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Editorial

CDKL5 mutations in early epileptic encephalopathy and in atypical forms of Rett syndrome

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Rett syndrome (RTT, MIM #312750) is a neurodevelopmental disorder defined by a distinct set of clinical features, notably a regression that robs the affected individuals of spoken language and volitional hand use [1]. Additionally, affected people develop characteristic hand stereotypies that are classically wringing or washing in nature, although they make take on a variety of forms such as clapping, finger rubbing, or hand mouthing. Gait is also impaired or absent: Those who can walk display a characteristic dyspraxic gait. Most affected individuals are girls, which is one of the features that lead to the discovery of the genetic cause for the majority of cases, mutations in *Methyl-CpG-Binding Protein 2* (*MECP2*) [2]. Ninety-five percent of people who fulfill the clinical criteria for typical, or classic RTT have mutations in *MECP2* [3].

In addition to the defining clinical characteristics outlined above, people with typical RTT have a number of additional clinical features such as irregular awake breathing patterns, growth failure, sleep disruption, dystonia, and scoliosis. The majority of individuals have seizures at some point in their life and have grossly abnormal electroencephalograms. Seizure onset is typically in school age and is very rare amongst infants. In contrast to the pattern of seizures found in people with typical RTT, a subset of individuals have been identified who have some features of RTT but have severe, early-onset epilepsy [4]. Mutations in *MECP2* are not typically found in these variants, which have been termed early seizure variant [1]. In the last couple of years mutations in a different genetic locus, *Cyclin dependent kinase 2* (*CDKL5*), have been identified in people with severe infantile epilepsy with infantile spasms and early infantile epileptic encephalopathy (EIEE2, MIM#300672), some of whom have also been characterized as having the early seizure variant of RTT [5,6].

In this issue of Journal of Pediatric Epilepsy, Martínez et al. [7] describe a Spanish experience looking for *CDKL5* mutations in a cohort of people characterized as having atypical RTT but lacking mutations in *MECP2*. They screened 53 of the collection of 150 people lacking *MECP2* mutations and found de novo genetic changes in eight individuals. Seven of the eight individuals presented had relatively early onset of seizures (between 25 days and 3 yr), however, this is a later and more variable presentation of seizure onset than has been previously reported, with seizures typically starting in the first 1-3 mo of life [8,9]. The authors also attempt

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to make some correlation between clinical severity and skewing of X-chromosome inactivation and specific genetic polymorphisms in *brain-derived neurotrophic factor*. However, the sample size is too small to gain useful information from such analyses.

A significant finding of this work is the identification of an individual with a sequence change in *CDKL5* but no history of any seizures. This is in contrast to the previous reports which indicate that seizures are a common feature in people with mutations in *CDKL5* [8,9]. One caveat that needs to be considered is whether the missense mutation reported in this paper is pathologically significant or rather is merely a polymorphism, albeit de novo, that does not affect protein function. Further work will be needed to prove with certainty that this sequence change is truly causative. However, this result does raise into question whether the spectrum of phenotypic abnormalities resulting from mutations in *CDKL5* may be broader than previously considered.

This raises another significant issue with this manuscript. Although all the people identified in this paper are classified as having some form of RTT, the exact reasons for this clinical designation are unclear. In fact, three of the eight people did not have any history of regression, a required feature in the diagnosis of any form of RTT [1]. In many ways, lumping individuals with *CDKL5* mutations into the "Rett syndrome" category may actually be doing a disservice to both clinical medicine and the patients with these mutations. The problem is that putting these individuals into the category "Rett syndrome" may prevent the recognition that they actually have a distinct clinical disorder with specific unique characteristics. This is a situation similar to that currently faced with people who have mutations in *forkhead boxG1* (*FOXG1*), who have been lumped into another variant RTT, the congenital variant. In fact, recently a call has been made to refer to these people as having *FOXG1*-disorder rather than variant RTT [10]. Perhaps we should refer to this disorder instead as *CDKL5*-disorder or early infantile epileptic encephalopathy rather than a variant of RTT. The ongoing challenge presented by these cases is determining what the exact clinical features define this disorder, to better predict whom should be screened for mutations in *CDKL5*. From there, understanding of the clinical course and the best treatment options can be generated.

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