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Full Length Research Paper

Genome examine meta-examination in systemic lupus erythematosus solid linkage with loci 6p22.3-p21.1 and 2q31.1-34

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The genetic contribution to development of system lupus erythematosus (SLE) is well established. Several genome scan studies have identified putative susceptibility loci to SLE. However; they have shown high level of inconsistency. Genome search meta-analysis (GSMA) which is a non-parametric method is used to identify genetic regions that rank high on average in terms of linkage statistics across genome scan studies. The validity of GSMA was proven when applied on various complex diseases. We applied the GSMA on 16 genome-wide scans of SLE in various ethnicities published from 1996 - 2008. The SLE GSMA resulted in identifying a total of 4 bins lie above 95% confidence level (P = 0.05) of which 2 bins were above 99% confidence level (P = 0.01); bins 6.2 (6p22.3-p21.1, (*Psumrnk* = 0.0054), 2.8 (2q31.1-q34) (*Psumrnk* = 0.0091), 16.2 (16p12.3-q12.2) (*Psumrnk* = 0.0386) and 6.1 (6p25.3-p22.3) (*Psumrnk* = 0.0419). The highest summed rank was observed at locus 6p22.3-p21.1 surrounding the HLA region and 2q31.1-q34 which locates various genes that were linked to autoimmunity such as CTLA4. In addition, GSMA identified several other putative regions that may contribute to SLE susceptibility. The application of the GSMA technique to 16 SLE genome-wide linkage studies confirmed linkage to loci 6p22.3-p21.1 and 2q31.1-q34.

Key words: SLE, linkage, genome scan, meta-analysis.

INTRODUCTION

Systemic lupus erythematosus (SLE, also called Lupus; MIM 152700) is a complex systemic autoimmune disease characterized by multiorgan pathology. The severity of the disease, the spectrum of the clinical manifestations and laboratory parameters differ among various ethnic groups where some ethnic groups were shown to have a very early onset of the disease and more severe than others (Hochberg and Petri, 1993; Lawrence et al., 1998). The etiology of SLE is very versatile, involving both envi-ronmental and genetic factors and probably also a synergistic relationship between these factors. Genetic factors are likely to play a significant role in susceptibility to SLE in determining the disease expression Wakeland et al. (2001).

The genetic involvement in SLE was studied in various various levels; the candidate gene association level, the genome-wide gene expression level and the genome scan linkage level. In the past few years several genes were implicated in human SLE such as; HLA Class II DRB and DQB alleles (Arnett and Reveille, 1992) and early components of the complement cascade (e.g. C1q, C3, C4A, C4B) Sestak et al. (2005). Recently a genome-wide gene expression profiling using micro-arrays was used by 4 independent groups to identify patterns of gene expression that distinguished most SLE patients from healthy controls (Baechler et al., 2003; Bennett et al., 2003; Han, 2003; Rus, 2002). In addition, several genome scans efforts in families enriched for SLE have identified several putative sus-ceptibility loci (Wakeland et al., 2001; Harley et al., 1998; Cantor, 2004; Gaffney et al., 1998; Gaffney PM et al., 2000; Gray-McGuire et al., 2000; Johansson et al., 2004; Koskenmies et al., 2004; Lindqvist et al., 2000; Moser et al., 1998; Nath et al., 2004a, b; Shai et al., 1999); however, there were always inconsistencies

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among these studies. This could be reasoned for the inadequate studied sample size which reduces the study power and the heterogeneity in the sample genetic background and the analytical method used. Genomescan Meta- analysis (GSMA) is been developed and yielded useful applications for genome scans of several complex diseases (Levinson et al., 2003; Lewis et al., 2003; Van Heel et al., 2004; Demenais et al., 2003; Chiodini BD and Lewis, 2003). GSMA allowed pooling the raw genotype linkage data across several studies, providing greater power to identify regions that showed only weak evidence for linkage in individual studies. The GSMA method is based on several studies of genetically diverse populations. Results from the meta-analysis should direct further studies toward single nucleotide polymorphism association (SNP) studies and positional cloning of SLE development genes.

