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Short report

Clinical features and molecular genetic analysis of thanatophoric dysplasia type I in a neonate with a *de novo* c.2419 T > C (p. Ter807Arg) (X807R) mutation in FGFR3

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ABSTRACT

We present a case report that entails prenatal ultrasonography, postnatal characteristics, and molecular genetic analysis of a newborn who presented with thanatophoric dysplasia type I (TDI) with a mutation in the fibroblast growth factor receptor 3 gene (FGFR3). A malformed newborn with tachypnea, delivered by caesarean at the gestational age of 39 weeks, was the first child of nonconsanguineous parents by a spontaneous pregnancy. Features in prenatal ultrasonography and postnatal radiography were consistent with the diagnosis of TDI, presenting with short body length (38 cm, < 3rd percentile), redundant skin folds, a narrow thorax with a bust of 29.5 cm (3-5th percentile), and macrocephaly with a head circumference of 36 cm (> 97th percentile). The proposita had postnatal dyspnea and unfortunately died of respiratory failure at the age of 13 days. Molecular genetic analysis revealed a mutation of c.2419 T > C (p. Ter807Arg) (X807R) in FGFR3. Live-born infants with TDI are exceedingly rare, and we hereby report a newborn with a c.2419 T > C mutation in FGFR3, emphasizing phenotype with clinical characteristics and ultrasonographic and X-ray findings, to raise awareness about the heterogeneous patterns of TD.

1. Introduction

Thanatophoric dysplasia (TD) is a sporadic, autosomal-dominant skeletal dysplasia caused by mutations in the fibroblast growth factor receptor 3 gene (FGFR3). It has an estimated incidence of 1/35,000 to 1/50,000 births, and is characterized by short long bones, a narrow thorax, macrocephaly, and flattened vertebral bodies (Wilcox et al., 1998). TD has been further divided into types 1 (TDI) and 2 (TDII), with TDI (MIM# 187600) being the most common subtype and characterized by curved femora and occasional cloverleaf skull; while cloverleaf skull and short-but-straight femora are the characteristic of TDII (MIM# 187601) (Tavormina et al., 1995a). The anomaly results due to different mutations in the FGFR3 gene which lead to increased activation of FGFR3, with the severity of the phenotype proportional to the activity of the receptor. TDI is caused by FGFR3 missense, insertion, or stop codon mutations (Table 1) (Tavormina et al., 1995a; Lindy et al., 2016; Rousseau et al., 1996; Gomes et al., 2018; Pannier et al., 2009; Xue et al., 2014; Chitty and Altman, 2002; Rousseau et al., 1995; Wilcox et al., 1998; Brodie et al., 1998); whereas TDII is only caused by 1 FGFR3 missense mutation of p. Lys650Glu (K650E) (Tavormina et al., 1995b; Lindy et al., 2016; Rousseau et al., 1996; Gomes et al., 2018; Pannier et al., 2009; Xue et al., 2014; Wilcox et al., 1998; Brodie et al., 1998). Although the most frequent mutations for TDI are p. Arg248Cys and p. Tyr373Cys —which together contribute to about 90% of the cases (Xue et al., 2014)—correlations between genotype and phenotype are not apparent due to the limited number of cases (Jung and Park, 2017), and molecular genetic analysis must be used for confirmatory purposes and genetic consultation. TD presents earlier in pregnancy with short limbs, small chest, and other features; thus ultrasonographic examination combined with a local biometric standard of the Chinese population (Leung et al., 2008) is straightforward with respect to diagnosing TD. However, it is not always possible to differentiate TD from other skeletal dysplasias by ultrasonography alone (Chitty et al., 2013; Jung and Park, 2017). Therefore, molecular genetic analysis is indispensable for TD diagnosis in the era of precision individualized medicine. The mutation of c.2419 T > C (p. Ter807Arg) (X807R) that causes TDI has been reported without a detailed description of clinical phenotype (Xue et al., 2014). We therefore reported here a full-term,

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Table 1
Different mutations in FGFR3 and amino acid change for thanatophoric dysplasia type I.

