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Sibling recurrence of total anomalous pulmonary venous drainage

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ABSTRACT

Many childhood syndromic disorders are associated with congenital heart defects, but few present specifically with total anomalous pulmonary venous drainage (TAPVD). Here, we report two siblings presenting with TAPVD, tracheo-oesophageal fistula and dysmorphic features in the neonatal period. Careful examination of the mother revealed subtle facial asymmetry and a pre-auricular tag, suggesting a potential variable expression of a dominant disorder. Whole exome sequencing identified a pathogenic heterozygous mutation in *EFTUD2*, a gene, normally associated with mandibulofacial dystosis Guion-Almeida type (MFDGA), in both siblings and the mother. This is the first report of TAPVD occurring as part of the MFDGA phenotype. It serves to highlight the importance of modern sequencing panels in identifying causative mutations for heterogeneous syndromes such as MFDGA and familial congenital heart defects whilst emphasising the relevance of variable expression when counselling parents.

1. Introduction

Total anomalous pulmonary venous drainage (TAPVD) is a rare cyanotic congenital heart defect (CHD) whereby the pulmonary veins fail to drain to the left atrium, leading to respiratory distress, circulatory collapse and hypoxia. This disorder, which affects 7.1 per 100,000 live births, is thought to arise from a complex interplay of genetic and environmental factors which affect cardiac modelling during embryogenesis (Seale et al., 2010).

Several previous reports have described isolated TAPVD affecting multiple members of the same family, supporting an inherited component, but very little is known about the molecular changes which drive these abnormalities (Seale et al., 2010; Bleyl et al., 2006). A cohort of TAPVD patients in Utah with a common Scottish ancestry has served as the best resource for studying the disease. Linkage mapping with highly polymorphic microsatellite markers identified 2.48 Mb region at chromosome 4q12 which was highly preserved throughout the kinship with an estimated penetrance of 40%. Labelled as the TAPVR-1 interval, this susceptibility region contains approximately 30 genes, many of which have proposed functions in embryonic vascular modelling (Bleyl et al., 2006).

Overall, TAPVD most frequently occurs as an isolated anomaly but it is also associated with several syndromic disorders including cat eye syndrome, Holt-Oram syndrome and several heterotaxy disorders (Bleyl et al., 2006; Khan et al., 2015; Ho-Sung Kim et al., 2014). These syndromes all present with distinct extra-cardiac features and are associated with well described independent molecular abnormalities. However, the fact that they may all present with TAPVD highlights the complex genetic landscape which contributes to cardiac modelling during embryonic development. In this work, we describe two siblings with TAPVD who both carry a familial mutation in *EFTUD2*, a further novel syndromic presentation of TAPVD.

1.1. Clinical report

Sibling 1, a female, was the first child born to an unrelated Caucasian couple. This was the mother's third pregnancy, the previous two having ended in early miscarriage. The baby had been born at term by vaginal delivery and there had been no antenatal concerns. An anomaly scan at 20 weeks with dedicated cardiac views had been reported normal. Soon after birth the infant developed respiratory compromise and a subsequent echocardiogram revealed TAPVD and a tracheo-oesophageal fistula (TOF). These were both repaired surgically and the patient was transferred to the high dependency unit. On review, several dysmorphic features were noted including a small, low set, right ear and long slim feet. Diagnoses of CHARGE syndrome and VACTERL association

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were considered, however, vertebral anomalies were absent and a renal ultrasound was normal. Chromosome microarray analysis gave a normal result. Sadly, the baby succumbed on day 81.

Sibling 2, a baby boy, was delivered at 39 + 4 weeks by vaginal delivery. Antenatal scans were undertaken and did not reveal any abnormalities but were unable to rule out TOF, otherwise the pregnancy was uneventful. The baby's birth weight was 3.7 kg (50-90th Centile) and his OFC was 35 cm (50th). Apgar scores were 8 at 1 min and 9 at 5 min but soon after, whilst breast feeding, he became dusky and increasingly breathless. An urgent echocardiogram demonstrated the presence of TAPVD and a TOF which were urgently repaired. On review, several dysmorphic features were noted. He had long slim feet, a broad nasal bridge, and asymmetric opening of the mouth on crying. Small cup shaped ears were also observed with a small pre-auricular tag on the right. Blood was taken for microarray analysis to search for likely genetic causes, including 22q deletion syndrome, but no copy number variants were identified.

Since both children had been affected in a similar way, the past medical histories of each parent were explored further. The father had no medical history of note however the mother had a several interesting features. She had attended mainstream school but as a child had suffered from recurrent infections and had been born with ankyloglossia. On careful examination, it was noted that she had mild facial asymmetry and prominent ears with a small left sided pre-auricular hillock. It was suspected that the mother and both children had the same autosomal dominant disorder but with variable expression. In view of the facial asymmetry, ear, cardiac and tracheo-oesophageal defects, CHARGE syndrome was excluded by analysis of the *CHD7* gene which gave normal results. The mother became pregnant again and was offered a detailed 3D-antenatal scan of the foetus which was normal. The mother subsequently delivered a healthy baby boy. The couple opted to participate into the Deciphering Developmental Disorders (DDD) study. DNA extraction, sequencing strategy, variant calling and filtering pipelines used in the DDD study are described elsewhere (Wright et al., 2014). Results demonstrated that the mother and two children shared a heterozygous frameshift mutation in the *EFTUD2* gene caused by a deletion (NM_004247.3:c.944delG) predicted to result in a loss of function frameshift mutation (p.Ser315fs). Details of this variant are available on DECIPHER under ID Number 271922. This mutation was confirmed by Sanger sequencing in both children and the mother in an NHS diagnostic laboratory.

