HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2013 September 01.

Published in final edited form as:

J Invest Dermatol. 2013 March ; 133(3): 836–839. doi:10.1038/jid.2012.366.

Association of Cardiovascular and Metabolic Disease Genes with Psoriasis

Yingchang Lu[1], **Haoyan Chen**[1], **Pernilla Nikamo**[2], **Hui Qi Low**[3], **Cynthia Helms**[4], **Mark Seielstad**[3,5], **Jianjun Liu**[3], **Anne M. Bowcock**[4], **Mona Stahle**[2], and **Wilson Liao**[1]

[1]Department of Dermatology, University of California, San Francisco, San Francisco, CA 94143, USA

[2]Unit of Dermatology and Venereology, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

[3]Human Genetics, Genome Institute of Singapore, Singapore, Singapore

[4]Division of Human Genetics, Department of Genetics, Washington University School of Medicine, Saint Louis, MO 63110, USA

[5]Institute for Human Genetics and Department of Laboratory Medicine, University of California, San Francisco, CA 94143, USA

To the Editor:

Psoriasis is a chronic immune-mediated and hyperproliferative disorder of the skin that affects 2–3% of the population. Psoriasis is associated with an increased incidence of several cardiovascular and metabolic co-morbidities, including coronary artery disease (CAD), hypertension, obesity, hyperlipidemia, and type 2 diabetes (T2D) (Davidovici *et al.*, 2010). The association of these cardiovascular and metabolic diseases with psoriasis could be due to shared genetic risk variants, shared environmental triggers, activation of common inflammatory pathways, or a combination of these factors. Here, we evaluated the hypothesis that some of the increased risk of cardiovascular and metabolic diseases in psoriasis is derived from shared genetic risk factors.

Using the genome-wide association studies (GWAS) Catalog (available at www.genome.gov/gwastudies and accessed in December 2011), we selected 363 SNPs that showed significant association with CAD, hypertension, body mass index (BMI), hyperlipidemia (total, LDL and HDL cholesterol levels and triglyceride levels), or T2D. Selected SNPs met genome-wide significance ($p < 5\times10^{-8}$) in at least two GWAS or were significant in the latest meta-analysis of GWAS. Additional SNPs or loci were also included

Correspondence: Wilson Liao, M.D., 2340 Sutter Street, Box 0808, San Francisco, CA 94143-0808, Tel: 415-476-8364, Fax: 415-476-8837, liaowi@derm.ucsf.edu.

Conflict of interest:
The authors state no conflict of interest.

based on the latest expert opinions (McCarthy, 2010; O'Donnell and Nabel, 2011; Peden and Farrall, 2011). Detailed information about the selected SNPs is provided in Table S1.

We evaluated the selected cardiovascular and metabolic SNPs for association with psoriasis in four psoriasis GWAS cohorts: the GAIN cohort including 1368 psoriasis cases and 1348 controls (Nair *et al.*, 2009), an unpublished psoriasis cohort from Sweden including 725 cases and 438 controls, a Washington University/University of California San Francisco cohort including 211 psoriasis cases and 502 controls (Liu *et al.*, 2008), and the Wellcome Trust Case-Control Consortium (WTCCC) cohort including 2178 psoriasis cases and 5175 controls (Strange *et al.*, 2010). Further details of the Swedish cohort are described in the Supplemental Methods. IMPUTE2 was used to impute the ungenotyped SNPs by using phase 3 HapMap and 1000 Genomes pilot project CEU haplotypes as a reference. SNPTEST was used to associate the imputed dosage for each SNP with psoriasis status separately in each study population with the adjustment of the first three principal components from an MDS analysis of population stratification. The association test results for these SNPs with relatively high confidence (PROPER_Info > 0.5) were then combined by meta-analysis with the META using inverse-variance method based on a fixed-effect model. The false discovery rate method was used to correct for multiple testing (FDR_q < 0.05).

