Arthritis & Rheumatology
Vol. 73, No. 7, July 2021, pp 1155–1166
DOI 10.1002/art.41655

American College of Rheumatology
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Contribution of a European-Prevalent Variant near *CD83* and an East Asian–Prevalent Variant near *IL17RB* to Herpes Zoster Risk in Tofacitinib Treatment: Results of Genome-Wide Association Study Meta-Analyses

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Objective. Tofacitinib is an oral JAK inhibitor for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis, and has been previously investigated for psoriasis (PsO). This meta-analysis of genome-wide association studies (GWAS) was performed to identify genetic factors associated with increased risk/faster onset of herpes zoster (HZ) in subjects with RA or PsO receiving tofacitinib treatment, and to determine potential mechanisms that could be attributed to the varying rates of HZ across ethnicities.

Methods. In an ethnicity/indication-specific, trans-ethnic, trans-population meta-analysis of GWAS in subjects with RA or PsO from phase II, phase III, and long-term extension studies of tofacitinib, 8 million genetic variants were evaluated for their potential association with time to an HZ event and incidence of an HZ event (case versus control) with tofacitinib treatment, using Cox proportional hazard and logistic regression analyses, respectively.

Results. In total, 5,246 subjects were included (3,168 with RA and 2,078 with PsO). After adjustment for age, baseline absolute lymphocyte count, genetically defined ethnicity, and concomitant methotrexate use (in RA subjects only), 4 loci were significantly associated with faster onset of HZ in European subjects ($P < 5 \times 10^{-8}$), including a single-nucleotide polymorphism (SNP) near *CD83* (frequency of risk allele ~2% in European subjects versus ~0.1% in East Asian subjects). In the trans-ethnic, trans-population meta-analysis, the *CD83* SNP remained significant. Four additional significant loci were identified in the meta-analysis, among which a SNP near *IL17RB* was associated with faster onset of HZ (meta-analysis hazard ratio 3.6 [95% confidence interval 2.40–5.44], $P = 7.6 \times 10^{-10}$; frequency of risk allele ~12% in East Asian subjects versus <0.2% in European subjects).

Conclusion. Genetic analysis of tofacitinib-treated subjects with RA or PsO identified multiple loci associated with increased HZ risk. Prevalent variants near the immune-relevant genes *CD83* and *IL17RB* in European and East Asian populations, respectively, may contribute to risk of HZ in tofacitinib-treated subjects.

INTRODUCTION

Tofacitinib is an oral JAK inhibitor for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC), and has been previously investigated for psoriasis (PsO). Tofacitinib is an orally bioavailable small molecule whose inhibitory activity involves blockade of the ATP binding site (1). In cellular settings where the various JAKs signal in combination, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK1 and/or JAK3, and has functional selectivity over

Sponsored by Pfizer Inc. The studies of CD4+ T cell subsets were supported by funding from Pfizer Inc. and Takeda Pharmaceutical Co., Ltd., and by a grant from RIKEN.

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Drs. Bing, Zhou, Zhang, and Clark were employees of Pfizer Inc. at the time of the analysis. Drs. Chen, Hirose, Valdez, Vincent, and Martin own stock or stock options in Pfizer Inc. Drs. Kochi, Tsuchida, Ishigaki, Sumitomo, and Fujio have received research funding from Chugai Pharmaceutical Co., Ltd., Pfizer Inc., and Takeda Pharmaceutical Co., Ltd.

JAK2 (1). The efficacy and safety of tofacitinib have been studied across multiple immune-mediated inflammatory diseases, including RA (2–7) and PsO (8–11).

The safety profile of tofacitinib in subjects with RA or PsO is generally similar to that of tumor necrosis factor inhibitors and other biologic disease-modifying antirheumatic drugs (bDMARDs), with the exception of herpes zoster (HZ) rates (12–15). HZ risk is elevated in subjects with RA in comparison to the general population (16), and the risk is further increased in tofacitinib-treated subjects (17), although multidermatomal or disseminated HZ cases have been infrequent (8% of HZ cases) in subjects receiving tofacitinib (13). This appears to be a class-specific effect, because use of other JAK inhibitors targeting JAK1 or JAK1/JAK2 has resulted in an increased risk of HZ (18). HZ risk in tofacitinib-treated subjects with RA increases with age, glucocorticoid use, tofacitinib dose, and enrollment within Asia (e.g., subjects from Japan and Korea have 2–3-fold higher rates of HZ versus those from other regions) (19). Similarly, in tofacitinib-treated subjects with PsO, HZ risk increases with age, tofacitinib dose, and Asian descent, and also prior bDMARD use (20). Subjects with UC and those with PsA receiving tofacitinib also experience higher rates of HZ when compared with subjects who have not been treated with tofacitinib (21–23). The higher HZ rates in Asian subjects observed in the RA and PsO studies (17,20) could be attributable to multiple factors, including ascertainment bias, prevalence of a genetic clade of virus prone to reactivation, enhanced response to tofacitinib, or an interaction between JAK inhibition and a genetic polymorphism more common in Japan and Korea.

