Letter to the Editor

An association study of 36 psoriasis susceptibility loci for psoriasis vulgaris and atopic dermatitis in a Japanese population

Keywords:
Genetic polymorphism; Genome-wide association study; Atopic dermatitis; Psoriasis vulgaris; Japanese population

To the Editor,

Psoriasis is a chronic inflammatory skin disease caused by interplay between genetic and environmental factors, and psoriasis vulgaris (PsV) is the most common form of the disease [1]. Recent genome-wide association studies (GWASs) and meta-analysis of GWAS of psoriasis in European individuals have identified a total of 36 susceptibility loci at a genome-wide level of significance ($P < 5 \times 10^{-8}$) [2]. Conditional analysis of the 36 loci was also conducted and further identified five additional SNPs, rs2111485, rs2910686, rs4379175, rs13437088 and rs12720356 with genome-wide significance. We conducted a validation study of these 41 SNPs among the 36 loci in Japanese patients with PsV. Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease, and recent linkage and association studies have identified overlapping susceptibility loci of psoriasis and AD [3,4]. Since identification of shared genetic components helps to highlight the key molecular pathways involved in chronic inflammatory skin diseases, we also explored the association of these 41 SNPs in Japanese patients with AD.

We recruited a total of 259 patients with PsV diagnosed by clinical and histopathological findings (median age 53, 11–85 years, male:female ratio = 2.4:1.0) and a total of 999 patients with AD diagnosed according to the criteria of Hanifin and Rajka (median age 29, 3–77 years, male:female ratio = 1.3:1.0). As controls, 938 individuals who had never been diagnosed with AD or PsV were recruited from Fukui University and Miyatake Clinic (median age 50, 20–75 years, male:female ratio = 2.0:1.0). All individuals were unrelated Japanese and gave written informed consent to participate in the study. The study was approved by the ethical committees of the hospitals involved, the University of Tokyo, the Jikei University School of Medicine, Fukui University, Miyatake Clinic and the Institute of Physical and Chemical Research (RIKEN). Genomic DNA was prepared in accordance with standard protocols. We selected a total of 41 SNPs achieving genome-wide significance in a previous meta-analysis of GWASs [2]. SNPs were genotyped by using the multiplex PCR-based Invader assay (Third Wave Japan). We calculated allele frequencies and tested agreement with Hardy–Weinberg equilibrium using a χ^2 goodness of fit test as described [5], and no SNP was excluded from the analysis. Among 41 SNPs, four (rs9988642, rs12188300,

Table 1
Summary of allele frequencies of 37 previously reported loci for psoriasis.

