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Case Report

A Child Carrying a Large Deletion in the 10p.15.3-p12.31 Region

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Abstract

Partial deletion of 10p is a rare disorder. Common features of this disorder include intellectual disability, developmental delay, dysmorphic features, hypoparathyroidism, deafness, and renal anomalies, but the phenotypes can vary between patients. We report an infant girl presented with global developmental delay, distinctive facial features with cleft lip, congenital exotropia, laryngomalacia, atrial septal defect, and sensorineural hearing loss. 46, XX, del (10p→ter) was observed on the G-banded analysis. A chromosomal microarray was performed to obtain more detail on the deletion size and gene involvement that might be related to the clinical phenotypes, medical problems, and management. The deletion involved the region of 10p15.3–p12.31, with an approximate size of 19.528739 Mb. The size of deletion could determine the variability in phenotypes, and microarray is necessary to comprehend the deletion size and gene involvement better.

Keywords
DiGeorge syndrome type 2; 10p deletion; chromosomal microarray

1. Introduction

Deletion of 10p is associated with multiple congenital anomalies in <1/1,000,000 of the population [1]. This chromosomal deletion resulted in variable clinical phenotypes, including congenital heart disease, T-cell deficiency, hypoparathyroidism/hypocalcemia, facial anomalies, development, and growth retardation, hearing loss and genitourinary anomalies [2]. However, compared to 22q11.2 microdeletions, congenital heart disease manifestations in partial monosomy 10p are more heterogeneous and of conotruncal type [3]. The clinical phenotypes in the partial monosomy of 10p are associated with two distinct regions: hypoparathyroidism, sensorineural hearing impairment, and renal disease 1 *(HDR1)* and DiGeorge critical region gene 2 *(DGCR2)* [4, 5].

Statistically, 22q11.2 deletions are more frequent and comprise >90% of patients with DiGeorge syndrome (DGS) or velocardiofacial syndrome (VCFS) [6]. Combined clinical examination and genetic analysis are essential to the deletions at chromosome 22q11.2 or 10p13-14 in patients with DGS phenotype.

We report a patient with multiple congenital anomalies, in concordance with DiGeorge Syndrome Type 2, which was confirmed on chromosomal microarray examination.

2. Case Presentation

2.1 Physical Examination

The patient's mother was a woman in her 20s, gravida 4 para 1 abortus 2, with a nonremarkable pregnancy. The mother experienced oligohydramnios in the 38th week of pregnancy. The baby was delivered at term with a birth weight of 2,300 grams (weight-for-age Z-score = -2.25 SD) and a birth length of 43 cm (height-for-age Z-score = -3.3 SD), indicating an intrauterine growth restriction (IUGR), and the baby was born grunting. She was then admitted into the neonatal intensive care unit for a week due to symptoms of difficulty breathing and cyanosis.

At 4 months, the proband was referred to a pediatric endocrinologist after being diagnosed with hypotonia, severe short stature, and failure to thrive. She also had a history of developmental delay (Denver Development Screening Test-II: personal-social age was 2.5 months old, fine motor age was normal according to age, language was newborn-old, and gross motor was newborn-old), with no history of seizures. Anthropometric measurement at the age of 5 months revealed that the baby had a body weight of 3,900-gram, body length of 55.5 cm (height-for-age Z-score = -3.75 SD, weight-for-age Z-score = -2.08 SD), and head circumference 36.5 cm (-3.81 SD (microcephaly)). Further examination revealed a dysmorphic and asymmetric face with hypertelorism, a right incomplete cleft lip with a high-arched palate, a depressed nasal bridge, bulbous tip and low set ears (Figure 1), along with craniosynostosis, a short neck, a wide-spaced nipple, and pectus excavatum. A sandal gap was noticed on her extremities, and her right hand had a simian crease. Chest x-ray indicated cardiomegaly and a 2 mm atrial septal defect was observed in echocardiography. An ophthalmologic examination indicated congenital left eye exotropia. Her ears were posteriorly rotated and low set

and were characterized by the pre-auricular pit, prominent antihelix and antitragus, and earlobes creases. The reduced function of outer hair cells was detected in otoacoustic emission (OAE) and tympanometry. A profound sensorineural hearing loss at 115/117 decibels was detected on brainstem evoked response audiometry (BERA). No abnormality was detected on renal sonography. She had calcium levels at 2.3 mmol/L (reference value 2.12-2.52 mmol/L).

