A familial case of *NOG*-related symphalangism spectrum disorder due to a novel *NOG* variant

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List of key features

Congenital Stapes Ankyloses
Broad Thumbs/Halluces
Brachytelephalangia

Introduction

Conductive and mixed hearing loss is described as a clinical symptom common to more than 70 different genetic syndromes, among which congenital stapes ankylosis is present in a non-negligible portion (Toriello and Smith 2013). Even if these conditions are rare, they should be recognized and differentiated from other similar pathologic conditions, to achieve a precise diagnosis, which might have relevant implications for surgical intervention and clinical prognosis (Thomeer *et al.*, 2012).

The present article describes the case of a boy and his mother with conductive hearing loss due to stapes ankylosis, for which clinical genetic evaluations revealed mild skeletal anomalies leading to an unexpected diagnosis.

All signs and symptoms suggested Teunissen-Cremers syndrome (TCS) or stapes ankylosis with broad thumb and toes (SABTT) as a diagnosis, two very similar and allelic syndromic entities. Sequence analysis of the *NOG* gene detected a single nucleotide heterozygous deletion at position 280 (c.280del). To our knowledge, this frameshift variant was not previously described, but it is predicted to lead to a premature stop codon p.(Ala94Glnfs*28) and prevents the normal translation of Noggin protein.

Materials and methods

Subjects

The probands, an 8-year-old child, and his 48-year-old mother, were referred to our Clinical Genetic Service for a genetic evaluation of a congenital bilateral conductive hearing loss. The mother underwent surgical intervention for conductive hearing loss with suspected otosclerotic-like stapes fixation.

Their family history did not show members affected by hearing loss or skeletal anomalies, or specific genetic conditions. In particular, the mother's sister and their parents are reported having normal audiological functions. The child has two healthy older sisters.

Clinical, physical and audiological examinations were performed by an otorhinolaryngologist and by a clinical geneticist on both mother and son.

X-rays of hands, feet, skull and spine were obtained for both patients. Also, we asked and obtained specific written consent forms, for genetic testing and for picture taking.

Genetic analysis

Genomic DNA was extracted from peripheral blood lymphocytes using the automated QIAsymphony Platform (Qiagen). A sequence analysis of the *NOG* gene was performed using the ABI PRISM_3130xl DNA sequencer (manufactured by Applied Biosystems, Foster City, California, USA). The full coding region of the gene was sequenced and primers are available upon request.

Results

The two individuals did not have dysmorphic facial characteristics (hypoplastic alae nasi and hemicylindrical nose were noticed) and had normal tooth shape and enamel. They had brachytelephalangy of the hands with broad terminal phalanges (Fig. 1a,b). Fifth finger clinodactyly is evident in the boy (Fig. 1a). Flexion at the proximal interphalangeal joints is limited, especially in the boy. Symphalangism (i.e. the ankylosis of the interphalangeal joints) was not radiologically evident. X-rays of the patients' hands confirmed the presence of brachytelephalangia, clinodactyly of the V finger (in the boy) and a short first metacarpal bone (Fig. 1c,d). The feet's radiographies of both persons (Fig. 1e,f) show short hallux, more evident in the mother (Fig. 1f), whereas cutaneous syndactyly of the second and third fingers is present only in the son.

No bone anomalies were detected through X-rays of the skull and spine in both individuals.

