Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 87–92

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

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*

Shin-Wen Chen [a], Chih-Ping Chen [a, b, c, d, e, f, *], Liang-Kai Wang [a], Schu-Rern Chern [b], Pei-Chen Wu [g], Yen-Ni Chen [a], Chen-Ju Lin [a], Wen-Ling Chen [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] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[i] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

ARTICLE INFO

Article history:
Accepted 20 December 2016

Keywords:
FGFR3
perinatal imaging findings
stop codon mutation
thanatophoric dysplasia type 1

ABSTRACT

Objective: We present perinatal imaging findings and molecular genetic analysis of thanatophoric dysplasia type I (TD1) in a fetus.
Case Report: A 28-year-old woman was referred for genetic counseling at 22 weeks of gestation because of abnormal prenatal ultrasound findings. Level II ultrasound examination revealed a narrow chest, shortened and curved long limbs, protrusion of the abdomen, and macrocephaly. A tentative diagnosis of TD1 was made. After genetic counseling, the pregnancy was terminated and a malformed fetus was delivered. Postnatal radiography findings were consistent with the diagnosis of TD1, with additional findings of short ribs, platyspondyly, and horizontal acetabular roofs. Molecular genetic analysis using umbilical cord tissue revealed a heterozygous mutation of c.2419T>G (p.Ter807Gly) (X807G) in the fibroblast growth factor receptor 3 gene *(FGFR3)*.
Conclusion: A second-trimester fetus with a heterozygous c.2419T>G mutation in *FGFR3* may present characteristic ultrasound and X-ray findings of TD1.

Introduction

Thanatophoric dysplasia (TD) is a neonatal, lethal, short-limb dwarfism syndrome, with a prevalence rate of approximately 1:20,000–1:12,000 in prenatal cases [1,2] and 1:47,000–1:33,000 in live births [3].

According to the clinical features, TD is classified as TD type 1 (TD1) and TD type 2 (TD2). TD1 is characterized by short limbs (below the 5th centile at 20 weeks gestation) and curved femurs with or without cloverleaf skull, whereas TD2 is characterized by short limbs with straight femurs and moderate-to-severe cloverleaf skull. The common features of TD1 and TD2 are short limbs, narrow thoracic cage, short ribs, macrocephaly, and brachydactyly [4–8].

TD is a sporadic, autosomal dominant skeletal dysplasia caused by mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*). TD1 is caused by *FGFR3* missense or stop codon mutations [4,9–11], whereas TD2 is caused by only one *FGFR3* missense mutation of p.Lys650Glu (K650E) [12–14]. The FGFR3 protein comprises three main parts: an extracellular region including three immunoglobulin (Ig) domains, a transmembrane segment, and an intracellular region comprising two tyrosine kinase (TK) domains (Figure 1) [15,16]. Here, we present perinatal imaging findings and molecular genetic analysis of TD1 in a fetus with a c.2419T>G (p.Ter807Gly) (X807G) mutation in *FGFR3*.

