

## Glucotransporters: clinical, molecular and genetic aspects

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### Abstract

Oxidation of glucose is the major source of obtaining cell energy, this process requires glucose transport into the cell. However, cell membranes are not permeable to polar molecules such as glucose; therefore its internalization is accomplished by transporter proteins coupled to the cell membrane. In eukaryotic cells, there are two types of carriers coupled to the membrane: 1) cotransporter Na<sup>+</sup>-glucose (SGLT) where Na<sup>+</sup> ion provides motive power for the glucose's internalization, and 2) the glucotransporters (GLUT) act by facilitated diffusion. This review will focus on the 14 GLUT so far described. Despite the structural homology of GLUT, different genetic alterations of each GLUT cause specific clinical entities. Therefore, the aim of this review is to gather the molecular and biochemical available information of each GLUT as well as the particular syndromes and pathologies related with GLUT's alterations and their clinical approaches.

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### Introduction

Glucose metabolism provides energy to the cell by means of adenosine-5'-triphosphate (ATP) biosynthesis, with glycolysis as the catabolic pathway. Glycemia homeostasis involves three processes: 1) glucose absorption in the small intestine; 2) glucose internalization and consumption by body tissues, and 3) hepatic production of glucose<sup>1-3</sup>.

For the above processes to be carried out, glucose internalization to the cell is primordially required. However, cell membrane is not permeable to polar molecules such as glucose, so it is necessary the participation of membrane-coupled carrier proteins<sup>4</sup>. Each transporter protein, expressed in different tissues, has

different affinity for carbohydrates<sup>1</sup>. In eukaryote cells there are two membrane-coupled transporter proteins: 1) Sodium-glucose co-transporters (SGLT), located in the small bowel and renal tissue, mainly responsible for the absorption and reabsorption of nutrients, and 2) glucotransporters (GLUT), which act by facilitated diffusion and are differentially distributed in body tissues<sup>4-6</sup>. The latter are included in the solute carriers (SLC) family 2<sup>7</sup>.

So far, 14 GLUTs have been described, which exhibit common structural features: 12 transmembrane alpha helix domains, whose amino and carboxyl end-groups are intracytoplasmically located, one highly glycosylated extracellular domain in the third or fifth loop, depending on the GLUT. GLUTs can be grouped in 3 main classes according to their homologous

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sequences and the glycosylation loop position<sup>8-10</sup>. Class I comprises GLUT1 to 4 and GLUT14. Class II (odd transporters) includes GLUT5, 7, 9 and 11. Class III (pair transporters) is comprised by GLUT6, 8, 10 and 12 and proton-propelled myo-inositol transporter (HMIT) or GLUT13<sup>10</sup>.

GLUT classes I and II have their glycosylation site at the first extracellular loop between transmembrane helices 1 and 2, whereas in class III, glycosylation occurs in loop 9. GLUT protein sequences possess 14 to 63% homology, while in preserved regions, homology increases from 30 to 79%<sup>10</sup>.

Next, we will describe biochemical and molecular information, protein function, as well as associated syndromes and phenotypes of each GLUT.

## GLUT1

GLUT1 is encoded by the *SLC2A1* gene with an extension of 33,802 bp and a mRNA of 3,687 bp and it is located at the chromosome 1. It contains 10 exons and 9 introns. The protein is composed of 492 amino acids and is found mainly in erythrocytes, blood-brain barrier, brain, placenta and kidney. There are 2 described isoforms for this GLUT, encoded by the same gene (*SLC2A1*), which differ by the number of glycosylated sites and molecular weight. The first 55-kDa isoform is located in blood-brain barrier endothelial cells (also in neurons) and erythrocytes, while the second 45-kDa isoform is found in astrocytes<sup>1,4,11-13</sup>. The main function of GLUT1 is to maintain cell respiration by means of basal glucose uptake and delivery to the brain. GLUT1 also carries other molecules such as galactose, mannose and glucosamine<sup>1</sup>. The  $K_m$  value of this GLUT for glucose is 3 mM<sup>10</sup>. It has an amino acid homology between species of 98% (human, rat, rabbit and pig)<sup>9</sup>.

The pathologies related with alterations of this gene are the following: Type 9 dystonia, type I and type II GLUT1 deficiency syndrome, exercise-induced paroxysmal dyskinesia, in addition to susceptibility to suffer generalized idiopathic epilepsy in 1% of cases<sup>13</sup>. GLUT1 overexpression in patients with different types of cancer and alterations in *p53* (tumor suppressor gene) expression probably contributes to an increase in glucose delivery to the tumor<sup>1,12,13</sup>.