Nucleotide mutation	Amino acid change	Reference
c.742C > T	p. Arg248Cys	(Tavormina et al., 1995a)
c.746C > G	p. Ser249Cys	(Tavormina et al., 1995a)
c.742_743insTGT	p. Arg248delinsLeuCys	(Lindy et al., 2016)
c.1108G > T	p. Gly370Cys	(Rousseau et al., 1996)
c.1111A > T	p. Ser371Cys	(Tavormina et al., 1995a)
c.1118A > G	p. Tyr373Cys	(Rousseau et al., 1996)
c.1130 T > C;c.1138G > A	p. Leu377Pro;Gly380Arg	(Gomes et al., 2018)
c.1620C > A;c.1454A > G	p. Asn540Lys;Gln485Arg	(Pannier et al., 2009)
c.1949A > T	p. Lys650Met	(Xue et al., 2014)
c.2419 T > A	p. Ter807Arg	(Rousseau et al., 1995)
c.2419 T > C	p. Ter807Arg	(Xue et al., 2014)
c.2419 T > G	p. Ter807Gly	(Wilcox et al., 1998)
c.2420G > C	p. Ter807Ser	(Xue et al., 2014)
c.2420G > T	p. Ter807Leu	(Chitty and Altman, 2002)
c.2421A > C	p. Ter807Cys	(Chitty and Altman, 2002)
c.2421A > T	p. Ter807Cys	(Rousseau et al., 1995)
c.2421A > G	p. Ter807Trp	(Brodie et al., 1998)

Table 2
Ultrasonography monitor of the baby during the pregnancy.

GA(weeks)	11	17	25	39
HC(cm)	–	14.6	22.9	35.1
AC(cm)	–	11.9	22.1	35.2
BPD(cm)	–	3.99	6.83	10.6
humerus length (cm)	–	1.07	2.35	2.41
ulna length (cm)		0.98	2.2	2.25
radius length (cm)		0.89	2.0	2.05
femur length (cm)	–	1.27	2.5	2.95
tibia length (cm)	–	1.01	2.0	2.21
fibula length (cm)	–	0.96	1.9	2.09
nasal-bone length (cm)	–	0.39	0.61	0.92
mandible length (cm)	–	1.89	3.1	4.83
AMN(cm)	3.0	3.3	8.3	12.8
Placental acreage (mm)	11	18.8	22	27
placental mature	0	0	0-I	II
HR(n/min)	168	158	153	153
PTD(mm)	–	–	11.3	–
CTR	–	–	0.54	0.74

GA: gestational age; HC: head circumference; AC: abdomen circumference; BPD: biparietal diameter; HR: heart rate; AMN: amniotic fluid maximcon depth; PTD: pulmonary transverse-diameter ; CTR:cardio-thoracic ratio; cm: centimeter; mm: millimeter.

live infant born with TDI and this specific mutation by analyzing clinical characteristics, ultrasonography, radiographs, and genetic sequence—as well as provided a short review of the literature.

2. Materials and methods

2.1. Study subjects

Members of the study family were included (consisting of the proband, mother, and father), in agreement with Chinese law and following genetic counseling for the parents, and the parents' informed consent was provided for genetic studies. The study protocol was approved by the Ethics Committee of Children's Hospital of Fudan University, People's Republic of China.

2.2. Whole exon sequencing

Genomic DNA fragments from study subjects were enriched for whole exon sequencing (WES) using an Agilent (Santa Clara, CA, USA) SureSelectXT Human All Exon 50-Mb kit. For all samples, we created DNA fragments ligated with adaptors and two paired-end DNA libraries, with an insert size of 500 bp. We sequenced DNA libraries after enrichment by polymerase chain reaction (PCR) on a HiSeq2500 sequencer according to the manufacturer's instructions (Illumina, San Diego, CA); this resulted in 90-bp paired-end sequencing reads with at least a 100-fold average sequencing depth for each sample. Clean reads were aligned to the reference human genome (UCSC hg19) using a Burrows-Wheeler Aligner (BWA) (v.0.5.9-r16). Subsequent processing of sorting, merging, and removing duplication of the BAM files was performed by using SAMtools and Picard (http://picard.sourceforge.net/index.shtml). We obtained variant calls—which differed from the reference sequence—using a Genome Analysis ToolKit 4 (GATK4), and variants with suboptimal quality scores were removed from consideration. We annotated the remaining variants with ANNO-VAR and VEP software, and compared these computationally with the list of reported pathogenic variations from the Human Gene Mutation Database (HGMD, professional version). Missense variants were assessed with SIFT, PolyPhen-2, and MutationTaster (Kumar et al., 2009; Adzhubei et al., 2010; Schwarz et al., 2010).

