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# The Genetics of Systemic Sclerosis

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## Abstract

Systemic sclerosis (SSc, scleroderma) is an autoimmune disease clinically characterized by progressive fibrosis in the skin and internal organs. While the pathogenesis of SSc is not completely understood, familial studies and genetic studies suggest that SSc is a complex polygenic disease. In the current review, we will discuss recent studies investigating genetic susceptibility to SSc. Candidate gene studies have identified critical immunoregulatory genes and gene regions including *BANK1, FAM167A-BLK, IL23R, IRF5, STAT4, TBX21,* and *TNFSF4* as susceptibility genes for the development of SSc. More recently a genome-wide association study has been performed and identified CD247 (CD3-zeta) as a novel genetic risk factor for the susceptibility to SSc. Together these genetic association studies have substantially advanced our understanding of SSc pathogenesis and form the foundation for future studies seeking to understand the complexities of SSc.

## Introduction

Systemic sclerosis (SSc, scleroderma) is an autoimmune disease clinically characterized by progressive fibrosis in the skin and internal organs (Charles et al., 2006). Clinically and pathologically SSc is epitomized by the triad of inflammation and autoimmunity, endothelial dysfunction, and fibrosis (Charles et al., 2006). Autoimmunity is best demonstrated by the presence of non-overlapping SSc-associated autoantibodies [e.g., anti-topoisomerase I (ATA), anti-centromere (ACA), and anti-RNA polymerase III (ARA)] in SSc patients which subcategorize patients into distinct clinical subsets (Reveille et al., 2001; Arnett et al., 2006). For example, ATA+ patients are at increased risk of developing interstitial lung disease while ACA+ patients are at increased risk of developing pulmonary hypertension (Arnett et al., 2006). Interestingly, ARA+ patients have been reported to be at increased risk of developing SSc renal crisis (Nguyen et al., 2010). Inflammation is present in early scleroderma skin biopsies, characterized by perivascular infiltrates of mononuclear inflammatory cells (Fleischmajer et al., 1977). Furthermore, patients with SSc have increased circulating levels of cytokines that have distinct patterns based on the SSc-associated autoantibodies, and similar to systemic lupus erythematosus, SSc patients have dysregulation of type I interferon pathways (Gourh et al., 2009b; Blanco et al., 2001; Baechler et al., 2003; Tan et al., 2006). Initially identified using gene expression profiling of SSc peripheral blood, the presence of type I interferon pathway activation has been confirmed in subsequent studies (Tan et al., 2006; York et al., 2007; Gardner et al., 2006). Together, these data place inflammation and autoimmunity in the pathogenesis of SSc. While the initiating events that lead to this immune dysregulation are unknown, current

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paradigms point to an underlying genetic predisposition in individuals which in turn influences their immune regulation and disease susceptibility.

SSc is a complex disease which occurs in genetically predisposed individuals who have encountered specific environmental exposures and/or other stochastic factors (Agarwal et al., 2008). Candidate gene studies have implicated multiple genetic factors that increase the risk of individuals to develop SSc (recently reviewed in Agarwal et al., 2008) These studies are often limited by small cohorts, the clinical heterogeneity of SSc, and lack of replication. Significant efforts have been made to develop large collaborative cohorts of SSc patients to identify and confirm candidate genes that are SSc susceptibility factors. Furthermore, given that the modest magnitude of the risks of individual genetic polymorphisms, these studies are now exploring how gene-gene interactions might impart greater risk than the individual gene. In the current review we will discuss the recent evidence from candidate gene studies that supports a strong genetic link to SSc.

## Familial Aggregation Studies

Estimates of prevalence and incidence rates of SSc in the general population have ranged from 3.1 to 20.8 per 100,000 and from 0.4 to 1.2 per 100,000, respectively (Medsger, Jr, and Masi, 1971; Steen et al., 1997; Michet, Jr, et al., 1985). More recently, the prevalence of SSc in the United States was estimated to be 24.2 per 100,000 adults with an annual incidence of 1.93 per 100,000 adults (Mayes et al., 2003). Several reports have suggested that familial clustering does occur (McGregor et al., 1988; Englert et al., 1999). Several subsequent studies have utilized large clinical databases to study the heritability of SSc. Using 3 cohorts in the United States with a total of 703 SSc patients, it was reported that SSc recurred in 1.6% of families compared to an estimated population risk of only 0.026% (Arnett et al., 2001; Mayes et al., 2003). These data suggested that siblings had approximately a 15-fold higher risk of SSc and while first-degree relatives had approximately a 13-fold higher risk of SSc (Arnett et al., 2001; Mayes et al., 2003).Hudson et al. (2008) reported that 2.1% and 2.8% recurrence rates in first-degree relatives of SSc patients using a Colombian and a Canadian cohort, respectively. Finally, first- and second-degree relatives of SSc patients were reported to have a relative risk of developing SSc of approximately 3.0 compared to relatives of controls, further demonstrating familial aggregation of SSc (Frech et al., 2010).

