Ethical Issues in Family/Pedigree Studies

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Background and Context

- Many types of genetic research involve the study of families
- Family-based designs require the collection and analysis of information about multiple family members:
  - Family composition and genetic relationships: Who is in the family and how are they related to each other?
  - Clinical data: Which family members are or are not affected?
  - DNA: What are the *biological* relationships among the family members? What genetic variants have been inherited by different family members?

Positional cloning: Steps in finding genes

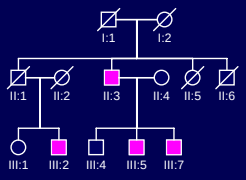
Find and clinically characterize families

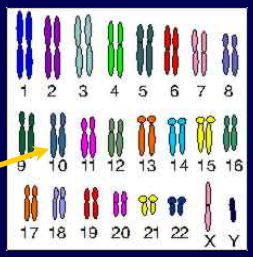
Linkage analysis

Localize a gene to a small chromosomal region

Sequence genes in the linked region

Identify a mutation in a specific gene that influences risk





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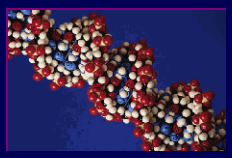


Study Participants

- Members of families containing several affected individuals
- Suspect they have a genetic susceptibility to the disorder
- May be motivated to participate in the research because they believe they will learn more about their genetic risks

Some Important Issues

- Privacy and confidentiality
  - In "family history" interviews, study participants provide information about family members (who may or may not wish to participate)
  - DNA test results in one family member have implications for others (e.g., nonpaternity)
  - Methods used to obtain informed consent more complex than in other types of research

Important Issues (Continued)

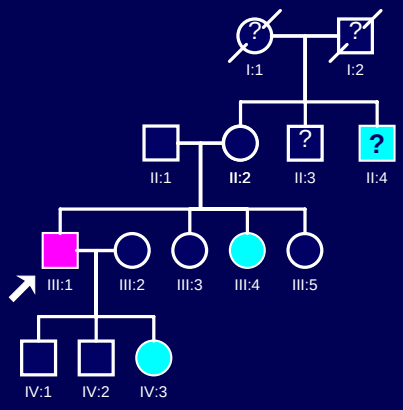
- Communication of risks and benefits
  - No individual benefits – research participants will not learn whether or not they carry a risk-raising gene
    - Statistical results in individual (small) families may not be interpretable, even if the overall result is significant
    - Results cannot be disclosed if obtained in a research laboratory rather than a clinical laboratory
  - Some benefits of participation
    - Newsletters to provide education and study results in the aggregate
    - Satisfaction from helping to provide information "for the good of future generations"

Process of Data Collection

- Studies usually begin with enrollment of an affected individual, or "proband" (who may provide information about his/her family history)
- How should information on the proband's family members be handled?
  - Should the family members be considered "subjects" even if they are not personally contacted?
  - What steps need to be taken to enroll the relatives in the study?

Scenario

- An affected subject is referred for study by his physician, who says he has a positive family history
- The subject agrees to participate, and you interview him (with informed consent)
- He tells you the names of his close relatives, and says his sister and daughter are also affected
- Is this a violation of the privacy of his sister and daughter? Of his other relatives?
- He also tells you he heard his mother may have had an affected brother, but he doesn't know much about this branch of the family, including their names



Next Steps

- You need to collect data from other family members:
  - To determine who really is and is not affected
  - To collect more clinical information about those affected
  - To collect DNA samples
- How do you enroll the other family members in the study?

Informed consent for the proband (EFSCU as an example)

- After referral (or self-referral), administer screen for eligibility by telephone
- If subject is eligible,
  - Explain study procedures
  - Mail an "Information Form" describing study procedures, risks and benefits (same as consent form, but no signature required at this stage)
- Call back after 1-2 weeks to confirm subject understands risks and benefits
- If subject agrees, administer telephone interviews regarding family composition and family history
- Obtain signed consent form at time of sample collection

Elements of Information Form and Consent Form

- Participation is voluntary
- All data will be kept confidential
  - None of the information subject provides will be given to anyone, *including other family members*
  - None of the information *family members* provide will be released to subject
- Genetic analysis may reveal sensitive information about genetic relationships (e.g., nonpaternity) and this will not be revealed
- Subjects will not receive any genetic or medical information about themselves, and will not learn whether or not they carry a risk-raising gene

Special risks for genetic studies disclosed in consent form

- Denial of insurance coverage. Sometimes occurs based on results of genetic testing. Advise subject THIS IS NOT GENETIC TESTING
- Social stigma or discrimination. Participation in a genetic study may be misunderstood by some (e.g., health care insurers, employers)
- Reinforcement of harmful stereotypes about group to which subject belongs. (e.g., discoveries may impact on women, Ashkenazi Jews, Hispanics, etc.)
- Distress because of increased awareness of family history of disease

Enrollment of Family Members

- Three approaches used
- Goals:
  - Protect privacy of relatives
  - Assure relatives can freely choose whether or not to participate

Method 1

1. Ask for proband's permission to contact relatives, and obtain full names and addresses of relatives with permission
2. Send proband a list of names and addresses of relatives with permission
3. Ask proband to sign the list and return it by mail, authorizing contact with relatives
4. Contact relatives directly by telephone after signed list is received
5. Use same informed consent procedure with each relative as with proband

Issues:

- ***Few probands returned the form***
- ***The identities of the relatives were given to us without their consent***
- ***Relatives were not given the option to refuse the initial contact***

Method 2

1. Ask for proband's permission to contact relatives and obtain full names and addresses of relatives with permission
2. Send proband a list of names and addresses of relatives with permission
3. *Ask proband to make any necessary corrections or modifications to the list, and return it only if changes are needed*
4. Contact relatives directly by telephone *if proband does not delete from list*
5. Use same informed consent procedure with each relative as with proband

Issues:
- ***The identities of the relatives were given to us without their consent***
- ***Relatives were not given the option to refuse the initial contact***

Method 3 (Preferred)

1. Ask for proband's permission to contact relatives
2. Ask proband to contact relatives with permission and ask them whether or not they want to be contacted by researchers
3. Call back 1-2 weeks later to see if proband has done this and if relatives are willing to be contacted
4. Obtain full names and addresses of relatives who are willing
5. Contact relatives who are willing directly by telephone
6. Use same informed consent procedure with relatives as with proband

Issues:
- ***Laborious and time-consuming***
- ***Gives relatives the option to refrain from contact***
- ***Proband can still provide information about relatives, as part of his/her family history***

Final thoughts

- Family-based research presents complex problems regarding privacy
- Each family member (whether proband or relative) has the right to choose his or her level of participation
- Subjects may be motivated to participate because they hope to learn about their genetic status – it is very important to avoid unrealistic expectations
- Many subjects derive satisfaction from helping to contribute to knowledge that may help future generations