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WHOLE EXOME SEQUENCING IDENTIFIED A PATHOGENIC VARIANT c.1620C>G IN THE *FGFR3* GENE IN A VIETNAMESE PATIENT

Duc Tien Nguyen[1,2,3], Thi Thanh Ngan Nguyen[1], Ngoc Lan Nguyen[4], Thi Anh Thuong Tran[5], Thi Bich Ngoc Can[5], Chi Dung Vu[5], Van Tung Nguyen[1], Thi Kim Lien Nguyen[1], Thanh Hien Nguyen[1], Duc Quan Nguyen[1], Thi Huong Giang Tran[1], Ke Long Phan[6] and Huy Hoang Nguyen[1,✉]

[1]*Institute of Genome Research, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*

[2]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*

[3]*19-8 Hospital, Ministry of Public Security, No. 9 Tran Binh street, Mai Dich ward, Cau Giay district, Hanoi, Vietnam*

[4]*Center for Gene and Protein Research, Hanoi Medical University, 1 Ton That Tung street, Dong Da, Hanoi, Vietnam*

[5]*Center for Rare Diseases and Newborn Screening, Department of Endocrinology, Metabolism and Genetics, Vietnam National Children's Hospital, 18/879 La Thanh, Dong Da, Hanoi, Vietnam*

[6]*Vietnam National Museum of Nature, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*

✉*To whom correspondence should be addressed. Email: nhhoang@igr.ac.vn*

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ABSTRACT

Fibroblast growth factor receptor (FGFR3)-related diseases can present a wide spectrum of symptoms, ranging from mild shortening of limbs to lethal skeletal dysplasia. Diagnosing FGFR3-related diseases can be challenging given phenotypic overlap with other skeletal dysplasia. The appropriate diagnosis of FGFR3-related diseases relies on a combination of clinical and radio-imaging data, and molecular analyses. In this report, we present a Vietnamese female with short stature, shortening of long bones, short and broad femoral neck, and squared and shortened ilia. Whole exome sequencing and variant filtering were performed in the proband to identify a disease-causing variant. Sanger sequencing was carried out to confirm the presence of the variant in the proband as well as in her parents. The result showed that a c.1620C>G (p.N540K) in the *FGFR3* gene was found in the proband. The parents and sister carried normal alleles. The variant in the proband is *de novo*. The variant was classified as a pathogenic variant in the ClinVar database. Therefore, the proband was diagnosed with hypochondroplasia. This is the first report of pathogenic variant c.1620C>G (p.N540K) in the *FGFR3* gene identified in the Vietnamese patient.

Keywords: c.1620C>G, FGFR3, hypochondroplasia, p.N540K, Vietnamese patient.

INTRODUCTION

Skeletal dysplasia is a group of rare conditions that affect the normal development, growth, and maintenance of the human skeleton (Mortier *et al.*, 2019). Skeletal dysplasia is divided into several types such as: epiphyseal dysplasia group I, metaphyseal dysplasia group II and; Group III bone dysplasia with altered bone density: osteoporosis or osteosclerosis. Among the metaphyseal dysplasia group, there are two relatively prominent bone dysplasia syndromes. Skeletal dysplasia is the most common form and the primary cause of disproportionate short stature, resulting from a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Notably, most individuals with skeletal dysplasia are born to parents without this condition (Savarirayan *et al.*, 2022).

In the 1990s, gain-of-function mutations in fibroblast growth factor receptor-3 (FGFR3) were found responsible for achondroplasia (ACH), the most common type of human dwarfism (Horton, 1997; Shiang *et al.*, 1994). Later on, gain-of-function mutations in FGFR3 were further identified in several other types of human skeletal dysplasias, including achondroplasia, hypochondroplasia and thanatophoric dysplasia (TD). Currently, there are no effective treatments for these skeletal dysplasia diseases *(Bonaventure et al.*, 1996). FGFR3 is a negative regulator of bone growth and all mutations of FGFR3 are gain-of-function mutations that lead to skeletal dysplasias (Almeida *et al.*, 2009; Prinos *et al.*, 1995). FGFR3-related diseases include thanatophoric dysplasia type 1 (OMIM # 187600), thanatophoric dysplasia type 2 (OMIM # 187601), severe achondroplasia with developmental delay (SADDAN, OMIM # 616482), achondroplasia (OMIM # 100800), hypochondroplasia (OMIM # 146000), camptodactyly, tall stature and hearing loss syndrome (CATSHL, OMIM # 610474), Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome, OMIM # 612247), craniosynostosis, Muenke type (OMIM # 602849), and Lacrimo-auriculo-dento digital syndrome (LADD) (OMIM # 149730) (Table 1). Each FGFR3-related disease has a typical variant; however, they have similar phenotypes, which make it difficult to classify.