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

http://dx.doi.org/10.1016/j.tjog.2016.12.013

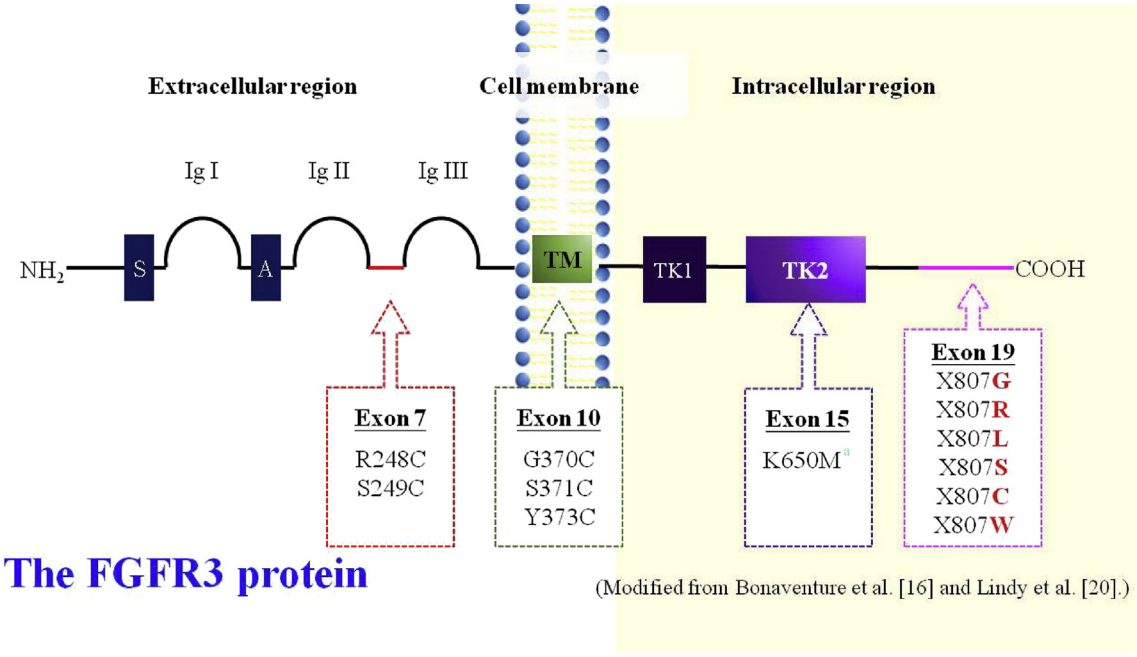

Figure 1. FGFR3 protein structure and reported locations of *FGFR3* gene mutations causing TD1. A = acid box; FGFR3 = fibroblast growth factor receptor 3; Ig, immunoglobulin-like domains (I, II, III); S = secretory peptide; TD1 = thanatophoric dysplasia type 1; TM = transmembrane domain; TK1 = first tyrosine kinase domain; TK2 = second tyrosine kinase domain. [a] Severe achondroplasia with developmental delay and acanthosis nigricans is caused by an amino acid change due to K650M in *FGFR3*.

Case Report

A 28-year-old gravida 1, para 0 woman was referred for genetic counseling at 22 weeks gestation because of abnormal prenatal ultrasound findings. She and her 28-year-old husband were healthy, with no family history of skeletal anomalies. Level II ultrasound examination revealed a narrow chest, shortened and curved long limbs, protrusion of the abdomen, and macrocephaly with a biparietal diameter of 59.7 mm (24 weeks). The lengths of the long limbs were all below the fifth centile of normal biometry: right humerus length (HL) = 18.9 mm (15 weeks), left HL = 18.2 mm (15 weeks), right radius length (RL) = 15.4 mm (15 weeks), left RL = 12.6 mm (14 weeks), right ulna length (UL) = 18.2 mm (16 weeks), left UL = 14.2 mm (15 weeks), right femur length (FL) = 18.1 mm (15 weeks), left FL = 20.1 mm (16 weeks), right tibia length (TL) = 14.7 mm (15 weeks), left TL = 14.0 mm (15 weeks), right fibula length = 14.0 mm (15 weeks), and left fibula length = 13.7 mm (15 weeks). The abdominal circumference (AC) was 175.5 mm (22 weeks) (Figures 2 and 3). The left- and right-side FL/AC ratios were 0.10 (18.1 mm/175.5 mm) and 0.11 (l20.1 mm/175.5 mm), respectively. Both were < 0.16. Parilla et al [17] reported that an FL/AC ratio < 0.16 implies a specific diagnosis of TD. The amount of amniotic fluid was normal. A tentative diagnosis of TD1 was made.

After genetic counseling, the pregnancy was subsequently terminated and a malformed fetus was delivered. Postnatal radiography findings were consistent with the diagnosis of TD1, with additional findings of short ribs, platyspondyly, and horizontal acetabular roofs (Figure 4). The fetal humerus and femur exhibited "telephone handle" bowing with metaphyseal flaring. Cytogenetic

