This is just a short review of most, but not all, of CDKL5 related studies that appeared in 2017. As research into CDKL5 proceeds, some of the molecular studies are getting increasingly technical and I have tried to simplify as best as I can without losing the basics of the results. For the sections of the CDKL5 Gene and Protein, it may be worthwhile reviewing those relevant pages on my website (www.supporting-cdkl5.co.uk). I have included the references if you want to look them up although not all full texts are available. I hope you find this useful.

The CDKL5 Gene

Hector, Ralph D., et al. "CDKL5 variants: Improving our understanding of a rare neurologic disorder." Neurology Genetics 3.6 (2017): e200.

In a previous paper, Ralph Hector et al (2016) produced an update on the characterisation of the CDKL5 gene and proposed new nomenclature for the 5 isoforms – denoted as hCDKL5_1 to hCDKL5_5. They commented that hCDKL5_1 was the predominant isoform in human brain development. In this paper the CDKL5 gene has been further analysed to gain a better understanding of the variants (in mutations) that can occur. Their study identified several variants that can be reclassified as benign or likely benign. With the addition of novel CDKL5 variants, they were able to show that pathogenic missense variants cluster in the catalytic domain of CDKL5, and also reclassify a purported missense variant as having a splicing consequence. They also suggest that missense variants in the final 3 exons (exons 19 - 21) are likely to be benign and not important to disease pathology. They describe benign splicing and nonsense variants within these exons, suggesting that one of the known isoforms, hCDKL5_5 , is likely to have little or no neurologic significance. The findings of their study have implications for genetic diagnosis and provide evidence for the reclassification of specific variants previously thought to result in CDKL5 deficiency. Their results support the view that the predominant brain isoform in humans (hCDKL5_1) is crucial for normal neurodevelopment and that the catalytic domain is the primary functional domain.

Hector, Ralph D., et al. "Characterisation of Cdkl5 transcript isoforms in rat." Gene 603 (2017): 21-26.

Hector et al have produced an updated model of the Cdkl5 gene in rats which will provide a framework for studies into its protein products and also provides a reference for the development of molecular therapies for testing in rat models of the CDKL5 disorder.

Allou, L., et al. "Rett-like phenotypes: expanding the genetic heterogeneity to the KCNA2 gene and first familial case of CDKL5-related disease." Clinical genetics 91.3 (2017): 431-440.

In their paper, Allou et al identified a missense mutation in the CDKL5 gene in a 21 month old girl presenting with a global psychomotor delay affecting in particular language and autistic disturbances. She also displayed microcephaly, hand stereotypies, strabismus and pyramidal signs but had good eye contact. Her asymptomatic mother also displayed the same missense mutation in CDKL5. However, the mother had a skewed X-inactivation associated with a preferential expression of the normal gene in 90% of her leucocytes compared to her affected daughter who expressed the mutated copy of CDKL5 in half her leucocytes. The authors suggest that missense mutations in this part of the CDKL5 protein might be associated with milder encephalopathies.

The CDKL5 Protein

Cortelazzo, Alessio, et al. "Inflammatory protein response in CDKL5-Rett syndrome: evidence of a subclinical smouldering inflammation." Inflammation Research 66.3 (2017): 269-280.

Inflammation is the body's response to an injury or insult. At the physiological level it is reflected by the presence of proteins which produce an acute phase response (APR). There has been some research suggesting an abnormal inflammatory response in patients with Rett syndrome. Cortelazzo et al in their study have identified for the first time, what they call a “subclinical smouldering inflammation pattern” in CDKL5 consisting of an atypical APR coupled with a dysregulated cytokine response - cytokines are small proteins involved in cell signalling that also have a role in the inflammatory response. The use of ω-3 polyunsaturated Fatty Acids, has previously been investigated in the treatment of Rett syndrome because of their anti-oxidant properties and the authors study suggests that these can improve illness severity through their action on inflammatory mediators.

Tramarin, Marco. Critical role of CDKL5 in AMPA receptor composition: underlying mechanism and functional outcome. Diss. Università degli Studi dell'Insubria, 2017.

The loss of Cdkl5 affects spine density and stabilization as well as synaptic activity although the underlying molecular mechanisms are not fully understood. This study from Tramarin shows evidence linking Cdkl5-associated synaptic defects to AMPA receptor expression and subunit composition. The suggestion is that the resulting alterations may contribute towards the synaptic dysfunctions and cognitive deficits in the CDKL5 disorder. The study also suggests that tianeptine, a drug previously reported to modulate AMPAR-mediated glutamatergic neurotransmission, is capable of restoring these defects in neurons devoid of CDKL5, and is therefore an interesting candidate drug for CDKL5-disorder.

