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ABCC8 genetic variants and risk of diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is a major health problem worldwide and it will rapidly increase. This disease is characterized by hyperglycemia caused by defects in insulin secretion, insulin action or both. DM has three types: T1DM, T2M and gestational DM (GDM), of them T2DM is more frequent. Multiple genes and their interactions are involved in insulin secretion pathway. Sulfonylurea receptor encoded by ABCC8 gene, together with inward-rectifier potassium ion channel (Kir6.2) regulates insulin secretion by ATP-sensitive K^+ (KATP) channel located in the plasma membranes. Disruption of these molecules by different mutations is responsible for risk of DM. Several single nucleotide polymorphisms (SNPs) of ABCC8 gene and their interaction are involved in pathogenicity of DM. This review summarizes the current evidence of contribution of ABC8 genetic variants to the development of DM.

1. Introduction

Diabetes mellitus (DM) is a common lifelong health condition. Approximately, 366 million people were diagnosed with DM in the world in 2011 and it will increase to 552 million by 2030 (Zimmet et al., 2014). This disease is a group of metabolic disorders characterized by hyperglycemia caused by defects in insulin secretion, insulin action or both (Alice et al., 2008). DM is associated with dysfunction and failure of different organs such as blood vessels, heart and kidneys (Wilkin, 2009). Development of diabetes is resulted from several pathogenic processes such as interruption of immune system. Autoimmunity damages pancreatic β-cells which results in insulin deficiency leading to resistance to insulin action (Jill et al., 2008). DM has been classified into three subtypes: type 1 (T1DM), type 2 (T2DM) and gestational DM (GDM).

Approximately, 5–10% and more than 90% of patients with DM are affected to T1DM and T2M, respectively. T1DM is caused by destruction of immune system which affects on production of insulin by pancreatic β-cells, therefore patients are dependent on exogenous insulin. T2DM is a chronic degenerative disorder, characterized by high levels of glucose and metabolic complications. It is caused by insulin secretion deficiency and insulin resistance. Resistance to insulin can be a consequence of reduced insulin receptors, failure in binding of insulin to receptor or disturbance in the glucose transportation into the cell. T1DM appears in children and young adults but T2DM is more common between 40 and 60 years (Thomas et al., 2012; Waldron-Lynch and Herold, 2011). GDM is a condition in which insulin receptors do not function properly leading to high blood glucose levels during pregnancy. Increase of human placental lactogen (hPL) up to 30-fold in pregnancy is likely associated to GDM. This protein stimulates insulin secretion from pancreas during pregnancy leading to inappropriately elevated blood sugar levels. GDM affects 3–10% of pregnancies in various populations (Prudente et al., 2012; Ryan and Enns, 1988).

Genetic and environmental conditions are predisposing factors for pathogenicity of DM. Multiple genes and their interactions are involved in insulin secretion pathway. Disruption of these molecules of this pathway by pathogenic (causative) and non-pathogenic (DNA polymorphism) mutations is responsible for risk of DM. Several single nucleotide polymorphisms (SNPs) have been reported to increase risk of DM. The aim of this review is to discuss the possible contribution of gene polymorphisms of ATP binding cassette, subfamily C, member 8 (ABCC8) gene as an element of this ABCC8 to the development of DM via their effects on SUR1 function.

2. Role of genetics in development of diabetes mellitus

DM is a multi-factorial disease influenced by both genetic and environmental factors. People with a family history of T1D and T2D have

Abbreviations: KATP, ATP-sensitive K^+; CALPN10, calpain 10; PRKACG, cAMP-dependent protein kinase catalytic subunit G; DM, diabetes mellitus; ENSA, endosulfine alpha; FOXA2, forkhead box A2; GWAS, genome-wide association studies; GDM, gestational diabetes mellitus; HVA, high-voltage activated; hPL, human placental lactogen; Kir6.2, inward-rectifier potassium ion channel; L, long-lasting; LVA, low-voltage activated; N, neural; NBD, nucleotide-binding domains; PPARγ, peroxisome proliferator-activated receptor-γ; KCNJ11, potassium inwardly-rectifying channel, subfamily J, member 11; P/Q, purkinje; RAPGEF4, rap guanine nucleotide exchange factor 4; R, residual; SNPs, single nucleotide polymorphisms; SUR1, sulfonylurea receptor; T, transient; TMD, transmembrane domains; T1DM, type 1 diabetes mellitus; T2M, type 2 diabetes mellitus; VDCC, voltage-gated calcium channels.

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more six and three times higher risk of developing this disease than unrelated individuals, respectively (Dorman and Bunker, 2000; Flores et al., 2003). More than 70% of T2D risk has been attributed to genetics, with multiple genes involved and different combinations of genes playing roles in different subsets of individuals (Ahlqvist et al., 2011).

Non-pathogenic genetic mutations account for development of DM. SNPs are the commonest type of genetic variation dispersed within or outside a gene region in human genome with a frequency < 1%. Approximately, 54% of these variants are not deleterious mutations (Mitchell et al., 2005). Many SNPs have been shown to be associated with the risk of diseases. These variants generally do not directly cause a disease, but alter the risk of developing a disease (Bailey-Wilson and Wilson, 2011). Recent genome-wide association studies (GWAS) have identified more than 60 loci for susceptibility to T1DM; 65 loci for s, encoding up to 500 different genes increase risk of T2DM (DIAbetes Genetics replication and meta-analysis DIAGRAM. Consortium, 2014; Hivert et al., 2014). Most of these genes are involved in pancreatic β cell function, insulin action/glucose metabolism, or other metabolic conditions that increase T2D risk (e.g., energy intake/expenditure, lipid metabolism). Amongst these genes, ABCC8, potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11), peroxisome proliferator-activated receptor-γ (PPARγ) and calpain 10 (CALPN10) were more under attention (Schwenk et al., 2013).