3. Case Report

3.1. Ultrasonographic analyses

A 25-year-old woman was referred for genetic counseling at 25 weeks of gestation because of abnormal prenatal ultrasonographic findings (Table 2). At 17 gestational weeks, ultrasonography of the fetus indicated macrocephaly, a narrow chest, and short limbs. We performed a comprehensive fetal biometric analysis by two-dimensional (2D) ultrasonography at 25 weeks (Fig. 1 A-E). The head and abdominal circumferences were 22.9 and 22.1 cm, respectively, which were both > 97th percentile; and all long-bone measurements were below the 5th percentile relative to normal biometry, as femoral length measured 2.5 cm, tibial length 2.0 cm, fibular length 1.9 cm, humeral length 2.35 cm, ulnar length 2. 2 cm, and radius length 2.0 cm. We quantified a severely narrowed thorax with pulmonary hypoplasia as a pulmonary transverse-diameter (PTD) of 11.3 mm (< 5th percentile) and a cardio-thoracic proportion of 0.54. We suspected a clinical diagnosis of thanatophoric dysplasia (TD), and suggested terminating pregnancy, which was refused by the primigravida and her husband for religious reasons as the couple was Christian. The couple had been healthy and not in contact with medical staff until the wife was in labor. Prior to the caesarean, we conducted three-dimensional (3D) ultrasonography of the fetus at 39 weeks (Fig. 1 F—H) and showed facial dysmorphism with frontal bossing, a depressed nasal bridge, short and bowing femurs, and increased subcutaneous tissues in the digits and limbs; fetal structural abnormalities had also previously been visualized by 2D ultrasonography at 25 weeks. Polyhydramnios was a

