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# A Comprehensive Review of Reported Heritable Noggin-Associated Syndromes and Proposed Clinical Utility of One Broadly Inclusive Diagnostic Term: *NOG*-Related-Symphalangism Spectrum Disorder (*NOG*-SSD)

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**ABSTRACT:** The *NOG* gene encodes noggin, a secreted polypeptide that is important for regulating multiple signaling pathways during human development, particularly in cartilage and bone. The hallmark of *NOG*-related syndromes is proximal symphalangism, defined by abnormal fusion of the proximal interphalangeal joints of the hands and feet. Many additional features secondary to *NOG* mutations are commonly but inconsistently observed, including a characteristic facies with a hemicylindrical nose, congenital conductive hearing loss due to stapes fixation, and hyperopia. The variable clinical presentations led to the designation of five different autosomal dominant syndromes, all subsequently found to have resulted from *NOG* mutations. These include (1) proximal symphalangism; (2) multiple synostoses syndrome 1; (3) stapes ankylosis with broad thumbs and toes; (4) tarsal-carpal coalition syndrome; and (5) brachydactyly type B2. Herein, we review the phenotypic features associated with mutations in the *NOG* gene, demonstrating the overlapping characteristics of these syndromes. Due to the variable phenotypic spectrum within families and among families with the same mutation, we propose a unifying term, *NOG*-related symphalangism spectrum disorder (*NOG*-SSD), to aid in the clinical recognition and evaluation of all affected individuals with these phenotypes. These *NOG* gene variants are available in a new locus-specific database (https://NOG.lovd.nl).
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**KEY WORDS:** *NOG*; noggin; proximal symphalangism; stapes ankylosis

## Background

The *NOG* (MIM# 602991) gene encodes a secreted protein called noggin that is essential for normal bone and joint development [Zimmerman et al., 1996]. *NOG* maps to human chromosome band 17q22 [Valenzuela et al., 1995] and consists of a single coding exon of 696 bp, encoding a 232 amino acid protein that is secreted as a homodimer. Noggin binds and inactivates bone morphogenetic proteins (BMPs) [Brunet et al., 1998], specific signaling proteins of the transforming growth factor-β (TGF-β) superfamily. BMPs function by binding to Type I and Type II bone morphogenic protein receptors (BMPRs) on the cell surface and triggering a phosphorylation cascade that eventually leads to activation of transcription factors [Zakin and De Robertis, 2010]. The 15 known members of the BMP family (BMP1–BMP15) are responsible for the differentiation of mesenchymal cells [Hogan, 1996], and thus may also be referred to as growth differentiation factors (GDFs), comprising another family within the TGF-β superfamily. BMPs and noggin have been implicated in regulating multiple processes during embryogenesis, including establishment of the dorsoventral axis, neural induction and neurogenesis, and formation of bones and joints in the developing skeletal system [Brunet et al., 1998; McMahon et al., 1998]. BMPs are responsible for osteogenic transformation of stem cells, activation of immature osteoblasts [Cheng et al., 2003], and induction of apoptosis at joint sites [Zou and Niswander, 1996]. A variety of skeletal dysplasias may result from abnormal signaling through the BMP pathway (reviewed by [Baldridge et al., 2010]). When noggin is absent, BMPs are unregulated, and chondrocytes undergo hyperplasia instead of apoptosis in the developing joint [Dawson et al., 2006].

Currently, noggin is the only secreted inhibitor of BMPs that has been associated with abnormal phenotypes in humans. Fusion of the proximal interphalangeal joints, known as proximal symphalangism, is the most widely recognized hallmark feature caused by *NOG* mutations. Proximal symphalangism displays minimal genetic heterogeneity, as mutations in only two other genes, *GDF5* (MIM# 601146) and *FGF9* (MIM# 600921), have been reported in a small number of families (see Diagnostic Relevance, below). Several additional features have been described that comprise overlapping clinical syndromes associated with *NOG* mutations, including proximal symphalangism (MIM# 185800), multiple synostoses syndrome 1 (MIM# 186500), tarsal-carpal coalition syndrome (MIM# 186570), stapes ankylosis with broad thumbs and toes (MIM# 184460), and brachydactyly type B2 (MIM# 611377). We propose a new term, *NOG*-SSD (*NOG*-related symphalangism spectrum disorder), to encompass these disorders.

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## Phenotypes

### Proximal Symphalangism (SYM1)

SYM1 is characterized by variable fusion of the proximal interphalangeal joints and occasionally the metacarpophalangeal joints in the hands. The third, fourth, and fifth digits are more frequently affected than the index fingers, and the thumb is almost always spared. In 1916, Cushing described a family with proximal symphalangism segregating as an autosomal dominant trait with complete penetrance [Cushing, 1916]. Affected individuals were noted to have "straight fingers," or symphalangism, and an inability to make a fist, as well as hearing loss, shortened middle fingers, and straight and/or webbed toes. A family with similar features with the exception of hearing loss was reported the next year by Drinkwater [1917]. In 1965, a follow-up report of Cushing's family described several members with talonavicular and calcaneocuboidal coalitions, resulting in a waddling or "duck-like" gait, in addition to bony fusions in the hands [Strasburger, 1965]. Numerous reports described families presenting with dominantly inherited symphalangism, hearing loss, and fusion of the carpals and tarsals [Bloom, 1937; Spoendlin, 1974; Sugiura and Inagaki, 1981]. Other features identified in affected individuals include hyperopia, fused cervical vertebrae, abnormal facies, absent flexion creases of the digits, shortened metacarpals, distal symphalangism, hypoplasia or aplasia of the distal phalanges in the hands and feet, and symphalangism in the toes. Premature ovarian failure was also reported in one Japanese female with SYM1 [Kosaki et al., 2004].

