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Dicentric Recombinant Chromosome 18 due to Maternal Paracentric Inversion Analyzed by Array CGH

Özlem Anlaş[a] Akgün Ölmez[b] Birsen Karaman[c] Füsun Düzcan[d] Selçuk Yüksel[e] Funda Tümkaya[f] Gülseren Bağcı[d] Cavidan Nur Semerci Gündüz[g]

[a]Department of Medical Genetics, Adana City Training and Research Hospital, University of Health Sciences, Adana, Turkey; [b]Pediatric Neurology Private Office, Denizli, Turkey; [c]Department of Medical Genetics, School of İstanbul Medicine, Istanbul University, Istanbul, Turkey; [d]Department of Medical Genetics, School of Medicine, Pamukkale University, Denizli, Turkey; [e]Department of Pediatric Nephrology, School of Medicine, Pamukkale University, Denizli, Turkey; [f]Department of Otolaryngology, School of Medicine, Pamukkale University, Denizli, Turkey; [g]Department of Medical Genetics, School of Medicine, Ankara Yıldırım Beyazit University, Ankara, Turkey

Established Facts

- Chromosomal inversions lead to unbalanced gametes.

Novel Insights

- This is the first report of a patient with dicentric chromosome 18 due to a parental paracentric inversion of chromosome 18.

Keywords
Dicentric chromosome 18 · Paracentric inversion · Array CGH · FISH · C-banding

Abstract

Introduction: Chromosomal abnormalities are mostly found in 0.5–0.8% of live-born infants with developmental and morphological defects. Paracentric inversions are structural intrachromosomal rearrangements resulting in a risk of chromosomally unbalanced gametes in carriers. ***Case Presentation:*** Herein, we report a patient with dicentric rearrangement of chromosome 18 due to maternal paracentric inversion of chromosome 18. The patient was a girl, aged 3 years and 11 months. She was referred due to multiple congenital abnormalities, severe intellectual disability, and motor retardation. She had microcephaly, prominent metopic suture, synophrys, epicanthic folds, telecanthus, wide-set alae nasi, wide columella, bilateral cleft lip and palate, pectus carinatum, umbilical hernia, pes planus, and anteriorly displaced anus. She had bilateral external auditory canal stenosis and mild right-sided and moderate left-sided

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Correspondence to:
Özlem Anlaş, dr.ozlemanlas@gmail.com

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sensorineural hearing loss. Echocardiography showed secundum-type atrial septal defect and mild tricuspid failure. Brain magnetic resonance imaging showed only thinning of posterior areas of the corpus callosum. Chromosome analysis showed 46,XX,dic rec(18) by GTG and C banding. Dicentric chromosome was confirmed by fluorescence in situ hybridization analysis. Paternal karyotype was normal 46,XY but maternal chromosome analysis showed a paracentric inversion in chromosome 18 with 46,XX,inv(18)(q11.2?q21.3?) karyotype. Array CGH was performed on a peripheral blood sample from the patient and showed duplication at 18p11.32p11.21 and 18q11.1q11.2, and deletion at 18q21.33q23. The patient's final karyotype is arr 18p11.32 p11.21(64,847_15,102,598)×3,18q11.1q11.2(18,542,074_22,666,470)×3,18q21.33q23(59,784,364_78,010,032)×1. ***Discussion:*** To the best of our knowledge, this is the first report of a patient with dicentric chromosome 18 due to a parental paracentric inversion of chromosome 18. We present the genotype-phenotype correlation with literature review.

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Introduction

Inversions are structural intrachromosomal rearrangements involving two breaks and the reinsertion of the chromosome segment after a rotation through 180°. If the inverted segment includes only one chromosome arm, not including the centromere, it is known as a paracentric inversion [Madan, 1995]. Inversion-loop formation is the mechanism which may lead to duplication or deletion of the entirety or parts of the inverted segment in the offspring. As a result of this, if the inverted loop contains a centromere, the resulting recombinant chromosome will be dicentric [Liehr, 2019]. Although paracentric inversions are harmless to the carrier, there is a risk for having an affected child due to recombination events, such as mitotic instability of the expected acentric and dicentric recombinants or duplicated and deleted segments [Madan and Nieuwint, 2002; Courtens et al., 1998]. Balanced paracentric inversions have also been reported to lead to multiple miscarriages in carrier women [Courtens, 1998].

