AIMS Medical Science

AIMS Medical Science, 10(2): 130–140.
DOI: 10.3934/medsci.2023011
Received: 04 January 2023
Revised: 24 April 2023
Accepted: 11 May 2023
Published: 26 May 2023

http://www.aimspress.com/journal/medicalScience

Case report

4q interstitial and terminal deletion: clinical features comparison in two unrelated children.

Piero Pavone[1,*,†], Xena Giada Pappalardo[2,3,†], Riccardo Lubrano[4], Salvatore Savasta[5], Alberto Verrotti[6], Pasquale Parisi[7] and Raffaele Falsaperla[8]

[1] Section of Pediatrics and Child Neuropsychiatry, Department of Child and Experimental Medicine, University of Catania, Italy
[2] National Council of Research, Institute for Biomedical Research and Innovation (IRIB), Unit of Catania, Italy
[3] Department of Biomedical and Biotechnological Sciences (BIOMETEC), University of Catania, Italy
[4] Department of Pediatrics, Sapienza University of Rome, Pediatric and Neonatology Unit, Hospital Goretti Polo Pontino, Rome, Italy
[5] Department of Pediatrics, University of Cagliari, Pediatric and Neonatology Unit, Cagliari, Italy
[6] Pediatric Clinic, Department of Medicine, University of Perugia, 06129 Perugia, Italy
[7] Child Neurology, NESMOS Department, Faculty of Medicine & Psychology, Sapienza University of Rome, Rome, Italy
[8] Pediatric and Pediatric Emergency Department, University Hospital, A.U.O "Policlinico Vittorio Emanuele", Catania, Italy

*** Correspondence:** Email: ppavone@unict.it.

† These two authors contributed equally.

Abstract: The 4q deletion syndrome defines a disorder, which may involve patients affected by either the deletion of the interstitial region from the centromere to 4q31 or by the deletion of the terminal region from 4q31 to 4qter. Here, we describe clinical phenotypes of two unrelated children of the same age followed at the same time, with case 1 presenting with 4q interstitial and case 2 with terminal 4q deletion, and compare them each other and with those reported in the literature. Both children showed complex, heterogeneous clinical manifestations, including craniofacial features, pre-postnatal growth failure, speech and developmental delay. In case 2, thyroid and cholesterol dysfunction were also found.

Analyzing these data, clinical differences between interstitial and terminal 4q deletions are scanty and no significant phenotype differences were found between the 4q regions deleted as observed in the comparison of the two children and the related cases of the literature. The term 4q deletion syndrome - inclusive for both the interstitial and terminal 4q regions deleted - seems to be appropriate. To note, the dysfunction of cholesterol metabolism and thyroid presented by case 2 may be clinically worthwhile, whether confirmed by other observations.

Keywords: 4q deletion syndrome; terminal 4q deletion; interstitial 4q deletion; craniofacial malformations; developmental delay/intellectual disability (DD/ID)

1. Introduction

The "4q deletion syndrome" is a clinical disorder manifesting phenotypic variability including developmental delay/intellectual disability (DD/ID), speech impairment, congenital heart defects, and digital anomalies [1–10]. Ockey et al. [1] first described the disorder in a 31-and half-month-old male infant presenting with limb abnormalities and a large deletion of the long arm of ch4. The child showed one bone in the left forearm, limitation of the extension of the left elbow, single finger on the left limb, and little toes bilaterally overriding. The term 4q deletion syndrome has been subsequently applied to include both the 4q interstitial and 4q terminal deletions, as their clinical features are variable but mainly overlapping [5]. The 4q deletion syndrome is an uncommon disorder with a reported incidence of 1/100.000 individuals [6]. Variability in the clinical presentation, diagnosis, and prognosis of the 4q deletion syndrome was shown by Strehle et al. [8] with a report on three affected children: a female fetus diagnosed with del4q33 following chorionic villus sampling at 14 weeks, with pregnancy terminated at 18 weeks; a 5-month-old boy with del4q31.3 plus ch6 duplication with complex congenital heart who died for cardiac failure; and a 2-year-old girl interstitial del4q22.1q23 with no major malformations, mild dysmorphic features, and only slight DD/ID. We followed two unrelated cases of the same age and in the same period, but differently affected by 4q deletions: a case 1 with a terminal deletion, previously published by our group [10], and a case 2 with an interstitial deletion. Given the fragmented knowledge on 4q syndrome, we attempted to provide a clinical and genetic comparison of our patients, underlining the similarity and diversity of their clinical manifestations based on criteria used by Lin et al. [4] in order to improve the diagnostic framework and medical experience.

