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RESEARCH LETTER

Prenatal Diagnosis of Cerebral Tubers by Magnetic Resonance Imaging Following Detection of Cardiac Rhabdomyomas by Prenatal Ultrasound in a Fetus With a Nonsense Mutation in the *TSC2* gene

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A 31-year-old, primigravid woman was referred to the hospital at 34 weeks of gestation because of fetal cardiomyopathy with ventricular hypertrophy. This was her first pregnancy. She and her husband were healthy, and there was no family history of tuberous sclerosis complex (TSC) or cardiac tumors. Level II prenatal ultrasound revealed multiple cardiac tumors with right and left ventricle flow obstructions (Fig. 1). Sonographic findings of the fetal brain were unremarkable. However, ultrafast magnetic resonance imaging of the fetal brain manifested multiple small subependymal tubers (Fig. 2). Fetal cord blood sampling revealed a karyotype of 46,XY and a heterozygous *de novo* nonsense mutation of the *TSC2* gene or *TSC2* c.1117C>T CAG>TAG (Gln>X) (Fig. 3). The C→T substitution at nucleotide 1117 in exon 10 of the *TSC2* gene predicts a substitution of p.Q373X or Gln373Stop (CAG→TAG). The 1117 C→T point mutation generates a stop codon and results in premature termination of a translation of a peptide chain.

The present case had a novel nonsense mutation in the *TSC2* gene and was associated with multiple cerebral tubers and cardiac rhabdomyomas. TSC is an autosomal dominant disorder. Mutations in the tumor-supressor genes, *TSC1* (OMIM 605284) and *TSC2* (OMIM 191092) cause TSC. The *TSC1* gene maps to chromosome 9q34 and encodes hamartin, and the *TSC2* gene maps to chromosome 16p13.3 and encodes tuberin. In Taiwanese TSC families, *TSC2* mutations are more frequent than *TSC1* mutations, and the clinical manifestations caused by *TSC2* mutations are more severe than those by *TSC1* mutations [1].

The present case had multiple cardiac rhabdomyomas and right and left ventricle flow obstructions. Prenatally

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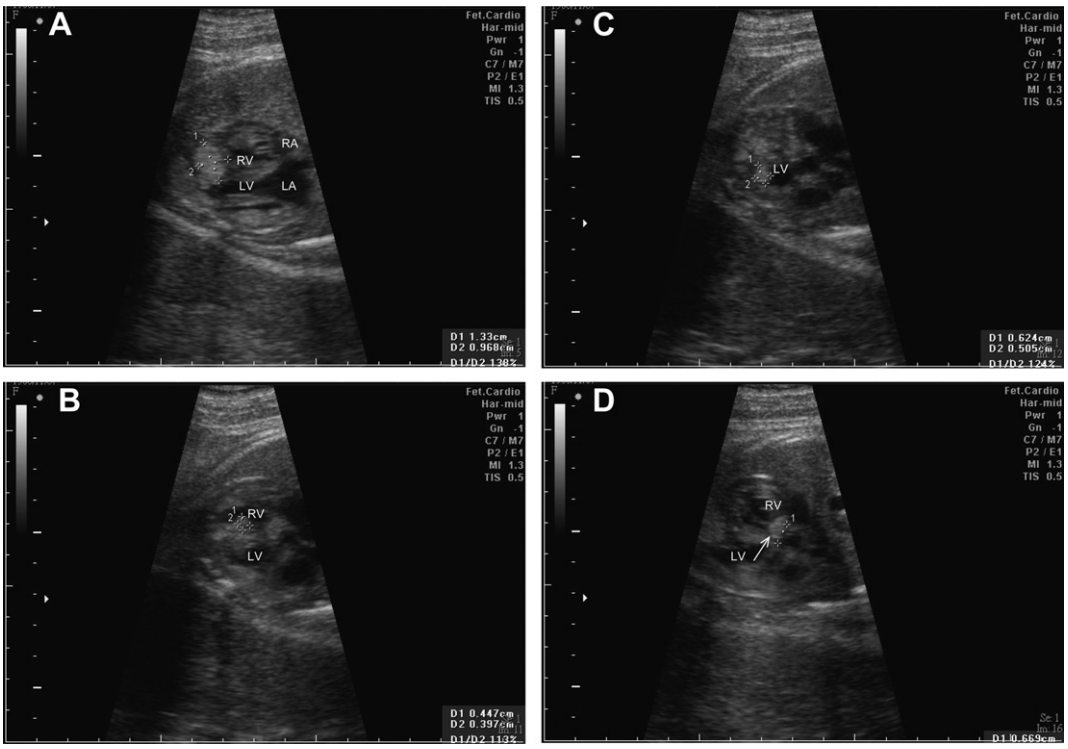

