Syndrome of the month

Edited by D Donnai and R Winter

The Nance-Horan syndrome

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In 1974 Nance *et al*¹ and Horan and Billson² described a type of uncommon X linked congenital cataract, distinctive because of the striking associated dental features. Possible earlier reports of the so-called 'Nance-Horan syndrome' are incomplete and vague, and only a further three families have been described in the past two decades. Van Dorp and Delleman³ were able to confirm and broaden the clinical description of the ophthalmological and facial manifestations and Bixler *et al*⁴ showed that the dental and ophthalmological features in female carriers could be more severe than previously recognised. We report a family (fig 1, table) who further illustrate the Nance-Horan syndrome. The male proband was developmentally delayed and had a dysmorphic facies, features which we believe are integral parts of the syndrome spectrum. Recently it has been suggested that the gene locus is in the Xp21.1-p22.3 region.⁵

Clinical features

Cataracts in association with the distinctive dental findings and characteristic facial features form the major features necessary to diagnose the Nance-Horan syndrome (table).

Ophthalmological features

X linked cataracts account for a minority of hereditary cataracts. In males with Nance-Horan syndrome the

Figure 1 Family pedigree.

Frequency of features in the Nance-Horan syndrome*.

	Previous reports		This family	
	Male	Female	Male	Female
Ocular				
Cataract	100%	38%	+	+
Microcornea	65%	NR	+	-
Posterior suture opacity	NR	75%	+	-
Dental				
Mesiodens	65%	80%	-	+
Tapering incisor crown	>50%	100%	+	+
Incisal notching	>65%	NR	+	+
Diastema	>50%	80%	+	+
Facial				
Prominent ears	94%	8%	+	+
Long face	+	NR	+	+
Prominent nasal bridge and nose	+	NR	+	+
Intellect				
Diminished	18%	NR	+	-
Skeletal				
Broad fingers	+	NR	+	-

*Approximate rates only because of incomplete reporting. Underestimation owing to edentulous subjects and probable under-reporting. NR=not reported.

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cataracts are severe, bilateral, and congenital. Microcornea (<10 mm diameter), microphthalmia, and nystagmus are usually present; this was true of our proband and the irides were pale and vascular.¹⁻³ Younger carrier females most frequently have localised posterior sutural lens opacities and normal vision is usually retained. These lens opacities can be of unequal density and can progress to true cataract formation that affects vision in later life. The adult female in this report (II.1, aged 43 years) had punctate lens opacities affecting the anterior nucleus and not restricted to the sutural area. The degree of eye involvement has been noted to parallel dental manifestations²⁻⁴ in both sexes and interfamilial variation in expression is likely.³

Dental features

It is most often the dental findings that make it possible to distinguish this syndrome from other forms of cataract. Mesiodens, that is, peg shaped, supernumerary teeth, most frequently medial and in the upper jaw, were present in several reported males. The proband's mother in our family had a single, characteristically placed mesioden as part of her primary dentition, but does not recall its fate. Characteristically, the incisors show tapering of the crown or are peg shaped, with a vertical notch ('screwdriver' shaped) and diastema. The close similarity to the incisor shape seen in congenital syphilis was noted by the original authors and described as Hutchinsonian.^{1,2} In our patient this provided us with the diagnostic clue (figs 2 and 3).

Facial features

Nance *et al*¹ described all affected males as having anteverted pinnae which are less frequently observed in females.⁴ The ears were long (II.1 and III.5, >97th centile) and prominent in our patients. That there is a characteristic facial appearance in Nance-Horan

Figure 2 The proband. The teeth show tapering of the crown with a vertical notch ('screwdriver' form) and diastema.

Figure 3 Mother of the proband. Despite extensive therapy, upper teeth still display diastema, tapering, and some notching, particularly of the incisors.

Figure 4 Mother and child with Nance-Horan syndrome. Major features evident are long facies with large, prominent ears, nose, and nasal bridge. III.5 has microphthalmos and severe congenital cataract.

syndrome is evident in our family (fig 4) and supported by reports that affected subjects have long faces and appear different from unaffected family members. The nasal bridge and nose are prominent, with synophrys in some subjects.^{2,3} This appearance in our index patient led to fragile X chromosome studies, which proved negative.

Intellect

Intellect has not been commented upon in the other

published reports, but it is noteworthy that four subjects, including our proband, that is over 20% of males reported with the Nance-Horan syndrome, are intellectually handicapped or have developmental delay.^{1 3 4} At the age of 2½ the proband (III.5) has significant delay in areas of fine/gross motor, social, language, and self help skills. He has no speech, poor concentration, is not walking, and has much self-stimulatory behaviour with vision assessed as 'adequate'. It is suspected that long term follow up will indicate mild to moderate intellectual deficit. There is no report of intellectual deficit in carrier females.

Skeletal features

Broad or short fingers without brachydactyly have been described in Nance-Horan syndrome, but there has been no confirmation of short fourth metacarpals as reported by Nance *et al.*¹ Bixler *et al.*⁴ commented that this is probably not a feature of the condition and it was not evident clinically or radiologically in our patients. Alkaline phosphatase levels were also normal.

Differential diagnosis

Other syndromes with X linked patterns of inheritance include congenital cataract with microcornea or microphthalmos, but none have the associated characteristic dental findings most apparent in males and evident in female Nance-Horan syndrome carriers reported so far, often to a minor degree.⁴⁻⁸ The dental abnormalities may be confused with those seen in congenital syphilis, so rare in modern times, but are unlikely to be confused with the pegged teeth of ectodermal dysplasia. The family described by Goldberg and McKusick⁶ featured dental diastema, possible tapering of incisors, and simple prominent ears. Only one affected male had cataracts, but all had colobomatous microphthalmos with marked microcornea and blepharoptosis. Nystagmus, esotropia, and pupils unresponsive to direct or consensual light were observed. Other features included microcephaly with intellectual retardation, short stature, kyphoscoliosis, and pes cavus. Females examined were normal.⁵

Lenz also described an X linked form of microphthalmos with dental anomalies and multiple congenital malformations which included micro-

cephaly, digital defects, and vertebral, renal, and heart anomalies.⁶

Counselling

Those families so far described with Nance-Horan syndrome most strongly support X linked recessive inheritance. Firstly, manifestations in the heterozygous female have been less marked than in the hemizygous male. There has been no example of male to male transmission. Segregation ratios in 67 persons from five pedigrees also favour X linked recessive inheritance. Linkage analysis of Nance-Horan syndrome segregating in four multigenerational families using X chromosome RFLP markers *DXS143* and *DXS84* (also *DXS43*, *DXS41*, *DXS67*) obtained peak lod scores of 3.08 at $\theta=0.05$ and 4.07 at $\theta=0.05$, respectively. These results place the gene locus broadly in the Xp21.1 and Xp22.3 region.⁵

Males with Nance-Horan syndrome generally have severe visual problems and most will be legally blind. The risk of mild intellectual handicap in males is probably about 20%. Bixler *et al.*⁴ have suggested that as the syndrome becomes better delineated it may prove to be a more common condition than currently recognised.⁴

The authors would like to thank Mrs Sue Conlan for her considerable assistance in preparing this manuscript.

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