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Case Report

Prenatal diagnosis and molecular genetic analysis of short rib-polydactyly syndrome type III (Verma-Naumoff) in a second-trimester fetus with a homozygous splice site mutation in intron 4 in the *NEK1* gene

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Abstract

Objective: To demonstrate perinatal imaging findings and to investigate the mutation in the *NEK1* gene in a fetus with type III short rib-polydactyly syndrome (SRPS) (Verma-Naumoff).

Case Report: A 34-year-old woman with no past history of fetal SRPS was referred to the hospital at 21 weeks of gestation because of sonographic diagnosis of short limbs in the fetus. Fetal ultrasound revealed a narrow thorax, short ribs, short limbs with marginal spurs, and postaxial hexadactyly in both the hands and feet. A diagnosis of SRPS III (Verma-Naumoff) was made. Amniocentesis was performed. The karyotype was 46,XY. Molecular genetic analysis of the amniotic fluid cells identified a homozygous splice site mutation in intron 4 (c.331-1 A > G) or IVS4-1 A > G in the *NEK1* gene. The parents were heterozygous for the mutation. The pregnancy was subsequently terminated and a malformed fetus was delivered with prominent forehead, a flattened nasal bridge, a narrow and short trunk, a protuberant abdomen, bilateral postaxial polydactyly and syndactyly of the hands and feet, and micromelic limbs. No facial cleft or genital abnormality was noted. The radiograph was consistent with SRPS III.

Conclusion: Polydactyly, micromelia, metaphyseal spurs, widened humeral metaphyses, and shortened ribs can be prominent prenatal ultrasound findings of SRPS III. The present case provides evidence for a correlation of a mutation in the *NEK1* gene with SRPS III.

Keywords: NEK1; prenatal diagnosis; short rib-polydactyly syndrome type III; ultrasonography; Verma-Naumoff

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Introduction

Short rib-polydactyly syndromes (SRPSs) are a group of autosomal recessive osteochondrodysplasias caused by ciliary dysfunction and characterized by short ribs, polydactyly, short limbs, multiple abnormalities of the internal organs including kidneys, heart, liver, pancreas, genitalia, and intestines. Five types of SRPS have been recognized such as SRPS I (Saldino-Noonan; OMIM 263530), SRPS II (Majewski; OMIM 263520), SRPS III (Verma-Naumoff; OMIM 263510), SRPS IV (Beemer-Langer; OMIM 269860), and SRPS V (OMIM 614091). The different subtypes of SRPS may be a single genetic disorder with variable expressivity because of significant phenotypic overlap in different subtypes [1]. SRPS III (Verma-Naumoff) is characterized by polydactyly, micromelia, metaphyseal spurs and occasional situs inversus totalis [2,3]. Here, we present our experience of prenatal diagnosis and molecular genetic analysis of SRPS III in a second-trimester fetus associated with a homozygous splice site mutation in intron 4 in the *NEK1* gene. Such an association is novel and has not been previously described.

Case report

A 34-year-old, gravida 3, para 1, woman had undergone amniocentesis at 17 weeks of gestation because of advanced maternal age, and the result revealed a karyotype of 46,XY. Her husband was 46 years old. The woman and her husband were non-consanguineous, and they had a healthy 6-year-old daughter. The woman had experienced spontaneous abortion twice, but cytogenetic analysis of the couple had revealed normal karyotypes. During this pregnancy, the pregnancy was uneventful until 21 weeks of gestation when level II ultrasound revealed a narrow thorax, short ribs, short limbs with marginal spurs, and postaxial hexadactyly in both hands and feet in the fetus (Fig. 1). The thoracic circumference (TC) was 12.17 cm (< 5th percentile), and the abdominal

