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Detection of Spondyloepiphyseal Dysplasia Phenotype with *CHST3* Mutation in an Asian Indian Family and Outcomes of Index and Subsequent Pregnancy

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Abstract

CHST3-related skeletal dysplasia is an autosomal recessive disorder with a prenatal onset. Variations in the *CHST3* gene are associated with spondyloepiphyseal dysplasia with short stature of prenatal onset; dislocation of the knees, hips or elbows; club feet; postnatal limitation of range of motion of large joints; and progressive kyphosis, occasional scoliosis and minor heart valve dysplasia. The identification of pathogenic variants in the family is helpful for carrier and prenatal testing. We describe the prenatal identification of spondyloepiphyseal dysplasia with *CHST3* mutation in the index pregnancy of an Asian Indian woman and the outcome of the subsequent pregnancy.

Keywords
- spondyloepiphyseal dysplasia
- *CHST3* mutation
- prenatal diagnosis
- pregnancy
- fetus

Introduction

CHST3-related skeletal dysplasia (SKD) is an autosomal recessive disorder characterised by short stature and shortening of long bones and the presence of clubfeet.[1] The common differential diagnosis for *CHST3*-related SKD includes autosomal dominant Larsen syndrome caused by changes in the FLNB gene[2] and spondyloepiphyseal dysplasia congenita (SEDC) that often occurs due to a new or de novo mutation with no previous family history.[3] In this case report, we describe the prenatal identification and phenotype of SED with *CHST3* mutation and the genetic workup required to reach the molecular diagnosis in the index pregnancy of an Asian Indian family and the outcomes of the subsequent pregnancy in the same woman.

Case Report

A 24 year old woman (G2P0L0A1) in a non-consanguineous marriage, with a history of anembryonic gestation in her first pregnancy, presented in the first trimester of pregnancy for antenatal assessments. The first trimester nuchal translucency

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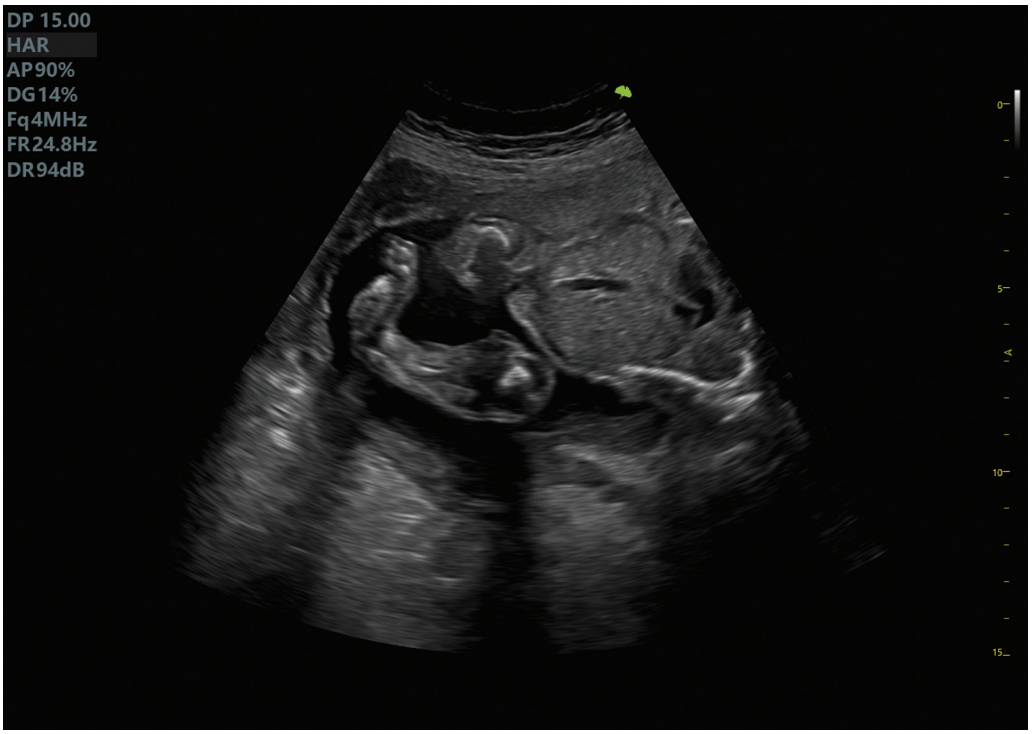

