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Array CGH-based Detection and Characterization of Combined 1p36 Deletion and 22q13 Duplication in a Boy and a Fetus from a Single Family

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Abstract

Purpose: 1p36 deletion syndrome is the most common terminal deletion syndrome, with an incidence of 1/5,000 newborns. But 22q13 duplications seem to be exceedingly rare. A combined 1p36 deletion and 22q13 duplication was more rarely observed and presented variability of clinical features, which increases the importance of reporting additional cases in order to better characterize genotype-phenotype correlations.

Methods: A boy and a fetus from a single family with combined 1p36 deletion and 22q13 duplication characterized by array CGH and MLPA were described here.

Results: The proband presented severe developmental delay, hypotonia, epilepsy, feeding difficulties with failure to thrive, tracheal malformation, clinodactyly, strephexopodia, fair skin, facial dysmorphism and died at 1 year of age. Array CGH uncovered a 9.3-Mb deletion of 1p36 plus a 6.655-Mb duplication of 22q13in the proband. This rearrangement was confirmed by MLPA. When his mother was pregnant again, array CGH detected an almost identical rearrangement with that of the proband. She terminated the pregnancy at 24 weeks gestation. The fetus was female and had similar facial dysmorphism as the proband. Karyotypes of parents are all normal.

Conclusions: Most of the features in the proband were similar to those associated with both isolated 1p36 deletions and 22q13 duplications. However, tracheal malformation, fair skin and strephexopodia were only observed in our patient. Given that 22q13 duplications are rare and not as well characterized as 1p36 deletions, we attributed these features to 22q13 duplications. Importantly, we emphasize importance of prenatal diagnosis of females who had such abnormal pregnancy.

Keywords: Combined1p36 deletion and 22q13 duplication; 1p36 deletion syndrome; 22q13 duplication; Developmental delay; Congenital anomalies

Introduction

The deletion of chromosome 1p36 (OMIM#607872) is the most frequent terminal chromosomal deletions observed in humans, affecting approximately 1 in 5,000 newborns [1,2]. The clinical manifestations of this syndrome include developmental delay/intellectual disability, hypotonia, epilepsy, brain anomalies, congenital heart defects, cardiomyopathy, renal anomalies, vision problems, hearing loss, short stature, and orofacial clefting. Distinctive facial features include microcephaly or brachycephaly, straight eyebrows, deep-set eyes, epicanthal folds, low-set ears, abnormal ears typified by their posterior rotation, midface dysplasia, a wide and depressed nasal bridge, a long philtrum, a pointed chin, and a large and late-closing anterior fontanel [2-4]. Additionally, patients with the 1p36 deletion have better functional skills during adolescence and adulthood [5]. In contrast, 22q13 duplications are rarely observed. The most prominent phenotypes associated with 22q13 duplications are psychomotor retardation, pre- and post-natal growth retardation, hypotonia, congenital heart defects, renal and genital anomalies, skeletal abnormalities, autism spectrum disorders, cleft palate with or without cleft lip, microcephaly, hypertelorism, low-set ears, and micrognathia. Almost half of all published patients died before reaching 12 years of age, which suggest that life expectancy is severely reduced [6-9]. A combined 1p36 deletion and 22q13 duplication is more infrequent,

with only four reported cases to date [10]. Array CGH- and MLPA-based characterization of a boy and a fetus from a single family with combined 1p36 deletion and 22q13 duplication are described in this study.

Case Presentation

The proband was born at 38 weeks gestation by cesarean delivery with a birth weight of 2.5 kg (< 3rd percentile) and a birth length of 47 cm (≤3rd percentile) as the second child of a 34-year-old father and a 30-year-old mother. His older brother was healthy. His psychomotor development was severely delayed since birth. He was unable to hold his head or sit by his first birthday, and he had no speech throughout his life. Hypotonia and feeding difficulties with failure to thrive were observed since birth. His weight was only 6kg until 1 year of age. The first seizure occurred at 6 months of age, with a frequency of 2-3 times per day, lasting about tens of seconds each. The dysmorphic features of the proband included microcephaly, straight eyebrows, deep-set eyes, hypertelorism, asymmetric and low-set ears, a high-arched palate, clinodactyly, tracheal malformation, strephexopodia, and fair skin. Additionally, the proband had a femoral hernia. He died at 1 year of age from septic shock following a severe infection. A single umbilical artery and mild bilateral ventriculomegaly (11mm) were detected by prenatal ultrasound at 22 weeks gestation. A ventricular septal defect was revealed by echocardiography after birth, and was repaired at 6months of age. The clinical information of the proband and the clinical characteristics of previously published patients with combined 1p36 deletion and 22q13 duplication patients with isolated 1p36 deletions or 22q13 duplications are summarized in table 1[10]. He was referred to our laboratory for genetic analysis at 5 months of age, the karyotype was 46, XY. However, array CGH detected a 9.3-Mb 1p36 deletion plus a 6.655-Mb 22q13 duplication which was confirmed by MLPA.