Genetic studies have identified variations in the HLA region as being associated with risk of HZ (24). We hypothesized that genetic factors may be associated with tofacitinib-related HZ, and that the genetic variation across ethnicities may contribute to the variance in HZ rates. Identifying such genetic factors could help reveal the mechanisms of, and hence the risk of, varicella zoster virus (VZV) reactivation related to tofacitinib. We therefore conducted a genome-wide trans-ancestry meta-analysis of HZ using DNA samples from RA and PsO subjects receiving treatment with tofacitinib in clinical studies. Furthermore, to understand the mechanism of an HZ-associated variant near *IL17RB*, we correlated the allele count and the expression of candidate genes in immune cell types via an expression quantitative trait loci (eQTL) analysis.

PATIENTS AND METHODS

Population. This analysis included subjects with RA or PsO from phase II and phase III index tofacitinib studies (ClinicalTrials.gov identifiers NCT00413660, NCT00550446, NCT00603512, NCT00687193, NCT01059864, NCT00960440, NCT00847613, NCT00814307, NCT00856544, NCT00853385, NCT01039668, NCT00678210, NCT01276639, NCT01309737, NCT01241591, NCT01186744, and NCT01519089) and the corresponding long-term extension (LTE) studies (ClinicalTrials.gov identifiers NCT00413699, NCT00661661, and NCT01163253) (for more details, see Supplementary Table 1 available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract). All subjects provided written informed consent.

Blood samples for genetic studies were genotyped, and passed sample quality control (QC). HZ events from both index and LTE studies were included in the analysis (data cutoff: April 2014).

Genotyping, imputation, and data QC. Germline DNA was extracted from peripheral blood. Single-nucleotide polymorphism (SNP) data were generated using Illumina Human OmniExpress Plus Exome genome-wide arrays, versions 1–4 (https://www.illumina.com/products/by-type/microarray-kits/infinium-omni-express-exome.html). The genotype calls were conducted through GenomeStudio by Illumina. SNPs were imputed using IMPUTE2 (25), using reference panels from the 1000 Genomes Project phase I integrated variant set. Subjects who failed the sex match based on self-reported sex or those who failed the heterozygosity check or relatedness test were excluded from the downstream analysis. Furthermore, SNPs that were estimated to have poor imputation performance (quality score <0.9) were removed from the analysis.

Up to 8 million autosomal SNPs were imputed. The allelic dosage of each genetic variant, ranging from 0 to 2 and calculated from posterior genotype probabilities from IMPUTE2, was used in each statistical model. As an additional QC step, allele frequencies of variants that produced the strongest association signals were compared with those reported in the gnomAD database (https://gnomad.broadinstitute.org/).

To determine the genetic ancestry of all subjects, we performed a principal components analysis (PCA) using EIGENSTRAT. Prior to PCA, the study data were combined with data from the 1000 Genomes Project. Independent autosomal SNPs across the

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Submitted for publication November 28, 2019; accepted in revised form January 12, 2021.

genome were selected after pruning, and chromosomal regions known to be associated with ethnicity were also removed before running SmartPCA. Empiric ancestry groups were then determined based on the distribution over the first 2 principal components in each self-reported population, using clinical data. Subjects who were more than 6 standard deviations from either of the 2 first principal components were removed in the final statistical analyses.

End points and analyses of associations. Two end points were evaluated: 1) time to HZ event with tofacitinib treatment, defined as the interval between the first tofacitinib treatment in either the index or the LTE studies and the earliest HZ event; and 2) numbers of HZ cases versus controls, in which HZ cases were subjects with investigator-reported HZ, and controls were subjects who received tofacitinib in the index or LTE studies and did not develop HZ during the study observation period. Cox proportional hazard and logistic regression analyses were used for assessing associations with the time to HZ event and incidence of an HZ event (cases versus controls), respectively. R version 3.2 software was used for the statistical analyses.

Covariates. A set of baseline clinical variables that are known to, or could potentially, affect the rate of HZ were evaluated for inclusion as covariates in the analysis model. The covariates considered in RA studies included age (in years), sex, baseline weight, baseline rheumatoid factor status, baseline RA severity based on the Disease Activity Score in 28 joints (26), erythrocyte sedimentation rate, RA duration, baseline absolute lymphocyte count (ALC), baseline neutrophil count, glucocorticoid use, and concomitant methotrexate use. The covariates considered in PsO studies included age (in years), sex, baseline weight, baseline ALC, baseline neutrophil count, PsO duration, presence versus absence of PsA at baseline, and proportion of subjects achieving a 75% decrease in the Psoriasis Area and Severity Index (27) at week 12 or week 16 (depending on the trial). Tofacitinib dose was not included as a covariate because of the potential for dose switching in the LTE studies.

