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CASE REPORT

A chromosomal microdeletion of 15q in a female patient with epilepsy, ID, and autism spectrum disorder: a case report

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Key Clinical Message

15q deletions have been described in association with intellectual disability and autism spectrum disorder (ASD). Previous reports have supported the role of 15q24 low copy repeats (LCRs) in mediating alternatively sized genomic rearrangements. Based on our reported finding of a 15q24 deletion coinciding with two LCR regions in a patient with epilepsy and ASD, we recommend that patients with 15q24 deletions be evaluated for ASD for early institution of therapy.

Keywords

Autism, clinical genetics, copy number variation, epilepsy, intellectual disability.

Introduction

Autism spectrum disorder (ASD) is comprised of a heterogeneous group of neurodevelopmental diseases characterized by impaired social interaction, repetitive behavior, and a remarkably rising global prevalence rate [1]. ASD is associated with intellectual disability (ID) in approximately 75% of patients and with epilepsy and/or EEG abnormalities in 20% of cases [2, 3]. The observed increased recurrence risk in families and concordance in twin pairs indicate a strong role for genetics in ASDs [4, 5].

The case presented here is part of a large body of family-based studies aimed at identifying rare, chromosomal abnormalities in complex, neurodevelopmental disorders [6]. Constitutional copy number variants (CNVs) affecting particular regions of the genome have been reported in association with epilepsy [7]. These include various deletions and duplications involving both single as well as subsets of genes [8]. Inherited or de novo CNVs account for as many as 1–3% cases of idiopathic ASD identified, reviewed by [9]. Pathogenic CNVs can be recurrent, arising by nonallelic homologous recombination among LCRs, or nonrecurrent arising from DNA replication errors, leading to dosage-sensitive gene loss or gain [10]. Most nonrecurrent CNVs are simple deletions or duplications; however, some are complex chromosomal rearrangements affecting a single or multiple chromosomal regions [11]. Studies of multiplex families have shown that patients with combined intellectual disability and epilepsy present with a threefold increase (10% vs. 3%) in epilepsy-associated CNVs than patients with epilepsy alone [12].

Here, we report a female patient with ASD, ID, and epilepsy presenting with a 2.5 Mb deletion of the long

arm of chromosome 15 (46,XX [del(15) q24.1-q24.2]). This case is part of a larger family-based study aimed at identifying gene variants associated with ASD and epilepsy phenotype.

Clinical Picture

The proposita is a six-year-old girl of Arabic ethnic origin, delivered at full term by Caesarean section with a birthweight of 2.7 kg. She sat without support at 8 months, crawled at 10 months, and walked at 18 months. She had a two-word vocabulary by the age of 3 years which she lost since then. The family history is positive for a mother with migraine and history of febrile convulsions as a child and the parents are third cousins.

At the age of 8 months, she presented with three episodes of generalized tonic–clonic seizures, one of which was febrile. She was treated with valproic acid with good seizure control that prompted its withdrawal after a seizure-free period of 4 years.

At 42 months of age, her cognitive development was assessed and she was diagnosed with developmental delay by CAPTURE (CAT/CLAMS) scale. Her behavioral development leads to the diagnosis of pervasive developmental disorder – not otherwise specified (PDD-NOS) by Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS).

Currently, her head circumference is 50.5 cm, which is at the 50th percentile and has no demonstrable dysmorphic features or associated congenital anomalies. She demonstrates considerable hyperactivity, communication deficits, abstract thinking, poor interaction with other children, and stereotypical patterns of behavior. She is nonverbal and uses pointing and gestures to communicate with her family. She is toilet trained.

Molecular Evaluation

The presented case is part of a larger study aimed at investigating ASD, ID, and epilepsy-associated gene variants. The case cohort consists of 34 families containing one or more, clinically ascertained, affected offspring. DNA was extracted from peripheral blood of the patients and available parents after obtaining informed consent. The consent forms and the research project were approved by the Qatar Biomedical Research Institute Institutional Review Board (QBRI-IRB), agreeing to the accords of the Declaration of Helsinki. Fragile-X (*FMR1*) and Rett syndrome (*MECP2*) were ruled out by molecular, diagnostic testing.

Genomewide SNP genotyping was done utilizing the OmniExpress array (700K) on the Illumina (San Diego, California) platform. Genotyping quality assessment, SNP calling and copy number variation (CNV) analysis were performed using the GenomeStudio V.2011 software (California, USA) (GRCh37/Hg19). Analysis of genomewide SNP array data revealed a de novo 2.52 Mb deletion (chr15q:72.97–75.48 Mb). The deletion is demarcated by the markers (rs12441929, rs11636245) and contains 47 protein-coding genes.

