LETTERS TO THE EDITOR

Laws regarding insurance companies

For several years now in a number of countries new laws have been passed dealing with the use that insurance companies may make of the genetic knowledge that new techniques may provide of the status of applicants for insurance cover. In other countries, such as the UK, the subject is under discussion. Austria is one of those countries which has already introduced such a law. According to federal law 510 of 1994 (the gene technique law) "Employers and insurance companies including also their representatives and collaborators are forbidden to obtain, request, take or otherwise use results of gene analyses of their employees, applicants for employment, or of those who wish to insure themselves". This appears definitive. But what is actually happening in practice?

Enquiries were made about applicants to the private insurance companies in Austria, as distinct from the state insurance system, in that the state system does not refuse cover to any applicant, but the private companies are able to refuse to grant cover or only grant it at the cost of an increased premium. The object was to discover whether applicants in whom there may be a genetic problem would be accepted and, if so, on what terms. Some illustrative examples are given in tables 1 and 2. Applicants with an existing expressed genetic disorder are not automatically excluded but are treated in the same way as any other applicant with a chronic condition, namely by granting cover with restrictive clauses and payment of increased premiums depending on the condition and its severity, assessed in terms of a "risk factor". The restrictive clauses in health insurance relate mainly to the exclusion of development of pathologies associated with the primary condition. For the life cover, some age groups may be excluded, insurance being available after a critical age has been reached, or only up to a certain age, depending on the age specific mortality risk of the disorder. Accident insurance is generally not available for those with severe mental handicap or with motor dysfunction. It should be stressed that the restrictions and risk factors given in tables 1 and 2 represent general levels. They may vary slightly from one insurance company to another, and may be modified slightly from one applicant to another according to the opinion of a company's medical advisor.

Table 1 Insurance policies for applicants with manifest genetic disorders (health policies exclude any pathological manifestation connected with the primary condition in the applicant, referred to below as "with exclusion")

Syndrome	*Life insurance*	*Health insurance*	*Accident insurance*
Huntington's disease	Not available	Available "with exclusion"	Not available
Friedreich's ataxia	Available from 25 years onwards	Available "with exclusion"	Not available
	in mild cases with risk 200–300%; not available if severe	Available "with exclusion"	Not available
		Available "with exclusion" or with high risk	Not available
Mucoviscidosis	Available only after 21 years;	Not available	Available
	with 500–700% risk between age 21 and 35,	Not available	Available
	after 35 years, 300–400% risk	Not available	Available
Down syndrome	Available but excludes infants and older adults (>40–50 years), risk depends on additional pathologies	Not available or available with high risk	Not available
Klinefelter syndrome	Available in mild cases with moderate risk	Available "with exclusion"	Available
Turner syndrome	Available if no pathologies,	Available "with exclusion"	Available
	with pathologies moderate risk	Available "with exclusion"	Available
Hereditary haemosiderosis	Not available if severe;	Not available	Available
	if mild available with 75–150% risk	Available "with exclusion"	Available
Muscular dystrophies			
Duchenne	Not available	Not available	Not available
Facioscapulohumeral	Available with 50–100% risk	Available "with exclusion"	Available
Juvenile spinal muscle atrophy	Not available	Not available	Not available
Coeliac disease	Available if good response to diet;	Available "with exclusion"	Available
	if not, available with 50–100% risk	Available "with exclusion"	Available
Thalassaemia minima	Available	Available	Available
Thalassaemia minor	Available with 0–50% risk	Available "with exclusion"	Available
Thalassaemia major	Available after age 20 with 200–400% risk	Available "with exclusion"	Available
Morbus Gaucher	Not available if manifestation in childhood;	Not available	Not available
	if mild manifestation in adults, available with 200–400% risk;	Available "with exclusion"	Available
	if severe, available with high risk or not available	Not available	Available
Diabetes mellitus	Available with individual risk depending on individual condition (100–500%)	Available "with exclusion"	Available
Psychiatric disorders (suicide, schizophrenia, paranoia)	Not available	Generally not available	Not available
Cardiovascular	Available with individual risk depending on individual condition (100–500%)	Available "with exclusion"	Available

Table 2 Insurance policies for applicants at risk for genetic disorders. Estimation of the applicant's risk of developing a particular genetic disorder is only based on family history

Syndrome	*Life insurance*	*Health insurance*	*Accident insurance*
Huntington's disease	Not available if a parent/grandparent died from it	Available "with exclusion"	Not available
Friedreich's ataxia	Available only after 25 years	Available (also before 25 years)	Available
Mucoviscidosis	Available only after 21 years	Available (also before 21 years)	Available
Hereditary haemosiderosis	Available	Available	Available
Muscular dystrophies:			
Duchenne	Available	Available	Available
Facioscapulohumeral	Available	Available	Available
Juvenile spinal muscle atrophy	Available	Available	Available
Coeliac disease	Available	Available	Available
Morbus Gaucher	Available	Available	Available
Diabetes mellitus	Available, if more than one first degree relative is affected, available with risk up to 25%	Available	Available
		Available "with exclusion"	Available
Psychiatric disorders (suicide, schizophrenia, paranoia)	Available, if more than 2 first degree relatives are affected, available with risk of 25–50%	Available	Available
		Available "with exclusion"	Avalable
Cardiovascular	If more than two first degree relatives are affected, available with risk 25–100%	Available "with exclusion"	Available

Applicants whose family history indicates 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 but 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 does not necessarily prevent an applicant for insurance from using that information to his own advantage.

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Microsatellite markers for the cone-rod retinal 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,[1] of which chorioretinal dystrophies are the most common subgroup; all are untreatable and incurable.

The cone-rod retinal dystrophy (CORD2; MIM 120970) locus on 19q13 is an example of a severe, early onset (first decade of life), choroidoretinal dystrophy, often leading to complete loss of visual function by middle age.[2,3] Mutations in a retina specific OTX-like homeobox gene, CRX, that codes for a 299 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.[4] 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.*[2] 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 rab escort protein-1 (REP-1) coding region.[5] Similarly, only 10-15% of X linked retinitis pigmentosa 3 (RP3) patients have a mutation in the retinitis pigmentosa GTPase regulator (RPGR) gene.[6,7]

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 yeast artificial chromosome (4X11A7) isolated from the ICRF library[8] that is positive for the polymorphic microsatellite markers D19S902 and C19S17.[9] D19S902 is a Genethon marker with a heterozygosity of 79%[10] and C19S17 (GenBank G29026) is a novel microsatellite with an observed heterozygosity of 53%,[11] amplified by primers 5'-TCA TGA ATT AAT CCC AGG AG-3' and 5'-CTG TAT CTT GGA TAA AGT GG-3' under previously described conditions.[12] Both of these polymorphic markers are non-recombinant 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, such as 2 (depending upon pedigree size and structure and polymorphic marker information), which can be taken to be confirmation of a previous linkage.[13] If these two polymorphic markers are uninformative, we suggest using any of the following polymorphic markers: D19S219, D19S112, D19S412, D19S606, D19S879, D19S604, or D19S246, the flanking polymorphic markers D19S219 and D19S246 encompassing approximately 5 cM of the CORD2 locus.[14] 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 northern analysis of 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 monochromacy[15] and forced expression of CRX affects rat retinal cell differentiation in vivo.[16] 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*[7] in order to explain the lack of mutations observed in the RPGR gene in RP3 patients.

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NOTICE

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" will be held 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 78 58 86 71, e-mail: 101711.2322@compuserve.com