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Research Letter

Prenatal diagnosis of a *de novo* 17p13.1 microduplication in a fetus with ventriculomegaly and lissencephaly

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A 27-year-old, gravida 3, para 1, woman was referred to the hospital at 31 weeks of gestation because of abnormalities of the fetal brain. Her husband was 30 years old. The woman and her husband were non-consanguineous, and there was no family history of congenital malformations. The couple had a 9-year-old healthy son. The present pregnancy was uneventful until 31 weeks of gestation when ventriculomegaly and a small size for gestational age were noted in the fetus. The fetal biometry was equivalent to 29 weeks, and the fetal cerebral ventricle was prominently dilated (Fig. 1). Ultrafast fetal magnetic resonance imaging (MRI) scans showed a smooth agyric brain with a "figure-of-eight" appearance of the shallow sylvian fissure and a thick cortex (Fig. 2). The MRI findings were consistent with the diagnosis of lissencephaly. Fetal blood sampling revealed a karyotype of 46,XX. However, bacterial artificial chromosome (BAC)-based array comparative genomic hybridization (aCGH) analysis using CMDX BAC aCGH CA3000 Chips (CMDX, Irvine, CA, USA) revealed a 0.5-Mb microduplication at 17p13.1, or arr cgh 17p13.1p13.1 (RP11-736G8 → RP11-8I18) × 3 (Fig. 3). Oligonucleotide-based aCGH analysis using Human CGH 12 × 135K Whole-Genome Tiling Array V3.1 (Roche NimbleGen, Madison, WI, USA) revealed a 1.3-Mb microduplication at 17p13.1, or arr cgh 17p13.1p13.1 (9,730,710 − 11,014,931) × 3 [University of California Santa Cruz (UCSC) genome browser on human, March 2006 (National Center for Biotechnology Information (NCBI) 36/human genome 18) assembly] (Fig. 4). The 1.3-Mb duplicated region encompasses the genes of *GLP2R*, *RCVRN*, *GAS17*, *MYH1*, *MYH2*, *MYH3*, *MYH4*, *MYH8*, *SCO1* and *PIRT*. The parental karyotypes were normal. The aCGH analysis of the parental blood did not reveal such a duplication. At 34 weeks of gestation, a dead fetus weighing 1996 g was delivered with hypertelorism, a depressed nasal bridge, a thin lip and enlarged low-set ears (Fig. 5).

The present case was associated with 17p13.1 microduplication and lissencephaly, but did not have the distinctive facial appearance of Miller-Dieker lissencephaly syndrome (MDLS; OMIM 247200) such as prominent forehead, bitemporal hollowing, a short nose with upturned nares, a protuberant upper lip, and a small jaw. MDLS is an autosomal dominant disorder and is caused by deletions or mutations of the *LIS1* (*PAFAH1B1*) gene (OMIM 601545) on 17p13.3 [1–3]. Trisomy 17p is characterized by mental and motor retardation, intrauterine growth restriction, postnatal growth retardation, hypotonia, skeletal anomalies, clinodactyly of the fingers, hypertrichosis, congenital heart defects, and distinctive craniofacial abnormalities such as microcephaly, downslanting palpebral fissures, ptosis, hypertelorism, low-set malformed ears, smooth philtrum, micrognathia, high-arched palate, and a short neck [4–7]. Duplication of distal 17p can be associated with phenotypic abnormalities. Ruiter et al. [8]

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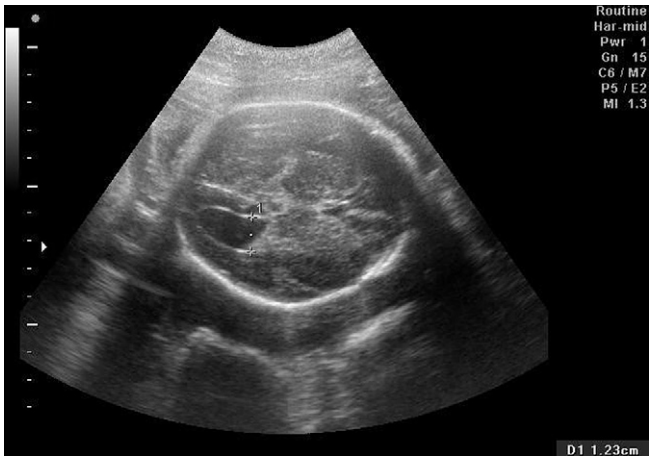

