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## Cerebrofaciothoracic Dysplasia: four new patients with a recurrent TMCO1 pathogenic variant

Running title: TMCO1-related Cerebrofaciothoracic Dysplasia

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### **Conflict of interest**

The authors declare no conflict of interest.

## **Abstract**

Biallelic loss of function variants in the *TMCO1* gene have been previously demonstrated to result in Cerebrofaciothoracic Dysplasia (CFTD; MIM #213980). The phenotype of this condition includes severe intellectual disability, as well as distinctive craniofacial features, including brachycephaly, synophrys, arched eyebrows, 'cupid's bow' upper lip, and microdontia. In addition, non-specific skeletal anomalies are common, including bifid ribs, scoliosis and spinal fusion. Only 19 molecularly confirmed patients have been previously described. Here, we present four patients with CFTD, including three brothers from a Pakistani background and an additional unrelated white Scottish patient. All share the characteristic craniofacial appearance, with severe intellectual disability and skeletal abnormalities. We further define the phenotype with comparison to the published literature, and present images to define the dysmorphic features in a previously unreported ethnic group. All of our patient series are homozygous for the same c.292\_293del (p.Ser98\*) *TMCO1* pathogenic variant, which has been previously reported only in an isolated Amish population. Thus we provide evidence that CFTD may be more common than previously thought. The patients presented here further delineate the phenotypic spectrum of CFTD and provide evidence for a recurrent pathogenic variant in *TMCO1*.

**Keywords: *TMCO1*, Cerebrofaciothoracic Dysplasia, Intellectual Disability**

## Introduction

Cerebrofaciothoracic dysplasia (CFTD; MIM #213980) is a rare, autosomal recessive, developmental disorder. It is characterized by distinctive craniofacial features (including brachycephaly, synophrys and microdontia), skeletal abnormalities, mostly affecting the ribs and vertebrae, and intellectual disability. CFTD is caused by biallelic (all reported are homozygous) loss of function variants in the TMCO1 gene (Alanay et al., 2013). Of note, Xin et al. (2010) identified a condition described as TMCO1 defect syndrome prior to the molecular basis of CFTD being identified (Alanay et al., 2013), although they did not make the link to CFTD clinically. It is now thought that TMCO1 defect syndrome is part of the CFTD spectrum (Alanay et al., 2013; Pehlivan et al., 2014).

Only 19 molecularly confirmed patients with CFTD have been reported to date (Alanay et al., 2013; Caglayan et al., 2013; Pehlivan et al., 2014; Xin et al., 2010). Here, we present three further familial patients together with an unrelated additional patient. All share a recurrent TMCO1 pathogenic variant. Description of these four new patients and review of those previously described allows further delineation of the genotypic and phenotypic spectrum of this condition.

## Subjects and Methods

### Editorial policies and Ethical Considerations

No ethical approval has been sought as this is a retrospective study with informed parental consent to publish.

## Methods

Patients 1 and 4 were identified through the Wellcome Trust Deciphering Developmental Disorders (DDD) study. Recruitment to this study was via UK regional Clinical Genetics centers after routine referral. The affected person and their parents had microarray and trio-based exome sequencing and analysis as per Wright et al. (2015). Variants identified as pathogenic were confirmed via Sanger sequencing in a clinical laboratory setting. Patients 2 & 3 were tested by Sanger sequencing for the variant found in their sibling.

## **Results**

### Clinical Reports

#### **Patient 1 (DECIPHER ID 259339)**

This male patient was born to consanguineous parents (second cousins) of North-West Pakistani origin. The pregnancy was uncomplicated. He was delivered at 35 weeks by elective cesarean section and birth weight was 3.40 kg (98<sup>th</sup> centile). He spent one day following birth in Special Care due to hypoglycemia. He first sat upright at one year of age, walked at two years, and first words were at 18 months of age.

He was initially referred to his local Genetics service at the age of 13 years and 8 months, with severe learning disability and a diagnosis of Autism Spectrum Disorder. His verbal communication was limited to sentences of a few words.

On examination, he had blue irides, synophrys, downslanting palpebral fissures, macroglossia, high arched palate, everted lower lip, low set ears, narrow chest, generalized joint laxity and adducted halluces (Fig. 1), and an intention tremor. Head circumference was on the 91<sup>st</sup> centile, height on the 98<sup>th</sup> centile and weight between the 50<sup>th</sup>-75<sup>th</sup> centiles. MRI brain and spine at the age of ten years demonstrated low lying cerebellar tonsils.

His parents advised they had two other similarly affected male children, therefore individual genetic evaluations were initiated.