3. ABCC8 gene produces protein

The ABCC8 gene is located at 11p15.1 and has more than 100 kb of genomic DNA (17,414,538–17,493,323) encoding SUR1 protein (Kapoor, 2010). This gene is a member of ABCC subfamily belonging to ABC family (Dean et al., 2001) (Fig. 1). Based on the mode of action, ABC transporter can be divided into two classes: active transporters such as ABCB subfamily and transport facilitators such as ABCC subfamily. ABCB transporters move molecules across membranes but ABCC molecules display nucleotide binding and a following conformation alters with a very low ATP hydrolysis. ABCC8 gene is a member of ABCC subfamily which encodes SUR1 protein. SUR1 contains three transmembrane domains (TMD0, TMD1 and TMD2), two cytoplasmic nucleotide-binding domains (NBD1 and NBD2) and two cytoplasmic loops 3 and 8. Each NBD consists Walker A and Walker B motifs with specific sequences for nucleotide binding proteins. SUR1 can couple ATP hydrolysis at the NBDs to supply energy and displace their substrates such as sugars, amino acids, and lipids (Biemans-Oldehinkel et al., 2006; Kapoor, 2010; Maa Bared, 2005; Pohl et al., 2005).

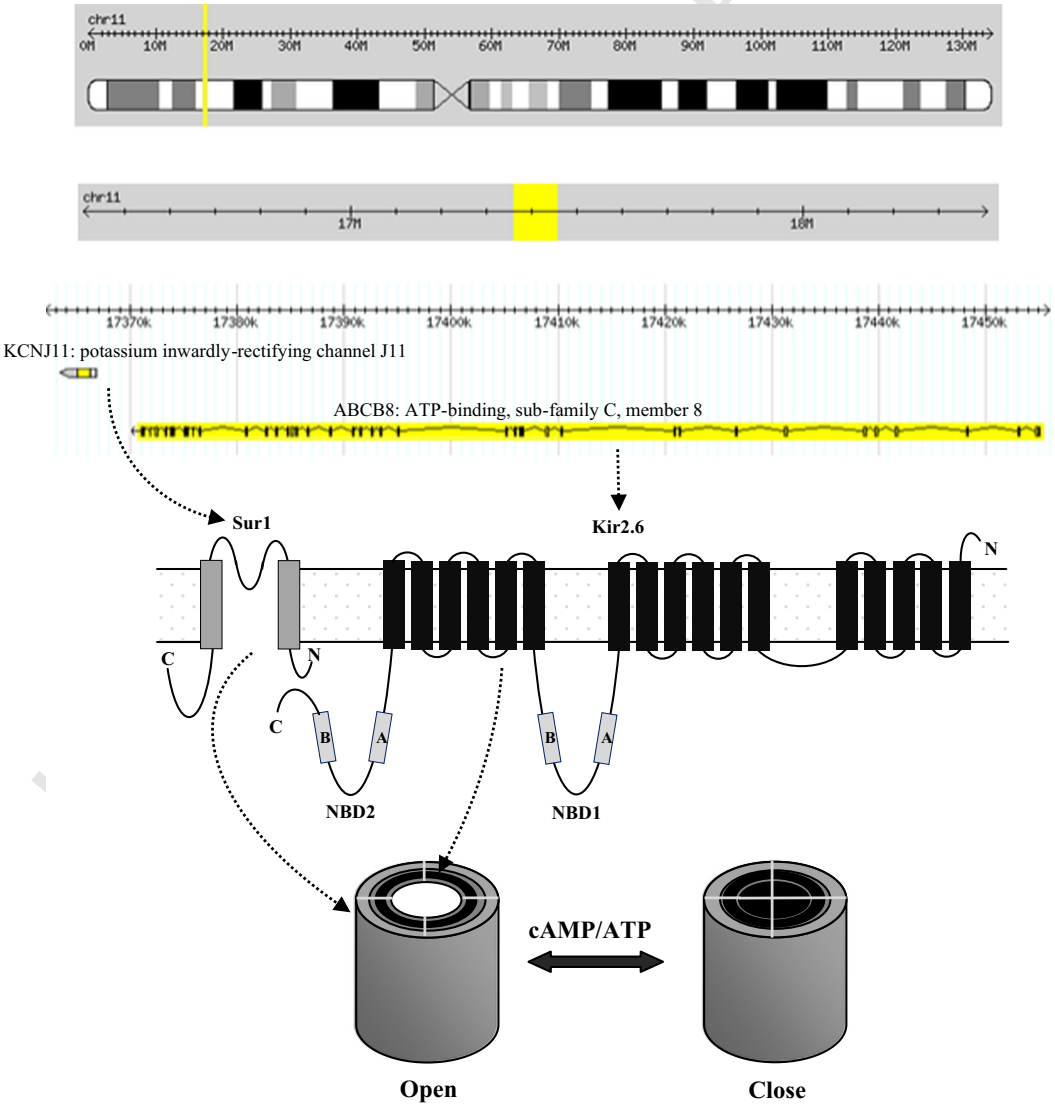

Fig. 1. Structure of ABCC8 and KNJ11 genes and their encoded proteins.

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