

A Chinese Family with Pseudoachondroplasia Caused by *COMP* Gene Mutation

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How to cite this paper: Han, X., Wang, Y. H., Yan, W. J., Dai, J., & Jiang, Q. (2019). A Chinese Family with Pseudoachondroplasia Caused by *COMP* Gene Mutation. *Advances in Anthropology*, 9, 95-102. <https://doi.org/10.4236/aa.2019.91007>

Received: November 21, 2018

Accepted: February 16, 2019

Published: February 19, 2019

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Abstract

Pseudoachondroplasia (PSACH; MIM 177170) is a rare disease which was characterized by disproportionate short stature, deformity of the lower limbs, brachydactyly, loose joints, and ligamentous laxity. It is an autosomal dominant osteochondrodysplasia presented in childhood, and usually resolved with age, but osteoarthritis is progressive and severe. Genetic testing using the whole exome sequencing and Sanger sequencing was performed for the patients, a 30-year-old woman and her affected son, who is only 8 years old. A heterozygous mutation in exon 15 of *COMP* (c.1675G > A, p.Glu559Lys, NM 000095.2) was identified. The Polyphen-2 predicted that the mutation may damage the *COMP* protein function. This study suggested that the heterozygous mutations in *COMP* were responsible for PSACH and demonstrated the genotype-phenotype relationship between mutations in *COMP* and clinical characteristics of PSACH.

Keywords

Pseudoachondroplasia, PSACH, *COMP*, Rhizomelic Dwarfism, Achondroplasia

1. Introduction

Pseudoachondroplasia (PSACH) is an autosomal dominant osteochondrodysplasia caused by mutation of the *COMP* gene on 19p13.1-p12 encoding cartilage oligomeric matrix protein (Briggs, Hoffman, King, et al. 1995). Main clinical characteristics of PSACH are short-limb dwarfism with body proportions re-

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sembling those of achondroplasia but with normal head and face, disproportionately long trunk with accentuated lumbar lordosis, mild to moderate scoliosis and laxity of all joints but the elbow. Radiographic examination can detect tongue-like anterior protrusion of the central portion of the vertebral bodies, small irregular capital femoral epiphyses in children and marked dysplasia of the femoral head in adults, and shortening of the tubular bones with expanded, markedly irregular metaphyses (McKeand, Rotta, & Hecht, 1996). Diagnosis of PSACH is mainly based on clinical manifestation, family history, physical examination and radiographic evaluation.

Cartilage oligomeric matrix protein (COMP) is an extracellular matrix (ECM) protein expressed by chondrocytes, tendon, ligament, synovium and smooth muscle (Posey, Alcorn, & Hecht, 2014). It has been reported that missense mutations of *COMP* gene can result in single-amino acid substitutions and in-frame deletions could cause defection of codon(s), and these mutations contribute to structural changes of COMP protein and then triggers activation of oxidative stress and inflammation, which promotes premature chondrocyte death and thus leads to development of PSACH (Hecht, Nelson, Crowder, et al., 1995).

Clinical presentation varies substantially among PSACH individuals and most radiographic changes are not disease-specific. Recently, whole-exome sequencing (WES) is performed to achieve unbiased clinical diagnosis in patients whose clinical findings are not specific. When WES reveals variants of unknown significance (VUS), it will offer clinically useful insights into disease pathogenesis and may ultimately unravel unexpected therapeutic options for the affected family (Virani & Austin, 2014). By doing this research, we are intended to evaluate the application of WES in diagnosis of PSACH and to provide practical suggestions to the patients.

2. Methods

Based on clinical and radiologic findings, the diagnosis of PSACH can be primarily made. To verify our speculation and to offer further suggestion to her families, we performed molecular analysis of the proband. After the written informed consent, genomic DNAs from peripheral blood of the proband and his family were extracted using a QIA-GEN DNA minikit (Qiagen, Hilden, Germany). Then WES was conducted. The genomic DNA was divided into smaller fragments of 200 - 250 bp by ultrasonic instrument (CovarisLE220, Massachusetts, USA). Subsequently, Ampure Beads (Beckman Coulter, California, USA) purification was applied to add poly A/joint reaction in the end of the purified DNA fragments. To hybridize with the purified DNA fragments of proband, the gene-trapping chip (Roche NimbleGen, Madison, USA) was then used. After hybridization, the captured DNAs were sequenced on Illumina HiSeq2500 Analyzers (Illumina, San Diego, USA) and read on Illumina Pipeline software (version 1.3.4). BWA v0.59 (9) was used to align sequence reads to the human genome reference (build 37) and removed duplicated reads from subsequent analyses. Sequences variants were identified by comparing to the NCBI reference

sequence (NM 000095.2) and annotated by ANNOVAR (<http://www.openbioinformatics.org/annovar>). The 20× coverage for the RefSeq coding region was 99.18%. A total of 356 suspicious genes like COL1A1, COL1A2 and COL11A1 were involved.