Table 1: Clinical characteristics of the proband, the fetus and the previously published combined 1p36 deletion and 22q13 duplication as well as isolated 1p36 deletion and 22q13 duplication.

	Combined 1p36 deletion and 22q13 duplication[Gajecka et al. 2008][10]				This study		Isolated 1p36 deletion [Slavotinek et al., 1999; Battaglia et al., 2008][2, 3]	Isolated 22q13 duplication [Feenstra et al., 2006][6]
	Case 128	Case 127	Case 42	Case 13	The proband	The fetus		Collected from review
General								
							39 reported cases	24 reported cases
Sex	M	M	M	M	M	F		
Low-birth weight		+	+					+
Small for gestational age		+						
Survival past neonatal age	+	+	+	+	Died at age 1	Aborted at 22 weeks gestation		
Reduced life expectancy					+			+
Facial features								
Microcephaly		+		+	+	+	+	+
Large anterior fontanelle		+	+	+			+	
Brachycephaly		+					+/-	
Prominent forehead							+	+
Straight eyebrows,					+		+	
Deep-set eyes		+			+	+	+	+
Short, narrow or slanting							+	+
Palpebral fissures								
Hypertelorism			+		+	+		+
Epicanthic folds							+	+
Flat nasal bridge	+		+				+	+
Asymmetric ears	+	+	+	+	+	+	+	
Posteriorly rotated ears		+					+	
Low-set ears		+	+	+	+	+	+	+
Small mouth							+	
Down turned corners of the mouth							+	+
Long philtrum							+	
Pointed chin		+	+	+			+	

Micro/retrognathia			+					+
High arched palate		+			+		+	
Webbed neck								+
Short neck			+					
Hypoplastic nipples								+
Orofacial clefting							+	+
Clinodactyly				+	+	+	+	
Tracheal malformation					+			
Small hands and/or feet		+						
Strephexopodia					+			
Developmental delay/	+	+	+	+	+		+	
Intellectual disability includes speech delay								
Behavioral difficulties							+	+
Hypotonia	+	+	+	+	+		+	+
epilepsy		+	+	+	+		+	+
MRI/CT[a]		a	a	a	a		a	
Visual problems								
Visual inattentiveness	+			+	+			
Strabismus		+					+	
Sixth nerve palsy							+	
amblyopia							+	
Refractive errors							+	
Bilateral cataracts							+	
Hearing loss				+	+		+	
Congenital heart defects								+
Patent ductus arteriosus			+	+			+	
Ventricular septal defect			+		+		+	
Ebstein anomaly		+					+	
Pulmonary valve stenosis								+
Feeding difficulty/failure to thrive	+			+	+		+	+
obesity							+/-	
Oropharyngeal dysphasia		+		+	+			
Gastroesophageal reflux		+	+		+			
Fair skin					+			
Delayed bone age				+				
Genital or renal anomalies								+
Ectopic left kidney								+
cryptorchidism				+			+	+
Small genitalia							+/-	
Early puberty							+/-	
Skeletal anomalies							+	+
Sacral cleft/dimple		+						
Karyotype	46,XY,der(1) t(1;22) (p36.3;q11.23)	46, XY, der(1)t(1:22) (p36.3;q13.3)	46,XY, der1t(1:22)	46,XY,	46,XY	46,XX		

Parental age(Mother/ Father)	35/36	34/36	18/un-known	29/45	28/32	30/34		
Parental chromosomes								
Father:	46,XY	46,XY, t(1:22)	46, XY	46,XY, t(1;22)	46,XY	46,XY		
Mother:	46,XX, t(1;22)	(p36.3;q13.3) 46, XX	46, XX, t(1;22)	(p36;q13) 46,XX	46,XX	46,XX		

[a]Abnormal MRI/CT include: dysgenesis of the corpus collosum (case 127), leukoencephalopathy (case 13), prominent ventricles (case 13), generalized cerebral atrophy(case 13), brain dysplasia with asymmetry (case 42), mild ventriculomegaly (the proband). Cerebral atrophy, ventricular asymmetry, ventricular enlargement, and hydrocephalus (isolated 1p36 deletion)

The proband's mother consented to amniocentesis and cytogenetic testing at 18 weeks of gestation for another pregnancy. A single umbilical artery and mild bilateral ventriculomegaly (11mm) were detected by ultrasound again at 22 weeks of gestation,the karyotype of the fetus was 46, XX. Array CGH detected the same chromosomal aberration as the proband. She terminated the pregnancy at 24 weeks of gestation. The aborted female fetus had similar facial features to the proband according to the description of the mother. The standard karyotypes of the parents performed by another laboratory were normal.

