Genetic Counseling and Ethical Issues for Autism

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Exciting progress is being made in the journey toward discovery of genes conferring risk for autism and autism spectrum disorders. Currently, genetic counseling for idiopathic autism rests on clinical diagnosis and empiric risk estimates. While no genetic test for risk of autism currently exists, it is possible that such a test may emerge in the near future, and that commercial availability may precede adequate understanding of test characteristics. The complexity of multifactorial conditions like autism raises a host of ethical and counseling challenges. For families to benefit from new genetic knowledge about autism, it will be important for their practitioners to be knowledgeable about the issues, utilize appropriate educational interventions and emerging management options, and help families across the cultural spectrum cope with these challenges.

KEY WORDS: autism; autism spectrum disorders; genetic counseling; genetic testing; ethics

INTRODUCTION

Genetic research on autism has increased remarkably since the first twin study was reported nearly 30 years ago [Folstein and Rutter, 1977]. Currently, several candidate genes have been claimed to have a role in at least some families. Oligogenic, polygenic, and multifactorial mechanisms have been proposed. While it is possible that no cases of autism result from major genes, it is also possible that some subset of cases will be found with a Mendelian mode of inheritance. In either case, families will seek guidance and clinicians will be challenged to understand and communicate the implications of the latest findings. In addition, research scientists, clinicians, families, and social policy agents will all face the daunting tasks of translating autism genetics findings into ethical practices. Historical precedents of eugenics, the stigma of psychiatric illness and increasing concerns about privacy and confidentiality make the genetics of autism a fertile field for students of bioethics. Genetic counseling, development of genetic testing, and diverse topics in the ethics of genetic research are becoming increasingly relevant issues for scientists, clinicians, and families concerned with autism. The purpose of our article is to summarize current knowledge and highlight potential future concerns involving these issues.

GENETIC COUNSELING

The first step for genetic counseling is to distinguish idiopathic autism from syndromes that include autism as a feature (5−10% of cases [Miles and McCathren, 2005]). Important syndromes with an autism component include tuberous sclerosis, fragile X syndrome, and Rett syndrome. However, autism also sometimes co-exists with other chromosomal and single gene disorders. For example, a chromosomal condition involving duplication of chromosomal region 15q is associated with autism with few associated phenotypic abnormalities [Battaglia, 2005]. This can be diagnosed by a fluorescent in situ hybridization (FISH) cytogenetic test, using probes specific for the 15q region. Correctly making a syndrome diagnosis aids the family and their medical practitioners in both management and the provision of reproductive information. Once these syndromes have been excluded, an individual with autism is considered to...
have idiopathic autism. The experience of one clinic focused on genetic counseling for autism has been summarized by Simonoff [1998], who lists common questions that may be posed by families seeking counseling for autism.

In the absence of genetic testing based on known loci or mutations, empiric risk estimates are the foundation for the genetic counseling. Recurrence risks to subsequent children of parents with one affected child range from 2% to 8% [Muhle et al., 2004], with 5% being a general risk for autism and the broader category of pervasive developmental disorders (PDD) [Simonoff, 1998].

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While recurrence risks for idiopathic autism and PDD in siblings are substantially higher (50–100 times) than population rates, they do not include the risks for other psychiatric symptoms and behavioral traits that have also been shown to be increased in families affected with autism. Psychiatric symptoms other than PDD in probands and family members may be coincidental or such symptoms may reflect components of neuropsychiatric genetic risk that contribute to autism susceptibility. The broader autism phenotype appears familial, with features similar to autism, but much milder in severity [Bailey et al., 1995]. This broader phenotype has been defined differently by different investigators but generally includes social, cognitive, and repetitive-behavior traits that are increased among relatives of probands with autism compared to controls [Piven et al., 1997; Pickles et al., 2000; Dawson et al., 2002; Lainhart et al., 2002; Constantino and Todd, 2005]. Familial rates of depression, social phobia, and other psychiatric disorders have been reported to be increased in families with autism [Piven et al., 1991; Cook et al., 1994; Smalley et al., 1995; Micali et al., 2004].

**DEVELOPMENT OF GENETIC TESTING FOR AUTISM**

Imagine that genetic loci are identified that are associated with autism. A basic question is how this information can be used to help children and families with autism or at risk for autism. Because autism is such a poorly understood condition at the molecular and pathophysiological levels, the discovery of a gene or genes associated with the condition could provide invaluable clues to the etiology. From a better understanding of the etiology, creative approaches to treatment might emerge. Given the history of limited success with treating neurodevelopmental abnormalities, such treatments are not likely to emerge quickly or easily. Nevertheless, this is the scenario that primarily justifies the investment in genetic research. A short-term consequence of the successful identification of a gene or genes associated with autism will be the development of a genetic test. Therefore, the generation of risk information and capabilities for effective treatment is the cause of most ethical, legal, and social concerns with genetic technology.