2. Materials and methods

2.1. Genetic testing

Genomic DNA was isolated from the peripheral blood of the proband and parents to analyze structural anomalies using Human Genome CGH Microarray (aCGH) Kit 8x60K, performed according to the manufacturer's recommendations (Agilent Technologies, Santa Clara, CA). Data analysis was performed using Cytogenomics (GRCh37assembly). For the copy number variants (CNVs) an interpretation was performed using public patient data on Database of Genomic Variants (DGV)

(dgv.tcag.ca), DECIPHER web-based resource (decipher sanger ac.uk), CNV dataset from Clinical Genome Resource (ClinGen), and Morbidity Map of Developmental Delay.

2.2. Ethics approval of research

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by ethics Committee of the University of Catania, Italy (Ethical Committee Catania 1 Clinical Registration n. 95/2018/PO). Written informed consent was obtained from the parents.

3. Results

3.1. Molecular results

Case 1. In the proband, the aCGH analysis revealed a 329.6 Kb deletion long in the 4q32.3 region (164.703.186-165.032.803)x1, inherited from his healthy mother. Normal results were observed in the father. The deletion size of the CNV harbored a partial fragment of the *MARCH1* (membrane associated ring-CH-type finger 1) gene (OMIM#513331), a member of the MARCH family of membrane-bound E3 ubiquitin ligases (Figure 1).

Case 2. In the proband, the aCGH analysis revealed a 6.3 Mb deletion long in the 4q13.3-q21.1 region (71.655.407-78.016.622)x1. Normal results were obtained in the parents in regard to genetic testing, a cholesterol test, and thyroid markers (Figure 1).

Case 1. The deletion detected of 329.6 Kb was located in the 4q32.3 region (164.703.186-165.032.803)x1, including a partial intronic fragment of *MARCH1* gene.

Case 2. The deletion of 6.3 Mb was located in the 4q13.3-q21.1 region (71.655.407-78.016.622)x1, including about 52 genes (*ADAMTS3, AFM, AFP, ALB, ANKRD17, AREG, ART3, BTC, C4ORF26, CCDC158, CCNI, CDKL2, CDKL2, COX18, CXCL1, CXCL3, CXCL5, CXCL6, CXCL10, CXCL9, CXCL11, DCK, EPGN, EREG, G3BP2, GC, GRSF1, IL8, MIR4450, MOB1, MTHFDL2, NAAA, NPFFR2, NUP54, PARM1, PF4, PF4V1, PPBP, PPBPP2, PPEF2, RASSF6, RCHY1, RUFY3, SCARB2, SDAD1, SEPT11, SHROOM3, SLC4A4, SOWAHB, THAP6, U7*, and *USO1*).

