Published in final edited form as:
Br J Dermatol. 2013 March ; 168(3): 639–642. doi:10.1111/bjd.12001.

Interactions between adiposity and genetic polymorphisms on the risk of psoriasis

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Abstract

Background—Adiposity is a known risk factor for psoriasis. Genome-wide association studies have identified a number of genes associated with risk of psoriasis while the evidence on gene-environment interactions in psoriasis is very sparse.

Objective—To investigate the effect modification by obesity measures on the association between SNPs from published GWAS and risk of psoriasis.

Methods—Our psoriasis GWAS dataset comprised 9,194 participants, including 337 individuals with psoriasis and 8,857 controls from six GWAS, nested within the Nurses' Health Study (NHS), NHS II, and Health Professionals' Follow-up Study. Clinician-diagnosed psoriasis was ascertained with high validity. For stratified analyses, BMI was dichotomized at 25, and waist circumference was dichotomized at 30 (women) and 36 inches (men), while WHR was dichotomized at 0.8 (women) and 1.0 (men).

Results—41 out of 44 previously GWAS reported SNPS were included in our GWAS datasets. After excluding those with high linkage disequilibrium, 33 remained in the analysis. There were significant interactions between BMI and two SNPs in the *IL12B* (rs3212227) and *IL23R* genes (rs7530511). Further analysis of these two SNPs indicated interactions between rs3212227 and waist circumference or WHR (P_{int}<0.05), but not for rs7530511. These observations were confirmed among participants without type 2 diabetes or coronary heart disease. The interactions remained after simultaneously adjusting for BMI as a continuous variable. In addition, we did not observe significant main effect for rs7530511.

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Disclosures:

This manuscript contains original unpublished work and is not being submitted for publication elsewhere at the same time. Abrar A. Qureshi has received a grant from Amgen/Pfizer to evaluate "Biomarkers in psoriasis and psoriatic arthritis." AAQ also serves as a consultant for Abbott, Centocor, Novaritis, and the Centers for Disease Control and Prevention. The other authors state no conflict of interest.

Conclusions—The association between a polymorphism in *IL12B* and psoriasis risk may be modified by measures of overall and central adiposity.

Psoriasis is a Th1 and Th17-mediated inflammatory disorder that has been associated with coronary heart disease (CHD) and type 2 diabetes (T2D).[1-2] Both genetic and environmental factors have been implicated in psoriasis pathophysiology.[3-8] Genome-wide association studies (GWAS) have identified a number of genes associated with risk of psoriasis. However, only a handful of these genes, such as *IL12B* and *IL23R*, show consistent supporting evidence from multiple studies.[8] Adiposity is a well-known risk factor for psoriasis and the chronic, low-grade inflammatory state associated with adiposity has been postulated as the key underlying mechanism.[4] The roles of genetic factors may be modified by obesity in psoriasis development although evidence is sparse.[9-11] In this study, we investigated the effect modification by obesity measures on the association between SNPs from published GWAS and risk of psoriasis.

Our psoriasis GWAS dataset comprised 9,194 participants, including 337 psoriasis cases and 8,857 controls from six GWAS, nested within the Nurses' Health Study (NHS), NHS II, and Health Professionals' Follow-up Study (Supplementary text and table 1 online). We utilized Illumina HumanHap550 array, Illumina HumanHap 610 Quad array, or Affymetrix 6.0 array for genotyping. MACH v1.0.16 was used to impute more than 2.5 million SNPs with HapMap CEU phase II data (release 22) as the reference panel.[12] The MACH dosage files were used for the analysis. Those genotyped SNPs passing quality control procedures and the imputed SNPs with minor allele frequency >2.5% and imputation R^2>0.3 in each study were finally included.

Details on the cohorts and ascertainment of psoriasis have been described previously.[2] Clinician-diagnosed psoriasis was ascertained with high validity. Anthropometric information on body mass index (BMI) and measures of central obesity (waist circumference and waist-hip ratio, WHR) were obtained in the main questionnaire.[13] For stratified analysis, BMI was dichotomized at 25 kg/m^2, in line with the criteria for definition of overweight by the World Health Organization. Waist circumference was dichotomized at 30 (women) and 36 inches (men), according to the median value in three cohorts, while WHR was dichotomized at 0.8 (women) and 1.0 (men).

For each SNP, an unconditional logistic regression model was fitted for the effect of the risk allele defined based on the previous GWAS in psoriasis. We used an additive model, adjusting for age, smoking, alcohol intake, and vigorous physical activity. We coded the genotype in the additive models and coded measures of obesity as dichotomized variables and tested the statistical significance of the single interaction term. We examined the association and interaction among all participants, and then confirmed the significant results among a subgroup of individuals without T2D (n=1,818) or CHD (n=421). To minimize multiple testing, genetic risk scores were calculated by summing the number of the risk alleles for each SNP. We analyzed the interaction between risk scores of all SNPs, as well as SNPs in the inflammatory pathways, and obesity on psoriasis. The protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

Characteristics of subjects are listed in Supplementary table 2. Psoriatics tended to have more alcohol intake, higher anthropometric measurements and were more likely to be current smokers.