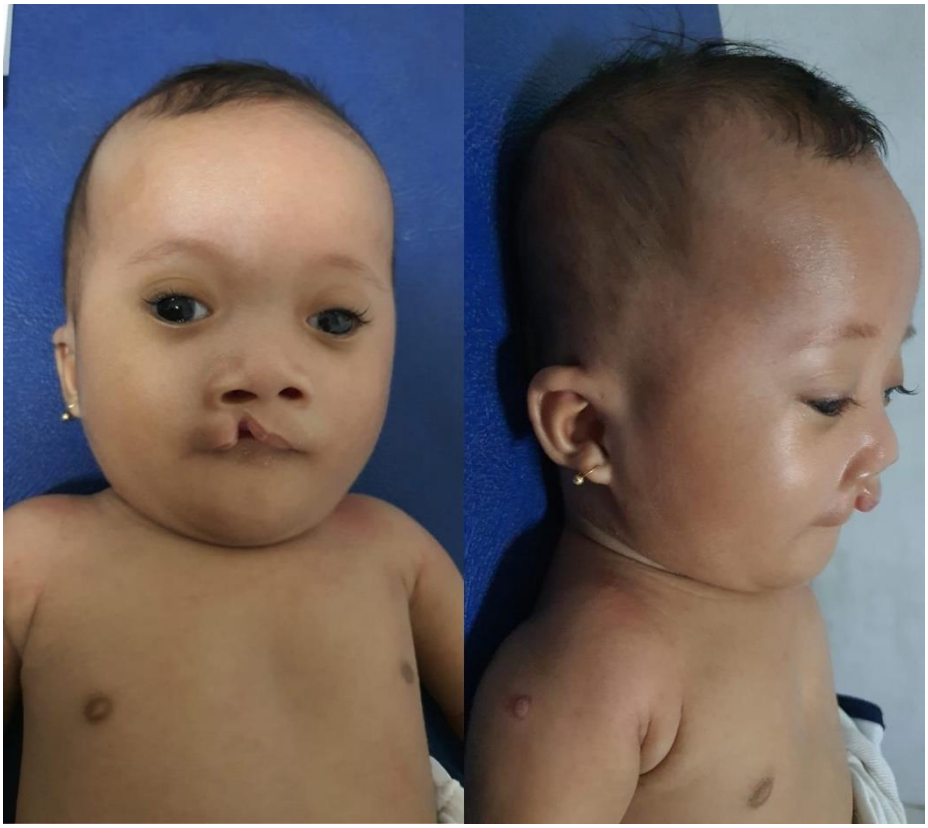

Figure 1 Clinical phenotypes demonstrating a dysmorphic and asymmetric face with hypertelorism, right incomplete cleft lip, depressed nasal bridge, bulbous tip, short neck, wide-spaced nipple, and pectus excavatum.

She was diagnosed with a global developmental delay, as a Denver II Developmental Screening Test conducted at the age of one year revealed that her personal-social age was 2.5 months old, fine motor age was 3 months old, language was 3 months old and gross motor was that of a newborn.

Written informed consent for physical examination, genetic analysis, and publication was obtained from the patient's parents.

2.2 Genetic Diagnosis

Genetic diagnostics were performed with chromosomal analysis and chromosomal microarray. The peripheral blood sample was collected and stored in heparin (for chromosome analysis) and EDTA (for chromosomal microarray). Metaphase chromosomes were stained with a G-banding technique and analyzed at approximately 550 band resolutions.

