Novel Stop-Gain TSC2 Gene Mutation in an Indian Child of Tuberous Sclerosis Complex

Dear Editor,

Tuberous sclerosis complex (TSC) is a rare autosomal dominant neurocutaneous disorder resulting from mutations in TSC1 or TSC2 genes.[1] It manifests with epilepsy, learning disorders, and skin manifestations.[1] Here, we report a classic case of TSC with a novel pathogenic mutation in the TSC2 gene.

A 10-year-old boy born of a non-consanguineous marriage presented with multiple facial skin-colored lesions since 9 months of age. He had a history of epilepsy since 6 months of age, with delayed speech and motor milestones. There was no similar family history. He was the only child, born at full term by cesarean section.

On examination, he had a solitary 2 × 2 cm skin-colored plaque on the forehead. Multiple, firm, skin-colored papules and nodules with smooth surface were distributed bilaterally symmetrically over the nose, cheeks, and chin, sparing the upper lip [Figure 1]. Multiple, discrete, firm plaques with "peau d'orange" surface were distributed posteriorly on the trunk, with few hypomelanotic macules [Figure 2]. Oral and other mucosae, hair, and nails were normal. Based on the presence of angiofibromas, shagreen patches, and ash-leaf macules, a diagnosis of TSC was made, after ruling out Multiple Endocrine Neoplasia type 1 (MEN1) and Birt–Hogg–Dube syndrome.

Blood investigations, echocardiography, and ultrasound abdomen were normal. A computed tomography (CT) scan of the brain revealed multiple subependymal nodules [Figure 3]. Genetic analysis with "Sanger sequencing" targeting the commonly involved exons in TSC initially failed to identify any mutation, but subsequent "whole-exome sequencing" revealed the pathogenic mutation in exon 12 of the TSC2 gene.

Epilepsy was well controlled with sodium valproate and facial angiofibromas were treated with topical sirolimus, as the parents were unwilling for surgical procedure. Parents were counseled about regular follow-up for early detection of new hamartomas and monitoring any rapid increase in

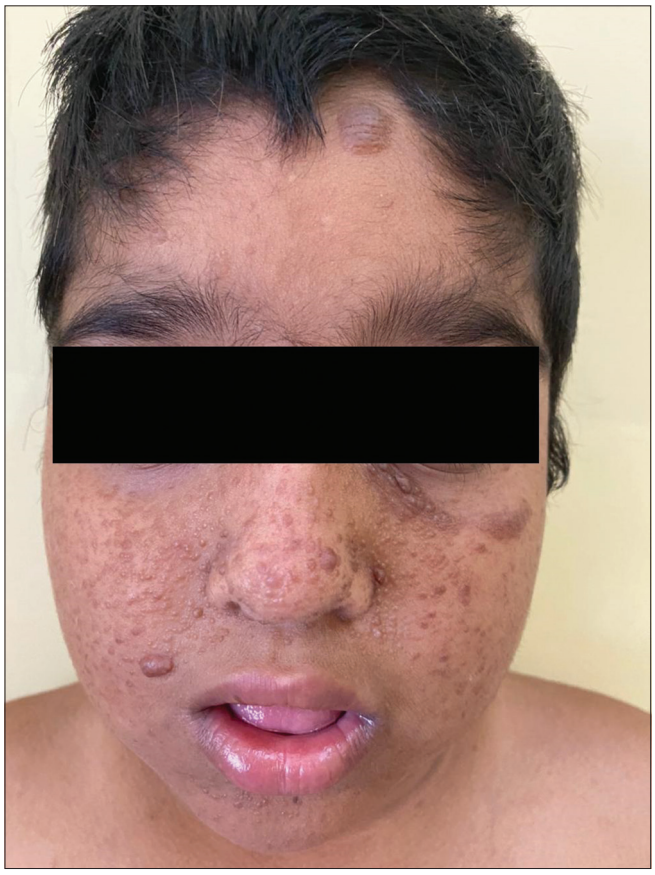

Figure 1: Solitary skin-colored plaque on the forehead with multiple grouped angiofibromas over the cheeks, nose, and chin

