CASE REPORT

HONG KONG JOURNAL OF PAEDIATRICS RESEARCH
Hong Kong J Pediatr Res 2021; 4(3):48-50

ISSN(e): 2663-5887
ISSN(p): 2663-7987

A Novel Variant of Tuberosclerosis: c.2458A>T in the 19th Exon

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Abstract

Rhabdomyomas are the most common congenital heart tumors. Rhabdomyomas are hamartomas of myocytes and benign heart tumors. In the postnatal period, it may be asymptomatic, or there may be findings such as murmur, arrhythmia, heart failure, and even hydrops. Echocardiography (ECHO) is a very valuable method in its diagnosis. Rhabdomyomas can regress spontaneously. Rhabdomyoma of the heart is seen in 43-60% of tuberous sclerosis cases. Tuberous sclerosis is an autosomal dominant inherited neurocutaneous disease that causes the development of benign tumors called hamartoma in many systems such as brain, retina, kidneys, heart, skin and lungs. In this article, we wanted to contribute to the literature by presenting a new pathogenic c.2458A> T (p.Lys820Ter) variant that developed de novo in the TSC1 gene by genetic analysis of a patient with multiple cardiac rhabdomyomas.

Keywords: Tuberous Sclerosis, Cardiac Rhabdomyoma, TSC1 Gene.

INTRODUCTION

Rhabdomyomas are hamartomas of myocytes and the most common congenital heart tumors and can be diagnosed by ultrasonographic examinations after 32 weeks of gestation [1]. Tuberous sclerosis is an autosomal dominant inherited neurocutaneous disease that causes the development of hamartoma in many systems such as brain, retina, kidneys, heart, skin and lungs, which is seen in 1 / 6000-1 / 10000 live births [2]. Cardiac Rhabdomyomas are seen in 43-60% of tuberous sclerosis cases, therefore, rhabdomyoma cases should be evaluated in terms of tuberous sclerosis [3].

CASE REPORT

The girl patient was born 39w3d, 3200 g, by vaginal delivery. When she was 1 month old, she was brought to the Pediatrics Clinic. In the physical examination, the general condition is good, active, IR ++ / ++, no hypopigmented macules, no angiofibromas on the face, no periungal fibromas (Figure 1Bb). S1 +, S2 +, 3/6 systolic murmur was heard during cardiac examination, and he was referred to Pediatric Cardiology. Left ventricular systolic functions were found to be normal in echocardiography. Multiple rhabdomyoma of 10x5 mm,16x9 mm and 12x8 mm in size was found in the right ventricle (Figure 1Ca and b). No arrhythmia was observed in the ECG and she was hemodynamically stable. Follow-up was planned, surgical intervention was not considered. Abdomen USG and urinary system USG were revealed normal. Retinal hamartoma was not detected on ophthalmological examination. The patient was referred to the Medical Genetics clinic to be evaluated for tuberous sclerosis. All exons and exon / intron junction regions encoding the TSC1 gene were sequenced in the patient by Sanger sequencing, and the c.2458A>T variant was found as heterozygous state in the 19th exon (Figure 1A)(Table 1). As far as we know, this change has not been previously identified in any genetic database and was considered a novel variant. As a result of the segregation analysis performed in the family, it was determined that the variant developed de novo and was evaluated as a pathogenic variant according to ACMG guidelines (Figure 1Ba) [9]. The family was informed about possible convulsions and other risks. Genetic counseling was given to the family. The patient was referred to Pediatric Neurology Clinic for follow up of convulsions and Pediatric Cardiology Clinic for follow-up of rhabdomyomas.

