

II. OBJECTIVES

Three strategies are proposed to reach the study's goal of identifying genes that determine an individual's risk of type 1 diabetes. First, raw linkage data from previously published studies will be assembled and jointly analyzed (n= ~1,200 affected sib-pair families). Second, affected sib-pair families (n= ~600) currently available will be genome scanned. Third, the collection of 2,800 new affected sib-pair (ASP) families as well as new single-case families (trios) and new cases with ethnically matched controls in populations with a low prevalence of disease will be undertaken via an international collaborative network of investigators.

In order to establish this combined resource of 4,600 ASP families and to carry out an appropriately powered search for type 1 diabetes susceptibility genes, a series of specific aims are proposed to fully utilize and update existing materials and to collect new clinical resources. The specific aims will be achieved by the concerted efforts of clinicians, geneticists and genetic epidemiologists. The specific aims of this study are:

- 1. Ascertain 2,800 new families with two or more type 1 diabetic siblings through an established Asia-Pacific Network (340), a European Network (1,200), a North American Network (1,100), and a United Kingdom Network (160).**

This collection will add to the existing resource of 600 families collected (on whom a genome scan has been requested) and 1,200 families that have been previously scanned. These new and existing data will create a repository for detailed statistical and molecular genetic analysis. All family members in the new set of 2,800 families will be evaluated for clinical and biochemical variables, including age at onset and duration of disease using standardized protocols. In unaffected family members, genetic data will be obtained. In newly collected type 1 diabetes families, peripheral blood will be collected and lymphoblastoid cell lines (LCLs) will be established to provide a renewable source of genomic DNA, in order to enable future studies of immune function. Participant samples, including DNA, cell lines, plasma and serum, will be sent to a central repository.

- 2. In order to detect the effects of HLA and other candidate regions/genes on the signals from the genome screen, all samples will be genotyped for HLA class II and class I genes (DRB1, DQB1, DPB1, DPA1, A, B, C), INS, and CTLA4 polymorphisms that have previously been implicated in susceptibility to type 1 diabetes.**

Statistical genetic analyses of the combined data will be conducted by the Coordinating Center as well as by Consortium members to assist in the localization of type 1 diabetes susceptibility genes, using methods specifically designed to evaluate interactions as well as main effects. Existing genome-screened families (n= ~1,200) and past/ongoing collections (n= ~600) will be genotyped for these same markers to allow integration with new data family collections.

3. Refine the localization of the five most promising regions identified from linkage and association studies.

Consortium members and collaborators will identify five linked regions, including the HLA region, and assay transmission of alleles of individual markers and haplotypes (using haplotype-tagged SNPs, ht-SNPs) to systematically and efficiently refine locations for type 1 diabetes loci. Further genetic analyses to identify and confirm candidate genes (using haplotype-tagged SNPs, functional candidate SNPs and contiguous maps of polymorphisms flanking disease-associated markers) will require joint investigation by Consortium laboratories and supplemental support using Consortium material (*e.g.*, DNA, data).

4. To aid in the confirmation and identification of diabetes susceptibility genes within linked regions, the Consortium will use existing and planned resources of single case families (trios, including an affected child and both biological parents) and single cases with ethnically matched controls to carry out detailed disease association analyses.

These collections have been identified through initiatives of individual investigators and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Juvenile Diabetes Research Foundation (JDRF). The Consortium will facilitate new collections of trio families and case-control collections through its Asia-Pacific, European and North American Networks to obtain diverse disease-associated haplotypes for fine mapping from low-prevalence populations.

The ultimate goal is to provide the fundamental clinical and genetic resources to achieve the necessary sample size and sample availability for gene identification. The Consortium will establish a mechanism to ensure that scientists will work together toward a better understanding of the genetic factors that underlies risk for type 1 diabetes. The Consortium will gain a better understanding of disease mechanisms, with a purpose of altering these mechanisms and pathways in individuals at risk of type 1 diabetes.