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CASE REPORT

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Prenatal diagnosis of a rare de novo 1q22-q25.1 chromosomal deletion syndrome using oligo array CGH

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Key Clinical Message

We present prenatal diagnosis of a case with a rare de novo interstitial deletion of 1q21-q25.1 by oligo array CGH and provide detailed information on unbalanced gene content and the breakpoints. The affected fetus was delivered at 37 weeks' gestation with a unique clinical phenotype.

KEYWORDS

1q22-q25.1, cleft lip/palate, oligo array CGH, small hands and feet

1 | INTRODUCTION

Unbalanced de novo copy number variants (CNVs) are relatively common in humans and are associated with a wide variety of congenital malformations.[1] Many publications have recently reported associations of such CNVs with these malformations.[2,3] CNVs pathogenicity has been proposed as due to haploinsufficiency of genes in CNV regions. In this regard, interstitial deletion of 1q22-q25.1 is a rare CNV for which detailed genotype-phenotype correlations are not yet well-established. The first case showed a partial deletion of 1q22-q25 following a pericentric inversion in a 4-year-old boy with mental and physical retardation.[4] The second case was described in 1980 by de Pablo.[5] The deletion was detected by G banding, Q banding, and C banding karyotypes. The third case was reported by Leber in 2006.[6] Prenatal ultrasound detected major abnormalities in this case but cultured amniocytes showed normal karyotype**.** After birth, karyotype analysis using lymphocyte culture revealed an interstitial deletion of 1q22-q25. Moreover, six cases with more proximal and larger deletion of 1q21-q25 have been published [7,8] (Table 1). However, these cases lack the molecular mapping of the breakpoints and the gene content by a currently-practiced genome technology like array CGH. The largest cohort of interstitial deletions of the long arm of chromosome 1, comprising 18 patients and two family cases, was published by Chatron et al.[9] Therefore, considering the small number of reported cases, the wide variability of the phenotypes associated with the previously-described deletions and the lack of molecular data about the size of deletions, the delineation of a precise deletion syndrome involving 1q22-q25.1 band is still challenging. Here we report, for the first time, the

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TABLE 1 Clinical features of this and three previously-reported patients with an interstitial deletion in 1q22-q25

	Interstitial deletion of 1q22-q25.1				Deletion partially overlapped with 1q22-q25					
	Present case	**Scwanitz 1977**	**D Pablo 1980**	**Leber R. R. ASHG 2006**	**Sekhon 1987**	**Schimzel 1980**	**Silengo 1984**	**Beemer 1985**	**Takano 1997**	**Melis De 1998**
Deleted region	1q22-q25.1	1q22-q25	1q2-q25	1q22-q25	1q21-q25	1q21-q25	1q23-q25	1q21-q25	1q24-q25.3	1q22-q24
Breakpoints	154559773-171639287	NA	NA	NA	NA	NA	NA	NA	NA	NA
Deleted OMIM genes	138	NA	NA	NA	NA	NA	NA	NA	NA	NA
Method of detection	CGH array	Karyotype	Karyotype	Karyotype	Karyotype	Karyotype	Karyotype	Karyotype	Karyotype	Karyotype
Sex of case	Female	Male	Male	Male	Male	Female	Female	Male	Male	Male
Parent	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy
Parental karyotype	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Low birthweight	+	−	+	+		+	+	+	+	+
Microcephaly	−	−	+	+		+	+	+	+	+
Bilateral cleft lip/palate	+	−	+	+		+	+	+	−	+
Malformed low-set ears	+	+	+	+		+	−	+	+	+
Small hands and feet	+	+	+	+		+	+	+	+	+
Hypotonia	+	+	−	+		+			−	+
Clinodactyly	−	−	+	+		−	−		+	−
Transverse palmar crease	+	−	+	+		−	−		+	−
Inguinal hernia	−	+	+	+		−	+		−	−
Congenital heart disease	−	−	−	−		+	+		+	−
Seizures	−	−	−	−						
Cryporchidism		−	+	+		+			+	−

prenatal diagnosis of a case with 1q22-q25 microdeletion, its gene mapping, and the exact breakpoints using an oligonucleotide array CGH.