MATERIAL AND METHODS

The search engines used to screen for the genome scan studies were the NIH PubMed site (http://www.ncbi.nlm.nih.gov/pubmed) and Genetic association database (http://geneticassociationdb.nih.gov/). The following initial keywords were used for the search: "genome-wide screen," "genome-wide scan," "genomic scan" and "genome-wide search." combined with SLE. Then genome scan database of SLE was established using all published studies on families with SLE. This database contained the following information: publication details (author, title, source, year of study); details of study population (ethnic background and studied population); sample-size details (number of probands, individuals, families and sib pairs); genotyping methods (type of markers, number of markers, average polymorphism information content, average spacing of markers); statistical methods and results obtained (All results were included including the positive markers concerning the individual threshold, with localization and marker term; maximum LOD score or *Z* score, nonparametric LOD score NPL and minimum P value) in addition to the markers with lower statistical value than the threshold. The database was checked by examination of both the discussion section and the reference list of the publications allowing the completeness of the database of genome scans.

All potentially eligible articles (were scrutinized for eligibility and potential overlap of the studied populations. Studies done in the same institution were checked thoroughly. In case of overlap, only the largest study was retained, in order to avoid duplication of data. Eligible studies were those that had performed whole genome scans for strictly defined SLE. Studies with a minimum of 100 microsatellite markers were selected regardless of the statistical analytical method and software employed. In the studies or subsets of subjects with data derived only for specific chromosomes or specific chromosomal regions were excluded. Twenty two genome scan articles were recovered in our search and used to establish the database. However, after applying our exclusion criteria GSMA technique was performed to only 16 SLE genome-wide linkage studies using 10,000 simulations. Data extraction was done independently and discrepancies, if any were carefully sorted out.

Genome scans meta-analysis

Several strategies are available for meta-analysis of linkage data. The approach selected here is the rank-based genome-scan meta-analysis (GSMA) method described by Wise et al (1999) and further generalized by Levinson DF et al. (2003). The GSMA method is widely used now and has already yielded useful applications for genome scans of several diseases (Shai et al., 1999; Levinson et al., 2003; Lewis et al., 2003; Van Heel et al., 2004; Demenais et al., 2003; Chiodini and Lewis, 2003) . With this method, the autosomal chromosomes were divided into 120 of 30 cM bins defined by Genethon markers (CEPH-Genethon Integrated Map web site http://www.cephb-genethon-map.htm) or the Marshfield map (http://www.marshfieldclinic.org/search-/genetics). Each marker was placed within one of these bins on the basis of its location on the Genethon or Marshfield map.

For each genome scan, all bins that showed significant or insignificant results were included. However, the most significant result of the test statistic obtained within the bin was used. Test statistics may include lod score, maximum logarithm of odds score (MLS), nonparametric linkage score (NLP), z-statistics and P- values, depending on the mode of analysis of the linkage data (Terwilliger JD and Ott, 1994). Each bin was assigned from each study a within- study rank based on the maximum linkage score within the bin. The average rank across studies was then computed for each bin (Ravg). Ravg is the average of bin's within- study rank or weighted ranks across all studies. All selected studies were weighted by the square root of the affected cases.

RESULTS

Reach results of SLE genome scan

Twenty two genome scan articles were recovered in our search and used to establish the database (Cantor, 2004; Gaffney et al., 1998; Gaffney et al., 2000; Gray-McGuire et al., 2000; Johansson et al., 2004; Koskenmies et al., 2004; Lindqvist et al., 2000; Moser et al., 1998; Shai R et al., 1999; Nath et al., 2004a, b, 2002, 2001; Rao et al., 2001; Namjou B et al., 2002; Namjou B et al., 2005; Scofield RH et al., 2003; Johansson et al. 2006; Xing et al., 2005, 2007, Slegen et al., 2008). The database included Authors, institution in which the study accomplished, year of publication, number and types of pedigrees, number of affected cases, ethnicities, number of markers used, linkage results. Seven articles were excluded (Moser et al., 1998; Tsao, 1997; Nath et al., 2004, 2002, 2001; Namjou et al., 2005; Johansson et al., 2006) as some had overlap in the screened families and others scanned only specific chromosomal region or detailed results were not included in their publication.

GSMA

An average of 342 microsatellite markers was ge-notyped across the 16 studies. In all studies around 184 markers showed significant linkage with SLE either by $p < 0.1$ or LOD > 1 or NPL > 2 of which 19% were overlapped between the various genome scan studies. For each chromosome, the summed ranks for each bin, the sumrank p-value and the OrderRank p-value in un-weighted and weighted analyses are shown in Table 1

Table 1. Regions with sumrank < 0.1 and < 0.05 (a) in both unweighted and weighted GSMA analysis.