Methods

DNA Extraction

Genomic DNA was extracted from peripheral blood lymphocytes of the proband as well as the amniotic fluid cells of the fetus using a QIAamp DNA mini kit (Qiagen, Valencia, CA, USA) Informed consent was obtained from parents of the children in the study.

Array CGH

An Agilent Sure Print G3 Human CGH Microarray Kit (8×60K, Agilent Technologies, Santa Clara, CA, USA) was used for genetic analysis of the proband and the fetus according to the manufacturer's instructions (Agilent Oligonucleotide Array-Based CGH for Genomic DNA Analysis, version 7.3). DNA hybridization was performed according to the standard procedures after labeling of 500ng of the sample DNA with cyanine-5 and control DNA with cyanine-3(Promega, USA). The signals were captured by Sure Scan microarray scanner (Agilent Technologies, Santa Clara, CA, USA). Microarray data was analyzed using Feature Extraction software and Workbench genomics software (Agilent Technologies, Santa Clara, CA, USA). The Aberration Detection Methods 2 algorithm (ADM2) was used to analyze data with a threshold of 6.0 and a moving average window of 2 kb. Log 2 ratios under 0.25 and variations with less than three consecutive probes were excluded. Genomic positions were based on the UCSC February 2009 human reference sequence (GRCh37/hg19) (NCBI build 37 reference sequence assembly). Then, the clinical relevance of observed chromosomal aberrations was estimated according to data found in the scientific literature and databases for each of the regions and genes involved, using the DECIPHER database (http://www.sanger.ac.uk/PostGenomics/decipher/) for known micro deletion or micro duplication syndromes and the Online Mendelian Inheritance in Man (OMIM,www.ncbi.nlm.nih.gov/Omim/getmorbid.cgi) for known disease-causing genes and gene functions.

MLPA

Multiplex Ligation-dependent Probe Amplification (MLPA) analysis was performed to confirm the rearrangements detected by array CGH using SALSA P070, P036 and P245 kit (MRC-Holland. Amsterdam, Netherlands). MLPA analysis was performed according to the manufacturer's instructions. The amplification products were identified and quantified by capillary electrophoresis on a genetic analyzer (ABI 3130XL, USA). The fluorescence signal intensities of the PCR products were determined with Coffalyser.Net software.

Results

Array CGH analysis uncovered a 9.3-Mb deletion of 1p36.33p36.22 plus a 6.655-Mb duplication of 22q13.31q13.33in the proband. This rearrangement was confirmed by MLPA P070 and P245 kit. A 9.231-Mb deletion of 1p36.33p36.22 plus a 6.655-Mb duplication of 22q13.31q13.33 was detected in the fetus, which was almost identical with the rearrangement of the proband. The family tree and array CGH results of the proband are showed in figure 1, and MLPA results are showed in figure 2. The deletion/duplication sizes of our patients and the reported patients are summarized in table 2.

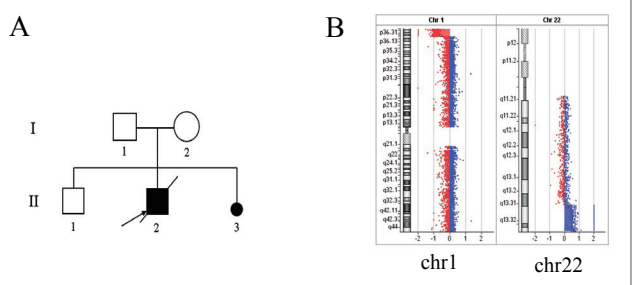
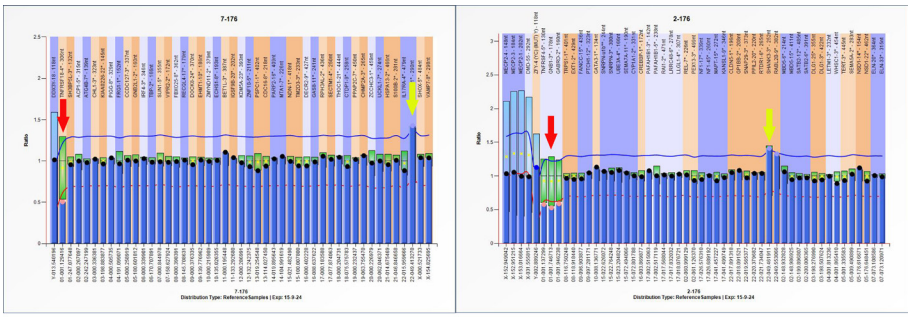


