Clinical Case Report

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Prenatal diagnosis of a 5q35.3 microduplication involving part of the *ADAMTS2* locus: a likely benign variant without apparent phenotypic abnormality

Case series

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Abstract

Rationale: Chromosomal duplications are associated with a series of genetic disorders. However, chromosome 5q duplications, especially pure 5q35.3 microduplications, have rarely been reported in the literature. Clinical phenotypes usually depend on the region of chromosome duplicated, its size, and loci.

Patient concerns: From 2011 to 2017, prenatal amniotic fluid samples were obtained from 6 pregnant women diagnosed with pure 5q35.3 microduplications following different prenatal indications at our center. We followed up the children of these pregnancies and determined their postnatal health conditions.

Diagnoses: Cytogenetic studies delineated that all patients had normal karyotypes, except for patient 6 who had 46,XX,inv(9)(p11q13). Single-nucleotide polymorphism array results showed 177–269 kb duplications of 5q35.3 (chr5:178728830–178997692) in these cases. All shared similar localization of *ADAMTS2*.

Interventions: All pregnant women chose to continue the pregnancies. Follow-up analysis showed that the children presented normal physical and growth developments.

Outcomes: We described six prenatal cases with similar 5q35.3 duplications involving part of the *ADAMTS2* locus with no apparent postnatal phenotypic abnormalities.

Lessons: Our research revealed that partial microduplication of *ADAMTS2* (chr5:178728830–178997692) might be benign and not correlate with disorders. And there might exist phenotypic diversities of 5q35.3 duplications.

Abbreviations: CMA = chromosomal microarray analysis, CNVs = copy number variations, DGV = database of genomic variants, FISH = Fluorescence in situ hybridization, ISCN 2013 = International System for Human Cytogenetic Nomenclature 2013, NCBI = National Center for Biotechnology Information, OMIM = Online Mendelian Inheritance in Man, SNP = single-nucleotide polymorphism.

Keywords: 5q35.3 microduplication, part of *ADAMTS2*, SNP array

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1. Introduction

Chromosomal duplications are commonly associated with intellectual disability (ID) and related disorders. Three main common manifestations of 5q duplications have been seen in the clinic: distal 5q, interstitial, and terminal duplications,[1–3] whereas Rodewald et al[4] divided 5q duplications into: the proximal duplication of 5q11-q22.1, the distal duplication of 5q31-qter, and the distal duplication of 5q34-qter. Other 5q duplication cases, such as 5q34 and 5q35, have also recently been described.[5]

Pure partial 5q duplications are rare, and coverage regions range across the long arm. 5q duplications often occur in association with other chromosomal deletions, which makes it difficult to establish phenotype–karyotype correlations. Two explanations have been put forward to explain the common formations: an unbalanced segregation of a parental balanced translocation between 5q and another chromosome, and a homologous chromosome producing a partial monosomy of 5p and trisomy of 5q resulting from a parental inversion on

chromosome 5. The parental insertion or direct duplication can also result in a pure 5q duplication.[6] Based on this information, it is not easy to determine the phenotypes of pure 5q duplications in the clinic.

For submicroscopic chromosomal imbalances and copy number variations (CNVs), the G-banding technique is not suited to detecting structural aberrations; however, chromosomal microarray analysis (CMA) can improve the detection yield because of its superior diagnostic resolution. CMA is performed either as array comparative genomic hybridization or single-nucleotide polymorphism array. Subchromosomal abnormalities in approximately 1% of structurally normal pregnancies and 6% with structural abnormalities can be diagnosed by CMA of prenatal samples with normal karyotypes.[7,8] It can also be used as a postnatal diagnostic tool for children with congenital abnormalities, developmental retardation, and intellectual disability.[9]

Here, we delineated 6 cases of prenatal diagnostic 5q35.3 duplication presenting with a normal phenotypic spectrum using the single-nucleotide polymorphism (SNP) array. We also reviewed related clinical data focusing on similar duplicated segments, and discussed the potential pathogenicity of a 5q35.3 microduplication involving part of the ADAMTS2 locus.

