Neurology Asia 2024; 29(1) : 269 – 271

The intronic variant of *SATB2* gene observed in an Indian Glass syndrome family

[1]Murugasamy Pradeepkumar, [2]Mohan Gomathi, [3]Mohandass Kaviya

[1]Department of Medical Genetics, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu, India; [2]Centre for Neuroscience, Department of Biotechnology, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu, India; [3]Department of Biochemistry, Dr. N. G. P. College of Arts and Science College, Coimbatore, Tamil Nadu, India

Abstract

The Glass syndrome is a rare genetic disorder that is associated with a multisystem disorder due to a *SATB2* gene mutation. The intellectual development delay and the delay in speech are the predominant characteristics of the disorder. The reports on Glass syndrome are very few and have not been reported in India. In the present study, we report the Glass syndrome disorder in an Indian mother and her child, both affected by the same likely pathogenic mutation c.1741-2A>C intronic variant at intron 11 of the *SATB2* gene. The mutation was observed as a heterozygous and autosomal dominant missense mutation through focused exome sequencing analysis. The variant identified has not been observed in the general population, and the clinical features like cleft palate, speech delay, and intellectual delay match the causative mutation. The present study is novel in exhibiting the intronic variant and identifying Glass syndrome in the Indian population.

Keywords: SATB2, intronic Variant, cleft palate, speech delay

INTRODUCTION

The Glass Syndrome is a rare neurogenic multisystem disorder that occurs due to a mutation in *SATB2* (OMIM-608148 and PMIM:612313). The clinical features of this syndrome include delay in development and speech, hypotonia, abnormal dental features, cleft palate, difficulty in behavior, seizures, and bone abnormalities.[1] The prevalence rate of this disorder is still unknown, as there have been few cases reported. The *SATB2* gene is located on chromosome 2. This syndrome was first reported in 1989 by Glass *et al*. (1989) in a 16-year boy who had microcephaly, mental retardation, craniofacial dysmorphism, and facial features of a large beaked nose, a cleft palate, and ptosis. Initially, it was diagnosed as a chromosomal interstitial deletion between 2q33.2-q33.1. The *SATB2* gene belongs to the family of special AT-rich binding proteins and influences craniofacial and skeletal developments.[2] The cleft palate symptom involved in the glass syndrome is strongly associated with a mutation in the *SATB2* gene.[3]

In a study conducted with the Glass Syndrome individuals, it was found that all had *de novo* mutations.[4] In the present study, we report a female patient of Glass syndrome and her daughter with a similar condition affected by the rare variant c.1741-2A>C mutation in the *SATB2* gene, found in the Indian population.

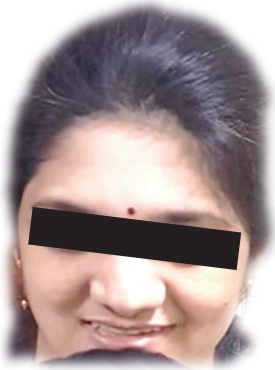
CASE REPORT

The female index patient, about 25 years old, was born of a non-consanguineous marriage. The family pedigree appeared to be normal. The index exhibited the features of cleft palate and developmental delay; initially, she was suspected to have Rubinstein-Taybi syndrome. The cleft palate of the index patient was normalised by surgery. She also displayed the bone deformities which is prominent in her left hand and craniofacial deformities. The observed height is 148 cms and the weight is about 49 kgs. Her daughter was also manifesting the symptoms of speech delay at three and a half years of age. The child had developmental delay but there were no evidential craniofacial anomaly or bone deformities observed. The height of the child is about 90 cms and her weights is about 12 kgs. The image of the affected index and her child

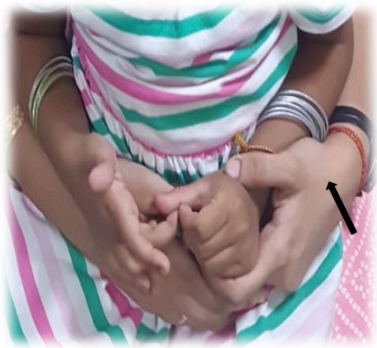
Address correspondence to: Dr. Kaviya Mohandass, PhD, Assistant Professor, Department of Biochemistry, Dr. N. G. P. Arts and Science College, Coimbatore - 641035, Tamil Nadu, India. Email: kaviyamohandass@gmail.com, kaviya.m@drngp.asc.ac.in

Date of Submission: 27 August 2023; Date of Acceptance: 16 October 2023

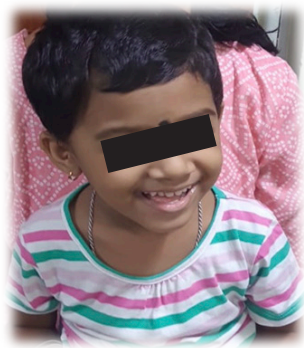
https://doi.org/10.54029/2024ttf



Craniofacial anomaly and normalized cleft palate



Skeletal deformity in left hand



Normal facial feature of affected chld

Figure 1. Features of Glass syndrome. The figure illustrates the normalized cleft palate observed in the index mother along with her bone deformities observed in the left hand and the normal facial feature of the child.

with the clinical features are given in the Figure 1. On genetic analysis through focused exome sequencing, it was found that index had a mutation in the *SATB2* gene with a rare variant c.1741-2A>C; at intron 11 (NM_015265.4). This is a substitution of base A for base C, two nucleotides before the initiation of the exon. This variant is reported to be pathogenic and causative of Glass syndrome.

