Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 123–127

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of short-rib polydactyly syndrome type III or short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3) associated with compound heterozygous mutations in *DYNC2H1* in a fetus

Chih-Ping Chen [a, b, c, d, e, f, *], Tsang-Ming Ko [g], Tung-Yao Chang [h], Schu-Rern Chern [b], Shin-Wen Chen [a], Shih-Ting Lai [a], Tzu-Yun Chuang [a], Wayseen Wang [b, i]

[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 Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[g] *Genephile Bioscience Laboratory, Ko's Obstetrics and Gynecology, Taipei, Taiwan*
[h] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[i] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

ARTICLE INFO

Article history:
Accepted 4 December 2017

Keywords:
DYNC2H1
Short-rib polydactyly syndrome type III
SRTD3
Targeted next-generation sequencing

ABSTRACT

Objective: We present the perinatal imaging findings and molecular genetic analysis in a fetus with short-rib polydactyly syndrome (SRPS) type III or short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3).

Case report: A 29-year-old, primigravid woman was referred for genetic counseling at 15 weeks of gestation because of abnormal ultrasound findings of short limbs, a narrow chest and bilateral polydactyly of the hands and feet, consistent with a diagnosis of SRPS type III. Chorionic villus sampling was performed, and targeted next-generation sequencing (NGS) was applied to analyze a panel of 25 genes including *CEP120*, *DYNC2H1*, *DYNC2LI1*, *EVC*, *EVC2*, *FGFR2*, *FGFR3*, *HOXD10*, *IFT122*, *IFT140*, *IFT172*, *IFT52*, *IFT80*, *KIAA0586*, *NEK1*, *PAPSS2*, *SLC26A2*, *SOX9*, *TCTEX1D2*, *TCTN3*, *TTC21B*, *WDR19*, *WDR34*, *WDR35* and *WDR60*. The NGS analysis identified novel mutations in the *DYNC2H1* gene. The fetus was compound heterozygous for a missense mutation c.8077G > T (p.Asp2693Tyr) of paternal origin in *DYNC2H1* and a frameshift mutation c.11741_11742delTT (p.Phe3914X) of maternal origin in *DYNC2H1*. The fetus had a karyotype of 46,XY, and postnatally manifested characteristic SRPS type III phenotype.

Conclusion: Targeted NGS is useful in genetic diagnosis of fetal skeletal dysplasia and SRPS, and the information acquired is helpful in genetic counseling.

Introduction

Short-rib polydactyly syndromes (SRPSs) are a group of autosomal recessive or digenic recessive skeletal dysplasias caused by ciliary dysfunction and characterized by short ribs, short limbs, polydactyly and associated anomalies of kidneys, heart, liver, pancreas, genitalia and intestines [1–6]. Currently, SRPSs have been classified into short-rib thoracic dysplasias with or without polydactyly types 1–17 (SRTD1~17): SRTD1 [Online Mendelian Inheritance in Man (OMIM) 208500] (gene locus: 15q13), SRTD2 (OMIM 611263) [gene locus: 3q25.33, *IFT80* (OMIM 611177), SRTD3 (OMIM 613091) [gene locus: 11q22.3, *DYNC2H1* (OMIM 603297), SRTD4 (OMIM 613819) [gene locus: 2q24.3, *TTC21B* (OMIM 612014), SRTD5 (OMIM 614376) [gene locus: 4p14, *WDR19* (OMIM 608151), SRTD6 (OMIM 263520) [gene locus: 4q33, *NEK1* (OMIM 604588), SRTD7

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan. Fax: +886 2 25433642, +886 2 25232448.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

https://doi.org/10.1016/j.tjog.2017.12.021

(OMIM 614091) [gene locus: 2p24.1, *WDR35* (OMIM 613602), SRTD8 (OMIM 615503) [gene locus: 7q36.3, *WDR60* (OMIM 615462), SRTD9 (OMIM 266920) [gene locus: 16p13.3, *IFT140* (OMIM 614620), SRTD10 (OMIM 615630) [gene locus: 2p23.3, *IFT172* (OMIM 607386), SRTD11 (OMIM 615633) [gene locus: 9q34.11, *WDR34* (OMIM 613363), SRTD12 (OMIM 269860), SRTD13 (OMIM 616300) [gene locus: 5q23.2, *CEP120* (OMIM 613446), SRTD14 (OMIM 616546) [gene locus: 14q23.1, *KIAA0586* (OMIM 610178), SRTD15 (OMIM 617088) [gene locus: 2p21, *DYNC2LI1* (OMIM 617083), SRTD16 (OMIM 617102) [gene locus: 20q13.12, *IFT52* (OMIM 617094) and SRTD17 (OMIM 617405) [gene locus: 3q29, *TCTEX1D2* (OMIM 617353). We previously reported prenatal diagnosis of SRPS associated with *NEK1* mutations [5,6]. Here, we present a case of SRTD3 associated with *DYNC2H1* mutations.

