Genetics of systemic lupus erythematosus

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Systemic lupus erythematosus remains a disease with an elusive etiology, and the search for genetic factors that trigger the autoimmune cascade has only been accelerated by recent advances in technology. Starting with the early observations that HLA type and complement deficiency had an impact on disease risk, genetic studies in lupus have now expanded to include genome-wide linkage and association scans, as well as hypothesis-driven candidate gene studies on nearly 200 different genetic loci. This review will classify the existing literature and report on the genes that most consistently contribute to systemic lupus erythematosus risk.

Systemic lupus erythematosus (SLE) is an autoimmune disease notable for its complex and varied presentation and its predilection for affecting women in their childbearing years. It is believed that a number of genetic risk factors combine to create susceptibility, and then environmental triggers, such as the Epstein–Barr virus [1], impact the genetically primed host to start the autoimmune cascade. There is the powerful and consistent observation that lupus occurs in families, such that up to 10% of SLE patients have a relative with lupus [2]. Increased concordance in monozygotic twins was observed over 30 years ago [3], and more current twin statistics continue to support this observation, with over 40% concordance in monozygotic twin pairs versus 4% concordance in dizygotic twins [4]. Except in the rare cases of complement deficiency [5], the inheritance pattern of SLE does not follow simple Mendelian rules, which suggests that genetic risk in most lupus patients arises from the combination of a number of relatively common variations in several different genes. The general consensus of those in the field is that the number of 'lupus genes' is likely to be in the order of 20–50. The search for the genes that cause SLE has been a subject of active investigation for nearly 20 years by dozens of groups all over the world, generating thousands of papers, many of which have conflicting results. In this review, I will attempt to summarize this body of work.

Keywords: association, complement, genetics, HLA, IRF5, linkage, lupus, SLE

future medicine part of fsg

Studies to elucidate the complex genetic causes of SLE

Two major approaches have been used to define the genetic factors in SLE: linkage studies and association studies (Table 1). To use a linkage approach, one must first gather families in which more than one person has SLE. Since only approximately 10% of SLE patients have a first-degree relative with lupus, this takes considerable time and effort. However, once gathered, these multiplex families can be used in genome-scan experiments, which examine the entire genome without bias. Historically, genome scans have been performed using microsatellite markers, which are heterozygous in over 85% of people. Since testing is laborious, approximately 300–400 markers spaced at 10–30 mb intervals were typically used in a genome-wide scan. Any peaks of linkage were then further typed using a technique called fine mapping, in which additional microsatellite markers spaced at 1–2 mb intervals within the linkage peak were assessed in the same multiplex cohort. Usually this approach would narrow the region of interest to 5–10 mb, depending on the size of the cohort used. Five groups have put together the resources to pursue genome-wide linkage scans [6–12], and the results are summarized in Table 2.

The second major approach to lupus genetics is to test for association. These studies are hypothesis driven and are usually focused on a single gene. Most commonly, a single polymorphism, often in a coding region, is tested in a case–control cohort. Some groups use a trio design, in which the patient and both parents are genotyped. Trio designs are stronger, statistically, per patient recruited, and they eliminate any bias that might be introduced when the cases and the controls are not well matched in genetic ancestry (i.e., stratification error). More recently, technological advances have made it more practical to test an array of SNPs across a gene of interest, such that a combination of alleles, known as a risk haplotype, emerges. Linkage studies are generally followed up with association studies in the

Table 1. Types of studies used in evaluating genetic risk factors for systemic lupus erythematosus.

	Traditional linkage study	Traditional association study	Association scan study
Cohort type	Multiplex families	Case–control or trio	Any
Marker type	Microsatellite	SNP	SNP
No. markers tested	300–400	One or more	100,000+
Findings	Linkage	Association	Association
No. regions	10–15, usually	One or more	100+
Size of region	20–40 mb	5–10 kb	5–10 kb
No. using the approach	Five major groups	>50 groups	A few in progress

linkage region, although there are far more candidate genes chosen on the basis of their function than on their location within a linkage region.

