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Novel *TSC1* and *TSC2* gene mutations in Chinese patients with tuberous sclerosis complex

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ABSTRACT

Objective: The study was designed to identify pathogenic *TSC1* or *TSC2* gene mutations and provide solid evidence for the diagnosis of tuberous sclerosis complex (TSC).
Methods: 11 unrelated Chinese patients with TSC were investigated in the present study. Characteristic skin lesions such as hypomelanotic macules and the central nervous system features such as the epilepsy, cortical tubers and subependymal nodules were the most common symptoms that were observed in the patients. All exons and exon-intron boundaries of the *TSC1* and *TSC2* gene of the patients were amplified by PCR.
Results: A total of 11 different *TSC2* and one *TSC1* mutations were identified in the present study, of which five *TSC2* and 1 *TSC1* gene mutations were novel. Among the 11 patients, 10 harbored *TSC2* mutations, whereas only one patient had a *TSC1* gene mutation. The identification of *TSC1*/*TSC2* gene mutations confirmed the diagnosis of the 11 patients with TSC.
Conclusions: Our study has expanded the spectrum of *TSC1* and *TSC2* gene mutations causing TSC. The identification of the *TSC1*/*TSC2* gene mutations confirmed the diagnosis of the 11 patients with TSC.

1. Introduction

Tuberous sclerosis complex (TSC), first described in 1862, is an autosomal dominant genetic disorder of high penetrance [1]. It has an incidence of 1/6000 to 1/10,000 live births and is characterized by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, and lung [2–4]. The phenotypic manifestations of the disease are highly variable. It often causes disabling neurologic disorders such as epilepsy and skin lesions such as hypomelanotic macules. Cardiac rhabdomyomas, retinal hamartomas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis can also occur.

Inactivating mutations in either the *TSC1* or *TSC2* gene are responsible for TSC [5,6]. The *TSC1* gene is located on chromosome 9q34, encompassing 55 kb of DNA, and encodes hamartin (130 kDa) [7]. The *TSC2* gene is located on chromosome 16p13.3, encompassing 40 kb of DNA, and encodes tuberin (200 kDa) [8]. Hamartin and tuberin are co-expressed in the cells of various organs and form a stable protein complex [9]. The hamartin-tuberin complex acts on the rheb GTPase to prevent the rheb-GTP dependent stimulation of cell growth through the mammalian target of rapamycin (mTOR) [10]. Disruption of the hamartin-tuberin complex results in upregulation of signal transduction through mTOR and leads to a constitutive growth phenotype with development of hamartomas in TSC. Molecular analysis of the *TSC1* and *TSC2* genes is helpful to make the diagnosis of TSC. It is recommended that the identification of a clearly pathogenic *TSC1* or *TSC2* gene mutation is sufficient to make a diagnosis of TSC, even in the absence of clear clinical signs [4].

In the present study, 11 unrelated Chinese patients with TSC were investigated. We analyzed both *TSC1* and *TSC2* gene in the 11 patients to identify the mutation spectrum in Chinese TSC patients. *TSC1* and *TSC2* gene mutation analysis can provide solid evidence for clinical diagnosis. Furthermore, it provides a better understanding of the molecular mechanisms underlying the pathogenesis of TSC.

