The Role Of Genetics In The Aetiology Of Diabetes Mellitus

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ABSTRACT

Diabetes the commonest endocrine- metabolic disorder is becoming a global epidemic with over 382 million of the world's population affected in 2013 and this figure is projected to be 592 million by the year 2035[1]
Diabetes is an endocrine disorder hugely influenced by genetic and environmental factors.
The genetic factors which are heritable, increases the risk of an individual to diabetes, while, environmental factors acts as a trigger in the development of overt diabetes.
Several genes have been associated with both Type 1 and Type 2 diabetes. These genes are important as they can act as potential site for pharmacologic and gene therapy interventions in stemming the tide of diabetes.
This write up explores these genes, however, as study in this interesting field progresses, more genes are being identified and associated with diabetes.

INTRODUCTION

Diabetes mellitus is a group of common metabolic disorders that is characterized by persistent hyperglycaemia
It is a complex and multifactorial pathologic process and is due to series of interactions between the environment and genes that make an individual susceptible
The chronic hyperglycaemia seen in DM leads to micro vascular and macro vascular complications. In the United States, for example, diabetes is the leading cause of end- stage renal disease (ESRD), non-traumatic lower extremity amputations, and adult blindness[2]
There are two main types of diabetes mellitus based on the pathologic leading to it; Type 1 and Type 2 DM
Type 1 DM is due to autoimmune destruction of the beta cells of the pancreas leading to insulin deficiency. Type 1 DM is further classified into Type 1A and Type 1B
In 1A, immunologic markers are found in the serum of the affected individual, whereas, in 1B, immunologic markers are not found, hence,

they develop insulin deficiency by unknown mechanisms and are prone to ketosis

Type 1 DM was referred to as insulin dependent diabetes mellitus (IDDM), but this classification is no longer used as some Type 2 DM individuals require insulin for glycaemic control[3]

Type 2 DM is a heterogeneous group of disorders characterized by insulin resistance and impaired insulin secretion. Several genetic defect and environmental factors have been studied in the pathogenic process leading to Type 2 DM

In type 2 DM, there is peripheral insulin resistance, which later precipitates or leads to a relative insulin insufficiency

Type 2 DM is commonly found in adults, but rare form called Maturity Onset Diabetes of the Young (MODY), is found in adolescents. This is an inheritable disorder and genetic defects responsible have been elucidated

EPIDEMIOLOGY

Diabetes mellitus arises as an interaction between genetic and environmental factors

Diabetes mellitus is one of the most common endocrine disorders affecting almost 6% of the world's population[4]

It is a rising epidemic, with over 552 million people projected to be affected by the year 2030 and majority of these (97%) will have Type 2 DM

Environmental factors like obesity, physical inactivity, viral infections, modify the expression of DM; hence, the incidence of DM vary from one geographical location to another

About 7.1 million people are estimated to be affected in Africa and it is expected to increase to over 18.6 million by 2030[5]. The prevalence of diabetes in Nigeria has increased to 4.9% affecting approximately 4 million people and diabetes accounts for significant number of death per year[6]

GENETICS AND DIABETES MELLITUS

Diabetes mellitus is largely a genetic disease with environmental modification

Genetics play a very important role in the susceptibility of individuals to developing DM. various genetic loci and chromosomal abnormalities have been identified in the aetiopathogenesis of DM

Studies conducted by the Africa America Diabetes Mellitus [AADM] study group has found that the strongest linkage signal in the genetics of DM in West Africa is on Chr. 20q13.3 and 12q 24[7]

Studies of the concordance rate among monozygotic twins compared to dizygotic twins have proven that genetics play a very prominent role in the development of DM

Genetics of Type 1 DM

Type 1 DM is commonly found in the younger age group before the age of 30. It is characterized by insulin deficiency due to autoimmune destruction of the beta cells of the pancreas

Several genes have been indicated as probably responsible for the development of Type 1 DM. As stated earlier, these genes increase the susceptibility of an individual, while, environmental factors most especially viral infections, acts as a trigger factor in the development of overt Type 1 DM

The incidence of type 1 DM in the general population is <1% compared to the incidence in individuals with first degree relative with Type 1 DM which is about 6%[8]. This further impresses the role of genetics in this endocrine disorder

Three main genes have been identified to influence the risk of Type 1 DM. They include IDDM 1 (insulin dependent diabetes mellitus 1) gene; INS (insulin) gene; CTLA 4 (cytotoxic T- lymphocyte associated) gene

The IDDM 1 gene is located on Chr 6p 1.3, the HLA (Histocompatibility leucocyte antigen) region of the Chr 6. This region is responsible for the anergy of leucocytes to self-antigens. It contains the HLA class II genes vis, HLA DR, DQ and DP

The presence of mutations in these genes increases the heritable risk of Type 1 DM by 40- 50%. Several haplotypes of this gene have been found in individuals from different ethnic groups. The presence of these haplotypes increases the risk of Type 1 DM in individuals from that ethnic group

