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Letter to the Editor

Delineating a new critical region for juvenile myoclonic epilepsy at the 22q11.2 chromosome

To the Editor:

We read with great interest the article entitled "The unexpected role of copy number variations in juvenile myoclonic epilepsy" by Helbig I. et al. [1] published in the supplemental special issue "Juvenile myoclonic epilepsy: What is it really?" [July 2013] of this journal. We thought that it would be appropriate to report the 22q11.2 chromosome as an additional proposed critical region for juvenile myoclonic epilepsy (JME) in order to raise awareness that 22q11.2 distal rearrangements may not be so uncommon in populations with epilepsy and to suggest the need to further study individuals with both microdeletions and duplications at 22q11.2.

In fact, epileptic seizures are frequent in chromosomal disorders, but only a few of these disorders are associated with specific seizure and EEG patterns [2–4]. Thus, it is assumed that causative chromosomal aberrations offer the opportunity to identify genes which may be involved in idiopathic epilepsies [3]. In patients with JME, several autosomal genes have been reported to show heterozygous (CACNB4, CLCN2, GABRA1, EFHC1) [5–8] and, in a single case, homozygous mutations (GABRD) [9]. Further loci have been linked to chromosomes 5q, 6p, and 15q [10–12]. However, most forms of JME seem to follow poly- or oligogenic inheritance. The 22q11.2 chromosome has long been implicated in several genomic disorders with neurological impairment including DiGeorge/velocardiofacial syndrome (DGS/VCFS), der(22) syndrome, and cat-eye syndrome (CES), which are associated with either decreased or increased gene dosage [13–16]. Recent evidence presumes that these different congenital anomaly disorders share a physical region of overlap containing chromosome 22-specific low-copy repeats (LCRs) composed of a complex modular structure with a high degree of sequence homology (>95%) over large stretches within the repeats. Low-copy repeats predispose to homologous recombination events and mediate meiotic nonallelic homologous recombinations (NAHR) resulting in genomic rearrangements of the 22q11.2 chromosome, including microdeletion and duplication [16–18]. While the cat-eye and der(22) syndromes are rare disorders characterized by duplications (tetrasomy and trisomy, respectively) of part of 22q11.2; on the contrary, 22q11.2 microdeletions, associated with DGS/VCFS, occur more often in the general population with an estimated frequency of 1/4000–6000 live births [19]. Even though recent data suggest that the frequency of 22q11.2 microduplications could be approximately half that of the deletions, relatively few duplications have been detected among human genomic disorders. Up to now, about 100 patients have been reported, and a high frequency of familial duplications has been detected [20]. This discrepancy may be due, in part, to the remarkable phenotypic variability of the duplications [21,22], which may complicate the clinical recognition of the corresponding syndromes.

So far, several studies focused on the potential connection between certain epilepsy phenotypes and the 22q11.2 locus. Kao et al. [23] reported a significantly increased prevalence of unprovoked seizures in individuals with del(22)(q11.2) and suggested generalized epilepsy as a primary manifestation of the disorder. Coppola et al. [24] described two patients with a del(22)(q11.2) and an epilepsy resembling Rolandic epilepsy. Both patients had sporadic Rolandic or occipital partial-onset seizures with clinical and electroencephalographic features of benign idiopathic childhood epilepsy. Baralle et al. [25] reported on a mother and her son who both had a 22q11.2 microdeletion; the mother presented with a tremor-like myoclonic movement disorder affecting the head, trunk, and limbs since infancy. Furthermore, there were single reports of patients carrying the deletion or the duplication and presenting with atypical absences [26] or generalized seizures [27–29]. Finally, Lemke et al. [30] and Piccione et al. [31] described two different patients with a diurnal pattern of myoclonias, generalized tonic–clonic seizures, and pathologic EEG with generalized spike waves (which are characteristic of JME) and respectively affected by 22q11.2 microdeletion and duplication.

Thus, based on the abovementioned features, although the syndrome's phenotype is well known to include epileptic seizures, putative epilepsy-causing genes are predicted within the 22q11.2 band. Therefore, a latent predisposition to seizures/JME, triggered by chromosomal imbalance and a decreased or increased gene dosage effect, could be assumed as well. In this view, it could be relevant to clarify the not yet known role of the *Rab36* gene at the 22q11.22 sub-band and its Ras-associated protein Rab36 currently localized by immunofluorescence studies at the Golgi body and hypothesized to be involved, like some other Rab family proteins, in vesicular transport [32]. Recently, Chen et al. [33] have shown that the overexpression of *Rab36* induced late endosome and lysosome clustering around the Golgi apparatus and that Rab36 can also interact with Rab-interacting lysosomal proteins. These data suggest that the haploinsufficiency or the overexpression of *Rab36* may interfere in neurotransmitter processing with an erroneous trafficking mechanism of release or other forms of unregulated secretion. Furthermore, this would seem to be mimicking and amplifying the recently recognized mechanism of the *Rab39B* gene that codified Golgi-associated GTPase with a critical role in vesicular trafficking, development of neurons, and human intellectual abilities. *Rab39B* mutations are, in fact, demonstrated to be responsible for a new X-linked syndrome characterized by milder phenotype, mental retardation, and epilepsy [34]. In conclusion, emphasizing the idea that the 22q11.2 chromosome should be considered a new critical region for epilepsy/JME, we propose that only by widening the scope of the patients tested and further investigating the function of the *RAB36* gene will we gain a better understanding of the JME's yet unrecognized cryptogenetic/idiopathic pattern.

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