Mini Review

Polymorphism Study on *SLC30A8* and Its Association with Type 2 Diabetes

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Polymorphism Study on SLC30A8 and Its Association with Type 2 Diabetes

M. Vignesh*, T. Sangeetha, T. Varsha
Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India.

*Correspondence: vigneshvickey585@rocketmail.com

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Abstract
Type 2 diabetes mellitus (T2DM) is one of the threatening disorders in the world. It affects people of all ages. Type 2 diabetes mellitus is a condition in which the glucose level in the blood is elevated due to improper function of the secretion of insulin from beta cells of the pancreas. It is a multifactorial disease because it is caused by both environmental and hereditary factors. One of the genes which play an important role in type 2 diabetes mellitus is SLC30A8 which encodes for zinc transporter ZnT8. The common polymorphic site for SLC30A8 is rs13266634. This single-nucleotide polymorphism leads to type 2 diabetes mellitus by replacing the arginine residue with tryptophan residue. This review mainly focuses on the polymorphic studies in the gene SLC30A8 and its association with type 2 diabetes mellitus.

Keywords: Diabetes; Polymorphism; SLC30A8 gene; rs13266634.

1. INTRODUCTION
Type 2 diabetes mellitus is the most common multifactorial disease which affects both men and women in the worldwide population. The abnormal function of pancreatic beta cells and their loss of secretion of insulin are the main reasons for the progress of the disease [1]. Environmental and genetic factors play a crucial role in causing type 2 diabetes mellitus [2]. Numerous genes are involved in the development of type 2 diabetes mellitus. They are TCF7L2, PPARG, IRS-1, IRS-2, KCNJ11, WFS-1, HNF1A, HNF1B, HNF4A, TCF7L2, SLC30A8, CDKN2A/B, and IGF2BP2. Totally there are 38 genetic variants associated with type 2 diabetes mellitus [3]. I have chosen this gene SLC30A8 because there are only few studies on this gene, and it has high potency for causing type 2 diabetes mellitus.

2. SOLUTE CARRIER FAMILY 30 MEMBER 8 (SLC30A8)
SLC30A8 gene encodes the largely endocrine pancreas-restricted zinc transporter ZnT8 and the secretory granule-resident [4]. SLC30A8 gene codes for a protein which is highly present in the pancreas (particularly in the islets of Langerhans), and that protein is involved in the storage and secretion of insulin. This provides a clear-cut mechanism by which it may be involved in conferring type 2 diabetes mellitus risk, and this interrelation has been coped in more than one studies in divergent populations. Interestingly, this gene has also been found to be interrelated with the development and progression of type 1 diabetes; however, it is not confirmed in all studies [3].

3. POLYMORPHISM STUDIES IN SLC30A8
The genetics study reveals that the common polymorphism of rs13266634 was interconnected with lowered beta-cell function and a 14% increase in diabetes risk for C allele [4]. The genetic polymorphisms of SLC30A8 are linked with type 2 diabetes in the Saudi population due to allele variants of SLC30A8 (rs13266634 [C/T]), and they also observed a link between allele variants of SLC30A8 (rs13266634 [C/T]) and type 2 diabetes. It has been suggested that there is no interlink between the obesity associated genes (rs9939609 [A/T]), the melanocortin 4 receptor genes (rs17782313 [C/T], rs12970134 [A/G]), the potassium voltage-gated channel (rs2237892 [C/T]) genes and type 2 diabetes in the Saudi population [5].

Shan et al. [6] suggested that the C-allele variant of SLC30A8, rs13266634, was involved in conferring type 2 diabetes mellitus, and higher plasma zinc was associated with lower odds type 2 diabetes mellitus. Variants of different genes such as SLC30A8, WFS1, JAZF1, KCNQ1, HMG20A, CDKN2A/B, TCF7L2, HNF4A, and DUSP9 are connected with type 2 diabetes in the population of Saudi [7]. The common polymorphisms of SLC30A8 (rs13266634) were linked with type 2 diabetes mellitus in the Tunisian population but not in Lebanese population after adjusting for gender and body mass index which was studied through genome-wide studies by analyzing single-nucleotide polymorphism [8].

