**Full Study Protocol**

**Study of the Genetic Causes of Neurologic & Psychiatric Disorders**

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A. BACKGROUND AND INTRODUCTION:

While the genetic etiology for some neurologic and psychiatric disorders has been discovered, the genetic anomalies in most people remain unknown. One of the main reasons for this has been the failure to capture large patient cohorts and families to facilitate the use of approaches such as linkage analysis, genome-wide association studies (including family-based association tests), and whole genome sequencing studies. These powerful techniques can be used to identify genetic etiologies in conditions with variable penetrance/expressivity, complex gene interactions or interactions between genetics and environment.

B. OBJECTIVES:

We propose to conduct genetics research at the Utah Foundation for Biomedical Research. This study will create an infrastructure to collect, organize, and maintain a bank of information describing neuropsychiatric phenotypes and clinical data for research participants who have been diagnosed with neurologic or psychiatric conditions. The purpose of such a resource is to provide researchers at (and/or affiliated with) the Utah Foundation for Biomedical Research with DNA and phenotype data, in order to improve our understanding of the genetic causes of complex disorders. These samples will be used for gene discovery studies conducted through the Utah Foundation for Biomedical Research consisting of genome-wide and family-based association studies (using single nucleotide polymorphism arrays), copy number variation analysis, whole exome sequencing, and whole genome sequencing. The samples may also be made available, with the participants’ informed consent, to other investigators for use in other hypothesis-driven research aimed at uncovering genetic etiologies and understanding genotype-phenotype relationships.

This study will test the hypothesis that a low number of highly penetrant genetic mutations will be shared in a relatively small combination (on the order of 1-3 such variants) among affected relatives within some pedigrees, and that these variants will not be present in the same combination in unaffected relatives or in other families in Utah with very little to no neuropsychiatric disorders. The alternative hypothesis is that some affected individuals in these families have these illnesses due to polygenic inheritance models, including additive and/or epistatic interaction among dozens to hundreds of loci within each person. The currently classified syndromes of schizophrenia, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), autism and other mental illnesses are quite heterogeneous between families, and these symptoms can be seen in known single locus disorders such as Fragile X and 22q11.2 velocardiofacial syndrome. We hypothesize that a set of 1-3 mutations will either singly or additively predispose to illness in each particular person within any one family. We will test our hypothesis with genotyping and whole genome sequencing (WGS) analysis of these families, particularly given that we expect to find various kinds of mutations in genes, noncoding regions, promoters, and other regulatory loci. Identifying mutations and carefully defining their resulting pathology in the context of well studied large families, coupled with cellular functional analyses, could also identify additive and epistatic contributions, along with genetic networks and biological pathways underlying this form of pathology seen within broader diagnostic groupings, e.g. autism and schizophrenia.

PARTICIPANT SELECTION CRITERIA:

Inclusion & Exclusion Criteria:

Criteria for the selection of participants are broad. This is consistent with the goal of creating a resource for the study of a variety of poorly understood neurologic and psychiatric conditions, including but not limited to:

• Attention Deficit Hyperactivity Disorder (ADHD)

• Mental retardation/Intellectual Disability

• Tourette syndrome

• Autism

• Obsessive compulsive disorder (OCD)

• Developmental delay

• Schizophrenia

• Depression

• Bipolar disorder

Participation will be solicited both for individuals who do and do not have neuropsychiatric disorders, as it is very important to not only have a database of participant with neurologic and psychiatric disorders, but also to have a control group without such disorders. Consent will also be solicited from family members of any identified probands to provide expanded pedigrees and aid in research aimed at discovering genetic links in neuropsychiatric disorders, including rare, family-specific genetic variants.

There are no broad exclusion criteria based on age, gender, race, or level of functional impairment. Individuals will be excluded if they are unwilling to consent to the banking of a sample of DNA, RNA and/or cell lines. Children and mentally impaired adults with a developmental age greater than or equal to seven years of age will be excluded if they do not give their assent to participation.

Participants will primarily be recruited from the community. Informed consent will be obtained by a research coordinator or study investigator. Both participants with and without neurologic and psychiatric disorders will have the opportunity to opt into the study. Research participants without neuropsychiatric disorders will be used as controls to help further the knowledge about the disorders being studied.

