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Identification of a novel mutation of NOG in family with proximal symphalangism and early genetic counseling

Cong Ma¹⁺, Lv Liu²⁺, Fang-Na Wang¹, Hai-Shen Tian¹, Yan Luo¹, Rong Yu³, Liang-Liang Fan^{4*} and Ya-Li Li^{1*}

Abstract

Background: Proximal symphalangism is a rare disease with multiple phenotypes including reduced proximal interphalangeal joint space, symphalangism of the 4th and/or 5th finger, as well as hearing loss. At present, at least two types of proximal symphalangism have been identified in the clinic. One is proximal symphalangism-1A (SYM1A), which is caused by genetic variants in *Noggin (NOG)*, another is proximal symphalangism-1B (SYM1B), which is resulted from *Growth Differentiation Factor 5 (GDF5)* mutations.

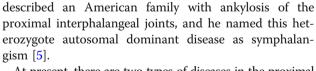
Case presentation: Here, we reported a Chinese family with symphalangism of the 4th and/or 5th finger and moderate deafness. The proband was a 13-year-old girl with normal intelligence but symphalangism of the 4th finger in the left hand and moderate deafness. Hearing testing and inner ear CT scan suggested that the proband suffered from structural deafness. Family history investigation found that her father (II-3) and grandmother (I-2) also suffered from hearing loss and symphalangism. Target sequencing identified a novel heterozygous *NOG* mutation, c.690C > G/p.C230W, which was the genetic lesion of the affected family. Bioinformatics analysis and public databases filtering further confirmed the pathogenicity of the novel mutation. Furthermore, we assisted the family to deliver a baby girl who did not carry the mutation by genetic counseling and prenatal diagnosis using amniotic fluid DNA sequencing.

Conclusion: In this study, we identified a novel *NOG* mutation (c.690C > G/p.C230W) by target sequencing and helped the family to deliver a baby who did not carry the mutation. Our study expanded the spectrum of *NOG* mutations and contributed to genetic diagnosis and counseling of families with SYM1A.

Keywords: Proximal symphalangism, Deafness, NOG mutation, Prenatal diagnosis

Background

Proximal symphalangism is a rare genetic disorder of congenital limb malformation, characterized by ankylosis of the proximal interphalangeal joints, carpal and tarsal bone fusion, and, in some cases, conductive deafness and premature ovarian failure [1, 2]. The typical features of proximal symphalangism are reduced proximal interphalangeal joint space, symphalangism of the 4th and/or 5th finger [3, 4]. As early as in 1916, Cushing has



At present, there are two types of diseases in the proximal symphalangism family: (1) Proximal symphalangism-1A (SYM1A, OMIM # 185800), which iss caused by genetic variants in *Noggin* (*NOG*) [6, 7]; (2) Proximal symphalangism-1B (SYM1B), which is resulted from *Growth Differentiation Factor 5* (*GDF5*) mutations [8, 9]. In addition, some other diseases may be also related to proximal symphalangism, such as tarsal-carpal coalition syndrome, multiple synostoses syndrome, and brachydactyly, etc. [10, 11].

In this study, we employed target sequencing to explore the genetic lesion of a Chinese family with symphalangism of the 4th and/or 5th finger and moderate

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deafness. A novel mutation (c.690C > G/p.C230W) of *NOG* was identified in all affected individuals in this family. Furthermore, after genetic counseling and prenatal diagnosis with us, the mother successfully delivered a baby girl who did not carry the mutation.

Case presentation

A family from North of China (Hebei Province) with eight members across three generations participated in the study (Fig. 1a). The proband (III-2) was a 13-yearold girl with normal intelligence but symphalangism of the 4th finger in the left hand (Fig. 1b) and moderate deafness (Fig. 1c). Inner ear CT scan found abnormal inner ear structure (cochlear hypoplasia) and abnormal calcification (inner ear bone thickening and increased density) (Fig. 1d). Family history investigation found that her father (II-3) and grandmother (I-2) also suffered from hearing loss and symphalangism (Fig. 1a, e). Her grandmother has died six years ago. Her father showed the symphalangism of the 4th finger in left hand (Fig. 1e, f). He had performed the vestibulotomy and recovered the hearing one year ago. They went to the Department of Reproductive Genetics, HeBei General Hospital because the mother was pregnant with the second baby. They wanted to detect whether the second baby was normal or not.

Genetic analysis

We selected the proband's genomic DNA to perform the target sequencing to detect the disease-causing mutations by Sinopath Diagnosis Company (Beijing, China). Target sequencing yielded 3.71 Gb of data with 99.088% coverage of the target region and 97.530% of the target covered over 10×. After filtering dbSNP132, 1000G, EXAC, and GenomAD database (MAF < 0.01), only 12 mutation were left. We then conducted the cosegregation analysis by Sanger sequencing and only seven variants were exist in affected individuals and were absent in healthy members (Table 1). We further performed the bioinformatics analysis including Mutation-Taster, SIFT, Polyphen-2, PANTHER, ToppGene function analysis, OMIM clinical phenotype analysis and ACMG classification (Table 1), we highly suspected the novel mutation (c.690C > G/p.C230W) of NOG, belonging to PM1 and PM2 in ACMG guidelines [12], was responsible for the family with SMY1A. This mutation resulted in a substitution of in polar amino acid cysteine by nonpolar amino acid tryptophan in the codon 230 of exon 1 of NOG gene, and was not presented in our 200 control cohorts. Noggin amino acid sequence alignment analysis suggested that this mutation was located in a highly evolutionarily conserved site (Fig. 2b). In addition, we also constructed a part model of the Noggin protein using SWISS-MODEL (https://swissmodel.expasy.org) (Fig. 2c) and, after applying SDM software (http://marid. bioc.cam.ac.uk/sdm2/prediction) to analyze the structure, it was found that this novel mutation might increase the solvent accessibility (WT:16.9% and Mutant: 39.9%) and reduce the stability of the Noggin protein.

