

Recurrent CPLANE1 splice site variant in Oro-facial-digital syndrome OFD VI

Case Report

Shalini Dhiman, Karandeep Kaur, Satya Swarup Tripathy, Karthik Adari, Inusha Panigrahi*

PhD Scholar Genetic Metabolic unit Dept. of Pediatrics APC, PGIMER Chandigarh 160012

ABSTRACT

Introduction: Oral-facial-digital syndrome VI (OFD VI) is a rare and complex hereditary disorder. It is characterized by developmental abnormalities such as dental anomalies, and facial, and digital anomalies: polydactyly, and duplication of thumb and halluces. Here, we characterize orofacial digital syndrome type VI in two families. **Methods:** Patients were evaluated clinically, and anthropometrically, and with X-ray examination of hands and feet, genetic testing by whole exome sequencing, and imaging by MRI Scan of the brain. **Results:** Both patients had facial dysmorphism, oral findings and digital anomalies including polydactyly. We found splice site variant pathogenic variation on the CPLANE1 gene in both the unrelated patients. **Discussion:** On X-ray radiometric examination of hands, we found hypo-plastic middle phalanges of hands. The identified CPLANE1 variant is possibly a recurrent variant in the gene causing OFD type VI in different ethnicities. Our findings reflect variable phenotypic presentations and add to the clinical spectrum of OFD VI.

Key Words: ciliopathy, orofacial digital syndrome (OFD), polydactyly, dental anomalies, short stature. .

Received: 13 April 2024, **Accepted:** 20 April 2024.

Corresponding Author: Shalini Dhiman , PhD Scholar Genetic Metabolic unit Dept. of Pediatrics APC, PGIMER Chandigarh 160012 **Mobile:** xxxx , **E-mail:** shalinidhiman622@gmail.com

ISSN: 2090-097X, June 2024, Vol. 15, No. 3

INTRODUCTION

Oral-facial-digital syndrome (OFDs) was first described in 1954, as hereditary malformation of the buccal mucous membrane [1]. The OFD syndromes are rare and complex disorders that consist of facial anomalies, abnormalities of the oral cavity, and malformations of fingers and toes [2]. There are different types of OFDs based on various clinical findings. The previous literature described 45% of patients with oral, buccal frenula, cleft palate, 30% to 50% of patients with pseudo upper lip cleft, and 70% with lobulated and bifid tongue, cleft palate. Oral-facial-digital syndrome type VI (OFD VI) is one of the rare types of OFD. It is a rare phenotypic subtype of ciliopathies which includes Joubert syndrome and related disorders (JSRD) [3- 5].

Oral-facial-digital syndromes VI (OFD VI) is characterized by developmental abnormalities as dental anomalies, facial, and digital anomalies: polydactyly, and duplication of thumb [6- 7]. OFD VI is inherited in an X-linked recessive and autosomal recessive manner. It is caused by dysfunction of the primary cilium, a mechano-sensory organelle, that facilitates developmental patterning and growth [8- 13]. However, the mechanistic spectrum of the OFDs has not yet been fully revealed, due to variations in the expression of the syndromes and overlap in the clinical phenotypes. There is significant genetic heterogeneity.

However, up to 40% of OFD syndromes are of unknown genetic basis. Here we describe two unrelated patients one male and female with classical presentations of OFD VI. A splice site CPLANE1: c.31501-G>T pathogenic variation was identified.

INTERPRETATIONS OF CASES:

Case 1

The first case of a girl child brought to Genetic clinic with bilateral deviation of eyes, flat occiput, forehead bossing, convergent squint, epicanthal folds, hypertelorism, depressed nasal bridge, low set ears, tongue nodules, polydactyly in hands, and deformed great toes in feet (Fig:1) Anthropometric measurements revealed short stature. Whole Exome sequencing (WES) and Sanger sequencing were performed using standard protocols from peripheral blood samples (Fig:2). A variant in the CPLANE1 gene on chromosome 5 c.31501-G>T, a splice acceptor variant was identified in the homozygous state. MRI brain, using standard protocols revealed hypoplastic superior cerebellar vermis and hypoplastic corpus callosum.

Case 2

In the second family a patient of 21 years old brought

to the outpatient clinic with phenotype as short stature, dental anomalies, cleft palate, forehead bossing, pre-axial polydactyly, and deviated toe in feet (Fig:3). The MRI of the brain of the patient predicted nodular heterotopia along the ependymal surface of the atrium of the right lateral ventricle. There was ribbon-shaped heterotopia/close lip schizencephaly along the left medial clefting lobe. There was anterior median clefting of the midbrain with thickening of superior cerebellar peduncles giving a molar tooth appearance. There was the presence of pedunculated right-sided hypothalamic hamartoma measuring 4.6mm x 4mm 3.9mm (Fig:4). there was duplication of the pituitary stalk with a relatively hypo-enhancing left-sided pituitary gland. There is evidence of cerebellar dysplasia with molar tooth transformation of the midbrain. Hand-foot images and MRI scans are shown in the figure. Genetic testing by WES was performed on the patient. The same genetic variant in CPLANE1: c.31501-G>T was identified, additionally a CNV (deletion) was detected in the patient on gene SLC34A1. The CPLANE1: c.3150 -1 G>T variant has been reported earlier and is a pathogenic variant. Genetic Counselling was done and further familial segregation was offered to the families.



