

# **National Disease Research Interchange**

## **Annual Progress Report: 2008 Formula Grant**

### **Reporting Period**

July 1, 2009 – December 31, 2009

### **Formula Grant Overview**

The National Disease Research Interchange received \$58,338 in formula funds for the grant award period January 1, 2009 through December 31, 2009. Accomplishments for the reporting period are described below.

### **Research Project 1: Project Title and Purpose**

*Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes* - The HBDI database is a vast repository of family and medical information focused on the study of type 1 diabetes (T1D) and its complications. A previous project confirmed that genetic factors likely influence susceptibility to microvascular complications of diabetes, including retinopathy, kidney disease and neuropathy. We will test for associations between specific genes and the presence or absence of complications by using HBDI samples newly typed by the T1DGC (Type 1 Diabetes Genetic Consortium). To enhance our analyses and maintain the scientific value of our dataset, we will continue our program of administering follow-up questionnaires, begun in 2007. Finally, we will begin a SNP saturation study of statistically important genes. The additional information we collect will better define the genetic contribution to diabetes complications.

### **Duration of Project**

1/1/2009 - 12/31/2009

### **Project Overview**

The overall goal of this project is to discover genes responsible for susceptibility to the microvascular complications of diabetes that function independently of T1D susceptibility, in order to predict which patients are at greatest risk for the blindness, kidney failure and nerve disease caused by diabetic microvascular disease. Our specific aims are to: 1) Analyze a large dataset of newly genotyped HBDI patients to explore the genetic susceptibility among T1D patients to microvascular complications using 3 separate statistical genetics methods, 2) Continue our annual follow-up program utilizing the updated family questionnaire to track the development and progression, or lack thereof, of microvascular complications among patients with both T1D and type 2 diabetes (T2D). This more precise assessment tool has already enhanced the specificity of data collection on microvascular complications and will continue to help better define the phenotypes. 3) Data gathered in aims 1 & 2 will be used to plan and

execute a high intensity genotyping study of the most promising genetic region found to be significant for association with susceptibility to diabetes microvascular complications.

The Human Biological Data Interchange (HBDI) maintains a database of 6,626 families, of which 5,014 are affected by T1D. Within this group is a subset of 540 families that have been previously recruited for genetic studies. Members of these families have had blood drawn, cell lines immortalized and DNA extracted. Our recently published analysis of data examining microvascular complications showed that familial factors do indeed predispose individuals not only to type 1 diabetes but also to the development of complications. Such factors include the sex of the patient, the presence of a complication in another family member and the presence of T2D in a parent, but not T1D in a parent. Also, using T1D cases with retinopathy as “cases” and T1D cases without retinopathy as “controls”, we tested association of retinopathy with a set of 50 SNPs and found an association between two SNPs and retinopathy. Preliminary analyses of 6000 SNPs obtained from the Type 1 Diabetes Genetics Consortium show a number of additional SNPs that are significantly associated with either predisposition to, or protection from, development of microvascular complications. We plan to extend these analyses and use new genetic data to discover specific SNPs responsible for the observed effects.

### **Principal Investigator**

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### **Other Participating Researchers**

Cathie Miller, PhD – employed by National Disease Research Interchange  
Davlyn Tang, BS – employed by National Disease Research Interchange  
Maria Cristina Monti, PhD – employed by Columbia University

### **Expected Research Outcomes and Benefits**

The clinical and familial data contained in the HBDI database is an immense and invaluable resource for the development and testing of hypotheses regarding the genetic and environmental factors leading to susceptibility to diabetic complications. It is the complications of diabetes that eventually take the biggest toll on the lives of T1D patients. 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, decreased blood flow and even 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 stem 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 next step is to discover which genes may be responsible for these observed differences in susceptibility. The information contained in the HBDI database, coupled with a newly available genetic data, provides us a unique opportunity to screen for these culprit genes. This research should provide a mechanism for better screening, prevention and treatment of complications with the ultimate aim of reducing the heavy burden on patients and society.

### **Summary of Research Completed**

#### Specific Aim 3 – SNP saturation study on the most promising genomic region

The chromosomal region selected for the SNP saturation study had 40 SNPs genotyped in the HBDI sample by T1D consortium, thus we chose an additional 30 SNPs to be genotyped providing an excellent coverage for a case-control analysis. To perform the SNP saturation study, a set of 191 cases and 128 controls were selected from the HBDI cohort genotyped by T1DGC. Cases were defined as patients with retinopathy, while controls were T1D patients without any complications after 20 years with T1D and without family history of complications in T1D siblings. Multivariate models that incorporated a cluster function to account for potential confounders such as age, duration of diabetes, sex, and clinical relevant information were carried out. These samples were sent to the University of Pennsylvania Molecular Diagnostics Laboratory for additional SNP determination within this chromosomal region which had been demonstrated to be associated with development of retinopathy in Specific Aim 1. These 30 additional SNPs were selected based on minimum allele frequency, linkage disequilibrium and distance from one another. Additionally, a thorough investigation of which of these SNPS had been previously significantly associated with any disease process was done. All SNPs are located within a specific gene as well as its promoter and 3' UTR regions. We are currently awaiting the conclusion of the SNP assay processing by the University of Pennsylvania Molecular Diagnostics Laboratory in order to perform the analysis.