Case report

A 29-year-old, primigravid woman was referred for genetic counseling at 15 weeks of gestation because of abnormal ultrasound findings of short limbs, a narrow chest and bilateral polydactyly of the hands and feet, consistent with a diagnosis of SRPS type III (Fig. 1). Her husband was 31 years old. The woman and her husband were non-consanguineous, and there was no family history of congenital malformations. An ultrasound examination revealed biparietal diameter (BPD) of 3.33 cm (15 weeks), an abdominal circumference (AC) of 9.67 cm (15 weeks), a femur length of 1.16 cm (13 weeks), a narrow chest, a protruding abdomen and bilateral polydactyly of the hands and feet. Chorionic villus sampling was performed at 15 weeks of gestation, and the DNA extracted from the chorionic villi was analyzed by targeted next-generation sequencing (NGS) by Illumina NGS platform (Illumina, San Diego, CA, USA) and Agilent SureSelect capture array (Agilent Technologies, Santa Clara, CA, USA). The bioinformatics analysis was made by Burrows-Wheeler Aligner (BWA) and GATA software in combination with Ensembl VEP affect estimation system. Targeted exon capturing and NGS were performed in 25 known skeletal disorder-related genes including *CEP120*, *DYNC2H1*, *DYNC2LI1*, *EVC*, *EVC2*, *FGFR2*, *FGFR3*, *HOXD10*, *IFT122*, *IFT140*, *IFT172*, *IFT52*, *IFT80*, *KIAA0586*, *NEK1*, *PAPSS2*, *SLC26A2*, *SOX9*, *TCTEX1D2*, *TCTN3*, *TTC21B*, *WDR19*, *WDR34*, *WDR35* and *WDR60*. The fetus was compound heterozygous for a missense mutation c.8077G > T (p.Asp2693Tyr) of paternal origin in *DYNC2H1* and a frameshift mutation c.11741_11742delTT (p.Phe3914X) of maternal origin in *DYNC2H1* (Fig. 2). The father carried the mutation c.8077G > T, and the mother carried the mutation c.11741_11742delTT. The c.8077G > T mutation in codon 2693 is a missense mutation that results in an aspartic acid to tyrosine substitution at amino acid position 2693, and the c.11741_11742delTT mutation in codon 3914 causes a frameshift that introduces a stop codon at amino acid position 3914, resulting in a truncated protein. These two mutations have not been reported in the Human Gene Mutation Database (HGMD) and ClinVar and dbSNP databases. The c.8077G > T mutation and the c.11741_11742delTT mutation in *DYNC2H1* are likely resulting in probably damaging according to the PolyPhen 2 and PROVEN pathogenesis prediction programs. The pregnancy was terminated at 16 weeks of gestation, and a 122-g malformed fetus was delivered with a phenotype consistent with SRPS type III (Fig. 3). The external genitalia were normal. The fetus had a karyotype of 46,XY. Postnatal mutational analysis of *DYNC2H1* using the DNA extracted from the placenta confirmed compound heterozygous mutations of c.8077G > T and c.11741_11742delTT in *DYNC2H1* (Fig. 4).

Discussion

SRTD3 with alternative titles of short-rib polydactyly syndrome type III (SRPS3) [Verma–Naumoff syndrome], asphyxiating thoracic dystrophy 3 (ATD3), short-rib polydactyly syndrome type I (SRPS1) [Saldino–Noonan syndrome], polydactyly with neonatal chondrodystrophy type I, polydactyly with neonatal chondrodystrophy type III, or short-rib polydactyly syndrome type IIB (SRPS2B) is caused by homozygous or compound heterozygous mutation in

