HNRNPH2

Patient Description:

MF was the product of an uncomplicated pregnancy, born with primary caesarean section because of failure to progress in the active phase of labor. Her infancy was unremarkable; however, during her first year of life, she experienced marked delay in her motor development. Though she seemed "socially connected," she never developed verbal language. In her first year, she was referred to NYS Early Intervention and began receiving physical, occupational and speech therapy, as well as special instructions. MF was evaluated by a medical geneticist, neurologist and development-behavioral pediatrician, and a work-up, including MRI of her head, microarray comparative genomic hybridization, fragile X testing, other blood work, and EEGs were all normal. Eventually, whole exome sequencing revealed a de novo pathogenic mutation in *HNRNPH2*.

Disease/Syndrome Features:

Missense variations in *HNRNPH2*, a gene on the X chromosome, cause a neurodevelopmental disorder in females that is characterized by intellectual or developmental disability and hypotonia. Several patients share additional neuropsychiatric phenotypes including acquired microcephaly, regression, autism spectrum disorder, attention deficit hyperactivity disorder, anxiety, and seizures. Individuals with *HNRNPH2* mutations appear also to have multisystem involvement. Patients are notable for dysmorphic facies, orthopedic abnormalities, and GI symptoms including GERD, difficulty feeding, and constipation. Facial features shared among multiple affected individuals include almond eyes, short palpebral fissures, short philtra, and micrognathia. As *HNRNPH2* is located on the X chromosome and no male patients have been identified, it has been speculated that *de novo* missense mutations in male fetuses are lethal [Bain 2016].

Protein/Pathway:

Heterogeneous Nuclear Ribonucleoprotein H2 (*HNRNPH2*) belongs to a ubiquitous family of RNA binding proteins that act as a shuttle between the nucleus and cytoplasm. These family members act on pre-mRNA and regulate spliceosome assembly, thereby controlling the transcriptional profile of cells across development and differentiation. HNRNPH2 shows nuclear co-localization across a variety of tissues including brain, intestine, spleen, lung, and skin [Honoré 1995, Bain 2016].

HNRNPH2 contains three RNA recognition motifs and two glycine-rich domains, one of which contains a nuclear localization sequence (NLS) that interacts with the import receptor transportin 1. Among the six individuals first identified with *HNRNPH2* mutations, five possessed mutations involving an arginine residue at position 206. The remaining patient had a mutation in a nearby proline. Both of these amino acids are within the NLS in the first glycine-rich domain. Additionally, both amino acids are highly conserved across the HNRNPH family and across the phylogenetic tree [Bain 2016].

A specific role for *HNRNPH2* has been identified in rat neurons. As neurons differentiate, alternative splicing generates a truncated isoform of rat telomere repeat-binding factor 2 (TRF2) that is termed (TRF2-S). TRF2 indirectly represses several neuronal genes. Unlike TRF2 which localizes to the nucleus, TRF2-S remains locked in the cytoplasm and thereby reverses the TRF2-mediated inhibition of genes required for neuronal differentiation. HNRNPH2 interacts with pre-mRNA of Trf2, inhibits the formation of TRF2-S and thus inhibits neurogenesis. During normal neuronal differentiation, HNRPH2 levels fall and TRF2-S levels rise. When *HNRNPH2* is knocked-down experimentally, TRF2-S levels rise and the rate at which pheochromocytoma cells differentiate into neurons increases. These experiments suggest an important role for *HNRNPH2* as a repressor of neurogenesis [Grammatikakis 2016].

Publications:

Bain, J. M., Cho, M. T., Telegrafi, A., Wilson, A., Brooks, S., Botti, C., … Chung, W. K. (2016). Variants in HNRNPH2 on the X Chromosome Are Associated with a Neurodevelopmental Disorder in Females. *American Journal of Human Genetics*, *99*(3), 728–734. https://doi.org/10.1016/j.ajhg.2016.06.028

Grammatikakis, I., Zhang, P., Panda, A. C., Kim, J., Maudsley, S., Abdelmohsen, K., … Gorospe, M. (2016). Alternative Splicing of Neuronal Differentiation Factor TRF2 Regulated by HNRNPH1/H2. *Cell Reports*, *15*(5), 926–934. https://doi.org/10.1016/j.celrep.2016.03.080

Honoré, B., Rasmussen, H. H., Vorum, H., Dejgaard, K., Liu, X., Gromov, P., … Celis, J. E. (1995). Heterogeneous nuclear ribonucleoproteins H, H', and F are members of a ubiquitously expressed subfamily of related but distinct proteins encoded by genes mapping to different chromosomes. *The Journal of Biological Chemistry*, *270*(48), 28780–28789. https://doi.org/10.1074/JBC.270.48.28780

Support Groups and Information:

Yellow Brick Road Project

Facebook groups:

HNRNPH2 mutations: Community for discussiong patients with mutations in HNRNPH2. Private group, >100 members

HNRNPH2: Simons Searchlight Community: Private group for anyone interested in HNRNPH2, including families and researchers. >60 members.

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