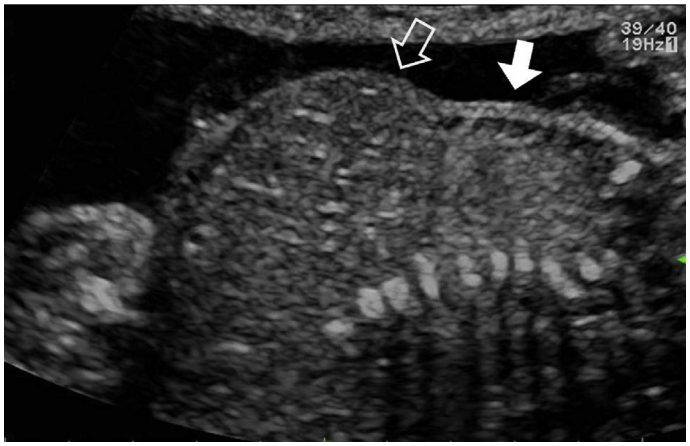

Figure 2. Prenatal ultrasound of fetus at 22 weeks gestation in profile reveals a narrow chest (solid arrow) and protrusion of the abdomen (hollow arrow).

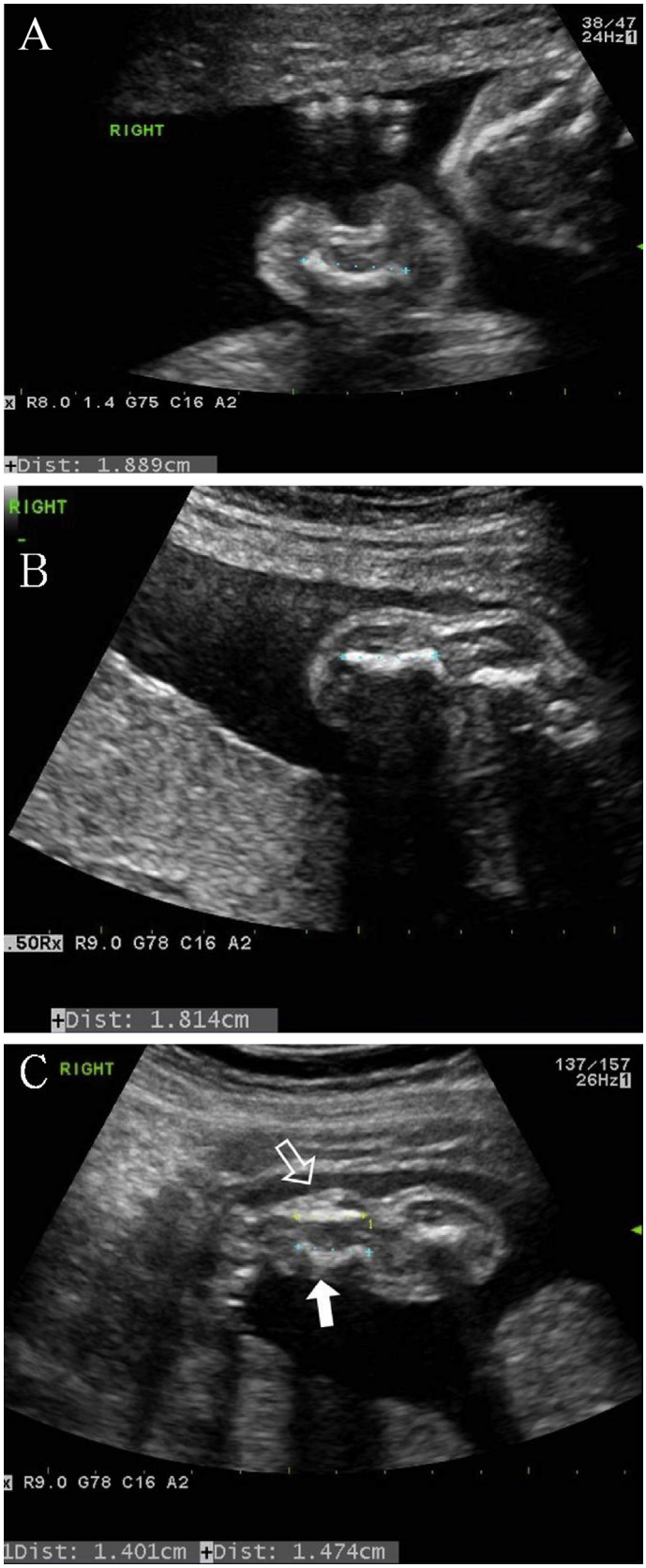

Figure 3. Prenatal ultrasound of fetus at 22 weeks gestation revealed short and curved limbs. (A) Right humerus with a length of 18.9 mm (15 weeks); (B) right femur with a length of 18.1 mm (15 weeks); (C) right tibia (solid arrow) with a length of 14.7 mm (15 weeks), and right fibula (hollow arrow) with a length of 14.0 mm (15 weeks).

