WWOX

Patient Description: (Add when available)

Disease/Syndrome Features:
Homozygous mutations in *WWOX* cause two rare autosomal recessive conditions which differ in severity but share epilepsy and intellectual disability as common features . These are spinocerebellar ataxia, autosomal recessive 12 (SCAR12) and epileptic encephalopathy, early infantile 28 (EIEE28). SCAR12 was found in two consanguineous families and is characterized by childhood onset of cerebellar ataxia, generalized tonic-clonic epilepsy, and intellectual disability. In one family, affected individuals also show upper motor neuron involvement reminiscent of spastic ataxia or paraplegia, with features including leg spasticity and positive bilateral extensor plantar response. Patients with SCAR12 are homozygous for missense mutations in *WWOX* [Mallaret 2014].

EIEE28 owing to biallelic perturbations of *WWOX* has been seen in six patients from five families and clusters into two groups based on severity. Patients with the most devastating form of the disorder have null genotypes and absent psychomotor development, poor spontaneous motility, absent eye contact, epilepsy starting in the first month of life, hypotonia, hypomimia, retinal degeneration, acquired microcephaly, and premature death. Patients with milder phenotypes have compound genotypes of one null allele and one missense mutation. Clinically, they have epilepsy, encephalopathy, and delayed psychomotor development but tend to survive childhood [Abdel-Salam 2014, Mignot 2015].

Protein/Pathway:
WW domain-containing oxidoreductase, *WWOX*, is located at the FRA16D fragile site, the second most common fragile site in the human genome. *WWOX* is composed of nine exons and is frequently involved in loss of heterozygosity (LOH) in many different cancer types. These somatic deletions of *WWOX* led to its elucidation as a tumor suppressor gene prior to the discovery of disease causing germline mutations. The WWOX protein contains two WW domains and an N-terminal short chain dehydrogenase/reductase (SDR) domain. WW domains contain conserved tryptophan and proline residues and bind to proline-proline-X-tyrosine motifs. The first WW domain in WWOX is phosphorylated by Src-family tyrosine kinases and binds to p73, a p53 homolog. WWOX overexpression causes p73 translocation from the nucleus to the cytoplasm and suppresses its other interactions. This first WW domain also binds to a proline-proline-proline-tyrosine motif in AP2γ [Iliopoulos 2006]. Interestingly, pathogenic mutations in SCAR12 are predicted to destabilize the first WW domain but neither patients nor heterozygous carriers show an increased susceptibility to cancer [Mallaret 2014].

Murine models of *WWOX* deficiency have several features in common with the human diseases. *Wwox* knock-out mice die by four weeks of age from failure to thrive, but develop spontaneous seizures by two weeks of age. Additionally, mice present with audiogenic tonic-clonic seizures when exposed to sustained sound. When challenged to walk on the edge of their cages, all of the knock-out mice show balance disturbances. From the fetus into adulthood, *Wwox* is expressed in wild-type mouse cerebral cortex and cerebellum. Finally, there is a similar, spontaneous rat model called *Ide* (lethal dwarfism and epilepsy) that presents with ataxia and audiogenic seizures [Mallaret 2014].

Publications:

Abdel-Salam, G., Thoenes, M., Afifi, H. H., Körber, F., Swan, D., & Bolz, H. (2014). The supposed tumor suppressor gene WWOX is mutated in an early lethal microcephaly syndrome with epilepsy, growth retardation and retinal degeneration. *Orphanet Journal of Rare Diseases*, *9*(1), 12. https://doi.org/10.1186/1750-1172-9-12

Iliopoulos, D., Guler, G., Han, S.-Y., Druck, T., Ottey, M., Mccorkell, K. A., & Huebner, K. (2006). Roles of FHIT and WWOX fragile genes in cancer. *Cancer Letters*, (232), 27–36. https://doi.org/10.1016/j.canlet.2005.06.048

Mallaret, M., Synofzik, M., Lee, J., Sagum, C. A., Mahajnah, M., Sharkia, R., … Koenig, M. (2014). The tumour suppressor gene WWOX is mutated in autosomal recessive cerebellar ataxia with epilepsy and mental retardation. *Brain*, *137*(2), 411–419. https://doi.org/10.1093/brain/awt338

Mignot, C., Lambert, L., Pasquier, L., Bienvenu, T., Delahaye-Duriez, A., Keren, B., … Philippe, C. (2015). WWOX-related encephalopathies: delineation of the phenotypical spectrum and emerging genotype-phenotype correlation. *Journal of Medical Genetics*, *52*(1), 61–70. https://doi.org/10.1136/jmedgenet-2014-102748

Support Groups and Information:

WWOX Foundation: wwox.org

Facebook Groups:

WWOX Gene Mutation- Support Group: private group, >50 members

WWOX Foundation – support and research group, >1000 members

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