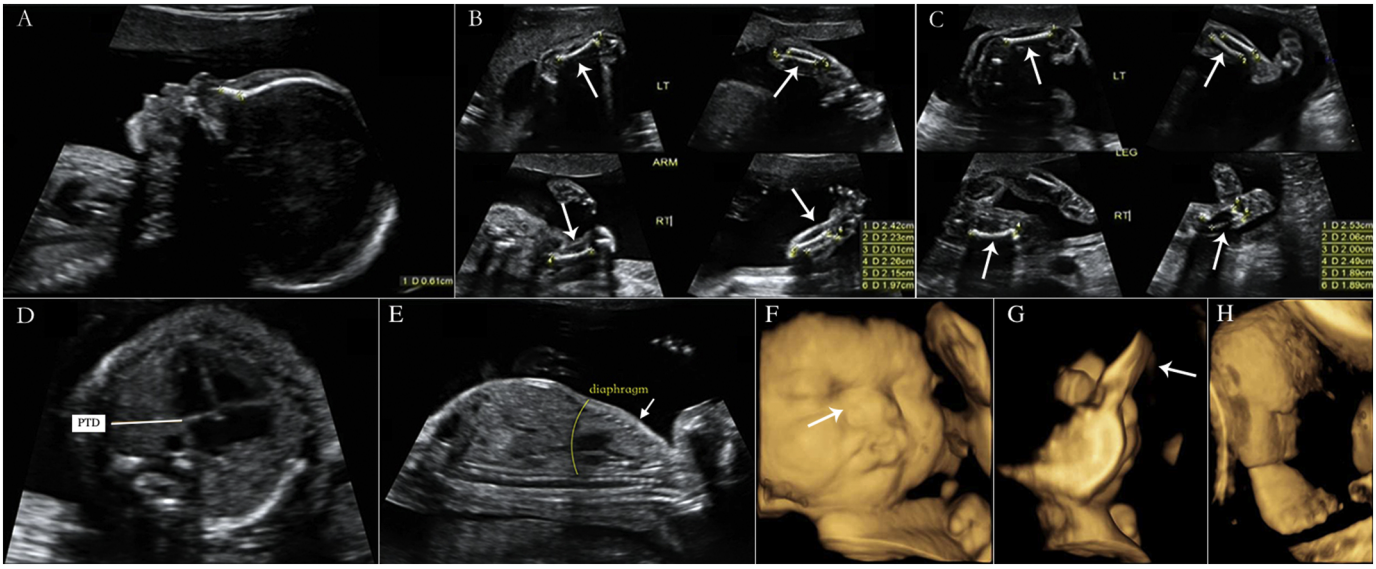

Fig. 1. Prenatal ultrasonography of fetus at 25 (A-E) and 39 weeks (F-H) of gestation revealed macrocephaly, short and curved limbs, and a narrow, bell-shaped thorax. (A) Macrocephaly with a head circumference > 97th percentile; (B) short arms with a humeral length of 2.35 cm, ulnar length of 2.2 cm and radius length of 2.0 cm (< 5th percentile); (C) short and curved legs with a femoral length measuring 2.5 cm, tibial length of 2.0 cm, and fibular length of 1.9 cm (< 5th percentile); (D) pulmonary hypoplasia with a pulmonary transverse-diameter (PTD) of 11.3 mm (< 5th percentile); (E) a narrow chest and protrusion of the abdomen; (F) a depressed nasal bridge; (G) facial dysmorphism with frontal bossing; and (H) short and bowing femurs.

distinguishing feature throughout pregnancy, and the maximal amniotic fluid depth was 128 mm at 39 weeks.

4. Clinical characteristics

The malformed infant was delivered by caesarean section at 39 gestational weeks, with Apgar scores of 9 and 10 at 1 and 5 min, respectively. The baby girl weighed 3000 g (50th percentile), had a head circumference of 36 cm (> 97th percentile), a thoracic circumference of 28 cm (< 3rd percentile), a body length of only 38 cm (< 3rd percentile), a short nose with depressed nasal bridge, protuberant abdomen, and micromelia with short stubby fingers and deep skin creases

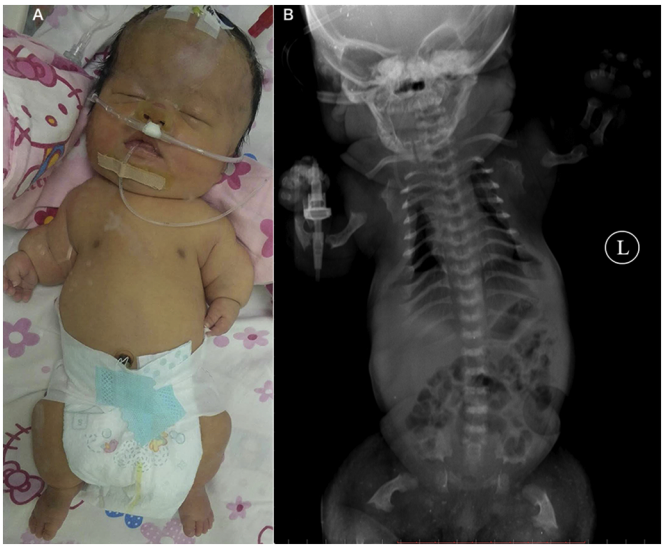

Fig. 2. Malformed female infant with thanatophoric dysplasia I. (A): Clinical photograph of the entire body on the 1st day of life showing macrocephaly (head circumference 36 cm [> 97th percentile]), narrow thorax (thoracic circumference of 28 cm), and short limbs. (B) Radiograph on the 1st day of life demonstrating a small thorax, bowing of the femora, and severe platyspondyly with H-shaped vertebrae.

(Fig. 2A). She was sent to the neonatal intensive care unit for dyspnea 20 min after birth. After 10 days of respiratory support by a high flow nasal cannula (FiO2 range, 45%–30%; flow rates, 5–4 L/min), the dyspnea was relieved and alleviated by nasal oxygen (flow rates, 1–2.5 L/min; FiO2 range, 21%–25%). The infant had difficulty suckling and required tube feeding. After 3 days of nasal oxygen, respiratory failure ensued, resulting in a bout of pneumonia. As her parents refused the more aggressive actions of tracheal intubation and mechanical ventilation, the girl died of respiratory failure at 13 days of age. An autopsy was declined, so histologic analyses were not available. A skeletal radiograph (Fig. 2B) showed severe rhizomelic shortness of the long bones and bowing of the femora. The thorax was small with a cardio-thoracic ratio of 0.75, and the iliac bones were short and wide. Macrocrania and frontal bossing were observed, but without a cloverleaf skull. Cranial ultrasonography displayed bilateral ventriculomegaly, while echocardiography manifested no anomalies. These clinical and radiologic findings are consistent with TDI.