### **GLUT1 deficiency syndrome**

This syndrome displays high phenotypical variability and is caused by *SLC2A1* gene mutations, which

encodes for GLUT1<sup>14</sup>. De Vivo et al. (1991) made the first clinical description of the syndrome in 2 pediatric patients who had neurological development delay associated with idiopathic epileptic encephalopathy<sup>9,14</sup>. GLUT1 deficiency diagnostic criteria are the following: seizures, developmental delay, complex movement disorder and fasting electroencephalographic changes<sup>15</sup>.

Classic presentation, which is the most severe and common form, is characterized by encephalopathy, early-onset epilepsy with developmental delay, acquired microcephaly, motor discoordination and spasticity. In addition, patients experience periods of apnea, absence seizures appearing within the first 4 months of life and seizures before the first 2 years of age in 90% of cases<sup>9</sup>.

Recently, 200 patients with this syndrome have been reported<sup>16</sup>. Both autosomal dominant and recessive inheritance patterns have been identified; however, in most described patients mutations are *de novo* reported<sup>14</sup>. Initial diagnostic approach of patients with suspicion of this pathology involves general laboratory tests such as urinalysis, without relevant findings, serum glucose concentration determination, where the result is normal<sup>11</sup>, which rules out hypoglycemia as the cause of seizures. Non-conventional diagnostic tests are carried out: the immunoreactivity-mediated erythrocyte membrane glucose uptake test, using 3-O-methyl-D-glucose. In patients with GLUT1 deficiency, this uptake is lower (< 74%) than in individuals without this pathology<sup>16</sup>.

The presence of seizures refractory to conventional treatment in these patients suggests the need to rule out lesions at the central nervous system (CNS) level with imaging studies such as magnetic resonance imaging (MRI). GLUT-deficient patients do not exhibit overt structural lesion data. At the absence of CNS structural lesions by MRI in patients with normoglycemia, positron-emission tomography (PET) with 18-fluorodeoxyglucose (18-FDG) is suggested. Patients with GLUT-1 deficiency show decreased glucose uptake at the cerebral cortex and increased uptake in the putamen and bitemporal and lingual cortex. Collaterally, a 4-6-h fasting hypoglycorrhachia (< 40 mg/dl) together with euglycemia support the diagnosis of this pathology<sup>11,13,16</sup>. However, to confirm the diagnosis, exon sequences amplification has to be carried out by means of polymerase chain reaction (PCR), with subsequent direct sequencing to identify specific mutations. For confirmatory diagnosis, the use of other techniques has been also reported, including single-strand

conformational polymorphisms (SSCP), restriction fragment length polymorphisms (RFLP) and fluorescent in situ hybridization (FISH)<sup>11,13</sup>.

Treatment is based on a 4:1 or 3:1 ketogenic diet (fat:carbohydrate and protein) from early stages of life keeping it until adolescence. Fat-rich and low-carbohydrate diet causes an increase in ketone bodies that, together with anticonvulsant therapy, control seizures. An important feature of ketonic bodies is the ability to cross the blood-brain barrier. At the presence of persistent hypoglycorrhachia in patients with GLUT1 deficiency, ketone bodies provide an alternate energy source for brain tissue metabolism<sup>11,15</sup>.

Therapies with alpha-lipoic acid and triheptanoin are still on investigational phase. Alpha-lipoic acid is an antioxidant with co-enzyme function. In in vitro studies, it has been shown to improve glucose transport by favoring translocation to GLUT4 cell membrane; however there is no evidence indicating a similar mechanism for GLUT1. With regard to triheptanoin, it is a triglyceride that has been used in the treatment of metabolic conditions, such as pyruvate carboxylase and type II palmitoyltransferase deficiency. This compound has the capacity to form 5-carbon ketone bodies that easily cross the blood-brain barrier. It should be mentioned that there are no clinical trials providing information in patients with GLUT1 deficiency<sup>11,15</sup>.

## GLUT2

The *SLC2A2* gene is located at the 3q26 chromosome, which is constituted by 10 exons and 10 introns, with an extension of 30,362 DNA bp and 3,210 mRNA bp. It encodes for the 524-amino acid protein GLUT2. It should be mentioned that this GLUT has 55.5% homology in the amino acid sequence with GLUT1<sup>17,18</sup>. This GLUT is highly glucose-specific, in comparison with other substrates such as galactose, fructose and mannose. However, an even higher affinity has been reported for glucosamine transport<sup>10</sup>. It is mainly found in hepatocytes plasma membrane, pancreatic islets beta cells, and to a lesser extent in small intestine and kidney epithelium<sup>18</sup>.

