

MONO- AND BIALLELIC DELETION OF NEUREXIN: A PROPOS OF 3 CASES

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Introduction

Autism spectrum disorder is a complex neurodevelopmental syndrome characterized by social communication deficits and stereotyped behaviors with restricted interests. Although the etiology of this disease is not fully understood, recent genomic and genetic studies have found that hundreds of genetic variants contribute to the occurrence of ASDs. Neurexin 1 (NRXN1) is a cell adhesion protein important for synapse integrity and function. Mutations of this gene are known to be associated with developmental disorders and psychiatric diseases.

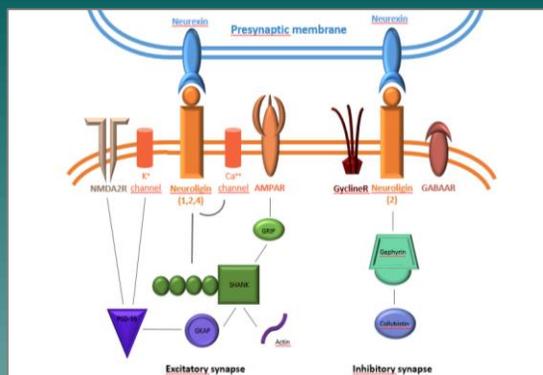
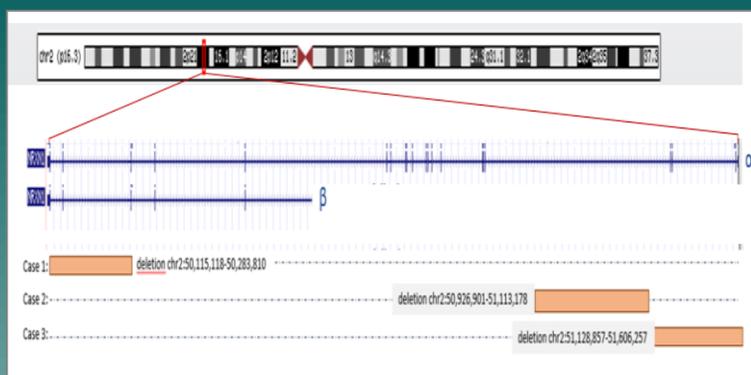
Material and methods

We describe three cases with mutation of NRXN1 and compare them with those of the literature. Two of them have a heterozygote exon deletion in this gene and present a global development delay. In the third patient who suffer from a typical severe autism, we discovered a rare biallelic mutation in NRXN1.

Case 1: the propositus is a full-term female child of an uneventful gestation pregnancy. Parents and siblings are healthy but some of her aunts and uncles present schizophrenia, epilepsy and developmental delay. The patient made her first steps at 17 month and began to walk at 24 month. At 2 years old, she showed behavioral disorders with aggressivity and auto-mutilation. She presents also language delay and hyperactivity. Although she has stereotyped movement of her right arm, she doesn't gather all criteria for typical autism because she continue to have multiple interests and a good nonverbal communication with the entourage. Further analysis demonstrate a normal cerebral RMN and a heterozygote deletion of 168kb in the gene 2p16.3 coding neurexin (chr2:50,115,118-50,283,810).

Case 2: this twenty years old patient suffer from typical severe autism with a strong developmental delay. His parents describe no smile and no visual contact since his birth. He can say only few words but no phrase and can't use nonverbal language. He present moreover restrictive interests and some motor stereotypies. He has also epilepsy for which Depakine is given. No contributory neonatal history. In his family, his sister and his mother suffers from autism to. The cerebral IRM performed in our patient is normal but genomics analysis with array-CGH demonstrate homozygote deletion of 232kb at the region 2p16.3 (chr2:50,926,901-51,113,178)

Case 3 (Schyns Noé 300113): This patient is a full-term male child of an uneventful gestation pregnancy. His parents and sister are in good health. Some of his cousins and uncles present a developmental delay. At 2 years old, the child doesn't walk and doesn't say word. No other deficit was found. Genetics analysis demonstrate a heterozygote deletion of 477kb in the gene 2p16.3 (chr2:51,128,857-51,606,257)



Figures: A left, the neurexin 1 gene (NRXN1) and the different mutations discovered in our patients. Case 1 and 3 exonic deletions, case 2 present intronic deletion; at right, a schema of the interactions between pre and postsynaptic proteins (GABA = gamma-aminobutyric acid A, GRIP = Glutamate receptor interacting protein, GKAP = guanylate kinase-associated protein, PSD-95= postsynaptic density protein 95)

Conclusion

We report on two patients with heterozygote deletion in the gene NRXN1, and one with a rare biallelic partial deletion of this gene. These cases emphasize the important role of NRXN1 and its implication in the development of autism and intellectual disability