In 1995, linkage analysis in Cushing's family identified a locus for proximal symphalangism on human chromosome band 17q21–q22 [Polymeropoulos et al., 1995], and subsequently, missense mutations in the *NOG* gene were reported in this family and five other families with proximal symphalangism [Gong et al., 1999]. Mutations causing proximal symphalangism are listed in Table 1 [Mangino et al., 2002; Takahashi et al., 2001].

### Multiple Synostoses Syndrome 1 (SYNS1)

SYNS1 was initially described as an autosomal dominant disorder characterized by progressive symphalangism and conductive hearing loss secondary to stapes fixation [Gorlin et al., 1970]. Multiple synostoses syndrome was clinically distinguished from proximal symphalangism based on the presence of characteristic facial features and by more severe and widespread joint involvement, especially in the vertebrae and hips [Maroteaux et al., 1972]. The joint fusions typically worsened with aging in the affected individuals [Gaal et al., 1987].

In multiple synostoses syndrome, the facies are characterized by low frontal hair implantation, a broad, tubular shaped (hemicylindrical) nose with lack of alar flare, thin vermilion of the upper lip, short philtrum, and microstomia [Higashi and Inoue, 1983]. Additional features include multiple joint fusions in the hands, feet, hips, and cervical vertebrae, brachydactyly, hypoplastic or absent phalanges in the hands, hypoplastic or absent nails, shortened metacarpals, subluxation of the radial heads, pectus carinatum, strabismus, and hyperopia [da-Silva et al., 1984; Gaal et al., 1987; Konigsmark and Gorlin, 1976].

Although some reports lacked formal audiological test results of individuals or did not differentiate sensorineural from conductive hearing loss, reported hearing impairment ranged from mild to severe [Gaal et al., 1987]. As in proximal symphalangism, the proximal interphalangeal joints of the ulnar-sided digits are generally affected first, followed by involvement of the radial-sided digits, with sparing of the thumbs. Most affected adults are unable to make a fist. Over time, affected individuals developed fusions of the cervical vertebrae, hips, and humeroradial joints. The cervical vertebral fusions began to develop in childhood and eventually led to significantly limited neck range of motion by adulthood.

Multiple synostoses syndrome has also been described as WL symphalangism-brachydactyly syndrome [Herrmann, 1974; Higashi and Inoue, 1983] and facioaudiosymphalangism [Hurvitz et al., 1985; van den Ende et al., 2005]. Linkage analysis of a family with multiple synostoses syndrome mapped to the same locus (17q21–q22) as proximal symphalangism [Krakow et al., 1998], and mutations in the *NOG* gene were later described in several families with multiple synostoses syndrome [Dawson et al., 2006; Debeer et al., 2005; Emery et al., 2009; Gong et al., 1999; Takahashi et al., 2001] (Table 1).

### Tarsal-Carpal Coalition Syndrome (TCC)

TCC syndrome was described as an autosomal dominant disorder characterized by fusion of the carpals, tarsals, and phalanges in addition to shortened first metacarpals, brachydactyly, and humeroradial fusion [Drawbert et al., 1985; Gregersen and Petersen, 1977]. Conductive hearing loss is not typically observed in tarsal-carpal coalition syndrome [Dixon et al., 2001]. Beginning at birth, affected members show progressive fusion of the proximal interphalangeal joints, starting at the fifth digit and proceeding sequentially to the second digit, with sparing of the thumb. With age, affected individuals may develop humeroradial fusion and elbow abnormalities. Other features may include flat feet, varus or valgus deformities of the heel, fixed pronation or supination of the forefoot, and low body height. The abnormalities of the ankle and foot can cause significant discomfort and disability in these affected individuals, often requiring palliative or surgical intervention. Four different *NOG* mutations have been identified in families with TCC [Debeer et al., 2004; Dixon et al., 2001; Drawbert et al., 1985] (Table 1).

### Stapes Ankylosis with Broad Thumbs and Toes (SABTT)

Stapes ankylosis with broad thumbs and toes was described as an autosomal dominant disorder characterized by bilateral conductive hearing loss secondary to stapes ankylosis, significant hyperopia, broad thumbs, and broad first toes [Teunissen and Cremers, 1990]. In contrast, fewer than 3% of total cases of SYM1 and SYNS1 report hyperopia [Hilhorst-Hofstee et al., 1997]. Fusion of cervical vertebrae, characteristic facies akin to multiple synostoses syndrome, strabismus, and syndactyly of the toes may also be observed [Brown et al., 2003]. However, SABTT differs from SYM1 and SYNS1 by the presence of hyperopia and the lack of fusions in the carpals or tarsals.

Nonsense mutations within the *NOG* gene were reported in two families with stapes ankylosis with broad thumbs and toes, one of which was previously described by Milunsky [Brown et al., 2002, 2003; Milunsky et al., 1999]. These two families had similar phenotypes, with the exception of tall stature ($>90\%$ percentile) and lack of childbearing by affected females in one family. Several additional *NOG* mutations associated with SABTT were subsequently reported [Hirshoren et al., 2008; Thomeer et al., 2011; Weekamp et al., 2005] (Table 1). Notably, in contrast to the missense mutations in *NOG* typically associated with SYM1, SYNS1, and TCC, six of the eight known mutations to cause