A new approach called association scanning is being used by a few studies now in progress. This type of study would not be possible without the recent advances in technology. Nevertheless, both Affymetrix and Illumina have created products that test over 100,000 SNPs distributed across the entire genome. Although the SNP markers still have the limitation that they are never more than 50% heterozygous, and are therefore not as informative as microsatellite markers, in combination they form informative haplotypes that can be used to trace ancestry. Genome scans can be performed on case–control, trio or pedigree collections. Like the linkage studies that precede them, an association scan is hypothesis generating, but the associated regions found will already be fine mapped, in a sense, because the markers used are so densely arrayed.

All three of these study designs share a common problem: they are prone to the production of false-positive results. Therefore, it is important that each finding be replicated in an independent cohort, and the scientific community as a whole recognizes the importance of such replication work. Unfortunately, every cohort is slightly different – they vary in size, ethnicity, selection and matching criteria, and likely a whole host of other variables that may not even be collected or recognized as contributing to this complex disease. Some cohorts are underpowered for the effect they attempt to define, and this can also lead to false negatives. In addition, each investigator has the choice of a large number of potential variants to test within each gene, and often different studies of the same gene have few or no SNPs in common. In part because of this variation, the resulting literature in the field is full of conflicting reports. For example, while there are 16 reports supporting an association with mannose-binding lectin, there are eight that find no association and 14 that find association only with a specific phenotype, such as lupus nephritis. When enough reports have been accumulated, meta-analysis can assist us in determining the true nature of the association, and a meta-analysis of mannose-binding lectin shows that there is a consistent, albeit weak, association with SLE [18]. Unfortunately, 32 of the 48 genes with conflicting reports have less than ten total reports in the literature as of October 2007, such that meta-analysis is impractical. In addition, there are unconfirmed associations, negative reports and associations with phenotype only that remain to be verified. Even among the 'confirmed' associations summarized below, eight of the 20 genes have only been tested in two cohorts. A summary of the nature of the candidate genes in SLE by the types of literature they have generated is given in Table 3.

Established genes

Complement

Work on complement began before the genotyping era, and reports of association with complement deficiency may or may not include genetic information. Nevertheless, it has been established that, in rare cases, complete deficiency of the elements of the classical pathway – C2, C4 and C1q – leads to SLE or lupus-like syndromes [5]. Immune complexes activate complement through these components, which are also important for keeping immune complexes in soluble form and clearing apoptotic bodies [19]. The genetic aspects of C4 deficiency are complicated by both the complex structure of the gene and its location within the HLA region. It has recently been discovered that individuals may carry anywhere between zero and six copies of the C4 cassette, although most carry four, and that decreased copy number is associated with SLE risk [20]. A partial deficiency, also known as *C4A*Q0* or C4 null, is also in linkage disequilibrium with

Table 2. Confirmed linkage regions.

Region	Group(s)	Cohort type	Associated gene(s)	Ethnicity
1q23	OMRF	Extended pedigrees	*FCGR2A*, *FCGR2B*, *FCGR3A*, *FCGR3B*	EA, AA
1q31–32	UU	Extended pedigrees		EU
1q41–43	UCLA, USC	Extended pedigrees	*PARP**	EA, HIS
2q37	UU	Extended pedigrees	*PDCD-1*	EU
4p16	OMRF	Extended pedigrees		EA
6p11–21	UMN	Sib-pairs	*HLA-DR*	EA, AA, HIS
10q23	OMRF, UCLA	Extended pedigrees, sib-pairs		AA
12q24	OMRF	Extended pedigrees		EA, HIS
16q12–13	UMN, OMRF	Extended pedigrees, sib-pairs		EA, AA, HIS

**PARP was initially associated in this linkage region [13], but subsequent studies have failed to confirm the association [14–17].*

AA: African–American; EA: European–American; EU: European; HIS: Hispanic; OMRF: Oklahoma Medical Research Foundation; UCLA: University of California, Los Angeles, CA, USA; UMN: University of Minnesota, MN, USA; USC: University of Southern California, CA, USA; UU: University of Upsala, Sweden.

HLA-DR3 [21], and *HLA-DR3* is strongly associated both with autoantibody profile and SLE on its own [22].

