

IRB Protocol for Simons Foundation

Title: Simons Variation in Individuals Project (Simons VIP)

IRB of Record: Columbia University Medical Center

Principal Investigators: Gerald Fischbach; Wendy Chung

Study Description

Study Purpose and Rationale: Twin and family studies suggest that genetic and/or epigenetic factors are important in the development of autism, although it is also clear that these influences are complex. Much past work in this field has been marred by inconsistent diagnostic methodology and poorly defined subject populations, which make it challenging to link particular genes to clinical subtypes. To rectify this weakness the Simons Foundation established a database of 2500 rigorously characterized simplex families in order to identify de novo mutations associated with autism. From this database, several genetic changes have been identified. The 16p11.2 deletion is the most common genetic disorder associated with autistic spectrum disorder (ASD). The Simons VIP has begun investigating these genetic etiologies by studying a large number of individuals with a particular recurrent genetic lesion (deletion or duplication at locus 16p11.2) that increases their risk of developing autism spectrum disorders (ASD) and other neurodevelopmental disorders. Since this approach has proved successful, additional genetic variants that have been observed to share dysmorphic features, global developmental delay, and behavioral abnormalities found in the autism spectrum (e.g., 1q21.1, 15q11q3, 7q11.2 or 7) will be studied as well. The Simons Foundation has funded four university based medical centers to (a) identify individuals with the relevant genetic mutation and recruit them into the study, (b) collect blood samples and an optional skin sample from these individuals and both biological parents and siblings, and (c) perform in depth medical, developmental, behavioral evaluation, and brain imaging of these individuals and control subjects who lack this mutation. The goal is to characterize the phenotype associated with these syndromes cross sectionally and longitudinally and identify factors that influence the expression of these genetic mutations in brain and behavioral development. Columbia University will act as the coordinating site for the overall study which will be led by Drs. Wendy Chung, principal investigator, and Gerald Fischbach, Scientific Director of the Simons Foundation. The database of results from these studies will be maintained by the Simons Foundation and contain only deidentified data; the Simons Foundation staff will not have contact with the families.

Study Design and IRB Procedures: This study aims to collect data on approximately 200 individuals with 16p11.2 deletion or duplication and an equivalent number of matched sibling control subjects and parents, which is a total of approximately 800 subjects. Phase II, which will take place simultaneously with the completion of Phase I (16p11.2), will enroll 100 individuals with 1q21.1 abnormalities and their parents and matched sibling controls. Other genetic variants may be added in the future. The information will be stored in a database without subject identifier information, and de-identified biological specimens will be stored in a centralized

repository at Rutgers University and shared with researchers in the future to facilitate the study of autism and related disorders.

This protocol submission will cover the coordinating and analytical activities of Columbia University and the Simons Foundation. No subjects will be studied at Columbia University. The organizational structure of the group is given above. Dr. Wendy Chung is the principal investigator at Columbia University. She will work closely with Gerry Fischbach, John Spiro, Marion Greenup, Connie Atwell, and Jennifer Tjernagel at the Simons Foundation who will provide administrator support for the project, facilitate communication with the group, and provide oversight for IRB approvals at each site. Although unexpected, any adverse outcomes will be reported to Dr. Wendy Chung on a monthly basis, and she will investigate and resolve any issues.

Emory School of Medicine will serve as the recruitment and retention core and will be led by Drs. David Ledbetter, Christa Lese Martin and Andy Faucett. Dr. Ellen Hanson will lead the phenotyping core with Fiona Miller. Dr. Elliott Sherr will lead the neuroimaging core. Dr. Roger Vaughan will lead the statistical analysis core at Columbia University. The Simons Foundation has funded four sites to conduct the clinical and structural imaging research studies described in this protocol submission: Children's Hospital, Harvard Medical School (Clinical PI: Ellen Hanson and Imaging PI: Ellen Grant); Baylor College of Medicine (Clinical PI Robin Kochel and Imaging PI: Jill Hunter); Emory University (Clinical PIs: Christa Martin and Imaging PI: TBD); University of Washington (Clinical PI: Raphe Bernier and Imaging PI: Elizabeth Aylward). Additional functional research imaging studies will be conducted at the Children's Hospital of Philadelphia (PI: Tim Roberts) and the University of California, San Francisco (PI: Elliott Sherr).