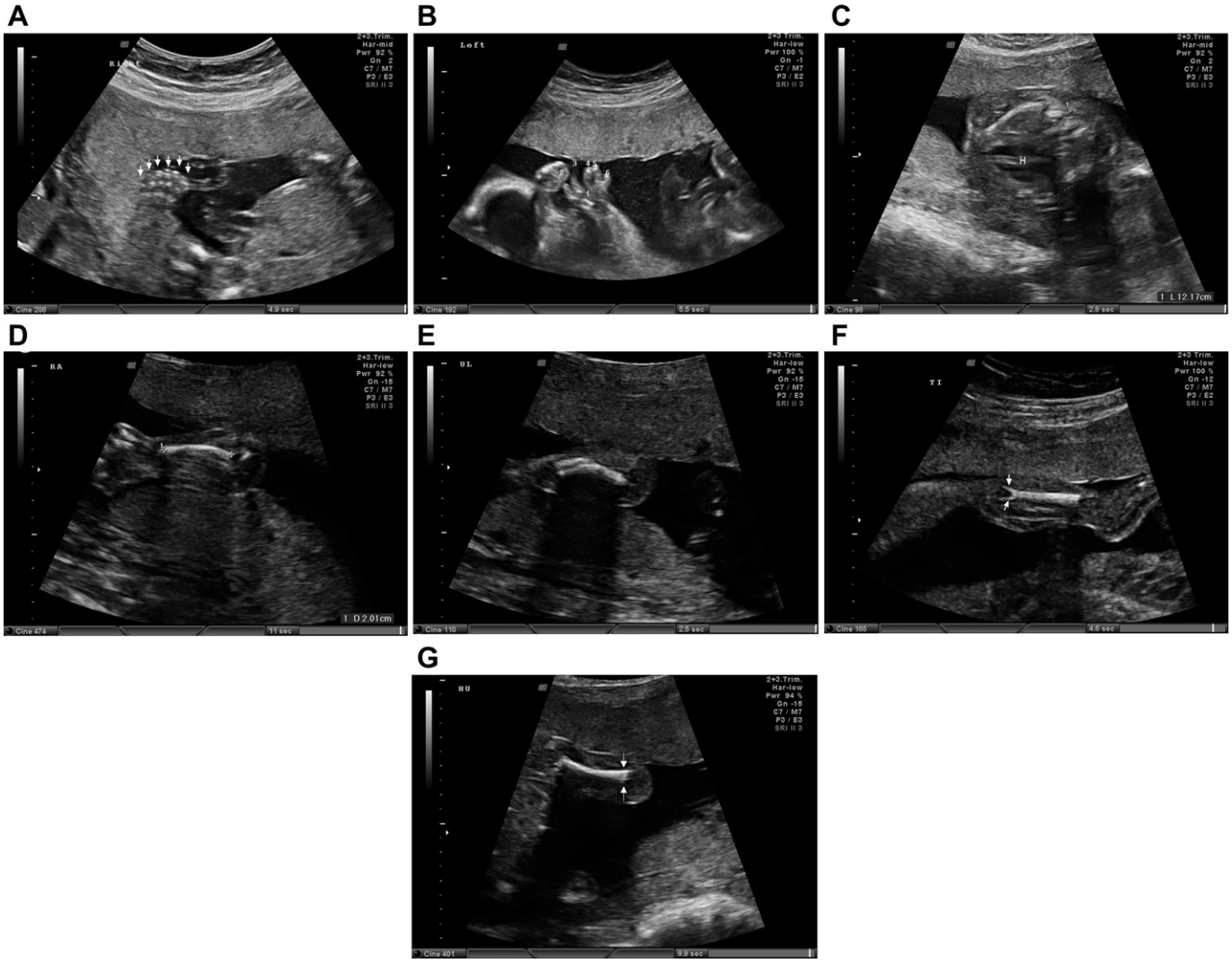

Fig. 1. Prenatal ultrasound at 21 weeks of gestation shows (A) polydactyly of the foot; (B) polydactyly of the hand; (C) short ribs and a narrow chest; (D) curved radius; (E) curved ulna; (F) marginal spurs (arrows) in tibia; (G) widened humeral metaphyses (arrows). H = heart.

