LETTERS TO THE EDITOR

A new dominant retinitis pigmentosa family mapping to the RP18 locus on chromosome 1q11-21

Retinitis pigmentosa (RP) is an inherited retinal degeneration affecting approximately 1 in 4000 people. Until recently, there were eight known loci for the autosomal dominant form, ADRP, on chromosomes 3q (rhodopsin), 6p (peripherin/RDS), 7p (RP9), 7q (RP10), 8q (RP1), 17p (RP13), 17q (RP17), and 19q (RP1). Mutations in the rhodopsin gene account for 20-50% of ADRP, while peripherin/RDS mutations account for less than 5%. Some insight into the frequencies of the remaining six ADRP loci can be gained by scanning the available published reports. Further ADRP families have been reported as linked to 7q, 8q, 17p, and 19q, suggesting that these might be commoner loci.

In 1996 a ninth locus, designated RP18, was reported by Xu et al as mapping to chromosome 1cen in a large Danish ADRP pedigree. Patients in this family were shown to have a classical RP fundus with peripheral bone spicule pigmentation, constriction of retinal arterioles, and visual field loss. Disease onset was consistently early, with no evidence of non-penetration. Night blindness was apparent from birth but central visual acuity was preserved until much later in the course of the disease process. Linkage analysis initially placed the locus in a 7 cm interval between markers D1S534 and D1S305, spanning the chromosome 1 centromere. However, further analysis in the same family excluded the centromere and placed RP18 in the 4 cM interval between D1S2858 and D1S534.

We now report an English ADRP family which also links to 1cen markers. Members of family RP1188 were examined at Moorfields Eye Hospital, London, and at Addenbrooke’s Hospital, Cambridge. Affected subjects are aware of night blindness in early infancy, experience field loss and decreased visual acuity over the third and fourth decades, but retain reasonably good central vision into late life. The reason for the severely affected subjects shows the typical fundus appearance of retinitis pigmentea, with diffuse retinal and retinal pigment epithelial atrophy and intraretinal pigmentation. The very early onset of night blindness with late preservation of central cone function is similar to that seen in “diffuse” (D type) ADRP. The family originate from Lancashire in north west England and there is no genealogical evidence of a link to the Danish RP18 family.

Microsatellite markers from known ADRP loci were typed in genomic DNA by PCR with incorporation of 32P labelled cytosine, followed by size fractionation on 6% polyacrylamide denaturing gels. Lod scores were calculated using the LINKAGE (version 5.1) suite of programs, both on a PC and on the Human Genome Mapping Project Resources Centre computing facility (Cambridge, UK). Crossovers were detected in family RP1188 at all of the eight previously reported loci (data not shown). When tested for linkage to RP18 markers, maximum lod scores of 3.42 and 2.43 were obtained with D1S534 (distal to RP18 on 1p1) and D1S498 (centromeric and within the RP18 interval) respectively, with no recombination. However, marker D1S305 (distal to RP18 on 1q1) detected two crossovers and gave a maximum lod score of 0.8 at a theta value of 0.16. In order to determine whether these crossovers refined the genetic interval for RP18, we tested additional markers in the interval D1S498-D1S305, selected from the integrated Whitehead physical and genetic map of chromosome 1 (available from http://www-genome.wi.mit.edu). D1S1664, a GATA repeat mapping in this interval, still detected one of the two crossovers, refining the locus proximal to this marker. Two point linkage analysis with D1S1664 gave a maximum lod score of 1.34 at a theta value of 0.08. Multipoint linkage analysis with D1S534, D1S498, and D1S1664 gave a maximum lod score of 3.86 at D1S534. The approximate physical map positions of the markers used are shown in fig 1. Fig 2 shows the linked family and its haplotypes for the markers used.

The latest published refinement of RP18 in the Danish family places the locus on 1q11-1q13, in the distal RP9 region. The distal flanking marker is D1S2858, from the 1996 Genethon genetic map. Haplotypes analysis in the UK family places the locus proximal to D1S1664, a marker from the Whitehead integrated physical map which is placed only approximately on the genetic map. However, D1S1664 is clearly itself proximal to D1S2346 on the physical map, and this marker is genetically indistinguishable from D1S2858 on the genetic map. Further, three CEPH YACs which contain D1S1664 do not contain either D1S2858 or D1S2346, so it is likely that the haplotype analysis shown in fig 2 has significantly further refined the distal boundary of the RP18 interval.

The identification of a second RP18 family confirms the original linkage and suggests that this may be among the more common forms of RP compared with, for instance, those at the RP9 and RP17 loci, which have as yet been implicated only in single families. It may also be significant that the phenotype in the Danish and UK RP18 families closely resembles that associated with many of the mutations found in the rhodopsin gene. Both are fully penetrant, with onset of night blindness in the first decade but with good preservation of central vision until later in life. In our experience, families with such symptoms have always proved to have rhodopsin-RP, with the sole exception of RP1188. This may imply that the defective gene, like rhodopsin and unlike a number of other genes recently implicated in RP causation, is a rod specific transcript.