**Table 1. DNA Variants in the *NOG* Gene and Predicted Functional Consequences**

| Nucleotide change[a] | Protein | Predicted and/or demonstrated effect on protein | Syndrome | previous publications |
|---|---|---|---|---|
| c.58delC | p.Leu20Cysfs*42 | Frameshift<br>Truncated protein with 60 amino acids<br>Missing cysteine-rich C-terminal domain | SYNS1 | Takahashi et al., 2001 |
| c.103C>G | p.Pro35Ala | Missense<br>Decreased affinity for BMP; prevents interaction with BMP type I receptors | BDB2 | Lehmann et al., 2007 |
| c.103C>T | p.Pro35Ser | Missense<br>Conformational change; prevents interaction with BMP type I receptors | SABTT<br>BDB2<br>SYM1 | Hirshoren et al., 2008<br>Lehmann et al., 2007<br>Mangino et al., 2002 |
| c.104C>G | p.Pro35Arg | Missense<br>Conformational change; prevents interaction with BMP type I receptors | SYM1<br>TCC | Gong et al., 1999<br>Dixon et al., 2001 |
| c.106G>C | p.Ala36Pro | Missense<br>Conformational change; prevents interaction with BMP type I receptors | BDB2 | Lehmann et al., 2007 |
| c.110C>G | p.Pro37Arg | Missense<br>Destruction of beta-sheet motif and conformational change; prevents interaction with BMP type I receptors | TCC | Debeer et al., 2004 |
| c.[124C>G; 149C>G] | p.[Pro42Ala; Pro50Arg] | Double missense mutation | SYNS1 | Debeer et al., 2004 |
| c. 125C>G | p.Pro42Arg | Missense | SYNS1 | Oxley et al., 2008 |
| c.129_130dup | p.Val44Glyfs*19 | Frameshift<br>Truncated protein with 61 amino acids<br>No functional noggin protein synthesized | SABTT | Weekamp et al., 2005 |
| c.142G>A | p.Glu48Lys | Missense<br>Conformational change; inhibits interaction with BMP type II receptors | BDB2<br>SYM1 | Lehmann et al., 2007<br>Kosaki et al., 2004 |
| c.252dup | p.Glu85Argfs*97 | Frameshift<br>Truncated protein with 180 amino acids<br>Missing cysteine-rich C-terminal domain | SABTT | Brown et al., 2002 |
| c.304del | p.Ala102Argfs*22 | Frameshift | SABTT | Thomeer et al., 2011 |
| c.328C>T | p.Gln110* | Nonsense<br>Truncated protein with 109 amino acids<br>Missing cysteine-rich C-terminal domain | SABTT | Brown et al., 2002 |
| c.386T>A | p.Leu129* | Nonsense<br>Truncated protein with 128 amino acids<br>Missing cysteine-rich C-terminal domain | SYM1 | Takahashi et al., 2001 |
| c. 391C>T | p.Gln131* | Nonsense<br>Truncated protein with 130 amino acids | SABTT | Thomeer et al., 2011 |
| c.499C>G | p.Arg167Gly | Missense<br>Conformational change; prevents interaction with BMP type II receptors | BDB2 | Lehmann et al., 2007 |
| c.551G>A | p.Cys184Tyr | Missense | SYM1 | Takahashi et al., 2001 |
| c.559C>T | p.Pro187Ser | Missense<br>Destabilizes binding of noggin homodimers; secretion of monomeric forms | BDB2 | Lehmann et al., 2007 |
| c.561del | p.Glu188Argfs*76 | Frameshift<br>Elongated protein with 262 amino acids.<br>Missing second finger structure and likely conformational change | SABTT | Weekamp et al., 2005 |
| c.565G>T | p.Gly189Cys | Missense<br>Secreted mostly in monomer form<br>Significantly decreased levels of dimeric noggin | SYM1 | Gong et al., 1999 |
| c.568A>G | p.Met190Val | Missense | SYNS1 | Oxley et al., 2008 |
| c.608T>C | p.Leu203Pro | Missense<br>Conformational change in second finger structure | SABTT | Weekamp et al., 2005 |
| c.611G>T | p.Arg204Leu | Missense | TCC | Dixon et al., 2001 |
| c.614G>A | p.Trp205* | Nonsense<br>Truncated protein with 204 amino acids | SYNS1 | Dawson et al., 2006 |
| c.615G>C | p.Trp205Cys | Missense | SYNS1<br>SYM1 | van den Ende et al., 2005<br>Emery et al., 2009 |
| c.649T>G | p.Trp217Gly | Missense<br>Loss of noggin secretion; unable to bind BMPs | SYNS1 | Gong et al., 1999 |
| c.659T>A | p.Ile220Asn | Missense | SYM1 | Gong et al., 1999 |
| c.[659_660delinsAT; c.664T>G] | p.[Ile220Asn; Tyr222Asp] | Double missense mutation | SYM1 | Gong et al., 1999 |
| c.665A>G | p.Tyr222Cys | Missense | SYM1<br>TCC | Gong et al., 1999<br>Dixon et al., 2001 |
| c.668C>T | p.Pro223Leu | Missense<br>Secreted in dimer form<br>Decreased levels of disulfide-linked dimeric noggin | SYM1 | Gong et al., 1999 |
| c.696C>G | p.Cys232Trp | Missense<br>Disrupts cysteine-rich C-terminal domain | SYNS1 | Rudnik-Schöneborn et al., 2010 |

SYNS1, multiple synostoses syndrome 1; BMP, bone morphogenetic protein; BDB2, brachydactyly type B2; SABTT, stapes ankylosis, broad thumbs and toes; SYM1, proximal symphalangism; TCC, tarsal-carpal coalition syndrome.

[a]Nucleotide and amino acid alterations are displayed in Human Genome Variation Society preferred format (www.hgvs.org/mutnomen) [den Dunnen and Antonarakis, 2000]. Nucleotide numbering is based on GenBank reference sequence NM_005450.4. All listed variants occur in exon 1, the single coding exon of *NOG*.

SABTT are inactivating mutations, suggesting that haploinsufficiency of *NOG* may specifically lead to the SABTT phenotype.