Fig. 1. Prenatal ultrasound at 29 weeks of gestation shows right ventriculomegaly.

reported severe mental retardation, epilepsy, ataxia, constipation behavior problems, and facial dysmorphism in a patient with a 0.5-Mb duplication of 17p13.3 → pter. Recently, a new microduplication syndrome encompassing the region of *LIS1* (*PAFAH1B1*) gene with phenotypic features of developmental delay, hypotonia, and facial dysmorphism has been suggested [9].

The present case has a 17p13.1 microduplication encompassing the genes of *GLP2R*, *RCVRN*, *GAS17*, *MYH1*, *MYH2*, *MYH3*, *MYH4*, *MYH8*, *SCO1* and *PIRT*. Of interest is the involvement of *SCO1* gene dosage increase in this case. The SCO1 protein (OMIM 603644) and SCO2 protein (OMIM 604272), functioning as copper-binding proteins, are constituents of the inner mitochondrial membrane and play a role in mitochondrial copper delivery to cytochrome c oxidase (COX) [10].

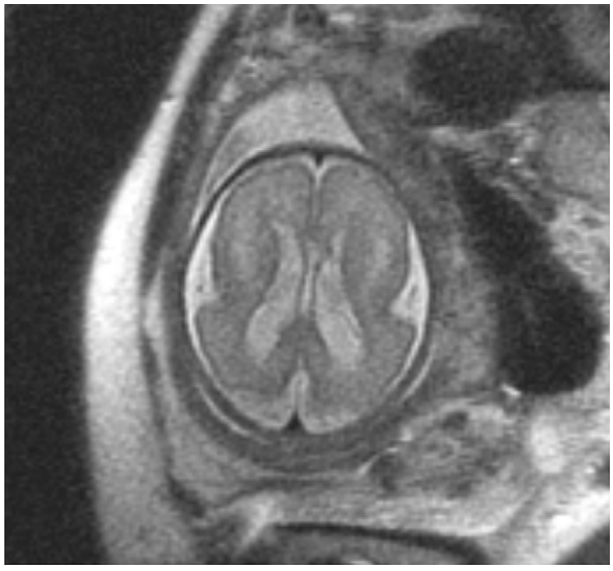

Fig. 2. Magnetic resonance imaging of the fetal brain at 29 weeks of gestation shows agyria, a "figure-of-eight" appearance of the brain, a wide and shallow sylvian fissure, and dilated lateral ventricles.