Extraction of genomic DNA was accomplished using a g-DNA purification kit using the manufacturer’s protocol. The quality and quantity of the DNA were measured using Qubit dsDNA HS (Thermo Fisher Scientific). Human CytoSNP-12 v2.1 Bead-Chip kit chromosomal microarray,

comprising 301,232 markers, was used to confirm the conventional chromosomal analysis. The array was performed using NextSeq (Illumina) in the Genetic Laboratory, National Center for Women and Children's Health Harapan Kita, Indonesia, and was analyzed using BlueFuse Multi v4.5 (Illumina).

While the parental chromosome analysis showed no structural abnormality, the child's chromosomal analysis revealed a karyotype of 46, XX, del (10p). Chromosomal microarray confirmed a deletion of chromosome 10p (arr10p15.3.p12.31(135,708-19,664,446)x1), which was approximately 19.528739 Mb in size (Figure 2), based on Genome Reference Consortium Human Build 37 (GRCh37/hg19). This deletion, involving 65 OMIM genes, overlaps the known diseases region of DiGeorge Syndrome/velocardiofacial syndrome complex 2 (OMIM 601362) and hypoparathyroidism, sensorineural deafness, and renal disease (OMIM 146255).

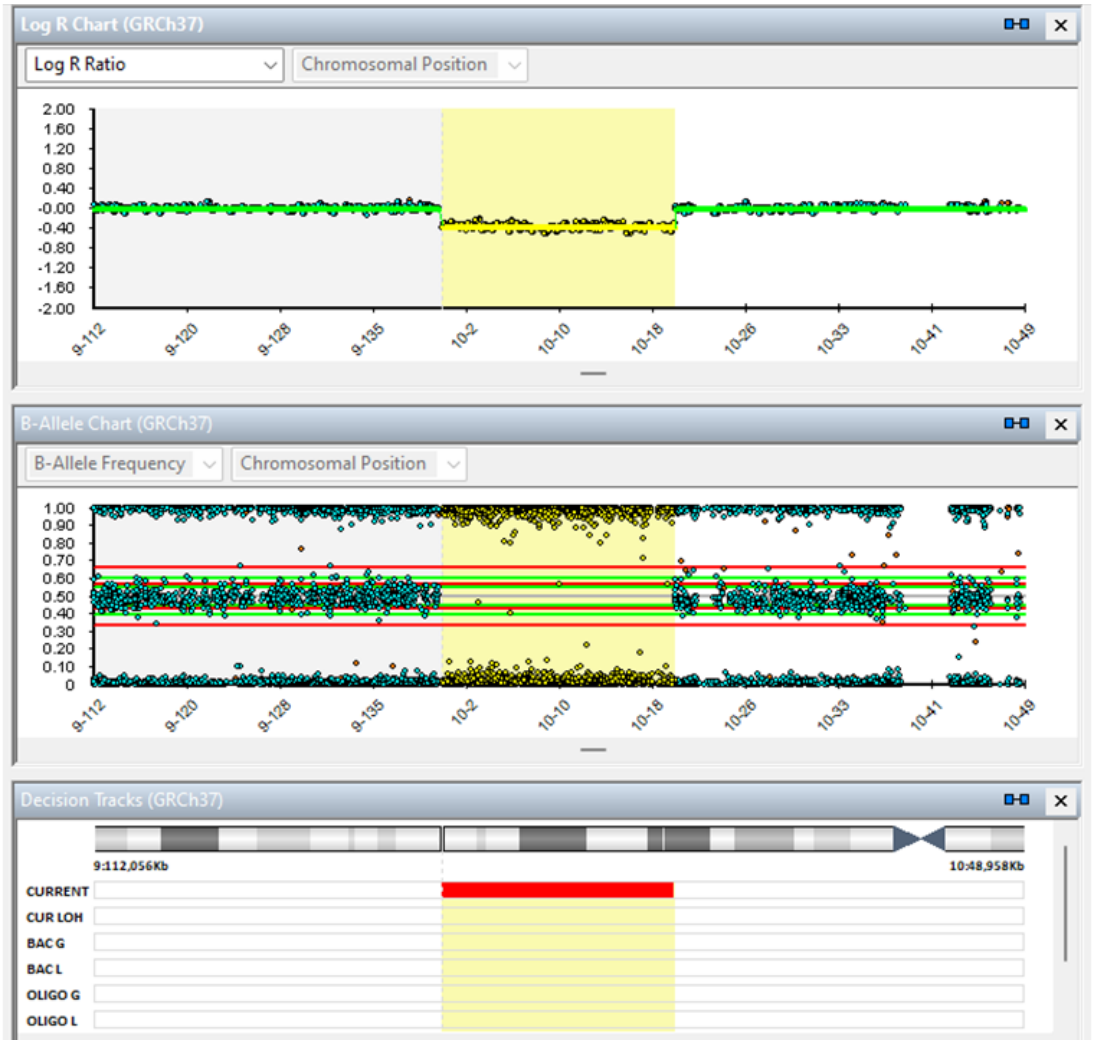

Figure 2 Chromosomal microarray analysis using Human CytoSNP-12 v2.1 Bead-Chip kit chromosomal microarray, comprising 301,232 markers, demonstrating the deletion in 10p region.

2.3 Outcome and Follow-Up

A corrective surgery was performed on the child for her cleft lip. She is being regularly monitored for growth, development, and potential complications. Her nutritional needs dictate her diet,

