DRCR Retina Network

Genetics in Retinal Diseases Project
(Protocol GEN)

Version 4.0
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By signing below, I acknowledge my approval of this protocol.

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VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Bambi Arnold-Bush	Adam Glassman	09NOV2011	Initial
2.0	Bambi Arnold-Bush	Adam Glassman	13MAR2014	Clarification added that additional information may be collected for the study
3.0	Adam Glassman	Cynthia Stockdale	06APR2018	Target goal increased from 2,000 to 5,000; background/rationale, study objective and research methods sections updated to include other retinal diseases, previously just DR. Participant reimbursement updated to allow sample redraw
4.0	Sandra Galusic	Cynthia Stockdale	22JAN2026	Revised formatting to current protocol template (title page, key roles, revision history), updated Network name throughout, clarified that DNA samples will be available (not blood) and no other samples or data collected (phenotype data is based on participation in other DRCR trials), expanded the study eligibility/enrollment section to better describe participating sites, and consent process, expanded data/sample collection to include more information on blood sample collection and DNA extraction process, updated repository name from RCB to BPB, updated miscellaneous section with more info on participant withdrawal and updated confidentiality risks to reflect current policies, and clarified that for (future) research efforts genotype will be available in public portals like dbGaP

TABLE OF CONTENTS

Chapter 1. BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background Information:

1.1.2 Public Health Impact of Retinal Diseases

Retinal disease is a common cause of visual impairment and blindness worldwide. In the United States (US), it is estimated that nearly 20 million Americans are affected by retinal pathology from diabetic retinopathy (DR), age-related macular degeneration (AMD), retinal vein occlusion, myopic choroidal neovascularization, retinopathy of prematurity, or inherited retinal diseases.[7-14] The US economic burden from retinal disorders totals as much as $8.7 billion per year.[15] Diabetic eye disease and AMD are the most frequent causes of vision loss and are projected to cause visual impairment in over 17 million Americans by the year 2050.[15] New approaches to the management of these conditions are needed in order to more effectively preserve vision across large segments of the growing and aging population.

Estimates suggest that by the year 2030, approximately 439 million individuals worldwide will be affected by diabetes mellitus.[28] The increasing global epidemic of diabetes implies an associated increase in rates of vascular complications from this chronic disease, including diabetic retinopathy (DR). Despite advances in diagnosis and management of ocular disease in diabetic patients, eye complications from diabetes continue to be the leading cause of vision loss and new onset blindness in working-age individuals throughout the United States.[29] Although therapies with anti-vascular endothelial growth factor (anti-VEGF) agents and laser are generally effective in improving visual outcomes, approximately 50% of patients with diabetic macular edema (DME) do not respond fully to these treatments. There is a critical and unmet need for safer and more effective novel therapies for DR and DME. The global epidemic of diabetes is projected to increase by 55% over the next 2 decades to affect 642 million people.[16] Retinopathy occurs in 40.3% of diabetic patients over 40 years of age; vision-threatening DME in 9.6%, and 4.4% develop advanced DR that could lead to blindness.[3, 10, 17] Patients with DR experience substantially worse quality of life compared with patients with no ocular disease.[18, 19] The cost of caring for patients with diabetes related blindness in the US is approximately $500 million annually.[20]

Age-related macular degeneration (AMD) is another leading cause of legal blindness throughout the western world.[21-24] AMD is expected to affect nearly 88 million older Americans in 2050.[28] Prior to anti-VEGF treatments, approximately 90% of vision loss in AMD was attributable to neovascular AMD.[25] Although the prognosis for patients with neovascular AMD improved dramatically in 2005 with the introduction of anti-VEGF agents, 10% of patients still become legally blind and another 50% experience substantial vision loss in the first few years of treatment.[26-29] With longer follow-up, many patients experience vision decreases despite initial treatment success.[30] In the largest cohort of neovascular AMD patients followed for 5 years, mean visual acuity at 5 years was worse than at baseline despite initial treatment success in many patients, and 20% of patients were legally blind.[30] The cost and treatment burden of anti-VEGF therapy necessary is high and clinical research efforts to improve therapeutic frequency and cost are needed.[31] For non-neovascular AMD, there are no effective treatments to date that reverse or prevent progression of geographic atrophy. Support for several factors determining one's risk for AMD, including smoking, systemic hypertension and cardiovascular disease, have been found.

