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Original Article

A familial 3q28q29 duplication induced mild intellectual disability: case presentation and literature review

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Abstract: The 3q29 duplication syndrome is an uncommon imbalanced chromosomal disorder with highly variable manifestations, mainly characterized by a mild mental anomaly, eye abnormalities, and developmental delay. Only a few such cases have been reported with significant phenotypic heterogeneity. Here, we reported a case with familial 3q28q29 duplication that was 8.5 Mb in length, covering all fragments from previous reports. A series of genetic detection techniques, including karyotyping, chromosomal microarray, and fluorescence in situ hybridization, demonstrated that the rearrangement, in this case, was due to a three-chromosome translocation of the paternal grandmother of the fetus. Interestingly, only mild intellectual disability in the father and slightly thick nuchal translucency (NT) in the fetus were observed. The fetus was delivered at term and showed normal developmental milestones. Our study increased the understanding of this syndrome and highlighted the necessity and importance of the rational use of multiple genetic techniques in prenatal diagnosis.

Keywords: 3q29 duplication, intellectual disability, SNP array, fluorescence in situ hybridization

Introduction

With the advancements in molecular cytogenetic techniques, many novel chromosomal rearrangements and copy number variations (CNVs) have been identified and recognized as phenotype-causing [1, 2]. For genome-wide assessment of CNVs, techniques like array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) array are considered to be first-tier methods for the postnatal evaluation of individuals suffering from intellectual disability, developmental delay, autism spectrum disorder, and/or multiple congenital anomalies, where the prenatal evaluation and detection of structural anomalies of fetuses are performed using ultrasound [3-5]. Specifically, although microdeletions and microduplications are both induced by the same mechanism that involves non-allelic homologous recombination and region-specific low copy repeats [6], the pathogenicity of the latter is less commonly recognized or reported, probably because of ascertainment bias and milder and/or more variable phenotypes [7].

The 3q29 microduplication syndrome (MIM #611936), first described by Lisi et al. in 2008, is characterized by mild to moderate mental retardation and mild dysmorphic characteristics [8]. Clinical features of this condition include microcephaly, round face, bulbous nose, short or downward-slanting palpebral fissures, excessive hand creases, and pes planus [8]. The phenotypic heterogeneity of the 3q29 microduplication syndrome makes it difficult to define a recognizable pattern and challenges appropriate genetic counseling and procreation guidance [9]. The phenotypic spectrum of the syndrome includes ocular defects like microphthalmia/aniridia, myelomeningocele and midline cranial defects, ventricular septal defect, palatal, renal, and structural brain anomalies, and musculoskeletal anomalies (chest-wall and finger deformities) [7, 8, 10, 11]. The psychiatric characteristics might be rare and subtle, mainly

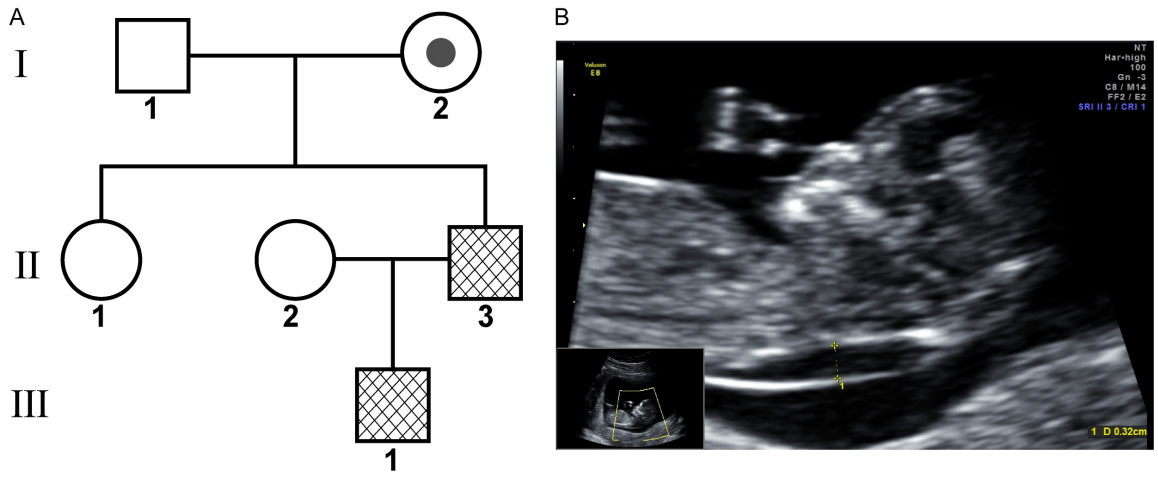

Figure 1. Clinical indications in the case. A. Pedigree diagram of the family. B. The fetus (III-1) in this case showed a thickened NT at 12w6d of gestation.

