

PRENATAL MAGNETIC RESONANCE IMAGING, ULTRASOUND IMAGING FINDINGS AND GENETIC ANALYSIS OF CONCOMITANT RHABDOMYOMAS AND CEREBRAL TUBEROUS SCLEROSIS

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A 32-year-old, gravida 3, para 1, woman had an uncomplicated pregnancy until 29 weeks' gestation when multiple fetal cardiac tumors were detected on routine ultrasound. She had experienced one abortion. Her first child was a 3-year-old healthy boy. This was her third pregnancy. She and her husband were healthy and did not have any family history of tuberous sclerosis complex (TSC) or cardiac tumors. Detailed sonographic examination of the fetal heart demonstrated seven cardiac rhabdomyomas including a 0.89 × 0.44 cm tumor in the lowest part of the interventricular septum (IVS) near the apex, a 0.84 × 0.64 cm tumor in the upper part of the IVS near the crus, a 0.34 × 0.20 cm tumor in the middle part of the IVS, two tumors measuring 0.37 × 0.30 cm and 0.30 × 0.18 cm in the lateral wall of the left ventricle, a 0.49 × 0.33 cm tumor in the lateral wall of the left ventricle near the aortic valve, and a 0.35 × 0.24 cm tumor in the lateral wall of the left atrium (Figure 1). Detailed sonographic examination of the fetal brain also demonstrated several suspicious echogenic foci around the cerebral ventricles (Figure 2). Ultrafast magnetic resonance imaging (MRI) revealed small subependymal tubers (Figure 3) and cardiac rhabdomyomas (Figure 4). Cordocentesis revealed a karyotype of 46,XX and a *de novo* frameshift mutation to the *TSC2* gene or *TSC2* exon 33 c.4420_4421delAG (Figure 5). DNA analysis

of the parents did not show the mutation. The woman had intrauterine fetal death at 30 weeks of gestation. A 1,376-g dead fetus was delivered vaginally.

The present fetus had multiple cardiac rhabdomyomas and cerebral tuberous sclerosis, and was associated with a frameshift mutation in the *TSC2* gene. Jóźwiak and Kotulska [1] suggested that prenatally diagnosed multiple cardiac rhabdomyomas are a sign of TSC because cardiac rhabdomyomas are the earliest and most frequently reported sign of TSC in the fetuses. Jóźwiak et al [2] found that cardiac rhabdomyomas were diagnosed in 83.3% (20/24) of TSC children under 2 years of age, in 21.4% (3/14) of the TSC children at 2–5 years of age, and in 21.1% (4/19) of TSC children at 5–9 years of age. Tworetzky et al [3] found that TSC was diagnosed in 95.3% (61/64) of fetuses and neonates with multiple cardiac tumors and in 23.3% (7/30) of patients with a single cardiac tumor. Tworetzky et al [3] also found that multiple cardiac tumors were significantly more likely to have TSC than in patients with a single tumor (relative risk, RR, 4.1; 95% confidence interval, CI, 2.1–7.8; $p < 0.001$) or in patients with a single ventricular tumor (RR, 3.1; 95% CI, 1.7–5.8; $p < 0.001$). With the advent of MRI technology, prenatal MRI has been shown to be a useful adjunct to ultrasound for the precise determination of the extent of cerebral involvement of TSC. Mirlesse et al [4] first reported the use of prenatal MRI in the evaluation of fetal cerebral tuberous sclerosis. Kivelitz et al [5] first described the use of prenatal MRI in the evaluation of fetal cardiac rhabdomyomas. Chen et al [6] first reported the prenatal MRI demonstration of concomitant fetal cardiac rhabdomyomas and cerebral tuberous sclerosis. The present case shows