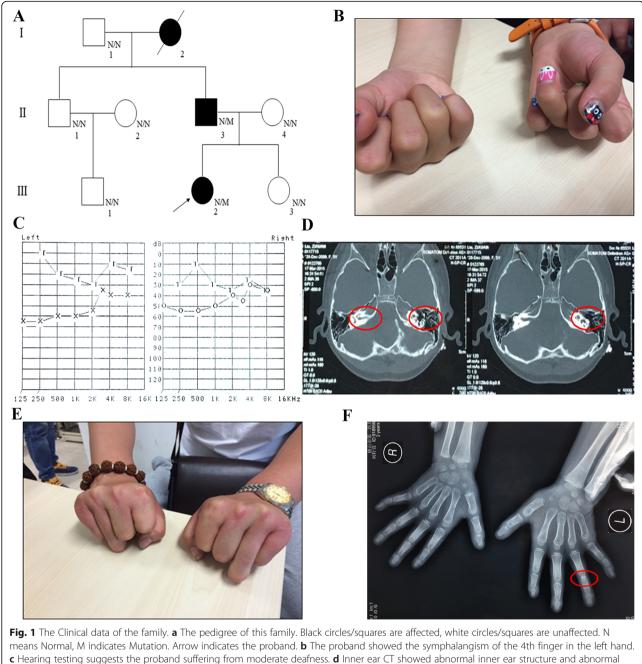
Prenatal diagnosis

When the parents came to our hospital, the mother has been pregnant with the second baby for 17 weeks and they wanted to have a healthy baby. According to ACMG classification, the novel mutation (c.690C > G/ p.C230W) of *NOG* belongs to PM1 and PM2. Simultaneously, target sequencing only identified this mutation as a pathogenic variant. So, we highly believed the novel mutation (c.690C > G/p.C230W) of *NOG* was the genetic lesion of the family with proximal symphalangism and hearing loss. We then performed the Sanger sequencing of amniotic fluid DNA to detect the mutation, fortunately, the results showed a normal allele of the second baby. And 22 weeks later, the mother delivered a 3.4-kg healthy girl (Fig. 2d).

Discussion

The human NOG gene encoding Noggin protein is located on chromosome 17q22, and it consists of one exon, spanning approximately 1.9 kilobases (kb) [6]. Noggin protein is involved in the development of many body tissues, including nerve tissue, muscles, and bones and the role of Noggin in bone development makes it significant for proper joint formation [13]. According to previous researches, Noggin protein can interact with bone morphogenetic proteins (BMPs) and regulate the development of bone and other tissues [14]. In detail, the Noggin protein regulates the activity of BMPs by binding to them and blocking them from attaching to the downstream receptor, which results in a decrease in BMP signaling [15]. In our research, the novel mutation (c.690C > G/p.C230W) of *NOG* can increase the solvent accessibility and reduce the stability of the Noggin, which may active the BMP signal pathway and lead to bone diseases.

In 1999, five *NOG* mutations were identified in unrelated families with symphalangism (SYM1A) and a de novo mutation in a patient with unaffected parents [6]. Interestingly, a wide variety of bone development anomalies, including tarsal/carpal coalition syndrome [10], brachydactyly [16], multiple synostoses syndrome [17], Stapes ankylosis with broad thumbs and toes [18], have been reported in patients with *NOG* mutations. Similar observations were also reported in the families even with the same mutation [16, 19]. Therefore, the pleiotropic types of bone diseases and significant genetic heterogeneity make it difficult to be diagnosed. We summarized the previous reports and found that approximately 57



calcification. The red circles marked the abnormal regions which indicated cochlear hypoplasia, inner ear bone thickening and increased density. e The symphalangism of the 4th finger in II-3. f Hands X-ray of III-2. The red circles marked the abnormal regions

mutations (60 patients) of *NOG* have been identified in different types of disorders (Table 2).

In this study, a family with symphalangism and moderate deafness was investigated by target sequencing. Genetic analysis found a novel mutation (c.690C > G/p.C230W) of *NOG* in two affected members. Of note, both of two patients with p.C230W in the family were associated with hearing loss. To date, 29 mutations have been reported in symphalangism patients related to deafness (Table 2) [11].

And the mutation p.C230W was the fifth report related to *NOG* mutation, although some Chinese journals have also published some reported mutations. Meanwhile, this difference also suggested that there were still a lot of novel mutations need to discovery in Chinese population.

The p.C230W mutation disrupts the cysteine knot motif of the C-terminal domain of Noggin (amino acids 155–232), which contains a series of nine cysteine residues and was shown to target the molecule

