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Ethical and Methodological Issues in Pedigree Stroke Research

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Abstract

Background—Stroke is a complex genetic disorder with a variable phenotype. Investigations of heritable factors in complex genetic disorders use pedigree and genetic techniques, which pose different ethical and methodological challenges than those routinely encountered in therapeutic research. Building consensus on acceptable research practices in this field is vital to the success of multicentered collaborations.

Summary of Review—We review important ethical and methodological concerns related to the collection, storage, and release of pedigree research information. The human studies aspects of pedigree research are complicated methodologically because individuals can be active or passive participants and pedigrees can be proband derived, partially validated, or fully validated. Current research ethics frameworks do not work well outside of a dyadic researcher-subject relationship. Privacy and confidentiality for family members must be considered in pedigree research. Investigators should anticipate potential conflicts of interest among family members when designing a pedigree research protocol.

Conclusions—We propose a “proband-initiated contact” methodology in which the proband or the proband’s designate allows identification of potential families without breaching the privacy of individuals in the family. In situations in which family history data are collected without direct contact between researchers and individuals in the proband’s family, an Institutional Review Board may waive consent by family members after appropriate review of the protocol and application of rules for granting waivers of consent. Certificates of Confidentiality should be considered.

Keywords

ethics; medical; family; patient selection; pedigree; stroke

Stroke can be viewed as a complex genetic disorder with variable expression and intermediate phenotypes such as carotid atherosclerosis. Technological advances and the human genome sequence have improved our ability to dissect out inherited components of complex disorders through 2 complementary strategies: pedigree and genetic research. These forms of research raise specific ethical and methodological issues not typically encountered in acute therapeutic trials or secondary prevention studies. Pedigree research relies on accurate ascertainment of family history. In its most rudimentary form, this approach is similar to that used in routine

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clinical care. Genetic research looks for mutations or polymorphisms of genes associated with a disease or an intermediate phenotype. Pedigree information remains crucial to the process of elucidating the genetics of multifactorial diseases.¹ Genetic research can incorporate pedigree studies, as in linkage analyses,² or be independent from family historical data, as in case-control association studies.³

Issues of privacy, consent, and confidentiality surround DNA samples in genetic research,^{4, 5} and concerns about consent for future uses of banked DNA have sparked unresolved national and international debate.⁶⁻⁸ Pedigree research presents equally challenging dilemmas that merit consideration.⁹ We present some of the major issues encountered in planning and executing pedigree studies of stroke and suggest practical ways to address some of them. We suggest neither that these are the only relevant ethical issues nor that the approaches discussed are the only viable solutions. Our purpose is to contribute to an informed debate. Because adequately powered pedigree and genetic studies typically require collaboration of many investigators at multiple sites, it is important to build consensus on acceptable research practices in this field.

Pedigree Research in Cerebrovascular Disease

The exact role of heritable factors in cerebrovascular disease remains poorly characterized. Large population-based studies have not consistently identified family history as an independent risk factor for cerebrovascular disease,¹⁰⁻¹² as they have for coronary disease. This may in part be due to diagnostic limitations inherent in relying solely on clinical and historical information in the era before routine use of CT. Nonetheless, stroke has been recognized as a common feature of single-gene disorders such as sickle cell disease¹³ and homocysteinuria.¹⁴ Recent pedigree-driven research has characterized single-gene stroke disorders, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).^{2,15} Established cerebrovascular risk factors such as hypertension¹⁶ and diabetes¹⁷ exhibit strong familial clustering.

Attempts to investigate heritable risk for stroke have followed many strategies. Lack of accurate and verifiable information on the occurrence and subtype of stroke has limited traditional population-based and cross-sectional epidemiological studies. Large-scale data banks with comprehensive clinical information, including family history, may serve as a starting point to investigate the genetics of cerebrovascular disease. Future studies should emphasize careful characterization of phenotype.