Family studies in SSc have also supported the emerging paradigm that autoimmune diseases may share genetic risk factors (Smyth et al., 2008). Using a cross-sectional study of two cohorts, it has recently been reported that first-degree relatives of SSc patients had an increased prevalence of rheumatoid arthritis and autoimmune thyroid disease (Hudson et al., 2008). Another study of 1,071 SSc probands reported that systemic lupus erythematosus and autoimmune thyroid diseases were more frequent in first-degree relatives compared to control families (Arora-Singh et al., 2010). Finally, it has also been reported that first-degree relatives of SSc patients have an increased risk of developing Raynaud's phenomenon and interstitial lung diseases (Frech et al., 2010). Together these studies suggest autoimmune diseases and manifestations of autoimmune diseases may share genetic risk factors. Indeed as will be discussed later in this review, recent candidate gene association studies in SSc further support this hypothesis.

## Human Leukocyte Antigen Associations

The human leukocyte antigen region is the most polymorphic region in the genome. Allelic variation in this region has been associated with a wide-range of autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, and *type 1 diabetes* mellitus (Arnett et al., 1989; Nepom et al., 1986; Laurent and Welsh, 1983). Polymorphisms in the HLA region have also been linked to susceptibility to SSc and these

studies have been reviewed elsewhere (Agarwal et al., 2008; Tan and Arnett, 2000; Tan et al., 2003). Recently, class II HLA associations with the SSc and the SSc-specific autoantibodies (ATA, ACA, and ARA) were investigated in a case-control series of white, black, and Hispanic SSc patients (Arnett et al., 2010). The *HLA-DRB1*1104, DQA1*0501, DQB1*0301* haplotype, and *DQB1* alleles encoding a non-leucine residue at position 26 *(DQB126* epi*) had strong positive associations in whites and Hispanics. In contrast, a negative association of SSc susceptibility in whites and Hispanics was associated with the *HLA-DRB1*0701, DQA1*0201, DQB1*0202* haplotype and *DRB1*1501*. SSc in blacks was associated with *HLA-DRB1*0804, DQA1*0501, DQB1*0301* alleles. Regarding the SSc-associated autoantibodies, *HLA-DPB1*1301* and *HLA-DRB1*1104* showed strong associations with ATA-positivity. *HLA-DQB1*0501* and *DQB1*26 epi* alleles showed the highest association with ACA-positivity. Lastly, *HLA-DRB1*0404, DRB1*11*, and *DQB1*03* alleles (whites and Hispanics) and *DRB1*08* (blacks) were associated with ARA-positivity. These data have recently been confirmed in an independent report from Spain which reported that *HLA-DRB1*11* was also associated with SSc susceptibility while the *HLA-DRB1*0701* had a protective effect (Simeon et al., 2009). These investigators also reported an association of *HLA-DRB1*1104* with ATA-positivity and *HLA-DRB1*01* and *HLA-DRB1*05* alleles with ACA-positivity. These data indicate unique and multiple HLA class II effects in SSc and that there are distinct associations with the SSc-associated *autoantibody* subsets.

Recently, the sequence feature variant type approach (SFVT) has been used to study the HLA region in SSc (Karp et al., 2010). SFVT is a novel method of investigating the HLA region that incorporates functional and structural information known about HLA molecules with allele-based associations to shed light on the biologic nature of the associations with diseases. Accordingly, the SFVT approach confirmed the association between SSc and *HLA-DRB1*1104* in whites and Hispanics. This allele contains the amino acids F at position 26, D at position 28, D at position 70, and Y at position 78 in peptide-binding pocket 4. Interestingly, these amino acids are common between *HLA-DRB1*1104 and HLA-DRB1*0804* in whites and Hispanics, while the *HLA-DRB1* allele is associated with SSc in blacks. These amino acids could explain why two different DRB1 alleles have similar associations with SSc but in different races. Furthermore, these data suggest that the amino acids within the peptide-binding pocket might influence the type of peptides presented to T cells leading to the development of autoimmunity in these SSc patients.