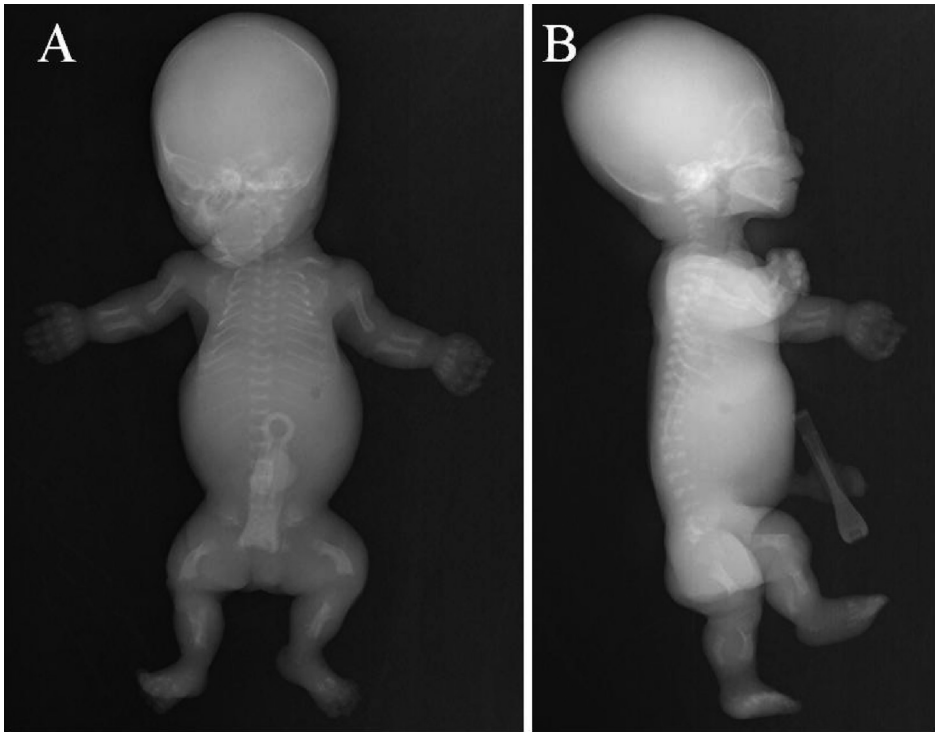

Figure 4. Postnatal radiography revealed a narrow chest, short limbs, short ribs, platyspondyly, horizontal acetabular roofs, and a large head. (A) Coronal view and (B) sagittal view.

analysis of the umbilical cord tissue revealed a karyotype of 46,XX. Molecular genetic analysis of the *FGFR3* gene using the genomic DNA sequence from the umbilical cord tissue revealed a heterozygous mutation of c.2419T>G (p.Ter807Gly) (X807G) (Figure 5).

Discussion

We present a rare case of TD1 with a c.2419T>G (p.Ter807Gly) (X807G) mutation in *FGFR3*. To date, at least 14 different cDNA nucleotide changes in *FGFR3* have been reported, representing 12 different protein sequence changes associated with TD1 (Table 1 and Figure 1) [4,5,9,16,18–20]. The reported six missense mutations result in six different protein amino acid substitutions. The mutations of c.742C>T (R248C) and c.746C>G (S249C) occur in Exon 7, which encodes the linker region between the Ig II and Ig III loops [16]. The mutations of c.1108G>T (G370C), c.1111A>T (S371C), and c.1118A>G (Y373C) occur in exon 10, which encodes the transmembrane domain [16]. The mutation of c.1949A>T (K650M) occurs in Exon 15, which encodes the TK2 domains [4,14,19]. Eight stop codon loss mutations in Exon 19, such as c.2419T>G (X807G), c.2419T>C (X807R), c.2419T>A (X807R), c.2420G>T (X807L), c.2420G>C (X807S), c.2421A>T (X807C), c.2421A>C (X807C), and c.2421A>G (X807W), result in six different protein sequence extensions, and an elongated coding frame caused by the mutations of chain termination stop codon [4,9,11,18,20].