The de-identified data repository will be held at a secure offsite storage facility (ipHouse, 331 2 Avenue South, Minneapolis, MN 55401) designed and maintained by Prometheus Research and paid for by the Simons Foundation. Data monitoring will be overseen by Wendy Chung at Columbia University in collaboration with staff at Prometheus Research. Data quality checks will be performed to check for missing data and data out of range as they are entered so more complete and accurate data sets are acquired. Any issues with data that are entered will be discussed with the site PI from whom the data were received. Data analysis will be performed by the statistical analysis core led by Dr. Roger Vaughan at Columbia University. Descriptive summary statistics will be compiled, and the characteristics of subjects with 16p11.2 deletions will be compared with 16p11.2 duplications and to participants in the Simons Simplex Collection as a representative group of children with autism. Similar analyses will be performed on the 1q21.1 groups, and the results for the chromosomal variants will be compared with each other.

All data will be de-identified when it is entered into the database by the individual site collecting the data. All files with photos of patients will be labeled with study ID numbers only and will be transferred to Columbia University or University of Massachusetts by mail.

Data and biospecimens will be stored indefinitely and will be made available as de-identified specimens and de-identified data to the research community. Applications to request data or biospecimens will be reviewed by the Simons Foundation staff based upon scientific merit, quality of the investigative team, capacity to complete the proposed studies, and successful IRB approval of the proposed studies.

Weekly or bi-weekly conference calls of the Executive Committee, clinical PIs, and imaging PIs allow discussion of study plans, review of IRB submissions, and in the future will review study progress and resolve any study related issues. Annual in person meetings will allow the group to review study progress and results.

To ensure collection of consistent and reliable data from the neuropsychiatric testing battery (see study procedures below), we have an extensive plan for training and reliability. Site Supervisors are responsible for the bulk of training site examiners. Supervision and training will be ongoing, frequent, face-to-face, and regular until site examiners have established reliability. Each site will have two Site Supervisors, one of which will be the Lead Clinician (PhD in clinical psychology, licensed, extensive clinical experience). The other Site Supervisor will be masters level or in a graduate program for clinical psychology. A licensed clinician will see each Simons VIP family. Sites that do not have a clinician meeting these prerequisites will have an examiner attend the research-level trainings and establish reliability with their Simons VIP consultant prior to taking on the role as lead clinician. Fiona Miller will train staff and evaluate reliability across the Simons VIP site prior to subject enrollment.

At the site level, the site supervisors will do the following to ensure adequate training and reliability of the staff:

Be research reliable with Simons VIP consultants or an approved independent trainer who works at their site on each of the instruments:

ADI-R

ADOS Modules 1, 2, 3, 4 & Toddler ADOS

Ensure that site examiners have completed ADI-R and ADOS research training

Examiners can begin onsite training with the site supervisor on the measures prior to attending the research trainings.

Establish reliability among site examiners. Site supervisors will provide ongoing training and supervision to get examiners reliable.

Reliably administer and code ADI-R, ADOS Modules 1&2, ADOS Modules 3&4, and the Toddler ADOS. Site supervisors will regularly give the measures on which they are supervising others (this is outlined in maintaining reliability below). Best practice guidelines are to administer an ADOS and ADI-R once a month to be able to supervise others' administrations adequately.

Monitor and maintain reliability for each examiner.

Sit in and co-code the first ADI-R and the first ADOS (M 1&2, 3&4 plus Toddler) that each examiner gives every quarter. Calculate reliability and resolve discrepancies as needed.

Train site examiners in cognitive measures, language measures and other phenotyping measures and sit in on the first administration of each. Site supervisors will sit in on a site examiner administration of the cognitive and language measures every 6 months after the initial

administration.

Conduct “in-house” trainings (about every 6 months) using training DVDs provided by University of Michigan or Dr. Miller.