Table 1. The information of FGFR3-related diseases

Disease	Inheritance	OMIM	Most variant	Phenotype	References
Thanatophoric dysplasia type 1	AD	187600		Micromelia with bowed femurs and, uncommonly, the presence of craniosynostosis of varying severity	(French & Savarirayan , 1993)
Thanatophoric dysplasia type 2	AD	187601		Micromelia with straight femurs and uniform presence of moderate-to-severe	(French & Savarirayan , 1993)

				craniosynostosis with cloverleaf skull deformity	
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	616482	c.1949A>T p.K650M	Extremely short stature, macrocephaly, rhizomelic or mesomelic limb shortening, severe tibial bowing, seizures, developmental delay, and acanthosis nigricans.	(Bellus *et al*., 1999)
Achondroplasia	AD	100800	c.1138G>A and c.1138G>C (p.G380R)	Rhizomelic shortening of the limbs, macrocephaly, distinctive facial features, small chest, brachydactyly, trident hands and hypotonia.	(Pauli, 2019)
Hypochondroplasia	AD	146000	c.1620C>A and c.1620C>G (p.N540K	Short stature with mild limb shortening, macrocephaly, lumbar lordosis, brachydactyly and tibial bowing.	(Cheung *et al*., 2024)
Camptodactyly, tall stature and hearing loss syndrome (CATSHL)	AD, AR	610474	c.862G>A (p.R621H)	Camptodactyly, tall stature, and hearing loss, kyphoscoliosis, a high palate, microcephaly, and intellectual disabilities	(Toydemir *et al*., 2006)
Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome)	AD	612247	c.1172C>A (p.A391E)	Craniosynostosis, proptosis, external strabismus and prognathism	(Wilkes *et al*., 1996)
Craniosynostosis, Muenke type	AD	602849	c.749C>G (p.P250R)	Coronal craniosynostosis, hearing loss, carpal and tarsal anomalies, and developmental/behavioral issues	(Murali *et al*., 2019)
Lacrimo-auriculo-dento digital syndrome (LADD)	AD	149730	c.1882G>A (p.D628N)	Dental and digital anomalies, aplasia, atresia or hypoplasia of the lacrimal and	(Talebi *et al*., 2017)

	c.1537G>A (p.D513N)	salivary systems, cup-shaped ears and hearing loss

AD: autosomal dominant; AR: autosomal recessive

Because of its phenotypic and genetic heterogeneity, the molecular diagnosis of osteochondrodysplasia remains a challenge. The usual strategies include performing targeted analysis of frequent mutations or phenotype-based panel sequencing, looking for previously identified mutations in the origin population of the patient (Almeida *et al.*, 2009). However, the performance of phenotype-based panel sequencing depends on the completeness of the panels. Moreover, most pathogenic variants have not been reported at a high enough frequency to allow the establishment of genotype/phenotype correlations, so the prognosis is sometimes difficult to discern. In this study, we investigated the phenotype and genotype of a Vietnamese patient with the pathogenic variant c.1620C>G (p.N540K) in the *FGFR3* gene.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Institute of Genome Research Vietnam Academy of Science and Technology (No: 01-2022/NCHG-HĐĐĐ on January 10, 2022, Institute of Genome Research, Institutional Review Board, Hanoi, Vietnam).

Genomic DNA samples were extracted from blood using the QIAamp DNA Blood Mini Kit (Qiagen, Germany). Whole exome sequencing and bioinformatics analyses were performed as described in the previous study (Nguyen *et al.*, 2020). Variants with minor allele frequency > 0.01 were excluded by comparing with the 1,000 Genome Database (http://browser.1000genomes.org). The filtering of pathogenic variants was performed within 437 genes related to dysplasia (Mortier *et al.*, 2019).

The primer set for amplification of exon 12 of *FGFR3* was designed using Primer blast (https://www.ncbi.nlm.nih.gov/tools/primer-blast). PCR conditions used for the amplification were, 95^{o}C for 12 min followed by 35 cycles at 95^{o}C for 45 s, 56^{o}C for 45 s, and 72^{o}C for 45 s, and final extension at 72^{o}C for 8 min. Amplified PCR product (380 bp) was checked on 1.5% agarose gel. Sanger sequencing was performed using ABI Big Dye Terminator on 3100 Genetic Analyzer (Applied Biosystems, USA). The target sequence was compared with the *FGFR3* gene sequence from the NCBI database (NM_000142). The effect of variants was predicted using the Mutation Taster (Steinhaus *et al.*, 2021) and PolyPhen_2 (Adzhubei *et al.*, 2013) tools. The pathogenicity of variants was interpreted according the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathologists (AMP) (Richards *et al.*, 2015).

