

Supporting CDKL5



CDKL5 and ARX mutations in males with early-onset epilepsy. Pediatric Neurology 2013.

This is a retrospective review from the University of Chicago of males who were referred for mutation analysis for CDKL5 and ARX. The clinical, molecular and neuroimaging findings were discussed for the two groups. For the CDKL5 group, there were 266 boys referred for analysis, of which 8 were found to have mutations.

Clinical - The boys with CDKL5 were aged 2 months to 14 years at the time of evaluation. All 8 experienced seizures with at least 6 displaying the characteristic [3 stages of epilepsy](#). All had profound developmental delay with minimal or no language and motor skills, severe tone abnormalities and cortical visual impairment. Many also had GI problems with gastroesophageal reflux and at least 7 required g-tube placement. The authors also noted that one boy had a maternal half-sister with the same missense mutation although her epilepsy was milder.

Molecular – There were 4 nonsense and 2 missense mutations identified. The remaining 2 were deletions, of exon 3 and a larger deletion of exons 10 – 15. Maternal testing revealed that 6 mutations were de novo. The mother of the boy with a maternal half-sister with the same missense mutation did not herself have the mutation, suggesting the possibility of germline mosaicism.

Neuroimaging – Early brain imaging was normal, but later imaging showed progressive changes including cerebral and cerebellar atrophy in several boys. Some changes were evident as early as 6 weeks of age in one boy.

In their discussion, the authors compare the results of this review with those other accounts of CDKL5 in males. They state that males with CDKL5 mutations do appear to be more severely affected than females. This review includes the second case where germline mosaicism may have played a role in the transmission of a CDKL5 mutation and the authors therefore emphasize the need for genetic counselling.

Note – The ARX gene is also located on the X-chromosome and is positioned relatively close to the CDKL5 gene. Mutations in this gene are also a cause of early-onset epilepsy and severe neurodevelopmental delay. This study presents considerable corroborative information about CDKL5 in boys. The role of germline mosaicism in transmitting a mutation arises again. One interesting comment the authors make is in relation to the term “epileptic encephalopathy” which perhaps most of us have heard in relation to our own child. The authors suggest that “developmental epilepsy” is more appropriate as the neurodevelopmental delay we see is more likely to be related to the underlying cause of the epilepsy than to the epilepsy itself - an issue that arises in the knockout mouse study below. The results of neuroimaging might be something that makes us all think uh-oh..! and there is another published report in relation to this aspect for which I have not yet produced a review. One of the tables in this paper also clearly reports that one of the subjects in the study is deceased. I may have missed it but I can't find a reference to this in the text - I have made an enquiry to the author about this.