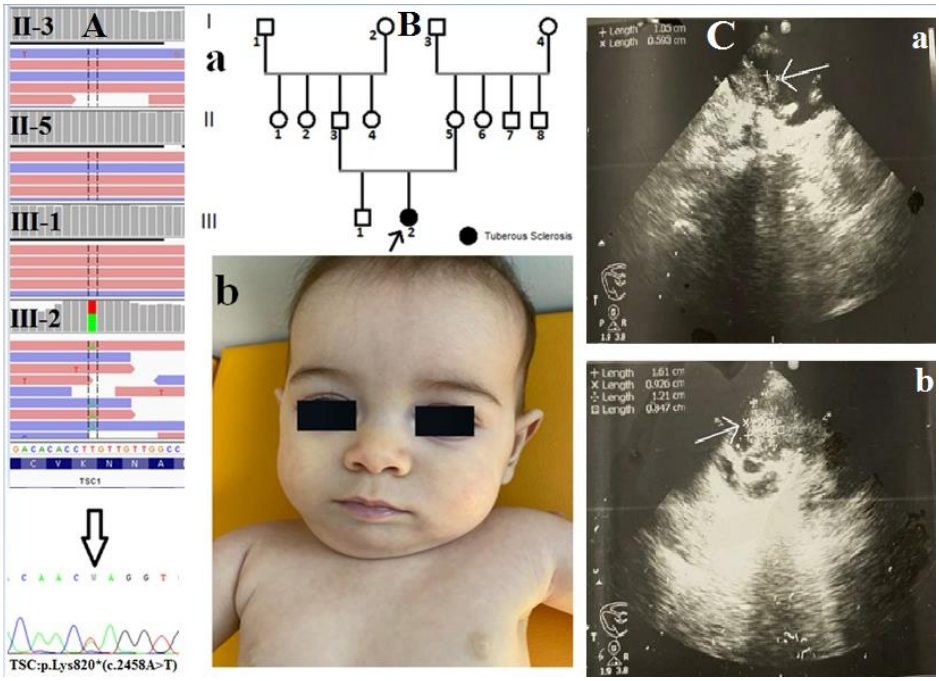

Figure 1: (A) Novel c.2458A>T p.(Lys820*) mutations in exon 19 of *TSC1*(NM_000368.5gene in probands(III-2). Normal sequence analysis appearance of *TSC1* gene in II-3 (father), II-5(mother) and III-1(sibling). (B) Pedigree of the family. III-2 is proband and patient. I-1, I-2, I-3, I-4, II-1, II-2, II-3, II-4, II-5, II-6, II-7, II-8 and III-1 are unaffected relatives. II-3 and II-4 are parents of our patient(a). The patient's facial appearance, No skin lesions were detected (b). (C) Echocardiography imaging findings of probands with rhabdomyoma (a and b).

Table 1: A Patient Who had a novel variant in TSC1 gene

GENE	***TSC1***
Transcript ID	NM_000368.5
dbSNP	Novel
Variant	c.2458A>T (p.Lys820*)
Variant Location	Exon 19
Variant Type	Nonsense
Mutation Taster	Disease causing
Provean	Damaging
SIFT	Damaging
GnomAD (exomes)	Not found
ClinVAR	Not found
Conservation	conserved
DANN score	0.9966
GERP score	NR:5.23 RS:5.23
ACMG Classification	Pathogenic
ACMG Pathogenity Criteria	PVS1,PM2,PP3

DISCUSSION

Tuberous sclerosis disease was first described by Desire-Magloire Bourneville as 'Bourneville disease' in 1880. It is a multisystemic, autosomal dominant disease that progresses with hamartomas in many organs such as the skin, central nervous system, kidney and lungs. Classical triad of Tuberosclerosis are seizures, mental retardation and cutaneous angiofibromas [4]. It is caused by the dysfunction of the TSC1 (9q34) and TSC2 (16p13) tumor suppressor genes. In these mutated cells, mTOR activation increases and it causes an increase in cell size and growth. 80% of the cases develop as a result of de novo mutation [5, 6].

Cardiac Rhabdomyomas are the most common congenital heart tumors. It has been reported to be detected with a frequency of approximately 0.027-0.08% in autopsy studies. Echocardiography (ECHO) is a very valuable method in its diagnosis [1]. Rhabdomyomas may be asymptomatic in the postnatal period, or there may be findings such as murmur, arrhythmia, heart failure, and even hydrops. Most of cardiac rhabdomyomas tend to shrink spontaneously. Postpartum regression is observed in 70% up to 4 years and 17% after 4 years [7]. It has been reported that a tumor size of 20 mm and above is significant in terms of fetal dysrhythmia and hydrops. Surgical treatment is recommended for cases that cause mechanical stenosis in the heart or cause life-threatening arhythmias [8].

CONCLUSION

In this article, we report a novel pathogenic c.2458A> T (p.Lys820Ter) variant that develops de novo in the TSC1 gene with the genetic analysis of a patient with multiple cardiac rhabdomyomas on his echocardiography and we want to contribute to the literature and remind again the association of cardiac rhabdomyoma with tuberosclerosis.

Conflict of Interest

None declared.

Financial Support

None declared.

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