manifested as attention-deficit/hyperactivity disorders, elimination disorders, and autism spectrum disorder [12]. Additionally, this condition follows an autosomal dominant inheritance pattern, so the offspring of patients have a 50% chance of being affected.

In this study, we enrolled a case with abnormal prenatal fetal indication and performed a comprehensive clinical evaluation and genetic detection of the extended family. A novel familial 3q28q29 duplication of 8.5 Mb, covering the entire core region of 3q29 microduplication syndrome, was identified and verified. However, it only caused mild intellectual disability in an adult carrier in the family. By full informed consent, the couple decided to continue the pregnancy with this genetic rearrangement, and a clinical follow-up was conducted.

Materials and methods

This study was reviewed and authorized by the Ethics Committee of the Beijing Haidian Maternal and Child Health Hospital (Approval No. 2021-23). All participants signed the informed consent. The procedures related to human participants in the research followed the Declaration of Helsinki 1964, its subsequent amendments, and similar ethical criteria.

Subjects

A 23-year-old woman with pregnancy at the 18th gestational week was referred to our center because the fetus was diagnosed with thick nuchal translucency (NT) at 12w6d (**Figure 1B**). Her husband was 25 years old with seemingly normal physical signs. The pregnant woman denied that she and her husband had a family history of any genetic condition. Routine clinical tests, such as amniocentesis and prenatal genetic diagnosis, were recommended. At the 20th gestational week, amniocentesis was performed to collect fetal samples. Then, peripheral blood samples of the couple and extended family members were also collected for follow-up tests.

Chromosomal karyotyping

Conventional G-banding technology was used for sampling the fetus and the other members to determine chromosomal abnormalities based on the AGT cytogenetics laboratory manual [13]. Standard laboratory procedures included PHA and colchicine-stimulated lymphocyte cultivation, chromosome specimen preparation, digestion via trypsin, G-band staining, and karyotype analysis, as per ISCN-2016 [14].

Chromosomal microarray analysis (CMA)

Genomic DNA extraction from fetal and paternal samples was performed with the QIAamp DNA Blood Mini Kit (Qiagen GmBH, Hilden, Germany), following the specifications of the manufacturer. Chromosomal microarray analysis (CMA) was conducted as previously described [15]. Briefly, a CytoScan 750K (Affymetrix, USA) microarray was used for

testing genome-wide copy number variations (CNVs), loss of homozygosity (LOH), uniparental disomy (UPD), and mosaicism, following the specifications of the manufacturer. The Affymetrix Gene Chip Command Console software (version 4.0) and Chromosome Analysis Suite (version 2.1) (Affymetrix, USA) were used to analyze the raw data. The obtained data were entered into the UCSC database (http://genome.ucsc.edu) for analysis and compared with the DGV database (http://projects.tcag.ca/variation), using the phenotypic DECIPHER database (https://decipher.sanger.ac.uk/), PubMed database (www.ncbi.nlm.nih.gov/pubmed/), and the OMIM database (www.ncbi.nlm.nih.gov/omim) to determine the pathogenicity of specific CNVs.

Fluorescence in situ hybridization (FISH)

Fluorescence *in situ* hybridization (FISH) was conducted with probes of 3pter/3qter and 20pter/20qter (Cytotest, USA) on the fetal and paternal metaphase cells.

Results

Clinical manifestation

The pedigree diagram is shown in **Figure 1A**. The fetus (III-1) displayed a slight thickness of the NT (0.32 cm) at the end of the first trimester (12w6d); during the second and third trimesters, there was no ultrasonic anomaly. So, the couple made a fully informed choice to continue this pregnancy. A boy was delivered after 39 weeks of gestation with normal birth weight. The Apgar score was 10 at 1 min, 5 min, and 10 min. Developmental milestones were normal at 42 days, three months, six months, and one year of age, and the boy had started to walk and develop normal speech. The father scored 70 by the standard Wechsler Intelligence Scale and was recognized as having a mild intellectual disability. Other members of the family had no obvious abnormalities, and the follow-up was continued.