Bin	Cytogenetic location	SumRank	SumRank p-value	OrderRank p-value
Unweighted analysis				
2.8	2q31.1-p34	687[a]	0.00476578	0.311569
6.2	6p22.3-p21.1	669.5[a]	0.00774341	0.111489
6.1	6p25.3-p22.3	626.5[a]	0.0427578	0.676432
16.2	16p12.3-q12.2	625.5[a]	0.0451052	0.461654
1.6	1p13.3-q23.3	623	0.0521986	0.354765
1.9	1q32.3-q43	616	0.077092	0.569043
5.1	5pter-p15.1	615.5	0.0789788	0.380562
4.7	4q32.1-q34.3	614.5	0.0824486	0.244076
20.3	20p11.22-q13.13	612.5	0.0891591	0.181382
Weighted analysis				
6.2	6p22.3-p21.1	697.251[a]	0.00540789	0.346065
2.8	2q31.1-q34	684.2[a]	0.00916315	0.146185
16.2	16p12.3-q12.2	644.435[a]	0.0386578	0.59584
6.1	6p25.3-p22.3	641.938[a]	0.0419368	0.39776
1.6	1p13.3-q23.3	631.127	0.058317	0.464554
1.9	1q32.3-q43	628.209	0.0635302	0.339366
6.3	6p21.1-q15	621.166	0.0776381	0.368663
20.3	20p11.22-q13.13	615.75	0.0902157	0.360864
2.1	2p25.3-p25.1	612.513	0.098617	0.30057

and Figures 1A and B, respectively. In the unweighted analysis, we observed 9 bins with a summed rank >612 with a significant p-value < 0.1, compared with 4 bins that had significant point-wise sum rank p-value < 0.05. (bin 6.2 sumrank p-value 0.0047, bin 2.8 sumrank p-value 0.0077, bin 16.2 sumrank p-value 0.042 and bin 6.1 sumrank p-value 0.045).

When the ranks from each study were weighted by square root of the affected cases, the summed ranks for all loci identified by unweighted analyses remained the most significant regions with minor differences in the sumrank p-value (bin 6.2 sumrank *p*-values 0.0054, bin 2.8 sumrank p-value 0.0091, bin 16.2 sumrank p-value 0.0386 and bin 6.1 sumrank p- value 0.0419) and variation in the ranking position (Table 1).

The other regions identified by weighted analysis that had a summed rank of > 612 with a significant sumrank p-value < 0.1 were bin 1.6 (1p13.3-q23.3), bin 1.9 (1q32.3-q43), bin 6.3 (6p21.1-p15), bin 20.3 (20p11.22-q13.13) and bin 2.1 (2p25.3-25.1) (Table 1). While the unweighted analysis has identified bins 5.1 (5pter-p15.1), bin 4.7 (4q32.1-q34.3) in addition to bins 1.6, 1.9 and 20.3 that had a significant sumrank p-value of < 0.1 (Table 1).

DISCUSSION

SLE is one of the complex diseases that have been intensively studies by various groups using genome scan searching for putative susceptibility loci. Although several susceptibility loci have been identified independently, most linkage effects remain inconsistent across these studies. GSMA technique, which is based on several studies of genetically diverse populations, used in pooling the data of the various genome scans has added power to linkage analysis by identifying regions that showed only weak evidence for linkage in individual studies.

Here we have applied GSMA technique to 16 SLE genome-wide linkage studies using 10,000 simulations which confirmed SLE susceptibility linkage to 4 bins representing chromosome 6p25.3-p21.1 (bins 6.1 and 6.2), 2q31.1-34 (bin 2.8) and 16p12.3-q12.2 (bin 16.2) at sumrank p < 0.05. Two of which (bins 6.2 and 2.8) were ranked above 99% confidence level at p < 0.01. Weighted and unweighted analyses gave largely similar results, except that the rank of the bins has shifted in the top 4 ranks. Five more loci were ranked at sumrank p < 0.1. Our result is close to what was recently published by