#### **Patient 2 (DECIPHER ID 358411)**

Patient 2 is the brother of Patient 1. The pregnancy was unremarkable. He was delivered at 42 weeks by emergency cesarean section due to cephalopelvic disproportion, with a birth weight of 4.89 kg (98<sup>th</sup>-99.6<sup>th</sup> centiles). He had bilateral talipes equinovarus. He first smiled at the age of six months, walked at seven years and first words were at four years of age.

On assessment at the age of twenty-nine years, he had synophrys, arched eyebrows, mild hypertelorism, 'cupid's bow' upper lip, everted lower lip, high narrow palate, grooved tip of the tongue and low-set ears. There was hypermobility of the distal joints of the hands, and he had a left-sided Sprengel deformity clinically (Fig.1). His head circumference was on the 99.6<sup>th</sup> centile. His behavior was generally affable.

A chest radiograph (Fig. 2) demonstrated a dorsal scoliosis concave to the right, fused left 4<sup>th</sup> and 5<sup>th</sup> ribs posteriorly, and an un-ossified posterior end of the left 6<sup>th</sup> rib. There was also a bony bridge leading to posterior fusion of the left 7<sup>th</sup> and 8<sup>th</sup> ribs. CT head demonstrated agenesis of the corpus callosum.

### **Patient 3 (DECIPHER ID 358412)**

Patient 3 is the brother of Patients 1 and 2. Antenatal ultrasound had demonstrated an abnormal bladder, polyhydramnios, kinking of the thoracic spine and an enlarged 3<sup>rd</sup> cerebral ventricle. He was delivered at 38 weeks by elective cesarean section, with a birth weight of 4.02 kg (91<sup>st</sup>-98<sup>th</sup> centiles). At birth he was noted to have scoliosis, prominent left-sided ribs, left talipes equinovarus, a systolic heart murmur, and congenital macrocephaly (above 99.6<sup>th</sup> centile). His length at birth was on the 97<sup>th</sup> centile.

He also had a left-sided inguinal hernia, undescended left testis, Fallot's tetralogy and scoliosis, all of which required surgical treatment. He had severe congenital bilateral sensorineural hearing loss and severe developmental delay . He first sat upright at the age of six years and has never walked, but is able to bottom shuffle. He is non-verbal, and cannot feed himself.

On assessment at the age of twenty-six years, he had synophrys, mild hypertelorism, 'cupid's bow' upper lip, everted lower lip, low set and posteriorly rotated ears, gingival hypertrophy, a short neck and an intention tremor (Fig.1) . He



still has his primary dentition. His head circumference was between the 75<sup>th</sup> and 91<sup>st</sup> centiles.

Chest and spinal radiographs showed abnormalities of the spine with multiple block vertebrae in the midthoracic region associated with scoliosis. Posterior fusion defects were seen in the cervical spine, and there were multiple bifid ribs. CT head demonstrated enlarged ventricles and subarachnoid space.

#### **Patient 4 (DECIPHER ID 267516)**

Patient 4 is a white Scottish male from a non-consanguineous family. Bilateral talipes equinovarus was noted on antenatal ultrasound. He was delivered at 41 weeks gestation by elective cesarean section, with a birth weight of 3.77 kg (50<sup>th</sup>-75<sup>th</sup> centile). He had severe developmental delay. He first walked at five years of age, first words were at two years and six months of age, and he is not toilet trained.

On assessment at the age of eight years, he had brachycephaly, a flat face, frontal hair upsweep, highly arched eyebrows, hypertelorism, epicanthic folds, long eyelashes, wide nasal bridge, thin upper lip and everted lower lip. (Fig.1). His ears were low set and posteriorly rotated, and his tongue had a grooved tip. His head circumference was between the 25<sup>th</sup> and 50<sup>th</sup> centiles and height and weight both between the 50<sup>th</sup> and 75<sup>th</sup> centiles. He had three café au lait patches, and the anus was anteriorly placed. He had scoliosis and bilateral talipes equinovarus, and also primary generalized epilepsy. Radiographs demonstrated abnormal modelling and fusion of his ribs, predominantly on the right.

### **Molecular testing**

Each patient was found to be homozygous for a c.292\_293del p.(Ser98\*) TMCO1 pathogenic variant (NM\_019026.4 transcript). This variant has previously been reported in an Amish population (Xin et al., 2010). Microarray analysis for patients 1 & 4 was normal, and no additional variants were identified on exome sequencing.