1.1.2 Genetics and Diseases of the Retina

There is agreement that several factors determine a person's risk for diabetic retinopathy, namely hyperglycemia, diabetes duration, and systemic hypertension. There is also increasing evidence supporting a genetic component in DR susceptibility given the heterogeneity of DR in patients with equally poor glycemic control. Several studies, including the Diabetes Control and Complications Trial, have provided evidence for a familial tendency toward DR development, independent of associated risk factors.[32] Therefore, studies on the genetic risk factors related to diabetic retinopathy are of public health importance.

Several family and twin-based studies have shown that the proportion of variability attributed to the risk of AMD has been estimated at 45% - 70%[27]. Variation at two loci, the Complement Factor H (*CFH*) gene and the *ARMS2/HTRA1* locus, account for almost half of the genetic risk for advanced AMD.[33] Other genes in the complement activation pathway, as well as genes with roles in extracellular matrix homeostasis and lipid metabolism, also contribute to risk for AMD.[34] These genetic insights into the pathophysiology of AMD have led to development of drugs that are currently in clinical trials for geographic atrophy.[35]

Though AMD and DR are very different diseases of the retina, genetic components are likely involved in both. Research extracted from The Health Improvement Network (THIN) database showed that when compared to those who were free from AMD, those who had diabetes carried a higher risk of AMD compared to nondiabetics.[29]

1.2 Study Objective and Study Overview

The DRCR Retina Network is pursuing this genetics initiative to collect, store, analyze, and distribute genetic material with accompanying phenotypic information. The initiative will provide a unique opportunity to combine data from multiple populations, to define genetic factors that confer risk for development and progression of diabetic retinopathy and other retinal diseases, and response to therapeutic intervention. The goal of this project is to create a repository of at least 5,000 participant's DNA samples with high-quality genetic material and clinical phenotype information as a resource for the research community, both public and private institutions. Specimens will be collected from consented participants from Network trials and sent to a qualified provider to extract DNA, and possibly plasma/serum, and store the materials. This bioresource will be made available to the researcher community (e.g., government, academic centers, and industry), who may request samples, together with detailed clinical data, for genotypic analyses. Requests will be approved by a transparent process by the DRCR Retina Network.

A focus of the DRCR Retina Network has been to conduct large-scale randomized comparative-effectiveness trials which therefore afford the opportunity to conduct well-powered pharmacogenetic analyses. Findings from genetic research may be adopted world-wide to assess risk of disease, prognosis and response to interventions. It also may promote development of international research collaborations that would improve the lives of people around the world or accelerate fundamental discoveries.

1.3 General Considerations

The project is being conducted in compliance with the policies described in the DRCR Retina Network Policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

When feasible, data will be directly collected in electronic case report forms, which will be considered the source data.

Chapter 2. STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT

2.1 Participant Recruitment and Enrollment

A minimum of 5,000 participants are expected to be enrolled. Participants who have signed consent may be permitted to continue into the study, even if the enrollment goal has been reached.

Study participants will be recruited from the approximately 80 clinical sites in the United States and Canada currently participating in DRCR Retina Network protocols. All eligible participants will be included without regard to race or ethnicity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal. Potential eligibility will be assessed during a routine examination by an investigator prior to obtaining informed consent, as part of usual care.

2.2 Informed Consent and Authorization Procedures

Potential eligible participants should be approached during either a routine care visit or DRCR Retina Network study visit. Prior to collecting a blood sample, consent must be obtained with the consent process documented by an appropriately signed written informed consent form.

The potential study participant will be given either the Protocol GEN Informed Consent Form (ICF) to read as part of the Genetics consent process, or may complete an opt-in/opt-out section for Genetics Repository Biospecimen collection when being consented in another protocol in which blood sample collection is being done. Potential study participants will be encouraged to discuss the study with family members, friends, or their personal physician(s) before deciding whether to participate in the study. Participants that do not give their permission for biospecimen banking in another trial will not be treated any differently and still be allowed to take part in the main study.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when either the Genetics informed consent form has been signed, or the participant opts in to the optional Genetics Repository biospecimen collection section in another protocol, as may be the case. Sample collection may be collected at any time during follow-up, if not obtained at Screening.