Tang, Sheng, et al. "Loss of CDKL5 in glutamatergic neurons disrupts hippocampal microcircuitry and leads to memory impairment in mice." Journal of Neuroscience 37.31 (2017): 7420-7437.

Tang et al studied how the loss of cdkl5 leads to memory impairment in male conditional knock-out mice. The found that ablating cdkl5 expression specifically from glutamatergic neurons in the forebrain caused hippocampal-dependent memory in the mice to be impaired. Hippocampal pyramidal neurons lacking cdkl5 showed morphological changes that were accompanied by an increase in the frequency of spontaneous neuronal electrical activity. Using voltage-sensitive dye imaging techniques they also found that certain pyramidal neurons lacking cdkl5 showed hyper-excitability in their dendritic domain that was constrained in a spatially and temporally distinct manner. The authors suggest that these results may indicate a novel role for CDKL5 in the regulation of synaptic function and a potential microcircuit mechanism underlying impaired learning and memory.

Barbiero, Isabella, et al. "CDKL5 localizes at the centrosome and midbody and is required for faithful cell division." Scientific Reports 7.1 (2017): 6228.

A centrosome is a small cellular organelle involved in and essential for cell division in animals - including humans. In this study, the authors have identified that the CDKL5 protein localizes at the centrosome and midbody and is required for faithful cell division. They point out that although defects in CDKL5 have mainly been associated with neurological disease, they believe that its influence on cell cycle progression may also be of relevance. They note that defects in centrosomal proteins are known to influence early neuronal development - which in turn may produce those early neural deficiencies that are known to be central to the development of many neurodevelopmental disorders. They therefore suggest the possibility that defects in early neuronal development may be linked to a function of CDKL5 at the centrosome. A further understanding of the precise role of CDKL5 in cell cycle progression and at the centrosome might be relevant in order to to recognize the origin of some features of the human pathology associated with CDKL5 deficiency.

Okuda, Kosuke, et al. "CDKL5 controls postsynaptic localization of GluN2B-containing NMDA receptors in the hippocampus and regulates seizure susceptibility." Neurobiology of disease 106 (2017): 158-170.

Another technical study, Okuda et al use Cdkl5 knockout mice to identify that in response to NMDA and postsynaptic over-accumulation of GluN2B-containing NMDARs in the hippocampus, neurons become hyper excitable - leading to seizure activity. The GluN2B-selective antagonist ifenprodil reverses this NMDA-induced hyper-excitability. This study therefore suggests that CDKL5 plays an important role in controlling postsynaptic localization of what is known as the GluN2B-SAP102 complex in the hippocampus, and that aberrant NMDAR-mediated transmission may underlie the pathological mechanisms of loss of function and seizure activity seen in CDKL5 deficiency.

Living with CDKL5

Seizures

Lim, Zhan, et al. "Use of the ketogenic diet to manage refractory epilepsy in CDKL5 disorder: Experience of > 100 patients." *Epilepsia* (2017).

This study came from data collected by The International CDKL5 Disorder Database (ICDD), which was established in 2012. They analysed data regarding the use of the ketogenic diet (KD) in the management of epilepsy. Their database contains information on 204 individuals with a pathogenic CDKL5 mutation. The median age of ascertainment to the database was 4.8 years (range 0.3–33.9 years) with a median age of seizure onset of 6 weeks (range 1 day–65 weeks). A history of KD use was reported for 51% (104/204) which was used for a median duration of 17 months (95% CI 9 to 24). Changes in seizure activity after commencing the ketogenic diet were reported for two-thirds of individuals (69/104), with positive effects reported for 88%. Nearly one-third (31.7%) experienced side effects during the diet. At ascertainment, only one-third (32%) remained on the diet with lack of long-term efficacy as the main reason for diet discontinuation (51%, 36/70). The authors therefore concluded that the benefits of the ketogenic diet in the CDKL5 disorder coincide with findings of previous trials on refractory epilepsy. However, poor long-term efficacy remains as a significant barrier and n view of its side effects, the ketogenic diet should be commenced under the guidance of a paediatric neurologist and/or specialist dietitian.

Baba, Shimpei, et al. "Amelioration of intractable epilepsy by adjunct vagus nerve stimulation therapy in a girl with a CDKL5 mutation." Brain and Development 39.4 (2017): 341-344.