3.2. Clinical results

3.2.1. Case presentation—Case 1

This 5-year boy was the first child of healthy, unrelated parents. Family history, pregnancy, birth, and perinatal period were uneventful. This case has been previously clinically reported (Pappalardo et al. [10]). He was followed from infancy to the present age due to a growth delay, minor craniofacial features, and generalized hypotonia. To note, the child showed crowded and precocious primary dentation. His clinical course was characterized by pre-post-natal failure to thrive, minor craniofacial anomalies, severe speech delay, and behavioral impairment with an outburst of anger and aggressivity (Table 1). There was mild/moderate intellectual disability with an intelligent quotient (IQ) of 55 at WISCH III. Encopresis, diurnal, and nocturnal enuresis were present. The child presents a high and rounded forehead, occipital plagiocephaly, mild asymmetric face, long eyebrows, small palpebral

fissures, a short nose with a large nasal bridge and round tip, long philtrum, thin upper lips, low-set ears with abnormal pinnae, and epicanthal folds. The thumbs are bilaterally adducted but mobile with digital hyperlaxity. Routine laboratory analysis is normal, including lipid profile analysis and thyroid markers. An EEG in awake state and during sleep, ECG, Echo, and RMN are normal. He undergoes speech-language therapy. At the last examination (at the age of 7 years), the clinical features of the child are unmodified.