Genetic findings

Initially, the karyotype of the III-1 was recognized as 46,XY,?der(20) (**Figure 2F**) because the exact source and the rearrangement form of the der(20) chromosome were not clear. The subject II-3 carried a similar derivative chromosome 20 as the fetus (**Figure 2E**), while the karyotype of II-2 was normal (**Figure 2D**). Through extensive investigation, we found that the paternal grandmother (I-2) could be a carrier for a triple-chromosomal reciprocal translocation involving chromosomes 3, 6, and 20, denoted by 46,XX,t(3;20;6)(q28;p13;p11.2) (**Figure 2B**). Thus, the der(20) was inherited from I-2 to II-3 and III-1, while the other derivative chromosomes were not transmitted.

Further validation experiments were conducted with the CMA and FISH methods on subjects II-3 and III-1. CMA identified a 8.5 Mb 3q28q29 microduplication, namely arr[hg19] 3q28q29(189,336,472-197,851,444)x3, and a 342.7 Kb 20p13 microdeletion, namely arr[hg19] 20p13(61,661-404,435)x1, in both the subjects (**Figure 3**). The 3q28q29 duplication covered the entire region of the 3q29 duplication syndrome [8], so it was determined as "pathogenic"; the clinical significance of the 20p13 microdeletion was uncertain. To verify the CMA result, FISH was conducted with 3pter/3qter and 20pter/20qter probes on subjects II-3 and III-1. The results indicated that they both carried an extra signal of the 3q probe. Hence, it was interpreted as ish der(20) t(3;20)(3q+,20p+,20q+) (**Figure 4**).

The karyotype of each subject was conclusively found to be 46,XY,der(20)t(3;20)(q28;p13) pat for III-1, 46,XY,der(20)t(3;20)(q28;p13) for II-3, and 46,XX,t(3;20;6)(q28;p13;p11.2) for I-2 (**Figure 2**).

Discussion

There is a risk of misdiagnosis and missed diagnosis during prenatal genetic diagnosis, especially for cryptic and complex structural variations. Multiplatform techniques and extensive family verification should be combined for a definitive diagnosis [15].

The 3q29 duplication syndrome, which was sporadically reported initially [16, 17], was not recognized as a syndrome till Lisi et al. summarized it [8]. Currently, over 35 cases with this condition have been reported [9, 18]. In the largest survey cohort to date, Pollak et al. concluded that patients of 3q29dup frequently encountered problems in the first year (80.6%),

