SLC29A3

Patient Description:
This is a case of a 7-year-old girl of consanguineous Pakistani origin with an apparently unique phenotype in whom WES identified a somewhat unexpected etiology. The proband, IR, has been followed since infancy for a series of progressive abnormalities, including failure to thrive, short stature, persistently patent anterior fontanel, exophthalmos, Rosai-Dorfman disease, pancreatic insufficiency, autoimmune hepatitis vasculitis and thrombocytopenia, sensorineural hearing loss and intellectual disability. Through the years, extensive genetic testing, including array CGH, high resolution chromosomes, mutational analysis for Robinow syndrome, Shwachman-Diamond syndrome, Smith-Lemli-Opitz syndrome, and disorders of glycosylation, yielded normal results. However, WES revealed that IR is homozygous for a deleterious mutation in *SLC29A3* (*E444X*), which was previously reported to be associated with Histiocytosis-Lymphadenopathy Plus syndrome. IR also carries a novel homozygous IVS6-2 A>C mutation in *LPIN1* predicted to be disease-causing. Though mutations in *LPIN1* are associated with autosomal recessive acute recurrent myoglobinuria (OMIM # 268200), IR has never had an attack of rhabdomyolysis or myoglobulinuria.

Disease/Syndrome Features:
Mutations in *SLC29A3* cause a group of related conditions that are together referred to as histiocytosis-lymphadenopathy plus syndrome or *SLC29A3*/hENT3 spectrum disorders. These individual conditions include H syndrome, pigmented hypertrichotic dermatosis with insulin-dependent diabetes (PHID), Faisalabad histiocytosis (FHC), and familial Rosai-Dorfman disease (RDD). There are a number of overlapping features between these disorders including hypertrichosis, hyperpigmentation, short stature, lymphadenopathy, sensorineural hearing loss/deafness, and hypogonadism. Interestingly, identical mutations in *SLC29A3* can give rise to different conditions, suggesting the importance of modifying genetic and/or environmental factors [Kang 2010, Morgan 2010].

H syndrome is an autosomal-recessive dermatosis named for its major findings of hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height, and hyperglycemia. H syndrome has been reported in ten Arab patients from six consanguineous families. Cutaneous legions mostly involved the middle and lower body and appeared within the first or second decade of life. Additional features include scrotal masses, gynecomastia, exophthalmos, angiopathy, and camptodactyly. Multiple patients also shared musculoskeletal abnormalities including hallux valgus, fixed flexion contractures of the toe and finger joints, and lateral tibial torsion [Molho-Pessach 2008].

PHID represents a rare instance where insulin-dependent diabetes is subject to Mendelian inheritance. It is an autosomal-recessive disorder characterized by pigmented, hypertrichotic skin lesions and an 83% frequency of autoantibody negative insulin-dependent diabetes mellitus. Both cutaneous lesions and diabetes mellitus appear in

childhood. PHID shares dermatological and histological phenotypes with H syndrome, but PHID patients have not been observed with deafness or clinodactyly [Cliffe 2009].

FHC and RDD are related autosomal recessive histiocytoses, or disorders defined by an abnormally large number of histiocytes. They are Class II histiocytoses, meaning they are macrophage-related disorders. FHC was first described in a consanguineous family from Pakistan and includes systemic phenotypes such as joint deformities, sensorineural hearing loss, lymphadenopathy, and swollen eyelids. RDD is also known as sinus histiocytosis with massive lymphadenopathy (SHML) and manifests as a painless lymphadenopathy. RDD is mostly a sporadic condition but familial cases occur and resemble FHC [Morgan 2010].

Protein/Pathway:
Solute Carrier Family 29, Member 3, *SLC29A3*, encodes a human equilibrative nucleoside transporter (hENT3). These facilitative transporters carry hydrophilic nucleosides and are involved in nucleotide synthesis by salvage pathways. hENTs are also permeable to nucleoside analogs used as anti-cancer or anti-viral agents. Unlike other hENT family members, hENT1, hENT2, and hENT4, hENT3 does not show cell surface expression and instead exhibits intracellular localization patterns. Different groups have identified hENT3 at the lysosome/late endosome or at the mitochondria. Additionally, hENT3 is unique in having a maximal activity at acidic pH, ranging from 5.5 – 6.5, where it is broadly specific for nucleosides [Baldwin 2005, Govindarajan 2009, Kang 2010].