RESULTS

Clinical presentation

The proband was the first child of the family. At the age of 4 years and 8 months, she was first referred to the pediatric department due to short state. She presented with a head circumference of 51.5 cm, height of 85 cm

(<-3 SD WHO), weight of 11.5 kg, no rib deformation, no bracelet legs, and loose ligaments. Biochemical analyses revealed a slight decreased level of calcium ions (1.03 mmol/L, normal range: 1.10-1.35 mmol/L) and elevated level of phospho (1.7 mmol/L, normal range 0.81-1.45 mmol/L), and normal levels of alkaline phosphatase, vitamin D, free thyroxine (FT4), and thyroid-stimulating hormone (TSH). The patient showed a normal karyotyping. The X-ray images indicated the proband presented with a shortening of long bones; short and broad femoral neck; and squared and shortened ilia (Figure 1). At the age of 8 years and 11 months, she presented with a height of 99.5 cm (-5.3 SD WHO), no rib deformation, a slightly decreased level of calcium ions (0.99 mmol/L), and normal levels of alkaline phosphatase and vitamin D. Genetic analysis was performed with the agreement of parents.

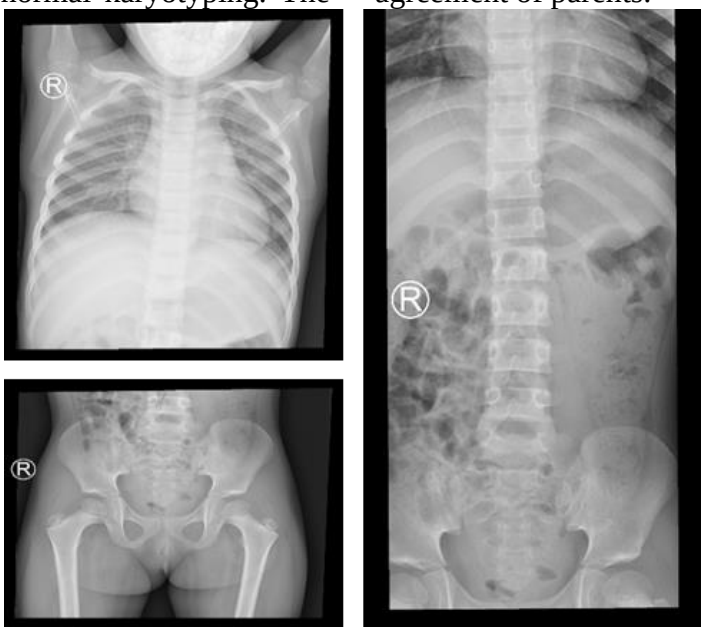

Figure 1. The X-ray images showed a shortening of long bones, short and broad femoral neck, and squared and shortened ilia in the patient.

Whole exome sequencing analyses

A total of 44,655,114 sequence reads with 6,624,729,745 nucleotides were generated from whole exome sequencing. The results showed that 99.8% of sequences were successfully aligned with the hg19 reference genome. After using Picard to remove the duplicate molecule, 90.1% of the sequences were retained, and 74.7% belonging to the targeted region. A total of 80,343 variants were identified in the patient, including 11,988 synonymous variants, 11,726 missense variants, 119 stop-gained variants, 38 stop-loss variants, 332 frameshift variants, 184 in-frame insertions, and 217 in-frame deletions.

Filtering results showed a total of 2,339 variants located on 437 genes related to dysplasia, of which 217 variants had allele frequency <0.01. After removing intron variants, 22 variants in 18 genes remained (Table 2). Out of them, 13 benign missense variants and 6 variants occurring in the in-house WES database (n = 350) were

eliminated. Three remaining variants included c.1620C>G (p.N540K) in the *FGFR3* gene and c.4547C>T (p.T1516M) and c.2795G>C (p.W932S) in the *DOCK6* gene. Two *DOCK6* variants were reported as likely benign variants in the ClinVar (Table 1). The variant c.1620C>G (p.N540K) in the *FGFR3* gene was evaluated as a pathogenic variant in the ClinVar (ID 16337) and predicted as "deleterious" in Mutation Taster, and "probably damaging" in PolyPhen_2. Therefore, c.1620C>G (p.N540K) was identified as disease-causing variant in the patient. The c.1620C>G variant was not found in the 1,000 Genome Database or 6,500 Exome database or gnomAD (https://gnomad.broadinstitute.org/gene/ENSG00000068078?dataset=gnomad_r4).