 Table 1 The mutations list after data filtering and co-segregation analysis

CHR	POS	RB	AB	Gene	Mutation	SIFT	PolyPhen- 2	MutationTaster	PANTHER	OMIM clinical phenotype	ToppGene function	ACMG classification
1	45, 481, 060	С	Т	UROD	NM_000374: c.994C > T, p.R332C	0,D	0.94,D	0.99,D	-	AD or AR: Porphyria cutanea tarda	heme biosynthetic process	BP5
2	149, 216, 410	G	A	MBD5	NM_018328: c.83G > A, p.R28H	0,D	0.99,D	0.99,D	Ρ	AD: Mental retardation	response to growth hormone	BP5
2	189, 953, 479	G	Т	COL5A2	NM_000393: c.587G > T, p.A196D	0.29, T	0.98,D	0.99,D	-	AD: Ehlers- Danlos syndrome	regulation of endodermal cell differentiation	BP4, BP5
3	38, 674, 642	G	A	SCN5A	NM_198056: 157G > A, p.R53W	0,D	0.36,B	0.95,D	Ρ	AD: Atrial fibrillation	voltage-gated sodium channel activity	BP4, BP5
3	184, 953, 112	G	A	EHHADH	NM_001966: c.317G > A, p.A106V	0,D	0.99,D	0.99,D	Ρ	AD: Fanconi renotubular syndrome	peroxisomal transport	BP5
17	48, 701, 856	G	A	CACN A1G	NM_018896: c.6365G > A, p.R2122H	0.04, D	0.01,B	0.8,D	Ρ	AD: Spinocerebellar ataxia	voltage-gated calcium channel	BP4, BP5
17	54, 672, 274	С	G	NOG	NM_005450: c.690C > G, p.C230W	0,D	0.99,D	0.99,D	D	AD: Symphalangism proximal	fibroblast growth factor receptor signaling pathway	PM1, PM2

CHR Chromosome, POS position, RB reference sequence base, AB alternative base identified, D damaging, P probably damaging, B Benign, T Tolerated, AR autosomal recessive, AD autosomal dominant, BP Benign Supporting, PM Pathogenicity Moderate

to a specific receptor protein [20, 21]. The similar mutations (p.C228G, p.C228S, p.C230Y and p.C232W) have been identified in patients with symphalangism and hearing loss, which indicated that mutations in cysteine residues may be related to abnormal development of auditory ossicles and hearing loss [19, 22–24].

In clinical genetics, the aim of mutation detection is to make contributions to genetic diagnosis and counseling. In this study, we identified the genetic lesion of the family by target sequencing. All the filtered data were shown in Table 1. We not only performed the informatics analysis of the novel mutation by multi-different algorithm based bioinformatics programs, but also followed the

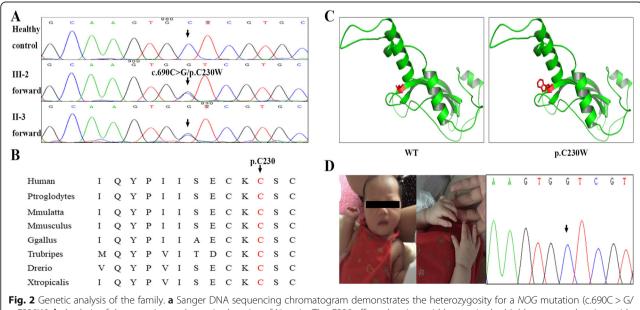


Fig. 2 Genetic analysis of the family. **a** Sanger DNA sequencing chromatogram demonstrates the heterozygosity for a NOG mutation (c.690C > G/ p.C230W). **b** Analysis of the mutation and protein domains of Noggin. The C230 affected amino acid locates in the highly conserved amino acid region in different mammals (from Ensembl). The black arrow and red words show the C230 site. **c** Swiss-model analyzed the Noggin structures of WT and Mutated (p.C230W). **d** The healthy hands of III-3 and normal sequences of amniotic fluid DNA