Three GLUT2 protein variants of 524, 405 and 351 amino acids have been reported so far. The 405 and 351-amino acid variants differ from the other both in their N-terminal region and in the untranscribed region (UTR), and in the lack of an exon at the 5' terminal region, which causes different downstream initiation sites in the gene promoter<sup>19</sup>. With regard to pathologies where GLUT2 is involved, a relationship has been

described between congenital deficiency of this transporter and the Fanconi-Bickel syndrome.

## Fanconi-Bickel syndrome

This syndrome is an autosomal recessive pathology caused by *SLC2A2* gene mutations, characterized by hepatomegaly and glycogen accumulation in the liver and the kidneys. Patients with Fanconi-Bickel syndrome have been reported in European, Asian and American populations, including Mexican patients<sup>20</sup>.

Patients with the Fanconi-Bickel syndrome (MIM 227810) show decreased function of the proximal convoluted tubule (glycosuria, hyperphosphaturia, hyperuricemia, hyperaminoaciduria), intermittent albuminuria, nephropathy, glucose and galactose intolerance, fasting hypoglycemia, as well as postprandial hyperglycemia and hypergalactosemia and hepatosplenomegaly<sup>20,21</sup>. Clinically, patients since six months of age can display "doll-like" facies, facial obesity, important abdominal distension, failure to thrive, polydipsia, chronic constipation and hyperlordosis<sup>20,22,23</sup>.

For the diagnosis of this syndrome, both urine and blood laboratory tests are carried out. Urinalysis reveals glycosuria that can be detected since the fifth day after birth, in addition to hyperphosphaturia, hyperuricemia and intermittent proteinuria. In blood, fasting glucose concentrations of up to 18 mg/dl (1 mmol/l) and postprandial hyperglycemias higher than 120 mg/dl have been reported, as well as hypercholesterolemia and hypertriglyceridemia. Glucose 6 phosphatase (G6PD) and amylo-1,6-glucosidase enzyme activities are normal in this pathology, differentiates this condition from that of glycogenosis. Hepatic biopsy usually shows steatosis and glycogen deposit<sup>20,22,23</sup>.

Fasting hypoglycemia episodes can be explained because there is a disturbance in glucose transport out of the liver. On the other hand, liver impaired glucose uptake activates gluconeogenesis, which increases intracellular glucose and inhibits hepatic glycogen breakdown (glycogenolysis), with an ensuing hepatic glycogen accumulation in hepatocytes, which causes secondary hepatomegaly. In addition, GLUT2 abnormalities generate glucose renal loss in the proximal convoluted tubule (glycosuria), which exacerbates hypoglycemia<sup>20</sup>.

So far, 30 different mutations have been reported for the *SLC2A2* gene, which can be deletions, insertions or single-nucleotide changes. Fanconi-Bickel molecular diagnosis is performed by means of PCR and exon sequencing<sup>23</sup>.

On the other hand, treatment focuses on symptom amelioration, and generally it consists in patient hydration, electrolyte replacement, vitamin D administration, galactose diet-restriction, avoidance of prolonged fasting periods (consuming small portions of food distributed throughout the day is recommended) and treatment with oral bicarbonate in those patients with metabolic acidosis. Of note, an adequate diet during childhood in these patients has been shown to revert hepatomegaly at puberty<sup>23</sup>.

### **GLUT3**

The gene that encodes for GLUT3 (*SLC2A3*) is located at the 12p13.3 chromosome. It is comprised by 10 exons and 9 introns. DNA extension is 17,069 bp and 3,938 bp for mRNA (NM\_006931). The amino acid sequence has 64.4 and 51.6% analogy with GLUT1 and GLUT2, respectively. The protein has a 496-amino acid extension with molecular weight of 54 kDa. GLUT3 is a GLUT with high affinity for glucose, and has also been reported to bind with lower affinity to galactose, mannose, maltose, xylose and dehydroascorbic acid. It is expressed mainly in the brain, in addition to the placenta, testicles and skeletal muscle (slow-contraction fibers). In *in vivo* studies, have shown that this glycoprotein is expressed in mouse pre-implanted embryo cells, which facilitates glucose transport from the placenta to fetal circulation<sup>10</sup> (MIM 138170).

### **GLUT3-related pathologies**

GLUT3 protein overexpression is associated with neonatal-stage hypoglycemia, increased risk for psychomotor development delay and intrauterine growth restriction (IUGR)<sup>24</sup>. IUGR diagnostic approach is accomplished with prenatal echo sonography. Patients with IUGR are at increased risk for cardiovascular conditions and type 2 diabetes mellitus (DM2) at adulthood<sup>6,8,10</sup>.

*SLC2A3* gene mutations have been associated with different malignant processes such as cancer cells increase and metastasis<sup>25,26</sup>. With this regard, GLUT3 overexpression has been reported in testicular lineage tumors by means of immunohistochemistry (IHC) and microarrays<sup>27,28</sup>.

