American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 369-373
DOI: 10.12659/AJCR.907329

Received: 2017.09.28
Accepted: 2017.12.19
Published: 2018.03.29

Placental Pathology in Placental Mesenchymal Dysplasia with 13q12.11 Deletion and a 25-Week Gestation Female Infant

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: —
Final Diagnosis: Placental mesenchymal dysplasia
Symptoms: Premature rupture of membranes
Medication: —
Clinical Procedure: Amniocentesis
Specialty: Obstetrics and Gynecology

Objective: Congenital defects/diseases

Background: Placental mesenchymal dysplasia (PMD) is a rare placental lesion that is associated with high perinatal morbidity and mortality. Grossly, PMD is characterized by placentomegaly with thick and tortuous chorionic vessels and abnormal branching over the chorionic plate. Histologically, enlarged edematous stem villi with dysplastic vessels and cistern formation are seen among normal intermediate and terminal villi. PMD has been previously associated with Beckwith-Wiedemann syndrome, paternal uniparental disomy 6, trisomies, Klinefelter syndrome, and androgenetic-biparental whole-gene mosaicism.

Case Report: We report a case of PMD in the setting of severe fetal growth restriction (FGR) (birth weight, 380 gm), with delivery at 25 weeks 1-day gestation. There was no maternal history of hypertension. The 25-week and 1-day gestation newborn infant died 20 minutes after delivery. Fetal cells obtained at amniocentesis had a 228kb deletion at 13q12.11 involving the gap junction beta-6 (*GJB6*) gene detected by single nucleotide polymorphism (SNP) microarray analysis. This finding was not previously reported in the setting of PMD. The histological findings of the placenta also showed some unique features that may have been associated with the specific molecular alteration that included inconspicuous cistern formation, stem villi and cell island complexes, features of shallow implantation, and a uterine pattern of chronic hypoxic placental injury.

Conclusions: A case of PMD in a 28-year-old woman with a female infant born at 25 weeks and 1-day gestation was associated with a 13q12.11 deletion in the *GJB6* gene and abnormal placental histological features.

MeSH Keywords: Congenital Abnormalities • Gene Deletion • Placenta Diseases

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/907329

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Background

Placental mesenchymal dysplasia (PMD) is a rare and poorly understood placental lesion, which can be unrecognized by general pathologists. The typical gross and histologic features of PMD are shown in Figure 1. Grossly, PMD is characterized by placentomegaly with marked ectasia and tortuosity of the vessels of the chorionic plate and stem villous vessels (Figure 1A). On cut section of the placenta, the large vessels appear as striae, running perpendicularly from the chorionic plate (Figure 1B). The findings can be mistaken for molar pregnancy, particularly a partial mole, both by ultrasound and gross examination, due to the cystic areas of the placental parenchyma. Histologically, enlarged edematous stem villi with peripherally arranged blood vessels and cisterns can be observed (Figure 1C), perhaps resulting from abnormally permeable vessels. Trophoblastic proliferation is not seen in PMD, and the terminal villi are relatively normal, in contrast to molar pregnancy.

Specific conditions previously described as being associated with PMD include Beckwith-Wiedemann syndrome (often seen with genetic and epigenetic defects on genes in the 11p15.5 region), neonatal diabetes mellitus, uniparental disomy 6, trisomy 13, aneuploidy, and Klinefelter syndrome [1–4]. The placental vascular abnormalities in PMD, which are the hallmark of the condition, can result in chorionic villous dysfunction, thrombosis, fetal growth restriction (FGR), and fetal death. However, although associated with high neonatal morbidity and mortality, PMD can also be seen with otherwise unremarkable pregnancies and newborn infants.

The most consistent molecular finding in PMD is androgenetic biparental mosaicism (ABM), in which a subset of cells in the placenta are diploid, but only have paternal chromosomes [5–8]. Immunohistochemistry for p57, the product of the *CDKN1C* gene, is widely used in the diagnosis of complete hydatidiform mole and is adjacent to the locus for the Beckwith-Wiedemann syndrome gene. The *CDKN1C* gene is expressed from the maternal chromosome but is silenced via methylation on the paternal chromosome. The usual immunohistochemical finding in PMD has been reported to be the absence of p57 staining in the villous stroma, with retention of staining in the villous trophoblast among the histologically abnormal stem villi [6]. The reason for the preferential distribution of the biparental cells to the trophoblastic epithelium and abnormal androgenetic cells to the extraembryonic mesoderm in PMD is unclear [8]. Normal villi and those in partial hydatidiform mole show nuclear staining for p57 in both the stroma and trophoblast, as opposed to the complete hydatidiform mole that shows neither types of immunostaining.