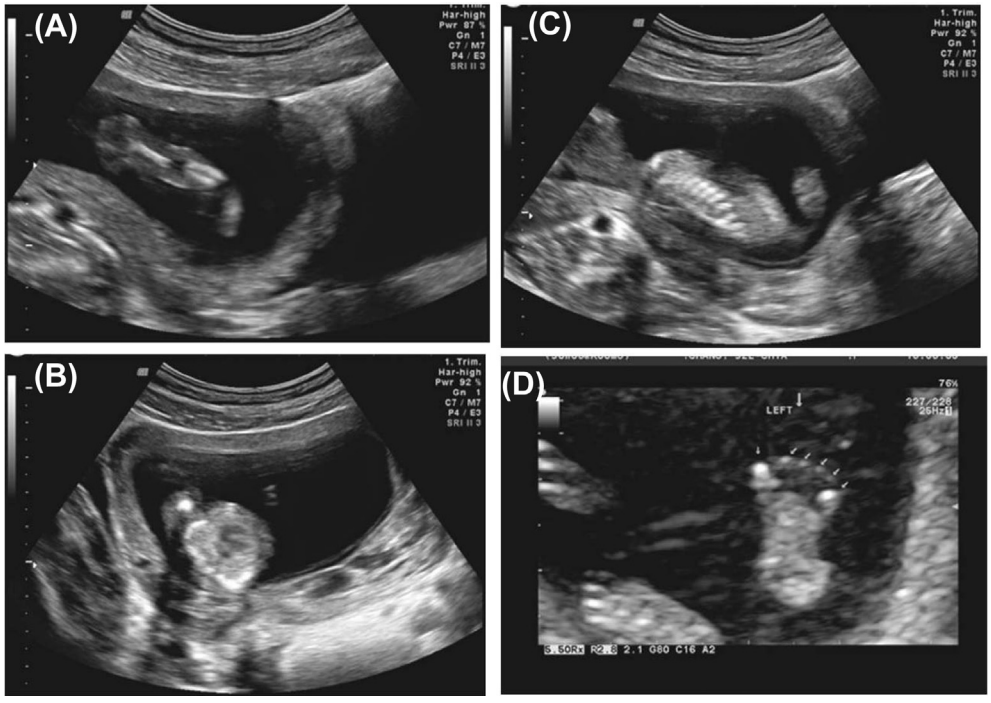

Fig. 1. Prenatal ultrasound at 15 weeks of gestation shows (A) short limbs (B) and (C) a narrow chest, and (D) polydactyly.

