GENETICS

New genetic approach confirms importance of *IRAK1* in SLE risk

The X-chromosome gene encoding interleukin-1 receptor-associated kinase 1 (*IRAK1*) was previously identified as a risk factor for systemic lupus erythematosus (SLE). Results of a study in a larger cohort confirm the gene's functional role in SLE pathogenesis.

“Together, the forward and reverse genetic studies establish the importance of *IRAK1* in SLE pathogenesis”

The investigators took a Bayesian approach to gene discovery by use of a bioinformatics tool termed ‘Function2Gene’, which they designed to take into account pre-existing knowledge of a disease—regardless of whether the information comes from genetic or non-genetic studies. This method sits

in contrast to the popular but expensive genome-wide association study (GWAS) approach, which first identifies genes and only then characterizes their potential functions in a disease.

The association between *IRAK1* and SLE was discovered using this approach in a family study of childhood-onset SLE. In the present study, a case–control approach tested the association in a large number of patients with childhood-onset and adult-onset SLE, as well as healthy controls. Five single nucleotide polymorphisms (SNPs) within *IRAK1* were significantly associated with SLE across the SLE cohort, and three of the five SNPs were associated with both childhood-onset and adult-onset disease.

Tests of the functional role of the gene in mouse models of SLE focused on two loci key to disease pathogenesis, *Sle1* and *Sle3*. *IRAK1*-deficiency attenuated the serological and cellular disease features attributed to *Sle1*, including levels of IgG

and IgM autoantibodies, lymphocyte activation and markers of renal disease, and also diminished the pathological autoimmunity attributed to *Sle3*. The results suggest that the lupus phenotypes contributed by *Sle1* and *Sle3* depend, at least in part, on *IRAK1* function.

Together, the forward and reverse genetic studies establish the importance of *IRAK1* in SLE pathogenesis. “The Function2Gene approach may have a major impact not only on SLE genetics but also on how researchers go about discovering the multiple genetic variations that commonly underlie inherited diseases other than SLE,” says Chaim O. Jacob, who led the study.

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Original article Jacob, C. O. *et al.* Identification of *IRAK1* as a risk gene with critical role in the pathogenesis of systemic lupus erythematosus. *Proc. Natl Acad. Sci. USA* **106**, 6256–6261 (2009).