Congenital nystagmus cosegregating with a balanced 7;15 translocation

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Abstract

We report a family in which autosomal dominant congenital nystagmus cosegregates with a balanced 7;15 translocation. Ophthalmic investigation showed predominantly horizontal nystagmus with a small rotatory component and no significant loss of visual function. This finding suggests a possible localisation for autosomal dominant congenital nystagmus (McKusick 164100).

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Congenital nystagmus is not uncommon in the population. The population frequency based on a survey of army recruits was estimated to be 1 in 6500, but in a population based study of school children in Sweden, it was estimated to be as frequent as 1 in 1500. In both these studies, the frequency in males was significantly higher than in females. In the Swedish study analysis of family data suggested X linked recessive inheritance to be the most frequent mode of inheritance.

Congenital nystagmus may have a variety of different aetologies and if inherited may show X linked recessive, autosomal dominant, or autosomal recessive inheritance. Virtually all of the reports of autosomal dominant inheritance predate the development of molecular genetics and only one study has attempted linkage data with common blood group polymorphisms.

In this report a family is described with autosomal dominant congenital nystagmus cosegregating with a balanced 7;15 translocation.

Case report

The couple (IV.2 and IV.3, fig 1) presented at the genetic clinic with two spontaneous miscarriages. No chromosomes had been cultured from the fetal material. On examination of the parents' karyotypes, it was found that IV.2 had a balanced 7;15 translocation (46,XY,t(7;15)(p11.2;q11.2)) (fig 2). He had also had congenital nystagmus. Further investigation of the family showed that III.2 also had the same balanced translocation and a rapid horizontal nystagmus without significant visual defect. The other family members tested showed normal chromosome patterns. The history of congenital nystagmus in this family extended over four generations with male to male transmission, indicating autosomal dominant inheritance, but the proband's grandfather and great grandfather were dead and therefore not available for further electrophysiological or genetic study.

OPHTHALMIC STUDIES

Patient IV.2 has had nystagmus from birth, but this has not significantly interfered with his vision. His visual acuity was 6/9 in each eye. Colour vision was normal. Slit lamp examination and fundoscopy showed no evidence of ocular albinism or abnormal retinal pigmentation. The optic discs were normal in size and colour. The nystagmus was evaluated by electronystagmography using external electrodes and analysed by Fourier analysis. This showed predominantly horizontal nystagmus with a small rotatory component. The null point of the nystagmus was straight ahead. The frequency of nystagmus was 3.5 Hz in the midline and 6 Hz in gaze to either side.

Patient III.2 also had nystagmus from birth. Her visual acuity was 6/9 in each eye and again ophthalmic examination was normal. Electronystagmography showed a similar 4 Hz horizontal nystagmus with a small rotatory component.

Figure 1 Pedigree showing inheritance of balanced chromosome translocation and congenital nystagmus.
IV.2. Congenital nystagmus cosegregating with a balanced 7;15 translocation

Figure 2  Balanced 7;15 translocation (46,XY,t(7;15)(p11.2;q11.2)) in subject 4V.2.

discussion

Nystagmus is a disorder of visual fixation in which the relationship between the visual system and the object it fixes on is disturbed. It may occur as a physiological adaptation to rapidly moving images in the visual field, for example, when looking out of a train window, but in the pathological setting is an attempt to correct a defect in the visual path or the neural pathways controlling eye movement.

The classification of nystagmus depends on two approaches. The first classification uses a functional assessment of the eye movements and the second classification is based on aetiology. The eye movements in nystagmus may be (1) horizontal, (2) vertical, (3) rotatory, or (4) non-directional. Horizontal nystagmus is further subdivided into pendular nystagmus, in which the oscillations are of equal amplitude, and jerk nystagmus, in which there is a slow phase where the eyes deviate from the fixation point and a rapid phase where the eyes are brought quickly back to fixation point. The amplitude of the oscillations in jerk nystagmus will vary depending on the position of the eyes and is minimal at one specific point, the null region. Patients with jerk nystagmus tilt or turn their heads in order to place the eyes in the null region and achieve maximum visual acuity. In some patients with nystagmus, the rapidly corrective phase of the eye movements may compensate sufficiently so that there is no impairment in visual acuity. However, in others there may be considerable decrease in visual acuity. Non-directional nystagmus or roving eye movements are seen in subjects with virtually total loss of vision and represents the uncoupling of the visual input from the motor control.

