

# Copy number variants in absence epilepsy

## Further complications of the picture

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After years of largely unsuccessful association studies attempting to detect genetic variants underlying common epilepsies, the recent identification of copy number variants (CNVs) in epilepsy has generated a lot of excitement. CNVs are defined as genomic deletions or duplications larger than 1 kb and up to several Mb in size. A proportion occur at genomic hotspots (recurrent CNVs), whereas others can occur anywhere in the genome. Although individually rare, these CNVs collectively constitute the single largest risk factor for sporadic epilepsies known to date. Depending on the exact phenotype, CNVs have been reported in up to 28% of patients with epilepsy.<sup>1</sup> Subsequently, exon-disrupting deletions in a range of genes previously implicated in a variety of neurodevelopmental disorders were also identified in patients with epilepsy.<sup>2–4</sup> Genetic generalized epilepsy (GGE), either associated or not associated with intellectual disability, is the most commonly reported phenotype in patients carrying these CNVs. The GGEs comprise a large group of phenotypically heterogeneous disorders with a known or presumed genetic cause, which may vary from rare monogenic cases to complex polygenic inheritance.

In the current issue of *Neurology*<sup>®</sup> *Genetics*, Addis et al.<sup>5</sup> used single-nucleotide polymorphism arrays to detect CNVs in a cohort of 144 previously collected patients with absence epilepsy, including 95 with childhood absence epilepsy, 23 with juvenile absence epilepsy, and 26 with unclassified absence epilepsy. They identified recurrent CNVs previously reported in patients with GGE in 4 individuals, recurrent CNVs previously associated with a range of neurodevelopmental disorders in 4 individuals, and novel CNVs disrupting a range of genes involved in neuronal development and function in 15 individuals. They observed the different categories of CNVs across the 3 types of absence epilepsy, lending support to the hypothesis that these different subtypes of epilepsy share common genetic mechanisms.

The present study is the first to systematically address the identification of CNVs in patients with

absence epilepsy specifically. Many previous studies have reported the presence of recurrent and novel CNVs in a variety of GGE syndromes, including absence epilepsies, but because of the heterogeneity of phenotypes included in these studies, the distribution of CNVs in this specific subtype of GGE is presently unclear. GGE, and epilepsy in general, is not a single disease, and the large variety of syndromes and inherent difficulties in classifying the epilepsies constitute a unique challenge to the elucidation of the underlying genetic and molecular pathways. Deep phenotyping and careful patient classification can help refine genotype–phenotype correlations and improve our insight into the underlying disease pathophysiology. As pointed out by the authors, the retrospective nature of the current study represents a major limitation in this respect. Detailed clinical information was lacking for several patients, and the availability of prospective clinical information could have helped to refine the diagnosis, particularly in those patients with unclassified absence epilepsy, some of whom were reported to also have febrile seizures and developmental delay.

The results further confirm the involvement of some of the known recurrent CNVs in GGEs. The identification of CNVs previously reported in neurodevelopmental disorders, including often ill-defined seizures, in 4 patients with absence epilepsy further widens the phenotypic spectrum associated with these variants. Despite the well-known association of some of these recurrent CNVs with epilepsy and other neuropsychiatric disorders, the exact pathophysiologic mechanisms remain largely unknown. It is also important to point out that most of these CNVs act as susceptibility factors for epilepsy, rather than providing the sole explanation for the phenotype. This is illustrated by the wide phenotypic variability and by the fact that these CNVs may also be detected in asymptomatic relatives, complicating genetic counseling. Interpretation of the significance of the novel gene-disrupting CNVs is even more problematic.

See article

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Although the authors used specific criteria to support the potential for pathogenicity, detection of a large, novel, gene-disrupting CNV does not equal causality. The sample size was relatively limited, and except for one, each of these CNVs was observed in single cases. The absence of familial, especially parental, DNA samples for testing further limits assumptions about the pathogenicity of these novel CNVs. It is also of note that the gene-disrupting CNVs identified in the current study do not show substantial overlap with CNVs recently reported in similar studies in GGE including large numbers of patients with absence epilepsies.<sup>2</sup>

The present study further confirms the genetic complexity underlying the absence epilepsies and the epilepsies in general. It remains to be seen to what extent the identified CNVs contribute to the pathophysiology of absence epilepsies and whether the newly identified CNVs are specific to absence epilepsy or any specific subtype thereof. Large-scale studies involving careful phenotyping are required to answer these questions. For the time being, and in the absence of a better understanding of the exact underlying pathophysiologic mechanisms, genetic

counseling will remain problematic in many of these cases.

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