1 1.0.005 Murdles yenesses and/once Toursham Toursham <th>No.</th> <th>No. Mutation</th> <th>Phenotypes</th> <th>Reference</th>	No.	No. Mutation	Phenotypes	Reference
pmddiam pmddiam	-	p. Leu2ofs	Multiple synostoses syndrome	Takahashi et al. (2001)
Pro155ct Turussen-Conner synchome Pr055ct Runssen-Conner synchome	2	p. Pro35Ala	Brachydactyly type B	Lehmann et al. (2007)
Preside Previnal Symphologian P M354 Previnal Symphologian P M354 Previnal Symphologian P M354 Previnal Symphologian P M354 Previnal Symphologian P Pedid Previnal Symphologian <td>m</td> <td>p. Pro35Ser</td> <td>Teunissen-Cremers syndrome</td> <td>Hirshoren et al. (2008)</td>	m	p. Pro35Ser	Teunissen-Cremers syndrome	Hirshoren et al. (2008)
p. Pr03/Set Bod/set p. Pr03/Set Pr04/Set p. Pr03/Set Test regist collition syndhome p. Pr03/Set Test regist collition syndhome p. Pr03/Set Pr04/Set p. Pr03/Set Test regist collition syndhome p. Pr03/Set Pr04/Set p. Pr04/Set Pr04/Set <	4	p. Pro35Ser	Proximal symphalangism	Mangino et al. (2002)
p fro35/d Pro437/vg p fro35/vg Pro437/vg p fro42/kg Pro447/vg p fro42/kg Pro447/vg <td>L)</td> <td>p. Pro35Ser</td> <td>Brachydactyly type B</td> <td>Lehmann et al. (2007)</td>	L)	p. Pro35Ser	Brachydactyly type B	Lehmann et al. (2007)
p PolSAG TarsH-carpfic caliform syndrome p Address TarsH-carpfic caliform syndrome p PolSAG TarsH-carpfic caliform syndrome p PolSAG TarsH-carpfic caliform syndrome p PolSAG Multiple syncrosses syndrome p PolSAG Multiple syncrosses syndrome p PolSAG Multiple syncrosses syndrome p PolSAG PolMalingian p GluBSIS Porimal symphalingian p AdSAG Porimal symphalingian p Porimal symphalingian Porimal symphalingian p AdSAG Porimal symphalingian p AdSAG Porimal symphalingian p AdS	9	p. Pro35Arg	Proximal symphalangism	Gong et al. (1999)
p. No.35No p. Ab36ho p. Por37Arg p. Por37Arg p. Por37Arg p. Por37Arg p. Por37Arg Majhe synonses syndrome p. Por37Arg Majhe synonses syndrome p. Por37Arg Provinal symphanism p. Aug55Tyr Stapes ankytosis with broad thumb p. Aug55Tyr Provinal symphanism p. Aug55Tyr Provinal symphanism p. Aug55Tyr Stapes ankytosis with broad thumb p. Aug55Tyr Provinal symphanism p. Aug55Tyr Provinal symphanism p. Aug55Tyr Provinal symphanism p. Aug55Tyr Provinal symphanism p. Aug55Tyr Provinal symphanism <td>7</td> <td>p. Pro35Arg</td> <td>Tarsal-carpal coalition syndrome</td> <td>Dixon et at. (2001)</td>	7	p. Pro35Arg	Tarsal-carpal coalition syndrome	Dixon et at. (2001)
Prio:374g Taraal-carpal contition syndrome Prio:374g Multiple synonouse syndrome Prio:474b Prio:474b Prio:474b Multiple synonouse syndrome Prio:445b Prio:445c/shy type B Prio:445b Prio:45c/shi Prio:45c/shi Prio:45c/shi Prio:45c/shi Prio:45c/shi Prio:45c/shi Prio:45c/shi	Ø	p. Ala36Pro	Brachydactyly type B	Lehmann et al. (2007)
p. ProdZkie Mutiple synotasies syndome p. ProdZhr Mutiple synotasies syndome p. ProdZhr Mutiple synotasies syndome p. Val445 ProdXival synthalargism p. Gu480, so ProdXival synthalargism p. Gu480, so ProdXival synthalargism p. Gu480, so ProdXival synthalargism p. Aug551 Stapes antyloxis with broad thumb p. Aug551 ProdXival synthalargism p. Aug755 ProdXival synthalargism p. Aug755 ProdXival symthalargism p. Aug755 ProdXival symthalargism p. Aug755 ProdXival symthalargism<	6	p. Pro37Arg	Tarsal-carpal coalition syndrome	Debeer et al. (2004)
P. Prod.Xet Provintal sympholangism P. Prod.Xet Multiple synonsuses syndrome P. Vak445 Multiple synonsuses syndrome P. Vak445 Multiple synonsuses syndrome P. Vak445 Provintal sympholangism P. Alg557v Provintal sympholangism P. Alg574 Provintal sympholangism P. Alg575 Provintal sympholangism P. Alg5655 Provintal sympholangism	10	p. Pro42Ala	Multiple synostoses syndrome	Debeer et al. (2005)
p Prod2Arg Multiple synotables syndrome p Prod3Arg Eurolises Cremers syndrome p Vald45 Eurolises Cremers syndrome p Prod3Arg Eurolises Cremers syndrome p Prod3Arg Prod3Arg p Prod3Arg Provinal symphalengism p Arg55 Syndrome Provinal symphalengism p Arg57 Syndrome Provinal symphalengism p Gry92Arg Provinal symphalengism p Arg57 Syndrome Provinal symphalengism p	11	p. Pro42Ser	Proximal symphalangism	Sha et al. (2019)
p. Pro42/Thr D. Pro42/Thr p. Valvids D. Valvids p. MagNis Provinal symphalangism p. AdpST Provinal symphalangism p. Glu92Acg Provinal symphalangism p. Glu92Acg Provinal symphalangism p. Glu12IX D. AdpST p. Ala1025 Provinal symphalangism p. Ala1025 Provinal symphalangism p. Lu123X Provinal symphalangism	12	p. Pro42Arg	Multiple synostoses syndrome	Oxley et al. (2008)