### Brachydactyly Type B2 (BDB2)

The brachydactylies are a group of autosomal dominant disorders characterized by shortened digits in the hands or feet due to abnormal development of the phalanges or metacarpals/metatarsals [Bell, 1951]. Brachydactylies are classified into subtypes A to E based on the degree and pattern of skeletal involvement [Fitch, 1979]. For example, in type A brachydactylies, only the middle phalanges are abnormal. Brachydactyly type B classically involves hypoplasia or aplasia of the middle and/or terminal phalanges and is the only subtype in which the terminal phalanges are abnormal. Brachydactyly type B2 was characterized by hypoplasia or aplasia of the distal and/or middle phalanges in combination with proximal symphalangism, carpal synostosis, syndactyly, and rarely, distal symphalangism [Lehmann et al., 2007]. Proximal symphalangism is commonly noted when the distal phalanges are present. Similar to SYM1, the fourth and fifth digits tend to be affected more frequently than the second or third digits in brachydactyly Type B2.

Truncating mutations in the tyrosine kinase-like orphan receptor 2 gene (*ROR2*; MIM♯ 602337) are responsible for brachydactyly type B1 (BDB1; MIM♯ 113000) [Oldridge et al., 2000]. BDB2 was described in a family in which every affected member exhibited absent or hypoplastic middle and/or terminal phalanges, consistent with brachydactyly type B, but no mutations in *ROR2* were found [Brunet et al., 1998]. Among six families with different *NOG* mutations causing BDB2 (Table 1), hearing loss was not reported, although it is unclear whether formal audiological testing was performed [Lehmann et al., 2007].

## *NOG* Mutation Database

A locus-specific mutation database has been created for the *NOG* gene using the LOVD platform (https://NOG.lovd.nl).

## Variants

There are few reported polymorphisms in the *NOG* gene (Table 2). The completed DNA sequence of human chromosome 17 demonstrated five variants in exon 1: a predicted frameshift, c.19delC; two nonsynonomous base substitutions, p.Asp60Asn and p.Trp150Gly, and two synonomous base substitutions [Zody et al., 2006]. As these DNA sequence variants were discovered in presumably asymptomatic individuals, no phenotypic information is available.

Several genetic association studies have investigated *NOG* as a candidate susceptibility gene for various disorders. Significant associations between single nucleotide polymorphisms (SNPs) mapping to human chromosome band 17q22–17q23 have been demonstrated for nonsyndromic cleft lip and palate [Mangold et al., 2010] and adult human height [Gudbjartsson et al., 2008]. No significant associations were detected between polymorphisms in the *NOG* gene and the incidence of osteoporosis phenotypes [Moffett et al., 2009] or the degree of volumetric bone mineral density [Yerges et al., 2009].

## Biological Relevance

In mice, homozygous *Noggin* null mutations led to a recessive lethal phenotype at birth with multiple abnormalities involving the neural tube, limbs, vertebrae, and tail [Brunet et al., 1998; McMahon et al., 1998]. Although null mice had normal induction of neural tissue, they subsequently displayed failure of neural tube closure, reduced amount of posterior neural tissue, and failure of ventral development in the posterior neural tube. Additionally, somite differentiation was deficient due to reduced induction and impaired survival of sclerotomal and myotomal derivatives in the trunk. Due to excess cartilage production, the skeleton was affected by widespread joint fusion involving the axial skeleton and limbs [Brunet et al., 1998]. It was also noted that GDF-5 expression was significantly decreased or absent in the affected joint cavities.

The phenotype of heterozygous *Noggin* null mice varied with the background strain, suggesting that modifier genes play a role

**Table 2. Polymorphisms in the *NOG* Gene**

| Region | Nucleotide change[a] | Affected codon | Reference number | Allele frequency[b] | Previous publications |
|---|---|---|---|---|---|
| 5′ UTR | c.−520G.A | p. = | NA | 0.98/0.02 | Moffet et al., 2009 |
| 5′ UTR | c.−385C>A | p. = | rs117249328 | ND | Zody et al., 2006 |
| 5′ UTR | c.−73G>A | p. = | NA | 0.81/0.19 | Moffet et al., 2009 |
| Exon 1 | c.19delC | p.Leu7* | rs34711886 | ND | NCBI SNPdb |
| Exon 1 | c.178G>A | p.Asp60Asn | rs117165670 | ND | Zody et al., 2006 |
| Exon 1 | c.448T>G | p.Trp150Gly | rs118090182 | ND | Zody et al., 2006 |
| Exon 1 | c.561C>T | p. = | rs116863344 | ND | Zody et al., 2006 |
| Exon 1 | c.582G>A | p. = | rs76347008 | 0.789/0.211 | Zody et al., 2006 |
| 3′ UTR | c.*80A>C | p. = | rs1442829 | ND | NCBI SNPdb |
| 3′ UTR | c.*110T>C | p. = | rs1236187 | ND | NCBI SNPdb |
| 3′ UTR | c.*130_*135del | p. = | rs71671792 | ND | Zody et al., 2006 |
| 3′ UTR | c.*130_*135del | p. = | rs67555616 | ND | Zody et al., 2006 |
| 3′ UTR | c.*130_*135del | p. = | rs71888945 | ND | Zody et al., 2006 |
| 3′ UTR | c.*136_*137del | p. = | rs71139919 | ND | Zody et al., 2006 |
| 3′ UTR | c.*153A>G | p. = | rs74256715 | ND | NCBI SNPdb |
| 3′ UTR | c.*303A>C | p. = | rs1348322 | ND | NCBI SNPdb |
| 3′ UTR | c.*567G>C | p. = | rs116716909 | ND | Zody et al., 2006 |

Nucleotide and amino acid alterations are displayed in Human Genome Variation Society preferred format (www.hgvs.org/mutnomen) [den Dunnen and Antonarakis, 2000] where "−" indicates nucleotides upstream of the initiation codon, *indicates nucleotides downstream of the termination codon, and +1 corresponds to the A of the ATG initiation codon; UTR, untranslated region; ND, not determined; NA, not available.

[a]Nucleotide numbering is based on GenBank reference sequence NM_005450.4.

