

Potential Role of Glucose Transporters in Glucose Homeostasis: a Narrative Review

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ABSTRACT

Background: The *GLUT2* (glucose transporter 2) is a glucose sensitive receptor gene found in the liver, pancreas, and sometimes in the CNS. The experiments conducted on the genetically modified mice revealed their role in the different regulatory mechanisms.

Objective: The current narrative review aims to elucidate the role of *GLUT2* in glucose homeostasis.

Methods: The recent related articles were reviewed with the help of different databases including PubMed, Google Scholar, Springer link, and Science direct. To ensure the credibility of data, articles published only in indexed journals were considered.

Results: In the liver (hepatocytes), it's reported that there is an unsuspected glucose pathway (output) that is dependent on the membrane mechanism is in progress. In humans, due to the mutation in the *GLUT2* gene, there is a syndrome known as "Fanconi–Bickel syndrome" which dictates a glycogen storage disease type 11 disease characterized by kidney and liver disorders.

Conclusion: It is concluded from the genome-wide association studies that the genetic mutations in *GLUT2* result in an increased risk of high cholesterol, cardiovascular diseases (CVDs), and fasting hyperglycemia.

Keywords: *GLUT2*, Fanconi–Bickel syndrome, CVDs, Glucose Transporter.

INTRODUCTION

Glucose transporter 2 (*GLUT2*), famously known as solute carrier family 2 (cellular glucose helper), member 2 (*SLC2A2*). The *SLC2A2* is approximate 30kb in size. This gene consists of ten introns and eleven exons. It stands as a transmembrane protein possessing the function of cellular glucose transport in cell membranes. The major contributor to this is the movement of blood glucose between the liver and blood. The gene is found amongst humans, where the respective protein is found encoded by the *SLC2A2* gene [1]. It is to note that the error in this gene is

linked with a typical kind of glycogen storage disease (GSD) i.e. Fanconi Bickel syndrome (FBS) [2].

In *SLC2A2* knockout mice suppress glucose stimulated insulin secretion and inhibit beta-cell glucose uptake, and the transgenic *GLUT2* gene has been shown to protect against a variety of disorders in the mice. However, while the lack of *GLUT2* adaptation is not well established [3], it is important to remember that the major cause of non-diabetes is likely to result in infants older than average. Large may be a good measure of good glycemic control and healthy *GLUT2* status. Establish the onset of blood sugar attacks between the blood vessels and the space within the kidney. *GLUT2* has been seen

playing a major part in osmoregulation, and prevents edema development, transient ischemic stroke especially when blood glucose levels are above average [4]. *GLUT2* may be referred to as "diabetic glucose transporter" or "stress hyperglycemia glucose transporter" [5].

Fanconi Bickel syndrome is a glycogen storage disorder caused by autosomal recessive pathways and also due to conformational polymorphisms in the *SLC2A2* gene causing to loss of *GLUT2* transporter expression. It is accepted as a rarely occurring disease owing to approximately 100 reported so far as seen through been in the literature review. *SLC2A2* gene is used for *GLUT2*, which is also a low-affinity transport protein that is involved in sugar-induced homeostasis, for instance as in pancreatic β -cells, hepatocytes, and the tubular cells. The FBS has a marked reduction in galactose and glucose utilization, hepato-renal glycogen accumulation and

tubular nephropathy. *GLUT2* deficiency and hypotension result in postprandial hyperglycemia, fasting hypoglycemia, hepatomegaly, diabetes mellitus (DM) galactose, and glucose deficiency, probable defiance against glucagon and adrenaline, malignant growths, and rickets. The part of *GLUT2* shortage in the origin of DM is not completely established [6].

Many mutations related to the *GLUT2* gene are well interpreted for FBS [7], to date, forty-six polymorphisms (missense, splice site variants, deletions, insertions, and nonsense) were identified in the *SLC2A2* gene which has a strong association with the Fanconi Bickel syndrome. Further research in FBS patients confirmed that a person must possess 2 pathogenic *SLC2A2* mutation with homozygous or compound heterozygous for the manifestation of the disease. Figure 1 explains the genetic polymorphisms in the *GLUT2* gene [8].

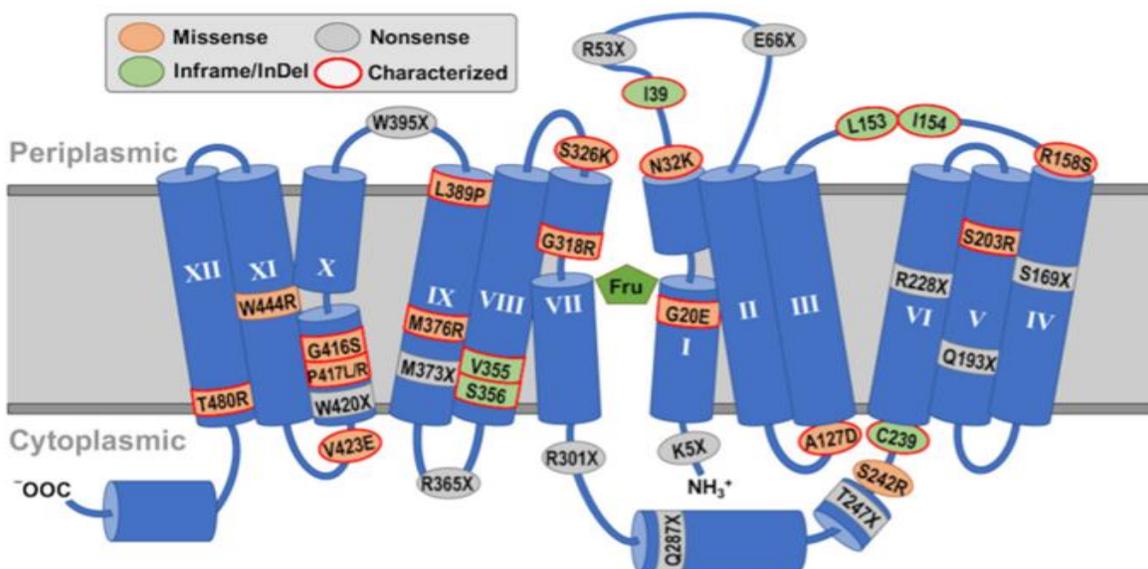


Figure 1. Mutation including missense, non-sense, inframe /Del and characterized within the *GLUT2* transporter which are associated with FBS. Roman numerals I-XII indicate *GLUT2* transmembrane helix, red border for functional characterization and "Fru" represents the fructose [8].