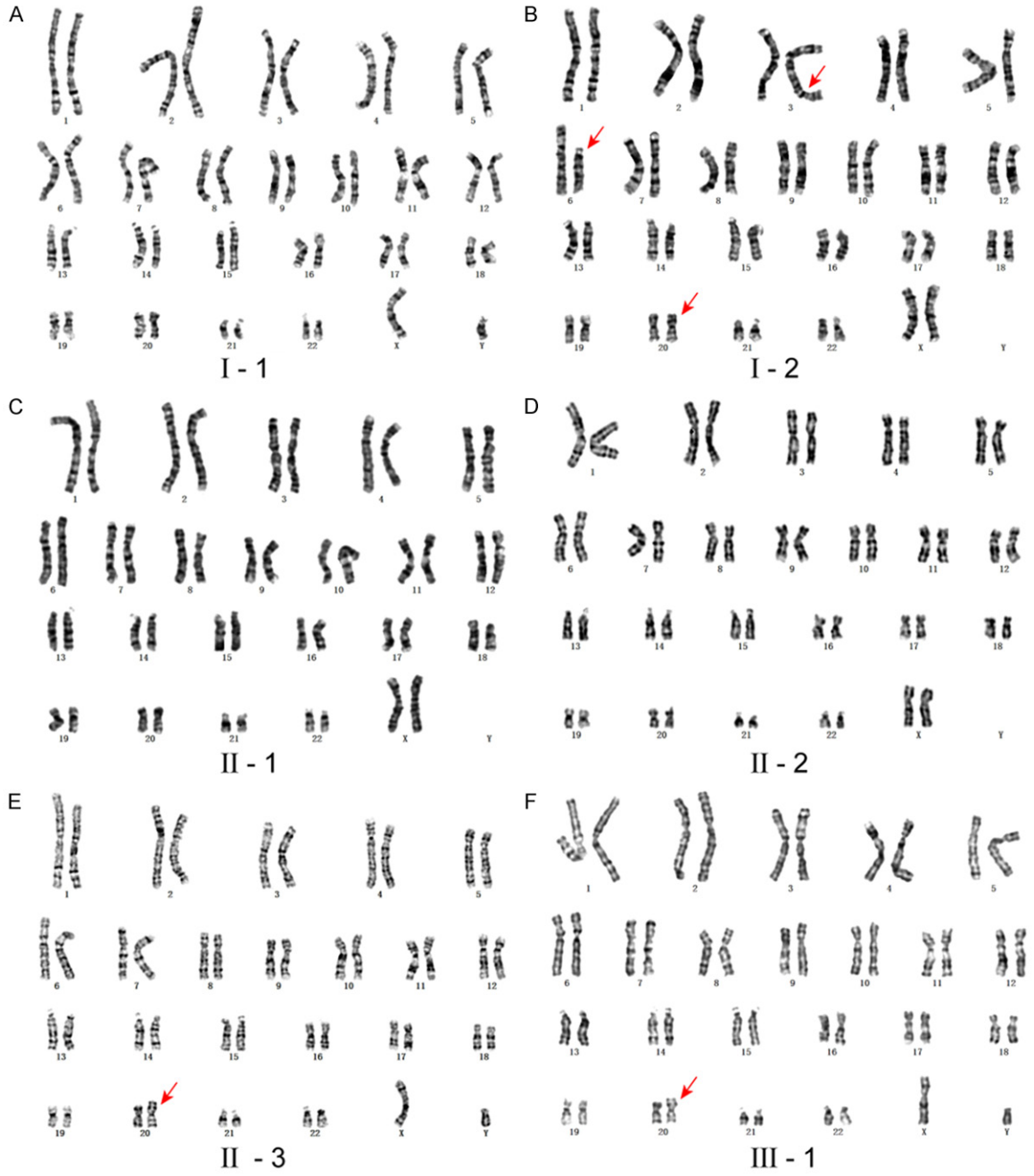

Figure 2. The karyotypes of key members of the family. A. Subject I-1: 46, XY. B. I-2: 46, XX, t(3;20;6)(q28;p13;p11.2). C. II-1: 46, XX. D. II-2: 46, XX. E. II-3: 46, XY, der(20)t(3;20)(q28;p13). F. III-1: 46, XY, der(20)t(3;20)(q28;p13)pat. Red arrows indicate the rearranged chromosomes.

such as feeding problems (55%), inability to gain weight (42%), hypotonia (39%), and respiratory distress (29%); while in early childhood, learning problems (71.0%) and seizures (25.8%) were common. Moreover, the self-reported autism spectrum disorder diagnosis rate (39%) was considerably higher than that of ordinary people, indicating the correlation of 3q29 duplication with an autism susceptibility locus [18]. Representative studies on 3q29dup and key information from such studies are summarized in **Table 1**. Goobie et al. proposed that the dosage effect of this segment was important for eye and cognitive development and that CNV of other segments might play a role in phenotypic changes. They proposed a set of recommended management guidelines for the disease [7]. Tassano et al. presented

