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Substance Use Disorder Genetic Research: Investigators and Participants Grapple with the Ethical Issues

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Abstract

Objective—This qualitative research examined the ethical concerns regarding the psychosocial issues, research design and implementation, and application of psychiatric genetic research on substance use disorders (SUD) from multiple perspectives.

Method—A literature review of the bioethics literature related to psychiatric genetics and focus groups explored the ethical implications of SUD genetic research. Twenty-six National Institute on Drug Abuse (NIDA) funded principal investigators in the field of psychiatric genetic research, 9 adolescent patients in residential SUD treatment, and 10 relatives of patients participated in focus groups (held separately). The focus groups were recorded, transcribed, and the content was analyzed. The themes that emerged from the literature and the focus group transcripts were organized using NVIVO7, a software package designed to manage, analyze and compare narrative data.

Results—Investigators and the literature expressed similar concerns regarding the ethical concerns associated with psychiatric genetic research including violation of privacy, misunderstanding about psychiatric genetics, stigmatization, commercialization, discrimination, eugenics, consequences of research on illegal behavior, unforeseen consequences, altered notion of individual responsibility, and others. Patients and their relatives demonstrated little familiarity with the ethical issues as identified by professionals and little concern regarding most of the potential risks. The exception was apprehension associated with potential criminal justice uses of stored genetic information and enforced therapy, which elicited some concern from all perspectives.

Conclusions—The challenge for further research is to identify risks and benefits of SUD research that are germane in a behaviorally disinhibited population and devise effective tools to communicate information to participants through an improved informed consent process.

Keywords

Substance use disorders; psychiatric genetic research; privacy; prevention and treatment; criminal justice; responsibility

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INTRODUCTION

Current high-throughput genotyping methods are producing staggering amounts of genetic data that will undoubtedly further our understanding of human variation associated with behavior and disease. As our understanding of the genetic basis of substance use disorder (SUD) expands, it is perhaps a fitting time to pause and consider proactively the ethical implications of this knowledge. Extensive evidence supports a genetic contribution to SUD (Goldman et al., 2005; Radel et al., 2005; Wang et al., 2004; Edenberg et al., 2004; Corbett et al., 2005). Yet, current studies report limited success in identifying loci influencing SUD vulnerability in adolescents, although this may be a function of time rather than inherent limitations within this population (Hall et al., 2008; Young et al., 2006; Lachman, 2006; Stallings et al., 2003). Researchers hope that the identification of the genes associated with SUD will clarify the biological underpinnings of differences in treatment response and potentially lead to future innovative prevention and/or treatment strategies (Berrettini et al., 2007; Li, 2006; Edenberg and Kranzler, 2005; Berrettini and Lerman, 2005). Understanding a complex behavior such as SUD will necessitate a full comprehension of the biological, social, psychological and environmental factors impacting the disorder, including their interactions with each other (Lessov, 2004; Shields et al., 2004).

The field of psychiatric genetics is not currently well prepared to address the ethical challenges that likely will accompany the promised scientific advances in this field (Applebaum, 2004). What are the ethical implications of genetic research on SUD and the concerns and perspectives of those involved? In this article we analyze and compare (a) the viewpoints of National Institute on Drug Abuse (NIDA) funded principal investigators in the field of psychiatric genetic research, (b) the bioethics literature related to psychiatric genetics and ethics, (c) adolescent SUD patients and (d) their relatives. The purpose of this pilot study was to explore the ethical concerns of those directly involved in psychiatric genetic research. Our hypothesis was that the concerns cited in the bioethics literature would differ from those of investigators and participants, based on a presumed difference in objectives and training among the groups. We expected: (a) scientists in general to focus on specific research questions that could lead to potential benefits for future patients, (b) bioethicists to reflect on the broad societal implications of psychiatric genetic research, and (c) bioethicists and participants to consider short term benefits and harms to research participants. All of these perspectives are noteworthy because any major differences identified can play a role in the development or improvement of research practices, particularly with regard to the process of informed consent.