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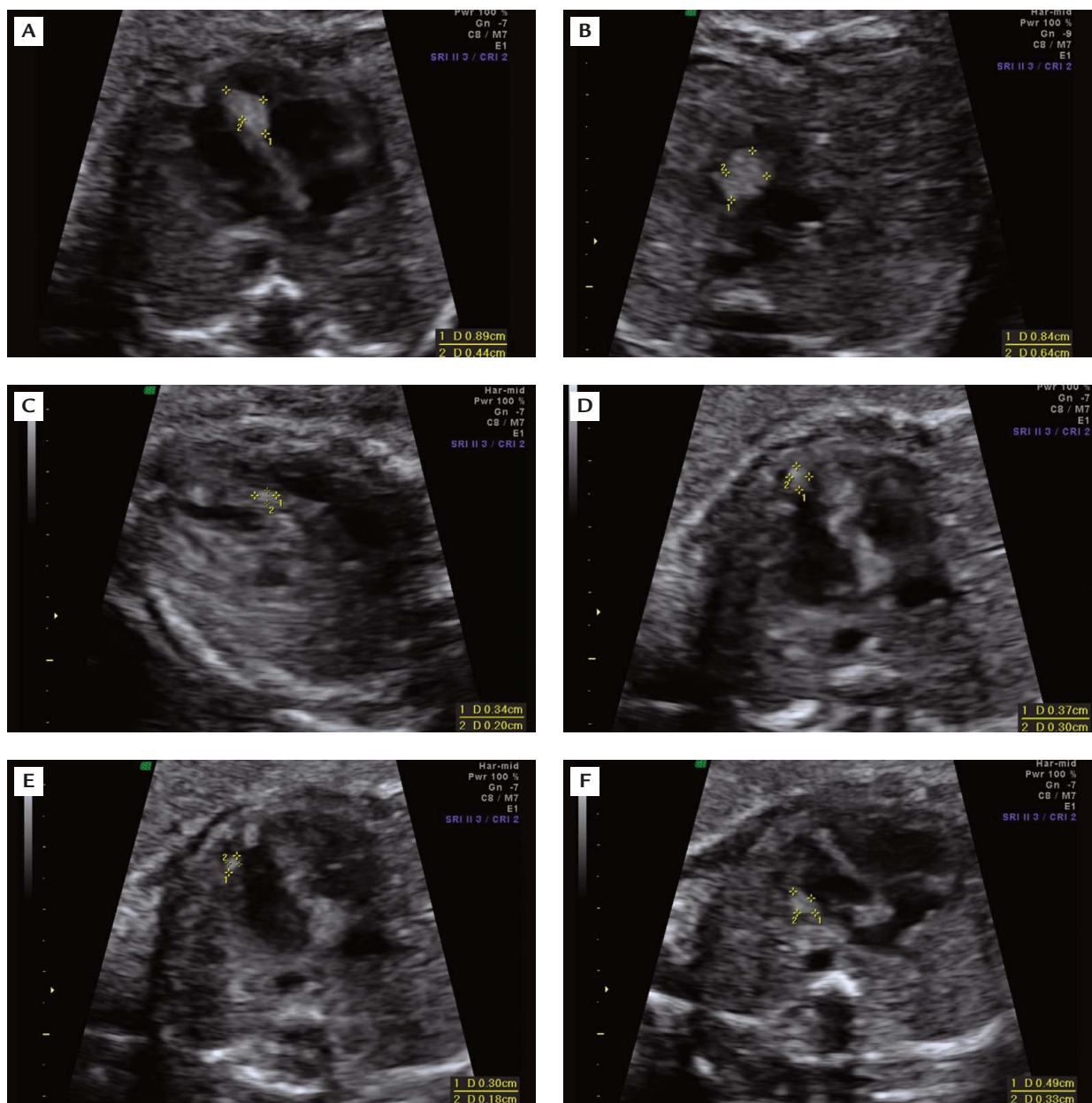


