The prenatal diagnosis and clinical outcomes of fetuses with 15q11.2 copy number variants: a case series of 36 patients

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Running title:

Case series of 15q11.2 copy number variants

Full Abstract

Objective: The prenatal genetic counseling of fetus diagnosed with the 15q11.2 copy number variant (CNV) involving the BP1-BP2 region has been difficult due to limited information and controversial opinion on prognosis.

Design: Case series.

Setting: This study uses data from National Taiwan University Hospital.

Sample: Data of 36 pregnant women who underwent prenatal microarray analysis from 2012 to 2017 and were assessed at National Taiwan University Hospital.

Methods: Data were collected by reviewing patients' medical record. Comparison of patient characteristics, prenatal ultrasound findings and postnatal outcomes between different cases involving the 15q11.2 BP1-BP2 region were presented.

Main outcome measured: Postnatal prognosis.

Results: Out of the 36 patients diagnosed with CNVs involving the BP1-BP2 region, 5 were diagnosed with microduplication and 31 with microdeletion. Abnormal ultrasound findings were recorded in 12 cases prenatally. De novo microduplications were observed in 25% of the cases and microdeletions were found in 14%. Amongst the cases, 10 pregnant women received termination of pregnancy and 26 gave birth to healthy individuals (27 babies in total).

Conclusion: The prognoses of 15q11.2 CNVs were controversial and recent studies have revealed its connection with developmental delay and autism. In our study, no obvious

developmental delay or neurological disorders were detected postnatally in the 1 case of 15q11.2 microduplication and 25 cases of microdeletion.

Keywords: 15q11.2 microdeletion, 15q11.2 microduplication, BP1-BP2, copy number variant, microarray

Abstract

Prenatal genetic diagnosis data of 36 pregnant women involving 15q11.2 copy number variant and their postnatal outcomes.

Introduction

Copy number variations (CNV) involving chromosome 15q11-q13 is a challenging issue for prenatal counseling. Prader-Willi syndrome (PWS), Angelman syndrome (AS), and 15q11-q13 duplication syndrome are the three most studied neurodevelopmental disorders occurring at the locus (1). Few studies have been conducted specifically on the Asian population, especially in the region involving non-imprinting breakpoints 1-2 (BP1-BP2) (2, 3).

There are five common breakpoints within 15q11-q13, defined as BP1 through 5. The most common breakpoints involved with deletions are BP1, BP2 and BP3, whereas duplications are more complicated (1). The copy number variant involving the BP1-BP2 region is more challenging in prenatal counseling due to its incomplete penetrance with variable expressivity. The four genes within the BP1-BP2 region would affect the clinical presentation and severity of neurological impairment, and this region is approximately 500 kb in size (2). The tubulin gamma complex associated protein 5 (TUBGCP5) gene is related to neurobehavioral disorders (4). Cytoplasmic fragile X mental retardation 1 interacting protein 1 (CYFIP1) gene product interacts which is responsible for Fragile X syndrome (5). Non-imprinted in Prader-Willi/Angelman syndrome 1 (NIPA1) has been associated with autosomal dominant hereditary spastic paraplegia (6-8), and non-imprinted in Prader-Willi/Angelman syndrome 2 (NIPA2) gene is related to childhood absence epilepsy (9, 10).

Previous studies have revealed that deletions have a more severe impact than duplications (11). Variable penetrance of this copy number variant is reported (3, 12). According to previous studies, the de novo frequency of 15q11.2 BP1-BP2 microdeletion is around 5-

22%. About 80% of the cases were inherited from their parents (2), of which around 50% got it from an apparently unaffected parent, while 35% came from an affected parent (1). Different origins of inheritance are associated with different phenotypes (13). As for duplication, no previous statistics on the inheritance pattern have been collected, and information about prognosis is extremely limited (14-16).

