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Case Report

Short rib-polydactyly syndrome type II (Majewski): Prenatal diagnosis, perinatal imaging findings and molecular analysis of the *NEK1* gene

Chih-Ping Chen [a,b,c,d,e,f,*], Tung-Yao Chang [g], Chen-Yu Chen [a], Tao-Yeuan Wang [h,i,j], Fuu-Jen Tsai [d,k,l], Pei-Chen Wu [g], Schu-Rern Chern [b], Wayseen Wang [b,m]

[a] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[d] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[e] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[f] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[g] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[h] *Department of Pathology, Mackay Memorial Hospital, Taipei, Taiwan*
[i] *Mackay Medicine, Nursing and Management College, Taipei, Taiwan*
[j] *Mackay Medical College, New Taipei City, Taiwan*
[k] *Department of Medical Genetics, China Medical University Hospital, Taichung, Taiwan*
[l] *Department of Medical Research, China Medical University Hospital, Taichung, Taiwan*
[m] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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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 II short rib-polydactyly syndrome (SRPS) (Majewski).

Case Report: A 34-year-old woman with a past history of fetal SRPS was referred to the hospital at 16 weeks of gestation because of sonographic diagnosis of short limbs in the fetus. Fetal ultrasound revealed short ribs, short limbs, absence of tibiae, polydactyly, syndactyly and choroid plexus cysts. At 21 weeks of gestation, polycystic kidneys were found. The pregnancy was terminated, and a fetus was delivered with facial dysmorphism, a median cleft lip, a narrow chest, micromelia, aplasia of tibiae, hypoplastic nails, syndactyly and postaxial polydactyly. The karyotype was 46,XX. Molecular analysis of fetal tissues showed a paternal-origin heterozygous splice site mutation in intron 7 (c.465-1 G>A) in the *NEK1* gene, but no mutations in the genes of *WDR35*, *DYNC2H1*, *IFT80*, *EVC* and *EVC2*. The *NEK1* mutation causes an alteration of the splice acceptor site of intron 7 (IVS7-1 G>A). No second mutation was identified.

Conclusion: Tibial aplasia, choroid plexus cysts and polycystic kidneys can be prominent prenatal ultrasound findings of type II SRPS. The present case provides evidence for a correlation of *NEK1* mutation with type II SRPS.

Keywords: NEK1; prenatal diagnosis; type II short rib-polydactyly syndrome (Majewski); ultrasound

Introduction

Short rib-polydactyly syndromes (SRPSs) are a heterogeneous group of lethal autosomal recessive osteochondrodysplasias, and four types of SRPS are recognized, although up to seven types have been proposed in some classifications [1]. Type I SRPS (Saldino–Noonan) (OMIM

* Corresponding author. Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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263530) is characterized by flipper-like extremities, polydactyly, polycystic kidneys and pointed metaphyses. Type II SRPS (Majewski) (OMIM 263520) is characterized by polydactyly, micromelia, cleft lip/palate, polycystic kidneys, disproportionately short ovoid tibia and occasionally hypoplastic epiglottis and larynx. Type III SRPS (Verma–Naumoff) (OMIM 263510) is characterized by polydactyly, micromelia, metaphyseal spurs and occasionally situs inversus totalis. Type IV SRPS (Beemer–Langer) (OMIM 269860) clinically resembles type II SRPS, except there is no polydactyly and more normally developed tibiae. Type III SRPS is similar but milder than type I. Both types I and III are classified together according to current nosology and classification of genetic skeletal disorders [2]. Recently, a new type V SRPS has been suggested. Type V SRPS (OMIM 614091) is most similar to type III SRPS, but is associated with acromesomelic hypomineralization and campomelia [3,4]. Because of overlap in the clinical and radiological manifestations in different types, it is hypothesized that the different subtypes may be a single genetic disorder with variable

