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THE GENETICS OF TYPE 2 DIABETES MELLITUS : A REVIEW

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ABSTRACT

Variants of a number of genes have been associated to Type 2 Diabetes Mellitus (T2D) among Europeans. However, the contributions of these genetic variants in other ethnic groups are unclear. Since the susceptibility of different ethnic groups differ due to different environmental factors and genetic background it is important to replicate the findings to unravel the genetics of T2D. According to WHO, India leads the world with largest number of Diabetic patients. Several recent studies in Asian Indian populations have replicated the association of a few genes with larger effect size compared to those reported for European populations. However, reports from several Indian populations give a heterogeneous picture owing to its diverse ethnicity. The major issue to address in diabetes biology is to identify the genetic changes in the disease and their occurrence in different populations. Uncovering these genetic changes in diabetes may be important in (a) defining the functional role of specific genetic alterations and (b) developing potential biomarkers.

Introduction :

Diabetes has become a common global health problem that affects >170 million people worldwide. It is one of the leading causes of death and disability. It is estimated that by 2030, the number will rise to 366 million (www.who.int). The majority of diabetes (~90%) is type 2 diabetes (T2D) caused by a combination of impaired insulin secretion from pancreatic beta cells and insulin resistance of the peripheral target tissues, especially muscle and liver. According to Wild et al. (2004) the 'top' three countries in terms of the number of T2D individuals with diabetes are India (31.7 million in 2000; 79.4 million in 2030), China (20.8 million in 2000; 42.3 million in 2030); and the US (17.7 million in 2000; 30.3 million in 2030). Clearly, T2D has become an epidemic in the 21st century where India leads the world with largest number of diabetic subjects.

This form of diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity and certain ethnicities. About 80% of people with T2D are overweight. Diabetes is

associated with long-term complications that affect almost every organ of the body. The disease often leads to blindness, heart and blood vessel disease, stroke, kidney failures, amputations and nerve damage. Uncontrolled diabetes can complicate pregnancy and birth defects are more common in babies born to women with diabetes.

Until recently, type 2 diabetes was typically regarded as a disease of the middle-aged and elderly. Though this age-group maintains a higher risk than younger adults, evidence is accumulating that even children and adolescents aged less than 30 years are now becoming caught up in the diabetes epidemic, which has mainly been attributed to the high level of obesity in these groups. T2D has already been reported in children in a number of countries, including Japan, USA, India, Australia and UK (Bloomgarden, 2004). The decrease in the age of onset of diabetes is of great concern as future generations may be burdened with morbidity and mortality at the height of their productivity, potentially affecting the workforce and healthcare resources of the countries across the world. So, prevention must be the main strategy for the future.

Genetics:

T2D is a complex polygenic disorder in which common genetic variants interact with environmental factors to unmask the disease. Genetic factors are known to play an important part in the development of T2D, as exemplified by rare monogenic subtypes, the high prevalence in particular ethnic groups and its modification by genetic admixture and the difference in concordance rates between monozygotic and dizygotic twins. However, the role genetics plays in the development of diabetes is poorly understood.

A large amount of data available on the genetics of T2D from association studies of candidate gene variation include variants of calpain-10 (**CAPN10**) (Horikawa et al., 2000; Weedon et al., 2003; Song et al., 2004; Cassell et al., 2002; Tsuchiya et al., 2006), peroxisome proliferator-activated receptor gamma (**PPARG**) (Barroso et al.,1999;Altshuler et al., 2000;Agostini et al., 2006), potassium inwardly rectifying channel, subfamily J, member 11 (**KCNJ11)** (Gloyn et al., 2003; Love-Gregory et al., 2003; Florez et al., 2004; Schwanstecher et al., 2002), ATP binding cassette, subfamilyC, member 8 (**ABCC8**) (Hart et al., 1999; Inoue et al.,1996; Gloyn et al., 2001, 2003; Laukkanen et al., 2004; Van Dam RM et al., 2005),hepatocyte nuclear factor-1A (**HNF1A**) (Triggs et al., 2002), hepatocyte nuclear factor-4A (**HNF4A**) (Weedon et al., 2004; Domcott et al., 2004; Love-Gregory et al., 2004; Muller et al., 2005), glucokinase (**GCK**) (Gloyn, 2003; Weedon et al., 2006), plasma cell glycoprotein-1/encoding ectonucleotide pyrophosphate phosphodiesterase 1 (**PC-1**/**ENPPI**) (Meyre et al., 2005; Abate et al., 2005; Bottcher et al., 2006;

Bochenski et al., 2006; Grarup et al., 2006), insulin receptor substrate-1 (**IRS-1**) (Hitman et al., 1995), protein tyrosine phosphatase 1B (**PTPNI**) (Bento et al., 2004; Florez et al., 2005), the nuclear lamina gene, **LMNA** (Owen et al., 2007). However, majority of genetic studies could not be reliably replicated (Mc Carthy, 2004, Mohan et al., 2007).