Fig. 1 Ultrasound assessment in the second trimester showing shortening of the lower limb with loss of perpendicular angulation between the long axis of the leg and foot.

scan and double marker screening test for aneuploidy were normal in this pregnancy (her second pregnancy; hereafter mentioned as the index pregnancy). An ultrasound assessment at 18 gestational weeks showed reduced fetal growth, shortening of the long bones (►**Fig. 1**) and talipes equinovarus (►**Fig. 2**). An ultrasound scan at 22 gestational weeks confirmed SKD with bilateral shortening of the femur, tibia, fibula, humerus, radius and ulna, and rocker bottom feet. There were no other skeletal abnormalities. The biparietal diameter (BPD), head circumference and abdominal circumference (AC) corresponded to the gestational age (GA). All long bones showed a growth lag of 2.2 to 4.5 standard deviations (SDs) below the mean for GA. Femur length (FL) was 4 SDs below the mean for GA (3.29 cm at 24 weeks 3 days, corresponding to a size of 20

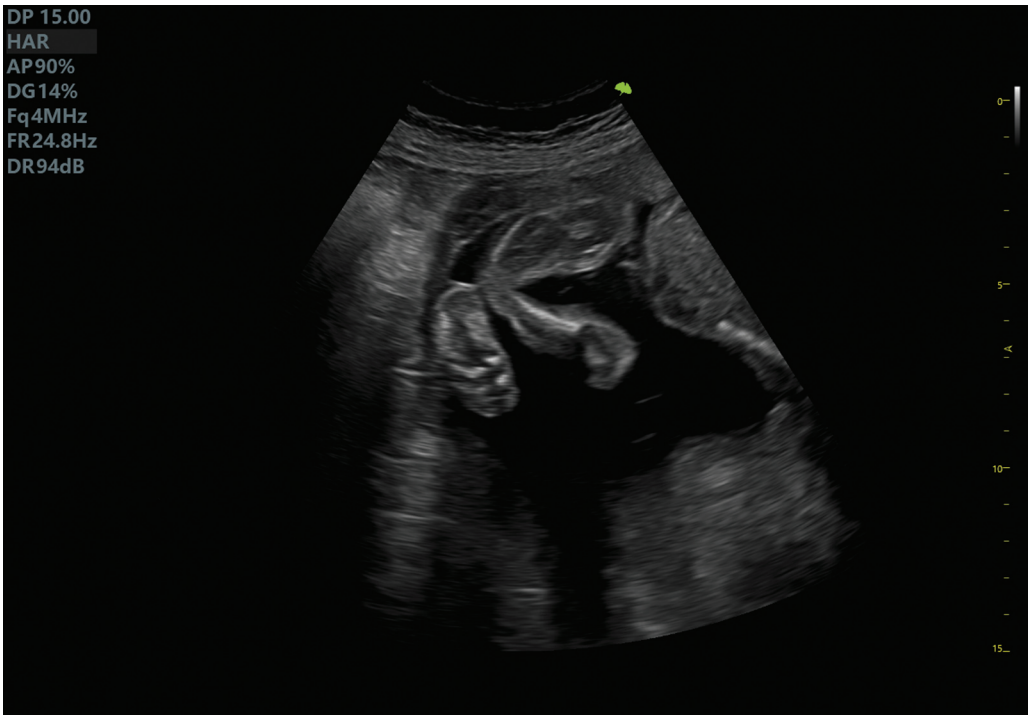

Fig. 2 Ultrasound image of the lower limb in the second trimester showing inward rotation of foot suggestive of talipes equinovarus.

weeks 2 days), femur to foot length ratio was 0.75 (1.0–1.1) and the FL/AC ratio was 0.17. The femur-to-foot length ratio below 0.87 discriminates between intrauterine growth restriction and severe SKD. Humeral length was 3.43 cm, corresponding to 21 weeks 5 days and was at –2.7 SD. There was no narrowing of the thoracic cage and chest circumference (CC)/AC ratio was 0.84. The fetus was considered suspect for a *non-lethal SKD* and skeletal abnormalities. There was no similar obstetric history or genetic or chromosomal anomaly in the family. The parents chose to terminate the pregnancy at 24 gestational weeks and agreed to further genetic assessments. The abortus (►**Fig. 3**) was sent for a fetal autopsy, an X-ray (►**Fig. 4**) and a whole-exome sequencing. The X-ray abortus confirmed the ultrasound findings and revealed an elbow joint dislocation.

