Clinical and Functional Significance of JIA-Specific Risk Alleles

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Project Summary/Abstract

In this project, we accomplish the preliminary steps required to undertake a "phenome-wide association study" (PheWAS) for juvenile idiopathic arthritis (JIA). We will test 3 JIA-associated genetic variants that we have shown to alter non-coding functions in CD4+ T cells and determine their association with 3 JIA sub-phenotypes: (1) disease presentation and course; (2) response to methotrexate; and (3) the development of uveitis. This study is intended to set the stage for a CARRA-wide PheWAS that will leverage our discovery of genetic variants with known biological effects and the resources of the CARRA network and registries.

PheWAS differ from genome-wide association studies (GWAS) in several respects. GWAS start with a given phenotype and compare the frequency of a large number of genetic variants in individuals with and without the phenotype. PheWAS, on the other hand, start with genetic variants whose biological effects are already characterized and ask whether the variants correspond to a specific phenotype.

In Aim 1, we will query 3 genetic variants, 2 of which attenuate enhancer function within the IL2RA locus and the 3rd of which is associated with ectopic binding of CTCF, and important regulator of 3-dimensional chromatin architecture. We will genotype 600 oligoarticular/polyarticular (RF negative) JIA patients and use standard statistical approaches to determine whether any of the 3 genotypes is associated with the sub-phenotypes of interest. In Aim 2, we will determine whether the genetic variants of interest are associated with alteration in gene expression, focusing on genes within the same chromatin loops as the genetic variants.

The current proposal uses existing resources in Buffalo and Atlanta, and represents crucial studies that have to be undertaken before we can compete for NIH funding. However, we are already beginning to plan the next phase of this study, which will be a CARRA-wide effort.

Lay Summary

This project is an important first step in our ability to use genetic information to guide how we monitor and treat juvenile idiopathic arthritis. In this study, we will examine 3 genetic variants associated with JIA and whose biological effects we have characterized. We will determine whether these genetic variants are associated with particular clinical features in JIA. If we are successful, this project will be the start of an ambitious second phase aimed to link genetic information to patient outcomes across the CARRA network.