Applicants whose family histories indicate that they are at risk of developing a particular genetic disorder, for example Huntington’s disease or Friedreich’s ataxia, are treated in the same way as if the disease were already expressed. They are treated with the risk premium correspondingly modified. In many cases the exact status of the applicant could be clarified by the use of DNA testing, but this must neither be requested nor required by the insurance companies according to the Austrian gene technique law (see quotation above). Consequently, the companies will not pay for such tests even if the applicant requests them. However, it may well be to his advantage to provide such information at his own expense. If it is positive he is not worse off, will pay the higher premium, and cover will remain subject to the same restrictions. If the results are negative, then the genetic problem is irrelevant, there would be no restrictions on the policy, and the premium would be normal. Of course this economic argument is only one of many, for example, religious, ethical, psychological, and social, which he would need to consider in coming to a decision.

This enquiry indicates that the existence of a law prohibiting insurers from using genetic test information necessarily prevents an applicant for insurance from using that information to his own advantage.

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Microsatellite markers for the cone-rod dystrophy gene, CRX, on 19q13.3

A large proportion of cases of visual loss in children in the developed world result from genetic aetiologies. Fifty percent of blindness in children in the United Kingdom has been classified as genetic, of which choroidal dystrophies are the most common subgroup; all are untreatable and incurable.

The cone-rod dystrophy (CORD2; MIM 120970) locus on 19q13.3 is an example of a severe, early onset (first decade of life), chorioretinal dystrophy, often leading to complete loss of visual function by middle age.1 Mutations in a retina specific OTX-like homeobox gene, CRX, that codes for a 290 amino acid protein have recently been shown to be the causative defect for cone-rod dystrophies linked to the 19q13 locus. Two mutations are described: a highly conserved glutamate at the first amino acid of the recognition sequence of the homeodomain is replaced by an alanine, and a 1 bp deletion leading to a protein truncated by 132 amino acid residues.2 We have, however, failed to determine a mutation in the three published coding exons of 1.4 kb of the CRX mRNA in the original CORD2 family described by Evans et al. This type of anomaly is not unknown in retinal dystrophies; for example, approximately one third of European choroideremia patients have no known mutation in the rod escort protein-1 (REP-1) coding region. Similarly, only 10–15% of X linked retinitis pigmentosa 3 (RP3) patients have a mutation in the retinitis pigmentosa GTGase regulator (RPGR) gene.3

In order to determine whether a similar phenomenon is occurring at the CORD2 locus, we have finely mapped the CRX gene to a 285 kb interval on chromosome 2 (X11A7) isolated from the ICRF library4 that is positive for the polymorphic microsatellite markers D19S902 and C19S17.5 D19S902 is a Genethon marker with a heterozygosity of 79%6 and C19S17 (Geneknow 29026) is a novel microsatellite with an observed heterozygosity of 53%,7 amplified by primers 5’TCA TGA ATT AAA CCC AGG AG-3’ and 5’CTG TAT CAT ACT GGA TAA CTT-3’ under previously described conditions.8 Both of these polymorphic markers are non-recombiant in the original CORD2 family and newly ascertained branches refine the locus further to a 2 cm interval between polymorphic markers D19S412 and glycogen synthase-1 (GYS1).9 We propose that investigators wishing to determine whether a cone-rod retinal dystrophy pedigree is linked to the 19q13.3 locus should attempt linkage with either D19S902 or C19S17. The close proximity of D19S902 and C19S17 to the CRX gene should enable other investigators to achieve a lod score indicative of linkage, as such 2 (depending upon pedigree structure and polymorphic marker information), which can be taken to be confirmation of a previous linkage.10 If these two polymorphic markers are uninformative, we suggest using any of the following additional markers: D19S219, D19S112, D19S506, D19S879, D19S604, or D19S246, the flanking polymorphic markers D19S219 and D19S246 encompassing approximately 5 kb of the CORD2 locus.11 It is then hoped that a greater spectrum of mutations in the CRX gene may be determined by other laboratories, and our own observations of a lack of a mutation in the presently known sequence may also be confirmed. In the case of the original CORD2 family, the mutation may lie in an as yet undetermined non-coding exon or an upstream regulatory element. We are currently investigating this area since non-coding exons in the CRX gene shows two retina specific transcripts, one highly expressed at 4.5 kb and a second, less highly transcribed mRNA of about 3 kb, though only 1.4 kb of mRNA sequence is known.4 Mutations in regulatory elements have been shown to cause blue cone monochromacy12 and forced expression of CRX affects rat retinal cell differentiation in vivo.13 Alternatively, the CORD2 locus may be exhibiting microheterogeneity, that is, there may be a mutation in another gene within the CORD2 interval that may be causing the phenotype, as postulated by Fujita et al in order to explain the lack of mutations observed in the RPGR gene in RP3 patients.

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Newer Aspects of Trace Element Research

The Fifth Conference of the International Society for Trace Element Research in Humans (ISTERH) on “Newer Aspects of Trace Element Research” was held at Peking University, Shangai, on 26-30 September 1998 at the newly established “Trace Element - Institute for UNESCO”, Lyon, France. For further details contact Trace Element - Institute for UNESCO, Immeuble Le Condorcet, 1 place de l’Ecole, BP 7021, 69342 Lyon Cedex 07, France. Tel: 33 (0) 4 72 80 82 90, fax: 33 (0) 4 72 85 86 71, e-mail: 101711.23522@compuserve.com

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