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Case Report

Detection of a *de novo* Y278C mutation in FGFR3 in a pregnancy with severe fetal hypochondroplasia: Prenatal diagnosis and literature review

Chih-Ping Chen [a,b,c,d,e,f,*], Yi-Ning Su [g,h], Tzu-Hung Lin [g], Tung-Yao Chang [i], Jun-Wei Su [a,j], Wayseen Wang [b,k]

[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] *Department of Obstetrics and Gynecology, School of Medicine, Taipei Medical University, Taipei, Taiwan*
[h] *Dianthus MFM Clinic, Taipei, Taiwan*
[i] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[j] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[k] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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Abstract

Objective: We describe a prenatal molecular diagnosis of hypochondroplasia (HCH) in a pregnancy not at risk of HCH and review the literature on prenatal diagnosis of HCH.

Case report: A 28-year-old primigravid woman was referred for genetic counseling at 30 weeks of gestation because of short-limbed dwarfism in the fetus. The woman had a body height of 152 cm. Her husband had a body height of 180 cm. Level II ultrasound showed a normal amount of amniotic fluid and a singleton fetus with fetal biometry equivalent to 30 weeks except for short limbs. Fetal biometry measurements were as follows: biparietal diameter = 7.38 cm (30 weeks); head circumference = 28.14 cm (30 weeks); abdominal circumference (AC) = 24.64 cm (30 weeks); femur length (FL) = 3.97 cm (<5th centile); FL/AC ratio = 0.161 (normal > 0.18); humerus = 3.64 cm (<5th centile); radius = 3.49 cm (30 weeks); ulna = 3.76 cm (<5th centile); tibia = 3.67 cm (<5th centile); and fibula = 3.72 cm (<5th centile). The digits and craniofacial appearance were normal. A tentative diagnosis of achondroplasia (ACH) was made. DNA testing for the *FGFR3* gene and whole-genome array comparative genomic hybridization (aCGH) analysis were performed using cord blood DNA obtained by cordocentesis. *FGFR3* mutation analysis revealed a *de novo* heterozygous c.833A > G, TAC > TGC transversion in exon 7 leading to a p.Tyr278Cys (Y278C) mutation in the FGFR3 protein. aCGH analysis revealed no genomic imbalance in cord blood. After delivery, the fetus had short limbs, a narrow thorax, brachydactyly, and relative macrocephaly. Cytogenetic analysis of cultured placental cells revealed a karyotype of 46,XX.

Conclusion: Prenatal diagnosis of abnormal ultrasound findings suspicious of ACH should include a differential diagnosis of HCH by molecular analysis of *FGFR3*.

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Keywords: FGFR3; hypochondroplasia; prenatal diagnosis

* 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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Introduction

Hypochondroplasia (HCH; OMIM 146000) is an autosomal dominant skeletal dysplasia caused by mutations in the *FGFR3* gene. *FGFR3* (OMIM 134934) encodes fibroblast growth factor receptor 3 and is located at 4p16.3. A heterozygous FGFR3 N540K mutation accounts for 70% of all reported patients [1,2]. HCH is characterized by short-limbed dwarfism, broad short hands and feet, mild joint laxity, macrocephaly, and roentgenographic findings of narrow inferior lumbar interpedicular distances, short long bones with mild metaphyseal flare, a short broad femur neck, and short square ilia [3]. Prenatal molecular diagnosis of HCH in a pregnancy not at risk of HCH is uncommon. Here, we present our experience of prenatal diagnosis of a *de novo* FGFR3 Y278C mutation in a pregnancy with fetal severe HCH and review the literature on prenatal diagnosis of HCH.