The extracted deoxyribonucleic acid libraries were sequenced[4,5] and copy number variants were detected from VarSeq 2.2.3 in addition to single nucleotide variants and small indels.[6] Clinically relevant mutations were annotated using published variants in literature and disease databases that included ClinVar, Online Mendelian Inheritance in Man, Genome-Wide Association Studies, Human Gene Mutation Database (v2020.2) and SwissVar.[7–11] The exome sequencing reported likely compound heterozygous variants (1a and 1b) in the *CHST3* gene and a heterozygous variant (2) in the *LBR* gene. Variant 1a: *CHST3* (NM_004273.5): c.491C > T, p.Pro164Leu. This variant has previously been reported in individuals affected by SED[10] and has been reported as pathogenic in the ClinVar database (Variation ID: 478823).[12] Variant 1b: *CHST3* (NM_004273.5): c.500A > G, p.His167Arg. At the time of analysis, the variant was not reported in association with the disease and was classified as a variant of uncertain significance, but considering recent evidence, it has been re-classified as likely pathogenic and reported as likely pathogenic in the ClinVar database (Variation ID: 1679884).[12] Variant 2: *LBR* (NM_0002296.4): c.746C > A, p.Ala249Asp. At the time of analysis, the variant was not reported in association with the disease and was classified as a variant of uncertain significance, but recently has been reported as likely benign in the ClinVar database (Variation ID: 295943).[13]

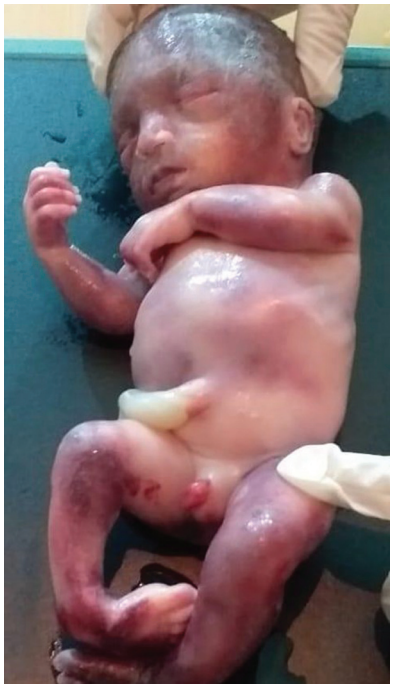

Fig. 3 Abortus showing shortening of long bones and bilateral talipes equinovarus.

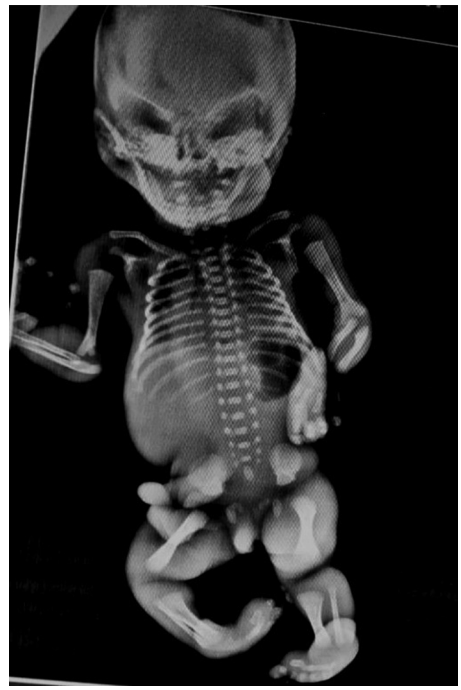

Fig. 4 X-ray abortus image: X-ray of the index child abortus at 24 weeks of gestation showing short and stubby femur, tibia-fibula and radius-ulna on both sides, bilateral talipes equinovarus and dislocation of the right elbow joint. Bilateral humeri also appear small. Central skeleton in the form of thoracic cage, spine, pelvis and skull shows no remarkable findings of skeletal dysplasia. Bone mineralisation of the axial and central skeleton both appears normal. There are no fractures or epiphyseal stippling. Bilateral scapulae and clavicles also appear normal.