5. Mutational analyses

Molecular genetic analysis using WES demonstrated a *de novo* 2419 T > C (p. Ter807Arg) mutation in the FGFR3 gene caused by a T > C transition at nucleotide 2419 on exon 19, leading to a Stop807Arg (TGA > CGA) substitution for the proband; while the proband's parents did not carry the mutation (Fig. 3A). This mutation in the chain termination stop codon for FGFR3 is expected to give rise to a protein elongation of 101 amino acids (NM_000142.4: exon19: c.2419 T > C(p.X807RfsTer102); the nucleotide and predicted amino acid sequences are depicted in Fig. 3B.

6. Discussion

We present herein a rare case of TDI with a c.2419 T > C (p. Ter807Arg) (X807R) mutation in the FGFR3. At least 18 different cDNA nucleotide changes in the FGFR3 gene have now been reported, representing different protein sequence changes associated with TDI (Table 1). Of these, Arg248Cys and Tyr373Cys account for 55.1%–66.5% and 21.6%–23.7% of TD1, respectively (Xue et al., 2014; Chen et al., 2017). Nine stop codon loss mutations on Exon 19—such as

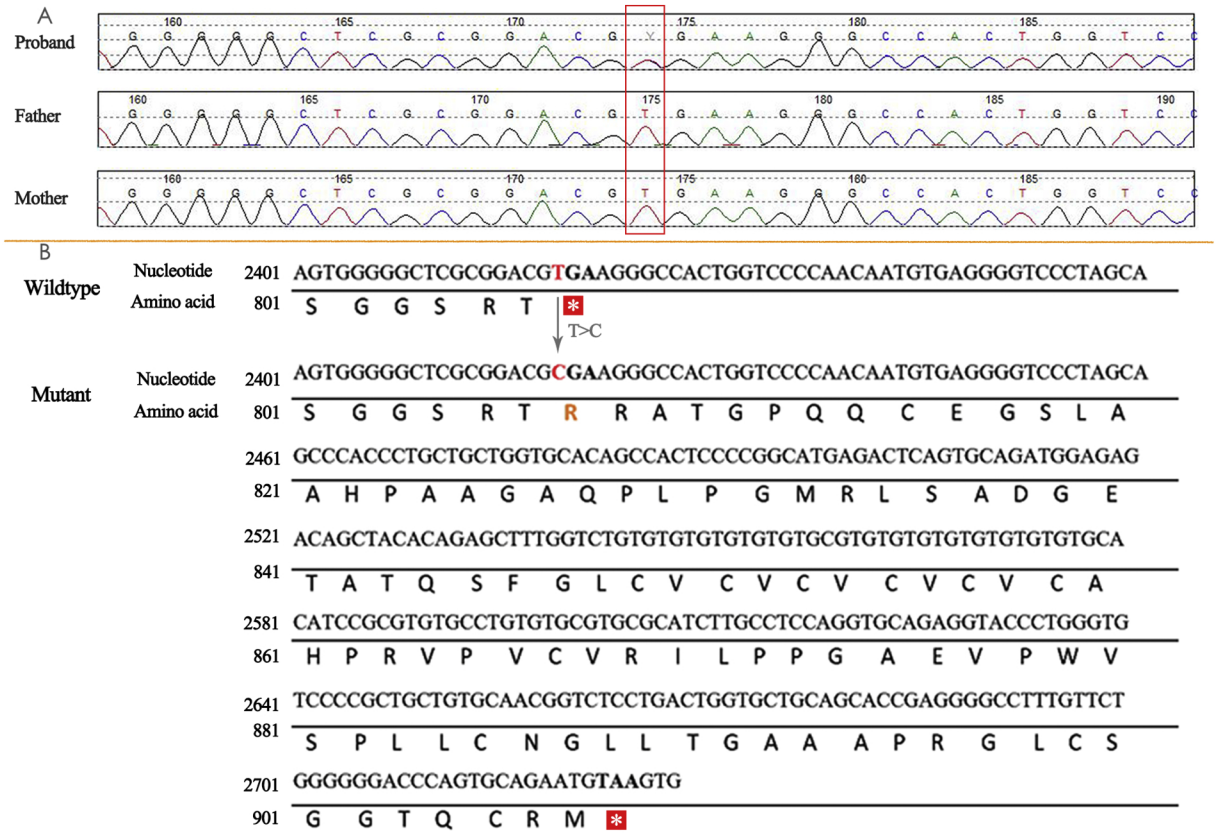

Fig. 3. Whole exon sequencing of the study family, with the nucleotide sequence and predicted amino acid sequence resulting from the X807R mutation. (A): Sanger sequencing demonstrated a mutation in the FGFR3 gene caused by a T > C transition at nucleotide 2419, leading to a Stop807Arg (TGA > CGA) substitution for the proband, while the parents did not carry the mutation. (B): Predicted sequence of the mutated protein with elongation of 101 amino acids (NM_000142.4: exon18: c.2419 T > C (p.X807RfsTer102).

c.2418G > T (Ter807Leu), c.2419 T > G (Ter807Gly), c.2419 T > C (Ter807Arg), c.2419 T > A (Ter807Arg), c.2420G > T (Ter807Leu), c.2420G > C (Ter807Ser), c.2421A > T (Ter807Cys), c.2421A > C (Ter807Cys), and c.2421A > G (Ter807Trp)—have resulted in six different protein sequence extensions and an elongated coding frame caused by mutations in the chain termination stop codon. In contrast to TDI, only the p. Lys650Glu mutation in FGFR3 has been found for TDII. To our knowledge, there is no published detailed description of the clinical characteristics of TDI with the c.2419 T > C (p. Ter807Arg) mutation. The present case therefore appears to be the first report on the clinical phenotype of TDI with the mutation c.2419 T > C (p. Ter807Arg), which results in a protein elongation of 101 amino acids (NM_000142.4: exon19: c.2419 T > C(p.X807RfsTer102); and is verified to impair signal transduction and lead to ligand-independent, constitutive activation of the FGFR3 receptor, inhibition of chondrocyte proliferation, and premature bone maturation (Bonaventure et al., 2007; Del-Piccolo et al., 2015).