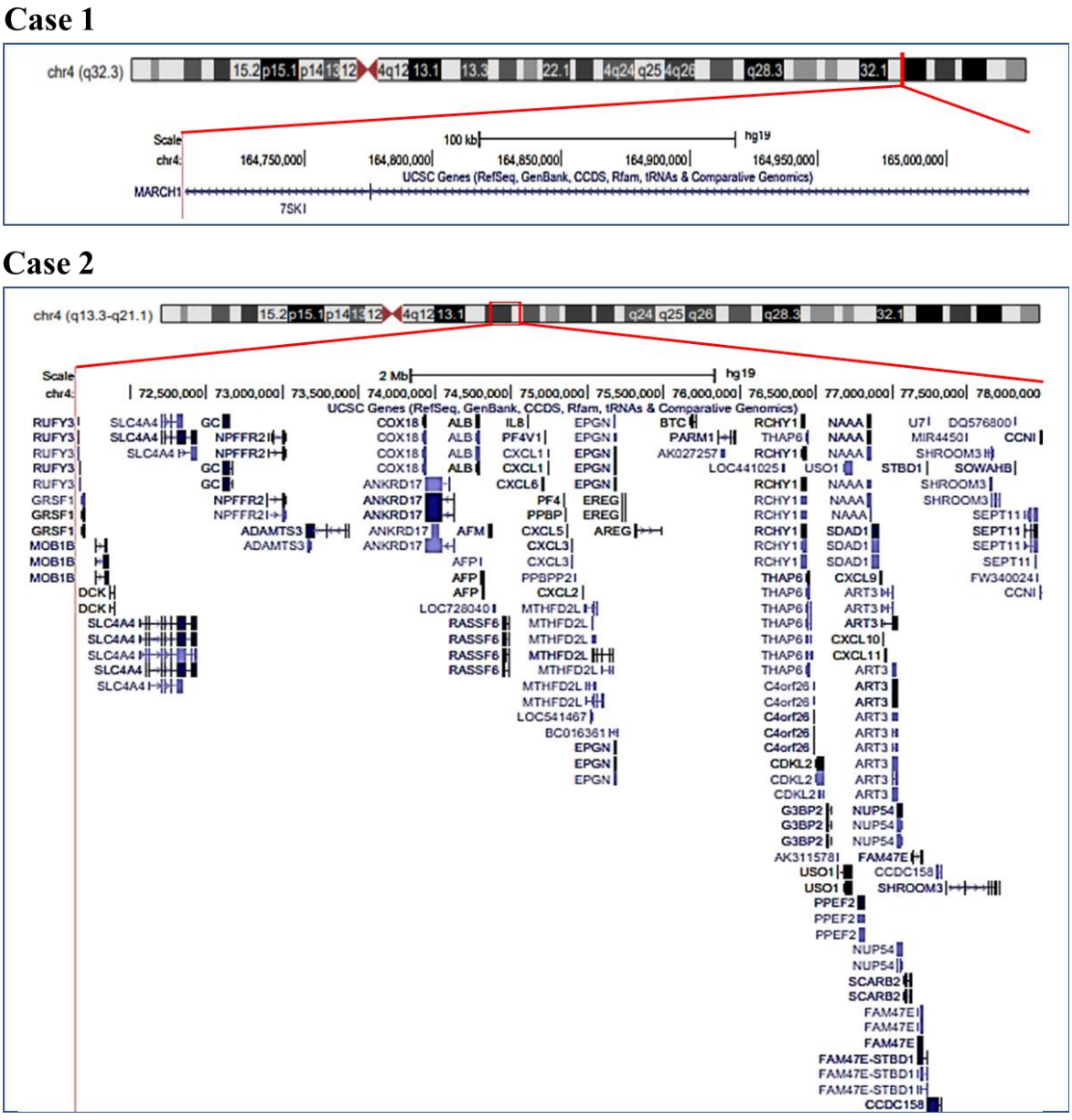

Figure 1. UCSC Genome Browser illustration (GRCh37/hg19) of aCGH results found in Case 1 and Case 2.

3.2.2. Case presentation—Case 2

This 4-year-old boy was the first born of healthy, unrelated parents. The Family history was irrelevant. The mother complained of epileptic seizures to the age of 10 years. During the pregnancy,

the mother suffered from gestosis. Oligohydramnios, fetal growth failure, and poor fetal movements were reported. The boy was born at 32 weeks by cesarean section with a birth weight of 1700 g, a height of 46 cm, and an occipitofrontal circumference (OFC) of 32 cm. The Apgar score was 6 and 8 at one and five minutes, respectively. At birth, he was kept in incubator for a week. The transfontanellar ultrasound was normal. In the first months of life, the growth was slow but constant, with a delay in developmental milestones and an OFC within normal range. At first admission, at the age of 4 years old, the child showed minor craniofacial features consisting of symmetrical plagiocephaly, a mild asymmetric face, very high and rounded forehead, long eyebrows, small palpebral fissures, epicanthal folds, low set ears, thin upper lips, a short nose with a large nasal bridge with round tip, abnormal pinnae, and micro and retrognathia. Primary dentation was complete. The thumbs were bilaterally adducted and mobile with digital hyperlaxity. There was talipes equino-varus. The child showed good cognitive and social functions but a marked speech delay. The behavior was good. At the age of 4 years old, the weight was 12.7 kg (>3rd), the height was 93 cm (>3rd), and the OFC was 51 cm (70th). The audiometric test and ophthalmologic examination were normal. No anomalies were found for the EEG, ECG, echocardiogram, and brain MRI. An abdominal ultrasound displayed an accessory spleen of 7 mm wide at the level of splenic ileus. Routine laboratory analysis including plasma and urinary amino acids, urine organic acids, and transferring isoelectric focusing gave normal results. Repeated TSH analysis showed high levels with values between 8–10 mcIU/ml (n.v. 0.20–6 mcIU/ml). The T3 level of 90 ng/dL (n.v. 80/190 ng/dL) and T4 level of 7.0 ng/dL (n.v. 5.0–12.5 ng/dL) were within normal range. The lipid profile analysis displayed high total cholesterol between 129 to 190 mg/dl (n.v. > 120 mg/ml) in serial examinations, and normal value for HDL-Cholesterol (40 mg/ml—n.v. < 40), LDL-Cholesterol (110 mg/dL—n.v.110–129), Triglycerides (75 mg/ml—n.v. 75–99 mg/ml). He undergoes speech-language therapy. No treatment for neither the high total cholesterol nor the thyroid dysfunction was started. At the present age of 6 years, the clinical features are unmodified, and the total cholesterol levels maintained high levels.

