Ethics, Public Policy and Behavioral Genetics

David Glick PhD and Hermona Soreq PhD

Department of Biological Chemistry, Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem , Israel

Key words: diagnosis, *in vitro* fertilization, late onset, pharmacogenomics, polygenic

Abstract

Behavioral genetics is the identification of behavioral traits that are genetically determined, the identification of the genes that are involved, and the discovery of modes of intervention to alter the expected course of the disease. Unlike the classical Mendelian traits, many specific aspects of behavior are, in part, determined by several genes. The corresponding abnormalities of behavior or deficiencies are therefore polygenic. New genetic techniques are leading to the discovery of these genes, and the techniques and knowledge developed in the Human Genome Project make it possible to screen the genome of any individual for the presence of known polymorphisms. This raises great hopes for diagnosis and the individualization of therapy. However, the genetic prediction of unacceptable behavior can further lead to social and occupational discrimination and enforced therapy. This raises serious concerns about how this information will be collected and who will have access to it.

IMAJ 2003;5:83–86

The New Biology offers exciting prospects for individualizing human health. However, the application of the associated technologies poses ethical problems. We now know a lot more about the genetic components of disease than when the monogenic disease paradigm was established by Archibald Garrod a century ago [1]. The possibility of individual genotyping changes the focus of medical policy-making from populations to individuals, and raises questions of privacy, public policy and general morality. Issues of financing and public health have traditionally been major concerns of the national healthcare systems of many countries, including Israel. Privacy and confidentiality are relatively recent concerns and have, with greater or lesser success, been grafted onto the existing systems. With the advent of individualized medicine, these peripheral issues are coming to the fore. This is particularly relevant for foreseeable developments in behavioral genetics, the implications of which may have serious consequences for the rights of individuals and the morality of society at large.

Behavioral genetics is:

- *The identification of behavioral traits*, such as aggression, intelligence and addiction, which are genetically determined, accepting that there is often an interaction between genetic predisposition and environment. One of the most widespread behavioral conditions for which there is a genetic component is alcoholism [2]. Obviously, any susceptibility to alcoholism will remain latent unless or until the social setting makes alcohol available and desired. The premise that any behavior might be, at least in part, genetically determined is denied by some, but this is not an issue we choose to engage in this article.

- *Identifying the genes that are involved*. Behavioral traits are characteristically polygenic, which makes them hard to analyze, but novel approaches to population genetics, such as finding quantitative trait loci [3], are beginning to yield some success [4].

- *Devising modes of intervention* to modify or reverse genetic traits that are perceived as undesirable. Avoidance of genetic risks through genetic counseling is relatively uncontroversial, but there is little agreement beyond this. There is no consensus on what modes of intervention are acceptable, or even on what genetically determined conditions are undesirable [5].

Polygenic diseases

Just as the study of monogenic diseases was instrumental in understanding normal metabolism, so the investigation of polygenic diseases helps to understand the genetics of behavior. We are familiar with monogenic heritable diseases (hemophilias, thalassemias, etc.). What the New Biology has brought us is the diagnosis of susceptibilities to the far greater number of polygenic diseases. The development of their symptoms in any individual is less certain, but the susceptibility to them can now be assessed in pre-symptomatic individuals or even in unborn children, and the prospect, based on preliminary indications, is bright for treatment of these diseases.

DNA chips and the individualization of diagnosis and therapy

Once the responsible genes are identified, the technology now exists to relatively easily analyze any particular gene and its known polymorphisms – in either an individual or an embryo. Briefly, the technology consists of a credit card-size plate (a DNA "display" or

"chip") that can identify in an individual's DNA, taken from a blood or saliva sample, tens of thousands of DNA sequences that are known to be indicative of a normal gene or a known mutation [6]. After exposure to the individual's DNA, the chip is scanned and the presence of the normal or mutated gene is recorded. It is foreseen that with this information, prediction may be made of the risk, but not necessarily the certainty, of a specific disease in an individual. In the case of late-onset diseases, this can serve as a signal for prophylactic treatment. Another version of the chip technology allows the analysis of expression levels of a set of genes in a given tissue or blood cells [7], and this version can tell us, for example, which oncogenes determine the growth of a tumor, which variant of the serotonin transporter gene is responsible for anxious behavior, which polymorphisms in receptor genes are causing depression [8], and which therapy would be most effective.