We first examined the associations between all selected SNPs and psoriasis status (Table 1 and Table S2). After adjusting for multiple testing with the false discovery rate method, seven SNPs were associated with psoriasis status (FDR_q < 0.05, Table 1). The alleles associated with increased risk of dyslipidemia (rs2247056, rs3177928, rs492602, and rs181362), increased blood pressure levels (rs805303, rs653178, and rs3184504), and increased CAD risk (rs3184504) were associated with increased risk of psoriasis (Table 1). The top three SNPs (rs2247056, rs3177928, and rs805303) were located in the HLA gene region which is a known psoriasis susceptibility locus. After further adjustment for the top psoriasis risk allele HLA-C*06:02 (determined by imputation as described in (Chen *et al.*, 2012), the associations for rs2247056 and rs3177928 were mitigated (p = 0.06 and 0.07, respectively), while the association for rs805303 persisted (p = 0.005). Since multiple psoriasis risk alleles are identified in HLA loci (Chen *et al.*, 2012), we cannot rule out the significant association for rs805303 is derived from linkage disequilibrium (LD) with other psoriasis HLA risk alleles. Interestingly, we identified 4 non-HLA SNPs with evidence of shared genetic risk between psoriasis and cardiovascular and metabolic diseases: rs492603 in *FUT2*, rs181362 in *UBE2L3*, and rs653178 and rs3184504 (in complete LD with each other) near or in *SH2B3*. *FUT2* encodes an alpha-(1,2)fucosyltransferase that determines secretor status of blood group antigens on epithelial cells and in bodily secretions and has been recently associated with susceptibility to psoriasis and Crohns's disease (Ellinghaus *et al.*, 2012), type 1 diabetes (Smyth *et al.*, 2011), primary sclerosing cholangitis (Folseraas *et al.*, 2012), and norovirus infection (Carlsson *et al.*, 2009). *UBE2L3* encodes an ubiquitin-conjugating enzyme involved in cell proliferation and immune function and is associated with susceptibility to celiac disease and rheumatoid arthritis (Zhernakova *et al.*, 2011), Crohn's disease (Fransen *et al.*, 2010), and systemic lupus erythematosus (Wang *et al.*, 2012). The adaptor protein encoded by *SH2B3* plays pleiotropic signaling roles in regulating lymphocyte differentiation, induction of VCAM-1 and E-selectin on endothelial cells by

TNF-α, and thrombus formation (Devalliere and Charreau, 2011), and thus might explain its dual role in susceptibility to multiple autoimmune diseases and endothelium-related cardiovascular diseases (Jin *et al.*, 2012).

With a combined 4482 psoriasis cases and 7463 controls, our meta-analysis had 80% power to detect genetic variants with OR = 1.2 at a significance level alpha of 0.05, assuming 5% of population allele frequency. Given that many cardiovascular and metabolic trait SNPs have ORs less than 1.2, we sought to determine whether cardiovascular and metabolic risk SNPs could be having a real, but more subtle effect on psoriasis susceptibility. We therefore constructed a weighted gene risk score (wGRS) to investigate the aggregate effects of the risk alleles associated with cardiovascular and metabolic traits between psoriasis patients and controls. Prior studies have shown that such genetic risk scores, which estimate an individual's overall genetic burden, have increased ability to discriminate between cases and controls (Chen *et al.*, 2011). The GRS were weighted according to the effect size of the risk alleles and a common set of SNPs were examined across all cohorts (see Supplemental Methods). A small but significant difference for the wGRS of CAD, total cholesterol levels, and TG levels was seen ($p < 0.006$ for adjusting for multiple testing of 8 traits, Table 2). The wGRS of total cholesterol levels did not reach significance after removing the top associated SNPs (rs3177928 and rs492602, $p = 0.42$, Table 1 and 2). No difference between psoriasis cases and controls was observed regarding the wGRS of hypertension, T2D, LDL cholesterol levels, HDL cholesterol levels, and BMI (Table 2).