p. Val.445 Teunissen-Cremers syndrome p. GukaBys p. GukaBys p. GukaBys P. GukaBys p. GukaBys P. GukaBys p. GukaBys Provimal symphalangism p. App55Tyr Sapes ankyots with broad thumb p. AlgSTS Sapes ankyots with broad thumb p. GugaBy Encolyspala ostificans progressiva p. AlgSTS Flocolyspala ostificans progressiva p. GugaBy Multiple synonses syndrome p. AlgSTS Multiple synonses syndrome p. AlgSTS Flocolyspala ostificans progressiva p. AlgSTS Proximal symphalangism p. AlgTSK Proximal symphalangism p. AlgTSK Proximal symphalangism p. AlgTSK <td>13</td> <td>p. Pro42Thr</td> <td>Multiple synostoses syndrome</td> <td>Aydin, H et al. (2013)</td>	13	p. Pro42Thr	Multiple synostoses syndrome	Aydin, H et al. (2013)
p. Guddlys p. Guddlys p. ProSONrg p. ModSAry p. ProSONrg p. ModSAry p. ProSONrg p. ModSAry p. ProSONrg p. ModSAry p. AdpS5Tyr Provinal symphalangism p. AdpS5Tyr Prosonal symphalangism p. AdpS5Tyr Stapes ankytosis with broad thumb p. AdpS7 Stapes ankytosis with broad thumb p. AdpS7 Stapes ankytosis with broad thumb p. AdpS7 Florodysplasia ossificans progressia p. AdpS7 Florodysplasia ossificans progressia p. AdjS7 Florodysplasia ossificans progressia p. AdjS7 Provinal symphalangism p. AlaS7 Provinal symphalangism p. AlaS7 Provinal symphalangism p. AlaS7 Provinal symphalangism p. AlaS7 Stapes ankytosis with broad thumb p. AlaS7 Provinal symphalangism p. AlaS7 Provinal symphalangism p. AlaT31X Stapes ankytosis with broad thumb p. AlaT36 Provinal symphalangism p. Ag136Cys Provinal symphalangism <	14	p. Val44fs	Teunissen-Cremers syndrome	Weekamp et al. (2005)
p. Gud8Uys Proximal symphalangism p. PoSGAg Tarsal-carpal coalition syndrome p. Ag875 P. Guu851s p. Ag875 Provinal symphalangism p. Ag875 Provinal symphalangism p. Ag875 Provinal symphalangism p. Ag875 Provinal symphalangism p. Ag875 Muthple sympatolangism p. Ag875 Muthple sympatolangism p. Ag875 Muthple sympatolangism p. Ag876 Provinal symphalangism p. Ag877 Provinal symphalangism p. Ala1025 Provinal symphalangism p. Ala1026 Provinal symphalangism p. Ala1027 Provinal symphalangism p. Ala1027 Provinal symphalangism p. Ala1027 Provinal symphalangism p. Just1204 Provinal symphalangism p. Just131X Provinal symphalangism p. Just135 P	15	p. Glu48Lys	Brachydactyly type B	Lehmann et al. (2007)
p. Pro50kig p. Asp55Tyr p. Asp55Tyr Profinal symphalangism p. Ag9515 Provinal symphalangism p. Ag9216 Provinal symphalangism p. Ag9515 Ag9216 p. Ag9516 Provinal symphalangism p. Ag9517 Provinal symphalangism p. Ag9517 Provinal symphalangism p. Al95517 Provinal symphalangism p. Al95517 Provinal symphalangism p. Al95517 Provinal symphalangism p. Al95517 Prosimal symphalangism p. Al95517 Proximal symphalangism p. Jal10255 Stapes ankylosis with broad thumb p. Leu129X Proximal symphalangism p. Leu129X Proximal symphalangism p. Leu129X Proximal symphalangism p. Jys133X Proximal symphalangism p. Jys133X Proximal symphalangism p. Jys133X Proximal symphalangism p. Jys133X Proximal symphalangism p. Cys135Fbe Proximal symphalangism p. Cys155Fbe Proximal symphalangism	16	p. Glu48Lys	Proximal symphalangism	Kosaki et al. (2004)
p. Ag55Tyr Proximal symphalangism p. Glu85fs Stapes ankylosis with broad thumb p. Ag875 Multiple synotroses syndrome p. Ag91Cys Florodysplasia ossificans progressiva p. Gly92Glu Florodysplasia ossificans progressiva p. Al95Thr Florodysplasia ossificans progressiva p. Gly92Glu Florodysplasia ossificans progressiva p. Al95Thr Florodysplasia ossificans progressiva p. Al95Thr Florodysplasia ossificans progressiva p. Ala102fs Florodysplasia ossificans progressiva p. Ala102fs Florodysplasia ossificans progressiva p. Ala102fs Florodysplasia ossificans progressiva p. Ja102fs Proximal symphalangism p. Ja102fs Stapes ankylosis with broad thumb p. Jy133X Proximal symphalangism p. Ly133X Proximal symphalangism p. Ly133X Stapes ankylosis with broad thumb p. Ly133X Proximal symphalangism p. Ly135Che Proximal symphalangism p. Cy135Che Proximal symphalangism p. Cy155Che Proximal symphalangism	17	p. Pro50Arg	Tarsal-carpal coalition syndrome	Debeer et al. (2005)
P. Glu85fs Stapes ankylosis with broad thumb and toes p. Ag87fs Multiple synostoses syndome p. Gly32Arig Florodysplasia ossificans progressiva p. Gly32Arig Florodysplasia ossificans progressiva p. Gly32Fit Florodysplasia ossificans progressiva p. Alaa02fs Florodysplasia ossificans progressiva p. Alaa02fs Proximal symphalangism p. din110X Stapes ankylosis with broad thumb p. din131X Stapes ankylosis with broad thumb p. Lu333X Proximal symphalangism p. Lys133X Stapes ankylosis with broad thumb p. Lys133X Proximal symphalangism p. Lys135X Proximal symphalangism	18	p. Asp55Tyr	Proximal symphalangism	Xiong et al. (2019)