[b]Allele frequency from NCBI Single Nucleotide Polymorphism Database [Sherry et al., 2001] or cited reference.

[Hwang and Wu, 2008]. $Nog^{+/-}$ embryos were reported as normal in one study [Brunet et al., 1998], whereas $Nog^{+/-}$ mice on a congenic C57BL/6J background demonstrated conductive hearing loss secondary to impaired mobility of the stapes [Hwang and Wu, 2008]. In contrast, $Nog^{+/-}$ mice on a mixed C57BL/6J/FVB background had normal hearing. Observations from mouse models as well as variability seen across the human spectrum may suggest epistatic modifiers for the *NOG* gene.

In vitro studies have examined the synthesis, secretion, and BMP binding activity of mutant noggin proteins (p.Gly189Cys, p.Pro223Leu, and p.Tryp217Gly) [Marcelino et al., 2001]. Although mutant noggin was transcribed and translated similar to wild-type noggin, the mutant polypeptides were less efficient at forming disulfide linkage bonds. Mutant proteins expressing p.Gly189Cys and p.Pro223Leu were secreted as monomers or dimers in lower amounts compared to wild type, and were able to interact with GDF-5. In contrast, the p.Tryp217Gly mutant protein failed to be secreted at all and was unable to interact with GDF-5. Interestingly, GDF-5 facilitated the formation of dimers in all three mutant proteins. The same three mutant proteins retained their ability to function as secreted dimers in *Xenopus laevis* embryos.

The C-terminal region of noggin contains a cysteine-knot motif of nine cysteine residues important for dimerization and disulfide-bond formation (between residues 155 and 192, 178 and 228, 184 and 230, and 207 and 215) [Groppe et al., 2002]. Truncations or alterations of the C-terminal region are therefore likely to alter protein function [Groppe et al., 2003]. Six of eight mutations associated with SABTT are nonsense mutations, which may result in truncation of the C-terminal domain or haploinsufficiency through nonsense-mediated decay (Table 1).

The known *NOG* mutations associated with abnormal phenotypes tend to cluster in areas that affect noggin's ability to bind to the Type I and Type II receptor pockets on BMPs (Table 1). The P35 amino acid appears to be crucial for binding to the Type I receptor pocket on BMPs via a hydrophobic interaction; thus, substitutions at this site may decrease affinity or induce steric hindrance [Lehmann et al., 2007]. Interestingly, three different missense mutations involving this residue have been reported (Table 1) (p.Pro35Ala in BDB2; p.Pro35Ser in SABTT, BDB2, and SYM1; and p.Pro35Arg in SYM1 and TCC). It has been suggested that when containing mutations associated with BDB2, noggin may either retain most of its function in binding BMPs/GDFs or act through a different mechanism [Lehmann et al., 2007]. For example, the BDB2 mutation p.Pro187Ser is thought to affect the dimerization domain of noggin and inhibit its ability to form a homodimer [Lehmann et al., 2007].

One study used computer simulation to calculate the free-binding energy between noggin and GDF5, comparing the loss of energy with a variety of noggin mutants in comparison to wild-type noggin [Lehmann et al., 2007]. The highest loss of free-binding energy was observed for p.Pro35Arg, with intermediate reduction in free energy observed for p.Pro35Ala and p.Pro35Ser, and negligible decreases were noted for p.Ala36Pro, p.Glu48Lys, and p. Arg167Gly. However, in chick limb buds, the p.Glu48Lys and p.Pro35Arg mutants were unable to inhibit chondrogenesis, indicating significantly decreased affinity for BMPs [Groppe et al., 2003].

BMPs and GDF5 bind to BMPR1 and BMPR2, which are specific transmembrane serine/threonine kinases located on the cell surface [Gilboa et al., 2000]. After ligand binding, the BMPRs form heterodimers, and BMPR2 phosphorylates BMPR1. If the BMP/GDF binds to a preformed heterodimer, the phosphorylated BMPR1 subsequently activates SMAD proteins by phosphorylation [Nohe et al., 2002]. The SMAD proteins enter the nucleus to regulate transcription of genes related to bone formation [von Bubnoff and Cho, 2001]. Thus, the level of activation of SMAD proteins is a means to assay *NOG* activity. Upregulation of BMPs and GDFs produces phenotypes similar to those associated with downregulation of *NOG*.

## Clinical Relevance

Despite the descriptions of several different syndromes to date and the wide spectrum of phenotypes arising secondary to *NOG* mutations, there are common overlapping features. These anomalies most commonly involve abnormal bone and joint formation, from the ears to the toes, but may also involve development of facial structures and vision. We propose that a more broadly inclusive clinical diagnostic term, *NOG*-related Symphalangism Spectrum Disorder (*NOG*-SSD), may offer significant clinical and research utility. Although recognizing *NOG* mutations as the common molecular etiology, this term also incorporates the hallmark feature of proximal symphalangism, whereas noting the variable spectrum of associated findings. The reported clinical findings in *NOG*-SSD are summarized in Table 3.

