

National Disease Research Interchange

Annual Progress Report: 2012 Formula Grant

Reporting Period

July 1, 2013 – December 31, 2013

Formula Grant Overview

National Disease Research Interchange received \$56,394 in formula funds for the grant award period January 1, 2013 through December 31, 2013. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Susceptibility Genes for Microvascular Complications in Patients with Type 1 Diabetes – Genetic factors likely influence susceptibility to microvascular complications of diabetes, including retinopathy, nephropathy and neuropathy. A linkage analysis of chromosome 6 identified three loci that contributed to Type 1 Diabetes (T1D) complications; the human leukocyte antigen (HLA) locus, which is the main locus for susceptibility to T1D itself, and 2 novel loci. One of the novel loci appears to relate to susceptibility to retinopathy and the other, possibly, to neuropathy. The fact that they could be identified by linkage analysis indicates that they are major contributors to complications susceptibility. We propose using dense single nucleotide polymorphism (SNP) typing in this area of chromosome 6 to identify the genes at these novel loci.

Duration of Project

1/1/2013 – 12/31/2013

Project Overview

The overall goal of this project is to identify the mutations within genes shown to contribute to susceptibility to microvascular complications of diabetes (MCD). Identifying such genes will allow us to predict which patients are at greatest risk for the blindness, kidney failure and nerve disease caused by MCD. Our linkage analysis of Human Biological Data Interchange (HBDI) families has indicated at least three loci involved in MCD, one of which is known (HLA) and two of which lie outside the HLA region and appear to be specific for MCD but have no apparent influence on T1D expression. Our specific aims are to: 1) Type dense SNPs at loci of interest on chromosome 6 and analyze the T1D families using our newly developed and extensively tested linkage methods, Efficient Analysis of Genetic Linkage: Estimation and Testing (EAGLET), to extract the maximum amount of information for linkage to retinopathy, nephropathy, and neuropathy, 2) Use our newly-developed association method to find disease-related genes within linkage-identified regions using both family-based and case-control tests of association and 3)

Continue our annual follow-up program to track the development and progression, or lack thereof, of MCD.

While previous SNP analysis led to the discovery of genes of potential interest, the odds ratios of loci discovered by association have indicated minimal impact on MCD expression. This is one of the few linkage analyses of MCD that has been attempted. The advantage of our linkage result is that it suggests that the discovered loci harbor major contributors to MCD expression.

Principal Investigator

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Other Participating Researchers

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Expected Research Outcomes and Benefits

The clinical and familial data in the Human Biological Data Interchange (HBDI) database is an invaluable resource for the development and testing of hypotheses about the genetic and environmental factors leading to susceptibility to diabetic complications. Since blood glucose is, with modern technology, controllable, it is the complications of diabetes that take the biggest toll on the lives of patients with Type 1 Diabetes (T1D). The most common complications include: 1) retinopathy of the eye – which distorts vision and leads to blindness, 2) neuropathy – a degenerative nerve condition that can cause excruciating pain in the extremities and decreased blood flow, sometimes necessitating amputation, and 3) nephropathy – a serious kidney disorder that prevents proper filtering of the blood and may require dialysis or transplantation.

Better ways of preventing, treating and curing diabetes will inevitably arise from a better understanding of those factors that contribute to complications. We have already shown that some families with T1D are more susceptible to developing complications than others. The information contained in the HBDI database, coupled with genetic data, provides us with a unique opportunity to screen these culprit genes for specific linkage SNPs to complication occurrence. The long-range aim is to provide a mechanism for better screening, prevention and treatment of complications with the ultimate aim of reducing the heavy burden of T1D on patients and society.

Summary of Research Completed

The milestones for the reporting period are:

Aims 1 and 2 - Complete data analysis

Aim 3 - Receive additional patient responses and utilize national address/search service to locate relocated families, send out additional questionnaires and follow up to increase compliance.

Progress on Aims:

Aim 1: Previously, linkage analysis of sparse SNP data on chromosome 6 has identified loci that influence risk for diabetic complications. During the last six months, results have been checked and a manuscript prepared for publication. This manuscript is now under review. A grant proposal to NIH to support the work was also prepared and submitted.

Status of dense SNP typing

Based on careful analysis of family structures, affectedness status and HLA types, specific families and individuals were selected for SNP genotyping. DNA samples were ordered for 300 individuals, representing 75 families. Their respective identification codes were cross referenced with the HBDI database at NDRI and with the HBDI repository at Coriell. The DNA was prepared, plated, and shipped from Coriell and sent for genotyping under the linkage peaks at 42 cM and 64 cM. Those typing results were received and we are in the process of cleaning and checking the data. Analysis of the data is expected to start shortly.

Aim 2: This aim will move forward as soon as the SNP typing has been cleaned, checked and incorporated into the data base and prepared for analysis.

Aim 3: During July – September an additional 354 questionnaires were sent to registry participants. The updated family questionnaire is designed to track development/progression or lack of development/progression of microvascular complications among patients with T1D and T2D. Of the 1003 questionnaires that were mailed, 228 questionnaires were completed and returned. This corresponds to a response rate of 23%. An additional 60 questionnaires were returned due to incorrect addresses. The information in these updates provides information on a subset of 4,256 of the individuals in the HBDI National Genetics Family Registry. Non-responding families were followed-up by email to increase the response rate.