Table 2. Analyses of three variants in the proband

	***FGFR3*: c.1620C>G**	***DOCK6*: c.2795G>C**			***DOCK6*: c.4547C>T**		
Location	chr4:1807371C>G	chr19:11339635C>G			chr19:11322772G>A		
Gene	*FGFR3*	*DOCK6*			*DOCK6*		
Genbank transcript ID	NM_000142	NM_020812			NM_020812		
UniProt peptide	P22607	Q96HP0			Q96HP0		
DNA change	c.1620C>G g.12338C>G	c.2795G>C g.33523G>C			c.4547C>T g.50386C>T		
Amino acid change	N540K	W932S			T1516M		
Known variants	rs28933068 allele 'G' was not found in the ExAC, 1000G, or gnomAD.	rs199649621	Hom	Het	rs181639639	Hom	Het
		1000G	0	4	1000G	0	4
		ExAC	0	37	ExAC	0	32
		gnomAD	0	84	gnomAD	0	82
ClinVar	Pathogenic 16338	Likely benign 723458			Likely benign 723457		
Mutation Taster	Deleterious						
PolyPhen_2	Probably damaging with a score of 1.00						
SIFT	Deleterious with a score of 0.002						
CADD	23.7						
ACMG	Pathogenic PS2, PS4, PM1, PM2, and PP3						

Hom: Homozygous; Het: heterozygous;

Sanger sequencing results

Sanger sequencing showed a heterozygous C>G at the c.1620 in exon 12 of the *FGFR3* gene in the patient (Figure 2). The missense variant causes a substitution of asparagine to lysine at position 540 (p.K540K) in the amino acid sequence. The parents and her

sister carried normal alleles; it means that the pathogenic variant c.1620C>G is *de novo* variant. According to ACMG/AMP classification, the variant c.1620C>G (p.N540K) was interpreted as a pathogenic variant with 2 strong evidence (PS2 and PS4), 2 moderate evidences (PM1 and PM2) and 1 supporting evidence (PP3).

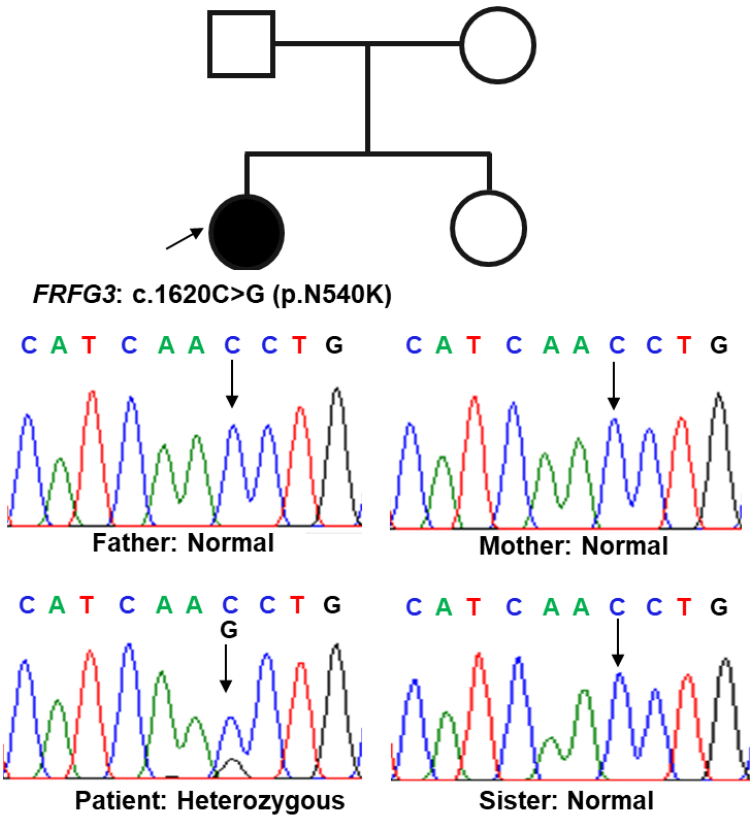

Figure 2. The pathogenic variant c.1620C>G (p.N540K) in the *FGFR3* gene in the family. Squares, males; circles, females; arrow, patient.