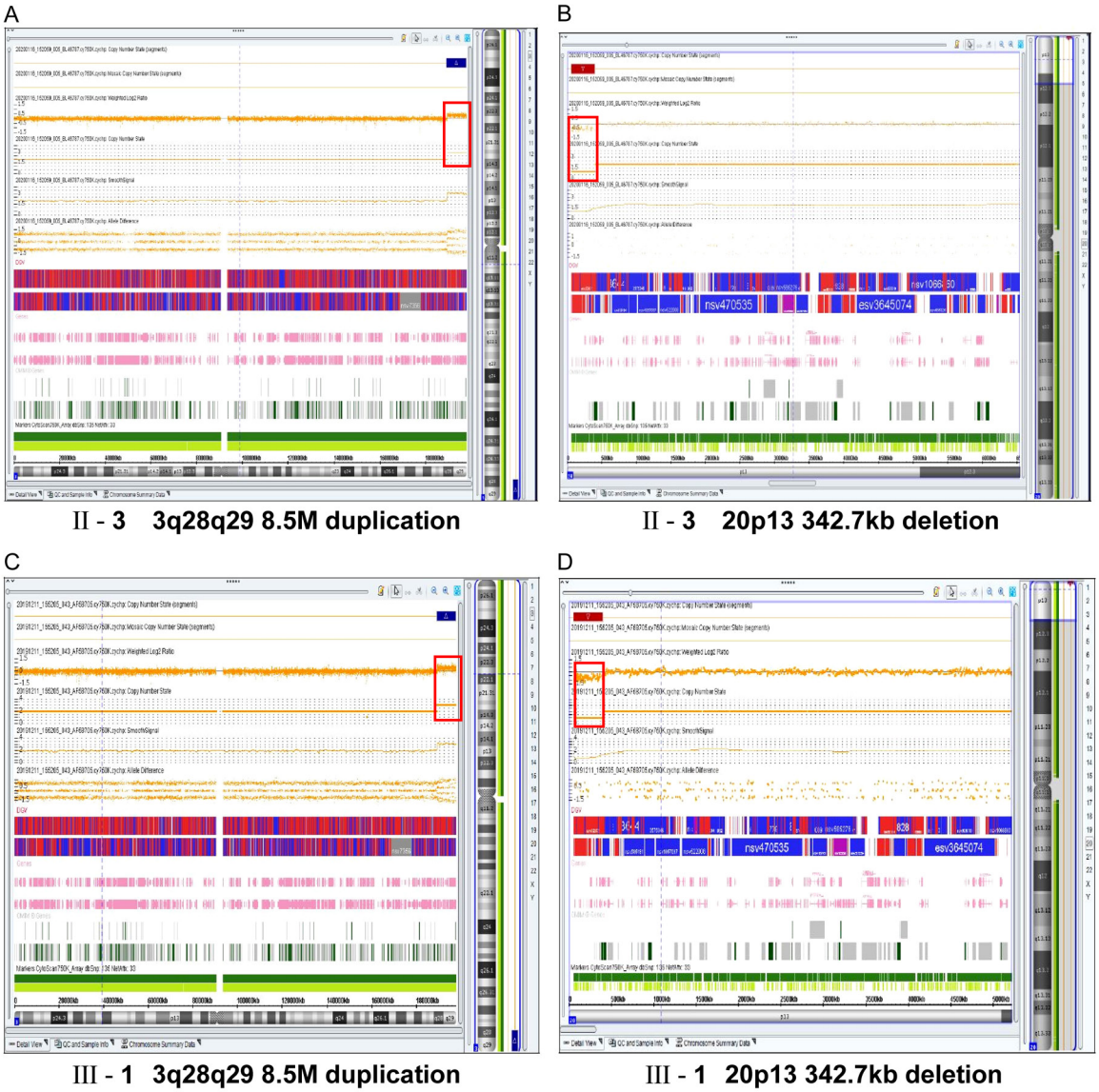

Figure 3. The diagnostic results of CMA of the subjects II-3 (A, B) and III-1 (C, D). Both individuals had a 8.5 Mb 3q28q29 microduplication, arr[hg19] 3q28q29(189,336,472-197,851,444)x3 (A, C), and a 342.7 Kb 20p13 microdeletion, arr[hg19] 20p13(61,661-404,435)x1 (B, D). Red blocks indicate the duplicated or deleted regions.

a case with a short duplicated segment of 448.8 kb, including the *DLG1* and *BDH1* genes, indicating that gain-of-dosage of these two genes was sufficient for the major clinical features related to the syndrome [19]. Ohshiro et al. demonstrated that in Drosophila, *Dlg* can mediate cortical protein targeting in mitotic neuroblasts differently during a common process [20]. Cotter et al. found that for Schwann cells, mammalian *Dlg1* interacts with *Pten* to prohibit axonal stimulation for myelination [21]. The *BDH1* expression level in the developing murine cortex reduces during later phases of cortex maturation [22]. In another case, Vinas-Jornet et al. detected a duplicated segment of 490 kb, containing key genes like *PAK2* and *FBXO45* [23]. *PAK2* is closely related to cerebral cortex development and might be a core determining factor of the mental phenotype [24, 25], while *FBXO45* affects the development of the central and peripheral nervous systems [26].