To confirm the identified deletions, quantitative real-time PCR (qRT-PCR) was performed using the SYBR® Green PCR Master Mix on a 7900 Fast Real-Time PCR system (Applied Biosystems, Foster City, CA). Primer sets were designed using the web-based tool Primer3 (http://bioinfo.ut.ee/primer3/) to amplify two exons contained within the deletion in the genes (*NPTN*, exon 4, 426 bp and *SEMA7A*, exon 9, 388 bp) and two intronic regions peripheral to the deletion (chr15q:72.96 Mbp, 509 bp; 75.48 Mbp, 417 bp) (Table S1). Copy number values were normalized against the house-keeping gene (*GAPDH*, exon 5–6, 384 bp).

The exonic fragments amplified within the deleted region showed one copy in the affected patient and two copies in both parents, thereby confirming the de novo deletion identified using SNP genotyping analysis (Fig. 1).

The identified CNVs were systematically compared to CNVs present in the Database of Genomic Variants (DGV) (http://dgv.tcag.ca/dgv/app/home) to assess its frequency in control populations. The CNV was considered novel because it did not overlap entirely with any CNVs reported in the database. No duplications matching or overlapping with the deletion identified here were found in control population studies upon searching the DGV database.

Furthermore, the identified CNV was compared to CNVs reported to cause known chromosomal imbalance syndromes that are documented in DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources) GRCh37 (https://decipher.sanger.ac.uk/index). Multiple reports of overlapping duplications on chromosome 15 in patients with comparable phenotypes, including seizures, autistic features, and intellectual disability, were identified (Table 1).

Using the SFARI database for ASD candidate genes, a number of chromosome 15 genes that have been implicated in various forms of de novo or inherited ASD, epilepsy, and/or intellectual disability were identified [13] (Table S2).

Discussion and Conclusion

Here, we report a female patient with clinical presentations of epilepsy, ASD, ID, and motor delay, in whom a 15q deletion was identified.

Studies have demonstrated a higher frequency for large, rare (frequency <1%), de novo CNVs in patients with ASD from consanguineous, simplex families than from

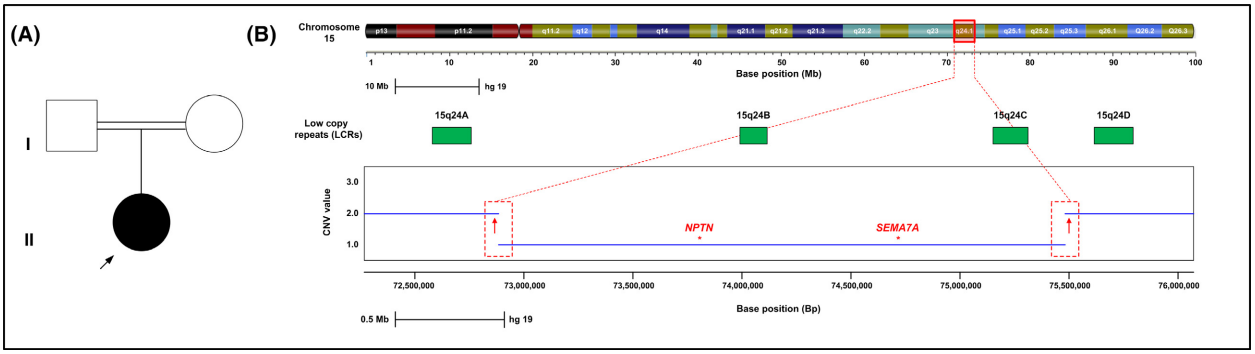

Figure 1. Illustration of pedigree investigated and qRT-PCR analysis. (A) Pedigree schematic showing clinically unaffected (unshaded) parents and affected (shaded) proband. Circle and square symbolize female and male gender, respectively. (B) qRT-PCR analysis of two regions (↑) 72.96 Mbp and 75.48 Mbp, peripheral to the (chr15q:72.97–75.48) deletion reveals two copies in the proband and parents. qRT-PCR of (*) marked regions at positions (*NPTN* exon 4, 73.87 Mbp) and (*SEMA7A* exon 9–10, 74.71 Mbp) revealed one copy in the proband relative to the parents, indicative of a de novo deletion. Four (LCR15q24A, LCR15q24B, LCR15q24C, and LCR15q24D) of the five reported LCR regions are shown according to scale. The breakpoints of the identified deletion coincide with two (LCR15q24A, LCR15q24C) of the reported LCRs.