Study participants will primarily be ascertained from the community and referrals, but participants will occasionally be enrolled via telephone and fax/mail if they are out of state and have a relative participating in the study locally.

Genetic studies generally require large sample sizes in order to detect multiple small disease effects and uncover rare genetic variants associated with complex disorders. The total number of participants expected to participate in this study is at most 5,000 over the course of 5 or more years. Approximately one-third of the participants are anticipated to be healthy controls without any of the disorders listed above. Both small and large families will be collected, as well as individual cases, although extended pedigrees offer advantages in disease-gene finding efforts. Ideally, index cases will present family histories indicative of 2 or more affected blood relatives distributed across 3 living generations. There are no limitations on how many family members can participate, and it is anticipated that equal numbers of adults and children will participate in this study.

Study Duration:

This study is not limited in duration, and it is anticipated that we will continue renewing this protocol for many years, while searching for disease-causing genes in complex neurologic and psychiatric disorders. Genetics studies often take 10 or more years, although with advances in technology such as whole genome sequencing, it is our hope that progress will be made much more quickly. All samples are anticipated to be kept indefinitely, unless participants request, in writing, to have their samples and personal information destroyed. In the event that funding is no longer available to continue to store DNA samples at the Utah Foundation for Biomedical Research, the samples (along with informed consent forms and accompanying study data) could be donated to a Co-Investigator (such as Dr. Lyon) for continued research.

C. SUB-INVESTIGATORS:

In addition to the Principal Investigator, Reid Robison MD MBA, there are several co‑investigators on this proposal, from a variety of clinical and research disciplines, including Gholson Lyon, MD PhD, Kai Wang, PhD, and Clark Johnson, MD. All of these individuals are involved in either clinical care or research, thus all of them will be contributing to this effort. Other individuals not listed, such as support staff and research scientists, may be involved in the analysis of de-identified study data (including genotype and phenotype information) at the Principal Investigator’s discretion, if they possess adequate training and experience to carry out their assigned responsibilities.

D. STUDY PROCEDURES:

Research participants taking part in the study will have a blood or saliva sample taken, possibly during home visits, and will be asked questions about their relevant medical history. Research participants will also be asked for permission to have their medical records obtained from their primary care providers, hospitals, and/or specialists they have seen, such as inpatient or outpatient psychiatrists or neurologists. In some instances, more detailed assessments will be administered, with consent from the research participant. Dr. Robison, and other study Sub-Investigators, are members of international consortia studying the genetic basis of obsessive compulsive disorder, ADHD, and Tourette Syndrome. One such example is the Psychiatric Genetics Consortium, in which Drs. Robison and Lyon currently participate. For these consortia, there are many assessments that are required, in order to provide detailed information concerning the diagnoses. This information may be collected from study participants either by mail/fax/email or in person, and then sent, in a de-identified manner, to the various coordinating sites.

Family Participation & Privacy/Confidentiality

When an individual with a neurologic or psychiatric disorder (proband) participates in this study, they will be asked if they have any relatives (unaffected or affected) who may be interested in participating as well. In order to respect privacy, participants in this study (probands) will be asked to give a brochure for the study (or business card for the Utah Foundation for Biomedical Research) to any relatives to may be interested and ask them to call the Foundation. We will therefore be collecting samples for parents, grandparents, uncles, aunts, cousins, and other members of the extended family.

Remote Participation via Telephone/Mail

Because this is a family-based genetics study, study participants will be asked to refer out-of-state relatives to participate in the study. Study participants will be given a study brochure or business card for the Foundation and instructed to have their relative call the Foundation if they are interested in participating. If the relative is interested in participating and they live near Salt Lake City, Utah, they will be invited to participate in person. If they would like to participate but do not live locally, the consent form will be mailed, emailed or faxed, and discussed in detail on the telephone with the potential participant by study staff. No study procedures will be conducted until informed consent has been obtained and the signed consent form has been collected via mail or fax. Once informed consent has been obtained, additional phenotypic information may be collected via telephone or mail/fax.

