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Point of View

Ethical Issues in Genetic Linkage Studies of Psychiatric Disorders

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Recent advances in molecular genetics have radically altered the prospects for determining the role of heredity in the transmission of major psychiatric disorders. Identification of the actual gene(s) involved, elucidation of their structure, and determination of their products are the steps which theoretically follow successful demonstration of linkage (Gurling, 1985; Baron & Rainer, 1988). Consideration of the ethical issues raised by genetic linkage studies is therefore now of paramount importance. This article focuses on the problems raised by the research process, and not on the ethical implications of the results eventually obtained.

The process of gathering clinical information for genetic linkage studies is considerably more complex from the ethical standpoint than would appear at first. Working with affected families, the researcher is often faced with dilemmas which are not covered by existing guidelines for the conduct of psychiatric research (President's Commission, 1983). Furthermore, issues such as informed consent, confidentiality, and access of the subject to results, which are central to all clinical research projects, may take on a different dimension in genetic linkage studies of psychiatric disorder.

Both our experience and the clinical examples quoted below stem primarily from an extensive linkage study of bipolar affective disorder in a series of Israeli families. Problems encountered in studies with a different diagnostic focus, e.g. schizophrenia, may differ in emphasis, but are generally similar in nature.

Clinical procedures and ethical issues in genetic linkage studies

Extended families with many affected members are the desired research population in genetic linkage studies, but willingness on the part of most of the family members to co-operate with the research is a cardinal prerequisite. The goal is to elicit the co-operation of the maximum number of family members (affected as well as healthy), while at the same time conducting the research according to ethical standards.

The following clinical procedures are the components of field work for any linkage study of psychiatric disorder:

(a) Identification of the proband: locating a person who has the disorder under study, and determining whether he has affected relatives as well as the size of his extended family.

(b) Screening the pedigree: to determine whether a family meets the criteria of the research study, information must be obtained from the proband and/or a close relative. For the research to be informative, the disorder should be inherited through only one parent, there must be similarly affected family members, and enough relatives, both affected and unaffected, must be willing to participate.

(c) Structured interviews with family members: each adult family member is a potential subject. Each willing subject undergoes a structured, diagnostic interview (e.g. the Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS–L; Endicott & Spitzer, 1978)), as well as any other standard diagnostic measures that are required.

(d) Family history interviews: each subject is asked for information on the psychiatric history of his immediate family, using a structured interview (e.g. Family History – Research Diagnostic Criteria (Andreasen *et al*, 1977)), to validate and add to the information given in the individual interviews.

(e) Ancillary information: each subject is asked for a release of confidentiality in order to obtain medical records, discharge summaries, and other relevant documents from other sources.

(f) Blood samples: each subject who appears informative for the genetic analysis is asked to give a blood sample, from which material for DNA analysis is extracted.

Protecting the privacy of the proband in the ascertainment process

The initial contact with the family, usually through the proband, is most significant for gaining co-operation; if the family meets research criteria, efforts are made to enlist the co-operation of all the family members. The proband or a relative might be willing to do this, which would circumvent some of the above ethical problems, and make it easier for all concerned.

However, not every potential subject who suffers psychiatric disorder is prepared to ask his relatives for their co-operation, in which case the researcher must undertake this task (with the proband's written permission). The initial contact is usually by telephone, and includes a brief explanation of purpose, efforts to engage co-operation, and a promise of confidentiality.

Family members approached in this fashion are often taken aback: an approach from a person connected with a mental health facility can provoke anxiety. There may be instances where distant branches of the family do not know each other, and do not know of the illness, but it is usually possible to elicit initial co-operation with a tactful explanation of the reason for the approach. There are, however, questions which are ethically complicated to deal with, such as: "Who gave you my name? How do you know that person? Who in my family is ill? What is their illness?"

At the time of obtaining the proband's permission to contact his relatives, it is important to clarify with him the precise limits of the consent he has given, with appropriate documentation on the consent form. The nature and limits of the information which may be divulged to his relatives should be clearly defined. It is also essential to determine the extent to which his relatives know him and are aware of his disorder. This information makes it easier to deal with the problem of what to divulge in contacts with his relatives, and protects the proband's right to privacy.