Develop and implement more intense training plans for clinical staff having difficulty maintaining reliability. This plan will be documented and reported to Simons VIP with frequent updates.

Attend bi-monthly calls with the phenotyping PI to maintain standards across the study.

The Simons Foundation will maintain tracking systems to ensure that this and each human subjects research activity supported under grants from the Simons Foundation will require prospective IRB approval and will obtain continuing review approval until completion of the study. The Simons Foundation will maintain records of all IRB approval letters at each site, all modifications, and renewals. Also, each investigator of each human subjects research activity will be responsible for tracking the enrollment of each subject and ensuring that informed consent has been obtained in accordance with IRB requirements.

If any human subjects research activity supported by this grant involves another institution, the Simons Foundation will ensure, through tracking systems, that each institution has an Assurance of Compliance approved by the Office for Human Research Protections (OHRP) prior to the involvement of the given institution in the human subject research activity. Also, the tracking system will monitor that: (1) IRB approval is obtained from each institution prior to their initiation of human subjects research; (2) for multicenter studies supported by this project, any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and (3) informed consent is obtained from each of their subjects in accordance with IRB approval and HHS regulations.

Study Participants: All subjects identified with the specific genetic mutation likely to be involved in ASD or other neurodevelopmental disorders are eligible for inclusion in the study, regardless of age, diagnosis, or other medical conditions.

The Simons VIP started with a focus on deletion (del) and duplication (dup) 16p11.2. The 16p11.2 deletion is the most common genetic disorder associated with ASD. Inclusion criteria will be any individual of any age with the 16p11.2 deletion or duplication (del/dup) defined as equal or smaller than 28.5 Mb-31.2 Mb. Exclusion criteria will include additional known genetic mutations resulting in effects on neurocognitive outcome, deletions or duplications that are larger than the indicated 2.7 Mb interval, or probands and parents who do not speak English fluently. Subjects are required to speak English since the behavioral and neuropsychological tests have only been validated and are only available in English. Findings from the deletion and duplication cases will be analyzed separately to avoid confusion about these distinct genetic conditions. Because of the success of the initial 16p11.2 efforts, the study will now be expanded to include other recurrent deletions or duplications. Initially this will include individuals with 1q21.1 deletions or duplications.

This study will enroll 200 individuals with del or dup 16p11.2 and 100 individuals with del or dup 1q21.1, approximately evenly divided, identified through the following sources: (1) prior participation in the Simons Simplex Collection, which is a multisite study to identify genetic variations in individuals with a well-documented ASD; (2) chromosome microarray analysis performed in the clinical diagnostic laboratories that make up the ISCA (International Standards for Cytogenomic Arrays) Consortium; (3) referral from other clinical genetic testing laboratories, hospitals, and web-based networks (such as the Interactive Autism Network [IAN]); and (4) self-referral by families who learn about the Simons VIP through internet search sites devoted to 16p (UNIQUE and Simons VIP Connect). We will also study the first degree relatives of the individuals with the del or dup 16p11.2 and 1q21.1, and unaffected siblings will serve as controls.

Study Procedures:

If not already performed, clinical genetic testing in a CLIA certified clinical lab for the 16p11.2 del/dup will be performed on the parents and any siblings to determine if the del/dup is inherited or de novo and to appropriately categorize all the participants based upon their genetic status. Pre and post test counseling will be provided to subjects by genetic counselors. Subjects will be provided with results of this testing through a genetic counselor from Emory University. Parents and siblings who are identified through this testing as being a carrier of the relevant variation may themselves become subjects in the study.

Comprehensive medical history information will be obtained from either the participant directly or from the primary caregiver and extracted from the medical record. This history will be taken by phone by a genetic counselor at Emory University with input from Dr. Chung and should take approximately 60 minutes to complete. Medical records released by the subject/family and collected by the recruitment core will be reviewed to verify the data reported in the medical history interview. Additionally, for participants who have a history of seizures, study investigators will conduct a seizure-specific interview over the phone with either the participants or their parents.

