**SLC17A5**

**Patient Description:**
3 year old boy with developmental delay first noted at about six months of age. He is a very happy, engaging child with slightly coarse facial features, an ataxic broad-based gait, and global hypotonia.

**Disease/Syndrome Features:**
Mutations in SLC17A5, or sialin, cause two autosomal recessive sialic acid storage disorders, Salla disease (SD) and infantile sialic acid storage disorder (ISSD). SD is a slowly progressive form of the disease and is most prevalent in Finland, particularly in the northeast region for which it is named. ISSD is a more severe neurodegenerative disorder affecting patients of different backgrounds. Additionally, there are rare cases of an intermediate phenotype or “severe SD” [Aula 2000].

SD was first described in 1979 in three Finnish brothers and their female third-cousin who all had severe intellectual disability and other shared clinical features. They all showed the first signs of developmental delay between ages 6 and 24 months, when they exhibited delayed walking, delayed speech, or delayed motor development. Three cases showed slight to marked deterioration beginning in the second decade, while one brother showed no obvious deterioration by age 31. All patients were united by coarse facial features, clumsiness, ataxia, dysarthria, diffuse EEG abnormalities, and thickened calvaria. An unidentified lysosomal storage disorder was suspected because of the presence of vacuolized lymphocytes in peripheral blood smears. Further histological and biochemical analysis revealed normal lysosomal hydrolase activity, cytoplasmic vacuoles in dermal fibrocytes and other cell types, and increased urinary excretion of sialic acid [Aula 1979]. Progressive cerebellar atrophy and dysmyelination have been observed by MRI [Aula 2000].

In 1982, ISSD was described, and several similarities to adult SD were noted. The first siblings reported had coarse facial features, severe intellectual and developmental delay, prominent motor impairments, fair complexion relative to healthy family members, and hepatosplenomegaly. Like in SD, patients had vacuolized lymphocytes, large cytoplasmic inclusions in numerous cell types, and increased urinary excretion of free sialic acid. [Tondeur 1982]. Whereas SD patients have been reported as surviving into their eighth decade, ISSD patients usually do not survive past two years of age [Aula 2000].

**Protein/Pathway:**
Solute carrier family 17 anion/sugar transporter, member 5, SLC17A5 or sialin, encodes a lysosomal sialic acid/H^+ transporter involved in sialic acid efflux [Verheijen 1999]. Elucidation of SLC17A5 function has been greatly informed by investigation into the clinical aspects of SD and ISSD. Specific symptoms in SD, for example, pointed towards a lysosomal storage disorder, but biochemical studies ruled out known disorders. The presence of increased urinary excretion of total sialic acid suggested that the causative gene might be involved in sialic acid metabolism or flux [Aula 1979]. It
was then shown that patient-derived lysosomes had a specific deficit in sialic acid egress, adding SD to a growing number of diseases caused by failed transport of a small molecule, in this case a monosaccharide, across the lysosomal membrane [Renlund 1986]. SLC17A5 was finally cloned in 1999. It is located on chromosome 6q and was predicted to encode a 495 amino acid, integral lysosomal transport protein belonging to a family of anion/cation symporters (ACS) and to the major facilitator superfamily (MFS) of transporters. Sialin is predicted to include 12 transmembrane domains and has a high degree of homology with human phosphate transporters and E. coli H+/glucuronate symporters [Verheijen 1999].

Around 95% of Finnish SD chromosomes carry a R39C substitution affecting a highly conserved amino acid just before the first transmembrane domain. This founder mutation has also been found in Swedish and non-Scandinavian patients. No patients with ISSD carry this particular mutation. The R39C mutation appears to confer a more mild phenotype than other pathogenic mutations, as compound heterozygotes with one or zero copies of this allele are more severely afflicted than homozygotes with two [Aula 2000].

Recently, extra-lysosomal functions for SLC17A5 have emerged. Miyaji and colleagues propose a role for sialin as a vesicular excitatory amino acid transporter (VEAT). They note that sialin is present in hippocampal synaptic vesicles and synaptic-like microvesicles (SLMV) of pinealocytes. Furthermore, they observe membrane potential-dependent uptake of aspartate and glutamate by sialin in proteoliposome preparations. Sialin with the SD R39C founder mutation has abrogated aspartate and glutamate uptake and reduced sialic acid transport activity. Sialin with ISSD mutations, on the other hand, has normal aspartate and glutamate uptake and completely absent sialic acid transport activity. As such, they propose a role for sialin in the vesicular storage and exocytosis of aspartate and glutamate neurotransmitters and that this mechanism may explain some of the neurological findings in SD [Miyaji 2008]. The physiological significance of sialin in this arena, however, is controversial. Finally, another group has reported that plasma membrane sialin in salivary gland acinar cells functions as an electrogentic 2NO$_3^{-}$/H$^+$ co-transporter. This activity is depressed in fibroblasts and salivary gland cells expressing disease-associated mutations, and suggests a role for sialin in systemic nitrogen balance [Qin 2012].

**Publications:**


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