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Disorders of Glucose Transport

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- **Four congenital defects of monosaccharide transport are known. Their clinical picture depends on tissue-specific expression and substrate specificity of the affected transporter. SGLT1 deficiency causes intestinal glucose-galactose malabsorption, a condition that presents with severe osmotic diarrhea and dehydration soon after birth.**
- **SGLT2 mutations result in isolated renal glucosuria, a harmless renal transport defect with normal blood glucose concentrations.**

- **In GLUT1 deficiency, also termed glucose transporter deficiency syndrome, clinical symptoms, usually microcephaly and an epileptic encephalopathy, are caused by impaired glucose transport at the blood brain barrier and thus into neurons and glia cells. The key finding is a low CSF glucose.**
- **Fanconi-Bickel syndrome is the result of a deficiency of GLUT2, an important glucose and galactose carrier within liver, kidney and pancreatic β-cells. Patients typically present with a combination of hepatic glycogen storage and a generalized renal tubular dysfunction which includes severe glucosuria.**

Congenital Glucose/Galactose Malabsorption (SGLT1 Deficiency)

Children with congenital glucose-galactose malabsorption (GGM), caused by SGLT1 deficiency present within days after a normal pregnancy

Genetics

- **GGM is a relatively rare autosomal recessive disorder although the exact prevalence is unknown.**
- **SGLT1, located on chromosome 22q13, codes for a protein of 664 amino acids that forms 14 transmembraneous loops.**
- **To date, approximately 60 different mutations have been found scattered all over the gene.**

Metabolic Defects

- **A congenital defect of the sodium-dependent monosaccharide transporter SGLT1 at the membrane of enterocytes is the basic defect of this disorder.**
- **SGLT1 contributes to the transcellular transport of these two monosaccharides which is completed by the transport out of the cell at the basolateral membrane either by facilitative diffusion or a membrane vesicle-associated transport.**
- **Fructose is not a substrate for SGLT1; it is absorbed by facilitative diffusion mediated by GLUT5 both on the apical and basolateral side.**

- **The SGLT1 protein has not yet been detected in normal human kidney; however, the fact that patients with glucosegalactose malabsorption show mild glucosuria, points to a physiological role of this transporter in renal glucose reabsorption.**

Renal Glucosuria (SGLT2 Deficiency)

Genetics

- **Most individuals with renal glucosuria have been found to carry mutations within the SGLT2 gene, located on chromosome 16p11.**
- **Its product is a low-affinity carrier that transports glucose but not galactose. Homozygosity or compound heterozygosity for SGLT2 mutations results in the severe types of renal glucosuria**

- **is associated with mild glucose excretion albeit not in all carriers. Therefore, inheritance of renal glucosuria is best characterized as a codominant trait with variable penetrance.**
- **To date, approximately 20 private SGLT2 mutations have been described which are scattered all over the gene.**

Metabolic Defects

- **Renal glucosuria is a non-disease; only individuals with massive glucose excretion may have a propensity to hypovolemia and hypoglycemia and can present with a delay of somatic maturation**

Glucose Transporter Deficiency Syndrome (GLUT1 Deficiency)

Genetics:

- **The majority of patients carry heterozygous de novo mutations in the GLUT1 gene located on the short arm of chromosome 1.**
- **Mutations are distributed at random and are of various types (missense, nonsense, and splice-site mutations) including cases of haploinsufficiency.**
- **Phenotype-genotype correlation is yet unclear, but missense mutations may cause a milder phenotype. Autosomal dominant GLUT1-DS has been identified in three unrelated families.**

Metabolic defect

- **GLUT1 is a membrane-spanning, glycosylated protein that provides basal glucose entry across most blood-tissue barriers.**
- **GLUT1 exclusively facilitates glucose transport across the luminal and abluminal membranes of brain capillaries representing the blood-brain barrier.**
- **Consequently, GLUT1 deficiency results in low glucose concentrations in the cerebrospinal fluid, termed hypoglycorrhachia.**
- **In addition, GLUT1 supplies glucose to neurons and glial cells . Since glucose is the principal fuel for cerebral energy metabolism, GLUT1 deficiency results in impaired energy supply to the brain.**