



Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2018 September ; 177(6): 589–595. doi:10.1002/ajmg.b.32673.

A rare exonic *NRXN3* deletion segregating with neurodevelopmental and neuropsychiatric conditions in a three-generation Chinese family

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Abstract

Members of the neurexin gene family, neurexin 1 (*NRXN1*), neurexin 2 (*NRXN2*), and neurexin 3 (*NRXN3*) encode important components of synaptic function implicated in autism and other neurodevelopmental/neuropsychiatric disorders. Loss of function variants have been reported predominantly in *NRXN1*, with fewer such variants detected in *NRXN2* and *NRXN3*. Evidence for segregating *NRXN3* variants has particularly been lacking. Here, we report identification by chromosomal microarray analysis (CMA) of a rare exonic deletion affecting the *NRXN3* alpha isoform in a three-generation Chinese family. The proband, a 7-year-old boy, presented with motor and language delay and met the clinical diagnostic criteria for autism. He also presented with moderate intellectual disability, attention deficit hyperactivity disorder (ADHD) and facial dysmorphic features. The mother and maternal grandfather, both deletion carriers, presented with variable degrees of language and communication difficulties, as well as neuropsychiatric problems such as schizophrenia and temper tantrums. A compilation of sporadic cases with deletions involving part or all of *NRXN3* revealed that 9 of 23 individuals (39%) displayed features of autism. The evidence for co-segregation in our family further supports a role for *NRXN3* in autism

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Author contributions

H.Y. carried out the cytogenetic studies and wrote the manuscript. Y.S. was responsible for the design of the project, data analysis, and manuscript write-up. Q.W., W.Y., and Y.L. made the clinical evaluation and collected clinical information of the patient in detail. J.G. was responsible for polishing this paper. Q.W. and Y.H. performed the experiments. J.S. performed data entry. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

and neurodevelopmental/neuropsychiatric disorders but demonstrates intra-family variable expressivity due to this *NRXN3* deletion, with schizophrenia and facial dysmorphism being potential novel features of *NRXN3* haploinsufficiency.

Keywords

NRXN3; intragenic deletion; autism; intra-family expressivity

Introduction

Neurexins are presynaptic cell-adhesion molecules encoded by paralogous genes, *NRXN1*, *NRXN2* and *NRXN3*. Each of these encodes alpha and beta isoforms [Sudhof, 2008]. Neurexins are cell-surface receptors that bind neuroligins to form a Ca²⁺-dependent neurexin/neuroligin complex at synapses in the central nervous system; they are required for efficient neurotransmission and play key roles in synaptic contacts and function [Tabuchi and Sudhof, 2002; Reissner et al., 2008]. All three genes had been implicated in autism spectrum disorders (ASD) [Feng et al., 2006; Autism Genome Project Consortium et al., 2007; Kim et al., 2008; Glessner et al., 2009; Rujescu et al., 2009; Ching et al., 2010; Gauthier et al., 2011; Liu et al., 2012; Gjørnlund et al., 2012; Stessman et al., 2017; Mohrmann et al., 2011; Dachtler et al., 2014; Born et al., 2015; Boyle et al., 2015; Vaags et al., 2012].

Loss of function variants had been mostly identified in *NRXN1* among patients with neurodevelopmental or neuropsychiatric disorders, supporting *NRXN1* as a susceptibility gene for ASD, schizophrenia and intellectual disability [Feng et al., 2006; Szatmari et al., 2007; Kim et al., 2008; Glessner et al., 2009; Rujescu et al., 2009; Ching et al., 2010; Gauthier et al., 2011; Liu et al., 2012; Gjørnlund et al., 2012; Stessman et al., 2017]. Variable expressivity and incomplete penetrance frequently were observed [Woodbury-Smith et al., 2017; Lowther et al., 2017]. Variants involving *NRXN2* and *NRXN3* are much rarer but reports are accumulating [Gauthier et al., 2011; Mohrmann et al., 2011; Dachtler et al., 2014; Born et al., 2015; Boyle et al., 2015; Vaags et al., 2012]. Several findings support a role for *NRXN2* in autism, but the contribution of *NRXN2* to brain function might be less than other NRXN genes since *NRXN2* deletion does not seem to impair cognitive competence [Gauthier et al., 2011; Mohrmann et al., 2011; Dachtler et al., 2014; Born et al., 2015; Boyle et al., 2015].