Figure 3: Patient 2 with post-axial polydactyly in left hand, deviated duplicated hallux (pre-axial polydactyly) in feet, with other digital anomalies.



Figure 1: Patient 1 with sloping forehead, hypertelorism, squint, epicanthic folds, tongue nodules, median cleft lip and digital anomalies including duplicated thumb.

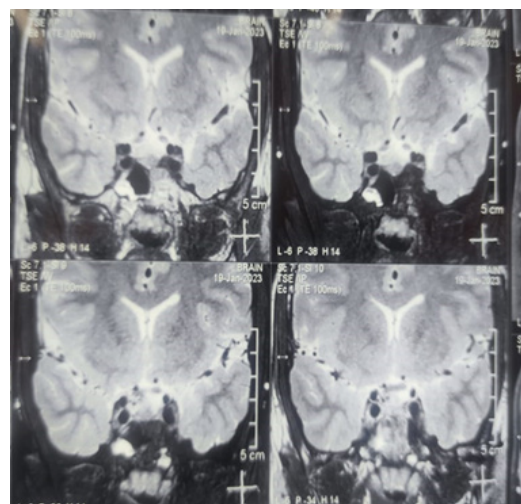


Figure 4: MRI scan of Patient :2, showing pedunculated right sided hypothalamic hamartoma measuring 4.6mm x 4mm 3.9mm (a). There is duplication of pituitary stalk with relatively hypo enhancing left sided pituitary gland and molar tooth sign (b).

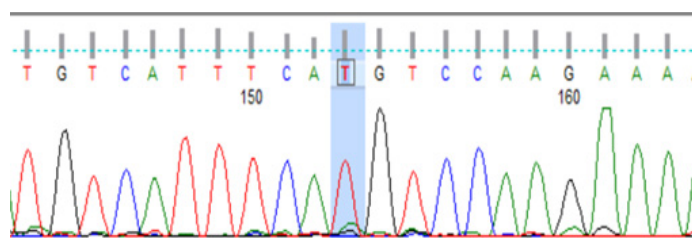


Figure 2: Sanger sequencing validation of CPLANE1 (c.3150-1G>T) homozygous splice site variant.

DISCUSSION

OFD VI is a rare autosomal recessive syndrome presenting with broad and bifid nasal tip, orofacial clefts, tongue nodules or lobulated tongue, short stature, and digital or brain anomalies [1-6]. OFDs have been characterized by high genetic heterogeneity. More than 18 different genes have been identified as causative variations [2,6-9]. OFD VI patients have also been reported to exhibit a more severe neuroimaging pattern in the brain. In severe cases, the patients have prenatal or neonatal presentations [10-12]. In the girl (patient 1), we observed flat occiput, forehead bossing, convergent squint, epicanthal folds, hypertelorism, low set ears, depressed nasal bridge, tongue nodules, polydactyly in hands, and deformed great toes in feet. On radiometric examination of hands, we found hypoplastic middle phalanges of hands.

In patient 2, the presentation included short stature, dental anomalies, cleft palate, frontal bossing, and pre-axial polydactyly, with deviated great toes in feet.

X-ray examination showed left-hand post-axial polydactyly and duplication of thumb in feet. The MRI of the brain of patient 2 revealed multiple brain abnormalities with cerebellar dysplasia and molar tooth transformation of mid brain. The identified heterozygous variant (c.3150-1G>T) lies in the essential splice acceptor site, in intron 17 of the CPLANE1 gene. The identified CPLANE1 variant is possibly a recurrent variant in the gene causing OFD type VI in Indians and a common variant for OFDVI in different ethnicities. Figure 5 shows different pathogenic and likely pathogenic variants in adjoining exons including exons 16 and 18.

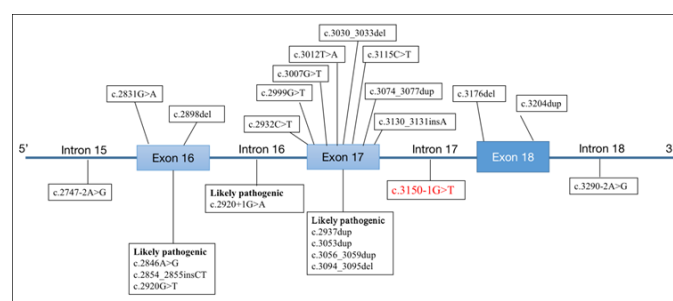


Figure 5: Selected pathogenic and likely pathogenic variants in the CPLANE1 gene adjoining intron 17 and exon 18. The variant in intron 17 found in two of our patients is shown in red.