Technically the incidence of deletions and duplications should be nearly equal, the actual case numbers of microduplication reported are fewer than microdeletion. Few publications have described patients with 15q11.2 microduplications between BP1 and BP2, which could cause developmental delay, motor or language delay, epilepsy, learning disabilities and behavioral issues (11, 14, 17). Variable penetrance and the severity of phenotypes increase the complexity of prenatal genetic counseling. Therefore, we retrospectively reviewed 36 cases that were diagnosed with 15q11.2 copy number variants involving the BP1-BP2 region.

Materials and methods

We collected the data of 36 pregnant women with copy number variants involving the 15q11.2 BP1 and BP2 region, whose microarray analyses were assessed at National Taiwan University from July 1st, 2012 to December 31th, 2017. Indications include advanced maternal age, karyotype abnormalities, abnormal ultrasound findings and maternal anxiety. Microarray data of all patients were analyzed retrospectively for microdeletion and microduplication involving the 15q11.2 BP1 and BP2 region.

The patients underwent amniocentesis or chorionic villus sampling, where 10 ml of amniotic fluid or chorionic villi was sampled through abdominal puncture under ultrasound guidance. Once received, genomic DNA was extracted from the amniotic fluid or chorionic villi using the DNA Extraction Kit (QIAamp® DNA Blood Mini Kit) according to the manufacturer's instructions. The outcome of the pregnancies was determined by conducting telephone interviews with the pregnant women until the baby was born or the pregnancy was over.

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Cytogenomic microarray analysis

The 8 × 60K oligonucleotide array (Agilent Technologies, Santa Clara, California, USA) and the Affymetrix CytoScan 750K SNP array analysis (Affymetrix Inc., Santa Clara, CA, USA) were used, and all procedures were carried out according to the manufacturer's protocols.

1. Array CGH Analysis

The SurePrint G3 Human CGH Microarray Kit 8 × 60K (Agilent Technologies, Santa Clara, California, USA) was used. DNA extraction was performed using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Slides were scanned using the SureScan Microarray Scanner (Agilent Technology, Santa Clara, CA, USA) and analyzed

with Feature Extraction Software v11.5 (Agilent Technology, Santa Clara, CA, USA) under designed parameters of the human reference genome hg19. Data analysis was conducted via the Agilent Cytogenomics software available on the company's website (https://www.genomics.agilent.com/en/CGH-Microarray-Data-Analysis/CytoGenomics-Software/?cid=AG-PT-111&tabId=AG-PR-1017, Agilent Cytogenomics v2.7.8.0).

2. SNP Array Analysis

The Affymetrix CytoScan 750K SNP array analysis (Affymetrix Inc., Santa Clara, CA, USA) was employed, with a size threshold of 400 kb used for all CNVs. All procedures were carried out according to the manufacturer's protocols. The sample DNA (250 ng) was digested, ligated, and amplified by PCR, followed by purification, fragmentation, labeling, hybridization, dyeing and scanning. Data analysis was performed using Chromosome Analysis Suite (ChAS) software (v3.1, r8004).

Results

Although different microarray platforms were used in our study, the SNP microarray analysis was used with the majority of our subjects. Of all 36 cases, we screened 9 cases using the 60K oligonucleotide array (Agilent Technologies Inc., Santa Clara, CA, USA), and 27 cases with the Affymetrix CytoScan 750K SNP array analysis (Affymetrix Inc., Santa Clara, CA, USA).

Of all 36 cases, 5 were diagnosed with microduplication and 31 with microdeletion. Ten cases received termination of pregnancy, while 26 patients (including one case of microduplication) delivered healthy babies (27 deliveries) without further complications.

1. Microduplication

We identified a duplication within the 15q11.2 region involving BP1 and BP2 in five patients. Only one case involved the four highly conserved genes (http://genome.ucsc.edu, NCBI build 36.1) (Fig. 1), and the size of duplication ranged from 2.15 Mb to 12.21 Mb of chromosome 15. Three cases were proven to be de novo, while the other one was maternal in origin. Case 2 was of unknown origin because further study was not conducted.

One patient delivered at term without major anomalies or complications. Four cases underwent termination of pregnancy due to the involvement of the PWS/AS region (case 2 to 5), with one diagnosed with tetralogy of Fallot prenatally.