Other associated findings and genetic and molecular alterations in cases of PMD have not been reported to involve the 11p15.5 region. A previously published report has shown that PMD was associated with trisomy 13, suggesting that key genetic factors could involve *loci* on chromosome 13 [9]. We present a case of PMD in which a 13q12.11 deletion in the gap junction beta-6 (*GJB6*) gene and abnormal placental histology were found.

Case Report

A 28-year-old (G1, P0) woman presented with premature rupture of membranes at 25 weeks gestation. The mother was noted to have a history of infertility and irregular menses. No prenatal infectious or other teratogenic exposures were known. There was no maternal history of hypertension. A thrombophilia screen was negative. Prenatal ultrasound was notable for severe fetal growth restriction (FGR), absent end-diastolic blood flow in a single umbilical artery, pericardial effusion, oligohydramnios, and a markedly thick placenta, suspicious for partial hydatidiform mole. However, at that time, placental mesenchymal dysplasia (PMD) was not suspected clinically. The combination of imaging features raised the possibility of triploidy and partial molar pregnancy.

Amniocentesis had been performed at 19 weeks gestation due to the multiple abnormalities noted by ultrasound, which

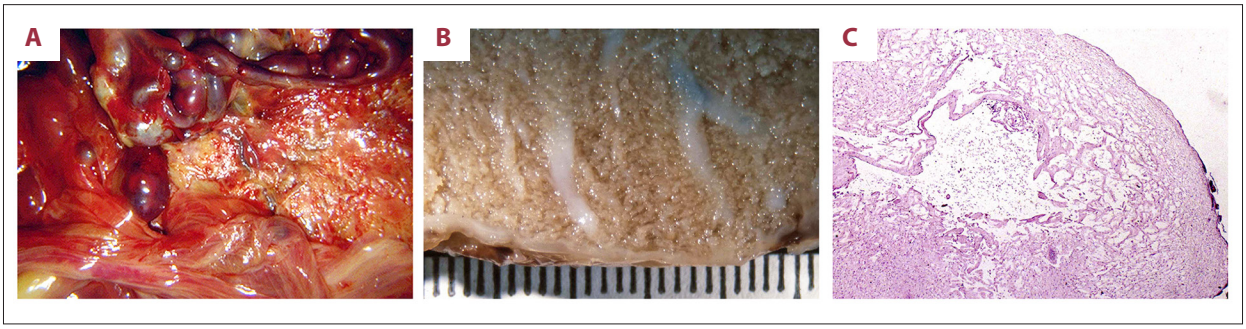

Figure 1. The typical gross morphology of placental mesenchymal dysplasia (PMD). (**A**) Large, tortuous vessels on the fetal surface of the placenta. (**B**) Prominent parallel striae of distended stem villi on a cross-section of the chorionic disc viewed using a dissecting microscope. (**C**) Enlarged stem villi with cistern formation.