p. Arg875 Mittiple synostoses syndrome p. Gly91Cys Florodysplasia ossificans progressiva p. Gly92Jdu Florodysplasia ossificans progressiva p. Ala95Thr P. Nal95Thr p. Ala95Thr P. Nal95Ts p. Ala95Thr P. Nal95Ts p. Ala102fs P. Nal95Ts p. Ala102fs P. Nal95Ts p. Ala102fs P. Nal95Ts p. Gln110X P. Nal95ts p. Gln110X P. Namel symphalangism p. Gln111X P. Namel symphalangism p. Leu129X Proximal symphalangism p. Lu128X Proximal symphalangism p. Juy1355 Proximal symphalangism p. Juy1355 Proximal symphalangism p. Juy136Cys Proximal symphalangism p. Arg136Cys Proximal symphalangism p. Try130Cys Proximal symphalangism p. Cys135The Proximal symphalangism	19	p. Glu85fs	Stapes ankylosis with broad thumb and toes	Brown et al. (2002)
 p. Gly91Cys p. Gly92Ag p. Gly92Gu p. Gly92Gu p. Ala95Thr p. Ala95Thr p. Ala95Thr p. Ala102fs p. Ala103fs p. Cys155Phe p. Cys155Phe p. Cys155Phe p. Cys155Phe 	20	p. Arg87fs	Multiple synostoses syndrome	Lee et al. (2014)
p. Glyg2diu Florodysplasia ossificans progressiva p. Ala95Thr Florodysplasia ossificans progressiva p. Ala95Thr Florodysplasia ossificans progressiva p. Ala102fs Florodysplasia ossificans progressiva p. Ala102fs Florodysplasia ossificans progressiva p. Ala102fs Proximal symphalangism p. Gln110X Stapes ankylosis with broad thumbs p. Gln131X Proximal symphalangism p. Leu129X Stapes ankylosis with broad thumbs p. Lu123X Stapes ankylosis with broad thumbs p. Lys133X Proximal symphalangism p. Lys135 Proximal symphalangism p. Cys1557ble Proximal symphalangism p. Cys1557ble Proximal symphalangism	21	p. Gly91Cys	Fibrodysplasia ossificans progressiva	Kaplan et al. (2008)
 p. GlygGlu Flbrodysplasia ossificans progressiva p. Alao5Thr p. Ala05Thr p. Ala102fs p. Ala102fs p. Ala102fs p. Ala102fs p. Ala102fs p. Gln110X p. Gln110X p. Gln110X p. Gln111X p. Lu129X p. Lu129X p. Lu129X p. Lu129X p. Lu129X p. Lu129X p. Lys133X p. Lys133X p. Lys133X p. Lys133X p. Typ150Cys p. Typ150Cys p. Cys155Phe p. Cys155Phe p. Cys155Phe 	22	p. Gly92Arg	Fibrodysplasia ossificans progressiva	Kaplan et al. (2008)
p. Ala95Th Fibrodysplasia ossificans progressiva p. Ala102fs P. Ala102fs p. Ala102fs Proximal symphalangism p. Gln110X Proximal symphalangism p. Leu129X Stapes ankylosis with broad thumb p. Leu129X Proximal symphalangism p. Lu121X Proximal symphalangism p. Lu123X Stapes ankylosis with broad thumb p. Lys133X and toes p. Lys133X Stapes ankylosis with broad thumb p. Typ156Cys Proximal symphalangism p. Cys155Phe Proximal symphalangism p. Cys155Phe Stapes ankylosis with	23	p. Gly92Glu	Fibrodysplasia ossificans progressiva	Kaplan et al. (2008)
p. Ala102fs Proximal symphalangism p. Gln110X Stapes ankylosis with broad thumb p. Leu129X Stapes ankylosis with broad thumbs p. Leu129X Proximal symphalangism p. Leu129X Proximal symphalangism p. Leu129X Proximal symphalangism p. Luy131X Stapes ankylosis with broad thumbs p. Lys133X and toes p. Lys133X Proximal symphalangism p. Cys155Phe Proximal symphalangism	24	p. Ala95Thr	Fibrodysplasia ossificans progressiva	Kaplan et al. (2008)
p. Gln110X Stapes ankylosis with broad thumb and toes p. Leu129X Proximal symphalangism p. Gln131X Proximal symphalangism p. Gln131X Stapes ankylosis with broad thumbs and toes p. Lys133X Stapes ankylosis with broad thumbs p. Lys133X Proximal symphalangism p. Lys133X Proximal symphalangism p. Lys135X Proximal symphalangism p. Lys135X Proximal symphalangism p. Lys155Phe Proximal symphalangism p. Cys155Phe Stapes ankylosis with	25	p. Ala102fs	Proximal symphalangism	Thomeer et al. (2011)
p. Leu129X Proximal symphalangism p.Gln131X Stapes ankylosis with broad thumbs p. Lys133X and toes p. Lys133X Stapes ankylosis with broad thumbs p. Lys133X and toes p. Lys133X Proximal symphalangism p. Lys135Cys Proximal symphalangism p. Arg136Cys Proximal symphalangism p. Cys155Phe Stapes ankylosis with broad thumb	26	p. Gln110X	Stapes ankylosis with broad thumb and toes	Brown et al. (2002)
p.Gln131X Stapes ankylosis with broad thumbs and toes p. Lys133X Stapes ankylosis with broad thumb and toes p. Arg136Cys Proximal symphalangism p. Trp150Cys Proximal symphalangism p. Cys155Phe Stapes ankylosis with symphalangism	27	p. Leu129X	Proximal symphalangism	Takahashi et al. (2001)
p. Lys133X Stapes ankylosis with broad thumb and toes p. Arg136Cys Proximal symphalangism p. Trp150Cys Proximal symphalangism p. Cys155Phe Stapes ankylosis with symphalangism	28	p.Gln131X	Stapes ankylosis with broad thumbs and toes	Takashi etal. (2014)
p. Arg136Cys Proximal symphalangism p. Trp150Cys Proximal symphalangism p. Cys155Phe Stapes ankylosis with	29	p. Lys133X	Stapes ankylosis with broad thumb and toes	Takano et al. (2016)
p. Trp 150Cys Proximal symphalangism p. Cys155Phe Stapes ankylosis with symphalanoism	30	p. Arg136Cys	Proximal symphalangism	Masuda et al. (2014)
p. Cys155Phe Stapes ankylosis with symbolia actions of the symbolia actions of	31	p. Trp150Cys	Proximal symphalangism	Pan et al. (2015)
	32	p. Cys155Phe	Stapes ankylosis with symohalanoism	Usami et al. (2012)

