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Short Communication

A Turkish family with Nance-Horan syndrome due to a novel mutation

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ABSTRACT

Nance-Horan Syndrome (NHS) is a rare X-linked syndrome characterized by congenital cataract which leads to profound vision loss, characteristic dysmorphic features and specific dental anomalies. Microcornea, microphthalmia and mild or moderate mental retardation may accompany these features. Heterozygous females often manifest similarly but with less severe features than affected males. We describe two brothers who have the NHS phenotype and their carrier mother who had microcornea but not cataract. We identified a previously unreported frameshift mutation (c.558insA) in exon 1 of the *NHS* gene in these patients and their mother which is predicted to result in the incorporation of 11 aberrant amino acids prior to a stop codon (p.E186Efs11X). We also discussed genotype–phenotype correlation according to relevant literature.

1. Introduction

Nance-Horan Syndrome (NHS) [MIM 302350], also known as cataract-oto-dental syndrome (Sonoda, 2001), X-linked cataract-dental syndrome (Stambolian et al., 1990), or X-linked congenital cataracts and microcornea (Ding et al., 2009), was first described in 1974, in Australia (Horan and Billson, 1974) and the United States (Nance et al., 1974), as a rare X-linked syndrome involving congenital cataract and dental anomalies (Burdon et al., 2003). Affected males have severe bilateral congenital dense nuclear cataracts which lead to profound vision loss and usually require surgery at an early age (Burdon et al., 2003; Florijn et al., 2006; Huang et al., 2006). Microcornea and microphthalmia have also been reported in some families (Florijn et al., 2006; Huang et al., 2006). Characteristic facial features such as large anteverted and simple pinnae, long-narrow face, prominent nose and nasal bridge, and distinctive dental anomalies such as supernumerary incisors and crown shaped permanent teeth are seen in affected males (Burdon et al., 2003; Ding et al., 2009). In addition, approximately 30% of cases have developmental delay (Brooks et al., 2004). Mild or moderate mental handicap was also a mentioned feature (Toutain et al., 1997a). Females who are carrier of the X-linked gene display milder variable symptoms of disease with lens opacities often involving the posterior Y sutures, and on occasion other associated anomalies described (Horan and Billson, 1974). To date 26 mutations in the *NHS* gene have been described (Brooks et al., 2004; Burdon et al., 2003; Chograni et al., 2011; Coccia et al., 2009; Florijn et al., 2006; Huang et al., 2007; Ramprasad et al., 2005; Reches et al., 2007; Sharma et al., 2008).

We describe two brothers and their carrier mother who has the NHS phenotype as a result of a novel mutation in the *NHS* gene. In addition we discussed genotype–phenotype correlation according to relevant literature.

2. Material and methods

2.1. Patient data

Both patients (brothers) were born spontaneously after an uneventful pregnancy. They had healthy and non-consanguineous Turkish parents. At the time of their births, the mother's age was 32 years and 36, respectively. The family history was unremarkable, except the mother who had microcornea and diastema. Pedigree analysis indicated X-linked recessive inheritance (Fig. 1). The demographic

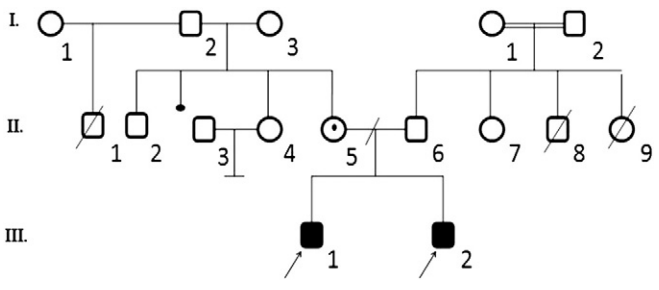

Fig. 1. Family pedigree with Nance Horan Syndrome.

Abbreviations: NHS, Nance-Horan Syndrome; *NHS*, *Nance-Horan Syndrome* gene; NHS-A, *Nance-Horan Syndrome* gene isoform A; NHS-B, *Nance-Horan Syndrome* gene isoform B; NHS-C, *Nance-Horan Syndrome* gene isoform C; MR, mental retardation.

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Table 1
The demographic features of patients. The percentiles are given in brackets.

Manifestations			Case 1	Case 2
Age			7.5 years old male	9 years old male
	At birth	Weight	3500 g (50–75th)	4000 g (90th)
		Height	50 cm (50th)	50 cm (50th)
		Head circumference	35 cm (50–75th)	35 cm (50–75th)
	At the time of presentation	Weight	30 kg (50–75th)	28 kg (75–90th)
		Height	139.5 cm (90th)	132 cm (90–97th)
		Head circumference	55 cm (75th)	53.5 cm (50–75th)
Psychomotor development		Neonatal hypotonia	Present	Present
		Head control	6 months of age	6 months of age
		Walking without help	18 months of age	12 months of age
		Speech with one word sentences	2 years	1.5–2 years
		Urine and feces control	3 years	2 years
		Enuresis nocturna	Up to 6 years	Still exist
Intellectual Function		IQ	Normal	Normal
Operation			Two times congenital cataract in his left eye	
Karyotype			46,XY	46,XY

features and developmental history of the patients are summarized in Table 1 and facial features are shown in Fig. 2.

