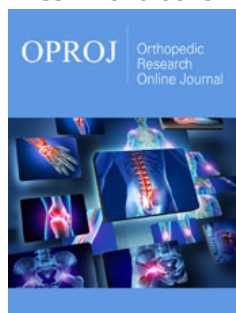


# A Novel NOG Variant Causes Brachydactyly Type B2: A Case Report

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## Abstract

**Background:** Brachydactyly type B2 (BDB2) is a very rare form of brachydactyly, characterized by hypoplasia or aplasia of the middle to distal phalanges of fingers and/or toes in combination with distal symphalangism. It is caused by dominant mutations in the NOG gene encoding noggin protein.

**Case presentation:** In the present study, we report a Tunisian family composed of three affected subjects showing varying degrees of BDB2. We performed a direct sequencing of NOG, and we identified a novel missense heterozygous mutation c.503T>C (p.F168S), which is likely pathogenic according to the prediction programs. This new variation enlarges the mutation spectrum of the NOG gene.

**Conclusion:** To the best of our knowledge, this is the first molecular study of BDB2 in Tunisian family.

**Keywords:** Brachydactyly type B2, NOG gene, Missense mutation, Tunisia

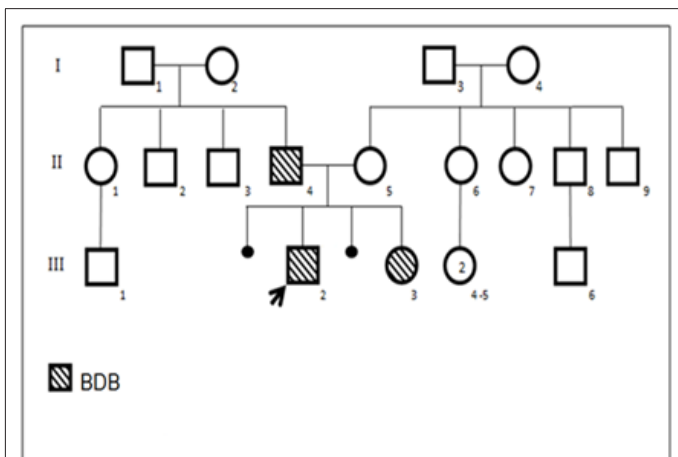
## Introduction

Brachydactyly ("short digit") is a rare skeletal malformation that is characterized by short fingers and toes [1]. It may be either isolated or a part of a complex malformation syndrome [2]. There are 11 types of isolated brachydactyly depending on which phalanges and metacarpals are involved [1,2]. Brachydactyly type B (BDB) is an autosomal dominant disorder characterized by aplasia or hypoplasia of the middle to distal phalanges and nails of the second to fifth digits and toes[2]. BDB has been classified into two subtypes BDB1 (MIM# 113000) and BDB2 (MIM# 611377) caused by mutations in ROR2 and NOG genes respectively [3]. BDB1 and BDB2 are two closely related forms and only the genetic study allows differentiating between them. Heterozygous truncating mutations in ROR2 (MIM# 602337) are most frequently involved in BDB.

BDB2 is caused by mutations in the NOG gene (MIM# 602991) on chromosome 17q22. It encodes noggin, a secreted polypeptide involved in signaling pathways in bone and cartilage development [4]. Noggin is a conserved protein during evolution [5]. It is an extracellular antagonist of bone morphogenetic proteins (BMP) and growth differentiation factors (GDF). BMPs and GDF activities are modulated by noggin which binds with varying affinities to each BMP, thus disturbing their interaction with their receptors [6]. BDB is caused by increased activation of BMP signaling. According to the Human Gene mutation database (<http://www.hgmd.cf.ac.uk/ac/index.php>), more than 60 dominant inherited variants in NOG gene were reported, associated with overlapping syndromes: Stapes ankylosis with broad thumb and toes, symphalangism proximal 1A, multiple synostoses syndrome 1, tarsal-carpal coalition syndrome and bradydactyly type B [4,7]. To date, only six missense variants in NOG have been reported to cause BDB2 [3].

Here we report a clinical and genetic study of BDB2 in a Tunisian family. We identified a novel heterozygous variant p.F168S in NOG that is predicted to be likely pathogenic. To the best of our knowledge, this is the first molecular study of BDB2 in a Tunisian family.

