EDITORIAL

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The neurodevelopmental spectrum seen with *CHD2* variants

There are many self-evident truths when it comes to genetic testing in epilepsies: classifying epilepsy and identifying the co-morbidities helps you pick the right panel; sending the test increases your chance of making that diagnosis; increased panel testing broadens the phenotype. The series of children with chromodomain helicase DNA-binding protein 2 (*CHD2*) variants reported by Feng et al.[1] are notable for a number of important reasons, including confirmation of another *CHD2* family.

The clinical relevance of variation in the *CHD2* gene is challenging to predict as we do not have the support of a biological or electrophysiological assay. Pathogenic variants are reported at many loci and result in a wide spectrum of disease phenotypes, which are typically *de novo*. Evidence from animal models support a neurodevelopmental role for *CHD2*. *Chd2*$^{+/-}$ mice demonstrate dysregulated cortical neural oscillations and synchrony as well as deficits in long-term memory and interneuron density, with the latter two findings related to a deficit in hippocampal inhibitory interneuron number and/or function.[2]

CHD2 myoclonic encephalopathy secondary to *de novo* point mutations or less commonly 15q26 deletions (which includes the entire *CHD2* gene)[3] has distinctive features of myoclonic epilepsy, exquisite photosensitivity, atonic-myoclonic-absence, and intellectual disability.[4] *CHD2* pathogenic variants more recently have been associated with treatment-resistant adult-onset epilepsy.[5] *CHD2* variants are also associated with neurodevelopmental disorders such as autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) with and without epilepsy.[4,6] Variants in *CHD2* are not infrequently seen in adult psychiatric patients with or without intellectual disability and ASD, with genetic positivity predicting a higher probability of seizures.[6] *De novo CHD2* mutations account for approximately 1.2% of all epileptic encephalopathy cases,[7] with developmental delay, and behavioral problems.[3,8]

It is now clear that *CHD2* variants can cause a spectrum of disease including epilepsy with intellectual disability and also epileptic and developmental encephalopathy. More than 90% of patients with *CHD2* pathogenic variants have epilepsy, most often generalized, with prominent photosensitivity.[5] *CHD2* genetic variants confer photosensitivity risk for individuals without intellectual disability, too.[9] The Feng et al.[1] series does not report a high level of reflex photic seizures, but the pattern-sensitive case is important and may represent a broader propensity towards reflex seizures.

Feng et al.[1] describe generalized tonic-clonic seizures in the majority of their cohort, with nearly 60% displaying multiple seizure types, and a significant proportion displaying features of ASD. Of particular clinical relevance, Feng et al.[1] reported a significant degree of treatment resistance among patients, with two patients completely resistant to treatment in a cohort of 17 patients, and 10 patients requiring polypharmacy. Frustratingly for parents and clinicians, and in concordance with the literature, no specific treatment was observed to be the most effective among patients.

Despite clear clinical descriptions among affected patients, a true genotype-phenotype correlation is yet to emerge. The heterogeneous nature of the *CHD2*-mutation-associated phenotype is certainly a cause for uncertainty for clinicians who are looking to estimate a patient's clinical trajectory, particularly with genetic results returned to families at ever earlier stages. As one of the more commonly reported genetic causes of epileptic encephalopathy, all early-onset epilepsy testing panels must include *CHD2*. The yield for older children and adults without complex epilepsy is yet to be ascertained. As re-iterated by Feng et al.,[1] *CHD2* reported variants even in people with the constellation of epilepsy, developmental delays, and behavioral problems are not always clearly pathogenic.

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Treating physicians and parents or guardians should be aware of the likelihood of multiple seizure types, photosensitivity, treatment resistance, developmental delay, and not under-estimate the behavioral disorders associated with pathogenic *CHD2* variants. In the absence of disease-modifying therapies and with no consensus as to suggested therapies, a genetic result is important for counseling and may facilitate timely support regarding educational and social development.

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CONFLICT OF INTEREST

None.

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