Identification of an unknown frameshift variant of NOG in a Han Chinese family with proximal symphalangism

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Proximal symphalangism (SYM1) is an autosomal dominant disorder manifested by ankylosis of the proximal interphalangeal joints of fingers, carpal and tarsal bone fusion, and conductive hearing loss in some cases. Herein, we clinically diagnosed a Chinese patient with fusions of the bilateral proximal interphalangeal joints in the 2–5 digits without conductive hearing loss. Family history investigation revealed that his mother and grandfather also suffered from SYM1. Whole exome sequencing was performed to detect the genetic lesion of the family. The candidate gene variants were validated by Sanger sequencing. By data filtering, co-segregation analysis and bioinformatics analysis, we highly suspected that an unknown heterozygous frameshift variant (c.635_636insG, p.Q213Pfs*57) in NOG was responsible for the SYM1 in the family. This variant was predicted to be deleterious and resulted in a prolonged protein. This finding broadened the spectrum of NOG mutations associated with SYM1 and contributed to genetic diagnosis and counseling of families with SYM1.

Introduction

Proximal symphalangism (SYM1) is a hereditary disorder manifested by ankylosis of the proximal interphalangeal joints, carpal and tarsal bone fusion, and conductive hearing loss in some cases [1]. The typical features of SYM1 are reduced proximal interphalangeal joint space, symphalangism of the 4th and/or 5th finger [2,3]. The estimated prevalence of SYM1 is less than 1/100000 with autosomal dominant inherited pattern [4,5]. And the first family with ankylosis of the proximal interphalangeal joints was reported and named as symphalangism in 1916 [6].

At present, at least two types of SYM1 have been identified in the clinic. One is proximal symphalangism-1A (SYM1A; OMIM 185800), which was caused by genetic variants in NOG (noggin), another is proximal symphalangism-1B (SYM1B; OMIM 615298), which resulted from GDF5 (growth differentiation factor 5) mutations [2,7]. However, due to the extensive pleiotropy, several other diseases may be also related to NOG, such as tarsal–carpal coalition syndrome, multiple synostoses syndrome, and brachydactyly, etc. [8]. Hence, detection the genetic lesion of the patients with SYM1 may further confirm the clinical diagnosis and help us to understand the development of bone.

In the present study, we enrolled a family with SYM1 from central south region of China. The aim of the present study was to detect the genetic lesion of the affected individuals by employing whole exome sequencing and bioinformatics analysis.
| Chr | Pos  | RB | AB  | Gene       | Mutation                  | OMIM                        | Allele frequency | Topp gene                          | ACMG                              |
|-----|------|----|-----|------------|---------------------------|-----------------------------|------------------|------------------------------------|-----------------------------------|
| 1   | 220275877 | C | T   | IARS2     | NM_018060; c.C790T: p.H264Y | AR: growth hormone deficiency | Unknown variant   | Isoleucyl-tRNA aminoaaclylation    | PM2, BP6                          |
| 2   | 196681652 | A | G   | DNAH7     | NM_018897; c.T9461C:p.V3154A | -                           | Unknown variant   | Inner dynein arm assembly          | PM2, PP1, PP3                      |
| 2   | 233388655 | G | A   | PRSS56    | NM_00119512; c.G1186A: p.E396K | AR: microphthalmia          | Unknown variant   | Serine-type endopeptidase activity | PM2, BP6                          |
| 5   | 118485627 | C | T   | DMXL1     | NM_001290321; c.C4105T:p.R1369C | -                           | Unknown variant   | Vacular acidification              | PM2, PP1, PP3                      |
| 8   | 99116733  | A | G   | HRSP12    | NM_005836; c.T335C: p.V112A | -                           | Unknown variant   | -                                  | PM2, PP1, PP3                      |
| 9   | 119481126 | G | A   | TRIM32    | NM_001099679; c.G1105A: p.G369R | AR: Bardet–Bied syndrome neuropathy | Unknown variant   | Tat protein binding                | PM2, BP6                          |
| 12  | 992601    | T | G   | WNK1      | NM_014823; c.T2789G: p.F930C | AR: neuropathy; AD: pseudohypoaldosteronism | Unknown variant   | Chloride channel inhibitor activity | PM1, PM2                           |
| 12  | 49522372  | A | C   | TUBA1B    | NM_006082; c.T275G: p.L242R | -                           | Unknown variant   | Fibroblast growth factor receptor signaling pathway | PM1, PM2, PM4, PP1, PP3, PP4 |
| 17  | 54672219  | G | G   | NOG       | NM_005450: c.635_636insG: p.Q213PfsX57 | AD: symphalangism | Unknown variant | Fibroblast growth factor receptor signaling pathway | PM2, PP1, PP3 |
| 17  | 71420107  | G | A   | SDK2      | NM_001144952; c.C1708T: p.R570W | -                           | Unknown variant   | Camera-type eye photoreceptor cell differentiation | PM2, PP1, PP3                   |
| 18  | 13071096  | G | A   | CEP192    | NM_003214; c.G5233A: p.E1745K | -                           | Unknown variant   | Phosphatase binding                | PM2, PP1, PP3                      |
| 19  | 39521974  | T | G   | ECH1      | NM_001398; c.A235C: p.N79H | -                           | Unknown variant   | Δ3,5-Δ2,4-Dienoyl-CoA isomerase activity | PM2, PP1, PP3                      |
| 19  | 56128115  | T | C   | ZNF865    | NM_001195605; c.T3131C: p.L1044P | -                           | Unknown variant   | –                                  | PM2, PP1, PP3                      |
| 20  | 25457050  | C | CA  | NINL      | NM_025176; c.2876_2877insT: p.E969Dfs15 | -                           | Unknown variant   | Calcium ion binding                | PM2, PP1, PP3                      |
| 20  | 30785333  | G | A   | PLAGL2    | NM_002667; c.C413T: p.T138M | -                           | Unknown variant   | Chylomicron assembly               | PM2, PP1, PP3                      |
| X   | 131188838 | G | T   | STK26     | NM_001042452; c.G222T:p.L74F | -                           | Unknown variant   | Microvillus assembly               | PM2, PP1, PP3                      |