3. Results

The proband, patient 1 shows typical features of PSACH. This 30-year-old woman of a Han nationality family in Southeast China presents disproportion stature (140 cm, -10% from the average height for the age and gender), genu varus, waddling gait, short forearms and short and broad hands (**Figure 1**). This proband has normal craniofacial appearance and intelligence.

Review of the family history was negative for any abnormality. Her birth weight was 3.0 kg, length 48 cm, and head circumference (HC) 33 cm. Those figures are indistinguishable from those of other children, but at the age of four, she was found short in stature due to gradually short hands, arms and legs. Her body length (BL) was 90 cm (-10% SD), weight 13 kg (-30% SD) and HC 50 cm. Though coxa vara had been noticed, it was symptomless at that time. By the age of eight, BL was 110 cm (-13% SD), body weight 18 kg (-14% SD). Since then, she started to feel hip pain, which became serious at puberty. It was worse when she was 20 years old, as she could not engage in any heavy physical activity due to unbearable hip pain. The radiographic examination shows typical serious hip osteoarthritis (**Figure 2**). She has been seeking for medical advice for many years and has tried several of therapies, including COX II inhibitor and traditional Chinese medical science. It has been increasingly difficult to control the pain. When she came to our outpatient, the obvious waddling gait suggested the limitation of hip motor. Radiographic examination showed severe hip osteoarthritis and physical examination revealed short in stature, especially in limbs. Though hip joints were found stiff, other smaller joints such as wrist and metacarpophalangeal joints were found lax. Adduction and flexion of hip was limited, which resulted in her abnormal gait.

Patient 2, her 6-year-old son, has relatively moderate symptom. His height is normal (110 cm). Brachydactyly and slight genu varus can also be noted. No trident positioning of the fingers was noted and thumbs were not deviated, while deformity of the hand is obvious and no symptoms have thus been caused so far (**Figure 2**). The birth weight was 3.5 kg, length 50 cm and head circumference 34cm, which were all normal. He learned walking at 12 months and has not complained about any pain of joint.

WES reveals the same mutation in patient 1 and patient 2. The result (**Figure 3**) indicates that there is a mutation (c.1675G > A) in exon 15 in chromosome 19, which has led to a protein change (p.Glu559Lys). But the outcome of patient 1's husband is normal.

Since the proband is still young and the pain is currently sustainable, conservative treatment is suggested, and joint replacement can be considered later when necessary. We also suggest her to have COX-II inhibitors to control the

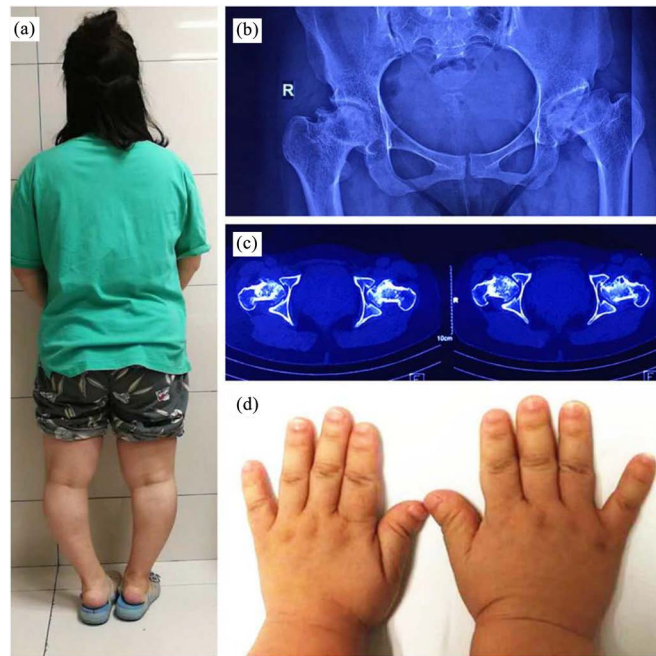


Figure 1. Clinical findings and radiographic features of patient 1, 30-year-old proband with pseudoachondroplasia. (a) Genu varus was noted and limbs were disproportionately short. (b) Anteroposterior radiograph of pelvis showed features of bilateral hip osteoarthritis, with narrow joint space, dysplasia of collum and caput femoris, sclerosis margin of acetabulum vault and osteophytes. (c) Computer Tomography feature of the pelvis showed destruction of surface of femoral heads. (d) Anteroposterior radiograph of pelvis showed features of bilateral hip osteoarthritis, with narrow joint space, dysplasia of collum and caput femoris, sclerosis margin of acetabulum vault and osteophytes.

