Journal of Genetics, Vol. 97, No. 1, March 2018, pp. 311–317
https://doi.org/10.1007/s12041-017-0879-3

RESEARCH NOTE

Case report of newborn with *de novo* partial trisomy 2q31.2–37.3 and monosomy 9p24.3

MAURIZIA COLANGELO[1]*, MELISSA ALFONSI[2], CHIARA PALKA[3], ELEONORA DI ZIO[1], SILVANA DI RENZO[1], PAOLO GUANCIALI-FRANCHI[1,2] and GIANDOMENICO PALKA[1,2]

[1] *Department of Medical Genetics, University G. D'Annunzio, Chieti 65100, Italy*
[2] *Department of Medical Genetics, SS Annunziata Hospital, Chieti 65100, Italy*
[3] *Department of Pediatrics, University G. D'Annunzio, Chieti 65100, Italy*
*For correspondence. E-mail: maurizia.colangelo@katamail.com.

Received 10 November 2016; revised 13 March 2017; accepted 21 March 2017; published online 24 February 2018

Abstract. We describe a newborn female with a *de novo* duplication of chromosomes 2q31.2 and 2q37.3, and a *de novo* monosomy 9p24.3. The clinical findings of this patient include congenital heart defects, dysmorphic facial features, hypotonia, feeding difficulties and microcephaly. Ultrasonographic prenatal findings were negative for foetal malformations. Only a mild pyelectasis was reported. This is the first report of molecular cytogenetic characterization of a partial trisomy 2q31.2–37.3 with monosomy 9p24.3.

Keywords. duplication of 2q31.2 and 2q37.3; monosomy 9p; array CGH.

Introduction

A *de novo* partial trisomy 2q syndrome, from q31.2 to q37.3, with a monosomy 9p24.3 was not previously reported. We describe the first case of *de novo* duplication of chromosomes 2q31.2 and 2q37.3 and a *de novo* monosomy 9p24.3.

Materials and methods

Case report

The proband was born by Cesarean delivery at 40 weeks of gestation from a 39-year old Caucasian female. She is the second child of healthy and nonconsanguineous parents. She has a healthy nine-year old brother. Family and gestational history are unremarkable. Prenatal sonograms identified only a mild pyelectasis. Prenatal noninvasive test (contingent test) was negative (risk 1 : 1356, free Beta hCG 0.69 multiple of the median (MoM), PAPP-A 0.45 MoM). The parents have normal karyotype. Her birth weight was 3.500 kg (50° percentile), length 56 cm (> 97° percentile), and occipito-frontal circumference (OFC) 33.5 cm (10° percentile). At birth, Apgar Index was 6 at 1st min and 8 at 5th min. She needed respiratory assistance. Further, there were severe feeding difficulties due to muscular hypotonia.

Physical examination revealed: (i) head/neck: microcephaly, prominent occiput, micrognathia and arched palate, atresia of the left choana, right choana pervia, mouth breathing, frequency 139 per min, guttural cried (figure 1a); (ii) abdomen, reduced abdominal circumference; (iii) limbs: incomplete Moro reflex, and global muscolar hypotonia. She showed microcephaly, feeding disease, ventricular septal defect, anorectal malformation with perianal fistula, bilateral cataract, severe muscular hypotonia and psychomotor developmental delay. The child was hospitalized in prenatal intensive care and was fed by gavage. Cytomegalovirus, herpesvirus, rubellavirus and toxoplasmosis were negative. Brain magnetic resonance imaging (MRI) documented a large ventricular system in place, with a great cisterna magna.

