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# Recent findings on genetics of systemic autoimmune diseases

Angélica Delgado-Vega[1], Elena Sánchez[2], Sara Löfgren[1], Casimiro Castillejo-López[1] and Marta E Alarcón-Riquelme[1,2,3]

Association studies of over 1 million SNPs capturing most of the human genome common variation became possible thanks to the information provided by the HapMap International project and the development of high-throughput genotyping technologies at accessible prices. Genome-wide scans analyzing thousands of individuals have now identified most if not all of the major genes involved in susceptibility for several systemic autoimmune diseases. In particular, results for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) are reviewed here. While most genes are shared between diseases, few seem to be unique reflecting that we still are long before knowing all genes, their interactions with other genes and the environment and their impact on biological functions.

**Addresses**
[1] Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Dag Hammarsjölds väg 20, 751 85 Uppsala, Sweden
[2] Arthritis and Immunology Program, Oklahoma Medical Research Foundation, 825 NE 13th St., Oklahoma City 73104, OK, United States
[3] Center for Genomics and Oncological Research Pfizer, University of Granada, Junta de Andalucía, Avenida de la Ilustración 114, Granada 18007, Spain

Corresponding author: Alarcón-Riquelme, Marta E (alarconm@omrf.org)

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## Introduction

Previous studies on the genetics of complex diseases used small sample sizes leading to inconclusive results, with the exception of the strong genetic association between genes within the major histocompatibility complex (MHC) and the various autoimmune diseases. While GWAS have provided some surprises, they have also confirmed a few of the old results, but not all. The most important genes identified previously, *IRF5* and *STAT4* for SLE and *PTPN22* and *STAT4* for RA stand [1]. In this review we focus only on those genes identified in the past two to three years. As GWAS with extensive coverage have been used, except for a few examples (*PDCD1* is a relevant one, as SNPs within this gene are lacking in the GWAS arrays), most of the genome has been screened with thousands of samples providing an overall picture of genetic susceptibility. We present only those genes that have been clearly replicated and whose role in genetic susceptibility is beyond doubt or the result of powerful GWAS with replication using large sample sizes.

## Genetics of SLE

SLE is considered as a prototypic autoimmune disease, characterized by production of antinuclear autoantibodies, immune-complex deposition, and subsequent multiple organ damage.

The understanding of the genetic basis of SLE has expanded enormously over the past couple of years, driven principally by technological advances and the assessment of six genome-wide association studies (GWAS) in the past two years, in Caucasians and Asians [2•,3•,4••,5••,6••,7].

The great majority of the identified genes are involved in innate and adaptive immune responses. The convincingly associated genes, as summarized in Table 1, are mainly implicated in immune-complex (IC) processing, T/B cell signaling and/or and Toll-like receptor (TLR), and type I interferon signaling. The strongest association in the GWAS era is undoubtedly the MHC region, but because it consists of strongly correlated polymorphisms in a ~6 Mb region involving more than 400 genes it remains a challenge. Recent observations by Fernando *et al.* have shown at least two independent genetic effects within the MHC region in SLE: one signal is provided by the *HLA-DRB1*0301* allele, and the second within the class III region specifically detecting the 6th intron of the *SKIVL2* gene [8]. A more recent study genotyping over 1400 variants within the MHC region and over 10,000 individuals with various autoimmune diseases including SLE and RA showed the top disease-specific signal for SLE to be SNP [8,9] located between *TNXB* and *CREBL1* and the HLA *DRB1*0301* [9].

Impaired IC clearance and deposition is an important pathological aspect in SLE. Susceptibility genes with important roles in IC processing known from previous studies are the FcGR family of genes and more recently *ITGAM* [10••] coding for the surface antigen CD11b (or CR3). Signal transduction in immune cells, particularly T and B cells, is another pathway that has revealed to contain multiple lupus susceptibility genes, modulating T cell signaling such as *TNFSF4* (OX40L) [11,12] and