circumference (AC) was 17.58 cm (75th percentile). The TC/AC ratio was 0.69. The lengths of the long bones were under the 5th percentile on nomograms. The femur, tibia, fibula, humerus, radius (curved) and ulna (curved) were measured 2.64 cm, 2.03 cm, 1.90 cm, 2.40 cm, 2.05 cm, and 2 cm, respectively. The biparietal diameter, head circumference and amniotic fluid amount were normal. Internal organs were unremarkable. A diagnosis of SRPS III (Verma-Naumoff) was made. Repeated amniocentesis was performed. Molecular genetic analysis of the amniotic fluid cells identified a homozygous splice site mutation in intron 4 (c.331-1 A > G) or IVS4-1 A > G in the *NEK1* gene (Fig. 2). The parents were heterozygous for the mutation (Fig. 2). Molecular analysis of the amniotic fluid cells revealed no mutations in the *DYNC2H1* gene. The pregnancy was subsequently terminated at 22 weeks of gestation. A 552-g male fetus was delivered with prominent forehead, a flattened nasal bridge, a narrow and short trunk, a protuberant abdomen, bilateral postaxial polydactyly and syndactyly of the hands and feet, and micromelic limbs (Fig. 3). No facial cleft or genital abnormality was noted. Postnatal molecular analysis of the fetal tissues confirmed the prenatal diagnosis. The radiograph was consistent with SRPS III (Fig. 4).

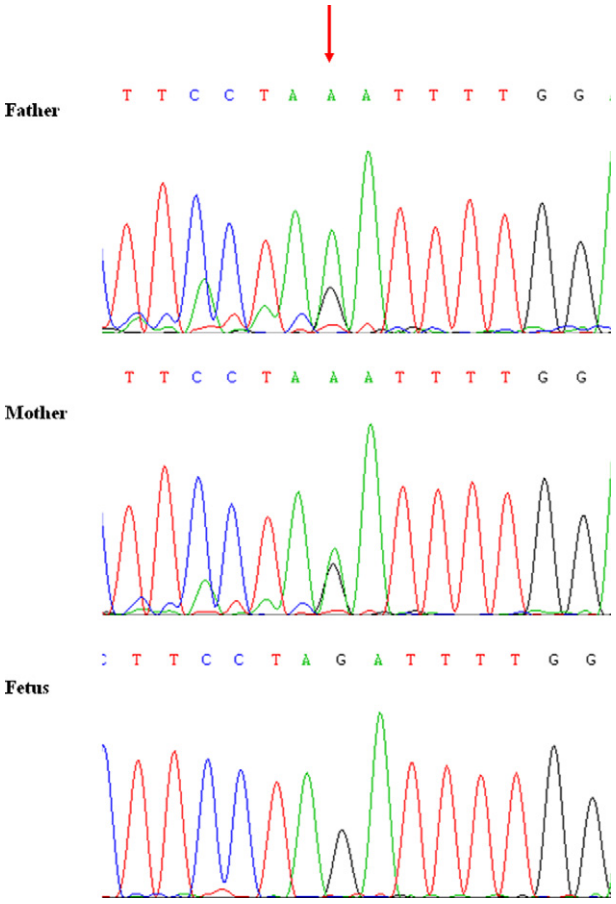

Fig. 2. A heterozygous splice site mutation in intron 4 (c.331-1, A > G) or *IVS4-1* A > G in the *NEK1* gene in the father and the mother, and a homozygous mutation of *NEK1*, *IVS4-1* A > G in the fetus.

Discussion

Prenatal diagnosis of SRPS III has been well described [2–5]. Characteristic ultrasound features include widened humeral metaphyses with marginal spurs, postaxial polydactyly, and shortened ribs [5]. The peculiar aspect of this case is the prenatal diagnosis of a *NEK1* mutation in a fetus with SRPS III.

