Progession of phenotype in Leber’s congenital amaurosis with a mutation at the LCA5 locus

M D Mohamed, N C Topping, H Jafri, Y Raashed, M A McKibbin, C F Inglehearn

Background: Leber’s congenital amaurosis (LCA) accounts for 5% of inherited retinal disease and is usually inherited as an autosomal recessive trait. Genetic and clinical heterogeneity exist. Mutations have been described in the RPE65, CRB1, RPGRIP1, AIP1, GUCY2D, and CRX genes and other pedigrees show linkage to the LCA3 and LCA5 loci. The latter is a new locus which maps to 6q11-q16. The ocular findings and the evolution of the macula staphyloma are described in five members of a Pakistani family with consanguinity and a mutation in the LCA5 gene.

Methods: 13 family members including five affected individuals consented to DNA analysis and ocular examination including fundal photography.

Results: Ocular abnormalities are described. The most striking feature was the progression of macula abnormalities in three brothers resulting in a colobomatous appearance in the eldest compared to only mild atrophy in the youngest. The phenotypic pattern of this mutation in this Pakistani family contrasts with the “Old Order River Brethren” who were of Swiss descent, in whom the mutation was first described.

Conclusion: The evolution of a new phenotypic picture is presented to a mutation in LCA5.

Figure 1 Family tree of subjects examined.
RESULTS
Linkage to the LCA5 locus was confirmed by linkage analysis. A multipoint lod score of 3.75 was generated using microsatellite markers D6S391 and D6S968 against LCA5. All affected individuals had a non-syndromic form of LCA with normal neurological examination and intelligence. Ocular examination revealed a best corrected visual acuity of perception of light. Pendular nystagmus was present in the three adults and roving eye movements in the two children (Table 1).

The anterior segment examination was essentially normal with no evidence of keratoconus or cataract. The vitreous was clear in the younger family members but a vitreous opacity was noticed unilaterally in the three elder brothers.

Fundal examination revealed bilateral and symmetrical retinal changes. Detailed fundal examination of the youngest child was not possible in view of the roving eye movements. In the other four individuals retinal vessel attenuation was noticed and “waxy” optic nerve pallor was seen only in the oldest affected brother. Examination of the posterior pole revealed the most striking features where a progressively more severe degenerate appearance was seen. In the 6 year old child, mild perifoveal atrophic changes were noted while in the 21 year old increasing pigmentary disturbance was noted (Fig 2). In the 25 year old a definite atrophic region surrounded by pigmentary changes were seen (Fig 3), while in the 30 year old an even more marked staphylomatus region of atrophy and pigmentary change was seen (Fig 4).

Table 1  Subject characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Eye movement</th>
<th>Vitreous</th>
<th>Macula</th>
<th>White dots</th>
<th>Spiculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2</td>
<td>2</td>
<td>Roving</td>
<td>Clear</td>
<td>Not seen</td>
<td>Not seen</td>
<td>Not seen</td>
</tr>
<tr>
<td>V1</td>
<td>6</td>
<td>Roving</td>
<td>Clear</td>
<td>Minimal atrophy</td>
<td>Equatorial</td>
<td>None</td>
</tr>
<tr>
<td>IV5</td>
<td>21</td>
<td>Pendular nystagmus</td>
<td>Opacity LE</td>
<td>Atrophy</td>
<td>Equatorial</td>
<td>Equatorial</td>
</tr>
<tr>
<td>IV4</td>
<td>25</td>
<td>Pendular nystagmus</td>
<td>Opacity RE</td>
<td>Atrophy and pigment clumps</td>
<td>Equatorial</td>
<td>None</td>
</tr>
<tr>
<td>IV3</td>
<td>30</td>
<td>Pendular nystagmus</td>
<td>Opacity LE</td>
<td>Staphyloma</td>
<td>Equatorial</td>
<td>Peripheral and equatorial</td>
</tr>
</tbody>
</table>

Figure 2  Subject IV5 aged 21: minimal atrophy at macula. (A) Right fundus, (B) left fundus

Figure 3  Subject IV4 aged 25: atrophy at macula with pigment rim and clumps. (A) Right fundus, (B) left fundus

Figure 4  Subject IV3 aged 30: macula staphyloma. (A) Right fundus, (B) left fundus
Similarly in the retinal periphery progressive changes were seen. Extensive white dots at the level of the retinal pigment epithelium (RPE) were seen in the 6 year old, and these appeared to take a larger rounder appearance with a grey-green hue in the three elder brothers.

**DISCUSSION**

This report presents the progressive features of LCA seen within a single pedigree arising from a mutation in the LCA5 gene. In this family, progression with age is seen with the development of nystagmus, vitreous opacity, peripheral retinal dots and, most strikingly, the macular staphylomatous appearance. However, despite this progressive picture the visual acuity is poor from birth.

The progressive nature of the condition is well known from examination of individual cases as well as larger studies of pooled patients in whom clinical heterogeneity is seen when looking across a broad age range. Here we present a unique view into the evolution of this disorder and particularly the progressive retinal changes seen within a single pedigree. As the affected individuals are all from the same consanguineous family we assume they have the same underlying defect. We acknowledge that environmental factors may also have had a role in the pathogenesis, but in the cases presented a strong correlation between severity of ocular fundus signs and age is demonstrated. Although not all the retinal dystrophies involve retinal degeneration, the end point of the majority of these diseases is photoreceptor cell death. Animal models suggest a mechanism of death by an apoptotic pathway and not a direct consequence of the biochemical abnormality.\(^7\) So, despite many different patterns of pigmented or atrophic fundus changes, they are the result of degeneration by a single path- way. The process by which these particular patterns arise is poorly understood.

This pedigree describes changes arising from a specific mutation in a single gene. In the field of retinal dystrophies, allelic variation is common resulting in different diseases arising from different mutations within a single gene. This is highlighted by the only other report of Leber’s congenital amaurosis from different mutations within a single gene. This is allelic variation is common resulting in different diseases arising from different mutations within a single gene. In the field of retinal dystrophies, poorly understood.

In contrast, LCA with CRB1 mutations have been noticed to have two fairly consistent phenotypic features: the relatively early appearance of white spots and pigment clumps and the presence of moderate to high hyperopia.\(^2\) Mutations in the GUCY2D and RPE65 genes both give a normal fundal appearance at birth followed by a “salt and pepper” appearance despite very different functional outcomes.\(^8\)

In the future we can expect to see extensive databases, which provide us with projected pattern of disease progress for specific mutations in individual genes, with essentially each variation being a specific disease process.

**ACKNOWLEDGEMENT**

The authors gratefully acknowledge the Wellcome Trust who funded this research (award 061682/dcp).

**REFERENCES**