Genetic Science Spotlight

University of Houston: Deciphering the Genetic Basis of Systemic Lupus Erythematosus (SLE) Patients Would Help Tailor Therapies

Systemic lupus erythematosus (SLE) is an autoimmune disorder that affects multiple organs, while up to 70% of patients will develop lupus nephritis (LN) and suffer from renal assaults. A number of genome-wide association studies on SLE have identified more than 50 genes, associated with SLE and/or LN. The molecular functions of these associated variations remain unclear, as multiple forms of variations have been identified, including coding region single nucleotide polymorphisms (SNPs), polymorphisms that lead to differential alternative splicing, polymorphisms in the 3' untranslated region (UTR) that influence gene expression, and copy number variants (CNVs).

Despite the complexity of genetic composition, the candidate genes have been divided into four function groups in murine models: genes that affect lymphocyte activation and hence adaptive immunity, particularly B cells; genes that affect innate immune signaling, i.e. innate immunity, notably NF-κB activation and IFN-I signaling; genes that affect renal functions and potentially cause tissue damages; and genes that influence the handling of apoptotic debris, chromatin, and immune complexes bearing these antigens.

Murine models have also shown that different genotypic combinations may affect development of SLE and/or LN. Firstly, genes that only affect lymphocyte function might lead to the production of antinuclear antibodies or IgM polyreactivity but not LN, implying the antibodies alone might not cause kidney damage. Secondly, innate immunity activating genes might lead to medially elevated anti-DNA antibody levels (compared with complete SLE) and non-proliferative glomerulonephritis. Finally, gene-gene interaction of more than one category is essential in triggering severe LN.

While SLE patients may each have unique genotype, knowing the molecular basis of disease could assist in clinical management. For instance, patients with B or T cell activating polymorphism might benefit from therapeutics that target specific signaling molecules or co-stimulatory pathways encoded by the disease genes; patients with end-organ inflammation predisposition might benefit from therapeutics that target the implicated pathways within the kidneys.

http://www.nature.com/nrneph/journal/v11/n6/full/nrneph.2015.33.html?foxtrotcallback=true