comprised of 640 ml of liquids, 110 kcal/kgBW/day, 1.5 g/kgBW/day of protein, and 1.5 g/kgBW/day of lipid. Recent follow-up demonstrated satisfactory nutritional status, average weight, and normal stature. Follow-ups on her Denver II Developmental Screening Test showed improvement in fine motor adaptive skills from 3 months to that of a 4-month-old.

3. Discussion

We reported a child with approximately 19.5 Mb deletion of chromosome 10p15.3 to p12.31 who was characterized by global developmental delay, distinctive facies with unilateral labioschisis and congenital exotropia, atrial septal defect, and sensorineural hearing loss. This patient exhibited the second-largest terminal deletion of chromosome 10p we found in the literature to date (Figure 3). The known disease regions, DGR2 (OMIM 601362) and HRD syndrome (OMIM 146255), are overlapped by the 10p15.3.p12.31 region covering 168 HGNC and 65 OMIM-curated genes.

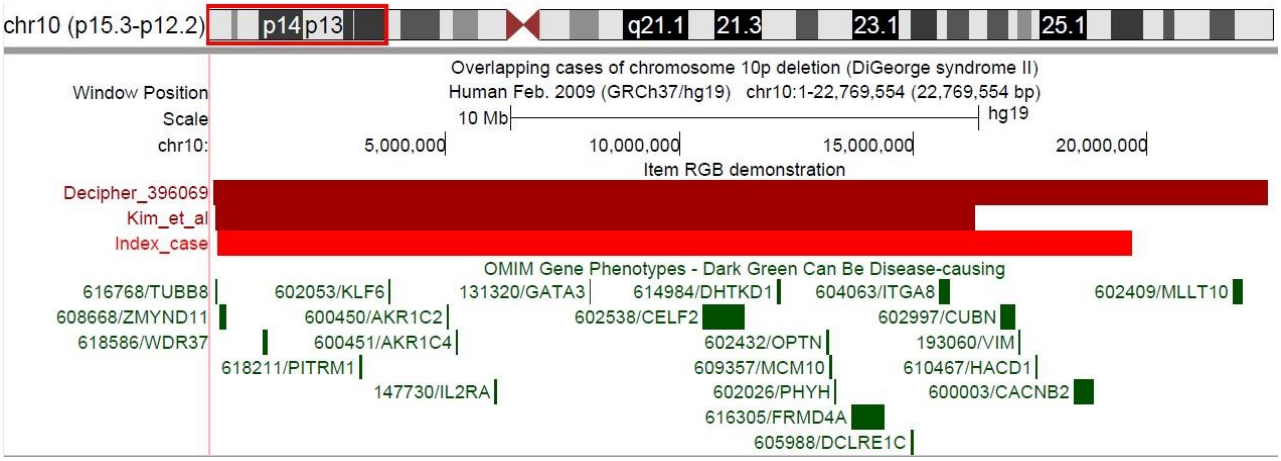

Figure 3 Comparison of the deleted regions in our case with previously reported cases from the literature and DECIPHER's database. A screenshot of the UCSC genome browser highlights part of chromosome 10 from 10p15.3 to 10p12.2. The brown bar indicates the present case, while the cases in the literature are shown in light gray. OMIM disease-causing gene locations have been represented with dark green bars. Genome coordinates for the DECIPHER case are converted to GRCh37. Our case coordinate is arr10p15.3.p12.31(135,708-19,664,446)x1), based on Genome Reference Consortium Human Build 37 (GRCh37/hg19).