For cytogenetic findings, see Fig.1. Genetic information is summarized in Table 1 and clinical details are listed in Table 2.

2. Microdeletion

We identified microdeletion of 15q11.2 involving BP1 and BP2 in 31 patients. The deletion involved the four highly conserved genes in 30 cases (Fig. 1), and one only involved partially, ranging from 0.31 Mb to 7.99 Mb of chromosome 15. Five of the microdeletion cases were proven to be de novo, six were maternal and nine were paternal in origin, while 11 were of unknown origin.

Six patients received termination of pregnancy, among which abnormal ultrasound findings were reported in four cases prenatally, including one with fetal chylothorax, two with congenital cardiac disease and one with nuchal edema.

The other 25 patients continued their pregnancy, with 4 delivering preterm due to obstetric complications (ranging from 27 to 35 weeks of gestational age) and 21 patients (22 deliveries) delivering at term without complication. Of the 25 patients who delivered, abnormal ultrasound findings were confirmed in 7 cases prenatally, including 3 cases of ventricular septal defect, one of duplex kidney, one of single umbilical artery, one of fetal ascites and one of oligohydramnios.

Discussion

1. Main findings

Prenatal genetic diagnosis has become a trend due to advanced maternal age, while the progress in genetic testing resolution provides more detailed information to clinicians. Microarray analysis is effective in screening for submicroscopic genomic imbalance, and may expand the scope of diagnosis by 8.2% compared with conventional karyotyping for those with abnormal ultrasound results (18). Clinical interpretations of the rare cases of microdeletion, microduplication and variants of unknown significance (VOUS) have also been a challenge. Copy number variants of 15q11.2 have always been a difficult issue for prenatal genetic counseling due to incomplete penetrance and variant phenotype expression. Because of its incomplete penetrance, this CNV is currently considered a risk locus. There have been some reviews investigating 15q11.2 microdeletion worldwide, but general population-based data are still lacking. As for microduplication, even less information can be found as it has not been extensively studied.

In Taiwan, there was no previous comprehensive or systematic study of this region. One case of 15q11.2 (BP1-BP2) duplication with abnormal prenatal ultrasound including ventriculomegaly, microcephaly and intrauterine growth restriction has been reported but underwent termination (19). Another patient who delivered in the end had undergone amniocentesis for fetal karyotyping, which revealed 46,XX. However, developmental delay was noted in this baby and her two siblings, and further genetic study revealed that the 15q11.2 duplication was inherited from their phenotypically normal father. Thus, incomplete penetrance has also been a challenge regarding 15q11.2 duplication, as a wide variety of phenotypes may be present in the same family (20). In our cases that involve duplication, only one was inherited from a phenotypically normal mother, and no developmental delay was noted in the following years. No detailed information on the penetrance and expressivity was available. Four out of five duplication cases received termination due to large size with involvement of the PWS/AS region, thus the clinical significance of 15q11.2 duplication is still uncertain.

2. Strengths

There was no previous study investigating 15q11.2 duplications with abnormal ultrasound findings. In our study, only one out of five cases of duplication was diagnosed with tetralogy of Fallot via ultrasound examination. The incidence of congenital heart disease is similar to a previous study, which found that the detection rate in an unselected population is around 16.9% (21). Thus it seems like there is no strong association between congenital heart disease and 15q11.2 CNVs.

3. Limitations

The first limitation of this study is the relatively small case number of diagnosed CNVs. The prevalence of 15q11.2 CNVs in our study seems to be lower than previous statistics. We could obtain the information of patients from other genetic centers. The larger study population may provide more information for us to offer a more detailed explanation to the patient. Second, the follow-up period of the offspring is too short and should be expanded, so that the growth development could be evaluated more thoroughly in the future.