## Candidate Gene Associations

Candidate gene association studies seek to determine specific single nucleotide polymorphisms (SNPs) associated with disease states or specific traits. It has become clear that the contribution of individual genes to the genetic risk for SSc may be quite modest and that multiple loci are involved. In this light, interpretation of genetic association studies in an uncommon and phenotypically heterogeneous disease, such as SSc, must be performed in large cohorts and confirmed in multiple populations to control for genetic heterogeneity, population stratification, and the extent and degree of linkage disequilibrium among genetic markers that vary among populations (Campbell and Rudan, 2002; Lohmueller et al., 2003). Of the candidate gene studies that have demonstrated associations of SNPs, the most intriguing genes seem to center in pathways involved in inflammation and autoimmunity, endothelial function, and extracellular matrix deposition. One theme that also emerges from the list of SSc candidate genes revolves around the concept of shared genetic risk factors for the development of autoimmune diseases. Similar to the familial aggregation studies discussed above, many of the genes that are associated with SSc susceptibility are also associated with other autoimmune diseases. For example, *PTPN22* has been associated with SSc susceptibility in two large studies and has also been associated with the development of

type 1 diabetes mellitus, RA, and SLE (Begovich et al., 2004; Onengut-Gumuscu et al., 2004; Orozco et al., 2005; Gourh et al., 2006). These studies implicate dysregulation of common immune pathways due to polymorphisms in several genes in the development of a variety of autoimmune diseases. Many of these associations have recently been reviewed (Agarwal et al., 2008). In the current review we have selected several of these candidate genes that have either been confirmed or have particular relevance to the pathogenesis of SSc and autoimmune diseases (Table 1).

## Connective Tissue Growth Factor (CTGF)

CTGF induces proliferation, extracellular matrix production, and chemotaxis of mesenchymal cells, which are processes central to fibrosis (Leask and Abraham, 2006; Igarashi et al., 1996). SSc skin biopsies as well as cultured fibroblasts from SSc patients contain high levels of CTGF relative to healthy controls (Igarashi et al., 1996; Igarashi et al., 1995; Leask et al., 2001). Mice engineered to over-express CTGF under the control of a fibroblast specific promoter develop accelerated fibrosis of the skin, lung, kidney, and vasculature (Sonnylal et al., 2010). Using two independent cohorts totaling 500 SSc patients and 500 healthy controls, an association of the G-allele at position −945 of *CTGF* with SSc susceptibility was identified (Fonseca et al., 2007). These data were confirmed in a Japanese cohort, and most recently other SNPs in the *CTGF* gene were found to be associated with SSc in a French cohort (Kawaguchi et al., 2008; Granel et al., 2010). Interestingly, in the Japanese study 46% of the patients had diffuse disease, 48% had interstitial lung disease, and 31% ATA+ (Kawaguchi et al., 2008). Subsequent analyses demonstrated that the association is primarily in patients within these groups. Despite these reports, two additional large studies were not able to replicate the association of the *CTGF −945* promoter polymorphism with SSc (Gourh et al., 2008; Rueda et al., 2009b). The North American cohort of 749 SSc patients (including 257 with diffuse SSc and 124 ATA+ patients) and 429 controls and a European study with 1,180 SSc patients failed to confirm this association (Gourh et al., 2008; Rueda et al., 2009b). Given the importance of CTGF in SSc and the intriguing observation of stronger associations in the diffuse and ATA+ patients, additional studies are needed to clarify these discrepancies.

## Signal Transducer and Activators of Transcription-4 (STAT4)

Cytokines regulate cellular behavior through binding of their receptors, which leads to the activation of signal transducers and activators of transcription (STATs). The IL-12 and IL-23 receptors signal through STAT4 and may also be activated in response to type I interferon receptors (Watford et al., 2004). STAT4 promotes T helper 1 (Th1) cell development and is a negative regulator for Th2 cell differentiation (Watford et al., 2004). *STAT4* polymorphisms have been associated with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Remmers et al., 2007).

