The Ethics of a Genetic Screening Study for Antisocial Personality Disorder With Mesoamericans

Case Study in the Ethics of Mental Health Research

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Abstract: This article contains an analysis of a research ethics committee's (REC) concerns about a study protocol involving genetic screening for antisocial personality disorder. The study was proposed by US university researchers and to be conducted with Mesoamerican populations in the United States and in their countries of origin. The analysis explains why the study was not considered ethical by the REC, pointing to issues with the choice of study population, informed consent, confidentiality, and posttrial obligations. Some recommendations are provided for ways in which the study could have been redesigned.

Key Words: Genetic screening, antisocial personality disorder, ethical issues.

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THE RESEARCH PROJECT

Antisocial personality disorder (ASPD) is defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV-TR*), as "a pervasive pattern of disregard for, and violation of, the rights of others occurring since age 15 years, as indicated by three (or more) of the seven criteria that include four in the interpersonal realm (including a failure to conform to social norms, irresponsibility, deceitfulness and indifference to the welfare of others); one in the behavioral realm (recklessness); one in both the behavioral and cognitive domain (a failure to plan ahead); and finally, one in the mood domain (irritability and aggressiveness)" (American Psychiatric Association, 2000; Million and Davis, 1996). The prevalence of ASPD in the United States is 3% in men and 1% in women (American Psychiatric Association, 2000).

In 2004, US university researchers proposed a genetic research protocol to be conducted in Mesoamericans, with the aim of identifying a gene for susceptibility to ASPD. Selection of this population was intended to overcome an important limitation mentioned in previous genetic studies of psychiatric diseases—genetic heterogeneity—by using a more genetically homogeneous population. The researchers identified the following features as further reasons for selecting this particular group:

1. The Hispanic population is now the largest single ethnic group in the United States, which makes it a timely population for genetic study.
2. Hispanics have been largely untapped in previous genetic studies of mental health disorders.
3. The Hispanic population is well suited to genetic studies because Hispanic families typically have more individuals than families from other ethnic groups; there exist multigenerational pedigrees, which are mostly descended from a small number of founders a short number of generations ago; and there is a great deal of environmental and phenotypic homogeneity.

Using a Mesoamerican population also permitted the study to be conducted simultaneously in the United States and in Mesoamerican countries of origin. For the non–United States parts of the study, local psychiatrists were to be hired and trained in the United States with specific tools for accurate psychiatric diagnosis.

Methodology

This study proposed the analysis of biological samples to localize genes that contribute to the genesis of ASPD and relevant endophenotypes. Endophenotype is a psychiatric concept referring to a special kind of biomarker or indicator that divides behavioral symptoms into more stable phenotypes with a clear genetic connection. The concept of endophenotype was adapted for filling the gap between available descriptors and between the gene and the elusive disease processes in psychiatric genetics (Gottesman and Gould, 2003). The long-term goals of the project, beyond the scope of this particular study, were to fine map and identify mutations in specific genes associated with loci identified by the study.

The study was to proceed as follows. First, patients with ASPD would be identified through an exhaustive search of medical records in public and private psychiatric hospitals and outpatient psychiatric units by the researchers, including in psychiatric units where the researchers did not work, and through media advertisements.

Second, once the patients were identified, their vital data would be collected in an Excel database, and those younger than 40 years would be prioritized. The patients would be contacted, and preliminary informed consent would be obtained for the collection of data such as the presence of siblings with ASPD and verification that all four grandparents were of Mesoamerican ancestry.

Third, if the family met the inclusion criteria, the researchers would attempt to enroll as many family members into the study as would agree to participate. The ideal family to be recruited would have two brothers or sisters with ASPD, both parents living, and an average of two unaffected siblings, and there should be an average of 20 subjects per pedigree. Both unaffected and affected siblings should be 15 years or older.

All participants (affected and nonaffected) would undergo the following procedures after signing the informed consent form:

1. Clinical and neuropsychological testing with special diagnostic tools
2. A physical examination
3. Magnetic resonance imaging
4. Phlebotomy to provide a blood sample for deoxyribonucleic acid (DNA) analysis

The samples would be sent to a central biobank located in the United States, where they would be analyzed using special software. They would be stored in this central gene bank and made available to qualified researchers at the end of the study, including, potentially, for commercial use. Family relationship information, ethnicity, and all

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Aspects of the research project described in this case study, including the precise condition under study, have been made anonymous to preserve the confidentiality of some of the people involved.