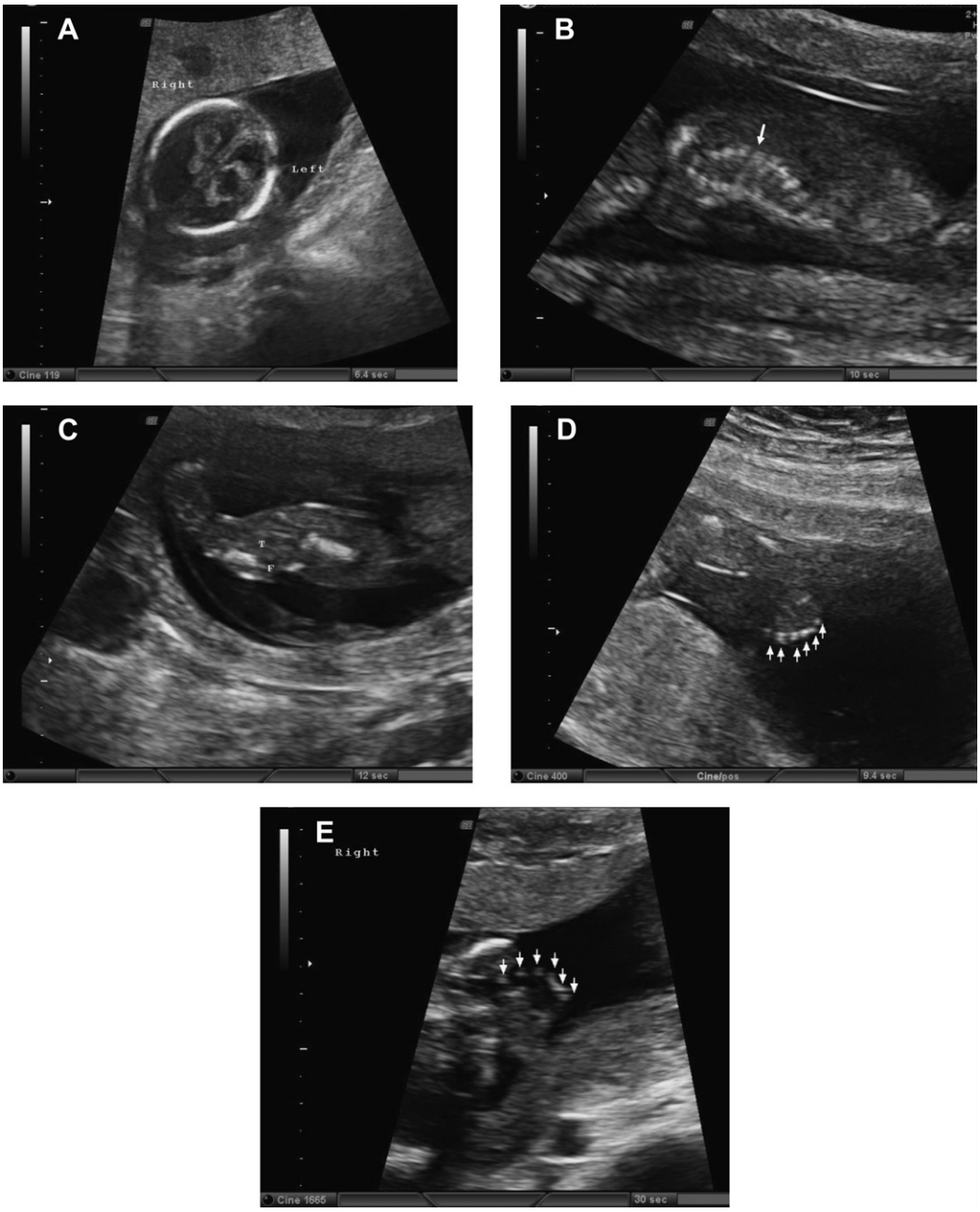

Fig. 1. Prenatal ultrasound at 16 weeks of gestation shows: (A) choroid plexus cysts; (B) short ribs and a narrow chest (arrow); (C) short fibula and tibial aplasia; and (D) and (E) polydactyly. F = fibula; T = tibia.

expressivity. Here, we present perinatal imaging findings and molecular investigation in a fetus with type II SRPS (Majewski).