2 | CASE PRESENTATION

A 26-year-old pregnant woman, G3P2, referred for prenatal diagnosis and genetic counseling at 12 weeks' gestation. In the first pregnancy, a normal girl was delivered. The second pregnancy was delivered by cesarean due to oligohydramnios, kidney problem, cleft lip/palate, and intrauterine death detected by ultrasound at 38 weeks' gestation. The VDRL, toxoplasmosis, cytomegalovirus, rubella, blood and urine tests were all normal. There was no family history of congenital malformations or other genetic disorders. Routine first-trimester screening [10] showed a low risk. The first-trimester screening is carried out for chromosomal defects. It was performed by a combination of maternal age, fetal nuchal translucency thickness at $11\text{-}13^{+6}$ weeks of gestation, and maternal serum biochemistry (free Ƀ-hCG and PAPP-A) to identify about 85%-90% of affected fetuses. Follow-up ultrasound monitoring at 20 weeks' gestation detected oligohydramnios, IUGR and small hands and feet. To check the chromosomal abnormalities, amniocentesis was performed. Then, DNA extracted from amniocytes was subjected to CGH array.

CGH array analysis on the DNA extracted from amniocytes detected a 17 Mb deletion at 1q22-q25.1, arr 1q22q25.1 (154559773-171639287,) X1 (Figure 1). This means that the breakpoints are at base pair 154559773-171559773. This deleted region contained 235 HGNC genes, including 138 OMIM genes. To confirm the deletion by the FISH analysis, Probe RP11-443G18 was ordered. However, we could not get the probe for the FISH analysis at the due time. Cytogenetic analysis for the woman and her husband revealed a normal karyotype. The possible phenotypes were explained for the parents, and they decided to continue the pregnancy. Finally, a female fetus was delivered at 37 weeks' gestation by cesarean. She was diagnosed with a bilateral cleft lip and palate, a transverse palmar crease in the right hand, a short neck, a normal head circumference, a broad nasal bridge, poorly-shaped and low-set ears, a birthweight of 1800 g, small hands and feet, hypotonia and a hemangioma on the back of the head (Figure 2). She was operated for her cleft lip and cleft palate (image not shown). After birth, the array CGH was again carried out using the DNA extracted from peripheral blood. It revealed the same microdeletion on 1q22-q25.1 and confirmed our prenatal array CGH results.

The whole-genome array-CGH analysis on the DNA extracted from amniocytes was performed using a BlueGnome cytochip 4×44K version 2.1 oligonucleotide array. The BlueGnome 4×44K cytochip ISCA array has 44 000 probes and a median resolution of 75 kb across the entire genome. According to the manufacturer's instructions, 0.5 µg of the extracted DNA was digested with Alu1 and Rsa1 (5 unit each) and subsequently labeled with Cy3 dye. Then it was compared with an equivalent amount of normal female genomic DNA labeled with Cy5 dye to perform the array CGH experiment. Finally, slides were scanned using an Innoypsis 900 microarray scanner and analyzed using Bluefuse multi V2.3 software. Although array CGH allows for a high-resolution investigation of DNA copy number alterations associated with chromosomal abnormalities, this method cannot detect