Loss of function sequence variants in *NRXN3* gene are very rare: only one stop gain variant was detected among 60,706 individuals in the Exon Aggregation Consortium (ExAC) database. While sporadic deletion cases have been reported in databases and publications, these presented limited segregation evidence to support a causal relationship between *NRXN3* deletion and autism [Schlade-Bartusiak et al., 2008; Cingoz et al., 2011; Vaags et al., 2012; Griswold et al., 2012; Riegel et al., 2014; Faheem et al., 2015; Nicita et al., 2015; <https://decipher.sanger.ac.uk/>]. Familial exonic *NRXN3* deletions were reported previously in autistic children from four unrelated pedigrees of Western origin. Among the four pedigrees, one deletion was inherited from a carrier mother without ASD diagnosis, another

from an unaffected father. The third deletion was inherited from an affected father with subclinical autism and the fourth deletion was *de novo*. Thus, the four pedigrees provided limited evidence for co-segregation of the deletion with a neurodevelopmental phenotype [Vaags et al., 2012]. *NRXN3* has also been implicated in neuropsychiatric disorders such as schizophrenia [Hu et al., 2013], but overall, studies of *NRXN3* in autism and other neuropsychiatric disorders are quite limited. Here, we describe a three-generation Chinese family carrying a deletion at 14q24.3–31.1 involving the *NRXN3* alpha isoform (Fig. 1). This pedigree provides important supporting evidence for the association between *NRXN3* and neurodevelopmental/neuropsychiatric conditions, including autism.

Case presentation

The proband (F-001) was one of two children of nonconsanguineous parents, the product of an uneventful pregnancy. His younger brother (F-002) was healthy. The proband was delivered at 38 weeks of gestation with normal birth measurements: weight 3.2 kg (40th centile), length 51 cm (65th centile) and head circumference 34.2 cm (40th centile). Apgar scores were all 9. No feeding problem was noted after birth. His growth development was within normal range: he weighed 24 kg (60th centile), his height was 121.8 cm (45th centile), and his head circumference was 51.4 cm (50th centile) at age of 7 years, but his motor development was delayed: he raised his head at 4 months, sat alone at 1 year and could walk independently at 2 years. His language development was significantly delayed, he only developed two-word sentences and displayed moderate intellectual disability with Intelligence Quotient (IQ) 50 by the Wechsler Intelligence Scale. The proband's abnormal behaviors included autism spectrum disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). He demonstrated poor eye contact, social difficulties and stereotyped behaviors as well as restricted interests, such as playing with building blocks and sand. He showed aggressive, depressive and anxious open field behaviors and was diagnosed with ASD after a clinical assessment at the age of 2-year-5-month. Reassessment at the age of 3-year-8-month confirmed that he met the clinical diagnostic criteria for autism based on the Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS) and Modified Checklist for Autism in Toddlers Revised (M-CHAT-R). He had distinctive facial features including high forehead, flat facial profile, auricle dysplasia, widely spaced eyes, blepharoptosis, flat nose bridge, long broad philtrum, dental dysplasia, micrognathia, sparse eyebrows and hair (Fig. 2). Brain magnetic resonance imaging (MRI) was normal.

The proband's father (F-003) was apparently healthy. The mother (F-004) presented with language delay, learning difficulties, anxiety, slightly impaired socialization skills as well as difficulty in communication. She had good eye contact, did not show stereotyped behaviors, and did not meet the criteria for ASD upon a clinical assessment. The maternal grandmother (F-009) was obviously unaffected. The maternal grandfather (F-008) was assessed by clinical review and was found to have language delay, mild impaired communication and social interaction issues, schizophrenia, temper tantrums, aggressive behavior and anxiety in unfamiliar situations, but had good eye contact and no evidence of stereotyped behaviors or restricted interests. An evaluation for autism was not performed. The maternal aunt (F-005) and her 10-year-old son (F-007) were both normal.

Material and methods

Chromosome karyotype analysis

Cytogenetic investigation (GTG banding) of 20 metaphases obtained from PHA-stimulated peripheral lymphocytes of the proband was performed following standard protocols.

FMR1 gene testing

FMR1 testing was carried out for the proband following the manufacturer's instructions as described elsewhere [Biancalana and Macpherson, 2004].