METHODS

Participants

As part of a larger ongoing family genetic study of antisocial drug dependence, we conducted focus groups with principal investigators in SUD genetic research (n=26), adolescent male patients in residential SUD treatment (n=9) and relatives of patients (n=10). One investigator focus group was conducted locally as a pilot (n=7); the second investigator focus group was conducted during a national meeting of principal investigators at the NIDA Genetics Consortium (NIDA-GC) (n=19). Inclusion criteria for the investigators included funding as a principal investigator through the NIDA Request for Applications entitled "Genetics of Drug Addiction Vulnerability" (DA 99-003) and valid informed consent.

The adolescent patient focus group (n=9) included males who had participated in a SUD genetics study and were: (1) adolescents in treatment at a male residential SUD treatment program described elsewhere (Crowley et al., 2003); (2) age 15–18 years; (3) full-scale IQ > 80 (or no obvious intellectual deficiency for subjects not so tested); (4) had conduct problems or a diagnosis of Conduct Disorder on the NIMH Diagnostic Interview Schedule for Children-

Version IV (DISC-IV) (Shaffer et al. 2000); (5) abuse or dependence on one or more substances according to the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), a structured instrument for lay interviewers (Cottler et al., 1995); (6) for subjects 17 years of age or younger, valid written consent from parent or guardian, together with assent from the subject, or if the subject is over 17, consent from the subject. Exclusion criteria for patients were (1) refusal to provide valid consent or assent, (2) psychosis, (3) obvious intoxication, (4) current risk of suicide, violence, or fire setting sufficiently great to interfere with evaluation or to endanger evaluator, and (5) insufficient English skills for consenting/assenting or interviews. We attempted to enroll all current clients at a residential treatment center (n=32 maximum) who had also participated in the SUD genetic study and whose stay coincided with the focus group schedule. Of those individuals who met the criteria for the study, nine subjects consented to participate. The relatives were selected on the basis of the nine subjects.

All of the patients in our sample had a diagnosis of SUD. Eight of the nine patients in the sample had diagnoses of both SUD and CD. The mean number of CD symptoms in this sample was 6.89 (out of 15 listed in the DSM-IV, standard deviation 3.89, range 0–12 symptoms. In this sample the mean number of DSM-IV abuse diagnoses was 1.56, standard deviation=1.81, range 0–5, and dependence diagnoses was 3.67, standard deviation=1.93, range 2–7. For a detailed breakdown by patient of abuse and dependence diagnoses see Table 1.

Inclusion criteria for relatives of patients included valid informed consent, having a son or brother currently in SUD residential treatment, participation in a SUD genetics study themselves, and the ability to come to the treatment center for a research interview. All of the relatives who participated had a son or brother who also participated in this pilot study. The patients and relatives were paid a nominal fee. Approval for the project was obtained from the Colorado Multiple Institution Review Board.

Data Collection and Analysis

Literature Review—A concentrated review of the bioethics literature related to psychiatric genetics for articles published between 2000 and 2008 was conducted using databases and search terms in Appendix A.

Investigator Focus Groups—Two in-depth 1½ hour focus groups were conducted with investigators by the first author following standard methodology for qualitative research (Fontana and Frey, 1994). The focus group addressed three open-ended questions: (1) What does ethics mean to you? (2) How do you evaluate current ethical oversight of genetic research? (3) What are the ethical implications of SUD genetic research?

Patients/Relatives Focus Groups—A guide for the patient and relative focus groups (held separately) was developed based upon the ethical concerns identified by the literature review and the NIDA-GC investigators. The guide included 18 open ended questions that explored patients' and relatives' understanding of genetics, commercialization, genetic discrimination, privacy, self and social stigmatization, treatment and prevention of SUD, consequences of research on illegal behavior, impact on family and friends, disclosure of research results, unforeseen consequences, and the concept of individual responsibility.

Analysis—The focus groups were audio tape-recorded and transcribed. A qualitative software package, NVIVO7, was used to organize and aid in the content analysis of the investigator and participant focus group transcripts and the literature search. The NVIVO7 package is designed to manage, analyze and compare narrative data. This method of qualitative

analysis facilitates cross-comparisons of content from the different data sources, but it does not produce quantitative summaries.

