HHS Public Access

Author manuscript

Clin Immunol. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Clin Immunol. 2015 December ; 161(2): 157–162. doi:10.1016/j.clim.2015.09.007.

Genetic associations of leptin-related polymorphisms with systemic lupus erythematosus

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Abstract

Leptin is abnormally elevated in the plasma of patients with systemic lupus erythematosus (SLE), where it is thought to promote and/or sustain pro-inflammatory responses. Whether this association could reflect an increased genetic susceptibility to develop SLE is not known, and studies of genetic associations with leptin-related polymorphisms in SLE patients have been so far inconclusive. Here we genotyped DNA samples from 15,706 SLE patients and healthy matched

controls from four different ancestral groups, to correlate polymorphisms of genes of the leptin pathway to risk for SLE. It was found that although several SNPs showed weak associations, those associations did not remain significant after correction for multiple testing. These data do not support associations between defined leptin-related polymorphisms and increased susceptibility to develop SLE.

Keywords

systemic lupus erythematosus; leptin pathway; gene polymorphisms

Introduction

The etiopathogenesis of systemic lupus erythematosus (SLE) generally considers an involvement of environmental factors (including epigenetic changes) that could trigger abnormal autoimmune responses, facilitated by sex and hormones, in individuals that carry a predisposing genetic background (1). Therefore, in SLE multiple genetic variants could create favorable conditions for a heightened sensitivity of autoreactive cells to an increased stimulation/activation.

Our group and others have previously shown that leptin is abnormally elevated in SLE patients (2–3). We also showed that leptin in mice could promote SLE autoimmunity (4–5). Whether these findings underlie genetic association(s) between selected leptin polymorphisms and SLE is not known. A recent study suggested an association of a leptin receptor gene polymorphism (LEPRQ223R) with increased susceptibility of SLE in 100 Kashmiri individuals (6). Since analyses on larger numbers of SLE patients and in multiple ethnic groups would better delineate the possibility of association(s) between leptin-related genes and increased risk for SLE, we performed genetic association studies for single nucleotide polymorphisms (SNPs) within multiple leptin-related genes. Criteria for selection were based on the following considerations. Leptin gene (*LEP*) polymorphisms (7) were studied because of their possible roles in abnormal function/catabolism of leptin. For leptin receptor (*LEPR*), which exists in six alternatively spliced forms with cytoplasmic domains of different length (8), we assessed polymorphisms of all isoforms (9) because any of them might influence catabolism and/or sustain leptin activity. The polymorphism of *PPARG* (10–12) was also studied because leptin can downregulate PPAR-γ expression for a subsequent increase in the release of pro-inflammatory IL-1β, IL-6 and TNF-α (13–14). Finally, the polymorphism of the growth hormone secretagogue receptor *GHSR* was studied because its opposing action on leptin results in the inhibition of the same pro-inflammatory cytokines (15–16).

Haplotype-tagging SNPs selected from these genes were genotyped by a customized SNP genotyping-array and assessed for association with SLE in 15,706 case-control subjects from four different ancestral groups including European American (EA), African American (AA), East Asian (AS) and Hispanic enriched for the Amerindian-European admixture (HS).

Materials and Methods

Subjects' samples collection and SNP genotyping

To test association of *LEPR*, *PPARG*, *GHSR* and *LEP* with SLE, we used a large collection of samples from case-control subjects from multiple ethnic groups. These samples were from the collaborative Large Lupus Association Study 2 (LLAS2) and were contributed by participating institutions in the United States, Asia and Europe. All SLE patients met the American College of Rheumatology (ACR) criteria for the classification of SLE (17). LLAS2 samples were processed at the Lupus Genetics Studies Unit of the Oklahoma Medical Research Foundation (OMRF). SNP genotyping was carried out on the Illumina iSelect platform. Subjects with individual genotyping call rate <0.90 were removed because of low data quality. Subjects that were duplicated or first degree related were also removed. Both principal component analysis and global ancestry estimation based on 347 ancestry informative markers (AIMs) were used to detect population stratification and admixture, as described in another LLAS2 report (18). After removing genetic outliers, a final dataset of 15,706 unrelated subjects (8,269 cases vs. 7,437 controls) was obtained.