In particular, the patient presented tachypnea and difficulties to suckling, swallowing with microinfusion, for

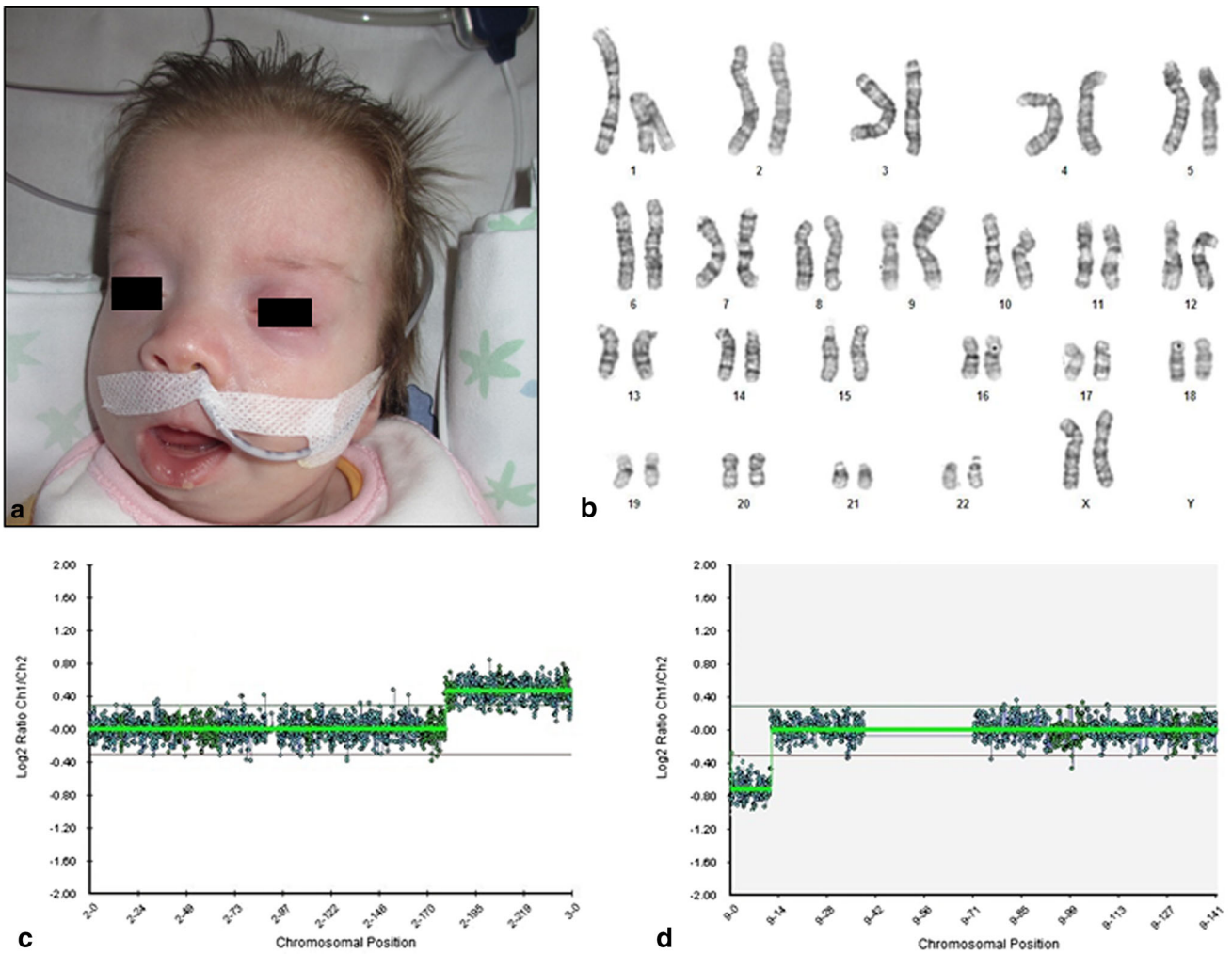

Figure 1. (a) Dysmorphic features of our patient. (b) Karyotype showing the derivative (9)t(2;9)(q31.2;p24.3). (c) Array CGH analysis revealed a 63.5 Mb duplication of 2q31 q37.3 (Chr2: 179, 536, 770–243, 068, 370, GRCh37). (d) Array CGH analysis revealed a 11.7 Mb deletion of 9p24.3p23 (Chr9: 204, 221–11, 904, 279, GRCh37).