Pedigree Research Paradigms

Pedigree research utilizes both single-family and multifamily pedigrees. Different issues attend these 2 strategies, although both raise concerns about privacy and confidentiality. In general, identities of participants in research are protected by techniques such as substituting coded information for personal identifiers or removing personal identifiers altogether, thereby rendering the data anonymous.¹⁸ Single-family pedigrees are usually documented exhaustively and contain multigenerational data. The completeness of family data makes ensuring anonymity more difficult, especially in small, defined communities or for rare diseases. A family tree may be uniquely identifiable by the nature of its branches. Strategies to protect family identity have included omission of sex information in unaffected family members or collapsing children into a single icon on published pedigree diagrams.¹⁸ Multifamily research uses portions of families such as twin, sibling, or parent-child pairs. The time these data remain linked to personal identifiers may be shorter than in studies using complete pedigrees. Greater assurances of privacy can be made when each pedigree is concealed within the collection of research units.

Pedigree Research and Bioethics

Research ethics gives considerable weight to voluntary informed consent to protect individuals from risk.¹⁹⁻²¹ Ethical principles outlined in the Belmont Report²² and their applications inform federal regulations governing human subjects research in the United States.^{23,24} Traditional interpretations of these principles and regulations offer guidance most explicitly in the realm of clinical trials, in which a dyadic researcher-participant relationship exists. Outside of that relationship, these interpretations sometimes fail to offer adequate guidance for investigators using other research paradigms such as health services,²⁵ epidemiological,²⁶ and pedigree research.

Collecting family history is an integral part of routine clinical care used in medical decision making and risk stratification for many diseases. Family history remains the most appropriate and efficient means of screening for and stratifying genetic risk for common, multigenic conditions such as stroke and is also an efficient and cost-effective way to screen for single-gene disorders. The advent of presymptomatic and carrier status testing for single-gene disorders has engendered debate about the rights of family members.²⁷ Genetic counseling often includes family members, and discussion has ensued regarding release of information to family members at risk for genetic disease.²⁸

Genetic exceptionalism, the belief that genetic information is unique among medical information and requires special additional safeguards, continues to influence policy and practice²⁹ and could potentially impede collection of complete family history data. Nevertheless, some public health authorities have called for a shift in policies regarding genetic information and advocated for routine pedigree collection for all patients.³⁰ Since the vast majority of diseases are likely caused by an interaction between genetic and environmental factors, the distinction between “genetic” and “nongenetic” diseases is increasingly blurred and could potentially justify this shift.³¹ However, there are precedents of discrimination based solely on family history,³² and many still legitimately fear discrimination for having a disease perceived to run in families.³³

Pedigree methodologies have been essential in identifying and characterizing a multitude of heritable diseases, but concerns about privacy in the era of genomics have brought new scrutiny to the use of family history data. For example, prompted by a complaint from a father of participants in a twin registry, the Office of Protection From Research Risk (OPRR) (now known as the Office of Human Research Protections) temporarily suspended all federal research funds at Virginia Commonwealth University (VCU).³⁴ The father objected to the gathering of information regarding his medical history without his consent during the process of gathering his daughter’s family medical history. The decision of OPRR to intervene was reportedly due in large part to the failure of the local Institutional Review Board (IRB) to document that they had sufficiently considered potential risks to family members, including breach of privacy and unauthorized release of information.

Responding to the VCU situation, the American Society of Human Genetics (ASHG) offered a framework for IRB review of pedigree research,³⁵ and the OPRR issued a statement admonishing all researchers and IRBs to consider risk to family members in their ethical assessment of research protocols.³⁶ Questions have arisen regarding to what extent researchers should consider risks to family members even when their medical histories are collected only from probands.³⁵

Pedigree Recruitment

Identification of Probands and Pedigrees

Potential probands referred for participation will typically have the following basic characteristics: a personal and family history of stroke and an ability to provide informed consent directly or through a surrogate. Screening for familial clustering of stroke is performed after the proband has agreed to participate. Approximately 1 in 10 patients who present with ischemic stroke reports having a living sibling with a history of stroke³⁷; therefore, a multifamily paradigm focusing on siblings offers an efficient methodology for pedigree stroke research. Surviving parents or children with premature disease can potentially provide information for linkage analysis in associated genetic studies.

Levels of Pedigree Participation and Pedigree Information

Levels of pedigree participation

Active participant

A member of a pedigree who is contacted, gives his/her own consent, and provides his/her own phenotypic data.