According to genetic ancestry, subjects were grouped into four ancestral groups including European American (3,966 cases vs. 3,543 controls), African American (1,527 cases vs. 1,812 controls), East Asian (1,272 cases vs. 1,270 controls) and Hispanic enriched for the Amerindian-European admixture (1,504 cases vs. 812 controls).

The study was approved by the Human Subject Institutional Review Boards or the Ethic Committee of each institution. All subjects were enrolled after informed consent had been obtained.

SNP selection and Statistical analysis

To avoid the genotyping of all SNPs for the genes of interest yet capture the majority of diversity within each region, we selected haplotype tag SNPs for genotyping according to the Hapmap Project (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap24_B36/; HapMap public release #24 of 11/26/2008). In addition, SNPs with potential functional consequences were selected as well for testing. In total, we selected 9 SNPs for *LEP*, 17 SNPs for *LEPR*, 5 SNPs for *GHSR* and 16 SNPs for *PPARG*, at an average density of 8.2kb per SNP. 32 SNPs that passed data cleaning and quality control measures (7 SNPs for *LEP*, 10 SNPs for *LEPR*, 3 SNPs for *GHSR* and 12 SNPs for *PPARG*, Table 1) were genotyped on the Illumina iSelect platform and subsequently used for genetic association test.

The Hardy-Weinberg equilibrium (HWE) test threshold was set at $P>0.01$ for controls and $P>0.0001$ for cases. SNPs failing the HWE test were excluded from association test. SNPs showing genotyping missing rate >5% or showing significantly different genotyping missing rate between cases and controls (missing rate >2% and $P_{missing}<0.05$) were excluded from association test. In each ancestral group, SNPs were assessed for association with SLE under a logistic regression model adjusting for gender and the first 3 principal components estimated using AIMs. The trans-ancestry meta-analysis was conducted across all four ancestral groups. For each SNP, if the Cochran's Q statistic showed no evidence of genetic heterogeneity ($P>0.05$), a fixed effect model was applied. Otherwise, a random effect model

was used. All analyses described above were performed using PLINK v1.07 (19). Pairwised LD values shown in Figure 1 were calculated using Haploview 4.2 (20)

Results

Genetic association between leptin-related polymorphisms and human SLE

To test the possibility of common leptin-related variants predisposing to SLE, genetic association studies using htSNPs for the four selected candidate leptin-related genes *LEP*, *LEPR*, *GHSR* and *PPARG* were performed in different ancestral groups. Information and SNPs scoring are reported in Supplementary Table 1. Using Illumina microarray platform, 15,706 case-control samples from four ethnic groups were genotyped in LLAS2 including European American (EA), African American (AA), East Asian (AS) and Hispanic enriched for the Amerindian-European admixture (HS).

In *LEP*, the A allele of rs12706832 showed association with decreased risk of SLE in AA (78.3% in cases vs. 80.6%w P=0.0063, OR=0.84, Table 1). In addition, the A allele of rs3828942 was associated with increased risk of SLE in AA (19.5% in cases vs. 17.7% in controls, P=0.029, OR=1.16, Table 1)

In *LEPR*, two SNPs rs6690625 and rs1892535 showed association with decreased risk of SLE in HS (C allele of rs6690625, 25.9% in cases vs. 28.7% in controls, P =0.0011, OR=0.79; A allele of rs1892535, 25.0% in cases vs. 26.8% in controls, P =0.0068, OR=0.82, Table 1).

In *GHSR*, the G allele of rs2948694 was associated with decreased risk of SLE in HS (13.7% in cases vs. 15.3% in controls, P =0.019, OR=0.81, Table 1).

