

HLA DRB1 Genotyping for the Type 1 Diabetes Trial net Nutritional intervention to prevent (NIP) type I diabetes pilot trial, subcontract from George Washington University

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Principal Investigator: Henry Erlich, PhD

Co-Investigators: Steven J. Mack, PhD

Synopsis:

Hypothesis: Spontaneous development of type-1-diabetes (T1D) can be attenuated by administering docosahexanoic acid to infants determined to be at medium to high genetic risk for type-1-diabetes.

Specific Aim: As subcontractors on this project, our aim is to identify DRB1 and DQB1 alleles that confer high and medium type-1-diabetes (T1D) risk, as well as DRB1 and DQB1 alleles that are neutral or protective with respect to T1D, in the subjects enrolled in the TrialNet NIP T1D pilot trial.

Background: Type 1 diabetes (T1D) is a chronic autoimmune disease that results from destruction of the insulin-producing beta cells of the pancreatic islets. Epidemiologic studies, as well as studies in mouse T1D models, have indicated that dietary manipulations can affect the spontaneous development of T1D (Suresh and Das, 2003); in particular, children are less likely to develop T1D when cod liver oil is consumed by the mother during pregnancy, and/or by the infant in the first year of life.

The Nutritional Intervention to Prevent (NIP) T1D study investigates the use of an omega-3 fatty acid (docosahexanoic acid) administered to pregnant mothers and "at risk" newborns under 6 months of age, to prevent the initial autoimmune process. For this project, T1D risk is, at least in part, determined by an individual's Human Leucocyte Antigen (HLA) DRB1 and DQB1 genotype.

The HLA class II molecules are cell surface glycoproteins encoded by genes in the HLA-D region of chromosome 6. These proteins (DR, DQ, and DP) are heterodimers comprised of an α and β chain found on the surface of antigen presenting cells. They bind and present peptides to CD4+ T lymphocytes, initiating a specific immune response. The β -chain loci (e.g. DRB1), are extremely polymorphic, and most sequence polymorphism is found in the second exon, which encodes the class II peptide-binding groove. Many different types of diseases (autoimmune, infectious disease, and cancer) as well as specific pathological responses to exogenous agents have been associated with specific HLA alleles.

For (T1D), the contribution of the HLA region to the overall genetic risk is greater than 50% (Noble et al., 1996). Multiple HLA genes contribute to susceptibility for T1D (see below), and for most HLA-associated diseases, particular combinations of alleles determine the extent of predisposition.

T1D risk is associated with HLA DR3 and DR4 alleles, and negative (protective) associations with DR2 alleles, and the DQB1*0602 allele) are well-established (reviewed in Nepom and Erlich, 1991). The association with DR4 is determined by a combination of DRB1 and DQB1 alleles. DRB1*0401, *0402, and *0405, coupled with DQB1*0302, confer high risk, while DRB1*0403 is protective for T1D, even when coupled to DQB1*0302 (Erlich et al., 1993, Noble et al., 1996). The highest risk genotype is the DRB1*0301-DQB1*0201/DRB1*04-DQB1*0302 heterozygote; the Odds Ratio for this genotype is around 30, and other genotypes (i.e., DR3/3, DR4/4, and DR4/8) confer reduced but significant risk for T1D (Noble et al., 1996).