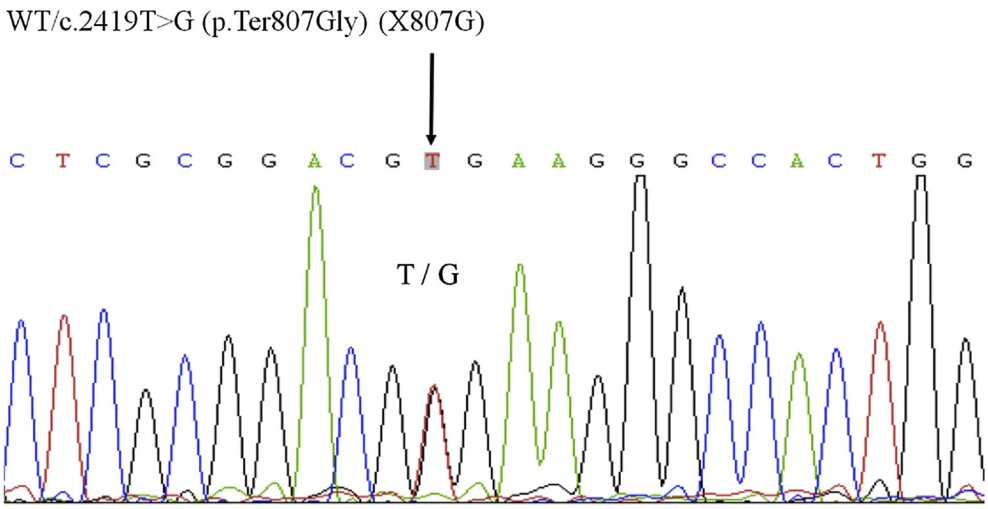

Figure 5. Molecular genetic analysis of the *FGFR3* gene using the genomic DNA sequence from umbilical cord tissue reveals a heterozygous mutation of c.2419T>G (p.Ter807Gly) (X807G).

Table 1
FGFR3 gene mutations in thanatophoric dysplasia type 1.

Mutation category	cDNA nucleotide change	Protein amino acid change		Exon
Missense mutations	c.742C>T	p.Arg248Cys	R248C	07
	c.746C>G	p.Ser249Cys	S249C	07
	c.1108G>T	p.Gly370Cys	G370C	10
	c.1111A>T	p.Ser371Cys	S371C	10
	c.1118A>G	p.Tyr373Cys	Y373C	10
	c.1949A>T[a]	p.Lys650Met	K650M	15
Stop codon mutations	c.2419T>G	p.Ter807Gly	X807G	19
	c.2419T>C	p.Ter807Arg	X807R	19
	c.2419T>A	p.Ter807Arg	X807R	19
	c.2420G>T	p.Ter807Leu	X807L	19
	c.2420G>C[b]	p.Ter807Ser	X807S	19
	c.2421A>T	p.Ter807Cys	X807C	19
	c.2421A>C	p.Ter807Cys	X807C	19
	c.2421A>G	p.Ter807Trp	X807W	19

Modified from Rousseau et al [9], Chen et al [5], Foldynova-Trantirkova et al [19], Xue et al [18], Karczeski et al [4], and Lindy et al [20].
[a] Severe achondroplasia with developmental delay and acanthosis nigricans is caused by an amino acid change due to K650M in *FGFR3*.
[b] The c.2420G>C mutation was reported by Xue et al [18] and Lindy et al [20].

In the cases of TD1, the c.742C>T (R248C) mutation has the highest frequency, followed by the c.1118A>G (Y373C) mutation, and stop codon lost mutations such as c.2419T>G (X807G), c.2419T>C (X807R), c.2419T>A (X807R), c.2420G>T (X807L), c.2420G>C (X807S), c.2421A>T (X807C), c.2421A>C (X807C), and c.2421A>G (X807W) [10,18]. The mutations of c.742C>T (R248C) and c.1118A>G (Y373C), account for 55.1–62.2% and 21.6–22.2% of TD1, respectively (Table 2) [10,18]. Passos-Bueno et al [10] reported that 11.9% (22 cases/185 cases) of TD1 were caused by stop codon mutations, and among the 22 cases with stop codon mutations, seven cases were caused by the c.2419T>G (p.Ter807Gly) (X807G) mutation. Xue et al [18] reported that 6.5% (12 cases/185 cases) of TD1 were caused by stop codon mutations, and among the 12 cases with stop codon mutations, three cases were caused by the c.2419T>G (p.Ter807Gly) (X807G) mutation.