Multiple cardiovascular and metabolic co-morbidities have been observed in psoriasis patients. Here we examined whether the co-manifestation of these conditions is a result of shared genetic factors. The data presented here suggest that patients with psoriasis are enriched for certain common genetic variants (*HLA*, *FUT2*, *UBE2L3*, *SH2B3*) that predispose to increased risk of dyslipidemia, hypertension, and increased CAD risk itself. Further evaluation of these genes and pathways may be important to elucidate whether particular subsets of psoriasis patients carry a higher burden of risk for the development of these cardiovascular and metabolic co-morbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The GAIN dataset was obtained from the database of Genotypes and Phenotypes (dbGaP) found at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs000019.v1.p1. Samples and associated phenotype data for the Collaborative Association Study of Psoriasis were provided by Drs. James T Elder (University of Michigan, Ann Arbor, MI), Gerald G Krueger (University of Utah, Salt Lake City, UT), Anne Bowcock (Washington University, St. Louis, MO) and Gonçalo R Abecasis (University of Michigan, Ann Arbor, MI). This study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for this study was provided in part by grants from the National Institutes of Health: AR050266 (A.M.B.), and K08AR057763 (W.L).

References

Carlsson B, Kindberg E, Buesa J, Rydell GE, Lidon MF, Montava R, et al. The G428A nonsense mutation in FUT2 provides strong but not absolute protection against symptomatic GII.4 Norovirus infection. PLoS One. 2009; 4:e5593. [PubMed: 19440360]

Chen H, Hayashi G, Lai OY, Dilthey A, Kuebler PJ, Wong TV, et al. Psoriasis Patients Are Enriched for Genetic Variants That Protect against HIV-1 Disease. Plos Genet. 2012; 8:e1002514. [PubMed: 22577363]

Chen H, Poon A, Yeung C, Helms C, Pons J, Bowcock AM, et al. A genetic risk score combining ten psoriasis risk loci improves disease prediction. PLoS One. 2011; 6:e19454. [PubMed: 21559375]

Davidovici BB, Sattar N, Prinz JC, Jorg PC, Puig L, Emery P, et al. Psoriasis and systemic inflammatory diseases and potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol. 2010; 130:1785–1796. [PubMed: 20445552]

Devalliere J, Charreau B. The adaptor Lnk (SH2B3): an emerging regulator in vascular cells and a link between immune and inflammatory signaling. Biochemical pharmacology. 2011; 82:1391–402. [PubMed: 21723852]

Ellinghaus D, Ellinghaus E, Nair RP, Stuart PE, Esko T, Metspalu A, et al. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. Am J Hum Genet. 2012; 90:636–647. [PubMed: 22482804]

Folseraas T, Melum E, Rausch P, Juran BD, Ellinghaus E, Shiryaev A, et al. Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci. J Hepatol. 2012

Fransen K, Visschedijk MC, van Sommeren S, Fu JY, Franke L, Festen EA, et al. Analysis of SNPs with an effect on gene expression identifies UBE2L3 and BCL3 as potential new risk genes for Crohn's disease. Hum Mol Genet. 2010; 19:3482–3488. [PubMed: 20601676]

Jin Y, Birlea SA, Fain PR, Ferrara TM, Ben S, Riccardi SL, et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. Nat Genet. 2012; 44:676–680. [PubMed: 22561518]

Liu Y, Helms C, Liao W, Zaba LC, Duan S, Gardner J, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet. 2008; 4:e1000041. [PubMed: 18369459]

McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med. 2010; 363:2339–2350. [PubMed: 21142536]

Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet. 2009; 41:199–204. [PubMed: 19169254]

O'Donnell CJ, Nabel EG. Genomics of cardiovascular disease. N Engl J Med. 2011; 365:2098–109. [PubMed: 22129254]

Peden JF, Farrall M. Thirty-five common variants for coronary artery disease: the fruits of much collaborative labour. Hum Mol Genet. 2011; 20:R198–R205. [PubMed: 21875899]

Smyth DJ, Cooper JD, Howson JM, Clarke P, Downes K, Mistry T, et al. FUT2 nonsecretor status links type 1 diabetes susceptibility and resistance to infection. Diabetes. 2011; 60:3081–3084. [PubMed: 22025780]

