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The Clinical Characteristics and the Pathogenic Gene Mutations in Two Sporadic Cases with Tuberous Sclerosis Complex

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Abbreviations:

TSC: Tuberous Sclerosis Complex; mTOR: Mammalian Target of Rapamycin; CT: Computed Tomography

1. Abstract

Background

Tuberous sclerosis complex (TSC) is an autosomal-dominant disorder characterized by hamartomas in multiple organ systems. Variants in the TSC1 and TSC2 gene lead to the dysfunction of the hamartin or tuberin proteins, respectively, which causes tuberous sclerosis complex.

Case Presentation

We report two sporadic cases of patients with TSC2 variants. Both patients showed multiple organ system involvement. Gene analysis showed that both patients had nonsense variants that led to the premature truncation of peptide chain synthesis. A novel nonsense variant of the TSC2 gene (c.94G>T, p.E32X) was identified. Another nonsense variant of the TSC2 gene (c.4515C>G, p.Y1505X) has been reported before.

Conclusion

We identified a novel pathogenic TSC2 variant, c.94G>T, which enriches the gene variant database.

2. Background

Tuberous sclerosis complex (TSC), otherwise known as Bourneville's disease, is a rare autosomal-dominant disease with an incidence of 1/6000 -1/10,000 [1]. TSC is a neurocutaneous disease that is characterized by the development of hamartomas in a variety of tissues and organs throughout the body, including the brain, skin, heart, lungs and kidneys [2]. Clinically, almost all patients suffer from the characteristic manifestations of facial angiofibromas, epilepsy and mental disorders, accompanied by behavioural abnormalities, shagreen patches, subependymal nodules (SENs), subependymal giant cell astrocytomas (SEGAs), cardiac rhabdomyomas, renal angiomyolipomas (AMLs) and renal cysts. Most cased of TSC are caused by genetic heterogeneity in the TSC1 and TSC2 genes located on chromosomes 9q34.3 and 16p13.3, respectively. TSC1 and TSC2 encode the hamartin and tuberin proteins, respectively, which act as tumour growth suppressors. Hamartin and tuberin control cell growth by negatively regulating S6 kinase 1 and eukaryotic initiation factor 4E binding protein 1, potentially through their upstream modulator mammalian target of rapamycin (mTOR) [3]. They constitute a functional complex to regulate cell proliferation, growth, adhesion, and vesicle transport. When a variant occurs in TSC1 or TSC2 gene, the mTOR pathway is triggered, causing uncontrolled cell growth and thereby tumour formation [4]. The two patients presented in this article were diagnosed with TSC according to the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference [5].

3. Case Presentation

Case 1

A 35-year-old female was admitted to our hospital with the complaint of intermittent right lumbago, which was characterized by distending pain. Bilateral nodular lesions appeared and had been increasing on the face since she was seven years old. She dropped out of junior high school because of poor grades and was diagnosed with epilepsy at the age of 15; seizures occurred many times but ceased in adulthood. Seven years ago, periungual fibromas began to appear. There is no history of marriage between close relatives in the family. Other family members did not show similar symptoms. Physical examination revealed densely distributed needle-tip red angiofibromas on the face (Figure 1a). Periungual fibromas could be seen on the toes (Figure 1b). In addition, there were scattered hypomelanotic macules on the back. No oral manifestations, such as dental pits and intraoral fibromas, were observed. Biochemical laboratory tests demonstrated that there were no obvious abnormalities in hepatic or renal function. Multiple calcified SENs and cortical dysplasia were demonstrated by skull CT (Figure 1c). Chest CT showed multiple small nodules in both lungs and partial patchy sclerotic lesions in the cone (Figure 1d). Abdominal CT revealed multiple small hamartomas in the right lobe of the liver and enlarged kidneys with multiple AMLs (Figure 1e). The largest AML was located at the lower pole of the right kidney, with a diameter of approximately 61.9*51.3*68.6 mm. Multiple AMLs of both kidneys gradually increased. The patient had symptoms of intermittent lumbago. In terms of treatment, we gave the patient the mTOR inhibitor everolimus for targeted therapy. We collected the peripheral blood of the patient and other family members for genetic analysis. The patient signed informed consent and obtained the approval of Second Affiliated Hospital of Anhui Medical University's ethical committee. Genomic DNA was isolated from peripheral blood leukocytes, and Sanger sequencing was performed. In the patient, a variant of the 94th base in exon 2 of TSC2 from guanine to thymine (c.94G>T) had led to the replacement of glutamate (E) with a termination codon and the termination of the amino acid chain (p.E32X). A novel nonsense variant (c.94G>T, p.E32X) of TSC2 was detected (Figure 1f), which is not listed in the Leiden Open Variation Database (LOVD). We did not find additional family members with this variant.