Two-dimensional ultrasound imaging, with or without three-dimensional examination, is useful for prenatal diagnosis of TD [4,21]. If the prenatal sonographic imaging examination demonstrates short limbs, an FL/AC ratio < 0.16, a narrow chest, femoral telephone handle bowing especially after 20 weeks of gestation, and no cloverleaf head deformity, TD1 is likely a preliminary diagnosis [4,17,22]. However, even patients with the same *FGFR3* mutation may have phenotypic differences. The TD variants occasionally lack typical characteristics, such as facial deformation or different degrees of femur bowing [5]. Wilcox et al [23] and Castori et al [24] suggested that the phenotypic variability of TD may be due to nonallelic genetic variability, epigenetic/environmental, and stochastic factors. For example, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), an allelic disease of TD1, is caused by an amino acid change due to c.1949A>T (K650M) in *FGFR3* [25–27]. The radiographic features and sonographic findings in SADDAN are similar to those in TD1, but the phenotypes are milder in SADDAN than in TD1 [14,28]. The most distinct difference between SADDAN and TD1 is longer-term survival, craniosynostosis, and acanthosis nigricans in patients with SADDAN [27,28].

Our case shows that a stop codon mutation of c.2419T>G (p.Ter807Gly) (X807G) can exhibit typical features of TD1. We suggest that prenatal diagnosis of TD1 by ultrasound should include a molecular genetic analysis of *FGFR3* to elucidate the molecular pathogenesis and the acquired information will provide useful information for genetic counseling.

Table 2
Reported FGFR3 gene mutations in TD1.

Mutations	cDNA nucleotide change	Protein amino acid change	Passos-Bueno et al 1999		Xue et al 2014	
			No. of cases[a]	%	No. of cases[b]	%
Missense	c.742C>T	R248C	102	55.1%	115	62.2%
	c.746C>G	S249C	13	7.0%	11	5.9%
	c.1108G>T	G370C	2	1.1%	4	2.2%
	c.1111A>T	S371C	1	0.5%	–[c]	–
	c.1118A>G	Y373C	40	21.6%	41	22.2%
	c.1949A>T	K650M	5	2.7%	2	1.1%
Stop codon	c.2419T>G	X807G	7	3.8%	3	1.6%
	c.2419T>C	X807R	–	–	2	1.1%
	c.2419T>A	X807R	5	2.7%	2	1.1%
	c.2420G>T	X807L	2	1.1%	1	0.5%
	c.2420G>C	X807S	–	–	1	0.5%
	c.2421A>T	X807C	5	2.7%	–	–
	c.2421A>C	X807C	1	0.5%	–	–
	c.2421A>G	X807W	2	1.1%	3	1.6%
Total No.			185		185	

[a] Including reports by Rousseau et al [9,11], Tavormina et al [13,29,30], Bonaventure et al [16], Nerlich et al [31], Pokharel et al [32], Bellus et al [33], Camera et al [34], Wilcox et al [23], Kitoh et al [12], Brodie et al [35,36], and Wilcox and Kitoh [10].
[b] Including 93 cases of thanatophoric dysplasia type 1 and platyspondylic lethal skeletal dysplasia, San Diego type (PLSD-SD) reported by Tavormina et al [13], Kitoh et al [12], Wilcox et al [23] and Brodie et al [35,36].
[c] no information.