Case report

A 28-year-old primigravid woman was referred for genetic counseling at 30 weeks of gestation because of short-limbed dwarfism in the fetus. The woman had a body height of 152 cm. Her husband was 30 years old and had a body height of 180 cm. Both were healthy and unrelated, and there was no family history of congenital malformations. The prenatal ultrasound was unremarkable until 28 weeks of gestation, when a short femur was noted, with a femur length (FL) of 3.9 cm equivalent to 24 weeks. The biparietal diameter (BPD) was 7.3 cm (28 weeks), abdominal circumference (AC) was 23.7 cm (28 weeks), and the FL/AC ratio was 0.165. Level II ultrasound at 30 weeks of gestation showed a normal amount of amniotic fluid and a singleton fetus with fetal biometry equivalent to 30 weeks except for short limbs. Fetal biometry measurements were as follows (30-week 5th–95th centile range): BPD = 7.38 cm (7.30–8.20 cm); head circumference (HC) = 28.14 cm (26.6–30.9 cm); AC = 24.64 cm (21.7–27.4 cm); FL = 3.97 cm (5.20–6.20 cm); HC/AC = 1.14 (0.97–1.18); HC/FL = 7.09 (4.54–5.38); FL/AC = 0.161 (normal > 0.18); humerus = 3.64 cm (4.4–5.6 cm); radius = 3.49 cm (3.4–4.9 cm); ulna = 3.76 cm (3.8–5.4 cm); tibia = 3.67 cm (4.1–5.6 cm); and fibula = 3.72 cm (3.8–5.2 cm). The digits and craniofacial appearance were normal. A tentative diagnosis of achondroplasia (ACH) was made. DNA testing for the *FGFR3* gene and whole-genome array comparative genomic hybridization (aCGH) analysis were performed using cord blood DNA obtained by cordocentesis. *FGFR3* mutation analysis revealed a *de novo* heterozygous c.833A > G, TAC > TGC transversion in exon 7 leading to a p.Tyr278Cys (Y278C) mutation in the FGFR3 protein (Fig. 1). Mutation analysis of parental blood samples did not reveal this mutation (Fig. 1). aCGH analysis revealed no genomic imbalance in cord blood. A 1586-g fetus was delivered at 31 weeks of gestation with a body length of 41 cm. The fetus had short limbs, a narrow thorax, brachydactyly, and relative macrocephaly (Fig. 2). Cytogenetic analysis of cultured placental cells revealed a karyotype of 46,XX.

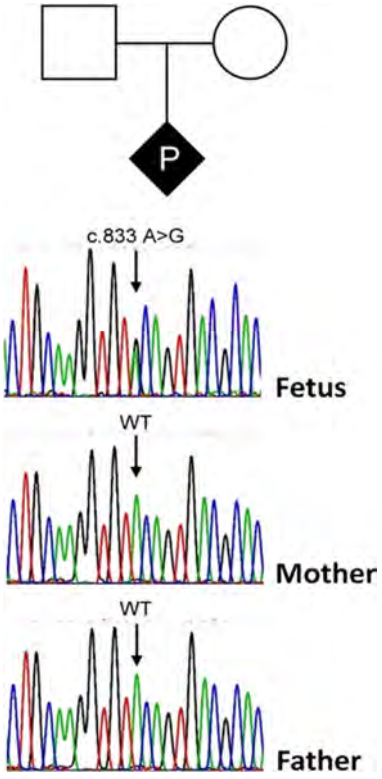

Fig. 1. *FGFR3* mutation analysis for cord blood and parental blood samples revealed a *de novo* heterozygous c.833A > G, TAG > TGC transversion in exon 7 leading to p.Tyr278Cys (Y278C) mutation in FGFR3 in the fetus.

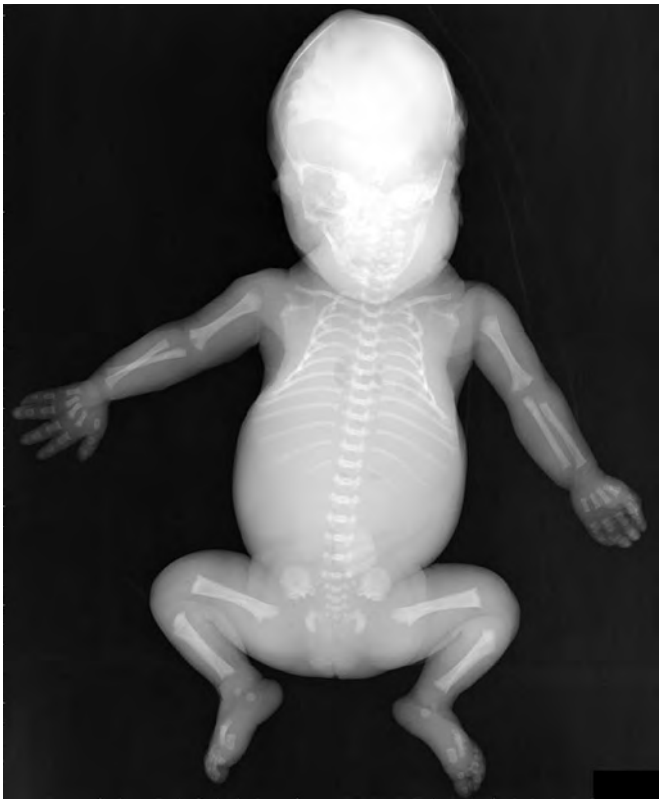

Fig. 2. Whole-body X-ray of the fetus at birth.

Table 1
Reported cases of hypochondroplasia with prenatal diagnosis.