4. Interpretation

Deletion involving the 15q11.2 BP1-BP2 region could be discovered in healthy individuals, but recent research has discovered that this part of deletion is associated with developmental and behavioral disorders, which are the most common clinical features in 15q11.2 deletion (2, 11, 22). According to previous studies, the estimated risk of an abnormal phenotype ranged from 10.4% to 83% for 15q11.2 deletions (23, 24). Most of our cases were of unknown origin, and for those with further information on origin, de novo accounts for 16%, maternal origin accounts for 19% and paternal accounts for 29%. The majority of the deletion cases chose to deliver their fetuses. Case 6 with de novo microdeletion of 15q11.1-q11.2 delivered a healthy baby without any complications. Her array report showed a relatively small deletion size (2.4 Mb) and didn't involve the whole 15q11.2 BP1-BP2 region. The other 25 cases that delivered healthy individuals also had a relatively small deletion size (ranging from 0.31-0.85 Mb). Most cases of termination in the microdeletion group were found to be larger in deletion size and some involved the PWS/AS region. Four cases of congenital anomalies were diagnosed via prenatal ultrasound scanning, including one diagnosed with Down syndrome by chorionic villus

sampling. Although most cases of microdeletion delivered without serious complications, the time for follow-up is relatively short. Long-term growth development and evaluation should be conducted in the future.

Not all of the patients underwent amniocentesis for genetic study at the beginning. Abnormal ultrasound findings were reported in some cases and needed further evaluation. Another interesting issue is whether there is a relationship between specific ultrasound features and 15q11.2 CNVs. Prenatal ultrasound is a very important tool for obstetricians nowadays. Some abnormal ultrasound findings might be related to specific chromosomal abnormalities or genetic syndromes. Dysmorphic feature (43%) is the most common sonographic characteristic noted in cases of chromosomal abnormalities, which was also noted in previous studies of 15q11.2 deletion, and cardiac diseases were also found in 10-20% of the cases of 15q11.2 deletion (12). The cardiac problems reported include complex left-sided malformations, atrial and ventricular septal defects, coarctation of the aorta, and tetralogy of Fallot. In our study, twelve cases of microdeletion had abnormal ultrasound findings diagnosed prenatally, including six with congenital cardiac defects, one with chylothorax associated with hydrops fetalis, one with a duplex kidney, one with isolated single umbilical artery, one with fetal ascites with echogenic bowel, one with nuchal thickening and one with oligohydramnios. For those with heart defects, the one with total anomalous pulmonary venous return and the one with hypoplastic left heart syndrome underwent termination of pregnancy. None of the cases had dysmorphic features. Given the wide variety and low prevalence of congenital heart defects in subjects with 15q11.2 (BP1-BP2) deletion, it remains questionable whether there is an association.

Conclusion

The prognostic accuracy of 15q11.2 CNVs was mostly unknown because some cases underwent termination of pregnancy. In our study, no obvious developmental delay or neurological disorders were detected in the one case of 15q11.2 microduplication and 25 cases of microdeletion. However, the prevalence of 15q11.2 CNVs is very low in the Taiwanese population, which suggests that our findings should be interpreted with caution and indicates the need for studies that include large numbers of control subjects to ascertain the impact.

Ethics approval

All the research methods used in this process were approved by the National Taiwan University Hospital Research Ethics Committee (201801010RINC)

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Conflict of interest: There is no conflict of interest.

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Author's contribution

JK contributed to the drafting of the main manuscript. MWL and YYT organized and analyzed the patient data. WWH and KYH drew and formatted the tables and the figure. CNL and YNS participated in the study design and data collection. SYL conceived the study and helped revise the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Cytogenetic results 15q11.2 CNV.