In *PPARG*, two SNPs rs12633551 and rs3856806 were associated with decreased risk of SLE in EA (A allele of rs12633551, 2.8% in cases vs. 3.3% in controls, P =0.022, OR=0.80; A allele of rs3856806, 11.1% in cases vs. 12.3% in controls, P =0.023, OR=0.88, Table 1).

Although we detected significant association signals at several loci, none of them showed consistent association (P<0.05) in multiple ancestral groups. The meta-analysis combining all four ancestral groups showed that multiple SNPs in *PPARG* exhibited association with SLE (P_{meta}=0.031, 0.024, 0.025, 0.0080 and 0.024 for rs6785890, rs10510410, rs12633551, rs4145574 and rs3856806, respectively, Table 1). After Bonferroni correction for multiple tests, only the association of rs6690625 in *LEPR* with SLE in HS remained significant (P=0.0011, which was less than the corrected P=0.05/32=0.0016).

Together, these data do not provide evidence that leptin-related genes can increase risk for SLE.

Discussion

In SLE, many candidate genes including MHC loci, complement components, mannose-binding protein, Fc-γ receptors and pro-inflammatory cytokines have been tested by genetic association studies for risk of SLE (21–22). Recently, the role of leptin receptor

polymorphism as a possible contributor to SLE risk was suggested (6). In the *LEPR*, several SNPs gene have been identified, including the Q223R polymorphism in which an A to G transition in exon 6 (that encodes for the extracellular domain of the leptin receptor) (23) could lead to altered signal transduction by altering binding to leptin and/or by impairing LEPR expression. Afroze and colleagues found that carriers of variant genotype (A/G+G/G) or G allele were at elevated risk for SLE (6). However, the number of SLE patients in that study was so low that it lacked power to reach any relevant conclusion as for the association between leptin receptor and SLE. Conversely, our study uses very large number of SLE subjects and is well powered, thus the conclusions can be considered highly significant.

Genetics plays a key role in the pathogenesis of autoimmune diseases because it can influence the expression and activity of genes that are relevant to the disease. Here we aimed to address whether the abnormally increased levels of leptin in SLE patients could associate to gene polymorphisms, i.e. whether certain leptin-related polymorphisms might contribute to a predisposing SLE background that would sustain hyperleptinemia. Although initial assessments suggested the possibility of associated polymorphisms, extensive analyses on 15,706 individuals of multiple ancestries did not confirm the findings. However, we acknowledge that our results do not exclude the possibility that other polymorphisms in genes different from the ones tested here and related to leptin activities could associate with increased susceptibility to develop SLE. Yet such genes should be indirectly related to leptin because both leptin and leptin receptor polymorphisms showed no association with increased SLE risk in this study.

The finding of a lack of polymorphisms association with the leptin pathway reminds the results obtained in genetic association studies of human BLyS and SLE. Like leptin, BLyS is an important pro-inflammatory cytokine that is abnormally elevated in SLE patients (24). However, no polymorphism in BLyS or BlyS receptor BCMA was found associated with SLE (25, 26). As for leptin, it might be possible that the increase of BLyS levels in SLE patients could be an indirect consequence of other gene(s) associated with SLE or a consequence of multiple interactions between genes and/or genes and environment. It derives that multivariate analyses on subsets of patients (i.e., based on autoantibody positivity, disease manifestations, organ involvement etc.) should be performed for possible identification of associations and assessment of functional significance. In our case, future studies will need to address whether stratification of SLE patients might identify associations of selected SNPs polymorphisms with defined subsets of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all subjects for participation in this study, and Erika Magdangal for help with DNA preparation and organization. This work was supported by the US National Institutes of Health grants AR53239 (A.L.C.) AR043814 and AR065626 (B.P.T.), AI083194 (J.B.H., K.M.S., R.P.K., L.A.C., T.J.V., M.E.A.R., C.O.J., B.P.T. and P.M.G.), AR049084 (R.P.K., J.B.H., J.C.E., E.E.B., G.S.A., J.D.R., R.R.G. and M.A.P.), AR064820 (E.E.B., M.A.P., R.R.G., J.D.R. and L.M.V.), TR001417 (J.C.E. and R.P.K.), CA141700 and AR058621 (M.E.A.R.), AR053308 and TR000004 (L.A.C.), AR062755 and RR029882 (G.S.G. and D.L.K.), AR057172 (C.O.J.),

