Identification of a key recombinant which assigns the incomplete congenital stationary night blindness gene proximal to MAOB

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Abstract
The gene for complete congenital stationary night blindness (CSNB1) has been assigned to the Xp11.3 region. However, little evidence has been provided for the assignment of the incomplete congenital stationary night blindness gene (CSNB2). Here we present the clinical and molecular data from a CSNB2 family which show a key recombinant assigning the CSNB2 gene proximal to MAOB.

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Congenital stationary night blindness is a non-progressive disturbance of night vision which occurs in an autosomal dominant, autosomal recessive, and X linked fashion. In contrast with the autosomal forms, the X linked form of CSNB (CSNBX) is frequently associated with high myopia, resulting in loss of visual acuity.

Miyake et al suggested that CSNBX can be divided into a "complete" and an "incomplete" type. The complete type lacks rod function by ERG and dark adaptometry, and myopia is usually severe. The incomplete type shows some rod function in scotopic testing and dark adaptometry, but also impairment of cone function. The refraction error ranges from moderate myopia to hyperopia.

The gene for complete congenital stationary night blindness (CSNB1) has been assigned to proximal Xp by linkage analysis. In a possible CSNB2 family, clinically described by Khouri et al, Musarella et al assigned CSNB2 proximal to DXS84 by recombination analysis.

Here we describe the clinical and molecular data in a CSNB2 family (according to the criteria of Miyake et al), which refines the localisation of the CSNB2 gene.

Materials and methods
PATIENTS
All patients underwent ophthalmological examination, including refraction, determination of visual acuity, slit lamp examination, and funduscopy. Colour vision was tested with Ishihara plates, AO-HRR plates, the tritan (F2) plate, and the Farnsworth Standard Panel D-15 in illuminant C.

Dark adaptation curves were obtained with the Goldmann-Weekers dark adaptermeter. Full field electoretinography (ERG) was recorded in three patients (III.2, III.5, and IV.1) in strict accordance with the guidelines of the International Standardization Committee (1989). For patient III.1 ERG recording was performed some years ago with another recording device: the results for this patient could not completely be compared with those obtained in the others.

LINKAGE ANALYSIS
Southern and PCR analyses were essentially carried out as previously described. Details concerning probes and primers used are described elsewhere. Statistical analyses were carried out using the computer program package LINKAGE 5.0.3. A gene frequency of 0.0001 was used. Penetrance values for carriers were set to 0.00.

Results
CLINICAL ASSESSMENT
Three patients (III.2, III.5, IV.1) showed a biphatic dark adaptation curve with a raised threshold of 1 or 2 log units (fig 1). The biphatic dark adaptation curve is characteristic of incomplete congenital stationary night blindness compared to the complete form in which a monophasic adaptation curve can be observed.

The single bright flash ERG in these patients showed a normal a wave and a reduced b wave (fig 2). The ratio of b wave to a wave was below 1:0, indicating a electronegative ERG. Oscillatory potentials were detectable, although abnormal in shape. The rod ERG showed a reduced, but detectable b wave. The b wave of the cone ERG was markedly depressed as were the responses to the 30 Hz flicker (fig 2). The ERG and dark adaptation curve for patient III.1, who was examined previously, showed a reduction in the amplitude of the cone responses, and the presence of some residual rod response (not shown). All patients were myopic with a range from −3.5 up to −16 dioptres, and their best corrected visual acuity was between 0.1 and 0.3. Colour vision examination showed a super-mild red-green colour deficiency.

DNA ANALYSIS
The CSNB2 family was studied with 11 DNA markers from proximal Xp and Xq, six of which yielded informative results (fig 3). Close linkage without recombination was found between CSNB2 and M276 (Zmax = 1.48) and both CA repeat polymorphisms corresponding to the DXS426 and ALAS2 loci (Zmax = 1.20).
A key recombinant assigns the CSNB2 gene proximal to MAOB

The segregation patterns of dys-11 and MAOB show that male patient III.2 is recombinant for these loci, while DXS426, DXS255, and ALAS2 fully cosegregate with CSNB2 (fig 3). Thus, these data suggest that CSNB2 is localised proximal to the MAOB locus. DXS7, DXS14, DXS453, DXY51X, and TIMP yielded uninformative results (not shown). DXS3 was only partially informative.

**Discussion**

Since the single bright white flash ERG showed an electronegative type in our patients, they may be classified as Schubert-Bornschein type of congenital stationary night blindness. The presence of residual rod function, as shown by the dark adaptation curves and ERG, is typical of the incomplete type of congenital stationary night blindness according to the classification of Miyake et al. In the study of Miyake et al., CSNB1 and CSNB2 appear to be distinct disease entities which do not coexist within the same pedigree. However, Pearce et al. suggested that CSNBX is a single disease entity with a highly variable clinical expression.

At present, it is also not clear whether or not CSNB2 represents the same disease entity as either CSNB1 or Aland Island eye disease (AIED). Some authors have suggested that CSNB1 and CSNB2 occur in the same family, and may therefore be different manifestations of the same disease entity. Others have suggested that CSNB2 and AIED are clinically the same disease entities. Glass et al. however, stated that the electrophysiological findings in their AIED patients were distinct from those found in both CSNB1 and CSNB2 patients. At present, all three genes (CSNB1, CSNB2, and AIED) have been assigned to approximately the same chromosomal region. CSNB1 has been localised between MAOA and DXS426. The AIED gene has been
localised to DXS7 and DXS255. Combining our CSNB2 data with the CSNB2 family data of Musarella et al., we suggest that CSNB2 is localised to proximal Xp, centromeric to MAOB, and closely linked to the DXS255 locus (θmax = 0.00, Zmax = 4.58).

Further clinical and molecular studies, especially in CSNB2 and AIED families, are needed to establish whether these diseases are allelic or represent genetically distinct disease entities.

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