**Table 1**

**Susceptibility Genes for SLE**

| Chromosome | *Gene* | SNPs | Population | References |
|---|---|---|---|---|
| 6p21 | *HLA region* | DRB1*0301 and several other alleles | European, several Asian, African-American, mixed European-Amerindian | [8,9] |
| 7q32 | *IRF5* | 5bp promoter indel, rs2004640, rs2070197, rs10954213 | European, several Asian, mixed European-Amerindian, African-American | [3•,4••,5••,7,20••] |
| 2q32 | *STAT4* | rs7574865, rs3821236, rs7601754 | European, mixed European-Amerindian, several Asian, African-American | [3•,4••,5••,7,20••] |
| 6q23 | *TNFAIP3* | rs5029939, rs2230926 | European, Asian, African-American | [2,3•,4••,5••,7,17•,20••] |
| 16p11 | *ITGAM* | rs9888739, rs1143679, rs4548893 | European, mixed European-Amerindian, Asian, African-American | [3•,4••,5••,7,10••,20••] |
| 4q24 | *BANK1* | rs10516487, rs17266594, rs3733197 | European, European-Amerindian, Asian | [3•,6••,7,14] |
| 1p13 | *PTPN22* | rs2476601 | European | [4••] |
| 8p23 | *BLK* | rs13277113, rs2736340 | European, several Asian | [3•,4••,5••,7,15,20••] |
| 2q37 | *PDCD1 (CD279)* | PD1.3A | European, European-Amerindian, Chinese | [49] |
| 1q25 | *TNFSF4* | Risk haplotype; rs3850641 | European, Asian | [3•,7,11,12,14,20••] |
| 18q22.3 | *CD226* | rs763361, rs727088 | European, European-Amerindian | [13•] |
| 1q21-23 | *FCGR2A* | ARG131HIS | European, European-Amerindian, African American | [4••,5••,20••] |
| 19p13.2 | *TYK2* | rs280519 | European | [20••] |
| 3p21.3 | *TREX1* | rs72556554, R114H and other 11 nonsynonimous substitutions | European | [16] |
| Xq28 | *MECP2-IRAK1* | rs2269368, rs17435 | European, Chinese, Korean, European-Amerindian (Mexican) | [18,19,20••] |
| 3p14.3 | *PXK* | rs6445975, rs2176082 | European | [4••,20••] |
| 2q24 | *IFIH1* | rs1990760 | European | [20••] |
| 11p15.5 | *KIAA1542 (PHRF1)* | rs4963128 | European | [4••] |
| 8p23.1 | *XKR6* | rs6985109 | European | [4••] |
| 6q21 | *ATG5-PRMD1* | rs6568431, rs2245214 | European, Chinese | [4••,20••] |
| 22q11.2 | *UBE2L3* | rs5754217 | European, Chinese | [2•,20••] |
| 5q33.3 | *PTTG1* | rs2431099 | European | [2•,20••] |
| 6p21 | *UHRF1BP1* | rs11755393 | European | [20••] |
| 5q32 | *TNIP1* | rs7708392 | European, Chinese, Thai | [3•,20••] |
| 7p15.2 | *JAZF1* | rs849142 | European | [20••] |
| 7p21.3 | *ICA1* | rs10156091 | European | [4••,20••] |
| 1q24 | *IL10* | rs3024505 | European | [20••] |
| 1q25.3 | *NMNAT2* | rs2022013 | European, Chinese | [3•,4••] |
| 11q23.3 | *ETS1* | rs6590330 | Chinese, Thai | [3•,7] |
| 10q11.23 | *WDFY4* | rs877819 | Chinese, Thai | [3•,7] |
| 7p12.2 | *IKZF1* | rs4917014 | Chinese | [3•] |
| 12q24.32 | *SLC15A4* | rs10847697, rs1385374 | Chinese | [3•] |
| 2p22.3 | *RASGRP3* | rs13385731 | Chinese | [3•] |

*CD226* on NKT cells [13•]. More recently *BANK1* and *BLK*, thought to be involved in B cell activation and tolerance [5••,6••], respectively have been now clearly established [3•,14,15].

One pathway that has been biologically and genetically strongly related to SLE pathogenesis is the type I interferon (IFN) pathway. Several genes for factors upstream and downstream of IFN production, such as *IRF5*, *STAT4*, and more recently *TNFAIP3*, *TYK2*, and *TREX1*, have been associated to susceptibility to SLE [2•,16,17•]. *IRAK1* has been an interesting candidate but it is closely linked to *MECP2*, a gene that can regulate expression of *IRAK1* also associated. It has proven as yet impossible to discern the genetic effects between these X chromosome genes [18•,19•,20••]. *TREX1* is mainly represented by rare but penetrant and mutations leading to high levels of type I interferon found in few patients with lupus, suggesting a potentially important role of rare variants that have remained undetected with the use of common variation mapping.