## Case Presentation



**Figure 1:** Pedigree of the family with BDB. The proband (III-2) is indicated by an arrow.

In this paper, we examined a Tunisian family with three affected individuals. The pedigree of this family shows an autosomal dominant mode of inheritance (Figure 1). The diagnosis of BDB was

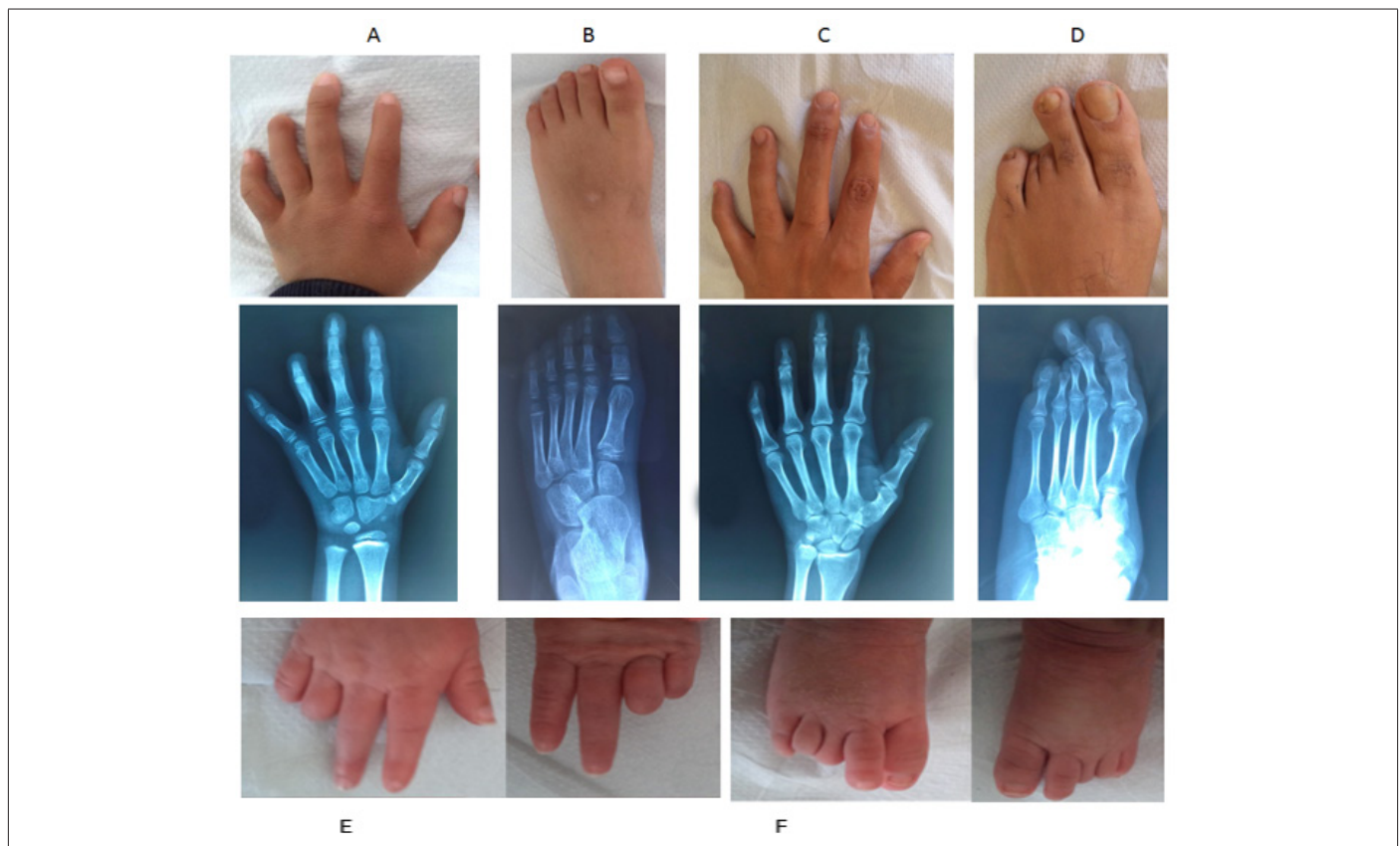
performed through clinical examination and x-rays of the hands and feet. Genomic DNA was extracted from peripheral blood samples using standard procedures [8]. The proband was screened first for mutations in ROR2 gene but no mutations were detected. We subsequently sequenced the NOG-coding exon as described by [3].

### Clinical presentation

Three affected individuals of the family exhibited, to varying degrees of severity, typical features of BDB.

Patient 1, the proband, a three-year-old boy, is the first born to non-consanguineous parents. He had bilateral aplasia of middle phalange with absent nail and distal symphalangism of 4<sup>th</sup> finger and hypoplasia of middle phalange of 5<sup>th</sup> finger. He also had aplasia/hypoplasia of distal phalange of 4<sup>th</sup> and 5<sup>th</sup> toes (Figure 2).