Authors	*FGFR3* mutation	Inheritance	Prenatal findings	Postnatal findings
Stoll et al [19]	NA	Familial (paternal)	Father 28 y, 134 cm, HCH; mother: 28 y, 160 cm Ultrasound (22 wk): FL = 3.4 cm (−2.4 SD)	Delivery at 25 wk; X-ray: short square iliac wings, reduced sacroiliac notch, flat acetabular roof with a spicule
Jones et al [20]	NA	Sporadic	Father 35 y, mother 35 y, both normal Ultrasound (26 wk): BPD = 6.5 cm (26−27 wk), FL = 3.8 cm (24 wk), HL = 3.9 cm (24 wk) Ultrasound (35 wk): BPD = 8.7 cm (35 wk), FL = 5.4 cm (27−28 wk), HL = 4.7 cm (27−28 wk) Ultrasound (39 wk): BPD = 9.62 cm (39.3 wk), AC = 33.8 cm (37.7 wk), FL = 5.89 cm (31.1 wk), HL = 5.44 cm (31.5 wk), FL/AC = 0.174	Delivery at 40 wk; X-ray: mildly short femora and humeri, slight narrowing of the sacroiliac notch; X-ray (12 m): narrowing of the interpediculate distances within the lumbar spine, flattening of the acetabular roofs, shortening of proximal and distal long bones, flattening of the base of the skull, HCH
Chitayat et al [21]	p.G380R p.N540K	Familial (biparental)	Father 20 y, HCH, N540K; mother 25 y, ACH, G380R Amniocentesis (16 wk): compound heterozygous FGFR3 G380R and N540K mutations Ultrasound (14 wk 6 d): BPD = 3.3 cm (15.6 wk), FL = 1.8 cm (15.1 wk), HL = 1.6 cm (14.4 wk), FL/AC = 0.186 Ultrasound (17 wk 6 d): BPD = 4.2 cm (18.4 wk), FL = 2.4 cm (17.4 wk), HL = 2.3 cm (17 wk), FL/AC = 0.189 Ultrasound (22 wk 1 d): BPD = 5.8 cm (23.6 wk), FL = 3.3 cm (20.2 wk), HL = 3 cm (20.2 wk), FL/AC = 0.167 Ultrasound (27 wk 3 d): BPD = 8 cm (32.2 wk), FL = 4.1 cm (23.2 wk), HL = = 3.6 cm (22.3 wk), FL/AC = 0.158 Ultrasound (31 wk 4 d): BPD = 9.1 cm (37.3 wk), FL = 3.9 cm (22.4 wk), HL = 3.7 cm (23 wk), FL/AC = 0.134	Delivery at 38 wk, 3325 g, high forehead, large skull, frontal bossing, depressed nasal bridge, narrow chest, trident position of the fingers, rhizomelic shortening of long bones with flare of the metaphyses, seizures and hypotonia at 9d; CT scan at 2 wk: partial agenesis of corpus callosum, cerebral dysplasia
Huggins et al [22]	p.N540K	Familial (paternal)	Father HCH, N540K; mother 23 y, ACH, G380R Ultrasound (15 wk 6 d): BPD = 3.8 cm (17.4 wk), FL = 1.8 cm (15.1 wk), HL = 1.8 cm (15 wk), AC = 10.9 cm (16.4 wk), FL/AC = 0.165 Ultrasound (18 wk 6 d): BPD = 4.7 cm (20.2 wk), FL = 2.6 cm (17.6 wk), HL = 2.6 cm (17.7 wk), AC = 14.7 cm (19.7 wk), FL/AC = 0.177 Ultrasound (21 wk 6 d): BPD = 5.6 cm (23.2 wk), FL = 3.2 cm (19.6 wk), HL = 3.2 cm (20 wk), AC = 18.7 cm (23.3 wk), FL/AC = 0.171 Ultrasound (24 wk 6 d): BPD = 6.7 cm (27.2 wk), FL = 3.8 cm (21.8 wk), AC = 21.9 cm (26.2 wk), FL/AC = 0.174 Ultrasound (28 wk 5 d): BPD = 7.6 cm (30.8 wk), FL = 4.4 cm (24.1 wk), HL = 4.0 cm (23.7 wk), AC = 26.3 cm (30.4 wk), FL/AC = 0.167 Ultrasound (31 wk 1 d): BPD = 8.6 cm (34.8 wk), FL = 4.3 cm (23.7 wk), AC = 29.5 cm (33.6 wk), FL/AC = 0.146	Delivery at 35 wk, 2706 g, rhizomelic shortening of all limbs, hypospadias; X-ray: short femora and humeri; cord blood and paternal blood: FGFR3 N540K mutation; maternal blood: FGFR3 G380R mutation
Kataoka et al [23]	c.1659C>G	Sporadic	Father 22 y, 170 cm; mother 23 y, 165 cm Ultrasound (37 wk): FL = 5.0 cm (28 wk), BPD = 9.15 cm (39 wk), FL/AC = 0.18	Delivery at 39 wk, 3000 g, mild short limbs; X-ray: narrow thorax, shortening of the greater sciatic notches of the ilia, lack of normal iliac flaring, oval radiolucent areas of the proximal femora; cord blood: 46,XY, *FGFR3* c.1659C > G (*de novo*) mutation

