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Case Report

Prenatal diagnosis of a 0.7-Mb 17p13.3 microdeletion encompassing *YWHAE* and *CRK* but not *PAFAH1B1* in a fetus without ultrasound abnormalities

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of 17p13.3 microdeletion encompassing *YWHAE* and *CRK* but not *PAFAH1B1* in a fetus without ultrasound abnormalities.
Case report: A 33-year-old woman underwent amniocentesis at 17 weeks of gestation because of a family history of spinocerebellar atrophy in the husband. Amniocentesis revealed a karyotype of 46,XX. Simultaneously array comparative genomic hybridization (aCGH) analysis (using 60,000 probes) revealed a 0.7-Mb 17p13.3 microdeletion or arr 17p13.3 (1,264,243–1,965,733) × 1 dn [GRCh37 (hg19)] encompassing *YWHAE* and *CRK* but not *PAFAH1B1*. Prenatal ultrasound findings were unremarkable. There were no structural abnormalities of the brain, heart, kidneys, skull, limbs and other internal organs. The parents elected to terminate the pregnancy, and a 268-g fetus was delivered at 19 weeks of gestation with mild facial dysmorphism. Postnatal high-resolution aCGH analysis of the placenta (using 630,000 probes) showed a 0.79-Mb 17p13.3 microdeletion or arr 17p13.3 (1,173,549–1,970,690) × 1 (hg19) encompassing *TUSC5*, *YWHAE*, *CRK* and *HIC1* but not *PAFAH1B1*. Metaphase fluorescence *in situ* hybridization analysis using the 17p13.3-specific probe of RP11-818O24 revealed a 17p13.3 deletion.
Conclusion: Fetus with 17p13.3 microdeletion without involving *PAFAH1B1* may present no brain abnormalities on fetal ultra sound.

Introduction

Miller-Dieker lissencephaly syndrome [MDLS; Online Mendelian Inheritance in Man (OMIM) 247200] including chromosome 17p13.3 deletion syndrome is an autosomal dominant contiguous gene deletion syndrome involving genes on chromosome 17p13.3 and is characterized by cerebral agyria/pachygyria or type I lissencephaly, ventriculomegaly, corpus callosum dysgenesis/agenesis, microcephaly, seizures, facial dysmorphism of prominent forehead and occiput, bitemporal narrowing, furrowed brow, small nose, anteverted nostrils, low-set ears, prominent lip and micrognathia, hypoplastic male external genitalia, intrauterine growth restriction (IUGR), mental retardation, cardiac defects, omphalocele and genitourinary abnormalities [1–9]. Mutations or deletions of *PAFAH1B1* cause isolated or classic lissencephaly 1 (LIS1; OMIM 607432). Deletion of the *PAFAH1B1* (OMIM 601545) in chromosome

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17p13.3 deletion syndrome is responsible for lissencephaly in MDLS. Facial dysmorphism and other abnormalities in MDLS have been suggested to be associated with additional genes such as *YWHAE* distal to *PAFAH1B1* [10].

We previously reported prenatal diagnosis of central nervous system (CNS) anomalies in fetuses with MDLS involving haploinsufficiency of *PAFAH1B1* [6–8]. Here, we present a case with 17p13.3 microdeletion including *YWHAE* and *CRK* but not *PAFAH1B1* in a fetus without CNS abnormalities on prenatal ultrasound.