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Figure 1 An approximate physical map of the RP18 region of chromosome 1cen. Distances in cR are based on the integrated Whitehead physical and genetic map of chromosome 1. Genetic distances estimated from the same source are shown on the right hand side.

Figure 2 Pedigree of family RP1188. Filled symbols denote subjects confirmed as having RP. Haplotypes for chromosome 1cen markers are shown below each symbol, with the affected haplotype denoted by a black bar. A crossover proximal to D1S1664 in III.9 refines the locus.
other had a ventral septal defect which closed spontaneously in childhood.

The frequency of familial transmission in our group of patients of 10% is nearer the figure of 5% reported by Driscoll et al in the only other large study than the 28% reported by the European collaborative study. It is difficult to explain the large discrepancy between these figures; however, we would stress that where possible we follow up all cases irrespective of parental phenotypes, and although the collaborative study is a far larger one, the authors recognise that patient selection for testing because of suggestive features may have inflated their frequency. If an assumption is made that no further deletions were present in the parents not tested by Ryan et al, then the minimal estimate of deletion from their study is 81/558 or 15%, a value closer to our frequency.

An accurate figure for parental transmission of 22q11 microdeletions is important when counselling parents of a child recently diagnosed, helping to allay anxiety, guilt, and also fears of recurrence. A risk of 28% coming as it does from such a comprehensive and well respected study is the one most likely to be used for counselling purposes; however, in view of our findings and those of Driscoll et al, we feel this may be too high and that more clinical data on non-selected patients are needed before a true frequency of familial transmission is known.

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The annual incidence of DiGeorge/velocardiofacial syndrome

The majority of cases with either DiGeorge syndrome or velocardiofacial syndrome are caused by a submicroscopic deletion in chromosome 22q11 (del22q11). Since the advent of a routine diagnostic test for this microdeletion, the number of patients diagnosed has increased dramatically, including many patients with either mild features or non-specific presenting symptoms. The del22q11 occurs much more frequently than previously thought, but the incidence figures are not known. Wilson et al. found a del22q11 in approximately 5% of children with a congenital heart defect (CHD), and therefore an estimated incidence of at least 1/4000 live births. A more direct way is to determine the annual incidence of cases with a del22q11, in a well defined region, with a known number of births. In a region in southern France, with an annual birth rate of approximately 23,000, Du Montcel et al. found 1/9700 as a minimum incidence of the del22q11 associated with the typical clinical picture.

In the Flemish region of Belgium, all genetic tests are performed in four genetic centres. The number of births was extracted from the annual reports of the Study Centre for Perinatal Epidemiology (Studiecentrum voor perinatale epidemiologie, SPE), which registers in Flanders over 95% of all live and stillborn children with a birth weight over 500 g. Routine genetic testing for a del22q11 by means of FISH became available during the years 1992-1993. A total of 151 Flemish cases have been diagnosed, of which 94 were born before 1992, six in 1997, and 51 in the five year period between January 1992 and December 1996. The annual birth rate in Flanders ranges from 68,613 in 1992 to 63,550 in 1996, with a total of 356,166 births during the five year study period of 1992-1996. Therefore, the estimated annual incidence of a del22q11 in 1992-1996 is 15.3/100,000 newborns (95% confidence intervals 13.3-17.2), or 1/6395 (table 1).

However, in the study of Du Montcel et al., it is evident that this represents a minimum estimate, since many cases with mild features remain undiagnosed. In the total group of patients with a del22q11, 81 of the 151 patients (54%) have a symptomatic congenital heart defect (CHD), compared to 37 of the 51 patients (72.5%) born during the last five years. This confirms the clinical experience that the diagnosis is delayed in patients without a heart defect. In our series of patients from 1992-1996, mean age at diagnosis of those with a heart defect was 8.3 months (range: day of birth to 15 months). During the last three years, the majority of infants with a conotruncal heart defect and a del22q11 were diagnosed during the first weeks of life. In contrast, patients without a heart defect were diagnosed at a mean age of 25.9 months (SD 17 months), when developmental delay or speech delay becomes evident. It can be estimated, therefore, that a large proportion of the children born during the last five years with a del22q11 but without a heart defect remain to be diagnosed.

Taken together, our observation is in good agreement with a maximal annual incidence of 1/4500 found in children born in 1993 in the study of Du Montcel et al and with an estimated incidence of 1/4000 as suggested by Wilson et al. We conclude that a del22q11 is among the most frequent causes of genetic syndromes.
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