The *NEK1* gene is located at 4q33 and encodes never in mitosis gene A-related kinase 1 (NEK1). NEK1 is the first mammalian ortholog of the fungal protein kinase of never in mitosis A in *Aspergillus nidulans* [6]. The NEK1 protein is localized to the basal body region of the cilium, and overexpression of NEK1 inhibits ciliogenesis [7]. The NEK1 is involved in a DNA damage sensing/repair pathway and functions in DNA damage response and checkpoint control [8,9]. The NEK1 also affected primary cilium formation [7]. Thus, NEK1 plays a role in centromere integrity affecting both ciliogenesis and chromosome stability [10]. Mutant mice for Nek1 kinase (*kat* mice) have been shown to present an autosomal recessive pleiotropic phenotype that includes progressing polycystic kidney disease, choroid plexus cysts, male sterility, dwarfing, abnormal olfactory lobes, facial dysmorphism, hydrocephalus, uremia and anemia [11–13]. Thiel and colleagues [14] first reported the association of *NEK1* mutations with SRPS. They identified a homozygous R127X mutation in the *NEK1* gene in an affected individual with SRPS II, a homozygous splice site mutation of c.869-2 A > G in intron 10 in the *NEK1* gene in another individual with SRPS II, and a heterozygous 1-bp insertion (c.1640_1641insA) in the *NEK1* gene and a heterozygous G3916D missense mutation in the *DYNC2H1* gene in the third individual with SRPS II. Thiel and colleagues [14] also found that absence of functional full-length NEK1 severely reduces cilia number and alters cilia morphology *in vivo*. Our report additionally shows the association of *NEK1* mutation with SRPS and provides evidence that a homozygous splice site mutation in intron 4 in the *NEK1* gene can cause SRPS III.

In addition to the *NEK1* gene, other genes such as *DYNC2H1* and *IFT80* have been reported to be associated with SRPS III. Dagoneau and colleagues [15] identified mutations in *DYNC2H1* in two fetuses with SRPS III. One fetus had compound heterozygous mutations of Q1537R and G2461V in *DYNC2H1*, and the other fetus had compound heterozygous mutations of T1987A and 10130delT in *DYNC2H1*. Merrill and colleagues [16] detected compound heterozygous mutations in *DYNC2H1* in two patients with SRPS III and homozygous mutation in one patient with SRPS III. One patient had a homozygous mutation of R587C in *DYNC2H1*, another patient had compound heterozygous mutations of R2205H and R2838X in *DYNC2H1*, and the third patient had compound heterozygous mutations of F209I and IVS33+1 G > T in *DYNC2H1*. Cavalcanti and colleagues [17] reported a homozygous mutation of G241R in *IFT80* in a fetus with SRPS III.

In summary, this presentation demonstrates perinatal imaging findings of polydactyly, micromelia, metaphyseal spurs, widened humeral metaphyses, and shortened ribs in