In considering the individualization of cancer chemotherapies, Evans and Relling [9] summarize the considerable body of knowledge on the ethnic and racial differences in polymorphisms that determine their effectiveness. The sub-discipline is, predictably, called pharmacogenomics. The same concerns are applicable to behavioral genetics, especially in light of the widespread pharmacologic treatment of psychiatric and behavioral conditions [10]. They state, "The marked racial and ethnic diversity in the frequency of functional polymorphisms . . . dictates that race be considered in studies aimed at discovering whether specific genotypes or phenotypes are associated with disease risk or drug toxicity." However, no ethnic group or race is uniform in the occurrence of these polymorphisms. Rather than helping a clinician decide on a course of therapy, this fact merely emphasizes the variability among individuals in the responsiveness or sensitivity to any particular treatment. The genetic make-up of an individual cannot safely be reconstructed based on his/her race or ethnicity; it must be determined in each case. Evans and Relling continue: "Because every individual represents a combination of drug-metabolizer phenotypes . . . it is apparent that some individuals are destined to have unusual reactions to drugs or to combinations of drugs due to the coincidental occurrence of multiple genetic defects in drug-metabolizing enzymes."

Thus, the New Biology offers relief from the one-size-fits-all approach, in which a diagnosis, e.g., of late-onset diabetes, carries with it a fairly standardized treatment [11]. Schizophrenia, for example, being a polygenic disease [12], cannot be strictly stereotypical. If we knew the detailed genetic make-up of each schizophrenic, we could design an individual therapy that would ideally suit each subject. Deciphering the multiple genes that contribute to such behavioral traits will open new avenues toward understanding and treatment of these disorders. Knowing the detailed genetic make-up of every person is certainly within reach, and the individualization of therapy seems realistic.

The present debates confront two familiar and not entirely independent issues, now raised in a new setting:

- *Confidentiality and the genetic diagnosis of pre-symptomatic diseases.* Who, and under what conditions, should have access to this information? Many individuals (relatives, fiancés) and agencies (employers, health insurers) have credible claims on the information. What balance should be struck between their claims and the individual's right to privacy? At another level, some inherited traits are already required to be reported to public health authorities; should dangerous behavioral phenotypes be added to the list? The practical and ethical issues posed by the New Biology make a confrontation with these issues inevitable [13,14]. Furthermore, these matters raise additional questions.
- *Conflicts between the rights of the individual and of society.* The individualization of diseases, which is promised by the New Biology, somehow runs contrary to the social traditions of healthcare in Israel, which, like in other social democracies, has been designed to cover the general public, not primarily to serve individuals. Now that we are presented with a new paradigm of healthcare, what accommodations should and can be made?

Confidentiality

While such discussions usually emphasize the dangers to individuals, there is another dimension to the issue. Few rights are absolute. They are limited by the rights of other individuals and those of society. If a person is a danger to others for whatever reason – be it genetic or non-genetic – there have to be limits to his/her rights. For instance, employers, or the State, should not be forced to hire someone in a sensitive position who has a known (or knowable?) disposition to dangerous unsocial behavior. That may apply without objection to military intelligence; does it also apply to kindergarten teachers?

However the genetic information will be applied in practice, enormous power will be put into the hands of those who administer it: the power to include or exclude individuals from the normal benefits of society and, because therapy for genetic disorders is in the offing, the power to reshape the human mind. If ever such programs are to be set into motion, the challenge to society is to first set appropriate guidelines, to continuously monitor the application of the procedures, and to hold the administrators of such programs to professional and public account.

Individual-centered vs. social-centered medicine

These issues are tied up with the concern for "rights." The rights of society to set norms of individual behavior are a defining feature of traditional cultures. The society may have been a tribe, a religion, a nation, or an aristocracy speaking for any of them. In the west, beginning in the eighteenth century, the dominance of society was challenged by the rise in esteem of the individual and the insistence on the rights of man. Nevertheless, as long as humans live in societies, they have to concede some of their independence to the community. A stable balance between the individual and society has not been achieved; indeed, the tension between them is one of the chief motors that drives politics and will continue to do so for the foreseeable future. How behavioral genetics is being dragged into the fray is exemplified by the recent case of a couple who elected to create, by *in vitro* fertilization and genetic analysis of embryos, a baby who would be, like them, deaf [5]. Here is clearly posed the conflict of the interests of individuals and society. The couple claims that what is seen as a disability by many, including

most deaf people, by the insurers who assist them and by society at large, is to them a matter of cultural identity, to which they have a "right." (The child's wishes have yet to be heard.) The case can only blunt the claim of most deaf people that their condition is a disability that deserves special consideration. Recognition of the couple's "right" impairs the "right" of other deaf people to have their condition treated as a medical disability, but few would argue that society's wishes should always take precedence. The history of the last century is all too grim a reminder of the evils that can be packaged as society's right to rid itself of undesirable traits; but the burden of that experience probably contributes to a lack of confidence in confronting the claims of hitherto undiscovered "rights."