Passive participant

A member of a pedigree who is never contacted or unsuccessfully contacted. Such individuals do not provide their own consent. Phenotypic data are usually provided by a proband or proband's designate. Family members may be contacted successfully but still elect to be passive participants.

Nonparticipant

A member of a pedigree who is contacted successfully and refuses to participate. These individuals do not give consent or provide their own phenotypic data. It may be appropriate to treat nonparticipants as passive participants as long as hearsay data are completely stripped of personal identifiers or data from nonparticipants can be omitted depending on the balance of ethical and scientific considerations.

Levels of pedigree information

Fully validated pedigree

All analyzed members of the pedigree are active participants.

Partially validated pedigree

Proband is an active participant, but 1 or more analyzed members of the pedigree are passive participants.

Proband-derived pedigree

Only proband is an active participant.

Identification of families with clustering of any disease depends on the ability of probands to recognize and report the occurrence of disease among family members. Lack of knowledge, misinformation, or poor recollection may complicate pedigree research. Stroke makes pedigree research even more problematic because the disease can compromise attention, arousal, and communication. There is a strong scientific justification for contacting family members to verify proband reported histories.

Identification of disease clustering requires accurate pedigree characterization. When designing a protocol, researchers must decide whether data will be collected solely from the

proband or if family history information will be validated through contacting family members. The decision of whether or not to validate data should be based on scientific, ethical, and logistical considerations and will have implications for the role of family members in the study.

Pedigree research participation can be classified as active or passive, and pedigrees can be categorized on the basis of degree of validation (Table). In studies in which the proband provides all information, family members are not contacted and can be considered passive participants. In this framework, the proband is the only person given the opportunity to provide informed consent. This would constitute a proband-derived pedigree. By contrast, probands and family members can all act as active participants, with each providing his/her own medical information and giving informed consent for participation, thereby creating a fully validated pedigree. When using this active participant framework, researchers attempt to contact all family members eligible for the protocol. In so doing, a picture of mixed participation will often occur, creating a partially validated pedigree. Some family members will be contacted successfully, and others will not. Of those contacted, some will give consent and join as active participants, some may opt for passive participation, and some will explicitly object to inclusion of their information. Investigators have at times chosen to put information about nondissenting members into the pedigree and left dissenting members in as “no information.”³⁸ Family members who are not successfully contacted could be considered passive participants. Family members who decline participation present a challenge since omitting family history information on these “nonparticipants” may render information from other consenting family members unusable. From an epidemiological point of view, there may be utility in including interested members and nonidentifiable basic demographic data of dissenting members to determine whether there are systematic differences between consenting, nondissenting, and dissenting “groups.”

Consent for Probands and Other

Active Participants—All potential active participants need to be approached for informed consent.^{20,22-24} Concerns about diminished capacity to provide informed consent for research apply to persons with stroke.³⁹ Pedigree research has some advantages over therapeutic research in its ability to address these concerns. Pedigree research is “noninterventional” and potentially as low risk as other observational studies. Researchers seeking informed consent from a patient of questionable capacity can formally assess capacity; wait for the return of capacity since family history data may not be time sensitive; or seek out guardians or surrogates. Statutes regarding surrogate consent for research differ by state, and interpretation of these statutes differs by institution. The Patient Self-Determination Act encourages the completion of advance directives and designation of surrogate decision makers in the clinical arena.⁴⁰ The precise role that advance directives and surrogate decision makers will play in the realm of research is still to be determined.⁴¹

Passive Participants—The recent VCU case raises the question of whether collecting family history information from research subjects ought to require explicit consent from each family member even when it is not necessary to contact them for scientific purposes. The ASHG expressed concern that requiring written informed consent from every member of a study pedigree could have a detrimental effect on pedigree research.^{28,42} Contacting all members of a pedigree could represent a broad-scale intrusion into their lives.