Other recently identified loci, such as *PXK*, *XKR6*, and *KIAA1542* close to *IRF7* [4••], with no known function or correlation to SLE pathology, have the potential to lead to the discovery of novel pathways involved in SLE. It is unclear if the genetic association of *KIAA1542* indeed represents an association with *IRF7*.

**Table 2**

**Susceptibility Genes for RA**

| Chromosome | *Gene* | SNPs | Population | Reference |
|---|---|---|---|---|
| 6p21.32 | *HLA-DRB1* | rs615672, rs660895, rs64576200, rs6910071, rs13192471 | European, Japanese | [21–23,24••,25•] |
| 1p13.2 | *PTPN22* | rs6679677, rs2476601 | European | [21–23,24••,30•] |
| 2q32.3 | *STAT4* | rs7574865 | European, Japanese | [24••,25•] |
| 9q34 | *TRAF1-C5* | rs3761847, rs881375 | European | [22,24••,30•] |
| 6q23.3 | *TNFAIP3, OLIG3* | rs10499194, rs6920220 | European, Japanese | [23,24••,25•,29•] |
| 6p21.32 | *HLA-DQA1, HLA-DQA2* | rs6457617 | European | [31] |
| 18q23 | *SALL3* | rs2002842 | European | [31] |
| 20q13.12 | *CD40* | rs4810485 | European | [23,24••] |
| 9p13.3 | *CCL21* | rs2812378 | European | [23] |
| 12q13.3 | *KIF5A,PIP4K2C* | rs1678542 | European | [23] |
| 1p36.32 | *TNFRSF14* | rs3890745 | European | [23,24••] |
| 10p15.1 | *PRKCQ* | rs4750316 | European | [23,24••] |
| 7q21.2 | *CDK6* | rs42041 | European | [23] |
| 2p16.1 | *REL* | rs13017599, rs13031237 | European | [24••,30•] |
| 2q33.2 | *CTLA4* | rs231735, rs3087243 | European | [24••,30•] |
| 8p23.1 | *BLK* | rs2736340 | European | [30•] |
| 2q11.2 | *AFF3* | rs11676922,rs10865035 | European | [24••] |
| 5q11.2 | *ANKRD55,IL6ST* | rs6859219 | European | [24••] |
| 14q24.3 | *BATF* | rs7155603 | European | [24••] |
| 5q21.1 | *C5orf30* | rs26232 | European | [24••] |
| 9p13.3 | *CCL21* | rs951005 | European | [24••] |
| 6q27 | *CCR6* | rs3093023, rs3093024 | Japanese | [24••,25•] |
| 1q24.2 | *CD247* | rs840016 | European | [24••] |
| 17q12 | *IKZF3* | rs2872507 | European | [24••] |
| 4q27 | *IL2,IL21* | rs13119723 | European | [24••] |
| 10p15.1 | *IL2RA* | rs706778 | European | [24••] |
| 7q32.1 | *IRF5* | rs10488631 | European | [24••] |
| 15q23 | *KIF3* | rs17374222 | European | [24••] |
| 1p34.3 | *POU3F1* | rs12131057 | European | [24••] |
| 3p14.3 | *PXK* | rs13315591 | European | [24••] |
| 4p15.2 | *RBPJ* | rs874040 | European | [24••] |
| 12q24.12 | *SH2B3* | rs3184504 | European | [24••] |
| 2p14 | *SPRED2* | rs934734 | European | [24••] |
| 21q22.3 | *UBASH3A* | rs11203203 | European | [24••] |

Finally, a very large replication study identified and replicated several genes among which are *JAZF1*, *TNIP1*, *PRDM1* (or *BLIMP1*), *UHRF1BP1*, *PTTG1* [2•], UBE2L3 [2•], IL10, IL21, and the IL21R [20••]. Importantly, several other genes were also confirmed in this study such as *ATG5*, *ICA1*, and *NMNAT2* found in a previous GWAS from the SLEGEN consortium [4••]. *ATG5* is an important component of the autophagy pathway. *JAZF1* and *UHRF1BP1* are transcription factors, while *TNIP1* interacts with *TNFAIP3*, its function in regulating *TNFAIP3* is not known. *TNFAIP3* (or A20) regulates inflammation by turning off NFκB through polyubiquitination and degradation.

