Neurological Sciences (2019) 40:2405–2406
https://doi.org/10.1007/s10072-019-03923-2

LETTER TO THE EDITOR

GRIN2A: involvement in movement disorders and intellectual disability without seizures

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Received: 27 December 2018 / Accepted: 4 May 2019 / Published online: 16 May 2019

The GRIN2A gene codes for the GluN2A subunit of N-Methyl-D-aspartate receptors (NMDARs) [1]. Inherited and de novo GRIN2A mutations are associated with Landau–Kleffner syndrome, continuous spike and wave during slow-wave sleep syndrome (CSWSS), atypical rolandic epilepsy, and speech impairment [2]. Recently, Fernandez-Marmiesse et al. [3] suggested that the phenotypic spectrum of GRIN2A-related disorders can also include neurodevelopmental and movement disorders without seizures.

We report here the case of a 19-year-old boy coming from southern Italy born from non-consanguineous parents after full-term pregnancy complicated by a risk of abortion. The proband showed a delayed psychomotor development (walking at 18 months) and language development restricted to vocalizations. Altered gait also appeared successively. Worsening in dystonic movements and postures, involving more evidently head and neck, and also upper limbs and feet, as well as an abnormal gait with dystonic postures, were also reported. The patient underwent karyotyping, which showed a balanced pericentric inversion of chromosome 9 (heterochromatic region), apparently not associated with neuropsychiatric disorders. The screening of the FMR1 gene was negative. An electroencephalogram (EEG) revealed no relevant findings. A brain magnetic resonance imaging (MRI) only reported asymmetric ventricular size.

At the age of 17 years, the patient was admitted to our hospital. Comparative genomic hybridization-array analysis (array-CGH) 60 k, genetic study for FBN1, eye examination, EEG, electrocardiogram, and abdominal ultrasound, as well as metabolic blood and urine screening, resulted to be within the normal range. A more recent brain MRI study documented asymmetric ventricular size and a prominent cortical and cerebellar sulci atrophy.

At the age of 18 years, the patient presented paroxysmal involuntary hyperkinetic movements involving both proximal limbs and trunk. The patient underwent multi-gene panel testing (90 genes including channelopathies and epileptic encephalopathies, see the Supplementary Table 1) which disclosed a heterozygous missense mutation, inherited from the mother, in the GRIN2A gene (NM_000833.4, c.3163G>C (p.Glu1055Gln)). In addition, the predictive test was performed with wANNOVAR (http://wannovar.wglab.org) [4]; 8/12 predictive test (SIFT, Polyphen_HDIV, Polyphen_HVAR, LRT, MutationTaster, M-CAP, fathmm-MKL_coding, and Mutation Assessor) considered the mutation as deleterious/probably damaging; only 4/12 (FATHMM, MetaSVM, MetaLR, and PROVEAN_pred) predictive test considered as tolerated the mutation. Moreover, the variant is placed in a conserved nucleotide as indicated by its Genomic Evolutionary Rate Profiling (GERP value) of 5.33. Finally, CADD score (26.5 value) for p.Glu1055Gln variant was indicative of a pathogenic mutation [4]. Screening of this variant was not detected in a population of 50 healthy controls (100 alleles) of the same geographic area, ruling out the possibility of a population polymorphism.

Lesca et al. [2] highlighted the possibility of both reduced penetrance in the GRIN2A gene (due to modifier genes and/or environmental factors) and the interfamilial phenotypic variability, also describing that some carriers were only affected by verbal dyspraxia (two missense mutations) as well as unaffected (four missense mutations).

We might conclude that the GRIN2A gene variant (c.3163G>C (p.Glu1055Gln)), also detected in healthy controls (Exome Aggregation Consortium (ExAC) 0.002%; The Genome Aggregation Database (gnomAD): 0.002%; 1000 Genomes: not found), is not conclusive of benignity, but it could also reflect a variable expressivity and incomplete

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10072-019-03923-2) contains supplementary material, which is available to authorized users.

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Table 1 Demographic, clinical, and genetic findings of patients with missense mutation in GRIN2A gene with nonepileptic neurodevelopmental and movement disorders

Number	Gender	Psychomotor development	Dystonic movements and posture	Hyperkinetic disorder movement	Abnormal gait	Language impairment	Intellectual disability	EEG findings	MRI findings	Missense mutation	Reference
1	Male	Delayed	Yes	No	Yes	Yes	Moderate	No	No	p.Ala643Asp	1
2	Female	Delayed	Yes	Yes	Yes	Yes	Moderate	No	No	p.Ala643Asp	1
3	Male	Delayed	Yes	Yes	Yes	Yes	Severe	No	Aspecific	p.Glu1055Gln	Our patient

EEG, electroencephalogram; *MRI*, magnetic resonance imaging

penetrance, frequently recurring in autosomal dominant epileptic disorders, as recently shown for those with PRRT2 frame shift mutations too [3, 5]. Moreover, the two siblings with missense mutation (p.Ala643Asp) as described by Fernandez-Marmiesse et al. [3] appear to be strongly similar to the clinical case reported here (Table 1). However, more investigations and cases are needed to understand the possible involvement of the GRIN2A missense variant c.3163G>C (p.Glu1055Gln) in movement disorders and intellectual disability.

In conclusion, the close phenotypic similarity between our patient and the two siblings described by Fernandez-Marmiesse et al. [3] seems to reinforce the possible involvement that missense mutations in the GRIN2A might represent a possible risk factor for movement and psychiatric disorders without seizures. Also, further investigations are needed to understand if mild encephalopathy with dystonia, without epileptic abnormalities is the primary clinical feature in some patients with the GRIN2A mutation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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