The aetiological classification aims to separate those causes that are congenital from those which are acquired and to divide each group into those which affect the sensory input and those which affect the neural control of eye movements. The causes of congenital nystagmus include albinism, retinal dystrophy or degeneration, congenital achromatopsia, cataract, and optic nerve hypoplasia. There are a significant number of inherited eye disorders or syndromes involving the eye in which nystagmus may be a feature. Some of these, such as ocular albinism, are well defined and their loci have been mapped, but this has not yet been achieved for the familial forms of congenital nystagmus in which there is no sensory abnormality.

The limitations of the present systems of classification should be recognised. It has been recognised that there may be intrafamilial variation in pattern of eye movements in inherited congenital nystagmus. It is also difficult to separate the motor and sensory components as these are mutually dependent. There is, for example, electrophysiological evidence that oculocutaneous albinism in which there is hypopigmentation of the retina also affects the development and integrity of the neural connections in the optic radiation in the occipital cortex. In McKusick's *Mendelian inheritance in man* there are three patterns of inheritance of isolated nystagmus, autosomal dominant (164100), autosomal recessive (257400), and X linked recessive (310700). It is usually suggested that X linked inheritance is the most frequent pattern. Forsman2 ascertainment 26 families in Southern Sweden and found 17 families with multiple affected members. Of these families, three showed clear X linked recessive inheritance with passage through unaffected female carriers, and in the remaining 14 families with multiply affected family members, it was proposed that there was sex linked, irregular, dominant transmission, since there was no male to male transmission found. It should, however, be noted that the sex ratio for affected members was equal in many of these dominant families and autosomal dominant inheritance with variable expressivity is an alternative explanation. A search of earlier published reports shows a number of extensive autosomal dominant families with male to male transmission. One aspect that may make the mode of transmission difficult to determine is the variable expressivity. Patients with congenital nystagmus may be asymptomatic and may not have sought medical attention. If the null region is wide, it will only show nystagmus at the extremes of visual gaze. On occasions, the nystagmus is only recognised by ophthalmoscopy.

The discovery of a balanced translocation cosegregating with a single gene disorder offers a significant clue for gene localisation. There may be more than one locus involved in autosomal dominant congenital nystagmus as the delicate balance of gaze fixation can be disrupted at many different points in the neural pathway. There has been one previous report of a balanced 5;16 translocation associated with familial nystagmus and hypoplasia of the macula. In the present report, the congenital nystagmus is not associated with any visual deficit and presumably reflects a predominantly motor defect in the neural integration of gaze fixation.

We would like to acknowledge the cooperation we have received from the family in the study, the cytogenetic analysis by Dr John Taylor, and also financial assistance from Guide Dogs...
For The Blind to support gene mapping of autosomal dominant nystagmus.

1 Hemmes GC, Over hereditaire nystagmus. Wageningen: H Veerman & Zonen, 1924.

Corrections

In the paper by Richards et al on 'Detailed genetic mapping of the von Hippel-Lindau disease tumour suppressor gene' (J Med Genet 1993;30:104-7), an important collaborator, Dr Per Enblad, was inadvertently omitted from the authorship. The correct authorship is as follows.


Cambridge University Department of Pathology, Cambridge, UK; *Laboratory of Immunobiology, National Cancer Institute, Frederick Cancer Research Facility, Frederick, USA; †Erasmus University, Rotterdam, The Netherlands; ‡University of Uppsala, Sweden; ¶Division of Community Medicine, Memorial University of Newfoundland, Canada; ‖Yorkshire Regional Genetics Service and ICRF Genetic Epidemiology Laboratory, Leeds, UK; *Surgery Branch, National Cancer Institute, USA.

In the paper by Padayachee et al on 'Mapping of the X linked form of hyper IgM syndrome (HIGM1)' (J Med Genet 1992;30:202-5), the primer sequence for DXS102 was referenced Luty et al. This is incorrect and should be:

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