Some have suggested that family member “participation” could be evaluated by an IRB for consideration of waived consent.³⁵ This mechanism, described in Title 45 of Code of Federal Regulations part 46 (45 CFR 46),²³ has strict requirements and is currently applicable only to research subjects. It is unclear whether waived consent would be an appropriate paradigm for considering hearsay information about family members. However, if investigators consider

these family members to be research participants, the option to waive consent is potentially available to them and their IRB. Whether or not passive participants are classified as research subjects, pedigree investigators designing research protocols need to consider the possibility that family members may incur bystander risks and implement mechanisms to minimize those risks.

Nonparticipants—Bioethical principles relating to privacy and autonomy of one family member can conflict with principles related to autonomy and justice for another. Similar questions about individual responsibility in a larger societal context are debated in other ethical traditions.⁴³⁻⁴⁶ Bioethicists are exploring relationships between group and individual rights and responsibilities in several contexts.⁴⁷⁻⁴⁹ Families may be considered unique communities with instances of higher mutual obligations. If so, family members may have some obligation to one another with regard to participation in pedigree research. However, there are no obligations to donate blood, bone marrow, or organs even among family members, and there is no duty to participate in research.

In multifamily studies, one dissenting member may preclude others from participating (eg, one twin can keep the other from being an eligible study subject). Some authors propose a concept of multiple ownership of family history, which still leaves open the question of prevailing rights.²⁸ In the clinical context, patients have the right to discuss their family history with their physician. Although family history information that has not been verified is considered hearsay,²⁸ it remains useful for medical decision making and risk stratification. Medical family histories have been treated as part of an individual's medical record, and privacy protections traditionally have not extended beyond routine safeguards. In research that is not focused on heritability, family historical information is often collected in an anonymous and dichotomous fashion (eg, family history of stroke is recorded as positive or negative). Pedigree research requires that medical data be linked to specific familial relationships. Including only those members of a pedigree who provide written informed consent could introduce scientific bias. If unverified family history data belong to the proband and other active participants, then we suggest that family history data may be used in research even over the objections of nonproband family members provided that the data are collected without personal identifiers and that identity cannot be inferred secondary to family relationships.

Proband-Initiated Contact Methodology

When designing pedigree research protocols using active participation, investigators must decide how to contact family members. Can a researcher approach family members on the basis of information collected from the proband (so-called cold contacting)? Does the answer to this question depend on the stigma or potential stigma associated with the disease under study? Stroke is a relatively nonstigmatized illness, but potential genetic risk may be stigmatizing. Discussion of ethical considerations surrounding subject recruitment in other research disciplines, such as epidemiological and social science research, may offer some guidance.^{26,50,51} Concepts such as “guardian consent” for groups or communities may have relevance to pedigree research.⁵² Similar to some cluster research scenarios in which a “guardian” for the group gives consent for the other members to be approached to participate, the proband may be able to give consent for researchers to approach family members. Each family member then gives or denies consent for his/her own active participation. In cluster research, guardian consent is used to avoid having one individual's decision to decline participation impinge on the involvement of others in the group.⁵²

If probands or other nonresearchers make the initial contact, family members can elect to be contacted by the investigator without the investigator needing to know any personal details a priori. In this proband-initiated contact methodology, potential families could be identified and

contacted without the investigator breaching the privacy of individuals in the family (Figure). Investigators can contact family members directly once a relationship has been established. This methodology undoubtedly adds complexity to pedigree research. Nevertheless, the proband-initiated contact method seeks to balance ethical and scientific considerations and can be subjected to empirical study for appropriateness and effectiveness in various research contexts.

Potentially coercive forces acting on family members change depending on who makes contact. If family members feel that their participation in research may affect the delivery of care to the proband, they may feel undue pressure to enroll in the study. Proband-initiated contact could be more or less coercive than investigator-initiated contact depending on the family. However, proband-initiated contact better simulates regular family decision-making dynamics.

Storage and Release of Information

Data Security

Investigators must consider how data will be stored and accessed for analyses. Generally, efforts to limit access to data still linked to potential identifiers improve both the security of the data set and allow for more objective assessment of the data. Reviewing source documents, data entry, and closeout of the data set may necessitate verification of information with the use of individual identifiers. Database management, storage, and statistical analyses usually can be performed with the use of coded information or information that has been rendered anonymous. Database safeguarding systems should help to prevent both intentional and accidental breaches of security. Advances in information technology offer new procedures that can improve the security in storage and management of research data.⁵³ Encryption and nonidentifiable codes facilitate protection of information.⁵⁴ The potential risk for and possible consequences of deducible identity and breaches of security ought to be reviewed with potential subjects during the informed consent process.

