PHENOTYPIC VARIABILITY IN A SOUTHERN ITALIAN FAMILY WITH 16p13.2 GRIN2A DELETION

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OBJECTIVES

We report the clinical and neurophysiological characterisation of a family with a GRIN2A microdeletion, exhibiting marked intra-familial phenotypic variability ranging from mild drug-responsive epilepsy to isolated language impairment.

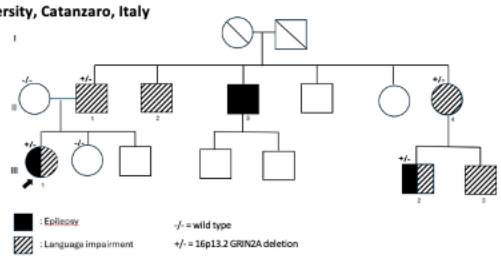

Fig. 1: Family pedigree illustrating segregation of the 16p13.3 deletion, with the proband indicated by an arrow.

MATERIALS AND METHODS

Clinical data were collected from all family members, and a pedigree was constructed. The diagnostic work-up included: neurological examination, standard EEG, brain magnetic resonance imaging (MRI), and a comprehensive neuropsychological assessment also including the 'Neuropsychological Examination for Aphasia' (ENPA) test. All individuals were Caucasian and originated from Calabria, southern Italy. Genetic testing using array CGH was performed on all included individuals.

RESULTS

The pedigree of the family is showed in Figure 1. The proband is a 16-year-old girl with normal birth and developmental milestones, except for delayed language acquisition: her first words emerged at the age of 3. At the age of 4, she experienced the first seizure during sleep, characterised by throat noises, head and gaze deviation, hypersalivation, and lasting approximately two minutes, followed by postictal confusion. She also manifested occasional focal impaired awareness seizures during wakefulness, accompanied by bimanual automatisms. General examination revealed low-set ears (Fig. 2) with a normal occipito-frontal circumference. Neurological examination was unremarkable. Neuropsychological evaluation using the ENPA test revealed a selective language impairment affecting both phonemic processing and semantic abilities, despite preserved overall cognitive function (Table 1). Ictal EEG recorded a paroxysmal arousal (i.e. focal frontal seizure following arousal from N2 sleep). Interictal EEG showed bifrontal sharp waves (Fig. 3). Brain MRI was unremarkable. Genetic analysis revealed a 16p13.2 (10,273,862–10,273,924) deletion involving the GRIN2A gene, inherited from the father (Fig1). The 52-year-old father, his 52-year-old sister (the proband's paternal aunt) and two cousins exhibited also language impairment with normal scores in other cognitive domains (Table 2). All affected individuals carried the same 16p13.2 deletion.

Fig.2: Low-set ears of the proband

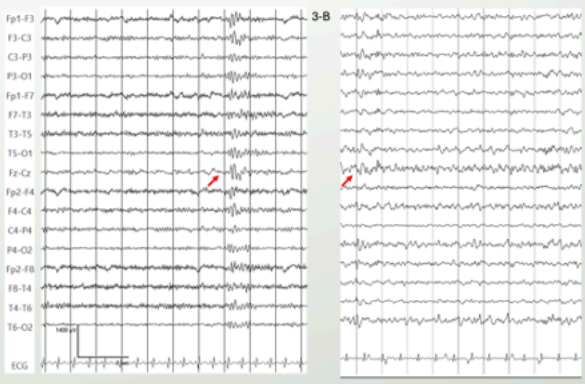

Fig 3: Interictal EEG features of the proband of both wakefulness (3A) and sleep (3B)

Table.1: Neuropsychological assessment of the proband

TEST	SCORE	RESULTS
Phonemic Fluency – Language	16	Below threshold
Semantic Fluency – Language	37	Below threshold
Lexical Naming – Language	43	Below threshold
Writing – Learning Skills	47	Below threshold
Reading – Learning Skills	99	Normal
Tower of London – Reasoning and Executive Functions	11	Normal
Selective Recall of Immediate Words – Verbal Memory	74	Normal
Selective Recall of Delayed Words – Verbal Memory	10	Normal
Digit Span – Working Memory	3	Below threshold

Table.2: Neuropsychological assessment of the family members

	PHONEMIC LANGUAGE (FAS TEST) CUT-OFF: >17.35	SEMANTIC LANGUAGE CUT-OFF: >28.34
Case II; 1	2.5	13
Case II; 4	14.3	42
Case III; 2	9.8	17

DISCUSSION

We report a novel paternally inherited 16p13.2 microdeletion involving the GRIN2A gene, segregating in four affected individuals with either mild epilepsy or isolated language disorder. This report further highlights the clinical heterogeneity of GRIN2A-related disorders[1]. To our knowledge, 'paroxysmal arousals' consistent with sleep-related hypermotor epilepsy[2] have not previously been associated with GRIN2A-related disorders. A detailed neuropsychological assessment using language-focused tools such as the ENPA test was crucial in detecting subtle deficits in affected family members. Finally, the presumed loss-of-function mechanism underlying the 16p13.2-GRIN2A deletion has relevant implications for precision medicine, as L-serine has recently been proposed as a potential therapeutic agent[3].

CONCLUSION

This report further highlights the clinical heterogeneity of GRIN2A-related disorders. A detailed neuropsychological assessment using language-focused tools may be essential to detect subtle language deficits associated with GRIN2A-related disorders

REFERENCES

[1] Strehlow V, Heyne HO, Vlaskamp DRM, Marwick KFM, Rudolf G, de Bellescize J, Biskup S, Brilstra EH, Brouwer OF, Callenbach PMC, Hentschel J, Hirsch E, Kind PC, Mignot C, Platzer K, Rump P, Skehel PA, Wyllie DJA, Hardingham GE, van Ravenswaaij-Arts CMA, Lesca G, Lemke JR; GRIN2A study group. GRIN2A-related disorders: genotype and functional consequence predict phenotype. Brain. 2019 Jan 1;142(1):80-92.
[2] Loddo G, Baldassarri L, Zenesini C, Licchetta L, Bisulli F, Cirignotta F, Mondini S, Tinuper P, Provini F. Seizures with paroxysmal arousals in sleep-related hypermotor epilepsy (SHE): Dissecting epilepsy from NREM parasomnias. Epilepsia. 2020 Oct;61(10):2194-2202.
[3] Juliá-Palacios N, Olivella M, Sigatullina Bondarenko M, Ibáñez-Micó S, Muñoz-Cabello B, Alonso-Luengo O, Soto-Insuga V, García-Navas D, Cuesta-Herraiz L, Andreo-Lillo P, Aguilera-Albesa S, Hedrera-Fernández A, González Alguacil E, Sánchez-Carpintero R, Martín Del Valle F, Jiménez González E, Cean Cabrera L, Medina-Rivera I, Perez-Ordoñez M, Colomé R, Lopez L, Engracia Cazorla M, Fornaguera M, Ormazabal A, Alonso-Colmenero I, Illescas KS, Balsells-Mejía S, Mari-Vico R, Duffo Viñas M, Cappuccio G, Terrone G, Romano R, Manti F, Mastrangelo M, Alfonsi C, de Siqueira Barros B, Nizon M, Gjerulfsen CE, Muro VL, Karall D, Zeiner F, Masnada S, Peterlongo I, Oyarzábal A, Santos-Gómez A, Altafaj X, García-Cazorla Á. L-serine treatment in patients with GRIN-related encephalopathy: a phase 2A, non-randomized study. Brain. 2024 May 3;147(5):1653-1666.