Subsequent segregation analysis was done on the parents for the *CHST3* gene variants. Variant 1a (c.491C > T) was detected in a heterozygous state in the mother, whereas variant 1b (c.500A > G) was detected in a heterozygous state in the father, thus confirming their carrier status of the disorder and the compound heterozygosity of the variants. As for the *LBR* gene variant, it was deemed less likely to be causative based on the limited phenotypic match, conflicting/benign in silico predictions, zygosity (heterozygous for an autosomal recessive disorder) and high population for an autosomal dominant disorder. The woman presented at 6 gestational weeks (G3P0L0A2) to confirm pregnancy after an inter-pregnancy interval of 8 months. The first-trimester ultrasound assessment at 11 weeks showed a single, live, normal fetus. Chorionic villus sampling (CVS) was done at 12 weeks of gestation, and Sanger sequencing was done. *CHST3* gene variant 1a was not detected in this fetus, while *CHST3* gene variant 1b was detected in a heterozygous state. The fetus was considered less likely to be affected by the *CHST3*-associated phenotype (SED with

congenital hip dislocation). The karyotype testing of the fetus was reported as normal. Second trimester and third trimester assessment at 33 gestational weeks showed normal interval growth, normal biometry and normal fetal Doppler studies. The assessment at 37 gestational weeks was normal except for late-onset stage 1 fetal growth restriction with mild oligohydramnios (amniotic fluid index of 8). The FL/AC ratio at 37 weeks was 22% (20–24%) and FL/BPD was 79% (71–87%) and the BPD was –1.4 SD, head circumference was –2.8 SD, AC was –1.7 SD and FL was –1.5 SD. The FL-to-foot length ratio was 1.02. The woman delivered a healthy male baby weighing 2.4 kg through a caesarean section at 37 gestational weeks. The newborn screening for inborn error of metabolism was normal.

Informed consent was obtained from the parents to use anonymised images for publication.

Discussion

This case highlights the importance of prenatal ultrasound assessment, appropriate genetic testing and a high index of suspicion to identify SED early in the prenatal phase. Variations in the *CHST3* gene are associated with SED with congenital joint dislocations,[1] which is a very rare bone disorder characterised clinically by short stature of prenatal onset, dislocation of the knees, hips, or elbows and club feet. There is a postnatal limitation of range of motion of large joints, progressive kyphosis and occasional scoliosis. In a few patients, minor heart valve dysplasia has also been described. Intellect, vision and hearing are usually normal.[1] At conception, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier and a 25% chance of being unaffected and not a carrier.[1] Ultrasound assessments in the second trimester of pregnancy are helpful in identifying skeletal abnormalities that can indicate SED.[14] Advancement in ultrasound resolution has led to prenatal diagnosis of SKD as early as the late first trimester. Differentiation between lethal and non-lethal ones is mainly based on criteria like FL (►**Fig. 5** shows normal range), lung volume, FL/AC, thoracic circumference (TC)/AC, FL/foot length ratio and bone mineralisation. Lethal ones present earlier than non-lethal, with narrow thoracic cavities playing a major role in lethality due to lung hypoplasia and respiratory difficulties. In lethal SKD, the FL is > 4 SD below the mean (–4 SD in this case), the CC/AC ratio is < 0.6 (0.84 in this case) and the FL/AC ratio is < 0.16 (0.17 in this case). Three-dimensional lung volume is < 5% for GA in lethal SKD. However, we did not measure lung volume in this case. FL/foot length ratio was 0.75 (1.0–1.1) in normal range, and > 0.87 is seen in intrauterine growth restriction, discriminating it from severe SKD (►**Table 1**).