HLA region

Although work on the HLA region pre-dates genotyping and linkage in this region is well established, there remains much to be done to define the nature of genetic alteration in the region and its role in autoimmune pathology. First, there are a number of genes with immune functions in tightly linked regions, including not only HLA class I, II and III genes, but also genes encoding complement components C2 and C4, TAP 1 and 2, and TNF-α and -β. Since these genes are so close together, they are often inherited as a unit, a phenomenon known as linkage disequilibrium (LD), and this creates confusion as to which variation within a risk haplotype is truly responsible for disease. For example, the *TNF-α* -308 variant, which is associated with overexpression, is often found in a haplotype block that includes *HLA-B8*, *C4A*Q0* and *HLA-DR3*. As such, it has been variably claimed that each of these variants is the 'real' cause of increased risk, and unfortunately, there are few studies that attempt to type them all, leading to competing claims rather than clarification work. To add to the confusion, both *HLA-DR3* and *HLA-DR2* have been found to be associated with disease, and the dual association cannot be explained by ethnic background alone [23]. It is possible that only one of these genes is important in disease, but it is also possible that some combination or combinations of genetic variants in this region is necessary to generate an autoimmune predisposition. Additional work on larger cohorts in which all of these variants are assessed will be necessary to sort out this established association and determine why and how the HLA region genes contribute to lupus pathology.

Meta-analysis

For those genes that have already been tested for the same variant in multiple cohorts, meta-analysis can be used to combine the results at a specific site. This site is usually a SNP (such as the -308 variant of *TNF-α*), but it could be an insertion/deletion (as in *ACE*), or even a microsatellite. Meta-analysis takes into account the size of the sample cohorts and the size of the effect for each report. A preliminary comparison is used to determine if the effects are all in the same direction. For example, two reports might both be in favor of association but have opposite risk alleles. In addition, a negative report may be in the same direction as other positive reports but be underpowered to achieve statistical significance on its own. Of the nine genes in Table 4, all but *ACE* were found to have association in meta-analysis.

Newly discovered associations

Unless it is by coincidence, confirmation work often lags behind an initial report by at least a year or two. In addition, since so many of these associations are likely to be either population-specific or false positives, attempts to confirm may be unsuccessful, and, if underpowered, negative reports should not be published at all. One exception to this pattern has been interferon regulatory factor 5 (*IRF5*). Following the initial

Table 3. Classification of lupus candidate genes by types of literature report.

Type of gene	No. genes	No. reports*	Examples
Causative mutations reported	11	18+	*C1q*, *C2*, *FasL*, *DNase 1*
Confirmed associations	20	75+	*HLA-DR*, *IRF5*, *APRIL*
Conflicting reports	48	532	*IL10*, *CTLA4*, *MBL*
Unconfirmed associations	28	28	*STAT4*, *CR2*, *IL-21*, *ICOS*
Phenotypic associations only	28	92	*CD38*, *BDNF*, *ITGA2*
Negative reports only	53	56	*NFκB1*, *RUNX1*, *CD40*
Total	***188***	***800+***	

*Excludes literature prior to 1995 on HLA and complement, which is a body of work of over 300 papers.

report in a large Nordic cohort in 2005 [36], several groups confirmed the association in quick succession [37–44]. Part of the success of this replication effort arises from the ability of groups who have assembled test cohorts to quickly assay newly reported associations in their own samples. Another factor may be that the large Caucasian cohorts assembled around the globe may be somewhat genetically heterogeneous to start with, and therefore more similar to each other. For example, in the USA, individuals of northern and southern European ancestry are freely mixed, and therefore there is considerable heterogeneity in appearance and ancestry among those who would be identified as 'white' and assembled into a European–American cohort. Perhaps Asian and Hispanic cohorts are more genetically specific to their regions of origin, and therefore we should not be surprised that an association found in Columbians might not be replicated in Mexicans, or an association found in Japanese might not be replicated in Koreans.