2. Subjects and methods

2.1. Subjects

From 2011 to 2017, prenatal amniotic fluid samples were obtained from 6 pregnant women diagnosed with pure 5q35.3 microduplications following different prenatal indications at the Center for Reproductive Medicine and Center for Prenatal Diagnosis of the First Hospital of Jilin University. We followed up the children of these pregnancies and determined their postnatal health conditions. The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University (No.2011–042), and all patients' parents had provided informed consent for publication of the cases. All experiments in our study, including cytogenetic analysis and molecular cytogenetics, were performed in accordance with relevant guidelines and standard protocols.

2.2. Cytogenetic analysis

Chromosome analysis was performed on G-band metaphases prepared from cultured amino fluid cells according to standard protocols. Twenty metaphases were analyzed for all samples. The International System for Human Cytogenetic Nomenclature (ISCN 2013) was used to describe the karyotype.[10]

2.3. SNP array

SNP array analysis was performed using the Human CytoSNP-12 BeadChip (Illumina, San Diego, CA). DNA was extracted from 10 mL of uncultured aminotic fluid cells using the QIAamp DNA Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Image data were analyzed using Illumina's Genome Studio software. The final results were analyzed using the Database of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources (DECIPHER), the database of genomic variants, Online Mendelian Inheritance in Man (OMIM), and the National Center for Biotechnology Information. Parents provided 5 mL of peripheral blood which was collected using a standard vacuum extraction blood-collecting system containing EDTA and heparin. Genomic DNA was then isolated from whole blood using the QIAamp DNA Mini kit (Qiagen) following the manufacturer's instructions.

3. Results

From 2011 to 2017, a total of 6 cases with pure 5q35.3 duplications were initially detected by SNP array. All cases shared the similar duplication of part of the *ADAMTS2* locus (chr5: 178728830–178772431). The distributions of indications for prenatal diagnosis were as follows: advanced maternal age (5/6), circular of umbilical cord (3/6), Down syndrome risk (2/6), cervical lymphatic hygroma in the fetus (1/6), abnormal childbearing history (1/6), and early embryonic death in previous pregnancies (1/6). Routine cytogenetic analysis showed that all fetuses had normal karyotypes except for P6. Cytogenetic, SNP array, and clinical findings of all cases are summarized in Table 1. The parents of fetuses P2 and P3 chose to undergo SNP array analysis themselves based on the abnormal microarray results of their fetuses. Both fetuses were found to have inherited their 5q35.3 duplications from their paternal side. Neither of the 2 fathers presented with physical or developmental abnormalities. Among the 6 fetuses, the smallest duplication was 177 kb, whereas the largest was 269 kb.

P1 and P5 shared the same duplicated localizations, although they had different prenatal indications. We then carried out a follow-up of the fetuses in childhood including: pregnancy ultrasound results, body stature, developmental retardation, intellectual disability, craniofacial dysmorphisms, and skeletal anomalies. Our findings are listed in Table 1.

4. Discussion

We presented 6 rare prenatal cases with pure 5q35.3 duplications ranging from 177 to 269 kb according to SNP array. Two of these were identified as arising from paternal origins. To the best of our knowledge, the pathogenicity of duplicated CNV has not previously been described before. This is also the first report focusing on pure 5q35.3 duplications with no apparent phenotypic abnormalities. Moreover, most reported distal duplication of chromosome 5q is distributed between 5q35.2 and 5q35.3, and seldom involves single 5q35.3 duplications.[3]

Chromosomal rearrangements such as duplications can result in a series of genetic diseases.[11] Indeed, partial duplication of distal chromosome 5q is associated with a wide range of clinical phenotypes including short stature, growth and mental retardation, microcephaly, skeletal anomalies, facial clefts, micrognathia, low-set ears, hypertelorism, almond-shaped eyes, down-slanted palpebral fissures, strabismus, epicanthal folds, a prominent widened nasal bridge, a long philtrum, small mouth, and thin upper lip. Other unusual characteristics include heart defects (ventricular septal defects, atrial septal defects, and a bicuspid aortic valve), hypoplastic phalanges, ambiguous genitalia, hypospadias, cryptorchidism, and inguinal hernias.[4,12–15]

Because of the limited number of reported cases, clinical manifestations involving 5q35.3 microduplications only appear to be associated with short stature and microcephaly.[3] Therefore, to delineate the phenotype–karyotype correlations more clearly, we summarized the clinical manifestations of patients involving or overlapping 5q35.3 duplications in Table 2.[3,14–21] The age of the patients ranged from 2 years 8

Table 1

Summary of the cytogenetic, SNP array, and clinical findings of our cases with 5q35.3 duplication.