Among all T2D susceptibility genes studied before 2006, only two were found to be convincingly associated, P12A variant in peroxisome proliferator-activated receptor gamma (**PPARG)** gene (encoding the target for the thiazolidinedione class of drugs used to treat T2D**)** by Altshuler et al., 2000 and E23K in potassium inwardly rectifying channel, subfamily J, member 11(**KCNJ11)** (which encodes part of the target for another class of diabetes drug, the sulphonylureas) by Gloyn et al., 2003. But these have only modest effect on disease risk (odds ratio~1.2). Replication of significant associations of **ENPPI** with risk of obesity and T2D in some (Bottcher et al., 2006; Bochenski et al., 2006) but not all (Weedon et al., 2006; Grarup et al., 2006; Keshavarz et al., 2006; Lyon et al., 2006) is intriguing. The basis of such heterogeneity is poorly understood.

In 2006, deCODE genetics identified common variation in the transcription factor 7-like 2 **(TCF7L2)** gene to have a substantial effect on T2D susceptibility (Grant et al., 2006). TCF7L2 encodes a transcription factor that is active in the Wnt-signaling pathway and had no track record as a candidate for T2D. The effect of TCF7L2 on T2D was detected through a search for microsatellite associations across a large region of chromosome 10 that had been previously implicated in T2D susceptibility by linkage analysis (Reynisdottir et al., 2003). Several T2D associated SNPs have been identified in a region of strong linkage disequilibrium within **TCF7L2** (odds ratio for T2D of~1.4 fold per allele). The association of **TCF7L2** with T2D has been demonstrated in US and Danish subjects (Grant et al., 2006; Zhang et al., 2006; Saxena et al., 2006). The association has also been replicated in diverse subjects of UK (Groves et al., 2006; Florez et al., 2006), Amish (Damcott et al., 2006), Finnish (Scott et al., 2006), French (Cauchi et al., 2006) Japanese (Hayashi et al., 2007; Horikoshi et al., 2007), Mexican American (Lehman et al., 2007) origin. Common variants in Wolfram syndrome1 (**WFS1**) gene have been found to confer risk of T2D (Sandhu et al., 2007).

The advent of Genome-wide association scans (GWAS) in 2007, led to identification of association of polymorphism in loci, solute carrier family 30, member 8 (**SLC30A8)** and two linkage disequilibrium (LD) blocks insulin degrading enzyme-kinesin factor11-hematopoietically expressed homeobox

(**IDE-KIF11-HHEX)** and exostoses (multiple) 2 (**EXT2-ALX)** (Sladek et al., 2007; Schulze et al., 2007). Further, T2D susceptibility variants were also found in and around CDK5 regulatory subunit associated protein 1-like 1 (**CDKAL1),** cyclin-dependent kinase inhibitors 2a and 2b (**CDKN2A/ CDKN2B**) & insulin-like growth factor 2 mRNA binding protein 2 (**IGF2BP2**) (Zeggeni et al., 2007; Saxena et al., 2007; Scott et al., 2007; Steinthorsdottir et al., 2007). Association has also been found between variants in the fat mass and obesity associated (**FTO)** gene and T2D in those studies in which cases and controls differed substantially in BMI (Frayling et al., 2007). The strong association found with variants in **TCF7L2** and **CDKAL1** and **CDKN2A/2B** to that of T2D implicate wnt-signaling pathway and cell cycle control in the pathogenesis of T2D (Frayling and McCarthy, 2007). Replication of the above six entirely novel T2D susceptibility loci was done in studies involving individuals of both European (Grarup et al., 2007) and Asian (Omori et al.,2008; Wu et al., 2008; Ng et al., 2008; Sanghera et al., 2008) origin.

Furthermore, a recent meta-analysis identified six novel variants viz. Juxtaposed with another zinc finger gene1 (**JAZF1**), calcium/calmodulin-dependent protein kinase 1D (**CAMK1D**), tetraspanin 8 (**TSPAN8**)/ leucine-rich repeat-containing G-protein coupled(**LGR5**), thyroid adenoma associated (**THADA**), ADAM metallopeptidase with thrombospondin type 1 motif 9 (**ADAMTS9**) and Notch homologue 2 (**NOTCH2**) that are associated with T2D (Zeggini et al.,2008; Omori et al., 2009). Among the six genes, only Notch homologue2, *Drosophila* (**NOTCH2**) is known to be involved in pancreatic development, for others the mechanisms involved remains unclear.