Proband-Initiated Contact - A proposed method for maximizing privacy of family members and the validity of phenotypic data

1. Treating physician identifies potential proband.
2. Treating physician discusses with the potential proband the possibility of participation in a research protocol and refers interested potential proband to an investigator.
3. Investigator approaches potential proband about participation in a pedigree research project.
4. Investigator determines if the proband has any living relatives with or without a shared phenotype, but the investigator does **not** obtain personal identifiers on any relative.
5. Proband provides written informed consent to personally participate in the protocol and to participate in contacting family members.
6. Investigator provides the proband (or the proband's designate) with invitation letters and reply cards to be sent to all approachable family members.*
7. The proband (or the proband's designate) forwards the invitation letters and reply cards to all approachable family members.
8. Interested family members indicate their willingness to participate by returning the reply card to an investigator.

9. Investigator contacts interested family members after receipt of the reply card.
10. Interested family members provide written informed consent to participate in the protocol.

* Protocols using Proband-initiated contact will need to avoid imposing undue burden and expense on probands by providing means of contact such as printed materials and postage or access to telephones as needed.

Publication and Other Intentional Release of Information

Researchers have a duty to subjects to make important findings publicly known but not at the expense of protection of privacy. Journals vary in the handling of single-family pedigrees,⁵⁵ and the acceptability of alteration of information to preserve anonymity is still debated.^{56,57} Two guidelines for publication of pedigrees both call for informed consent by the patient for publication of identifying information.^{56,57} These recommendations do not clarify what information is “identifying,” nor do they specify whether all family members in a pedigree constitute “patients.” Publishing potentially identifying information without consent may constitute forcing an investigator-subject relationship on family members without consent.⁵⁸ The risk of accidental discovery of published personal clinical information without proper counseling needs to be considered.⁵⁹

When any release of clinical data is planned, potential legal and fiduciary obligations to the proband and family members, who have or have not consented, merit consideration during the planning phase.

Release of data to future researchers for exploratory analyses and systematic overviews is increasingly common. Although all future analyses cannot be anticipated, the potential for them should be discussed, and options for informed consent should be planned.

Proband Access to Information

During the informed consent process for many types of clinical research, participants are routinely offered access to relevant individual data and the results of the research on study completion. In pedigree research this practice may not be appropriate since the clinical implications of the results may not be known with certainty. Adequate comprehension of the implications of pedigree and genetic information may be difficult to achieve outside of formal genetic counseling. During the design phase of a study, decisions should be made and procedures specified for relaying or withholding information about risk for the disease under investigation and for other inherited diseases identified during the course of research or subsequent analyses. Decisions about who on the research team bears the responsibility of relaying information and to whom the information should be conveyed ought to be made before subject recruitment.

Family Access to Information

In the clinical setting, release of information to at-risk family members outside of a patient-physician relationship can be appropriate and, at times, is imperative.²⁸ In the research setting, the degree of risk is likely less certain, and therefore arguments in favor of releasing information to family members may not carry the same weight. Additionally, persons who decline to contribute to the pedigree may have diminished rights to request access to information collected even though it may affect their understanding of genetic risk.

Decisions about disclosure to other family members can be discussed with active participants in pedigree research at the time of initial consent. In fully validated pedigrees, family members

can discuss issues about disclosure within the family and agree on how to handle disclosure. In research using proband-derived pedigrees, direct disclosure by the researchers to other family members is less likely to be an issue but could be decided on by the proband. Partially validated pedigrees have unique problems since concealment of identity within the family may not be possible. Information on children in a pedigree may allow accurate inference about the risk status of their parents analogous to asymptomatic genetic testing in autosomal dominant diseases in clinical practice. Conflict may occur, such as when one member of a family asks to see pedigree information and another family member gives information with the stipulation that no one in the family finds out about it.