the risk of aspiration has been fuelled by gavage. The incidence of anorectal malformation (ARM) is 1 : 5000 live births (Elsevier 2005). Our case presented an ARM with perianal fistula, also known as imperforate anus. Only the last part of the rectum is placed before the orifices sphincter. The rectum and the vagina are well separated. The sphincter mechanism is good and so also the prognosis. For this type of malformation, the colostomy is not necessary. The timing of surgery is within two months, which aims to lower the rectum until the skin can rebuild more accurately the sphincter complex that ensures continence stool (posterior sagittal anorectoplasty).

Cytogenetic studies

Karyotype from peripheral lymphocytes with a resolution of 550 bands revealed a 46,XX,der(9)t(2;9)(q31.2;p24.3) karyotype (figure 1b).

Array CGH

Microarray-based comparative genomic hybridization (array CGH, a-CGH) was performed to specify the size of chromosomal alterations, using 4 per 44 K oligo ISCA design according to manufacturer's instructions. Data were analysed with BlueFuse multi v4.1 software (BlueGnome, Cambridge, UK). The Human NCBI Build GrCh37 (Hg 19/2009) was used as the reference genoma. Array CGH analysis revealed a 63.5 Mb duplication of 2q31 and 2q37.3 (Chr2: 179, 536, 770–243, 068, 370, GRCh37), which included 298 OMIM genes, and a 11.7 Mb deletion of 9p24.3p23 (Chr9: 204, 221–11, 904, 279, GRCh37), which included 32 OMIM genes (figure 1, c & d).

Discussion

Several cases with trisomy 2q3 were reported in literature, often associated with monosomy of another chromosomal

