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Letter to the Editor

Expanding the spectrum of Grik2 mutations: intellectual disability, behavioural disorder, epilepsy and dystonia

To the Editor:

Intellectual disability (ID) is a common neurodevelopmental disorder that involves impairments of general mental abilities that impact adaptive functioning (1). Noteworthy advances in the research of the genetic causes of non-syndromic ID have been observed in recent years. Most of these advances have depended on the introduction of next generation sequencing technologies, which have revolutionized this field allowing the identification of causative DNA mutations in several new genes (2). Some of them are related to glutamatergic neurotransmission, such as GRIK2, which was proposed as the genetic cause of isolated moderate to severe ID in an Iranian family (3).

However, it still remains unclear, which are, if any, the typical phenotypic features linked to defects on glutamate pathways. The spectrum seems to be very wide including epilepsy, ID and psychiatric disorders (4, 5). Furthermore, occasional clinical-genetic descriptions in unique families need to be confirmed and expanded in other non-related subjects before the genetic cause of a familial disorder could be confidently established. We report here clinical features present in two siblings from a consanguineous family affected with variable degrees of cognitive impairment, epilepsy, dystonia and behavioral disorders where a homozygous non-sense mutation in the ionotropic glutamate receptor type 6 gene, GRIK2, was identified through whole-exome sequencing.

The proband (individual IV: 2 in Fig. 1a) is a 31-year-old male patient that was born after a normal pregnancy. His perinatal history did not show any relevant data. He had delay in social and cognitive development during infancy. The behavioural impairment did not change over time. At the age of 13, he presented a first atonic seizure. A diagnosis of epilepsy was made after the occurrence of new seizures. Treatment with valproate was begun with good clinical response. At the age of 16, he developed cervical dystonia. Tremor and myoclonus started a few years later. The neurological evaluation showed ID, Addenbrooke's cognitive examination (ACE) revealed a total score of 53 with impairment in all cognitive domains. His physical exam was remarkable for the presence of overt cervical dystonia. The patient presented generalized pyramidal tracts dysfunction,

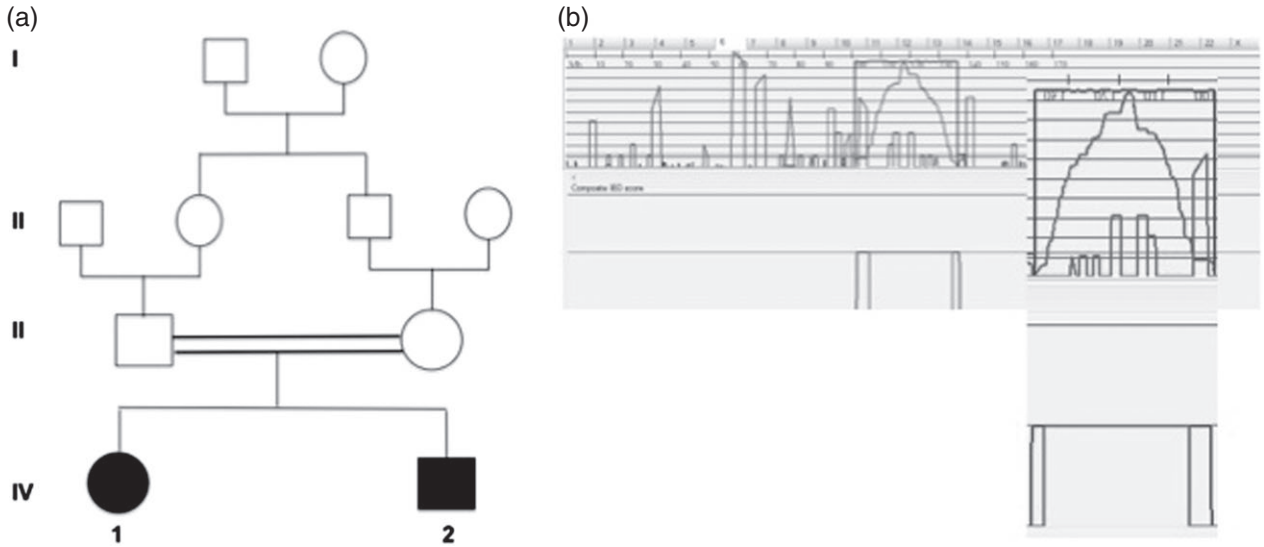

Fig. 1. (**a**) The family history shows consaguinity between the parents of the probands. (**b**) Genotypes derived from whole exome data were utilized to identify homozygous runs and possible identity by descent (IBD) regions using *AgileVariantMapper* (Available at http://dna.leeds.ac.uk/ibdfinder) tools. Here was analyzed chromosome 6 and the IBD region that correspond to GRIK2 is pointed in a bigger size.