On the other hand, mutations of this gene have been associated with Huntington's disease, because the variation in the number of copies of the *SLC2A3* gene modulates pathogenesis and the appearance of symptoms of the disease, i.e., the higher the number of copies of this gene, pathology occurs at earlier stages<sup>29</sup>.

The *SLC2A3* gene is sequenced in patients with Huntington's disease with the purpose to find out the number of existing copies. GLUT3 gene expression quantification and tissue localization is carried out by means of quantitative PCR and IHC, respectively<sup>24,26,29</sup>.

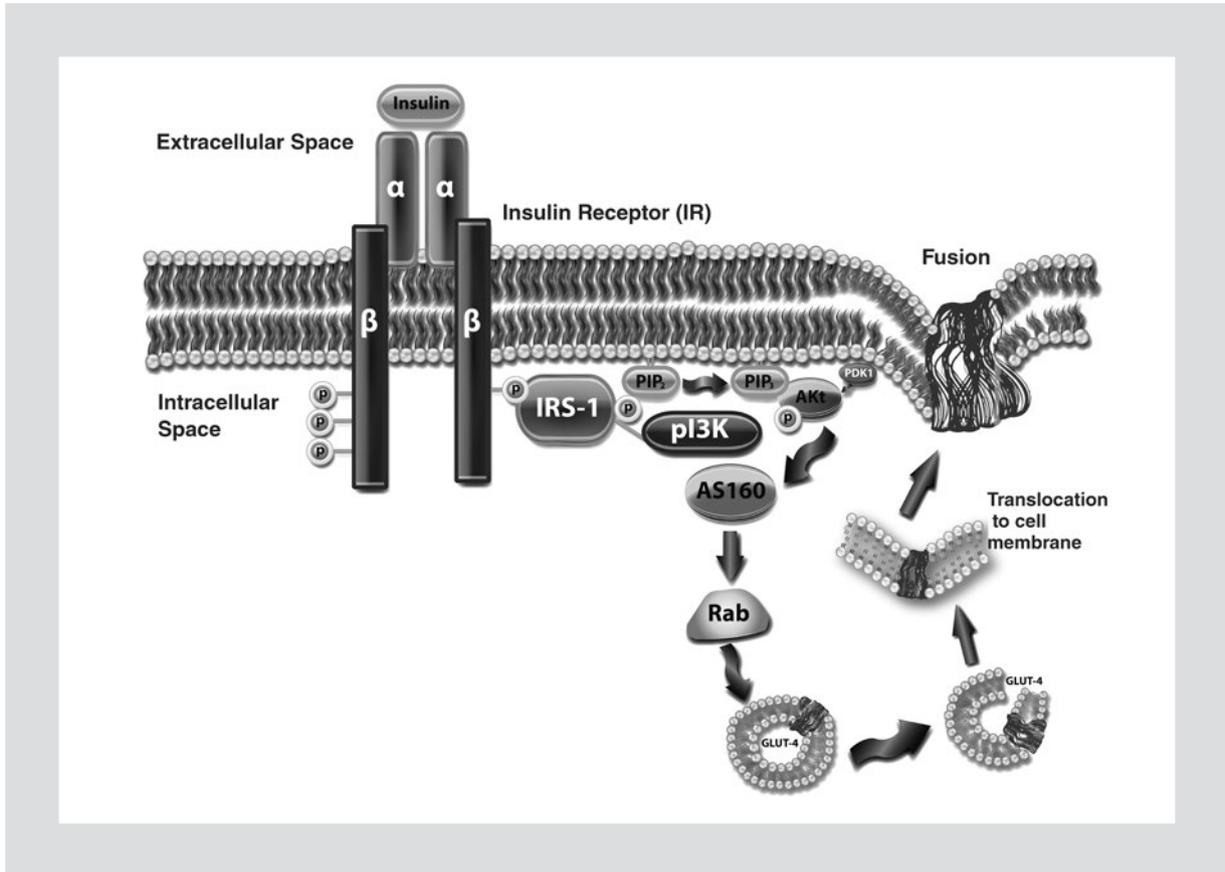
### **GLUT4**

*SLC2A4* gene chromosomal location is 17p13; it has an extension of 6,314 DNA bp and 3,159 linear mRNA bp and a structure comprising 10 introns and 11 exons that encode for a 509-amino acid protein (MIM 138190).

This GLUT displays high affinity for glucose ( $K_m = 5$  mM), and is expressed in skeletal and cardiac muscle and adipose tissue (insulin-sensitive tissues). In these tissues, glucose transport into the cell is increased by insulin-mediated GLUT4 action. GLUT4 insulin-mediated translocation is due to the presence of phenylalanine residues at the amino-terminal region, dileucine residues at the carboxy-terminal region, acidic domains and an insulin-responsive motif (IRM) domain<sup>8,30,31</sup>.