2.3 Participant Inclusion Criteria

To be eligible for this project, a patient must currently be enrolled in an applicable DRCR Retina Network study or previously been enrolled in an applicable study. The DRCR Retina Network procedures manual will indicate which protocols are applicable for study enrollment.

Chapter 3. DATA AND SAMPLE COLLECTION AND STORAGE

3.1 Blood Sample Collection

Blood samples will be collected from consented participants enrolled in DRCR Retina Network protocols. It is anticipated that a minimum of 5,000 participants will have a sample collected.

Clinical sites can obtain blood specimens according to their own office procedures. Venipuncture should only be performed by qualified and trained staff, as determined by the investigator, while observing Universal Precautions. Samples are collected from each participant using the blood sample collection kits provided by the DRCR Retina Network.

Details regarding collection, sample labeling, storage, and shipment can be found in the DRCR Retina Network procedures manuals.

3.2 DNA Extraction

High-quality genomic DNA will be extracted from venous blood samples collected from DRCR Retina Network study participants. The amount of DNA is determined by spectrophotometry, using a relative purity optical density 260/280 ratio. Any sample falling outside of the recommended ranges for purity will be re-extracted if possible. Following all harvesting and processing steps, stock DNA will be made into 9 aliquots of 2 µg each with a concentration of 100 ng/µl using 1:10 DNA hydration solution and stored at -20ºC.

When requested, DNA aliquots will be made available for genome-wide or targeted SNP analyses, whole exome, whole genome sequencing, methylation analyses, or other analyses. At some high enroller sites, an additional blood sample may also be collected and used for serum extraction. Blood serum will be processed and aliquoted by clinical site, shipped frozen to the repository for storage in ultralow (-80ºC) freezers. With this serum, scientists might conduct proteomic or other analyses.

3.3 Sample Storage

Both DNA and serum samples will be stored at the Biospecimen Processing & Biorepository (BPB), formerly Research Cell Bank, at the Fred Hutch Cancer Center research laboratory located in Seattle, Washington. Samples will be stored in a locked freezer for an indefinite amount of time. Patient samples are identified by anonymized barcode and aliquot number only. The sample is stored such that no automated links exist between the patient's sample and information that would identify them.

3.4 Collection of additional information

Information collected as a part of the DRCR Retina Network study the participant is enrolled in will be stored in the DRCR Retina Newtork study's database. Additional information, including photographs of the participant's eye(s), other lab samples, an eye exam, visual acuity testing,or other testing may also be collected, if necessary to supplement the parent study. This associated clinical data will be available as part of a uniquely detailed phenotype, alongside the genotype dataset as already described.

3.5 Samples and Data Requests

Researchers may request access to biospecimen samples, genetic and clinical data through the DRCR.net public website. Requests for access to data available on the DRCR.net public website

will be reviewed by the DRCR Retina Network Steering Committee, with input from the Genetics Protocol Chair, and at least one geneticist, as needed.

Chapter 4. MISCELLANEOUS CONSIDERATIONS

4.1 Participant Reimbursement

Participants will receive a separate $25 gift card for their participation in this study, unless the genetics sample is provided as part of the parent study and covered by the main study consent. In those cases, participant payment is already included in the parent's study reimbursement and no additional gift card is given, even if the participant consents to future biobanking. If the DNA sample is of insufficient quality, the participant may be asked to have blood redrawn at a subsequent visit. In this case, an additional $25 gift card will be provided.

4.2 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. While participants have the right to request that their biological samples (DNA, plasma/serum) be destroyed if feasible, the DRCR Retina Network will not attempt to withdraw or destroy any genetic materials that have already been distributed.

Participants may also cancel their authorization for sharing personal information at any time by providing written request to either their study doctor or the JCHR IRB Office. When authorization is cancelled, study participation is ended. No new personal information will be shared for the study, however any requesting researchers will receive all information that was collected up to the time that authorization was cancelled or participant was withdrawn.

