Diabetic Retinopathy Clinical Research Network

Genes in Diabetic Retinopathy Project

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Chapter 1. BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background Information:

1.1.1. Public Health Impact of Diabetic Retinopathy

Over the last 10 years, the age-adjusted incidence of diabetes mellitus (DM) in the United States has doubled,[1] and recent estimates suggest that by the year 2030, approximately 439 million individuals worldwide will be affected by this chronic disease.[2] 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.[3]

Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) demonstrated that 15 years after diagnosis of DM, the prevalence of DME ranges from 14% to 25% in patients with type 1 and 2 DM.[4] In a review of three early studies concerning the natural history of diabetic macular edema, Ferris and Patz found that 53% of 135 eyes with DME, presumably all involving the center of the macula, lost two or more lines of visual acuity over a two year period.[5] Without intervention, 33% of 221 eyes included in the Early Treatment Diabetic Retinopathy Study (ETDRS) with center-involved DME experienced "moderate visual loss" (defined as a 15 or more letter decrease in visual acuity score) over a three year period.[6]

1.1.2. Rationale for Genetics Studies on Diabetic Retinopathy

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.[7] Therefore, studies on the genetic risk factors related to diabetic retinopathy are of public health importance.

The DRCR.net 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, including the Type 1 and Type 2 diabetic populations in the US, to define genetic factors that confer risk for development and progression of diabetic retinopathy, and response to therapeutic intervention.

1.2 Study Objective and Study Overview

The goal of this project is to create a repository of at least 2000 participant's blood samples with extracted 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 serum, and store the materials. This bioresource will be made available to researchers (including industry), who may request samples, together with detailed clinical data, for genotypic analyses. Requests will be approved by a transparent process by the DRCR.net.

The database may provide the opportunity to assess genetic susceptibility and resistance to DR and also variants impacting visually-important biomarkers for macular edema and neovascularization. A focus of the DRCR.net 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.net 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.

The DRCR.net Procedures Manuals provide details of examination procedures and blood sample collection procedures.

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 Identifying Eligible Study Participants and Obtaining Informed Consent

A minimum of 2000 participants are expected to be enrolled. Potential eligible participants should be approached during either a routine care visit or DRCR.net 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 the Informed Consent Form to read as part of the consent process. 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.

2.2 Study Participant Eligibility Criteria

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

Chapter 3. SAMPLE COLLECTION AND STORAGE

3.1 Blood Sample Collection

Blood samples will be collected from participants from DRCR.net protocols. It is anticipated that a minimum of 2000 participants will have a sample collected.

Procedures for collecting blood samples are outlined in the Procedures Manual.

3.2 DNA Extraction

High-quality genomic DNA will be extracted from venous blood samples collected from DRCR.net study participants. The DNA will be made available for genome-wide or targeted SNP analyses, whole exome, whole genome sequencing, methylation analyses, or other analyses.

At some sites, an additional blood sample may also be collected and used for serum extraction. With this serum, scientists might conduct proteomic or other analyses.

3.3 Sample Storage

Blood samples will be stored at the Research Cell Bank at Fred Hutchinson Cancer Research Center laboratory located in Seattle, Washington. Samples will be stored in a locked freezer for an indefinite amount of time. Patient blood samples are identified by ID number. The sample is stored such that no automated links exist between the patient's sample and information that would identify them.

3.4 Samples and Data Requests

Researchers may request access to samples through the DRCR.net public website. Requests for access to data available on the DRCR.net public website will be reviewed by the DRCR.net Project Access Committee. The Project Access Committee may be composed of, but is not be limited to, the project principal investigator, project manager, DRCR.net Network Chair, the DRCR.net NIH representative, at least one geneticist, and a DRCR.net investigator.

Chapter 4. MISCELLANEOUS CONSIDERATIONS

4.1 Participant Reimbursement

Participants that are currently receiving reimbursement for study related costs for completing a DRCR.net study visit will not receive monetary reimbursement for participation in the Genes in Diabetic Retinopathy Project. If a participant is not receiving reimbursement for study related costs for a DRCR.net study, they will receive a $25 gas card or a gift card to cover any travel costs related to the study visit.

