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Identification of a *GDF5* Mutation in a Korean Patient with Brachydactyly Type C without Foot Involvement

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Brachydactyly type C (BDC) is characterized by shortening of the middle phalanges of the index, middle, and little fingers. Hyperphalangy of the index and middle finger and shortening of the first metacarpal can also be observed. BDC is a rare genetic condition associated with the *GDF5* gene, and this condition has not been confirmed by genetic analysis so far in the Korean population. Herein, we present a case of a 6-yr-old girl diagnosed with BDC confirmed by molecular genetic analysis. The patient presented with shortening of the second and third digits of both hands. Sequence analysis of the *GDF5* gene was performed and the pathogenic mutation, c.1312C>T (p.Arg438Cys), was identified. Interestingly, this mutation was previously described in a patient who presented with the absence of the middle phalanges in the second through fifth toes. However, our patient showed no involvement of the feet. Considering intrafamilial and interfamilial variability, molecular analysis of isolated brachydactyly is warranted to elucidate the genetic origin and establish a diagnosis.

Key Words: Brachydactyly, *GDF5* gene, Mutational analysis

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INTRODUCTION

Brachydactyly is a condition that results in the shortening of digits due to an abnormal development of the phalanges, metacarpals, or both [1]. Brachydactyly may present as an isolated feature or as a part of a complex malformation syndrome. Isolated brachydactyly can be classified into 5 types on the basis of anatomy and genetics. Brachydactyly type A can be further classified into 5 subtypes. Brachydactyly type C (BDC) is characterized by the shortening of the middle phalanges of the index, middle, and little fingers. Hyperphalangy of the index and middle fingers can also be observed and is associated with the shortening of the first metacarpal. Usually, in BDC, the ring finger appears unaffected and is the longest digit in affected patients.

Growth differentiation factor-5 (*GDF5*) gene, also known as cartilage-derived morphogenetic protein-1 (*CDMP1*), is the only gene known to be associated with BDC. BDC is associated with multiple inherited genotypes of the *GDF5* gene including autosomal dominant, autosomal recessive, and even a semidominant pattern of inheritance has been reported [2]. Mutations in the *GDF5* gene also result in recessive acromesomelic dysplasias of Hunter-Thompson type, Grebe type chondrodysplasia, and Du Pan syndrome, characterized by short stature, severe limb shortening, and profound brachydactyly [3]. Moreover, phenotypic variability is a typical hallmark of BDC, and variation is found in individuals of the same family harboring identical mutations [4]. Therefore, elucidating the genetic origin and establishing a genetic diagnosis are important for understanding the role of *GDF5* gene in cartilage and bone formation and the molecular pathogenesis of isolated brachydactyly.

Although the incidence and prevalence have not been well established, isolated brachydactyly is expected to be rare in the

Korean population [5]. To the best of our knowledge, no BDC case has been confirmed by molecular genetic analysis in this population. Herein, we report the *GDF5* mutation identified in a Korean BDC patient with relevant clinical findings.

CASE REPORT

A 6-yr-old girl presenting with shortening of the second and third digits on both hands was admitted for evaluation. She had normal stature and development compared to the general Korean standards. She had normal prenatal and birth history as well as no family history of shortened digits. Hand examination revealed that the first, second, and third digits were short. The fourth digit was the longest and appeared normal. The distal phalanx of the left second digit was deviated to the ulnar side and that of the left third digit was deviated to the radial side. Mild clinodactyly was present in the fifth digit of both hands. Range of motion of individual joints was normal and her feet were unaffected. She had no other skeletal or non-skeletal dysmorphisms. Radiographs showed shortening of the thumb metacarpals and middle phalanges of the second, third, and fifth digits (Fig. 1).

Informed consent was obtained and whole blood was collected from the patient in EDTA blood collection tubes. DNA was extracted and PCR was performed using primers specific for 2 coding exons (data not shown). The amplified products were sequenced on an ABI 3730 analyzer (Applied Biosystems, Foster City, CA, USA) using a BigDye Terminator v3.1 Cycle sequencing kit (Applied Biosystems,) (Reference cDNA sequence: NM_000557.2). Sequence analysis of *GDF5* revealed a missense mutation at c.1312C>T that resulted in a change in the protein level of p.Arg438Cys (Fig. 2). Mutation analysis and clinical review of this patient were approved by the institutional review board of Inje University, Sanggye Paik Hospital.