Studies in Asian populations have identified new susceptibility genes for lupus and replication of the hitherto identified genes in Europeans has revealed the presence of some genes but not others [3•,7,14]. Two genes were clearly identified, *ETS1* and *WDFY4* [3•,7]. *ETS1* is involved in the development of TH17 cells while *WDFY4* codes for a protein of unknown function. *STAT4*, *IRF5*, *BANK1*, *BLK*, *TNFAIP3*, and *TNFSF4* have been confirmed in Asians [3•,7]. Studies on African Americans and European-Amerindian admixed populations are ongoing.

## Genetics of RA

Multiple GWAS have corroborated the MHC genes as major genetic contributors to the risk of developing RA [21–23,24••,25•]. Within the MHC, the strongest contribution to risk is given by the *HLA-DRB1* gene, which codes for the third hypervariable region of the HLA-DR molecule β chain. Since the original report of Peter Stastny, diverse *HLA-DRB1* alleles have been associated in European, Asian, African, and European-Ameridian populations [26]. All the associated alleles were unified by Peter Gregersen under the hypothesis of the shared epitope (SE). SE alleles are associated with anti-citrulline antibody production, a major biomarker for RA and determine severity. A study analyzing over 1400 SNPs within the HLA regions from the IMAGEN Consortium found the peak association for RA between the gene *BTNL2* and HLA-*DRA* (SNP rs2395175) and the allele for the *DQA1* gene *DQA1*0301* [9]. Dense typing of the

MHC have revealed several *DRB1*-independent associations, including a signal at *MICA*, one in the border between class I and class III region and some in the class I region [27].

Although any other association outside the MHC is rather modest in RA, and the SE accounts for 18–37% of the genetic heritability [28], fine mapping of candidate non-MHC linkage regions successfully identified important susceptibility genes such as *PTPN22* (1p13), *PADI4* (1p36), and *STAT4* (2q32). To date, seven GWAS conducted in collections of thousands of patients with RA and healthy controls reliably detect several new susceptibility genes [21–23,25•,29•,30•,31] (Table 2). The loci supported by the best evidence are the *TRAF1-C5* [22,24••,30•] and the 6q23 region [23,24••,25,29•], both with strongest effect in anti-CCP+ patients. GWAS studies have also confirmed the association of *PTPN22* and *STAT4*, as well as previously reported candidate genes identified by studies that did not have enough power such as *CTLA4* and *CD40*. The maximum power has been achieved by a recent meta-analysis of GWAS conducted in a total of 12,307 patients and 28,975 controls of European ancestry [24••]. This allowed the identification and confirmation of *IL6ST*, *SPRED2*, *RBPJ*, *CCR6* [25•], *IRF5*, and *PXK* [24••]. While *SPRED2* has been found to be a negative regulator of the Ras-ERK cascade, *IL6ST* and *CCR6* are inflammation regulators and *RBPJ* is a transcription factor important in dendritic cell function.

It is important to note that major differences across racial groups have been noticed; for example, *PTPN22* and *CTLA4* were associated in Europeans whereas *PADI4* and *SLC22A4* are confirmed only in Asian population groups. By contrast, the *STAT4* association is valid for European, Asian, and European-Amerindian but not African Americans [32]. All these findings add evidence of the complexity and the heterogeneity of the genetic basis of RA and justify the study of diverse populations. One GWAS has been performed in Japanese [25•] but none in admixed populations of European-Amerindian or African American. The observed heterogeneity highlights the importance of conducting well-powered GWAS in non-European populations in order to dissect all the genetic contribution to the disease.