Chromosomal microarray analysis (CMA)

Genomic DNAs were isolated from peripheral blood samples using a commercial kit (Qiagen Valencia, CA, USA). Chromosomal microarray analysis was carried out for all members of the large Chinese family using Affymetrix Cytoscan 750K platform (Affymetrix, Santa Clara, CA, USA). Labeling and hybridization procedures were performed according to the manufacturer's instructions. The raw chromosomal microarray data were analyzed by Affymetrix Chromosome Analysis Suite Software. The pathogenicity of the copy number variants was interpreted according to the American College of Medical Genetics (ACMG) guidelines [Kearney et al., 2011].

Whole Exome Sequencing (WES)

Whole exome sequencing (Illumina, San Diego, CA, USA) was performed for F-001, -004, and -008. Library preparation, cluster generation and sequencing were performed according to manufacturer's protocols. Bcl2fastq tool (v2.15.0.4) was used for extracting Fastq files from Illumina bcl sequencing file. BWA (0.7.10-r789), Picard (v1.128) and Genome Analysis Toolkit (GATK v3.5) were employed for genome alignments and variant detection. The Annovar tool was applied for variant annotation and the copy number variants (CNVs) were analyzed using ExomeDepth (v1.1.4). Common variants were filtered based on their frequencies in the databases of the Exome Aggregation Consortium (ExAC) (<http://exac.broadinstitute.org>), the Exome Sequencing Project (<https://esp.gs.washington.edu>), or 1000G (<http://www.1000genomes.org>), and our internal database. The pathogenicity of the sequence variants was interpreted according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines [Richards et al., 2015].

All data were collected with the informed consent of the patients. Ethical approval for the present study was obtained from Dongguan Maternal and Child Health Care Hospital

Results

The proband had a normal karyotype and a normal *FMR1* repeat number but chromosomal microarray analysis detected a 222 Kb heterozygous microdeletion at 14q24.3q31.1 with genomic coordinates 79,258,267–79,480,738 (GRCh37/hg19), encompassing exons 6–12 of the alpha isoform of *NRXN3* (Fig. 3). The *NRXN3* deletion was also detected in the mother and the maternal grandfather. The other members of the large Chinese family showed

normal copy number in this region. We also performed WES tests for F-001, -004, and -008 to search for variants that might contribute to the phenotype. No clinical significant sequence variants were identified.

Discussion

CNVs involving *NRXN1* have been associated with intellectual disability, language delay, autism, and several psychiatric disorders, in particular, schizophrenia [Feng et al., 2006; Kim et al., 2008; Glessner et al., 2009; Rujescu et al., 2009; Ching et al., 2010; Gauthier et al., 2011; Liu et al., 2012; Gjørnlund et al., 2012; Stessman et al., 2017], indicating a broad phenotypic spectrum for *NRXN* mutations. In the four previously reported pedigrees with *NRXN3* deletion, the deletion carrying probands were all diagnosed with autism. In addition, three of the probands also presented with aggression, anger and anxiety. One deletion-carrying father presented with subclinical autism and one deletion-carrying mother presented with social difficulties, language delay and anxiety but no autism [Vaags et al., 2012]. These data indicated variable clinical presentations of individuals with *NRXN3* deletion, as well as reduced penetrance of *NRXN3* deletion for autism. The exonic *NRXN3* deletion detected in the Chinese family was absent from 5,163 healthy individuals of Chinese ethnicity (<http://database.gdg-fudan.org/>) and 3,397 normal controls in our internal database. We also excluded to the degree possible other known genetic causes of autism in the proband. Based on current evidence, it is reasonable to conclude that this deletion is likely to be causally linked with proband's phenotype. Interestingly, the same CNV deletion was present in the mother, who did not meet the criteria of ASD diagnosis but had language delay, learning difficulties, anxiety, slightly impaired socialization skills as well as difficulty in communication. The proband's deletion-negative younger brother had a normal development. The deletion was also detected in the maternal grandfather who had deficits in language, mild impaired communication and social interaction issues, schizophrenia, temper tantrums, aggressive behavior and anxiety in unfamiliar situations, but did not have a formal ASD diagnosis. The unaffected maternal aunt did not inherit the deletion and had a 10-year-old healthy son. In view of the phenotypes displayed by the proband, mother and maternal grandfather, this pedigree demonstrates co-segregation of this *NRXN3* deletion with neurodevelopmental/neuropsychiatric phenotypes, but also provides evidence for variable expressivity of phenotype associated with *NRXN3* haploinsufficiency.