4. Discussion and conclusions

The 4q deletion syndrome is often evaluated and classified by a missing genetic fragment; however, from a clinical perspective, there is a grey area of investigations due to the rare incidence and the phenotypic heterogeneity combined with the overlapping features of symptoms and signs, either within the same or different molecular finding. Due to the overlapping features, patients with interstitial and terminal 4q deletions have been recently labeled under a common term “4q deletion syndrome”, characterized by craniofacial features, pre- and postnatal growth failure, developmental delay, speech and language impairment, complex congenital heart defects (CHD), digital anomalies [4], and pointed fifth finger and nail. These latter ones indicated as pathognomonic diagnostic signs [5]. To strengthen this prospect, while maintaining the genetic distinction, we compared two unrelated patients showing two different deletions of 4q and noted a similar facial resemblance among them, with a comparable shape of the forehead, nose, and chin. Moreover, both children showed a pre-post-natal growth retardation, mild DD (while speech delay was marked), and unusual adducted position of the thumbs. The diversity consisted of a notable aggressivity and precocious, crowed dentation and an accessory spleen, and dysfunction involving thyroid and cholesterol metabolism for case 2 (Table 1).

In order to recapitulate the strengths and limitations of the diagnostic procedure based on clinical findings, we briefly summarized the most important literature data on this issue. According to the greatest case collection by Strehle and Bantock [6] with 101 patients, craniofacial features are the most common signs observed in 99% of the cases, followed by digital (88%), skeletal (54%), and cardiac (50%) anomalies with an overall mortality in 28%. Moreover, nearly all surviving patients had DD/ID and approximately two third showed pre- postnatal growth failure [6]. Coherently, Strehle et al. [7] states that the recurrent malformations are craniofacial, developmental, digital, skeletal and cardiac anomalies. Interesting insights come from Lin et al. [4], who reviewed a total of 45 patients, with 29 presenting with 4q terminal deletions and 16 with interstitial deletions. The patients manifest an identifiable phenotype with abnormal skull shape, hypertelorism, cleft palate, apparent low-set abnormal pinnae, a short nose with an abnormal bridge, virtually pathognomonic pointed fifth finger and nail, congenital heart and genitourinary defects, moderate-severe mental retardation, poor postnatal growth, and hypotonia. Moreover, patients with various interstitial deletions proximal to 4q31 have a less specific phenotype, though DD and minor craniofacial anomalies are always observed [4]. Ultimately, Xu et al. [9] found ID, cleft palates, and micrognathia in 94% of cases, craniofacial anomalies including broad nasal bridge in 92% of cases, post-natal growth deficiency in 83% of cases, digital anomalies mainly involving the fifth finger in 50-88% of cases, rotated ears in 56% of cases, and complex CHD in 50% of cases. Additional anomalies associated with 4q deletion syndrome include bilateral thumbs anomalies, left side hypoplasia, bilateral ptosis, erythroderma [11], ocular [12] and hearing impairments [13], ulnar defects [14,15], and occipital encephalocele [16].

In case 2, a high level of total cholesterol and TSH have been found in the absence of specific clinical signs. The increased level of TSH and total cholesterol have not been previously reported. In attempting to explain the metabolic anomaly, it is interesting to note a plausible link with the results of Zhang et al. [17]. In fact, they identified the genomic trait of LDL-associated clusters in the 4q13.3-q21.1 region, which are located in the albumin (*ALB*) and platelet factor 4 (*PFF4*) genes.

In conclusion, the lucky coincidence of following two unrelated coetaneous patients, in the same period, from infancy to the age of seven years, allowed to us a great opportunity to enrich the data availability.

The two cases affected by different 4q deletions (interstitial vs terminal deletion) showed a partial similarity, such as some craniofacial features, pre- and postnatal growth failure, speech, and DD; alternatively, they also displayed distinct clinical elements, such as precocious and crowded dentition in case 1, and accessory spleen and talipes equino-varus in case 2. Neither CHD nor severe congenital systemic anomalies [18] were reported in the probands. Still, based on the double comparison of clinical features between the probands and between each proband with those reported by Lin et al. [4], the general term 4q deletion syndrome seems more appropriate, even if the clinical manifestations may be various and include different body-organs (Table 2). It is difficult to explain the different clinical signs in these children: the genes in these two deleted fragments may either be functionally associated or maybe have a different influence on gene regulation. As a result of a combinatorial approach of conventional and genetic methods, the genotypic-phenotypic correlations depending on the breakpoint and size of terminal deletion have been characterized (Figure 1). The clinical signs of individuals with 4q deletion syndrome are not distinctive, hence a more correct diagnosis may only arise following the genetic investigation.