Opposition by family members to contact with other relatives

Any subject has the right to refuse to participate. But should the researcher honour a request from one family member (not the proband) not to contact another? This may happen in instances where one family member will feel overprotective to another, e.g. to his own (adult) offspring, or to a relative who has been ill. The question of opposition to contacting others is really a tactical and not an ethical one; the approach used should seek to minimise confrontation, and thus reduce the risk of losing co-operation of both relatives. Often, the subjects need sufficient time and experience with the research team to build up trust and willingness to refer other family members.

Special problems of informed consent

Informed consent includes an explanation of the purpose of the research, the different stages of co-operation requested, the possible risks and potential benefits, as well as a promise of total confidentiality. The subject should understand that his participation is voluntary, and that it is his right to withdraw at any stage.

The process of obtaining informed consent gives the subject an opportunity to think about the nature and causes of mental illness and to raise many questions, often before agreeing to participate. Full disclosure raises the possibility that the subject may be deterred because of fears, e.g. finding 'the gene' in himself or in his children. It is important to permit discussion of these issues, and where appropriate, to take the opportunity to give the potential subject some background which he may be lacking in genetics. In some cases, the subject may resist considering genetics as a causative factor in mental illness: this is understandable and can help maintain defences. In other cases, there are subjects who are relieved that there are medical or biological theories of mental illness, and are willing to accept possible genetic causes. Clinical judgement, in addition to ethical principles, must be used in handling cases such as these.

While disclosure of the research aims is a cardinal requirement for obtaining informed consent, the amount of detail required by internal review boards may differ from site to site. Within the constraints imposed by the consent form it is important to evaluate carefully both the subject and the specific questions he asks, and to determine the level of information he is able to handle. It is not necessary to give more information than is required, unless it is felt that this will be understood by the subject and be beneficial to the interaction. It is also not necessary for the subject to accept the research hypothesis.

Some of the family members in these studies are inevitably in an episode of illness, or even in hospital when they are contacted, so there can be questions about their competence to give informed consent. Stanley *et al* (1981) found that "severely disturbed psychiatric patients evaluate participation in research in a manner similar to the way medical patients do . . . [Their] autonomy . . . may be compromised unnecessarily by giving them protection they may not require . . . [and] there may be little opportunity to conduct research if the mentally ill are seen as incapable of consenting". This would occasion the loss of potential benefits from research progress, in which the patient may well be very interested. The legal aspects of a psychiatric patient's right to sign a research consent form may vary in different places. It is therefore important to clarify whether the patient

(in hospital or ambulatory) may legally consent to participate in research.

Therapeutic interventions

In the course of conducting this work, questions may arise which require clinical judgement about the need for therapeutic intervention. The nature of the diagnostic interview is such that the subject must be made to feel comfortable, and there must be rapport with the interviewer. This atmosphere, together with the private nature of some of the questions, encourages the subject to talk freely about himself and his family. There may be subjects who are diagnosed in the course of the interview as suffering from psychiatric disorders, who report that they have never sought treatment. Others may directly ask for therapeutic help or referrals. The subjects may also be concerned about their relatives and may ask for advice about dealing with them, or for active intervention outside the interview setting. There may also be requests for assistance which are not strictly therapeutic, such as help with social problems, government agencies or military deferments.

As researchers, we have come to our possibly vulnerable or even 'at risk' subjects and 'intruded', stirring up muddled feelings, asking distressing questions, even gently challenging defensive and cherished myths. We must relate to these issues with sensitivity and sound clinical judgement. Since not all interviewers have therapeutic experience, the research project should have a staff member who is responsible for relating to these clinical aspects. Each subject should be made aware of how to reach this person who can clarify and evaluate the situation. This consultation might be enough, or it might become clear that more extended contact is advisable, in which case, the research obligation would be to make the appropriate referral.

A previous study has addressed questions concerning the intrusiveness of the interview and the potential distress it might cause. Turnbull *et al* (1988) considered the possibilities of 'respondent harm'. Their empirical studies did find a small percentage of respondent discomfort with the use of the SADS–L interview, although more respondents enjoyed the interview and wished to go on talking. They also found that clinically experienced interviewers elicited more response from research subjects, perhaps because of the trained use of empathy. They state that the investigator should be capable of evaluating and dealing with stressful after-effects of the interview. Merikangas *et al* (1989) also recommended the use of clinically trained interviewers, as a measure to ensure replicability of the study.