Case	Dup/del	CNV detected by	Size (pb)	Boundaries	Origin	Phenotype of parent with CNV
1	Dup	60K array[a]	2,149,626	chr15:22,765,628-24,915,254	Maternal	Normal
2	Dup	60K array	12,213,310	chr15:20,686,219-32,899,529	N/A	
3	Dup	60K array	6,181,306	chr15:23,656,965-29,838,271	De novo	
4	Dup	60K array	6,312,880	chr15:23,072,800-29,385,680	De novo	
5	Dup	60K array	5,391,222	chr15:23,300,238-28,691,460	De novo	
6	Del	60K array	2,398,848	chr15:20,686,219-23,085,067	N/A	
7	Del	60K array	7,994,780	chr15:20,686,219-28,680,999	N/A	
8	Del	60K array	7,873,154	chr15:20,686,219-28,559,373	De novo	
9	Del	60K array	7,873,154	chr15:20,686,219-28,559,373	De novo	
10	Del	SNP array[b]	511,465	chr15:22,770,421-23,281,886	De novo	
11	Del	SNP array	436,120	chr15:22,770,421-23,206,541	Maternal	Normal
12	Del	SNP array	855,364	chr15:22,770,421-23,625,785	Maternal	Normal
13	Del	SNP array	855,364	chr15:22,770,421-23,625,785	De novo	
14	Del	SNP array	506,184	chr15:22,770,421-23,276,605	De novo	
15	Del	SNP array	311,816	chr15:22,770,421-23,082,237	Maternal	Normal
16	Del	SNP array	512,377	chr15:22,770,421-23,282,798	Maternal	Normal
17	Del	SNP array	444,234	chr15:22,770,421-23,214,655	N/A	
18	Del	SNP array	845,348	chr15:22,770,421-23,615,769	Paternal	Normal
19	Del	SNP array	444,234	chr15:22,770,421-23,214,655	Maternal	Normal
20	Del	SNP array	512,377	chr15:22,770,421-23,282,798	Paternal	Normal
21	Del	SNP array	507,015	chr15:22,770,421-23,277,436	Paternal	Normal
22	Del	SNP array	444,234	chr15:22,770,421-23,214,655	Maternal	Normal
23	Del	SNP array	512,377	chr15:22,770,421-23,282,798	Paternal	Normal
24	Del	SNP array	855,364	chr15:22,770,421-23,625,785	Paternal	Normal
25	Del	SNP array	506,184	chr15:22,770,421-23,276,605	Paternal	Normal
26	Del	SNP array	507,015	chr15:22,770,421-23,277,436	Paternal	Normal
27	Del	SNP array	507,015	chr15:22,770,421-23,277,436	N/A	
28	Del	SNP array	507,015	chr15:22,770,421-23,277,436	N/A	
29	Del	SNP array	506,184	chr15:22,770,421-23,276,605	N/A	
	Del	SNP array	506,184	chr15:22,770,421-23,276,605	N/A	
30	Del	SNP array	425,304	chr15:22,770,421-23,195,725	N/A	
31	Del	SNP array	311,816	chr15:22,770,421-23,082,237	Paternal	Normal
32	Del	SNP array	5,933,629	chr15:22,770,421-28,704,050	N/A	
33	Del	SNP array	444,234	chr15:22,770,421-23,214,655	De novo	
34	Del	SNP array	506,184	chr15:22,770,421-23,276,605	Paternal	Normal
35	Del	SNP array	512,377	chr15:22,770,421-23,282,798	N/A	
36	Del	SNP array	506,184	chr15:22,770,421-23,276,605	Paternal	Normal