Thanatophoric dysplasia is one type of skeletal dysplasia, and as the name “thanatophori” suggests, the condition is frequently lethal *in utero* or shortly after birth; with severe disturbances in bodily proportions, shortening and deformation of the long bones, and maldevelopment of the chest, leading to severe respiratory failure and early death. Almost all neonates with TD require oxygen therapy or mechanical ventilation; and although most patients die of respiratory failure within about one month (Sahin et al., 2016), 4–9-year survivals have been reported (Baker et al., 1997). Our proband also died of respiratory failure at the age of 13 days, caused by narrowing of the thorax and pulmonary hypoplasia. Respiratory insufficiency may have been secondary to the narrowed chest cavity—with a cardio-thoracic proportion of 0.54, and hypoplastic lungs with a PTD of 11.3 mm (< 5th percentile) at 25 weeks—or due to brain stem compression because of the narrowed foramen magnum, or a combination of both. Cranial ultrasonography of the proband displayed bilateral ventriculomegaly and the baby had difficulty in suckling, indicating that the brains of infants with TD possess developmental alterations that significantly affect cerebral cortical structure and function (Foldynova-Trantirkova et al., 2012).

During pregnancy in this study, the ultrasonogram showed a fetus with apparent polyhydramnios, macrocephaly, a depressed nasal bridge, chest narrowing, and femoral bowing using 2D ultrasonography. With 3D ultrasonography, we additionally visualized the fetal structural abnormalities. Therefore, we believe that 3D is a useful adjunct to 2D ultrasonography in third-trimester prenatal diagnosis and parental counseling regarding TDI. Although TDI is likely a preliminary diagnosis, even patients with the same FGFR3 mutation may exhibit phenotypic differences (Chitty et al., 2013). The TD variants occasionally lack typical characteristics, such as facial deformation or different degrees of femoral bowing. We therefore also assert that molecular genetic analysis is beneficial to confirming diagnosis and recommend its use prior to genetic counseling.