Third Party Access to Information

Society is currently conflicted about its preferences over privacy and confidentiality; the Office of Management and Budget recently proposed increased public access to data collected as part of federally funded medical research,⁶⁰ while privacy concerns have dominated discussions of the Health Insurance Portability and Accountability Act.⁶¹ Although family history data are not equivalent to genetic information, third party access to family history data could affect an individual's access to affordable healthcare.³² When pedigree data are linked to genetic data, third parties may attempt to get access to the information to look at other areas of the genome for disease genes. Release of research data to such third parties without consent by research participants is a significant violation of confidentiality. However, many research participants do not realize that some healthcare coverage agreements have clauses that include, or could be construed to include, consent for the agency to collect information from researchers. Some investigators are informing potential research participants of this possibility.

Third parties may attempt to compel disclosure if information is stored in any identifiable way. In the United States, Certificates of Confidentiality may offer some legal protection for researchers from compelled disclosure.⁶² They have typically been used in mental health and substance abuse research⁶³ and may have applications in pedigree and genetic research.⁶⁴ However, these certificates offer no protection in the aforementioned situation in which a researcher is presented a signed consent for release of information. The only protection when this type of release is truly undesired—on the part of the researcher or on the part of the participant, even if signed consent was obtained—may be maintaining the data without any personal identifiers rendering them completely anonymous. One of the authors (J.F.M.) obtained a Certificate of Confidentiality from the National Institute of Mental Health for the Siblings With Ischemic Stroke Study, a multicentered trial investigating genetic causes of ischemic stroke.⁶⁵ Obtaining Certificates of Confidentiality may become increasingly important as pedigree, genetic, and genomic research continues to progress at a rapid rate.

Individual and the Greater Community Issues

Recently, DeCode, a commercial venture in Iceland, obtained a license for a national database linking medical records to genetic material, renewing concerns about community versus individual rights in the era of genetic research.⁶⁶ This is notable because the company sought and obtained authorization to create this database using the ideas of “community consent” and “presumed consent” for individuals with an anonymous option to “opt out” for those who wish to decline participation.⁶⁷ This has led to extensive public⁶⁸ and professional debates,^{67,69} particularly on the potential linking of medical records to DNA data that may not be sufficiently secure.⁷⁰ However, since use of the database for genotypic exploration requires explicit individual consent, those in charge of the database believe that the potential for unchecked exploration of genetic foundations for diseases will be low.⁶⁷ Public opinion strongly favors the database,⁶⁸ although approximately one tenth of the Icelandic population has declined to participate.⁶⁹ Some have raised the concern that in such a small country as few as 3 pieces of

basic information may allow identification of individuals despite efforts to de-identify the data.
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Concerns about use of data and cultural implications of data are receiving renewed attention in communities such as Native American tribes. Disclosure of population-based data could adversely affect group privacy.⁴⁸ The rights and responsibilities of groups may also depend on their degree of identification as a community.^{47,72} These unresolved issues are being actively discussed in the public health arena, and how they are resolved will likely affect pedigree and genetic research in discrete populations. The issues around privacy and disclosure are on the forefront of national debate not only because of advances in genetics but also because of the increased potential for and recent steep rise in rapid information sharing in this electronic information age.

Conclusions

Pedigree research can establish the heritability of disease whether by itself or in conjunction with genetic techniques such as linkage analyses. Pedigree research begins with interviewing a proband. Family members can then participate either actively or passively. There is greater confidence in assigning phenotype in active participants. Stroke patients may have diminished capacity to consent or an impaired ability to provide accurate information about family members. When the data set is adequately secured, it may be appropriate for governing IRBs to grant a waiver of consent for passive participant family members if they are considered research subjects. Certificates of Confidentiality may offer additional protections to active participants in pedigree research. We have proposed a proband-initiated contact method as an ethical means of recruiting family members to be active participants. This method avoids cold contacting of potential study subjects and protects the privacy of all family members. Addressing ethical issues in pedigree research is complicated methodologically because the unit of study is a group and because individuals can participate at multiple levels, creating potential for conflict between individual and group rights and responsibilities. Pedigree and genetic research can benefit from further advances in applicable research ethics that are carefully considered, internally consistent, clearly articulated, and well accepted.

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