Deletions involving *NRXN3* have rarely but sporadically been reported in databases and publications, so we compiled and compared these cases in Table 1 and Fig. 4. We compared the phenotypes of all 23 cases carrying *NRXN3* deletions and found that 9 patients (39%) had ASD, as the most consistent feature of individuals with *NRXN3* deletion. Other features included language delay, social difficulties, intellectual disability, ADHD, temper tantrums, anxious, aggressive and obsessive behaviors [Schlade-Bartusiak et al., 2008; Cingoz et al., 2011; Vaags et al., 2012; Griswold et al., 2012; Riegel et al., 2014; Faheem et al., 2015; Nicita et al., 2015; <https://decipher.sanger.ac.uk/>]. Our proband's maternal grandfather was diagnosed with schizophrenia, which was a rare phenotype in *NRXN3* deletion patients. It was interesting to note that our proband had distinctive facial features which had not been described in those patients who carried exonic deletions within *NRXN3*. However, we found that four patients who carried large deletions at 14q24.3-q32 that overlap *NRXN3* and other

genes also presented with facial dysmorphism. We observed that our proband and these four patients shared similar facial features, such as hypertelorism, flat nose bridge, long broad philtrum, auricle dysplasia and mild micrognathia [Schlade-Bartusiak et al., 2008; Cingoz et al., 2011; Riegel et al., 2014; Nicita et al., 2015]. Whether or not the *NRXN3* deletion is responsible for facial dysmorphism requires further investigation.

In conclusion, we identified a rare exonic deletion of *NRXN3* in a three-generation Chinese family. The co-segregation evidence further supported a role for *NRXN3* in autism and other neurodevelopmental/neuropsychiatric disorders. By comparing the clinical phenotypes of all 23 patients with *NRXN3* deletions, we confirmed that patients carrying exonic *NRXN3* deletions display variable clinical features and reduced penetrance for autism. Facial dysmorphism and schizophrenia might be novel phenotypes which need to be further studied.

Acknowledgments

We would like to thank the family of the proband for their cooperation with this study. This study was supported by the Dongguan Social development project (2013108101021; 20161081101023).

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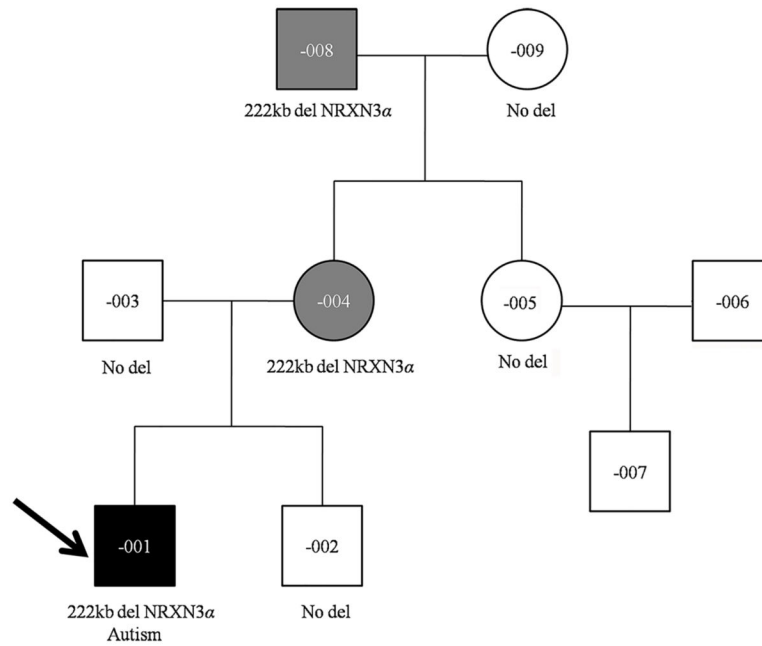


Fig. 1:
Pedigree of our large Chinese family with deletion at the *NRXN3* locus
Black-filled symbol represents ASD affected individual, gray-filled symbols represent affected individuals, and unfilled symbols represent apparently unaffected individuals. Proband is marked with an arrow. Clinical diagnosis and segregation of the *NRXN3* deletion are shown.