CHR, chromosome; POS, position; RB, reference sequence base; AB, alternative base identified; AR, autosomal recessive; AD, autosomal dominant; BP, benign supporting; PP, pathogenicity supporting; PM, pathogenicity moderate; PVS, pathogenicity very strong. The data of allele frequency were obtained from 1000G, ESP, and ExAC databases.
Figure 1. The clinical data of the family with SYM1

(A) The pedigree of this family. Black circles/squares are affected, white circles/squares are unaffected. Arrow indicates the proband. The question mark indicates that the illness is uncertain. (B) The proband showed the symphalangism of second to fifth fingers. (C) Hands X-ray of III-2. The red circles and arrows marked the abnormal regions.

Materials and methods

Subjects and ethical approval

The proband (Figure 1A, III:2) was a 6-year-old boy from a non-consanguineous Chinese family. According to the family history investigation, mother (II:4) and grandfather (I:1) of proband also had the phenotype of limited fingers bilaterally, they may be patients with SYM1. We found the fourth to fifth fingers bilaterally of his mother were limited after preliminary diagnosis. Unfortunately, the proband’s mother refused further diagnosis and treatment and grandfather has already passed away. The photographs showed the second to fifth fingers and toes bilaterally of the proband were limited and cannot make a fist (Figure 1B). The radiographs indicated the reduced proximal interphalangeal joint space and further confirmed the clinical diagnosis (Figure 1C). No other significant phenotypes were found, such as hearing loss.

The Review Board of the Xiangya Hospital of the Central South University approved the present study. Given the proband is too young, written consent forms were signed by his parents as guardians.

Genetic analysis

Genomic DNA was prepared from peripheral blood of the patients and other all participants using a DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA, U.S.A.). Genomic DNA was extracted from the peripheral blood lymphocytes of all family members by using a DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA, U.S.A.) following the manufacturer’s instruction. The central part of the whole exome sequencing was provided by the Novogene Bioinformatics Institute (Beijing, China). The exomes were captured using Agilent SureSelect Human All Exon V6 kits, and high-throughput sequencing was performed using Illumina HiSeq X-10. The necessary bioinformatics analyses, including reads, mapping, variant detection, filtering, and annotation, were also endowed by Novogene Bioinformatics Institute [9].