Home Visits

In the event that research participants cannot come to the foundation for participation, then we will visit them in their homes as necessary to finish the assessments and obtain blood or saliva. Sometimes, we will mail saliva collection kits, particularly for relatives living out of state.

Blood Collection

If blood is taken, it will be used to extract DNA, RNA and/or to create lymphoblastoid or induced pluripotent cell lines using established protocols (Anderson and Gusella, 1984). Approximately 10-30 milliliters of blood will be collected from adult participants. Only 8 ml of blood will be collected from children weighing less than 25 kg. The minimum weight for participation in the blood draw is 10 kg. The DNA from infants and children weighing less than 10 kg will be collected via buccal swab instead. A total of 8-16 ml of blood will be collected from children weighing between 25-50kg. Children over 50kg will be treated as adults for blood draw calculations. Blood will be collected in yellow-top tubes designed for genomic DNA collection.

Saliva Collection. In cases where participants are unwilling to consent to phlebotomy for themselves or their children, or if participants are recruited via the Internet from the Foundation website and blood sample collection is not feasible, we may ask for consent to obtain genetic material from samples of saliva and/or epithelial cells scraped from the inside of the cheek (buccal swab), using saliva DNA collection kits from Oragene or Nortek.

After signing the informed consent form (or providing an electronic signature via the study website), participants will be assigned a family ID and an individual ID. Blood and saliva samples will be labeled with this is unique ID number, rather than with identifying information. If blood samples are being obtained, phlebotomy will be done by individuals with adequate training and experience, under the supervision of study physicians.

Blood samples are preferred over saliva, due to better DNA quality derived from blood samples. However, blood samples are less convenient to collect. The determination of which type of sample will be collected from which research participants will be made as follows: if participants are unable or unwilling to provide a blood sample, but are still willing to provide a saliva sample, a saliva sample with be obtained. Furthermore, if providing a blood sample is not practical as the participant is participating in the study remotely via telephone and fax, then a saliva kit will be sent via mail to the participant. When sending in saliva via mail, the participant will be sent an addressed, stamped mailing envelope designed for saliva shipment and instructions for the participant regarding how to provide the saliva sample will be included. On occasion, when a blood sample is desired from a study participant who enrolls in the study remotely via telephone and fax, the participant may be provided with yellow-top collection tubes via mail, as well as, an addressed stamped mailing enveloped designed for the shipment of blood. The participant will be instructed to take this to their primary care physician office, or to the nearest laboratory (such as Labcorp) for phlebotomy.

Samples are received by laboratory technicians at the following DNA company:

**Affiliated Genetics**

2749 East Parleys Way Suite 100

Salt Lake City, UT 84109

It is possible that we will use other laboratories or core facilities to process DNA, RNA and cell lines.

All samples are labeled with a 2D barcode. After DNA and RNA extraction, genomic DNA and RNA will be stored in refrigerators or in freeze-dried aliquots, and an aliquot of the DNA will be returned to the Utah Foundation for Biomedical Research for backup. Additionally, if lymphoblastoid cell lines are not created upon receipt of blood samples, a small cell pellet will be frozen for later transformation into cell lines, if needed. It is anticipated that samples will be stored indefinitely; there is no planned date for destruction of samples. If genomic DNA is depleted throughout the course of this study, lymphoblastoid cell lines will be created from frozen cell pellets, and genomic DNA will be extracted from these cells to replenish the supply of genomic DNA. If a participant requests in writing to be removed from the study, their DNA sample and phenotype data files will be destroyed.

Upon written request, information indicating a participant’s willingness to be screened and/or contacted will be excluded from the database.

Consent will be obtained either in person or via telephone or fax (if the participant is not living near Salt Lake City, Utah). All records, including the electronic and/or paper version of the consent form, will be stored in a locked file cabinet (for paper records) or on a secure, password-protected server (for scanned or electronic copies).

In the event that a consent form is partially filled out or if a signature is missing, the participant will be contacted in order to finish filling in the form, which can be sent to them via mail or fax, or when they come in for their next appointment.

A demographics questionnaire will be included with the consent, so as to provide research participants with the opportunity to provide additional information that could assist with choosing which research studies that they could be eligible for in the future. This questionnaire includes questions related to their medical and psychiatric health. This questionnaire, as is the case with all study questionnaires and assessments, is optional.