Table 1 (*continued*)

Authors	*FGFR3* mutation	Inheritance	Prenatal findings	Postnatal findings
Bonnefoy et al [24]	p.N540K	Sporadic	Father 35 y; mother 34 y Ultrasound (12 wk & 22 wk): normal Ultrasound (32 wk): FL = 5.3 cm (28 wk), HL = 4.7 cm (28 wk) Ultrasound (35 wk): FL = 5.7 cm (30 wk), HL = 5.0 cm (30 wk), BPD = 9.8 cm (40 wk), FL/foot = 0.81 3D ultrasound: lack of normal iliac flaring, depressed nasal bridge, femoral metaphyseal abnormalities, horizontalization of the roof of the cotyla, radiolucent areas of the proximal femora Amniocentesis (36 wk): 46,XX, FGFR3 N540K (*de novo*) mutation	Delivery at 38 wk; X-ray: narrow thorax, lack of normal iliac flaring, oval radiolucent areas of the proximal femora
Karadimas et al [25]				
Case 1	p.N540K	Sporadic	Father 35 y; mother 27 y, both average height Ultrasound (21 wk 2 d): normal Ultrasound (23 wk 4 d): all long bones <5th centile, FL/foot <0.87, FL/AC = 0.18, ventriculomegaly, bowing femora and humeri Amniocentesis: 46,XY, exclusion of FGFR3 G380R for ACH Decreased long bone development at 27 wk Retrospective study of prenatal DNA: FGFR3 N540K (*de novo*) mutation	Delivery at 27 wk, 1020 g, short stature, bowed lower limbs, mildly stubby hands and feet, normal craniofacial appearance
Case 2	p.N540K	Sporadic	Father 33 y, mother 28 y, both average height Ultrasound (22 wk 2 d): all long bones 5th–10th centile Ultrasound (24 wk 6 d): mild bowing of femora and humeri (<5th centile), FL/foot <0.87, FL/AC <0.18 Amniocentesis: 46,XX, exclusion of FGFR3 G380R for ACH Ultrasound (28 wk): normal BPD, AC, foot length, FL = 4.3 cm (<3rd centile), HL = 4.2 cm (<3rd centile), FL/foot = 0.74, FL/AC = 0.17 Retrospective study of prenatal DNA: FGFR3 N540K (*de novo*) mutation	Delivery at 28 wk, 1280 g, short stature, bowed lower limbs, mildly stubby hands and feet, brachydactyly, normal cranium and face, borderline increase in HC
Hatzaki et al [26]	p.N540K	Familial (maternal)	Mother 31 y, HCH CVS (12 wk): FGFR3 N540K mutation	TOP
Park et al [27]				
Two cases	p.N540K	Familial (maternal)	Mother <27 y, HCH, N540K CVS: FGFR3 N540K mutation in two pregnancies	TOP in two pregnancies
Wang et al [12]	p.G342C	Familial (maternal)	Father 170 cm; mother 25 y, 131 cm, HCH Ultrasound (13 wk): normal Ultrasound (23 wk): FL = 3.43 cm (20 wk 6 d), FL/foot = 0.8, FL/AC = 0.18, BPD normal Ultrasound (28 wk): FL = 4.6 cm (25 wk), BPD normal	Delivery at 29 wk; X-ray: HCH; cord blood and maternal blood: FGFR3 G342C mutation
Present case	p.Y278C	Sporadic	Father 30 y, 180 cm; mother 28 y, 152 cm Ultrasound (13 wk, 16 wk, & 24 wk): normal Ultrasound (28 wk): BPD = 7.3 cm (28 wk), FL = 3.9 cm (24 wk), AC = 23.7 cm (28 wk), FL/AC = 0.165 Ultrasound (30 wk): BPD = 7.38 cm (30 wk), FL = 3.97 cm (<5th centile), AC = 24.64 cm (30 wk), FL/AC = 0.161 Cordocentesis: FGFR3 Y278C (*de novo*) mutation	Delivery at 31 wk, 1586 g; X-ray: short limbs, brachydactyly, relative macrocephaly

AC = abdominal circumference; ACH = achondroplasia; BPD = biparietal diameter; CVS = chorionic villus sampling; FL = femur length; HC = head circumference; HCH = hypochondroplasia; HL = humerus length; NA = not available; SD = standard deviation; TOP = termination of pregnancy.