Case report

A 34-year-old, gravida 5, para 2, woman with a past history of fetal SRPS was referred to the hospital at 16 weeks of gestation following sonographic diagnosis of shortening of the limbs in the fetus. She and her husband were non-consanguineous and had two normal daughters, aged 6 years and 3 years, respectively. Eight years previously, she had given birth to a female fetus with type II SRPS (Majewski). The fetus manifested a median cleft lip, a narrow chest, a protuberant abdomen, ovoid short tibiae, postaxial polydactyly and micromelia [5]. Five years previously, recurrent SRPS occurred in her third pregnancy that resulted in a malformed male fetus. During this pregnancy, level II ultrasound at 16 weeks of gestation revealed a singleton fetus equivalent to 16 weeks with short ribs, short limbs, absence of tibiae, polydactyly, syndactyly and choroid plexus cysts (Fig. 1). The lengths of four limbs were less than fifth centile. At 21 weeks of gestation, polycystic kidneys were evident on prenatal ultrasound (Fig. 2). The pregnancy was subsequently terminated. A 404-g malformed female fetus was delivered with prominent forehead, low-set ears, a short and flat nose, micrognathia, a median cleft lip, a narrow chest, micromelia, aplasia of tibiae, hypoplastic nails, syndactyly, and postaxial polydactyly of the hands and feet (Fig. 3). The phenotype and radiological manifestations were consistent with the diagnosis of SRPS II (Majewski) (Fig. 4). Pathological examinations showed multiple small cysts in the kidneys (Fig. 5). The fetal karyotype was 46,XX. Molecular analysis of the tissues of the affected fetus showed no mutations in the genes of *WDR35*, *DYNC2H1*, *IFT80*, *EVC* and *EVC2*. However, there was a paternal-origin heterozygous splice site mutation in intron 7 (c.465-1 G>A) in the *NEK1* gene. The mutation causes an alteration of the splice acceptor site of intron 7 (IVS7-1 G>A) (Fig. 6). No second mutation could be identified in this case.

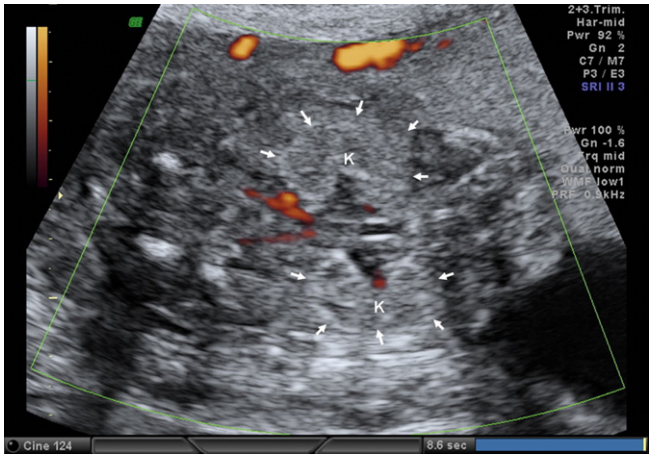

Fig. 2. Prenatal ultrasound at 21 weeks of gestation shows bilateral enlarged echogenic kidneys (K) (arrows) consistent with polycystic kidneys.

Discussion

The present case prenatally manifested choroid plexus cysts and absence of tibiae in addition to short ribs, micromelia, enlarged echogenic kidneys and polydactyly. SRPS has been reported to be associated with increased nuchal translucency, cystic hygroma and choroid plexus cysts on prenatal ultrasound [6–9]. The unique aspect in the present case is tibial aplasia on prenatal ultrasound. Round hypoplastic tibia is a characteristic finding of type II SRPS. Radiological manifestations of type II SRPS include underdeveloped mandible, short and horizontally located ribs, mesomelia, extremely short tibiae, rounded metaphyseal ends of long bones, precocious ossification of proximal femoral epiphysis, polydactyly, syndactyly and distal phalangeal hypoplasia [1].

