ETHICS WATCH

Genetic discrimination — an overblown fear?

The fear of insurance companies or employers using genetic information to discriminate against individuals is an important concern for geneticists to be aware of as such fear could hamper their studies by preventing individuals from participating in research. But just how real is this fear?

Although there is much talk of "genetic discrimination", so far there is little evidence of its extent. Most reports are anecdotal collections of cases (Billings *et al.*) or are based on surveys with low (<10%) response rates (Geller *et al.* 1996). In one survey (which avoided the word discrimination), US genetics professionals reported 693 cases of patients or family members who had been refused life insurance or employment on the basis of carrier status or genetic predisposition in the absence of symptoms (Wertz 1999). However, refusals were rare relative to overall patient volume in this study, in which 1,084 geneticists with ~9 years experience each saw an average of six patients a week, making a total of ~2,900,000 patients in all. In a separate survey, 476 patients at 12 North American genetics clinics reported 43 instances of refusals of insurance or employment because of genetic disability or disease (including relatives). But their descriptions indicated that many believed that a wide range of common conditions were inherited. For example, patients reported being denied a job as a firefighter because of chronic bronchitis and being denied disability insurance because of obesity (in the absence of a known genetic syndrome). Most patient reports fell within the vagaries of insurance practice generally, including being refused cosmetic surgery for Down syndrome because the company did not cover cosmetic surgery or procedures, such as late abortions, that were only available outside the individual's home state.

Perhaps such fears mirror a more general "genetic dread" that pervades society. Will refusals of insurance or employment increase in the future, as more people take genetic tests? Probably not. In the past, some refusals were caused by ignorance. As insurance companies learn more about genetic disorders, illogical refusals, such as refusing life insurance to sickle cell carriers, will decrease. However, refusals based on sound actuarial evidence can still be unethical (Rothstein & Anderlik 2001). For example, individuals with cystic fibrosis require more health care and die earlier than others. But it would be unethical to deny health-care coverage to them or to prevent them from purchasing a house in countries where mortgages require life insurance. This is where social justice and community obligation to protect the vulnerable come into play. Laws that protect rights to employment for people with disabling symptoms (such as the Americans with Disabilities Act) should be extended to preclude discrimination on the basis of carrier status or predisposition in the absence of symptoms. Only system-wide safeguards can solve the problem, such as government-sponsored health-insurance systems and guarantees of a basic amount of life insurance in nations (including much of Europe) that require it to secure home mortgages.

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SEX DETERMINATION

Secrets of masculinity

A crucial event during early development of the testis is the specification of somatic cell lineages — among them, the Leydig cells. Little is known about the origin of fetal Leydig cells, or of the signals that induce them to differentiate, but Blanche Capel and colleagues now provide evidence that the Desert Hedgehog (Dhh)–Patched 1 (Ptch1) pathway triggers Leydig cell differentiation.

Fetal Leydig cells are responsible for the initial masculinization of an embryo. They are first identifiable in the interstitium of XY gonads, where they express enzymes needed for the production of male sex hormones. They are present in the gonad by embryonic day (E)11.5 and some evidence indicates that Leydig cell precursors migrate there from the mesonephros.

Because *Ptch1* is expressed in the interstitium of XY gonads at E12.5, the authors wondered whether this receptor — and its ligand, *Dhh* — might be involved in Leydig cell differentiation. The expression patterns of the *Ptch1*, *Dhh* and *P450* side-chain cleavage enzyme (*Scc*) genes (Scc is a marker for fetal Leydig cells) confirmed previous reports that Dhh comes on at E11.5 in XY gonads. At E12.5, most of the interstitial cells also expressed $Ptch1^{lacZ}$ — but not *Scc*. However, by E13.5, most of the $Ptch1^{lacZ}$-positive cells were also expressing *Scc*.

These expression patterns support the idea that Dhh signalling is involved in the early development of Leydig cells. So, to determine what happens in the absence of the Dhh signal, Capel and colleagues analysed the expression of *Scc* in $Dhh^{+/+}$, $Dhh^{+/-}$ and $Dhh^{-/-}$ XY gonads at E13.5–E14.5. Scc was seen at the centre of $Dhh^{+/+}$ and $Dhh^{+/-}$ gonads at E13.5, but it was absent from 70% of the $Dhh^{-/-}$ gonads at this stage. Even by E14.5, the $Dhh^{-/-}$ gonads showed only very sparse staining for Scc.

So why is it that the loss of Dhh signalling leads to defects in Leydig cell differentiation? The authors showed that two obvious candidate processes, cell migration from the mesonephros to the gonad and the proliferation or survival of Leydig cell precursors, were unaffected in $Dhh^{-/-}$ gonads.

Capel and colleagues think that the main role of Dhh signalling is to upregulate Scc in Leydig precursor cells. Scc is the target of the steroidogenic factor 1, and there is evidence that this, too, is upregulated in Leydig cells. By upregulating these factors, the Dhh pathway could trigger the differentiation of precursors into Leydig cells. However, as the authors point out, not all cells that express *Ptch1* differentiate as Leydig cells, so other signals probably combine with the Dhh pathway to specify Leydig cell fate.

Alison Mitchell, Editor,
Nature Reviews Molecular Cell Biology

References and links

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WEB SITE

Blanche Capel's laboratory: http://note.cellbio.duke.edu/Faculty/Capel