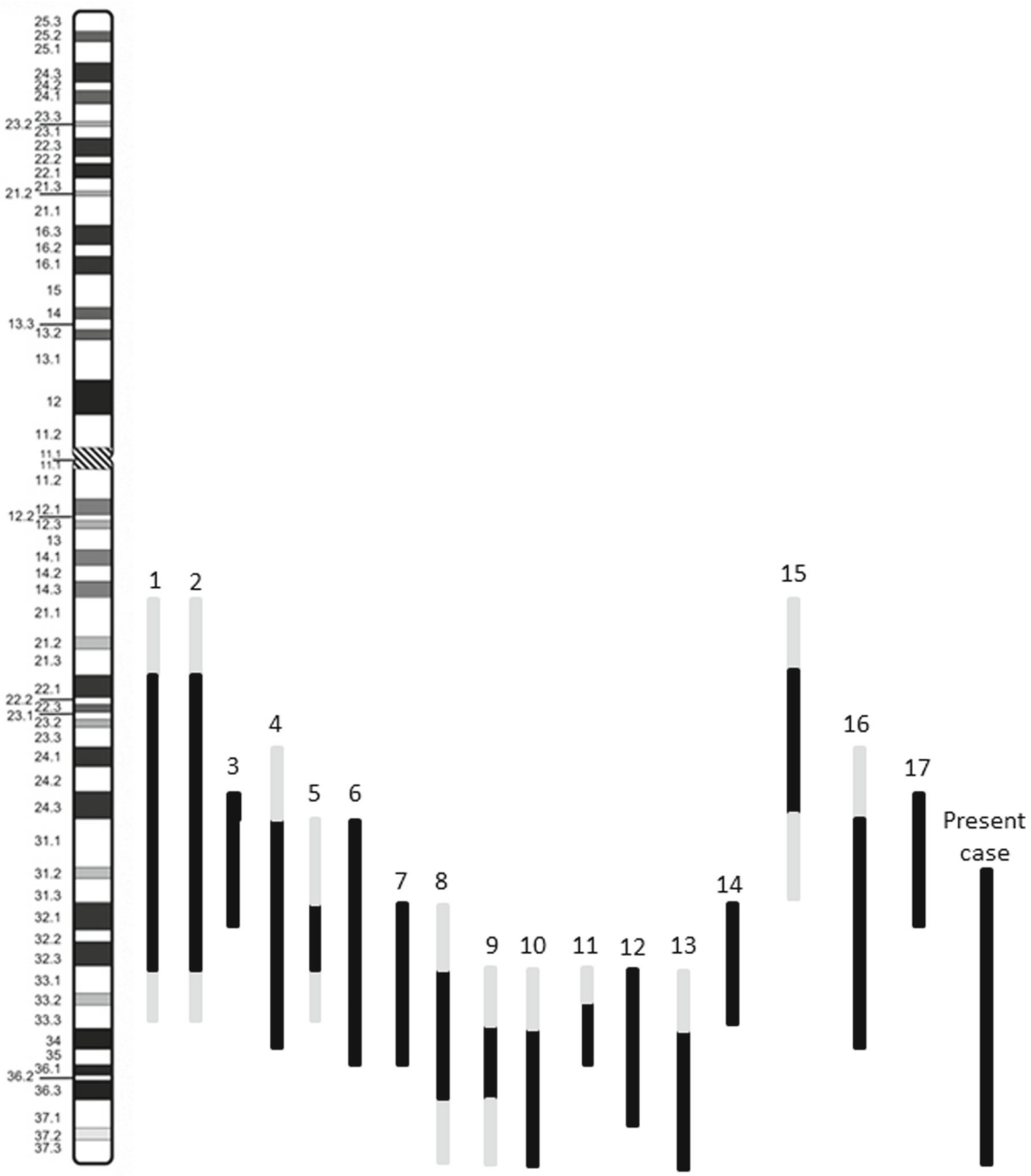

Figure 2. Schematic representation of the previously reported duplications of 2q. The black bar and gray bars indicate certain and uncertain regions of the duplications, respectively.

segment (Couturier *et al*. 1977; Dennis *et al*. 1978; Schumacher *et al*. 1983; Romain *et al*. 1994; Barnicoat *et al*. 1997; Matos *et al*. 1997; Lukusa *et al*. 1999; Seidahmed *et al*. 1999; Bird and Mascarello 2001). To the best of our knowledge, a *de novo* partial trisomy 2q syndrome, from q31.2 to q37.3, with a monosomy 9p24.3 was not previously reported. Majority of trisomy 2q3 is the result of an abnormal segregation of a chromosomal rearrangement carried by a parent (Slavotinek *et al*. 2003; Sebold *et al*. 2005). On the contrary, pure duplication of 2q3 is relatively rare (Elbracht *et al*. 2009). Patients with different sizes of the involved chromosomal segments were compared in some reports (Ramer *et al*. 1990). The duplication of chromosome 2 included 298 OMIM genes. We report a schematic representation of the previously reported duplications of 2q (Ikeuchi 1984; Gurrieri *et al*. 1992; Usui *et al*. 2013) (figure 2). The present case share several facial dysmorphisms with the previously reported patients with 2q duplication, such as prominent forehead, depressed nasal bridge, long philtrum and ear anomaly. Other common features are muscular hypotonia, brain and genital anomaly (table 1).

Table 1. Clinical features of patients with 2q duplication.