SRPS is an autosomal recessive disorder with a recurrence rate in 25% of cases. Genetic counseling of fetal SRPS should include differential diagnosis of Jeune asphyxiating thoracic dystrophy (JATD) and Ellis–van Creveld syndrome (EvCS). SRPS, JATD and EvCS belong to ciliopathy. Ciliopathy is associated with defects in a variety of ciliary proteins necessary for intraflagellar transport (IFT), primary cilia, basal body and centrosome. JATD (OMIM 208500) is an autosomal recessive disorder characterized by thoracic dystrophy, chondrodysplasia, short ribs, short long bones, inconstant polydactyly, trident acetabular roof and occasional involvement of hepatic and retinal degeneration and cystic renal disease. JATD is caused by mutations of the *IFT80* gene (OMIM 611177) and *DYNC2H1* gene (OMIM 603297). JATD and type III SRPS have been suggested to be variants of a single ciliary disorder [10]. EvCS (OMIM 225500) is an autosomal recessive disorder characterized by short ribs, short limbs, postaxial polydactyly of the hands, occasional polydactyly of the feet, ectodermal dysplasia such as dysplastic nails and teeth, sparse hair and an absent gingival sulcus, and congenital heart defects such as a common atrium, atrioventricular septal defects and patent ductus arteriosus [11]. EvCS is caused by mutations in the *EVC* gene (OMIM 604831) or *EVC2* gene (OMIM 607261). SRPSs share similar findings in the phenotypic and radiological manifestations with JATD and EvCS. Merrill et al [12] suggested that SRPS, JATD and EvCS comprise a family of disorders that may be functionally related. Recently, SRPS has been found to be caused by mutations in the genes of *IFT80*, *DYNC2H1*, *NEK1* (OMIM 604588) or *WDR35* (OMIM 613602).

The *WDR35* gene is located at 2p24.1. WDR35 is a WD40 domain-containing protein and functions in intraflagellar transport [13]. Gilissen et al [13] first identified compound heterozygous mutations in the *WDR35* gene in patients with cranioectodermal dysplasia 2 (CED2; OMIM 613610). Mill et al [4] later mapped the SRPS disease locus to 2p24 from two siblings affected by type II SRPS and subsequently identified an in-frame homozygous 2,847-bp deletion spanning exon 5 of the *WDR35* gene. Mill et al [4] additionally identified compound heterozygous mutations in the *WDR35* gene in an unrelated fetus with type V SRPS. The fetus inherited a nonsense mutation of R545X from the mother and a missense mutation of W261R