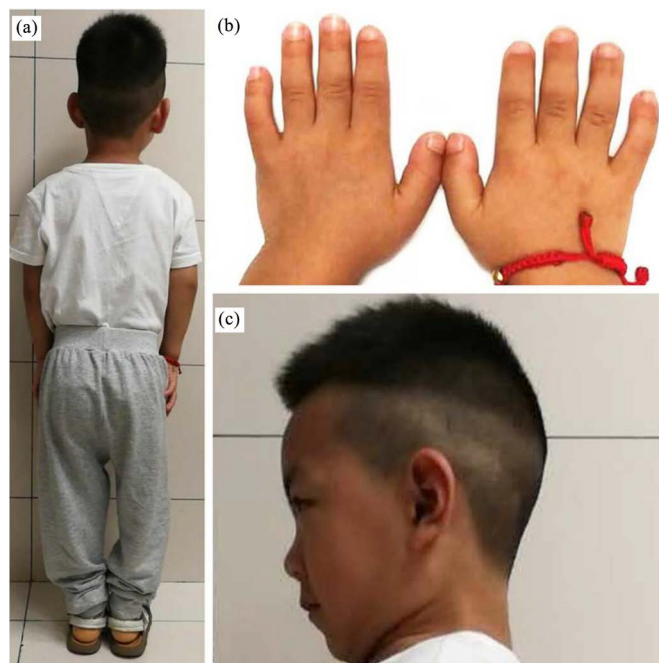


Figure 2. Patient 2, 10 years old, the son of patient 1. (a) The body proportions resembled those of achondroplasia with a long trunk and short extremities, and mild genu varus deformity was seen. (b) The head and face were as normal as children of the same age. (c) Fingers were short and broad, and laxity of interphalangeal joints was also found.

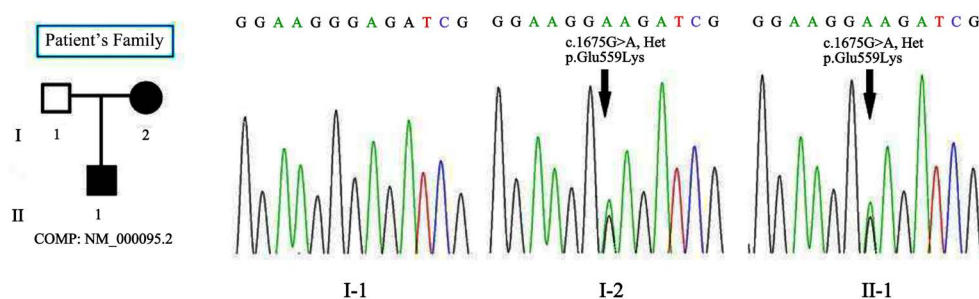


Figure 3. Pedigree of the family pseudoachondroplasia (PSACH) for mutation c.1675G > A and amino acid sequence alignment of cartilage oligomeric matrix protein (COMP).

pain when necessary. Fortunately, the regular follow-up shows that the pain of this woman has been milder in the past year, so total hip arthroplasty is not on the schedule currently. For her son, to keep the balance of calcium and phosphate, a daily intake of vitamin D is recommended. Until now, that boy has accepted twice orthopedics surgery to reform the hip malformation and wears a brace every night. The last time this boy came to the outpatient was 3 months ago, and we were pleasant to see that he looked nearly normal in appearance and gait, and he was competent of moderate daily activities. It is suggested that both of them are never exposed to exaggerated physical activities.

4. Discussion

PSACH should be differentiated with several similar diseases. Achondroplasia is an autosomal dominant bone dysplasia caused by a G1138A mutation of the *FGFR3* gene on chromosome 4 (4p16.3) with disproportionate short-limb like PSACH, but has some characteristic features: depressed nasal bridge, prominent fore head, mild hypoplasia of midface with narrow passages (Trotter & Hall, 2005). Multiple epiphyseal dysplasia (MED) shows short stature and prominent, frequently painful joints are sometimes difficult to be distinguished from PSACH. MED and PSACH constitute a bone dysplasia family, while patients with MED patients usually have normal or moderately short stature with normal body proportions compared with those with PSACH. PSACH is almost exclusively caused by mutations in cartilage oligomeric matrix protein (COMP) while MED may be caused by mutations in the genes encoding COMP, type IX collagen (COL9A1, COL9A2, and COL9A3), matrilin-3 (MATN3), and solute carrier member 26, member 2 gene (SLC26A2) (Newman, Donnah & Briggs, 2000).