300. (5/315/cProtonal symphalangian31p. (3/67/c)Ben/Mittary/Mitt	No.	Mutation	Phenotypes	Reference
 p. Arg16/Gly p. Arg16/TCys p. Gy188/Tyr p. Cy188/Tser p. Pro187/Ser p. Pro187/Ser p. Gu188/5 p. Gu188/5 p. Gu188/5 p. Gu188/5 p. Gu188/5 p. Gu188/5 p. Gy189/Gln p. Gy189/Gln p. Arg204/en p. Trp205/5 p. Sy23207 p. Sy2327 		p. Cys155Ser	Proximal symphalangism	Usami et al. (2012)
 p. Arg16/Cys p. Cys184ftyr p. Fyo187/Ser p. Glu188f5 p. Met190Val p. Arg204Leu p. Arg204Leu p. Arg204Leu p. Trp205K5 p. Cys228Ha p. Cys228Ha p. Cys228Ha p. Cys228Ha p. Cys228Ha 		p. Arg167Gly	Brachydactyly type B	Lehmann et al. (2007)
 p. Gys184fbre p. Pro1875er p. Pro1875a p. FN1875 p. Glu1885 p. Glu1885 p. Glu1885 p. Met190Val p. Arg203461n p. Arg203461n p. Arg203461n p. Arg203461n p. Arg203461n p. Trp205Cys p. Trp205Cys p. Trp205Cys p. Tyr22254s p. Tyr22254s p. Tyr22254s p. Tyr22254s p. Gys2381a p. Gys2381a p. Gys2381a p. Gys2381a p. Gys2381a 		p. Arg167Cys	Proximal symphalangism	Liu et al. (2015)
 Cys184Pte Pro1875er Pro1875a Fu1875 Glu1885 Glu1885 Glu1885 Glu1885 Heu203Pro Arg2046in Arg2046in Arg2046in Arg2046in Trp205Cys Trp205Cys Trp205Cys Trp22056 Trp22056 Trp22056 Ty7222568 Ty7222568 Cys22864a Cys22864a Cys22864a Cys22864a Cys22864a Cys22864a Cys22864a Cys22864a Cys22874 		p. Cys184Tyr	Proximal symphalangism	Takahashi et al. 2001
 p. Pro187/Ser p. Pro187/Ala p. Gu/188fs p. Gu/188fs p. Mu203Pro p. Mu204Gin p. Arg204Leu p. Arg204Leu p. Arg204Leu p. Arg204Leu p. Arg204Leu p. Trp2055X p. Trp2055 p. Sys23077 p. Sys23077 		p. Cys184Phe	Proximal symphalangism	Usami et al. 2012
 p. Pro187Ala p. Giv18865 p. Met190Val p. Met203Pro p. Meg204Leu p. Arg204Gin p. Trp205Cys p. Trp205Cys p. Trp20555 p. Sys23075 p. Sys233075 		p. Pro187Ser	Brachydactyly type B	Lehmann et al. (2007)
 p. Glu1885 p. Met190Val p. Met190Val p. Leu203Fro p. Arg204Leu p. Arg204Leu p. Arg204Leu p. Trp205Cys p. Trp20555 p. Trp20555 p. Trp22055 p. Cys228A1a 		p. Pro187Ala	Proximal symphalangism	Ganaha et al. (2015)
p. Gly (39C/ys p. Met 13004leu p. Arg204lein p. Arg204lein p. Trp205K p. Trp205Ks p. Trp205fs p. Trp205fs p. Trp217Gly p. Cys215K p. Trp2204sn p. Ho2224sp p. Ty222Cys p. Ty222Cys p. Ty222Cys p. Ty222Cys p. Ty222Cys p. Ty222Cys p. Cys2384la p. Cys2384la p. Cys2384la p. Cys2387Tp p. Cys2387Tp		p. Glu188fs	Teunissen-Cremers syndrome	Weekamp et al. (2005)
 p. Met190Val p. Leu203Pro p. Arg204Gin p. Trp205X p. Trp205fs p. Trp205fs p. Trp205fs p. Trp205fs p. Trp217Gly p. Trp2204sn p. Trp2205fs p. Trp2205fs p. Trp2205fs p. Trp2205fs p. Trp223fs p. Cys228fia p. Cys22301rp p. Cys23301rp 		p. Gly189Cys	Proximal symphalangism	Gong et al. (1999)
 p. Leu203Pro p. Arg204Leu p. Arg204Gin p. Trp205K p. Trp205K p. Trp205f5 p. Cys215X p. Cys215K p. Cys215K p. Tyr22C4sp p. Tyr222C4sp p. Tyr222C4sp p. Tyr222C4sp p. Tyr222C4sp p. Cys236F p. Cys236F p. Cys230Trp p. Cys230Trp 		p. Met190Val	Multiple synostoses syndrome	Oxley et al. (2008)
 p. Arg204Leu p. Arg204Gin p. Trp205Ky p. Trp205K p. Trp205f5 p. Trp205f5 p. Trp217Gly p. Frp217Gly p. Ie2204sn p. Ie2204sn p. Ig22C4ss p. Ty722C4ss p. Ty722C4ss p. Ty722C4ss p. Ty722C4ss p. Cy52361a p. Cy523017p p. Cy523017p 		p. Leu203Pro	Teunissen-Cremers syndrome	Weekamp et al. (2005)
 p. Arg204GIn p. Trp205K p. Trp205f5 p. Cys215X p. Cys215X p. Trp217Gly p. He2204sp p. Tyr222Asp p. Tyr2224sp p. Cys236fy p. Cys236fy p. Cys2367tp p. Cys2337tp 		p. Arg204Leu	Tarsal/carpal coalition syndrome	Dixon et al. (2001)
 p. Trp205Cys p. Trp205fs p. Trp205fs p. Cys215X p. Cys215X p. Trp217Gly p. Ile2204sn p. Ile2204sn p. Ile2204sn p. Ile2204sn p. Tyr222Cys p. Tyr222Cys p. Tyr222Cys p. Tyr222Cys p. Tyr222Cys p. Cys236Ty p. Cys230Trp p. Cys230Trp 		p. Arg204GIn	Tarsal-carpal coalition syndrome	Das et al. (2018)
 p. Trp2056s p. Cys215X p. Cys215X p. Trp2176jy p. He2204sn p. He2204sn p. Tyr2226sp p. Tyr2226sp p. Tyr2226sp p. Tyr2226sp p. Tyr2225sp p. Cys2361y p. Cys2301rp p. Cys2301rp 		p. Trp205X	Multiple synostoses syndrome	Dawson et al. (2006)
 p. Trp205fs p. Cys215X p. Trp217Gly p. Ile2204sn p. Ile2204s p. Tyr222Cys p. Tyr222Cys p. Tyr222Cys p. Tyr222Cys p. Cys236Gly p. Cys236Gly p. Cys230Trp p. Cys233Trp 		p. Trp205Cys	Facioaudiosymphalangism syndrome	van den Ende et al. (2005)
 p. Trp217Gly p. Trp217Gly p. Ile2204sn p. Ile220fs p. Tyr222dsp p. Tyr222dss p. Tyr222dss p. Tyr222ds p. Tyr222ds p. Cys236dly p. Cys230Trp p. Cys230Trp 		p. Trp205fs	Stapes ankylosis with broad thumb and toes	Emery et al. (2009)
 p. Trp217Gly p. Ile2204sn p. Ile2204s p. Tyr2224sp p. Tyr2225ys p. Tyr2225ys p. Tyr2250s p. Cys236Jy p. Cys228Ala p. Cys230Tyr p. Cys230Tyr 		p. Cys215X	Stapes ankylosis with broad thumb and toes	Usami et al. (2012)
p. Ile2204sn p. Ile220fs p. Tyr2224sp p. Tyr2224ss p. Cys228Gly p. Cys228Ala p. Cys2230Tyr p. Cys2330Trp		p. Trp217Gly	Multiple synostoses syndrome	Gong et al. (1999)
 p. Ile220fs p. Tyr222Asp p. Tyr222Cys p. Tyr222Cys p. Pro223Leu p. Cys23Bdla p. Cys228dla p. Cys230Tyr p. Cys230Trp 		p. Ile220Asn	Proximal symphalangism	Gong et al. (1999)
 p. Tyr2224sp p. Tyr222cys p. Tyr222cys p. Pro223Leu p. Cys236ly p. Cys228Ala p. Cys230Tyr p. Cys230Tyr p. Cys230Typ 		p. Ile220fs	Proximal symphalangism	Gong et al. (1999)
 p. Tyr222Cys p. Tyr222Cys p. Pro223Leu p. Cys228Gly p. Cys228Ala p. Cys2230Tyr p. Cys230Tyr 		p. Tyr222Asp	Proximal symphalangism	Gong et al. (1999)
p. Tyr222Cys p. Pro223Leu p. Cys228Gly p. Cys228Ala p. Cys230Trp p. Cys230Trp		p. Tyr222Cys	Proximal symphalangism	Gong et al. (1999)
p. Pro223Leu p. Cys228Gly p. Cys228Ala p. Cys230Trp p. Cys230Trp		p. Tyr222Cys	Tarsal-carpal coalition syndrome	Dixon et al. (2001)
p. Cys228Gly p. Cys228Ala p. Cys230Trp p. Cys232Trp		p. Pro223Leu	Proximal symphalangism	Gong et al. (1999)
p. Cys228Ala p. Cys230Tyr p. Cys230Trp p. Cys232Trp		p. Cys228Gly	Stapes ankylosis with broad thumb and toes	Ishino et al. (2015)
p. Cys230Tyr p. Cys230Trp p. Cys232Trp		p. Cys228Ala	Multiple synostoses syndrome	Ganaha et al. (2015)
p. Cys230Trp p. Cys232Trp		p. Cys230Tyr	Multiple synostoses syndrome	Bayat et al. (2016)
p. Cys232Trp		p. Cys230Trp	Proximal symphalangism	Present study
		p. Cys232Trp	Multiple synostoses syndrome	Rudnik-Schöneborn et al. (2010)

