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Association of Cardiovascular and Metabolic Disease Genes with Psoriasis

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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 comorbidities, 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 for 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 single-nucleotide polymorphisms (SNPs) that showed significant association with CAD, hypertension, body mass index (BMI), hyperlipidemia (total, low-density lipoprotein (LDL), and high-density lipoprotein (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 on the basis of latest expert opinions (McCarthy, 2010; O'Donnell and Nabel, 2011; Peden and Farrall, 2011). Detailed information about the selected SNPs is provided in Supplementary Table S1 online.

We evaluated the selected cardiovascular and metabolic SNPs for association with psoriasis in four psoriasis GWAS cohorts: the GAIN cohort including 1,368 psoriasis cases and 1,348 controls (Nair *et al.*, 2009), an unpublished psoriasis cohort from Sweden including 725 cases and 438 controls, a Washington University/University of California San Francisco cohort including 211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 cohort including 2,178 psoriasis cases and 5,175 controls (Strange *et al.*, 2010). Further details of the Swedish cohort are described in the Supplementary Methods online. IMPUTE2 was used to impute the ungenotyped SNPs using phase 3 HapMap and 1,000 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 adjustment of the first three principal components from a multidimensional scaling 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 the 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 Supplementary Table S2 online). After adjusting for multiple testing with the false discovery rate method, seven SNPs were found to be associated with psoriasis status (FDR_q < 0.05, Table 1). The alleles associated with increased risk for dyslipidemia (rs2247056, rs3177928, rs492602, and rs181362), increased blood pressure levels (rs805303, rs653178, and rs3184504), and increased risk for CAD (rs3184504) were associated with increased risk for 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), whereas the association for rs805303 persisted ($P=0.005$). As multiple psoriasis risk alleles are

Abbreviations: BMI, body mass index; CAD, coronary artery disease; GWAS, genome-wide association studies; HDL, high-density lipoprotein; LD, linkage disequilibrium; LDL, low-density lipoprotein; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes; wGRS, weighted gene risk score

Table 1. Top 10 metabolic SNPs associated with psoriasis status in the meta-analysis of four studies

Chromosome	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[2]
					GAIN[1,3]	Sweden[1,3]	WashU/UCSF[1,3]	WTCCC[1,3]			
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: CAD, coronary artery disease; CI, confidence interval; DBP, diastolic blood pressure; HDLC, high-density lipoprotein cholesterol levels; HTN, hypertension; LDLC, low-density lipoprotein cholesterol levels; OR, odds ratios; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; TC, total cholesterol levels; T2D, type 2 diabetes; TG, triglyceride levels; WTCCC, Wellcome Trust Case–Control Consortium.

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

[2]FDR_q, false discovery rate-adjusted *P*-value based on 358 SNPs in Supplementary Table S3 online.

[3]All *P*-values were adjusted by the first three principal components from a multidimensional scaling analysis of population stratification.

identified in HLA loci (Chen *et al.*, 2012), we cannot rule out that the significant association for rs805303 is derived from linkage disequilibrium (LD) with other psoriasis HLA risk alleles. Interestingly, we identified four 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 the 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* has pleiotropic signaling roles in regulating lymphocyte differentiation, induction of VCAM-1 and E-selectin on endothelial cells by tumor necrosis factor-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 4,482 psoriasis cases and 7,463 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 the 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 the ability to discriminate between cases and controls (Chen *et al.*, 2011). The GRS was weighted according to the effect size of the risk alleles, and a common set of SNPs were examined across all cohorts (see Supplementary Methods online). 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 eight traits, Table 2). The wGRS of total cholesterol levels did not reach significance after removing the top associated SNPs (rs3177928 and rs492602, $P = 0.42$, Tables 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 comorbidities 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 for