Table 1. Chromosomal duplications reported in the DECIPHER database.

CNV	Size (Mb)	Number of genes	Inheritance	Chromosomal makeup	Clinical phenotype
Loss chr15:73483899-75762535	2.28	56	*DeNovo*	46XX	Anal atresia, Inguinal hernia, Intellectual disability, Proximal placement of thumb, Seizures, Small for gestational age
Loss chr15:71959135-75893502	3.93	82	*DeNovo*	46XY	Abnormality of the foot, Abnormality of the kidney, Abnormality of the outer ear, Adducted thumb, Brachycephaly, Coarctation of aorta, Conductive hearing impairment, Low-set ears, Pointed chin, Slender finger, Ventricular septal defect, Wide nasal bridge
Loss chr15:72963970-75535330	2.57	49	*DeNovo*	46XY	Abnormality of the thumb, Broad nasal tip, Delayed speech and language development, Frontal bossing, Hearing impairment, Intellectual disability, Long face, Pointed chin, Seizures, Slender finger
Loss chr15:72884575-75753300	2.87	65	*DeNovo*	46XY	Hip dysplasia, Hydrocephalus, Intellectual disability, Laryngomalacia, Meningomyelocele
Loss chr15:72907808-75166304	2.26	43	*DeNovo*	46XX	Global developmental delay
Loss ch15:72963770-75434301	2.47	47	*DeNovo*	46XY	Intellectual disability
Loss chr15:70788924-73322524	2.53	31	*Unknown*	46XY	Broad forehead, Mild global developmental delay

Chromosomal deletions with similar clinical presentations reported to overlap with (chr15: q24.1-q24.2) in the DECIPHER database. The size, number of genes, inheritance, chromosomal makeup, and clinical phenotype for each reported deletion is shown.

nonconsanguineous or multiplex families [14]. These findings suggest a role for inherited risk factors in families with shared ancestry, such as the case described here, and provide evidence for the contribution of de novo variants with large effects to ASD liability. Furthermore, although a strong male bias in ASD has been reported, females with ASD are thought to be carriers of a higher heritable etiological/genetic load [15]. Subsequently, a higher proportion of large, de novo CNVs disrupting a greater number of genes has been noted in ASD female cases than in males [16]. These findings correspond to the de novo case identified here.

Reported key features of 15q24 microdeletion syndrome include developmental delay, atypical facial appearance, growth retardation, microcephaly, bowel anomalies, hearing loss, hypotonia, and dysmorphic and congenital malformation [17, 18]. Unlike these reported cases, the case presented here did not display any of the hallmark physical malformations of 15q24 deletion, but did present with several of the major cognitive findings reported due to deletions overlapping with the one reported here, including developmental delay, ID, seizures, and ASD [19, 20]. Our findings are also supported by several cases with overlapping chromosome 15

duplications reported in the DECIPHER database that present with comparable neurological phenotypes and no gross dysmorphic presentations (Table 1). The observed disease phenotype in this patient may also be explained by findings of genes previously implicated in ASD in the deleted region identified including *BBS4*, *UBL7,* and *RPP25* may explain (Table S2) [21–23].

Several low-copy repeat clusters (LCRs) that likely mediate the formation of alternatively sized 15q24 genomic rearrangement have been mapped across the region [24]. The proximal and distal breakpoints of the deletion identified here fall within two of the five reported 15q24 LCR regions (LCR15q24A and LCR15q24C). The deletion also overlaps with a duplication reported by the same authors [24]. This finding lends further support to the involvement of the mapped 15q24 LCRs in CNV formation.

In conclusion, the findings presented here demonstrate the genetic as well as phenotypic heterogeneity of complex neurodevelopmental disorders due to copy number variations (CNVs).

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Authorship

All authors on this manuscript have contributed toward the research presented. DFA: performed and interpreted all molecular analyses and wrote the manuscript. YS: contributed the analysis and interpretation of chromosomal copy number variation investigation. RZT: contributed to the validation of the identified CNV using qRT-PCR. SFE and FAA: contributed to clinical phenotyping and ascertainment. MK: was involved in molecular data analysis, interpretation, and manuscript writing. HE: was in charge of clinical ascertainment and recruitment of the family as well as molecular data analysis, interpretation, and manuscript writing.

Conflict of Interest

We would like to declare that none of the participating authors have any competing interests to disclose.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Details of primers utilized in qRT-PCT analysis.
Table S2. Genes reported in the SAFARI gene database to be implicated in ASD on chromosome 15 and a list of additional, supplementary references, which appeared in Table S2.
Data S1. Supplementary Data File.