Each participant will be evaluated at one of four clinical sites: Harvard University, Emory University, Baylor College of Medicine or the University of Washington. At the evaluation each participant will receive a standard neurological evaluation, measurements of height, weight, and head circumference, and will have photographs taken to evaluate for dysmorphic features.

A blood sample (up to 40 cc but not more than 3 cc/kg body weight for children) will be collected on participants in order to prepare DNA and establish lymphoblastoid cell lines. Blood samples (up to 40 cc) will also be obtained from the parents. A separate consent form will be signed for each participating individual.

In selected patients a 2 mm x 2 mm piece of skin at the incision site with surgery (done for routine clinical purposes) or a 3 mm in diameter circular punch skin biopsy will be performed to

create induced pluripotential stem (iPS) cells. An experienced physician will perform this procedure. A punch skin biopsy will be performed after injecting numbing medicine to minimize the pain. The punch skin biopsy will be performed on the inner arm or outer thigh under sterile conditions to prevent infection. The skin biopsy is not required for study participation and is an optional procedure.

Skin biopsies will be used to make induced pluripotential stem cells (iPS cells). The specimens will be used to identify additional genetic factors that may modify the expression of the 16p11.2 or 1q21.1 del/dup and to understand the mechanism through which the 16p11.2 or 1q21.1 del/dup exerts its effect on brain function. These specimens will be held indefinitely until they are exhausted.

In addition to the diagnostic and medical evaluations, all study participants with the del/dup 16p11.2 or 1q21.1 mutation will undergo an age-appropriate cognitive and behavioral evaluation including an Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS) and cognitive testing by research reliable staff. Assessment of intellectual, language, and behavioral functioning is a core component of subject characterization, so the following tools will be administered as appropriate for the age of the participant:

Mullen Scales of Early Learning
Differential Ability Scales (Early Years & School Years versions)
Wechsler Abbreviated Scale of Intelligence
Vineland Adaptive Behavior Scales
Autism Diagnostic Observation Schedule
Autism Diagnostic Interview – Revised
Autism Diagnostic Observation Schedule - Toddler
Infant Toddler Social Emotional Assessment
Behavior and Stereotyped Interest Questionnaire
Social Responsiveness Scale
Social Responsiveness Scale - Adult Research Version
Delis-Kaplan Executive Function System
Natural Language Sample
MacArthur Communicative Development Inventory
Childrens Communication Checklist - 2
PLS-4 - Preschool Language Scale - 4th edition
CASL - Comprehensive Assessment of Spoken Language
WIAT - Wechsler Individual Achievement Test - Third Ed
NEPSY - II
Child Behavior Checklist
Edinburgh Handedness Inventory
Purdue Pegboard
Visual-Motor Integration
Diagnostic Interview Schedule for Children – Revised

Symptom Checklist 90 - Revised
Goldman Fristoe Test of Articulation – Second Edition
Social Communication Questionnaire
Movement ABC-2

Parents and siblings without the 16p11.2 or 1q21.1 mutation will also undergo cognitive and behavioral evaluation with an age-appropriate subset of these instruments to measure verbal, nonverbal, social-communication and motor development skills. Some of these assessments may be videotaped for training, validation, and additional analysis purposes; consent for videotaping will be obtained. Neuropsychological testing scores will only be released directly to a licensed psychologist or a clinician, upon request.

3D and 2D images will be taken of all probands, siblings and parents for analysis of dysmorphology. Consent for these photographs will be obtained from all individuals. These images will be sent to Columbia School of Medicine for analysis by Dr. Wendy Chung and storage. The 3D images may be sent to the Eunice Shriver Kennedy Center at the University of Massachusetts for further analysis of morphometrics. If any of these photographs are published, a black line will be placed through the eyes to decrease the likelihood of recognition of the patient.

All probands and siblings who can tolerate it (usually over age 6) will have a structural MRI of the brain performed without sedation and without contrast. If they have had a previous clinical MRI scan of good quality, they may not need a new one for the purposes of this study and we will simply get copies of the previous MRI. Additional imaging protocols may be instituted for selected individuals. These selected participants will undergo resting state fMRI and MEG (magnetoencephalography) evaluation at UCSF or CHOP to include assessments of auditory processing, language lateralization, emotion/facial processing, attention shifting, and Stroop conflict testing.