The authors independently reviewed the literature search and the focus group transcripts to develop lists of potential codes based on common themes and patterns that emerged from the narrative data. The lists of potential codes were compared and the differences resolved through a critical reanalysis of the transcripts that resulted in additions, deletions, and modifications to the codes. The codes (themes) that emerged determined the questions for the patient and relative focus groups. The process was repeated with the addition of the transcripts from the patient and relative focus groups. The final codes had the capacity to include all of the content from the literature, the investigators, the patients, and the relatives. The final content analysis included a process to double check the analysis for individual interpretations.

Specifically, the authors analyzed the data by identifying pieces of text from the literature and transcripts and attaching the appropriate codes in the database in order to enable cross-comparisons (Kohler-Riessman, 1993). The cross comparisons of text within the codes identified similarities and differences in perspective among the groups.

RESULTS

Psychiatric Genetics and Ethics Literature Review Data

The literature search identified 48 articles specifically addressing the ethical implications of psychiatric genetic research published between 2000 and 2008. Table 2 lists the ethical concerns cited in the bioethics literature and broadly categorized as psychosocial issues, research design and implementation, and application of psychiatric genetic research; several pertinent references are provided for each issue. The ethical issues cited both in the literature and independently by investigators in the focus groups are bolded in Table 2. Ethical issues cited only in the literature are italicized. Contrary to our hypothesis, Table 2 illustrates the general agreement among scientists and the literature regarding their ethical concerns associated with psychiatric genetic research. A brief description of each concern in Table 2 is provided in Appendix B with the exception of those discussed in particular detail below.

Focus Group Data

Investigators: What does ethics mean to you?—Investigators were asked to describe the meaning and role of ethics in their work. A widely accepted definition of ethics is: "...a framework within which agents can reflect on the acceptability of actions and can evaluate moral judgments and moral character" (Beauchamp and Childress, 1994). Comments by the investigators demonstrated a clear understanding of the meaning of ethics.

Investigators: How do you evaluate current ethical oversight of genetic research?—Investigators acknowledged the importance of institutional oversight, but stated that reviews are frequently more driven by regulatory compliance to protect institutions and less to protect research subjects. Moreover, review boards vary in arbitrary ways among institutions. There was a call for evidence-based guidelines that include a thoughtful ethical approach and are flexible enough to anticipate ethical considerations in time for policy intervention. Several investigators were in favor of ethics discussions with the opportunity to discuss concerns without the time pressure and stress of protocol reviews.

Investigators and Patients/Relatives: What are the ethical implications of SUD genetic research?—Patients and relatives were receptive to participation in focus groups, but their grasp of the ethical issues listed above was limited. Investigators' comments in the focus groups demonstrated that they were well-informed about the ethical issues involved with

SUD genetic research and amenable to openly discussing their concerns. Investigators were asked independently to list the top 5 ethical issues that concerned them with regard to psychiatric genetic research. The three issues that they most frequently cited are discussed below.

Privacy and Confidentiality: The most frequently cited concern of investigators was “threat to privacy and confidentiality”. Privacy in regard to psychiatric genetic research refers to the protection of personal genetic information in research databases from unanticipated disclosure to third parties without specific consent. Many investigators expressed concern regarding the impact of long-term shared access to subjects’ banked genotypic and phenotypic information because identification of a research participant may be possible even when identifiers are properly coded or removed. In contrast to the uneasiness expressed by the investigators, patients and relatives expressed little concern about confidentiality with regard to their retained DNA. Participants’ responses reflected a lack of understanding of data protection, the inherent limits to that protection, and the potential risks of identification through matching with a second comparative DNA sample.

Stigma: The second most frequently cited concern of investigators was “stigmatization of patients”. The concern is that identification of a genetic predisposition to SUD may lead to social or self-labeling of individuals and their relatives based on genes associated with increased risk for SUD or other undesirable or illegal behaviors. In contrast, the National Alliance for the Mentally Ill and others consider that a genetic etiology of illicit behavior could actually diminish the stigma associated with SUD and other disorders (DeCamp and Sugarman, 2004).

Representative comments from the patients and relatives echoed investigators’ concerns. Research participants indicated that they were apprehensive about stigmatization, specifically with regard to increased surveillance by the criminal justice system. A comment that summarizes the strong sentiment expressed in both the patient and relative focus group discussion is: “We have cops in our town that they label bad kids, and they follow them around waiting for them to make their one wrong mistake” (relative comment).

