Clinical observation and genetic analysis of a SYNS1 family caused by novel NOG gene mutation

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Abstract
Objective: Analyze the clinical and genetic characteristics of a rare Chinese family with Multiple synostoses syndrome and identify the causative variant with the high-throughput sequencing approach.
Methods: The medical history investigation, physical examination, imaging examination, and audiological examination of the family members were performed. DNA samples were extracted from the family members. The candidate variant was identified by performing whole-exome sequencing of the proband, then verified by Sanger sequencing in the family.
Results: The family named HBSY-018 from Hubei province had 18 subjects in three generations, and six subjects were diagnosed with conductive or mixed hearing loss. Meanwhile, characteristic features including short philtrum, hemicylindrical nose, and hypoplastic alae nasi were noticed among those patients. Symptoms of proximal interdigital joint adhesion and inflexibility were found. The family was diagnosed as Multiple synostoses syndrome type 1 (SYNS1). The inheritance pattern of this family was autosomal dominant. A novel mutation in the NOG gene c.533G>A was identified by performing whole-exome sequencing of the proband. The substitution of cysteine encoding 178th position with tyrosine (p.Cys178Tyr) was caused by this mutation, which was conserved across species. Co-segregation of disease phenotypes was demonstrated by the family verification.

Conclusion: The family diagnosed as SYNS1 was caused by the novel mutation (c.533G>A) of NOG. The combination of clinical diagnosis and molecular diagnosis had improved the understanding of this rare disease and provided a scientific basis for genetic counseling in the family.

Keywords: conductive hearing loss, multiple synostoses syndrome 1, mutation, NOG

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1 | INTRODUCTION

Multiple synostoses syndrome (SYNS) was a group of rare autosomal dominant genetic diseases in which bone hypoplasia syndrome was characterized by multi-joint fusion, characteristic facial appearance, and progressive conductive hearing loss secondary to stapes fixation (Nakashima et al., 2021). Its clinical manifestations were diverse.

Four different types of SYNS had been reported, SYNS1 (OMIM# 186500), SYNS2 (OMIM# 610017), SYNS3 (OMIM# 612961), and SYNS4 (OMIM# 617898), respectively related to NOG (Gong et al., 1999), GDF5 (Dawson et al., 2006), FGF9 (Wu et al., 2009), and GDF6 (Wang et al., 2016) gene mutations. Different types of SYNS had similar phenotypes, suggesting common pathogenic mechanisms and regulatory pathways (Wang et al., 2016).

The NOG gene (OMIM# 602991) was mapped in the region between D17S790 and D17S794 of 17q22, (https://www.genenames.org) with a single exon. Noggin, encoded by NOG gene, is a secreted protein consisted of 232 amino acid residues and a BMP (bone morphogenetic protein) functional antagonist. Noggin interacts with BMP-7 by binding and masking the type I and type II receptor sites located on BMP (Groppe et al., 2002). The balance between BMPs and Noggin was critical for proper skeletal formation including cartilage, joints (Gong et al., 1999), and neural tube (Groppe et al., 2003). The C-terminal region of noggin contains a cysteine-knot motif of nine cysteine residues, which is important for dimerization and disulfide bond formation (Groppe et al., 2002).

The most identified mutations in NOG gene have been frequently associated with phenotypes, such as SYNS and other clinical spectra. A new term, NOG-related symphalangism spectrum disorder (NOG-SSD) was proposed by Potti et al. (2011). Conductive hearing loss was a common symptom for patients with these syndromes. The clinical manifestations of a proband who had been diagnosed with conductive hearing loss were analyzed in this study. Biological analysis of samples from the patient’s family was conducted, and the causative variant in this family was a novel heterozygous mutation of the NOG gene, and the diagnosis was Multiple synostoses syndrome type 1 (SYNS1). The specific reports were as follows.

2 | MATERIALS AND METHODS

2.1 | Patients and samples

The study protocol was approved by the Institutional Review Board of General Hospital of Central Theater Command (Wuhan, China). Informed consent was obtained from the recruited subjects before their participation. The proband of the family was from Honghu, Hubei, China. A detailed medical history inquiry, physical examination, audiology test including pure tone audiometry (at frequencies from 250 to 8000 Hz), acoustic immittance, and radiological test including temporal bone CT scan, x-rays of hands and feet were conducted. Peripheral blood sample of 10 ml were conducted for all recruited family members.