## Genetics of systemic sclerosis

Systemic sclerosis (SSc) or scleroderma is an autoimmune disease characterized by an extensive fibrotic process that affects multiple organs and tissues. Until now genetic studies have not been particularly successful in the identification of risk factors for SSc. The controversial results found for the majority of genes, such as, *PTPN22*, *CTGF*, or *TGF-β*, suggest that those studies were often limited by small sample size and clinical heterogeneity. Some were finally replicated when large sample sizes were used (Table 3). One of the first discoveries was the contribution, as in other autoimmune diseases, of HLA class II genes, which seem to be predominantly associated with the presence of specific autoantibodies rather than with SSc itself. These associations have been confirmed in a recent GWAS in SSc in the Korean population [33]. The first GWAS in a sample of European ancestry including 2296 SSc patients and 5171 controls has firmly established the role of the *HLA* genes in SSc [34••]. *STAT4* and *IRF5* that had previously been identified as risk factors for SSc through candidate gene studies [35,36], were also identified in the GWAS of European patients with SSc [34••]. The consistent association of these genes with SSc susceptibility provides compelling evidence that variation in genes with key functions in the innate immune system are involved in the pathogenesis of the disease.

The identification of the association of connective tissue growth factor (*CTGF*) gene with risk to SSc provides one of the most conflicting results to date. The potential

**Table 3**

**Susceptibility Genes for SSc**

| Chromosome | *Gene* | SNPs | Population | Reference |
|---|---|---|---|---|
| 6p21.32 | *HLA-DPB1,DPB2* | rs3128930, rs7764491, rs7763822, rs3128965, rs3117230, rs7763822, rs7764491, rs3117230,rs 3128965 | Korean, European | [33,34] |
| | *HLA-DQB1* | rs6457617 | European | [34] |
| 2q32.3 | *STAT4* | rs7574865, rs11889341, rs8179673, rs10181656, rs3821236 | European, Japanese | [34,44] |
| 7q32 | *TNPO3-IRF5* | rs2004640, rs2280714, rs10954213, rs10488631, rs12537284, rs4728142 | European, Japanese | [34–36] |
| 4q24 | *BANK1* | rs10516487, rs17266594 | European | [41] |
| 8p23.1 | *C8orf13-BLK* | rs2736340, rs13277113 | European | [42,43] |
| 17q21.32 | *TBX21* | rs11650354, rs17699436 | European | [44] |
| 1q25.1 | *TNFSF4* | rs1234314, rs2205960, rs844644, rs844648 | European | [47] |
| 10q24 | *FAS* | rs1800682 (G-670A) | European | [45,46] |
| 6q23.1 | *CTGF* | rs6918698 (G-945C), rs9399005 | European, Japanese | [37–40] |
| 1q22-23 | *CD247* | rs2056626 | European | [34] |

functional -945 G allele of *CTGF* gene was primarily associated with susceptibility to SSc in Europeans and Japanese [37]. However, three additional studies in Europeans failed to replicate the association [38–40]. A recent study suggests that variant rs9399005 in the 3′UTR region of the *CTGF* gene is associated with both subtypes of SSc [39]. The lack of replication of the *CTGF* polymorphisms in three large cohorts of SSc suggests that *CTGF* may not be a strong genetic determinant for SSc susceptibility.

Genes involved in B cell receptor signaling contribute to SSc susceptibility. Association with diffuse SSc (dcSSc) has been identified with *BANK1* [41]. The *C8orf13-BLK* region has been associated in European and Japanese patients with SSc [42,43]. These findings suggest an important role of B cells in the pathogenesis of SSc.