Lee et al. (2005) on meta-analysis for susceptibility loci in systemic lupus erythematosus, which was limited to nine genome scan studies. We replicated their results when performing GSMA to the same 9 genome scans data they used (Cantor, 2004; Gaffney et al., 1998; Gaffney et al., 2000; Gray-McGuire et al., 2000; Johansson et al., 2004; Koskenmies et al., 2004; Lindqvist et al., 2000; Nath et al., 2004b; Shai et al., 1999). However, when including the data from an additional five genome scans (Nath et al., 2004a; Namjou et al., 2002; Scofield et al., 2003; Johansson et al., 2006;

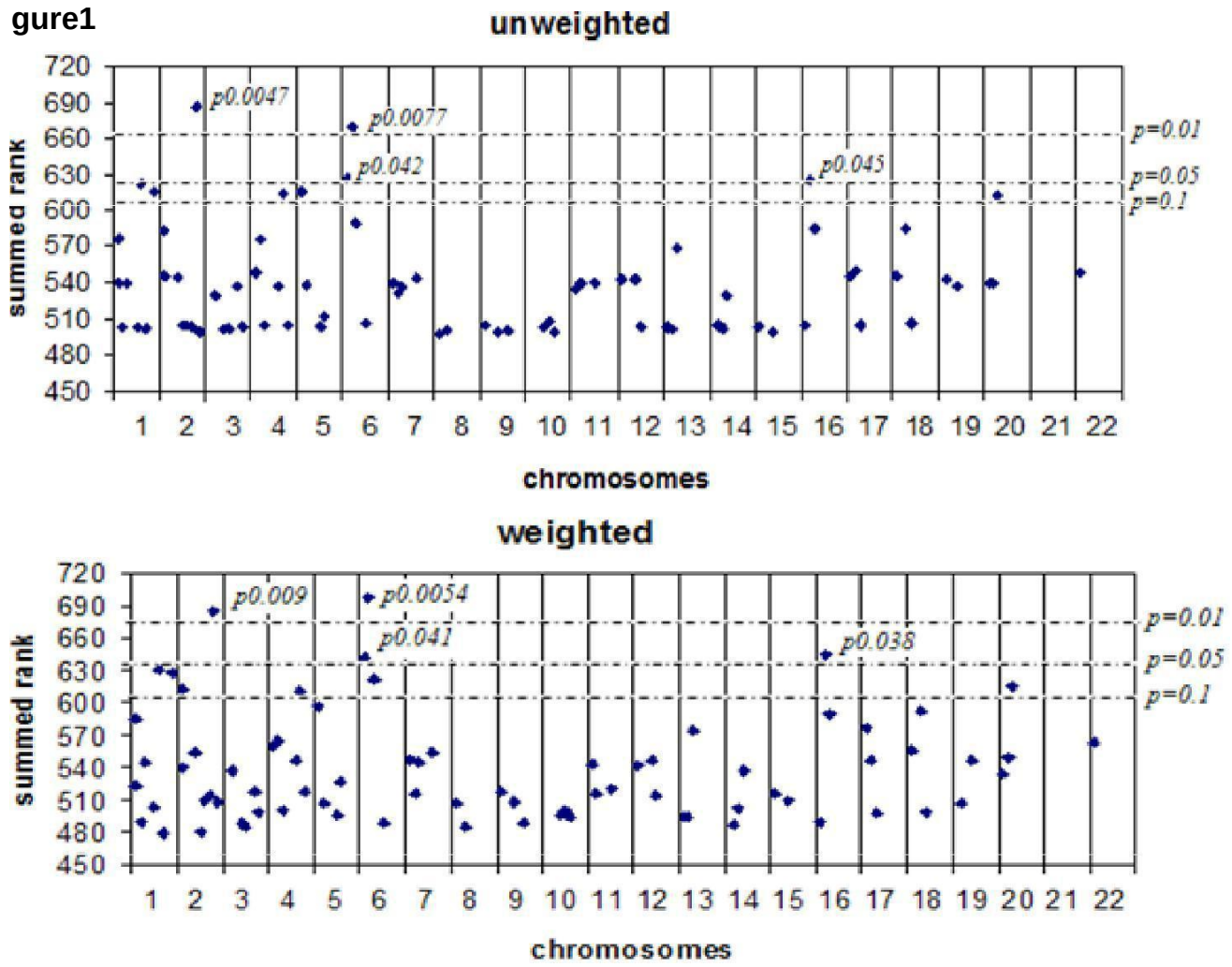

Figure 1. Results from the GSMA, the SumRanks for each bin for the unweighted and the weighted analysis (weighted by the square root of the number of affected cases in each study). Significant levels corresponding to 99% (SumRank p< 0.01), 95% (SumRank p < 0.05), and 90% (SumRank p< 0.1) are shown by horizontal lines.