2. Discussion

This case highlights the association of syndromic TAPVD with mutation of the *EFTUD2* gene. This gene encodes for the highly conserved GTPase U5-116KD which forms a major part of the spliceosome (Lehalle et al., 2015). In murine models this protein is widely expressed during embryogenesis and appears to be particularly upregulated in regions of mesenchymal outgrowth, suggesting an important regulatory function (Gordon et al., 2012). Mutations in *EFTUD2* are known to cause mandibulofacial dystosis Guion-Almedia type (MFDGA). A recent review of *EFTDU2* haploinsufficiency-related phenotypes demonstrated the variable

Table 1
Differential Diagnoses. This table highlights the phenotypic similarities and differences between several differential diagnoses for *EFTDU2* mutations. OAVS: Oculo-Auriculo-vertebral syndrome. VSD: Ventricular Septal Defect. AVS: Atrioventricular Septal Defect. TOF: Tetrology of Fallot. HLHSL: Hypoplastic Left Heart Syndrome. DORV: Double Outlet Right Ventricle.

	OAVS	22qDel	CHARGE	VACTERL	*EFTUD2*
Facial Asymmetry	Present in 83%	Present in 14%	Absent (Facial Nerve Palsy in 21%)	Unusual	Facial Palsy or Asymmetry Common
Neurocognitive Phenotype	Delay in Speech (9%) and Motor (14%) Development	Developmental Delay in 80% of Patients	Developmental Delay in 70% of Patients	Patients Do Not Tend to Have Neurocognitive Impairment.	Psychomotor Delay (96%)
Auricular Phenotype and Hearing	• Almost All Have Microtia or Pre-Auricular Tags • 85% Are Hearing Impaired	• Small Ears • Hearing Impairment Documented in 20–60%	• Cup shaped in 95–100% • Absent semi-circular canals & Deafness	Unusual	• Hearing Loss (77%) • Pre-auricular Tags (43%)
Tracheo/Oesophageal Abnormalities	**5%** Tracheoesophageal Fistula and Atresia	Unusual	**38%** Laryngotracheal Defects	**50–80%** Most Commonly Tracheo-Oesophageal Fistulas	**37%** Most Commonly Oesophageal Atresia
Limb Abnormalities	**12%** (Thumb Hypoplasia/Pes Adductus/Polydactyly)	Most Patients Have Characteristic Long Tapered Fingers	**37%** (Classically Polydactyly or Abnormal Palmer Creases)	**40–50%** (Classically Radial Anomalies or Thumb Aplasia)	**40%** (Proximally Placed or Hypoplastic Thumbs)
Congenital Heart Defects	**15%** (50% VSD/12.5% AVS)	**75%** (26% TOF/43% VSD)	**66%** (20% TOF/10% HLHS)	**67%** (58% VSD/7% TOF/7% DORV)	**41%** (19% VSD/19% ASD)
Anogenital abnormalities	**13%** Hypospadias/ Cryptorchidism	Very Rarely Affected	**50–70%** Genital Hypoplasia	**21%** Cloacal Anomalies/GU Fistulae	**9%** Cryptorchidism
Renal Anomalies	**7%** (75% Renal Agenesis or Hypoplasia)	**36–37%** (17% Absent or Dysplastic/ 10% Obstruction/4% Reflux)	**20%** (6% Horseshoe Kidney/6% Reflux/4% Cysts)	**50–80%** (Renal Agenesis/Horseshoe Kidney/Cysts)	**9%** (21% Renal Agenesis/7% Reflux)
Orofacial clefting	**40%** (43% Lateral/24% Palate)	**10%** Cleft Palate	**36%** (64% Lip & Palate)	Unusual	**33%** Cleft Palate
Common Ocular Abnormalities	Coloboma	Coloboma, Anterior Segment Dysgenesis	Coloboma (70%)	Absent	Epibulbar Dermoid, Strabismus, Astigmatism
Vertebral anomalies	**19%** Hemi-Vertebrae/ Hypoplasia	**47%** Scoliosis	**13%** Bony Scoliosis	**60–80%** Hemi-Vertebrae/Fusions	**17%** Kyphosis/Scoliosis
Other Features	• Short stature (13%) • Microcephaly (8%)	• Neonatal Hypocalcaemia • Immune Deficiency	• Choanal atresia (65%) • Immune Deficiency	• Imperforate Anus (55–90%)	• Epilepsy (22%)
Molecular Abnormality	No Consistent Molecular Cause Identified.	Microdeletion of Chromosome 22q11.2	Heterozygous Mutations or Deletions Affecting *CHD7*	No Consistent Molecular Cause Identified.	Mutations in *EFTUD2*