Another strong new association is in *STAT4*. The initial report provides evidence that a polymorphism in this gene is associated with both rheumatoid arthritis and SLE [45]. Work supporting this association in SLE is already in progress by a number of groups. Other strong initial reports with confirmation work in progress include *CR2* [46], *ICOS* [47] and *IL-21* [48]. As genome-wide association scans near completion, no doubt a number of other candidate genes will be confirmed or refuted, and new candidates will arise.

Future perspective

If you consider the large body of literature in lupus genetics as a whole, you cannot help but be dismayed that so much has been done and yet so little is truly known. Serious attempts to resolve the conflicts in the literature, to define the scope of each genetic effect, and to determine the interactions of the genetic factors that lead to disease risk must be attempted before true clarity is achieved. Large-scale collaborations that allow for cross-typing of different cohorts for the same markers in the same genes will be critical for determining the relative impact of each genetic variant on disease risk and for generating more complex models of disease that include epistatic interactions and clinical outcome variables. We already know that SLE is a complex disease with a pleomorphic presentation; we should expect that the final equation will also be complex to include multiple genes and encompass multiple phenotypes.

Another area in which we must improve and refine our techniques is in the consideration of racial heritage. The genetic background of the human species is varied, and even though we attempt to group patients by ancestry when matching controls, for example, this is fraught with inherent errors. Each racial subcategory we designate must be broad, so as to include as many samples as possible, but ancestry is not a simple categorical variable; it is a scalar, and will remain so no matter how we try to draw the lines in the sand. For example, African–Americans have admixture of European genes contributing anywhere from 10 to 30% of their ancestry, and this proportion can affect disease risk [49]. Our understanding of the effects of ancestral heritage will improve as we begin to characterize all participants in our genetic studies by their proportion of ancestral genotypes and use these variables as cofactors to combine all of our data. Over the next 10 years, the use of ancestry informative markers to characterize the ancestry of any individual will likely replace the use of questionnaires and self-designated racial categories. This revolution will refine our definitions of race immeasurably and will enable meaningful world-wide collaborations to confirm and further define genetics effects, wherein patient cohorts of different ethnicities will truly be combined for maximum power and not merely run side by side for economic convenience.

Table 4. Genes subjected to meta-analysis.

Gene	Location	Reports for	Reports against	Meta analysis	Ref.
ACE	17q23	4	9	Negative	[24]
CTLA4	2q33	9	11	Positive	[25,26]
FCGR2A	1q23	15	21	Positive	[27–30]
FCGR3A	1q23	11	9	Positive	[30]
IL10	1q32	13	9	Positive	[31]
MBL2	10q11	16	8	Positive	[18;32]
PTPN22	1p13	8	2	Positive	[33]
TNFα	6p21	19	12	Positive	[34]
TNFRSF1B	1p36	4	10	Positive	[35]

New technology has enabled us to gather more data than ever before, but we are currently attempting to lift our heads above the rising tide in the search for understanding. It is not enough to have some data on some of the patients some of the time, we must make efforts to combine and correlate what we know and to fill in the gaps. Much work remains to be done to resolve the apparent conflicts in the literature, as well as to combine the findings we are reasonably certain of into a coherent final picture. There is also much work in progress to define the exact nature of the causative polymorphisms within each risk allele, and the transition from an associated variant with no obvious functional consequence to a meaningful model of autoimmune pathogenesis will be an active area of investigation for many groups over the decade to come. This important work should raise us to a new level of understanding of the pathophysiology of SLE.

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Executive summary

Studies to elucidate the complex genetic causes of systemic lupus erythematosus

- Linkage studies type microsatellite markers across the whole genome in pedigrees with at least two systemic lupus erythematosus (SLE) patients and define a large linkage region.
- Association studies type SNPs in cases and controls, looking for differences in frequency at a specific base.
- Both linkage and association studies must be confirmed with work in a second, independent cohort. These attempts to confirm reported associations have led to a large body of conflicting literature.

Established genes

- Complement deficiencies in C1q, C2 and C4 cause SLE, but these are responsible for less than 1% of lupus cases.
- The HLA region is well known to be associated with disease, but there are a number of genes inherited with HLA that could be responsible for the increased risk. It is possible that a combination of factors is necessary.
- Other genes with both positive and negative reports in the literature have been established through meta-analysis.
- Newly discovered associations with promise include *IRF5* and *STAT4*.

