Prenatal Diagnosis of Rhabdomyomas and Cerebral Tuberous Sclerosis by Magnetic Resonance Imaging in One Fetus of a Dizygotic Twin Pregnancy Associated With a Frameshift Mutation in the *TSC2* Gene

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A 28-year-old woman, gravida 3, para 0, was referred to our hospital at 30 weeks of gestation for evaluation of cardiac tumors in one fetus of a twin pregnancy. The woman had not undergone any assisted reproductive technology. She and her husband were healthy and had no family history of tuberous sclerosis complex (TSC) or cardiac tumors. Previous sonographic examination had revealed a dichorionic and diamniotic twin pregnancy. Detailed sonographic examination of the fetuses demonstrated a normal heart in one male co-twin and multiple rhabdomyomas in the left ventricle (LV) in the other male co-twin. The affected co-twin had six intracardiac tumors, including three tumors measuring 1.87 × 1.42 cm, 1.12 × 1.04 cm and 0.84 × 1.00 cm, respectively in the inlet of the LV, a 1.41 × 0.74-cm tumor in the apex of the LV, and a 0.52 × 1.12-cm tumor in the LV side of the interventricular septum near the apex. There was no significant regurgitation and color Doppler mapping showed adequate flow in the LV and right ventricle. Ultrafast magnetic resonance imaging revealed small subependymal tubers (Figure 1A) and cardiac rhabdomyomas arising from the interventricular septum and the lateral wall of the LV (Figure 1B) in the affected co-twin. Fetal growth and amniotic fluid volume were normal. The unaffected co-twin (2,344 g) and affected co-twin (2,818 g) were delivered uneventfully by cesarean section at 37 weeks of gestation because of malpresentation. Neonatal computed tomography scans of the affected infant demonstrated small subependymal tubers (Figure 2A) and intracardiac rhabdomyomas in the LV (Figure 2B). The results of brain and renal ultrasound were unremarkable. The infant's ventricular outlet was not obstructed, and his cardiac function remained within normal limits. Cytogenetic analysis of cord blood from the twins revealed a karyotype of 46,XY. A zygosity test showed dizygosity. Molecular analysis of cord blood from the affected co-twin revealed a *de novo* frameshift mutation in the *TSC2* gene or *TSC2* exon 33 c.4472_4473delAA (Figure 3). No such mutation was detected by DNA analysis in the parents or the unaffected co-twin. The affected infant was doing well at 2 years of age, with no episodes of seizures or cardiac discomfort. The cardiac tumors persisted but became smaller in size.

Prenatal magnetic resonance imaging has been shown to be a useful adjunct to ultrasound for the precise determination of the extent of cerebral involvement in TSC [1–4]. TSC is caused by mutations in the tumor suppressor genes *TSC1* and *TSC2*. The *TSC1* gene (OMIM 605284) maps to chromosome 9q34 and encodes the protein hamartin, while the *TSC2* gene (OMIM 191092) maps to chromosome 16p13.3 and

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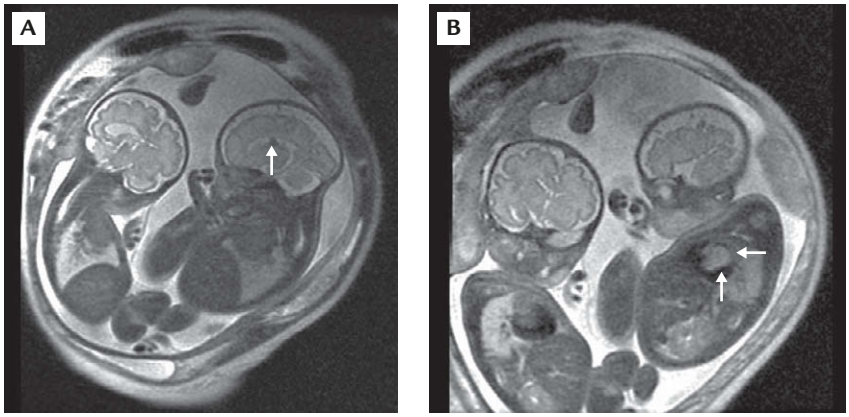

Figure 1. Ultrafast magnetic resonance imaging showing (A) small subependymal tubers and (B) intracardiac tumors in the co-twin affected with tuberous sclerosis complex.