dbSNP	Gene	Control $n=938$	PsV $n=259$	AD $n=999$	*P* value	PsV	*P* value	AD
		MAF	MAF	MAF		OR (95% CI)		OR (95% CI)
rs11121129	*SLC45A1*, *TNFRSF9*	0.222	0.230	0.227	7.19E−01	1.04 (0.83–1.32)	7.16E−01	1.03 (0.88–1.20)
rs7552167	*IL28RA*	0.192	0.141	0.196	8.12E−03	0.69 (0.53–0.91)	7.86E−01	1.02 (0.87–1.20)
rs7536201	*RUNX3*	0.388	0.344	0.358	6.55E−02	0.83 (0.67–1.01)	5.40E−02	0.88 (0.77–1.00)
rs6677595	*LCE3B*, *LCE3D*	0.412	0.363	0.417	4.52E−02	0.81 (0.67–1.00)	7.33E−01	1.02 (0.90–1.16)
rs62149416	*FLJ16341*, *REL*	0.039	0.043	0.038	6.70E−01	1.11 (0.68–1.81)	8.73E−01	0.97 (0.70–1.36)
rs10865331	*B3GNT2*	0.315	0.347	0.311	1.67E−01	1.16 (0.94–1.42)	7.97E−01	0.98 (0.86–1.13)
rs2111485	*IFIH1*	0.173	0.181	0.174	6.72E−01	1.06 (0.82–1.36)	9.03E−01	1.01 (0.85–1.19)
rs17716942	*KCNH7*, *IFIH1*	0.000	0.000	0.001	–	–	3.30E−01	–
rs27432	*ERAP1*	0.406	0.373	0.382	1.73E−01	0.87 (0.71–1.06)	1.30E−01	0.90 (0.79–1.03)
rs2910686	*ERAP2*	0.484	0.516	0.510	2.10E−01	1.13 (0.93–1.38)	1.19E−01	1.11 (0.97–1.26)
rs1295685	*IL13*, *IL4*	0.302	0.274	0.346	2.18E−01	0.87 (0.70–1.08)	3.54E−03	1.22 (1.07–1.40)
rs2233278	*TNIP1*	0.089	0.174	0.086	3.50E−08	2.15 (1.63–2.84)	7.34E−01	0.96 (0.77–1.20)
rs4379175	*IL12B*	0.430	0.311	0.450	1.25E−06	0.60 (0.49–0.74)	2.02E−01	1.09 (0.96–1.23)
rs9504361	*EXOC2*, *IRF4*	0.217	0.234	0.213	4.00E−01	1.10 (0.88–1.39)	7.51E−01	0.98 (0.84–1.14)
rs4406273	*HLA-B*, *HLA-C*	0.011	0.045	0.010	5.86E−07	4.12 (2.26–7.51)	6.13E−01	0.85 (0.46–1.59)
rs13437088	*MICA*	0.290	0.278	0.269	5.94E−01	0.94 (0.76–1.17)	1.38E−01	0.90 (0.78–1.04)
rs33980500	*TRAF3IP2*	0.017	0.050	0.021	9.39E−06	3.13 (1.84–5.32)	2.96E−01	1.28 (0.80–2.05)
rs582757	*TNFAIP3*	0.056	0.060	0.063	7.20E−01	1.08 (0.71–1.63)	3.70E−01	1.13 (0.86–1.48)
rs2451258	*TAGAP*	0.029	0.021	0.021	3.14E−01	0.72 (0.37–1.38)	1.05E−01	0.72 (0.48–1.07)
rs2700987	*ELMO1*	0.094	0.109	0.094	2.87E−01	1.19 (0.86–1.63)	9.86E−01	1.00 (0.81–1.25)
rs11795343	*DDX58*	0.224	0.241	0.257	4.23E−01	1.10 (0.87–1.38)	1.92E−02	1.19 (1.03–1.39)
rs10979182	*KLF4*	0.399	0.442	0.416	8.14E−02	1.19 (0.98–1.45)	2.89E−01	1.07 (0.94–1.22)
rs1250546	*ZMIZ1*	0.473	0.417	0.422	2.43E−02	0.80 (0.66–0.97)	1.65E−03	0.82 (0.72–0.93)
rs645078	*RPS6KA4*, *PRDX5*	0.239	0.234	0.239	8.33E−01	0.98 (0.78–1.23)	9.94E−01	1.00 (0.86–1.16)
rs4561177	*ZC3H12C*	0.365	0.371	0.382	8.24E−01	1.02 (0.84–1.25)	2.95E−01	1.07 (0.94–1.22)
rs3802826	*ETS1*	0.269	0.301	0.292	1.45E−01	1.17 (0.95–1.45)	1.12E−01	1.12 (0.97–1.29)
rs2066819	*STAT2*, *IL23A*	0.046	0.027	0.037	6.15E−02	0.58 (0.33–1.03)	2.01E−01	0.81 (0.59–1.12)
rs8016947	*NFKBIA*	0.479	0.454	0.471	3.15E−01	0.90 (0.74–1.10)	6.23E−01	0.97 (0.85–1.10)
rs367569	*PRM3*, *SOCS1*	0.094	0.081	0.099	3.59E−01	0.85 (0.60–1.21)	5.87E−01	1.06 (0.86–1.31)
rs12445568	*PRSS53*, *FBXL19*	0.085	0.093	0.066	5.77E−01	1.10 (0.78–1.54)	2.60E−02	0.76 (0.60–0.97)
rs28998802	*NOS2*	0.009	0.010	0.009	8.09E−01	1.13 (0.41–3.11)	9.97E−01	1.00 (0.50–1.99)
rs963986	*PTRF*, *STAT3*, *STAT5A/B*	0.372	0.442	0.377	4.18E−03	1.33 (1.09–1.63)	7.89E−01	1.02 (0.89–1.16)
rs11652075	*CARD14*	0.409	0.440	0.413	2.17E−01	1.13 (0.93–1.38)	7.98E−01	1.02 (0.89–1.16)
rs545979	*POL1*, *STARD6*, *MBD2*	0.024	0.029	0.022	5.31E−01	1.21 (0.67–2.19)	6.97E−01	0.92 (0.60–1.40)
rs892085	*ILF3*, *CARM1*	0.275	0.285	0.260	6.54E−01	1.05 (0.85–1.30)	2.92E−01	0.93 (0.80–1.07)
rs1056198	*RNF114*	0.315	0.308	0.341	7.51E−01	0.97 (0.78–1.19)	8.67E−02	1.13 (0.98–1.29)
rs4821124	*UBE2L3*	0.357	0.375	0.371	4.40E−01	1.08 (0.88–1.33)	3.80E−01	1.06 (0.93–1.21)