Gu has recently reported that the levels of plasma COMP significantly decreased in patients with this *COMP* mutation, but only in presymptomatic carriers (Gu, Yang, Tan, Zhang, Lu, & Ma, 2017). PSACH is correlated with carboxyl-terminal globular region of mutation *COMP* and is caused by both intra- and extracellular pathogenic pathways (Briggs, Mortier, Cole, et al., 1998). The Unfolded protein response (UPR) of COMP caused the decrease in cellular viability and less organized collagen fibers in the extracellular matrix (ECM) (Dinsler, Zaucke, Kreppel, et al., 2002). Apoptosis of chondrocyte is primarily mediated by serious UPR-independent pathways, such as activation of NF- κ B sig-

nalizing, downregulation of PRDX2 and peroxiredoxin 2 (Suleman, Gualeni, Gregson, et al., 2012). Also, the accumulation of mutant *COMP* can detract the tolerance of ER stress or stimulate the toxic level, leading to the increase of chondrocytes death and thus the limb shortening (Posey, Alcorn, & Hecht, 2014). In addition, it broke the integrity of cartilage by affecting thrombospondins and other extracellular matrix protein (Acharya, Yik, Kishore, Van Dinh, Di, & Haudenschild, 2014). It has been reported that *COMP* mutation is a biomarker for cartilage degeneration associated with osteoarthritis and a prognostic marker for joint injury (Posey, Coustry, & Hecht, 2018).

PSACH usually arises in the second year of life or later. It has been reported that pain of lower limbs is the first presented symptom (Gamble, Nguyen, Hashmi, & Hecht, 2015). Similar to our research, another article also reveals that abnormal gait is the most significant clinical finding (Tamaro, Pederiva, Dibello, et al., 2018). The development appears normal during the first 12 to 18 months of life. Early onset osteoarthritis frequently begins in the hips and knees in late adolescence to early adulthood and further influences the shoulders, elbows, ankles and feet. The intellectual development and life expectancy are unimpaired. The adult height ranges between 90 and 148 cm (McKeand, Rotta, & Hecht, 1996). Radiographic examination can detect early lesions in childhood, including moderate flattening of the vertebral bodies with biconvex deformity and various degrees of irregularity of the upper and lower end plates, tongue-like anterior protrusion of the central portion of the vertebral bodies (Manabe, Nakamura, Ikegawa, & Kimizuka, 1998).

In this case, the development of patient 1 appeared normal until the age of four, later than the average age of manifestation. The pain of the hip became serious in adolescence but tended to be moderate in adulthood. Scoliosis was not obvious and other complications like neurologic complication and cervical instability were not noted. As signs and symptoms are relatively moderate than other cases reported before, it is supposed that this mutation is associated with a late-onset and mild phenotype. Patient 2, the son of patient 1, showed even milder clinical findings than those of patient 1 and was expected to be almost normal in daily activities.

The progress can be retarded by in taking vitamin D but finally, most of patients need surgical intervention to correct deformities and cervical stabilization procedures to alleviate neurologic symptoms and signs of cervical cord compression (Li, Song, Mahajan, Suh, & Lee, 2007). Considering the pathological progress of PSACH, some novel therapies focusing on dampening inflammation and oxidative stress are approaching, which has defined an early treatment window (Posey, Coustry, Veerisetty, Hossain, Alcorn, & Hecht, 2015).

5. Conclusion

High-throughput sequencing is vital for accurate diagnosis of PSACH. A mutation (c.1675G > A) in exon 15 in chromosome 19 can lead to a protein change (p.Glu559Lys) and cause this disease.

Acknowledgements

This work was supported by the Projects of International Cooperation and Exchanges NSFC (81420108021), Key Program of NSFC (81730067), Excellent Young Scholars NSFC (81622033), Jiangsu Provincial Key Medical Center Foundation, Jiangsu Provincial Medical Outstanding Talent Foundation, Jiangsu Provincial Medical Youth Talent Foundation and Jiangsu Provincial Key Medical Talent Foundation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

PSACH: Pseudoachondroplasia;

COMP: Cartilage oligomeric matrix protein;

MED: Multiple epiphyseal dysplasia;

WES: Whole exome sequencing.