Figure 1. Prenatal ultrasound of the heart at 29 weeks' gestation shows: (A) a 0.89×0.44 cm tumor in the lowest part of the interventricular septum (IVS) near the apex, (B) a 0.84×0.64 cm tumor in the upper part of the IVS near the crus, (C) a 0.34×0.20 cm tumor in the middle part of the IVS, (D) a 0.37×0.30 cm tumors in the lateral wall of the left ventricle, (E) a 0.30×0.18 cm tumor in the lateral wall of the left ventricle, and (F) a 0.49×0.33 cm tumor in the lateral wall of the left ventricle near the aortic valve.

that prenatal MRI is particularly useful for the confirmation of the cerebral tuberous sclerosis lesions when prenatal ultrasound reveals suspicious cerebral lesions. Symptomatic rhabdomyomas may present poor prognosis. Kagan et al [7] reported ventricular outflow obstruction, valve aplasia, bradyarrhythmia, pulmonary hypoplasia, hydrops fetalis, and fetal death of a fetus with a large rhabdomyoma and unknown tuberous sclerosis at 32 weeks of gestation. Lin et al [8] reported intrauterine fetal death of a fetus with intrauterine rhabdomyomas at 30 weeks of gestation.

TSC is caused by mutations of the tumor suppressor genes, *TSC1* and *TSC2*. The *TSC1* gene (OMIM 605284) is mapped to chromosome 9q34 and encodes the protein hamartin [9]. The *TSC2* gene (OMIM 191092) is mapped to chromosome 16p13.3 and encodes the protein tuberlin [10,11]. In a mutation analysis of the *TSC1* and *TSC2* genes in 84 Taiwanese TSC families, Hung et al [12] identified mutations in 76.2% (64/84) of the cases, including nine *TSC1* mutations (seven sporadic and two familial) and 55 *TSC2* mutations (47 sporadic and eight familial), and found that diseases resulting from the