In conclusion, our case shows that a stop codon mutation of c.2419 T > C (p. Ter807Arg) (X807R) engenders typical features of TDI. We suggest that prenatal diagnosis of TDI include ultrasonography and a molecular genetic analysis of FGFR3 to elucidate the molecular pathogenesis and the genetic predisposition for the disease, thereby providing important information for genetic counseling.

Disclosure

Authors have no potential conflicts of interest to disclose

Author contributions

Research conception & design: Liling Qian. Performed experiments: Gaoli Jiang and Dan Dai. Data acquisition: Xuexin Chen and Li Cao. Data analysis and interpretation: All authors. Drafting of the manuscript: Gaoli Jiang. Critical revision of the manuscript: Liling Qian. Receiving grant: Liling Qian. Approval of final manuscript: all authors.

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References

Adzhubei, I.A., Schmidt, S., Peshkin, L., Ramensky, V.E., Gerasimova, A., Bork, P., Kondrashov, A.S., Sunyaev, S.R., 2010. A method and server for predicting damaging missense mutations. Nat. Methods 7, 248–249. https://doi.org/10.1038/nmeth0410-248.

Baker, K.M., Olson, D.S., Harding, C.O., Pauli, R.M., 1997. Long-term survival in typical thanatophoric dysplasia type 1. Am. J. Med. Genet. 70, 427–436 (PMID:9182787).

Bonaventure, J., Horne, W.C., Baron, R., 2007. The localization of FGFR3 mutations causing thanatophoric dysplasia type I differentially affects phosphorylation, processing and ubiquitylation of the receptor. FEBS J. 274, 3078–3093. https://doi.org/10.1111/j.1742-4658.2007.05835.x.

Brodie, S.G., Kitoh, H., Lipson, M., Sifry-Platt, M., Wilcox, W.R., 1998. Thanatophoric dysplasia type I with syndactyly. Am. J. Med. Genet. 78, 274–281 (PMID:9843049).

Chen, S.W., Chen, C.P., Wang, L.K., Chern, S.R., Wu, P.C., Chen, Y.N., Lin, C.J., Chen, W.L., Wang, W., 2017. Perinatal imaging findings and molecular genetic analysis of thanatophoric dysplasia type 1 in a fetus with a c.2419T > G (p.Ter807Gly) (X807G) mutation in FGFR3. Taiwan. J. Obstet. Gynecol. 56, 87–92. https://doi.org/10.1016/j.tjog.2016.12.013.

Chitty, L.S., Altman, D.G., 2002. Charts of fetal size: limb bones. BJOG 109, 919–929 (PMID:12197373).

Chitty, L.S., Khalil, A., Barrett, A.N., Pajkrt, E., Griffin, D.R., Cole, T.J., 2013. Safe, accurate, prenatal diagnosis of thanatophoric dysplasia using ultrasound and free fetal DNA. Prenat. Diagn. 33, 416–423. https://doi.org/10.1002/pd.4066.

Del-Piccolo, N., Placone, J., Hristova, K., 2015. Effect of thanatophoric dysplasia type I mutations on FGFR3 dimerization. Biophys. J. 108, 272–278. https://doi.org/10.1016/j.bpj.2014.11.3460.

Foldynova-Trantirkova, S., Wilcox, W.R., Krejci, P., 2012. Sixteen years and counting:the current understanding of fibroblast growth factor receptor 3(FGFR3) signaling in skeletal dysplasias. Hum. Mutat. 33, 29–41. https://doi.org/10.1002/humu.21636.

Gomes, M.E.S., Kanazawa, T.Y., Riba, F.R., Pereira, N.G., Zuma, M.C.C., Rabelo, N.C., Sanseverino, M.T., Horovitz, D.D.G., Llerena, J.C., Cavalcanti, D.P., Gonzalez, S., 2018. Novel and recurrent mutations in the FGFR3 gene and double heterozygosity cases in a cohort of Brazilian patients with skeletal dysplasia. Mol. Syndromol. 9, 92–99. https://doi.org/10.1159/000486697.