Fig. 2:
Clinical pictures of the proband at 7 years old age. Note cranial dysmorphism, high forehead, flat facial profile, auricle dysplasia, widely spaced eyes, blepharoptosis, flat nose bridge, long broad philtrum, dental dysplasia, micrognathia, sparse eyebrows and hair.

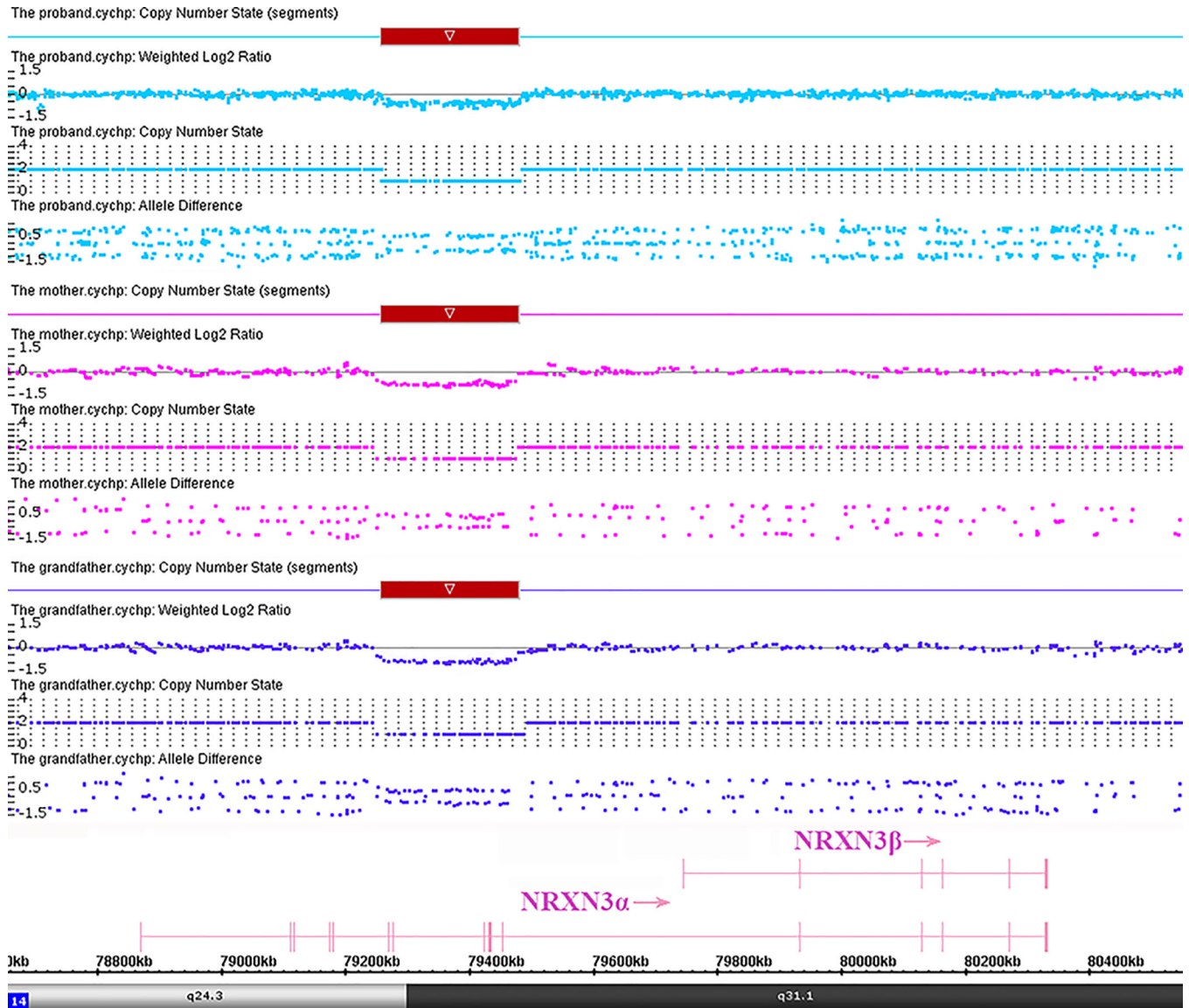


Fig. 3: Affymetrix Cytoscan 750K analysis including weighted log₂ ratio (upper), copy number state (middle) and allele difference (lower) are shown for chromosome 14. The result shows hemizygous microdeletion at 14q24.3q31.1, extending from chr14:79,258,267–79,480,738 (GRCh37/hg19), a region that overlaps exons 6–12 of the alpha isoform of *NRXN3*. The microdeletion region is denoted by a red bar. The *NRXN3* deletions were detected in the proband, the mother and the maternal grandfather.