GLUT4 is found in the cytoplasm, stored in the form of vesicles. GLUT4-storage vesicles, or insulin-response vesicles, translocation from the cytoplasm to the plasma membrane is regulated by the action of insulin. In physiological conditions, when the GLUT4 vesicle is translocated from the cytoplasm to the cell membrane by exocytosis, it gets integrated to the membrane, with subsequent glucose uptake<sup>32-34</sup>. GLUT4 translocation is influenced by type 1a phosphatidylinositol 3 kinase (PI3K), protein kinase B (PKB), serine/threonine kinase (AKT) and the atypical protein kinase isoform (PKC $\zeta$ )<sup>30,32</sup>. GLUT4 translocation via the PI3K pathway is shown in figure 1.

Recently, the diacylglycerol and ceramides deposit in skeletal muscle and adipose tissue has been hypothesized to alter GLUT4 translocation and to produce an inflammatory state that leads to insulin resistance (InRe). The latter physiopathological state is commonly found in DM2 and obesity<sup>33,34</sup>. In studies with murine models, GLUT4 protein deficiency has been observed to be associated with mRNA higher expression and retinol-binding protein-4 (RBP4) biosynthesis, a protein that favors InRe. However, this mechanism has not been fully elucidated in humans<sup>16,31</sup>. In models with GLUT4-knockout (KO) mice, a possible mechanism has been proposed, whereby RBP4 causes InRe. This mechanism produces muscle and liver signaling alterations. In muscle tissue, it decreases PI3K phosphorylation activity, as well as phosphorylation



**Figure 1.** PI3K-mediated GLUT4 translocation in skeletal muscle cells. When insulin binds to its receptor, insulin receptor (IR) subunit beta ( $\beta$ ) is phosphorylated, which in turn causes insulin receptor substrate-1 (IRS-1) phosphorylation. Subsequently, phosphatidylinositol-3,4,5-triphosphate ( $PIP_3$ ) is synthesized from phosphatidylinositol-3,4-bisphosphate ( $PIP_2$ ) by means of IRS-1 binding to phosphatidylinositol-3-kinase (PI3K). As a result, the protein kinase-dependent 1 (PDK1) is activated, which in turn activates protein kinase-B (PKB/AKT) by means of its phosphorylation. Consequently, AS160 and RaB are activated to subsequently favor GLUT4-vesicles translocation mechanism to the plasma membrane.

capacity at the insulin receptor substrate 1 (IRS-1) (amino acid 612), which is an important site for interaction with PI3K p85 subunit. Conversely, PI3K and IRS-1 activity is not altered in the liver<sup>36</sup>.

On the other hand, GLUT4 protein missense point mutations are mainly associated with DM2 and obesity<sup>6,8</sup>.

## DM2

DM2 is a chronic degenerative disease characterized by insulin secretion and/or action defects that cause hyperglycemia. It accounts for 90-95% of DM reported cases<sup>37-39</sup>.

In diabetic patients, altered glucose transport is due to defects in the insulin signaling pathway caused by decrease or changes in insulin receptor (IR) and IR substrate (IRS) activity. IR and IRS serine kinase activity is normal, whereas tyrosine kinase activity is decreased. This causes an alteration in the signaling

cascade and, as a consequence, a decrease in PI3K and PKB/AKT activity. This produces a deficient translocation of GLUT4 to the cell membrane surface<sup>40-42</sup>. DM2 diagnostic criteria were proposed by the National Diabetes Data Group (NDDG), the International Diabetes Federation (IDF) and the World Health Organization (WHO). Serum glucose concentration is determined in fasting state and, according to pre-established cutoff values, DM2 diagnosis is established<sup>38,43</sup>.

DM2 is a multifactorial disease, with insulin resistance and increased secretion occurring at early stages with the purpose to maintain euglycemic concentrations. DM2-triggering causes are unknown in 70-85% of cases; however there are nutritional, environmental and genetic factors involved (multigenic inheritance). The latter include GLUT4 alterations that contribute to the onset of hyperglycemias and associated complications secondary to serum glucose concentration chronic elevation<sup>38,43-45</sup>.

**GLUT5**

*SLC2A5* gene location is on the 1p36.23 chromosome; it contains 14 exons and 13 introns, and possesses an extension of 53,372 DNA bp and 2,454 mRNA bp. There are two isoforms, one encodes for a 501-amino acid protein, while the second isoform, owing to the loss of exons at the 3' extreme of isoform 1 transcript, only contains 244 amino acids, and has a different carboxi-terminal end as related to isoform 1 (MIM 138230)<sup>46</sup>. This GLUT is characterized for a high specificity to fructose. It is found in jejunal enterocyte membrane apical cells, in addition to the kidney, brain, muscle tissue and adipose tissue<sup>8,10,47,48</sup>.