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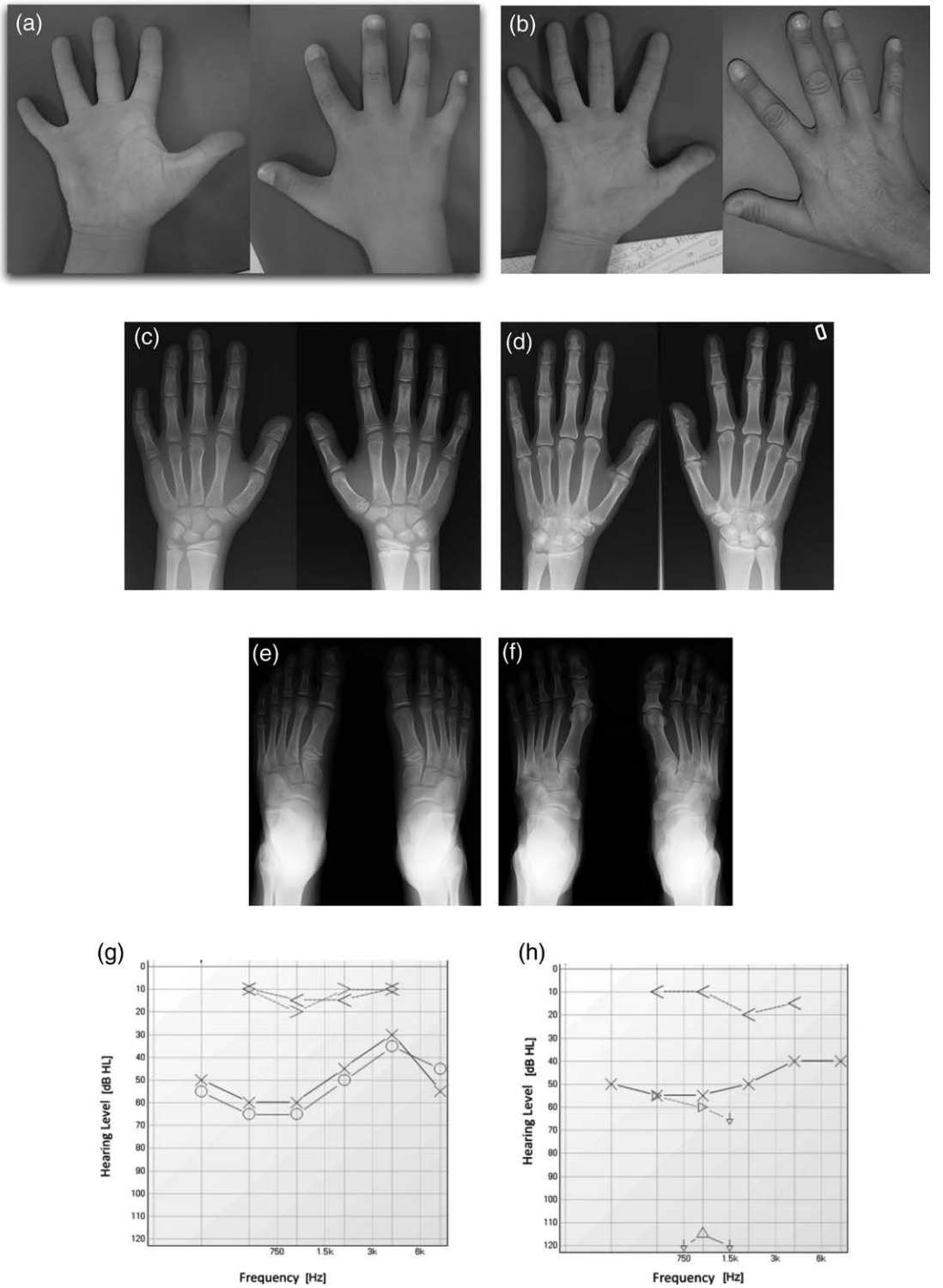
Fig. 1



Pictures of the boy's hands (a) showing brachytelephalangia with broad terminal phalanges and V finger clynodactyly. Pictures of the mother's hands (b) showing brachytelephalangia with broad terminal phalanges and V finger clynodactyly. X-rays of the patients's hands (c: boy and d: mother) confirmed the presence of brachytelephalangia, clinodactyly of the V finger (in the boy) and a short first metacarpal bone. The feet radiographies of both patients show short hallux (more evident in the mother; e), while only the son presents cutaneous syndactyly of the second and third fingers (f). (g) Pure tone audiometry of the boy showing bilateral pure conductive hearing loss. (h) Pure tone audiometry of the mother showing a moderate conductive hearing loss on the left side, and a profound mixed hearing loss on the right side due to a complication of previous surgery.