Initial questions about any test pertain to its analytic and clinical validity [Burke et al., 2002]. Analytic validity for genetic tests relates to the ability of the test to accurately identify the genetic sequences it is designed to identify. How often does the test accurately identify a functional mutation in the target sequence? Clinical validity relates to the ability to predict the clinical phenotype based on the genotype. A test may be perfectly accurate in identifying a set of mutations in a gene but clinical validity of the test will be low if the penetrance is low and/or there are other genetic loci or environmental etiologies for the condition. Given the obvious complexity of conditions like autism, any genetic test that emerges is likely to have limited clinical validity. That is, there are likely to be a significant number of false positive results and/or false negative results from testing. And because autism is a developmental disorder, it may be difficult to tell for many months or years whether a test done in, say, the newborn period, is a false positive or negative result.

Limited clinical validity, however, may not prevent a test from being sold in the marketplace. The FDA has nominal

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authority over genetic tests but has never had the resources or expertise to regulate these technologies [Burke and Zimmern, 2004]. The imperative to test is often furthered by public media coverage that simplifies and oversells the efficacy of genetic tests. Direct-to-consumer marketing may also drive test usage, and often biotechnology companies and other practitioners in the medical community disagree about the readiness of genetic tests for the mass market. Consumers may struggle to find authoritative, yet client centered, information about the myriad of genetic tests that are predicted in the future. The prevalence of autism makes it attractive for the development of new genetic tests. Well-organized parent support groups frequently advocate for progress in genetic tests and treatments (e.g., PXE) [Terry and Boyd, 2001]. Although this advocacy may bring energy, funding, and engagement to researchers working on specific genetic diseases, it may also contribute to the headlong rush to bring tests to market before there are adequate support services to aid families in using these tests.

For all of the reasons listed above, tests can move relatively rapidly from the research bench to the clinic without having achieved any specific guarantees for analytic or clinical validity. Clinicians must shoulder the burden of knowing the validity of the test and how to adequately interpret the results. The point is that a genetic test for autism could be marketed to clinicians without necessarily having high clinical validity. A high level of uncertainty involved with testing significantly increases the complexity of the ethical issues.

So how might a genetic test for autism be used? One application would be to help confirm a diagnosis in a symptomatic child. Because autism is a clinical diagnosis and a genetic test is likely to have limited clinical validity, a positive or negative test would not provide definitive information. In this situation, a positive test might be more useful for other family members. That is, if a symptomatic child were to test positive for a particular mutation, the test might be used for predictive purposes for other family members. A second child could be tested at birth to provide information about risk. Similarly, the test could be used prenatally by parents who might consider pregnancy termination for an “affected” fetus.

The ethical concerns in these contexts are significant. A positive test in a symptomatic child might falsely label the child as autistic and thereby foreshorten a more thorough evaluation. Or the test result might be considered sufficiently definitive even though the child does not otherwise fulfill the diagnostic criteria. Use of the test in asymptomatic children or fetuses may run a serious risk of labeling and subsequent stigma or, in the case of prenatal testing, pregnancy termination based on information of limited validity. Parents are often eager for any information about their children and a number of studies have shown that parents want genetic testing for children even when the results cannot be used to effectively prevent or treat the condition [Campbell and Ross, 2005]. Whether pregnant couples would terminate a pregnancy for risk of autism is unknown but research and experience show that couples are most concerned about preventing the birth of children with neurological impairments.

An additional consideration is how a genetic test might impact parents who are carriers of the relevant genetic risk factors. Less than 40 years ago, “refrigerator mothers” were blamed for their autistic children [Bettelheim, 1967]. The stigma of failed motherhood has been largely eliminated as a better understanding of autism has emerged. Yet the detection of specific hereditary causes for autism may revive this type of personal and social concern. Heritable traits do foster guilt in parents and a genetic test might more clearly delineate which parent was “responsible” for the condition. Social pressures may emerge to encourage prenatal carrier screening for prospective parents so that they might make allegedly prudent decisions about reproduction. Learning as a young adult that you were at increased but poorly defined risk of producing a child with autism would be a difficult psychological burden, until such a day that autism is treatable.