Covariates were selected via stepwise variable selection, using a *P* value cutoff of 0.05. In this analysis, age, baseline ALC, genetic population stratification, and concomitant methotrexate use (in RA subjects only) were included as covariates in the association test. Additionally, the first 3 principal components defined by genetic data within each ancestry subgroup were included in the analysis model.

Ancestry-specific and trans-ancestry genome-wide association study (GWAS) meta-analyses. Genetic ancestry subgroups of subjects (European, East Asian, South Asian, Hispanic, and Black) were defined as those clustering in principal component space, as estimated from genome-wide genotype data in combination with self-reported ethnicities. Ancestry-specific GWAS were performed for European, East Asian, and Hispanic subgroups. The sample sizes for the Black and South Asian populations were small; these subgroups were therefore excluded from the GWAS.

Each SNP with a minor allele frequency (MAF) of >2% in each ethnicity subgroup within either the RA or PsO populations was tested for association, under an additive model with adjustment for covariates. A meta-analysis across the ancestry subgroups and populations was conducted via a fixed effects model, with significant association defined as *P* values less than or equal to 5×10^{-8}. The meta-analysis included any SNPs with an MAF of >2% in at least 1 ethnicity subgroup; rarer alleles were not included, as the sample size would not be expected to provide adequate power for the risk estimate. Trans-ethnicity allelic heterogeneity was assessed with Cochran's Q test using the meta-analysis random effects model, with a statistically significant level defined, using the conservative Bonferroni correction, as 0.005 (0.05 divided by 10). In an additional analysis, we restricted the meta-analysis to variants with an MAF of >2% in all ethnic subgroups. Significant loci were labeled according to the gene nearest to the lead SNP, unless a compelling biologic candidate was mapped nearby. The overall design of the trans-ancestry and trans-population GWAS meta-analysis is illustrated in Figure 1.

Assessment of associations between genetic variants and proportions of CD4+ T cell subtypes. To identify the role of genetic variants in regulating immune phenotypes, flow cytometry was performed on freshly isolated peripheral blood mononuclear cells (PBMCs) from 82 healthy Japanese individuals (see Supplementary Methods, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).

Standardized human immunophenotyping was performed to classify CD4+ T cells into conventional Th1, Th2, Th17, and Treg cell types. Association of the genetic variants with the proportions of these CD4+ T cell subtypes was evaluated using an additive genetic model via linear regression analysis. In this analysis, only the association of the candidate SNP on CD4+ T cell subtypes

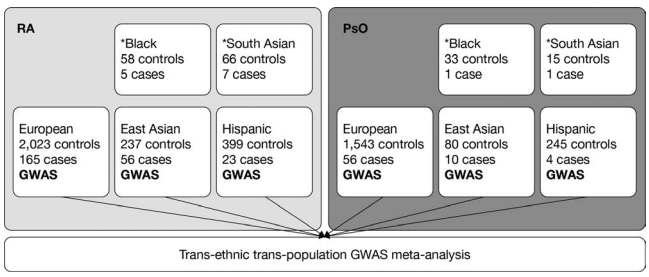

Figure 1. Overall design of the trans-ancestry and trans-population genome-wide association study (GWAS) meta-analysis in subjects with rheumatoid arthritis (RA) or psoriasis (PsO). *Black and South Asian subgroups were excluded from the GWAS meta-analysis due to small sample sizes.

was reported. Significance of the associations was defined as a *P* value cutoff of 0.05.

T cell subtype–specific eQTL analysis. Blood samples were collected from 29 healthy Japanese individuals. Naive CD4+ T cells from these individuals were collected via fluorescence-activated cell sorting. These cells were cultured for 72 hours and differentiated into T cell subtypes via stimulation of CD3/CD28 (for Th0 cells), CD3/CD28 plus interferon-γ (IFNγ) (for Th1 cells), CD3/CD28 plus interleukin-4 (IL-4) (for Th2 cells), CD3/CD28 plus IL-1β plus IL-6 plus IL-23 plus transforming growth factor β (TGFβ) (for Th17 cells), or CD3/CD28 plus IL-2 plus TGFβ plus all-*trans*-retinoic acid (for Treg cells). Gene expression of each cell type was measured using RNA sequencing with Illumina HiSeq 2000. Genotyping was conducted via Infinium OmniExpressExome BeadChips. Gene expression levels were quantified using Hisat2 (28) and HTSeq (29) using the GENCODE annotation (version 25), followed by normalization using probabilistic estimation of expression residuals (30,31); the residuals were further treated by quantile normalization, and each gene expression value was then rank-transformed to fit normal distribution. The association between variants and normalized expression values was analyzed using linear regression with an additive effects model. Within this analysis, only the eQTLs of the candidate SNP on the candidate gene are reported. Significant association was defined as a *P* value cutoff of 0.05.