Jung, M., Park, S.H., 2017. Genetically confirmed thanatophoric dysplasia with fibroblast growth factor receptor 3 mutation. Exp. Mol. Pathol. 102, 290–295. https://doi.org/10.1016/j.yexmp.2017.02.019.

Kumar, P., Henikoff, S., Ng, P.C., 2009. Predicting the effects of coding non- synonymous variants on protein function using the SIFT algorithm. Nat. Protoc. 4, 1073–1081. https://doi.org/10.1038/nprot.2009.86.

Leung, T.N., Pang, M.W., Daljit, S.S., Leung, T.Y., Poon, C.F., Wong, S.M., Lau, T.K., 2008. Fetal biometry in ethnic Chinese: biparietal diameter, head circumference, abdominal circumference and femur length. Ultrasound Obstet. Gynecol. 31, 321–327. https://doi.org/10.1002/uog.5192.

Lindy, A.S., Basehore, M.J., Munisha, M., Williams, A.L., Friez, M.J., Writzl, K., Willems, P., Dougan, S.T., 2016. Identification of a novel insertion mutation in FGFR3 that causes thanatophoric dysplasia type 1. Am. J. Med. Genet. Part A. 170, 1573–1579. https://doi.org/10.1002/ajmg.a.37609.

Pannier, S., Martinovic, J., Heuertz, S., Delezoide, A.L., Munnich, A., Schibler, L., Serre, V., Legeai-Mallet, L., 2009. Thanatophoric dysplasia caused by double missense FGFR3 mutations. Am. J. Med. Genet. Part A. 149A, 1296–1301. https://doi.org/10.1002/ajmg.a.32880.

Rousseau, F., Saugier, P., Le Merrer, M., Munnich, A., Delezoide, A.L., Maroteaux, P., Bonaventure, J., Narcy, F., Sanak, M., 1995. Stop codon FGFR3 mutations in thanatophoric dwarfism type 1. Nat. Genet. 10, 11–12 (PMID:7647778).

Rousseau, F., El Ghouzzi, V., Delezoide, A.L., Legeai-Mallet, L., Le Merrer, M., Munnich, A., Bonaventure, J., 1996. Missense FGFR3 mutations create cysteine residues in thanatophoric dwarfism type I (TD1). Hum. Mol. Genet. 5, 509–512. 8845844.

Sahin, S., Ograg, H., Aslan, E.A., Akcan, A.B., Turkmen, M.K., Moosa, S., Elcioglu, N.H., 2016. A thanatophoric dysplasia type I case with a p. R248C mutation and survival beyond the neonatal period. Genet. Couns. 27, 513–517 (PMID:30226972).

Schwarz, J.M., Rodelsperger, C., Schuelke, M., Seelow, D., 2010. Mutation taster evaluates disease-causing potential of sequence alterations. Nat. Methods 7, 575–576. https://doi.org/10.1038/nmeth0810-575.

Tavormina, P.L., Shiang, R., Thompson, L.M., Zhu, Y.Z., Wilkin, D.J., Lachman, R.S., Wilcox, W.R., Rimoin, D.L., Cohn, D.H., Wasmuth, J.J., 1995a. Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. Nat. Genet. 9, 321–328 (PMID:7773297).

Tavormina, P.L., Rimoin, D.L., Cohn, D.H., Zhu, Y.Z., Shiang, R., Wasmuth, J.J., 1995b. Another mutation that results in the substitution of an unpaired cysteine residue in the extracellular domain of FGFR3 in thanatophoric dysplasia type I. Hum. Mol. Genet. 4, 2175–2177 (PMID:8589699).

Wilcox, W.R., Tavormina, P.L., Krakow, D., Kitoh, H., Lachman, R.S., Wasmuth, J.J., Thompson, L.M., Rimoin, D.L., 1998. Molecular, radiologic, and histopathologic correlations in thanatophoric dysplasia. Am. J. Med. Genet. 78, 274–281 (PMID:9677066).

Xue, Y., Sun, A., Mekikian, P.B., Martin, J., Rimoin, D.L., Lachman, R.S., Wilcox, W.R., 2014. FGFR3 mutation frequency in 324 cases from the international skeletal dysplasia registry. Mol. Genet. Genomic. Med. 2, 497–503. https://doi.org/10.1002/mgg3.96.