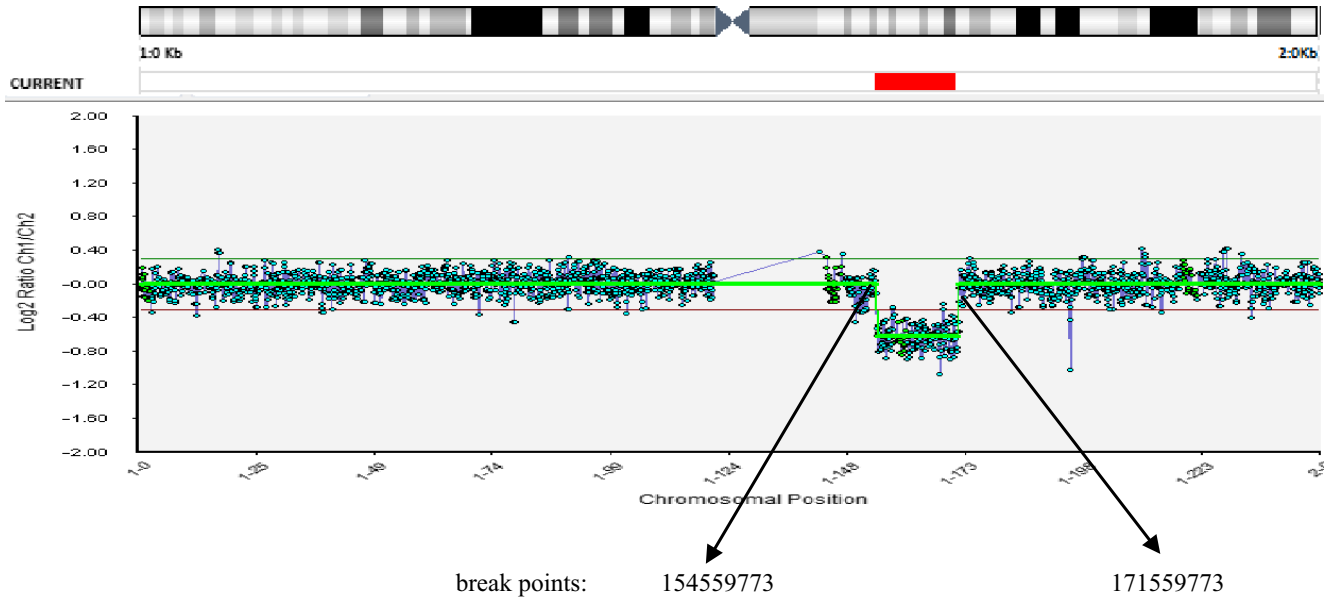

FIGURE 1 Array-CGH genomic chromosme1 profile from BlueGnome cytochip ISCA4x44K array confirming an interstitial deletion of 17 Mb (1q22-q25.1)

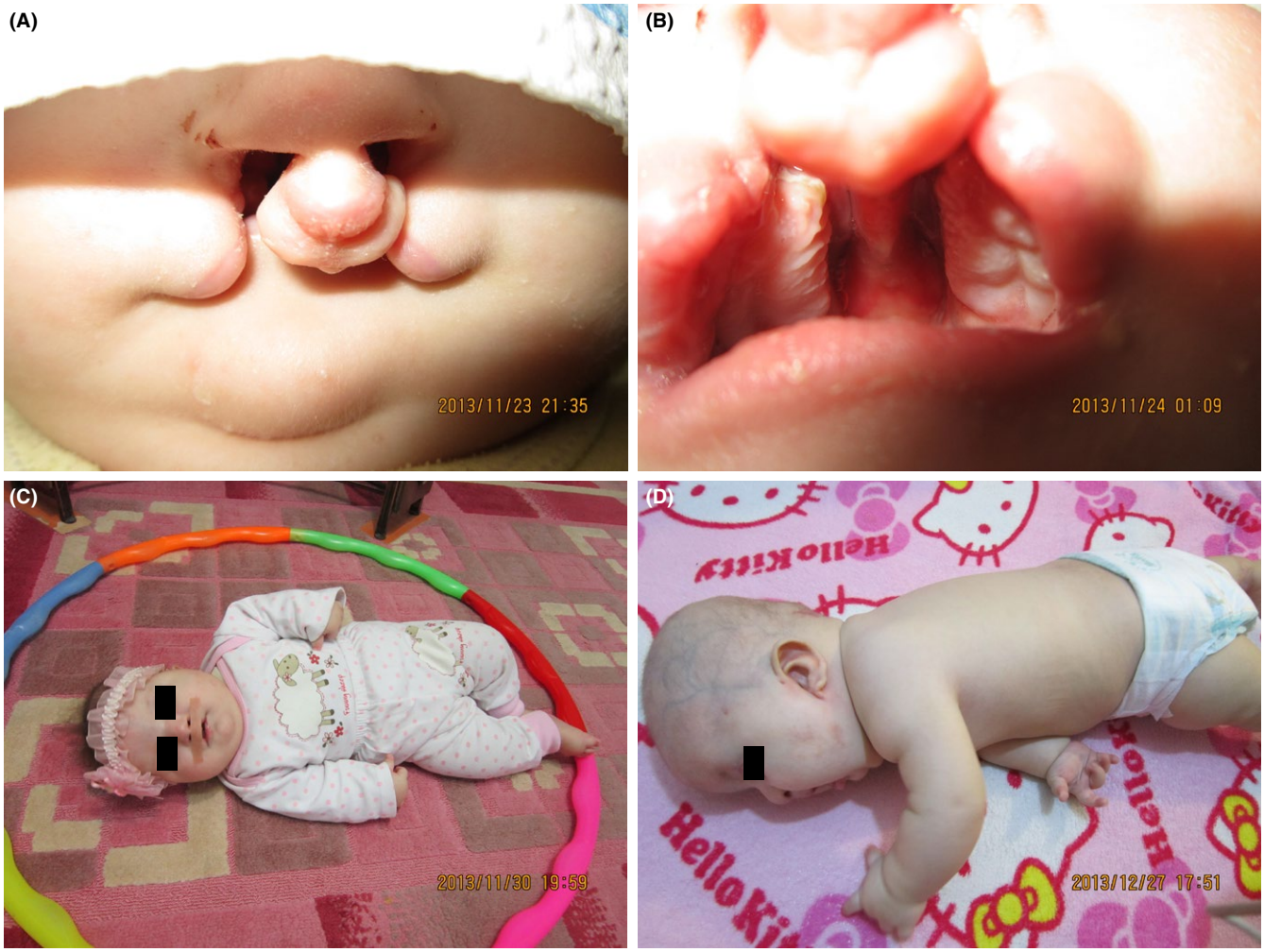

FIGURE 2 A and B, Frontal view demonstrating the bilateral cleft lip/palate. C, Supine view of whole body demonstrating small hands and feet. D, lateral view of body showing a hemangioma on the occipital part of the head and a single palmar crease in right hand

