First Trimester Identification of a Recurrent Case of Short-rib Thoracic Dysplasia due to Novel *NEK1* Variations with Small Thorax and Polydactyly

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Dear Editor,

Skeletal dysplasias comprise a very heterogeneous group of disorders, which include more than 400 types and affect the development of the bones.[1] Among these, short-rib thoracic dysplasia (SRTD) with or without polydactyly is a handful of autosomal recessive skeletal ciliopathies, characterized by a small thoracic cage, short ribs, shortened tubular bones, and a trident acetabular roof. We here report a prenatal case of *NEK1*-associated SRTD diagnosed in the first trimester.

A 30-year-old woman requested genetic counseling in the first trimester of pregnancy because of a positive reproductive history. The couple was healthy and nonconsanguineous. They had a healthy son. Their second pregnancy ended with interruption at 18 weeks due to short limbs and polydactyly in the female fetus. At this referral, the first trimester ultrasound showed a normal nuchal translucency (NT) with a crown-rump length of 55 mm. A small thorax and postaxial polydactyly of the right hand were demonstrated [Figure 1a-c]. Chorionic villus sampling was performed, and exome sequencing was used as the first-tier test, considering the possibility of a recessive disorder due to recurrence of the same anomaly. This approach revealed two novel heterozygous *NEK1* variants, c. 607-1G>C (pathogenic) and EX25-26del (likely pathogenic) in the fetus, inherited from the father and mother, respectively. Homozygous or compound heterozygous loss-of-function *NEK1* variants have been associated with SRTD type 6.[2]

At 18 weeks, a follow-up ultrasound identified shortened long bones, short ribs, narrow thorax, and postaxial polydactyly of the right hand [Figure 1d-g]. The pregnancy was terminated by parental request. External examination of the aborted male fetus confirmed prenatal findings. The couple declined X-rays.

Multidisciplinary team discussions determined that the *NEK1* variants were likely to fully explain the phenotypic findings in the fetus, which are in accordance with SRTD.

SRTD can be diagnosed in utero, usually based on second-trimester ultrasound examination. The findings include short ribs, constricted thorax, shorten long bones, and possible associated anomalies in major organs such as the brain, heart, kidneys, and genitalia. However, first-trimester identification of SRTD is challenging. For example, in recent ISUOG practice guidelines of 11–14-week ultrasound scan,[3] assessments of limbs only demonstrate the presence of the three segments of arms and legs, and the presence and normal orientation of the two hands and feet. In this study, a positive reproductive history triggered a detailed first trimester scan. The identification of small thorax and polydactyly promoted the use of exome sequencing to achieved a confirmative diagnosis.

Earlier identification of fetal structural anomalies gives patients more time for genetic diagnosis, and as a result for considering their options. Although early anatomical evaluation requires trained and experienced sonographers and high-resolution machines with debated cost/benefit ratio in the general population,[4] we believe this technique should be available at least in high-risk pregnancies. To date, at least 123 genes have been reported to be associated with skeletal dysplasias.[5] Exome sequencing has become the choice in the diagnostic workup of genetically heterogeneous disorders. This case report presents another example that showcases the effective usefulness of first-trimester ultrasound, combined with genomic testing, in early prenatal diagnosis of genetic syndromes.

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Received: 16-07-2024 **Revised:** 31-08-2024 **Accepted:** 03-09-2024 **Available Online:** 11-06-2025

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_88_24

How to cite this article: Chen YS, Li DZ. First trimester identification of a recurrent case of short-rib thoracic dysplasia due to novel *NEK1* variations with small thorax and polydactyly. J Med Ultrasound 2025;33:287-8.

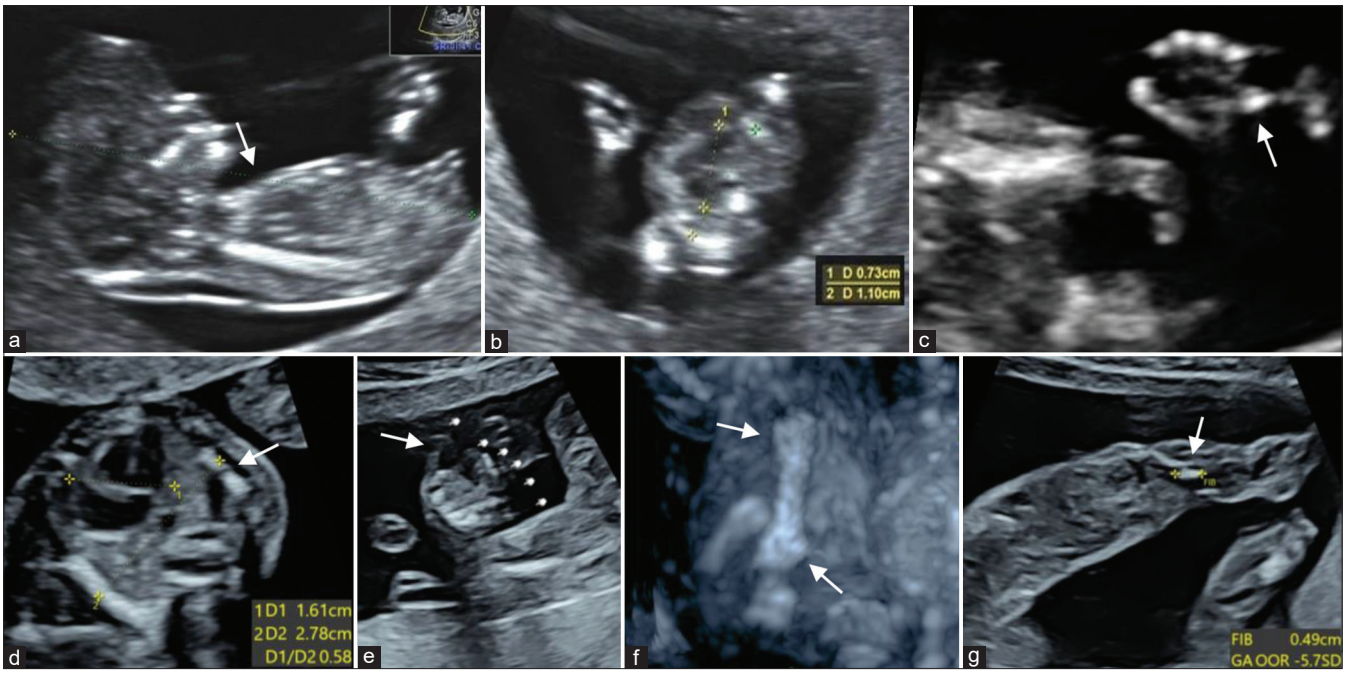

Figure 1: A fetus of short-rib thoracic dysplasia caused by *NEK1* variants. (a) The sagittal plane of the fetus showing a small chest at 12 weeks; (b) a narrow thorax characterized by an increased cardiothoracic ratio (CTR; 0.66) at 12 weeks; (c) polydactyly of the right hand at 12 weeks; (d) a narrow thorax characterized by an increased CTR (0.58) and short rib (arrow) at 18 weeks; (e) polydactyly of the right hand at 18 weeks (arrow); (f) large metaphyses of the femur (arrows) at 18 weeks; (g) very short fibula at 18 weeks

Abbreviations

del	Deletion
EX	Exon
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
NEK1	NIMA Related Kinase 1
NT	Nuchal translucency
SRTD	Short-rib thoracic dysplasia

Ethics statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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