Patient 2, his father, a 35-year-old, had bilateral aplasia/hypoplasia of middle phalange of fingers 3-5 with proximal symphalangism on corresponding rays. We did not note carpal fusion. The toes were also affected. There was aplasia of middle and distal phalange of toes 3-4 with absence of nails of the corresponding rays and aplasia of middle phalange of 5<sup>th</sup> toe (Figure 2).



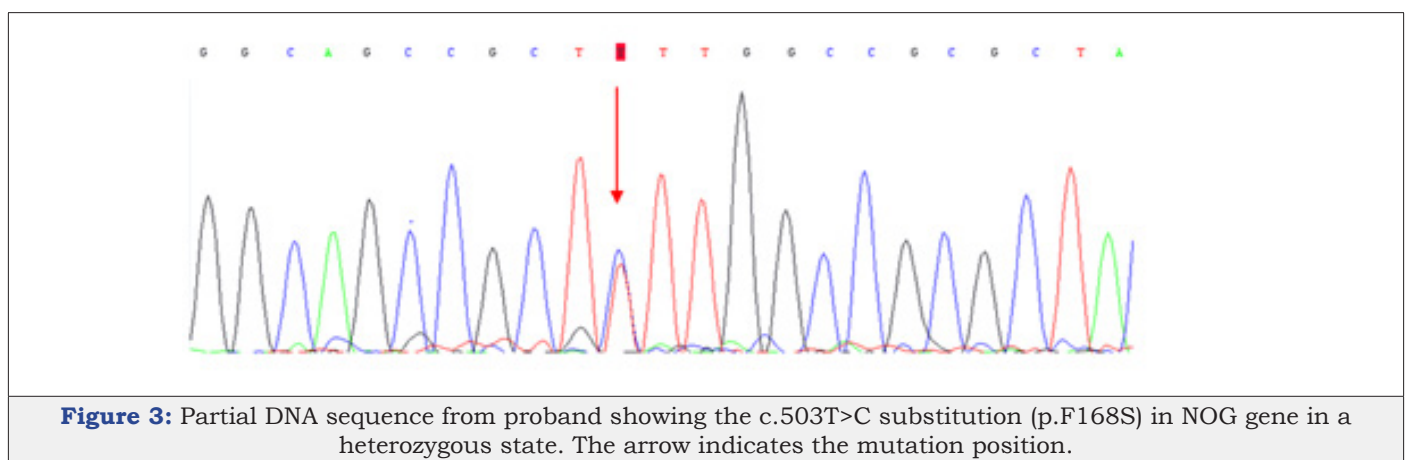
**Figure 2:** A & B: Photographs and radiographs of the hand and foot of the proband : aplasia of middle phalange and nail with distal symphalangism of 4<sup>th</sup> finger and hypoplasia of middle phalange of 5<sup>th</sup> finger, aplasia of distal phalange of 4<sup>th</sup> toe and hypoplasia of distal phalange of 5<sup>th</sup> toe.  
C & D: Photographs and radiographs of the hand and foot of the father (II-4) : aplasia/hypoplasia of middle phalange of fingers 3-5 with proximal symphalangism on corresponding rays, aplasia of middle and distal phalanges of 3-4 toes and absence of nails of the corresponding rays, aplasia of middle phalange of 5<sup>th</sup> toe.  
E & F: Photographs of the hands and feet of sister's proband (III-3): complete absence of middle and distal phalanges of 4<sup>th</sup> and 5<sup>th</sup> fingers and nails of the corresponding rays. Anomalies of feet are like her father.

Patient 3, his sister, a 5-month-old, was severely affected. We observed an amputation-like phenotype with a complete absence of middle and distal phalanges of 4<sup>th</sup> and 5<sup>th</sup> fingers and nails of the corresponding rays. She had the same feet abnormalities as her father (Figure 2). We did not find any other congenital anomalies. All three individuals have normal height and intelligence. There are no other affected members in the family.