2.2 | Research method

2.2.1 | Target region capture and sequencing

The genomic DNA was extracted from the blood of recruited family members using standard procedures (MagPure Buffy Coat DNA Midi KF Kit). The whole exons and flanking regions were captured and enriched by the BGIseq Human Exome V4 Kit. The libraries were sequenced by MGISEQ-2000 sequencing platform. Sequencing data quality control indicators were the average sequencing depth of the target area was ≥180X, and the proportion of sites with the average depth of the target area>20X was >95%.

2.2.2 | Data analysis

The sequenced fragments were compared with the UCSC hg19 human reference genome by BWA (Li & Durbin, 2009), and then duplicates were removed. GATK for base quality correction SNV, INDEL, and genotype detection were used. Copy number variation at the exon level by ExomeDepth was detected. The results of base polymorphism in the target region were generated, while annotated and screened the suspicious mutations were found (San Lucas et al., 2012). SWISS-MODEL and Swiss-PdbViewer4.1, used to predict the effect of mutation on protein function.

2.2.3 | Sanger sequencing

The suspected pathogenic variant of NOG gene from the results of the whole-exome sequencing bioinformatics analysis were confirmed by Sanger sequencing in the proband and family members.

2.2.4 | Pathogenicity analysis

Performed pathogenicity analysis according to the standards and guidelines for the interpretation of sequence
variants (ACMG/AMP) (Biesecker & Harrison, 2018; Gelb et al., 2018; Richards et al., 2015; Zastrow et al., 2018).

3 | RESULTS

3.1 | Clinical features of the family

The proband was a 19-year-old male who had hearing loss in both ears since 4 years old, with no dizziness, tinnitus, ear stuffiness, or other symptoms. The proximal interphalangeal joint could not be flexed. Growth and intellectual development were normal. The characteristic facial features with narrow eye splits, short philtrum, hemicylindrical nose, hypoplastic alae nasi were found (Figure 1a). The proximal phalanges of both hands were long, the middle phalanges and the distal phalanges were short, some skin folds of the proximal interphalangeal joints were missing, and the proximal interphalangeal joints could not be flexed (Figure 1b). The first toe was short, deep gap between the first and second toe, the skin folds of the proximal interphalangeal joints were missing, some of the proximal interphalangeal joints could not be flexed, the flat feet. (d) The proband’s x-rays of the hands and feet: The proximal and middle phalanx of the left second-fifth fingers and the right fourth to fifth fingers were fused, and the corresponding joint space disappeared. The bone of the proximal and middle phalanges of the second toe, middle, and distal phalanges of the third and fourth toes were fused, the corresponding joint space disappeared, the tarsal joint space was unclear, and the structures of bilateral cuneiform was not clearly displayed.

FIGURE 1 (a) The proband accompanied by characteristic facial features: Short philtrum, hemicylindrical nose, and hypoplastic alae nasi. (b) The characteristic of proband’s hands: The proximal phalanges of both hands were long, the middle phalanges, and the distal phalanges were short, some skin folds of the proximal interphalangeal joints are missing, and the proximal interphalangeal joints could not be flexed. (c) The characteristic of proband’s feet’s: The first toe was short, deep gap between the first and second toe, the skin folds of the proximal interphalangeal joints were missing, some of the proximal interphalangeal joints could not be flexed, the flat feet. (d) The proband’s x-rays of the hands and feet: The proximal and middle phalanx of the left second-fifth fingers and the right fourth to fifth fingers were fused, and the corresponding joint space disappeared. The bone of the proximal and middle phalanges of the second toe, middle, and distal phalanges of the third and fourth toes were fused, the corresponding joint space disappeared, the tarsal joint space was unclear, and the structures of bilateral cuneiform was not clearly displayed.
some of the proximal interphalangeal joints could not be flexed, the flat feet (Figure 1c). Both auricles were normal, both external auditory canals were unobstructed, the tympanic membranes are intact, and those characteristics were distinct. Pure tone audiometry reported that binaural mixed hearing loss, acoustic immittance reported binaural tympanic pressure were A, stapedius reflex in both ears were not elicited. Temporal bone CT scan was normal. X-rays of hands shown the proximal and middle phalanx of the left second to fifth fingers and the right fourth to fifth fingers were fused, and the corresponding joint space disappeared (Figure 1d). X-ray of feet shown the bone of the proximal and middle phalanges of the second toe, middle, and distal phalanges of the third and fourth toes were fused, the corresponding joint space disappeared, the tarsal joint space was unclear, and the structures of bilateral cuneiform were not clearly displayed (Figure 1d).