hENT family members are predicted to have 11 transmembrane (TM) α-helices, a cytoplasmic N-terminal domain, an extracellular C-terminal domain, and a large cytoplasmic loop between TM6 and TM7. hENT3 is a protein composed of 475 amino acids. Relative to other family members, hENT3 has a long, hydrophilic N-terminal region with a dileucine targeting motif. When this motif is perturbed, hENT3 re-localizes to the cell surface. With both leucines intact, hENT3 co-localizes with the lysosomal marker CD36 [Baldwin 2005]. Pathogenic mutations in *SLC29A3* have been shown to impair hENT3 activity in vitro. Mutant transporters show reduced nucleoside transport activity, altered adenosine transport kinetics, and cellular trafficking anomalies. Additionally, G437R and E444X mutations cause accelerated lysosomal degradation of hENT3 [Kang 2010].

SLC29A3 mutations cause insulin-dependent diabetes in PHID and shows genetic interaction with the insulin signaling pathway in *Drosophila*. Ubiquitous knockdown of the fly ortholog, *dENT1*, is lethal. Milder knockdown produces adult flies with abnormally short sensory bristles and ectopic bristles, a phenotype similar to knockdown of the *Drosophila* ortholog of *Islet.* Importantly, *dENT1* knockdown phenotypes were rescued by over-expression of insulin signaling pathway components *dInR, dPI3K and dAkt* [Cliffe 2009].

Publications:
Baldwin, S. A., Yao, S. Y. M., Hyde, R. J., Ng, A. M. L., Foppolo, S., Barnes, K., … Young, J. D. (2005). Functional characterization of novel human and mouse

equilibrative nucleoside transporters (hENT3 and mENT3) located in intracellular membranes. *Journal of Biological Chemistry*, *280*(16), 15880–15887. https://doi.org/10.1074/jbc.M414337200

Cliffe, S. T., Kramer, J. M., Hussain, K., Robben, J. H., de Jong, E. K., de Brouwer, A. P., … Buckley, M. F. (2009). SLC29A3 gene is mutated in pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and interacts with the insulin signaling pathway. *Human Molecular Genetics*, *18*(12), 2257–2265. https://doi.org/10.1093/hmg/ddp161

Govindarajan, R., H Leung, G. P., Zhou, M., Tse, C.-M., Wang, J., & Unadkat, J. D. (2009). Facilitated mitochondrial import of antiviral and anticancer nucleoside drugs by human equilibrative nucleoside transporter-3. *Am J Physiol Gastrointest Liver Physiol*, *296*, 910–922. https://doi.org/10.1152/ajpgi.90672.2008.-human

Kang, N., Jun, A. H., Bhutia, Y. D., Kannan, N., Unadkat, J. D., & Govindarajan, R. (2010). Human equilibrative nucleoside transporter-3 (hENT3) spectrum disorder mutations impair nucleoside transport, protein localization, and stability. *The Journal of Biological Chemistry*, *285*(36), 28343–28352. https://doi.org/10.1074/jbc.M110.109199

Molho-Pessach, V., Lerer, I., Abeliovich, D., Agha, Z., Libdeh, A. A., Broshtilova, V., … Zlotogorski, A. (2008). The H Syndrome Is Caused by Mutations in the Nucleoside Transporter hENT3. *The American Journal of Human Genetics*, *83*, 529. https://doi.org/10.1016/j.ajhg.2008.09.013

Morgan, N. V., Morris, M. R., Cangul, H., Gleeson, D., Straatman-Iwanowska, A., Davies, N., … Maher, E. R. (2010). Mutations in SLC29A3, Encoding an Equilibrative Nucleoside Transporter ENT3, Cause a Familial Histiocytosis Syndrome (Faisalabad Histiocytosis) and Familial Rosai-Dorfman Disease. *PLoS Genetics*, *6*(2), e1000833. https://doi.org/10.1371/journal.pgen.1000833

Support Groups and Information:

Facebook support groups:Rosai-Dorfman Disease aka SHML , private group, >250 members

Connecting with Rosai-Dorfman Disease, private group, >120 members

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