Consequences of Genetic Research on Illegal Behavior: The third most frequently cited concern of investigators was “studying illicit/illegal behavior”. Investigators’ concerns included: (a) criminal justice uses of DNA in research repositories to link individuals to crime, and (b) enforced therapy inappropriately based on genetic information. A representative comment that summarizes the investigators’ concern: “Certainly it is my hope that one day we’ll have medications that will affect the protein products of those genes and will favorably influence that behavior, and that people could volunteer to take those medications. But society has a strong interest in suppressing those behaviors. And first, if we do come up with such a medication, are they going to force people to take it? Second, in the absence of such a medication, are they going to apply monitoring and controls that they don’t otherwise apply to people, based on our genetic findings?”

Patients shared the concern that the results of psychiatric genetic research may be used improperly by the criminal justice system. A representative comment reflects a common theme opposing enforced therapy in the patient focus group: “That gene is probably what makes me, me. And if they mess up on that little gene with that pill, then that’s it, I’m not down for that.” In contrast, most relatives supported enforced treatments for SUD because: “It would have saved him and me and all of us a lot of heartache”. Two relatives also thought that their sons would be amenable to therapy if the adolescents knew that they had a gene(s) that predisposed them to SUD.

DISCUSSION

We discuss two main conclusions from this pilot study. *First, investigators and the literature cite similar concerns regarding the potential for misinterpretation or misuse of the results of SUD research.* The broad agreement on the ethical concerns is notable (See Table 2), in particular the openness of investigators to grapple with the ethical challenges involved in their research. The agreement is especially striking since the investigators were presented with three open-ended questions and yet came up with specific issues that tracked the literature quite well. While investigators were critical of ethicists, that critique does not translate to a disregard for ethics or lack of awareness of the ethical implications of this sensitive research.

In the discussion of ethical issues regarding SUD genetic research, investigators are candid about their concern that they are opening a “Pandora’s Box” (investigator comment). In general, their comments reveal an underlying anxiety that the ramifications of psychiatric genetic research could entail both good and harm for humankind. Investigators’ recognize that, despite strict regulations that protect research databases, they may be unable to prevent ethically questionable or objectionable uses of their research once results become publicly available. The data from this project indicate that an interdisciplinary response to the challenges of translating this research into practice could be constructive. These findings provide a basis to develop methods and expand opportunities for scientists, ethicists and others to jointly contemplate the use of psychiatric genetic technology proactively and together influence the design, implementation and application of research.

Second, patients and relatives demonstrate little familiarity with the issues as identified by professionals and little concern regarding most of the potential risks. The exceptions are apprehension associated with potential criminal justice uses of stored genetic information and enforced therapy. There are several possible explanations for this finding. Some of the above comments from patients and relatives indicate that they fail to understand the science involved and likely misunderstand the theoretical concept of risk associated with participation in SUD genetic research. It is unrealistic to expect most research participants to fully understand complex genetic concepts, even following a robust informed consent process that describes the potential risks and benefits of participation in psychiatric genetic research.

However, there are several distinctions in this population. First, the patients and relatives in this study may have insufficient information or experience to address such complex issues. It is possible that a more informed group of participants might produce responses more similar to those of the investigators and the literature. Second, the diagnoses in our sample include a propensity to pursue exciting risky behaviors and a disregard of adverse consequences for that behavior. This behavioral disinhibition likely exacerbates the lack of concern regarding most of the potential harms cited by investigators and the literature.

In the lives of these adolescents and their families, the risks of participation in psychiatric genetic research probably pale in comparison with their daily experiences (Robbins, 2004). Youths with a diagnosis of SUD have a propensity to engage in novel, dangerous, or deviant acts that have unpredictable reinforcing or punishing consequences (Crowley et al., 2006). Thus, even if subjects are informed about the potential harms, they may be more likely than others to participate in risky research. If we accept this possibility, the obligation for professionals is twofold: (a) collect data on how risk is understood *in situ* by behaviorally disinhibited research participants, and (b) balance the requirement to protect the autonomy of this population to participate in potentially risky research.