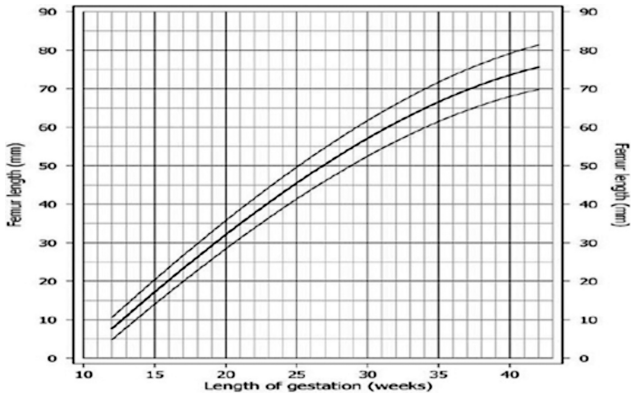

Fig. 5 Normal range of femur length.

Table 1 Discriminants of lethality in skeletal dysplasia

Parameter	Likely lethal	Likely non-lethal
Short femur	> 4 SD below mean for GA	< 4 SD
3D lung volume [up to 32 wk]	< 5% for GA	≥ 5% for GA
FL/AC	< 0.16	> 0.16
CC/AC	< 0.6	> 0.6

Abbreviations: 3D, three-dimensional; AC, abdominal circumference; CC, chest circumference; FL, femur length; GA, gestational age; SD, standard deviation.

The prenatal differential diagnosis for *CHST3*-related SKD includes autosomal dominant Larsen syndrome,[2] caused by a mutation in the FLNB gene, with ultrasound features of clubfoot and joint dislocations, facial dysmorphism with hypertelorism, mid-facial hypoplasia, prominent forehead, depressed nasal bridge, square-shape fingertips, shortened long bones, cleft palate and spine curvature abnormality. Spatulate thumb and kyphoscoliosis differentiate it from the CHST3 mutation phenotype. The most common joints involved are the hip, knee and elbow.[2] The other differential diagnosis is autosomal recessive diastrophic dysplasia caused by mutations in SLC26A2. Along with long bone shortening and club foot, there is a peculiar "hitchhiker thumb." The spine is usually normal, and instead of joint dislocation, there is joint stiffness and restricted movements (arthrogryposis).[15] Desbuquois dysplasia caused by homozygous or compound heterozygous mutation in the CANT1 gene shares a common finding of long bone shortening and joint dislocations with specific coronal clefts in the spine and mid-facial hypoplasia with prominent eyes. Autosomal dominant SEDC caused by COL2A1 gene mutation or de novo, shows long bone shortening and joint dislocation. Homozygous mutations in IMPAD1 cause chondrodysplasia with joint dislocations. The characteristic features apart from the shortening of long bones are facial dysmorphism, micrognathia, cleft palate, high forehead and broad nasal bridge. Brachydactyly, short metacarpals and radial deviation of first phalanx known as the "hitchhiker" thumb are also seen as very similar to that in diastrophic dysplasia. The absence of significant vertebral anomalies distinguishes it from desbuquois dysplasia and CHST3 mutation. The presence of knee dislocation and facial dysmorphism differentiate this condition from diastrophic dysplasia.[16]

In this case, the prenatal identification of SKD on ultrasound helped to counsel the parents for genetic testing of the abortus and themselves. This helped to identify the different

carrier statuses of the parents to counsel for CVS tests and develop a customised antenatal care schedule for the woman in the subsequent pregnancy.

Data Availability Statement

The data pertaining to this case can be shared on reasonable request and for reasonable purposes.

Patient Consent Statement

The patient provided informed consent for the anonymised use of images and case descriptors.

Authors' Contributions

S.G. performed the ultrasound and X-ray fetogram of the index pregnancy, clinical counselling for the parents, the ultrasound assessments of the subsequent pregnancy and wrote the manuscript. O.P.G. and N.K.J. provided the obstetric care and management for the patient, clinical counselling for the parents and reviewed the manuscript. G.M.T. performed the first and second trimester ultrasound assessments of the index pregnancy and reviewed the manuscript. S.C. and S.K. were involved with the genetic testing protocols and genetic counselling and reviewed the manuscript.

Conflict of Interest

None declared.

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