Findings from the MRI scans will be reported via the following procedure: MRI scans will be reviewed by a designated board certified neuroradiologist at UCSF. The neuroradiologist will generate an MRI report (see attached MRI Report Template_Radiology Review) that documents the neuroradiologist's name/institutional affiliation, scan logistics, the Incidental Finding (IF) category and a description of any clinically significant IFs. IF category selection will be based on the seriousness of the condition and the anticipated importance or benefit of the finding to the participant. The neuroradiologist and neurologist will discuss IFs (Categories 1, 2 and 3 below) together before a final selection is made to confirm that the appropriate category has been chosen. Each IF category along with the participant follow-up procedure is explained below.

Incidental Finding Category 1 – Strong Net Benefit: A finding of strong net benefit is likely to reflect a problem that is serious and that may be treatable. For example, a finding leads the neuroradiologist to suspect a serious condition such as a brain tumor or an aneurysm.

Participant Follow-up: The coordinator will arrange an in-person or remote video/phone conference if an in-person meeting is not feasible (see below for detail). The purpose of the conference is for the site neurologist to communicate the MRI finding directly to the participant and advise the participant to follow up with his/her primary care physician if the participant has remaining questions and/or if clinical care is needed to address the finding. Coordinators will mail to the participant a packet containing a cover letter with details about the conference (see attached SVIP MRI Cover Letter_Neuro Conf + CD), his/her MRI report and a CD/DVD with MRI images. To the best of the coordinator's ability, receipt of the packet should closely coincide with the conference so that the neurologist can quickly address any questions the participant may have after looking at their MRI report.

During the consent process, participants will read information about Category 1 IFs in the SVIP Consent Addendum_MRI IF and are asked to choose if they want their MRI results shared with their personal physician and to provide that contact information if they wish to share the results.

Incidental Finding Category 2 – Possible Net Benefit: IFs of possible net benefit may or may not reflect a problem that is real and possibly treatable. An example of this type of IF in a brain MRI is an increase in the number of white matter spots that may have been caused by brain injury, is stable and does not require treatment. However, the white matter spots may reveal a treatable condition such as hypertension or type 2 diabetes. Because these findings are of uncertain origin and they may not be treatable, there may be little benefit to learning such results.

Participant Follow-up: Follow-up regarding IFs in this category are based on the choices that are made in the SVIP Consent Addendum_MRI IF. If the participant chose to opt-in for this kind of result, the coordinator will arrange an in-person or remote video/phone conference (see below for detail) to communicate the MRI findings directly to the participant and advise the participant to follow up with his/her primary care physician if the participant has remaining questions and/or if clinical care is needed to address the findings. Coordinators will send a packet to the participant containing a cover letter with details about the conference (see attached SVIP MRI Cover Letter_Neuro Conf + CD), his/her MRI report, and a CD/DVD with MRI images. To the best of the coordinator's ability, receipt of the packet should closely coincide with the conference so that the neurologist can quickly address any questions the participant may have after looking at his/her MRI report.

If the participant chose to opt-out of receiving Category 2 results, the coordinator will send a packet to the participant containing a cover letter (see attached SVIP MRI Cover Letter_Report Opt Out + CD) and a CD/DVD with MRI images. The MRI report will not be included.

Incidental Finding Category 3 – Unlikely Net Benefit: IFs of unlikely net benefit may reflect a condition that is not likely to be of serious health importance or whose health importance is unknown at this time. An example of this type of finding is an arachnoid cyst, or a fluid filled sac located inside the brain or spine. Usually, arachnoid cysts do not have symptoms and do not

require treatment. Because arachnoid cysts and other findings of unlikely net benefit are of unknown significance or are known to have no health significance, there may be little to no benefit to learning such results.

Participant Follow-up: A cover letter (see attached SVIP MRI Cover Letter_No Clin Findings + CD) and CD/DVD of MRI images will be provided to the participant. An MRI report will not be shared with the participant.