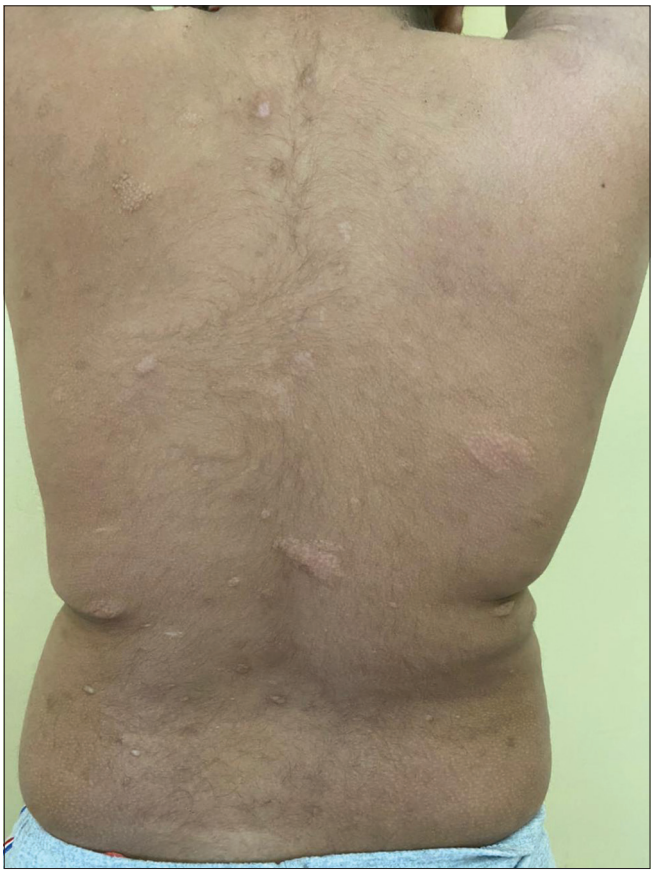

Figure 2: Multiple skin-colored plaques on the back with a few hypomelanotic macules

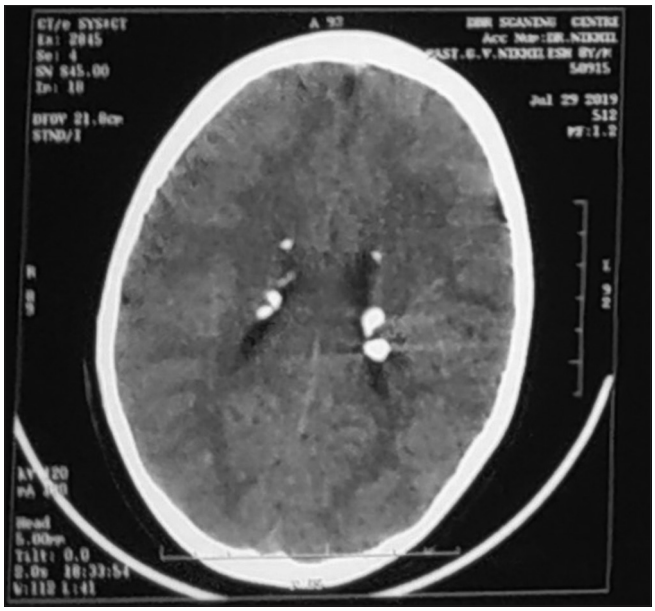

Figure 3: CT brain scan showing multiple subependymal nodules

the size of subependymal nodules, to rule out giant cell astrocytomas.

Tuberous sclerosis (first described in 1880 by Bourneville) characteristically manifests with skin and systemic hamartomas. Recent studies suggest a prevalence of approximately one in 20,000 live births.[2] TSC1 and TSC2 are tumor suppressor genes, located on chromosomes 9q34.3 and 16p13.3, respectively.[3,4] Their products, "hamartin" and "tuberin," inhibit the mammalian target of rapamycin (mTOR), which is an immunosuppressive agent.[4] Thus, their mutations occurring at 7 to 20 weeks of gestation lead to abnormal tissue structures. Three-quarters of TSC patients are sporadic (spontaneous mutations in 65%), and the remaining are familial. The ratio of TSC2 to TSC1 mutations in familial cases is 1:1, whereas it is 5:1 in sporadic cases.[3]

Sudarshan *et al.*,[4] in an Indian study of 98 TSC patients, reported that TSC2 variants were ten times more common than TSC1, compared with five times in other populations. TSC2 mutations produce a more severe phenotype than TSC1 mutations, except in some missense TSC2 mutations producing milder disease phenotypes.[5,6] In individuals harboring TSC2 mutations, as in our case, Al-Saleem reported greater risk of renal malignancy and Dabora *et al.* reported greater severity of seizures, learning disability, mean number of subependymal nodules, tuber count, kidney angiomyolipomas, facial angiofibromas, forehead plaque, and retinal hamartomas.[3,7] Au *et al.* found that male patients have frequent neurological and eye symptoms and renal and ungual fibromas.[8]

In our patient, genetic analysis by "whole-exome sequencing" of the blood deoxyribonucleic acid (DNA) was performed on the Illumina sequencing platform. A novel, pathogenic, heterozygous stop-gain variant in exon 12 of gene TSC2 (Chr16:2061972C > A; depth 56X) NM_000548.5:c.C1221A: p.Tyr407* was identified. This variant results in a pre-mature termination codon and has not been reported previously in population databases, such as 1000 Genomes, Exome Variant Server, Genome Aggregation Database, ClinVar, Online Mendelian Inheritance in Man and Human Genome Mutation Database or in the latest reviews.[9] It is classified as "pathogenic" according to the American College of Medical Genetics and Genomics guidelines.

