefore, when analysing individual SNPs, the GWAS misses such signals since these are usually embedded in a genome-wide sea of noise. Rare variants are usually also missed by GWAS, following the fact that existing GWAS platforms are not designed to capture such variants. These rare variants may contribute to the heritability of many traits and diseases, and missing such variants may contribute to "missing heritability" [43]. Missing heritability has been attributed to the gene-environment, gene-gene interactions and epigenetics. The epigenetic factors include DNA methylations and histone modifications that might be contributing to the environmental exposures leading to T2DM risk [44].

7. Heterogeneity of type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a heterogeneous disease with a genetic predisposition and environmental influences. Rapid changes in environmental factors such as lifestyle factors are the most likely contributing factors resulting in the global T2DM epidemic [45]. T2DM heterogeneity can be classified into different heterogeneity categories, namely clinical heterogeneity, locus heterogeneity and allelic heterogeneity.

Clinical heterogeneity incorporates clinical related factors that increase susceptibility to development of diabetes. Obesity is a strong modifiable factor contributing to T2DM development. Obesity leads to ectopic fat deposition in insulin-sensitive organs such as skeletal muscle and liver that affect the insulin-signalling pathway [46]. This enhances insulin resistance due to a defective non-oxidative glucose pathway metabolism; increased intramyocellular lipid content in the liver and viscera [47–49]. Therefore, an obese individual is more likely to develop T2DM. Interestingly, an obese adolescent has a faster beta cell failure with a deterioration rate of approximately 15% per year when compared to an obese adult beta cell deterioration rate of 7% yearly [50–52].

The age of onset of diabetes plays a role in the clinical heterogeneity of diabetes. Traditionally, the age of onset of uncontrolled hyperglycaemia was used as the distinguishing factor to identify the type of diabetes mellitus an individual was suffering from. However, nowadays this is of minimal clinical value especially between 20 and 50 years, where different types of diabetes can present. Very young children are those most likely to suffer from type 1 diabetes mellitus due to autoimmune destruction of the pancreatic beta cell and insulin deficiency, in which case these require lifelong insulin. In fact, administering of insulin improves their hyperglycaemic state [53,54]. The latent autoimmune diabetes of adults (LADA) presents with hyperglycaemia in middle age individuals. Until some time ago, the development of hyperglycaemia in middle age implied that the individual was suffering from T2DM. However, administering oral hypoglycaemic agents does not improve this condition (LADA) over a period of time. LADA has an autoimmune pathophysiology with the presence of GAD autoantibodies and ultimately results in an insulin-dependent state [55]. Hyperglycaemia presenting at an early age (before 25 years) with a strong family history of hyperglycaemia, is liable to be classified as Type 1 diabetes due to its early onset. However, in actual fact these individuals are not insulin dependent but require oral hypoglycaemic agents. These individuals suffer from monogenic diabetes. In a recent Italian study, it was reported that 23% of adults with a multigenerational T2DM had monogenic disease [56]. Monogenic diabetes (MODY) occurs due to beta cell dysfunction and results from one genetic mutation unlike T2DM, which is a multigenetic disease and therefore shows 'locus heterogeneity' [57–59].

Locus heterogeneity implies that mutations in different genes may explain one variant phenotype. T2DM also shows 'allelic heterogeneity', which is a feature of genetic architecture where different alleles in the same gene contribute to similar phenotype variant. An example of allelic heterogeneity was reported at the TCF7L2 locus [60].

8. Conclusion

Type 2 diabetes is a complex disease resulting from genetic and environmental interactions. Having a susceptible genetic variant does not imply that the individual would develop the disease unless environmental cues are present. SNPs are the basis of complex diseases' genetic variations, with their identification providing a means of predicting the possibility of development of metabolic abnormalities within the population. The environmental susceptible factors for type 2 diabetes are well reported but it is now time to incorporate the genetic side of the disease in preventive and management action plans. Targeted genetic and environmental pharmacotherapy with possible individual optimized treatment depending on the genetic susceptibility of the individual is the way forward.

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Declaration of conflicts of interest

The Author(s) declare(s) that there is no conflict of interest.

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