At the present time there is no consensus regarding how to assess or manage the actual risks of participation in research with stored DNA, but there are several possible strategies in the bioethics literature focusing on DNA repositories (Foster and Sharp, 2006; Church, 2005;

Eskenazi et al., 2005). In summary, the articles stress extensive education of participants, detailed discussion of possible future risks, inclusion of participants in the management of data in biobanks, and community consultation with groups targeted for data collection and storage to evaluate risk.

If the eventual outcome of genetic research is an effective prevention or treatment for SUD, it could alleviate significant suffering for all concerned and place increased emphasis on the autonomy of patients and the role of their families. Comments such as those above indicate that the patients' perspective, while limited, could provide useful input to describe and assess potential pitfalls early in the reporting of research results and the development, testing, and marketing of new treatments and therapies. Moreover, the comments of participants in this study suggest that a robust consent process does not necessarily equate with understanding, and there is evidence from other sources that participant comprehension actually decreases with lengthy consent forms (Sharp, 2004). Thus, the challenge for future research is to identify the risks and benefits of SUD research that are germane in a behaviorally disinhibited population and devise effective tools to communicate that information to participants through an improved informed consent process.

Limitations

It is difficult to compare ethical issues cited by investigators in a one and one-half hour focus group and a review of the psychiatric genetics and ethics literature due to overwhelming discrepancies in the context. In addition, the inherent subjectivity of qualitative analysis may produce misinterpretations of the data. A reasonable comparison of the personal views of research participants is equally difficult to substantiate, given the small sample of nine adolescents with varied SUD and comorbid CD and ten relatives. Yet, an analysis of the issues cited by the investigators, research participants and the literature is informative as a first step in developing evidence-based ethical guidelines for genetic research in a risk prone population.

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APPENDIX A: Literature Search in Psychiatric Genetics and Ethics

Terms Searched: addiction; drug abuse; behavioral genetics and ethics; psychiatric genetics and ethics; molecular genetics and ethics; psychophysiological research and ethics; ethics and genetics and nicotine, ...and alcohol, ...and drugs, ...and addiction eugenics, ...and antisocial behavior.

Databases Searched: Journals @Ovid Full Text; CINAHL; MEDLINE; PubMed; INFOTRAC - Health Reference Center – Academic; INFOTRAC - Expanded Academic ASAP; Academic Search Premier

APPENDIX B: Ethical Issues Cited by Investigators and the Literature in Table 2

Psychosocial Issues

Altered Notion of Individual Responsibility

Psychiatric genetic research may identify genetic variants associated with a predisposition to behavioral traits that call into question the concepts of free will and individual responsibility.

Family Impact

Research participants may want genetic information kept confidential, while parents or other blood relatives want access to research results and vice versa. In addition, parents may experience guilt related to passing on behavioral traits to offspring.

Impact of one's genetic make-up on sense of self

Psychiatric genetic information could affect how persons view their personality and traits, possibly influencing self-image.

Misunderstanding about Psychiatric Genetic Variants

Misinformation in the press and the media, especially extravagant speculation about genetic risk factors, contributes to the public's misunderstanding about the genetic contribution to complex behaviors.

Research & Implementation Issues

Bioethicists Block Research

Scientists assert that bioethicists should anticipate ethical considerations and address them proactively, in time for evidence-based guidelines that provide flexible frameworks for dealing with rapid advances in research.

Commercialization, Ownership and Access

There is a call for regulations to guide the commercialization of genetic data banks in order to promote their future sustainability and development, while allaying public concern about transparency and fairness.

Disclosure of Research Results

Scientists have a responsibility, in accord with existing codes of ethics, to clearly communicate the meaning and limitations of research results that have implications for the subjects' health concerns.

Informed Consent/Reconsent

Two approaches to consent for retained DNA in adolescent research are: (1) blanket consent, which doesn't provide information about how retained DNA will be shared and used, and a parent or surrogate provides it when the participant is under 18 years of age; or (2) reconsent after 18 years of age that provides information about possible future research and the choice to opt out, which is preferable.

