SHORT COMMUNICATION

Evidence for Further Genetic Heterogeneity in Autosomal Dominant Retinitis Pigmentosa

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We have investigated the possible involvement of further genetic heterogeneity in autosomal dominant retinitis pigmentosa using a previously unreported large Irish family with the disease. We have utilized polymorphic microsatellite markers to exclude the disease gene segregating in this family from 3q, 6p, and the pericentric region of 8, that is, each of the three chromosomal regions to which adRP loci are known to map. Hence, we provide definitive evidence for the involvement of a fourth locus in autosomal dominant retinitis pigmentosa.

ZMK-92 is an Irish kindred (Fig. 1) in which RP segregates in an autosomal dominant fashion. Affected individuals initially present with hearing difficulties in their teens. In their twenties patients notice symptoms referable to night vision impairment and peripheral visual field loss. Affected individuals show abnormal electroretinographic responses before the onset of symptoms. These consist of reduced amplitude rod responses that are prolonged in latency. Cone isolated responses likewise are reduced in amplitude and delayed in timing. Individuals in the fifth and sixth decades characteristically have no detectable rod or cone responses. Two-color dark adaptometry in affected individuals shows a Massof and Finkelstein Type 2 pattern (15).

Nineteen affected and 15 unaffected members of pedigree ZMK-92 were typed for highly polymorphic markers on chromosomes 3q, 6p, and 8 (Table 1). Recombination events were observed between adRP and intragenic markers in both the rhodopsin and peripherin/RDS genes, hence excluding the possibility of mutations in these genes as being causative of adRP in this kindred. Using two-point (Table 1) and multipoint analyses (Fig. 2c), we have excluded the possibility of the adRP gene in this family being present within a 26-cM region flanking peripherin/RDS. Due to the absence of linkage, obviously the phase of the disease locus cannot be determined with respect to peripherin/RDS. Considering the two possible phases, either three or five recombination

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FIG. 1. Kindred ZMK-92 segregating adRP. Affected individuals are indicated by closed squares (males) and circles (females). Similarly, unaffected individuals are indicated by open squares (males) and circles (females). The disease is fully penetrant (youngest affected individual aged 10 years and youngest unaffected individual aged 20 years) with a segregation ratio of approximately 0.5 as expected for an autosomal dominant gene. However, note there is no occurrence of male to male transmission of the disease.
<table>
<thead>
<tr>
<th>Locus/(chromosome)</th>
<th>0.001</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1S102 (1)</td>
<td>-9.69</td>
<td>-3.06</td>
<td>-1.92</td>
<td>-1.32</td>
<td>-0.90</td>
<td>-0.59</td>
<td>(22)</td>
</tr>
<tr>
<td>D1S103 (1)</td>
<td>-13.0</td>
<td>-5.04</td>
<td>-1.53</td>
<td>-0.78</td>
<td>-0.35</td>
<td>-0.09</td>
<td>(23)</td>
</tr>
<tr>
<td>D5S47 (8)</td>
<td>-17.2</td>
<td>-5.09</td>
<td>-1.86</td>
<td>-0.83</td>
<td>-0.34</td>
<td>-0.08</td>
<td>(25)</td>
</tr>
<tr>
<td>RHO (3)</td>
<td>-1.69</td>
<td>-0.63</td>
<td>0.14</td>
<td>0.16</td>
<td>0.19</td>
<td>0.18</td>
<td>(21)</td>
</tr>
<tr>
<td>DSS621 (3)</td>
<td>-10.5</td>
<td>-2.36</td>
<td>-1.18</td>
<td>-0.61</td>
<td>-0.29</td>
<td>-0.10</td>
<td>(10)</td>
</tr>
<tr>
<td>RDS (6)</td>
<td>-17.0</td>
<td>-4.41</td>
<td>-2.38</td>
<td>-1.35</td>
<td>-0.75</td>
<td>-0.37</td>
<td>(11)</td>
</tr>
<tr>
<td>TCTE1 (6)</td>
<td>-7.65</td>
<td>-2.32</td>
<td>-1.25</td>
<td>-0.68</td>
<td>-0.45</td>
<td>-0.15</td>
<td>(13)</td>
</tr>
<tr>
<td>D8S84 (6)</td>
<td>-6.40</td>
<td>-2.10</td>
<td>-1.31</td>
<td>-0.89</td>
<td>-0.63</td>
<td>-0.45</td>
<td>(21)</td>
</tr>
<tr>
<td>D8S87 (8)</td>
<td>-6.79</td>
<td>-1.84</td>
<td>-1.08</td>
<td>-0.69</td>
<td>-0.45</td>
<td>-0.22</td>
<td>(24)</td>
</tr>
<tr>
<td>D8S165 (8)</td>
<td>-2.98</td>
<td>-0.54</td>
<td>-0.37</td>
<td>-0.29</td>
<td>-0.23</td>
<td>-0.16</td>
<td>(20)</td>
</tr>
<tr>
<td>ANK1 (8)</td>
<td>-18.0</td>
<td>-4.76</td>
<td>-2.69</td>
<td>-1.64</td>
<td>-1.00</td>
<td>-0.59</td>
<td>(19)</td>
</tr>
<tr>
<td>DXS426 (X)</td>
<td>-16.8</td>
<td>-5.11</td>
<td>-3.24</td>
<td>-2.25</td>
<td>-1.60</td>
<td>-1.18</td>
<td>(4)</td>
</tr>
<tr>
<td>DXS7 (X)</td>
<td>-7.248</td>
<td>-2.30</td>
<td>-1.55</td>
<td>-1.18</td>
<td>-0.90</td>
<td>-0.77</td>
<td>(16)</td>
</tr>
<tr>
<td>DMD-49 (X)</td>
<td>-18.66</td>
<td>-5.38</td>
<td>-3.29</td>
<td>-2.21</td>
<td>-1.63</td>
<td>-1.06</td>
<td>(3)</td>
</tr>
</tbody>
</table>