Compensation. Some families have expressed the concern that the studies can cost them time, effort and lost income. Accordingly, for those families who express such a concern, we have decided to offer a minor amount of compensation, in the form of $10 for each participant. For a family of two parents and six children, that would be $80 paid to them to participate and to compensate for their effort, if they request compensation. The funding for UFBR is limited, so we only wish to provide this compensation if a family needs and requests it.

E. DATA ANALYSIS AND INTERPRETATION:

Information regarding a participant’s decision to be screened and contacted will be entered into a secure database of clinical information maintained at the Utah Foundation for Biomedical Research. Access to this database will initially be accessible to the investigators administering the study database. Ultimately, the intent of this proposal is to make participants and information in the database available to other investigators affiliated with the Utah Foundation for Biomedical Research. Requests for access to this material will be contingent on IRB approval, so that each proposal’s procedures, scientific design, and potential risks and benefits can be evaluated on a case-by-case basis, including the need to obtain further consent from the participant or whether a waiver of consent is appropriate.

Initial genetics studies planned to be conducted using these samples include single nucleotide polymorphism (SNP) and copy number variant (CNV) microarrays, as well as, whole exome and whole genome sequencing, performed by affiliated laboratories and investigators on de‑identified samples and information. Sequencing data will be analyzed according to broadly accepted software algorithms, such as the Short Oligonucleotide Analysis Package (SOAP) including SOAPaligner and SOAPsnp. Variants identified using SNP calling algorithms will then be processed using functional annotation software, such as ANNOVAR, in order to determine if variants have an impact on protein coding. Candidate variants will be checked against publicly available database, such as dbSNP and SNPs from the 1000 genomes project and then analyzed for sharing among affected individuals both within and across families. Plausible candidate variants will then be validated using Sanger sequencing by a genetics laboratory affiliated with the Foundation. SNP/CNV arrays will be used to assess SNP calling accuracy, and also to examine the genome for any structural variation (such duplications or deletions) associated with phenotype.

All phenotypic information, including results of the medical and family histories, physical exams, digital imaging, karyotypes, and other studies might be kept in research paper charts or entered into a database of clinical information maintained at the Utah Foundation for Biomedical Research. Access to these charts or this database will initially be accessible only to the investigators administering the program.

F. ADMINISTRATIVE RESPONSIBILITIES:

All study data will be kept in locked file cabinets and/or secure computers at the Utah Foundation for Biomedical Research. A designated coordinator will maintain the data. Participants will always have an opportunity to speak to a staff member and/or investigator from this protocol before signing the informed consent document. DNA samples and other biological material will be kept at the Utah Foundation for Biomedical Research or one of the laboratories it contracts with for DNA extraction, storage and/or genotyping, such as Affiiated Genetics, Cold Spring Harbor Laboratory or the Children’s Hospital of Philadelphia.

This study is funded internally by Foundation funds at this time, although we anticipate applying for external grants to support this going forward.

G. RECRUITMENT:

Research participants will receive an informed consent form as part of their initial patient packet or will be given the consent form by a coordinator. After reading and understanding the purpose of the study, the patient will have the choice to opt into the study.

Flyers will be printed with the following text (and may include the UFBR logo and other graphic design elements such as stock photos) and given to prospective study participants. Recruitment cards will also be left with neurology, psychiatry, primary care, and specialty clinics that agree to distribute these study recruitment materials:

Utah Foundation for Biomedical Research

Family-based Genetic Study of Neurologic & Psychiatric Conditions

Recruiting for the following conditions:

Autism, Developmental Delay, OCD, Tourette’s Syndrome, Mental Retardation, Schizophrenia

Eligible participants may be paid for their time & travel

Phone: 801-449-1246, Email: info@utahresearch.org, Web: [www.utahresearch.org](http://www.utahresearch.org)

Additionally, flyers or cards will be printed with just one disorder listed at a time to be given to specialty clinics or facilities who agree to distribute cards to prospective participants, such as at Autism schools, and other disorders listed in this protocol. Flyers or cards recruiting for a single condition will include text similar to this:

Utah Foundation for Biomedical Research

Now recruiting for a family genetics study of Autism Spectrum Disorders

Eligible participants may be paid for their time & travel

Phone: 801-449-1246, Email: info@utahresearch.org, Web: [www.utahresearch.org](http://www.utahresearch.org)

Advertising for study recruitment may also take place via the Internet or newspaper, by directing visitors to the Utah Foundation for Biomedical Research homepage (<http://www.utahresearch.org>) to call or email if they are interested in participating.