Psychiatric Genetic Information Viewed Differently

Some bioethicists argue that psychiatric genetic information warrants policy considerations separate from other genetic research because it is particularly sensitive information and may influence self-perception to a profound degree.

Application of Research Findings

Conflicts of Interest

Conflicts of interest are conditions in which professional judgment concerning psychiatric genetic research is unduly influenced by financial gain, professional recognition, competition for research funding, etc.

Discrimination

Employers, insurers and others may use psychiatric genetic information to deny employment, increase insurance rates unfairly, or deny insurance despite federal sanctions, thus violating the right to medical privacy.

Eugenics

Psychiatric genetic technology could be used to: (1) select offspring lacking variants associated with the predisposition to undesirable or illegal behavior, (2) or eradicate undesirable variants through enforced sterilization or genetic alteration.

Medicalization

This places increased emphasis on genetic determinants of complex disease and tends to ignore social, cultural and environmental factors as important contributors to health or disease.

Unforeseen Consequences

History reveals that unknown aspects of research and technology can entail unforeseen and potentially harmful consequences. For example, the discovery that pooled DNA doesn't protect anonymity was not considered a possibility until recently. Scientists now realize that it is possible to identify a particular individual in a large public pool of DNA, even if that person's DNA sample is less than 1% of the total (Couzin, 2008).

Table 1

Substance Abuse and Dependence Diagnoses by Patient

Patient	Abuse Diagnoses	Dependence Diagnoses
1	Cannabis	Alcohol, Tobacco
2	Amphetamines, Cannabis, Club Drugs, Cocaine, Hallucinogens	Alcohol, Tobacco
3	Opiates	Alcohol, Amph, Cannabis, Cocaine, Hallucinogens, Sedatives, Tobacco
4	Opiates	Alcohol, Amphetamines, Cannabis, Cocaine, Inhalants, Tobacco
5	None	Cannabis, Tobacco
6	Alcohol, Amphetamines, Club Drugs, Cocaine	Cannabis, Hallucinogens, Tobacco
7	Cocaine, Hallucinogens	Alcohol, Cannabis, Club Drugs, Tobacco
8	None	Alcohol, Amphetamines, Cannabis, Opiates, Tobacco
9	None	Cannabis, Tobacco

Ethical Issues Expressed in Literature and by Investigators

Table 2

Ethical Issues	Reference(s)
<u>PSYCHOSOCIAL ISSUES</u> *	
Altered notion of individual responsibility	Vohs and Schooler, 2008; Levitt and Manson, 2007; Morse, 2004
Familial impact	Wilson, 2005; Kendler, 2005; DeCamp and Sugarman, 2004
<i>Impact of one's genetic make-up on sense of self</i>	Farah, 2005; Appelbaum, 2004
Misunderstanding about psychiatric genetic variants	de Melo-Martin, 2005; Baldwin, 2004; Silva, 2002
Stigma	Spriggs et al., 2008; Caron et al, 2005
<u>RESEARCH DESIGN & IMPLEMENTATION</u> *	
Commercialization	Flemming, 2007
Disclosure of research results	Wensley and King, 2008; Merriman and Cameron, 2007
Bioethicists block research	Fortun, 2005; Hall et al., 2003
Informed Consent/Reconsent	Clayton, 2008; Hall et al., 2004; Uhl, 2003
Privacy and Confidentiality	Burke and Diekema, 2006; Biesecker and Peay, 2003; Fry, 2002
Psychiatric genetic information viewed differently	Dinwiddie et al., 2004; Newson, 2004
<u>APPLICATION OF RESEARCH FINDINGS</u> *	
Conflicts of interest	Weinfurt et al., 2006; Bekelman et al., 2003
Eugenics	Savulescu et al., 2006; Baldwin, 2004
Genetic Discrimination	Appelbaum, 2004; Friedrich, 2002
<i>Medicalization</i>	Shields et al., 2004; Caron et al., 2005; Midanik, 2004
Research on Illegal Behavior	Farah, 2005; Hall et al., 2004
Unintended Consequences	Bird and Sherwin, 2006; Cooper and Patsy, 2003

* Ethical issues raised in common by psychiatric genetics literature review and NIDA funded investigators are in bold print. Ethical issues in italics were raised only in the literature.