Case#	Sex	Pregnancy history	Birth		At investigation		Karyotype results	SNP array result	Duplicated size, kb	De novo/ inherited	Duplicated gene	Prenatal diagnosis indications/reason of study	Follow-up outcome
			Weight, kg	Length, cm	Weight, kg	Length, cm	Age						
P1	M	G4P1	4.2	59	10	72	7 mo	46, XY	arr[hg19]5q35.3(178728830 –178931310)×3	202	N.A.	Partial ADAMTS2	Advanced maternal age; ultrasound results: cervical lymphatic hygroma in fetus; circulor of umbilical cord	No apparent abnormalities
P2	F	G1P0	3.9	51	9.5	72	8.5 mo	46, XX	arr[hg19]5q35.3(178754468 –178931310)×3	177	Paternal inherited	Partial ADAMTS2	DS: 1/131; ultrasound results: circulor of umbilical cord	No apparent abnormalities
P3	M	G2P1	2.9	50	9	70	9.5 mo	46, XY	arr[hg19]5q35.3(178750377 –178931310)×3	181	Paternal inherited	Partial ADAMTS2	Advanced maternal age; abnormal childbearing history: a child with cerebral palsy	Ventricular septal defect at birth and heal now
P4	M	G1P0	2.85	49	9	71	10.5 mo	46, XY	arr[hg19]5q35.3(178728830 –178997692)×3	269	NA	Partial ADAMTS2; part RUFY1	Advanced maternal age	No apparent abnormalities
P5	M	G2P1	2.9	NA	10	NA	13 mo	46, XY	arr[hg19]5q35.3(178728830 –178931310)×3	202	NA	Partial ADAMTS2	Advanced maternal age, early embryonic death(2 times) in previous pregnancies, ultrasound results: circulor of umbilical cord	No apparent abnormalities
P6	F	G2P1	4	52	7	70	5.5 mo	46, XX, inv(9) (p11q13)	arr[hg19]5q35.3(178740070 –178931310)×3	191	NA	Partial ADAMTS2	advanced matemal age	No apparent abnormalities

NA = not available, SNP = single-nucleotide polymorphism.

months to 39 years. Most duplications were located in the region of 5q35.2q35.3 (15/18), with the remainder in 5q35.3 (3/18). The duplicated region ranged from 0.26 to 6.4 Mb. Among the duplications, 6 of 18 patients were *de novo*, 4 of 18 were maternally inherited, and 8 of 18 patients were not available. The high incidence rate of clinical characteristics was as follows: short stature (16/18), growth retardation (15/18), microcephaly (14/18), intellectual disability (14/18), language retardation (12/18), and motor delay (11/18), which is consistent with previous reports of 5q duplications.[4,12–15] Facial dysmorphisms are also important common manifestations for these patients and included: flat philtrum (12/18), long face (11/18), prominent nasal tip (11/18), thin upper lip (11/18), periorbital fullness (9/18), down-slanting palpebral fissures (9/18), strabismus (6/18), low-set ears (5/18), epicanthic folds (5/18), downturned mouth (4/18), a prominent nasal bridge (3/18), and hypertelorism (2/18). The irregular bone age was as follows: delayed (3/18), normal (2/18), and advanced (1/18). Mood swings and autistic symptoms were also reported in these patients (6/18).

Seven cases with similar overlapping 5q35.3 duplications are described in DECIPHER (patients 289927, 331005, 351756, and 300119) and ISCA databases (patients nssv 58214, nssv1608492, and nssv1608492) (Fig. 1). Patients 289927, 331005, and 351756 had a 16p13.2 microduplication, 5q35.3 microdeletion, and 7q36.1 microduplication, respectively, as well as the 5q35.3 duplication. In contrast, patient 300119 had a pure 5q35.3 duplication, presenting with truncal obesity, an abnormal facial shape, autistic behavior, and global developmental delay. Patient nssv 58214 presented with abnormalities of the skeletal system, a cleft upper lip, and Duane anomaly whose pathogenicity is uncertain. However, the pathogenicity of the duplicated region in the other 2 cases (nssv1608492 and nssv1608493) is largely benign, with the manifestation of developmental delay and/or other notable developmental or morphological phenotypes. Therefore, the pathogenicity of these duplicated regions is still uncertain.