Paracentric inversions are usually found incidentally during routine karyotype analysis and can be difficult to identify using standard chromosome analysis [Madan and Nieuwint, 2002; Rowe et al., 2009]. Advances in molecular cytogenetic and molecular methods, following conventional cytogenetic methods, may result in better understanding of the causes of complex chromosomal rearrangements. Herein, we report the clinical, cytogenetic, and molecular cytogenetic findings of a patient with an unbalanced rearrangement of chromosome 18 due to maternal paracentric inversion of chromosome 18.

Case Presentation

A girl, aged 3 years and 11 months, was referred due to multiple congenital abnormalities (Fig. 1) and mental and severe cognitive impairment. She was born at 39 weeks of gestation by cesarean section after an uneventful pregnancy with a birth weight of 3,200 g. Her parents were second cousins. Although cleft lip and palate was noted at birth, there were no other problems. She had a history of operations because of diaphragmatic hernia at 9 months old and for her cleft lip and palate at 18 months of age. She also had a history of recurrent urinary tract infections (UTI). Her mental and motor developmental milestones were delayed; she had head control at 12 months and sat without support at 24 months.

On physical examination, her weight was 12 kg (3rd-10th centile), her length was 90 cm (3rd centile), and her head circumference was 45.5 cm (<3rd centile). As shown in Figure 1, she had microcephaly, a prominent metopic suture, biparietal narrowing, synophrys, epicanthic folds, telecanthus, wide-set alae nasi, wide columella, bilateral cleft lip and palate, low-set malformed auricles, and hypoplasia of the tragus. In addition, she had pectus carinatum, umbilical hernia, pes planus, a wide gap between first and second toes, sacral dimple, and anteriorly displaced anus. She had operation scars on the philtrum and abdomen, and she still had partial cleft palate. Her speech was delayed, and she could only say a few words, like "mom" and "food," but could express herself by simple hand signs. She had prominent spasticity in the lower extremities, especially in the Achilles tendons, but truncal hypotonia. She could stand on tip-toes with support and take a few steps (Fig. 1). She had bilateral genu recurvatum. Bruxism was observed during the examination.

Her laboratory investigation showed normal whole blood count, blood biochemistry, and thyroid function tests. Urinalysis and urine culture showed current UTI, so renal ultrasonography was performed. Ultrasonography showed normal kidneys but bladder trabeculation and thickening. A voiding cystourethrography investigation detected grade II vesicoureteral reflux. Normal left kidney cortical function but hypoactive area and irregularity in the right kidney were recorded by renal cortical scintigraphy using Tc-99m DMSA. Echocardiography showed secundum-type atrial septal defect and mild tricuspid failure; magnetic resonance imaging of brain showed only thinning of posterior areas of the corpus callosum. Electroencephalogram showed no epileptiform activity. She had bilateral narrowing of the external auditory canal and mild and moderate sensorineural hearing loss in the right and left ears, respectively.

She was put on a special education and a physical rehabilitation programme, both at home and at a private school. Due to the history of recurrent UTI and her vesicoureteral reflux, antibiotic prophylaxis was commenced by pediatric nephrology. On follow-up visits, her progress in motor skills was evident. Her spas-

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Fig. 1. The patient.

ticity gradually decreased without muscle relaxant treatment. She began to walk greater distances using the whole sole of her foot and still needed support, but without genu recurvatum. Her vocabulary did not increase, but her communication with family members and strangers increased.