GM103510, GM104938, AR053483, AI101934 and AI082714 (J.A.J.), AI063274 (P.M.G.), AR043274 (K.M.S.), AI083790, AI071651 and RR024999 (T.B.N.), AR43727 (M.A.P.), AR002138, AR066464 and TR001422 (R.R.G.), RR023417 (J.D.R.), AR051545 and RR025014 (A.M.S.), AI070304 (S.A.B.), AR042460, AR062277, RR020143 and AI024717 (J.B.H.), AR048311 and AR055385 (E.E.B.), AR033062 (R.P.K.). Additional funds were from the Lupus Foundation of America (B.P.T.), the Alliance for Lupus Research (B.P.T., Y.D., K.M.S., T.B.N., L.A.C., C.O.J. and S.A.B.), the Lupus Research Institute (B.P.T. and T.B.N.), the US Department of Veterans Affairs (Merit Awards; J.B.H. and G.S.G.), the US Department of Defense (PR094002, J.B.H.), the Arthritis National Research Foundation (Eng Tan Scholar Award; J.Z. and T.B.N.), the Arthritis Foundation (A.M.S. and P.M.G.), the Korea Healthcare Technology R&D Project, Ministry for Health and Welfare, Republic of Korea (HI13C2124 to S.C.B and HI14C1277 to Y.W.S.), the European Science Foundation RNP (BIOLUPUS Research Network), the Wellcome Trust (T.J.V.), Arthritis Research UK (T.J.V.), a Kirkland Scholar Award (L.A.C.), the Wake Forest School of Medicine Center for Public Health Genomics (C.D.L.), and UCLA Clinical and Translational Science Institute (CTSI) RR033176 and TR000124.

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Highlights

- 15,706 individuals of four difference ancestral groups were genotyped for polymorphisms in four genes related to the leptin pathway, for possible association with systemic lupus erythematosus (SLE).
- Several SNPs showed weak associations that did not remain significant after correction for multiple testing.
- None of the tested leptin-related polymorphisms associated with increased risk for SLE.