This study was the first to report a hereditary imbalanced 3q28q29 duplication resulting from a complex balanced translocation of

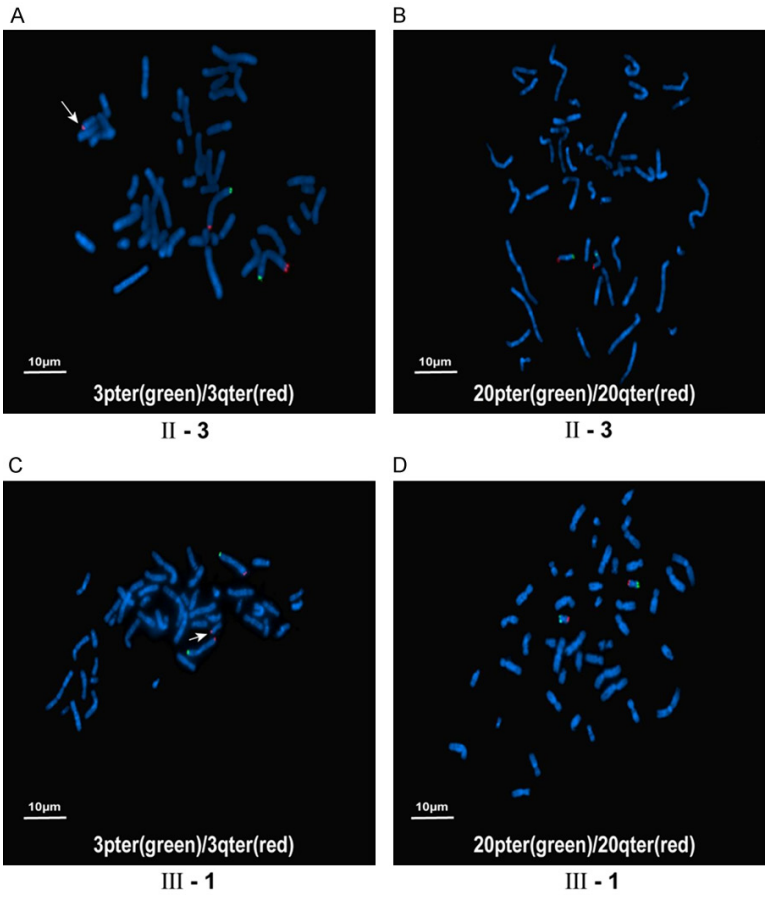

Figure 4. FISH results of the subjects II-3 (A, B) and III-1 (C, D). (A) Probe signals of 3pter (green) and 3qter (red) indicate an extra 3qter in II-3. (B) Probe signals of 20pter (green) and 20qter (red) are normal in II-3. (C) Probe signals of 3pter (green) and 3qter (red) indicate an extra 3qter in III-1. (D) Probe signals of 20pter (green) and 20qter (red) are normal in III-1. White arrows indicate the derived chromosome carrying the extra 3qter signal.

three chromosomes, and the size of the duplicated segment was 8.5 Mb, which covered all of the previously reported regions accounting for the 3q29dup syndrome. However, it only caused mild intellectual disability in an adult and no other significant abnormalities. This suggested that the phenotype is probably regulated by other factors, either genetic or environmental. Moreover, the thick NT symptom had not been discussed previously and might provide hints about this syndrome in early pregnancy. The duplicated region contains 108 genes, including those mentioned above and 14 OMIM genes (Table S1). We also considered the possible effect of 20p12 microdeletion on the phenotype. There are 13 genes in that fragment, including one OMIM gene (*RBCK1*), associated with the autosomal recessive polyglucosan body myopathy 1 in the presence or absence of immunodeficiency that causes the onset of progressive proximal muscle weakness in childhood, causing difficulties in ambulation (Table S1) [27].

We recommended an MRI of the brain to be conducted at an appropriate time to ensure normal brain development and to pay attention to the development of vision and hearing. Goobie's suggestions for long-term health monitoring and early intervention services should be referred to [7]. Additionally, we suggested that a full-length sequencing of *RBCK1* should be performed to avoid missing a possible variation in another allele. The recurrent risk for further pregnancy of this couple is unpredictable, and thus, we recommended that necessary measures should be taken, including prenatal and pre-implantation diagnoses.