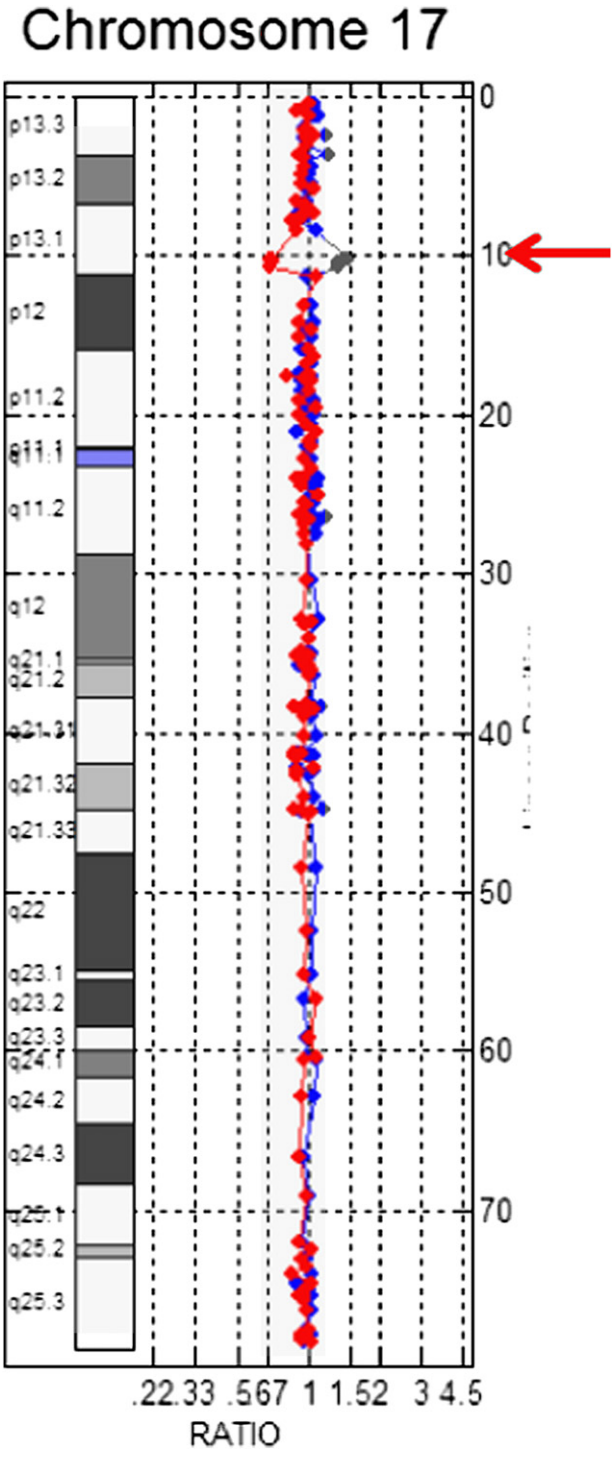

Fig. 3. Bacterial artificial chromosome (BAC)-based array comparative genomic hybridization (aCGH) analysis of fetal blood using CMDX BAC aCGH CA3000 Chips (CMDX, Irvine, CA, USA) shows a 0.5-Mb microduplication at 17p13.1 (arrow), or arr cgh 17p13.1p13.1 (RP11-736G8 → RP11-8I18) × 3.

SCO1 is predominantly expressed in the tissues characterized by high rates of oxidative phosphorylation such as muscle, heart and brain [11]. Leary et al [10] found that overexpression of either wild-type SCO protein will result in a dominant-negative phenotype. In their study of overexpression of SCO1 in