Table 1 Prevalent signs/symptoms of SSD and of the reported family

	SYNS1	SYM1	TCC	SABTT/TCS	Our family
Stapes ankylosis	+	+	−	+	+
Typical face	+/−	−	−	+	+
Hyperopia	−/+	−	−	+	−
Vertebral/limbs anomalies	+	−	+	−/+	−
Symphalangism	+	+	+	−	−
Brachytelephalangia with broad terminal phalanges	+	−	+/−	+	+
Limited flexibility of hand proximal interphalangeal joints	+	+	−/+	+	+
Fusion of carpal and tarsal bones	+	+/−	+	−	−
Broad thumbs/halluces	−	−	−	+	+/−

SABTT, stapes ankylosis with broad thumb and toes; SYM1, symphalangism; SYNS1, multiple synostosis syndrome; TCC, tarsal-carpal coalition syndrome; TCS, Teunissen-Cremers syndrome.

Pure tone audiometry of the probands showed bilateral moderate hearing loss in the boy (Fig. 1g), whereas the mother presented a moderate conductive hearing loss on the left side and a profound mixed hearing loss on the right side, which was treated with surgery for stapes fixation (Fig. 1h).

The ophthalmic examination of the boy was normal, ruling out hypermetropia and showing a normal length in the eye axis. For the mother, an ophthalmic examination was not available.

A sequence analysis of the *NOG* gene (NM_005450 accession number) detected a single nucleotide heterozygous deletion at position 280 (c.280del), both in the son and in the mother, while the same was not available for the two healthy sisters. This frameshift variant of the gene, with only one exon and without expected nonsense-mediated decay, is expected to cause a premature stop codon p.(Ala94Glnfs*28) and a truncated, nonfunctional Noggin protein.

Discussion

Conductive hearing loss in children is most frequently due to ear infections. Only rarely this type of auditory impairment is congenital (Esteves *et al.*, 2014). These congenital types, however, are often due to ear malformations ranging from deformities of the external and middle ear to isolated malformations of the ossicular chain. Moreover, congenital stapes ankylosis is an extremely rare condition.

Ossicular chain malformations are often a sporadic condition, but about 25% of cases show monogenic syndromes with a conductive or mixed hearing impairment, such as Crouzon syndrome, Pfeiffer syndrome, Klippel-Feil syndrome or Branchiootorenal syndrome (Thomeer *et al.*, 2012). Congenital stapes ankylosis is described in different syndromic conditions, including Mayer-Rokitansky-Küster-Hauser syndrome (Ledig and Wieacker 2018), Stickler syndrome (Baijens *et al.*, 2004), Saethre-Chotzen syndrome, Osteogenesis Imperfecta (Pedersen 1984), Multiple epiphyseal dysplasia (Beighton *et al.*, 1978) and X-linked Stapes Ankylosis with Perilymphatic Gusher (de Kok *et al.*, 1995). Consequently, the detection of familial cases of congenital conductive hearing loss should be considered a red flag for possible syndromic conditions and should call for genetic counseling and eventual testing.

We have described a family where the presence of a very similar audiological pattern between mother and son led to an in-depth evaluation of the subjects. Their phenotypes were strongly suggestive of TCS/SABTT because of the association of stapes ankylosis and skeletal specific findings, however, subtle. This prompted us to perform a targeted investigation of the *NOG* gene, resulting in the detection of a loss-of-function variant in both mother and son, consisting of a frameshift in the 94th codon and leading to the expected early termination of an anomalous protein: p.(Ala94Glnfs*28). Another frameshift variant near this codon, associated with the TCS/SABTT phenotype [*NOG*, c.304del (p.Ala102fs)], was reported (Thomeer *et al.*, 2011) along with two heterozygous nonsense variants at codons 110 and 129 (Brown *et al.*, 2002; Takahashi *et al.*; 2001). Clinical data for these are consistent with the same phenotypic spectrum. Moreover, it was reported (Laurell *et al.*, 2013) that signs of the TCS/SABTT spectrum are present in subjects with gross deletion of *NOG* in 17q22, supporting the haploinsufficiency of *NOG* as a cause for the condition.