Considering the follow-up outcomes of our patients, all children presented with normal growth and mental development, and there were no limb or facial feature anomalies. This differs from previous findings. P3 presented with a ventricular septal defect at birth, which was the only transitory symptom after birth. To further demonstrate the diverse clinical phenotypes, we made detailed comparisons of the cases encompassing the 5q35.2q35.3 duplication (Fig. 1).

According to the DECIPHER database, a total of 13 morbid genes exist in the 5q35.3 region (Table 3), which are associated with a diverse range of clinic phenotypes. The gene dosage effect appears to be involved in some abnormal clinical phenotypes.[22] Our cases all share similar partial duplications of *ADAMTS2* (OMIM 604539; chr5:178728830–178772431) (Fig. 1). *ADAMTS2* contains 22 exons and is a member of the *ADAMTS* gene family. It encodes an enzyme that excises the *N*-propeptide of type I and type II procollagens. *ADAMTS2* haploinsufficiency is associated with the dermatosparaxis type of Ehlers–Danlos syndrome (EDS; OMIM 225410) which is inherited in an autosomal recessive manner.[23–25] EDS is a heterogeneous group of disorders that affect the fragility of soft connective tissues, leading to hypermobile joints and hyperextension of the skin and other organs and tissues. The dermatosparaxis type of this syndrome is characterized by extreme skin fragility, characteristic craniofacial features, easy bruising, and growth retardation.[26,27]

Table 2

Clinical data of patients involving/overlapping 5q35.3 duplication.

References	Chen et al[14]	Kirchhoff et al[17]	Franco et al[18]		Zhang et al[19]	Kasnauskiene et al[16]	Dikow et al[3]									Jamsheer et l[15]	Žilina et al[20]	Reis et al[21]
			Case 1	Case 2			Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient9			
Duplicated region	5q35.2q35.3	5q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3	5q35.2q35.3
Age/sex	11 y/F	4 y 9 mo/F	33 y/M	8 y/M	14 y/M	4 y/F	17 y/M	15 y/M	13 y/F	39 y/F	9 y/M	35 y/F	7 y/M	2 y 8 mo/M	4 y/M	8.5 y/M	13.5 y/F	4 y/M
Duplication size, Mb	6.4	0.52∼0.65	>1.2	>1.1	∼2.1	0.264	1.6	1.6	1.6	1.6	1.5	1.5	0.26; 0.2	1.9	2.08	5.4–5.6	2.03	∼3.04
Inheritance	De novo	De novo	De novo	NA	NA	De novo	Mat	Mat	Mat	NA	Mat	NA	NA	NA	De novo	NA	NA	De novo
Growth retardation	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	+
Short stature	+	+	+	+	+	NA	+	+	+	−	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	NA	+	+	+	NA	+	−	+	+	+	−	+	+
Micrognathia	−	+	NA	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	−	NA
Long face	Oval	+a	+a	+a	−	+	+	+	+	+a	+	+	+	−	Oval	−a	NA	NA
Epicanthic folds	NA	+a	N	−	+	NA	−	+	−	−	−	−	−	−	+	NA	+	NA
Periorbital fullness	NA	+a	NA	−	+	NA	+	+	+	+	−	−	+	+	+	NA	NA	NA
Palpebral fissures	NA	NA	Short	Short	Short	Down slanting	Short	Short	Short	Short	Short	Down slanting	−	−	Short	NA	NA	NA
Strabismus	+	−	−	−	−	NA	+	+	−	−	−	−	+	−	−	+	−a	+
Hypertelorism	−	NA	−a	−a	−	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+
Nose	Small	NA	Small[a]	Small	Short	Small	Long	Long	Long	Long	NA	NA	NA	NA	NA	Small	NA	NA
Flat philtrum	NA	+	NA	+a	+a	−	+	+	+	+	+	+	+	+	+	NA	NA	NA
Prominent/high nasal bridge	+	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	−	+	NA	NA
Prominent/bulbous nasal tip	+	+	−	+	−	NA	+	+	+	+	+	+	Broad	−	−	+	+	NA
Downturned mouth	+	NA	NA	NA	+	NA	NA	NA	NA	+	+	NA	NA	NA	NA	NA	NA	NA
Thin upper lip	+	+	−a	−a	+	NA	+	−	+	−	+	+	−	+	+	+	+	NA
Low set ears	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	+	NA	NA	NA	+	+	NA	+
Brachydactyly	+	NA	NA	NA	+	NA	−	−	−	−	−	−	−	+	−	NA	+	NA
Heart defects	−	NA	NA	NA	−	NA	−	−	−	−	−	−	−	−	−	+	−	NA
Motor delay	+	+	+	−	+	+	+	+	+	NA	−	NA	+	+	+	−	NA	NA
Language retardation	+	+	+	+	+	NA	+	+	NA	NA	+	+	+	−	+	NA	NA	+
Intellectual disability	IQ54	+	IQ69	IQ62	+	NA	IQ 78	IQ 78	IQ53	+	IQ 55–58	+	IQ65	−	NA	NA	+	+
Bone age	NA	NA	NA	Delayed	Delayed	Advanced	NA	NA	Normal	NA	NA	NA	Normal	NA	Delayed	NA	Delayed	NA
Others	Inguinal hernias		Cryptorchidism			Prominent forehead	Hypospadias, mood swings	Mood swings, behavioral problems	Emotional reactions		Aggressive reactions		Cryptorchidism; restless, autistic features	Hypoplastic toe nails	Autistic features	Cryptorchidism; hypothyroidism left hypocausts.		Balanic hypospadias