The strategies of data filtering refer to our previous study [9]: (a) variants within intergenic, intronic, and UTR regions as well as synonymous mutations were excluded for later analysis; (b) variants with MAF>0.01 in the 1000 Genomes project, dbSNP132 were excluded; (c) variants with MAF>0.01 in genome aggregation database (gnomAD)
Table 2 The summary of reported mutations in NOG

| No. | Mutation | Phenotypes                | PMID    |
|-----|----------|---------------------------|---------|
| 1   | c. 58delC | p. Leu20fs S1            | –       |
| 2   | c. 103C-G | p. Pro35Ala BDB          | –       |
| 3   | c. 103C-T | p. Pro35Ser TCC          | Hyperia |
| 4   | c. 103C-T | p. Pro35Ser SYM1         | –       |
| 5   | c. 103C-T | p. Pro35Ser BDB          | –       |
| 6   | c. 104C-G | p. Pro35Arg SYM1         | –       |
| 7   | c. 104C-G | p. Pro35Arg TCC          | –       |
| 8   | c. 106C-G | p. Ala36Pro BDB          | –       |
| 9   | c. 110C-G | p. Pro37Arg TCC          | Hyperia |
| 10  | c. 124C-G; c. 149C-G | p. Pro42Ala; p. Pro50Arg SYM1 | – |
| 11  | c. 124C-T | p. Pro42Ser SYM1         | –       |
| 12  | c. 125C-G | p. Pro42Arg SYNS1        | –       |
| 13  | c. 124C-A | p. Pro42Thr SYNS1        | –       |
| 14  | c. 125C-T | p. Pro42Leu SYNS1        | –       |
| 15  | c. 130_131insGG | p. Val44fs SYNS1 Hearing loss | Hyperia |
| 16  | c. 137T-C | p. Leu46Pro SYM1         | –       |
| 17  | c. 142G-A | p. Glu48Lys BDB          | –       |
| 18  | c. 142G-A | p. Glu48Lys POF and SYM1 | Hyperia |
| 19  | c. 163G-T | p. Asp55Tyr SYM1         | –       |
| 20  | c. 252_253insG | p. Glu85fs SYM1 Hearing loss | Hyperia |
| 21  | c. 261_262insG | p. Pro88fs SYNS1 Hearing loss | Hyperia |
| 22  | c. 271G-T | p. Gly91Cys FOP          | –       |
| 23  | c. 274G-C | p. Gly92Arg FOP          | –       |
| 24  | c. 275G-A | p. Gly92Glu FOP          | –       |
| 25  | c. 283G-A | p. Ala95Thr FOP          | –       |
| 26  | c. 304delG | p. Ala102fs SYM1        | Hyperia |
| 27  | c. 328C-T | p. Gin110X SABTT        | Hyperia |
| 28  | c. 386T-C | p. Leu128X SYM1         | –       |
| 29  | c. 391C-T | p. Gin131X SABTT        | Hyperia |
| 30  | c. 397A-T | p. Lys133X SABTT        | Hyperia |
| 31  | c. 406C-T | p. Arg136Cys SYM1       | –       |
| 32  | c. 450G-C | p. Trp150Cys SYM1       | –       |
| 33  | c. 452C-A | p. Ser151X SYNS1        | Hyperia |
| 34  | c. 463T-A | p. Cys155Ser SYM1       | –       |
| 35  | c. 499C-G | p. Arg167Gly BDB        | –       |
| 36  | c. 499C-T | p. Arg167Cys SYM1       | –       |
| 37  | c. 511G-A | p. Cys184Tyr SYM1       | –       |
| 38  | c. 511G-T | p. Cys184Phe SYM1       | Hyperia |
| 39  | c. 559C-G | p. Pro187Ser BDB        | –       |
| 40  | c. 559C-G | p. Pro187Ala SYM1       | Hyperia |
| 41  | c. 561delC | p. Pro187fs SYNS1       | –       |
| 42  | c. 565C-T | p. Gly189Cys SYM1       | –       |
| 43  | c. 568A-G | p. Met190Val SYNS1      | –       |
| 44  | c. 608T-C | p. Leu203Pro TCS        | Hyperia |
| 45  | c. 611G-T | p. Arg204Leu TCC       | Hyperia |
| 46  | c. 615G-G | p. Arg204Gln TCC         | –       |
| 47  | c. 615G-A | p. Trp205X SYNS1        | –       |
| 48  | c. 615G-C | p. Trp205Cys Facioaudiosymphalangism syndrome Hearing loss Hyperia |
| 49  | c. 615G-C | p. Trp205Cys SABTT      | Hyperia |
| 50  | c. 659C-G | p. Cys215X SYM1         | –       |
| 51  | c. 659C-G | p. Cys215X SABTT        | Hyperia |
| 52  | c. 695T-G | p. Trp217Gly SYNS1      | –       |
| 53  | c. 695T-A | p. Leu220Asn SYM1       | –       |