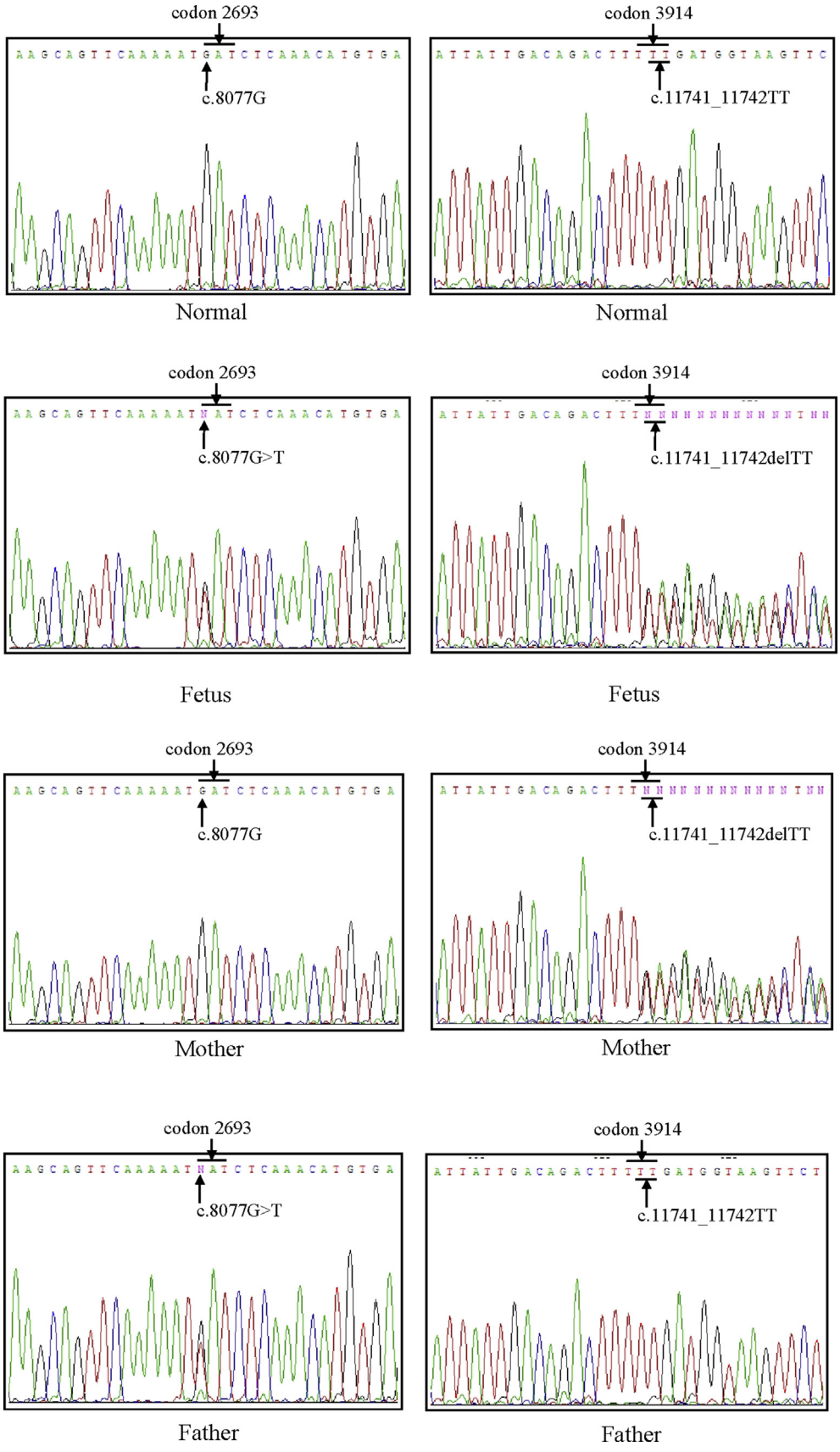

Fig. 2. Mutational analysis of the *DYNC2H1* gene on the DNAs extracted from the chorionic villi and parental bloods shows that the fetus is compound heterozygous for a missense mutation c.8077G > T (p.Asp2693Tyr) in codon 2693 and a frameshift mutation c.11741_11742delTT (p.Phe3914X) in codon 3914, the father carries the mutation c.8077G > T, and the mother carries the mutation c.11741_11742delTT.