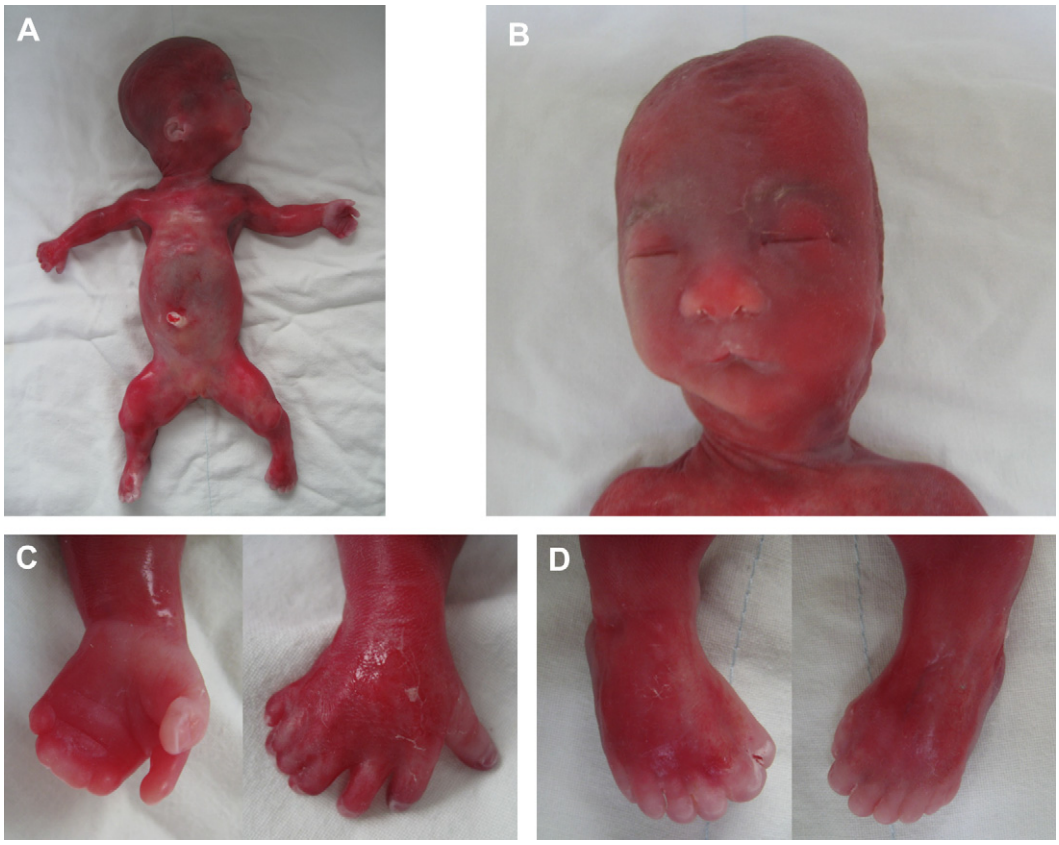

Fig. 3. The fetus at birth: (A) whole-body view; (B) characteristic facial features of prominent forehead, malformed low-set ears, a median cleft lip, a short and flat nose and micrognathia; (C) polydactyly and syndactyly of the hands; (D) polydactyly and syndactyly of the feet with hypoplastic nails.

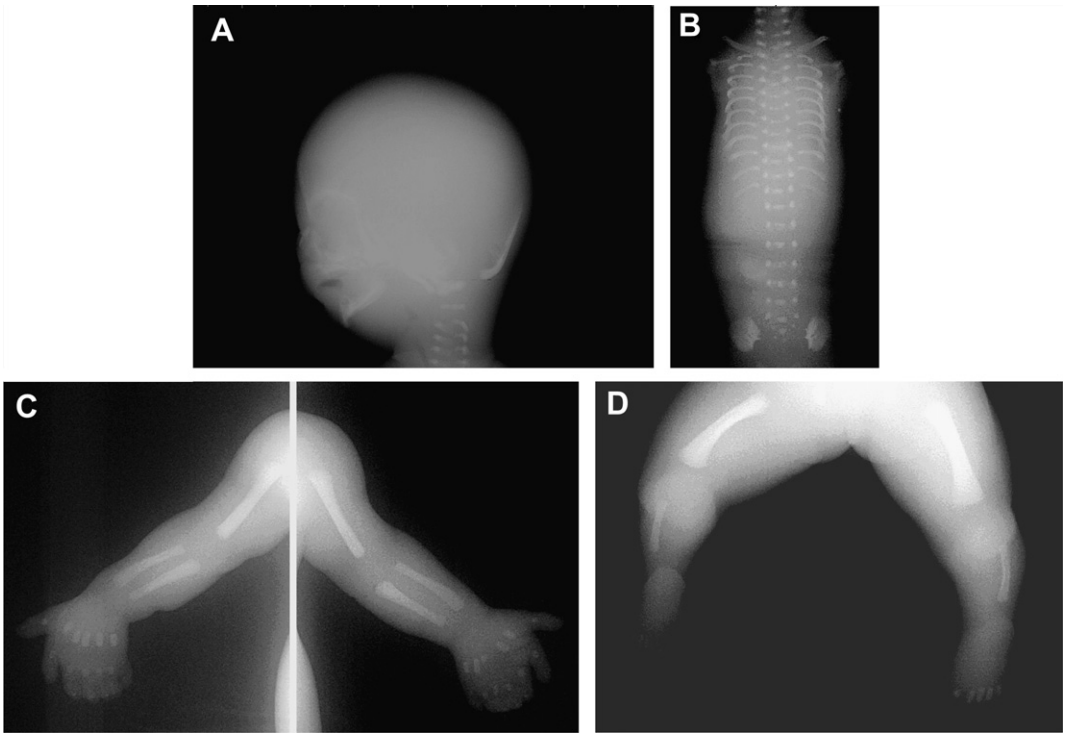

Fig. 4. Radiological manifestations: (A) skull with underdeveloped mandible; (B) short and horizontally located ribs; (C) precocious humeral ossification, polydactyly, distal phalangeal hypoplasia and symphalangism; (D) precocious femoral ossification and aplasia of the tibiae.