+=feature present, −=feature absent, a=presumed from the patient picture in the paper, F=female, IQ=intelligence quotient, M=male, NA=not available.

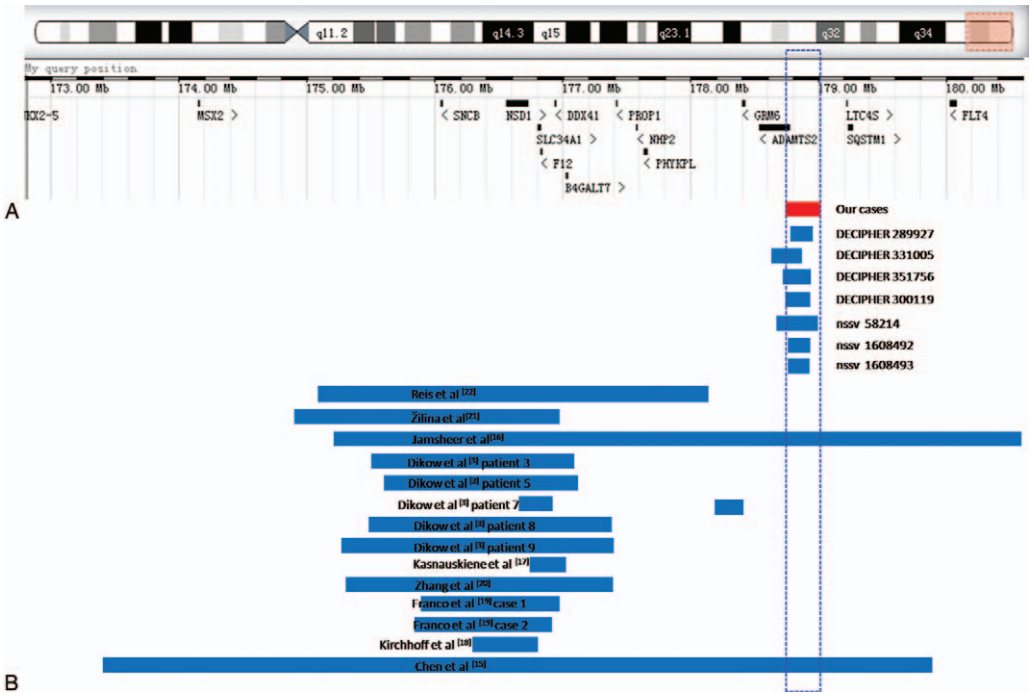

Figure 1. Scale representation of the duplicated region in the distal long arm of chromosome 5 (5q35.2–5q35.3) (https://decipher.sanger.ac.uk/) (A) Location of morbid genes in the region. (B) Duplicated fragments in the present cases (red) and previously described duplications in the region (blue).

