Genetics, Environmental Exposures, and Type I Diabetes

The development of **beta cell autoantibodies** and subsequent **type 1 diabetes** is causally associated with genetic susceptibility (e.g., HLA D3 or D4 haplotypes), early exposure to coxsackie (or other viral) infections, early exposure to cow's milk protein or other dietary components, and interactions between those factors.

General Information	
Broad Focus Area	Genetic Environment Interactions
Background and Justification	The etiology of type 1 diabetes remains unclear. Epidemiologic patterns, including the dramatic geographic variations in type 1 diabetes incidence rates, variation in risk by ethnicity, the peak age at onset at puberty, and the more frequent diagnosis of the disease during the cold winter months, suggest that viruses, nutrition, and socioeconomic factors are involved.[1] Potential environmental risk factors have been investigated in numerous populations, but the studies have yielded conflicting results. This has been due, in part, to a failure to account for disease susceptibility genes. Although genome screens found evidence of linkage to 15+ potential genes, the primary locus of susceptibility (*IDDM1*) is located in the HLA region of chromosome 6.[2,3] Estimated relative (odds ratios range from 10 - 100) and absolute risks (~3-6% through age 20 years) associated with high-risk HLA genotypes have been studied in many populations.[4] Although lifelong insulin therapy is the only treatment for type 1 diabetes, there are currently several large clinical trials designed to evaluate a variety of approaches for primary (i.e., avoidance of cow's milk formula) and secondary disease prevention (i.e., high doses of nicotinamide, oral/nasal insulin).[5] Newborns, children, and young adults who have a first-degree relative with type 1 diabetes are currently being screened for early pre-clinical markers (i.e., beta cell autoantibodies) and/or high-risk HLA susceptibility alleles. Those who are positive are eligible for randomization. However, approximately 90% of individuals who develop type 1 diabetes have no family history of the disease and are not eligible for these trials.[6] Thus, for the public health impact of any of these interventions to be realized, they must be based on the general population and not high-risk family members. As a result, several natural history studies are now following newborns who screen positive for high-risk HLA susceptibility alleles.[7,8] However, only one-half of the children who eventually develop type 1 diabetes carry these genes. Thus, approximately half of the remaining future incident cases will occur among those who screen negative for high-risk HLA genotypes. These individuals are being excluded from follow-up. The NCS offers an unprecedented opportunity to complement the ongoing investigations of high-risk children by evaluating a range of different disease susceptibility genes and environmental exposures. For example, there is considerable evidence to suggest that the contribution of HLA susceptibility alleles varies by age.[9] The largest relative and absolute risk estimates for children who carry high-risk genotypes are strongest for the youngest children (less than age 5 years). The contribution of the same genotypes is much less dramatic among children with an older age at onset (>10 years). This suggests that around the time of puberty, loci other than those in the HLA region and/or environmental exposures may play a more important etiologic role. Thus, the evaluation of gene-environmental interactions in the development of type 1 diabetes must be evaluated

	among children with and without high-risk HLA susceptibility alleles.
Prevalence/ Incidence	Type 1 diabetes is one of the most common chronic diseases in children, with prevalence rates approximating one in every 400 to 500 children in the U.S.[10] The incidence of the disorder has been increasing worldwide at an estimated rate of 3% per year,[11] particularly among young children (less than age 5 years) and ethnic minorities.
Economic Impact	Studies that describe the economic costs of diabetes often consider the direct or medical costs of the disease. Less frequently, the indirect costs of diabetes are evaluated. Examples of indirect costs include the value assigned to morbidity, disability and premature mortality associated with type 1 diabetes. From an economic perspective, the most important medical costs relate to the daily management of the disease and the treatment of late-stage complications. The annual costs of type 1 diabetes typically range between $1500 per person, for the standard insulin regimens, to nearly $6000 for insulin pump protocols.[12] Out-of-pocket health care costs for families with type 1 diabetes in the U.S. typically exceed $1,000 per year.[13] These costs increase substantially after the development of long-term complications. In 2002, the direct medical and indirect costs attributable to diabetes were estimated at $132 billion.[14]

Exposure Measures			**Outcome Measures**	
Primary/ Child	Measures of diabetes susceptibility: - Genetic markers (e.g., insulin gene VNTR - insulin-dependent diabetes mellitus gene) - Family history of type 1 diabetes and other autoimmune disorders Environmental exposures: - Viruses, infant/childhood nutrition; pesticides or other chemical exposures		***Primary/ Child***	- Beta cell and other autoantibodies - Manifestation of Type I Diabetes (e.g., average blood sugar level (HgbA1C), lipid profile, serum insulin levels, cortisol)
Methods	Blood test; Questionnaire; Periodic environmental sampling; Medical record review		Methods	Blood sample; Physical exam; Medical record review; Questionnaire
Life Stage	Periodically, beginning in infancy		Life Stage	Periodically

Important Confounders/Covariates	
Unknown environmental factors	Increase in risk associated with Type 1 diabetes not sufficiently explained by genetic susceptibilities; probably significant contribution by environmental factors.[14]
Family, medical history factors	Several genetic loci implicated in risk for T1D, e.g., CTLA4 exon 1 A49G polymorphism; genotype higher in patients (12.6%) than controls (4.2%); may be family association (p = 0.0229) [15, 16, 17, 18]
Obesity	Lower risk for TID associated with obesity, even among genetically susceptible children [19]

Population of Interest		**Estimated Effect that is Detectable**

Children with high-risk polymorphisms (Population currently unknown)		Though the NCS may not be large enough to examine rare outcomes in the overall population, it can be useful for analyses of subgroups at high risk of a generally uncommon condition. For instance, Type 1 DM has an estimated prevalence of approximately 3 per 1,000 in the general US adolescent population. However, it is much more common (estimated prevalence of 5-6%) among the approximately 2% of individuals with certain HLA haplotypes. Given those estimates, the NCS is large enough to describe a two to three-fold increase in risk associated with an exposure affecting 10% of the genetically susceptible population.

Other Design Issues	
Ethical/Burden Considerations	There may be ethical considerations associated with genetic tests, but such considerations underlie the overall NCS and would not be unique to this specific hypothesis. For non-genetic factors, the study will need to have a formal strategy and process for an effective communication of the results of physiological and biochemical measures to the child's parents and to a responsible health care provider. The study also will need to have a formal strategy and process for effective communication of the results of environmental monitoring to the child's parents along with appropriate and feasible recommendations regarding the correction of any unhealthful environmental findings.
Cost/Complexity of Data Collection	Case/parent trios may be considered as a possible sampling unit.
Cost of Sample Analysis	The use of outcome dependent sampling from stored or archived samples would provide efficiency

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