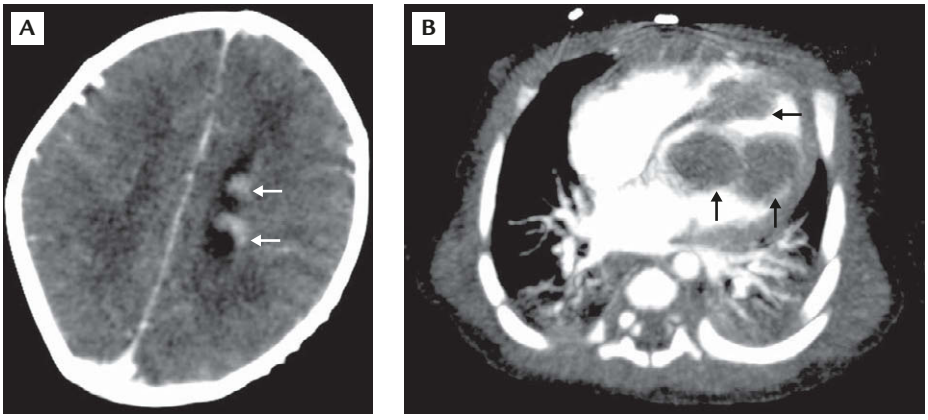

Figure 2. Neonatal computed tomography scan of the affected infant demonstrating (A) subependymal tubers and (B) intracardiac rhabdomyomas in the left ventricle.

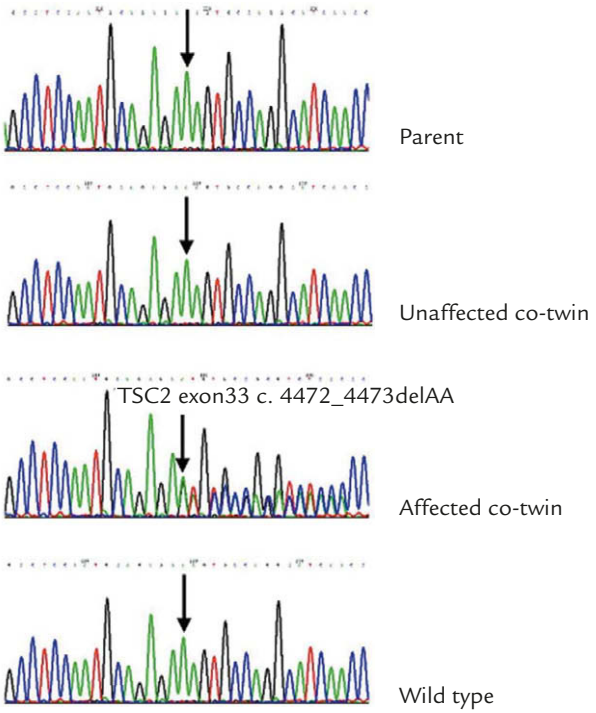

Figure 3. Molecular analysis shows a *de novo* frameshift mutation of *TSC2* exon 33 c.4472_4473delAA in the affected infant.

encodes the protein tuberin. Cardiac rhabdomyomas are more frequent in cases with *TSC2* mutations than in those with *TSC1* mutations; the clinical manifestations are also more severe in the *TSC2* group than in the *TSC1* group [5]. The present case was associated with a frameshift mutation in the *TSC2* gene and manifested prenatally with both cerebral subependymal tubers and intracardiac rhabdomyomas in the third trimester. In a mutational analysis of the *TSC1* and *TSC2* genes in Taiwanese TSC families, Hung et al [6] found that *TSC2* mutations were more frequent than *TSC1* mutations and that diseases arising as a result of *TSC1* mutations were less severe than those associated with *TSC2* mutations. The present case had a frameshift mutation in *TSC2* exon 33 associated with a *de novo* deletion. Frameshift mutations in *TSC2* exon 33 as a result of deletions have previously been documented in Chinese patients [4,6,7]. TSC is an autosomal dominant disorder; parents and siblings of affected infants may have the same TSC disorders, but exhibit reduced penetrance with no significant external manifestations. Prenatal diagnosis of rhabdomyomas and cerebral involvement of TSC should include molecular genetic analysis of the *TSC1* and *TSC2*

genes in the index fetuses and the parents to exclude polymorphisms and familial inheritance [8–11].

Acknowledgments

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