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clinical and genotype data would be included in the database. However, genetic information would be separated from the donor's personally identifying information, so no one could match the samples to its donor.

During the consent process, participants would be informed of possible future uses of their samples and made aware that they have no rights concerning any subsequent use of the materials.

The goal was to recruit 385 families, including 500 pairs of affected siblings, for a total of 3000 participants.

BACKGROUND: ANTISOCIAL PERSONALITY DISORDER

The concept of a personality disorder with callousness and lack of emotion, plus disregard for social norms is well established in psychiatry. Such people share a combination of traits including violence, aggression, callousness, lack of empathy, and repeated acts of criminality against social norms. However, the classification and definition from this point onward are not clear (Chaturaka et al., 2010). The *DSM-IV-TR* classifies it as antisocial personality disorder, whereas the corresponding diagnosis in the 10th revision of the World Health Organization's (WHO) International Classification of Diseases (ICD-10), published by the WHO, is dissocial personality disorder (World Health Organization, 2007).

Even the United Kingdom's National Clinical Guidelines note ambivalence and debate concerning this disorder among mental health professionals, including over the establishment of definition-supporting criteria for a more specific diagnosis, leading to treatment. Some of the outstanding problems in this debate are the overlap between different personality disorder diagnoses, heterogeneity among individuals with the same diagnosis, the inadequate capture of personality psychopathology, and growing evidence in favor of a dimensional rather than a categorical system of classification (National Collaborating Centre for Mental Health, 2010).

In terms of physiology, current research indicates a role of serotonin, cortisol, and testosterone in aggressive and antisocial behavior (Glenn and Raine, 2008). The role of genetics in determining violence and aggressive behavior has also been examined recently. Evidence from a meta-analysis of 50 studies suggests that children often develop ASPD as a result of their environment, as well as their genetic line. Genes seem to account for approximately 50% of population variation in antisocial behaviors, whereas environmental factors shared by family members account for about 20% (Moffit, 2005; Rhee and Waldman, 2002).

A meta-analysis searching for risk factors found that family risk factors such as parenting styles, parents' antisocial behavior, and parental disharmony/separation in the combined family measure in adolescence, presented an odds ratio (OR) of 2.50 (95% CI, 1.82 to 3.41), although there were slightly less data on social risk factors in a combined analysis of factors associated with social deprivation, with an OR of 2.39 (95% CI, 1.89 to 3.04; National Collaborating Centre for Mental Health, 2010).

Corley et al. (2008) analyzed single nucleotide polymorphisms in a sample of adolescents with antisocial behavior and drug dependence. They reported significant gene-based associations for two genes, *CHRNA2* and *OPRMI*, compared with controls, with an OR of 1.60 (95% CI, 1.19 to 2.15); $p = 0.002$ and an OR of 1.47 (95% CI, 1.11 to 1.36); $p = 0.006$, respectively (Corley et al., 2008). Rhee and Waldman (2002) also found a genetic connection on a dual diagnosis of substance abuse and conduct disorder symptoms, showing evidence for linkage to 9q34 chromosomal region when both vulnerability to drug dependency and conduct disorder symptoms were considered. There was also evidence for linkage to the 17q12 region for conduct disorder symptoms alone. Later analysis has shown that the influence of heredity is greater in children with antisocial behavior with callous and unemotional traits compared with those without callousness (Viding et al., 2005, 2007).

Knowledge from other studies recognizes that the heritability coefficient indexes not only the direct effects of genes but also the effects of interactions between genes and family-wide environments. In such interactions, the effect of an environmental risk may be even larger among the subgroup of individuals with a vulnerable genotype.

ETHICAL ISSUES

The research ethics committee (REC) in one of the proposed host Mesoamerican countries had to assess the study before subjects in that country could be enrolled. It identified several ethical concerns with the study, including fair participant selection, confidentiality, and failure to transfer technology to local researchers. This analysis will elaborate on the REC's concerns, explain why the study was not considered ethical, and recommend some ways in which the study could have been redesigned.

