proved or fancied genetic component were excluded from insurance coverage?

The debate over insurance coverage of infertility treatment highlights the fundamental flaw in financing health care through insurance. The interests of the health insurance industry are contrary to the interests of society and individuals. The interest of the insurance industry is in selling insurance, preferably to those who are unlikely to make claims, while the interests of society and individuals is in providing health care to those who need it the most. In support of their objectives, insurance companies seize on any argument, no matter how flimsy, to try to limit insurance coverage to those who do not need it.

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Evidence against a Second Autosomal Dominant Retinitis Pigmentosa Locus Close to Rhodopsin on Chromosome 3q

To the Editor:

In 1989 McWilliam et al. reported close linkage of the autosomal dominant retinitis pigmentosa (adRP) locus to chromosome 3q marker D3S47 in a large Irish pedigree (McWilliam et al. 1989). Subsequent studies confirmed linkage in two other adRP families (Lester et al. 1990; Olsson et al. 1990). Shortly afterward, mutations in the rhodopsin (RHO) gene, mapping to 3q21-24, were implicated in disease causation, and it is now known that around one-third of adRP results from such mutations (Dryja et al. 1991; Sung et al. 1991; Inglehearn et al. 1992*a*).

At that time, sequencing studies had failed to find rhodopsin mutations in the three families first linked to 3q. In the Irish family, linkage between D3S47 and phenotype gave a lod score of 16.5 at a theta of 0. In contrast, the other two families, adRP3 (Lester et al. 1990) and family 20 (Olsson et al. 1990), gave lod scores of 6.1 and 4.78, respectively, at theta values of .05 and .08, respectively. Several adRP families in which rhodopsin mutations had been found gave lod scores that, when pooled, had a peak of 4.47 at a theta of .12 (Inglehearn et al. 1992*b*). The apparent lack of mutations in families TCDM1, adRP3, and 20, together with the linkage data in these and the proved RHO-RP families, led to speculation that two adRP loci existed on chromosome 3q (Olsson et al. 1990; Inglehearn et al. 1992*b*). Such a situation is known to exist on the short arm of the X chromosome, where two loci for X-linked RP have been clearly demonstrated (Ott et al. 1990).

However this situation has been reversed by more recent analysis, since rhodopsin mutations have now been found in all three families. The phenotype in adRP3 results from a mutation in codon 178 (TAC→TGC; Tyr→Cys; Bell et al. 1992); the Irish family TCDM1 has a codon 207 mutation (ATG→AGG; Met→Arg) (Farrar et al. 1992); and family 20 proved to have a codon 58 mutation (ACG→AGG; Thr→Arg) (J. Keen, M. Horn, A. Gal, and C. Inglehearn, unpublished data). There is therefore no longer any evidence to support the hypothesis that a second adRP locus exists close to rhodopsin on chromosome 3q.

Linkage data can therefore now be pooled in families adRP3, TCDM1, and 20 and in the previously proved RHO-RP families. The lod score obtained thus between rhodopsin and D3S47 gives a peak of 29.28 at a theta of .04 (the 2-lod confidence interval extends from a theta value of .01 to a theta value of .12). With these data, it will be possible to provide accurate risk estimates for adRP carrier testing using D3S47 linkage. This would only be applicable in large families where linkage could first be proved but may nevertheless be useful in light of the range of rhodopsin mutations observed.

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Distribution of a Pseudodeficiency Allele among Tay-Sachs Carriers

To the Editor:

Recently Triggs-Raine et al. (1992) identified a new mutation in the gene coding for the α-subunit of β-hexosaminidase A (hex A), the enzyme whose deficiency causes Tay-Sachs disease. This mutation, a C_{739}-to-T transition in exon 7, results in an altered enzyme that is active (albeit at reduced levels) in cells but that has essentially no activity in serum. This so-called pseudodeficient allele was first detected in compound heterozygotes who also carried a Tay-Sachs disease allele and therefore had no detectable hex A in their serum but who were in good health.

Carriers of this apparently benign mutation are generally indistinguishable from carriers of a lethal mutation by means of routine enzyme-based screening tests, because the product of the pseudodeficient allele is not detectable in serum and has decreased activity in cells. This suggests that some individuals who have been classified as Tay-Sachs carriers are actually carriers of the pseudodeficient allele and are not at risk to have a child affected with Tay-Sachs disease. The pseudodeficient allele may also be responsible for some inconclusive diagnoses, where leukocyte values fall below the normal range but are still above the carrier range.

To begin to determine the frequency with which this allele occurs, Triggs-Raine et al. (1992) tested 98 enzyme-defined carriers from the Boston, California, and Toronto screening programs who did not have any of the three most common Tay-Sachs mutations, according to an earlier study (Triggs-Raine et al. 1990). They found the pseudodeficient allele present in 20 of 62 non-Jewish enzyme-defined carriers but in 0 of 36 Jewish enzyme-defined carriers. The absence of the C_{739}-to-T allele among Jewish carriers was unexpected, because five of the original seven pseudodeficient subjects in that same study were Jewish.

We have conducted a similar survey among enzyme-defined carriers from our screening program who did not have any of the common mutations. The common mutations, i.e., the insertion, splice junction, and adult mutations, were identified as described in an earlier