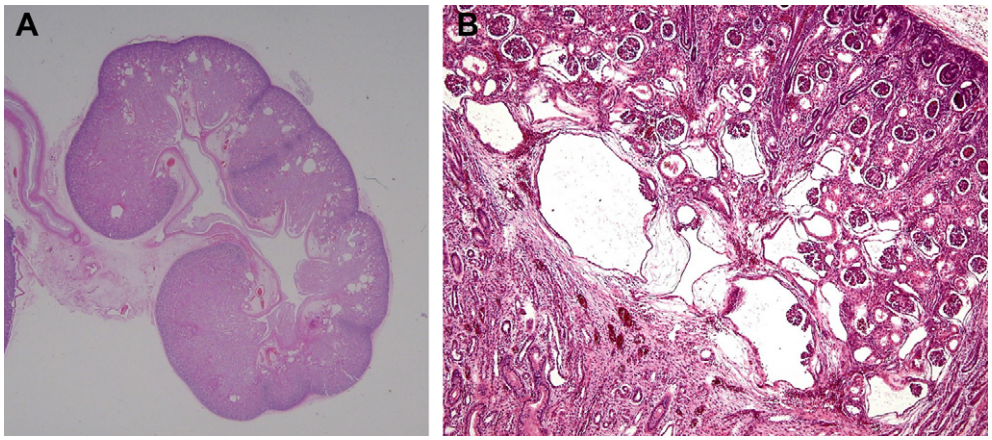

Fig. 5. Pathological manifestations: (A) polycystic kidney, hematoxylin–eosin (H&E) stain 1×; (B) polycystic kidney, H&E stain 40×.

from the father. Mill et al [4] showed that the endogenous WDR35 localizes to cilia and centrosomes throughout the developing embryo, and that mouse and human fibroblasts lacking the WDR35 protein fail to produce cilia.

The *NEK1* gene is located at 4q33. NEK1 is a mammalian protein relative of the fungal NIMA (never in mitosis gene A) regulator [14]. Thiel et al [15] mapped the SRPS disease locus to 4q32.1-q34.3 from the affected probands of type II SRPS from two consanguineous families, and identified a homozygous R127X mutation in the *NEK1* gene in an affected individual with type II SRPS and a homozygous splice site mutation of c.869-2 A>G in *NEK1* in another individual with type II SRPS. Thiel et al [15] additionally identified a heterozygous 1-bp insertion (c.1640_1641insA) in the *NEK1* gene,