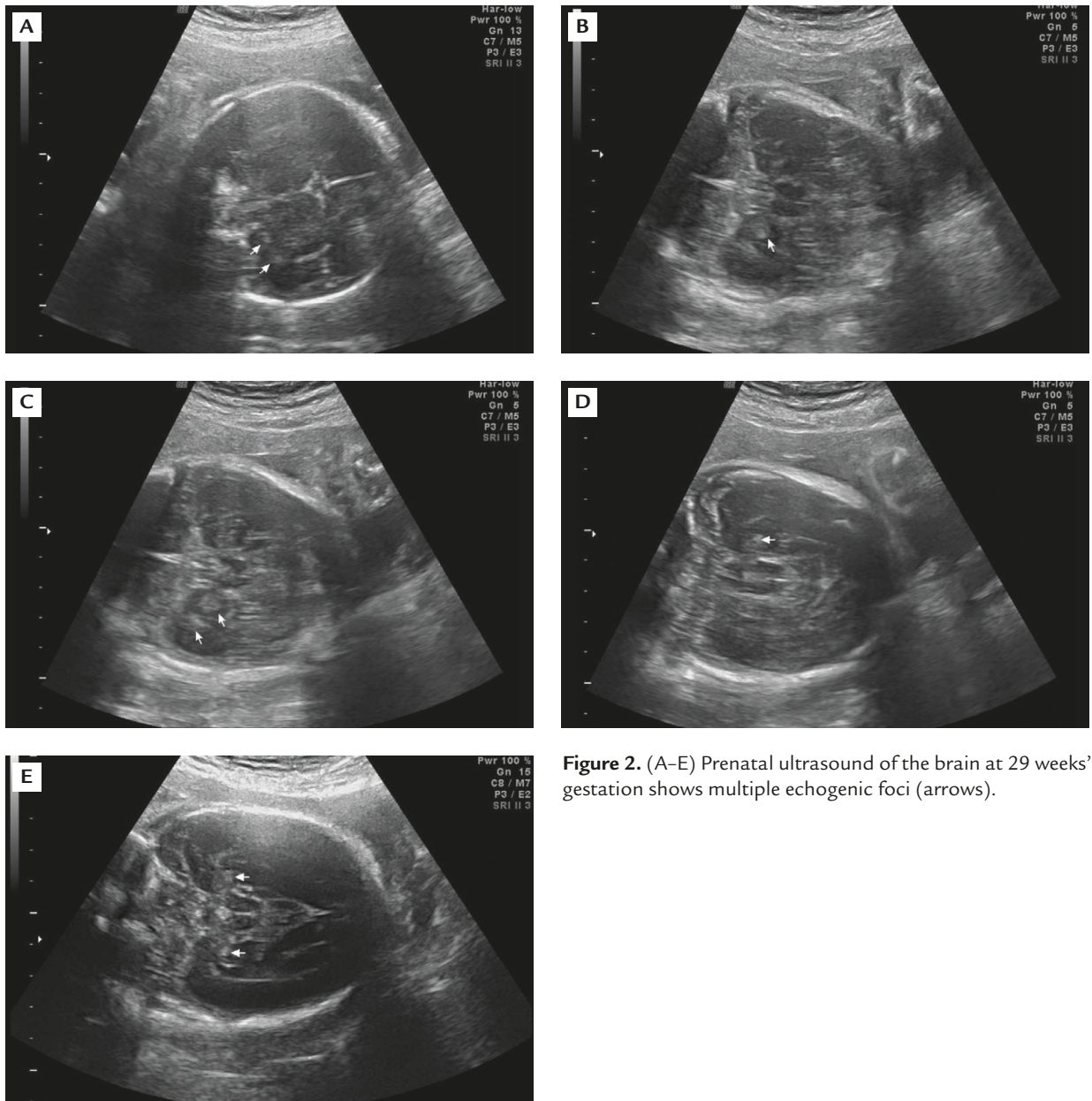


Figure 2. (A-E) Prenatal ultrasound of the brain at 29 weeks' gestation shows multiple echogenic foci (arrows).

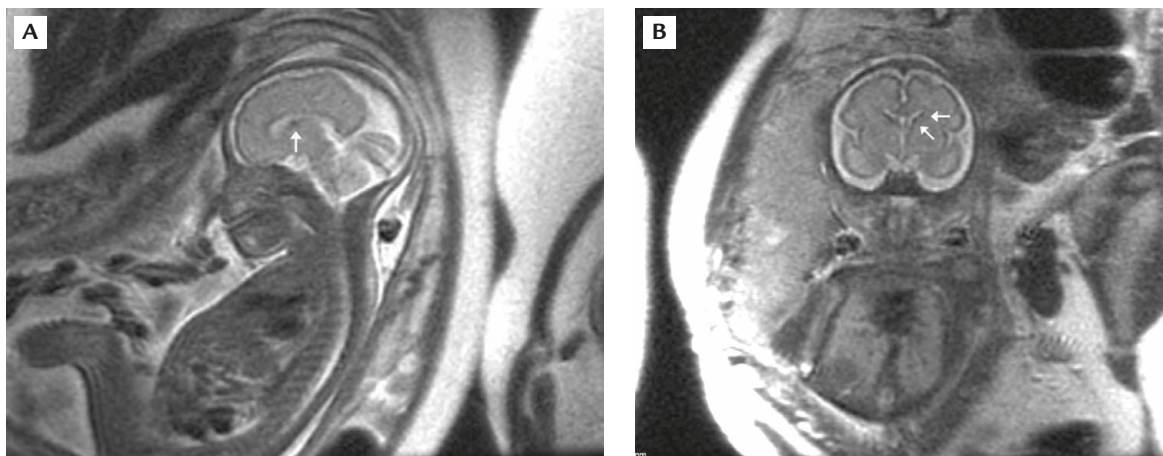


Figure 3. (A, B) Ultrafast magnetic resonance imaging of the brain reveals small subependymal tubers (arrows).

