CDKL5

Disease/Syndrome Features:

Mutations in *CDKL5* are associated with early-onset, difficult to control seizures, X-linked intellectual disability, hypotonia, motor disability, and cortical visual impairment [Olson 2019]. Pathogenic variants in *CDKL5* affect one in 40,000 to 60,000 live births with a female:male ratio of 4:1 [Olson 2019].

Individuals with mutations in *CDKL5* show considerable phenotypic overlap with Rett syndrome, a disorder most often caused by mutations in *MECP2*, a gene also located on the X chromosome that is involved in transcriptional silencing and epigenetic regulation of methylated DNA. Features in common include a period of normal development followed by regression, minimal or absent speech, the inability to walk unassisted, hand stereotypies, breathing abnormalities, and autistic features. Infantile seizures are universal in CDKL5 disorders, and not typical of Rett. Individuals with *CDKL5* mutations may also suffer from scoliosis, gastrointestinal difficulties, spasticity, hyperreflexia, and visual impairment. The full spectrum of *CDKL5*-related diseases is still being elucidated and mutations in the gene have so far been found in children previously diagnosed with Rett syndrome, Angelman syndrome, Lennox-Gastaut syndrome, and autism spectrum disorders [Tao 2004, Weaving 2004].

In terms of neuroimaging, most case reports have documented normal brain anatomy or occasional cortical atrophy or T2 fluid-attenuated inversion recovery hyperintensities in the white matter [Olson 2019], however neuroimaging has not yet been systematically reported in affected individuals. With regard to neuropathology, a single case report described the brain as the solely affected organ in a postmortem examination [Paine 2012]. Findings included cortical and cerebellar atrophy, ventricular enlargement, cerebral cortical gliosis, neuronal heterotopias in the white matter of the cerebellar vermis, gliosis of cerebellar cortex with loss of Purkinje cells and axonal swellings, and perivascular lymphocytes and axonal swellings in the anterior horn of the spinal cord.

Protein/Pathway:

Cyclin-dependent kinase-like 5, *CDKL5*, is a gene located on the X chromosome encoding a protein with a conserved serine/threonine kinase domain that is homologous to mitogen-activated protein kinase and cyclin-dependent kinase family members [Mari 2005]. It is highly expressed in the brain and localizes predominantly to neuronal nuclei and dendrites. Expression peaks in early postnatal life, near the onset of symptoms [Rusconi 2008]. The CDKL5 protein is involved with cell proliferation, neuronal migration, axonal outgrowth, dendritic morphogenesis and synapse formation [Zhu 2019].

Because of the clinical similarities between patients with *MECP2* and *CDKL5* mutations, much research has focused on the relationship between these two genes. In situ hybridization studies in mice have shown considerable overlap between the expression patterns of *Cdkl5* and *Mecp2*, the ortholog of the gene responsible for Rett syndrome. In these animals, both genes are expressed in the olfactory bulb, cerebral cortex, cerebellum, hippocampal formation, basal ganglia, thalamus, and superior and inferior

colliculi. *Cdkl5* expression is not, however, dependent on *Mecp2* expression as expression patterns are unchanged in *Mecp2* knockout mice [Weaving 2004]. MECP2 and CDKL5 have, however, been shown to directly interact by *in vitro* glutathione S-transferase pull-down assays and in human cells by coimmunoprecipitation experiments. Furthermore, the kinase activity of CDKL5 has been confirmed by *in vitro* experiments where CDKL5 is shown to phosphorylate itself and MECP2 [Mari 2005]. Based on these findings, a current working model posits that CDKL5 works upstream of MECP2, directly or indirectly influencing its phosphorylation state and specific functions of the methyl-binding protein. In the absence of functional CDKL5, the phosphorylation-dependent activities of MECP2 would be altered to cause a subset of Rett symptoms. Phosphorylation targets other than MECP2 may explain the features that are distinct from Rett syndrome. CDKL5 has been shown to shuttle between the cytoplasm and the nucleus, and its C-terminal tail is involved in localizing the protein to the cytoplasm. Cultured neurons expressing mutant CDKL5 with disease-causing truncations of the C-terminus have a constitutively nuclear expression of CDKL5, suggesting that these mutations may cause a gain of function in this cellular compartment [Rusconi, 2008].