Case report

A 33-year-old, gravida 2, para 0, woman underwent amniocentesis at 17 weeks of gestation because of a family history of spinocerebellar atrophy in the husband who was 31 years old. Amniocentesis revealed a karyotype of 46,XX. Simultaneously array comparative genomic hybridization (aCGH) analysis using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA) (60,000 probes) revealed a 0.7-Mb 17p13.3 microdeletion or arr 17p13.3 (1,264,243–1,965,733) × 1 dn [GRCh37 (hg19)] encompassing *YWHAE* and *CRK* but not *PAFAH1B1*. The parents did not have such a deletion. Prenatal ultrasound findings were unremarkable. There were no structural abnormalities of the brain, heart, kidneys, skull, limbs and other internal organs. The parents elected to terminate the pregnancy, and a 268-g fetus was delivered at 19 weeks of gestation with mild facial dysmorphism of low-set ears, anteverted nostrils, prominent forehead and occiput, bitemporal narrowing, furrowed brow, a broad nasal root and micrognathia (Fig. 1). Postnatal high-resolution aCGH analysis of the DNA extracted from the placenta using Roche ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA) (630,000 probes) showed a 0.797-Mb 17p13.3 microdeletion or arr 17p13.3 (1,173,549–1,970,690) × 1 [GRCh37 (hg19)] encompassing 29 OMIM genes including *BHLHA9*, *TUSC5*, *YWHAE*, *CRK*, *MYO1C*, *INPP5K*, *PITPNA*, *SLC43A2*, *SCARF1*, *RILP*, *PRPF8*, *MIR22*, *WDR81*, *SERPINF2*, *SERPINF1*, *RPA1*, *RTN4RL1*, *DPH1*, *OVCA2*, *MIR132*, *MIR212*, *HIC1* and *SMG6* (Fig. 2). Metaphase fluorescence *in situ* hybridization (FISH) analysis on the cultured chorionic villi cells using the 17p13.3-specific probe of RP11-818O24 and the 17q25.3-specific probe of RP11-196O11 confirmed a 17p13.3 deletion (Fig. 3).

Discussion

We previously reported three cases of 17p13.3 deletion syndrome associated with haploinsufficiency of *PAFAH1B1*, and all cases manifested abnormalities on fetal ultrasound. The first case had a karyotype of 46,XY,del(17)(p13.3) and manifested polyhydramnios, IUGR, ventriculomegaly and lissencephaly on prenatal ultrasound [6]. The second case had a karyotype of 46,XX,del(17)(p13.2) and manifested IUGR, tetralogy of Fallot and ventriculomegaly on prenatal ultrasound, and lissencephaly on postnatal magnetic resonance imaging (MRI) [7]. The third case had a karyotype of 46,XX,del(17)(p13.3) with a 3.17-Mb deletion encompassing *YWHAE*, *CRK* and *PAFAH1B1* and manifested lissencephaly, corpus callosum dysgenesis, ventriculomegaly, microcephaly, IUGR, polyhydramnios and a single umbilical artery on prenatal ultrasound [8]. Chromosome 17p13.3 deletion including haploinsufficiency of *PAFAH1B1* may manifest severe brain abnormalities on prenatal ultrasound [8].

Genetic counseling of *de novo* 17p13.3 microdeletion without involving *PAFAH1B1* detected during routine aCGH analysis at amniocentesis in pregnancy without sonographic abnormalities such as this case remains a challenge to genetic counselors and obstetricians. The present case had a 0.79-Mb 17p13.3 microdeletion encompassing *TUSC5*, *YWHAE*, *CRK* and *HIC1* but not *PAFAH1B1*. *TUSC5* (OMIM 612211) encodes tumor suppressor candidate 5 protein and is expressed in brown adipocytes [11,12]. *YWHAE* (OMIM 605066) encodes 14-3-3ε protein which plays important roles in neuronal migration [10]. *CRK* (OMIM 164762) is an oncogene that encodes v-crk avian sarcoma virus CT10 oncogene homologue which is an adaptor protein that has a role in cell proliferation and migration [13,14]. *HIC1* (OMIM 603825) encodes hypermethylated in cancer 1 protein which is expressed in mesenchymes of the sclerotomes, lateral body wall, limb and craniofacial regions during embryonic differentiation [15]. In Hic1-