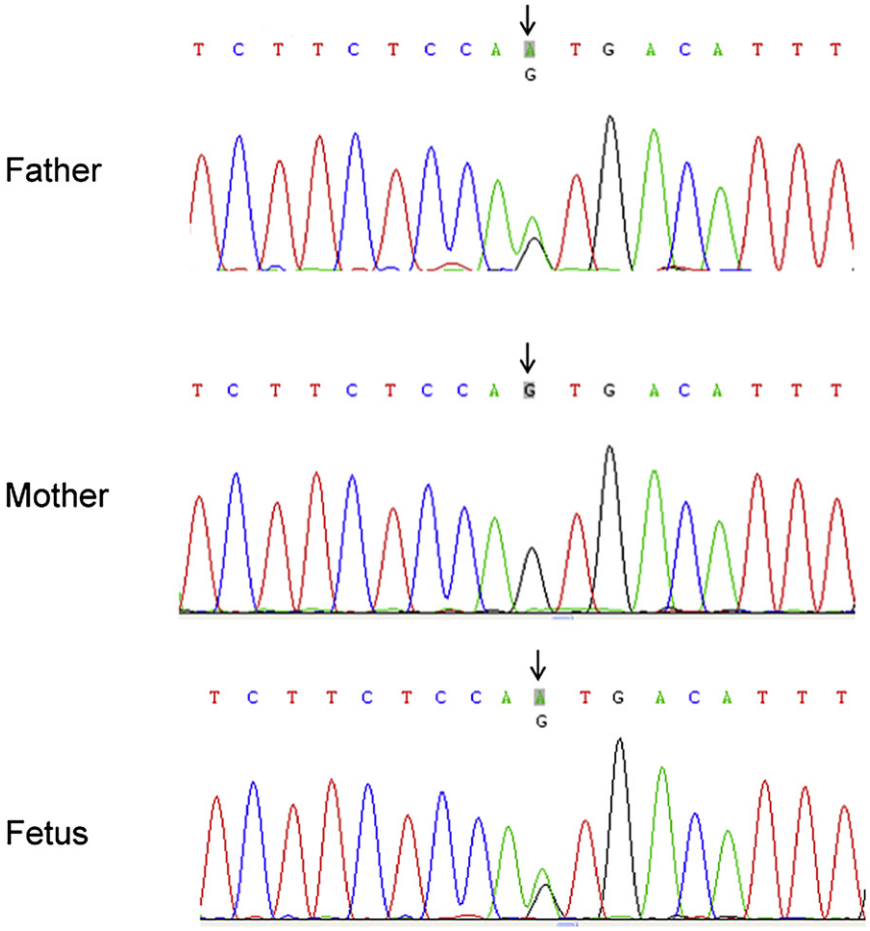

Fig. 6. A heterozygous splice site mutation in intron 7 (c.465-1 G>A) in the *NEK1* gene in the father and the fetus. The mutation causes an alteration of the splice acceptor site of intron 7 (IVS7-1 G>A).

and a heterozygous G3916D missense mutation in the *DYNC2H1* gene in the third individual with type II SRPS. Thiel et al [15] found that absence of functional full-length NEK1 severely reduces cilia number and alters cilia morphology *in vivo*.

The *IFT80* gene is located at 3q25.33. IFT80 is a protein component of the intraflagellar transport complex B and is essential for the development and maintenance of motile and sensory cilia [16]. Cavalcanti et al [17] reported a homozygous missense mutation of G241R in exon 8 of the *IFT80* gene in a fetus with type III SRPS. In an Ift80 mouse model of SRPS, Rix et al [18] demonstrated defects in hedgehog signaling without loss or malformation of cilia and suggested that Ift80 is required in hedgehog signaling, but low-level expression of Ift80 permits ciliogenesis.

The *DYNC2H1* gene is located at 11q22.3. DYNC2H1 is a cytoplasmic dynein involved in retrograde transport in the cilia. Dagoneau et al [10] identified compound heterozygosity for missense mutations of Q1537R and G2461V in the *DYNC2H1* gene in a fetus with type III SRPS. Dagoneau et al [10] additionally identified compound heterozygosity for a missense mutation of T1987A inherited from the father and a frameshift mutation of 10130delT or 1-bp deletion in exon 67 inherited from the mother in the *DYNC2H1* gene in three fetuses with type III SRPS. Merrill et al [12] detected homozygosity for a missense mutation of R587C in the *DYNC2H1* gene in four affected offspring with type III SRPS from first-cousin parents. Merrill et al [12] identified compound heterozygosity for a missense mutation of R2205H and a nonsense mutation of R2838X in the *DYNC2H1* gene in a patient with type III SRPS. Merrill et al [12] additionally identified compound heterozygosity for a substitution of consecutive basepairs in exon 5 (624_625 GT>AA) resulting in a missense mutation of F209I, and for an alteration of the splice donor site of intron 33 (IVS33+1 G>T) resulting in nonsense-mediated decay in the *DYNC2H1* gene in an individual with type III SRPS. A heterozygous G3916D missense mutation has also been observed in a patient with type II SRPS [15].

In summary, this presentation demonstrates perinatal imaging findings of a median cleft lip, tibial aplasia, choroid plexus cysts and polycystic kidneys in addition to short ribs, short limbs and polydactyly in a fetus with type II SRPS. The present case provides evidence for a correlation of a mutation in the *NEK1* gene with type II SRPS.

Acknowledgments

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