Xing et al., 2005) the rank of some loci has altered.

Although bin 6.2 remains the top ranked in both analysis, bin 2.8 shifted to the second position when it was ranked in the fourth position in Lee's meta-analysis. While bin 16.2 was in the third rank in our meta-analysis, it had the second rank in Lee's (Table 2).

Forabosco et al. (2006) has also performed a meta-analysis study on SLE; their results showed strong evidence of linkage in two bins 20.3 and 6.3 representing loci 20p11.22-q13.13 and 6p21.1-p15. We have also identified these two bins with significant linkage at sumrank p < 0.1 in the weighted analysis. Table 2 is used to compare the ranking of the bins that showed evidence of linkage in the three meta-analysis performed on SLE.

The locus that has the strong linkage evidence 6p25.3-p21.1 (bin 6.1 and 6.2) is surrounding the HLA region. Notably, the 2q31.1-34 locus (bin 2.8) identified herein has evidence for linkage to SLE with p-value as 0.0001, 0.0009 and 0.02 in three of the screened genome scan analysis of Scofield et al. (2003), Namjou et al. (2002) and Cantor et al. (2004) respectively and in one of the excluded genome scans of Moser et al. (1998) which showed evidence of linkage at LOD 2.09. This locus was also shown to be linked with other autoimmune diseases such as Osteoarthritis Lee et al. (2006). When we screen this locus for potential genes that could be related to autoimmunity we have found several such as CD28 antigen (MIM;186760), which is Involved in T-cell activation, the induction of cell proliferation and cytokine production and promotion of T- cell survival; Auto antigen La (SSB) (MIM;109090), which was originally defined by its reactivity with auto antibodies from patients with Sjogren syndrome and systemic lupus erythematosus; Engulfment adaptor PTB domain containing (GULP1) (MIM 608165), which is involved in the clearance of cells

Table 2. Comparison between the three SLE GSMA (weighted) in terms of the ranking of chromosomal region that showed evidence of linkage at $p < 0.1$.

Bin	Cytogenetic band	AlFadhli *Psr*; (Rank)	Lee and Nath*Psr*; (Rank)	Forabosco et al. *Psr*; (Rank)
6.2	6p22.3-p21.1	0.00540789 (1)	0.00002 (1)	0.0099 (4)
2.8	2q31.1-q34	0.00916315 (2)	0.0033 (4)	0.0268 (5)
16.2	16p12.3-q12.2	0.0386578 (3)	0.00017 (2)	0.0087 (3)
6.1	6p25.3-p22.3	0.0419368 (4)	0.01588 (6)	NS*
1.6	1p13.3-q23.3	0.058317 (5)	0.02655 (7)	NS*
1.9	1q32.3-q43	0.0635302 (6)	0.07023 (8)	NS*
6.3	6p21.1-q15	0.0776381 (7)	0.00103 (3)	0.0056 (2)
20.3	20p11.22-q13.13	0.0902157 (8)	0.01254 (5)	0.0044 (1)
2.1	2p25.3-p25.1	0.098617 (9)	0.07825 (9)	NS*

*NS; non significant.

undergoing apoptosis; Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), this gene is a member of the immunoglobulin superfamily and encodes a protein which transmits an inhibitory signal to T cells. Mutations in this gene have been associated with insulin-dependent diabetes mellitus, Graves disease, Hashimoto thyroiditis, celiac disease, systemic lupus erythematosus, thyroid-associated orbitopathy and other autoimmune diseases and Inducible T-cell co-stimulator precursor (ICOS) (MIM 604558) . The protein encoded by this gene belongs to the CD28 and CTLA-4 cell-surface receptor family. It forms homodimers and plays an important role in cell-cell signaling, immune responses and regulation of cell proliferation.

Locus 16p12.3-q12.2 (bin 16.2) was also identified as the most significant loci in genome scan meta- analysis of Rheumatoid arthritis (RA), inflammatory bowel disease Fisher et al., 2003. CARD15/Nod2 gene which is located in this locus was proven to be associated with Crohn's disease Oostenbrug et al. (2006).