There is currently no available evidence for the triplosensitivity in association with *ADAMTS2*. Moreover, P2 and P3 separately inherited the 5q35.3 duplication from their father, presenting without abnormal clinical phenotypes. Therefore, we speculate that the partial duplication of 5q35.3 (chr5: 178728830–178997692), including part of *ADAMTS2*, might be a benign variant. A partial *RUFY1* duplication was also seen in P4; this gene might be involved in endolysosomal transport, which plays an important role in the development of Alzheimer disease.[28] It is therefore likely that this gene has no evident relevance with our subject.

Our research has some limitations. First, the age of individuals at follow-up was typically too young to assess prospective growth and development, especially regarding language and intellectual disability. Table 2 shows that the youngest age reported in previous studies was 2 years 8 months, whereas our youngest subject was 13 months' old; therefore, regular follow-up for our cases should be carried out in the future. Second, only 2 of the

Table 3

Genes in the region of 5q35.3 and the associated diseases.

Gene	OMIM	Description	Disease
NSD1	606681	Nuclear receptor binding SET domain protein 1	Sotos syndrome 1, leukemia, acute myeloid; AML
SLC34A1	182309	Solute carrier family 34 member 1	Nephrolithiasis/osteoporosis, hypophosphatemic, 1, fanconi renotubular syndrome 2, hypercalcemia, infantile, 2
F12	610619	Coagulation factor XII	Factor XII deficiency, angioedema, hereditary, type III
DDX41	608170	DEAD-box helicase 41	Myeloproliferative/lymphoproliferative neoplasms, familial (multiple types), susceptibility to
B4GALT7	604327	Beta-1,4-galactosyltransferase 7	Ehlers-Danlos syndrome, spondylodysplastic type, 1
PROP1	601538	PROP paired-like homeobox 1	Pituitary hormone deficiency, combined, 2
NHP2	606470	NHP2 ribonucleoprotein	Dyskeratosis congenita, autosomal recessive 2
PHYKPL	614683	5-phosphohydroxy-L-lysine phospho-lyase	Phosphohydroxylysinuria
GRM6	604096	Glutamate metabotropic receptor 6	Night blindness, congenital stationary (complete), 1B, autosomal recessive
ADAMTS2	604539	ADAM metallopeptidase with thrombospondin type 1 motif 2	Ehlers-Danlos syndrome, dermatosparaxis type
LTC4S	246530	Leukotriene C4 synthase	Leukotriene C4 synthase deficiency
SQSTM1	601530	sequestosome 1	Paget disease of bone 3, frontotemporal dementia and/or amyotrophic lateral sclerosis 3, Neurodegeneration with ataxia, dystonia, and gaze palsy, childhood-onset, myopathy, distal, with rimmed vacuoles
FLT4	136352	Fms-related tyrosine kinase 4	Lymphedema, hereditary, IA, hemangioma, capillary infantile

OMIM = Online Mendelian Inheritance in Man.

present couples chose to investigate whether their chromosomal duplications are inherited, which is not sufficient evidence to explain pathogenicity of the duplicated region. Additionally, because few reports of similar 5q35.3 duplications have been made previously, further research is needed to confirm our findings.

5. Conclusion

We analyzed 6 prenatal cases with similar 5q35.3 microduplications ranging from 177 to 269 kb involving part of the *ADAMTS2* locus by SNP array. The application of molecular cytogenetic techniques provides an effective approach to improve the diagnosis rate of chromosomal microrearrangements and locate functional genes. Our report revealed that the partial 5q35.3 duplication (chr5: 178728830–178997692) might be benign and have no association with human disorders. However, the children involved in this study should undergo an assessment of their growth and intelligence during childhood and adulthood. All cases in our report currently present with normal physical development and clinical manifestations, with no apparent phenotypic abnormalities. This suggests the existence of phenotypic diversities associated with 5q duplications.

Author contributions

Conceptualization: Hongguo Zhang, Shibo Li, Ruixue Wang.
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