Counseling for Multifactorial Disease

Idiopathic autism may be multifactorial in etiology. Susceptibility genes have been associated with other multifactorial diseases (e.g., breast/ovarian cancer, Alzheimer disease) and are likely to be identified in families with autism. Counseling families regarding genes that confer susceptibility requires communicating complex concepts of probability. There is the probability of inheriting a gene mutation from a parent, the probability of the mutation resulting in the phenotype, as well as the possibility of genotype–genotype and genotype–phenotype interactions. This complex picture raises the question of how much counseling families need to understand their options, and the best modes of delivering information and counseling.

Alzheimer disease is a particularly instructive example. Different ApoE genotypes are associated with different levels of risk for Alzheimer disease. ApoE genotyping is a relatively easy and inexpensive genetic test that can be ordered by any physician. However, the testing is often done without extensive counseling about the possible outcomes and preparation for adjusting to the impact of the information. Testing has relatively low predictive value, and has not generally been recommended by professional genetics organizations [American College of Medical Genetics/American Society of Human Genetics Working Group on APOE and Alzheimer’s Disease, 1995; AGS Ethics Committee, 2000]. A large study is in progress to investigate the utility of testing [Roberts et al., 2004; LaRusse et al., 2005]. A potential challenge to patient communication arises because the same ApoE test used for Alzheimers also predicts coronary artery disease (CAD) and is routinely used to determine relative risk of CAD. ApoE testing for CAD is appealing because of the availability of treatments that lower the probability of symptomatic CAD. The clear therapeutic benefit from testing for CAD risk is not matched by testing ApoE for Alzheimer risk. When more
Efficacious treatments become available for Alzheimer disease, the balance of risk to benefit of testing will change. This will likely drive the imperative for testing, but is also likely to result in more tests with less counseling available to individuals being tested. Currently, patients may receive unanticipated information about Alzheimer risk when they are expecting information about risk for CAD. For an interesting discussion of the ethical implications of this “pleiotropic genetic test,” see Wachbroit [1998]. Alzheimer disease is also an example of a disease in which multiple Mendelian conditions are being identified. Some families with autosomal dominant early-onset Alzheimer disease have mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) [Campion et al., 1999; Sisodia et al., 1999]. These families can be counseled based on a more straightforward Mendelian model. It is important to develop protocols that aid individuals and their families to incorporate all of the necessary information from genetic testing into their healthcare, as well as other aspects of their lives.

Cultural Sensitivity

The scenario will be even more challenging in situations where the practitioner and consumer of genetic services are from different cultures [Browner et al., 2003]. This may occur in situations in which the culture is defined by geography (e.g., country of origin), demography (e.g., gender, socioeconomic, religion), or ability (e.g., intelligence, handicaps such as hearing loss or mental health conditions). In families with parents having mild mental retardation, the parents may not perceive a similar level of functioning in their children as a problem. Similarly, there are families in which a parent, although not diagnosed with autism, has many mild manifestations in the autistic spectrum. In this situation, a balanced discussion of the full spectrum of risks to offspring may be helpful. Parents may welcome a child with a similar set of strengths and weaknesses, but may not welcome a child with severe autism. In this context, it can be challenging to the health care professional to judge the line between respecting the family’s autonomy and appropriate intervention in the best interests of the family. This is already an issue in the case of medications for mental health conditions, and will surface again when treatments can be targeted to specific genotypes. One of the challenges of the future will be availability of culturally appropriate genetic counseling to help families understand and process complex information and make informed decisions that are consonant with their values.

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The Uncertainty Principle

One of the common reasons for genetic testing is to reduce uncertainty. Yet while genetic testing may reduce some types of uncertainty, the testing often results in new types of uncertainty. For example, individuals who elect presymptomatic testing for breast/ovarian cancer gene mutations often feel stress from uncertainty about whether or not they will develop the disease. Yet once an individual has positive test results, the uncertainty often shifts to other areas, such as whether and when cancer will occur, whether the family will experience problems with obtaining or retaining insurance, or whether the family can access appropriate medical care [Baty et al., 2006]. Potential sources of ambiguity associated with autism include probable etiologic heterogeneity, incomplete penetrance (the chance that an individual inheriting a gene mutation will express the phenotype), variable expressivity (severity of symptoms), as well as whether the family can obtain appropriate medical and financial services. Incomplete penetrance and variable expressivity could be particularly problematic in the arena of reproductive decision-making.

In the long term, genetic information will foster better treatments and preventions. In the short term, genetic testing may produce a host of complicated choices and dilemmas.

Ethical Issues in Genetic Research in Autism

Investigators pursuing genes associated with autism currently face a number of ethical concerns. Most of the potential harms of research do not arise from physical interventions but from knowledge of new genetic information by the subject, by his or her family members, and/or others who may be in a position to promote stigma or discrimination.