Study Population

The Belmont report says,

> *An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly… For example, the selection of research subjects needs to be scrutinized to determine whether some classes of subjects are being systematically selected simply because of their availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied.* (The National Commission for the Protection of Human subjects of Biomedical and Behavioral Research, 1979)

This research project throws up two issues of justice. First, the selection of Hispanic participants (and the exclusion of other groups) does not seem to be based on good scientific reasons. Second, even if there were scientific reasons to use a Hispanic population, the study might be exploitative if the benefits of the research are unlikely to accrue to populations from which the participants were drawn.

Regarding the first, the protocol said that the target population was chosen because Hispanic families are big and the chance of finding a pair of affected siblings in a homogeneous population is high. However, the protocol's background did not mention any epidemiological study concerning this population to support this argument. The study's methodology was built on the supposition that the research team might find more than one affected member of the family. The target population was also chosen on the belief that Hispanic families are more homogenous, genetically and environmentally. Again, no scientific evidence was cited in support of this claim. On the contrary, according to the one genetic study on this population that is previously published, there seems to be a great deal of genetic heterogeneity (Silva-Zolezzi et al., 2009).

Regarding the second, the project was justified on the grounds that ASPD is a major public health problem in the United States. However, no evidence was provided to show that it is a particular problem for Hispanics within the United States, which raises concerns about fair subject selection. Likewise, there was no evidence given to show that ASPD is a major public health problem for this population in Mesoamerican countries, and, crucially, no explanation of how genetic findings might lead to benefits for non–United States populations. If the burden of disease in the population under study is not sufficiently high to make it a health priority for that population, then the research risks being exploitative.

Study Design

Research studies that are not able to meet their scientific objectives are usually considered unethical because they expose participants to risks or burdens without the prospect of gaining valuable knowledge.

Because there was no direct benefit to recruited subjects in this study, at the very least, it should produce valuable generalizable knowledge. The study showed several weaknesses in its design.

First, as noted above, there is still debate among mental health professionals on how to define the disease, which has implications for diagnosis. If the definition and diagnostic criteria are still not clear and some features overlap with other personality disorders, the study risks, including subjects who have been given wrong diagnoses, might lead to a mistaken association. The heterogeneity among individuals with the same diagnosis could also lead the researchers to miss a weak association. This introduces a problem of internal validity for the study.

To all this, we could also add that there are no special considerations for vulnerable subjects who could be included in the study, such as minors, mentally and emotionally impaired persons, and substance abusers, which is a common problem for people with ASPD.

Informed Consent: Voluntariness

Some genetic research studies involve the investigation of individuals within a certain family pedigree or a social or ethnic group. The design of these studies may lead to pressure being placed on people's decisions about whether to participate. For example, family members who are not interested in participating are likely to experience pressure to participate to enhance the quality of the study because a decision not to participate affects more than just them. The ethical review of pedigree studies must take into account the potential coercion of family members and be aware of alternative recruitment strategies (Larsen, 2006).

As noted above, in this protocol, the ideal family to be recruited would have two brothers or sisters with ASPD, both parents alive, and an average of two unaffected siblings. This means that it would be highly desirable to enroll a large number of people from each family. If insufficient family members agreed to participate, the study's analysis would be affected. This could lead to a lot of pressure for the researchers to recruit most members from a family and therefore lead to the researchers or interested potential participants pressuring others. Because the nonaffected members of the family would be what the study design needed to have many nonaffected family members participating to be successful, this could cause more pressure on individuals, compared with other studies that do not need a big pedigree to achieve their goals.

Risks and Benefits: Confidentiality

Although confidentiality of research data is important in all studies, it is particularly crucial in genetic research studies because of the sensitivity of the data. Article 4 of the International Declaration on Human Genetic Data states,

> *(a) Human genetic data have a special status because:*
> *(i) They can be predictive of genetic predispositions concerning individuals;*
> *(ii) They may have a significant impact on the family, including offspring, extending over generations, and in some instances on the whole group to which the person concerned belongs;*
> *(iii) They may contain information the significance of which is not necessarily known at the time of the collection of the biological samples…*(United Nations Educational, Scientific and Cultural Organization, 2003)

Genetic studies concerning an individual's behavioral characteristics deserve special attention with respect to confidentiality because many behavioral conditions carry a social stigma. For example, schizophrenia is a mental disease that has been associated with social isolation because of the violent behavior produced by patients even toward their own families (Palazzola et al., 2005). Disclosing an individual's genetic risk of developing schizophrenia could lead to discrimination even when the disease has not yet developed and may even never develop. Release of information about someone's diagnosis may therefore put them at risk. This type of information could also adversely affect an individual's future insurability and employability.