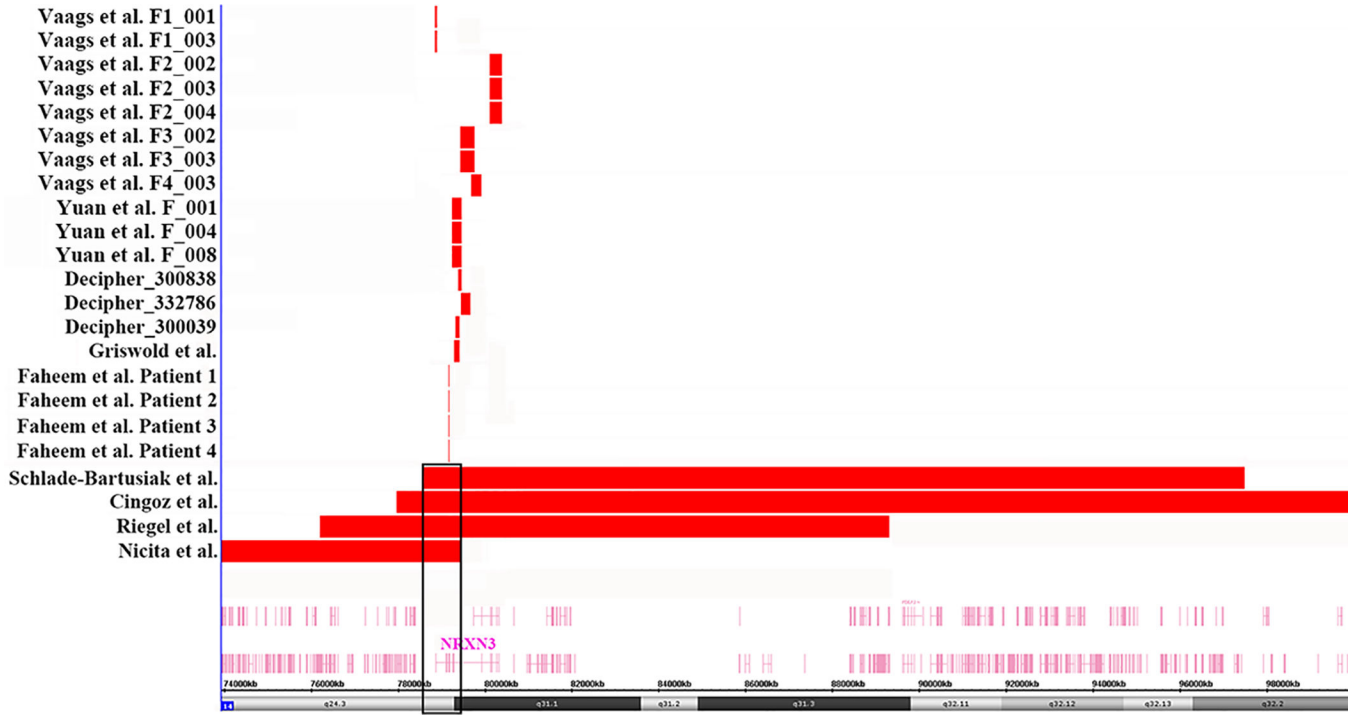


Fig. 4:
The panel shows a genome view of all deletion cases (red colored custom tracks) relative to the genomic coordinates at 14q24.3q31.1 region, extracted from Human Genome Build 37 (hg19). The minimal overlapping region of deletion in the four patients who carry large deletions involves only *NRXN3*, which is surrounded by black boxes.

Table 1.

Clinical features observed in patients with deletion involving *NRXN3*. The genomic coordinates are based on GRCH37/hg19.

