Severe short rib thoracic dysplasia-16 associated with the c424C>T pathogenic variant in the Intra Flagellar Transport 52 (*IFT52*) gene

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Introduction

Short-rib thoracic dysplasia (SRTD) refers to a group of autosomal recessive inherited disorders with an incidence of 1:100,000[1-5]. It is categorized as a skeletal ciliopathy characterized by constricted thoracic cage, short ribs, shortened tubular bones, and a 'trident' appearance of the acetabular roof. The group includes Ellis-van Creveld syndrome, Jeune syndrome or asphyxiating thoracic dystrophy, short rib-polydactyly syndrome, and Mainzer-Saldino syndrome[6]. Some forms of SRTD are lethal in the neonatal period due to respiratory insufficiency secondary to a severely restricted thoracic cage, whereas others are compatible with life[6]

An important gene associated with SRTD-16 is Intra Flagellar Transport 52 (*IFT52*) which is essential for the maintenance of the IFT-B core and the overall IFT-B complex, which in turn is involved in anterograde transport[7]. *IFT52* mutant cells demonstrate reduced synthesis of IFT74, IFT81, IFT88 and ADP Ribosylation Factor like GTPase 13B (ARL13B), other key anterograde complex members[7]. IFT complexes are vital for the functioning of primary cilia. *IFT52* mutations result in a ciliopathy with primary effects on the skeleton[7]. Defects in several components of IFT complexes cause a spectrum of ciliopathies with variable involvement of skeleton, brain, eyes, ectoderm and kidneys giving phenotypic heterogeneity[8].

There are only a few reported cases of SRTD-16 associated with *IFT 52* (Humam Gene Mutation Database). Girisha KM, *et al*[8] (2016) reported the first human skeletal ciliopathy associated with a nonsense variant in *IFT52*, in a child from a consanguineous family who had characteristic skeletal abnormalities and pigmentary retinopathy[8]. Chen X et al described a patient with homozygous missense variation in *IFT52* having ciliopathy suggesting mild SRTD and Leber congenital amaurosis (retinal ciliopathy)[9].

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We report two siblings, the offspring of consanguineous parents, affected with SRTD-16. Both showed similar skeletal abnormalities (short limbs, polydactyly, narrow thorax) and both died within the first few weeks of life due to respiratory compromise. Whole-exome sequencing in the second child revealed a homozygous c424C>T, p. Arg142* of the *IFT52* gene, which confirmed the diagnosis of SRTD type 16.

Case report

A newborn baby boy of a consanguineous couple presented at birth with respiratory distress. The baby was delivered at 38 weeks of gestation by elective lower segment caesarean section with a birth weight of 4 kg. Her antenatal scan showed the fetus to have short limbs with polyhydramnios. The Apgar score was 4 at 1 minute, 8 at 5 minutes and 9 at 10 minutes and the baby needed resuscitation at birth.

On examination, the baby had short limbs, a short, constricted thorax with protuberant abdomen, postaxial-polysyndactyly and brachydactyly in both upper and lower limbs. He also had frontal bossing, a flat, broad nasal bridge, low set ears, posterior cleft palate and small genitalia (Figures 1-3).

Figure 1: ***Polydactyly in upper limbs***

Figure 2: ***Bell shaped thorax***

Figure 3: ***Polydactyly in lower limbs***

His skeletal survey revealed a narrow, bell-shaped thorax with short, horizontally oriented ribs and high riding clavicles (Figure 4).

Figure 4: ***Chest x-ray showing bell-shape thorax with horizontally oriented ribs and high riding clavicles***

There were shortened tubular bones and a 'trident' appearance of the acetabular roof. The abdominal ultrasound scan revealed increased echogenicity in both kidneys, multiple liver calcifications and mild hepatomegaly. Ultrasound scan of the brain showed mildly dilated lateral and fourth ventricles. Echocardiography revealed an atrial septal defect. His ophthalmic evaluation was unremarkable. His blood investigations were normal apart from mildly elevated liver enzymes.

His respiratory distress was initially managed with continuous positive airway pressure (CPAP) but progressively worsened with significant respiratory acidosis. Hence, from day 4 onwards the baby was mechanically ventilated. He had one episode of pneumonia and necrotizing enterocolitis. It was difficult to wean the baby off the ventilator and he had to be kept in low ventilatory settings for a month. He was discharged on domiciliary oxygen and nasogastric feeds on day 45. Both parents were informed regarding the seriousness of the disorder, the predicted quality of life and the risks and benefits of treatment. He succumbed at home, three days after discharge.

Whole-exome sequencing revealed homozygous pathogenic variants affecting *IFT52* which is reported in association with SRTD 16 with polydactyly. He was the second child of this family. The elder child too had similar clinical and radiological features and was on a ventilator until day 33 when he passed away due to ventilator-associated pneumonia. However, genetic testing has not been performed on him. Having had two infantile deaths with similar features compounded by the consanguinity and the relatively young age of the mother, both parents were deeply concerned about their future pregnancies. Hence, genetic counselling was arranged. We were unable to confirm the carrier status in the parents due to financial constraints but there is a likely risk of 25% for their future pregnancies.

Discussion

SRTD is a genetically heterogeneous group of autosomal recessive skeletal ciliopathies characterized by a constricted thoracic cage, short ribs, shortened tubular bones, and a trident appearance of the acetabular roof. There is a phenotypic overlap in the various forms of SRTD depending on the presence of visceral malformation and metaphyseal appearance. Non-skeletal involvement includes craniofacial, brain, cardiac, gastrointestinal, and genitourinary system abnormalities[4].

A newborn born to consanguineous parents, presenting with respiratory distress, having short limbs, a short, constricted thorax with a history of a sibling who had similar features, were the key factors leading to our clinical diagnosis of SRTD syndrome. Characteristic radiological features such as a narrow, bell-shaped thorax with short, horizontally oriented ribs and high riding clavicles, shortened tubular bones and a 'trident' appearance of the acetabular roof, further supported this diagnosis.

Phenotypic and genetic heterogeneity led us to perform whole exome sequencing, which revealed homozygous *c424C>T, p.Arg142** of the *IFT52* gene, confirming the diagnosis of SRTD type 16.

Only a few cases of SRTDP-16 have been described in the literature (Humam Gene Mutation Database). Chen X *et al*[9] (2018) reported a 5-year-old child with mild SRTD and Leber congenital amaurosis having homozygous missense variation in *IFT52*. Dupont MA, *et al*[2] (2019) reported *IFT52* mutations associated with SRTD and multi-cystic dysplastic kidneys. Girisha KM, *et al*[8] (2016) reported a 3-year-old Indian girl with the same *IFT52 c424C>T* mutation. There are several similar clinical features between the two (short and narrow thorax with a protuberant abdomen, short limbs, post axial polydactyly, brachydactyly, depressed nasal bridge, low set ears). However, in contrast to our patient she had only mild respiratory complications.

Even though whole exome sequencing is helpful in making a diagnosis and genetic counselling, caution regarding prognosis is needed based on a single case report. Since the patients with this disorder have variable disease expression[4] and can live up to adulthood if they survive the neonatal period, it is worthwhile managing the neonatal period intensively.

Declaration of parental consent for publication

The authors certify that they have obtained written informed consent from the parents of the neonate to publish the case report.

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