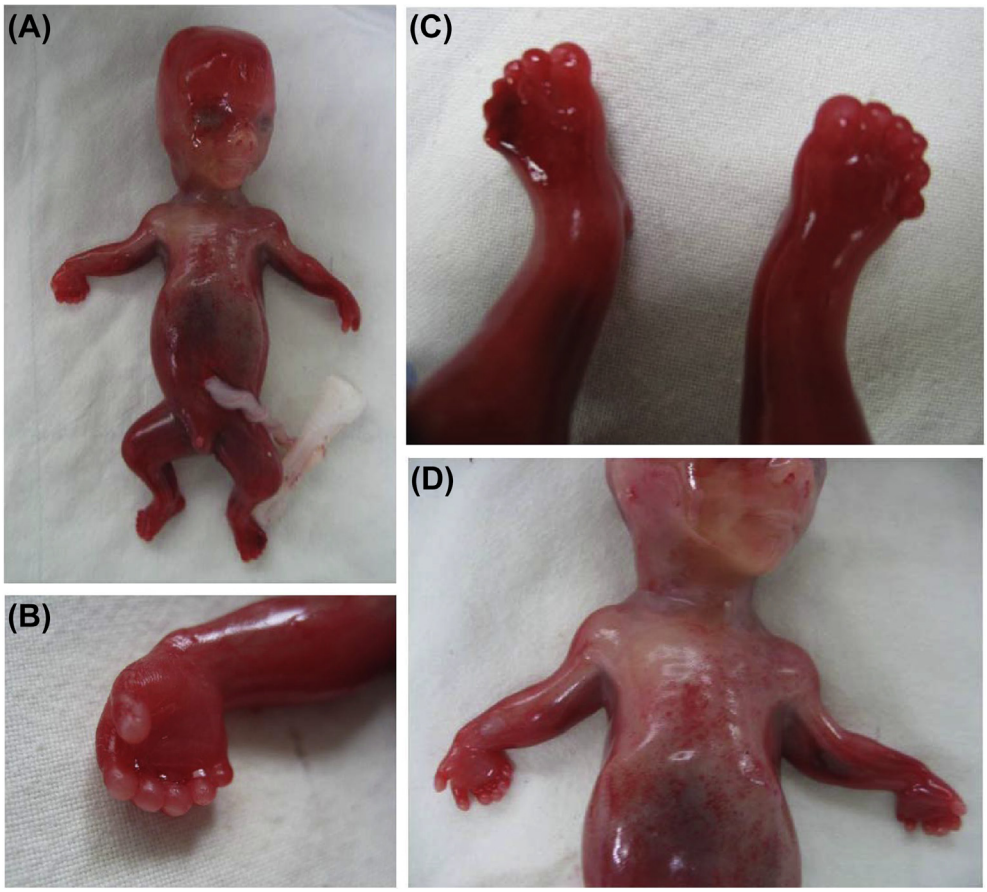

Fig. 3. The fetus at birth. (A) Whole body view, (B) right hand with polydactyly, (C) bilateral feet with polydactyly, and (D) a narrow chest.

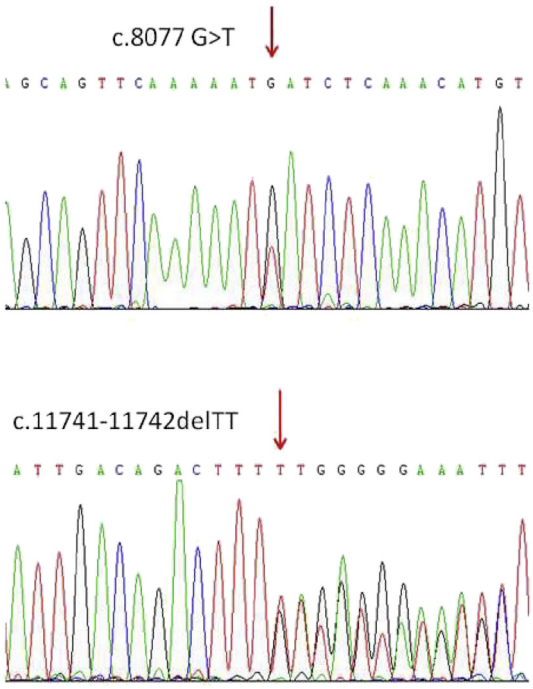

Fig. 4. Postnatal mutational analysis of the *DYNC2H1* gene on the DNA extracted from the placenta confirms the compound heterozygous mutations of c.8077G > T and c.11741_11742delTT in *DYNC2H1*.

DYNC2H1 on chromosome 11q22.3. SRTD3 can also be caused by digenic biallelic mutations in *DYNC2H1* and *NEK1* [7]. *DYNC2H1* is located at 11q22.3 and encodes dynein, cytoplasmic 2, heavy chain 1, which is a cytoplasmic dynein involved in retrograde transport in the cilia [8]. The *NEK1* gene is located at 4q33 and encodes mammalian protein relative of the fungal *NIMA* (never in mitosis gene A) receptor [9].

DYNC2H1 mutations have been observed in families with SRPS type III, ATD, SRPS type II and SRPS type I. Dagoneau et al. [10] reported *DYNC2H1* mutations in three families with ATD and two families with SRPS type III. The mutations in three families with ATD included homozygous c.5971A > T (p.Met1991Leu) and c.11284A > G (p.Met3762Val), compound heterozygous c.654_655insTTTATAACTTGGACAGTCTATCCTTACTA (p.Glu219-LeufsX2) and c.9044A > G (p.Asp3015Gly), and compound heterozygous c.3719T > C (p.Ile1240Thr) and c.10063G > T (p.Gly3355X). The mutations in two families with SRPS type III included compound heterozygous c.4610A > G (p.Gln1537Arg) and c.7382G > T (p.Gly2461Val), and compound heterozygous c.5959A > G (p.Thr1987Ala) and c.10130delT (p.Leu3377CysfsX34). Merrill et al. [11] reported *DYNC2H1* mutations in three families with SRPS type III. The mutations included homozygous c.1759C > T (p.Arg587Cys), compound heterozygous c.6614G > A (p.Arg2205His) and c.8512C > T (p.Arg2838X), and compound heterozygous c.624_625GT > AA (p.Phe209Ila) and c.IVS33 + 1G > T (splicing). Thiel et al. [7] reported *DYNC2H1* mutation and *NEK1* mutation in a family with SRPS type II. The digenic biallelic mutations included heterozygous c. 11747G > A (p.Gly3916Asp) in *DYNC2H1* and

