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X-linked Ohdo syndrome due to a novel *MED12* variant detected by Rapid Exome Sequencing

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List of key features

Blepharophimosis
Ptosis
Bulbous nasal tip
Long philtrum
Full cheeks
Maxillary hypoplasia
Micrognathia
Tetralogy of Fallot
Cleft palate

Clinical summary

Rapid exome sequencing detects a novel *de novo* hemizygous *MED12* missense variant NM_005120.2:c.4831C>T p.(Arg1611Cys) in a neonate with clinical features of X-linked Ohdo Syndrome (XLOS, OMIM 300895). The proband is the youngest of six siblings, born to a nonconsanguineous couple. During the pregnancy, the antenatal scans showed polyhydramnios, tetralogy of Fallot, cleft palate and mild bilateral cerebral ventriculomegaly. The prenatal array-CGH analysis was normal and testing for cytomegalovirus IgM was negative. The proband was born by normal delivery at 39 weeks gestation and did not require resuscitation. He had symmetrical foetal growth restriction with birth weight <0.4th centile and head circumference on 0.4–2nd centile. He was admitted to the neonatal ICU for management of his cardiac abnormality. His facial profile was of a round face, broad forehead, hypertelorism, ptosis, blepharophimosis, downslanting palpebral fissures, bulbous tip of the nose, a long, smooth philtrum, maxillary hypoplasia full cheeks and retromicrognathia. The

anomalies found on detailed examination and imaging were a unilateral cleft palate, tetralogy of Fallot and a left aortic arch, severe gastro-oesophageal reflux and a Morgagni-type diaphragmatic (paraoesophageal) hernia diagnosed on contrast study, left unilateral camptodactyly of the finger flexors and a tight thumb, hypermobile joints, a shawl penis/scrotum. There was initial hypertonia, but now profoundly hypotonia. Cranial ultrasound showed a normal corpus callosum but mild-moderate bilateral dilatation (ventricular index left 15.5 mm, right 17.2 mm (normal range at 40 weeks 9–13 mm) with multiple septations in the lateral ventricles. No abnormalities were seen on renal scan or brain MRI, except slightly increased extra-axial spaces on the latter. There were difficulties in taking oral feeds requiring full nasogastric feeding. Clinical photography can be found in Fig. 1. He had feeding difficulties and episodes of possible cyanotic spells due to tetralogy of Fallot requiring ongoing admission. He was transferred to the paediatric ICU at 2 months of age for ongoing cardiology and surgical care. At 11 months of age, he remained an inpatient with intermittent admission to intensive care, requiring multidisciplinary specialist care. During elective surgery for fundoplication and gastrostomy insertion, he was unexpectedly difficult to intubate and a tracheostomy was inserted. He has frequent desaturations and copious respiratory secretions, requiring positive pressure ventilation. He had surgical intervention for tetralogy of Fallot with a good outcome. He is fed via a gastrostomy tube and is growing along appropriate centiles. He was hypotonic and had minimal head control and a paucity of spontaneous movements, with no purposeful movements. He has a significant global developmental delay, bilateral ptosis with a degree of visual impairment undergoing investigation and mixed sensorineural and conductive hearing loss necessitating hearing aids.

Investigations

In view of his dysmorphic features and cardiac abnormality, rapid trio exome sequencing was requested. This detected a novel *de novo* hemizygous *MED12* missense variant NM_005120.2:c.4831C>T p.(Arg1611Cys), classified in line with American College of Medical Genetics and Association for Clinical Genomic Science 2019 guidelines as likely pathogenic and absent from the population database, gnomAd. This is consistent with a diagnosis of X-linked Ohdo syndrome.

Discussion

X-linked Ohdo syndrome belongs to the group of x-linked *MED12* disorders, most closely related to the Maat-Kievit- Brunner Type OSMKB/ XLOS (Maat-Kievit *et al.*, 1993; Patil *et al.*, 2017). *MED12* disorders also comprise Opitz– Kaveggia syndrome and Lujan–Fryns syndrome (Vultovan Silfhout *et al.*, 2013). All *MED12* disorders have a variable degree of intellectual disability and a wide range of overlapping features (Graham and Schwartz, 2013).

The main features associated with XLOS are intellectual disability, blepharophimosis, ptosis and bulbous tip of the nose, long philtrum (Lyons, 2008). The mediator complex subunit 12 (*MED12*) gene encodes a subunit of the mediator complex that plays an integral role in RNA polymerase II transcription, thought to affect growth, differentiation, gene silencing and signalling pathways (Charzewska *et al.*, 2018). Comparative features with other reported cases can be found in Table 1. Vulto-van Silfhout *et al.*, (2013) first sequenced three unrelated patients with X-linked Ohdo syndrome, identifying missense mutations in *MED12* inherited in an X-linked pattern common to all three and sub-dividing them into a fifth distinct subtype of the known group of blepharophimosis-intellectual disability syndromes. As shown in Table 1, the key phenotypic features described in those patients are found in the proband. Narayanan and Phadke (2017), described a pathogenic missense variant located close to the proband's, in a patient with intellectual disability and facial dysmorphism but without blepharophimosis. However, this patient was 5 years old without significant medical problems, in contrast to the multisystem features in our case. Rubin *et al.*, (2020) reported an affected family with similar features of microcephaly, facial dysmorphism and congenital heart defects (specifically tetralogy of Fallot) which are reported in only 10% of XLOS syndrome patients (Patil *et al.*, 2017). Unique B-cell immunodeficiency was also reported. There has been no immunological testing on our patient to date. Micrognathia is previously reported, particularly striking in a family with two affected male siblings with an inherited missense variant (Prescott *et al.*, 2016). The elder boy required a tracheostomy in the first year of life, due to a Pierre-Robin sequence. Langley *et al.*, (2015) reported another two affected siblings with a novel missense mutation with feeding difficulties, hypotonia, microcephaly and speech delay, all of which are seen in our case. Facial features are shared in many of the cases (Table 1), including reports of long, curled eyelashes. Oligohydramnios and hydrops fetalis have been reported, however, polyhydramnios was seen in this case. Awareness that there may be airway difficulty in XLOS is important where anaesthesia is being considered, as this has not been previously documented. With the increasing availability of exome and genome sequencing, more variants in *MED12* disorders are being identified. Published variants are shown in Fig. 2. Features not noted in reviews including cleft palate, paraoesophageal hernia, tetralogy of Fallot, cerebral ventriculomegaly, and severe hypotonia could co-exist with the diagnosed *MED12* variant, or more likely represent an expansion of the known phenotype with a more severely-affected presentation. More information from long-term follow-up and other emerging cases and variants are needed.