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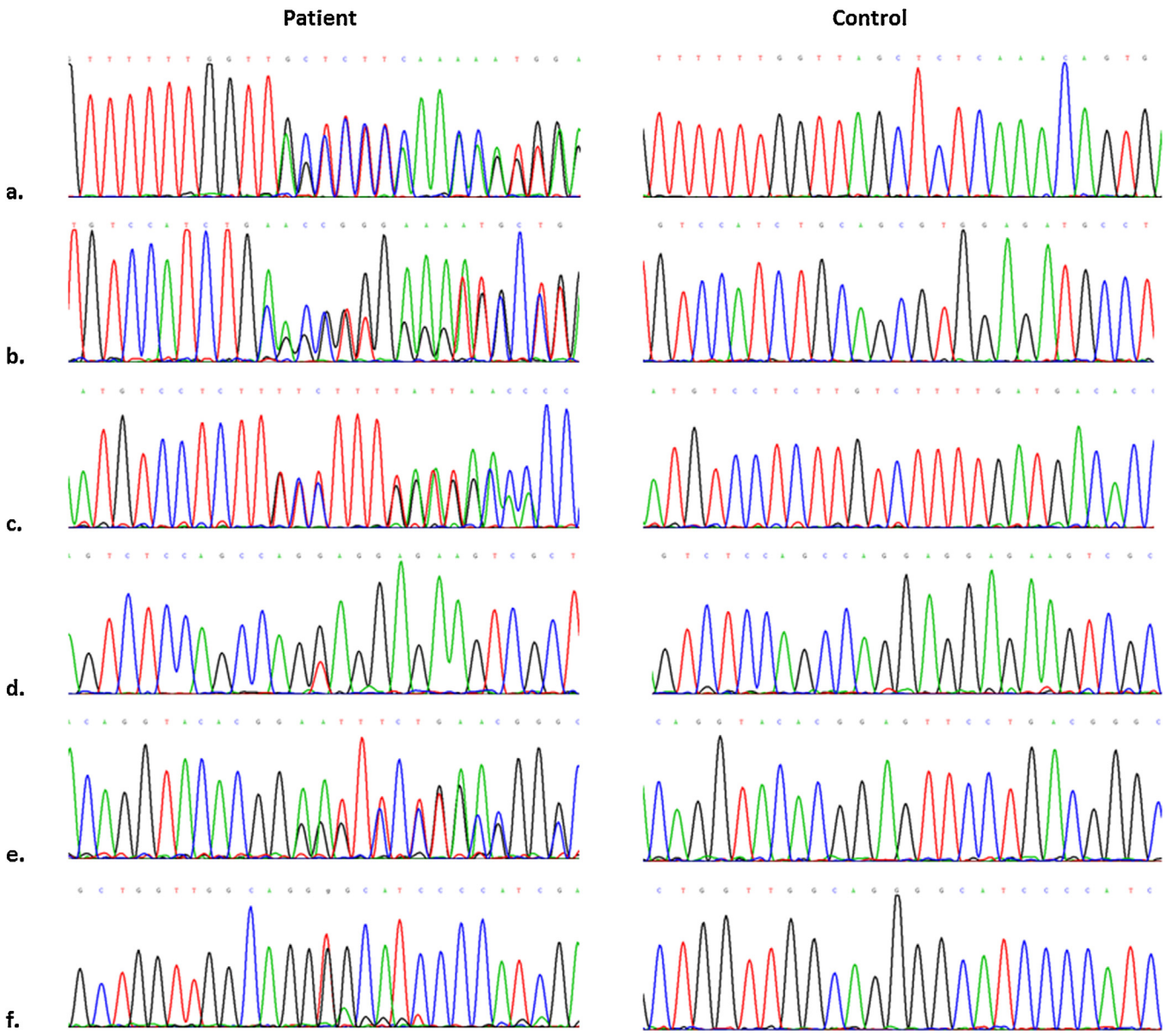

Fig. 1. Molecular analysis identified 1 novel *TSC1* gene mutation and 5 novel *TSC2* gene mutations. **Panel a**. *TSC1* c.2503-2delA; **Panel b**. *TSC2* c.2433delC; **Panel c**. *TSC2* c.2766delG; **Panel d**. *TSC2* c.4027G > T; **Panel e**. *TSC2* c.4717dupG; **Panel f**. *TSC2* c.4066G > T.

2. Materials and methods

2.1. Patients

A total of 11 unrelated Chinese patients with a clinical diagnosis of TSC were enrolled in the present study. All the patients were referred to our facility between August 2014 and July 2015 for epilepsy and/or dermatologic manifestations. They all meet the diagnostic criteria revised by the 2012 International Tuberous Sclerosis Complex Consensus Group [4]. Their ages ranged from 5 months to 15 years (median: 2 years) at the time of diagnosis. Their medical records were examined and the family histories were investigated. Their clinical characteristics were listed in Table 1. The 11 TSC patients we studied were all born to non-consanguineous parents. Available family members of the patients were also invited to participate in the study. All the TSC patients and their family members were tested for mutations in the *TSC1* and *TSC2* genes. An additional group of 105 Chinese subjects with no history of TSC were recruited as controls for *TSC1* and *TSC2* molecular testing. The ethics committee of the Shanghai Children's Medical Center approved the present study, and informed consents were obtained from each study participant.

2.2. Molecular analysis of TSC1 and TSC2 genes

Ethylenediaminetetraacetic acid (EDTA)-peripheral blood samples were obtained from the TSC patients, their parents, and 105 control individuals. Genomic DNA was isolated from the peripheral blood leukocytes using the QIAmp DNA Blood kit (Qiagen, Hilden, Germany). All exons and exon-intron boundaries of the *TSC1* and *TSC2* gene of the patients were amplified by PCR (primer sequence available on request). The PCR products were analyzed by direct DNA sequencing using an ABI 3700 sequencer (Applied Biosystems, Foster City, CA, USA). Only genomic fragments containing the mutation identified in the TSC patients were amplified and sequenced for the corresponding parents and the normal controls.