Incidental Finding Category 4: No Findings: MRIs in this category do not have IFs.

Participant Follow-up: A cover letter (see attached SVIP MRI Cover Letter_No Clin Findings + CD) and a CD/DVD of MRI images will be provided to the participant. An MRI report will not be shared with the participant.

Remote Video/Phone Conference

Research participants for whom an in-person conference is not practical for logistical reasons will have their clinically relevant MRI findings reviewed with them using established telemedicine technologies. These technologies, such as tablet computers and secure videoconferencing systems, will enable the board-certified pediatric neurologist who saw the participant at the study site to conduct a virtual conference with the participant, even after they have returned home. During this conference, the neurologist and the participant will review the participant's relevant medical data, both visually and audibly, in real time. All data reviewed with the participant will be transmitted using encrypted and HIPAA-/HITECHcompliant media.

These conditions are stated on the consent form and on the cover letters that will be included with the released data (see attached: SVIP MRI Cover Letter_Neuro Conf + CD; SVIP Cover Letter_Report Opt Out + CD; SVIP MRI Cover Letter_No Clin Findings +CD).

Participants may be recontacted in the future to collect data on medical and neurocognitive follow up, to repeat the cognitive and behavioral evaluation to determine how it changes over time, and to participate in future ancillary studies that may arise after the primary data are analyzed. Participants will be given the option to allow or not to allow their contact information to be shared with other researchers conducting related studies.

For probands under age 5, families will be presented with the option to opt-in to a longitudinal portion of the study. Specifically, at an 18-month update visit, the Mullen, ADOS-T, Vineland, MCDI, education and intervention history, HTWHC, PSI, BSIQ, MHI and CBCL will be administered. These participants will also be asked to undergo additional brain imaging at a 36-month follow-up visit.

The cost of travel to the study site, lodging, and meals will be provided by the Simons Foundation. Each subject who completes the study will be provided with a \$100 gift certificate

as a token of appreciation. Additional compensation will be provided for participation in longitudinal study visits.

Confidentiality of Study Data: Participant recruitment will be coordinated centrally by Emory University. After patients are enrolled, the recruitment core will work with each of the 4 evaluation sites to schedule evaluations. The recruitment core at Emory University will be conducting the medical history interview, collecting medical records/genetic test results/MRIs, and assisting to schedule study visits at the 4 clinical sites (Harvard University, Emory University, Baylor College of Medicine or the University of Washington) and the neuroimaging sites (Harvard, UCSF, and Children's Hospital of Philadelphia). For coordination of scheduling, personal identifying information will be shared among the recruitment core, the clinical sites, and the neuroimaging sites by fax and mail. Each evaluation site will maintain personal identifying information for each participant in addition to data collected from medical, cognitive, and behavioral evaluations. All data will be stripped of personal identifying information, encrypted and transmitted electronically to a central database, under the direction of the site Principal Investigator. Prometheus Research staff will review all data for completeness and will contact coordinators at local sites to correct errors or obtain missing data. All such communications will be conducted using the research identifier; no personal identifying information will be disclosed. Global unique identification numbers will be assigned for all participants to facilitate development of non-overlapping data sets from different studies and to link with other research databases.

The data will be stored in a central database and will be made accessible to other researchers. Any use of Simons Foundation data will require review and approval by the Simons Foundation and the investigator's local IRB. Researchers will not be provided access to identifying information under any circumstances without IRB approval, subject informed consent, or a waiver of consent granted by the IRB. Should an investigator wish to conduct any kind of follow up study on subjects, separate IRB review will be sought in conjunction with sites responsible for those subjects.

Blood will be submitted to the Rutgers University Cell and DNA Repository (RUCDR) and will be used to establish lymphoblast cell lines and extract DNA. Blood samples will be coded and all identifying information will be removed before sending the samples to the RUCDR. No clinical information will be sent to RUCDR. Only researchers who are approved by the Simons Foundation will be allowed to access the cell lines.

