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First prenatal case of proximal 19p13.12 microdeletion syndrome: New insights and new delineation of the syndrome

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ABSTRACT

Proximal 19p13.12 microdeletion has been rarely reported. Only five postnatal cases with intellectual disability, facial dysmorphism, branchial arch defects and overlapping deletions involving proximal 19p13.12 have been documented. Two critical intervals were previously defined: a 700 kb for branchial arch defects and a 350 kb for hypertrichosis-synophrys-protruding front teeth. We describe the first prenatal case, a fetal death in utero at 39 weeks of gestation. Agilent 180K array-CGH analysis identified a heterozygous interstitial 745 kb deletion at 19p13.12 chromosome region, encompassing both previously reported critical intervals, including at least 6 functionally relevant genes: *NOTCH3*, *SYDE1*, *AKAP8*, *AKAP8L*, *WIZ* and *BRD4*. Quantitative PCR showed that the deletion occurred *de novo* with a median size of 753 kb. *NOTCH3* and *SYDE1* were candidate genes for placental pathology whilst *AKAP8*, *AKAP8L*, *WIZ* and *BRD4* were highly expressed in the branchial arches. Molecular characterization and sequencing of candidate genes for placental pathology and branchial arch defects were carried out in order to correlate the genotype-phenotype relationship and unravel the underlying mechanism of proximal 19p13.12 microdeletion syndrome. This case also contributes to define the novel critical interval and expand the clinical phenotype spectrum of proximal 19p13.12 microdeletion syndrome.

1. Introduction

Microdeletion of 19p13.12 has been rarely reported. Individuals with 19p13.12 deletion display variable clinical features including mild to severe developmental delay, ear malformations, hearing impairment, cardiac anomalies, brain malformations, facial dysmorphic features, synophrys and hypertrichosis. Moreover, no fetal phenotype of 19p13.12 microdeletion was reported to date. Patients with distal 19p13.12 microdeletion share a common 359 kb SRO encompassing six annotated genes: *LPHN1/CIRL1*, *CD97*, *DDX39*, *PKN1*, *PTGER1*, *GIPC1* and show typical clinical features including moderate to severe psychomotor impairment, language delay, hearing loss, facial dysmorphism, mild congenital cardiac anomalies and/or rhythm disturbance (Bonaglia et al., 2010). Recently, several postnatal cases involving proximal 19p13.12 submicroscopic rearrangements were reported. All previously reported patients had branchial arch defects including ear malformations, branchial pits and high palate (Table 1). As shown in Table 1, patients with proximal 19p13.12 microdeletion present distinctive facial dysmorphism, branchial arch defects with ear malformations, hearing loss, psychomotor and language delay. A 700 kb critical region for branchial arch defects in proximal 19p13.12 microdeletion was previously defined by Kosaki et al. (2011) while a 305 kb candidate interval for hypertrichosis-synophrys-protruding front teeth was documented by Jelsig et al. (2012).

We report a fetal death in utero at 39 weeks of gestation carrying the smallest 753 kb microdeletion of proximal 19p13.12. Having reviewed the literature data, the genotype-phenotype correlation in the present case has been delineated and the new critical region of proximal 19p13.12 microdeletion syndrome refined.

2. Clinical report

A healthy 33-year-old woman (gravida 2, para 1) went into spontaneous labor at 39 weeks of gestation after an uneventful pregnancy. The stillbirth was discovered with no fetal cardiac activity by electronic fetal heart rate monitoring just before the labor. Autopsy showed a mildly macerated female fetus presenting facial dysmorphism including square face, hypertelorism, downturned corners of the mouth, preauricular skin tag and cupped ears (Fig. 1A). Her weight, length and head circumference were respectively 3145 g (28^{th} centile), 53 cm (90^{th} centile), 34 cm (50^{th} centile). Internal examination revealed small kidneys (combined weight: 16.2 g; expected: 27 + 7.5 g) with normal cortico-medullary differentiation histology. Placenta was slightly hypertrophic (460 g; expected weight: 425 ± 5 g; foetoplacental ratio: 6.8; expected: 7.5 ± 0.1). The cord was marginally inserted. Placenta histology showed a global villous hypoplasia with massive perivillous fibrin depositions (MPVFD). Ischemic villous changes with increased syncytial knots were diffusely present (Fig. 2). The family history was unremarkable.

3. Materials and methods

3.1. Conventional cytogenetic analysis

Patient-index placental trophoblasts were cultured in AmnioMAXTM-C100 Supplement (ThermoFisher Scientific, France) and metaphase

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Table 1
Detailed phenotype in previously reported patients with 19p13.12 interstitial deletion. Note that all patients had branchial arch defects and distinctive dysmorphic features in previously reported cases.

		High forehead	Synophrys	Thick eyebrows	Epicanthal folds	Downslanting palpebral fissures	Hypertelorism	Clinical features		Low-set or malformed ears	Preauricular tags	Preauricular or branchial pits	High/ Cleft palate	Long philtrum	Micrognathia
								Dysmorphic features							
								Strabismus	Depressed nasal bridge						
Postnatal diagnosis cases	Kosaki et al. (2011)	-	–	+	+	+	+	-	+	+	+	+	-	-	+
	Jelsig et al. (2012)	-	+	+	-	+	–	+	-	+	–	–	+	-	-
	Van der Aa et al. (2010)	-	+	+	+	+	–	-	+	+	–	–	+	-	-
	Engels et al. (2007)	-	+	-	+	-	–	-	-	+	+	–	-	+	-
	Jensen et al. (2009)	+	–	-	+	+	+	+	+	+	–	+	-	+	+
	Bonaglia et al. (2010) (case 1)	+	+	-	–	–	–	–	+	+	–	–	+	+	–
	Bonaglia et al. (2010) (case 2)	–	+	-	+	–	–	–	+	+	+	–	–	+	–
	Decipher 255839	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Decipher 265764	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Decipher 249355	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fetal phenotype	Our case	-	–	–	-	-	+	NA	+	+	+	–	-	–	-

Other malformations											aCGH or MLPA result
Postnatal diagnosis cases		Microcephaly	Hearing loss	Intellectual disability or psychomotor delay	Language delay	Stenosis of the external auditory canal	Hypertrichosis	Congenital heart defect	Renal hypotrophia	Placental anomalies	Growth restriction	
	Kosaki et al. (2011)	+	+	+	+	+	-	-	–	ND	ND	arr[GRCh37] 19p13.12(15439339_16203271)x1 dn [0.76 Mb]
	Jelsig et al. (2012)	+	+	+	+	+	+	-	–	ND	ND	mlpa 19p13.12(14,382,780-15,583,)x1 dn [1.4 Mb]
	Van der Aa et al. (2010) [Decipher 255743]	+	ND	+	+	-	+	-	ND	ND	ND	mlpa[GRCh37] 19p13.12(14,382,780-15,492,848)x1 dn [1.11 Mb]

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