Genetic determinism and the overprotection of human subjects

Advances in genetic research have raised questions about the protection of human subjects. The usual concern is whether existing protections are sufficient[1–2], but an escalation of protections can also create problems, as illustrated in the following example.

Epidemiologists were planning a study of learning problems in healthy children. One hypothesis was that ordinary genetic variations in metabolism might make some children more vulnerable to neurotoxic effects of household pesticides. Investigators planned to collect cheek swabs from children to determine genetic metabolic variants. An ethicist was asked to help with the consent form. The ethicist recommended advising the parents of these children as follows:

"Genetic information about [your child] could alter the way in which you think about them…Some individuals may feel anxious, depressed or additionally stressed by learning genetic information about their children…Your child could experience problems in school as a result of participation in genetic research…"

These warnings are directly based on NIH guidelines for human genetic research[3]. Although these guidelines do not carry the force of law or regulation, they are highly influential in the deliberations of Institutional Review Boards (IRBs). The current guidelines reflect an assumption of genetic determinism in which all alleles are expected to have direct and powerful consequences on health. In contrast, the common varieties of metabolism genes in the example above are neither necessary nor sufficient to produce disease.

Highly penetrant alleles have become the paradigm for discussions of genetic research. This assumption of strong genetic effects has, in turn, prompted calls for more stringent warnings in any studies that include the collection of genetic material[2]. A more balanced approach would be to recognize a broad distinction between disease alleles (rare alleles with strong health effects) and susceptibility alleles[4] (common alleles with weak effects).

Disease alleles have been characterized as rare, highly penetrant alleles that generally produce rare diseases[4]. Perhaps 2% of human illness can be attributed directly to the inheritance of specific alleles[5]. Even among the genes that fit this paradigm, the phenotype produced by a specific DNA sequence can be unpredictable. For example, not everyone who is homozygous for cystic fibrosis alleles shows clinical signs of disease, and severity can vary widely among those with the disease[6]. Inconsistency of gene penetrance may reflect interaction with other genes, cellular mechanisms that regulate gene expression and interactions with nutritional and environmental factors[7].

The contribution of specific alleles to the remaining 98% of human illness is largely unknown. In this second paradigm of genetic effect, a single allelic variant is but one component in a web of factors that lead to disease. Genetic variations in physiologic function that are adaptive for the species as a whole may be either good or bad for individuals depending on other factors. Gene-gene and gene-environment interactions presumably have a strong role.

Unlike disease alleles, susceptibility alleles in themselves have little predictive power for individual carriers. Their significance lies in what they might reveal (in combination with other factors) about the molecular processes that lead to common diseases. Better understanding of the pathways of disease causation in genetically susceptible people will provide new possibilities for disease treatment and prevention.

Policies on the protection of human subjects frequently fail to distinguish between the study of rare alleles with strong effects and the study of common alleles with weak effects. (For example, see current guidelines from the US Office for Protection from Research Risks[3].) Genetic studies of high-risk families or clinical studies of disease alleles with high penetrance require a higher level of protection for participants than population-based studies of common, low-penetrance alleles for which no risk has been established.

The indiscriminate application of more stringent cautions can cause harm. Warnings geared to highly penetrant genes may distract study participants from other, more immediate risks of a study. Another problem is that misplaced warnings may discourage healthy people from participating in studies in which they receive no particular benefit. Although ethicists acknowledge that harsher warnings may decrease research participation, they deem this a reasonable price to pay[2]. The costs, however, are greater than some ethicists may realize. A reduction in participation rates can damage the scientific validity of epidemiologic studies[8].

Informed consent is a moral imperative in human research, but more protection of research subjects is not necessarily better protection. The assumptions of genetic determinism can lead to unreasonable requirements for informed consent. It is a particular challenge in genetic research to calibrate the protection of human subjects to the actual level of risk.

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1. *Assessing Genetic Risks: Implications for Health and Social Policy* (eds Andrews, L.B., Fullarton, J.E., Holtzman, N.A. & Motulski, A.G.) (National Academy Press, Washington DC, 1994).
2. Reilly, P.R., Boshar, M.F. & Holtzman, S.H. *Nature Genet.* **15**, 16–20 (1997).
3. NIH Office of Protection from Research Risks *Protecting Human Research Subjects: Institutional Review Board Guidebook* (US Government Printing Office, Washington DC, 1993).
4. Caporaso, N. & Goldstein, A. *Pharmacogenetics* **5**, 59–63 (1995).
5. Dyson, F. *Am. Scholar* **62**, 513–525 (1993).
6. Centers for Disease Control *MMWR Morb. Mortal. Wkly Rep.* **46**, 1–24 (1997).
7. Strohman, R.C. *Nature Biotech.* **15**, 194–200 (1997).
8. Lilienfeld, A.M. & Lilienfeld, D.E. *Foundations of Epidemiology* (Oxford, New York, 1980).