Table 1. Candidate genes localized in probable *Identity by Descend* regions[a]

Chromosome	Gene	Variants	Pathogenic prediction by bioinformatic tools	Related gene disease	Phenotype OMIM number
Ch1	GLMN	c.1669+19_1669+19 Hom splice site	Benign	Glomuvenous Malformations	*138000
Ch3	PROS1	p.arg233lys Hom non-synon	Benign	Protein S Deficiency, autossomal recessive	*614514
Ch3	SI	c.374-12_374 12delATTTTTTTTinsATTTTTTT Hom splice site	Uncertain	Sucrase-isomaltase deficiency, congenital	*222900
Ch5	SLC26A2	p.Ile574Thr Hom non-synon	Benign	Diastrophic Dysplasia Achondrogenesis Atelosteogenesis	*600972 *256050 *222600
Ch5	SLC22A5	c.652+6A>G Hom splice site	Moderate	Primary Systemic Carnitine Deficiency	*212140
Ch6	**GRIK2**	p.Arg198* Hom stop gain	Pathogenic	Mental retardation, autosomal recessive, 6	*611092
Ch6	ENPP1	c.2101-15_2101-15 delATTTTinsATTT Hom splice site	Moderate	Susceptibility to Insulin Resistance, Diabetes Mellitus, or Obesity	*125853
Ch15	SLC12A1	T→C,C Hom non-synon	Benign	Bartter Syndrome Type 1	*601678
Ch15	FBN1	p.Cys472Tyr Hom non-synon	Benign	Marfan Syndrome	*154700
Ch15	NR2E3	c.684ACCCCC>ACCCC Hom splice site	Uncertain	Enhanced S-Cone Syndrome - Retinitis Pigmentosa 37	*268100 *611131
Ch15	ACAN	p.Ile1651Val Hom non-synon	Benign	Spondyloepiphyseal Dysplasia Spondy-loepimetaphyseal Dysplasia, Aggrecan Type Osteochondritis Dissecans, Short Stature, and Early-onset Osteoarthritis Susceptibility to Lumbar Disc Degeneration	*165800
Ch20	CTSA	c.1002+7G>A Hom splice site	Uncertain	Galactosialidosis	*256540

[a]Whole exome sequencing in proband IV: 2 generated 69,347,380 sequence reads, which resulted in an average coverage of targeted regions of 112.8X. Before filtering the data, 74,161 SNVs and 7,621 INDELs were found. Filtering for variants localized in IBD regions (Supportinf Information, Tables S1 and S2) yielded a list of 12 disease-causing genes, which harbor homozygous variants. Among them, only the non-sense variant p.Arg198* in GRIK2 could be considered a plausible candidate to cause the phenotype observed in this family. Sanger sequencing validated this mutation and confirmed its familial co-segregation with ID.

intermittent bilateral postural and kinetic tremor and symmetrical myoclonus in arms. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) showed no abnormalities.

A 34-year-old woman (individual IV: 1 in Fig. 1a), born to the same parents as the proband. Product of a normal pregnancy and an uncomplicated delivery. Mild cognitive delay was evident since her infancy. Impairments in social interaction and in verbal and non-verbal communication were more pronounced than in her brother. She had significant problems developing non-verbal communication skills, such as eye contact, facial expressions and body postural responses. Nowadays, she is engaged in a restricted range of activities in her daily routine. At the age of 16, she presented atonic seizures that were well controlled with clobazam. She did not show any neurological motor or sensory deficit, or any abnormal movement. Brain MRI and EEG were normal. She is still under treatment for epilepsy with good response.

Whole Exome sequencing was performed in proband IV: 2. Considering that both affected siblings were born from consanguineous parents, bioinformatic analysis was made in order to identify homozygous functional variant located in a Identity by descent region (Fig. 1b). A non-sense mutation in GRIK2, p.Arg198*

was identified as the possible etiology of this syndrome (Table 1). Validation and familial segregation analysis of GRIK2 non-sense mutation was confirmed by Sanger sequencing. Non-sense mediated decay will probably occur with this truncated transcript precluding its expression. Nevertheless, if it is expressed it would lack its three transmembrane domains and a pore loop resulting in a non-functional protein.

To date, there was only one family previously reported where non-syndromic ID was caused by mutations in GRIK2. Motazacker et al. (3) identified a complex mutation in GRIK2 that resulted in the deletion of 84 aminoacids of this receptor in five members of a consanguineous family showing a wide range of cognitive impairment with no other neurological symptoms. Considering that both mutations are comparable (i.e. both led to premature stop codons), clinical differences could obey to other *genetic and not* unidentified factors.

In conclusion, we described a second family showing ID as a consequence of a loss of function mutation in GRIK2 gene and expanded the phenotype associated with a dysfunction in GluK2 receptor, demonstrating the utility of whole exome sequencing in the diagnosis approach of heterogeneous disorders affecting higher brain functions.

Supporting Information

The following Supporting information is available for this article:

Table S1. Homozygous variants found in probable IBD regions.
Table S2. Probable IBD regions.

Additional Supporting information may be found in the online version of this article.

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