[a]: 60K array = Agilent 8 x 60K oligonucleotide array

[b]: SNP array = Affymetrix CytoScan 750K SNP array

Dup: duplication; del: deletion; N/A: not applicable; CNV: copy number variants

Table 2. Findings of fetuses with 15q11.2 CNV and newborn characteristics

Case	Sex	Dup/del	Size (Mb)	Origin	Prenatal ultrasound finding	Growth IUGR	Delivery mode	Gestational age at birth	Birth body weight (g)	Apgar score	Postnatal finding	Follow-up years	DD
1	M	Dup	2.15 Mb	Maternal		-	C/S	38+2	2994	9-9		3	-
2	F	Dup	12.21 Mb	N/A		-	Termination	22	445				N/A
3	M	Dup	6.18 Mb	De novo		-	Termination	21	405				N/A
4	F	Dup	6.31 Mb	De novo		-	Termination	27+6	730				N/A
5	M	Dup	5.39 Mb	De novo	Tetralogy of Fallot	-	Termination	23+4	495				N/A
6	M	Del	2.4 Mb	N/A		-	VD	38+4	2840	9-9		8	-
7	M	Del	7.99 Mb	N/A		-	Termination	23	480				N/A
8	F	Del	7.8 Mb	De novo	Chylothorax with fetal hydrops	-	Termination	23+4	850		Hydrops fetalis		N/A
9	F	Del	7.8 Mb	De novo	Total anomalous pulmonary venous return	-	Termination	26	580				N/A
10	F	Del	0.55 Mb	De novo	Ventricular septal defect	-	VD	38+4	3125	8-9		4	-
11	M	Del	0.43 Mb	Maternal	Echogenic intracardiac focus	-	C/S	38+2	2620	8-9		4	-
12	F	Del	0.85 Mb	Maternal	Left duplicated kidney	-	C/S	38+1	3080	8-9		3	-
13	M	Del	0.85 Mb	De novo	Ventricular septal defect	-	C/S	32+1	1840	7-8		2	-
14	F	Del	0.5 Mb	De novo		-	VD	39+1	2645	8-9		5	-
15	F	Del	0.31 Mb	Maternal		-	VD	40+1	3780	8-9		3	-
16	F	Del	0.51 Mb	Maternal		-	C/S	31+3	1740	6-8		2	-
17	F	Del	0.44 Mb	N/A		-	VD	39+5	3310	9-10		4	-
18	M	Del	0.84 Mb	Paternal		-	VD	39+2	2276	8-9		2	-
19	F	Del	0.44 Mb	Maternal	Hypoplastic left heart syndrome	-	Termination	22+6	540				N/A
20	M	Del	0.51 Mb	Paternal	Single umbilical artery	-	VD	39+1	3040	9-9		2	-
21	F	Del	0.5 Mb	Paternal		-	VD	39+4	2844	9-10		2	-
22	M	Del	0.44 Mb	Maternal	Fetal ascites, echogenic bowel	-	C/S	38+1	3320	9-10		2	-
23	M	Del	0.51 Mb	Paternal		-	VD	27+2	884	6-8		2	-
24	F	Del	0.85 Mb	Paternal	Ventricular septal defect	-	VD	39+5	2986	9-9		2	-
25	M	Del	0.5 Mb	Paternal		-	VD	40	3522	9-9		2	-
26	F	Del	0.5 Mb	Paternal		-	VD	35+4	2296	8-9		2	-
27	M	Del	0.5 Mb	N/A		-	C/S	39+2	3110	9-9		4	-
28	M	Del	0.5 Mb	N/A		-	VD	39+3	3630	9-10		3	-
29	M	Del	0.5 Mb	N/A		-	C/S	37+6	2734	9-9		4	-
	F	Del	0.5 Mb	N/A		-	C/S	37+4	4070	9-10		2	-
30	F	Del	0.42	N/A		-	VD	37	2534	9-10		3	-

31	F	Del	0.31 Mb	Paternal		-	VD	38+1	2884	9-10		4	-
32	M	Del	5.93 Mb	N/A		-	Termination	21+2	360				N/A
33	F	Del	0.44 Mb	De novo		-	VD	39	3210	9-10		5	-
34	F	Del	0.5 Mb	Paternal	Oligohydramnios	-	C/S	40	3075	9-10		3	-
35	M	Del	0.51 Mb	N/A	Nuchal thickness 5.2mm	-	Termination	13+5	46		Nuchal edema		N/A
36	M	Del	0.5 Mb	Paternal		-	VD	40+1	3310	8-9		2	-

Dup: duplication; Del: deletion; N/A: not applicable; VD: vaginal delivery; C/S: Cesarean section; IUGR: intrauterine growth restriction; DD: developmental delay

Table 2. Findings of fetuses with 15q11.2 CNV and newborn characteristics

Figure legends

Figure 1. Schematic map of the 15q11.2 BP1-BP2 region. The reported microduplications and microdeletions are shown at the bottom drawn to scale