H. PROTOCOL MANAGEMENT & ADMINISTRATION

Procedures for obtaining informed consent:

Potential participants will be presented with the consent form by a research coordinator or investigator. Participants will have the opportunity to read and sign the form and return it at the time of that visit; or they will have the opportunity to take the form home and return it at a later time, if they would like more time to consider their decision to give consent. There is no set time limit in which the consent form must be returned to be able to participate. Participants will always have an opportunity to speak to a staff member and/or investigator about this protocol before signing the informed consent document.

It is our experience that when presenting consent forms that ask research participants about their willingness to participate in a study, having separate forms for obtaining parental consent and the assent from the child is cumbersome and confusing to the participant. Therefore, in an effort to both simplify and clarify the consent process for the participant, we have merged the consent and assent forms onto one document.

The patient's decision whether or not to participate in research will in no way affect their care at the clinics that have referred them to this study. Research participants will not be pressured to opt into the study, and they will experience no adverse side effects for choosing not to opt into the study. Contact phone numbers for the principal investigators will be listed on the form for potential participants to contact with any question regarding the study. Study coordinators will also be available to answer any questions.

In the event that participants are not 18 years of age or older or if they do not have capacity to provide informed consent on their own, then consent will be obtained from their parent or any legally authorized representative. Assent will also be obtained for children and impaired adults determined to have the capacity to provide assent. Many of these research participants will have neuropsychiatric disorders (such as autism, mental retardation, or developmental delays), which might affect their ability to understand and provide informed consent for the screening of their medical records along with permission to contact for future research. For example, research participants who cannot read, speak, and/or write will clearly be unable to complete this informed consent process. In fact, some of these research participants may not be able to provide assent either, as it might not be possible to engage them in a conversation about this. This is akin to the fact that many children under the age of seven are deemed unable to provide assent, so their parents solely provide consent for their children's participation.

The number of signature blocks creates the possibility that a potential participant will sign the wrong one or perhaps forget to fill something in. A research coordinator will be present to make sure the form is filled out correctly. Nonetheless, if we do discover that a consent form has not been fully filled out, we will contact the participant to ask them either to come in to finish it OR for us to mail a copy (or new consent) to them so that they can finish it or correct it and return it to us.

Procedures for protecting privacy and confidentiality of specimens:

Privacy will be protected by only allowing study investigators to review the medical records of research participants that have consented to allow review of their medical records to determine eligibility for research studies. At any time, participants have the right to withdraw from the study and have any information they have shared destroyed. Allowing participants to withdraw at any time ensures that the participant has control over their information, thus further ensuring privacy. The database of research participants will be kept on a secure computer server within the Utah Foundation for Biomedical Research. Only approved members of this research protocol and specifically designated support staff will have access to this database, and any information (medical or otherwise) will be kept confidential and will not be shared with anyone not affiliated with the studies.

All study data will be kept in locked file cabinets and secure computers at the Utah Foundation for Biomedical Research. A designated coordinator will maintain the data. Strict efforts will be made to store and use de-identified data. A key with names and ID numbers that allows linking of de-identified study records will be stored in a locked file cabinet and/or secure computer for future use if needed.

Procedures for Maintaining Participant Confidentiality & Privacy

When study investigators and coordinators meet with potential study participants to discuss the study and obtain informed consent, this will be done in a private interview room to maintain strict confidentiality. Any identifying data will be stored in a locked file cabinet at the Utah Foundation for Biomedical Research or on a secure password-protected server in order to avoid both unauthorized and accidental access to study records by individuals not involved in the study. When conducting genetics research using these DNA samples and accompanying phenotypic information, study ID numbers will be used rather than names, in order to maintain participant confidentiality and privacy.