The limitation of this study is that the root cause of the mild intellectual disability in the adult patient could not be accurately measured, and a genotype-phenotype association could not be established in the same way. Further studies on the functions of the above genes associated with central neural development are important to understand the pathogenesis of this syndrome.

In conclusion, we reported an inherited 3q28q29 duplication arising from a complex three-chromosome translocation using a multiplatform genetic approach and reviewed the important studies on 3q29 duplication. Our study highlighted the need and importance of the rational use of multiple genetic techniques in prenatal diagnosis.

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Table 1. The 3q29 duplication cases reported in representative literature

Authors; year	PMID*	Size (Range) of duplication*	Number of patients	Detection methods*	Clinical manifestations*
Rooms et al.; 2006	16451137	NA	2	MLPA	Case 1: moderate ID, behavioral problems Case 2: mild mental retardation, some dysmorphic features, and neurological signs
Rosenberg et al.; 2006	15980116	0.4 Mb (probe GS-196F4 to GS-56H22)	1	aCGH; FISH	Moderate ID, facial dysmorphism, ataxia
Lisi *et al.*; 2008	18241066	~1.61-1.8 Mb (Chr3: 197,145,041_198,910,079)	5 in one family	G-banding; FISH; aCGH; SNP array	Mild to moderate ID; microcephaly
Goobie *et al.*; 2008	19287140	~1.9-2.4 Mb (range varies)	7 from 4 families	G-banding; FISH; aCGH; SNP array; MLPA	(Variable) mainly developmental delay and significant ophthalmological anomalies
Ballif *et al.*; 2008	18471269	200 kb-2.4 Mb	19	aCGH	7 patients: mild to moderate ID (common); craniosynostosis, high palate, seizures, and ventricular septal defect (each found twice)
Fernandez-Jaen *et al.*; 2014	24838842	1.607 Mb (Chr3: 195,731,956_197,339,329)	1	SNP array	Cerebral palsy, epilepsy, and severe intellectual disability
Lawrence *et al.*; 2017	28763312	2.94 Mb (Chr3: 195,495,220_197,851,986)	1	SNP array; FISH	Neonate: a lower lumbar and sacral kyphosis, myelomeningocele, nerve root-injury, dilation of the lateral ventricles, pulmonary hypertension, hypoplastic in Right cerebellar hemisphere andoptic nerves
Tassano *et al.*; 2018	29501613	~1.89 Mb (Chr3: 195,633,970_197,532,175); 448.8 Kb (Chr3: 196,892,527_197,339,329)	2	aCGH	Case 1: mental and developmental delay; autism spectrum disorder; scattered nodules of heterotopic gray matter Case 2: dyslalia, celiac disease, growth failure, microcephaly, mild inferior vermis hypoplasia
Vinas-Jornet *et al.*; 2018	29882083	492 kb [(Chr3: 196,022,728_196,515,371)×4, mat-pat]	2	CMA	Case 1: mild ID, post-traumatic stress disorder, facial dysmorphology Case 2: severe ID, autism spectrum disorder
Zhang et al.; 2018	29467824	9.0 Mb (Chr3: 188,823,885-197,851,986)	1	G-banding; FISH; SNP array;	With a 1.7 Mb deletion at22q13.33 Mental and motor developmental delay, facial dysmorphism
Reis et al.; 2020	32269882	Not mentioned	1	aCGH	Moderate ID, psychiatric anomaly (emotional dysregulation, incoherence)
Streata *et al.*; 2020	32874693	~1.65 Mb (Chr3: 195,979,518_197,638,922)	1	aCGH	Late-onset, mild ID, progressive cortical atrophy, recurrent mucosal infections with *Candida albicans*

*PMID, PubMed ID (https://pubmed.ncbi.nlm.nih.gov/). NA, not applicable; FISH, fluorescence in situ hybridization; aCGH, array comparative genomic hybridization; MLPA, multiplex ligation-dependent probe amplification; QF-PCR, quantitative fluorescent polymerase chain reaction; SNP, single nucleotide polymorphism; ID, intellectual disability.

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Disclosure of conflict of interest

None.

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