	1 Schumacher *et al.* (1983) 2q21q33	2 Matos *et al.* (1997) 2q21q33	3 Barnicoat *et al.* (1997) 2q24.3q32.1	4 Couturier *et al.* (1977) 2q24q34	5 Ramer *et al.* (1990) 2q31q33	6 Romain *et al.* (1994) 2q31.1q35	7 Lukusa *et al.* (1999) 2q32.1q35	8 Seidahmed *et al.* (1999) 2q32q37	9 Dennis *et al.* (1978) 2q33q37
Brachycephaly	(+)		(+)		(+)		(+)	(−)	(+)
Microcephaly				(−)	(+)	(−)			
Prominent occiput				(+)					
Prominent forhead	(+)	(+)	(+)				(+)	(+)	(+)
Hypertelorism	(−)	(+)	(+)	(+)		(+)			(−)
Upslanting palpebral fissures	(+)		(+)	(+)					(+)
Epicanthal folds			(+)	(+)	(+)	(+)	(+)	(+)	
Depressed nasal bridge	(+)		(+)	(+)	(+)	(+)	(+)		(+)
Anteverted nares	(+)		(+)	(+)					(+)
Long philtrum	(+)		(+)		(−)	(+)	(+)	(+)	(+)
Thin upper lip			(+)	(+)	(−)	(+)	(+)	(+)	
Ear anomaly	(+)	(+)	(+)		(−)		(+)	(+)	(+)
Micrognathia					(−)			(+)	(−)
Arched palate	(−)				(+)			(+)	
Developmental delay/mental retardation			(+)	(+)	(+)	(+)	(+)		(+)
Genital abnormality	(+)	(+)		(+)			(+)		(+)
Muscular hypotonia				(+)			(+)	(+)	
Brain anomaly	(+)	(+)						(+)	
Cardiac abnormality	(+)	(+)							(−)
Nail hypoplasia	(+)			(+)				(−)	(+)
Feet equinovarus		(+)		(+)					
Epilepsy	(+)								
Iris coloboma			(+)	(+)					
Feeding difficulties								(+)	
Atresia choana									
Renal abnormality									
Anorectal malformation									
Cataract									

Table 1(*contd*)

	10 Elbracht *et al.* (2009) 2q33q37.3	11 Sebold *et al.* (2005) 2q33.1q35	12 Bird and Mascarello (2001) 2q33.3q37.1	13 Slavotinek *et al.* (2003) 2q33q37.3	14 Usui *et al.* (2013) 2q32.1q33.3	15 Gurrieri *et al.* (1992) 2q21q31	16 Ikeuchi (1984) 2q24q34	17 Marchese et al. (1984) 2q24.3q32.1	18 Present case 2q31.2q37.3	Total
Brachycephaly		(+)			(−)					5/18 (27%)
Microcephaly			(+)		(−)				(+)	3/18 (16%)
Prominent occiput					(−)				(+)	2/18 (11%)
Prominent forhead	(+)	(−)		(+)		(+)	(+)	(+)		11/18 (61%)
Hypertelorism		(−)	(+)	(+)	(+)		(+)	(+)		9/18 (50%)
Upslanting palpebral fissures		(−)	(−)		(+)	(+)	(+)	(+)		8/18 (44%)
Epicanthal folds			(+)		(−)					7/18 (39%)
Depressed nasal bridge		(+)	(+)	(+)	(+)	(+)	(+)	(+)		14/18 (77%)
Anteverted nares										4/18 (22%)
Long philtrum	(+)	(+)	(+)	(+)	(−)			(+)		11/18 (61%)
Thin upper lip		(+)	(+)		(−)					7/18 (39%)
Ear anomaly	(+)	(+)	(+)	(+)	(+)	(+)	(−)	(+)		13/18 (72%)
Micrognathia		(+)		(+)	(+)				(+)	5/18 (27%)
Arched palate			(+)	(+)	(+)				(+)	6/18 (33%)
Developmental delay/mental retardation		(+)	(+)		(+)		(+)	(+)	(+)	12/18 (66%)
Genital abnormality			(+)		(−)	(+)	(+)	(−)		8/18 (44%)
Muscular hypotonia		(+)	(+)		(+)				(+)	7/18 (39%)
Brain anomaly	(+)				(−)				(+)	5/18 (27%)
Cardiac abnormality			(+)	(−)	(−)	(−)	(−)	(−)	(+)	4/18 (22%)
Nail hypoplasia					(−)		(+)	(−)		4/18 (22%)
Feet equinovarus			(+)		(−)					3/18 (16%)
Epilepsy		(+)			(+)					3/18 (16%)
Iris coloboma			(+)		(−)					3/18 (16%)
Feeding difficulties			(+)		(−)				(+)	3/18 (16%)
Atresia choana									(+)	1/18 (5%)
Renal abnormality						(+)	(−)	(−)		1/18 (5%)
Anorectal malformation									(+)	1/18 (5%)
Cataract									(+)	1/18 (5%)