Discussion

The present case was associated with a *de novo* heterozygous Y278C mutation in FGFR3 and HCH. The patient carried a single base substitution (c.833A > G, TAC > TGC) that substitutes tyrosine 278 with cysteine (Y278C) in the first half of the third immunoglobulin-like loop of FGFR3. Approximately 70% of patients affected with HCH have a heterozygous mutation in *FGFR3*, and ~72% of patients with FGFR3 mutations have N540K (Asn540Lys) resulting from *FGFR3*

c.1620C > A (70%) and *FGFR3* c.1620C > G (30%) [3–8]. Other rare mutations include S84L [9], R200C [9], N262H [9], G268C [9], Y278C [9], L324V [10], N328I [11], G342C [12], V381E [9], I538V [13], N540S [14,15], N540T [16], K650N [17], K650Q [9,18], and K652Q [17]. In a study of 74 patients with HCH, Heuertz et al found 10 (14%) familial cases and 64 (86%) sporadic cases with the following mutations: N540K (63.5%; 47 cases), K650Q (1.4%; 1 case), N328I (1.4%; 1 case); novel mutations of S84L, R200C, N262H, G268C, Y278C and V381E (8%; 6 cases); and no FGFR3 mutation (25.7%; 19 cases) [9]. Heuertz et al first reported a Y278C FGFR3 mutation in a patient with severe HCH [9]. The patient had a phenotype of ACH at birth, manifest as rhizomelic dwarfism, macrocephaly with midface hypoplasia, thoracolumbar kyphosis, short trident hands, and mild hypotonia at the age of 6 months; and a phenotype of HCH with normal craniofacial features, small stature with relatively short upper arms and thighs, and lumbar hyperlordosis at the age of 3.5 years.

To date, at least 12 cases of HCH with prenatal diagnosis have been reported [12,19–27]. Table 1 lists the *FGFR3* mutations and prenatal and postnatal findings for 13 cases of HCH with prenatal diagnosis, including the present case. Among the 13 cases, six were sporadic and seven were familial, of which three involved paternal HCH [19,21,22] and four involved maternal HCH [12,26,27]. Five cases were carried to term delivery [20–24]. In the two cases with ACH and HCH in either parent, the parents decided to continue with the pregnancy even though prenatal ultrasound and/or molecular genetic analysis confirmed familial inherited skeletal dysplasia [21,22]. The data in Table 1 show that fetuses with HCH can present with a short femur and humerus, relative macrocephaly, and an FL/AC ratio <0.18 in late second trimester without the associated abnormalities of ventriculomegaly, congenital heart defects, polydactyly, narrow thorax, and polyhydramnios. Prenatal findings for HCH are very similar to those for ACH. Therefore, prenatal diagnosis of abnormal ultrasound findings suspicious of ACH should include a differential diagnosis of HCH by molecular analysis of FGFR3 G380R and N540K mutations and other rare *FGFR3* mutations associated with ACH and HCH if necessary. In the present case, the mother had a short stature but no molecular evidence of HCH. Prenatal diagnosis of short-limbed dwarfism in the presence of parental short stature other than ACH should raise a suspicion of familial HCH. For instance, Stoll et al reported prenatal diagnosis of paternally inherited HCH with a paternal height of 134 cm [19] and Wang et al reported prenatal diagnosis of maternally inherited HCH with a maternal height of 131 cm [12]. Prenatal diagnosis of HCH can be achieved by molecular analysis of fetal DNA extracted from amniotic fluid cells [19,24,25], chorionic villi cells [26,27], cord blood lymphocytes (present case), or single-cell analysis by blastomere biopsy [27]. Park et al reported on a successful pregnancy and birth with preimplantation genetic diagnosis using single-cell PCR and sequencing in a 27-year-old woman with HCH, FGFR3 N540K mutation, and two consecutive abortions of HCH-affected fetuses diagnosed by molecular sequencing of chorionic villus samples [27].

In summary, we have described prenatal molecular diagnosis of a *de novo* Y278C FGFR3 mutation in a pregnancy with fetal severe HCH and reviewed the literature on prenatal diagnosis of HCH. We emphasize the importance of molecular analysis of the *FGFR3* gene in prenatally detected short-limbed dwarfism suspicious of ACH and HCH.

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