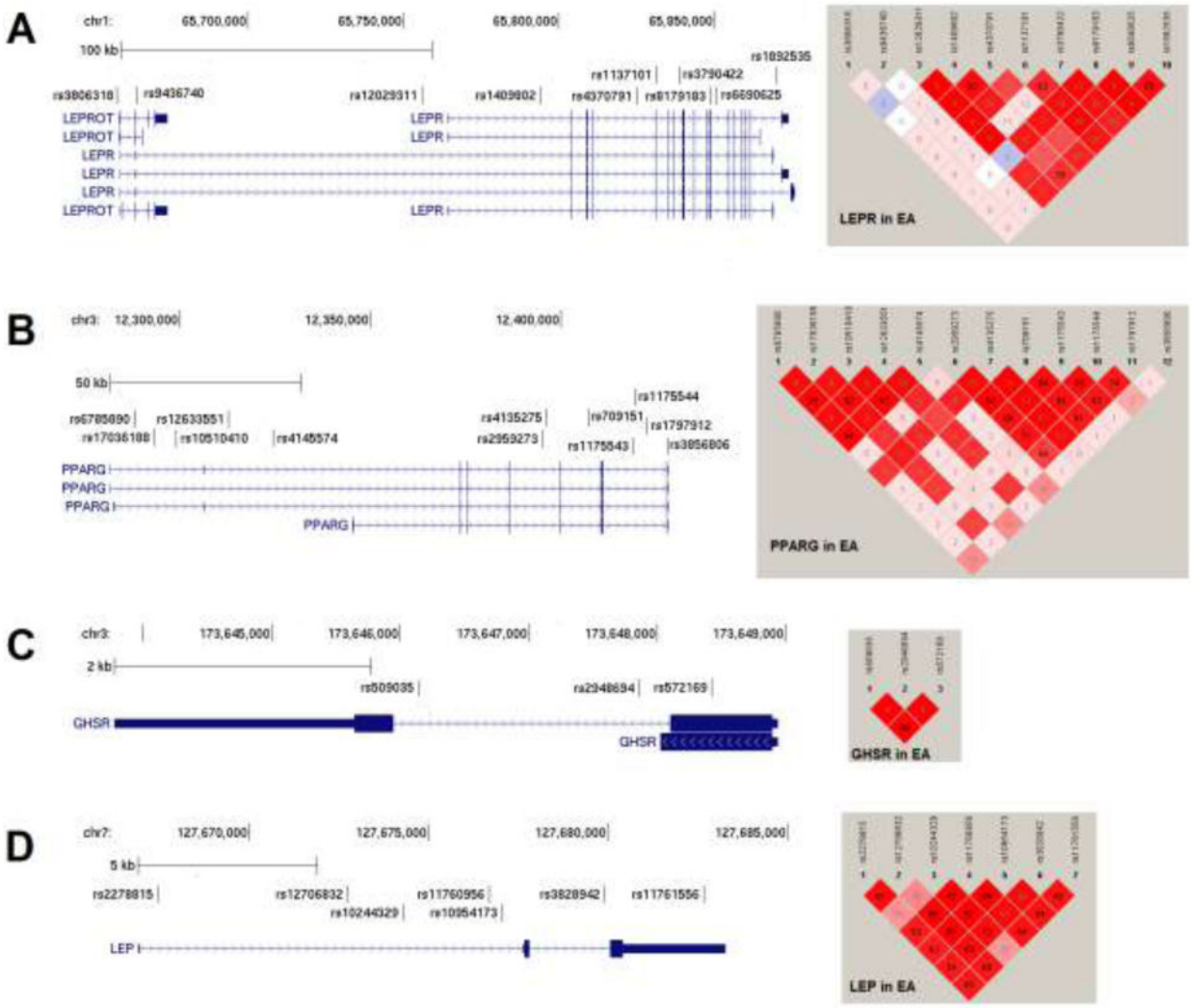

Figure 1. SNPs in leptin-related genes assessed for association with SLE

Genomic structure, SNP location and pairwise linkage disequilibrium (described as r^2) between SNPs are indicated for A) LEPR, B) PPARG, C) GHSR and D) LEP, respectively.