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ACMG guidelines to estimate the pathogenicity of the novel mutation strictly (PM1 and PM2). Finally, we highly believed that the novel mutation (p.C230W) of *NOG* may be the genetic lesion of the family. We then assisted the family to get a healthy baby by amniotic fluid DNA sequencing referring to other people's research [25]. Prenatal diagnosis not only helped the patient to delivery healthy baby and improved the population quality but also relieved psychological and financial stress [26]. Our study provided a successful example for genetic counseling and prenatal diagnosis of patients with SYM1A.

Conclusions

We reported a novel *NOG* mutation (c.690C > G/ p.C230W) in a three-generation family with SYM1A. And we helped them delivery a girl baby who did not carry the mutation by genetic counseling and prenatal diagnosis. Our study not only presented the important role of *NOG* in proximal symphalangism and deafness but also expanded the spectrum of *NOG* mutations and contributed to genetic diagnosis and counseling of families with SYM1A.

Abbreviations

BMPs: Bone morphogenetic proteins; GDF5: Growth Differentiation Factor 5; kb: Kilobases; NOG: Noggin; SYM1A: proximal symphalangism-1A; SYM1B: proximal symphalangism-1B

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Authors' contributions

C M and L L carried out the sample collecting and genetic testing, F-N W, H-S T and Y L collected the clinical data, R Y performed the bioinformatics analysis, Y-L L and L-L F designed the project and wrote the manuscript, and L-L F revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent was obtained from each individual and the investigation was approved by the Institutional Review Board of HeBei General Hospital.

Consent for publication

Written consent was obtained from all the participants or their guardians for the publication of this study.

Competing interests

The authors declare that they have no competing interests.

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