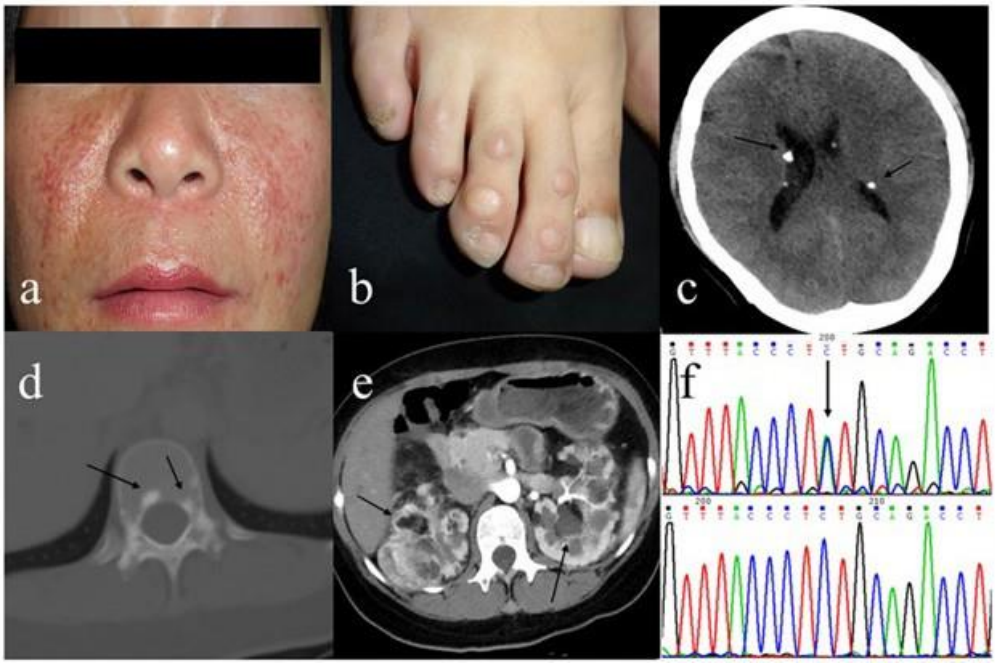

Figure 1: a. Facial multiple angiofibromas. **b**. Periungual fibromas on the toe. **c**. BrainCT indicates multiple calcified SENs. **d**. Spine images suggest partial patchy sclerotic lesions in the cone. **e**. Abdominal CT reveals multiple AMLs in both kidneys. **f**. A novel nonsense *TS*C2 variant (c.94G>T, p.E32X) was identified in case 1.

Case 2

A 15-year-old boy was born with hypomelanotic macules; he had facial angiofibromas (Figure 2a) at the age of 3 and shagreen patches at the age of 5 years (Figure 2b). Epilepsy occurred without obvious cause at age 12. Later, the boy was treated regularly with sodium valproate to control epilepsy. Skull CT identified multiple cortical nodules and SENs (Figure 2c). Abdominal ultrasound suggested multiple haemangiomas in the liver and bilateral renal cysts. The cardiac ultrasound, chest radiograph, ECG and EEG revealed no abnormalities. Similar symptoms did not appear in other family members. The patient's legal guardians signed informed consent and obtained the approval of Second Affiliated Hospital of Anhui Medical University's ethical committee. Genetic analysis showed a nonsense variant (c.4515C>G, p.Y1505X) in exon 35 of TSC2, resulting in the replacement of tyrosine (Y) with a termination codon and the termination of the amino acid chain (Figure 2d).