The studies involving blood samples from healthy Japanese individuals were approved by the Ethics Committees of RIKEN and the University of Tokyo. Written informed consent was obtained from each volunteer.

RESULTS

Subjects. Overall, 9,640 subjects with RA or PsO were recruited in the 17 phase II, phase III, and LTE studies (Supplementary Table 1 [http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract]). DNA samples were collected from 5,605 subjects; 5,246 subjects (3,168 RA subjects and 2,078 PsO subjects) remained in the genetic studies following sample QC. A total of 5,027 subjects received ≥1 dose of tofacitinib in the index or LTE studies, and thus were retained in the analysis. The other 219 subjects were initially included in the placebo or comparator arms in the index studies and were not switched to tofacitinib in the LTE studies.

Of the tofacitinib-treated subjects, 328 cases of HZ were reported (256 cases among RA subjects and 72 cases among PsO subjects). The numbers of subjects within each genetic ancestry subgroup were as follows: 3,787 European (75.3%), 671 Hispanic (13.3%), 383 East Asian (7.6%), 97 Black (1.9%), and 89 South Asian (1.8%) (Figure 1 and Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract). The HZ rates and distribution of demographic and clinical characteristics of the subjects in this genotyped cohort were consistent with those in the overall trial populations (see details in Supplementary Tables 3 and 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).

Identification of 4 genetic loci associated with increased HZ risk in European ancestry GWAS. Ancestry-specific GWAS were performed in European, Hispanic, and East Asian ethnicity subgroups within the RA or PsO populations (Figure 1 and Supplementary Table 2 [http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract]). European ancestry–specific GWAS identified 4 loci (1 in RA subjects and 3 in PsO subjects) that were significantly associated with a faster time to an HZ event ($P < 5 \times 10^{-8}$) in tofacitinib-treated subjects (Table 1 and Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).

In the European RA population, the variant rs59967896, located on chromosome 20 within 6.7 kb 3′ of the prostate transmembrane protein androgen induced 1 (*PMEPA1*) locus, was significantly associated with time to an HZ event (hazard ratio [HR] 3.8, $P = 8.3 \times 10^{-10}$) and showed a marginal association (odds ratio [OR] 4.1, $P = 2.3 \times 10^{-7}$) in the HZ case versus control analysis. The variant rs59967896 had an alternative allele with a "CAA" insertion that, to our knowledge, had no reported functions (see Supplementary Figure 2A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract). The *PMEPA1* locus showed no associations with the HZ end points in the European PsO population, nor were there any associations evident in the Hispanic and East Asian populations of either RA or PsO subjects.

In the European PsO population, 3 genetic loci at *CD83* (rs112817503), *UGDH* (rs150665541), and *VWF* (rs200638456) were associated with faster time to HZ (Supplementary Figures 2B–D [http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract]). SNP variant rs112817503 was associated with a faster time to onset of HZ (HR 5.7, $P = 1.4 \times 10^{-10}$) and increased risk of occurrence of an HZ event (OR 7.7, $P = 6.3 \times 10^{-8}$). *CD83* was the closest coding gene to rs112817503, which was 155 kb away. Variant rs150665541 was associated with a faster time to onset of HZ (HR 4.9, $P = 2.1 \times 10^{-8}$) and increased risk of occurrence of an HZ event (OR 5.5, $P = 3.6 \times 10^{-6}$); it was located in the second intron of *UGDH*. Variant rs200638456 was associated with a faster time to onset of HZ (HR 3.5, $P = 2.9 \times 10^{-8}$) and increased risk of occurrence of an HZ event (OR 4.0, $P = 1.1 \times 10^{-6}$). The rs200638456 variant was located within an intronic region of *VWF*, with a repeated sequence of the dinucleotide "AC." The alternative allele of rs200638456 had an additional insertion of the dinucleotide "AC."

In the Hispanic and East Asian ancestry subgroups of RA and PsO subjects, GWAS analysis did not reveal any significant results

Table 1. Genetic loci found to be associated with increased HZ risk in the European ancestry GWAS*

Disease, ethnicity	Locus	Chr	Reference SNP ID	Position	Allele			Time to HZ event†		Incidence of HZ (case versus control)‡	
					Reference allele	Alternative allele	Alternative allele frequency	HR (95% CI)	*P*	OR (95% CI)	*P*
RA											
European	*PMEPA1*	20	rs59967896	56216698	T	TCAA	0.03	3.75 (2.46–5.71)	8.34×10^{-10}	4.1 (2.51–6.69)	2.34×10^{-7}
PsO											
European	*CD83*	6	rs112817503	14292820	C	T	0.03	5.74 (3.38–9.77)	1.14×10^{-10}	7.71 (4.02–14.8)	6.25×10^{-8}
European	*UGDH*	4	rs150665541	39536523	C	T	0.03	4.86 (2.79–8.45)	2.10×10^{-8}	5.46 (2.88–10.3)	3.57×10^{-6}
European	*VWF*	12	rs200638456	6102826	T	TAC	0.07	3.5 (2.25–5.46)	2.94×10^{-8}	4.04 (2.42–6.75)	1.08×10^{-6}