### **Discussion**

TMCO1 plays an important role in the maintenance of intracellular calcium homeostasis through dynamic interaction with the endoplasmic reticulum (ER). The ER is the principle reserve of intracellular calcium. TMCO1 forms a transmembrane channel to allow calcium release in the presence of excess ER stores. Tmco1 knockout mice demonstrate several of the features of CFTD patients, including intellectual disability, craniofacial dysmorphic features and abnormal bone formation (Wang et al., 2016).

Our patient series demonstrates the characteristic features of CFTD (Fig. 1), including distinctive craniofacial dysmorphic features (4/4; 100%), rib (3/4; 75%) and vertebral (2/4; 50%) abnormalities, and severe intellectual disability (4/4; 100%). The feature of an anteriorly placed anus is novel (although this was unconfirmed by measurement or specialty consultation in this case). Further reports are needed to determine if this is part of the phenotype. The phenotype of these patients has some overlap with Kleefstra syndrome, particularly in relation to the brachycephaly, synophrys, 'cupid's bow' upper lip and low set ears. Synophrys and 'cupid's bow' upper lip are also features of Coffin-Siris syndrome. Additionally, the dysmorphic

features, especially including synophrys, and neurodevelopmental phenotype have some similarity to Cornelia de Lange syndrome. These conditions should be considered in the differential, especially in the context of normal microarray.

Xin et al. (2010) reported a series of Amish patients, sharing the same p.(Ser98\*) TMCO1 pathogenic variant as seen here. They have similar craniofacial dysmorphic features and a high prevalence of rib and/or vertebral anomalies. However, there are some notable differences. For example, all of the Amish patients had hypotonia and feeding problems; these were not seen in our series. In addition, Xin et al. (2010) reported gingival hyperplasia was a prominent feature whereas only 1 of 4 patients presented here have this. Overall, however, the two series share a strikingly similar phenotype.

Combining our series of four patients with those previously reported (Alanay et al., 2013; Caglayan et al., 2013; Pehlivan et al., 2014; Xin et al., 2010) allows further delineation of the phenotypic spectrum of this rare condition (Table 1). The majority of patients (22/23; 96%) were from consanguineous families. Neonatal hypotonia and poor feeding were seen in 16/21 (76%) patients. All patients have global developmental delay, with 4/18 (22%) non-verbal and 9/20 (45%) not able to walk. All patients have severe intellectual disability.

Common dysmorphic features include macrocephaly (12/21; 57%), brachycephaly (19/23; 83%), flat face (19/23; 83%), arched eyebrows (20/23; 87%), synophrys (22/23; 96%), hypertelorism (21/23; 91%), long eyelashes (16/21; 76%), wide nasal bridge (18/23; 78%), low set ears (23/23; 100%), microdontism (13/18; 72%) and

gingival hyperplasia (11/15; 73%). Affable behavior is often present (4/8; 50%). Rib (17/22; 77%) and vertebral anomalies (16/23; 70%) are common radiographic findings. Bilateral bifid and fused ribs are frequently seen, as well as scoliosis and spinal fusion.

As discussed, the p.(Ser98\*) TMCO1 pathogenic variant has previously been found only in a multiply consanguineous Amish community (Xin et al., 2010). This is therefore the first report of the variant outside this population. The variant is predicted to result in nonsense-mediated decay. Interestingly, the brothers reported here and the additional unrelated patient share the same variant, indicating this is a recurrent variant in TMCO1 and may represent a mutational hotspot. This variant has a small but appreciable allele frequency of 0.0001974 in Non-Finnish Europeans, according to gnomAD data (Lek et al., 2016).

In conclusion, we present four patients with CFTD due to a recurrent TMCO1 pathogenic variant, expanding the genotypic spectrum and further delineating the associated phenotype.

## **Acknowledgements**

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## **Conflict of Interest**

The authors do not have any conflict of interest to disclose.

## **Consent**

Informed consent was obtained for all subjects for inclusion in this study.

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## **Titles and legends to figures**

**Figure 1.** Patient photographs (age in years). Patient 1 a-c (13), Patient 2 d-g (29), Patient 3 h-i (26), Patient 4 j-k (1), l-o (8). Note characteristic craniofacial appearance including synophrys and arched eyebrows. Patients 1 and 2 have hypermobility of the fingers. Patient 2 also has a Sprengel deformity.

### **Figure 2.**

PA chest radiograph patient 2, age 25 years. Note likely dorsal scoliosis concave to the right. The left 4<sup>th</sup> and 5<sup>th</sup> ribs are fused posteriorly, giving the appearance of a single broad rib (arrows). The posterior end of the left 6<sup>th</sup> rib is unossified (triangle). There is a bony bridge leading to posterior fusion of the left 7<sup>th</sup> and 8<sup>th</sup> ribs (\*)