ETHICS WATCH

Genetics services and market forces

For years, commentators have been speculating on the potential adverse implications of market forces on the implementation and use of genetic services. Although the involvement of industry is both necessary and desirable for developing and disseminating genetic technologies, the resulting commercialization process is associated with social, ethical and health policy concerns.

In this issue, for example, Lori Andrews comments on the potential adverse implications of gene patents on the research environment and on the public's access to important genetic testing services. Myriad Genetics' recent decision to actively enforce its patents on the technologies associated with two breast cancer genes, *BRCA1* and *BRCA2* (as discussed by Andrews), highlights the impact that gene patents have on this access. According to a recent survey in Canada, the public generally support gene patents, but they have serious concerns about equity and access[1].

In addition to such concerns, gene patents might also contribute to the "overselling" of a given technology. Patent holders have a natural and understandable desire to see their inventions used rapidly and by as large a market as possible. But might this market pressure lead to the premature implementation of genetic services? Some have speculated that this might be so, and that financial interests and professional enthusiasm led to the premature commercialization of the tests for the *APOE4* and the BRCA mutations[2]. For example, it has been suggested that "commercial interests" led to the marketing of *APOE4* genotyping for "predicting the future development of [Alzheimer disease] in asymptomatic individuals"[3], despite uncertainty about the clinical utility of the test. Market pressures might also cause commercial labs to market their services to an inappropriately broad sector of the population (the broader the definition of "at risk", the larger the market). Indeed, it can be argued that creating a demand is a natural consequence of private sector involvement.

To maximize the health care benefits promised by the genetic revolution, we need policies that mitigate the inevitable ramifications of market forces in this context. For example, governments must develop systems to allow for the independent evaluation of the efficacy and utility of genetic services. The marketing of genetic services, as with other health care products, should also be carefully monitored. In addition, the international community needs to give serious consideration to the reform of the existing patent system, including the possible adoption of new patent licensing schemes, as discussed by Andrews.

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By fostering public trust and a high quality of care, the appropriate regulation of genetic technologies will benefit both the public and, in the long term, the biotech industry.

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REFERENCES [1]Report for the Biotechnology Assistant Deputy Minister Coordinating Committee (BADMCC). *Public Opinion Research into Biotechnology Issues*, *Third Wave* (Pollara & Earnscliffe, Ottawa, Canada, 2001) | [2]Healy, H. BRCA genes — bookmaking, fortunetelling, and medical care. *N. Engl. J. Med.* **336**, 1448–1449 (1997) | [3]Relkin, N. *et al.* The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer disease. *Ann. NY Acad. Sci.* **802**, 149–171 (1996)

HUMAN GENETICS

Sticking together

Nephronophthisis is the most common genetic cause of chronic renal failure in children. Mutations in three different loci contribute to this recessive phenotype, one of which, *NPHP1*, encodes nephrocystin — a novel docking protein that is involved in cell adhesion. Now, Mollet *et al.* and Otto *et al.* report the characterization of a fourth locus, *NPHP4*, that contributes to this disorder. Mollet *et al.* also show that its product interacts with nephrocystin, probably functioning in the same pathway.

Because of genetic heterogeneity of nephronophthisis, Mollet *et al.* and Otto *et al.* embarked on finding new loci that are linked with this disorder. To this end, both groups used genome-wide linkage and haplotype analysis in families in which there was no linkage between the disorder and the previously identified loci. The results implicated a small region on chromosome 1 that contained six candidate genes, so both groups screened affected individuals for mutations in a subset of candidates that were known to be expressed in the kidney. Collectively, the two groups found 16 mutations in one ORF that encodes a novel hydrophilic protein. Mollet *et al.* call this protein nephrocystin-4, whereas Otto *et al.* call it nephroretinin, to reflect the fact that the mutations in *NPHP4* are found in some individuals who not only suffer from nephronophthisis but also retinitis pigmentosa.

The product of *NPHP4* has been conserved during evolution — the mouse orthologue is 86% identical with the human protein at the amino-acid level, and there is also a previously uncharacterized worm orthologue. Although novel, the NPHP4 protein contains a proline-rich region with a consensus motif that is known to interact with SH3 domains, one of which is present in nephrocystin. Mollet *et al.* showed that *NPHP4* interacts with nephrocystin, at least *in vitro*. But domains other than SH3 must also be involved in this interaction because it was not abolished by a mutation that disrupts the SH3 domain of nephrocystin.

Given that nephrocystin interacts with several proteins that are involved in cell adhesion, the authors speculate that the product of *NPHP4* also affects the same process and that pathogenic changes that are associated with nephronophthisis result from the abnormal adhesion of cells in the renal tubules.

The results of both studies indicate the existence of a new cell-adhesion pathway that is important in the nephronophthisis disease process. But the pathway remains to be investigated in detail. The fact that Otto *et al.* failed to detect mutations in *NPHP4* in some of the affected families indicates a greater genetic heterogeneity than expected for nephronophthisis that awaits additional studies.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPERS Mollet, G. *et al.* The gene mutated in juvenile nephronophthisis type 4 encodes a novel protein that interacts with nephrocystin. *Nature Genet*. 9 Sep 2002 (doi:10.1038/ng996) | Otto, E. *et al.* A gene mutated in nephronophthisis and retinitis pigmentosa encodes a novel protein, nephroretinin, conserved in evolution. *Am. J. Hum. Genet*. 29 Aug 2002 [epub ahead of print].