

# Anti-Genetic Exceptionalism in Complex Disorders: Making a Case for Disclosure of Polymorphic Genetic Results in Clinical Research Studies

## Abstract

It is increasingly common for clinical research studies to include a genetic component. In complex genetic disorders, disease is associated with variation in many genes, each of which contributes only a small, discrete effect. The nature of the genetic information generated by such studies increasingly necessitates re-examination of the ethical precepts underlying their research questions, study designs, and disclosure practices. This article addresses the ethical basis for decisions whether to disclose the results of testing for polymorphic genetic variation to individual research participants, who often express great interest in knowing "Do I have the gene?" The paper argues that information about polymorphic genetic variation is unexceptional when compared to other data commonly collected in clinical research studies, such as age, blood pressure readings, or family history. This lack of exceptionalism should be considered in the procedures for disclosure in research studies of complex disorders involving polymorphic genetic variation.

## Introduction

Legend has it that in the early 1950s, after a particularly good day in the laboratory, Francis Crick walked into a Cambridge pub and announced, "We have found the secret of life". He was, of course, referring to his discovery, with James Watson, of the double helix structure of the DNA molecule [1]. This 'molecularizing' of DNA fundamentally and permanently altered the study of human genetic diseases. Within a short period after the molecular structure of DNA had been determined, the molecular genetics of sickle cell anemia were described as a single amino acid substitution. Recombinant DNA technology was introduced in the 1990s. Today, human genetics medical research is experiencing unprecedented progress and rapid discovery. In the past decade alone, significant accomplishments include completion of the Human Genome Project, Phase 1 of the HapMap project, and the initial stage of the ENCYclopedia of DNA Elements (ENCODE) [2], as well as the launch of the 1000 Genomes Project [3,4]. Having advanced by orders of magnitude from its first 'molecular' discoveries in the 1950s, the scope of human genomics is now vast, encompassing not only the genome, but also epigenetics, gene expression, exomics, proteomics and more.

As scientific knowledge of genes and their relationship to diseases has advanced, so too has the scope of clinical disease amenable to genetic research. Until relatively recently, monogenic disorders, in which a single genetic mutation inexorably causes disease, dominated human medical genetics. Sickle cell, Tay-Sachs and Huntington's diseases, and Marfan's syndrome are a few well-known examples of monogenic disorders, from a catalog of more than 1800. In recent



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years, however, the field of human medical genetics has undergone a paradigm shift. A significant proportion of research studies now focus on "complex genetic disorders", in which disease is associated with variation in many genes, not just one [5].

## Monogenic versus Polygenic Inheritance and the Ethics of Disclosure

Complex disorders can be oligogenic, a combination of variants in several genes, or polygenic, the cumulative result of polymorphic variation in tens, hundreds, or even thousands of genes, each of which contributes only a small discrete effect. Rather than *determining* disease destiny, quite literally whether or not disease will occur, as is generally the case for monogenic mutations, polymorphic genetic variation confers *susceptibility*, and permits at best a probabilistic statement about the likelihood that disease will develop. In the etiology of complex disorders, genetic variation is merely one factor among many that interact with each other and with the environment in complicated and poorly understood ways. Cancer, diabetes, Alzheimer's disease, and asthma are examples of this relatively new category of genetic disease.

As the scope of knowledge and information about disease subsumed under the rubric of genetics has exponentially broadened, and as dramatic advances in available technology have continually moved the cutting edge of gene discovery, clinical research ethics in genetic studies of complex disorders have not entirely kept pace. The nature of the genetic information generated by complex disorder studies -- polymorphic, polygenic, and conferring susceptibility rather than monogenic-like causality -- requires that we re-examine ethical issues in the design of research studies that investigate them, for ethical precepts may no longer apply in traditional or expected ways.

One area in which ethical flux is especially notable is the decision whether to disclose the results of testing for polymorphic genetic variation to individual research participants, who often are highly interested in knowing "Do I have the gene?" When complex disorders are under investigation, this is an unsophisticated question, as there is no single causative gene. Unfortunately, the answer from

most research studies, and the rationale for that answer, often betray a comparable lack of sophistication. The current practice in most research studies involving polymorphic genetic variation is explicitly one of nondisclosure of individual results [6]. The ideas invoked by researchers as the basis for this stance are in part appropriate and necessary ingredients of the disclosure decision: the nature of the scientific enterprise and fundamental principles of research ethics. In traditional clinical research studies this combination has been a successful recipe. However, in complex disorders, it fails.

