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*Genetic and Phenotypic Polymorphisms of Complement C4 in the Pathogenesis of Sjögren’s Syndrome*

**Research Description:**
Sjögren’s syndrome is one of the most common autoimmune diseases in the US. It affects multiple tissues and organs, and shares many features with other autoimmune diseases such as lupus and rheumatoid arthritis. Low complement C4 protein levels are often observed in Sjögren’s syndrome, and are linked to severe clinical manifestations such as lymphoma. Low C4 levels can be due to genetic deficiency or continuous protein consumption during inflammation. The cause and consequences of low C4 levels in Sjögren’s syndrome are not known. In this study, we will investigate the genetic and protein variations of C4 in patients with Sjögren’s syndrome only and in patients with Sjögren’s syndrome with accompanying lupus or rheumatoid arthritis. We will determine the cause of low C4 protein levels in Sjögren’s syndrome, analyze protein markers, and evaluate the utility of combining genetic stratification and new protein markers in the diagnosis and management of Sjögren’s syndrome.

**Scientific Abstract:**
Sjögren’s syndrome is a systemic autoimmune disease with overlapping clinical features with diseases such as lupus. Low levels of complement C4 protein are often observed in Sjögren’s syndrome, and are associated with cryoglobulinemia and lymphoma. Genetic deficiency and low gene copy numbers of complement C4 have been shown to be an important risk factor for lupus. Activation of C4 protein during inflammation consumes C4 protein and mediates tissue injuries. We hypothesize that C4 genetic and protein polymorphisms are engaged in disease predisposition and in modulating the clinical presentation of Sjögren’s syndrome. We will analyze patient samples using accurate molecular assays for determining C4 gene copy numbers, immunoassays for activated complement protein products, and transcriptomic analyses to i) determine the cause of low C4 in Sjögren’s syndrome, and to ii) evaluate the utility of combining genetic stratification of C4 and new protein markers in the diagnosis and management of Sjögren’s syndrome.