Acknowledgements

H.M. wrote the article; V.G., J.B., H.G. and S.N. conceptualised, supervised and reviewed the article. Written consent was obtained from the patient's parents prior to publication. The variant detailed has been uploaded to the NHSconsortium DECIPHER repository.

Conflicts of interest

There are no conflicts of interest.

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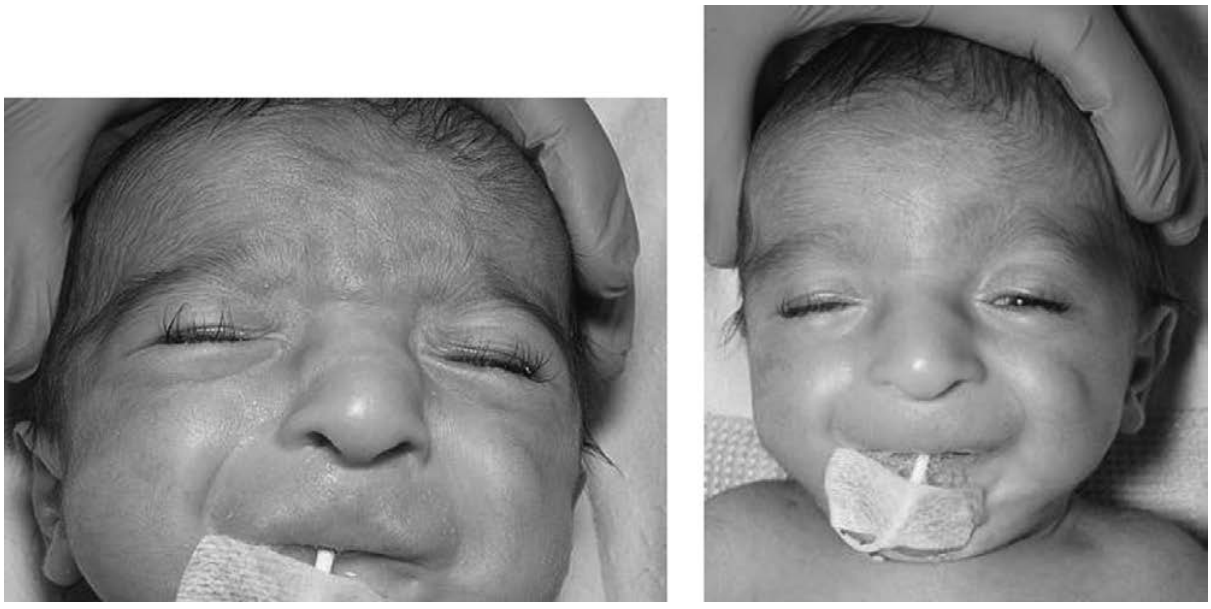

Figure 1. Facial profiles in neonatal period with prominent forehead, ptosis, blepharophimosis, hypertelorism bulbous nasal tip, smooth and long philtrum, full cheeks and micrognathia.

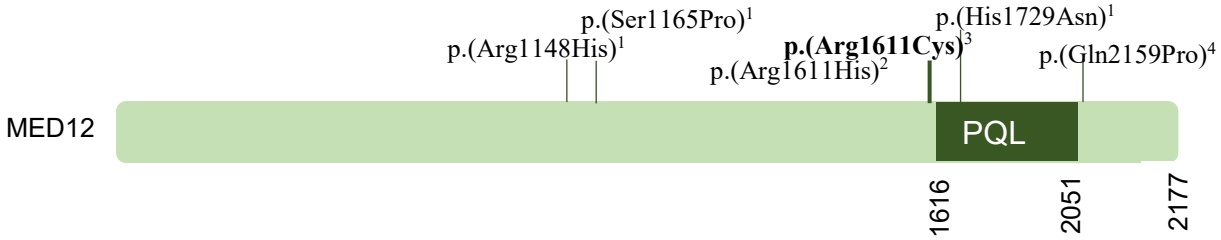

Figure 2. *MED12* variants described in patients with Ohdo syndrome. [1]Vulto-van Silfhout, A.T., et al, 2013. [2]Narayanan D.L. and Phadke S.R., 2017.[3]Described in the present study. [4]Variant reported by Rubin Z. et al, 2020.