### **Ethical Breakdown: Genetic Exceptionalism and Polygenic Disorders**

The crux of the failure lies in treating polymorphic genetic variants as though they too convey predictive information comparable to that of monogenic mutations, where possessing a documented mutation determines whether or not one will develop the disease in question. As a result, disclosure decisions are often based on standards for scientific validity, clinical utility, and ethical behavior that are applicable to monogenic genetic information. These standards are unwittingly predicated on what is now an outmoded idea: that genetic information is exceptional, different from other biomedical indices because it is uniquely individualized and powerfully predictive of future health events [7,8]. As a consequence of this perspective, genetic information seems qualitatively different from other biomedical data collected in clinical research. But in fact, the opposite is true. For purposes of predicting future disease outcomes, knowledge of whether one possesses a given polymorphic genetic variant is comparable to knowing a detail from the family history, or one's height or handedness: simply one detail among many that collectively determine future risk. Compared to other types of data likely to be collected in a clinical research study, information about polymorphic genetic variation is wholly *unexceptional*. This anti-exceptionalism perspective should be the *sine qua non* of the disclosure decision in research studies of complex disorders involving polymorphic genetic variation.

Irrespective of the type of genetic information under study, certain basic ethical principles are relevant to the issue of whether to disclose individual genetic results to research participants. Most prominent among them are autonomy and beneficence [9]. Autonomy is the principle that recognizes that individuals must be treated as agents capable of self-determination, and that decisions made in service of that self-determination must be respected. Autonomy underlies the requirement for informed consent, the disclosure of all relevant information about the nature of the study that permits a potential participant to make a reasoned decision about whether to take part in it. In some studies with a genetic component, participants may be asked during the informed consent process to make a decision about whether they are interested in learning the results of genetic testing. Much more commonly, they may be told explicitly that the study design prohibits disclosure of such results. Autonomy also incorporates the ideas of privacy and confidentiality, both increasingly contentious issues in virtually all areas of genetic research involving human subjects.

The principle of beneficence requires that researchers endeavor to maximize benefit (beneficence) and to minimize harm (nonmaleficence), and thus ensure the well-being of research participants. Beneficence exhorts researchers to 'do good'. Disclosure

of genetic information may provide psychological benefit, as participants may find it reassuring to acquire information about their risk for future disease, especially if that risk appears to be low. If the risk appears to be higher, knowledge might prompt salubrious lifestyle modification or other preventive measures, potentially producing direct physical benefit. In most circumstances, nondisclosure is unlikely to be beneficial, as it is difficult to ascribe direct benefit to not knowing one's genetic information. In contrast to beneficence, nonmaleficence demands that researchers 'do no harm.' Participants in research studies that involve a genetic component may face minor physical harm, as most studies will require venipuncture to obtain a blood sample for genetic analysis. (Some studies may require only a buccal swab, in which case the potential for even minor harm is obviated). Greater risks for potential harm in genetic research studies arise from possible psychological distress or socioeconomic disadvantage. Psychological harm may occur if a research participant experiences anxiety, which can arise from not knowing their genetic status in the case of nondisclosure of results, or from knowing that they possess a genetic mutation or susceptibility allele in the case of disclosure. Learning that their genetic results indicate either no predisposition to disease or that a protective factor is present can instill a false sense of security and could contribute to increased risk-taking behavior (e.g. "who cares if I eat that donut, then smoke a cigarette? My genes say I will not have a heart attack"). Mistrust of the investigators can develop if participants are required to receive information they do not want (in the case of disclosure) or if they are not provided with information that they do want (in the case of nondisclosure). The potential for socioeconomic harm arises from possible stigmatization or discrimination, particularly in obtaining a job or securing an insurance policy.

