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# A Novel Variant that may be Associated with Congenital Malformation in *HOXD13*

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## Abstract

**Background:** *HOX* genes, a subgroup of homeobox genes, found in as gene clusters in mammals, are the most important regulators of morphogenesis and cell differentiation, and also these genes control the main body axis during embryogenesis. One of these genes, *HOXD13*, known to be associated with developmental disorders especially congenital lower/upper limb abnormalities such as syndactyly and polydactyly.

**Case Report:** In this report we present two patients, one case of syndactyly and one case of polydactyly. In the first case, there was a syndactyly in the between 2$^{nd}$ and 3$^{rd}$ fingers of right hand, and there were extra fingers in both hands in the other case.

**Conclusion:** This case report provides a new variation (c.204G > A) which can be associated with dactyly malformations in *HOXD13* gene.

***Key words:*** *HOXD13; Next generation sequencing; Polydactyly; Syndactyly*

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## Introduction

Dactyl malformations are developmental disorders, and they are the most common congenital extremity anomalies in hand and foot. Brachydactyly, syndactyly and polydactyly are the most common types of dactyl malformations, and the phenotypic reflections of these malformations differ. Brachydactyl phenotype is characterized by disproportionately short hands and/or toes. Syndactyly is formed by the failure to break apart of the curled-combined hand and/or toes in embryo, more than 5 finger shaped in hand and/or feet is observed in polydactyly [1-2]. And also, many subclasses of typed malformations have been described in the literature. Especially the classification of the syndactyly and polydactyly anomalies is made according to morphology and settlement place of the anatomical structure which is excess or united [3]. The studies have shown that inheritance model of syndactyly and polydactyly, which are seen as isolated, is the autosomal dominant, while inheritance is autosomal recessive when the phenotype coexists with additional pathologies [4].

The homeodomain containing *HOX* genes are a family of highly conserved primer transcription factors that control the fate and local identity of the cell throughout the body and extremity axis [5]. *HOXD13* is the first HOX gene known to be associated with developmental disorders in human. Mutations in *HOXD13*, which have a critical role in limb development, may play a role in the development of variable expression of clinical manifestations in malformations such as syndactyly and polydactyly [2]. The goal of this report is to identify the genetic etiology of dactyl malformations as associated with *HOXD13* gene. For this, two cases were included in the study and the cases were screened for possible mutations in *HOXD13* using next generation sequencing (NGS) method.

## Case Presentation

The study was approved by the Ethics Committee of XXX University. Blood samples were collected after informed consent was obtained. We evaluated two family which are containing one polydactyly and syndactyly cases. In the first case, there was a syndactyly in the between 2nd and 3rd fingers of right hand (Figure 1). In the other case, there were extra fingers in both hands (Figure 2). In the case of two patients, no signs of disease were found in the other organ systems.

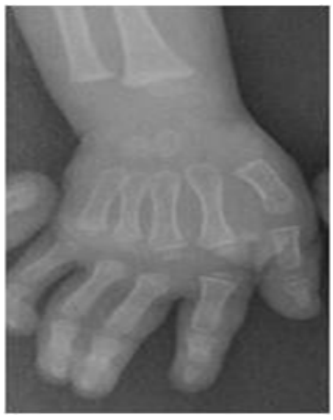

***Figure 1:*** *X-ray image of the first case; the syndactyly malformation between 2nd and 3rd fingers of the right hand.*

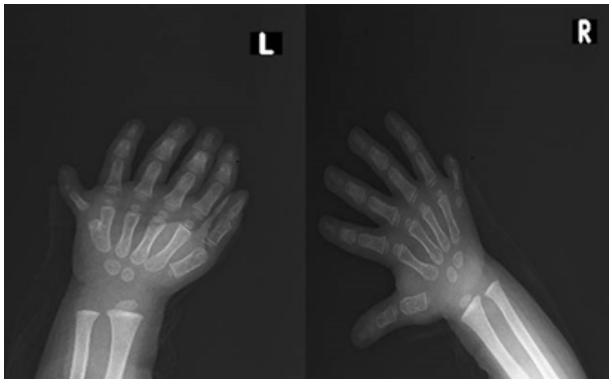


***Figure 2:*** *X-ray image of the second case; extra fingers in left and right hands.*

In the first case, the combined 2nd and 3rd fingers of right hand have been separated with the surgical operation. For polydactyly excision additional fingers on both hands in second case have been disjointed with surgery. And also, according to the pedigree analysis, it was determined that no other individuals with similar anomalies were present in the patients' families (Figure 3,4).