* GWAS = genome-wide association study; Chr = chromosome; SNP ID = single-nucleotide polymorphism cluster identification; HR = hazard ratio; 95% CI = 95% confidence interval; OR = odds ratio; RA = rheumatoid arthritis; PsO = psoriasis.
† Results of the Kaplan-Meier analyses of time to herpes zoster (HZ) event are presented in Supplementary Figure 4 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).
‡ C-statistics for the case versus control logistic regression model are presented in Supplementary Table 5 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).

Table 2. Genetic loci achieving genome-wide significance in either the time to HZ event or HZ case versus control trans-ancestry and trans-population GWAS meta-analyses*

				Allele			Time to HZ event		Incidence of HZ (case versus control)	
Locus	Genetic variant	Chr	Position	Reference allele	Alternative allele	Allele frequency†	HR (95% CI)	*P*	OR (95% CI)	*P*
IL17RB	rs58861611	3	54118714	T	C	0.093	3.6 (2.40–5.44)	7.6×10^{-10}	3.8 (2.17–6.67)	3.0×10^{-6}
CD83	rs112817503	6	14292820	T	C	0.022	3.6 (2.43–5.32)	1.5×10^{-10}	3.7 (2.35–5.87)	2.1×10^{-8}
GPR141	rs56114331	7	37802731	C	T	0.019	3.7 (2.37–5.73)	6.3×10^{-9}	3.4 (2.05–5.49)	1.5×10^{-6}
TOX3	rs79025327	16	52505167	G	A	0.072	2.9 (2.04–4.22)	6.4×10^{-9}	3.8 (2.28–6.23)	2.2×10^{-7}
ACSF3	rs142820005	16	89211411	T	A	0.055	2.3 (1.72–3.09)	2.3×10^{-8}	2.5 (1.81–3.45)	2.7×10^{-8}

* The threshold for genome-wide significance was defined as $P < 5 \times 10^{-8}$. HZ = herpes zoster; GWAS = genome-wide association study; Chr = chromosome; HR = hazard ratio; 95% CI = 95% confidence interval; OR = odds ratio.
† Allele frequency was calculated based on weighted allele frequency in each ancestry group by the standard deviation of the association effects.

(at the threshold of $P < 5 \times 10^{-8}$), likely because the sample sizes were modest. Other meta-analyses across ethnicity subgroups and populations could reveal additional loci, especially those with consistent effects across these subgroups.

Identification of 4 additional genetic loci associated with increased HZ risk in trans-ancestry and trans-population GWAS meta-analyses. A meta-analysis of the ancestry- and population-specific GWAS identified SNPs at 5 loci achieving genome-wide significance (combined meta-analysis $P < 5 \times 10^{-8}$) in the HZ case versus control analysis and/or in the time to HZ event analysis (Table 2 and Figure 2; see also Supplementary Figure 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract). These 5 loci included *IL17RB*, *CD83*, *GPR141*, *TOX3*, and *ACSF3/CDH15*. The strength of the genetic association with time to an HZ event and incidence of an HZ event (case versus control) for these loci and the ancestry/population-specific effects of the top variants in the loci are presented in Supplementary Table 6 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).

The association of *CD83* was driven by the significant association observed in the European subgroup, as reported above. The frequency of the *CD83* locus variant was lower in Hispanic subjects (~1%) than in European subjects (~2%), and was much rarer in East Asian subjects (~0.1%). The genetic effects in East Asian subjects could not be accurately estimated, due to the extremely low variant frequency. The trans-ethnic and trans-population meta-analysis did not improve the significance levels for the *CD83* variant in the European PsO population. Top variant rs56114331 in the *GPR141* locus had a low allele frequency (1.7–2.1%) in Europeans, but was nevertheless higher than that in East Asian or Hispanic subjects (<1%). The significance of the *GPR141* locus identified by meta-analysis was mainly driven by the significant association in the European population of PsO subjects, although the sample size of the European population was not large enough to show significance in the European ancestry GWAS. Top variant rs79025327 in the *TOX3* locus had a higher allele frequency in East Asian subjects (7–11%) compared with European or Hispanic subjects (~1–2%). The significant association of the *TOX3* locus was mostly driven by the significant