**Table 3. Physical Features Characteristic of *NOG*-Symphalangism Spectrum Disorder**

| Site | Features |
|---|---|
| Face | Broadened, hemicylindrical nose with bulbous tip and lack of alar flare |
| | Shortened philtrum |
| | Thin vermilion of upper lip |
| | Malar flattening |
| | Posteriorly sloping forehead |
| | Asymmetric mouth |
| | Prominent supraorbital ridges |
| Eyes | Hyperopia |
| | Strabismus |
| Ears | Conductive hearing loss, unilateral or bilateral |
| Neck | Limited neck flexion, extension, and lateral bending |
| Hands | Proximal symphalangism, inability to flex proximal interphalangeal joints of second through fifth digits and/or inability to make a fist (medial digits more commonly affected) |
| | Shortening or absence of distal portions of fingers (medial-sided digits affected preferentially) |
| | Broad and/or short thumbs |
| | Limited wrist flexion and extension |
| | Absent creases on flexor and/or extensor surfaces of interphalangeal joints |
| | Absent or shortened fingernails |
| | Clinodactyly |
| | Syndactyly |
| Elbows | Limited flexion and extension of the elbow |
| | Limited pronation and supination of the forearm |
| Chest | Pectus carinatum |
| | Pectus excavatum |
| Hips | Limited range of motion |
| Feet | Inability to flex toes |
| | Broad first toes |
| | Waddling "duck-like" gait |
| | Syndactyly |
| | Absent or shortened toenails |
| | Fixed valgus or varus deformity of heel |
| | Fixed pronation or supination of forefoot |
| | Limited inversion or eversion |
| | Pes planus |
| | Shortened or absence of distal portions of toes |

## Joint and Bone Anomalies

Most affected individuals with *NOG*-SSD express some degree of joint or bone deformity, although the severity of the deformities demonstrates both significant inter- and intrafamilial variability. Both hands and feet may display syndactyly, shortening or complete absence of the distal portions of the phalanges, shortening or complete absence of fingernails, and abnormally broad first digits ("hammer" thumbs and toes). Joint ankyloses in the cervical vertebrae, elbows, and/or hips are commonly observed. Thorough visual inspection of the hands and feet, in addition to range-of-motion testing in the neck, elbows, hands, hips, and feet, is essential in these patients.

The hands display the greatest amount of variation in *NOG*-SSD. Narrowing and eventual fusion of the proximal interphalangeal (PIP) joints occurs most frequently, with the ulnar-sided digits being affected more frequently than the radial-sided digits. In milder cases of *NOG*-SSD, the proximal interphalangeal joints are spared. The severity of PIP involvement tends to diminish toward the radial side of the hand (i.e., the fourth and fifth digits are much more likely to be affected than the second or third digits) [Strasburger, 1965]. Fusion of the PIP joints in the hands leads to decreased ability to flex the fingers and make a fist, as well as abnormalities in the pattern of interphalangeal creases (loss of creases or additional creases) on the flexor and/or extensor sides of the digits. However, these anomalies are not traditionally described as debilitating.

Fusion between any of the carpal bones is a rather common occurrence in *NOG*-SSD. Other possible findings include shortened or elongated metacarpals, and broadened metacarpals or thumbs. The distal and/or middle phalanges may be hypoplastic or completely absent, leading to shortened digits. In rare cases, there may be distal interphalangeal joint fusion, but these joints as well as the metacarpophalangeal joints are not typically affected.

In the feet, there may be fusion of the proximal or distal interphalangeal joints and broad phalanges, especially the hallux. Unlike the fingers, the toes do not demonstrate a pattern of joint involvement. The distal and/or middle phalanges of the feet may be hypoplastic or absent, resulting in shorter toes. The metatarsals may occasionally become fused with the tarsals or phalanges. Positioning abnormalities such as pes planus, fixed varus or valgus angulation of the heel, and fixed pronation or supination of the forefoot are also observed, which may result in painful callosities on the lateral portions of the feet [Drawbert et al., 1985]. Fusion between any of the tarsal bones is extremely common and debilitating, causing pain and difficulty with ambulation, sometimes described as a "duck-like" gait.

Limited range of motion due to joint ankylosis may involve the spine, elbows, and hips, and, rarely, the shoulders. Joint ankylosis tends to worsen over time and may not be noticeable until later in life. For example, one affected adult lacked the mobility to tie a necktie or to fold his legs in a pretzel or Indian-style fashion but otherwise had no limitations of daily activities. In the spine, fusion may develop between two or more adjacent vertebrae. The majority of fusions occur in the cervical vertebrae, leading over time to difficulties with neck flexion and extension. Other findings may include degeneration of the vertebrae, broadening of the spinal processes and laminae, narrowing of the intervertebral space, schmorl nodes, and spinal canal stenosis. The head of the radius is frequently deformed, resulting in subluxation of the radial head or humeroradial synostosis.

Radiological imaging may be helpful in the diagnosis and treatment of individuals with *NOG*-SSD (Table 4). The types of defects range from altered shapes of bones, shortened or absent bones, fusion between bones, and narrowed or absent joint spaces. Advanced bone age may also be noticed in children. Individuals with *NOG*-SSD may exhibit premature fusion of phalangeal growth plates, leading to short phalanges. In normal individuals, phalangeal growth plates fuse by age 25, and therefore imaging at a younger age is necessary to detect premature fusion.

**Table 4. Radiological Findings Characteristic of *NOG*-Symphalangism Spectrum Disorder**

| Site | Features |
|---|---|
| Head | Deformities of stapes |
| | Narrowing of oval window |
| Hands | Symphalangism of the proximal interphalangeal joints (medial digits affected preferentially) |
| | Hypoplastic or absent distal and/or middle phalanges (medial digits affected preferentially) |
| | Narrowed interphalangeal joint spaces |
| | Broadened and/or shortened thumb |
| | Broadened, shortened, or elongated metacarpals |
| | Carpal fusions |
| Elbow | Subluxation of the radial head |
| | Humeroradial fusions |
| Spine | Vertebral fusions (most commonly in cervical vertebrae) |
| | Narrowed intervertebral spaces |
| | Broadening of spinal processes and laminae |
| | Degenerative changes |
| Feet | Fusion of the proximal or distal interphalangeal joints |
| | Hypoplastic or absent distal and/or middle phalanges |
| | Broadened toes |
| | Metatarsal fusions |
| | Tarsal fusions |

Joint fusions in the hands, elbows, or spine rarely warrant surgical intervention, and attempts to create interphalangeal joints have been largely unsuccessful [Smith and Lipke, 1979]. Tarsal coalition may result in severe, disabling pain that can be treated by nonsteroidal anti-inflammatory medications, ankle-stabilizing orthotics, or casting. Surgical options include excision of the coalitions and arthodesis of the joints [Thometz, 2000]. Specific success rates of standard procedures such as osteotomy and arthroplasty in patients affected by *NOG*-SSD have not been described.