The AA genotype of SLC30A8 (rs11558471) was found more commonly in type 2 diabetes patients than in controls (46 vs 24%). The frequency of the A-C-A haplotype of SLC30A8 was particularly higher in type 2 diabetes mellitus patients than
in controls (0.331 vs 0.120). The frequency of the A-C-G haplotype was crucially lower in type 2 diabetes mellitus patients than in controls (0.160 vs 0.365). This highlighted that type 2 diabetes mellitus is interlinked with the AA genotype of rs11558471 in the human SLC30A8 gene. The A-C-A haplotype reveals to be increasing the risk of type 2 diabetes mellitus, and the A-C-G haplotype may act as a preventive factor against type 2 diabetes in Chinese Han population [9]. Single-nucleotide polymorphisms in TCF7L2 (rs7903146), CDKAL1 (rs10946398), HHEX (rs1111875, rs7923837, and rs5015480), and SLC30A8 (rs13266634, rs3802177, and rs11558471) genes are linked with type 2 diabetes mellitus in a Han Chinese population [10].

The genetic variants of SLC30A8 (rs13266634), HHEX (rs1111875), and LOC387761 (rs7480010) are more likely to provide the signals of type 2 diabetes mellitus in the Tunisian population [11]. The meta-analysis's results provide evidence for the significant interconnection between SLC30A8 (rs13266634), C/T polymorphism, and type 2 diabetes mellitus and impaired glucose tolerance. This study also reveals that there is no connection between this polymorphism and type 1 diabetes mellitus [12]. The meta-analysis study of SLC30A8 (rs13266634) C-allele polymorphism carriers could increase the risk factor of type 2 diabetes, particularly in European and Asian populations [13].

4. ASSOCIATION STUDIES IN SLC30A8

Genetic variants of multiple genes such as SLC30A8 (rs13266634), FTO (rs8050136), CDKAL1 (rs10946398), WFS1 (rs10010131), CDKN2A/B (rs10811661), KCNJ11 (rs5219), CDC123/CAMK1D (rs12779790), JAZF1 (rs864745), and HHEX/IDE (rs5015480) are connected with type 2 diabetes mellitus in Chinese population [14]. The genetic variants of rs13266634 (SLC30A8), rs7923837 (HHEX), rs10811661 (CDKN2A/2B), rs4402960 (IGF2BP2), rs12779790 (CDC123/CAMK1D), and rs2237892 (KCNQ1) genes of the Mexican Mestizo population are associated with type 2 diabetes [15]. The SLC30A8 (rs13266634) gene polymorphism does not provide any evidence to a genetic basis for the co-occurrence of schizophrenia and type 2 diabetes mellitus in Chinese Han population [16].

Single-nucleotide polymorphisms of rs11558471 (SLC30A8) and rs11196218 (TCF7L2) genes may be involved in the progression of diabetic retinopathy and diabetic neuropathy [17]. The six genes (SLC30A8, KCNJ11, TCF7L2, HHEX, FTO, and CDKAL1) identified in genome-wide association studies (GWAS) suggests that there is no link between this type 2 diabetes associated genes and polycystic ovary syndrome in Korean women [18].

Single-nucleotide polymorphism in or near insulin-like growth factor–binding protein 2 (IGFBP2), CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1), solute carrier family 30 (zinc transporter), member 8 (SLC30A8), hematopoietically-expressed homeobox (HHEX), and transcription factor 7-like2 (TCF7L2) were obviously linked with diabetes, and there is no evidence for an association to coronary-artery calcification [19]. Single-nucleotide polymorphism in or near PPARα, TCF7L2, FTO, CDKN2A/2B, HHEX/IDE, IGF2BP2, SLC30A8, KCNQ1, JAZF1, IRS1, KLF14, CHCHD9, and DUSP9 genes confers an increased risk of type 2 diabetes in Pakistani population [20]. Common single-nucleotide polymorphism at GCK, SLC30A8, IGF2BP2, and MTNR1B genes influence to different extents the progression of impaired fasting glucose and the transition from impaired fasting glucose to type 2 diabetes [21].

The common polymorphism of rs13266634 (SLC30A8) was associated with the capability of insulin sensitizer (Repaglinide or Rosiglitazone) monotherapy on insulin secretion in patients with newly diagnosed type 2 diabetes mellitus in Shanghai, China [22]. SLC30A8 rs13266634 and rs16889462 polymorphisms were associated with repaglinide therapeutic efficacy in Chinese type 2 diabetes mellitus patients [23]. The new evidence under immunohistochemistry study shows that type 2 diabetes mellitus can be detected by tissue typing [24].

5. CONCLUSION

In this review of the SLC30A8 gene, a summary of its polymorphism studies, sites where polymorphism occur, and its association with type 2 diabetes mellitus, were discussed in detail. Most of this study is carried out in the countries like China, Japan, Korea, Saudi Arabia, Europe, and some parts of Asia. So this paper would provide useful information and good knowledge for the studies going on in diabetes in South Asian and other countries. Details furnished in this review will further help in exploring more about SLC30A8 gene associated with type 2 diabetes mellitus.

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Author Contributions
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Conflict of Interest
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