In conclusion, the GSMA results we are presenting here with the other two published GSMA show no contradic-tion, however, it emphasizes the complexity of SLE and the polygenic characteristics of this disease. We believe that the ranking of loci 6.2, 6.3, 16.2, 2.8 or 20.3 is not the major issue but the involvement of all of these loci provides evidence that there is or are complex pathway(s) that leads to various manifestation of SLE. All these loci have to be taken in consideration when further stratify SLE cases when doing association study to a denser level.

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REFERENCES:

Arnett FC, Reveille JD (1992). Genetics of systemic lupus erythematosus. Rheum. Dis. Clin. North. Am. 18(4): 865-892.

Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, Shark KB, Grande WJ, Hughes KM, Kapur V, Gregersen PK, Behrens TW (2003). Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus, Proc. Natl. Acad. Sci. U. S. A. 100(5): 2610–2615.

Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, Pascual V (2003). Interferon and granulopoiesis signatures in systemic lupus erythematosus blood, J. Exp. Med. 197(6): 711– 723.

Cantor RM, Yuan J, Napier S, Kono N, Grossman JM, Hahn BH, Tsao BP (2004). 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: 3203–3210.

Chiodini BD, Lewis CM (2003). Meta-analysis of 4 coronary heart disease genome-wide linkage studies confirms a susceptibility locus on chromosome3q.*Arterioscler Thromb Vasc Biol*. 23(10): 1863-1868.

Demenais F, Kanninen T, Lindgren CM, Wiltshire S, Gaget S, Dandrieux C, Almgren P, Sjogren M, Hattersley A, Dina C, Tuomi T, McCarthy MI, Froguel P, Groop LC (2003). A meta-analysis of four European genome screens (GIFT Consortium) shows evidence for a novel region on chromosome 17p11.2-q22 linked to type 2 diabetes. Hum. Mol. Genet. 12(15): 1865-1873.

Fisher SA, Lanchbury JS, Lewis CM. (2003). Meta-analysis of four rheumatoid arthritis genome-wide linkage studies: confirmation of a susceptibility locus on chromosome 16. Arthritis Rheum. 48(5): 1200-1206.

Forabosco P, Gorman JD, Cleveland C, Kelly JA, Fisher SA, Ortmann WA, Johansson C, Johanneson B, Moser KL, Gaffney PM, Tsao BP, Cantor RM, Alarcon-Riquelme ME, Behrens TW, Harley JB, Lewis CM, Criswell LA (2006). Meta-analysis of genome-wide linkage studies of systemic lupus erythematosus. Genes. Immun. Oct. 7(7): 609-614.

Gaffney PM, Kearns GM, Shark KB, Ortmann WA, Selby SA, Malmgren ML, Rohlf KE, Ockenden TC, Messner RP, King RA, Rich SS, Behrens TW (1998). A genome-wide search for susceptibility genes in human systemic lupus erythematosus sibpair families. Proc Natl Acad Sci USA 95:14875–14879.

Gaffney PM, Ortmann WA, Selby SA, Shark KB, Ockenden TC, Rohlf KE, Walgrave NL, Boyum WP, Malmgren ML, Miller ME, Kearns GM, Messner RP, King RA, Rich SS, Behrens TW (2000). Genome screening in human systemic lupus erythematosus: results from a second Minnesota cohort and combined analyses of 187 sib-pair families. Am. J. Hum. Genet. 66: 547–556.

G.M. Han, S.L. Chen, N. Shen, S. Ye, C.D. Bao and Y.Y. Gu (2003). Analysis of gene expression profiles in human systemic lupus erythematosus using oligonucleotide microarray, Genes Immun.4(3): 177–186.