At the beginning of the study, before informed consent is given, patients' files were to be reviewed by researchers to identify prospective participants. Researchers would have access to files in psychiatric hospitals and outpatient clinics, and they would recover private data, such as telephone numbers for identification of the patients and their families. This would clearly breach confidentiality.

There is also the issue about protecting confidentiality in the family because subjects with ASPD may represent a threat to their family members, and the whole situation of the research process could exacerbate pre-existing dysfunctional relationships.

After the samples of DNA from this population were analyzed, they were to be sent to be kept in a US central bank, still with the population source identifying information attached. The samples could be shared with other researchers in studies unrelated to this one and could even be used commercially. Given concerns about immigration from Latin American countries, participants or their families might well be concerned that law enforcement officials could make use of the data. For example, data about specific individuals or families could be used to deny permanent or temporary residency petitions or support deportation on the grounds of public health or overloading the health system.

It is true that the participants were to be informed of these possibilities in the narrative summary and be made aware that they would have no rights to any subsequent use of the materials. However, consent to the terms with which they were presented is not enough: subjects should be given a choice on how they want their samples to be used. For example, they should be allowed to decide whether they want their samples to be discarded at the conclusion of the study or if they want them to be used in future studies. In multisite studies like the present one, they could also be given the option of having their samples used by local researchers to improve the knowledge of this disease in their own population.

It also seems that the risks of harming this population through stigmatization has not been considered in its full extent. This mental disorder has been linked to criminality, and this population is one of the major (and rapidly growing) minority groups in the United States, as a result of immigration as family gathering, high fertility index of people already in the United States, or simply because current immigrants are an inspiration to people left behind. This study could be used to link criminality to this population, as has been already insinuated by anti-immigrant groups.

Posttrial Obligations

Guideline 20 of the Council for International Organizations of Medical Sciences' International Ethical Guidelines for Biomedical Research states,

> *In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research… Capacity-building may include, but is not limited to, the following activities: …*
>
> - Strengthening research capacity
> - Developing technologies appropriate to health-care and biomedical research

- Training of research and health-care staff

… The specific capacity-building objectives should be determined and achieved through dialogue and negotiation between external sponsors and host-country authorities. (Council for International Organizations of Medical Sciences/World Health Organization, 2002)

According to the protocol, local researchers were to be trained in the host country on using specific tools (psychiatric interviews) for accurate psychiatric diagnosis. However, these researchers already had their psychiatric specialization and were licensed to work in their home country, so it was not clear that these tools would be adding to their skill sets. There were no plans to train local geneticists and local researchers who would not have the opportunity to share in the analyses of the ASPD gene bank in future research. Moreover, no effort had been made to contact national authorities to negotiate the implementation of a gene bank for the region in one of its countries. Indeed, there was no technology transfer planned that would facilitate any future genetic research in each country by local researchers. In sum, the minimal amount of training offered did not seem enough to be considered strengthening host country research capacity.

A proposal on how to redesign multinational genetic studies like this one are not intrinsically unethical. In this section, I return to each of the ethical issues highlighted above and suggest ways in which the study design could be changed to make it ethically acceptable.

Study Population

Fair subject selection requires that the study population be selected for scientific reasons, rather than for reasons of convenience. Unfairly selected populations risk being exploited for the benefit of other groups. To show that this population has been fairly selected, the researchers need to present adequate data from epidemiological studies on the distribution of ASPD in Hispanic populations and the degree of genetic homogeneity they can expect. If the data do not exist to back up the researchers' background assumptions, then the design of the study may have to be more radically revised, either to expand the study population or amend the scientific questions the study addresses.