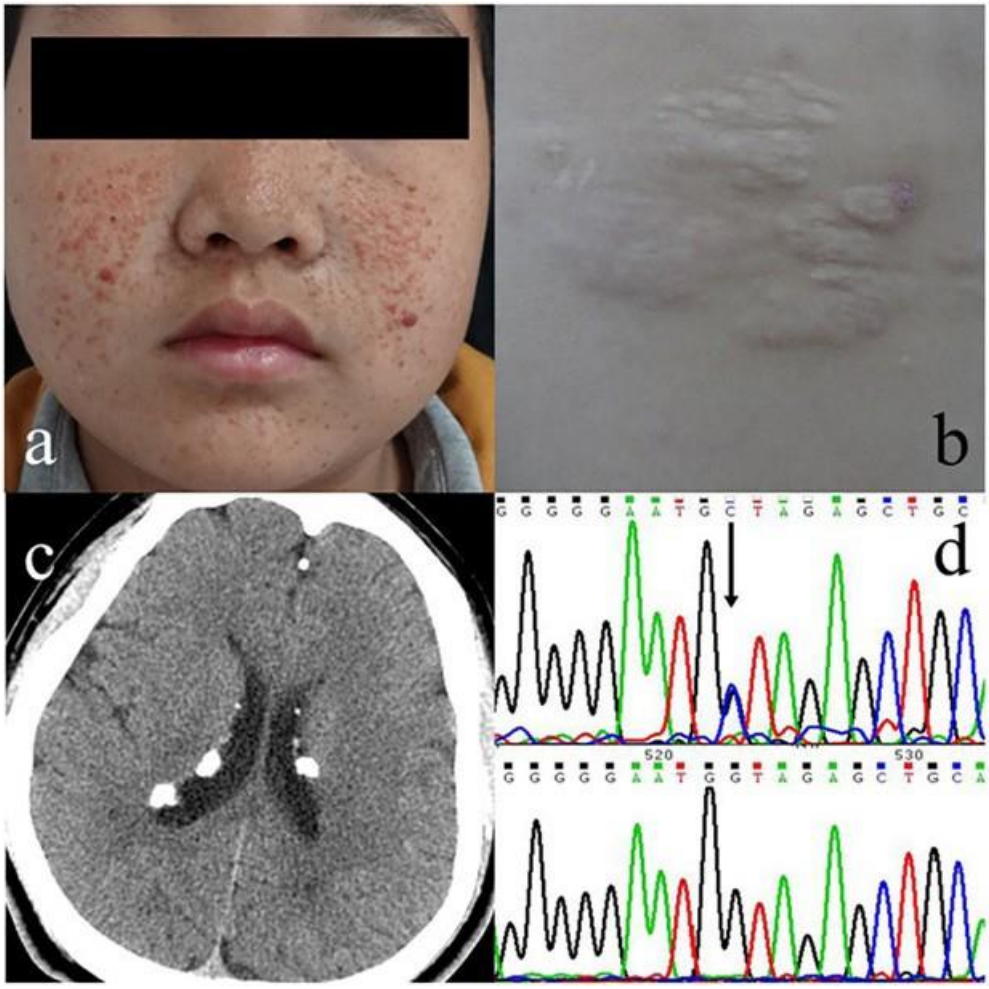

Figure 2: a. Facial multiple angiofibromas. **b**. Shagreen patches. c. Skull CT showed multiple cortical nodules and SENs. **d**. A nonsense *TSC2* variant (c.4515C>G, p.Y1505X) was identified in case 2.

4. Discussion and Conclusion

TSC is an autosomal-dominant disorder, but just one-third of patients inherit variants, and approximately two-thirds of cases are sporadic [6]. Generally, TSC2 variants are more frequent than TSC1 variants. Approximately seventy percent of TSC patients have TSC2 variants, and twenty percent have TSC1 variants. To date, more than 3000 unique DNA variants of TSC2 have been recorded in the LOVD, including all types, such as nonsense, missense, insertions and deletions. We reported two variants of TSC2. Variant c.94G>T is novel, and variant c.4515C>G is pathogenic and has been listed in the LOVD previously. The two patients reported are both sporadic cases. The two variants of TSC1 and TSC2 we found before were also sporadic cases [7, 8]. This may also indicate that TSC patients are mostly sporadic cases and that the variants are mainly located in TSC2. Genotype and phenotype analyses of TSC have attracted increasing attention in recent years. Variants c.94G>T and c.4515C>G are located in the same gene, TSC2, but in exons 2 and 35, respectively. Variants c.94G>T and c.4515C>G are both nonsense variants that result in premature truncation of peptide chain synthesis. Ultimately, the normal function of the tuberin protein was affected. The manifestations and severity of the two variants are equally different. Lin [9] indicated that in 45 cases of TSC2 patients, 82% and 71% had SENs and facial angiofibromas, respectively. In this study, both of the patients had SENs and facial angiofibromas, which also confirms the previous report that TSC2 patients are prone to symptoms of SENs and facial angiofibromas. TSC involves multiple organs and systems and mainly manifests as hamartomas. Clinical manifestations of TSC are highly diverse from patient to patient. CNS involvement is the most consistent feature, present in approximately 90% of TSC patients [10]. The main manifestations are epilepsy, mental retardation, abnormal neurobehaviour, cortical nodules, subventricular nodules, and SEGAs. These structural CNS lesions are associated with neurological signs and symptoms, such as epilepsy and neuropsychiatric disorders. CNS lesions are part of the leading causes of death in TSC. In this study, both patients showed symptoms of epilepsy as teenagers, accompanied by subependymal nodules and cortical abnormalities. Epilepsy onset is primarily diagnosed at the age of 3 months in clinical practice [11]. The appearance of epilepsy in the two patients was late, which may be related to the severity of cortical damage. Kaczorowska stated that a higher tuber count correlation may lead to a quicker onset of epilepsy [12]. In addition to the CNS, the skin is usually involved. Angiofibromas are generally found between ages two and five and