Table 1. Similarity and diversity reported in 4q terminal (Case 1) and interstitial (Case 2) region deleted.

	Case 1	Case 2
Diversity	Deletion in 4q32.3 region (164.703.186-165.032.803)x1.	Deletion in 4q13.3-q21.1 region (71.655.407-78.016.622)x1.
	Precocious and crowded dentition, behavioral disturbances.	Spleen accessory, talipes equino-varus.
Similarity	Pre-postnatal growth delay, rounded and very high forehead, symmetrical plagiocephaly, asymmetric face, palpebral fissure small, epicanthus, short nose with large nasal bridge and rounded tip, microretrognathia, low-set ears, bilateral adducted thumbs with digital hyperlaxity. Mild DD with marked speech delay, infantile hypotonia.	

Table 2. Main features of Case 1 and Case 2 of the present study compared with 29 patients showing terminal 4q deletion and 16 patients with interstitial 4q deleted region [4].

		Terminal [4]	Case 1	Interstitial [4]	Case 2
General features	Male (M)/Females (F)	13/16	M	5/11	M
	Birth weight >3rd	4	+	6	+
	Gestation >37th weeks	5	+	3	+
Craniofacial features	Abnormal skull	19	+	9	+
	Asymmetric face	5	+	1	+
	Palpebral fissures small	7	+	1	+
	Palpebral fissures upslanting	8	−	2	−
	Hypertelorism	14	−	6	−
	Epicanthal folds	10	+	7	+
	Short nose	16	+	2	+
	Abnormal nasal bridge	22	+	7	+
	Anteverted nares	12	−	3	−
	Cleft lip	8	−	1	−
	Cleft palate	23	−	3	−
	Microretrognathia	26	+	7	+
	Pierre Robin sequence	9	−	-	−
	Low ears, +/− set rotation	14	+	12	+
	Abnormal pinnae	18	−	12	−

Continued on next page

		Terminal [4]	Case 1	Interstitial [4]	Case 2
Limbs	Absent digits	3	−	1	−
	Clinodactily	11	−	2	−
	Camptodactyly	5	−	-	−
	Abnormal thumb/hallux impl.	12	+	-	+
	Tapering 5th finger	13	−	1	−
	Pointed/duplicated 5th nail	9	−	-	−
	Simian crease	15	−	6	−
	Absent/hypoplastic flexion crease	14	−	1	−
	Overlapping toes	8	−	3	−
Congenital heart defects		16	−	4	−
Neurodevelopmental	Seizures	4	−	4	−
Hypotonia		10	+	8	+
Developmental Delay/Intellectual Disability (DD/ID)	Absent	2	−	-	−
	Mild	2	+	-	+
	Moderate/severe	19	−	14	−
Other organs/systems	Postnatal growth failure	17	+	8	+/−
	Genitourinary defect	12	−	6	−
	Gastrointestinal defect	4	−	3	−

Note: +: present; −: absent.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Authors' contributions

PP, XGP, and RF worked with and helped gather patient data. PP and XGP drafted the present manuscript. RL, AV and PP revising the work critically for important intellectual content. All authors read and approved the final manuscript.