Informed Consent: Voluntariness

The enrollment of a pre-established number of family members along with the identified patient is currently one of the main pillars for the success of the study. The concerns about pressure to enroll noted above suggest that the protocol needs to be redesigned in this regard, making it more flexible about the number of members of the family included. This should make it possible to include patients even if their family members do not want to participate. Family members should be invited to participate, but the inclusion of the patient should not be linked to their acceptance. The study should also have two different kinds of informed consent processes, one for the patients and another for family members affected and not affected by the disorder.

Confidentiality

The concerns about confidentiality can be addressed without radical changes to the study design. First, instead of going through the clinics' files and patients' personal data, the researchers should publish advertisements for patients and contact psychiatrists to inform them about the study. In this way, only those patients who are willing to participate will contact the researchers and reveal personal information. Second, researchers should provide guarantees to participants that their health information will remain private. For example, in the United States, they might obtain a Certificate of Confidentiality issued by the National Institutes of Health for research that works with sensitive data, which protects the data against compelled disclosure. Although information on the effectiveness of Certificates of Confidentiality is limited and they might not provide absolute protection, they have been used to block the disclosure of participant data in several cases (Beskow et al., 2008; Wolf and Zandecki, 2006). Third, participants should be asked about future uses of their samples. They should be given sufficient control over them that they can participate in this ASPD study without having to give permission for unspecified future research.

Finally, local control over biological samples should be maintained. This would assuage some of the concerns over uses that might be made of the biobank out of the host country and facilitate future research by local researchers according to local needs. One way to achieve this would be to create a local in-country bank for the selected country so they could keep their biological samples after this research study ends. If this is not possible, the samples could be kept abroad, but local authorities could still be given rights over the samples so they could judge how to use them in future research.

Posttrial Obligations

Building capacity for future research of local value is an important goal for multinational collaborative research. As proposed, this study would seem not to provide any substantial long- terms gains for the country participating. As suggested above, principal researchers should try to identify local genetics professionals and involve them in the genetic analyses process so they can conduct research in their own country in the future. Similarly, the development of a local or regional genetic bank would be a significant step toward the empowering local research. Researchers should pay more attention to the needs of participating countries needs so that international research can be truly collaborative, not just a source of scientifically interesting samples.

CONCLUSIONS

Genetic testing for behavioral research is mentioned in all ethical guidelines for RECs as a research that poses challenges for the ethical review process, including the selection of participants, confidentiality, disclosure of information, and storage of data and samples. The protocol discussed here illustrates these issues, as well as the additional difficulties posed by multinational genetic research. As proposed, the REC involved considered that they could not approve the protocol. However, with appropriate amendments, including better justification of the selection of participants, protection against coercion, the safeguarding of confidentiality, and appropriate transfer of technology, such a study would be acceptable.

FURTHER READINGS

Textbooks on Ethics in Research

Dunn CM, Chadwick GL (2004). *Protecting Study Volunteers in Research: A Manual for Investigative Sites*, 3rd Edition. Boston, MA: Thomson Center Watch.

Derenzo E, Moss J (2006). *Writing Clinical Research Protocols: Ethical Considerations*. Burlington, MA: Elsevier Press.

International Guidance on Genetic Studies

Several international documents contain guidance that can help in decision making while evaluating studies that involve genetic data:

The Universal Declaration on the Human Genome and Human Rights states the basic principles of respect for human rights while conducting genetic research. The Declaration was adopted by the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1997 and endorsed by the United Nations General Assembly the following year.

The International Declaration on Human Genetic Data was adopted by UNESCO in 2003. It sets out principles governing the

collection processing, use and storage of human genetic data and biological samples for clinical care and research.

Mental Disorders and Genetics

More reflection on this issue can be found in the following:

Nuffield Council on Bioethics, (1998) *Mental disorders and genetics: The ethical context.* The Council. London, England: Nuffield Council on Bioethics.

This report is intended to define and consider ethical, social, and legal issues arising from work on the genetic aspects of mental disorders and identify those which are additional or complementary to the issues dealt with in the Council's report *Genetic Screening: Ethical Issues*.

Genetic Heterogeneity in Hispanic Populations

Some discussion can be found in the following:

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DISCLOSURE

The author has nothing to disclose.

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