There are 18 members in three generations of the family, two members were diagnosed as mixed hearing loss and four members were diagnosed with conductive hearing loss (Figure 2b).

Characteristic facial features similar to the proband and different degrees of adhesion of the finger/toe joints were found in affected members.

3.2 | Identification of pathogenic genes

Mutation detection results: A heterozygous mutation in NOG gene NM 005450.4: c.533G>A (p.Cys178Tyr) was identified in the proband by performing whole-exome sequencing. The same mutation was detected in all other patients (II:2, III:3, III:5, IV:2, IV:3, and IV:4) of this family but not in normal members by Sanger sequencing (Figure 3a). This heterozygous mutation and phenotype were co-segregated in this family.

The formation of disulfide bonds between Cys178 and Cys228 (Figure 3b) was prevented by the mutation
of Cys178Tyr, found by the protein spatial structure simulation analysis of Noggin. It was highly conserved among multiple species (Figure 3c) by conservation analysis of NOG gene. A variety of statistical methods predicted that the mutation causes harmful effects on genes or gene products (SIFT, Mutation Taster, Condel, PhyloP Vertebrates, PhyloP Placental Mammals, GERP++).

4 | DISCUSSION

A Chinese family diagnosed as SYNS1 was reported in this study. A novel mutation c.533G>A (p.Cys178Tyr) in the NOG gene was identified by the high-throughput sequencing.

The family patients had been experienced varying degrees of hearing loss since childhood, and their hearing
### TABLE 1  Clinical manifestations of patients in the family HBSY-18

| Patients' ID | II:2 | III:3 | III:5 | IV:2 | IV:3 | IV:4 |
|-------------|------|-------|-------|------|------|------|
| Age (y)     | 75   | 46    | 42    | 19   | 17   | 10   |
| Sex         | male | male  | female| male | male | male |
| Clinical manifestations | | | | | | |
| Types of hearing loss | mixed | conductive | conductive | mixed | conductive | conductive |
| Characteristic facial features (Broad hemicylindrical nose with lack of alar flare) | + | + | + | + | + | + |
| Knuckle adhesions | The proximal and middle phalanx of the right fifth finger were fused. | Bilateral proximal and middle phalanges of the fifth finger were fused. | The proximal and middle phalanx of the left fifth finger were fused. | The proximal and middle phalanges of the left second-fifth fingers and the right fourth to fifth fingers were fused. | The proximal and middle phalanx of the left fifth finger were fused. | Bilateral proximal and middle phalanges of the fifth finger were fused. |
| Toe joint adhesions | Bilateral proximal and middle phalanges of the third and fourth toes were fused. | Bilateral proximal and middle phalanges of the third and fourth toes were fused. | − | Bilateral proximal and middle phalanges of the second toe, middle, and distal phalanges of the third and fourth toes were fused. | Bilateral proximal and middle phalanges of the second, third, and fourth toe were fused. | Bilateral proximal and middle phalanges of the second, third, and fourth toe were fused. |
| Short first finger | + | + | + | + | − | − |
| Short first toe | + | + | + | + | + | + |
| Deep gap between the first and second toes | + | + | + | + | + | + |
| Flat feet | + | + | + | + | + | + |
loss became worse when aging, accompanied by characteristic facial features with narrow eye splits, short philtrum, hemicylindrical nose, hypoplastic alae nasi, and varying degrees of the finger or toe joint adhesion. The affected members III:3, III:5, IV:3, and IV:4 in this family had different degrees of conductive hearing loss. Patient II:2 was diagnosed with severe mixed hearing loss, which was considered to be caused by aging. The proband IV:2 was the most severe case of mixed hearing loss. In addition to hearing loss, abnormal bone, and joint development were found, but the severity of joint adhesion was different. Specifically, the finger/toe joints of the proband were the most severe while only one or two little fingers and a few toe joints were found among other patients. According to the analysis of clinical data and the OMIM database (http://www.omim.org), this family was consistent with a diagnosis of Multiple synostoses syndrome type 1 (SYNS1) (Table 1).