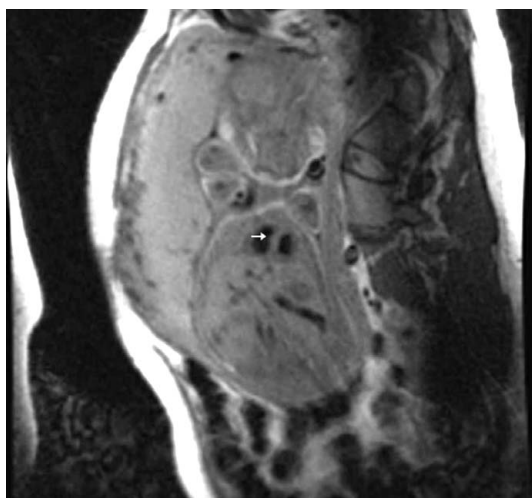


Figure 4. Ultrafast magnetic resonance imaging of the heart shows a cardiac rhabdomyoma (arrow).

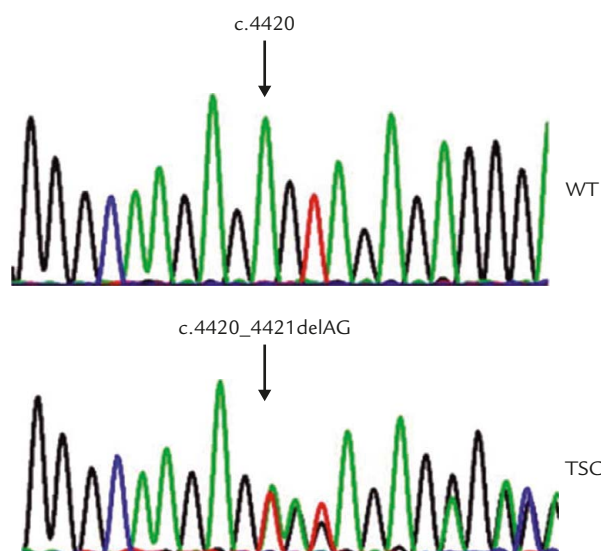


Figure 5. The denaturing high-performance liquid chromatography analysis and direct sequencing of exon 33 of the *TSC2* gene shows that the fetus is heterozygous for a frameshift mutation c.4420_4421delAG (lower panel, tuberous sclerosis complex [TSC]), compared with the control wild-type (WT) DNA (upper panel).

TSC1 mutations were less severe than those with the *TSC2* mutations. In the clinical and genotype studies of cardiac tumors in patients with TSC, Jóźwiak et al [13] found that mutations in the *TSC1* and *TSC2* genes were detected in 85% (108/127) of the cases, with cardiac rhabdomyomas being more frequent in the *TSC2* group (50/93; 53.8%) than in the *TSC1* group (3/15; 20%), with clinical manifestations being more severe in the *TSC2* group than in the *TSC1* group. Prenatal diagnosis of rhabdomyomas should prompt molecular genetic analysis of the *TSC1* and *TSC2* genes of the index fetuses and the parents to exclude polymorphism and

familial inheritance [14–17]. With the advent of modern molecular technology, prenatal molecular diagnosis of TSC is possible. Milunsky et al [17] reported successful DNA analysis of the *TSC* genes in 96% (48/50) of the tested fetuses. The present case had a frameshift mutation in *TSC2* exon 33 and was associated with *de novo* deletions. Frameshift mutations in *TSC2* exon 33 as a result of deletions have been documented in Chinese patients [12,18], and exon 33 in the *TSC2* gene is a hot spot of mutations in the Chinese population.

In conclusion, we have presented the prenatal ultrasound, MRI findings and molecular analysis of concomitant rhabdomyomas and cerebral tuberous sclerosis. We suggest that tuberous sclerosis should be suspected in all fetuses with prenatally diagnosed cardiac rhabdomyomas.

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