Samples and data will be shared according to the following terms of use for the data and cell repository: (1) Recipient-investigators will not be provided access to the identities of donor-subjects or to information through which the identities of donor-subjects may readily be ascertained; (2) The collection of data and specimens obtained through this study is subject to oversight by local IRBs convened under applicable OPRR-approved Assurances; (3) Written informed consent/assent will be obtained from each donor-subject. The sample consent form includes a clear description of (i) the operation of the biospecimen repository; (ii) the specific

types of research to be conducted; (iii) the conditions under which data and specimens will be released to recipient-investigators; and (iv) procedures for protecting the privacy of subjects and maintaining the confidentiality of data; (4) A sample collection protocol and informed consent document has been developed for distribution to collector-investigators and their local IRBs.

Potential Risks

The risks or discomforts associated with drawing blood from a vein include pain, bruising, bleeding, or local infection.

The risk to the patient from a punch skin biopsy is slightly increased over minimal risk but is still low. To minimize the discomfort of the skin biopsy, patients will be given a local injection of 1% lidocaine with skin biopsies. Sterile technique will be used to obtain the skin biopsy to minimize the risk of infection. When possible, skin biopsies on children will be obtained at the time of surgery for unrelated medical purposes to further minimize the risk.

Genetic testing of family members as part of this study may reveal a previously undetected chromosomal abnormality. Most families find this information helpful. This is because it may explain why the person has a developmental disability, and/or pregnancy loss. It also provides the information needed for thorough genetic counseling. But, sometimes learning that a person has a genetic abnormality can cause emotional problems or a disruption in family relationships. In order to lessen these risks, results are given to participants through doctors and genetic counselors who have experience in helping people and families understand the results and implications of genetic testing. The doctors and genetic counselors associated with the study can provide support, information, and referrals to other medical or counseling specialists in order to help people and families adjust to results of genetic testing in a healthy manner.

When comparing the genes of parents and their child, it is possible to tell if the man identified as the child's father is his or her biological father. If the results of this comparison, done as part of this study, show that the father who offered the blood sample and signed the consent is not the biological father of the child, this information will not be revealed to the patient, family, or referring physician.

There is a risk of potential diminished capacity for insurability due to insurance companies learning of a genetic condition. This risk will be minimized by receipt of a certificate of confidentiality from the National Institutes of Health to protect against unauthorized disclosure of information obtained as a result of this research study (application pending). Families are provided detail on the extent of certificate protections in the consent forms.

There are no known risks to the cognitive and behavioral evaluations that are included in this protocol other than possible fatigue during their administration. Attempts will be made to minimize fatigue through use of frequent breaks or temporary discontinuation of an evaluation session. There is a potential risk that testing of siblings or parents could identify a psychological

condition of which they are previously unaware. If that should occur, the study psychologist will refer them for additional testing and consultation and explain the reason for the referral.

Standard structural MRI of the brain evaluation involves the following risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during the examination. Precautions will be taken to insure that no loose metal objects are in the room. Subjects who have any pieces of metal in their bodies will not be allowed in the MRI room and will not receive an MRI evaluation. There may be some discomfort associated with the MRI procedure, in particular, feelings of claustrophobia and discomfort from the loud banging noise during the study. Participants will be asked to wear earplugs to prevent temporary hearing loss that has occasionally been reported from the loud noise. There are no known risks associated with MEG testing other than potential fatigue or boredom.

Potential Benefits

Participants will receive a summary of the results of their cognitive testing and MRI of the brain. Participating family members will also receive the results of their genetic testing for the 16p11.2 del/dup. The subjects and/or families are not anticipated to benefit directly from participating in this research study. Other individuals with the genetic variations investigated in this study may benefit in the future from a better understanding of the factors that contribute to their differential brain and behavioral development, including potential therapies.

Alternatives

All of the procedures being done for this research protocol are available through standard medical care except for the advanced imaging studies. Subjects are not required to donate a skin sample; this is an optional part of the study. Subjects are not required to participate in the imaging studies, and would only have imaging studies if sedation is not required. Subjects may choose not to participate in this research study at all or to discontinue participation at any time without prejudice.