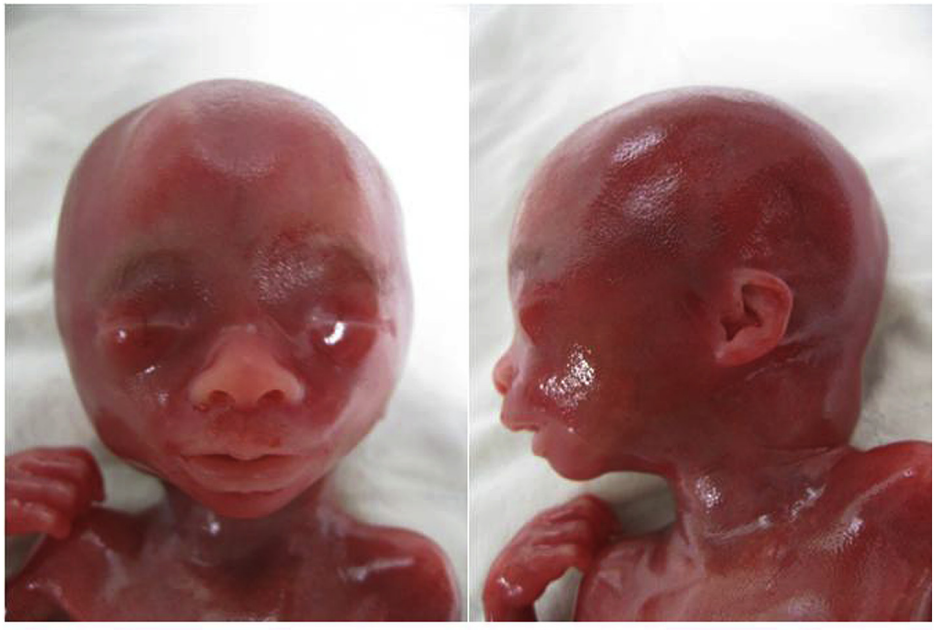

Fig. 1. The craniofacial appearance of the fetus at birth.