The positive or negative impact of behavioral genetics on social and environmental issues places society at the center. In a way, behavioral genetics reflects one aspect of the originally well-intentioned but now thoroughly discredited science of eugenics (http://www.eugenicsarchive.org/eugenics). The Nazi-era purification of the race by elimination of those deemed unsuitable – we all know the list – is a dark episode in European history. However, as it did not begin with them, it did not end with them, since only recently was it acknowledged that between 1936 and 1976 thousands of Swedish women were forcibly sterilized because alcoholism, mental illness, mental retardation or epilepsy were taken to indicate their genetic inferiority [15]. But not every intervention is malign. Changes in diet can ameliorate some diseases, even behavioral abnormalities [16], as is well known to students of the Hanoverian Dynasty and to moviegoers (*The Madness of King George III*).

The power of behavioral genetics makes it most controversial; it offers the possibility to change the human personality or ostracize those with the genes for unpopular traits. Western civilization has had experience with such attempts in the past, and our record is not good. Society has been "improved" by shaping populations to homogeneity of religious practice, theories of race, or the dialectics of history. All these seemed to be good ideas at the time, at least to enthusiasts, and our challenge is not to merely improve on the science behind such efforts. This being said, there may be a real social benefit to identifying the genetic basis of antisocial behavior, and, within limits of medical ethics and general morality, to limit the consequent damage. This may mean altering the personality of the extremely antisocial individual through as yet unavailable therapeutic protocols that can be developed once the corresponding genes are identified, an effort that will require much thought and debate.

Prenatal testing

The dangers of the New Biology are as wide as the opportunities it offers. There is the issue of the interests of parents in their children. It is now possible to screen embryos for many known genetic diseases. The argument has been forwarded that, given the choice through *in vitro* fertilization and the ability to test for behavioral traits, parents have a right to select the child that best suits them, even selecting for non-disease traits [17]. Others take a much more conservative stance on these issues [18]. When the genes that contribute to shyness, self-assuredness and declarative memory are identified, where should the line be drawn, and who should draw it? History gives no reassurance that genetic information will be used judiciously. For a growingly narcissistic culture, such as in the west, or sexually biased societies, such as in the Far East, these are real concerns. It would be flying in the face of experience to depend on the self-restraint of the public or of the medical profession alone to regulate these matters. Since 1998 Israel forbids human cloning, but some countries do not. Moreover, the public, the medical profession and the different government offices may have divergent interests; no one group has the ethical high ground. The best protection is probably to give all groups some voice in making collaborative decisions that will be public, and settle supervision over their implementation in non-governmental bodies.

Routine testing

What tests should be routinely performed? As "routine" inevitably means government-authorized and publicly financed, the only reasonable criteria are that the tests:

- *are voluntary*. In the absence of an over-riding health concern, the government should not coerce testing.
- *are reasonably inexpensive*. If testing is expensive, it will compete with more urgent health issues for the same limited government funds.
- *offer clear-cut results*. In order that the public have confidence in the procedure and the system that administers it, both positive and negative results must be reliable, or lead to follow-up tests that are.
- *offer the possibility of effective therapy or prevention of risk*. If tests are only to satisfy a curiosity, and do not offer an effective therapy for an identified genetic risk, the program is at best a waste of time and money and an intrusion into the private affairs of individuals who are tested.

The dilemmas that may be encountered are endless. For instance, the public at large may benefit from a program to screen for genetic disposition toward violent behavior, but would it target individuals before any violent act is committed, or only afterward? Who shall be tested and under what circumstances? The law requires that for research purposes, testing be done only with informed consent, but several treatable genetic disabilities are now screened in newborns without requiring parental consent. What criteria will apply for genetically determined behavioral traits? Perhaps the same safeguards that apply to informed consent for other medical procedures should apply in these cases as well. No safeguard is foolproof, and the same failures and abuses of the present systems will probably apply also to genetic testing. Still, although we live in an imperfect world, this should not paralyze us.

The fleeting gap between the public's expectation to partake of the highly publicized opportunities offered by the Human Genome Project, of genetic testing in particular, and the public's general wariness of any innovation, perhaps gives the biomedical community a chance to offer some leadership in the ethical, responsible and effective use of these opportunities for the well-being of our society before we are presented with an array of ethically and morally questionable *faits accomplis*.

