International Journal of Contemporary Pediatrics
Sinha R et al. Int J Contemp Pediatr. 2022 Jun;9(6):623-626
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221385

Case Report

De novo SOX6 variant: Tolchin-Le Caignec syndrome

Rahul Sinha[1]*, Sonali Singh[2], Gautam Kamila[3]

[1]Department of Pediatrics and Pediatric Neurology, Command Hospital, Chandimandir, Panchkula, Haryana 134109, India
[2]Department of Pediatrics, Institute of Neurosciences, Kolkata, India
[3]Department of Pediatrics, All India Institute of Medical Sciences, Delhi, India

Received: 27 March 2022
Revised: 22 April 2022
Accepted: 05 May 2022

***Correspondence:**
Dr. Rahul Sinha,
E-mail: drrahul_2000@yahoo.com

ABSTRACT

Tolchin-Le Caignec syndrome (TOLCAS) is a developmental disorder characterized by intellectual impairment and behavioural issues such as autism, hyperactivity, aggressive episodes and mood swings and lack of sleep. The other manifestations include osteochondroma, craniosynostosis, dysmorphic facies, arachnodactyly, prominent occiput and bitemporal narrowing. We reported this rare syndrome in a 5 and half year old female child who presented with global developmental delay (language and cognitive predominant), autistic features, hyperactivity, aggressive behaviour and dysmorphism (high forehead, bitemporal narrowing, micrognathia, low set ears, hypertelorism, wide nasal bridge, scaphocephaly, clinodactyly). The whole exome sequencing detected *de novo* heterozygous missense pathogenic variant c.1378A>C, p. (Asn460His) in exon 11 of SOX6 gene with no similar variant found in either of the parents confirmed the diagnosis of TOLCAS. This rare case report highlighted the phenotypic variation due to SOX6 gene mutation which the clinician should be aware of while dealing with dysmorphic child with cognitive and language delay with autistic features.

Keywords: Autistic, Dysmorphism, Hyperactivity, Developmental delay

INTRODUCTION

TOLCAS is a neurodevelopmental disorder characterized by developmental delay and behavioural issues like autistic features, attention deficit hyperactivity disorder (ADHD), labile personality and aggressive behaviour. The dysmorphic features include high forehead, bitemporal narrowing, micrognathia, low set ears, hypertelorism, wide nasal bridge, scaphocephaly, clinodactyly, palatal defects with many patients have bony abnormalities, including osteochondroma, craniosynostosis, arachnodactyly and large head circumference. This syndrome is due to mutation in the SOX6 gene which belongs to a family of 20 SRY-related HMG-box-containing (SOX) genes that encode transcription factors responsible for many developmental, physiological and pathological changes.[1-3] Variants in half of the SOX genes have been shown to cause severe developmental and adult syndromes, referred to as SOXopathies.[4,5] The heterozygous mutations in the SOX6 gene that were identified in most patients with TOLCAS.

CASE REPORT

5 and half year old female child, born to a non-consanguineous marriage presented with global developmental delay (language predominant), speech impairment, abnormal behaviour and dysmorphic features. She was born at term by lower segment caesarean section with a birth weight of 2.25 kg. The

baby was found to have dysmorphic features in the form of high forehead, bitemporal narrowing, micrognathia, low set ears, hypertelorism, wide nasal bridge, scaphocephaly, clinodactyly. She developed respiratory distress and features of sepsis on D2 of life and was kept in NICU for 2 weeks. The initial screening for an inborn error of metabolism was negative (tandem mass spectrometry/gas chromatography-mass spectrometry/ammonia normal).

Figure 1: (a) Depicts dysmorphic features in the form of high forehead, bitemporal narrowing, low set ears, hypertelorism, wide nasal bridge, long philtrum; (b) depicts low set ears, scaphocephaly, prominent occiput, mild retrognathia; (c) depicts clinodactyly with short fingers.

