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A novel developmental encephalopathy with epilepsy and hyperkinetic movement disorders associated with a deletion of the sodium channel gene cluster on chromosome 2q24.3

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Deletions involving the sodium channel gene cluster on chromosome 2q24.3, which includes *SCN1A, SCN2A, SCN3A, SCN7A, and SCN9A*, have been associated with variable phenotypes including Dravet syndrome, migrating partial seizures of infancy, and various occasional non specific dysmorphic features including ear abnormalities, microcephaly, micrognathia and brachysyndactyly [1] (Fig. 1). None of the 72 previously published patients with 2q24.3 deletions exhibited movement disorders (Fig. 1).

Reported here is a 21 months-old boy who was born after in vitro fertilization.

A first generalized seizure appeared during a febrile rotavirus gastroenteritis at 5 months. A severe developmental delay was evident since the first months of life (head control was achieved at the age 15 months while trunk is not controlled yet).

He came to our attention after myoclonic jerks with staring appeared at age 8 months.

On examination the child exhibited sub-continuous bursts of hyperkinetic movements including choreic dyskinesias of limbs and trunk associated with dystonic posturing of hands and feet, stereotypies such as alternate flex-extension of lower limbs and head nodding (online video shows the patient at the age of 21 months). Movement disorders were exacerbated by pain, fever or seizure worsening. EEG disclosed generalized sharp waves and a photoparoxysmal response at very low frequencies (also at 1 Hz). Brain MRI revealed fronto-temporal cortical atrophy and mild corpus callosum hypoplasia. Daily tonic and myoclonic seizures were observed in the following months. Two prolonged episodes of status epilepticus were controlled with the administration of intravenous levetiracetam. Seizures were partially improved with a combination of levetiracetam, clobazam and stiripentol after failure with valproate and clonazepam. A targeted next-generation sequencing (NGS) gene panel including 147 genes associated with epilepsy was performed using a SureSelect custom capture (Agilent). NGS data analysis including both single nucleotide variant calling and exon copy-number variations analysis by CONVaDING tool was performed. Copy-number analysis detected a heterozygous deletion including the *SCN1A* and *SCN2A* NGS targeted genes, both located within the 2q24 region. *SCN1A* MLPA analysis (P137–B2, MRC-Holland) confirmed the SCN1A gene deletion· Array-CGH analysis defined the boundaries of a 6.1 Mb microdeletion on 2q24.3q31.1, between the regions 164375953 and 170535670, including the genes: *SCN1A, SCN2A, SCN3A, SCN7A, SCN9A, GRB14, SLC38A11, GALNT3, TTC21B, XIRP 2 and STK39* (Fig. 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.09.016

All the diagnostic evaluations were realized after having obtained a parental informed consent. Molecular genetic investigations were approved by the institutional ethic committee and followed the tenants of the Declaration of Helsinki.

In the patient reported herein a complex epilepsy phenotype, a several developmental delay and a hyperkinetic movement disorder were associated with a deletion of the whole sodium channel gene cluster. Whether this unusual phenotype results from leading to haploinsufficiency of either *SCN1A or SCN2A,* or the combination of both, remains subject of speculation. However, there is no indication that any of the numerous reported patients with truncating mutations in *SCN1A* has ever manifested such a clinical phenotype [2].

An early onset hyperkinetic movement disorder was previously reported in 10 patients with Dravet syndrome carrying three different *SCN1A* missense point mutations (c.677C > T, c.4033C > T and c.1264G > T) and in about 7% of children with *SCN2A* encephalopathy [2–4]. The pathomechanisms causing these motor manifestations could reside in either loss or gain of function of Nav1.1 and Nav1.2 channels that are both expressed in the basal ganglia [3]. In some patients with Dravet syndrome paroxysmal hyperkinetic movement disorders are precipitated by treatment with phenytoin or carbamazepine [3].

Even though 2q24.3q31.1 deletion includes *STK39* gene, which has been associated with Parkinson disease in adults [5], to date parkinsonism is no part of the phenotype of our patient.