References

1. Garrod AE. Inborn errors of metabolism (Croonian Lecturers). *Lancet* 1908;ii:1–7, 73–9, 142–8, 214–20.
2. Lewohl JM. Dodd PR, Mayfield RD, Harris RA. Application of DNA microarrays to study human alcoholism. *J Biomed Sci* 2001;8:28–36.
3. Rannala B. Finding genes influencing susceptibility to complex diseases in the post-genome era. *Am J Pharmacogenomics* 2001;1:203–21.
4. Shifman S, Bronstein M, Sternfeld M, et al. A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet* 2002;71:1296–302.
5. McLellan F. Controversy over deliberate conception of a deaf child. *Lancet* 2002;359:1315.
6. Zammatteo N, Hamels S, De Longueville F, et al. New chips for molecular biology and diagnostics. *Biotechnol Annu Rev* 2002;8:85–101.
7. Polyak K, Riggins GJ. Gene discovery using the serial analysis of gene expression technique: implications for cancer research. *J Clin Oncol* 2001;19:2948–58.
8. Krishnan KR. Biological risk factors in late life depression. *Biol Psychiatry* 2002;52:185–92.
9. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999;286:487–91.
10. Tribut O, Lessard Y, Reymann JM, Allain H, Bentue-Ferrer D. Pharmacogenomics. *Med Sci Monit* 2002;8:RA152–63.
11. Collins FM. Current treatment approaches to type 2 diabetes mellitus: successes and shortcomings. *Am J Manag Care* 2002;8:S460–71.
12. Prasad S, Semwal P, Deshpande, S, Bhatia T, Nimgaonkar VL, Thelma BK. Molecular genetics of schizophrenia: past, present and future. *J Biosci* 2002;27:35–52.
13. Bird TD. Risks and benefits of DNA testing for neurogenetic disorders. *Semin Neurol* 1999;19:253–9.
14. Bird TD, Bennett RL. Why do DNA testing? Practical and ethical implications of new neurogenetic tests. *Ann Neurol* 1995;38:141–6.
15. Anonymous. Sweden plans to pay sterilization victims. *The New York Times* 27 January 1999:A8.
16. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. *Int J Clin Pract* 2002;56:272–8.
17. Savulescu J. Procreative beneficence: why we should select the best children. *Bioethics* 2001;15:413–26.
18. Spriggs M. Genetically selected baby free of inherited predisposition to early-onset Alzheimer's disease. *J Med Ethics* 2002;28:290.

Correspondence: Dr. H. Soreq, Dept. of Biological Chemistry, Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem 91904, Israel.
Phone: (972-2) 658-5109
Fax: (972-2) 652-0258
email: soreq@cc.huji.ac.il

Capsule

T cell memory

Using mice carrying a viral-specific transgenic T cell receptor, Kaech et al. performed a genome-wide profile of CD8+ T cells and correlated this with function and phenotype of these cells, before and after viral infection. Predictably, genes controlling migration, cytokine expression, and cytotoxicity were active during infection. In contrast, transcription of other genes increased only in memory cells that persisted several weeks after viral clearance. Among these were genes associated with cell cycle regulation, response to homeostatic cytokines, and receptor-mediated signals. Thus, precursors for CD8+ memory T cells emerge during the height of a viral immune response, but only later become fully equipped to self-maintain and to respond rapidly to subsequent infection.

Cell 2002;111:837

Capsule

Anemia gene discovered

A rare type of anemia found mainly in Bedouins may provide insight into the disease. Scientists at Schneider Children's Medical Center, Tel Aviv University, and the Weizmann Institute of Science identified the gene *CDA-1* (congenital dyserythropoietic anemia-1) responsible for a type of anemia found in several Bedouin families. These findings (*Am J Hum Genet*, December 2002) could lead to effective detection and eventually treatment. Also, understanding the role of this gene's protein product could provide important clues to other types of anemia and to general mechanisms of blood cell formation. CDA-1 is characterized by a medium to high deficiency in blood production, and critical patients receive blood transfusions throughout their lifetime. It is a rare disease worldwide, but the most vulnerable group is the Negev Desert's Bedouin population, which practices consanguineous marriage. The high disease prevalence in this Israeli population was crucial to the identification of the *CDA-1* gene. The researchers observed that mutations in this specific gene correlate with the disease. These mutations modify a previously unknown protein called codanin-1, which is likely present in the nuclear envelope of bone marrow cells that divide and give rise to red blood cells. Studies of this protein, which may become an important pharmaceutic target similar to erythropoietin, may yield a better understanding of blood cell maturation and anemia and eventually lead to an effective remedy for CDA-1.

Israel High-Tech & Investment Report 2003;19:7.