Mutations on *SLC2A5* gene associated with hypertriglyceridemia, hyperinsulinemia and urea metabolism disturbances have been described. In experiments carried out in vivo, GLUT5<sup>+/+</sup> mice have been reported to develop systemic hypertension when subjected to a fructose-rich diet, with this owing to fructose co-transport with sodium. In contrast, GLUT5<sup>-/-</sup>-KO mice develop gastrointestinal disorders caused by fructose poor absorption together with hypotension<sup>10</sup>.

On the other hand, GLUT5 increased expression has been reported in colorectal, lung and clear cell renal cell carcinoma (CCRCC), and preferential fructose consumption has been evidenced as the energetic source in this type of cancer<sup>1,47,49</sup>. Furthermore, presence of hyperglycemia, hyperuricemia, increased creatinine serum concentration, proteinuria and hematuria has been reported in patients with CCRCC as a result of renal dysfunction<sup>47</sup>. Histologically, GLUT5 alteration is assessed in a renal tumor tissue biopsy by means of IHC using anti-GLUT5 antibodies, with positivity being observed in cell membrane and cytoplasm. In addition, metabolic alteration in patients with CCRCC is determined by assessing glycogen deposits by means of periodic acid Schiff staining and lipid deposits using oil red, sudan III or sudan IV staining. In CCRCC cases, high energy requirement of the tumor has been described using fructose as a substrate, which is supplied to the cell interior by means of GLUT5 overexpression. Finally, *SLC2A5* gene expression is assessed at the molecular level by means of gene amplification quantification by PCR in patients with the aforementioned histological alterations<sup>47</sup>.

**GLUT6**

The *SLC2A6* gene is located on chromosome 9q34.2 with an extension of 8,061 bp of DNA and has 10 introns

and 9 introns. The zone that flanks exon 1 contains a GC-rich region, a 36-bp CAAT box upstream the start codon and several binding domains to a lymphocyte-specific transcription factor<sup>50</sup>. The *SLC2A6* gene encodes for a 507-amino acid protein and shares 44.8% homology with GLUT8 (MIM 606813)<sup>50</sup>. Two variants of the protein have been reported: the first one, the previously-described 507-amino acid one, and the second, of 445 amino acids owing to the absence of one exon. This GLUT has a  $K_m$  of 5 mM for glucose and is expressed predominantly in the brain, leukocytes and the spleen<sup>8,48</sup>.

Twelve mutations of the *SLC2A6* gene have been associated with developmental delay, morphological changes and malignant melanoma; specifically, the c.1279>G variant that causes a change of arginine for glycine at position 427 of the protein (p.Arg427Gly) (rs267602153).

**GLUT7**

The *SLC2A7* gene is located on chromosome 1p36.23, has an extension of 1,539 bp and contains 12 exons. It encodes for a 524-amino acid protein and shares 58% homology with GLUT5 (MIM 610371)<sup>51</sup>. GLUT7 is a transporter with high affinity for glucose and fructose<sup>52</sup>. It is expressed in testicles, prostate, small intestine and colon<sup>10</sup>. GLUT7 isoforms have been described, which display a region (transmembrane helical domain) that is responsible for fructose transport affinity<sup>10,53</sup>.

Mutations reported in this gene are two single nucleotide polymorphisms (SNPs), which are associated with malignant melanoma. The polymorphisms are c.472G>A (p.Glu158Lys) and c.531C>T (p.Ile177Ile) with reference numbers s267598763 and rs267598762, respectively.

**GLUT8**

The *SLC2A8* gene is found on chromosome 9q33.3 with an extension of 2,172 bp. It contains 10 exons that encode for a 477-amino acid protein also known as GLUTX1 with a molecular weight of 50.8 kDa. GLUT8 protein sequence in humans has been described to be 85% homologous to that of mouse. In contrast, mouse GLUT8 shares an homology of 20-25% in the amino acid sequence with mouse GLUT1, GLUT3 and GLUT4 (MIM 605245)<sup>8,10,54</sup>. This GLUT transports glucose and fructose. It expresses in hepatic tissue, heart, testicles, intestine, adipose tissue, brain and blastocyst<sup>10,55</sup>.

GLUT8 is important for blastocyst metabolism, development and implantation<sup>54</sup>.

So far, 106 polymorphisms (SNP) have been reported in the *SLC2A8* gene (Gene ID: 29988, updated in 2014), associated with steatosis and testicular adenocarcinoma<sup>55,56</sup>. Additionally, *SLC2A8* gene overexpression has been described in patients with Alzheimer's disease<sup>57</sup>.