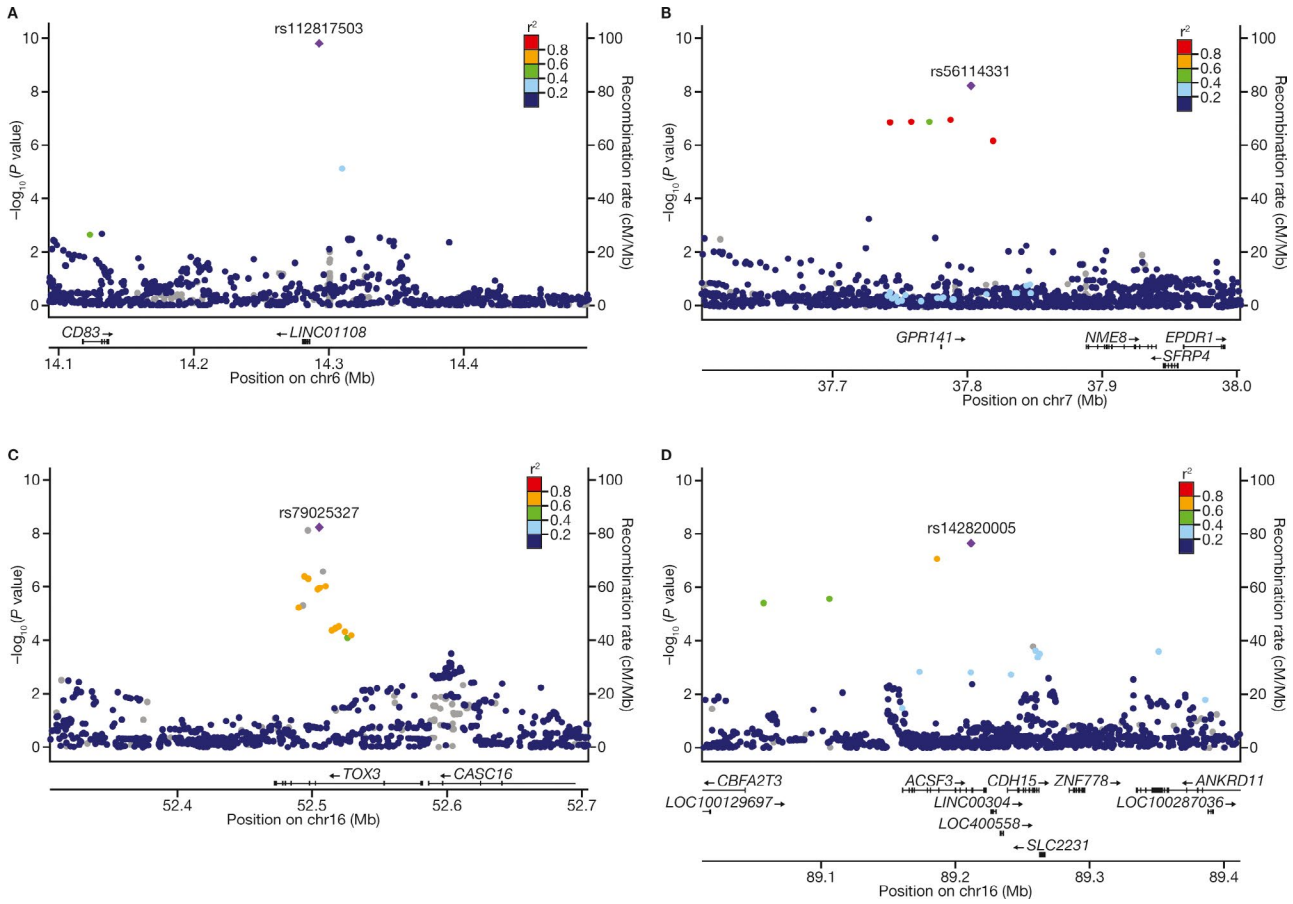

Figure 2. Regional association plots assessing the association of time to herpes zoster event with 4 genetic loci, at *CD83* (**A**), *GPR141* (**B**), *TOX3* (**C**), and *ACSF3* (**D**), in subjects with rheumatoid arthritis or psoriasis.