Continued over
### Table 2 The summary of reported mutations in NOG (Continued)

| No. | Mutation | Phenotypes | PMID          |
|-----|----------|------------|---------------|
| 54  | c. 659_660delinsAT | p. Ile220Asn | SYM1 – – | 10080184 |
| 55  | c. 664T>G   | p. Tyr222Asp | SYM1 – – | 10080184 |
| 56  | c. 665A>G   | p. Tyr222Cys | SYM1 – – | 10080184 |
| 57  | c. 665A>G   | p. Tyr222Cys | TCC – – | 11545688 |
| 58  | c. 668C>T   | p. Pro223Leu | SYM1 – – | 10080184 |
| 59  | c. 682T>G   | p. Cys228Gly | SABTT Hearing loss | Hyperopia 26211601 |
| 60  | c. 682T>A   | p. Cys228Ala | SYNS1 Hearing loss | Hyperopia 25391606 |
| 61  | c. 689G>A   | p. Cys230Tyr | SYNS1 – | Hyperopia 26994744 |
| 62  | c. 690C>G   | p. Cys230Trp | SYM1 Hearing loss – | 31694554 |
| 63  | c. 696C>G   | p. Cys232Trp | SYNS1 Hearing loss | Hyperopia 20503332 |

SYNS1, multiple synostosis syndrome; BDB, brachydactyly type B; TCC, Trasal–Carpal coalition syndrome; SYM1, proximal symphalangism; TCS, Teunissen–Cremers syndrome; POF, premature ovarian failure; SABTT, stapes ankylosis with broad thumbs and toes; FOP, fibrodysplasia ossificans progressiva.

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**Figure 2. The genetic analysis of the variant**

(A) Sanger DNA sequencing chromatogram demonstrates the heterozygosity for a NOG variant (c.635_636insG, p.Q213Pfs*57).

(B) Rope diagram of noggin–BMP7 complex (SMTL ID: 1m4u.1), the upper and lower parts are noggin dimer and BMP7 dimer, respectively. The arrows and words indicate the Q213 site, the red amino acids rope after Q213 was affected in the patient. (C) Alignment of the amino acid sequences of noggin. The affected amino acids locate in the highly conserved amino acid region in different species (from Ensembl). The arrow and words show the Q213 site.

(http://gnomad.broadinstitute.org/) were further precluded; (d) SIFT, Polyphen-2 and MutationTaster were utilized to predict the possible impacts of variants. (e) Co-segregation analysis was conducted in the family.

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**Result**

The WES raw data had a mean depth of 125.66 on target, target region coverage of 98.05%, target region coverage (at least 10×) of 97.27%, indicating the high sequencing quality. After data filtering, only 16 variants were included in Table 1. We then further performed bioinformatic analysis including Inheritance pattern and OMIM clinical phenotypes analysis (https://www.omim.org/), ToppGene gene function analysis (https://toppgene.cchmc.org/) and The American College of Medical Genetics and Genomics (ACMG) classification, we highly suspected the unknown variant (NM_005450, c.635_636insG, p.Q213Pfs*57) of NOG, belonging to PM1, PM2, PM4, PP1, PP3, and PP4 (likely pathogenic) in ACMG guidelines [10], was the genetic lesion of the family (Figure 2A). The result of co-segregation...
analysis showed the same unknown variant exist in mother of proband but not in his father. The unknown variant, which led to alteration of amino acid residues after position 212 and a prolonged protein (Figure 2B), was predicted as “Disease Causing” (0.99) by MutationTaster (http://www.mutationtaster.org/) and not found on the 1000 Genome Browser, the gnomAD Browser and the Exome Variant Server, and was not presented in 200 control cohorts. Multiple alignment of noggin orthologs in other animal species showed that amino acid sequence after position 212 was highly conserved (Figure 2C).