Several studies have now demonstrated that *STAT4* polymorphisms are also associated with SSc. A comparison of 1,317 SSc patients and 3,113 healthy controls in five European cohorts, an association of STAT4 rs7574865 T allele with limited SSc but not diffuse SSc was reported (Rueda et al., 2009a). The association of *STAT4 rs*7574865 with limited SSc was subsequently confirmed in a Japanese cohort, and which also demonstrated an association with the ACA positivity (Tsuchiya et al., 2009). Two additional reports have confirmed the association of *STAT4* with SSc susceptibility in both limited and diffuse SSc (Dieude et al., 2009b; Gourh et al., 2009a). Together these studies identify and confirm that *STAT4* is an important genetic risk factor for the development of SSc.

### Interferon regulatory factor 5 (IRF5)

Type I interferons (IFN) are potent regulators of innate and adaptive immunity and multiple lines of evidence suggest that type I IFN are important in the pathogenesis of SLE (Blanco et al., 2001; Baechler et al., 2003; Agrawal et al., 2009). IRF5 is involved in toll-like receptor signaling, and is a critical transcription factor in the activation of IFN associated genes; *IRF5* polymorphisms have been associated with SLE susceptibility (Graham et al., 2006; Graham et al., 2007). Similar to SLE, the type I IFN signature is observed in peripheral blood and skin of SSc patients (Tan et al., 2006; Gardner et al., 2006). Therefore it was of interest to determine if *IRF5* polymorphisms are also associated with SSc.

The association of *IRF5* polymorphisms with SSc susceptibility was first reported in a discovery cohort of 427 SSc patients and a confirmatory cohort of 454 SSc patients (Dieude et al., 2009a). The association was noted with the *IRF5* rs2004640 functional polymorphism with limited and diffuse SSc as well as ATA+ and ACA+ SSc. Multivariate analyses suggested that the association was strongest in the ATA+ group and in patients with interstitial lung disease. A study using a Japanese cohort of SSc patients and unpublished data from our group in collaboration with multiple European groups have confirmed the association *IRF5* polymorphisms with SSc susceptibility (Ito et al., 2009). The consistent associations of *IRF5* with SSc susceptibility places *IRF5* as an important gene for the SSc development.

### B cell scaffold protein with ankryn repeats (BANK1)

The importance of B cells in SSc pathogenesis is best supported by the presence of multiple SSc-associated autoantibodies (Reveille et al., 2001; Arnett et al., 2006). BANK1 is a B cell adaptor protein that links the B cell receptor (BCR) to downstream kinases including Lyn. Polymorphisms in *BANK1* have been associated with SLE and RA (Orozco et al., 2009; Kozyrev et al., 2008). Similar to SLE, these BANK1 SNPs have now been associated with SSc susceptibility in a large study of 2,380 white SSc patients and 3,270 controls (Rueda et al., 2010). An association with the rs10516487 G and rs17266594 T alleles was observed, which was strongest in the diffuse SSc and ATA+ groups. These data were confirmed by other studies, suggesting that BANK1 polymorphisms are most strongly associated with the diffuse SSc subset (Dieude et al., 2009c).

### FAM167A-BLK region

Two genome wide association studies have identified the *FAM167A-BLK* (previously referred to as *C8orf13-BLK)* region of chromosome 8p23.1 as a susceptibility locus for SLE (Hom et al., 2008; Harley et al., 2008). B lymphoid kinase (Blk) is a Src kinase that is expressed in thymocytes (Dymecki et al., 1992). Blk transduces signals downstream of the B cell receptor (Tretter et al., 2003). Using two independent case-control series totaling 1,416 SSc patients, we recently demonstrated an association of two variants in the *FAM167A-BLK* region with limited and diffuse SSc (Gourh et al., 2010a). No association with ATA+ patients was observed. However, rs2736340 was associated with ACA+ patients and rs13277113 was associated with both ACA+ and ARA+ patients. Functional studies using microarray expression profiling of peripheral blood demonstrated alterations in B cell receptor pathways in patients grouped according to their genotype. The association of SNPs in the *FAM167A-BLK* region has also been reported in a cohort of 309 Japanese SSc patients (Ito et al., 2010). This study also found an association with the rs13277113 variant, with a tendency towards the association in the ACA+ and the diffuse SSc patients.