Conflict of interest

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

Acknowledgments

This work was supported by research grants MOST-104-2314-B-195-009 and MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-105-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

[1] Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for the skeletal dysplasias. J Med Genet 1986;23:328–32.
[2] Donnelly DE, McConnell V, Paterson A, Morrison PJ. The prevalence of thanatophoric dysplasia and lethal osteogenesis imperfecta type II in Northern Ireland – a complete population study. Ulster Med J 2010;79:114–8.
[3] Waller DK, Correa A, Vo TM, Wang Y, Hobbs C, Langlois PH, et al. The population-based prevalence of achondroplasia and thanatophoric dysplasia in selected regions of the US. Am J Med Genet A 2008;146a:2385–9.
[4] Karczeski B, Cutting GR. Thanatophoric dysplasia. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20301540. Updated September 12, 2013; [Accessed 1 October 2016].
[5] Chen CP, Chern SR, Shih JC, Wang W, Yeh LF, Chang TY, et al. Prenatal diagnosis and genetic analysis of type I and type II thanatophoric dysplasia. Prenat Diagn 2001;21:89–95.
[6] Langer Jr LO, Yang SS, Hall JG, Sommer A, Kottamasu SR, Golabi M, et al. Thanatophoric dysplasia and cloverleaf skull. Am J Med Genet Suppl 1987;3:167–79.
[7] Spranger J, Maroteaux P. The lethal osteochondrodysplasias. Adv Hum Genet 1990;19. 1–103, 331–2.
[8] Norman AM, Rimmer S, Landy S, Donnai D. Thanatophoric dysplasia of the straight-bone type (type 2). Clin Dysmorphol 1992;1:115–20.
[9] Rousseau F, Saugier P, Merrer ML, Munnich A, Delezoide A-L, Maroteaux P, et al. Stop codon FGFR3 mutations in thanatophoric dwarfism type 1. Nat Genet 1995;10:11–2.
[10] Passos-Bueno MR, Wilcox WR, Jabs EW, Sertie AL, Alonso LG, Kitoh H. Clinical spectrum of fibroblast growth factor receptor mutations. Hum Mutat 1999;14:115–25.
[11] Rousseau F, el Ghouzzi V, Delezoide AL, Legeai-Mallet L, Le Merrer M, Munnich A, et al. Missense FGFR3 mutations create cysteine residues in thanatophoric dwarfism type I (TD1). Hum Mol Genet 1996;5:509–12.
[12] Kitoh H, Brodie SG, Kupke KG, Lachman RS, Wilcox WR. Lys650Met substitution in the tyrosine kinase domain of the fibroblast growth factor receptor