Strange A, Capon F, Spencer CC, Knight J, Weale ME, Allen MH, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet. 2010; 42:985–990. [PubMed: 20953190]

Wang S, Adrianto I, Wiley GB, Lessard CJ, Kelly JA, Adler AJ, et al. A functional haplotype of UBE2L3 confers risk for systemic lupus erythematosus. Genes Immun. 2012

Zhernakova A, Stahl EA, Trynka G, Raychaudhuri S, Festen EA, Franke L, et al. Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. PLoS Genet. 2011; 7:e1002004. [PubMed: 21383967]

Table 1

Top 10 metabolic SNPs associated with psoriasis status in the meta-analysis of four studies.

Chr.	SNP	Nearby Gene	Minor/major allele	Effect on metabolic phenotypes (allele effect)[1]	Effect on psoriasis (allele effect/p value)				β/p value (meta-analysis)	OR (95% CI)	FDR_q value[3]
					GAIN[1,2]	Sweden[1,2]	WashU/UCSF[1,2]	WTCCC[1,2]			
6	rs2247056	HLA-C	T/C	C↑TG	C↑/3.32E-04	C↑/0.02	C↑/0.45	C↑/4.21E-38	0.43/3.25E-35	1.53(1.43–1.64)	< 0.0001
6	rs3177928	HLA-DRA	A/G	A↑TC, LDLC	A↑/5.59E-07	A↑/0.07	A↑/0.21	A↑/2.66E-29	0.45/1.20E-32	1.57(1.46–1.69)	< 0.0001
6	rs805303	BAT2, BAT5	A/G	A↓SBP, DBP, and HTN	A↓/6.17E-02	A↓/3.42E-01	A↓/7.69E-01	A↓/3.13E-07	−0.15/8.30E-07	0.86(0.81–0.91)	< 0.0001
19	rs492602	FUT2	A/G	G↑TC	G↑/3.30E-03	G↑/6.64E-01	G↑/7.16E-01	G↑/6.59E-05	0.13/8.23E-06	1.14(1.07–1.20)	0.0007
22	rs181362	UBE2L3	T/C	T↓/HDLC	T↑/1.40E-01	T↑/8.18E-01	T↑/2.62E-01	T↑/2.77E-04	0.14/1.43E-04	1.15(1.07–1.23)	0.0102
12	rs653178	ATXN2, SH2B3	C/T	T↓DBP	T↓/2.56E-02	T↑/6.65E-01	T↓/1.07E-02	T↓/5.77E-03	−0.11/2.08E-04	0.90(0.85–0.95)	0.0124
12	rs3184504	SH2B3	T/C	T↑CAD, DBP, SBP	T↑5.60E-02	T↓/4.76E-01	T↑/1.00E-02	T↑/6.51E-03	0.10/6.22E-04	1.11(1.04–1.17)	0.0318
12	rs11065987	BRAP	G/A	G↓TC, LDLC	G↑/6.61E-02	G↓/8.57E-01	G↑/2.59E-02	G↑/2.39E-02	0.09/1.81E-03	1.09(1.03–1.16)	0.0811
2	rs7593730	RBMS1	T/C	C↑T2D	C↑/3.01E-01	C↑/8.17E-03	C↓/5.81E-01	C↑/1.73E-02	0.11/2.34E-03	1.11(1.04–1.19)	0.093
10	rs7901695	TCF7L2	C/T	C↑T2D	C↓/1.87E-01	C↓/3.81E-01	C↓/1.98E-01	C↓/4.49E-02	−0.09/5.26E-03	0.92(0.86–0.97)	0.1881

Abbreviations: TC, total cholesterol levels; LDLC, low-density-lipoprotein cholesterol levels; HDLC, high-density-lipoprotein cholesterol levels; TG, triglyceride levels; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; CAD, coronary artery disease; T2D, type 2 diabetes; OR (odds ratios); 95% CI (95% confidence interval).

[1] ↑/↓, increasing/decreasing effects on relevant metabolic traits and psoriasis risk.

[2] All p values were adjusted by the first three principal components from an MDS analysis of population stratification.