The tests for congenital adrenal hyperplasia was also normal. She was discharged on D14 of life and was asked to follow up in high-risk neonatal clinic. The initial milestones were delayed (both motor and language but language predominant); neck holding at 6 months, sitting independently at 10month, walking at 15 months, pincer grasp at 12 months, drinking with cup at 2 years, bisyllable at 20 month, 2-3 words 3.5 years. For the last two years, she developed behavioural issues in the form of hyperactivity and inattention, stereotypies. There was no history of similar illness in the last three generations of the family tree. The examination revealed weight 15 kg (-2.26 SD), height 101 cm (-1.78 SD), OFC 48 cm (-2 SD). She had dysmorphic features in the form of high forehead, mild retrognathia, low set ears, hypertelorism, wide nasal bridge, long philtrum, scaphocephaly, bitemporal hollowing, clinodactyly and short fingers (Figure 1 a-c). The neurological examination was essentially normal. The Malins intelligent score for Indian children (MISIC) score for overall intelligence was 45 (moderate intellectual disability) and childhood behaviour checklist (CBCL T score) for inattention was 78, hyperactivity 75, aggressiveness 76 (normal score, <65; borderline 65-70; and clinically impaired >70). The eye and hearing assessment was normal. The Echocardiography and ultrasonography of abdomen and kidney were normal. MRI (brain) did not reveal any abnormality. The skeletal survey was normal. The karyotype was 46, XX The screening for MECP2 gene mutation was negative. The whole exome sequencing detected *de novo* heterozygous missense pathogenic variant c.1378A>C, p. (Asn460His) in exon 11 of SOX6 gene with no similar variant found in either of the parents. In silico prediction tools the identified variant was found to be damaging by SIFT, Polyphen2. This confirmed the diagnosis of TTOLCAS. The genetic analysis for used only for diagnostic purpose so institute ethical clearance was not required. The parental consent was taken for the study and publication of images.

Table 1: Clinical phenotypes of patients with SOX6 variants.[1]

Variants	Occipitofrontal circumference	Weight/ height	ID	Facial dysmorphism	Osteochondromas	Behaviour issues	Other features
SOX6 variants	-1 SD to +3 SD	General ly normal	Mild to severe	Scaphocephaly (Saggital craniosynostosis), prominent occiput, hypertelorism, long forehead, short palpebral fissures, hooded eyelids, wide nasal bridge, low set ears, long philtrum, depressed bridge of nose	Single/multiple	ADHD, Autism, Mood swings, Restlessness, aggressiveness, short attention span, anxiety disorders	Bilateral inverted nipple, sensorineural hearing loss, vestibular dysfunction, high arched palate, long tapering fingers, hypotonia, clinodactyl, flat feet with valgus heels, arachnodactyly, precocious puberty

Continued.

Variants	Occipitofrontal circumference	Weight/ height	ID	Facial dysmorphism	Osteochondromas	Behaviour issues	Other features
TOLCAS (Our case)	-2 SD	-1 SD to -2.5 SD	Moderate	High forehead, mild retrognathia, low set ears, hypertelorism, wide nasal bridge, long philtrum, scaphocephaly	Absent	Inattention, aggressiveness hyperactivity, emotional lability	Bitemporal hollowing, clinodactyly, short fingers

Presently the child was on physiotherapy, occupational, speech and behavioural therapy and is under follow up in outpatient department.

DISCUSSION

The SOX6 gene is responsible for encoding member of the D subfamily of sex determining region Y-related transcription factors that are characterised by a conserved DNA binding domain called as high mobility group box and by their ability to bind the minor groove of DNA. The encoded protein was a transcriptional activator which was responsible for normal development of central nervous system, chondrogenesis and maintenance of cardiac and skeletal muscle cells.[6,7] The spectrum of SOX6 mutation varied from a balanced chromosomal translocation to partial or complete gene deletions and to nonsense, missense and other single nucleotide variants. The linking of SOX6 variants with a neurodevelopmental syndrome is mostly due to dynamic expression of this gene in the human developing brain especially in neuronal progenitors in the developing dorsal telencephalon which induced differentiation of the cells. SOX6 was also strongly expressed in the medial ganglionic eminence, where it was necessary for the normal positioning and maturation of cortical interneurons.[8-10] Most of the affected individuals with SOX6 variants had inactivated one SOX6 allele and thus caused a disease that revealed SOX6 haploinsufficiency.[11] These variants were microdeletions and frameshift and nonsense variants. The missense variants in the HMG domain might have inactivated the protein made from the SOX6 carrier allele and by evidence that many variants in the HMG domain, including those detected in affected individuals, have been shown in other SOX genes to cause SOXopathies. The SOX6 plays a role in neurogenesis and chondrogenesis, which could explain the phenotypic features. Table 1 provides the key clinical features SOX6 related along with TOLCAS features as was present in our case. In our patient there was global developmental delay (language and cognitive predominant), autistic features, hyperactivity, aggressive behaviour and dysmorphism (high forehead, bitemporal narrowing, micrognathia, low set ears, hypertelorism, wide nasal bridge, scaphocephaly, clinodactyly) and next generation sequencing was suggestive of TOLCAS. There was no effective treatment for this syndrome, only supportive treatment in the form of speech therapy, physiotherapy, behavioural and cognitive therapy can be prescribed.

CONCLUSION

This rare case report highlights the phenotypic variation due to SOX6 gene mutation which the clinician should be aware of while dealing with dysmorphic child with cognitive and language delay with autistic features.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sinha R, Singh S, Kamila G. De novo SOX6 variant: tolchin-le caignec syndrome. Int J Contemp Pediatr 2022;9:623-6.