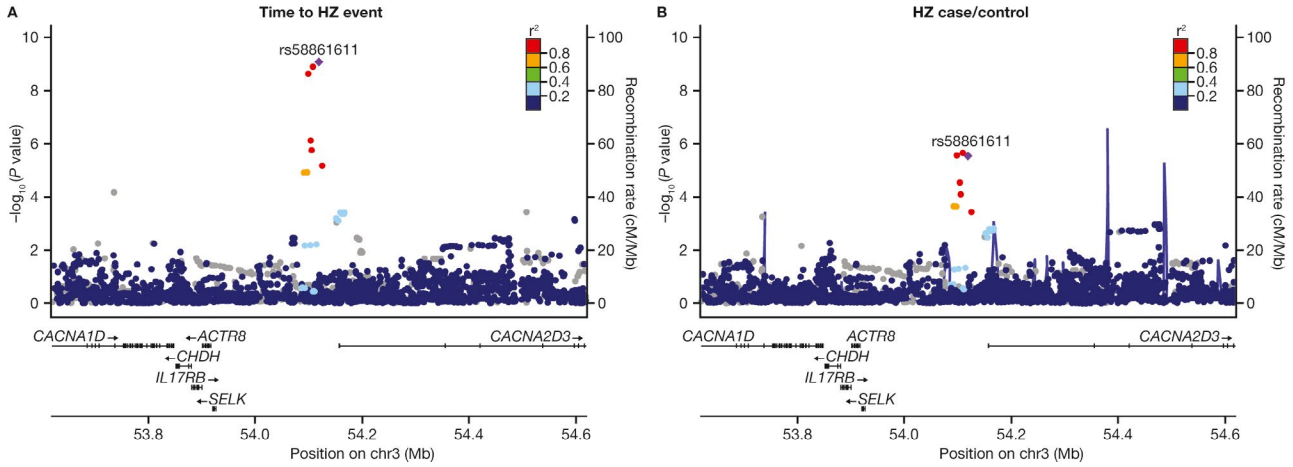

Figure 3. Regional association plots assessing the association of *IL17RB* with time to herpes zoster (HZ) event (**A**) and incidence of HZ (case versus control) (**B**) in subjects with rheumatoid arthritis or psoriasis. Each point represents a single-nucleotide polymorphism (SNP) passing quality control in the trans-ancestry meta-analysis, plotted with its *P* value (on a $-\log_{10}$ scale) as a function of genomic position. The purple diamond indicates the lead SNP. Color coding of all other SNPs indicates linkage disequilibrium with the lead SNP (estimated using r^2 values from East Asian populations in the 1000 Genomes Project database): red = $r^2 \geq 0.8$; gold = $0.6 \leq r^2 < 0.8$; green = $0.4 \leq r^2 < 0.6$; cyan = $0.2 \leq r^2 < 0.4$; blue = $r^2 < 0.2$; gray = r^2 unknown.

associations observed in the East Asian population of RA subjects. The *ACSF3/CDH15* locus variant had the highest allele frequency in Europeans (~5.6%), and the significant association was mostly driven by European subjects with RA. The validity of these results requires further investigation, as many of them are associated with low-frequency variants.

The robustness of the top associations was evaluated in several further analyses. We did not observe substantial deviations in allele frequencies for the top variants compared with those reported in the gnomAD database (Supplementary Table 7 [http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract]). In addition, no significant trans-ethnic allelic heterogeneity effects were found after adjustment of the *P* values for multiple tests (see Supplementary Table 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract). However, when we restricted the meta-analysis to variants with an MAF of >2% in all ethnic groups (5,685,609 SNPs), only 2 loci retained genome-wide significance (*CD83* and *ACSF3*), and 1 locus had suggestive genome-wide significance (*TOX3*) (see Supplementary Table 9 at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract), suggesting that the findings presented herein are sensitive to the allele frequency threshold.

Association of *IL17RB* with a shorter time to HZ, suggesting a potential contributory role for Th2 shift. A SNP near *IL17RB* (rs58861611) was associated with faster time to HZ (meta-analysis HR 3.6, $P = 7.6 \times 10^{-10}$) at the genome-wide significance level, and was suggestively associated with HZ in the case versus control analysis (meta-analysis OR 3.8, $P = 3.0 \times 10^{-6}$) (Table 2). Results from the Kaplan-Meier analysis of time to HZ event are presented in Supplementary Figures 4A–F, and C-statistics for the case versus control logistic regression model are presented in Supplementary Table 5 (http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract).

As shown in the detailed regional plots for the genetic association of the *IL17RB* locus and the ancestry/population-specific effects of this SNP on HZ end points (Figure 3 and Supplementary Table 6 [http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract]), the association of *IL17RB* was driven by a risk allele common in East Asian subjects (~8–17%) but rare in European subjects (<0.2%). Within the ancestry- and population-specific analyses, the most significant association with the HZ end points was seen in the East Asian subgroup of subjects with RA (HR 3.4, $P = 3.2 \times 10^{-7}$; OR 5.06, $P = 2.4 \times 10^{-6}$) (Supplementary Table 6).

Observation of altered T helper cells in rs58861611 carriers in healthy Japanese individuals. To elucidate the potential role of rs58861611 (*IL17RB* locus variant) in regulating immune phenotypes, flow cytometry was performed on freshly isolated PBMCs from 82 healthy Japanese individuals. Subjects were genotyped in parallel for the *IL17RB* rs58861611 SNP. Two subjects with the "CC" genotype were observed among these 82 healthy Japanese individuals, which is concurrent with the ~12% frequency of the "C" allele of rs58861611 in the overall Japanese population. As such, with the sample size being 82 subjects, the study had limited power to detect the variant impact on immune phenotypes.