## GLUT9

The *SLC2A9* gene is located on chromosome 4p16.1, with an extension of 1,927 bp. It contains 16 exons and two isoforms of 511 and 540 amino acids have been described, the latter with a molecular weight of 58.7 kDa (MIM 606142). cDNA complete sequence is 44.5 and 38% homologous to GLUT5 and GLUT1 sequence, respectively. GLUT9 contains an extracellular domain that can display glycosylation between transmembrane segments 1 and 2, which is important for carbohydrate (glucose and fructose) transport by facilitated diffusion. It is almost exclusively localized in the kidney and liver, and it is also expressed to a lesser extent in the small intestine, the placenta, kidney and leukocytes. An additional feature of this GLUT is high affinity for urates, whereby it participates in kidney urate reuptake, specifically in the proximal convoluted tubule<sup>58-61</sup>.

So far, there are two isoforms and 141 SNPs reported. Mutations in this gene are associated with states of hyperuricemia, hyperuricosuria, nephropathy, moderate renal failure, spontaneous abortion and renal hypouricemia (MIM 612076)<sup>6,10,58,59</sup>.

### **Type 2 renal hypouricemia**

Renal hypouricemia is a condition that is transmitted with a recessive autosomal inheritance pattern. Two types of hypouricemia have been described: type 1 renal hypouricemia, which is caused by mutations in the *SLC22A12* gene (also known as *URAT 1*), and type 2 hypouricemia, recently associated with *SLC2A9* gene mutations (MIM 612076)<sup>62</sup>. Hypouricemia main clinical characteristics are due to a decrease in urate renal reuptake, and patients occasionally experience vigorous exercise-induced acute renal failure and nephrolithiasis<sup>61,62</sup>.

Medical history is important for hypouricemia diagnosis due to the relevance of a past history of vigorous exercise-induced acute renal failure episodes. This pathology is suspected when blood urate concentration is lower than 3 mg/dl in several independent

determinations. It is important to rule out *SLC22A12* gene mutations, since these are more common than those described for the *SLC2A9* gene<sup>61,62</sup>. For molecular diagnosis, Matsuo et al. propose amplification of one *SLC2A9* gene region to subsequently identify two isoforms by means of digestion with restriction enzymes. Finally, the diagnosis is confirmed through identification of mutations by sequencing<sup>61</sup>.

## GLUT 10

The *SLC2A10* gene is located on chromosome 20q13.12, with an extension of 4,368 bp. It contains 5 exons that encode for a 541-amino acid protein with molecular weight of 56.9 kDa. This transporter exhibits high affinity for deoxy-D-glucose and galactose (MIM 606145)<sup>63</sup>. GLUT10 homology is 28 and 34% with GLUT3 and GLUT8, respectively. In GLUT10 structure, residues presenting on intracellular helices 9 and 10 show a N-glycosylation domain and a hydrophilic region between intracellular residues 6 and 7; however, the PESPR preserved domain is absent in this GLUT, which is a unique feature of this transporter<sup>6,63,64</sup>. It is predominantly expressed in the liver, pancreas, lung, heart, skeletal muscle, brain, placenta and kidney<sup>63,65</sup>.

GLUT10 deficiency is associated with arterial tortuosity syndrome (MIM 208050). The chromosomal locus where the *SLC2A10* gene is found is associated as DM2-susceptibility loci<sup>6,10,63,66</sup>.

### **Arterial tortuosity syndrome**

This syndrome is characterized for alterations in blood vessels connective tissue, large vessels tortuosity, aortic aneurisms, skin connective tissue hyperextensibility and joint hypermobility<sup>63</sup>. It has been reported with an autosomal recessive inheritance pattern<sup>10</sup>. Mortality rate caused by aneurisms, dissections and ischemic events before the first 5 years of life is considerably elevated, around 40%<sup>67</sup>. Loss of function of this GLUT causes decreased decorin transcription in response to glucose in this syndrome. Decorin is an inhibitor of transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling pathway. In patients with decreased levels of decorin, the expression of elements of response to TGF- $\beta$  and connective tissue growth factor is up-regulated, finally influencing on the formation of extracellular matrix, particularly of elastogenesis<sup>67</sup>. Clinically, these patients display elongated facies, blepharophthalmosis, inferior palpebral fissures, high-arch palate and

micrognathism. With regard to the limbs, reported abnormalities are arachnodactyly and distal contractures (MIM 208050)<sup>67</sup>.