Fig. 1. Prenatal ultrasound of the heart at 34 weeks of gestation shows (A) a 1.33 cm × 0.968 cm tumor in the lowest part of the interventricular septum (IVS) near the apex; (B) a 0.447 cm × 0.397 cm tumor in the middle part of the IVS; (C) a 0.624 cm × 0.505 cm tumor in the wall of the left ventricle; and (D) a 0.669 cm tumor in the left ventricle outflow tract. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

detected cardiac rhabdomyomas have been shown to be the earliest and the most frequently reported sign of TSC in the fetuses [2]. Jóźwiak et al [3] reported that cardiac rhabdomyomas were diagnosed in 83.3% (20/24) of the TSC children younger than 2 years. Tworetzky et al [4] reported that TSC was diagnosed in 95.3% (61/64) of neonates and fetuses with multiple cardiac tumors and in 23.3% (7/30) of the patients with a single cardiac tumor. Niewiadomska-Jarosik et al [5] reported that TSC was diagnosed in 100% (12/12) of fetuses with multiple cardiac tumors and in 9.1% (1/11) of patients with a single cardiac tumor. From the cardiovascular standpoint, cardiac rhabdomyomas are benign [6]. Prenatal detected cardiac rhabdomyomas have a favorable natural history with most tumors regressing beyond the third trimester and a 4—6% risk of fetal demise [6,7].

The present case had multiple cerebral tubers. The prognosis of TSC with prenatally detected cerebral lesions is poor [8]. The prenatally detected cerebral tubers do not regress; will be progressive in size and numbers; and are correlated with epilepsy, mental retardation, and

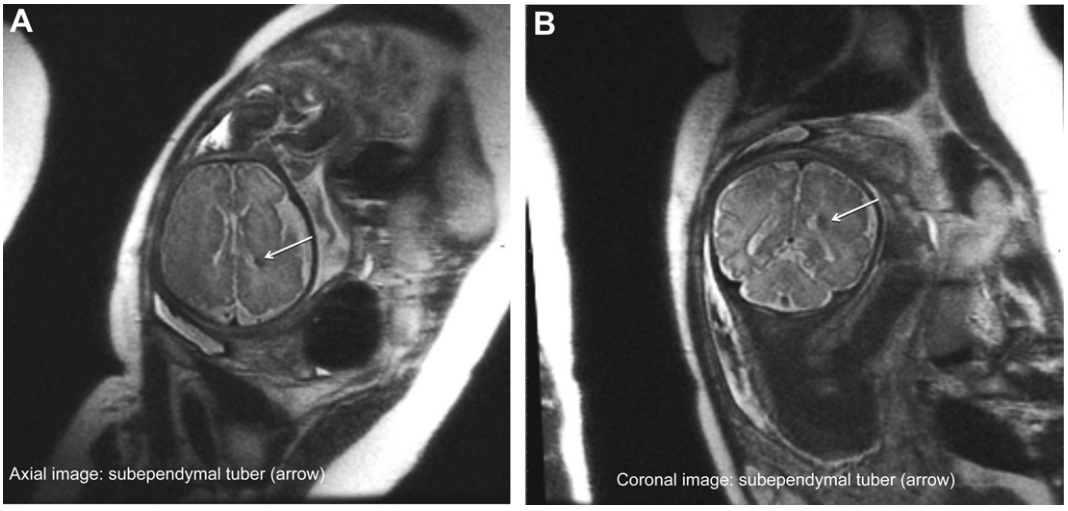

Fig. 2. (A and B) Ultrafast magnetic resonance imaging of the brain reveals small subependymal tubers (arrows).

