

## CASE REPORT

# Prenatal detection of congenital bilateral cataract leading to the diagnosis of Nance-Horan syndrome in the extended family

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**Objectives** To describe a family in which it was possible to perform prenatal diagnosis of Nance-Horan Syndrome (NHS).

**Methods** The fetus was evaluated by 2nd trimester ultrasound. The family underwent genetic counseling and ophthalmologic evaluation. The *NHS* gene was sequenced.

**Results** Ultrasound demonstrated fetal bilateral congenital cataract. Clinical evaluation revealed other family members with cataract, leading to the diagnosis of NHS in the family. Sequencing confirmed a frameshift mutation (3908del11bp) in the *NHS* gene.

**Conclusion** Evaluation of prenatally diagnosed congenital cataract should include a multidisciplinary approach, combining experience and input from sonographer, clinical geneticist, ophthalmologist, and molecular geneticist Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: prenatal diagnosis; congenital cataract; Nance-Horan syndrome

## CASE

The patient (Individual II:2, Figure 1), a healthy 27-year-old woman, was in her second pregnancy (III:1). She previously had a spontaneous miscarriage. The first half of the pregnancy was uneventful, including genetic screening tests, serology, and second-trimester maternal serum biochemical screening.

Sonographic examinations were performed using high-resolution equipment (4–8-MHz transabdominal transducers Voluson 730 Expert System, GE Medical Systems, Milwaukee, WI). Nuchal translucency measurement was 1.4 mm. An early detailed sonographic system scan, performed at 16 weeks of gestation, revealed no malformations and the fetus was appropriate for the gestational age. Both orbits and lenses appeared equal in size, with normal opacity. However, a detailed follow-up scan performed at 24 weeks, demonstrated bilateral hyperechogenic lenses, suggestive of bilateral cataract (Figure 2). No blood

flow was demonstrated in the hyaloid artery. Normal eye movement was observed. No other malformations were noted and the fetus was appropriate for gestational age.

Family history revealed that her 23-year-old brother (II:4) has congenital bilateral cataract. He was born prematurely at 32 weeks gestation, a co-twin in a monozygotic pregnancy. He was delivered by emergency cesarean delivery due to apparent fetal distress and suspected twin-to-twin transfusion syndrome. During childhood, he underwent a series of operations for congenital cataract in both eyes, with suboptimal results. He was evaluated and treated by numerous experts from several countries.

Major psychomotor milestones were characterized by some developmental delay, and remedial education was provided. Currently, he has normal intelligence and is a volunteer in the military.

His co-twin (II:3) died from complications of prematurity a few days after delivery. Autopsy revealed that he also had bilateral congenital cataracts, but no other malformations. At the time, the congenital cataract in both co-twins was attributed to viral infection *in utero*, possibly rubella.

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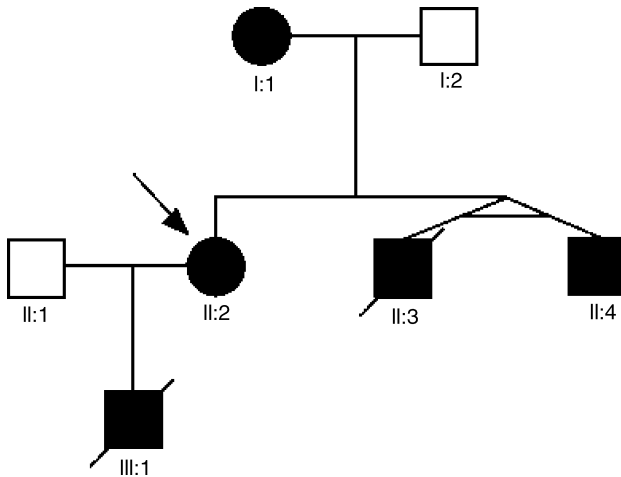


Figure 1—Three-generation pedigree. Circles represent females, squares males. Solid symbols indicate affected individuals. The proband II:2 is marked with an arrow. The affection status of the deceased co-twin is not confirmed molecularly but is suspected to be affected based on cataract at autopsy