Table 1

Association of SNPs in Leptin-related genes with SLE susceptibility

				EA				AA			
				Frequency				Frequency			
SNP	Gene	Location	Tested allele	SLE	CTRL	*P*	OR	SLE	CTRL	*P*	OR
rs3806318	LEPR	chr1:65657945	G	27.2%	26.8%	0.35	1.04	5.3%	5.4%	0.91	1.01
rs9436740	LEPR	chr1:65664489	A	27.7%	28.0%	0.84	0.99	47.9%	48.4%	0.93	1.00
rs12029311	LEPR	chr1:65755938	A	0.3%	0.2%	0.33	1.45	0.2%	0.3%	0.14	0.45
rs1409802	LEPR	chr1:65793939	A	24.4%	24.4%	0.92	1.00	18.5%	18.3%	0.54	1.04
rs4370791	LEPR	chr1:65824816	G	25.7%	25.4%	0.69*	1.02	29.6%	28.6%	0.31	1.06
rs1137101	LEPR	chr1:65831101	G	42.3%	43.0%	0.69	0.99	56.0%	54.7%	0.13	1.08
rs3790422	LEPR	chr1:65838587	A	36.7%	37.0%	0.74	0.99	56.5%	55.5%	0.22	1.07
rs8179183	LEPR	chr1:65848540	C	18.8%	18.0%	0.11	1.07	20.3%	18.5%	0.23	1.08
rs6690625	LEPR	chr1:65850178	C	17.7%	17.8%	0.82	0.99	33.2%	31.5%	0.097*	1.10
rs1892535	LEPR	chr1:65869769	A	17.0%	17.3%	0.70	0.98	14.9%	14.6%	0.61	1.04
rs6785890	PPARG	chr3:12310816	A	24.0%	24.7%	0.26	0.96	28.0%	23.3%	0.88	1.01
rs17036188	PPARG	chr3:12315925	G	2.6%	3.0%	3.11	0.84	3.4%	3.4%	0.47	1.11
rs10510410	PPARG	chr3:12321738	C	23.6%	24.4%	0.26	0.96	29.7%	30.6%	0.52	0.96
rs12633551	PPARG	chr3:12335494	A	2.8%	3.3%	***0.022***	0.80	0.7%	0.4%	0.071	1.93
rs4145574	PPARG	chr3:12347074	G	22.2%	23.1%	0.13	0 94	21.1%	21.1%	0.99	1.00
rs2959273	PPARG	chr3:12417731	A	39.4%	38.9%	0.61	1.02	20.6%	21.4%	0.57	0.96
rs4135275	PPARG	chr3:12418844	G	19.9%	19.2%	0.18	1.06	5.6%	5.7%	0.73	0.96
rs709151	PPARG	chr3:12429999	A	35.1%	34.6%	0.72	1.01	13.3%	13.5%	0.68	1.03
rs1175543	PPARG	chr3:12441433	G	35.2%	35.1%	0.93	1.00	13.4%	13.7%	0.71	1.03
rs1175544	PPARG	chr3:12442044	A	33.1%	32.4%	0.32	1.04	10.3%	10.7%	0.86	0.98
rs1797912	PPARG	chr3:12445239	C	37.1%	36.9%	0.97	1.00	14.3%	13.9%	0.29*	1.08
rs3856806	PPARG	chr3:12450557	A	11.1%	12.3%	***0.023***	0.88	5.5%	5.8%	0.89	1.02
rs509035	GHSR	chr3:173646143	A	29.0%	29.5%	0.27	0.96	8.9%	8.7%	0.83	1.02
rs294S694	GHSR	chr3:173647857	G	10.4%	10.3%	0.83	1.01	10.1%	10.6%	0.65	0.96
rs572169	GHSR	chr3:173648421	A	28.3%	29.6%	0.17	0.95	8.9%	8.9%	0.89	0.99

				EA				AA			
				Frequency				Frequency			
SNP	Gene	Location	Tested allele	SLE	CTRL	*P*	OR	SLE	CTRL	*P*	OR
rs2278815	LEP	chr7:127669087	G	44.7%	44.6%	0.97	1.00	85.3%	86.4%	0.17	0.90
rs12706832	LEP	chr7:127674375	A	45.3%	45.1%	0.77	1.01	78.3%	80.6%	***0.0063***	0.84
rs10244329	LEP	chr7:127675925	T	49.9%	49.8%	0.92	1.00	47.5%	46.1%	0.26	1.06
rs11760956	LEP	chr7:127678323	A	36.6%	37.0%	0.70	0.99	18.6%	16.7%	0.14	1.10
rs10954173	LEP	chr7:12767S676	A	36.6%	37.1%	0.72	0.99	18.4%	16.7%	0.16	1.10
rs3828942	LEP	chr7:127681541	A	43.2%	43.5%	0.64	0.98	19.5%	17.7%	***0.029***	1.16
rs11761556	LEP	chr7:127684305	C	45.3%	45.4%	0.91	1.00	82.2%	83.0%	0.38	0.94

Position of each SNP is based on NCBI36/hg18. Significant association signals ($P<0.05$) are highlighted in bold. For SNPs not passing our criteria of quality control, the P value is annotated with "*".