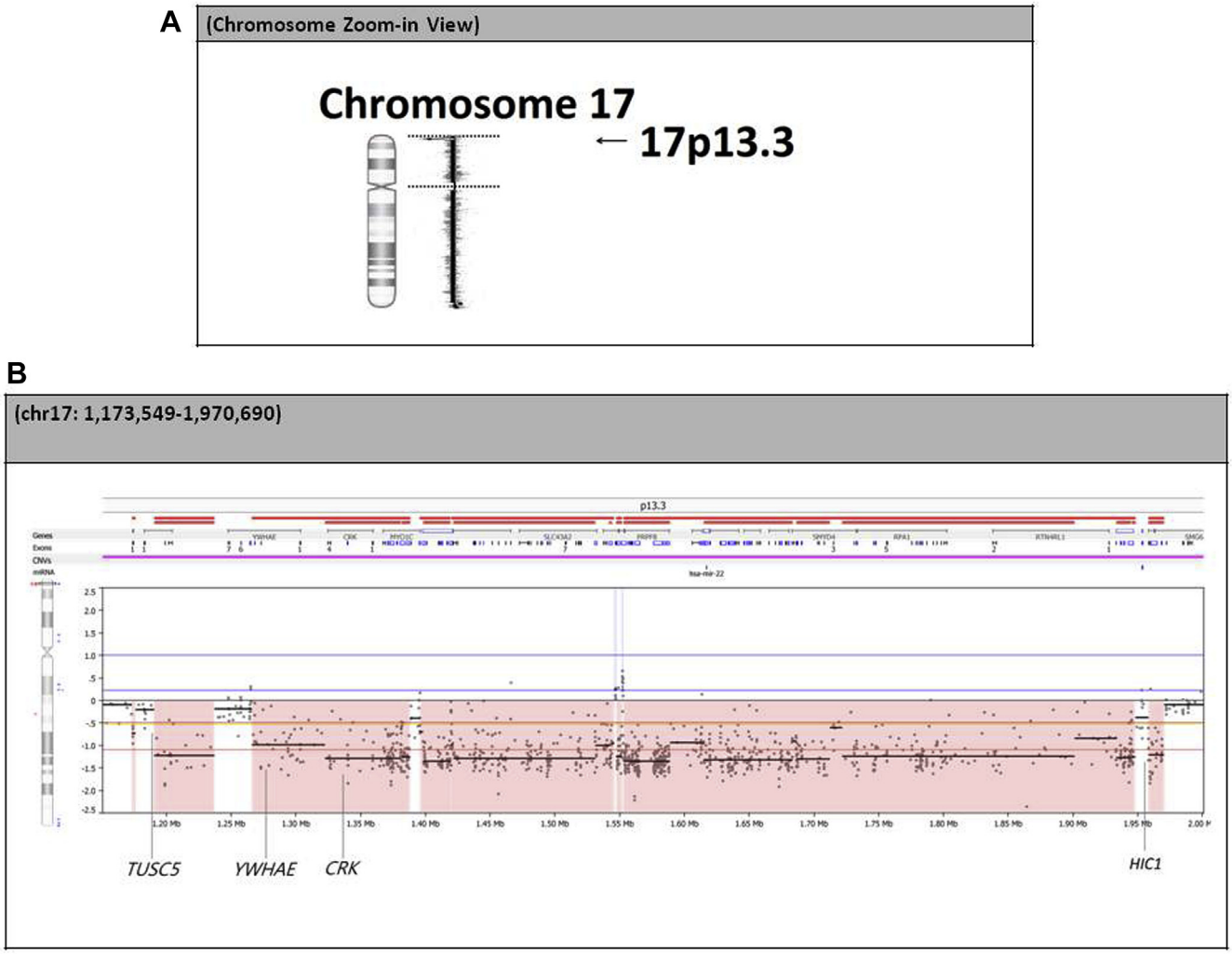

Fig. 2. Array comparative genomic hybridization analysis on the DNA extracted from the placenta shows a 0.79-Mb 17p13.3 microdeletion, or arr 17p13.3 (1,173,549–1,970,690) × 1 encompassing *TUSC5*, *YWHAE*, *CRK* and *HIC1*. (A) and (B) Chromosome zoon-in views.

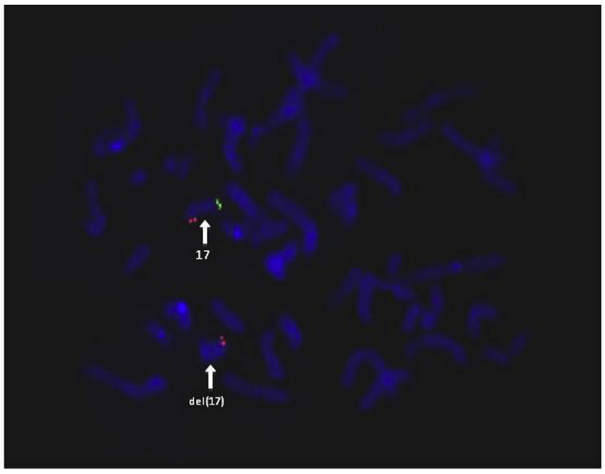

Fig. 3. Metaphase fluorescence *in situ* hybridization analysis on the cultured chorionic villi cells using the 17p13.3-specific probe of RP11-818O24 [fluorescein isothiocyanate (FITC), spectrum green] and the 17q25.3-specific probe of RP11-196O11 (Texas red, spectrum red) shows absence of the green signal on del(17), indicating a 17p13.3 microdeletion. del = deletion.

deficient mice, Carter et al. [16] observed gross developmental defects including acrania, exencephaly, cleft palate, limb anomalies and omphalocele. It has been suggested that the phenotypic features of facial dysmorphism of the nose and jaws and anomalies of the heart, kidneys, gastrointestinal tract and the limbs in MDLS may correlate with haploinsufficiency of *HIC1*.