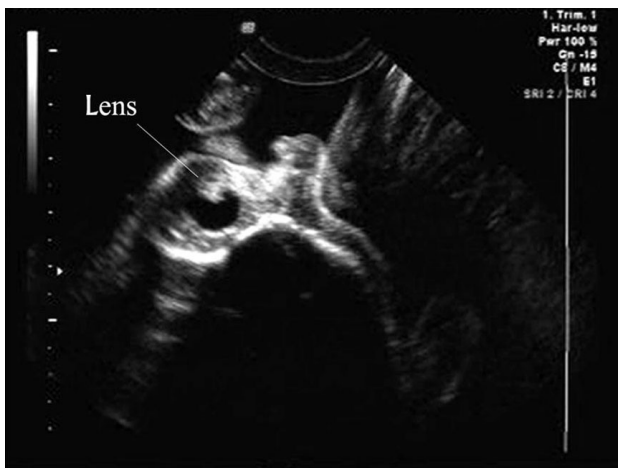


Figure 2—Transvaginal sonographic image showing homogeneous opacity of the lens

On examination, the affected brother (II:4) was noted to have high myopia, nystagmus, strabismus, microphthalmia and postsurgical corneal scarring. Additional manifestations include supernumerary, abnormally shaped teeth, a thin long face, prominent jaw, dry palms and relatively short fingers. These craniofacial findings were initially attributed to prematurity (Cartledge *et al.*, 1988)

Given the presentation of severe congenital bilateral cataracts in a male fetus and 2 maternally related male co-twins, a hereditary form of cataract, possibly an X-linked condition, was suspected. The pregnant patient and her mother (I:1) were therefore referred for ophthalmologic examination, demonstrating in both a characteristic Y-suture cataract (Figure 3). A 3-generation pedigree was suggestive of X-linked semidominant mode of inheritance, with partial manifestations in obligate

female carriers (Figure 1). An OMIM search was suggestive of X-linked congenital cataract, possibly Nance-Horan syndrome (Horan, 1974; Nance *et al.*, 1974). Following extensive genetic counseling, the couple opted for termination of pregnancy, which was carried out at 26 weeks of gestation. On autopsy, the male fetus was appropriate for gestational age. Bilateral cataracts were observed. A DNA sample was obtained from the fetus for further investigation.

Subsequently, DNA samples from the affected brother and fetus, mother and maternal grandmother were analyzed for mutations in the coding regions of the *NHS* gene on the X chromosome, which is responsible for the Nance-Horan syndrome (Burdon *et al.*, 2003). Complete sequencing revealed a novel 11 bp deletion in exon 6 of the *NHS* gene (designated 3908del11 bp) in both affected male individuals as well as both mildly affected obligate carriers. This mutation disrupts the reading frame, introducing a frameshift at amino acid Ile1302 and causes a premature truncation of the protein seven residues later.

## COMMENT

Cataract is a major cause of blindness throughout the world. It is defined as opacity of the lens, although clinically it usually refers to opacities that reduce visual acuity. Most cataracts occur in the elderly, but a small percentage of the pediatric population is also affected. Prenatal diagnosis of congenital cataract was reported as early as 14 weeks of gestation (Mashiach *et al.*, 2004). The incidence of congenital cataract is 1–6 per 10 000 live births (Francis *et al.*, 2000). There are many different causes of congenital cataract, including intrauterine infections (i.e. rubella), metabolic disorders, trauma, medication and chromosomal abnormalities. Cataracts may also be inherited as an isolated ocular abnormality, or as part of a genetic syndrome. The inherited form is usually autosomal dominant but both autosomal recessive and X-linked forms have been described.

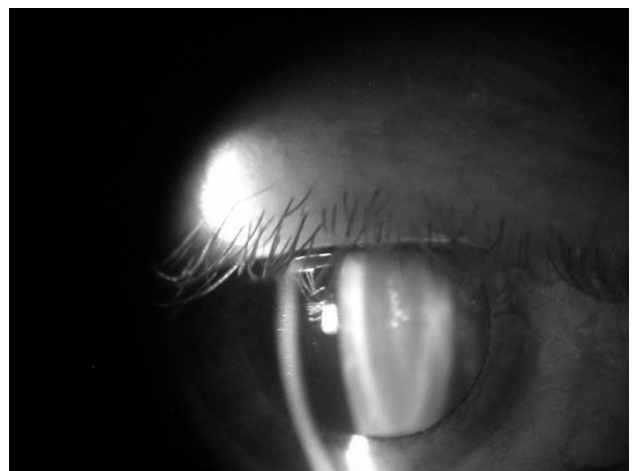


Figure 3—Ophthalmological examination of the maternal grandmother demonstrating a Y-suture cataract

Several X-linked conditions are associated with congenital bilateral cataract including Lenz syndrome, Lowe syndrome and the Nance-Horan syndrome.