Chromosome analysis showed 46,XX,dic rec(18) by GTG- and C-banding (Fig. 2a, b). Dicentric chromosome was confirmed by fluorescence in situ hybridization (FISH) analysis with a chromosome 18-specific α-satellite probe (Fig. 2c). Subtelomeric FISH analysis showed that there was a deletion in the long arm and a duplication in the short arm of chromosome 18 (Fig. 2d). Paternal karyotype was a normal 46,XY but maternal chromosome analysis showed a paracentric inversion on chromosome 18 with 46,XX,inv(18)(q11.2?q21.3?) karyotype. Array CGH was performed on a SurePrint G3 CGH + SNP Microarray Platform (Agilent, Santa Clara, CA, USA), and analysis was performed on DNA extracted from a peripheral blood sample. The array CGH showed duplication at p11.32p11.21 and q11.1q11.2, and deletion in the q21.33q23 regions of chromosome 18 (Fig. 3). The patient's final karyotype was arr 18p11.32 p11.21(64,847_15,102,598)×3,18q11.1q11.2(18,542,074_22,666,470)×3,18q21.33q23(59,784,364_78,010,032)×1 [ISCN, 2020].

Discussion

Numerical and structural abnormalities are frequently observed in chromosome 18 because it has a high number of specific repeat sequences which leads to an increase in the tendency to rearrangements. We described a girl with multiple congenital anomalies and severe cognitive impairment who had a 15-Mb duplication at 18p11.32p11.21, a 4.1-Mb duplication at 18q11.1q11.2, and a 19.1-Mb deletion at 18q21.33q23 due to maternal paracentric inversion of chromosome 18. There are 64 genes in the deleted segment and 106 genes in the duplicated segments.

Feenstra et al. [2007] reported genotype-phenotype mapping of 18q deletions by high-resolution array CGH. In their patients with 18q deletion syndrome, the most common clinical findings are short stature, microcephaly, midface hypoplasia, hypertelorism, congenital aural atresia (CAA), foot deformities, severe cognitive impairment, and hypotonia. All of these findings were present in our patient. Less common features are IgA deficiency, obesity, hyperlaxity, strabismus, eczema, and behavioral problems, all of

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Table 1. Clinical features of patients with del18q/dup18p and del18p/dup18q chromosomal aberrations

	Present case	Bartels et al. [2011]	Vianna-Morgante et al. [1976]	Teyssier and Bajolle [1980]	Hu et al. [2013]	Courtens et al., 1998		Israels et al. [1996]
						case 1	case 2	
Chromosomal aberration	del(18)(q21.33q23) (19.1 Mb) dup(18)(p11.32p11.21) (15 Mb) dup(18)(q11.1q11.2) (4.1 Mb)	del(18)(q22.3) (13.2 Mb) dup(18)(p11.32) (2.2 Mb)	del(18)(q21) dup(18)(p11)	del(18)(q21) dup(18)(p11)	del(18)(q21.33) (17.7 Mb) dup(18)(p11.21) (12.4 Mb)	del(18)(q22.3) dup(18)(q12.2q21.1)		dup(18)(q21.1) del(18)(p11.2)
Origin	Maternal paracentric inversion	De novo	Maternal pericentric inversion	Paternal pericentric inversion	Maternal pericentric inversion	Maternal paracentric inversion		Paternal pericentric inversion
Sex	Female	Male	Male	Male	Male	Male (monozygotic twins)	Male	Male
Age	4 years	13 years	18 months	Newborn	Newborn	Newborn	Newborn	13 months
Cognitive impairment	+	+	+	N/A	N/A	N/A	N/A	+
Speech delay	+	–	N/A	N/A	N/A	N/A	N/A	–
Hypotonia	+	+	+	+	N/A	+	+	–
Hearing impairment	+ (sensorineural)	–	N/A	–	N/A	N/A	+ (conductive)	–
Aural atresia	–	–	–	–	N/A	–	–	–
Microcephaly	+	–	+	+	–	+	+	–
Epicanthal folds	+	–	+	–	+	+	+	+
Cleft lip/palate	+ (bilateral cleft lip and palate)	–	–	–	–	–	–	–
Congenital heart malformation	Sec ASD	N/A	N/A	+ (left-right shunt)	Aortic coarctation	ASD	ASD	VSD, ASD
Limb anomalies	+ (genu recurvatum)	–	–	–	–	–	–	+
IgA deficiency	–	N/A	N/A	N/A	N/A	N/A	N/A	–
Thinning of corpus callosum	+	N/A	N/A	–	N/A	N/A	N/A	–
Vesicoureteral reflux	+	+	–	–	–	–	–	–
Other	Umbilical hernia	Anal atresia	–	Tracheolaryngomalacia, ploric stenosis; died because of cardiac malformation	Died 1 day after birth because of pulmonary hypoplasia	Webbed neck; died at the age of 2 months from cardiogenic shock	–	–