[3] FDR_q, false discovery rate adjusted p value based on 358 SNPs in supplementary table 3.

Table 2

Metabolic weighted gene risk score between controls and psoriasis cases.[1]

Studies	CAD	Hypertension	T2D	TC	LDLC	HDLC	TG	BMI
Gain								
Control	2.17±0.30	1.78±0.20	3.59±0.43	39.44±4.69	26.52±5.18	25.94±3.23	105.74±15.44	3.62±0.52
Case	2.20±0.30	1.79±0.20	3.59±0.43	39.73±4.78	26.22±5.33	25.82±3.20	107.40±15.13	3.65±0.49
P1[2]	*0.01*	*0.59*	*0.96*	*0.12*	*0.17*	*0.34*	*0.01*	*0.10*
Sweden								
Control	2.13±0.29	1.84±0.19	3.47±0.41	39.56±4.83	25.71±5.03	25.76±3.18	104.68±14.85	3.66±0.54
Case	2.14±0.30	1.81±0.20	3.51±0.43	39.59±5.07	26.04±5.41	25.96±3.31	104.87±14.82	3.69±0.52
P1[2]	*0.52*	*0.01*	*0.28*	*0.60*	*0.39*	*0.28*	*0.77*	*0.34*
WashU/UCSF								
Control	2.18±0.31	1.78±0.19	3.57±0.44	39.78±4.61	26.23±5.49	25.84±3.27	106.01±15.27	3.59±0.53
Case	2.19±0.28	1.76±0.20	3.57±0.42	39.82±4.64	26.47±4.75	26.26±2.99	109.62±15.93	3.54±0.52
P1[2]	*0.81*	*0.33*	*0.52*	*0.77*	*0.61*	*0.10*	*0.04*	*0.31*
WTCCC								
Control	2.16±0.30	1.78±0.20	3.54±0.44	39.39±4.70	26.27±5.27	26.01±3.19	105.1±15.26	3.64±0.52
Case	2.18±0.30	1.79±0.20	3.55±0.43	39.77±4.88	26.51±5.33	25.98±3.27	106.24±15.12	3.67±0.52
P1[2]	*0.002*	*0.22*	*0.95*	*0.003*	*0.003*	*0.69*	*0.001*	*0.03*
Meta OR(95%CI)	1.31(1.15–1.50)	0.88(0.60–1.29)	1.01(0.92–1.10)	1.01(1.01–1.02)	1.01(0.99–1.02)	1.00(0.99–1.01)	1.01 (1.00–1.01)	1.11(1.02–1.20)
P2[3]	*<0.0001*[5]	*0.50*	*0.91*	*0.0025*	*0.35*	*0.97*	*<0.00015*	*0.01*
P3[4]	*0.73*	*0.02*	*0.66*	*0.64*	*0.05*	*0.17*	*0.47*	*0.41*

Abbreviations: CAD, coronary artery disease; T2D, type 2 diabetes; TC, total cholesterol levels; LDLC, low-density-lipoprotein cholesterol levels; HDLC, high-density-lipoprotein cholesterol levels; TG, triglyceride levels; BMI, body mass index.

[1]Mean ± SD was presented; in total, 1348 controls and 1368 cases, 438 controls and 725 cases, 502 controls and 211 cases, and 5175 controls and 2178 cases, were included in the Gain, Sweden, WashU/UCSF, and WTCCC studies, respectively; the SNP lists used for constructing the weighted gene risk score for each trait were listed in Supplementary Table 2; the statistical significance for testing 8 traits was 0.006.

[2]P1, p value for 1 unit increase of weighed gene risk score with adjustment for gender and the covariates for population stratification using the logistic regression model.

[3]P2, p value for the meta-analysis over four studies.

[4] P_3, p value for Cochran's Q test of the heterogeneity.

[5] P value = 0.0003 after removing rs3184504 from the weighted gene risk score of CAD; P value = 0.42 after removing rs3177928 and rs492602 from the weighted gene risk score of TC; P value = 0.0025 after removing rs2247056 from the weighted gene risk score of TG.