The Nance-Horan syndrome was first described in 1974 by Nance (Nance *et al.*, 1974) and Horan (Horan, 1974) as an X-linked condition manifested by congenital bilateral cataract and dental anomalies. Males with the Nance-Horan syndrome have severe, bilateral congenital cataracts, as well as other ocular abnormalities: microcornea (<10 mm diameter), microphthalmia, nystagmus, esotropia and pupils unresponsive to direct or consensual light. Affected males usually require cataract surgery within the first few months of life and most will be considered legally blind. Younger female carriers frequently have localized posterior inverted Y-suture lens opacities with little or no visual loss. The lens opacities in such female carriers can be of unequal density and may progress to true cataract later in life (Bixler *et al.*, 1984). Intrafamilial and individual interocular variation in expression is possible (Van Dorp and Delleman, 1979).

The characteristic dental findings in Nance-Horan syndrome help distinguish this condition from other forms of cataract. These include, mesiodents (a supernumerary centrally situated upper incisor), cone-shaped or tapering of the incisors ('screwdriver' shape). Dental anomalies have also been described in female carriers, albeit to a lesser extent.

Affected males have distinct facial features, including prominent, anteverted pinnae and prominent ears and nasal bridge. The fingers may be broad and/or short. Developmental delay, in areas of fine gross motor, social, language skills have all been described (Ian, 1990). Mental retardation is also possible in some affected individuals, whereas others, even within the same family, may be of normal intelligence. The risk of mild intellectual handicap in males is probably about 20–30% (Bixler *et al.*, 1984; Toutain *et al.*, 1997; Brooks *et al.*, 2004). There is no report of intellectual deficit in female carriers.

In 2003, Burdon *et al.* reported that mutations in the *NHS* gene are responsible for this disorder (Burdon *et al.*, 2003). *NHS* is a large gene of unknown function. Studies in animals support a regulatory role for the *NHS* protein in the development of ocular, craniofacial, and neural tissue. Conservation of the gene in other vertebrates such as mouse, rat and zebra-fish, supports an important role for *NHS* in development and regulation of eye, tooth, brain and craniofacial development (Burdon).

This is, to the best of our knowledge, the first report of prenatal diagnosis of the Nance-Horan syndrome. The frameshift mutation in the *NHS* gene (3908del11bp) is also identified here for the first time.

The discovery of the causative *NHS* mutation allowed the establishment of a single-cell multiplex nested Polymerase chain reaction, which could then be used for preimplantation genetic diagnosis (PGD). Following the

first PGD cycle, the patient conceived and is now awaiting confirmation by amniocentesis.

In the case described here, the cooperation between sonographer, clinical geneticist, ophthalmologist, pathologist and molecular geneticist, enabled the prenatal diagnosis of the Nance-Horan syndrome, unveiling a previously undiagnosed familial condition, and allowed up-to-date reproductive options. This highlights the importance of such a multidisciplinary approach in the management of prenatally diagnosed malformations.

#### ACKNOWLEDGEMENT

We thank the family for their trust, cooperation and support

#### Electronic Database Information

Accession numbers and URLs for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), [http://www.ncbi.nlm.nih.gov/Omim/\[Nance-Horan Syndrome \(MIM#302350\), cataract, congenital total, with posterior sutural opacities in heterozygotes; CCT \(MIM #302200\)\]](http://www.ncbi.nlm.nih.gov/Omim/[Nance-Horan%20Syndrome%20(MIM#302350),%20cataract,%20congenital%20total,%20with%20posterior%20sutural%20opacities%20in%20heterozygotes;%20CCT%20(MIM%20#302200)]).

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