Future perspective

- Collaborations that result in the testing of larger cohorts will make confirmation and characterization of the existing candidate genes easier.
- Complex models of disease risk will incorporate multiple genetic elements, as well as clinical and demographic variables.
- A set of markers that more clearly define ancestry will be characterized and used routinely to assess all samples, such that ethnicity can be incorporated as a cofactor, rather than be used as a dividing line.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Harley JB, Harley IT, Guthridge JM, James JA: The curiously suspicious: a role for Epstein–Barr virus in lupus. *Lupus* 15(11), 768–777 (2006).
2. Sestak AL, Shaver TS, Moser KL, Neas BR, Harley JB: Familial aggregation of lupus and autoimmunity in an unusual multiplex pedigree. *J. Rheumatol.* 26(7), 1495–1499 (1999).
3. Block SR, Christian CL: The pathogenesis of systemic lupus erythematosus. *Am. J. Med.* 59(4), 453–456 (1975).
4. Block SR: A brief history of twins. *Lupus* 15(2), 61–64 (2006).
5. Sullivan KE, Winkelstein JA: Genetically determined deficiencies of the complement system. In: *Primary Immunodeficiency Diseases: A Molecular and Genetic Approach*. Ochs HD, Smith C, Puck J (Eds). Oxford University Press, NY, USA, 397–416 (1999).

• Excellent review of the complement deficiencies associated with systemic lupus erythematosus.

6. Moser KL, Neas BR, Salmon JE *et al.*: Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African–American pedigrees. *Proc. Natl Acad. Sci. USA* 95(25), 14869–14874 (1998).
7. Edberg JC, Langefeld CD, Wu J *et al.*: Genetic linkage and association of Fcγ receptor IIIA (*CD16A*) on chromosome 1q23 with human systemic lupus erythematosus. *Arthritis Rheum.* 46(8), 2132–2140 (2002).
8. Lindqvist AK, Steinsson K, Johanneson B *et al.*: A susceptibility locus for human systemic lupus erythematosus (*hSLE1*) on chromosome 2q. *J. Autoimmun.* 14(2), 169–178 (2000).
9. Shai R, Quismorio FP Jr, Li L *et al.*: Genome-wide screen for systemic lupus erythematosus susceptibility genes in multiplex families. *Hum. Mol. Genet.* 8(4), 639–644 (1999).
10. Gray-McGuire C, Moser KL, Gaffney PM *et al.*: Genome scan of human systemic lupus erythematosus by regression modeling: evidence of linkage and epistasis at 4p16–15.2. *Am. J. Hum. Genet.* 67(6), 1460–1469 (2000).
11. Cantor RM, Yuan J, Napier S *et al.*: Systemic lupus erythematosus genome scan: support for linkage at 1q23, 2q33, 16q12–13, and 17q21–23 and novel evidence at 3p24, 10q23–24, 13q32, and 18q22–23. *Arthritis Rheum.* 50(10), 3203–3210 (2004).
12. Tsao BP, Cantor RM, Grossman JM *et al.*: Linkage and interaction of loci on 1q23 and 16q12 may contribute to susceptibility to systemic lupus erythematosus. *Arthritis Rheum.* 46(11), 2928–2936 (2002).
13. Tsao BP, Cantor RM, Grossman JM *et al.*: *PARP* alleles within the linked chromosomal region are associated with systemic lupus erythematosus. *J. Clin. Invest.* 103(8), 1135–1140 (1999).
14. Hur JW, Sung YK, Shin HD, Park BL, Cheong HS, Bae SC: Poly(ADP-ribose) polymerase (*PARP*) polymorphisms associated with nephritis and arthritis in systemic lupus erythematosus. *Rheumatology (Oxford)* 45(6), 711–717 (2006).
15. Criswell LA, Moser KL, Gaffney PM *et al.*: *PARP* alleles and SLE: failure to confirm association with disease susceptibility. *J. Clin. Invest.* 105(11), 1501–1502 (2000).
16. Chen JY, Wang CM, Lu SC, Chou YH, Luo SF: Association of apoptosis-related microsatellite polymorphisms on chromosome 1q in Taiwanese systemic lupus erythematosus patients. *Clin. Exp. Immunol.* 143(2), 281–287 (2006).
17. Delrieu O, Michel M, Frances C *et al.*: Poly(ADP-ribose) polymerase alleles in French Caucasians are associated neither with lupus nor with primary antiphospholipid syndrome. GRAID Research Group. Group for Research on Auto-Immune Disorders. *Arthritis Rheum.* 42(10), 2194–2197 (1999).
18. Lee YH, Witte T, Momot T *et al.*: The mannose-binding lectin gene polymorphisms and systemic lupus erythematosus: two case–control studies and a meta-analysis. *Arthritis Rheum.* 52(12), 3966–3974 (2005).
19. Sullivan KE: Genetics of systemic lupus erythematosus. Clinical implications. *Rheum. Dis. Clin. North. Am.* 26(2), 229–256 (2000).
20. Yang Y, Chung EK, Wu YL *et al.*: Gene copy-number variation and associated polymorphisms of complement component C4 in human systemic lupus erythematosus (SLE): low copy number is a risk factor for and high copy number is a protective factor against SLE susceptibility in European Americans. *Am. J. Hum. Genet.* 80(6), 1037–1054 (2007).