heterozygous c.1640_1641insA (p.Asn547LysfsX2) in *NEK1*. El Hokayem et al. [12] reported *DYNC2H1* mutations in four families with SRPS type III. The mutations included compound heterozygous c.1012A > G (p.Arg338Gly), c.1288C > T (p.Arg430Cys) and c.4267C > T (p.Arg1423Cys), compound heterozygous c.7985G > A (p.Arg2662Gln) and c.7486C > T (p.Pro2496Ser), compound heterozygous c.988C > T (p.Arg330Cys) and c.8534delA (p.Asn2845IlefsX8), and compound heterozygous c.1483A > G (p.Lys495Arg) and c.12478-2A > G (splicing). Ellard et al. [13] reported heterozygous *DYNC2H1* variants in a couple with five fetuses with SRPS. The *DYNC2H1* variants included c.2819-14A > G (splicing) and c.7577T > G (p.Ile2526Ser). McInerney-Leo et al. [14] reported compound heterozygous c.1421T > G (p.Leu474Arg) and c.11312C > T (p.Ala3771Val) in *DYNC2H1* in a fetus with SRPS, and compound heterozygous c.2443G > C (p.Gly815Arg) and c.11417G > A (p.Arg3806His) in *DYNC2H1* in a child with Jeune asphyxiating thoracic dystrophy (JATD). Mei et al. [15] reported *DYNC2H1* mutations in a family with SRPS type III. The mutations included compound heterozygous c.1151C > T (p.Ala384Val) and c.4351C > T (p.Gln1451X). Okamoto et al. [16] reported *DYNC2H1* mutations in a family with SRPS type III. The mutations included compound heterozygous c.5682_5683delAA (p.Glu1894fsX10) and c.9010C > T (p.Arg3004Cys). Chen et al. [17] reported *DYNC2H1* mutations in a family with SRPS type III. The mutations included compound heterozygous c.8313A > T (p.Arg2771Ser) and c.10711_10714delTTTA (p.Phe3571ArgfsX3). Cossu et al. [18] reported homozygous mutation of c.3694G > A (p.Asp1232Asn) in *DYNC2H1* in a family with JATD. Badiner et al. [19] reported *DYNC2H1* mutations in three families with SRPS type I. The mutations included compound heterozygous c.6834G > T (p.Trp2278Cys) and c.10886G > C (p.Arg3629Pro), compound heterozygous c.6387G > T (p.Trp2129Cys) and c.8339T > C (p.Leu2780Ser), and compound heterozygous c.4267C > T (p.Arg1423Cys) and c.10594C > T (Arg3532X).

Recently, targeted next-generation panel sequencing and whole exome sequencing have been successfully applied in identification of *DYNC2H1* mutations in families with SRPS [13–15,17]. Our case provides an additional example that targeted NGS is useful in genetic diagnosis of fetal skeletal dysplasia and SRPS, and the information acquired is helpful in genetic counseling.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grants MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-106-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

[1] Chen C-P, Tzen C-Y. Short rib-polydactyly syndrome type III (Verma-Naumoff) in a third-trimester fetus with unusual associations of epiglottic hypoplasia, renal cystic dysplasia, pyelectasia and oligohydramnios. Prenat Diagn 2001;21:1101–2.

[2] Chen C-P, Chang T-Y, Tzen C-Y, Lin C-J, Wang W. Sonographic detection of situs inversus, ventricular septal defect, and short-rib polydactyly syndrome type III (Verma-Naumoff) in a second-trimester fetus not known to be at risk. Ultrasound Obstet Gynecol 2002;19:629–31.

[3] Chen C-P, Chang T-Y, Tzen C-Y, Wang W. Second-trimester sonographic detection of short rib-polydactyly syndrome type II (Majewski) following an abnormal maternal serum biochemical screening result. Prenat Diagn 2003;23:353–5.

[4] Chen C-P, Shih J-C, Tzen C-Y, Lin Y-H, Wang W. Recurrent short-rib polydactyly syndrome: prenatal three-dimensional ultrasound findings and associations with congenital high airway obstruction and pyelectasia. Prenat Diagn 2005;25:417–8.