rs34536443 and rs12720356) were found to be monomorphic in this study. We compared differences in the allele frequencies of the 37 polymorphisms between case and control subjects by using a contingency χ^2 test or Fisher's exact test, and calculated odds ratios (ORs) with 95 percent confidence intervals (95% CI). We then applied Bonferroni corrections, the multiplication of P values by the number SNPs assessed ($n = 37$). Statistical significance was set at $P < 0.05$.

All genotype frequencies and statistical results are shown in Table 1 and Supplementary Tables S1 and S2. We found significant associations with PsV in four SNPs, *TNIP1* (rs2233278, $P = 3.5 \times 10^{-8}$), *IL12B* (rs4379175, $P = 1.2 \times 10^{-6}$), the MHC class I region (rs4406273, $P = 5.9 \times 10^{-7}$) and *TRAF3IP2* (rs33980500, $P = 9.4 \times 10^{-6}$), after Bonferroni correction for 37 tests with $P < 1.4 \times 10^{-3}$ (0.05/37) (Table 1). The direction of associations of susceptibility to PsV was similar to that in the recent study [2], and confirmed previous Japanese studies that have shown significant associations with *IL12B* [6], *TRAF3IP2* [7] and the MHC class I region [8]. The strongest association was observed in Japanese patients with PsV for the first time at *TNIP* for SNP rs2233278, and *TNIP* encodes ABIN-1, an A20-binding protein that links A20 to NEMO/IKKγ and results in inhibition of NF-κB by facilitation of A20-mediated deubiquitination of NEMO/IKKγ [9].

A recent GWAS of childhood-onset AD showed the genetic relationship between AD and psoriasis [4]. The study examined SNPs previously shown to associate with psoriasis by a GWAS, and approximately two-thirds of those associated variants exhibited opposite risk profiles for AD versus psoriasis. The most significant association with AD in that study was observed at SNP rs1295685 in the *IL13* locus at a genome-wide level that exhibited opposing effects in AD and psoriasis. In this study, we observed marginal associations between AD and the two susceptibility SNPs for psoriasis, *IL13* (rs1295685, $P = 3.5 \times 10^{-3}$) and *ZMIZ1* (rs1250546, $P = 1.7 \times 10^{-3}$), in the opposite and same direction, respectively. *ZMIZ1* encodes a member of the PIAS (protein inhibitor of activated STAT) family of proteins that regulates the activity of several transcription factors [10]. The *IL13* and *ZMIZ1* loci might contain common genetic factors shared by these two common skin diseases.

Our data strongly suggests the importance of the *TNIP*, *IL12B*, *TRAF3IP2* loci and the MHC class I region in the susceptibility to PsV in the Japanese population. However, there are two limitations in our study. First, the sample size was relatively small. Second, we conducted the validation study using only SNPs reported in previous GWASs of psoriasis. Therefore, the associations of the other SNPs within the susceptibility loci remain unclear and further studies are necessary to achieve better understanding the genetic components of these chronic inflammatory skin diseases.