Considering the specificity of the phenotype, its vertical transmission, the type of variant found in *NOG*, the cosegregation of the variant, its absence in population databases and the presence in pathological mutation databases of similar variations nearby, we believe that this variant can be considered pathogenic for TCS/SBTT, according to American College of Medical Genetics and Genomics guidelines (Richards *et al.*, 2015).

The reported boy and his mother show the association of conductive hearing loss due to stapes ankylosis with only a few, not severe, additional skeletal and joint anomalies (brachytelephalangia, II-III toe syndactyly, V finger clinodactyly, short broad hallux and joint limitation of finger movement). These are typical signs of SABTT/TCS (Teunissen and Cremers 1990; Weekamp *et al.*, 2005) and some of them are shared with other *NOG*-symphalangism spectrum disorder (SSD) syndromes, such as SYNS1 and SYM1.

However, SABTT/TCS differs from SYM1, SYNS1 and Brachydactyly type B2 for hyperopia. This, in fact, is

almost constant in the first two conditions, but rare in the others, and differs from Tarsal-Carpal coalition syndrome because of the lack of fusions in carpals or tarsals.

Both our individuals lack the proximal symphalangism and the ocular hyperopia or other visual defects that are usually present in Teunissen-Cremers patients [only one case without these signs is indeed described in the literature (Brown *et al.*,2002)]. However, in our subjects, finger motility was found to be impaired.

Pathogenic variants in the *NOG* gene produce different rare syndromes, some of them with stapes ankylosis characterized by specific phenotypic defects but also with overlapping ones, that could make a differential diagnosis difficult (Table 1).

For this reason, the unifying term *NOG*-related SSD (*NOG*-SSD) was proposed (Potti *et al.*, 2011). These syndromes are Brachydactyly type B2 (BDB2: MIM# 611377 (Lehmann *et al.*, 2007), Multiple synostoses syndrome 1 (SYNS1: MIM#186500) (Gong *et al.*, 1999; Dixon *et al.*, 2001; Declau *et al.*, 2005; Van den Ende *et al.*, 2005; Lee *et al.*, 2014), Stapes ankylosis with broad thumb and toes or Teunissen-Cremers syndrome (SABTT: MIM#184460) (Teunissen *et al.*,1990; Weekamp *et al.*, 2005; Hirshoren *et al.*, 2008), Symphalangism, proximal 1A (SYM1: MIM #185800) (Ensink *et al.*,1999; Gong *et al.*, 1999; Potti *et al.*, 2011; Yuan *et al.*, 2020), Tarsal-carpal coalition syndrome (TCC: MIM#186570) (Dixon *et al.*, 2001). All these conditions are transmitted as autosomal dominant traits, they are completely penetrant, and most of them share the presence of proximal symphalangism defined as the abnormal fusion of the proximal interphalangeal joints of hands and feet.

The *NOG* gene encodes the Noggin protein which, in dimeric structure, binds to the bone morphogenetic proteins signaling of the transforming growth factor-b superfamily (Smith and Harland, 1992; Zimmerman *et al.*, 1996; Beck *et al.*, 2001; Seemann *et al.*, 2009; Song *et al.*, 2010), inhibiting their activities. Therefore, the *NOG* gene has an important role in cartilage morphogenesis and joint formation (Brunet *et al.*, 1998). Pathogenic variants of the gene reduce the secretion of functional Noggin with an excess of bone morphogenetic proteins activity, resulting in a cartilage excess and in failure to start normal joint formation. To date, the literature reports more than 65 human pathological variations of *NOG* (Usami *et al.*, 2012; Ishino *et al.*, 2015; Takano *et al.*, 2016; Ma *et al.*, 2019; Yuan *et al.*, 2020).