Data availability statement

The data used to support the findings of this study may be released upon application to the corresponding author who can be contacted at ppavone@unict.it.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ockey CH, Feldman GV, Macaulay ME, et al. (1967) A large deletion of the long arm of chromosome No. 4 in a child with limb abnormalities. *Arch Dis Child* 42: 428–434. https://doi.org/10.1136/adc.42.224.428
2. Golbus MS, Conte FA, Daentl DL (1973) Deletion from the long arm of chromosome 4 (46,XX,4q-) associated with congenital anomalies. *J Med Genet* 10: 83–85. https://doi.org/10.1136/jmg.10.1.83
3. Townes PL, White M, Di Marzo SV (1979) 4q-syndrome. *Am J Dis Child* 133: 383–385. https://doi.org/10.1001/archpedi.1979.02130040037008
4. Lin AE, Garver KL, Diggans G, et al. (1988) Interstitial and terminal deletions of the long arm of chromosome 4: further delineation of phenotypes. *Am J Med Genet* 31: 533–548. https://doi.org/10.1002/ajmg.1320310308
5. Strehle EM, Ahmed OA, Hameed M, et al. (2001) The 4q-syndrome. *Genet Couns* 12: 327–339.
6. Strehle EM, Bantock HM (2003) The phenotype of patients with 4q-syndrome. *Genet Couns* 14: 195–205.
7. Strehle EM, Yu L, Rosenfeld JA, et al. (2012) Genotype-phenotype analysis of 4q deletion syndrome: proposal of a critical region. *Am J Med Genet A* 158A: 2139–2151. https://doi.org/10.1002/ajmg.a.35502
8. Strehle EM, Gruszfeld D, Schenk D, et al. (2012) The spectrum of 4q- syndrome illustrated by a case series. *Gene* 506: 387–391. https://doi.org/10.1016/j.gene.2012.06.087
9. Xu W, Ahmad A, Dagenais S, et al. (2012) Chromosome 4q deletion syndrome: narrowing the cardiovascular critical region to 4q32.2–q34.3. *Am J Med Genet A* 158A: 635–640. https://doi.org/10.1002/ajmg.a.34425

10. Pappalardo XG, Ruggieri M, Falsaperla R, et al. (2021) A novel 4q32.3 deletion in a child: additional signs and the role of *MARCH1*. *J Pediatr Genet* 10: 259–265. https://doi.org/1055/s-0041-1736458
11. Kuldeep CM, Khare AK, Garg A, et al. (2012) Terminal 4q deletion syndrome. *Indian J Dermatol* 57: 222–224. https://doi.org/10.4103/0019-5154.96203
12. Sandal G, Ormeci AR, Oztas S (2013) De novo terminal 4q deletion syndrome with new ocular findings in Turkish twins: case report. *Genet Couns* 24: 217–222.
13. Vona B, Nanda I, Neuner C, et al. (2014) Terminal chromosome 4q deletion syndrome in an infant with hearing impairment and moderate syndromic features: review of literature. *BMC Med Genet* 15: 72. https://doi.org/10.1186/1471-2350-15-72
14. Meaux T, Zeringue A, Mumphrey C, et al. (2015) Bilateral absence of the ulna in 4q terminal deletion syndrome: evidence for a critical region. *Clin Dysmorphol* 24: 122–124. https://doi.org/10.1097/MCD.0000000000000078
15. Lurie IW (2016) A critical region for ulnar defects in patients with 4q deletions may be narrowed. *Clin Dysmorphol* 25: 133. https://doi.org/10.1097/MCD.0000000000000131
16. Quadrelli R, Strehle EM, Vaglio A, et al. (2007) A girl with del(4)(q33) and occipital encephalocele: clinical description and molecular genetic characterization of a rare patient. *Genet Test* 11: 4–10. https://doi.org/10.1089/gte.2006.9995.
17. Zhang QS, Browning BL, Browning SR (2015) Genome-wide haplotypic testing in a Finnish cohort identifies a novel association with low-density lipoprotein cholesterol. *Eur J Hum Genet* 23: 672–677. https://doi.org/10.1038/ejhg.2014.105
18. Maldžienė Ž, Vaitėnienė EM, Aleksiūnienė B, et al. (2020) A case report of familial 4q13.3 microdeletion in three individuals with syndromic intellectual disability. *BMC Med Genomics* 13: 63. https://doi.org/10.1186/s12920-020-0711-4