### T-box expressed in T cells (T-bet, TBX21)

The *TBX21* gene encodes for the Th1 transcription factor, T-bet (Szabo et al., 2000). Initially identified in CD4+ T cells where it is the critical transcription factor for the development of Th1 cells, it has also subsequently been shown to regulate dendritic cell and B cell function (Glimcher et al., 2007). Mice lacking T-bet develop more severe dermal fibrosis in the mouse models of dermal fibrosis (Lakos et al., 2006; Aliprantis et al., 2007). Given these observations, it was of interest to determine if *TBX21* SNPs were associated with SSc. In a recent study involving two independent cohorts of North American White SSc patients and controls, the rs11650354 variant of *TBX21* was associated with SSc susceptibility with a recessive pattern of inheritance (Gourh et al., 2009a). The association was observed in limited and diffuse SSc patients as well as the ACA+, ATA+, and ARA+ subsets. In addition, plasma from SSc patients with the susceptible "TT" genotype of the *TBX21* demonstrated elevated levels of Th2 cytokines. In contrast, the "CC" genotype was associated with the type I IFN pathways by whole genome expression analysis. These data must be replicated in additional cohorts.

### Tumor Necrosis Factor Superfamily-4 (TNFSF4)

TNFSF4 encodes for the protein OX40 ligand (OX40L) which is expressed on dendritic cells, macrophages, B cells, T cells, as well as non-immune cells such as endothelial cells (Redmond et al., 2009). OX40L binds to OX-40 on T cells, where it imparts a costimulatory signal to the T cell (Redmond et al., 2009). Polymorphisms in *TNFSF4* gene region have been associated with SLE susceptibility (Cunninghame Graham et al., 2008; Chang et al., 2009; Delgado-Vega et al., 2009). Using a cohort of 1,059 North American Caucasian SSc cases and 698 controls, several polymorphisms in the *TNFSF4* gene region were associated with limited and diffuse SSc susceptibility. Furthermore, specific SNPs were associated with ATA-positive, ACA-positive, and ARA-positive subjects (Gourh et al., 2010b). Although these observations were made in a large cohort, they must be confirmed in other cohorts.

### Other intriguing candidate genes

Reviewing the published literature of candidate gene studies, it has become clear that many individual genes contribute to the genetic risk for SSc with modest odds ratios. In addition to the above list of genes, several other genes, from pathways involved in inflammation and autoimmunity, endothelial function, and extracellular matrix production, have also been reported to be associated with SSc. However, these genes have yet to be confirmed in other cohorts. For example, polymorphisms in *IL23R*, a gene that encodes for the IL-23 receptor (a key factor in the Th17 pathway) was found to be associated with ATA-positive SSc patients (Agarwal et al., 2009). Interestingly, the association also was noted in those patients with pulmonary hypertension. Recently, polymorphisms in *KCNA5*, which encodes for a potassium voltage-gated channel, were associated with SSc and with pulmonary hypertension as well (Wipff et al., 2010). Another report recently demonstrated an association of a functional polymorphism of *FAS* with SSc susceptibility in a large cohort of SSc patients from multiple centers, confirming a previous study in Italian SSc patients (Liakouli et al., 2009; Broen et al., 2009). Finally a recent study has suggested that polymorphisms in *MMP12*, which encodes for the matrix degrading enzyme, matrix metalloproteinase-12, were demonstrated to be associated with SSc susceptibility (Manetti et al., 2010). While these are intriguing candidate genes, confirmatory studies are needed.

## Genome-wide Associations Studies in Scleroderma

The use of genome-wide association studies (GWAS) has resulted in significant advances in our understanding of the genetics of complex genetic diseases. Genome-wide association studies allow for the analysis of up to 1 million SNPs throughout the genome. A recent

review noted that over 600 genome-wide association studies in 150 distinct diseases and traits have been published (Manolio et al., 2010). Genome-wide association studies have been particularly productive with regards to autoimmune diseases, shedding light on the genetic background of diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and Crohn's disease (Plenge et al., 2007; Stahl et al., 2010; Harley et al., 2008; Burton et al., 2007; Duerr et al., 2006). Two genome-wide association studies have recently been published in SSc (Zhou et al., 2009; Radstake et al., 2010). The first used a small discovery cohort of Korean patients to identify an association of SNPs in the region of HLA-DPB1 and DPB2 with SSc susceptibility. Fine mapping of the region confirmed this association, particularly in the ATA+ subset. Finally these SNPs were subsequently confirmed in a large group of SSc patients and controls from a United States cohort. Unfortunately, the discovery phase of this study was underpowered to detect SNPs associated with SSc outside of the HLA region.