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An initial question in the design of a protocol is whether results will be revealed to participants. There is a number of considerations in this regard. The key question is whether the information generated in the research has any clinical significance.
with early phase projects to identify genes, research data will be of uncertain significance and validity. In other situations, the data, even if validated, would not be useful information for clinical or personal decisions. The general consensus is that research data that has not been validated or is of unknown or no clinical significance need not be disclosed to research participants [Glass et al., 1996; NBAC, 1999]. There are, of course, gray areas in this regard and unanticipated situations may arise during the conduct of the study. A second constraint on the disclosure of results is that the laboratory analysis must be conducted in a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory (http://www.phppo.cdc.gov/clia/default.aspx). A research laboratory that is not CLIA approved may not disclose results to research participants.

A significant concern for the national human genome initiative has been insurance and employment discrimination. This set of issues has been the primary focus of the Ethical, Legal, and Social Implications program at the National Human Genome Research Institute. The primary concern is that predictive information will be used by insurers and employers to deny insurance coverage or to deny employment due to health risks. As a result, many informed consent documents state that a risk of participation in genetic research is the potential loss of insurance or employability. In the context of autism research, the concern would be for the future employability or insurability of a child found to be at risk.

Fortunately, experience over the last decade demonstrates that the actual level of insurance and employment discrimination is very low [Hall and Rich, 2000]. Many anecdotal instances of health insurance problems are due to discrimination against people who are ill—a general problem that is not unique to genetic diseases. More than 30 states have enacted legislation to protect individuals against employment discrimination and more than 40 have protections against insurance discrimination (http://www.genome.gov/PolicyEthics/LegDatabase/pubMapSearch.cfm). There are serious limitations to state level genetic discrimination laws due to narrow definitions of what constitutes a genetic test and the inability of state insurance regulations to govern self-insured employers—often a majority of a state’s workforce [Rothenberg, 1995]. Federal legislation under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) protects individuals in group plans from genetic discrimination but does not protect people with individual plans (http://www.hhs.gov/ocr/hipaa/finalreg.html). HIPAA also permits insurers to charge higher rates to individuals with a genetic predisposition to disease and it does not prevent insurers from requiring genetic testing. Therefore, HIPAA protects some individuals from denial of insurance but does not guarantee that individuals can afford to buy a policy. Federal employees are protected from genetic discrimination by presidential order under President Clinton. More comprehensive federal legislation to address genetic discrimination has been under consideration in congress for years. So although the legal safety net to protect individuals from genetic discrimination is incomplete, the actual level of discrimination is low. Unfortunately, it is not uncommon for people to refuse participation in genetic research due to concerns about insurance or employment discrimination.

While there is some risk from the disclosure of genetic information to external social agents, there may be greater sensitivity for genetic or other health information within the participant’s own family. Medical or behavioral conditions are sometimes held secret within the family, particularly from members of the extended family. Therefore as investigators work with families and kindreds, it is particularly important not to assume that personal information is uniformly or widely known.

More than 30 states have enacted legislation to protect individuals against employment discrimination and more than 40 have protections against insurance discrimination. Paradoxically, the protection of confidentiality and privacy may be most important within an individual’s extended family.

The process of recruitment of extended family members for genetic research poses risk to a participant’s confidentiality. A research project to identify a genetic locus or loci associated with the disease requires recruitment of both affected and unaffected family members. Typically a proband is identified with a condition and, if the family is interesting to an investigator from a research perspective, he or she provides a family history. One concern is the confidentiality of the proband as investigators contact other family members. A second concern is the privacy of family members who may have sensitive health information told to the investigator by their kin before they have the opportunity to agree to participation.

Beskow et al. [2004] have provided an overview of the issues in recruitment for genetic research. There is an inherent tension between obtaining high participation rates of key family members and infringements on their privacy. The literature suggests that active recruitment, that is, direct calls
by the investigator to the potential subject, tend to have higher recruitment rates compared to passive methods. Passive methods include waiting for potential participants to call the investigator after contact by the proband or by letter. Yet active recruitment usually requires knowledge of the target individual’s condition and, potentially, unsolicited intrusions by phone. Beskow et al. [2004] recommend an intermediate approach whereby the investigator gives explanatory information to the proband for distribution to family members. Investigators can then contact family members directly or wait to be contacted for additional information. In all cases, they recommend that family members be told why they are being contacted and how the investigator obtained knowledge about the individual.

CONCLUSIONS
The complexity of a multifactorial condition(s) like autism raises a host of ethical and counseling challenges. For families to benefit from new genetic knowledge about autism, it will be important for their practitioners to be knowledgeable about the issues, utilize appropriate educational interventions and emerging management options, and help families across the cultural spectrum cope with these challenges.

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