There are instances where a subject will ask questions about his own mental health or that of others in his family, including requests for specific diagnoses to be divulged. It is clearly unethical to answer questions about anyone else in the family, but the subject has the right to know his own diagnosis. Imparting this information can often be helpful. A subject suffering depression may define his condition as 'laziness' or in some other pejorative fashion, and this view may be shared by members of his family. Knowing that a mental health professional has diagnosed depression may relieve him of guilt and open the way for him to seek treatment. On the other hand, the subject might not be able to accept or deal with the information appropriately. The interviewer should be competent to make a careful judgement or postpone the decision to a subsequent meeting and consult with a supervisor in the interim.

Sharing the results of the study is an integral component of informed consent and the logical outcome of the research process. It is clear that explaining the complex results of a genetic linkage study to people without the necessary background is a formidable task. Subjects can easily receive the wrong impression if, for example, positive linkage is communicated to them without the limitations of this concept being made absolutely clear.

A uniform approach should be established at the outset and the actual communication should be the responsibility of senior researchers who are well versed in the overall aspects of the project. The most appropriate approach is to inform subjects when results can be made available to them but to leave the option of whether to obtain the information to the subject themselves. If the subject decides to exercise this option, the results are best communicated in person. The subject should then be made clearly aware of the nature and limitations of the findings. If this information has already been imparted at an earlier stage of the project, difficulties caused by unrealistic expectations (and attendant anxiety in many cases) can be avoided.

Directions for empirical research

There are several areas of empirical inquiry which might be fruitful in considering the ethics of linkage research with psychiatric patients and their families:

(a) The degree to which the subject really understands the purpose of the research should be examined. Benson *et al* (1985) asked this question with regard to psychiatric in-patients and out-patients participating in medication trials. They found that it

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was not clear to the subjects that they had any choice about co-operating and their level of understanding of the project was low. In the case of genetic linkage studies in psychiatry, it is interesting whether understanding of the research goals and of genetics influences the level of participation in the project, and if there is a relationship, whether this is direct or inverse.

(b) The impact of the research process on the subject. If respondent harm is present during or after the interview, to what is it related, e.g. level of interviewer training, or diagnostic status of the subject? Similar questions may be asked about sharing the diagnosis with the subject. Expectations should be evaluated and the impact of communicating the diagnosis examined.

(c) Sharing of results. This complex question demands preparatory work in evaluating subjects' understanding of what the results of the project in fact represent, to what extent they really wish to know them and how results should be made available. When results are communicated, their actual impact on the subjects should be examined and compared with expectations.

(d) The effect of the research process on the subject's attitude to mental illness in general, and to his family's illness in particular, is of considerable interest. Also, how does participation in the project influence the subject's attitudes to research and the likelihood of his willingness to participate again at a later stage?

(e) The interaction between diagnostic category and all of the above questions must also be considered. Are there differences in understanding of goals, level of respondent harm and willingness to participate, among families afflicted by different disorders, and among affected and unaffected members of the same family?

(f) From a tactical rather than an ethical standpoint, the questions of what promotes co-operation and what is inimical are extremely important. Cassel (1987) discusses the "partnership of investigator and subject in the enterprise of research", in cases when the researcher is convinced that the work he is doing is ethical and beneficial. The impression is that subjects respond more positively and with more motivation to an explanation of purpose which emphasises the significance of the research and the contribution the subject can make by his participation. This impression should be empirically studied.

(g) Research personnel. What is the nature of the personnel being used in this type of research? What are the significant variables in this group? Which type is more successful? Is clinical experience significant?

Conclusions

This paper has considered questions that arise in the course of conducting genetic linkage studies of psychiatric illness involving families of people who are known to suffer from these disorders. This procedure, however delicately and sensitively handled, is intrusive and demanding. Because of the vulnerability of the subjects, careful consideration must be given to the ethical aspects of gathering the research data and sharing the results. In addition to being sensitive to ethical issues, researchers must exercise their best clinical judgement in carrying out this work.

There are currently an increasing number of genetic linkage studies in different parts of the world. The results they yield have the potential to revolutionise the entire field of psychiatry. Headlong pursuit of potentially informative families, insensitivity to subtle aspects of interaction with the subjects and failure to take ethical aspects of the process into account can, however, do substantial harm. Both the psychological well-being of the subjects and the research endeavour as a whole can be jeopardised. On the other hand, careful ongoing evaluation of the process, pooling of ethical experience and focused empirical research can be cardinally important and greatly enhance potential success in reaching families and gaining their co-operation. Without this co-operation, technological advances in molecular genetics cannot be effectively applied and research goals cannot be realised.

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