Discussion
In the present study, we enrolled a family with SYM1 from China. By employing whole exome sequencing, we identified an unknown frameshift variant (c.635_636insG, p.Q213Pfs*57) in the affected members. The variant resulted in the extension of noggin protein which may affect the function of the protein. Bioinformatics analysis further predicted this variant as disease-causing variant. Our study is consistent with previous studies which indicated that variants in NOG gene may lead to SYM1 and other bone diseases [11].

The human NOG gene encoding noggin protein is located on chromosome 17q22, and it consists of one exon, spanning approximately 1.9 kilobases (kb). Noggin, the first identified BMP antagonist, is posttranslationally modified and secreted as a disulfide-bonded homodimer. BMPs play essential roles in skeletogenesis including recruiting mesenchymal cells, promoting mesenchymal cell proliferation and differentiation into chondroblasts and osteoblasts, and inducing apoptosis to form joints [12–14]. Noggin can bind to BMPs and inhibit the interactions of BMPs and BMP-specific receptors, and therefore negatively regulates BMP-induced osteogenesis [15,16]. In the present study, the unknown variant was not located at the interface between the two molecules in noggin–BMP7 complex (SWISS-MODEL Template Library, ID:1m4u.1), and no templates of sufficient quality to build a homology model were found for the changed sequence (Figure 2B). Whereas, according to the complex model and the prolonged sequence, we suspected the variant presumably affected the binding of noggin homodimer and further disrupt the structure of noggin–BMP7 complex, which activated the BMP signal pathway and lead to bone diseases. Further research is needed to confirm this hypothesis.

On the basis of reported papers, multiple bone diseases are associated with NOG mutations [17]. For example, at present, over 50 mutations of NOG involved in wide variety of bone development anomalies, including tarsal/carpal coalition syndrome, brachydactyly, multiple synostoses syndrome, stapes ankylosis with broad thumbs and toes, have been reported [5,18]. Even the same variants of NOG can lead to different phenotypes between different families or different affected members of the same family, see Table 2 [19,20]. Meanwhile, the variant was the sixth unknown variant reported in Chinese population, which indicated there were still a lot of unknown variants to be discovered in Chinese population. Here, we summarized the reported NOG mutations in Table 2, which may make us to understand the function of noggin better.

In additional to major bone diseases, patients with NOG mutations are often accompanied by other phenotypes, such as conductive hearing loss and hyperopia. In Table 2, we can find that these phenotypes are not always present in the same mutations or in different mutations at the same sites. Besides, in some papers, hearing loss do not exist in all affected members of same families [5,18]. These results seem to indicate that conductive hearing loss and hyperopia may appear randomly in patients with NOG mutations; whereas, in contrast with most NOG mutations that have been reported in kindreds with SYM1 and SYN1, the mutations observed in families with stapes ankylosis without SYM1 are predicted to disrupt the cysteine-rich C-terminal domain [21,22]. In short, the relationship between NOG and these phenotypes is still unclear, further research is needed to understand that. Some patients with NOG mutations can also have nasal bone, elbow, shoulder, and spine anomalies except for hands and feet [11,14], suggested noggin protein plays an essential and extensive role in bone development.

In summary, we investigated a Chinese family with SYM1 and an unknown frameshift variant (c.635_636insG, p.Q213Pfs*57) was detected by whole exome sequencing. According to ACMG standards and guidelines, this variant was categorized as likely pathogenic (PM1, PM2, PM4, PP1, PP3 and PP4) and identified as the genetic lesion of the family. Our study expanded the spectrum of NOG mutations and contributed to genetic counseling and diagnosis of patients with SYM1.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.
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Author Contribution
Z.-Y.Z. and F.Y. carried out the sample collecting and genetic testing, J.-Y.J. and Z.-J.J. collected the clinical data, Z.-Z.Y. and J.-Y.J. performed the bioinformatics analysis, J.-Y.T. and R.X. designed the project and wrote the manuscript. All authors read and approved the final manuscript. All authors reviewed the manuscript.

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Abbreviations
ACMG, The American College of Medical Genetics and Genomics; GDF5, growth differentiation factor 5; gnomAD, genome aggregation database; NOG, noggin; OMIM, Online Mendelian Inheritance in Man; SYM1, proximal symphalangism; SYM1A, proximal symphalangism-1A; SYM1B, proximal symphalangism-1B; SYNS1, multiple synostosis syndrome.

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