The mutation detected by next-generation sequencing showed that the cysteine (Cys) at position 178 of its encoding was replaced with tyrosine (Tyr) in patients with multiple syndrome symptoms, which caused by a mutation of guanine (G) to adenine (A) in the 533rd base of coding region on the \textit{NOG} gene. This mutation was not detected in normal members of the family. The mutation co-segregated with the disease phenotype of the family. This mutation was novel according to the comparison of database alignment and previous reports (Table 2) (Gong et al., 1999; Takahashi et al., 2001; Dawson et al., 2006; Oxley et al., 2008; Shimizu et al., 2008; Rudnik-Schöneborn et al., 2010; Aydin et al., 2013; Lee et al., 2014; Ganaha et al., 2015; Pan et al., 2020).

The protein spatial structure simulation analysis of Noggin revealed the cysteines at the two positions of Cys178 and Cys228 were close in structure, which could form disulfide bonds. The formation of disulfide bonds was prevented by the mutation of Cys178Tyr (Figure 3b) that the stability and function of the structure might affected by the mutation. From Noggin protein structure, six conserved cysteines formed three disulfide bonds, which is cyclic cystine knots (CCK) I–VI. Specifically, the formation included I (p.Cys155)–IV (p.Cys192), II (p.Cys178)–V (p.Cys228), and III (p.Cys184)–VI (p.Cys230), each pair formed homodimers in the C-terminal region of \textit{NOG}. Cellular models demonstrated that disulfide bonds played an important role in protein structure and function. Those mutations in \textit{NOG}, that affecting disulfide bond formation could lead to dysfunction of Noggin (Marcelino et al., 2001). A Danish and a Japanese family suffering from SYNS1 due to a \textit{NOG} gene mutation p.Cys230Tyr and p.Cys228Ser, respectively were reported (Bayat et al., 2016; Ganaha et al., 2015). A \textit{NOG} gene mutation p.Ser185Cys reported by a Chinese SYNS1 family was near CCK III–VI (Pan et al., 2020).

Performing pathogenicity analysis according to the standards and guidelines for the interpretation of sequence variants (ACMG), the c.533G>A of the \textit{NOG} gene was mutated from guanine to adenine (Figure 3a). The result was the replacement of cysteine at position 178 with tyrosine, and the formation of disulfide bonds between Cys178 and Cys228 (PP3) was prevented by the mutation.

| Nucleotide | Protein | Type of mutation | Reference |
|------------|---------|-----------------|-----------|
| c.58del    | p.Leu20CysfsTer42 | Frameshift | Takahashi et al. (2001) |
| c.124C>A   | p.Pro42Thr | Missense | Aydin et al. (2013) |
| c.125C>T   | p.Pro42Leu | Missense | Lee et al. (2014) |
| c.125C>G   | p.Pro42Arg | Missense | Oxley et al. (2008) |
| c.261dup   | p.Pro88AlafsTer94 | Frameshift | Lee et al. (2014) |
| c.452C>A   | p.Ser151Ter | Stop_gained | Lee et al. (2014) |
| c.533G>A   | p.Cys178Tyr | Missense | This report |
| c.554C>G   | p.Ser185Cys | Missense | Pan et al. (2020) |
| c.568A>G   | p.Met190Val | Missense | Oxley et al. (2008) |
| c.614G>A   | p.Trp205Ter | Stop_gained | Dawson et al. (2006) |
| c.649 T>G  | p.Trp217Gly | Missense | Gong et al. (1999) |
| c.682 T>A  | p.Cys228Ser | Missense | Ganaha et al. (2015) |
| c.689G>A   | p.Cys230Tyr | Missense | Bayat et al. (2016) |
| c.696C>G   | p.Cys232Trp | Missense | Rudnik-Schöneborn et al. (2010) |
| 17q22 deletion | | | Shimizu et al. (2008) |

Note: Nucleotide numbering is based on the GenBank reference sequence NM_005450.4.
of Cys178Tyr (Figure 3b). It was highly conserved among multiple species that found by conservation analysis of the Noggin (Figure 3c). This mutation was a novel mutation, and it was not found in the gnomAD database (PM2). The phenotype of family patients with this mutation was highly consistent with the diagnosis of SYNS1 (PP4). The disease phenotype was co-segregated, which suggested that this mutation was a pathogenic mutation in the HBSY-018 family (PP1-Strong), confirmed by family verification. In conclusion, this novel mutation of NOG gene was the causative mutation in this family.

5 | CONCLUSION

In summary, a novel NOG gene heterozygous mutation c.533G>A (p.Cys178Tyr) in the Chinese family diagnosed as SYNS1 was identified. The understanding of this rare disease was improved and provided a valuable information and basis for further genetic counseling for patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of General Hospital of Central Theater Command (No. [2018]016–1; approved on 16th March 2018).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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