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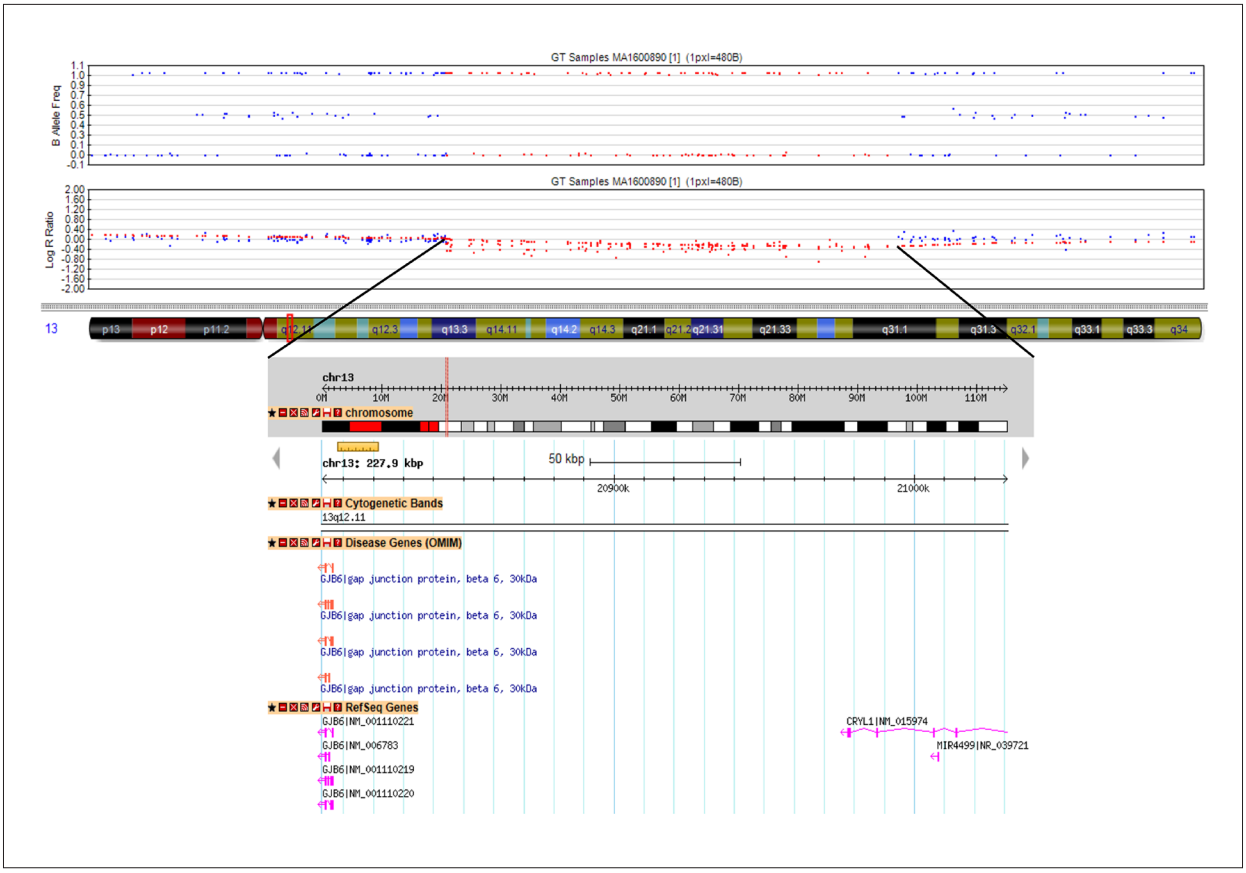

Figure 2. Single nucleotide polymorphism (SNP) microarray from the amniotic fluid sample. The amniotic fluid sample was determined to have a 228kb deletion at 13q12.11 involving the gap junction beta-6 (*GJB6*) gene by single nucleotide polymorphism (SNP) microarray, highlighted in red. The deletion encompassed all but the ultimate exon of the *GJB6* gene.

demonstrated a normal female karyotype, 46 XX. Microarray analysis of fetal cells obtained at amniocentesis demonstrated a 13q12.11 deletion involving the gap junction beta-6 (*GJB6*) gene (Figure 2). Polymerase chain reaction (PCR) analysis of the amniotic fluid for microorganisms including *Toxoplasma gondii*, herpes simplex virus (HSV)1, HSV2, cytomegalovirus (CMV), and parvovirus, was negative.

At 25 weeks 1-day gestation, the mother presented with preterm premature rupture of membranes (PROM). The neonate was born weighing 380 gm (normal mean weight=660±134 gm at 25 weeks gestation) and died 20 minutes after delivery. No macroscopic abnormalities were seen on examination of the neonate at the time of delivery, and an autopsy was not requested. The placenta was examined by the pathologists. Additional medical records were requested, although only limited past clinical history was available.

The fresh trimmed placental weight was 218.8 gm (75th to 90th percentile) (normal mean weight=184 gm at 25 weeks gestation). The placenta was fixed in formalin and was sectioned. No free membranes or umbilical cord was received, but slides requested from an external institution included sections from the placental disc, membranes, and umbilical cord.

