Autosomal recessive epilepsy associated with contactin 2 mutation is different from familial cortical tremor, myoclonus and epilepsy

Pasquale Striano,1 Federico Zara,2 Salvatore Striano3 and Carlo Minetti1

1 Paediatric Neurology and Muscular Diseases Unit, Institute “G. Gaslini”, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy
2 Laboratory of Neurogenetics, Paediatric Neurology and Muscular Diseases Unit, Institute “G. Gaslini”, Genova, Italy
3 Epilepsy Centre, Department of Neurological Sciences, Federico II University, Napoli; Italy

Correspondence to: Dr. Pasquale Striano, Paediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Institute “G. Gaslini”, Genova, Italy
E-mail: strianop@gmail.com

Sir, In a recent interesting paper, Stogmann et al. (2013) described a consanguineous Egyptian family with autosomal recessively inherited condition featuring focal epilepsy, neuropsychiatric features, borderline cognitive level, and myoclonus. Exome sequencing in this family revealed a homozygous deletion (c.503_503delG) leading to a frameshift in the coding region of CNTN2 and segregating in the five affected family members. The gene CNTN2 encodes for contactin 2, a glycosylphosphatidylinositol-anchored neuronal membrane protein, necessary to maintain voltage-gated potassium channels at the juxtaparanodal region. Given the severity of the mutation and the function of the protein, the authors considered this mutation as the most likely cause of the clinical phenotype in this family (Stogmann et al., 2013). However, we would recommend caution when describing this family as affected by ‘familial cortical myoclonic tremor with epilepsy’ (FCMTE). This condition is defined by an autosomal dominant inheritance, adolescence or adult onset of myoclonus, infrequent epileptic seizures, photosensitivity, and a non-progressive course (Striano et al., 2005; van Rootselaar et al., 2005). Several Japanese and European families with these features have been reported under various names and linkage studies have shown that Japanese families are linked to 8q24 and non-Japanese to 2p11.1-q12.2 in most cases (Madi et al., 2008; Uyama et al., 2005). This condition is acknowledged worldwide (Crompton et al., 2012). Moreover, despite mild phenotypic differences and genetic heterogeneity within the different families, the clinical and electrophysiological data point toward one syndrome (Striano et al., 2005; van Rootselaar et al., 2005). In particular, the diagnosis is confirmed by electrophysiological features favouring cortical reflex myoclonus (i.e. enhanced long loop reflex I or C-reflex at rest, giant somatosensory evoked potentials, and premyoclonus cortical spikes detected by the jerk-locked back-averaging) (Ikeda et al., 1990). Stogmann et al. (2013) failed to show any evidence of these electrophysiological features in the investigated members from their studied family, which also did not show autosomal dominant inheritance of the clinical manifestations. In addition, cortical myoclonic tremor is improved by the use of anti-myoclonic drugs, such as clonazepam, valproate and levetiracetam, whereas it can be worsened by other anticonvulsants, such as carbamazepine, lamotrigine and gabapentin, sometimes resulting even in refractory, life-threatening status epilepticus (Dhuna et al., 1991; Genton, 2000; Striano et al., 2007). All the affected members from the Egyptian family described by Stogmann et al (2013) were on carbamazepine, which in Subject V-6 was associated to lamotrigine, which could even potentially increase the plasma level of carbamazepine and its metabolites. Therefore, one wonders whether these drugs may have played a role in causing the action and postural, shivering-like twitching movements of the patients that also appeared later than epileptic seizures, differently from most patients with FCMTE (Striano et al., 2005; van Rootselaar et al., 2005).

The family described by Stogmann et al. (2013) showed clinical, electrophysiological, and in one case even neuroimaging (temporal...
sclerosis) findings suggestive of focal epilepsy of temporal lobe origin. Focal epilepsy is also a main clinical features of the Old Order Amish children showing a homozygous mutation in \textit{CNTNAP2} (Strauss \textit{et al.}, 2006), the gene encoding contactin associated protein-like 2 (also known as CASPR2), another transmembrane protein that—together with contactin 2—clusters voltage-gated potassium channels (K$_{v}$.1.1) at the nodes of Ranvier. Similar to the Egyptian pedigree described by Stogmann \textit{et al.} (2013), the family reported by Strauss \textit{et al.} (2006) showed autosomal recessive inheritance and—in the latter kindred—analysis of temporal lobe specimens showed evidence of abnormalities of neuronal migration and structure and widespread astrogliosis. An appropriate terminology and classification of this peculiar and rare phenotype is essential for the diagnosis and correct clinical management. Clearly, nosological difficulty is predictable given the constraints of arbitrary classification of biological conditions.

**References**


van Rootselaar AF, van Schaik IN, van den Maagdenberg AM, Koelman JH, Callenbach PM, Tijssen MA. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. \textit{Mov Disord} 2005; 20: 665–73.