Recently, the first GWA scans for T2D in East Asian subjects have revealed novel susceptibility loci, the potassium voltage-gated channel, KQT-like subfamily, member 1 gene (**KCNQ1**). Variants in **KCNQ1** have been shown to influence diabetes risk (Yasuda et al., 2008; Unoki et al., 2008; Liu et al., 2009; Tan et al., 2009). This new discovery, using samples of East Asian origin, highlights the importance of extending these studies to a wider range of populations. Variants in another new gene, melatonin receptor 2 (**MTNR1B**) have been shown to be associated with increased risk of type 2 diabetes and impaired early insulin secretion (Lyssenko et al., 2009). It has also been reported that variants in MTNR1B influence fasting glucose levels in European population (Prokopenko et al., 2009; Nabila Bouatia-Nagi et al., 2009).

Converging points of evidence from population based studies suggests that Indians are apparently genetically more prone to diabetes and insulin resistance. Moreover, Asian Indians are more susceptible to developing truncal

obesity, which might account for their tendency to insulin resistance referred to as "Asian Indian phenotype" (Banerji et al., 1999; Chandalia et al., 1999; Raji et al., 2001; Ramachandran et al., 2001; Mohan et al., 2006).

In Asian Indians, the D1057D genotype of insulin receptor substrate 2 (**IRS-2**) gene is susceptible to diabetes by interacting with obesity (Bodhini et al., 2007). Association of **lipoprotein lipase** Hind III (T-G) and Ser447Thr (C-G) polymorphism with dyslipidemia has been studied in Asian Indians by Radha et al., (2006) and it was shown that H+Ser and H-Ter were the 'high-risk' and 'low-risk' haplotypes for low HDL cholesterol and elevated triglyceride levels respectively. It has also been shown that –T93G SNP of lipoprotein lipase gene is associated with obesity but not T2D, whereas the –G53C SNP appears to be protective against both obesity and T2D (Radha et al., 2007).

A few studies in North western Indian Punjabi populations show association of apolipoprotein E (**APOE**) (Hha1), angiotensin-1 converting enzyme (**ACE**) I/D, **APOA1-CIII-AIV** gene cluster with lipid levels in T2D and CHD (Singh et al., 2006; Singh et al., 2007) and **Paraoxonase (PON1**) activity to CAD and T2D (Singh et al., 2007). Studies in North Indians show genetic association of **interleukin-1 beta** (-511C/T) and **interleukin-1 receptor antagonist (86bp repeat)** polymorphism with T2D (Achvut et al., 2007). Thr394Thr (G-A) polymorphism of peroxisome proliferator activated receptor-co-activator-1 alpha (**PGC-1 alpha**) gene has been shown to be associated with T2D in Asian Indian subjects and also with total, visceral and subcutaneous body fat (Vimaleswaran et al., 2005; 2006).

Two North Indian populations showed significant association of **PGC-1 alpha** variants (Thr394Thr & Gly482Ser) with T2D (Bhatt et al., 2007a). Analysis of **mitochondrial G10398A/T16189C** haplotypic combinations suggests susceptibility of these alleles to T2D independently as well as together (Bhatt et al., 2007b). A comparison of risk genotype combinations of uncoupling protein-2 (**UCP2)** -866GG, **mtDNA** 10398A and **PGC1** alpha p.Thr394Thr or p.Gly482Ser against the protective genotypes **UCP2**- 866XA, **mtDNA** 10398G and **PGC1 alpha** p.Thr394Thr or PGC1 alpha p.Gly482Ser showed a highly significant difference and increased ORs, showing significance of additive interaction of multiple small effects of the studied candidate gene variations in a complex disease like T2D.

Among all the association studies with T2D in Indian populations, **TCF7L2** has been shown to be most promising in South Indian (Bodhini et al., 2007) and Western Indian (Chandak et al., 2007; Chauhan et al., 2010) populations, where intronic SNP (rs12255372, rs7903146, rs4506565) show

association with T2D. Chauhan et al. (2010) have also replicated association of eight well established genetic variants with T2D in North Western Indian populations showing higher effect size compared to the Europeans.

Conclusion :

The number of loci robustly implicated in the development of T2D has climbed from just 3 in 2006 to almost 20 today. Across all the GWAS completed, **TCF7L2** clearly shows the largest effect size with an odd ratio (OR) of 1.37. So far, all other confirmed loci display more modest effect sizes (OR between 1.1 and 1.20) (Frayling, 2007). **KCNQ1** has been shown to have second largest effect size (OR 1.29) next to **TCF7L2** (Yasuda et al., 2008; Unoki et al., 2008). In spite of a large volume of published work on the disease, no gene(s) has been directly implicated. However, susceptibility to several genetic markers is coming to the fore, however the molecular mechanism by which they exert their biological functions is still not known. The role of all the variants in increasing susceptibility will be known only by gaining further knowledge of the underlying biology. Further association studies for TCF7L2 and KCNQ1 and other variants are needed to assess their role in other populations, especially populations with a high prevalence of type 2 diabetes such as in India.

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