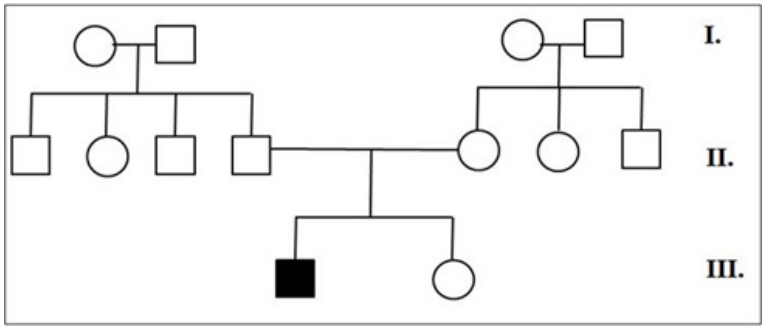


***Figure 3:*** *Pedigree analysis of the first case.*

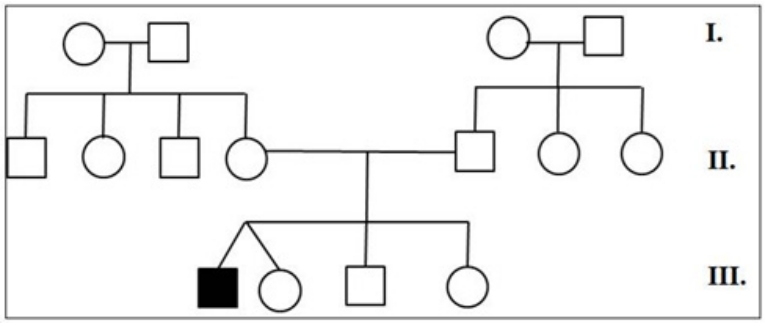


***Figure 4:*** *Pedigree analysis of the second case.*

According to the results of the NGS analysis; in the first case, no mutation was found in the *HOXD13* gene. In the second case, c.204G > A single nucleotide exchange was observed in exon 1 of *HOXD13* gene. And then, the patient's parents were screened for *HOXD13* mutations. According to the results, while the same variation was detected in the father of the patient, c.441G > A variation was determined in the mother of the patient addition to c.204G > A in exon 1 of *HOXD13* gene. Nonsynonymous or amino acid-altering mutations are further classified into missense and nonsense mutations. A point-nonsense mutation differs from a missense mutation, which is a point mutation where a single nucleotide is changed to cause substitution of a different amino acid. Summarly, we were performed with appropriate primers to generate *HOXD13* carrying the c.204G > A and the other c.441G > A mutation. The specific base changes were verified by DNA sequencing using NGS. *HOXD13* sequencing revealed a heterozygous G-to-A transition in exon 1 at position 204 of the coding sequence in all the affected people of this family. The c.204G > A and c.441G > A from novel mutations accounted for the clinical phenotype.in this study. Furthermore, circumstances, determine or these mutations occur when the change of a single DNA nucleotide within a protein-coding portion of a gene does not affect the sequence of amino acids that make up the gene's protein. A change in one nucleotide, however, doesn't always change the triplet's meaning; the mutated triplet may still add the same amino acid. And when the amino acids of a protein stay the same, we believed, so do its structure and function.

## Discussion

The *HOXD13* gene, located at the 5' end of the *HOXD* gene cluster localized on chromosome 2q31, is 1365 bp and its coding region is 1008 bp. The first exon located at the 5' end of the gene, comprising of two exons, contains the triple repeat sequences forming the chain of polyalanine, while the second exon located at the 3' end encodes a highly conserved homologous box domain [6]. HOXD13 gene mutations are known to cause variable expression in a wide spectrum of clinical manifestations of extremity malformations [7].

The mutations observed in the *HOXD13* gene are examined in three groups; loss of function mutations, increase in N-terminal polyalanine repeat, and missense mutations [8]. Until now five missense mutations (R298W, R298Q, S308C, I314L, and Q317R), are placed in gene's homeodomain and are associated with dactyly malformations in different phenotypes, have been identified [9]. Nonsense and

frame-shift mutations are thought to cause haploinsufficinency of the *HOXD13* protein, but this has not yet been confirmed experimentally [10,11].

Two cases, included in this study, were syndactyly and polydactyly. According to the pedigree analysis of the cases, there was no dactyl malformation in the family's story of the patients.

According to the NGS analysis results, no mutation in the *HOXD13* gene was detected in the case of the syndactyly. In addition to the *HOXD13* gene, other members of *HOX* gene family can be effective in developmental malformation. It is known that the expansion of the polyalanine in the *HOXA13* gene is responsible for the development of the syndactyly. It is thought that the responsible gene can be *HOXA13* in this case, too; so further analysis should be extended to cover all *HOX* gene cluster members.

However, in the case of polydactyly, c.204G > A variation was detected in the exon 1 of *HOXD13* gene. The same variation was also found in the parents of the patient. And, it was observed that the patient's mother had also carried a c.441G > A variation. In the literature, there have been no studies showing the association of these variants observed in the *HOXD13* gene with dactyl malformations. Dactyly malformations usually show autosomal dominant inheritance. In agreement with this, the variation observed in our polydactyly case was also detected in parents. However, the phenotype observed in the patient did not appear in the family. As the reasons of this, the differences of penetrance/expressivity in reflection of genotype to phenotype can be shown.

It is important to investigate whether the disease has emerged due to a new mutation in a person, has normal parents, with an autosomal dominant inherited disorder. In this study, we evaluated the association of dactyly malformations known to be autosomal dominantly inherited and *HOXD13* gene variants. The results show that a new variant may be associated with dactyly malformations. However, this variation should be scanned in large populations to arrive at a definite judgment. In addition, gene expression studies should be performed to clarify the underlying mechanisms of phenotypic differences observed within the family.

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