More recent reports have focused on effects that *CDKL5* mutations may have independent of *MECP2*. For example, CDKL5 has been shown to localize to excitatory synapses and has been implicated in ensuring normal dendritic spine morphology and overall synaptic activity through its phosphorylation of the cell adhesion molecule NGL-1. Accordingly, both rodent models and iPSC-derived neurons from individuals with *CDKL5* mutations display abnormal dendritic spines [Ricciardi 2012].

Clinical Trials:

An open-label phase 2 clinical trial of cannabidiol in CDKL5 and three other early onset genetic epileptic encephalopathy syndromes has shown promise for improvement in frequency of motor seizures. A phase 2 randomized, placebo-controlled crossover study of ataluren, a drug that targets pathogenic nonsense mutations in other genetic disorders such as Duchenne muscular dystrophy, is in process in CDKL5 disorders. Another phase 2 trial is underway for TAK-935, a medication that modulates the NMDA receptor system. A phase 3 randomized, placebo-controlled study is ongoing using ganaxolone, a synthetic methyl derivative of allopregnanolone, a neurosteroid that has shown promise in treating infantile spasms, status epilepticus, and protocadherin 19-related epilepsy. It is thought to work by restoring microtubule dynamics in CDKL5 disordered states.
For more information, see clinicaltrials.gov

Publications:

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Olson, H.E., Demarest, S.T., Pestana-Knight, E.M., Swanson, L.C., Iqbal, S., Lal, D., Leonard, H., Cross, J.H., Devinsky, O., Benke, T.A. (2019). Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review *Pediatric Neurology,* 97:18-25

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Rusconi, L., Salvatoni, L., Giudici, L., Bertani, I., Kilstrup-Nielson, C., Broccoli, V. Landsberger, N. (2008). CDKL5 expression is modulated during neuronal development and its subcellular distribution is tightly regulated by the C-terminal tail. *J Biol Chem* 283(44):30101-11.

Tao, J., Van Esch, H., Hagedorn-Greiwe, M., Hoffmann, K., Moser, B., Raynaud, M., … Kalscheuer, V. M. (2004). Mutations in the X-Linked Cyclin-Dependent Kinase–Like 5 (CDKL5/STK9) Gene Are Associated with Severe Neurodevelopmental Retardation. *The American Journal of Human Genetics*, *75*(6), 1149–1154. https://doi.org/10.1086/426460

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Zhu, Y.C., Xiong, Z.Q. (2019). Molecular and Synaptic Bases of CDKL5 Disorder *Dev Neurobiol* 79(1):8-19.

Support Groups and Information:

International Foundation for CDKL5 Research (cdkl5.com): family education and resources, private research funding.

CDKL5 Alliance (cdkl5alliance.org): worldwide membership organization that raises awareness of the condition amongst medical, scientific, and pharmaceutical communities, whilst supporting children and families. Comprises 14 active patient group member organizations from around the globe including USA, UK, Ireland, Canada, Italy, Spain, Netherlands, Germany, Austria, Switzerland, Slovkia, and Japan

CDKL5 Research Collaborative (cdkl5research.org): information on CDKL5, research collaborative group

Hope 4 Harper (hope4harper.com): support group, private research funding

Loulou Foundation (louloufoundation.org): private non-profit UK foundation dedicated to advancing research into the understanding and development of therapeutics for CDKL5 deficiency disorder.
CDKL5 UK (curecdkl5.org)
CDKL5 Canada (cdkl5canada.ca)
CDKL5 Ireland (cdkl5.ie)
CDKL5 Italy (cdkl5insiemeversolacura.it)
CDKL5 Japan (cdkl5japan.com)
CDKL5 France: (cdkl5.fr)
CDKL5 Germany: (cdkl5-verein.de)
CDKL5 Netherlands (cdkl5.nl)
CDKL5 Slovakia (cdkl5.sk)

Facebook:

- CDKL5 Parents Support Group: 1.1K members – A support group for parents, grandparents, and full time caregivers of children with CDKL5
- CDKL5 World – United in Hope, 700+ members – Support group
- CDKL5 Extended Family and Provider Support Group – 400+ members, private Facebook support group
- Numerous other regional, family, or community-oriented CDKL5 groups.

Last Updated: March 30, 2020, MKR