Characteristic clinical findings and comparison with previously reported patients with NHS are shown in Table 2.

2.2. Molecular analysis

Written informed consent was obtained from the patients' guardians for genetic analysis. Genomic DNA was extracted by the salting out method from peripheral blood leukocytes (Aljanabi and Martinez, 1997). All ten exons and the flanking regions of the *NHS* gene were screened for mutations as described previously (Toutain et al., 1997b). Sequence analysis was carried out using an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems) automated DNA sequencer and protocols provided by the manufacturer. We identified a causative hemizygous *NHS* gene mutation c.558insA where position +1 is the first base of the initiation codon leading to a p.E186Efs11X (GenBank accession number NM_198270) in exon 1 in both patients. Following the insertion, it is predicted that 11 aberrant amino acids would be incorporated prior to a stop codon. The mother is heterozygous for the same mutation (Fig. 3).

3. Discussion

The NHS gene, which is mapped to Xp21.1-p22.3 comprises at least 10 exons that encompass approximately 650 kb of genomic DNA, and at least three isoforms of NHS transcripts have been generated by alternative splicing (Burdon et al., 2003; Lewis et al., 1990; Sharma et al., 2006, 2009; Stambolian et al., 1990). Isoform A (NHS-A), the major isoform, has eight exons encoding a 1630-amino acid protein. Isoform B (NHS-B) is transcribed from exon 1b and translated from exon 4 encoding a 1335-amino acid protein. Isoform C (NHS-C) is transcribed and translated from exon 1a coding for a 1453-amino acid protein (Burdon et al., 2003; Florijn et al., 2006; Sharma et al., 2006). Isoform A is known to be important in the pathogenesis of NHS, because patient mutations identified in exon 1 are only predicted to affect this isoform (Brooks et al., 2004; Burdon et al., 2003). NHS protein has an important regulatory role in the development of ocular, craniofacial and neural tissues. It has been demonstrated that NHS protein is expressed in midbrain, lens, tooth and retina (Burdon et al., 2003; Sharma et al., 2006). There is allelic heterogeneity in NHS as well as variability of clinical phenotype (Liao et al., 2011).

We describe the first Turkish NHS patients, specifically two brothers who have a typical NHS phenotype. We identified a previously unreported frameshift mutation in exon 1 of the *NHS* gene in these patients and their mother which is predicted to result in the incorporation of 11 aberrant amino acids prior to a stop codon (p.E186Efs11X). This mutation may lead to nonsense mediated decay. To date, 26 pathogenic mutations have been identified in 4 coding exons and 2 introns of the NHS gene (Brooks et al., 2004; Burdon et al., 2003; Chograni et al., 2011; Coccia et al., 2009; Florijn et al., 2006; Huang et al., 2007; Ramprasad et al., 2005; Reches et al., 2007; Sharma et al., 2008).

The most frequent mutations associated with NHS are nonsense mutations, all of which are predicted to result in a truncated NHS protein (Burdon et al., 2003; Chograni et al., 2011; Coccia et al., 2009; Florijn et al., 2006; Huang et al., 2007; Ramprasad et al., 2005; Reches et al., 2007; Sharma et al., 2008) and one missense mutation

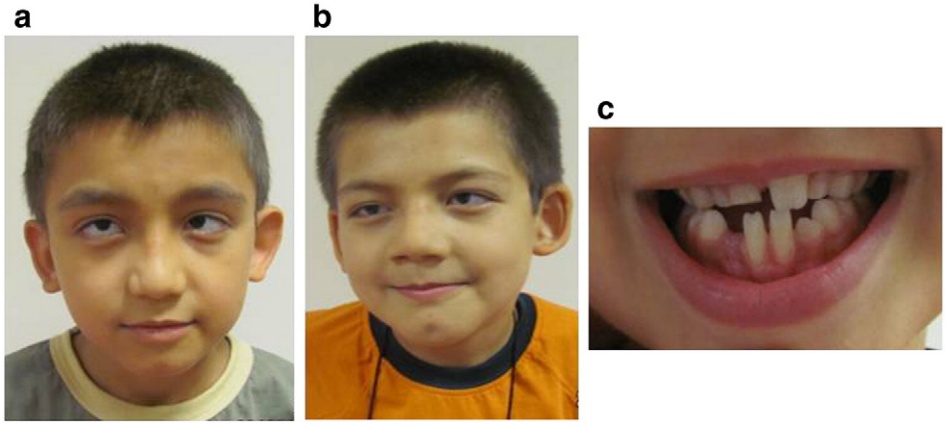

Fig. 2. a. Older brother (III-1); b. Younger brother (III-2); c. Screwdriver shaped incisors and diastema of III-2.