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Table 1 (continued)

	Andrieux et al. [2008]	Li et al. [1998]	Vermeulen et al. [2005]	Balasubramanian et al. [2016]	Liehr et al. [2019]	
					case 1	case 2
Chromosomal aberration	del(18)(q21.2q21.32) 6.2 Mb	dup(18)(p11.2p11.32)	del(18)(q23) and dup(18)(pterp11.22)	dup(18)(p11.32p11.31)	del(18)(q22.3q23) and dup(18)(p11.32p11.22)	
Origin	De novo	De novo	Paternal pericentric inversion	Paternal dup(18) (p11.32p11.31)	Maternal pericentric inversion	
Sex	Male	Male	Female	Female	Male	Male
Age	12 years	8 months	16 years	6 years	17 years	6 years
Cognitive impairment	+	+	–	+	+	+
Speech delay	+	N/A	–	+	N/A	N/A
Hypotonia	–	+	–	–	N/A	N/A
Hearing impairment	–	–	–	–	+ (sensorineural)	+ (sensorineural)
Aural atresia	–	–	–	–	–	–
Microcephaly	+	–	–	Relative microcephaly	+	+
Epicanthal folds	–	+	–	–	N/A	N/A
Cleft lip/palate	–	–	–	–	–	–
Congenital heart malformation	–	–	–	–	–	–
Limb anomalies	+	–	–	–	–	–
IgA defficiency	–	N/A	–	–	N/A	N/A
Thinning of corpus callosum	+	–	–	–	N/A	N/A
Vesicoureteral reflux	–	N/A	–	–	N/A	N/A
Other	Thin eyebrows, up-slanting palpebral fissures, anteverted nostrils, dysplastic ears, long philtrum with thin upper lip, and prominent central incisors	Deep-set eyes, short upturned nose, and micrognathia	Deficient social behavior and high-grade myopia	Social immaturity and difficult behavior	Dwarfism and facial dysmorphism	Facial dysmorphism

ASD, atrial septal defect; VSD, ventricular septal defect. N/A: not available.

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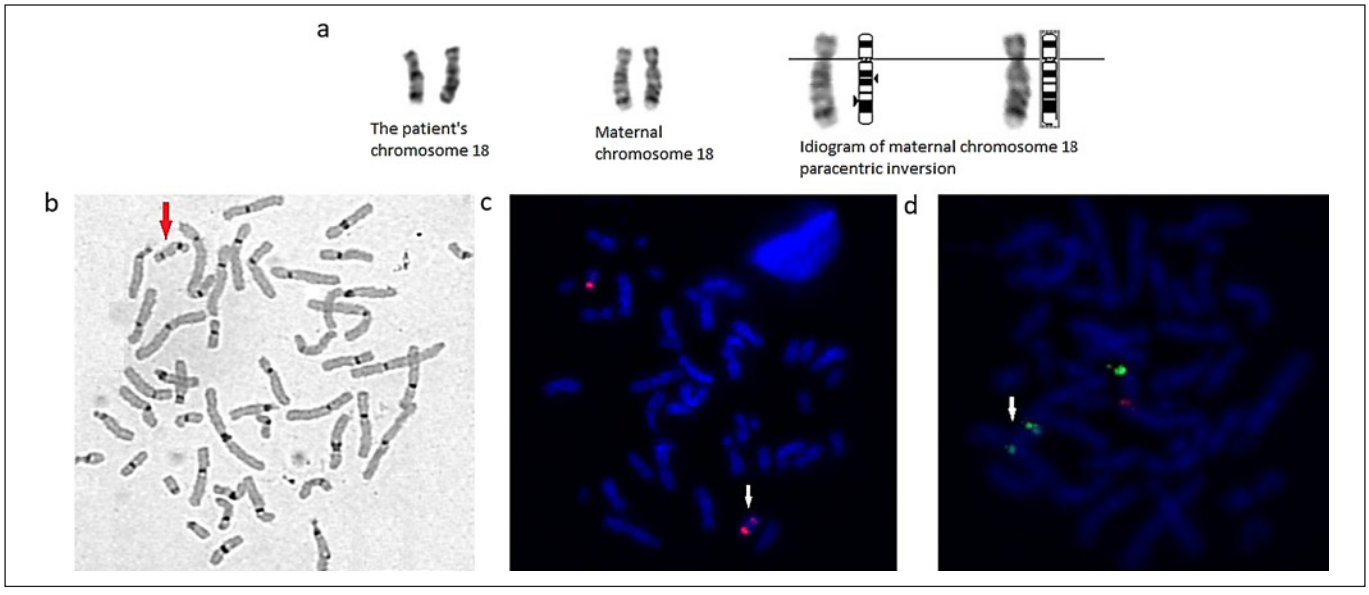