### **Scientific Validity and the Disclosure Decision**

Along with these basic ethical precepts, the scientific enterprise itself becomes an important ingredient in the rationale for disclosing or withholding individual information about polymorphic genetic variation. The most fundamental purpose of scientific research is to generate valid knowledge that is generalizable. The requirement for generalizability is explicit and often provides the rationale for nondisclosure of individual research results, whatever the nature of the study. (Exceptions are possible, however, especially in the case of potentially harmful incidental findings. For example, suppose a research study of midlife risk factors for Alzheimer's disease includes structural brain MRI and an asymptomatic mass lesion is discovered on a participant's scan. Few would argue that individual notification of this result is not justified).

The requirement that knowledge be valid before it can be thought of as scientific raises a thornier issue in the genetic disclosure debate. In 1999 the National Bioethics Advisory Commission (NBAC) recommended that disclosure of individual genetic research results should take place only under exceptional conditions, and should be permissible only if the findings are scientifically valid and confirmed, if they possess significant implications for the individual's health, and if an ameliorating or therapeutic course of action is readily available [10]. This standard can be applied to a monogenic disorder, such as Huntington's disease (HD), with little difficulty. The trinucleotide repeat in HD is valid and confirmed as causative, the individual health consequences of eventual disease onset are unquestionable and, while no cure or even effective treatment exists, it can be argued

that foreknowledge enables decision-making and planning, and that such activities have therapeutic benefit of a sort.

The NBAC standard does not apply nearly so easily in the case of polymorphic genetic variation in complex disorders. Such variants number in the millions, most have decidedly modest impact on their own, they interact with one another in dizzyingly complicated ways, and their interactions with nongenetic factors seem, at present, to be nearly limitless in their potential scope and variability. In this setting, genetic information loses its ‘exceptional’ quality entirely. As a recent commentary noted, polymorphic genetic variants do not “necessarily provide information that is inherently different from the other predictors commonly used in health care, such as age, gender, blood pressure, smoking status, cholesterol level or family history” [7]. In other words, polymorphic genetic variation is “not much more informative than a short family history” [8]. Put another way, should disclosure to a research participant of his weight, or his cholesterol level, or his score on a mental health screening test, or any of the scores of other, unexceptional, clinical data points collected in research studies be prohibited because of ethical concerns? Because of insufficient generalizability? Because the measurement is not valid enough? If the answer to these questions is no, then why answer yes for polymorphic genetic results, as so many research studies now do?

If researchers are to liberalize their disclosure procedures, they will need to take other steps as well. Clinical research participants should be provided with a brief description of the polymorphic genetic variants included in the study, with no special treatment. If the main focus of the study is genetic association, the associations and hypotheses being tested should be explained in simple, clear language. The possible outcomes – and the meaning of these outcomes – should be provided, with an emphasis on gradations of meaning. For example, a statistically-significant genetic association at the level of  $10^{-8}$  will not necessarily have clinical meaningfulness discernible by research participants. Researchers should make themselves available to answer questions about the research they are doing at regular intervals during the research project, and should expect to review concepts such as susceptibility, epigenetics, and probability at these meetings. In most cases, participants know that the study was investigating a ‘genetic’ question and (rightly) believe that they should have access to their results, with reasonable accommodation to an informed layperson’s understanding.

If researchers are not willing to provide this minimal degree of information, then research participants can hardly be blamed if they stop participating or opt to seek their answers elsewhere, such as the internet. Given the amount of biomedical and genetic information currently available in public domains, we do our research participants

no favors if we continue to shroud their genetic predispositions in secrecy. To take these logical steps may require revision of current guidelines that emphasize nondisclosure of any genetic information, to make appropriate provision for both polymorphic and monogenic genetic information, understanding and reflecting the differences between the two categories, rather than inappropriately conflating them. Protections, along the lines of the 2008 Genetic Information Nondiscrimination Act, may need to be extended and enhanced.

## Conclusion

Polymorphic genetic variants are neither deterministic nor exceptional. They are but one piece in an exceedingly intricate array of factors, some predisposing to risk and some to protection, some genetic and many not, that cumulatively tilt the balance either toward the occurrence of disease, or no disease. At present, knowing which way the balance tilts at a given time, and knowing whether it will eventually culminate in disease, is beyond our power to understand. But we should reassess the manner in which we decide who gets to know and for what reasons. Both ethical behavior in disclosure decisions and respect for the scientific enterprise should compel us.

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