Defining Complex and Monogeneic Systemic Lupus Erythematosis with Genome-wide Association Studies and Exome Sequencing

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Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by presence of autoantibodies to nuclear antigens and augmented interferon type 1 production, leading to inflammation that results in multiple organ damage, notably kidneys. There is an ethnic and gender bias in SLE incidence and severity which may be contributed by genetic, hormonal and environmental factors. SLE can be inherited as complex or monogenic disease, which have been investigated by genome-wide association studies and exome sequencing respectively. Twin studies and sibling risk ratio suggesting a high heritability of SLE of 60%.

Genome wide association studies (GWAS) of SLE have identified over 50 potential candidate genes which explain less than 30% of the heritability of SLE. These 50 genes are involved in apoptosis and clearance of apoptotic debris; lymphocyte and innate immunity signaling as well as intra-renal signaling. The limitations of GWAS include not being optimal to identify rare genetic variants and structural variants, requiring large number of subjects and controls for sub-phenotyping. The future genomic studies include investigating role of HLA, micro RNAs, epigenetics and copy number variations.

Exome and genome sequencing (EGS) has identified many types of monogenic SLE. Monogenic SLE include complement deficiencies of C1q, C1r/s, C2 and C4, as well as type 1 interferonopathies with defects in cytosolic DNA and RNA sensing and clearance, which can be due to mutations in DNASE1, DNASE1L3, TREX1, TMEM173, SAMHD1, RNASH2, ADAR1 and IFIH1.