In the 2q33.3 region, there are two genes (*CTRCT4* and *CTRCT2*) correlated to the cataract in an autosomal dominant matter (Heon *et al.* 1998). Several previously reported cases share this duplicated segment, but unexpectedly, the present case is the only one presenting cataract. In Decipher database, none of the chromosome 2 duplications had the clinical features of our case.

Partial *de novo* monosomy 9p appears to be caused by early spontaneous errors in embryonic development. Monosomy 9p seems to affect females more frequently than males. Since the disorder was originally described, more than 100 cases have been reported (Durmaz *et al.* 2016). Findings of monosomy 9p include intellectual disability, distinctive malformations of skull and craniofacial region, such as an abnormally shaped forehead (trigonocephaly), palpebral fissures and midfacial hypoplasia; congenital heart defects; genital anomalies in affected males and females; and other additional abnormalities (Sirisena *et al.* 2013). According to literature, approximately one-third to two-thirds of affected infants may have structural heart malformations at birth (Recalcati *et al.* 2012). Such cardiac defects may include ventricular septal defects, pulmonary stenosis and/or patent ductus arteriosus (PDA). Genital defects in some cases with partial monosomy 9p could present with hypoplastic/hyperplastic vaginal labia minora. Additional physical abnormalities were also reported in association with partial monosomy 9p as choanal atresia (Durmaz *et al.* 2016). Commonly observed phenotypic features of trisomy 2 are developmental delay and a number of minor anomalies. Characteristic facial features like broad flat nasal bridge, anteverted nostrils, long philtrum, thin upper lip, low-set ears, Cupid's bow lip and micrognathia including hypertelorism and epicanthic folds. Minor visceral anomalies reported in some patients mainly involve cardiac, kidney or brain defects and external genitalia malformations (Ma *et al.* 2015).

Chromosome 9 monosomy included 32 OMIM genes and specific correlations between the genes and the phenotype are not reported. In the Decipher database, five cases are described with monosomy 9p with clinical manifestation similar to our patient, with atresia of choana, muscular hypotonia and ventricular septal defect, but the common denominator mentioned in all these cases is the intellectual disability and global developmental delay. Therefore, it is possible to assume that our patient, probably will manifest the same phenotype regarding the psychomotor developmental delay, although not quantifiable with objective neurological criteria.

The reported patient shows the typical features of monosomy 9p as muscular hypotonia, distinct facial features and congenital heart defects. It is not possible to establish the exact percentage of prenatal ventricular septal defect (VSD), but Yoshikane *et al.* (2012), evaluated the accuracy of prenatal diagnosis of congenital heart defect (CHD). To date, the sensitivity and specificity of foetal echocardiography for CHD are higher than 90% in most leading countries. This paper included 132 cases with CHD. In this paper, it is interestingly stated that prenatally, false negatives were all ventricular septal defect (VSD) diagnosed at birth. In this review, the diagnostic accuracy was 89.7% for sensitivity and 95.7% for specificity. The authors suggest that the possible determinant factors for misdiagnosis are disease orientation, the timing of diagnosis (in this review, the mean gestational age is 31.3 weeks) and the skills of sonographers.

