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CAN WE CONSIDER SLC2A1 POLYMORPHISMS AS A GENOMIC MARKER FOR COGNITIVE PROBLEMS?

BİLİŞSEL PROBLEMLERDE SLC2A1 POLİMORFİZMLERİNİ GENETİK BELİRTEÇ OLARAK DİKKATE ALABİLİR MİYİZ?

Kadir Sinan Arslan[1], Korkut Ulucan[*2]

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To Editor;

Glucose is the most important carbon source and energy supplier molecule for almost every cell in our body. It is very important not only for muscle cells, but also for neurons, especially the neurons of central nervous system. Its availability influences the cellular metabolism and physiological processes of the cells and tissues. Its distribution through blood and transportation from cell membrane to cells are important for aerobic capacity of the cell. All animal cells contain a plasma membrane protein involved in transporting glucose into the cell (Elbrink et al.,1975).

GLUT1 or glucose transporter 1 (OMIM 138140), also known as solute carrier family 2 facilitated glucose transporter member 1 (SLC2A1), is a uniporter carrier protein encoded by SLC2A1. GLUT1 exist in two isoforms, one with 45 kDa in astrocytes and 55 kDa in brain endothelial cells (Simpson., 2007). It mediates the basal level cellular uptake of glucose into many tissues (Mueckler et al., 1985) as well as into the brain tissue. GLUT1 has important roles in the endothelial cells of the blood brain barrier (BBB) for transporting glucose to brain (Maher et al., 1994), but its expression is not seen in neurons (Zlokovic et al., 2008). The BBB acts as a boundary between capillaries and the surrounding brain; also protects the nerve tissue by preventing different types of hazardous molecules from entering the brain. The GLUT1 protein also moves glucose between cells in the brain called glia, which protect and maintain neurons.

SLC2A1 is located at 1p34.2 and has 10 exons (Figure 1). It has over 50 variations, some of which are associated with diseases like type 2 diabetes mellitus (T2DM), diabetic nephropathy (DN), diabetic retinopathy, renal cell carcinoma, and, more recently, breast cancer and age-related macular degeneration. Mutations in the SLC2A1 are responsible for GLUT1 deficiency (de Vivo disease), which is a rare autosomal dominant disorder. This disease is characterized by a low cerebrospinal fluid glucose concentration (hypoglycorrhachia), neuroglycopenia, which results from unbalanced glucose transport across the blood–brain barrier (Seidner et al., 1998). These individuals generally have frequent seizures (epilepsy), and the probable first signs of the disorder are the involuntary eye movements, which are mainly irregular and rapid. Babies with common GLUT1 deficiency have a normal head size at birth, but due to slow development of the brain and skull, microcephaly may be seen in these individuals. As they mature, developmental delays or intellectual disabilities, some neurological problems like spasticity, ataxia and dysarthria may be observed. Episodes of confusion, lethargy, headaches, or muscle twitches (myoclonus) are the other important features of the anomaly (Pearson et al., 2013).

One of the widely analyzed polymorphism in SLC2A1 is the Variant rs841853 (also termed SLC2A1 XbaI G>T polymorphism). This polymorphism is located approximately 4.5 kbp upstream of exon 3 and affects the glucose transport ability of GLUT1, and in conjunction with the neighboring SNPs, these variations form haplotype groups. Several studies have indicated that significant association exists between rs841853 polymorphism and increased risk in Type-2 diabetes, but this association is population-specific and varied, which generated some controversies (Du, 2013). There are other case-control studies that have investigated the association between

[1]Üsküdar University, Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics, Istanbul, Turkey
[*2]Marmara University, Faculty of Medical Biology and Genetics, Department of Medical biology and Genetics, Istanbul, Turkey
Corresponding Author: Haluk Türksoy Sok. No:14, Altunizade, Üsküdar, Istanbul, Turkey, 34662 E- mail: korkutulucan@hotmail.com, Tel:+902164002222-2409; M:+905326921922

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the diabetes-related complications, such as nephropathy, and the XbaI polymorphism in the SLC2A1, but their results were inconclusive. Some studies urge that this polymorphism is a risk factor for developing diabetic nephropathy (Liu et al., 1999; Hodgkinson et al., 2001; Ng et al., 2002), but other studies report no genetic association (Gutierrez et al., 1998;Tarnow et al., 2001) and other studies suggest the protection role of this polymorphism against diabetic nephropathy (Grzeszczak et al., 2001). To date, no study associated the related polymorphism with any kind of neurological and physiological conditions, if any, no significant associations were hold.

Another important polymorphisms is the variant rs1385129 (also termed SLC2A1 HaeII T>C polymorphism). This variation is located at the exon 2 of the GLUT1 gene (Tao et al., 1995). Like SLC2A1 XbaI polymorphism, this variation was analyzed in diabetes, but the results were not adequate to associate the polymorphism and the related disease.

There are other variations within the gene, which are considered to be an important biomarker for certain diseases and SLC2A1. As this protein is important in glucose balance through BBB, we consider that variation within the gene encoding GLUT1 may be associated with development and structure of the brain tissue. By affecting the neuro-developmental process, these variations could effect cognitive functions, which later may have an impact on physiological problems. With the help of these information, we can suggest the potential role of GLUT1 protein and its coding gene, SLC2A1, as a biomarker for cognitive problems.

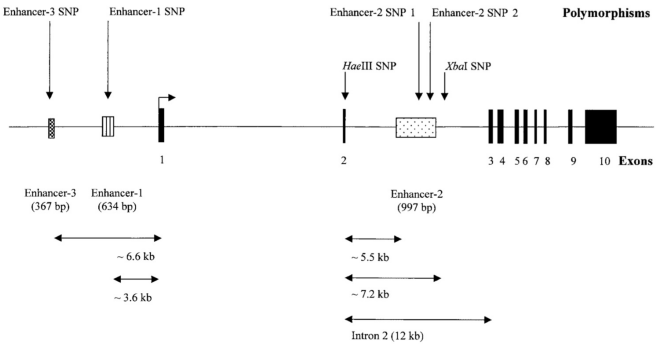

Figure 1: Structure, 5'-UTR, exons and putative enhancers (1, 2 and 3) of GLUT1. Vertical arrows indicate the important polymorphism in the gene (Ng. et al., 2002)

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