4.3 Benefits and Risks for Participants

Information obtained as a result of this research is unlikely to be of direct medical benefit to the participants. The major benefit to society is the possibility of better understanding how genetics might be associated with Diabetic Retinopathy, Age-Related Macular Degenertaion, and other retinal diseases. This information could lead to ways to prevent or better treat the effects of retinal disease in others in the future.

The risks of the study are minimal. The blood draws could result in discomfort or bruising or rarely a blood clot.

The risk of disclosure of protected health information is very small. Efforts are taken to assure that this does not occur, in compliance with HIPAA. See section 4.4 for additional information on confidentiality.

4.4 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Data will be entered on the Jaeb Center for Health Research's secure website. The study website is password-protected and restricted to users who have been authorized by the Coordinating Center to gain access. Deidentified participant information, i.e., identified only by the study-specific identifier, may be provided to research sites involved in the study.

Blood samples will be labeled with a barcode that will have no components that could identify the participant. The barcode of each sample will be linked in the Jaeb Center's database to the participant's DRCR Retina Network identification number.

Samples will be sent to the Biospecimen Processing & Biorepository, formerly Research Cell Bank, at Fred Hutch Cancer Center laboratory located in Seattle, Washington for processing, DNA extraction and sample storage.

To help protect participant's privacy, the National Institutes of Health has issues a Certificate of Confidentiality to the Jaeb Center for all studies conducted under the current grant award. With this certificate, the Jaeb Center cannot be forced to disclose identifying information for use in any federal, state, or local civil, criminal, administrative, legislative, or other court proceeding, even if faced with a court subpoena. The Jaeb Center will use the Certificate to resist any demands for information that would identify participants except as explained below.

The Certificate cannot be used to resist a demand from the Department of Health and Human Services or other offices in the United States Government for audit and evaluation purposes, nor does it preclude voluntary disclosure. A Certificate of Confidentiality does not prevent a participant or a member of their family from voluntarily releasing information about themselves or their involvement in this research. Each site participating in a DRCR Retina Network protocol is covered by the Certificate of Confidentiality.

Chapter 5. FUTURE RESEARCH STUDIES AND STATISTICAL METHODS

The long term goal of this project is to elucidate the genetic architecture of various retinal diseases. Repository samples will be used to identify genetic susceptibility variants associated with diabetic retinopathy and diabetic macular edema, age related macular degeneration, and other retinal diseases.

5.1 Research Studies

The Network will prioritize the genetic repository database of clinical phenotypes and genotype information to create the initial bioresource using criteria set from several high priority research topics. During or after completion of the genetic repository database, separate statistical analysis plans will be developed for each DRCR Retina Network topic of interest, with sequencing of interim dataset for genome-wide association testing, as applicable. The topics are not limited to, but may include any or all of the following:

1. Pharmacogenomic studies – Study participants who have a good response to treatments shown to be beneficial compared to those who do not have a good response
2. Theranostics – Study participants who have a good response initially and then fail to sustain a good response
3. Rapid vs. delayed onset – Study participants with shorter or longer duration of diabetes who develop PDR or DME.
4. Pharmacogenetic studies of side effects – Study participants who develop drug side effects, such as steroid-induced intraocular pressure rise with intravitreous steroids, compared to those who do not develop that side effect

The extensive and carefully-evaluated prospective longitudinal phenotype data that have been collected in many of the DRCR Retina Network populations may allow subgroup analyses focusing on endophenotypes, such as proliferative diabetic retinopathy, diabetic macular edema,disease worsening, and disease regression. Statistical estimations support that such analyses can be undertaken on a candidate gene basis.

5.2 Contributing to Other Cohorts or Metanalyses of Associated Diseases

As described in section 3.4, genotype and phenotype data will be made available to the research community. From this database, it may be possible for researchers to identify those individuals from the DRCR Retina Network studies with certain environmental or personal risk factors for whom genotype information is available through public portals such as the NIH's database of Genotypes and Phenotypes (dbGaP).

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