balanced chromosomal rearrangements, some polyploidies, single-base changes, and gains and losses in regions not covered by the array.

3 | DISCUSSION

To our best knowledge, this is the first prenatal case of partial deletion of the long arm of chromosome 1, 1q22-q25.1, by array CGH. There have been three previously-reported cases in the literature (Table 1). The first case showed a partial deletion of 1q22-q25 following a pericentric inversion. The patient was a 4-year-old boy with mental and physical retardation.[4] His clinical features include prominent occiput, small chin, deep-seated and dysplastic ears, abnormal vortices of the hair, divided tip of the tongue, high palate, small finger and toes, inguinal hernia of both sides, undescended but normal sized testes, hypotonic musculature and overextensible joints, retardation of ossification in the left hand by 6-12 months, and slight osteoporosis. The second case showed a de novo interstitial deletion of 1q22-q25. The case had a birthweight of 1720 g, 40 cm tall, small head circumference and 11 months later, microbrachycephaly with closed fontanels and fused sutures, frontal bossing, sparse eyebrows, bilateral exophthalmos, epicanthus and hypertelorism, low-set ears, cleft lip and cleft palate. Finally, the third case was presented in program Nr. 798 for the 2006 ASHG annual meeting.[5] The phenotypes were quite variable among these cases. The second and the third case, with similar deletion to our case (1q22-q25), presented microcephaly, inguinal hernia, and clinodactyly.[5,6] However, our patient was not affected by microcephaly, inguinal hernia, and clinodactyly. Common clinical characteristics included low birthweight, bilateral cleft lip/palate, malformed and low-set ears, and hypotonia. To compare the variability of phenotypes in accordance with genotypes, we do not have the molecular mapping of breakpoints and the gene content in those three previously-reported cases. Our case is the first to be delineated by array CGH. The size of the deletion was 17 Mb in

chromosomal 1q22-q25.1 region and its breakpoints were at base pair 154559773-171639287. The deleted region overlapped 138 OMIM (Online Mendelian Inheritance in Man) genes. Several of these genes are involved in known OMIM diseases. For example, mutation of DNM3 gene has been reported to associate with palate abnormalities.[9] Deleted regions overlapping PBX1, LMX1A, and RXRG are also reported to be associated with renal and cardiac malformations. [9] Dermaunt et al[11] evaluated the contribution of genetic variations in NCSTN gene in two large series of patients with early and late onset of the Alzheimer's disease. Lisi reported the contribution of PEX genes in a peroxisomal disorder and hypotonia.[12] Deletion of PEX19 gene in our patient and its haploinsufficiency may be involved in hypotonia. Moreover, through mutation analysis and transient transfection of human kidney cells, it was found that the N terminus of DEDD gene induces apoptosis and that C terminus has antiapoptotic activity.[13] In summary, due to the limited information about the function of these genes, we cannot hypothesize the exact contribution of the deletion of each gene to the clinical phenotype of the patient. There were also six previously-reported cases with interstitial deletion of the long arm of chromosome1, which partially overlapped with the deletion in our case and a few similar phenotypes. Three cases have a more proximal and larger deletion (1q21-q25) compared with the deletion in our patient (1q22-q25.1).[7,14,15] However, the other three cases had a smaller deletion which overlapped the distal part of the deletion in our case.[8,16,17] Congenital heart problems were present in two cases; one of them had a larger, more proximal deletion (1q21-q25.1)[14] than the one in our case while other cases had a smaller deletion (1q23-q25).[16] What is more, we do not have detailed information about the gene content and breakpoints in these six cases. Moreover, Chatron et al[9] published the largest series of patients carrying a deletion involving 1q24q25 region and the associated phenotypes including growth retardation, microcephaly, intellectual disability, brachydactyly, and facial dysmorphism.