• Provides an example of how copy number variations can contribute to disease risk.

21. Hartng K, Baur MP, Coldewey R *et al.*: Major histocompatibility complex haplotypes and complement C4 alleles in systemic lupus erythematosus. Results of a multicenter study. *J. Clin. Invest.* 90(4), 1346–1351 (1992).
22. Kelly JA, Moser KL, Harley JB: The genetics of systemic lupus erythematosus: putting the pieces together. *Genes Immun.* 3(Suppl. 1), S71–S85 (2002).
23. Behrens TW, Graham RR, Kyogoku C *et al.*: Progress towards understanding the genetic pathogenesis of systemic lupus erythematosus. *Novartis Found. Symp.* 267, 145–160 (2005).
24. Lee YH, Rho YH, Choi SJ, Ji JD, Song GG: Angiotensin-converting enzyme insertion/deletion polymorphism and systemic lupus erythematosus: a metaanalysis. *J. Rheumatol.* 33(4), 698–702 (2006).
25. Lee YH, Harley JB, Nath SK: *CTLA-4* polymorphisms and systemic lupus erythematosus (SLE): a meta-analysis. *Hum. Genet.* 116(5), 361–367 (2005).
26. Barreto M, Santos E, Ferreira R *et al.*: Evidence for *CTLA4* as a susceptibility gene for systemic lupus erythematosus. *Eur. J. Hum. Genet.* 12(8), 620–626 (2004).
27. Karassa FB, Bijl M, Davies KA *et al.*: Role of the Fcγ receptor IIA polymorphism in the antiphospholipid syndrome: an international meta-analysis. *Arthritis Rheum.* 48(7), 1930–1938 (2003).
28. Karassa FB, Trikalinos TA, Ioannidis JP: Role of the Fcγ receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Arthritis Rheum.* 46(6), 1563–1571 (2002).
29. Trikalinos TA, Karassa FB, Ioannidis JP: Meta-analysis of the association between low-affinity Fcγ receptor gene polymorphisms and hematologic and autoimmune disease. *Blood* 98(5), 1634–1635 (2001).
30. Karassa FB, Trikalinos TA, Ioannidis JP: The role of FcγRIIA and IIIA polymorphisms in autoimmune diseases. *Biomed. Pharmacother.* 58(5), 286–291 (2004).
31. Nath SK, Harley JB, Lee YH: Polymorphisms of complement receptor 1 and interleukin-10 genes and systemic lupus erythematosus: a meta-analysis. *Hum. Genet.* 118(2), 225–234 (2005).
32. Garred P, Voss A, Madsen HO, Junker P: Association of mannose-binding lectin gene variation with disease severity and infections in a population-based cohort of systemic

lupus erythematosus patients. *Genes Immun.* 2(8), 442–450 (2001).