Acknowledgments

We thank all the individuals who participated in the study. We also thank M.T. Shimizu, H. Sekiguchi, A.I. Jodo, N. Kawaraichi and the technical staff of the Center for Genomic Medicine for providing technical assistance and K. Barrymore for proofreading this manuscript. This work was supported by Health Science Research Grants from the Ministry of Health, Welfare and Labor of Japan and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2014.08.005.

References

[1] Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361:496–509.
[2] Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet 2012;44:1341–8.
[3] Elder JT, Bruce AT, Gudjonsson JE, Johnston A, Stuart PE, Tejasvi T, et al. Molecular dissection of psoriasis: integrating genetics and biology. J Invest Dermatol 2010;130:1213–26.
[4] Weidinger S, Willis-Owen SA, Kamatani Y, Baurecht H, Morar N, Liang L, et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. Hum Mol Genet 2013;22:4841–56.
[5] Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Sakashita M, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. Nat Genet 2012;44:1222–6.
[6] Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, et al. Interleukin-12 p40 gene (IL12B) 3′-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. J Dermatol Sci 2002;30:161–6.
[7] Hayashi M, Hirota T, Saeki H, Nakagawa H, Ishiuji Y, Matsuzaki H, et al. Genetic polymorphism in the TRAF3IP2 gene is associated with psoriasis vulgaris in a Japanese population. J Dermatol Sci 2014;73:264–5.
[8] Oka A, Tamiya G, Tomizawa M, Ota M, Katsuyama Y, Makino S, et al. Association analysis using refined microsatellite markers localizes a susceptibility locus for psoriasis vulgaris within a 111 kb segment telomeric to the HLA-C gene. Hum Mol Genet 1999;8:2165–70.
[9] Mauro C, Pacifico F, Lavorgna A, Mellone S, Iannetti A, Acquaviva R, et al. ABIN-1 binds to NEMO/IKKgamma and co-operates with A20 in inhibiting NF-κB. J Biol Chem 2006;281:18482–88.
[10] Li X, Thyssen G, Beliakoff J, Sun Z. The novel PIAS-like protein hZimp10 enhances Smad transcriptional activity. J Biol Chem 2006;281:23748–56.

Mayumi Tamari[a,1], Hidehisa Saeki[b,1,*], Mitsuha Hayashi[c], Yoshinori Umezawa[c], Toshihiro Ito[c], Osamu Fukuchi[c], Yoshimasa Nobeyama[c], Koichi Yanaba[c], Hidemi Nakagawa[c], Yuichiro Tsunemi[d], Toyoaki Kato[e], Sayaka Shibata[e], Makoto Sugaya[e], Shinichi Sato[e], Yayoi Tada[f], Satoru Doi[g], Akihiko Miyatake[h], Kouji Ebe[i], Emiko Noguchi[j], Shigeharu Fujieda[k], Tamotsu Ebihara[l], Masayuki Amagai[l], Hitokazu Esaki[m], Satoshi Takeuchi[m], Masutaka Furue[m], Tomomitsu Hirota[a]

[a]*Laboratory for Respiratory and Allergic Diseases, Center for Integrative Medical Sciences, RIKEN, Japan*; [b]*Department of Dermatology, Nippon Medical School, Japan*; [c]*Department of Dermatology, The Jikei University School of Medicine, Japan*; [d]*Department of Dermatology, Tokyo Women's Medical University, Japan*; [e]*Department of Dermatology, Faculty of Medicine, University of Tokyo, Japan*; [f]*Department of Dermatology, Teikyo University School of Medicine, Japan*; [g]*Osaka Prefectual Medical Center for Respiratory and Allergic Diseases, Japan*; [h]*Miyatake Asthma Clinic, Japan*; [i]*Takao Hospital, Japan*; [j]*Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan*; [k]*Department of Otorhinolaryngology-Head and Neck Surgery, School of Medicine, University of Fukui, Japan*; [l]*Department of Dermatology, Keio University School of Medicine, Japan*; [m]*Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Japan*

[*]Corresponding author at: Department of Dermatology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
Tel.: +81 3 3822 2131; fax: +81 3 3823 6731

E-mail address: h-saeki@nms.ac.jp (H. Saeki).

[1]These authors contributed equally to this article.

Received 5 June 2014

http://dx.doi.org/10.1016/j.jdermsci.2014.08.005