DISCUSSION

The clinical and genetic analyses supported a definitive diagnosis of the patient with hypochondroplasia. The variant *FGFR3*: c.1620C>G (p.N540K) account for over 50% of all hypochondroplasia cases (Bellus *et al.*, 1999; Linnankivi *et al.*, 2012; Xue *et al.*, 2014). The asparagine at codon 540 is highly conserved (Figure 3A). The change from asparagine to lysine at the amino acid 540 (p.N540K) resulted in a loss of H-bond (Figure 3B). The functional analyses of the mutant protein show significant reductions in protein expression and kinase activity (Krejci *et al.*, 2008; Raffioni *et al.*, 1998).

From the time of diagnosis at the age of 4 to 8 years and 11 months, the patient had clinical characteristics of the disease with a much shorter stature than her actual age. The average height of 8-year-old girls is approximately 126.6 cm according to WHO, however the patient was only 99.5 cm tall at 8 years and 11 months. The growth chart of children is often assessed based on those at the neonatal period and puberty. Here, the patient only had data from 2 times of

examination at 4 years and 8 years and 11 months. During nearly 5 years of development from 4 to 8 years and 11 months, the patient only grew 5.5 cm in height, reflecting the very slow growth rate of the patient's height. Although biochemical tests for the patient revealed that the results were within the normal range, the X-ray image was indicative that the patient had shortened long bones, short and wide femoral neck, and short and square pelvis. Therefore, it can be concluded that the patient has clinical manifestations of osteodysplasia. Whole coding region sequencing led to the identification of 3 pathogenic variants, of which the c.1620C>G (p.N540K) variant in the FGFR3 gene was identified as the causative variant. From the patient's family pedigree, it was shown that the parents and sister carried normal alleles. The variant in the patient was *de novo* and classified as a pathogenic variant in the ClinVar database. Therefore, the patient was diagnosed with achondroplasia.

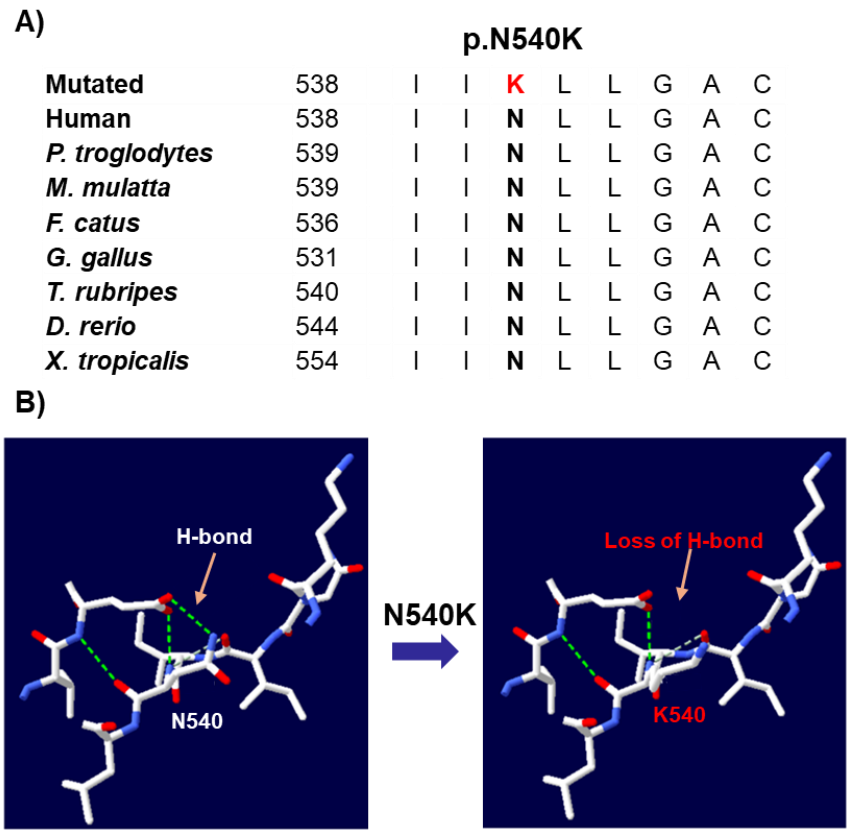

Figure 3. (A) Evolutionary conservation of the variant p.N540K among different species. (B) Structural illustration of the mutation in FGFR3 protein

CONCLUSION

In conclusion, whole-exome sequencing identified a variant c.1620C>G (p.N540K) in the *FGFR3* gene in a Vietnamese with hypochondroplasia. With the initial results of genetics of metabolic disorders in Vietnamese children that we report in the

present study, the patients' families could learn more genetic understandings for themselves and their children after becoming mature. Hopefully, in the future, in combination with the results achieved from screening statistic projects of Vietnamese children and our research, we will be able to have a database of mutant genes in Vietnamese people with hypochondroplasia disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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