33. Lee YH, Rho YH, Choi SJ *et al.*: The *PTPN22* C1858T functional polymorphism and autoimmune diseases – a meta-analysis. *Rheumatology (Oxford)* 46(1), 49–56 (2007).
34. Lee YH, Harley JB, Nath SK: Meta-analysis of TNF-α promoter -308 A/G polymorphism and SLE susceptibility. *Eur. J. Hum. Genet.* 14(3), 364–371 (2006).
35. Horiuchi T, Kiyohara C, Tsukamoto H *et al.*: A functional M196R polymorphism of tumour necrosis factor receptor type 2 is associated with systemic lupus erythematosus: a case–control study and a meta-analysis. *Ann. Rheum. Dis.* 66(3), 320–324 (2007).
36. Sigurdsson S, Nordmark G, Goring HH *et al.*: Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Am. J. Hum. Genet.* 76(3), 528–537 (2005).
37. Graham RR, Kozyrev SV, Baechler EC *et al.*: A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat. Genet.* 38(5), 550–555 (2006).
38. Graham RR, Kyogoku C, Sigurdsson S *et al.*: Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. *Proc. Natl Acad. Sci. USA* 104(16), 6758–6763 (2007).

• Outlines the work in delineating the complex effects at the *IRF5* locus.

39. Kozyrev SV, Lewen S, Reddy PM *et al.*: Structural insertion/deletion variation in IRF5 is associated with a risk haplotype and defines the precise IRF5 isoforms expressed in systemic lupus erythematosus. *Arthritis Rheum.* 56(4), 1234–1241 (2007).
40. Shin HD, Sung YK, Choi CB, Lee SO, Lee HW, Bae SC: Replication of the genetic effects of IFN regulatory factor 5 (*IRF5*) on systemic lupus erythematosus in a Korean population. *Arthritis Res. Ther.* 9(2), R32 (2007).
41. Demirci FY, Manzi S, Ramsey-Goldman R *et al.*: Association of a common interferon regulatory factor 5 (*IRF5*) variant with increased risk of systemic lupus erythematosus (SLE). *Ann. Hum. Genet.* 71(Pt 3), 308–311 (2007).
42. Cunninghame Graham DS, Manku H, Wagner S *et al.*: Association of *IRF5* in UK SLE families identifies a variant involved in polyadenylation. *Hum. Mol. Genet.* 16(6), 579–591 (2007).
43. Ferreiro-Neira I, Calaza M, Alonso-Perez E *et al.*: Opposed independent effects and epistasis in the complex association of *IRF5* to SLE. *Genes Immun.* 8(5), 429–438 (2007).
44. Reddy MV, Velazquez-Cruz R, Baca V *et al.*: Genetic association of *IRF5* with SLE in Mexicans: higher frequency of the risk haplotype and its homozygozity than Europeans. *Hum. Genet.* 121(6), 721–727 (2007).
45. Remmers EF, Plenge RM, Lee AT *et al.*: *STAT4* and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N. Engl. J. Med.* 357(10), 977–986 (2007).
46. Wu H, Boackle SA, Hanvivadhanakul P *et al.*: Association of a common complement receptor 2 haplotype with increased risk of systemic lupus erythematosus. *Proc. Natl Acad. Sci. USA* 104(10), 3961–3966 (2007).
47. Graham DS, Wong AK, McHugh NJ, Whittaker JC, Vyse TJ: Evidence for unique association signals in SLE at the CD28–CTLA4–ICOS locus in a family-based study. *Hum. Mol. Genet.* 15(21), 3195–3205 (2006).
48. Sawalha AH, Kaufman KM, Kelly JA *et al.*: Genetic association of *IL-21* polymorphisms with systemic lupus erythematosus. *Ann. Rheum. Dis.* (2007) (Epub ahead of print).
49. Wassel Fyr CL, Kanaya AM, Cummings SR *et al.*: Genetic admixture, adipocytokines, and adiposity in Black Americans: the health, aging, and body composition study. *Hum. Genet.* 121(5), 615–624 (2007).

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