Figure 1: The family tree and array CGH results of the proband. A: The family tree, the white square represents normal males, the white circle represents normal females, the black square with a slash represents patients who has died, the relatively small black circle represents aborted fetuses; B: results of array CGH analysis. A 9.3Mb deletion on chromosome 1; A 6.655 Mb duplication on chromosome 22.



P070 P245

Figure 2: Results of MLPA of the proband. P070 and P245 show combined 1p36 deletion and 22q13 duplication. Red arrows indicate 1p36 deletion, yellow arrows indicate 22q13 duplication.

Table 2: The deletion/duplication sizes of patients in this study and the reported patients.

		Sizes (Mb)	
		1p36 deletion	22q13duplication
[Gajecka et al.][10]	Case 13	9.96	0.12
	Case 42	7.77	1.94
	Case 127	3.98	6.58
	Case 128	2.59	9.74
	The proband	9.3	6.655
This study	The fetus	9.231	6.655

Discussion

In this study, we described the clinical and molecular characteristics of a boy and a female fetus from a family with combined 1p36 deletion and 22q13 duplication. The proband was born at term with mild intrauterine growth retardation. His postnatal growth and psychomotor development were severely delayed, and he died at 1year of age from septic shock following a severe infection. He weighted 6kg (< 3rd percentile) when he died. His mother consented to amniocentesis for another pregnancy, and the array CGH analysis revealed an almost identical rearrangement to the proband. The pregnancy was terminated at 24 weeks of gestation, and the fetus had similar facial features to the proband.

Combined 1p36 deletion and 22q13 duplication was rarely seen in the literatures with only four patients reported by Gajecka et al. [10]. We compared the clinical features observed in our patient to whose of and the patients reported by Gajecka et al. and to those of patients with isolated 1p36 deletions or 22q13 duplications. Most features identified in the proband were similar to those reported for patients by Gajecka et al. [10]. The following features were seen in the proband and in at least one of the four reported patients: low birth weight (2.5kg), developmental delay/intellectual disability, hypotonia, epilepsy, microcephaly, asymmetric ears, low-set ears, deep-set eyes, hypertelorism, a high-arched palate, clinodactyly, visual inattentiveness, hearing loss, a ventricular septal defect and feeding difficulties with failure to thrive. Most of these features were similar to those associated with 1p36 deletion syndrome and with 22q13 duplications. However, some features seen in at least one of the four reported patients were not observed in our patient, including large anterior fontanelle, brachycephaly, short neck, flat nasal bridge, posteriorly rotated ears, pointed chin, micrognathia, small hands and/or feet, strabismus, patent ductus arteriosus, ebstein anomaly, cryptorchidism and a sacral cleft. Features that were only seen in our patient, included tracheal malformation, straight eyebrows, strephexopodia and fair skin. With the exception of straight eyebrows, these features are not common for 1p36 deletion syndrome [2-4]. Given the poor characterization of 22q13 duplication phenotypes, we hypothesize that these features are specific to 22q13 duplications.

Early death, which has been reported for distal 22q duplications [11,12], was not observed in the reported patients who had combined 1p36 deletion and 22q13 duplication [10], but it was observed in our patient. Because a reduced life expectancy was not reported for 22q13.2 and 22q13.3 duplications, Gajecka et al. hypothesized that a reduced life expectancy was associated with duplications of 22q12-22q13.1, that were more proximal than 22q13.2 [6,13]. This contradiction may reflect an ascertainment bias. Whether reduced life expectancies are associated with 22q13 duplications requires further investigations using large cohorts. Additionally, a single umbilical artery and mild ventriculomegaly which were seen in both the proband and the fetus are important indications of chromosome abnormalities, and the ultrasound physician should pay attention to these recurrent indicative features.

The female fetus was aborted at 24 weeks of gestation, and according to the parents' description, it has similar facial features to the proband. Echocardiography was not performed for the fetus. Therefore, whether the fetus had congenital heart defect remains uncertain.