Gross examination of the placenta showed wide, pale striae running perpendicular to the chorionic plate towards the maternal bed, consistent with the enlarged stem villi, as well as laminated blood clots under the chorionic plate and along the margins of the placental disc. The placental disc showed marked thickening, measuring 9.5×8.2×4.7 cm (Figure 3A, 3B).

Histologic examination of the placental disc showed markedly enlarged stem villi with thick dysplastic vessels surrounded by a myxoid edematous stroma with rare inconspicuous cistern formation (Figure 3C). The density of cell islands was increased, some of which demonstrated pseudocysts (Figure 3D). Occasional cell islands were seen directly adjacent to the large stem villi (Figure 3E). Also, multiple intervillous laminated thrombi with surrounding infarction (infarction hematomas) were seen (Figure 3F). Clusters of multinucleated cells were seen in the decidua basalis, consistent with shallow implantation of the placenta (Figure 3G). Atherosis of spiral arterioles was also evident. The terminal villi showed unremarkable morphology, although

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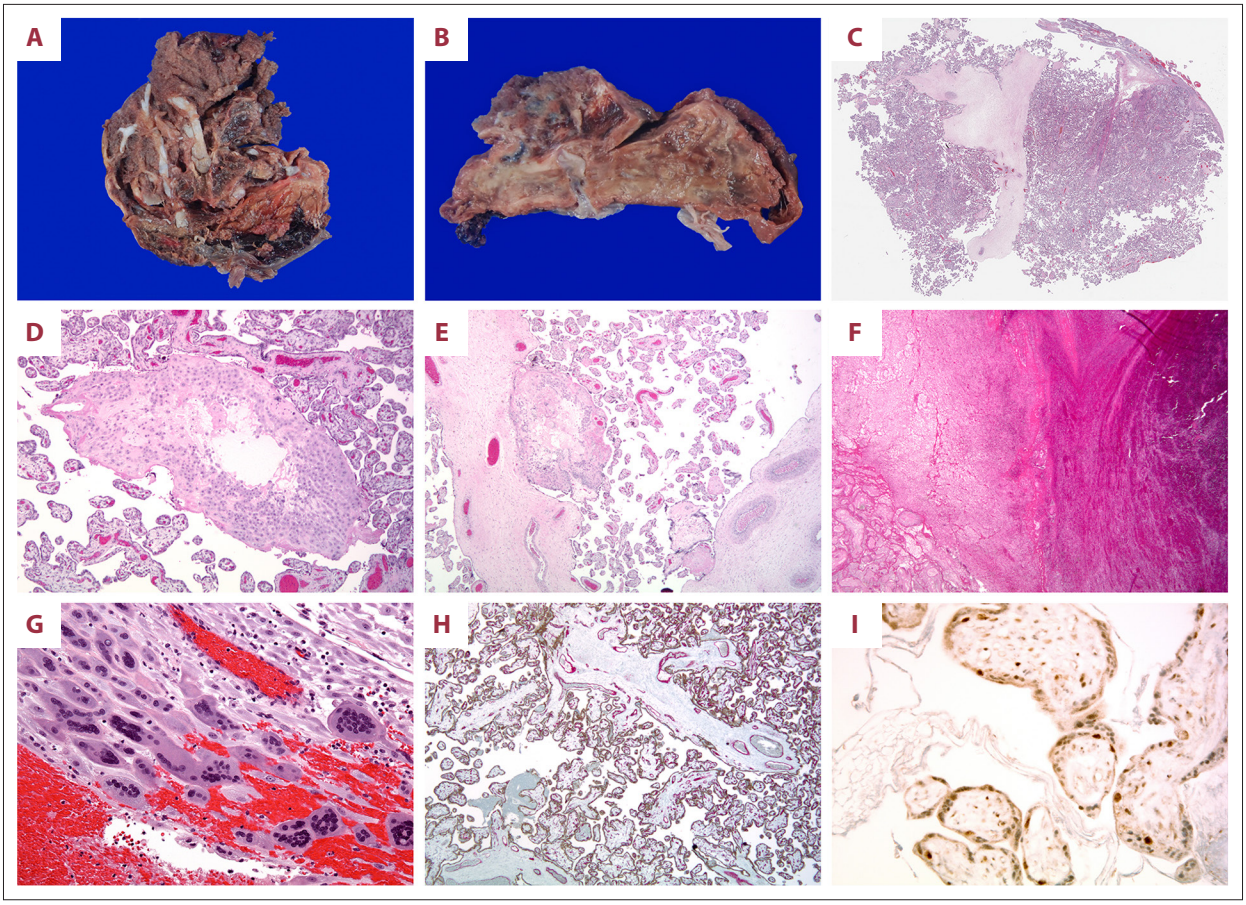