Gray-McGuire C, Moser KL, Gaffney PM, Kelly J, Yu H, Olson JM, Jedrey CM, Jacobs KB, Kimberly RP, Neas BR, Rich SS, Behrens

TW, Harley JB (2000). Genome scan of human systemic lupus erythematosus by regression modeling: evidence of linkage and epistasis at 4p16–15.2. Am J. Hum. Genet. 67: 1460–1469.
Harley JB, Moser KL, Gaffney PM, Behrens TW (1998). The genetics of human systemic lupus erythematosus. Curr. Opin. Immunol, 10(6): 690-696.
Hochberg MC, Petri M (1993). Clinical features of systemic lupus erythematosus. Curr. Opin. Rheumatol. 5(5): 575-586.
Inter national Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, Alarcón-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, Tsao BP, Vyse TJ, Langefeld CD, Nath SK, Guthridge JM, Cobb BL, Mirel DB, Marion MC, Williams AH, Divers J, Wang W, Frank SG, Namjou B, Gabriel SB, Lee AT, Gregersen PK, Behrens TW, Taylor KE, Fernando M, Zidovetzki R, Gaffney PM, Edberg JC, Rioux JD, Ojwang JO, James JA, Merrill JT, Gilkeson GS, Seldin MF, Yin H, Baechler EC, Li QZ, Wakeland EK, Bruner GR, Kaufman KM, Kelly JA (2008). Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat. Genet. 40(2): 204-10.
Johansson CM, Kristjansdottir H, Grondal G, Steinsson K, Alarcon-Riquelme ME (2006). Characterization of a susceptibility locus for SLE, SLEB5, on chromosome 4p14-13. Scand J. Immunol. 64(3): 308-313.
Johansson CM, Zunec R, Garcia MA, Scherbarth HR, Tate GA, Paira S, Navarro SM, Perandones CE, Gamron S, Alvarellos A, Graf CE, Manni J, Berbotto GA, Palatnik SA, Catoggio LJ, Battagliotti CG, Sebastiani GD, Migliaresi S, Galeazzi M, Pons-Estel BA, Alarcon-Riquelme ME (2004). Chromosome 17p12–q11 harbors susceptibility loci for systemic lupus erythematosus. Hum. Genet. 115: 230–238.
Koskenmies S, Lahermo P, Julkunen H, Ollikainen V, Kere J, Widen E 2004. Linkage mapping of systemic lupus erythematosus (SLE) in Finnish families multiply affected by SLE. J. Med. Genet. 41: e2–5.
Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F (1998). Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 41(5): 778-799.
Lee YH, Rho YH, Choi SJ, Ji JD, Song GG (2005). Osteoarthritis susceptibility loci defined by genome scan meta-analysis. Rheumatol. Int. 26(11): 959-963.
Levinson DF, Levinson MD, Segurado R, Lewis CM (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part I: methods and power analysis. Am. J. Hum. Genet. 73: 17–33.
Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lonnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoega T, Helgason T (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. Am. J. Hum. Genet. 73: 34–48.
Lindqvist AK, Steinsson K, Johanneson B, Kristjansdottir H, Arnasson A, Grondal G, Jonasson I, Magnusson V, Sturfelt G, Truedsson L, Svenungsson E, Lundberg I, Terwilliger JD, Gyllensten UB, Alarcon-Riquelme ME (2000). A susceptibility locus for human systemic lupus erythematosus (hSLE1) on chromosome 2q. J. Autoimmun. 14: 169–178.
Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, Bruner GR, Fox J, Kelly J, Henshall S, Bacino D, Dietz M, Hogue R, Koelsch G, Nightingale L, Shaver T, Abdou NI, Albert DA, Carson C, Petri M, Treadwell EL, James JA, Harley JB (1998). Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. Proc. Nat. Acad. Sci. USA 95: 14869–14874.
Namjou B, Kelly JA, Kilpatrick J, Kaufman KM, Nath SK, Scofield RH, Harley JB. (2005). Linkage at 5q14.3-15 in multiplex systemic lupus erythematosus pedigrees stratified by autoimmune thyroid disease. Arthritis Rheum. 52(11): 3646-3650.
Namjou B, Nath SK, Kilpatrick J, Kelly JA, Reid J, James JA, Harley JB (2002). Stratification of pedigrees multiplex for systemic lupus erythematosus and for self-reported rheumatoid arthritis detects a systemic lupus erythematosus susceptibility gene (SLER1) at 5p15.3. Arthritis Rheum. 46(11): 2937-2945.