gene causes thanatophoric dysplasia Type I. Mutations in brief no. 199. Online. Hum Mutat 1998;12:362–3.
[13] Tavormina PL, Shiang R, Thompson LM, Zhu YZ, Wilkin DJ, Lachman RS, et al. Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. Nat Genet 1995;9:321–8.
[14] Bellus GA, Spector EB, Speiser PW, Weaver CA, Garber AT, Bryke CR, et al. Distinct missense mutations of the FGFR3 lys650 codon modulate receptor kinase activation and the severity of the skeletal dysplasia phenotype. Am J Hum Genet 2000;67:1411–21.
[15] Perez-Castro AV, Wilson J, Altherr MR. Genomic organization of the human fibroblast growth factor receptor 3 (FGFR3) gene and comparative sequence analysis with the mouse Fgfr3 gene. Genomics 1997;41:10–6.
[16] Bonaventure J, Rousseau F, Legeai-Mallet L, Le Merrer M, Munnich A, Maroteaux P. Common mutations in the fibroblast growth factor receptor 3 (FGFR 3) gene account for achondroplasia, hypochondroplasia, and thanatophoric dwarfism. Am J Med Genet 1996;63:148–54.
[17] Parilla BV, Leeth EA, Kambich MP, Chilis P, MacGregor SN. Antenatal detection of skeletal dysplasias. J Ultrasound Med 2003;22:255–8.
[18] Xue Y, Sun A, Mekikian PB, Martin J, Rimoin DL, Lachman RS, et al. FGFR3 mutation frequency in 324 cases from the International Skeletal Dysplasia Registry. Mol Genet Genomic Med 2014;2:497–503.
[19] Foldynova-Trantirkova S, Wilcox WR, Krejci P. Sixteen years and counting: the current understanding of fibroblast growth factor receptor 3 (FGFR3) signaling in skeletal dysplasias. Hum Mutat 2012;33:29–41.
[20] Lindy AS, Basehore MJ, Munisha M, Williams AL, Friez MJ, Writzl K, et al. Identification of a novel insertion mutation in FGFR3 that causes thanatophoric dysplasia type 1. Am J Med Genet A 2016;170:1573–9.
[21] Chen CP, Chang TY, Chern SR, Wang W. Third-trimester 3D ultrasound evaluation of thanatophoric dysplasia type I. Taiwan J Obstet Gynecol 2007;46:281–3.
[22] Chen CP, Chern SR, Chang TY, Lin CJ, Wang W, Tzen CY. Second trimester molecular diagnosis of a stop codon FGFR3 mutation in a type I thanatophoric dysplasia fetus following abnormal ultrasound findings. Prenat Diagn 2002;22:736–7.
[23] Wilcox WR, Tavormina PL, Krakow D, Kitoh H, Lachman RS, Wasmuth JJ, et al. Molecular, radiologic, and histopathologic correlations in thanatophoric dysplasia. Am J Med Genet 1998;78:274–81.
[24] Castori M, Morlino S, Radio FC, De Bernardo C, Grammatico P. The “old theme” of variability versus transitory phenotypes in thanatophoric dysplasia type 1: two 19-week-old fetuses with (“San Diego” variant) and without ragged metaphyses due to the same FGFR3 mutation. Am J Med Genet A 2013;161a:2675–7.
[25] Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, et al. Nosology and classification of genetic skeletal disorders: 2015 revision. Am J Med Genet A 2015;167a:2869–92.
[26] Lemyre E, Azouz EM, Teebi AS, Glanc P, Chen MF. Bone dysplasia series. Achondroplasia, hypochondroplasia and thanatophoric dysplasia: review and update. Can Assoc Radiol J 1999;50:185–97.
[27] Bellus GA, Bamshad MJ, Przylepa KA, Dorst J, Lee RR, Hurko O, et al. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN): phenotypic analysis of a new skeletal dysplasia caused by a Lys650Met mutation in fibroblast growth factor receptor 3. Am J Med Genet 1999;85:53–65.
[28] Farmakis SG, Shinawi M, Miller-Thomas M, Radmanesh A, Herman TE. FGFR3-related condition: a skeletal dysplasia with similarities to thanatophoric dysplasia and SADDAN due to Lys650Met. Skeletal Radiol 2015;44:441–5.
[29] Tavormina PL, Rimoin DL, Cohn DH, Zhu YZ, Shiang R, Wasmuth JJ. 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 1995;4:2175–7.
[30] Tavormina PL, Bellus GA, Webster MK, Bamshad MJ, Fraley AE, McIntosh I, et al. A novel skeletal dysplasia with developmental delay and acanthosis nigricans is caused by a Lys650Met mutation in the fibroblast growth factor receptor 3 gene. Am J Hum Genet 1999;64:722–31.
[31] Nerlich AG, Freisinger P, Bonaventure J. Radiological and histological variants of thanatophoric dysplasia are associated with common mutations in FGFR-3. Am J Med Genet 1996;63:155–60.
[32] Pokharel RK, Alimsardjono H, Takeshima Y, Nakamura H, Naritomi K, Hirose S, et al. Japanese cases of type 1 thanatophoric dysplasia exclusively carry a C to T transition at nucleotide 742 of the fibroblast growth factor receptor 3 gene. Biochem Biophys Res Commun 1996;227:236–9.
[33] Bellus GA, Baker A, Spector EB, Hunter AGW, Hecht J, Lewanda AF, et al. Mutational analysis of FGFR3 in thanatophoric dysplasia type I. Am J Hum Genet 1997;61(Suppl.):A326.
[34] Camera G, Baldi M, Baffico M, Pozzolo S. An unusual radiological finding in thanatophoric dysplasia type 1 with common mutation of the fibroblast growth factor receptor-3 (FGFR3) gene (Arg248Cys). Am J Med Genet 1997;71:122–3.
[35] Brodie SG, Kitoh H, Lachman RS, Nolasco LM, Mekikian PB, Wilcox WR. Platyspondylic lethal skeletal dysplasia, San Diego type, is caused by FGFR3 mutations. Am J Med Genet 1999;84:476–80.
[36] Brodie SG, Kitoh H, Lipson M, Sifry-Platt M, Wilcox WR. Thanatophoric dysplasia type I with syndactyly. Am J Med Genet 1998;80:260–2.