The CPLANE1 is known as the C5orf42 gene which plays an important role in ciliogenesis. In silico splice prediction tools (ASSP, NCBI blast, and BDGP) predict that this variant is likely to impede splicing at the junction of intron 17 and exon 18 of the CPLANE1 gene. The identified variant has been reported in the dbSNP database with identification number rs606231258. In the ClinVar database, the identified variant has been reported as 'pathogenic' (VCV000157512.1) concerning OFD VI. Our findings reflect variable phenotypic presentations and add to the clinical spectrum of OFD VI. Thus, detailed neuro-imaging, cardiac assessment, hand-feet radiological findings, and dental evaluation provide additional data to better delineate this rare syndrome. The treatment strategy involves surgical correction of hands and feet and dental surgery along with other symptomatic therapies.

CONCLUSION

OFD VI is one of the faciodigital syndromes, although described as rare ciliopathy. The CPLANE1 splice variant in intron 17 is a pathogenic cause of OFD VI. In MRI supratentorial cerebral malformations on neuroimaging predict more severe OFD VI. High throughput sequencing analyses enable identifying the molecular basis of OFD VI and family counseling for management and preventive options.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

Acknowledgements:

We thank the junior residents posted in the unit for help in the patient evaluation and the parents for allowing us to publish the photographs.

REFERENCES:

- Zhang X, Shen Y, Li P, Cai R, Lu C, Li Q, Chen C, Yu Y, Cheng T, Wang X, Luo M. Clinical heterogeneity and intrafamilial variability of Joubert syndrome in two siblings with CPLANE1 variants. *Mol Genet Genom Med* 2021 Jun;9(6):e1682.
- Cuppari C, Salpietro A, Chimenz R, Colavita L, Ceravolo MD, Gitto E, Sallemi A, Fusco M, Ceravolo I, Farello G, Iapadre G. Joubert Syndrome with Oral-Facial-Digital Defect (JS-OFD): A Brief Overview on Clinics and Genetics. *J Ped Neurol* 2023 Feb;21(01):58-61.
- Toriyama M, Lee C, Taylor SP, Duran I, Cohn DH, Buel AL, Tabler JM, Drew K, Kelly MR, Kim S, Park TJ et al. The ciliopathy-associated CPLANE proteins direct basal body recruitment of intraflagellar transport machinery. *Nat Genet* 2016;48(6):648-656.
- Strong A, Simone L, Krentz A, Vaccaro C, Watson D, Ron H, Kalish JM, Pedro HF, Zackai EH, Hakonarson H. Expanding the genetic landscape of oral-facial-digital syndrome with two novel genes. *Am J Med Genet Part A*. 2021 Aug;185(8):2409-2416.
- Zhang C, Sun Z, Xu L, Che F, Liu S. Novel compound heterozygous CPLANE1 variants identified in a Chinese family with Joubert syndrome. *Int J Dev Neurosci* 2021 Oct;81(6):529-538.
- Bönnemann CG, Krishnamoorthy KS, Johnston JJ, Lee MM, Fowler DJ, Biesecker LG, Holmes LB. Clinical and molecular heterogeneity of syndromic hypothalamic hamartoma. *Am J Med Genet Part A*. 2023 Sep;191(9):2337-2343.
- Patra S, Goyal G, Lone YA, Gupta G. Novel variant CPLANE 1: c. 5051C> A (p. Ser1684Ter) in an Indian neonate with Joubert syndrome. *BMJ Case Reports CP*. 2023 May 1;16(5):e255561.
- Queiroz A, Pina PS, Novaes MS, Dutra B, de Sousa SC, Azevedo LH. Bilateral lipomatous hamartoma of the tongue: A case report in a child with oral-facial-digital syndrome type VI. *Special Care Dentistry*. 2024 Jan 7. <https://doi.org/10.1111/scd.12958>

9. Lopez E, Thauvin-Robinet C, Reversade B, Khartoufi NE, Devisme L, Holder M, Ansart-Franquet H, Avila M, Lacombe D, Kleinfinger P, Kaori I. C5orf42 is the major gene responsible for OFD syndrome type VI. *Hum Genet* 2014 Mar;133: 367377-.

10. Darmency-Stamboul V, Burglen L, Lopez E, Mejean N, Dean J, Franco B, Rodriguez D, Lacombe D, Desguerres I, Cormier-Daire V, Doray B. Detailed clinical, genetic and neuroimaging characterization of OFD VI syndrome. *Eur J Med Genet* 2013 Jun 1;56(6):301308-.

11. Bonnard C, Shboul M, Tonekaboni SH, Ng AY, Tohari S, Ghosh K, Lai A, Lim JY, Tan EC, Devisme L, Stichelbout M. Novel mutations in the ciliopathy-associated gene *CPLANE1* (C5orf42) cause OFD syndrome type VI rather than Joubert syndrome. *Eur J Med Genet* 2018 Oct 1;61(10):585595-.

12. Dordoni C, Prefumo F, Iascone M, Pinelli L, Palumbo G, Bondioni MP, Savoldi G, Donzelli C, Sartori E, Valente EM, Izzi C. Prenatal findings in oral-facial-digital syndrome type VI. Report of three cases and literature review. *Prenat Diagn.* 2019 Jul 1;39:652625-.