There were also other uncertainly significant mutations found in the CDCD42BP and SMARCC2 with variants c.3658C>T; NM_006035.4; and c.2527G>A; NM_003075.5 subjective of Chilton-Okur-Chung neurodevelopmental syndrome and Coffin-Siris syndrome 8, respectively.

DISCUSSION

In a Thai man, the Glass syndrome was found to be associated with the clinical features of isolated cleft palate, generalized osteoporosis, mental retardation, and gum hyperplasia with a mutation in the *SATB2* gene (c.715C>T, p.R239X variant.[5] In the present study, the clinical features of cleft palate matched those in the above case, but the variants differed with significant variations in the clinical features. In a three-year-old girl, the glass syndrome was identified with a mutation in the *SATB2* gene with the p.R239X variant, and she had the symptoms of severe speech delay, mental retardation, hypotonia, and cleft palate.[6] In a study by Leiden *et al*. (2014)[7], the Glass syndrome was identified in a 20-year-old boy, and it was a *de novo* mutation in the *SATB2* gene identified by means of array CGH analysis. The *de novo* mutation in the *SATB2* gene was also identified by Kaiser *et al*. (2015)[8], in a 10-year-old girl. However, in the present study, the identified mutation is not *de novo* as the mother and the daughter have both been affected, and the focused exome sequencing is an higher technique than that of CGH array, which is a chromosome-based technique. In about 19 cases of *SATB2* mutations studied by Bengani *et al*. (2017)[9], they observed about 11 loss-of-function mutations and 8 missense mutations. In the present study, the mutation observed is a missense mutation, which is the minimal type of mutation observed in the previous study. The Glass syndrome has also been observed in the Japanese population, where there is a case study on two patients with the *SATB2* mutation identified by means of whole exome sequencing as a heterozygous mutation, which is similar to the present study.

REFERENCES

1. Zarate YA, Kaylor J, Fish J. *SATB2*-associated syndrome. 2017 Oct 12. In: Adam MP, Mirzaa GM, Pagon RA, *et al*., Eds: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: Https://Www.Ncbi.Nlm.Nih.Gov/Books/NBK458647/.
2. Huang X, Chen Q, Luo W, *et al*. *SATB2*: A versatile transcriptional regulator of craniofacial and skeleton development, neurogenesis and tumorigenesis, and its applications in regenerative medicine. *Genes Dis* 2022;9(1):95-107. doi:10.1016/j.gendis.2020.10.003
3. Van Buggenhout G, Van Ravenswaaij-Arts C, Mc Maas N, *et al*. The del(2)(q32.2q33) deletion syndrome defined by clinical and molecular characterization of four patients. *Eur J Med Genet* 2005;48(3):276-89. doi:10.1016/j.ejmg.2005.05.005

4. Leoyklang P, Suphapeetiporn K, Srichomthong C, *et al*. Disorders with similar clinical phenotypes reveal underlying genetic interaction: *SATB2* acts as an activator of the UPF3B gene. *Hum Genet* 2013;132(12):1383-93. doi:10.1007/s00439-013-1345-9
5. Leoyklang P, Suphapeetiporn K, Siriwan P, *et al*. Heterozygous nonsense mutation *SATB2* associated with cleft palate, osteoporosis, and cognitive defects. *Hum Mutat* 2007;28(7):732-8. doi:10.1002/humu.20515
6. Döcker D, Schubach M, Menzel M, *et al*. Further delineation of the *SATB2* phenotype. *Eur J Hum Genet* 2014;22(8):1034-9. doi:10.1038/ejhg.2013.280
7. Liedén A, Kvarnung M, Nilssson D, Sahlin E, Lundberg ES. Intragenic duplication--a novel causative mechanism for *SATB2*-associated syndrome. *Am J Med Genet A* 2014;164A(12):3083-7. doi:10.1002/ajmg.a.36769
8. Kaiser AS, Maas B, Wolff A, *et al*. Characterization of the first intragenic *SATB2* duplication in a girl with intellectual disability, nearly absent speech and suspected hypodontia. *Eur J Hum Genet EJHG* 2015;23(5):704-7. doi:10.1038/ejhg.2014.163
9. Bengani H, Handley M, Alvi M, *et al*. Clinical and molecular consequences of diseaseassociated de novo mutations in *SATB2*. *Genet Med* 2017;19(8):900-8. doi:10.1038/gim.2016.211