To date, more than 1000 gene mutation sites have been reported.[10] Frameshift mutations, missense mutations, nonsense mutations, splicing mutations, deletions, and insertions have been described.[10] The stop codon variant (nonsense mutation), as seen in our case, was detected in 15% of cases of TSC2 gene mutations.[4]

The diagnosis of tuberous sclerosis remains a clinical one, but genetic testing is helpful in managing the genetic implications for the family. Even if no mutation is found in the parents of a child with the TSC mutation, there remains a 2% chance of having another child with TSC due to gonadal mosaicism. Therefore, genetic prenatal diagnosis is advised in subsequent pregnancies.

Recent advances in molecular genetics have shed light on disease pathogenesis and genotype–phenotype correlation and contributed to the development of new treatment modalities.[4] Our case with a novel TSC2 gene mutation adds to the existing database of pathogenic genetic variations causing TSC, but the clinical implications of this mutation are yet to be elucidated.

Declaration of consent

The authors certify that they have obtained all appropriate consent forms, duly signed by the parent(s)/guardian(s) of the patient. In the form, the parent(s)/guardian(s) has/have given his/her/their consent for the images and other clinical information of their child to be reported in the journal. The parents understand that the names and initials of their child/children will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgements

The authors acknowledge the valuable contribution of Dr. Ashwin Dalal (MD Paediatrics, DM Medical Genetics), Head, Diagnostics Division Centre for DNA fingerprinting and Diagnostics, Hyderabad, for his help in conducting whole-exome sequencing on our patient.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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References

1. Curatolo O, editor. Tuberous Sclerosis Complex: From Basic Science to Clinical Phenotypes. London, England: MacKeith Press; 2003.
2. Triono A, Herini ES, Iskandar K, Hadiyanto ML, Diantika K, Wijayanti VW. De novo mutation of the TSC2 gene in patient with tuberous sclerosis complex-associated neuropsychiatric disorders (TAND) phenotype: A case report. Ann Med Surg 2023;85:2102-7.
3. Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, *et al.* Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet 2001;68:64-80.
4. Sudarshan S, Kumar A, Gupta A, Bhari N, Sethuraman G, Kaushal T, *et al.* Mutation spectrum of tuberous sclerosis complex patients in Indian population. J Pediatr Genet 2020;10:274-83.
5. Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, *et al.* Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: Genotype–phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. Eur J Hum Genet 2005;13:731-41.
6. Astrinidis A, Khare L, Carsillo T, Smolarek T, Au KS, Northrup H, *et al.* Mutational analysis of the tuberous sclerosis geneTSC2 in patients with pulmonary lymphangioleiomyomatosis. J Med Genet 2000;37:55-7.
7. Al-Saleem T, Wessner LL, Scheithauer BW, Patterson K, Roach ES, Dreyer SJ, *et al.* Malignant tumors of the kidney, brain, and soft tissues in children and young adults with the tuberous sclerosis complex. Cancer 1998;83:2208-16.
8. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, *et al*. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genetics in Medicine 2007;9:88-100.
9. Quintero Vásquez CA, González IF, Quevedo Camera ML, García Ordoñez AM, Celis Regalado LG. Detection of new mutations in 3 cases de novo tuberous sclerosis. Scientific J Genet Gene Ther 2019;5:1-6.
10. Gao S, Wang Z, Xie Y. Two novel TSC2 mutations in pediatric patients with tuberous sclerosis complex: Case report. Medicine (Baltimore) 2018;97:e11533.

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Quick Response Code

DOI: 10.4103/idoj.idoj_469_23

How to cite this article: Haqqani R, Rana S, Haneef NS, Farooq O, Rao VR. Novel stop-gain TSC2 gene mutation in an Indian child of tuberous sclerosis complex. Indian Dermatol Online J 2024;15:657-9.

Received: 17-Jun-2023. **Revised:** 19-Sep-2023.
Accepted: 01-Oct-2023. **Published:** 20-May-2024.