Variations in clinical phenotypes characterize 10p terminal deletions. A comparison between the present case and two other cases has been shown in Table 1. The case we found in the DECIPHER database is 22.5 Mb, the most extensive deletion to our knowledge [7].

Table 1 Comparison between our case (Index case) and previous publications.

	Index case	**Kim et al. [8]**	**Decipher #396069 [7]**
Age, gender	1y, Female	Neonate, Female	7y, Male
CMA results (GRCh37/hg19)	(arr 10p15.3.p12.31(135,708-19,664,446)x1)	(arr 10p15.3p13(100,047-16,314,195)x1)	(arr 10p15.3.p12.31(60,001-22,559,994)x1); (arr 5q35.3

			(176,667,394-180,905,260)x3)
Deletion size	19.528 Mb	16 Mb	22.5 Mb
Hypoparathyroidism	-	+	hypocalcemia
Hearing loss	Sensorineural	Sensorineural	Sensorineural
Renal/urinary tract disease	no abnormalities from renal sonography	+	Multiple cysts, renal dysplasia, vesicoureteral reflux, recurrent urinary tract infections
Cardiac anomalies	ASD, cardiomegaly	+	ASD, VSD
Thymus hypoplasia/aplasia	N/A	+	N/A
Autism	N/D	N/D	N/D
Dysmorphism	Labioschizis, high arched palate, depressed nasal bridge, bulbous nasal tip, low set ears, short neck, widely spaced nipples	+ (broad nasal root, small mouth with thin upper lips, retromicrognathia and low-set malformed posteriorly rotated ears, widely spaced nipples)	Broad neck, depressed nasal bridge, downslanted palpebral fissure, hypoplastic philtrum, low posterior hairline, redundant neck skin, short neck, short palpebral fissure, short philtrum, telecanthus, wide nasal bridge, widely spaced nipples
Cognitive/behavioral delay	+	N/D	+
Motor delay	+	Expected	+
Speech/language delay	+	N/D	+
Craniofacial dysmorphism	Microcephaly	+ (disproportionately large head for her face)	Frontal bossing, malar flattening
Brain anomalies	N/A	+ (Brain MRI c DWI shows patchy diffusion restrictive lesions in the left frontoparietal white matter)	EEG abnormality

DGS2 is considered a contiguous gene syndrome; however, the role of deletions of different sizes in the phenotype variability remains unclear. An approximately 4.19025 Mb deletion in the 10p14 region showed only psychomotor delay, palpebral ptosis, epicanthic folds, anteverted nares, cryptorchidism, hand/foot abnormalities, and sensorimotor deafness. It showed no cardiac defect, cleft palate, or abnormal T cell levels [4]. A study by Lindstrand et al. demonstrated intellectual disability, autism, language impairment, and dysmorphic features in four cases involving an overlapping region in 10p14-p15 [9]. A 16 Mb deletion at 10p15.3p13 on a neonate, associated with respiratory difficulties at birth, dysmorphic facial features, thymus hypoplasia, genitourinary

abnormalities, cardiac anomalies, hypocalcemia, sensorineural deafness, and brain abnormalities has previously been reported [8].

Poluha *et al.* described a 1.08 Mb deletion in 10p15.3 with similar but more severe phenotypes since it involved brain abnormalities of Chiari malformation type I and spinal cord edema [10]. A report by DeScipio *et al*. also indicated the involvement of brain abnormalities, including cortical atrophy, hydrocephalus, and arachnoid cysts in one patient [11]. A partial monosomy of 10p involving 10p12.31-ter resulted in severe psychomotor delay, growth failure, congenital heart defect, multicystic kidney disease, grade V vesicoureteric reflux, and neurosensory hearing impairment [12].