It's difficult to perform a genotype-phenotype correlation analysis because only five children and a fetus have been reported to date. The deletion sizes and breakpoint locations of our patients were different from those of the reported patients (Table 2), without the common size or breakpoints of 1p deletion or 22q duplication [10]. Moreover, we did not observe correlations between the deletion/duplication sizes and phenotypes from these patients. Eight commonly observed clinical features for isolated 1p36 deletion syndrome were chosen for analysis as follows: a large anterior fontanel, hearing problems, structural heart defects, seizures, hypotonia, feeding difficulties, speech delay, and strabismus [10,14]. Our patient exhibited five of these features, most of which were specific for the 1p36 deletion syndrome rather than for 22q13 duplications as the reported patients (Table 1). This confirms that the presence of a chromosomal deletion has a stronger impact on phenotype compared with a duplication [10].

The chromosomal abnormalities in our patients were not detected by a conventional karyotype analysis. The karyotypes of the parents were normal, but the recurrence of the rearrangements in this family strongly indicate da germinal mosaic translocation in one parent or translocation derivatives that were too cryptic to distinguish from the normal karyotype [15]. Unfortunately, FISH analysis cannot be performed on the parents to confirm this because of their poor coherence. However, the recurrence of a rearrangement involving two chromosomes in a single family, where the parents have normal karyotypes, highlights array CGH as an essential pre- and post-natal diagnostic technology.

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References

1. Shaffer LG, Lupski JR (2000) Molecular mechanisms for constitutional chromosomal rearrangements in humans. Annu Rev Genet 34: 297-329.
2. Battaglia A, Hoyme HE, Dallapiccola B, Zackai E, Hudgins L, et al. (2008) Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics 121: 404-410.
3. Slavotinek A, Shaffer LG, Shapira SK (1999) Monosomy 1p36. J Med Genet 36: 657-663.
4. Heilstedt HA, Ballif BC, Howard LA, Lewis RA, Stal S, et al. (2003) Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. Am J Hum Genet 72: 1200-1212.
5. Brazil A, Stanford K, Smolarek T, Hopkin R (2014) Delineating the phenotype of 1p36 deletion in adolescents and adults. Am J Med Genet A 164A: 2496-2503.
6. Feenstra I, Koolen DA, Van der Pas J, Hamel BC, Mieloo H, et al. (2006) Cryptic duplication of the distal segment of 22q due to a translocation (21;22): three case reports and a review of the literature. Eur J Med Genet 49: 384-395.
7. Okamoto N, Kubota T, Nakamura Y, Murakami R, Nishikubo T, et al. (2007) 22q13 Microduplication in two patients with common clinical manifestations: a recognizable syndrome? Am J Med Genet A 143A: 2804-2809.
8. Peeters H, Vermeesch J, Fryns JP (2008) A cryptic duplication 22q13.31 to qter leads to a distinct phenotype with mental retardation, microcephaly and mild facial dysmorphism. Genet Couns 19: 365-371.
9. Magri C, Marchina E, Bertini V, Traversa M, Savio G, et al. (2015) SNP array and FISH analysis of a proband with a 22q13.2- 22qter duplication shed light on the molecular origin of the rearrangement. BMC Med Genet 16: 47.
10. Gajecka M, Saadeh R, Mackay KL, Glotzbach CD, Spodar K, et al. (2008) Clinical and molecular cytogenetic characterization of four patients with unbalanced translocation der(1)t(1;22)(p36;q13). Am J Med Genet A 146A: 2777-2784.
11. Bendel RP, Baldinger S, Millard C, Arthur DC (1982) Two successive partial trisomies for opposite halves of chromosome 22 in a mother with a balanced translocation. J Med Genet 19: 313.
12. Schinzel A (1981) Incomplete trisomy 22. II. Familial trisomy of the distal segment of chromosome 22q in two brothers from a mother with a translocation, t(6;22) (q27;q13) Hum Genet 56: 263-268.
13. Wieczorek D, Holtvogt J, Thonig S, Gillessen-Kaesbach G (1998) A female patient with partial duplication 22 (q13-->qter). Clin Dysmorphol 7: 289-294.
14. Gajecka M, Mackay KL, Shaffer LG (2007) Monosomy 1p36 deletion syndrome. Am J Med Genet C Semin Med Genet 145C: 346-356.
15. Di Gregorio E, Savin E, Biamino E, Belligni EF, Naretto VG, et al. (2014) Large cryptic genomic rearrangements with apparently normal karyotypes detected by array-CGH. Mol Cytogenet 7: 82.