More recently, a genome-wide association study was performed in 2,296 SSc patients and 5,171 matched controls from the United States, Spain, Germany, and the Netherlands. As expected, the strongest association was in the HLA region at the 6p21 locus. Outside of the HLA region, 5 gene polymorphisms were observed to be associated with SSc at a p-value of less than $10^{-7}$. Two genes, *TNPO3-IRF5* and *STAT4*, had previously been reported (Dieude et al., 2009a; Dieude et al., 2009b; Gourh et al., 2009a; Rueda et al., 2009a). Among the other three genes (*CD247, CDH7*, and *EXOC2-IRF4*) only *CD247* was independently confirmed in a replication cohort consisting of 2,753 SSc patients and 4,659 controls. CD247, also known as the CD3 zeta, is part of the T cell receptor complex (Call and Wucherpfennig, 2004). Upon T cell activation, CD247 is phosphorylated and subsequently acts as a docking site for ZAP-70, a critical *tyrosine kinase* involved in T cell activation. Interestingly a *SNP* in the 3′-UTR region of CD247 has been associated with susceptibility to SLE (Warchol et al., 2009). As with all genome-wide association studies, the association with CD247 needs to be followed up with fine mapping and/or sequencing of the CD247 gene as well as functional studies. However, this study highlights the usefulness of the genome-wide association studies in their ability to identify novel genes and pathways that had not previously been identified with a specific disease.

## Conclusions

From the published literature it is clear that scleroderma is indeed a complex genetic disease. These genetic studies in SSc also have provided major insights into the pathogenesis of SSc, pointing to immune dysregulation at the center of the development of SSc. A wealth of data is yet to be uncovered in these studies, particularly in the recent genome-wide association studies, and they are only the beginning of the process. We must increase our understanding of how these polymorphisms lead to SSc and further our understanding of the complex gene-gene and gene-environment interactions as well. Functional studies investigating the biological significance of the genetic variants are essential to determine whether these associations are in fact causal. Lastly, efforts must also focus on translating these findings into the management of SSc patients. In particular, recent advances in the genetics of SSc may ultimately lead to novel approaches to diagnosis, prognosis, and treatments of SSc.

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**Table 1**

Candidate Gene Associations with Scleroderma Susceptibility

| Gene | Reference | Single/Multiple Cohorts | Number of Subjects | | Independent Replication | |
|---|---|---|---|---|---|---|
| | | | SSc | Controls | Yes | No |
| *PTPN22* | Gourh et al., 2006 | Multiple | 1120 | 816 | Dieude et al., 2008 | Balada et al., 2006; Wipff et al., 2006 |
| *BANK1* | Rueda et al., 2010 | Multiple | 2380 | 3270 | Dieude et al., 2009c | - |
| *CTGF* | Fonseca et al., 2007 | Multiple | 500 | 500 | Kawaguchi et al., 2009; Granel et al., 2010 | Gourh et al., 2008; Rueda et al.,2009c |
| *FAM167A-BLK* | Gourh et al., 2010a | Multiple | 1639 | 1416 | Ito et al., 2010 | - |
| *IL23R* | Agarwal et al., 2009 | Single | 1402 | 1038 | - | Farago et al., 2007; Rueda et al., 2009b |
| *IRF5* | Dieude et al., 2009a | Multiple | 881 | 760 | Ito et al., 2009 | - |
| *STAT4* | Rueda et al., 2009a | Multiple | 1317 | 3113 | Dieude et al., 2009b; Tsuchiya et al., 2009; Gourh et al., 2009a | - |
| *FAS* | Liakouli et al., 2009 | Single | 350 | 232 | Broen et al., 2009 | |
| *TBX21* | Gourh et al., 2009a | Multiple | 1402 | 1038 | - | - |
| *TNFSF4* | Gourh et al., 2010b | Single | 1059 | 698 | - | - |
| *KCNA5* | Wipff et al., 2010 | Multiple | 1576 | 1033 | - | - |

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