Procedures for Communicating Results:

New technologies are making it possible to sequence whole exomes, and even whole genomes, for a reasonable price. As we proceed to sequence such genomes, it is likely that we will encounter “incidental findings”, i.e. mutations in genes that may or may not result in an elevated risk for a certain illness or disease. In the event that we identify such possibly deleterious mutations that study investigators deem significant, we will alert research participants and their physicians that there might be a mutation needing to be verified in a CLIA-certified laboratory. We will NOT convey specific details about any particular mutation to the research participant, but we will provide any details necessary to the CLIA-certified laboratory in order that they can efficiently conduct the necessary testing. Since results will not be conveyed directly to study participants, but rather they will be referred to their primary care physician for CLIA-certified laboratory testing at the discretion of the treating physician, the decision regarding the need for genetic counseling will be deferred to the participant’s primary care provider.

Procedures for Obtaining Consent from Parents

It is common practice in research studies for consent to be obtained from ONE parent of a child. However, we have found that obtaining consent from both parents (mother and father) is best, so as to avoid confusion; for example, sometimes one parent will sign the consent but then not inform the other parent that they did this, thereby later resulting in the other parent being upset or confused about the enrollment of their child or children in a research study. Therefore, every effort will me made to get participation and consent from both the mother and father, which is better anyway, as having the DNA from mother and father is better for the genetics studies. However, in the event that consent cannot be obtained from both parents, it will be sufficient to obtain consent from only one parent for participation of their children. This is also most practical, as most times, only one parent brings the children to the foundation, so only one parent is actually present to give consent. It would create an enormous burden to require written consent from both parents, prior to any blood draws from their children.

Procedures for Obtaining Consent when Children reach Adulthood

When children who have participated in this study by parental consent (and the child’s assent if they were 7-17 at time of participation) become adults (age 18), attempts will be made to re‑consent these participants using the adult consent as follows: a letter will be sent to the address of record asking the participant to call the Utah Foundation for Biomedical Research. If the individual responds to this letter and calls the foundation, they will be asked if they would like to consent to continued participation in this study. If so, informed consent will be obtained as an adult now, in person or via telephone. If the individual does not respond to the letter, two attempts will be made to contact the participant by telephone. If the participant consents to participate in this study as an adult, a follow-up assessment will be performed. If we are unable to reach the participant after three attempts as outlined above, their de-identified DNA sample and accompanying clinical data will remain in the study database.

Procedures to Withdraw from this Study:

Participants, including children, may choose to withdraw from this study at anytime, by sending a request in writing to the Principal Investigator, Dr. Robison, via email at info@utahresearch.org, or via mail at the following address:

Reid J. Robison, MD, MBA

Utah Foundation for Biomedical Research

1208 East 3300 South, Suite 100

Salt Lake City, Utah 84106

Phone: 801-449-1246

Immediately upon receipt of such requests, the individual’s DNA sample and accompanying phenotypic information will be destroyed. In the event that de-identified DNA samples have already been submitted to genetic research consortia, such as the Psychiatric Genetics Consortium, it will not be possible to destroy the aliquot of DNA that has already been sent. However, since the key linking the individuals study ID and name will have been destroyed, there will be no way to trace this DNA sample back to an individual.

The Utah Foundation for Biomedical Research may decide to terminate this study at any time, if sufficient successful genetic findings have been obtained or if resources to continue funding sample collection are limited. In this case, investigators may decide to contribute the DNA samples and accompanying phenotype data to research scientists involved in studying these neurologic and psychiatric disorders with current IRB-approved protocols.

I. DATA SAFETY AND MONITORING

This project poses minimal risk to participants. Blood draw may produce bruising, pain, fainting, or rarely, infection. These adverse reactions are best managed by sterile technique by experienced venipuncturists. Confidentiality will be assured by assigning participant numbers for data analysis. Potential anxiety resulting from diagnosing family members may be managed by educating family members about the condition, and referring them for treatment when appropriate.

Reporting of Adverse Events

Any adverse events will be reported via email as soon as possible to the Principal Investigator. Serious adverse events, such as infection related to blood draw, will be reported within 24 hours. Minor adverse events, such as fainting during venipuncture, will be reported within two business days.

REFERENCES AND APPENDICES:

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