For example, in African Americans, it has been found that haplotype DRB1*07-DQA1*0301-DQB1*0302 increases the risk of T1D; while, in the Caucasians, haplotypes DQA1*0501-DQB1*0201 and DQA1*0301-DQB1*0302 increase the risk of Type 1 DM

A haplotype has been found to reduce the risk of the carrier to developing Type 1 DM in many populations. This haplotype DRB1*15-DQA1*0602-DQB1*0102, acts as a protective factor in these individuals

INS (insulin) gene is also known as the IDDM 2 gene. It is located on Chr 11p 15.5 and is transcripted to the insulin mRNA. There are variants of this gene; the class I variant predisposes to Type 1 DM, while the class III variant is protective. The class III variant is longer and it generates more insulin mRNA

CTLA- 4 (cytotoxic T lymphocyte associated 4) gene is located on Chr 2q 31-35. It is associated with other autoimmune diseases.

Genetics of Type 2 diabetes

Type 2 DM is characterized by peripheral and central insulin resistance, which precipitates a relative insulin deficiency leading to hyperglycaemia

Type 2 DM is usually found in individuals >45 years, however, a rare variant called Maturity- Onset Diabetes of the Young has been found in younger age group

The incidence of Type 2 DM is on the increase and this has been attributed to environmental modifications especially physical inactivity in the presence of surplus energy supply. Diabetes patients are at least five MI units heavier than the general population of Nigeria and Ghana[9]

First degree relatives are three times more likely to develop Type 2 DM than the general population[10]. Type 2 DM is commoner among monozygotic twins than dizygotic twins, the concordance rate reaching 60- 90% in monozygotic twins

More than 50 candidate genes for Type 2 DM have been studied in various populations worldwide, however results have been conflicting. This is due to variations in environmental exposure, differences in genetic susceptibility to Type 2 DM across ethnic groups and variations in gene- environment interactions

Of the studied candidate genes, the most promising include PPARy gene (Peroxisome proliferator- activated receptor y); ABCC 8 gene (ATP- binding cassette, subfamily C member 8); KCNJ 11 gene (Potassium channel inwardly rectifying, subfamily J member 11); CALPN 10 (calpain 10)

The PPARy gene (Peroxisome proliferator- activated receptor y) is important in adipocyte and lipid metabolism. The most common variant PPARy gene (Pro) decreases insulin sensitivity in tissues. About 98% of European carries at least one copy of the Pro allele[11]. This contributes 25% risk of Type 2 DM among Caucasians. This gene is a target for hypoglycemic drugs known as thiazolidinediones

The ABCC 8 gene (ATP- binding cassette, subfamily C member 8), encodes the high affinity sulfonylurea receptor (SUR 1) subunit that is coupled to the Kir 6.2 subunit. The Kir 6.2 subunit is encoded by KCNJ 11 gene (Potassium channel inwardly rectifying, subfamily J member 11), which is also a gene of interest in the risk of Type 2 DM

Both genes are part of the ATP- sensitive potassium channel and this play a key role in regulating the release of hormones like insulin and glucagon from the islet o the pancreas

Both genes are very close together (just about 4.5 kbps apart) and are close to the INS gene. Current studies are looking into whether these genes work independently or in concert with each other

CALPN 10 (Calpain 10) gene encodes an intracellular calcium dependent cysteine protease[12]. Variations in calpain 10 activity affect insulin secretion and contribute to Type 2 DM risk. However, this gene has been found to play a very limited role in the risk of Type 2 DM in Africa[13]

Maturity- Onset Diabetes of the Young (MODY)

An uncommon form of Type 2 DM (<5% of Type 2 DM cases), It generally occurs before the age of 25 years. It is characterized by slow onset of symptoms, absence of obesity and ketosis with no evidence of beta cell autoimmunity

There are 6 forms of MODY genes and they are inherited in autosomal dominant mode (see table 1 below)

All MODY genes are expressed in the islet cells of the pancreas and play a role in metabolism of glucose, regulation of insulin and other genes involved in glucose transport.

Table1*

Type	Gene	Locus	#Mutations	% MODY
MODY 1	HNF4A	20q12- q13.1	12	-5%
MODY 2	GCK	7p15-p13	-200	-15%
MODY3	HNF1A	12q 24.2	>100	-65%
MODY4	IPF1	13q 12.1	Few	
MODY5	HNF1B	17cen- q21.3	Few	<3%
MODY6	NEUROD1	2q32	Few	

**culled from Genetics and diabetes- World Health Organization*

FUTURE ROLE OF GENETICS IN DIABETES MELLITUS

As studies into the genetics of DM widens, more genes associated with the development of DM will be identified. This will provide more insight to researchers and the scientific community about the aetiopathogenesis of DM and help in the accurate assessment of an individual's risk in developing DM

They are also potential pharmacologic targets in the development of drugs and pharmacotherapies in preventing, treating and controlling the disease (pharmacogenetics)

CONCLUSION

Genetics play a very prominent role in the aetioplathogenesis of DM. Genetics increases the risk of an individual above the general population in the development of DM. Interactions with the environment vary from one ethnic group to the other and is essential for the phenotypic appearance of Diabetes Mellitus

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