Reference	Genomic location	Size	Methods	Origin	NRXN3 exons	Autism	Other phenotype
Our proband	chr14:79258267–79480738	222Kb	microarray	Inherited from mother	exons 6–12 (α)	Yes	ID, ADHD, facial dysmorphism, motor delay, aggression, depression, anxiety
The mother	chr14:79258267–79480738	222Kb	microarray	Inherited from father	exons 6–12 (α)	No	Language delay, social impairments, learning difficulties and anxiety
The maternal grandfather	chr14:79258267–79480738	222Kb	microarray	Unknown	exons 6–12 (α)	No	Schizophrenia, social impairments, temper tantrums, aggression, anxiety
Vaags et al., F1-proband	chr14:78864063–78927002	63Kb	microarray	Inherited from mother	exon 1 (α)	Yes	Aggression, anger, anxiety, depression
Vaags et al., F1-mother	chr14:78864063–78927002	63Kb	microarray	Unknown	exon 1 (α)	No	High energy, social difficulties, anxiety, language-processing difficulties
Vaags et al., F2-proband	chr14:80125165–80416882	292Kb	microarray	Inherited from father	exons 14–17 (α) and 3–7 (β)	Yes	None
Vaags et al., F2-sister	chr14:80125165–80416882	292Kb	microarray	Inherited from father	exons 14–17 (α) and 3–7 (β)	Yes	None
Vaags et al., F2-father	chr14:80125165–80416882	292Kb	microarray	Inherited from father	exons 14–17 (α) and 3–7 (β)	No	Color blind
Vaags et al., F3-proband	chr14:79433698–79769716	336Kb	microarray	Inherited from father	exons 10–12 (α) and 1 (β)	Yes	Aggression, self harm, obsession, delusional and persecutory ideas, sleep issues and obesity
Vaags et al., F3-father	chr14:79433698–79769716	336Kb	microarray	Unknown	exons 10–12 (α) and 1 (β)	No	Learning difficulties, social avoidance, depression, alcohol-related issues
Vaags et al., F4-proband	chr14:79696374–79943510	247Kb	microarray	De novo	exon 13 (α) and 1–2 (β)	Yes	Aggression, anger, anxiety, temper tantrums
Faheem et al., Patient 1	chr14:79176037–79183213	7.2Kb	microarray	De novo	exon 5 (α)	No	Developmental delay, seizure
Faheem et al., Patient 2	chr14:79176037–79183213	7.2Kb	microarray	De novo	exon 5 (α)	No	ID, ADHD, difficulty in communication
Faheem et al., Patient 3	chr14:79176037–79183213	7.2Kb	microarray	Unknown	exon 5 (α)	No	Seizure, motor delay, obsession
Faheem et al., Patient 4	chr14:79176037–79183213	7.2Kb	microarray	Unknown	exon 5 (α)	Yes	ID, seizure
Decipher 300039	chr14:79328112–79433755	106Kb	microarray	Inherited from mother	exons 8–10 (α)	Yes	GDD
Decipher 300838	chr14:79388255–79473346	85Kb	microarray	Unknown	exons 8–12 (α)	No	ID, behavioral abnormality
Decipher 332786	chr14:79448118–79683009	235Kb	microarray	De novo	exons 12 (α)	No	GDD, hypotonia, seizures
Griswold et al., patient	chr14:79303752–79436470	133kb	microarray	Inherited from mother	exons 8–11 (α)	Yes	NR
Nicita et al., patient	chr14:73939850–79446043	5.5Mb	microarray	De novo	exon 1–11 (α)	No	Developmental delay, language delay, dysmorphic face, seizures
Riegel et al., patient	chr14:76211806–89327656	13Mb	microarray	De novo	the whole <i>NRXN3</i>	No	ID, ADHD, motor delay, language delay, dysmorphic features, hypotonia

Reference	Genomic location	Size	Methods	Origin	NRXN3 exons	Autism	Other phenotype
Schlade-Bartusiak et al., patient	14q24.3q32.2	19Mb	FISH	De novo	the whole <i>NRXN3</i>	No	GDD, short stature, absent speech and auditory neuropathy, minor dysmorphic features, feeding difficulty, hypotonia
Cingoz et al., patient	14q24.3q32.2	21Mb	FISH	De novo	the whole <i>NRXN3</i>	No	ID, no speech, motor delay, facial dysmorphism, short stature, hypotonia

ID intellectual disability, *ADHD* attention deficit hyperactivity disorder, *GDD* global developmental delay