Figure 3. The gross, histological, and immunohistochemistry findings of the placenta in placental mesenchymal dysplasia (PMD). (**A**) A formalin-fixed chorionic disc featuring thick and tortuous chorionic vessels. (**B**) A cross-section of the placenta shows a thick placental disc with distended stem villi. (**C**) A large stem villus with myxoid stroma, inconspicuous cistern formation, dysplastic vessels, and surrounded by heterogeneously hypermature villi. Hematoxylin and eosin (H&E). (**D**) A cell island with a microscopic chorionic pseudocyst. (H&E). (**E**) A cell island/stem villus complex. (H&E). (**F**) Infarction hematoma (laminated intervillous thrombus surrounded by placental infarct). (H&E). (**G**) Clusters of multinucleate trophoblast in the decidua basalis. (H&E). (**H**) Immunohistochemistry for E-cadherin and CD34 highlights the terminal villi with stromal karyorrhexis and hypovascularity (right) in a lobular pattern, not observed on the H&E stain, with normal staining demonstrated in the lower left of the microphotograph, consistent with fetal vascular malperfusion and incipient fetal thrombotic vasculopathy. (**I**) Immunohistochemistry for p57 shows retention of staining in the villous cytotrophoblast and stromal cells.

lobules with villous hypovascularity and stromal and endothelial disintegration were identified, consistent with fetal vascular malperfusion or fetal thrombotic vasculopathy. Dual immunohistochemical staining for E-cadherin and CD34 highlighted the vascular abnormalities (Figure 3H). Immunohistochemical staining for p57 was retained in both the trophoblast and stromal cells. (Figure 3G). Laminar necrosis and acute chorioamnionitis were seen in the placental membranes. Acute funisitis was seen in the two-vessel umbilical cord.

Discussion

This reported case of placental mesenchymal dysplasia (PMD) showed macroscopic and histologic features previously described in the literature, but also some unique histological findings. The gross findings of a thickened placental disc with striae perpendicular to the chorionic plate are typical for PMD and supported the diagnosis at the time of gross examination of the placenta. Microscopic examination showed enlarged stem villi with dysplastic vessels and terminal non-edematous villi without abnormal trophoblastic proliferation, which are typical features of PMD. In this case, the unusual placental findings included inconspicuous cistern formation in stem villi, and cell island stem villous complexes, which could be related to the 228 kb deletion at 13q12.11 involving the gap junction beta-6 (*GJB6*) gene detected by single nucleotide polymorphism (SNP) microarray analysis demonstrated in this case.

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Also, this case showed multiple intervillous thrombi with adjacent infarction and infarction hematoma, as well as foci of distal villous karyorrhexis [10]. A full spectrum of fetal thrombotic vasculopathy has been previously described in cases of PMD, which are most likely to be related to the altered vascular dynamics associated with the placental vascular abnormalities [2,7]. In this case, the terminal villi showed features of a uterine pattern of chronic hypoxic placental injury, including heterogeneous hypermaturity and increased extravillous trophoblast, which are features of shallow placental implantation. As the pregnancy was not complicated by a hypertensive disorder, the possibility that these hypoxic developmental patterns and lesions are also due to the underlying genetic abnormality cannot be excluded.