The deletion in our case covers several essential genes, including *ZMYND11, DIP2C, WDR37, KLF6, AKR1C2, AKR1C4, PITRM1, IL2RA, GATA3, DHTKD1, CELF2, OPTN, MCM10, PHYH, FRMD4A, DCLRE1C, CUBN, VIM, HACD1, and CACNB2* genes. *ZMYND11* (OMIM #608668) and *DIP2C* (OMIM #611380), associated with severe neuropsychiatric disorders and brain abnormalities, were known to be located within the 10p15.3 region [10, 11]. The deleted *WDR37* gene might be the explanation for patient's developmental delay, exotropia, atrial septal defect, and cardiomegaly, as reported by Sorokina et al. in 2023 that *WDR37* variant c.778G>A p.(Asp260Asn) which caused a lower level of WDR37 protein compared to wild-type [13]. The deleterious variant in the *DHTKD1* gene was reported to cause amyotrophic lateral sclerosis (ALS) phenotypes in two European cohorts [14]. A study in a large Chinese family pedigree found that a nonsense mutation in exon 8 of the *DHTKD1* gene (c.1455T>G, p.Tyr485X) caused Charcot-Marie-Tooth disease type 2 [15]. The *PHYH* gene is one of the genes involved in phytanic acid metabolism. Deleting the gene might lead to an enzymatically inactive protein, causing the buildup of phytanic acid. This condition is called Refsum disease, and some of its phenotypes are present in our patients: sensorineural hearing loss, developmental delay, motor problems, and skeletal malformations [16]. A loss of the *GATA3* gene (OMIM #131320), resulting from a deletion in the 10p14 region, will produce HDR phenotypes since it is the critical gene involved in the development of parathyroid glands, kidneys, thymus, auditory system, and central nervous system [5]. In our patient, we found only sensorineural hearing loss, not HDR phenotypes' other features. In a review by Barakat et al., among patients with a *GATA3* gene defect, 1 patient (0.6%) showed deafness without hypoparathyroidism and renal disease [17]. This patient was reported by Belge et al. in a familial case of *GATA3* c.856A>G (p.N286D) substitution, whose father had HDR syndrome and whose sister had hypocalcemia and deafness [18]. HDR syndrome is associated with a highly variable inter- and intrafamilial phenotype.

It seems to be challenging to conclude genotype-phenotype correlation. For example, every patient, including ours with the same deleted region did not exhibit renal abnormality, indicating that this inconsistency was probably due to variable penetrance [19]. It is also possible that the presence of another genetic rearrangement will influence the clinical phenotypes. An example of this case is the report of a patient with DGS carrying monosomy 10p13-pter and a trisomy 10q26-qter resulting from the meiotic recombination of a maternal inversion (10)(p13q26) demonstrated similar clinical phenotypes characterized by intellectual disability, abnormally shaped skull, hypertelorism, low nasal bridge, micrognathia, dysmorphic low set ears, short neck, foot abnormalities, cardiac defect, hypoplastic thymus, T-cell defect, hypocalcemia, and hypoparathyroidism [20]. It is also possible that some phenotypes might not appeared/developed yet due to this patient's young age.

4. Conclusions

The large deletion in 10p15.3.p12.31 region might cause clinical phenotypes related to the DiGeorge Syndrome type 2, as well as hypoparathyroidism, sensorineural deafness, and renal disease (HRD syndrome). However, the variable phenotypes shown in this type of deletion still need more studies.

Acknowledgments

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Author Contributions

Nani Maharani assisted the physical examination and wrote the initial draft of the case report; Agustini Utari was the first encountered with the patients, did the physical examination and genetic counseling; Nydia Rena Benita Sihombing assisted the physical examination, collected pictures and created figures; Tri Indah Winarni coordinated the writing and finalized the report. All authors contributed to revision of the draft and approved the final draft.

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Competing Interests

The authors have declared that no competing interests exist.

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