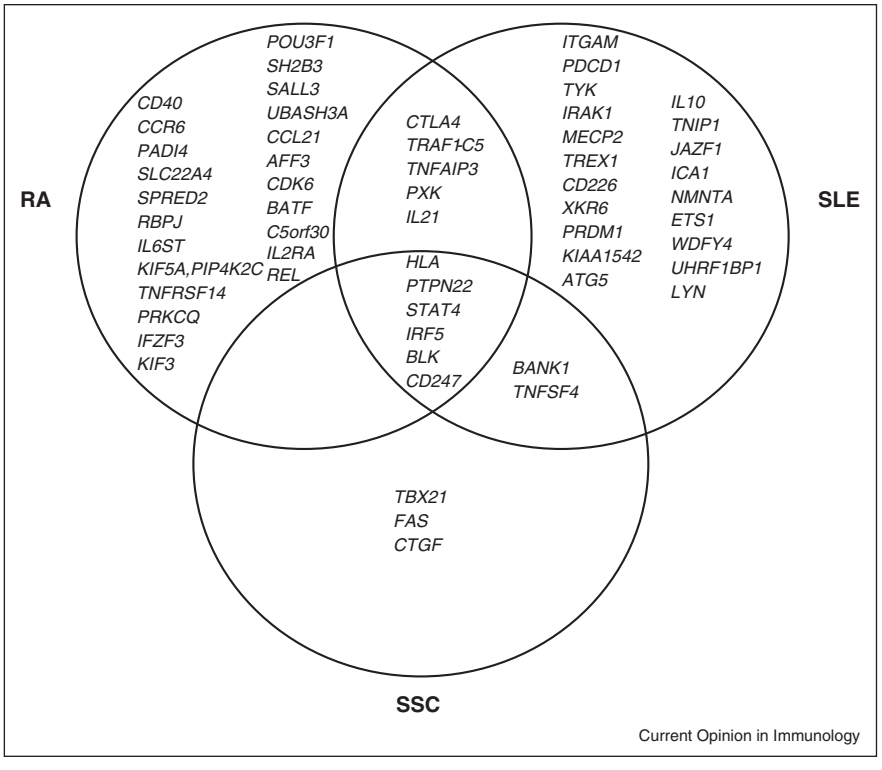
A large multicenter study in Europeans found two polymorphisms (rs11650354 and rs17699436) in the *TBX21* gene associated with SSc [44]. In addition, they also showed a gene–gene interaction between the *TBX21* and *STAT4*.

Some other genes that appear to play a role in susceptibility to SSc are *FAS*, *TNFSF4*, and *CD247*. The promoter rs1800682 polymorphism in the *FAS* gene is a confirmed susceptibility variant for SSc in different populations [45,46]. In addition, the SLE susceptibility gene *TNFSF4* [11,12,14] was associated with SSc in a large case–control study [47]. The *CD247* gene, which encodes the T cell receptor zeta (CD3ζ) subunit, was a new susceptibility gene for SSc in a GWAS and this association has been confirmed in an independent cohort [34••].

## Conclusions

The genetics results deriving from GWAS are just the beginning of a new era of research, but new insight on disease genetics has been acquired. First, the risk alleles identified for these diseases explain only between 5 and 15% of the whole genetic contribution to disease and with odds ratios ranging from 1.01 to 2.4 at the most. Clearly, gene–gene interactions, gene–environment interactions, and other genomic structural variation such as copy number variation, the role of rare variants, and epigenetics need to be adressed. In this regard, the recent identification of rare, but highly penetrant mutations in the sialic acid acetylestarase gene (SIAE) involved in SLE and RA susceptibility and with an important functional impact in the gene [48••] suggests that rare variants may have an important role not yet fully comprehended. Second, most autoimmune diseases, in particular systemic autoimmune diseases, share several susceptibility genes. The differences seem to reside on the contribution of each gene in each disease. HLA alleles have been known to be differ-

**Figure 1**




Unique and shared genes between SLE, RA and SSc.

ent from disease to disease, but the risk alleles for non-MHC genes appear, until now to be the same. However while *IRF5* and *STAT4* are prominent genes in SLE, *PTPN22* and *TNFAIP3* are major genes in RA and *CD247* in SSc. Very few genes are unique for each disease (Figure 1) and whether some genes may predominate in individuals with certain clinical manifestations is still a difficult nut to crack. Phenotyping of samples studied in genetics lack the detail required to define the correlation between clinical maifestations and genes. One possible exception is *ITGAM* in SLE, a unique gene for lupus importantly associated with kidney disease. Third, studies in different populations are important. Differences and similarities will not only lead to a comprehensive picture of genetic susceptibility, but may also pave the way to the very needed studies on gene–environmental interactions in autoimmune disease, a theme about which we know practically nothing.

Genetics studies are a starting point to cell biology and immunology studies aimed at understanding disease pathogenesis and the influence of susceptibility genes on cell function. Indeed, we have challenging and exciting times ahead of us.

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- • of special interest
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This study is one of the two first GWAS fir SLE. Primarily ITGAM was identified as a major gene for lupus.

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The other first GWAS in SLE. The risk polymorhisms close to the promoter of BLK and 3′ of C8orf13 (now FAM146A) correlate with expression levels of both genes.

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