It is still a matter of debate whether cases with trisomy 2q share a recognizable phenotype. Distinction between proximal and distal trisomy 2q phenotypes is often made. Duplications proximal to 2q33 seem to cause a more severe phenotype with major malformations and marked growth with intellectual disability, while duplications distal to 2q33 show a milder phenotype (Angle *et al.* 2000; Slavotinek *et al.* 2003). The facial phenotype could be due to the distal trisomy 2q, in region 2q35-qter (Dahoun-Hadorn and Bretton-Chappius 1992; Angle *et al.* 2000). While interstitial duplications of other segments of 2q have been reported, only two previous papers on a duplication of a segment extending from 2q33.1 to 2q35 were reported (Romain *et al.* 1994; Sebold *et al.* 2005). Similarities between our patient and that previously reported patients include reactive airway disease, hypotonia, micrognathia, septal defect and developmental delay. The severe intellectual disability is probably due to the both monosomy 9p and duplication 2q, considering the length of duplication (from 31.2 to 37.3). The parental origin of the duplicated material is unknown in our patient as well as in the previously reported patients.

In conclusion, we report the first case of a chromosomal duplication of 2q31.2–37.3 with a monosomy 9p24.3. Our patient has a constellation of minor anomalies such as micrognathia, atresia coana, microcephaly, arched palate, ventricular septal defect, cataract and perianal fistula. On the contrary, major anomalies are represented by feeding difficulties and global hypotonia, clearly evident only after birth. This could explain the discrepancy between the anomalies documented prenatally compared with postnatal phenotype.

Acknowledgement

Authors wish to thank the parents for their cooperation and for providing the photographic documentation.

References

Angle B., Hersh J. H., Yen F. and Christensen K. M. 2000 Case of partial duplication 2q3 with characteristic phenotype: rare occurrence of an unbalanced offspring resulting from a parental pericentric inversion. *Am. J. Med. Genet.* **91**, 126–130.

Bakiler A. R., Ozer E. A., Kanik A., Kanit H. and Aktas F. N. 2007 Accuracy of prenatal diagnosis of congenital heart disease with fetal echocardiography. *Fetal Diagn. Ther.* **22**, 241–244.

Barnicoat A. J., Abusaad I., Mackie C. M. and Robards M. F. 1997 Two sibs with partial trisomy 2q. *Am. J. Med. Genet.* **70**, 166–170.

Battista Parigi G. 2005 *Chirurgia pediatrica. Approccio e gestione del bambino con problemi chirurgici.* Elsevier, Milan.

Bird L. M. and Mascarello J. T. 2001 Chromosome 2q duplications: case report of a de novo interstitial duplication and review of the literature. *Am. J. Med. Genet.* **100**, 13–24.

Couturier J., Aurias A., Prieur M. and Barois A. 1977 Partial trisomy for the long arm of chromosome 2 due to malsegregation of a maternal insertion: ins(6;2) (p22;q24q34). *Ann. Genet.* **20**, 52–55.

Dahoun-Hadorn S. and Bretton-Chappius B. 1992 De novo inversion duplication of 2q35-2qter without growth retardation. *Ann. Genet.* **35**, 55–57.

Dennis N. R., Neu R. L. and Bannerman R. M. 1978 Duplication 2q33 leads to 2q37 due to paternal ins (12;2) translocation. *Am. J. Med. Genet.* **1**, 271–277.

Durmaz C. D., Yararbaş K., Kutlay N. Y., Türedi Ö., Akın İ., Gürbüz C. *et al.* 2016 Unusual chromosomal rearrangement resulted in interstitial monosomy 9p: case report. *Cytogenet. Genome Res.* **148**, 19–24.

Elbracht M., Roos A., Schonherr N., Busse S., Damen R., Zerres K. *et al*. 2009 Pure distal trisomy 2q: a rare chromosomal abnormality with recognizable phenotype. *Am. J. Med. Genet. Part A* **149**, 2547–2550.

Gurrieri F., Sammito V., Bellussi A. and Neri G. 1992 New autosomal recessive syndrome of mental retardation, epilepsy, short stature, and skeletal dysplasia. *Am. J. Med. Genet.* **44**, 315–320.

Heon E., Liu S., Billingsley G., Bernasconi O., Tsilfidis C., Schorderet D. F. and Munier F. L. 1998 Gene localization for aculeiform cataract, on chromosome 2q33-35. (Letter) *Am. J. Hum. Genet.* **63**, 921–926.