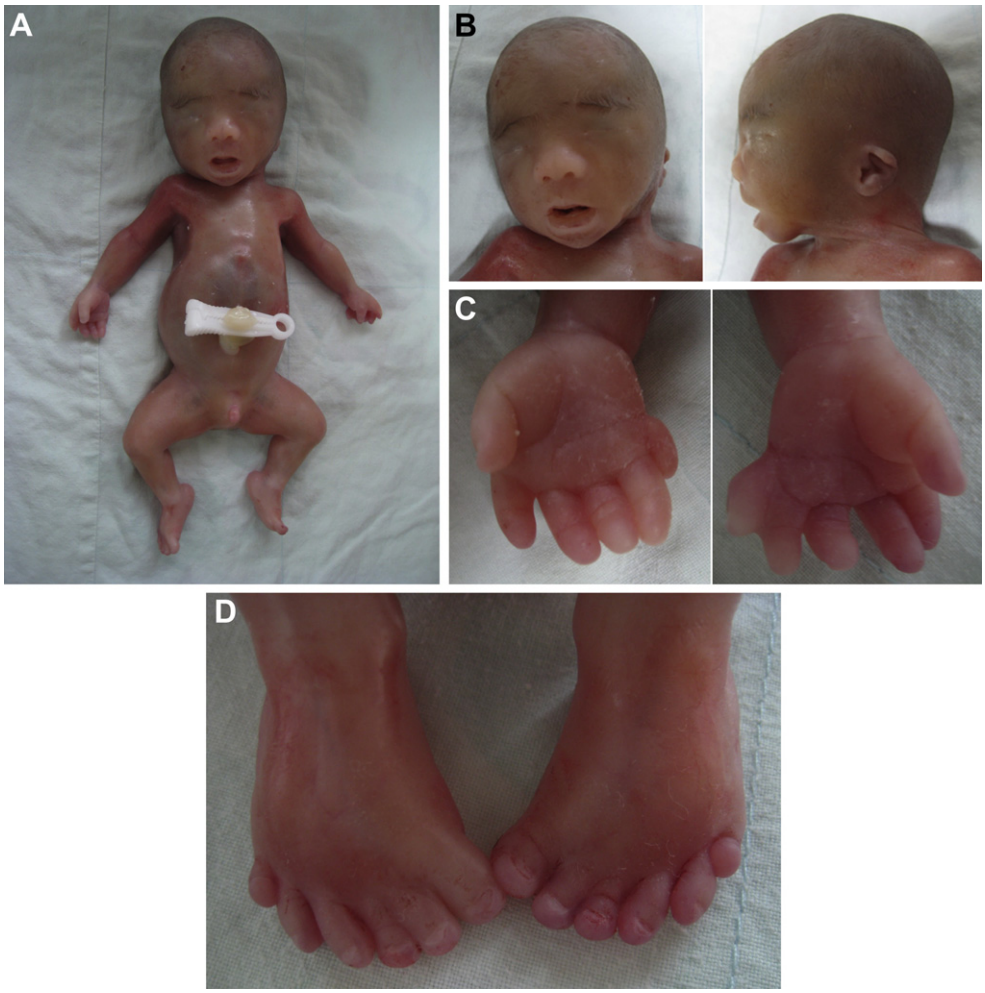

Fig. 3. The fetus at birth. (A) Whole body view; (B) craniofacial appearance; (C) polydactyly and syndactyly of the hands; (D) polydactyly and syndactyly of the feet.

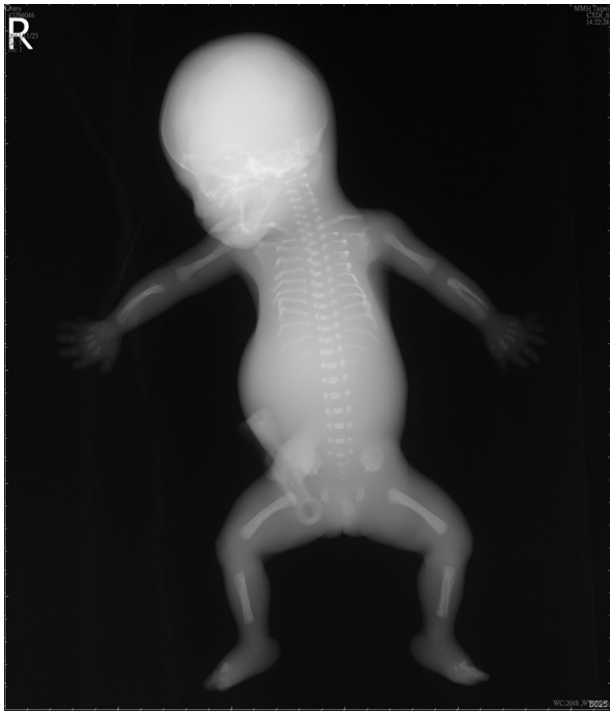

Fig. 4. Radiograph of the fetus.

a fetus with SRPS III. The present case provides evidence for a correlation of a mutation in the *NEK1* gene with SRPS III.

Acknowledgments

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