## Facial Features

Multiple families with *NOG*-SSD demonstrated characteristic facial features in multiple generations. The most prominent feature is a broad, hemicylindrical or tubular nose with a bulbous tip, hypoplastic nasal alae, and short philtrum [Higashi and Inoue, 1983]. A posteriorly sloping forehead, prominent supraorbital ridges, clefting of the nasal tip, malar flattening, synophrys, and a cleft chin may also be evident (Fig. 1). Other facial features may include a thin vermilion of the upper lip and upslanting palpebral fissures.

## Otologic and Audiologic Findings

Congenital conductive hearing loss due to stapes ankylosis is a well-defined feature in *NOG*-SSD. The conductive hearing loss presents in childhood, and onset may be difficult to determine in patients born before 2000, when newborn hearing screening became widely adopted [Vesell, 1960]. Moderate conductive hearing loss may be stable for years, but progression of stapes ankylosis is commonly described in families with SYM1 [Baschek,

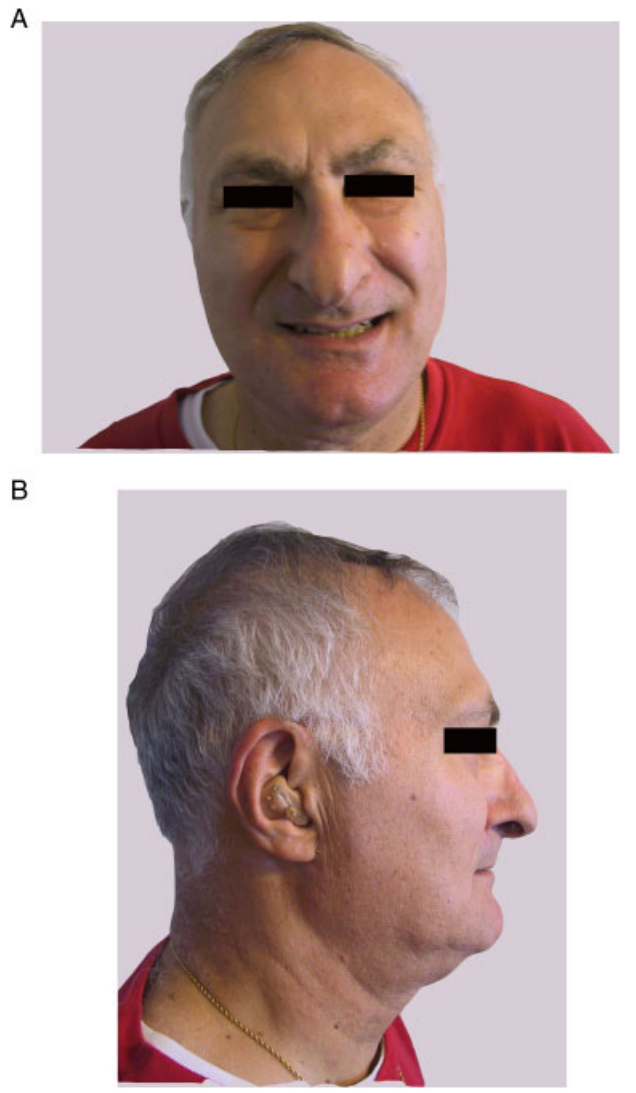


**Figure 1.** **A**: Frontal photograph of a 67-year-old male diagnosed with stapes ankylosis, broad thumbs and toes, demonstrating posteriorly sloping forehead, prominent supraorbital ridges, broad hemicylindrical nose with bulbous tip, short columella, and nasal tip cleft, short philtrum, malar flattening, synophrys, and prominent chin with midline cleft. **B**: Lateral view. [Color figures can be viewed in the online issue, which is available at www.wiley.com/humanmutation.]

1978; Cremers et al., 1985; Gorlin et al., 1970; Spoendlin, 1974; Stenger and Gloede, 1972]. The penetrance of hearing loss in *NOG*-SSD may range from low (33–50%) [Declau et al., 2001; Takahashi et al., 2001] to complete [Ensink et al., 1999].

Audiological evaluation typically demonstrates absent stapedial reflexes and absent otoacoustic emissions unilaterally or bilaterally. Typical of conductive hearing loss, speech discrimination is usually normal while the speech reception threshold is increased. The severity of hearing impairment can range from 20 to 80 dB, although most affected individuals have at least moderate hearing loss ($>40$ dB). Audiometric evaluation is imperative for children possibly affected by *NOG*-SSD.

Surgical exploration of the middle ear is necessary to evaluate the mobility of the ossicular chain by palpation. Fixation of the short process of the incus, elongation of the long process of the incus, and fixation of the malleoincudal joint or other ossicular articulations may also be observed [Ensink et al., 1999; Stephan, 2006; Thomeer et al., 2011; Weekamp et al., 2005]. Previous histological reports on resected stapes have noted an abnormal bony bridge between the crura and footplate, local bony fusion of the stapes footplate with thickened bone in the oval window niche, and abnormal ossification in the vestibular area of the footplate with calcification of the annular ligament [Declau et al., 2001].

Temporal bone CT may reveal narrowing of the oval window and deformities of the stapes [Brown et al., 2003]. However, high-resolution CT and MRI scans of the temporal bone are often normal in patients with *NOG*-SSD [Declau et al., 2001; Thomeer et al., 2011]. As stapes ankylosis is a clinical diagnosis, imaging may be most useful to exclude other causes of conductive hearing loss.