We identified 44 SNPs from previous reports, while 41 were included in our dataset. We excluded 8 because of the high linkage disequilibrium (LD) with other SNPs in the Hapmap database ($R^2 \geq 0.8$). The main effects of the remaining 33 SNPs are listed in Supplementary table 3. There were significant interactions between BMI and two SNPs in the *IL12B* (rs3212227) and *IL23R* genes (rs7530511) (Supplementary table 4). Further analysis of these two SNPs indicated interactions between rs3212227 and waist circumference or WHR ($P_{int}<0.05$), but not for rs7530511. These observations were confirmed among participants without T2D or CHD (Table 1). The interactions remained after simultaneously adjusting for BMI as a continuous variable. In addition, we did not observe significant main effect for rs7530511 (Supplementary table 3). We examined the interaction between obesity and the risk score of all SNPs, or SNPs in the inflammatory pathways, but did not find any significant interactions (Supplementary table 5 online).

Little is known about gene-environment interactions in psoriasis. With a number of published GWAS in psoriasis since 2007, we have the opportunity to evaluate gene-environment interactions in our cohort studies. We undertook a post-GWAS approach to identify the effect modification of obesity on the association between genetic variants and psoriasis. We confirmed the elevated risk of psoriasis associated with the SNP in *IL12B*, but only among overweight individuals. Those carrying the risk allele (*T* in rs3212227) with BMI >25 had an increased risk of psoriasis. Measures of central obesity may also influence the effect of *IL12B* SNP on risk of psoriasis. The total genetic risk score of the 33 SNPs ranged from 23 to 47. We did not observe an interaction between the genetic risk score and obesity, suggesting there is no cumulative effect of multiple SNPs modified by obesity. The *IL12B* gene encodes the IL12-p40 subunit of both IL-12 and IL-23, which have been shown to induce the expansion of interferon-γ–producing T-helper (Th) 1 and IL-17-producing Th-17 cells respectively, and may play a critical role in autoimmune inflammatory diseases.[14] Carriers of the risk allele of rs3212227, which is located in the 3′-UTR region, may therefore have an increased risk for autoimmune diseases, while obesity could further induce the inflammatory state required for development of psoriasis. Further evidence on the mechanisms of this interaction is warranted. In summary, our study provides evidence that the association between a polymorphism in *IL12B* and psoriasis risk may be modified by measures of overall and central adiposity. Our results should be interpreted with caution due to the possibility of multiple comparisons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work is partly supported by Department of Dermatology, Brigham and Women’s Hospital, CA87969, CA50385, CA055075 and CA49449.

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What's already known about this topic?

- Adiposity has been associated with psoriasis in prospective study and the chronic, low-grade inflammatory state associated with adiposity has been postulated as the key underlying mechanism.
- Prior genome-wide association studies have identified a number of genes associated with risk of psoriasis, with *IL12B* and *IL23R* demonstrating the most consistent associations across multiple studies.
- Evidence on the gene-environment interactions in psoriasis has been very sparse.

What does this study add?

- In a post-GWAS approach, we confirmed the elevated risk of psoriasis associated with the rs3212227 SNP in *IL12B*, but only among overweight individuals.
- The association between a polymorphism in *IL12B* and psoriasis risk may be modified by measures of overall and central adiposity.
- Our study indicated that gene-environment interaction could play important roles in development of psoriasis.

Table 1

Interaction between body mass index, waist circumference, waist/hip ratio, and genetic polymorphisms of *IL23R* (rs7530511) and *IL12B* (rs3212227) on risk of psoriasis

	All participants			Excluding those with type 2 diabetes or coronary heart disease		
	Cases/ controls	rs7530511 OR* (95% CI)	rs3212227 OR* (95% CI)	Cases/ controls	rs7530511 OR* (95% CI)	rs3212227 OR* (95% CI)
Overall BMI	337/8857	0.89 (0.71-1.11)	1.43 (1.15-1.77)	238/6717	0.83 (0.64-1.08)	1.43 (1.10-1.84)
Stratified by body mass index (kg/m^2)						
<25	123/4057	0.66 (0.47-0.92)	1.07 (0.77-1.48)	110/3551	0.63 (0.44-0.90)	1.00 (0.72-1.40)
≥25	214/4800	1.09 (0.81-1.47)	1.75 (1.31-2.34)	128/3166	1.11 (0.75-1.64)	2.09 (1.40-3.14)
P_{int}		0.030	0.026		0.044	0.005
Stratified by waist circumference						
Median low†	61/2262	0.79 (0.48-1.30)	0.94 (0.60-1.48)	59/2013	0.78 (0.47-1.31)	0.95 (0.60-1.50)
Median high†	210/4688	0.92 (0.69-1.23)	1.77 (1.32-2.37)	136/3257	0.85 (0.60-1.20)	1.91 (1.31-2.78)
P_{int}		0.56	0.022		0.85	0.021
Stratified by waist-hip ratio						
Median low†	153/4756	0.82 (0.59-1.12)	1.19 (0.88-1.60)	121/3861	0.77 (0.54-1.10)	1.23 (0.88-1.73)
Median high†	118/2194	1.01 (0.68-1.50)	2.28 (1.47-3.54)	74/1410	0.95 (0.58-1.55)	2.28 (1.30-4.01)
P_{int}		0.39	0.012		0.528	0.049

Abbreviations: CI, confidence interval; OR, odds ratio; P_{int}, *P* for interaction.

*OR per one test allele (C in rs7530511, T in rs3212227). P_{int} was obtained by adjusting for age (continuous), smoking (never, past, current with 1-14, 15-24 or ≥25 cigarettes/day), alcohol intake (none, <4.9, 5.0-9.9, 10-14.9, 15-29.9, or ≥30 g/d), and physical activity (in quintiles, metabolic equivalent hours/wk), and body mass index (continuous).

†According to the median value of waist circumference and waist/hip ratio in three cohorts, waist circumference was dichotomized at 30 (women) and 36 inches (men), while waist-hip ratio was dichotomized at 0.8 (women) and 1.0 (men)