SLC17A5

Tutorial with Parents (November 9, 2017)
A face-to-face meeting of the parents and their affected son (and one of the son's care givers) occurred on the afternoon of November 9, 2017, with the child's pediatrician, Dr. Wasserstein and Drs. Walkley and Dobrenis (scientists) present. Dr. Walkley had met this Bronx family through a friend of a friend who knew of Dr. Walkley's interests in lysosomal diseases. He subsequently told them about Dr. Wasserstein who they later met and decided to choose as their son's physician. At the start of the tutorial the parents shared much about their diagnosis, and earlier misdiagnoses (e.g., cerebral palsy) and how their son had progressed over time. The mother, a Julliard-trained opera singer, had had to stop her career due to his illness. Following the parents, Dr. Wasserstein further reviewed patient's history and diagnosis by WES of mutations in *SLC17A5* which cause the ultra-rare lysosomal disorder known as Salla disease (sialic acid storage disease, see details below). Drs. Dobrenis and Walkley next presented a lay summary of what is known about this disorder, as well as the reality that it was an "orphan" disease even within the category of lysosomal disorders and that little work was being reported on it following the death of a prominent Finnish physician whose lab had earlier pursued some studies. The parents were encouraged to think about the possibility of starting a foundation/patient support group for this very rare disease since none presented existed. At the end of the tutorial the parents expressed considerable gratitude for the thoughtful interactions and explanations about the disease.

Six weeks following the tutorial the mother contacted Dr. Walkley with the idea that they would indeed start such a foundation. A foundation has now been established (https://www.sallaresearch.org/). Funding by the foundation led to a first one-day scientific meeting (Salla disease "think-tank") hosted by Drs. Walkley and Wasserstein (in Tarrytown NY) which was attended by 12 scientists from the US and Europe. It was also attended by a number of Salla families and their affected children from the US and Europe that had been discovered (through Facebook) by the mom. The Bronx parents have hosted multiple fund raisers and their foundation is supporting research at Einstein (Dr. Dobrenis) and at the NIH (with Dr. Bill Gahl, an attendee at the think-tank meeting).

In February, 2018, the entire family participated in Einstein's Rare Disease Day program in LeFrak auditorium, sponsored by the Rose F. Kennedy IDDRC, and were written up as an example of the IDD Gene Team concept in the Kennedy Center newsletter in the fall 2018 issue.

Drs. Walkley and Wasserstein remain actively engaged with the family. This includes speaking engagements in early September at a fund raiser for the foundation at Strathmore in Bethesda and an International Salla Disease Walk at Van Cortland Park in the Bronx.

Patient Description:

BF is a 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 hypertonia.

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 electrogenic $2NO_3^-/H^+$ 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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Support Groups and Information:
Salla Treatment And Research (STAR) Foundation

Facebook Groups:
Salla Disease Support Group – private group, 49 members
Salla disease – Sallan tauti – Sallas sjukdom – public group, 136 members

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