This is a case report of an 8-year-old girl with CDKL5 who underwent vagal nerve stimulation (VNS) therapy for 2 years. She had developed epilepsy at the age of 6 months and initially had had tonic and tonic–clonic seizures. At about the age of 5 years, she also developed epileptic spasms. Her seizures were never completely controlled by conventional medical treatment. At the age of 7, after VNS initiation, her seizure frequency markedly reduced, and abnormal electrical activities on her electroencephalography tests strikingly decreased. Furthermore, an improvement in her quality of life in terms of alertness and activity was also documented. Although the efficacy of VNS therapy for patients with intractable epilepsy associated with a genetic anomaly has not been fully established, adjunctive VNS therapy may widen the scope of treatment choices available to these patients.

Sleep and Respiration

Lo Martire, Viviana, et al. "CDKL5 deficiency entails sleep apneas in mice." Journal of sleep research (2017).

Disorders of respiratory control are a prominent feature of Rett syndrome. A previous study has suggested a similar issue with CDKL5 (Hagebeuk, Eveline EO et al 2013). However, evidence is still limited, both in children with CDKL5 deficiency, and in particularly in adults. In this study, Lo Martire et al test whether the breathing pattern during sleep differs between adult Cdkl5 knockout and wild-type mice. Using whole-body plethysmography, sleep and breathing were recorded non-invasively for 8 h during the light period. Sleep apnoea occurred more frequently in Cdkl5-knockout than in wild-type mice. Statistical analysis (receiver operating characteristic (ROC) analysis) discriminated Cdkl5-KO significantly from WT mice based on sleep apnoea occurrence. This study therefore demonstrated that sleep apnoea is a core feature of the CDKL5 disorder and a respiratory biomarker of CDKL5 deficiency in mice, and suggest that sleep-disordered breathing should be evaluated routinely in CDKL5 patients.

Lee, Kun-Ze, and Wenlin Liao. "Loss of CDKL5 disrupts respiratory function in mice." Respiratory physiology & neurobiology (2017).

In their study, Lee and Liao examined the respiratory pattern of male Cdkl5 knockout mice at 1–3 months of age during resting breathing and respiratory challenge. Their results demonstrated that the resting respiratory frequency and tidal volume of knockout mice was unaltered compared to that of wild-type mice at 1 month of age. However, the knockout mice exhibit transient reductions in tidal volume during a respiratory challenge even after the challenge was removed at 2 months of age. In particular, the sigh-breathing pattern was changed in knockout mice, showing a transient reduction in sigh volume at 1–2 month of age and long-term attenuation of peak expiratory airflow from 1 to 3 month of age.
The authors therefore conclude that loss of CDKL5 causes breathing deficiency, supporting a CDKL5-mediated regulation of respiratory function in mice.

Visual Impairment

Mazziotti, Raffaele, et al. "Searching for biomarkers of CDKL5 disorder: early-onset visual impairment in CDKL5 mutant mice." Human Molecular Genetics 26.12 (2017): 2290-2298.

In a previous study, Pizzo et al (2016) had published research which basically showed that lack of Cdkl5 in a knockout mouse disrupts the organization of the neural network in the visual cortex. In this study from Mazziotti et al, they analysed the development of visual responses in a CDKL5 null male mice, heterozygous females and controls.
They found that defective responses appeared from 27 to 28 days after birth both in heterozygous and homozygous mice and that these defective responses persisted when re-tested at 60 to 80 days. The level of visual impairment in the adult significantly correlated with the reduction in visual responses observed during development. Support vector machine (which is a supervised learning model !) showed that multidimensional visual assessment can be used to automatically classify mutant and wild-type mice with high reliability. Thus, the authors believe that monitoring visual responses represents a promising biomarker for preclinical and clinical studies on CDKL5 disorder.

Impact on family and carers

Mori, Yuka, et al. "Impacts of caring for a child with the CDKL5 disorder on parental well-being and family quality of life." Orphanet journal of rare diseases 12.1 (2017): 16.

This is another study from The International CDKL5 Disorder Database (ICDD),in which they evaluate the impact of caring for a child with the CDKL5 disorder on parental well-being and family quality of life. They look at the child's mutation group, functional abilities, sleep and hospitalisations, as well as examining the primary care giver's well-being and family quality of life. There is a lot of detail in this publication and is worth a read if you haven't done so already - below is a direct link to an on-line version.

https://pdfs.semanticscholar.org/47e3/cd92b81eb98820b0f11dd136e9c748f57170.pdf

Although the authors acknowledge that the study has some shortcomings they nevertheless conclude by saying that emotional well-being was considerably impaired in the caregiver population, and was particularly associated with increased severity of child sleep problems and family financial difficulties. They go on to say that family quality of life was generally rated lowest in those using respite care extensively, suggesting that these families may be more burdened by daily care giving.

Martyn Newey
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