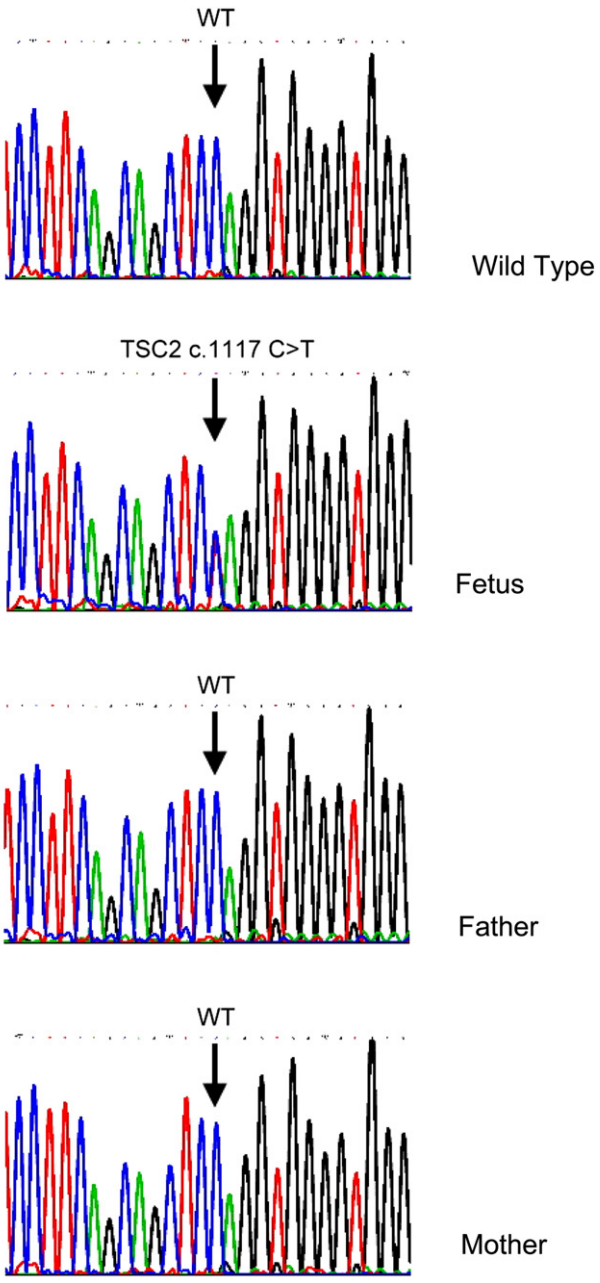

Fig. 3. A heterozygous nonsense mutation (c.1117C>T, p.Q373X) in exon 10 of the *TSC2* gene in the fetus but not in the parents. WT = wild type.

behavioral problems [8]. The neurological manifestations of TSC include infantile spasms, intractable epilepsy, cognitive disabilities, and autism [9]. In patients with TSC, about 90% have epilepsy, and about 30% have profound mental retardation [10]. Kassiri et al [10] suggested that the total number and location of cortical tubers play a significant role in the extent of mental retardation in patients with TSC. Patients with *TSC2* mutations tend to have increased tuber numbers, infantile spasms, and severe cognitive decline [10,11].

Prenatal MRI has been demonstrated to be a helpful adjunct to ultrasound for the precise evaluation of fetal cerebral tubers [12—14]. The present case shows the prenatal MRI is useful for the diagnosis of cerebral tubers even when prenatal ultrasound fails to detect suspicious cerebral lesions. Early diagnosis of cerebral lesion in TSC will help in parental counseling for the prognosis, postnatal follow-up, and anticipation on treatable neurological sequels.

Acknowledgments

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