Fig. 2. Cytogenetic and FISH analysis. **a** Chromosome 18 of the patient (left) and of the mother (middle). The idiogram shows the break points of the maternal chromosome 18 (right). **b** C banding of the patient. Red arrow shows the dicentric chromosome 18 due to maternal paracentric inversion. **c** FISH analysis with chromosome 18-specific α-satellite probe, which marks centromere with red, shows the dicentric chromosome 18 (white arrow shows that there are two centromeres of chromosome 18). **d** Subtelomeric FISH analysis, using CytoCell subtelomere-specific probe, which marks p arm with green and q arm with red, shows a deletion in the long arm (q arm) of chromosome 18 and a duplication in the short arm (p arm) of chromosome 18 (two green signals show the duplication of p arm of chromosome 18 and lack of one red signal shows the deletion of the q arm of chromosome 18).

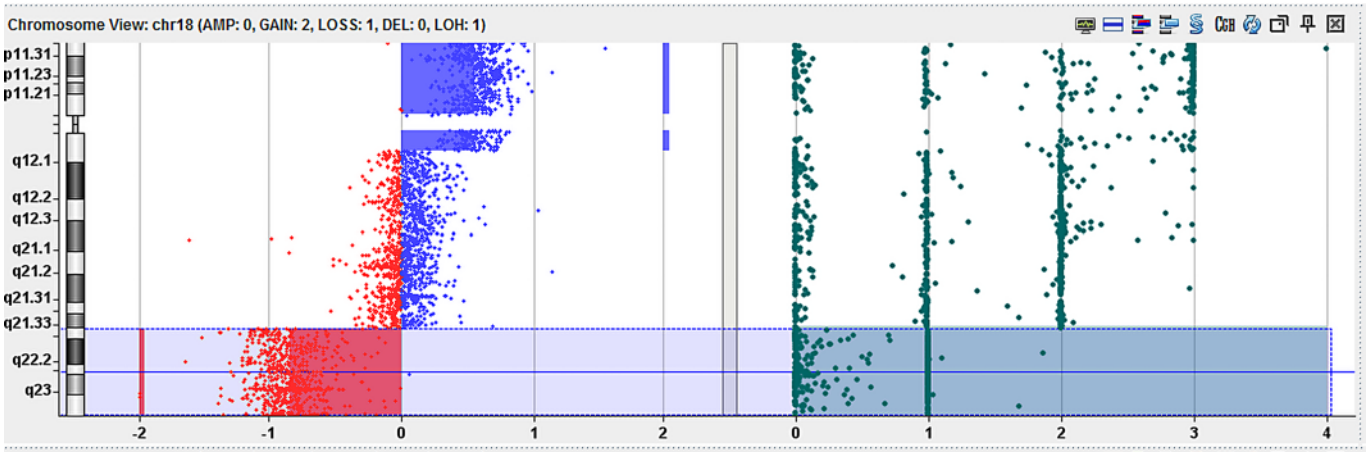


Fig. 3. Array CGH analysis indicates duplication at p11.32p11.21 and q11.1q11.2 and deletion at the q21.33q23 region of chromosome 18. (Agilent's SurePrint G3 CGH + SNP Microarray Platform).

which were absent in the present case, with the exceptions of strabismus and behavioral problems. Starke et al. [2001] reported a healthy woman who has identical derivative chromosomes ins(18)(pterp11.32::q12.2q11.2::p11.32q11.2 ::q12.3qter). She had three fetuses, from three different pregnancies, which had different derivative chromosomes due to her complex derivative chromosome structure [Starke et al., 2001]. As we summarized in Table 1, clinical findings of duplication and deletion of both the short and long arms of chromosome 18 have been previously described. Table 1 also shows that most cases are due to a parental pericentric inversion, an indication that paracentric inversions of chro-

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mosome 18 are rare. As is evident from these publications and also from our patient, deletions appear to cause a more severe phenotype than duplications [Brewer et al., 1998].