In a subject diagnosed as SABTT, no pathogenic variant was found in the *NOG* gene, (nor in other possibly interested genes, such as GDF5 or FGF9) suggesting the possibility of genetic heterogeneity (Ganaha *et al.*, 2015).

In general, no strict correlation between pathological variants and specific phenotypes was found. Several reports underline that the same *NOG* sequence pathogenic variation can produce different inter or intrafamilial phenotypes, in particular concerning the degree of joint or bone deformities (Hirshoren *et al.*, 2008; Masuda *et al.*, 2014; Ganaha *et al.*, 2015; Ishino *et al.*, 2015; Takano *et al.*, 2016; Shu *et al.*, 2019, Yu *et al.*, 2020). No definite correlation was found between the protein position in different domains and the phenotype, even if it was pointed out that in cases with stapes ankylosis without SYM1 the cysteine-rich C-terminal domain is primarily disrupted (Dixon *et al.*, 2001; Usami *et al.*, 2012; Lee *et al.*, 2014; Ganaha *et al.*, 2015; Ma *et al.*, 2019).

Finally, the disease expression does not seem connected to the type of *NOG* variant (Ma *et al.*, 2019). The same clinical picture produced by missense variants (the most frequently found ones) can also be due to completely inactivating sequence variations. In summary, it seems likely that other factors (disease-modifying genes, epigenetic variations or environmental influences) can modulate the clinical expression of *NOG* variants, determining variable phenotypes.

Even if familial stapes ankylosis detected in adulthood is more commonly due to nonsyndromic otosclerosis, it is important to collect a detailed audiological and medical history of subjects and their families, and to perform a careful physical examination looking for associated dysmorphic features. Particular attention should be paid, for instance, to the presence of even mild and not easily recognizable bony abnormalities of hands, feet and spine, in order not to miss syndromic conditions.

In subjects with stapes ankylosis with even minor skeletal anomalies, the analysis of the *NOG* gene is particularly useful for diagnosis purposes, whereas the examination of first-degree relatives is crucial. Moreover, the *NOG* gene analysis could be useful even to differentiate *NOG*-SSD from other syndromes (for instance Osteogenesis Imperfecta) where stapes ankylosis could be present (Usami *et al.*, 2012).

Although bone conduction hearing aids provide efficient rehabilitation for conductive hearing loss, it is important to remember that conductive hearing loss due to *NOG* variants generally benefits greatly from stapes surgery (Vincent *et al.*, 2016; Westergaard *et al.*, 2018). The surgical skills of the operator and the choice of appropriate prosthesis that can adapt to the potential anatomic anomalies of the ossicular chain present in Teunissen-Cremers syndrome/SABTT are crucial (Coombs and Bird 2016). However, the possible risks of a surgical procedure are still present, as well as the risk of bony reclosure of the oval window after surgery, and may have a major impact on the audiological outcome of the procedure.

Conclusion

This report adds a novel pathogenic variant of *NOG*, causing a TCS/SABTT phenotype, and provides further

data about *NOG*-associated phenotypes and intrafamilial variability.

In case of familial history of congenital conductive hearing loss, radiologic imaging is required to evaluate the possible presence of middle ear anomalies and stapes fixation signs. This is crucial for surgical planning, and it is useful for a following genetic evaluation that should be recommended for the non-negligible risk of underlying syndromic conditions.

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An informed consent form was obtained from all the participants whose identifying information is included in this article.

No non-human animal studies were carried out by the authors for the purpose of this article.

Informed consent has been obtained from patients that grants permission for the publication of images as part of this work.

G.P. and A.S. confirm that they had full access to all data in the study, and take responsibility for the integrity and accuracy of the data analysis. All of the authors gave final approval for this version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest

There are no conflicts of interest.

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