[5] Chen C-P, Chang T-Y, Chen C-Y, Wang Y-T, Tsai F-J, Wu P-C, et al. Short rib-polydactyly syndrome type II (Majewski): prenatal diagnosis, perinatal imaging findings and molecular analysis of the *NEK1* gene. Taiwan J Obstet Gynecol 2012;51:100–5.

[6] Chen C-P, Chern S-R, Chang T-Y, Su Y-N, Chen Y-Y, Su J-W, et al. 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. Taiwan J Obstet Gynecol 2012;51:266–70.

[7] Thiel C, Kessler K, Giessl A, Dimmler A, Shalev SA, von der Haar S, et al. *NEK1* mutations cause short-rib polydactyly syndrome type Majewski. Am J Hum Genet 2011;88:106–14.

[8] Schmidts M, Arts HH, Bongers EMHF, Yap Z, Oud MM, Antony D, et al. Exome sequencing identifies *DYNC2H1* mutations as a common cause of asphyxiating thoracic dystrophy (Jeune syndrome) without major polydactyly, renal or retinal involvement. J Med Genet 2013;50:309–23.

[9] Letwin K, Mizzen L, Motro B, Ben-David Y, Bernstein A, Pawson T. A mammalian dual specificity protein kinase, Nek1, is related to the NIMA cell cycle regulator and highly expressed in meiotic germ cells. EMBO J 1992;11:3521–31.

[10] Dagoneau N, Goulet M, Geneviève D, Sznajer Y, Martinovic J, Smithson S, et al. DYNC2H1 mutations cause asphyxiating thoracic dystrophy and short rib-polydactyly syndrome, type III. Am J Hum Genet 2009;84:706–11.

[11] Merrill AE, Merriman B, Farrington-Rock C, Camacho N, Sebald ET, Funari VA, et al. Ciliary abnormalities due to defects in the retrograde transport protein DYNC2H1 in short-rib polydactyly syndrome. Am J Hum Genet 2009;84:542–9.

[12] El Hokayem J, Huber C, Couve A, Aziza J, Baujat G, Bouvier R, et al. *NEK1* and *DYNC2H1* are both involved in short rib polydactyly Majewski type but not in Beemer Langer cases. J Med Genet 2012;49:227–33.

[13] Ellard S, Kivuva E, Turnpenny P, Stals K, Johnson M, Xie W, et al. An exome sequencing strategy to diagnose lethal autosomal recessive disorders. Eur J Hum Genet 2015;23:401–4.

[14] McInerney-Leo AM, Harris JE, Leo PJ, Marshall MS, Gardiner B, Kinning E, et al. Whole exome sequencing is an efficient, sensitive and specific method for determining the genetic cause of short-rib thoracic dystrophies. Clin Genet 2015;88:550–7.

[15] Mei L, Huang Y, Pan Q, Su W, Quan Y, Liang D, et al. Targeted next-generation sequencing identifies novel compound heterozygous mutations of *DYNC2H1* in a fetus with short rib-polydactyly syndrome, type III. Clin Chim Acta 2015;447:47–51.

[16] Okamoto T, Nagaya K, Kawata Y, Asai H, Tsuchida E, Nohara F, et al. Novel compound heterozygous mutations in *DYNC2H1* in a patient with severe short-rib polydactyly syndrome type III phenotype. Congenit Anom (Kyoto) 2015;55:155–7.

[17] Chen LS, Shi SJ, Zou PS, Ma M, Chen XH, Cao DH. Identification of novel *DYNC2H1* mutations associated with short rib-polydactyly syndrome type III using next-generation panel sequencing. Genet Mol Res 2016;15(2). gmr.15028134.

[18] Cossu C, Incani F, Serra ML, Coiana A, Crisponi G, Boccone L, et al. New mutations in *DYNC2H1* and *WDR60* genes revealed by whole-exome sequencing in two unrelated Sardinian families with Jeune asphyxiating thoracic dystrophy. Clin Chim Acta 2016;455:172–80.

[19] Badiner N, Taylor SP, Forlenza K, Lachman RS, University of Washington Center for Mendelian Genomics, Bamshad M, et al. Mutations in *DYNC2H1*, the cytoplasmic dynein 2, heavy chain 1 motor protein gene, cause short-rib polydactyly type I, Saldino-Noonan type. Clin Genet 2017;92:158–65.