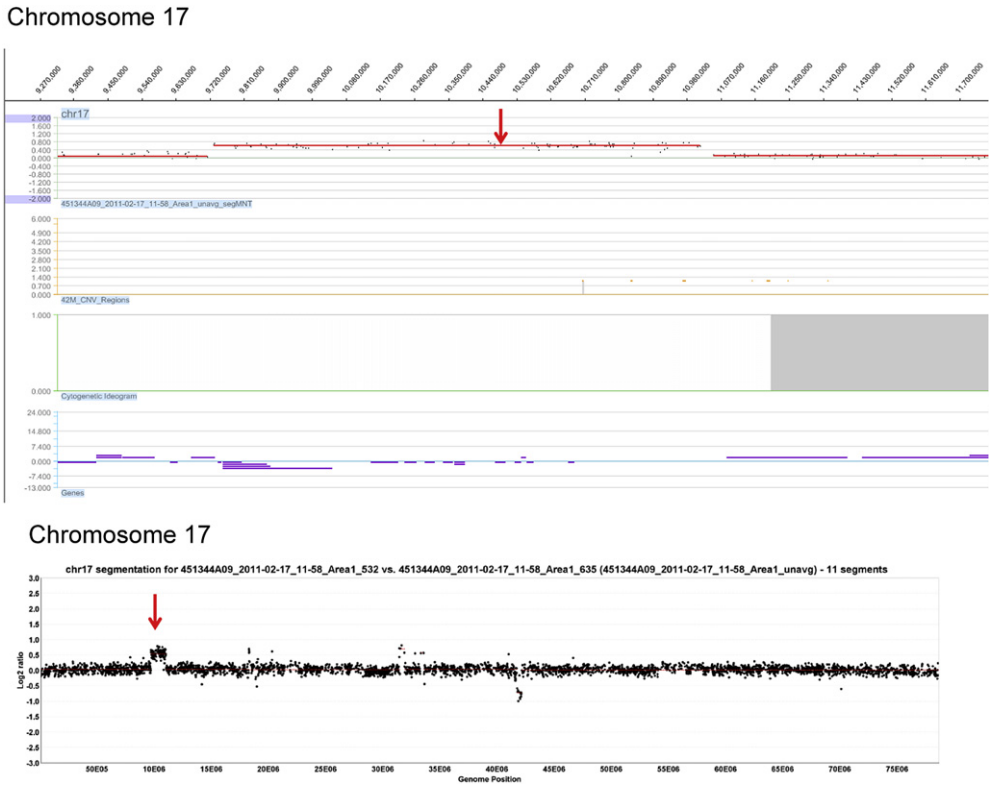

Fig. 4. Oligonucleotide-based aCGH analysis of fetal blood using Human CGH 12 × 135K Whole-Genome Tiling Array V3.1 (Roche NimbleGen, Madison, WI, USA) shows a 1.3-Mb microduplication at 17p13.1 (arrows), or arr cgh 17p13.1p13.1 (9,730,710 − 11,014,931) × 3 (UCSC, Mar 2006; NCBI 36/hg 18).

a *SCO2* patient background, overexpression of SCO1 will decrease COX activity. COX, a respiratory protein, is a multi-heteromeric enzyme embedded in the mitochondrial inner membrane. COX deficiency will cause respiratory chain defects in humans affecting those organs with high-energy demand such as the brain, heart, and skeletal muscle. The increased gene dosage effect of the other genes involved in this case such as the genes responsible for the myosin heavy chains (*MYH1*, *MYH2*, *MYH3*, *MYH4*, and *MYH8*), phosphoinositide-interacting regulator of transient receptor potential channels (*PIRT*), glucagon-like peptide 2 receptor (*GLP2R*) and recoverin (*RCVRN*), however, is unclear at the present time.

In summary, we report the first case of lissencephaly associated with 17p13.1 microduplication. Our report provides

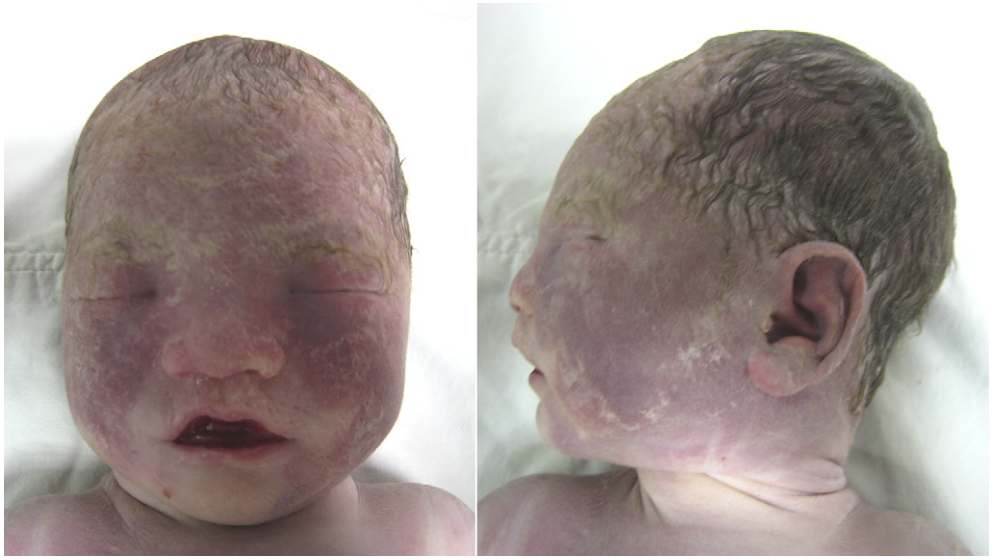

Fig. 5. Craniofacial appearance of the fetus at birth.

evidence that gene dosage increase in the 17p13.1 region may cause lissencephaly.

Acknowledgments

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