Infantile Epileptic Spasms Syndrome in a patient with heterozygous *NRXN1* deletion and *CNTNAP5* duplication: a potential case of digenic inheritance

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Background

Genetics of Infantile Epileptic Spasms Syndrome (IESS):

- Around 20% of the cases have a definite genetic etiology.
- Over 28 copy number variants (CNVs) are definitely associated.
- Biallelic microdeletions in *NRXN1* are a known cause of IESS.

Role of the gene *NRXN1*:

- *NRXN1* encodes a presynaptic cell-adhesion protein functioning as a ***cerebral synaptic organizer***.
- **Monoallelic microdeletions** are a **risk factor** - with incomplete penetrance and variable expressivity - for **epilepsy and neuropsychiatric disorders** including autism spectrum disorder, schizophrenia, and Tourette syndrome.
- Deletions primarily associated with **epilepsy** are non-recurrent and involve **exons 1-6**.
- In a single reported case of early-onset epileptic encephalopathy with respiratory depression, *NRXN1* has also been implicated in a **potential digenic inheritance model** with *NRXN2*, a gene encoding a functionally similar synaptic protein.
- Biallelic variants in both *NRXN1* and *CNTNAP2*, belonging to the neurexin superfamily, have been associated with Pitt-Hopkins-like syndrome.

Role of the gene *CNTNAP5*:

- *CNTNAP5* is a member of the **neurexin superfamily**.
- *CNTNAP5* **haploinsufficiency** has been suggested as a **risk factor** for schizophrenia and autism spectrum disorder.
- Two patients with intellectual disability have been described carrying 2q14.3 deletions involving only the *CNTNAP5* gene - one de novo and one inherited from an unaffected mother.

Materials and Methods

- Clinical and electrophysiological assessment.
- Trio-based Clinical Exome Sequencing (CES) + Trio-based Array-based Comparative Genomic Hybridization (array-CGH).

Results

Clinical assessment:

- A 3-month-old infant presented with epileptic spasms associated with hypsarrhythmia on EEG, consistent with a diagnosis of IESS.
- Partial improvement was achieved with vigabatrin, followed by complete clinical and EEG resolution with tetracosactide.
- At the 18-month follow-up, after gradual withdrawal of vigabatrin, EEG was well-organized during wake and sleep, without any relevant abnormality. Psychomotor development remained age-appropriate and brain MRI was unremarkable.

Genetic assessment:

- Trio-CES resulted negative.
- Trio-based array-CGH:
  - **Intragenic *NRXN1* deletion** (exons 3-5) inherited from the unaffected mother.
    arr[GRCh37] 2p16.3(51105765_51226229)x1
  - **Partial *CNTNAP5* duplication** (exons 1-6) inherited from the father, who had idiopathic generalized epilepsy with tonic-clonic seizures with onset in adolescence and remission in adulthood.
    arr[GRCh37] 2q14.3(124134952_125224778)x3

Conclusion

The proband carries an intragenic *NRXN1* deletion combined with a partial *CNTNAP5* duplication.

Given the **functional similarity** between *NRXN1* and *CNTNAP5*, we hypothesize that, while the isolated *NRXN1* deletion is clinically silent in the carrier mother, its **combination** with the paternally inherited *CNTNAP5* duplication may account for the patient's phenotype within a **digenic inheritance model**.