4.2 Sample Withdraw

Participants have the right to request at any time that their blood sample be destroyed. A sample can be destroyed (if deemed feasible by the DRCR.net) on written request. The DRCR.net will not attempt to withdraw or destroy any samples that already have been distributed to scientists.

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 detecting risk factors for vision loss from diabetes. This information could lead to ways to prevent or better treat the effects of diabetes on the eye 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

The participant's DRCR.net identification number will be used to identify all data. 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.

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

Samples will be sent to Research Cell Bank at Fred Hutchinson Cancer Research Center laboratory located in Seattle, Washington for sample storage.

To help protect participant's privacy, the Jaeb Center has obtained a Certificate of Confidentiality from the National Institutes of Health. 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.

Chapter 5. RESEARCH STUDIES AND STATISTICAL METHODS

The long term goal of this project is to elucidate the complete genetic architecture of Type 1 / Type 2 diabetes, in particular, the complication of retinopathy. Repository samples will be used to identify genetic susceptibility variants associated with diabetes and diabetic retinopathy.

Because of the heterogeneity of diabetic retinopathy present in patients who participate in a variety of Network protocols, it is anticipated that these samples will come from a broad range of retinal pathology from diabetes not otherwise readily available from other studies including eyes with no diabetic retinopathy (approximately 10%), to diabetic retinopathy without macular edema or proliferative disease (10%) undergoing evaluations of preventive treatment, to macular edema undergoing treatment (approximately 60%), to proliferative diabetic retinopathy (approximately 20%) previously treated or undergoing treatment. It is anticipated that approximately 10% of these participants will have Type 1 diabetes. The results of participants with Type 2 diabetes likely will apply to those with Type 1 diabetes since there is no evidence to suggest that the diabetic retinopathy progression or response to treatment differs by type once retinopathy develops.

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.net topic of interest. 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. Analysis of worsening of diabetic retinopathy – Study participants who develop severe PDR before or despite panretinal (scatter) photocoagulation versus study participants who have not developed any PDR after different durations of diabetes
5. Analysis of DME worsening – Study participants who develop DME with less or more amounts of thickening versus study participants who have not developed any DME despite different durations of DM.

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

5.2 Identifying Genetic Variants Associated with Treatment Response

By the time that the repository collection has reached 2000 participants, over 1200 individuals will have received intravitreal monoclonal anti-VEGF therapy for diabetic macula edema in at least 5 Network trials. This cohort, for which extensive follow-up data are available, including

endpoints as continuous variables, likely is satisfactorily powered to evaluate the pharmacogenetics of treatment response. Recent data support that genetic variants in the VEGF gene may be associated with retinopathy in patients with diabetes and one purpose of this study will be to further evaluate this finding and potentially identify new variants predictive of outcome.[8]

Assuming a repeated analysis of variance is performed, (assuming groups are divided into 'responders' and 'non-responders', and at least baseline and end-of-study measures), an empirical genome-wide *P* of $5x10^{-7}$, this study would have statistical power of 0.80 to detect an effect size (*f*) of 0.045, a suitably small effect size. If an ANOVA were performed, assuming an empirical p of $5x10^{-7}$, a minor allele frequency of 0.05, means of the three genotypes of 7, 9 and 11 ETDRS letters respectively (based on published data from the DRCR.net Protocol I) with a standard deviation of 3 we will have 96% power to detect an effect (effect size = 0.2054).

5.3 Contributing to Other Cohorts or Metanalyses of Associated Diseases

As described in section 3.4, genotype and phenotype data will be made available. From this database, it may be possible for researchers to identify those individuals from the DRCR.net studies with certain environmental or personal risk factors for whom genotype information is available. This dataset can be analyzed as part of genome-wide analyses of diseases associated with diabetes.

Chapter 6. REFERENCES

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