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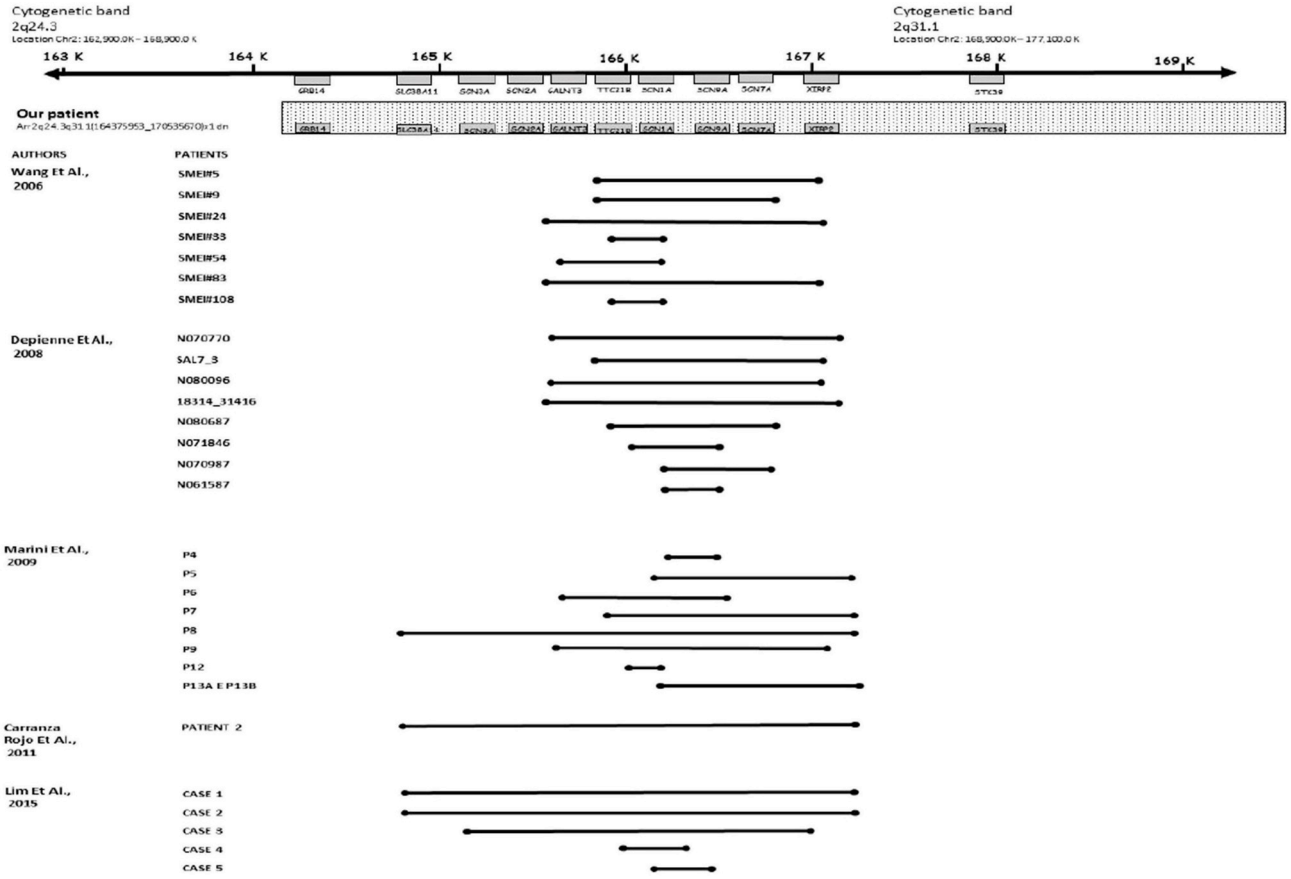

Fig. 1. Comparison between the deletion detected in the present patients and those in reported in previously published cases on the base of available array CGH data. References of the previously published cases.

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The genetic alteration underlying the phenotype of the present case was detected through an extended NGS analysis also including exon copy-number variations analysis. This approach, although not yet extensively included in the diagnostic process, allows a remarkable increase of the diagnostic yield.

The reported patient highlighted a new cause of early onset epilepsy and movement disorders in children, which widens the phenotypic spectrum associated with chromosome 2q24.3 deletions.

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