Glucose Transporter (GLUT2)

It was first cloned in 1988 from human liver cDNA libraries and rats. These glucose transporter 1 showed 55% similarity and 80% homology with the glucose transporters 1. It is composed of five hundred and twenty-four amino acids. It is mainly present in the liver, where it plays an essential role in the transportation of hexose, intestine, kidney, and islet

cells [9]. It consists of fourteen isoforms. It has a high affinity for glucosamine and a low affinity for glucose, fructose, mannose, and galactose. It has a key role in the transepithelial glucose transport in the kidney [10].

Liver Glucose Sensing and GLUT2

The hepatoportal supply is mainly regulated by the afferents [11], which operate after glucose is activated by the shield made by the hepatoportal sensor,

requiring *GLUT2* expression, and was further regulated by a flow of 5' AMP-stimulated protein kinase [12]. It has been shown that in situ, the regulation of the first degree of insulin depends on a physiological signal that glucose is entering the hepatportal artery, and may have been transmitted leading to neural beta cells.

Glucose Transport Mechanism

It is known that glucose travels into the enterocyte making way from the brush border membrane in the intestine via sodium glucose cotransporter 1 (*SGLT1*). It thereby is discharged all over the basolateral membrane, traveling down the concentration gradients through utilizing the *GLUT2*. However, Na^+/K^+ pump, found in the basolateral membrane plays a major part in the maintenance of the applicable gradient of *SGLT1*. It is also noted that fructose is also transferred from the brush border membrane and forced out bilaterally. This is accomplished by the well-known mechanism of facilitated diffusion by way of *GLUT5*.

Fanconi-Bickel Syndrome

It is a state depicting the sparse occurrence of glycogen storage disease (GSD). As a result of heterozygous or homozygous mutations in *GLUT2*, the gene further promotes the interaction of pancreatic b-cells, enterocytes, hepatocytes, and other human cells. Most patients have a common form of chronic disease: hepatomegaly seconds with glycogen build-up, galactose and sugar imbalance, fasting hypoglycemia, distinct tubular nephropathy, and severe tumor growth. The efficacy of *GLUT2* in DM is still debated because it is not the major cause of glucose tolerance in pancreatic cells in humans. [13, 14].

FBS results as mutations in *SLC2A2* including eleven exons up to 30-kb region on chromosome 3 (3q26.1-26) [15]. The long-acting transporter 2 (*GLUT2* or *GTR2*) proteins, that are highly implied in enterocytes, hepatocytes, pancreatic β -cells, stem, and neural cells [16]. *GLUT2* functions as a glucose sensor, monosaccharide transporter, and plasma membrane sugar that stimulates homeostatic sugar in the body [17]. Until now, greater than 80 *SLC2A2* mutations are noted to cause FBS at one time worldwide.

Amongst many pathways with *SLC2A2*, the gene used for circulating glucose, *GLUT2*, has been linked to FBS, is also rare with elevated glycogen content, and also reported in the 100 published articles. These

deficiencies rarely reduce *GLUT2* transporter activity, causing significant downstream effects. To date, 46 *SLC2A2* mutations are found to be associated with Fanconi Bickel syndrome. FBS is a dominant disease; autosomal and for FBS to be expressed in humans, it must be caused by homozygous or heterozygous cells and two pathogenic *SLC2A2* mutations.

In addition to people who are at risk of *GLUT2*-related FBS events, those with less than one are small (medium frequency between 1% to 5 %) or normal (low injection > 5%). The *SLC2A2* allele may be at stake for several metabolic characteristics. For instance, a genome-wide sequence analysis (GWAS) has specified the most widespread genes in *SLC2A2* that are associated with a heightened risk of type 2 diabetes [18].

Genome-Wide Association Studies

GLUT2 is responsible to regulate impairment glucose (fasting) for the sake of risk of type 2 diabetes Mellitus and Heart Attack. The only transporter required for glucose homeostasis and its metabolism is *GLUT2*. Genome-wide studies have reported that *GLUT2* variants are associated with fasting hyperglycemia and enhanced risk of type 2 diabetes in humans, the association of *GLUT2* mutation with diabetes in infant, high-risk, and potentially fatal, type 2 diabetes may be best described as a glucose disorder and may cause loss of first-phase insulin resistance, immune control, and progression forward development of the cream is not acceptable.

In conclusion, in humans, several polymorphisms in this gene showed to be associated with the Fanconi-Bickel syndrome, which is well known for being an autosomal recessive disorder as seen in the metabolism of carbohydrates. The *GLUT2* inactivation in mice due to homologous recombination incites drastic glucosuria. Certainly, it turned out as per the report that *GLUT2* cell surface expression influences glucose induced insulin secretion. *GLUT2* also possesses the ability to allow a consistent message to the entire body via signals sent out to both sugar scarcity and abundance. Moreover, novel opportunities for the re-evaluation of *GLUT2* in obesity, diabetes, and insulin resistance may help in the future prevention of the diseases.

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