In conclusion, we report an interstitial deletion of 1q22-q25.1 in a prenatal case and provide detailed information on unbalanced gene content and the breakpoints. This information is helpful for prenatal genetic counseling of fetal viability and phenotype prediction. In fact, the comparison of our case with the eight formerly-reported cases is difficult given the inherent problem of accurate breakpoint delineation by classical karyotyping in the previous cases. However, it seems that the common phenotypic features are low birthweight, bilateral cleft lip/palate, malformed and low-set ears, and hypotonia. An emerging genotype-phenotype correlation could also be established in this rare deleted region (1q22-q25.1). However, we need further cases with accurate delineation by array CGH to determine the molecular basis of these clinical features.

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AUTHORSHIP

GS and HG: performed Genetic Consultation. AS: performed array CGH analysis and writing manuscript. MH: involved in manuscript writing. AS: is patient clinician. NA: performed array CGH experiment.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest regarding this article.

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REFERENCES

1. Sibbons C, Morris JK, Crolla JA, Jacobs PA, Thomas NS. De novo deletions detected by array CGH: a study of parental origin in relation to mechanisms of formation and size of imbalance. *Eur J Med Genet*. 2012;20:155-160.
2. Pinkel D, Segraves R, Sudar D, et al. High-resolution analysis of DNA copy number variation using comparative genome hybridization to microarray. *Nat Genet*. 1998;20:207-211.
3. Ballif BC, Sulpizio SG. R, M. Lloyd, S. L. Minier, A. Theisen, B. A. Bejjani, L. G. Shaffer, The clinical utility of enhanced subtelomeric coverage in array CGH. *Am J Med Genet*. 2007;143A:1850-1857.
4. Schwanitz G, Schmid P, Hägele C, Daffner HW, Grosse KP. Partial deletion of 1q, following a pericentric inversion, in a boy with multiple minor morphologic anomalies and mental retardation. *Acta Genet Med Gemellol (Roma)*. 1977;26:173-175.
5. de Pablo CE, Garcia Sagredo IM, Ferro MT, Ferrando P, San Romance C. Interstitial deletion in the long arms of chromosome 1: 46, XY, del (1) (pter->q22-q25->qter). *J Med Genet*. 1980;17:483-486.
6. Leber RR, Shutt BJ. Chromosomal deletion syndrome1q22-q25. Program Nr:798 for the 2006 ASHG annual meeting.
7. Schinzel A, Schmid W. Interstitial deletion of the long arm of chromosome1, del (1) (q21 leads to q25) in a profoundly severed 8-year-old girl with multiple anomalies. *Clin Genet*. 1980;18:305-313.
8. Daniel M, Peron L, Sperando MP, et al. Mild phenotype associated with an interstitial deletion of the long arm of chromosome 1. *J Med Genet*. 1998;35:1047-1049.

9. Chatron N, Haddad V, Andrieux J, et al. Refinement of genotype-phenotype correlation in 18 patients carrying a 1q24q25 deletion. *Am J Hum Genet*. 2015;167A:1008-1017.
10. Nicolaides KH. *The 11–13 + 6 weeks scan*. London: Fetal Medicine Foundation; 2011.
11. Dermaut B, Theuns J, Sleegers K, et al. The gene encoding nicastrin, a major gamma-secretase component, modifies risk for familial early-onset Alzheimer disease in a Dutch population-based sample. *Am J Hum Genet*. 2002;70:1568-1574.
12. Lisi EC, Cohn RD. Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature. *Dev Med Child Neurol*. 2011;53:586-599.
13. Stegh AH, Schickling O, Ehret A, et al. DEDD, a novel death effector domain-containing protein, targeted to the nucleolus. *EMBO J*. 1998;17:5974-5986.
14. Beemer FA, Klep-de Pater JM, Sepers GJ, Janssen B. Two cases of interstitial deletion of the long arm of chromosome 1: del(1)(q21—q25) and del (1) (q41—q43). *Clin Genet*. 1985;27:515-519.
15. Sekhon GS, Hulman RE, Yu R, Aronson MM, Green AE, Coriell LL. Deletion in the long arm of chromosme 1 from a subject with multiple congenital anomalies. *Cytogenet Cell Genet*. 1978;21:176.
16. Silengo MC, Davi GF, Bianco R. Interestitial deletion of chromosome 1 (1q23-q25). Report of a case. *Clin Genet*. 1984;25:549-552.
17. Takano T, Yamanouchi Y, Mori Y, et al. Interestitial deletion of chromosme 1q [del(1)(q24q25.3)] identified by fluorescence in situ hybridization and gene dosage analysis of apolipoprotein A-II coagulation factor V, and antithromobin III. *Am J Med Genet*. 1997;68-207-210.

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