### Molecular findings

The direct sequencing analysis of NOG identified a novel missense mutation involving a heterozygous T-C transition at nucleotide position 503 (c.503T>C), resulting in the exchange of a codon for phenylalanine with serine at amino acid position 168 (p.F168S) (Figure 2). The sequence variant was then screened in the rest of the family members and was found only in affected

individuals. We assessed the possible functional impact of the new variant p.F168S using three prediction programs (PolyPhen2, SIFT and Mutation Taster). These programs showed a consistent result of the deleterious effect of this mutation [Polyphen-2: probably damaging with a score of 0.997 (sensitivity: 0.27; specificity: 0.98); SIFT: Damaging (score: 0, median: 2.85) and Mutation Taster: disease causing (p-value: 1)]. In addition to that, the p.F168S mutation was not reported in several databases : Human Gene Mutations Database (HGMD) (<https://www.hgmd.org/>), the Exome Aggregation Consortium database (ExAC) (<http://exac.broadinstitute.org>) and the 1000 Genomes database (<https://gnomad.broadinstitute.org/>) (Figure 3). Partial DNA sequence from proband showing the c.503T>C substitution (p.F168S) in NOG gene in a heterozygous state. The arrow indicates the mutation position.



**Figure 3:** Partial DNA sequence from proband showing the c.503T>C substitution (p.F168S) in NOG gene in a heterozygous state. The arrow indicates the mutation position.

### Discussion and Conclusion

BDB2 is a rare genetic disorder with no available data on its incidence as the literature is poor with less than ten cases reported. In the current study, we analysed a Tunisian Family with BDB. As ROR2 gene is the most gene causing BDB[3], we first pre-screened the proband for variants in this gene. Due to the absence of pathogenic variants within the ROR2 gene, we further sequenced the NOG gene in the affected individuals. We identified a novel missense variant p.F168S (c.503C>T) in NOG. The co-segregation of this variant with the disease was confirmed. To the best of our knowledge, this variant has not been reported before in the literature and it was considered likely pathogenic according to the guidelines of the American college of medical genetics and genomics. At least, three prediction algorithms (polyphen2, SIFT and mutation taster) showed that the novel variant identified in the present study is classified as likely pathogenic. Additionally, the variant is absent from public databases including GnomAD, dbSNP and the 1,000 Genome Project.

In our case, the variant p.F168S resulted in a change of phenylalanine with serine at the 168 position. There are large physicochemical differences between these two amino acids. Moreover, Phenylalanine residue is very probably important for structure or function of noggin protein since it is totally conserved up to frog and is located in a functional domain of noggin, disulfide

bond domain. To date, more than 60 variants of NOG gene have been associated with the symphalangism spectrum diseases: proximal symphalangism 1A, multiple synostosis syndrome 1, Tarsal-Carpal Coalition syndrome, stapes ankylosis with broad thumb and toes and brachydactyly type B2. Only six NOG variants have been closely associated with BDB2 [3]. They are all heterozygous missense variants, presumed to decrease the BMPs binding affinities to noggin leading to increase activation of BMP pathway.

Previously, two different variants in the adjacent codon, R167G and R167C, have been reported to cause BDB2 and proximal symphalangism respectively [3,9]. These findings supported the hypothesis that our novel variant F168S may be the cause of the BDB2 in our family. Consistent with literature, our patients showed varying degree of severity. In fact, found a significant phenotypic heterogeneity even between patients with the same variant [3]. Cutaneous syndactyly and fusion of carpal and tarsal bones are also observed in BDB2 families [3]. None of our patients had any of these anomalies. According to the literature, the tarsal and/or carpal fusion makes it possible to orient the diagnosis of BDB2 [3]. Therefore, the absence of this abnormality does not exclude the diagnosis of BDB2. Thus, only the molecular study can differentiate the two subtypes of BDB because of the high clinical similarity. NOG variants may also be associated with sensorineural hearing impairment [10,11]. A study conducted by Hwang et al. on an

animal model confirmed the existence of a relationship between haploinsufficiency of the NOG gene and deafness. Reported neurosensory deafness in some patients with BDB2 [3]. In our study, deafness was not found.

In conclusion, we report a novel mutation in NOG that enriches the human gene mutation database. In this study, patients who carry the same F168S mutation had different phenotypic presentations. The findings reported here are consistent with literature data where phenotypic variability suggested a lack of genotype-phenotype correlation.

### Author Contribution

Faten Hsoumi and Yasmina ELARIBI wrote the manuscript; Imen Rejeb: Methodology; Houweyda Jilani, Syrine Hizem, Hela Sassi and Molka Sebai: Clinical investigation; Lamia Ben Jemaa: Validation

### Ethics Approval and Consent to Participate

Informed and written consent for genetic analyses was obtained from the parents. The ethical approval of the study was obtained from Ethical Committee of the Mongi Slim Hospital, Tunisia.

### Consent for Publication

Consent for publication of respective case presentations was obtained from patients' parents.

### Conflicts of Interest

The authors have no conflict of interest to declare.

### Acknowledgements

We would like to express our gratitude to all the participants of this study.

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