In this case, the gross and histologic findings of the placenta were consistent with PMD, but immunohistochemical staining with p57 showed retained staining of the stromal and trophoblast nuclei, and in such cases, additional genetic studies are recommended [7]. Amniocentesis showed a normal female karyotype, 46 XX. However, microarray analysis showed a 228kb deletion at 13q12.11 involving the *GJB6* gene detected by single nucleotide polymorphism (SNP). The *GJB6* gene has been associated with a risk of hearing loss, while other abnormalities associated with deletions in this region include fetal and neonatal developmental delay, minor dysmorphic features, choanal atresia, malformed extremities, and brain and spinal malformations [11,12]. The at 13q12.11 involving the *GJB6* gene has not been previously associated with placental pathology. PMD has previously been associated with trisomy 13, suggesting that imbalance of chromosome 13, or an as yet unidentified gene or gene region could play a role in the development of PMD.

The wide variation in fetal and infant findings in PMD are possibly related to the timing and degree of involvement of the molecular event, with early and widespread involvement possibly leading to intrauterine fetal growth restriction (FGR) or fetal death, while less significant involvement or later mutations allow for unimpeded growth of the fetus [6]. The variability of presentation in PMD is likely to be related to the precise molecular change. In this case, the deletion was seen in 13q12.11, detected in fetal cells obtained at amniocentesis, a finding that has not been previously reported. Additional molecular studies of future cases of PMD may confirm or add further information to the relationship of the PMD lesion with the 13q12.11 deletion. The 13q12.11 deletion may be an additional locus of interest in the development of PMD. The findings of this case report have highlighted the importance of molecular studies, including karyotype and microarray analysis, in improving the understanding of the molecular genetics and pathogenesis of PMD, to allow for appropriate genetic counseling and clinical management.

Conclusions

In this case, placental mesenchymal dysplasia (PMD) was associated with deletion at 13q12.11 involving the *GJB6* gene and showed previously unreported placental histological features that included inconspicuous cistern formation, stem villi and cell island complexes, features of shallow placental implantation, and a uterine pattern of chronic hypoxic placental injury.

Acknowledgements

The authors wish to thank Chris Woods for assistance with preparation of the photomicrographs.

Conflict of interest

None

References:

1. Pawoo N, Heller DS: Placental mesenchymal dysplasia. Arch Pathol Lab Med, 2014; 138: 1247–49
2. Paradinas FJ, Sebire NJ, Fisher RA et al: Pseudo-partial moles: Placental stem vessel hydrops and the association with Beckwith-Wiedemann syndrome and complete moles. Histopathology, 2001; 39: 447–54.
3. Lange JM: Placentomegaly with massive hydrops of placental stem villi, diploid DNA content, and fetal omphaloceles: Possible association with Beckwith-Wiedemann syndrome. Hum Pathol, 1991; 22: 591–97
4. Cohen MC, Roper EC, Sebire NJ et al: Placental mesenchymal dysplasia associated with fetal aneuploidy. Prenatal Diagnosis, 2005; 25: 187–92
5. Hamida D, Yacoubi T, Chaieb A et al: Placental mesenchymal dysplasia with Beckwith-Wiedemann syndrome fetus in the context of biparental and androgenic cell lines. Placenta, 2008; 29: 454–60
6. Faye Petersen OM, Kapur RP: Placental mesenchymal dysplasia. Surg Pathol, 2013; 6: 127–51
7. Gibson BR, Muir-Padilla J, Champeaux A, Suarez ES: Mesenchymal dysplasia of the placenta. Placenta, 2004; 25: 671–72
8. Kaiser-Rogers KA, McFadden DE, Lavasy et al: Androgenetic/biparental mosaicism causes placental mesenchymal dysplasia. J Med Genet, 2006; 43: 187–92
9. Munger E, Dundar O, Muhcu M et al: Placental mesenchymal dysplasia associated with trisomy 13: Sonographic findings. J Clin Ultrasound, 2008; 36: 545–46
10. Khong TY, Mooney EE, Ariel I et al: Sampling and definition of placental lesions. Arch Pathol Lab Med, 2016; 140: 698–713
11. Pavone P, Briuglia S, Falsaperia R et al: Wide spectrum of congenital anomalies including choanal atresia, malformed extremities, and brain and spinal malformations in a girl with de novo 5.6-Mb deletion of 13q12.11-13q12.13. Am J Med Genet, 2014; 164A: 1734–43
12. Der Kaloustian VM, Russel L, Aradhya S et al: A *de novo* 2.1-Mb deletion of 13q12.11 in a child with developmental delay and minor dysmorphic features. Am J Med Genet, 2011; 155: 2538–42

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