Ikeuchi T. 1984 Inhibitory effect of ethidium bromide on mitotic chromosome condensation and its application to high-resolution chromosome banding. *Cytogenet. Cell Genet.* **38**, 56–61.

Lukusa T., Devriendt K., Jaeken J. and Fryns J. P. 1999 Mild dysmorphic signs in two male sibs with partial trisomy 2q32.1–>q35 due to maternal ins(14;2) translocation. *Clin. Dysmorphol.* **8**, 47–51.

Ma R., Peng Y., Zhang Y., Xia Y., Tang G., Chang J. *et al*. 2015 Partial trisomy 2q33.3-q37.3 in a patient with an inverted duplicated neocentric marker chromosome. *Mol. Cytogenet.* **8**, 10.

Marchese S., Diggans G., Garver K. and Stadler M. 1984 De novo 46,XX,dup(2)(q21–q31) ascertained by prenatal cytogenetic analysis. *Am. J. Hum. Genet.* **36**, 1035.

Matos A., Nogueira A., Criado B., Pereira S., Castedo S. and Montenegro N. 1997 Prenatal diagnosis of partial trisomy 2q. Case report. *Prenat. Diagn.* **17**, 874–876.

Ramer J. C., Mowrey P. N., Robins D. B., Ligato S., Towfighi J. and Ladda R. L. 1990 Five children with del (2)(q31q33) and one individual with dup (2)(q31q33) from a single family: review of brain, cardiac, and limb malformations. *Am. J. Med. Genet.* **37**, 392–400.

Recalcati M. P., Bellini M., Norsa L., Ballarati L., Caselli R., Russo S. *et al*. 2012 Complex rearrangement involving 9p deletion and duplication in a syndromic patient: genotype/phenotype correlation and review of the literature. *Gene* **502**, 40–45.

Romain D. R., Mackenzie N. G., Moss D., Columbano-Green L. M., Smythe R. H., Parfitt R. G. *et al.* 1994 Partial trisomy for 2q in a patient with dir dup (2) (q33.1q35). *J. Med. Genet.* **31**, 652–653.

Schumacher R. E., Rocchini A. P. and Wilson G. N. 1983 Partial trisomy 2q. *Clin. Genet.* **23**, 191–194.

Sebold C. D., Romie S., Szymanska J., Torres-Martinez W., Thurston V., Muesing C. and Vance G. H. 2005 Partial trisomy 2q: report of a patient with dup (2)(q33.1q35) *Am. J. Med. Genet. Part A* **134**, 80–83.

Seidahmed M. Z., Rooney D. E., Salih M. A., Basit O. B., Shaheed M. M., Abdullah M. A. *et al.* 1999 Case of partial trisomy 2q3 with clinical manifestations of Marshall–Smith syndrome. *Am. J. Med. Genet.* **85**, 185–188.

Sirisena N. D., Wijetunge U. K., de Silva R. and Dissanayake V. H. 2013 Child with deletion 9p syndrome presenting with craniofacial dysmorphism, developmental delay, and multiple congenital malformations. *Case Rep. Genet.* (https://doi.org/10.1155/2013/785830).

Slavotinek A. M., Boles D. and Lacbawan F. 2003 A female infant with duplication of chromosome 2q33 to 2q37.3. *Clin. Dysmorphol.* **12**, 251–256.

Usui D., Shimada S., Shimojima K., Sugawara M., Kawasaki H., Shigematu H. *et al*. 2013 Interstitial duplication of 2q32.1-q33.3 in a patient with epilepsy, developmental delay, and autistic behavior. *Am. J. Med. Genet. Part A* **161**, 1078–1084.

Yoshikane Y., Yoshizato T., Otake Y., Fusazaki N., Obama H., Miyamoto S. and Hirose S. 2012 Four-year experience with prenatal diagnosis of congenital heart defects at a single referral center in Japan with focus on inaccurately diagnosed cases. *J. Med. Ultrason.* **39**, 235–240.

Corresponding editor: Dhavendra Kumar