Congenital aural atresia is a common feature that is observed in 52% of the patients. Dostal et al. [2006] researched the genes in the 18q region which, through haploinsufficiency, may cause CAA. They suggested that haploinsufficiency of *ZNF407*, *ZADH2*, *SDCCAG33*, *ZNF516*, *FLJ44313*, *FLJ44881*, *ZNF236*, *MBP*, and *GALR1* genes in the 18q22.3-18q23 region are candidate genes for the CAA. All of these genes were deleted in our patient, except for *FLJ44313* and *FLJ44881*. Congenital aural atresia is a clue for clinicians to consider 18q deletion syndrome. Perry and Cody [2014] also investigated the association between hearing impairment and 18q deletion. Conductive hearing impairment was identified in 49.5%, sensorineural hearing loss was identified in 28%, and eustachian tube dysfunction was found in 78% of 18q deletion syndrome patients. Our patient had bilateral narrowing of the external auditory canal and mild and moderate sensorineural hearing loss in the right and left ears, respectively, which is consistent with these earlier reports.

Kline et al. [1993] suggested that haploinsufficiency of the *BCL2*, *FVT1*, and *VPS4B* genes was the potential reason for microcephaly in 18q deletion syndrome. These genes were deleted in our patient, who had microcephaly.

Orofacial cleft is a common clinical feature in 18q deletion syndrome. Dostal et al. [2009] reported that deletion of *FBXO1*, *C18ORF55*, *CYB5A*, *FAUP1*, *C18ORF51*, *CNDP2*, *CNDP1*, *ZNF407*, *ZADH2*, *ZNF516*, *FLJ44313*, *FLJ44881*, *ZNF236*, *MBP*, *GALR1*, and *SALL3* in the 18q22.3 region was the potential reason for orofacial cleft in this syndrome. Our patient had bilateral cleft lip and palate, and these genes were also deleted, again with the exception of *FAUP1*, *FLJ44313*, and *FLJ44881*.

In conclusion, we described a girl with multiple congenital anomalies and severe cognitive impairment who had duplication of the 18p11.32p11.21 and 18q11.1q11.2 regions and deletion of 18q21.33q23 region due to maternal paracentric inversion of chromosome 18. This is the third report [Chia et al., 1992; Courtens et al., 1998] of offspring with an unbalanced inversion due to a parental paracentric inversion of chromosome 18 and also the first report of dicentric chromosome 18 due to a parental paracentric inversion of chromosome 18. Conventional cytogenetic analysis is still an important and first-step genetic test to diagnose balanced chromosomal aberrations such as inversions and translocations. Although paracentric inversions are usually harmless to the carrier, there is a risk to their offspring, as in the case presented. Considering all this, prenatal diagnosis is important for an inversion involving a chromosome, such as 18, for which large structural abnormalities are compatible with live birth [Pettenati et al., 1995].

Statement of Ethics

Our study was accepted from the Adana City Training and Research Hospital Ethical Committee. The acceptance number is 2055, and the acceptance date is August 8, 2022. We obtained written informed consent from participant's parents for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Özlem Anlaş created the concept and design of the case report. Akgün Ölmez examined the patient, performed the neuropsychological assessment of the patient, supervised the work, and revised the case report. Birsen Karaman carried out the genetic examination using array CGH. Füsun Düzcan carried out the FISH analysis. Selçuk Yüksel performed the nephrological assessment. Funda Tümkaya performed the hearing assessment. Gülseren Bağcı carried out the cytogenetic analysis. Cavidan Nur Semerci Gündüz performed the physical examination and revised the case report.

Data Availability Statement

The authors declare that data supporting the findings of this study are available within the article.

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