Nath SK, Quintero-Del-Rio AI, Kilpatrick J, Feo L, Ballesteros M, Harley JB (2004)a. Linkage at 12q24 with systemic lupus erythematosus (SLE) is established and confirmed in Hispanic and European American families. Am. J. Hum. Genet. 74: 73–82.
Nath SK, Namjou B, Hutchings D, Garriott CP, Pongratz C, Guthridge J, James JA (2004b). Systemic lupus erythematosus (SLE) and chromosome 16: confirmation of linkage to 16q12–13 and evidence for genetic heterogeneity. Eur. J. Hum. Genet. 12: 668–672.
Nath SK, Kelly JA, Reid J, Lam T, Gray-McGuire C, Namjou B, Aston CE, Harley JB (2002). SLEB3 in systemic lupus erythematosus (SLE) is strongly related to SLE families ascertained through neuropsychiatric manifestations. Hum. Genet. 111(1): 54-8.
Nath SK, Kelly JA, Namjou B, Lam T, Bruner GR, Scofield RH, Aston CE, Harley JB (2001). Evidence for a susceptibility gene, SLEV1, on chromosome 17p13 in families with vitiligo-related systemic lupus erythematosus. Am. J. Hum. Genet. 69(6): 1401-6.
Oostenbrug LE, Nolte IM, Oosterom E, van der Steege G, Te Meerman GJ, van Dullemen HM, Drenth JP, de Jong DJ, van der Linde K, Jansen PL, Kleibeuker JH (2006). CARD15 in inflammatory bowel disease and Crohn's disease phenotypes: An association study and pooled analysis. Dig. Liver Dis. Nov. 38(11): 834-45.
Rao S, Olson JM, Moser KL, Gray-McGuire C, Bruner GR, Kelly J, Harley JB (2001). Linkage analysis of human systemic lupus erythematosus-related traits: a principal component approach. Arthritis Rheum. 44(12): 2807-2818.
Rus V, Atamas SP, Shustova V, Luzina IG, Selaru F, Magder LS, Via CS (2002). Expression of cytokine- and chemokine-related genes in peripheral blood mononuclear cells from lupus patients by cDNA array, Clin. Immunol. 102(3): 283–290.
Scofield RH, Bruner GR, Kelly JA, Kilpatrick J, Bacino D, Nath SK, Harley JB (2003). Thrombocytopenia identifies a severe familial phenotype of systemic lupus erythematosus and reveals genetic linkages at 1q22 and 11p13. Blood 101(3): 992-997.
Sestak AL, Nath SK, Harley JB (2005). Genetics of systemic lupus erythematosus: how far have we come? Rheum. Dis. Clin. North Am. May 31(2): 223-244.
Shai R, Quismorio FP Jr, Li L, Kwon OJ, Morrison J, Wallace DJ, Neuwelt CM, Brautbar C, Gauderman WJ, Jacob CO (1999). Genome-wide screen for systemic lupus erythematosus susceptibility genes in multiplex families. Hum. Mol. Genet. 8: 639– 644.
Terwilliger JD, Ott J (1994). Handbook of human genetic linkage. Johns Hopkins University Press. Baltimore.
Tsao BP, Cantor RM, Kalunian KC, Chen CJ, Badsha H, Singh R, Wallace DJ, Kitridou RC, Chen SL, Shen N, Song YW, Isenberg DA, Yu CL, Hahn BH, Rotter JI (1997). Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. J. Clin. Invest. 15, 99(4): 725-731.
Van Heel DA, Fisher SA, Kirby A, Daly MJ, Rioux JD, Lewis CM (2004). Inflammatory bowel disease susceptibility loci defined by genome scan meta-analysis of 1952 affected relative pairs. Hum. Mol. Genet. 13: 763–770.
Wakeland EK, Liu K, Graham RR, Behrens TW (2001). Delineating the genetic basis of systemic lupus erythematosus. Immunity 15(3): 397-408.
Wise LH, Lanchbury JS, Lewis CM (1999). Meta -analysis of genome searches. Ann. Hum. Genet. 63(Pt 3): 263–272.
Xing C, Gray-McGuire C, Kelly JA, Garriott P, Bukulmez H, Harley JB, Olson JM (2005). Genetic linkage of systemic lupus erythematosus to 13q32 in African American families with affected male members. Hum. Genet. 118(3-4): 309-321.
Xing C, Sestak AL, Kelly JA, Nguyen KL, Bruner GR, Harley JB, Gray-McGuire C (2007). Localization and replication of the

systemic lupus erythematosus linkage signal at 4p16: interaction with 2p11, 12q24 and 19q13 in European Americans. Hum. Genet. 120(5): 623-631.