Most patients with pure conductive hearing loss will be successful hearing aid users, but many patients may opt for surgery to improve their hearing by restoring function of the ossicular chain. Stapedotomy or stapedectomy followed by placement of a piston is the most commonly performed procedure. In the short-term after surgery, most patients show immediate improvement in hearing and a reduction in the air-bone gap, sometimes with complete closure. Other patients have no change in hearing or, in rare instances, worsening of the hearing loss. Long-term follow-up often shows recurrence of hearing loss, with need for reexploration and revision surgery after two years [Ensink et al., 1999; Weekamp et al., 2005].

In postoperative patients with recurrence of hearing loss, temporal bone CT may reveal incudomallear ankylosis, piston extrusion, or regrowth of bone over the stapes footplate [Brown et al., 2003]. Patients may also develop an additional sensorineural component to the hearing loss [Brown et al., 2003]. The suboptimal long-term surgical results likely reflect the inability of a mutant noggin protein to inhibit bone regrowth. Although caution must be used when comparing surgical results from years ago to modern approaches, overall results of surgery are thought to be poorer in patients with congenital stapes fixation than in patients with nonsyndromic otosclerosis [Massey et al., 2006].

## Ocular Findings

Hyperopia is a prominent feature in *NOG*-SSD, specifically in patients without proximal symphalangism or other widespread joint fusions. The hyperopia presents in early childhood, and corrective lenses are often required at an early age. Eyeglasses and contact lenses are effective treatments. The severity of the hyperopia may possibly require up to $+14$ diopters correction or more. Strabismus occurs quite frequently and can lead to amblyopia if untreated. Ophthalmologic evaluation is warranted in all children being evaluated for *NOG*-SSD.

## General

Height, weight, intelligence, and life expectancy are generally normal. Tall stature has been reported in individuals with SABTS [Brown et al., 2002] and SYNS1 [Rudnik-Schoneborn et al., 2010], particularly in childhood [Oxley et al., 2008]. The disability in these patients mainly arises from difficulties with hearing, vision, and/or painful ambulation. Although limited range of motion and impaired flexibility of various joints may be evident on physical examination, these features may not significantly limit activities of daily living. In general, conservative treatments are recommended to improve function and reduce pain in patients with *NOG*-SSD.

## Diagnostic Relevance

The constellation of joint fusions, stapes ankylosis, and abnormalities of the hands and feet (Table 2) is overall highly predictive of a *NOG* mutation, but there is some evidence of genetic heterogeneity. Mutations in the *GDF5* gene have been reported in patients with clinical features of multiple synostoses syndrome 2 [Akarsu et al., 1999; Dawson et al., 2006] and proximal symphalangism [Seemann et al., 2005; Wang et al., 2006; Yang et al., 2008]. Multiple synostoses syndrome 3 was described in a family segregrating a mutation in the fibroblast growth factor 9 gene (*FGF9*; MIM# 600921) [Wu et al., 2009]. It has been suggested that the FGF and BMP signaling pathways may have overlapping roles in specifying the developing joints [Baldridge et al., 2010]. Interestingly, mutations in *GDF5* and *FGF9* are not associated with hearing loss, suggesting that the bony abnormalities spare the ossicles.

Stapes ankylosis is a feature of multiple syndromes, such as osteogenesis imperfecta [Pedersen, 1984], multiple epiphyseal dysplasia [Beighton et al., 1978], and X-linked stapes ankylosis with perilymphatic gusher [de Kok et al., 1995]. Isolated stapes ankylosis is more commonly due to nonsyndromic otosclerosis, which has a prevalence of 0.3 to 0.4% in Caucasians [Declau et al., 2001]. However, many individuals who are thought to have nonsyndromic otosclerosis may actually have stapes ankylosis as part of a genetic syndrome, and, in addition to a thorough family history, genetic testing may be useful in discriminating between the two [Emery et al., 2009].

## Future Prospects and Nomenclature Recommendations

Of the several secreted proteins now known to modulate BMP activity, noggin was one of the first recognized and most studied antagonists of BMP function [Marcelino et al., 2001; Smith and Harland, 1992]. Noggin has been shown to interact with BMP-7 by binding and masking both the Type-I receptor and Type-II receptor sites located on the BMP [Groppe et al., 2003]. Missense mutations may lead to misfolding, decreased stability, decreased affinity to BMPs, or reduced/undetectable secretion of noggin [Groppe et al., 2003; Lehmann et al., 2007; Marcelino et al., 2001]. It is currently unknown whether truncating mutations cause the same decrease in noggin secretion as the missense mutations, although it is expected there would be a decreased affinity for BMPs. It has been suggested that the more severe pathology in SYNS1 results from upregulation of GDF5 due to lack of inhibition [Dawson et al., 2006]. Therapeutic approaches may include treatments to upregulate *NOG* or to downregulate *BMP/GDF* activity.

For many genetic disorders with a common molecular etiology, a diverse set of syndromes were initially characterized on phenotypic grounds. Incorporating molecular genetic data into the nomenclature without losing an extensive body of clinical information often presents a challenge [Biesecker, 1998]. Remarkably, the need to simplify classification of syndromes associated with proximal symphalangism was noted over 30 years ago [Nixon, 1978]. We propose a unifying term, *NOG*-related Symphalangism Spectrum Disorder (*NOG*-SSD), to aid in the clinical diagnosis and evaluation of affected individuals. Proximal symphalangism is the hallmark feature most consistently noted, although it may vary in extent and distribution. The spectrum varies from milder phenotypes (SABTT, BDB2) to moderate (TCC) to severe (SYM1, SYNS1). Within a family, certain features are more consistently observed across generations than others. Furthermore, the same mutation (such as p.Pro35Ser) has been described in patients diagnosed with different clinical disorders (Table 1). Use of one common diagnostic term may help simplify the establishment and dissemination of clinical diagnostic criteria and enable the development of more focused and robust counseling, evaluation, and educational tools for patients.

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