Cases with chromosome 17p13.3 deletion but not involving *PAFAH1B1* have been reported to manifest phenotypic abnormalities [17–28]. Nagamani et al. [17] reported five patients involving *YWHAE* but not *PAFAH1B1* and concluded that microdeletion of 17p13.3 involving *YWHAE* presents growth restriction, tall vertex, prominent forehead, broad nasal root, epicanthic folds, cognitive impairment, and abnormal brain imaging findings of Virchow-Robin spaces, periventricular and white matter signals, Chiari I malformation and abnormal corpus callosum. Nagamani et al. [17] also suggested that *CRK* plays a role in growth restriction in 17p13.3 deletion syndrome. Mignon-Ravix et al. [19] reported a 3-year-7-month-old boy with 400-kb 17p13.3 microdeletion involving *TIMM22*, *ABR*, *BHLHA9*, *TUSC5* and *YWHAE*, who manifested facial dysmorphism of high forehead with bitemporal hollowing, hypertelorism, epicanthus, down-slanting palpebral fissures, anteverted nares, pronounced Cupid's bow and small low-set ears, and abnormal MRI findings of corpus callosum hypoplasia, ependymal and periventricular nodular

heterotopias and malformation of cortical development. Bruno et al. [18] studied eight patients with 17p13.3 microdeletion and identified a 258-kb MDLS telomeric critical region encompassing six genes of *TUSC5*, *YWHAE*, *CRK*, *MYO1C*, *SKIP* and *PITPNA*, and suggested that *YWHAE* plays a role in facial dysmorphism, and *CRK* is responsible for IUGR. Schiff et al. [20] reported four patients with 17p13.3 microdeletion involving *YWHAE* but distal to *PAFAH1B1* and found a distinct phenotype of mild mental retardation, moderate to severe growth restriction, white matter abnormalities and developmental defects in brain and eye. Shimojima et al. [21] reported a patient with 17p13.3 microdeletion involving *YWHAE* and *CRK* but not *PAFAH1B1* and identified a phenotype of intractable epilepsy, facial dysmorphism and growth retardation. Tenney et al. [22] reported two patients with 17p13.3 microdeletion involving *YWHAE* but not *PAFAH1B1* and identified a clinical syndrome with macrocephaly, small stature, facial dysmorphism, generalized epilepsy, developmental delay and non-specific white matter changes. Enomoto et al. [23] reported a 5-year-old girl with a 2.3-Mb 17p13.3 deletion involving *YWHAE* and *CRK* but not *PAFAH1B1*. The girl showed normal brain structure on MRI, mild developmental delay, a distinct facial appearance and severe growth retardation. Enomoto et al. [23] suggested the dosage effect of *YWHAE* varies from severe to very mild structural brain abnormalities. Østergaard et al. [24] reported a case with a 284-kb 17p13.3 microdeletion involving *CRK* but not *YWHAE* and *PAFAH1B1*, and identified a distinct phenotype of mental retardation, postnatal growth restriction, facial dysmorphism, clinodactyly and syndactyly. Dias et al. [25] reported a patient with 17p13.3 microdeletion involving *HIC1* and the congenital malformations of hypoplastic left heart syndrome, bilateral cryptorchidism and diaphragmatic hernia. Barros Fontes et al. [26] reported a 3-year-old boy with a 2.1-Mb 17p13.3 microdeletion involving *YWHAE*, *CRK*, *HIC1* and *OVCA1* but not *PAFAH1B1*, and identified a phenotype of minor facial dysmorphism, a cleft palate, neurodevelopmental delay and behavioral disorder with no structural malformation of the brain. Heide et al. [27] reported a patient with a 2.05-Mb 17p13.3 microdeletion (18,902–2,071,058) × 1 (hg19) involving *YWHAE* but not *PAFAH1B1*, and the phenotype of partial corpus callosum agenesis. Noor et al. [28] reported an 8-year-4-month-old boy with a 12.6-kb 17p13.3 microdeletion (1,254,694–1,258,917) × 1 (hg19) involving the entire exon 6 of *YWHAE* and identified a phenotype of myoclonic epilepsy, Chiari I malformation, thin corpus callosum, cavum pellucidum and cavum vergae, dysgraphia and learning disability.

In summary, we present molecular cytogenetic characterization of prenatally detected 17p13.3 microdeletion involving *TUSC5*, *YWHAE*, *CRK* and *HIC1* but not *PAFAH1B1*. We review previously reported cases and discuss the genotype–phenotype correlation of the genes of *TUSC5*, *YWHAE*, *CRK* and *HIC1* that are deleted within 17p13.3 in this case.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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