Note. The most significant lod score (where significant exclusion is indicated by a lod score of -2 or less) for each marker locus has been underlined. The PCR was carried out as described previously (10). Mapping data were compiled with the data management package LINKSYS Version 4.11 (1) and calculations performed with LIFED (18).

**FIG. 2.** Support for exclusion of adRP from chromosomes 3q, 8, 8p, and Xp using LINKMAP (14). Male and female recombination rates were taken to be equal, and full penetrance of the disease gene was assumed. The Haldane mapping function was used to convert recombination fraction to map distance in all analyses. (a) The marker DSS621 was arbitrarily set at 0.00 cM, and DSS47 and Rhodopsin positioned 10.06 and 21.1 cM centromeric from it. Genetic distances were fixed according to the map of this region by Kumar-Singh et al. (12). (b) The marker D8S84 was arbitrarily set at 0.00 cM, and D8S165 and ANK1 placed 21.08 and 29.43 cM, respectively from D8S84. Genetic distances between marker loci were fixed according to the map of Tomohide et al. (20). A total of 72 haplotypes were considered simultaneously on a VAX 6200. (c) Support for exclusion of adRP in ZMK-92 from the region of the peripherin/RDS gene. TCTE1 was set arbitrarily at 0.00 cM, and peripherin/ RDS placed 4.02 cM distal from it according to the maps of Kumar-Singh et al. (11) and Kwiatkowski (13). (d) Support for exclusion of adRP from Xp. The marker locus DXS426 was arbitrarily placed at 0.00, and the markers DXS7 and DMD placed distal to it at 6.28 and 24.64 cM, respectively. Genetic distances between marker loci were fixed according to the CEPH database (version 4.5) and (4).
events were observed, including a minimum of two affected individuals in either case. It is worth noting that only a single recombination event was observed between adRP and rhodopsin due to the low PIC of the intragenic marker. This recombination event occurred in an unequivocally unaffected 23-year-old individual. Furthermore, using multipoint analyses with the rhodopsin polymorphism and the recently identified (25) microsatellite at D5S47 and D3S621, the adRP gene has been significantly excluded for a 35-cM distance (Fig. 1a) in this region of 3q. The extension of this exclusion was important in view of two recent observations. First, tentative evidence has been provided for the existence of two adRP loci on chromosome 3q (8)—one allelic with rhodopsin (RP4) and the other in the vicinity of C17/D3S47 (RP5). Both of these key regions have been excluded in this study. Second, the gene encoding cellular retinal-binding protein (RBPI) has also been physically assigned to a region of overlap with rhodopsin (17). Blanton et al. (2) have reported an adRP gene (RP1) in the pericentric region of chromosome 8. Multipoint analyses (Fig. 2b) with several loci in this region (D5S84, D5S165, and ANK1) have enabled us to exclude the possibility of the same disease gene segregating in ZMK-92.

Usher syndrome (US) is the name most commonly given to the association of RP and congenital deafness, either profound (Type I) or partial (Type II), and is usually inherited in an autosomal recessive pattern. Due to the moderate hearing loss reported by members of ZMK-92, and the recent observation of rhodopsin causing both dominant and recessive RP (7), we thought it prudent to exclude the possibility that Type II US, which maps to 1q (9), may be segregating in ZMK-92. Using two-point (Table 1) and multipoint analyses (data not shown), we have excluded the possibility of the existence of this adRP locus in the putative US region. A total of 58 cM flanking D1S102 and D1S103 have been shown to exclude a dominant RP gene.

There is no occurrence of male to male transmission of RP in ZMK-92. This we believe to be a coincidence due to a lack of matings by affected males. Nevertheless, we have excluded the possibility of an xlrp locus in ZMK-92 using multipoint analyses (Fig. 2d) across an 80-cM region on Xp shown to contain two xlrp genes (7).

In conclusion, this study again emphasises the genetically heterogeneous nature of adRP. We have excluded the adRP gene in ZMK-92 from all of the key regions of the genome known to harbor an adRP locus and thereby have provided conclusive evidence for at least one further, as yet unlocalized, autosomal dominant RP gene. The atypical clinical phenotype in this family of retinal degeneration combined with hearing impairments warrants further investigation to localize the gene(s) causing this debilitating disorder.

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Note added in proof. Since the submission of this paper we have obtained exclusion of an adRP gene on chromosome 3q,6p, and 8 in a family of Spanish origin (Jordan et al., in press).

REFERENCES