can be mistaken as acne during adolescence. Angiofibromas can result in decreased quality of life for patients because they affect appearance, may cause disfigurement and are prone to bleeding, which increases the possibility of infection [13]. Shagreen patches, periungual fibromas and hypomelanotic macules are also observed in patients. AMLs and cysts are the most characteristic renal findings in TSC patients and usually manifest as abdominalgia and haematuria. AMLs are highly vascular, often bilateral lesions that are composed of adipose and smooth muscle tissue derived from the renal parenchyma. The vascular nature of these tumours makes them prone to aneurysm formation, and patients are at high risk of spontaneous haemorrhage, especially when these tumours exceed 4 cm in diameter [14]. Therefore, systematic follow-up and management are necessary. Both patients reported manifestations of renal involvement, but the condition of the patient with the c.94G>T variant was more serious. The patient showed gradually increasing AMLs in both kidneys and had developed intermittent lumbago. In addition, the largest AML had exceeded 4 cm in diameter. The patient with the c.4515C>G variant had only cysts in the kidneys, with no symptoms. The severity of renal involvement may be related to the position of the nonsense variant in TSC2. Earlier termination of the amino acid chain may have a greater impact on tuberin protein function. The phenotype may be more severe when the variant is located at the beginning of an exon. Sirolimus and everolimus as mTOR inhibitors have been proven to be effective for some TSC manifestations [15,16]. Early topical application of sirolimus can reduce facial angiofibromas and prevent recurrence [17]. However, the withdrawal of the drug causes the reappearance of most disease symptoms. Therefore, patients often need lifelong medication. New and better drugs or treatments for patients are worth exploration. In summary, we identified a novel nonsense variant of TSC2 (c.94G>T, p.E32X). This further expands the TSC variant database and provides the basis for genetic counselling.

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References

1. Zhang R, Wang J, Wang Q, Han Y, Liu X, Bottillo I. Identification of a novel TSC2 c.3610G>A, p.G1204R mutation contribute to aberrant splicing in a patient with classical tuberous sclerosis complex: a case report. BMC Medical Genetics. 2018; 19(1): 173.
2. Hoogeveen-Westerveld M, Ekong R, Povey S, Karbassi I, Batish SD, den Dunnen JT. Functional assessment of TSC1 missense variants identified in individuals with tuberous sclerosis complex. Human Mutation. 2012; 33(3): 476-479.
3. Krymskaya VP: Tumour suppressors hamartin and tuberin: intracellular signalling. Cellular Signalling. 2003; 15(8): 729-739.
4. Franz DN. Everolimus in the treatment of subependymal giant cell astrocytomas, angiomyolipomas, and pulmonary and skin lesions associated with tuberous sclerosis complex. Biologics: Targets & Therapy. 2013; 7: 211-221.
5. Northrup H, Krueger DA. International Tuberous Sclerosis Complex Consensus G: Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurology. 2013; 49(4): 243-254.
6. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. Journal of the American Academy of Dermatology. 2007; 57(2): 189-202.
7. Zhang ZZ, Lv YM, Mou YZ, Yang H, Yang P, Liu YP. Analysis of TSC gene mutation in a patient with tuberous sclerosis. Chin J Med Genet. 2015; 32(4): 511-513.
8. Lv YM, Zhang ZZ, Chen L, Mou YZ. Gene mutation detection for a patient with tuberous sclerosis complex. Journal of Practical Dermatology. 2016; 9(03): 168-170.
9. Lin S, Zeng JB, Zhao GX, Yang ZZ, Huang HP, Lin MT. Tuberous Sclerosis Complex in Chinese patients: Phenotypic analysis and mutational screening of TSC1/TSC2 genes. Seizure. 2019; 71: 322-327.
10. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. The Lancet Neurology. 2015; 14(7): 733-745.
11. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA: The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010; 51(7): 1236-1241.
12. Kaczorowska M, Jurkiewicz E, Domanska-Pakiela D, Syczewska M, Lojszczyk B, Chmielewski D. Cerebral tuber count and its impact on mental outcome of patients with tuberous sclerosis complex. Epilepsia. 2011; 52(1): 22-27.
13. Hofbauer GF, Marcollo-Pini A, Corsenca A, Kistler AD, French LE, Wüthrich RP. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. The British Journal of Dermatology. 2008; 159(2): 473-475.
14. van Baal JG, Smits NJ, Keeman JN, Lindhout D, Verhoef S. The evolution of renal angiomyolipomas in patients with tuberous sclerosis. The Journal of Urology. 1994; 152(1): 35-38.
15. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet (London, England). 2016; 388(10056): 2153-2163.
16. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex

(EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet (London, England). 2013; 381(9861): 125-132.

17. Okanishi T, Fujimoto A, Enoki H, Ogai M. Early Sirolimus Gel Treatment May Diminish Angiofibromas and Prevent Angiofibroma Recurrence in Children With Tuberous Sclerosis Complex. Frontiers in Medicine. 2020; 7: 1.