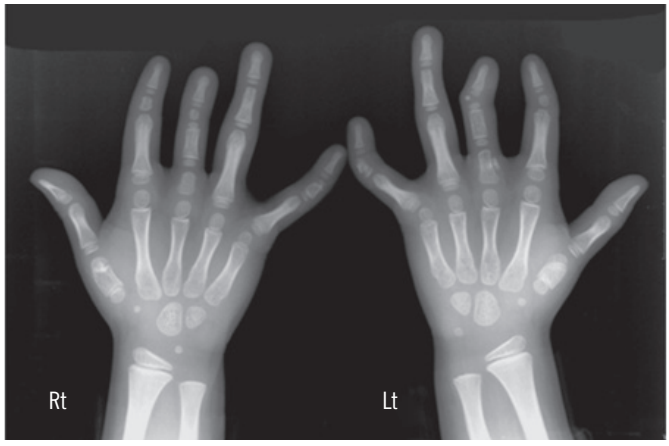

Fig. 1. Radiographic findings of both hands at age 5 yr and 7 months. The bilateral short first metacarpals show large pseudoepiphyses. The middle phalanges of the second, third, and fifth fingers are short, with clinodactyly of the fifth fingers. The fourth fingers are unaffected. The proximal phalanges of both third fingers are short. Note the segmentation anomaly with accessory ossification along the proximal phalanx and an accessory ivory dense epiphysis at the base of the distal phalanx of the left third finger. Note the ulnar deviation of the left second finger and radial curvature of the third finger. The carpal bone age is retarded.
Abbreviations: Rt, right; Lt, left.

DISCUSSION

This is the first genetically confirmed case of isolated brachydactyly in the Korean population. Isolated brachydactyly, including BDC, is a clinically and genetically heterogeneous disorder. In addition to the characteristic features of brachydactyly, BDC patients may have ulnar deviation of the index finger as well as hypersegmentation of the proximal or middle phalanges [6]. Interestingly, the first case report characterizing BDC with the same mutation identified in this study, described that the patient had no middle phalanges in their second through fifth toes [7]. Our patient showed no involvement of the feet. These findings suggest that this disorder may vary in its phenotype even within individuals with the exact same gene mutation. Concerning intrafamilial and interfamilial phenotypic variability, different genetic background and/or environmental factors associated with each patient are suggested to be involved in the pathogenesis [2].

The *GDF5* gene may be associated with various types of disorders including BDC. Among the 34 known mutations of the *GDF5* gene listed in the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=*GDF5*), only 15 are known to cause BDC [2, 6-9]. In addition to BDC, other disorders such as brachydactyly type A2, Du Pan syndrome, Grebe type chondrodysplasia, Hunter-Thompson type acromesomelic

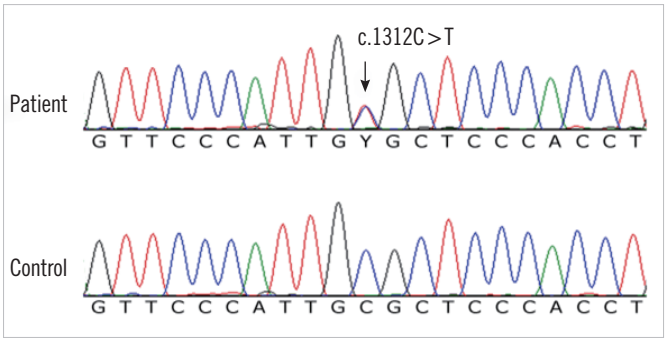

Fig. 2. Sequence analysis of the *GDF5* gene. A heterozygous mutation of c.1312C>T in exon 2 is noted.

dysplasia, multiple synostoses, and proximal symphalangism are also associated with *GDF5* gene abnormalities. Interestingly, while some mutations that decrease *GDF5* expression seem to be the main basis for the development of brachydactyly, other mutations that increase the activity of *GDF5* result in proximal symphalangism [10]. In a recent study, a novel missense mutation in *GDF5* was shown to cause brachydactyly type A1 [11]. Furthermore, some heterozygous mutation carriers of *GDF5* showed phenotypes similar to brachydactyly type E [2]. Therefore, molecular characterization of the *GDF5* gene will be helpful to diagnose and reclassify isolated brachydactyly on the basis of genetic background rather than clinical phenotype. These findings will also help in understanding the role of *GDF5* in normal cartilage and bone development.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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