Some clinical characteristics of this syndrome are present in the recessive cutis laxa syndrome (MIM 219100) and in the Loeys-Dietz syndrome (MIM 609192) and, therefore, they should be taken into consideration for differential diagnosis. This way, when the only findings are hyperextensibility and joint hypermobility without involving other systems, the diagnosis is recessive cutis laxa. Conversely, if there is a family history of aortic aneurism as a main finding, probable diagnosis is Loeys-Dietz syndrome. This syndrome is associated with *TGFBR1* gene alteration and with vascular complications occurring in DM2<sup>66</sup>.

The characteristic tortuous arterial trajectory of this syndrome is verified with ultrasonography and large vessels angio-resonance. By the same means, aorta, left carotid and subclavian artery aberrant origins can be evidenced. Other findings are aortic and pulmonary root dilatation. The histopathology analysis reveals medium and large caliber arteries tunica intima and media fragmentation. Diagnostic confirmation is accomplished by gene amplification (PCR) and subsequent sequencing of the *SLC2A10* gene<sup>67</sup>.

### GLUT11

The *SLC2A11* gene is located on chromosome 22q11.23 with an extension of 3,219 bp and is comprised by 14 exons. This GLUT possesses 41.7% homology in the amino acid sequence with regard to GLUT5, and its molecular weight is 54.4 kDa (MIM 610367). GLUT11 transports glucose with high affinity ( $K_m$  0.16 mM). However, it transports fructose as well, which is determined by the NAI domain found on helix 7 of its protein structure<sup>10</sup>.

So far, 3 isoforms have been described, GLUT11-A, GLUT11-B and GLUT11-C, resulting from changes in exon 1. These isoforms encode for proteins with 496, 503 and 499 amino acids, respectively. Each isoform is tissue-specific. GLUT11-A is expressed in the heart, skeletal muscle and kidney; GLUT11-B in the placenta, adipose tissue and kidney, and GLUT11-C has been detected in adipose tissue, heart, skeletal muscle and pancreas<sup>3,10</sup>.

### GLUT12

The GLUT12 gene is located on chromosome 6q23.2 with an extension of 4,469 bp. It contains 6 exons that encode for a 617-amino acid protein with molecular

weight of 66.9 kDa. GLUT12 transports glucose and is expressed in skeletal muscle, adipose tissue, small intestine, prostate, placenta, mammary gland, kidney and brain<sup>6,63,68</sup>. In human skeletal muscle, GLUT12 translocation to the plasma membrane occurs in response to insulin<sup>10</sup>.

There is GLUT12 overexpression in breast ductal carcinoma in situ, diabetic nephropathy, hyperglycemia and hypertension<sup>6,10</sup>.

### GLUT13

The *SLC2A13* gene is located on chromosome 12q12 with an extension of 7,003 bp. This gene is comprised by 11 exons that encode for a 648-amino acid protein with molecular weight of 70.3 kDa (CCDS8736.2). GLUT13 protein homology in humans is 90% with regard to that reported in the rat. Three N-glycosylation sites, a signal sequence for retention in the endoplasmic reticulum and a dileucine residue at the N-terminal region are found in the protein (MIM 6110369). This GLUT specifically transport myo-inositol and produces a decrease of extracellular pH to 5.0; this is why it is also known as H<sup>+</sup>-coupled myo-inositol symporter (HMIT)<sup>6,10,69,70</sup>. GLUT13 is found distributed in the brain, specifically in the hippocampus, hypothalamus, cerebellum and brainstem regions<sup>10</sup>.

Inositol regulation anomalies in brain tissues owing to mutations in GLUT13 are associated with bipolar disorder, lung adenocarcinoma and squamous cell lung carcinoma. In addition, the association of *SLC2A13* gene rs289605 (G>A) and rs11564162 (A>G) polymorphisms together with exposure to caffeine and smoking has been demonstrated to be a gene-environment interaction that increases the risk for the development of Parkinson's disease<sup>10,71-73</sup>.

### GLUT14

The *SLC2A14* gene is found on chromosome 12p13.31 with an extension of 4,125 bp. Two isoforms have been reported: a long (GLUT14-L) and a short isoform GLUT14-S). Both isoforms are expressed in the testicle; however, its expression has been reported in the CNS as well. The protein structure shows glycosylation sites and carbohydrate transport domains. GLUT14-S contains 10 exons encoding for a 497-amino acid protein with molecular weight of 54 kDa, whereas GLUT14-L differs from GLUT14-S by the presence of an additional exon (known as exon 1b) that encodes

for a 520-amino acid protein with molecular weight of 56.3 kDa. GLUT14-S isoform shares 94.5% homology with GLUT3 amino acid sequence<sup>31,74,75</sup>. It has high affinity for glucose<sup>71</sup>. *SLC2A14* gene rs10845990 polymorphism has been associated with late onset Alzheimer's disease; however, the effect of this polymorphism on this pathology has so far not been elucidated<sup>75</sup>.

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