The HZ risk allele of rs58861611 was significantly associated with lowered proportions of Th17 cells ($P = 0.045$) and Treg cells ($P = 0.025$) (Figures 4C and D). Similarly, a trend toward lowered

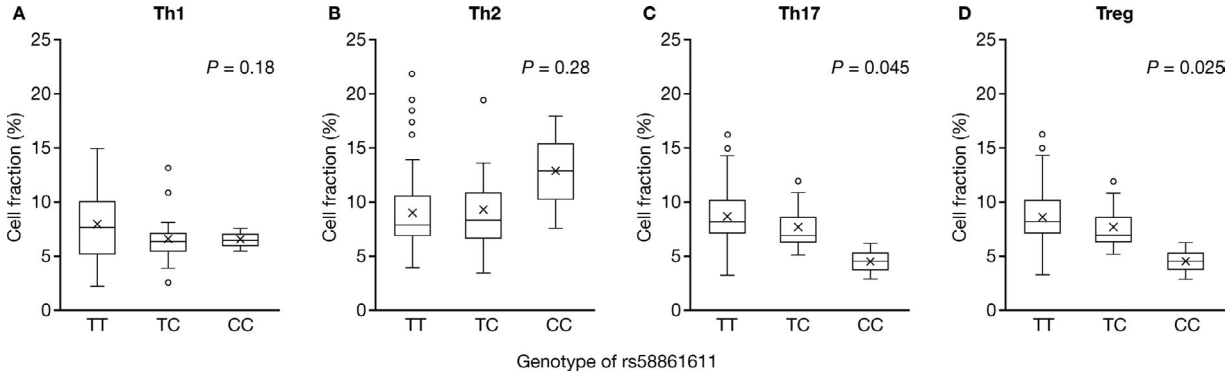

Figure 4. Correlation between genotype and cell fraction in peripheral blood CD4+ T cells from 82 healthy Japanese individuals. The test for significance of the data from the regression analyses of correlations between proportions of Th1 (**A**), Th2 (**B**), Th17 (**C**), and Treg cells (**D**) and genotype was performed using *t*-statistics. The horizontal axis indicates the rs58861611 genotype groups. Data are shown as box plots, where each box represents the 25th to 75th percentiles, lines inside the boxes represent the median, the X indicates the mean, and lines outside the boxes represent the 10th and 90th percentiles. Circles indicate outliers.

proportions of Th1 cells was observed in rs58861611 variant carriers, although this was not statistically significant (Figure 4A). The effects of rs58861611 on Th2 cell proportions were also not significant (Figure 4B). These results suggest that rs58861611 may be associated with alterations in the proportions of T cell populations. However, due to the small sample size in this functional assessment, and the limited number of subjects with the *IL17RB* gene variant in the present study, this observation needs to be further evaluated in a larger cohort.

Lack of association of rs58861611 with *IL17RB* gene expression in T helper cell–type specific eQTL analysis in a small cohort of healthy subjects. To further address the alterations in T cell proportions by the *IL17RB* variant, an eQTL analysis was performed to evaluate whether the rs58861611 variant impacts the gene expression of *IL17RB* or a nearby antisense sequence (AC012467.2) in T cell subpopulations. Th0, Th1, Th2, Th17, and Treg cells were induced from naive T cells from 29 healthy Japanese individuals. In this small cohort, there was only 1 "CC"-homozygous subject, as expected. Low expression levels of *IL17RB* were observed in naive T cells, and its overall expression remained low in Th0, Th1, and Th17 cells, while the expression of *IL17RB* was increased in Th2 and Treg cells (see Supplementary Figures 5A–E, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41655/abstract), which has also been shown in other studies (32). Results of eQTL analysis did not reveal a significant association between the rs58861611 genotypes and *IL17RB* gene expression or the expression of AC012467.2, a potential antisense sequence, in any of the induced T cell subtypes. This result could be attributed to the low power of the analysis, since the sample size was small, or it is possible that rs58861611 may affect *IL17RB* expression in an untested cell type or through a mechanism unrelated to the messenger RNA expression of the *IL17RB* gene.

DISCUSSION

In this analysis, we sought to identify genetic factors contributing to the occurrence of HZ related to tofacitinib treatment. The GWAS identified numerous loci associated with an increased risk of VZV reactivation (i.e., faster time to HZ onset), including 5 loci identified in a meta-analysis of the total pool, and loci identified in both ancestry- and population-specific settings. These data indicate that 1 gene, *IL17RB*, may account for some of the HZ cases seen among East Asian subjects receiving tofacitinib (C-statistic in the East Asian RA population = 0.78); however, no single gene accounts for all or the majority of cases of HZ in subjects receiving tofacitinib. Rather, the incidence of HZ in these populations is likely a result of interactions between many factors, including genetics and environmental factors.

In the ancestry- and population-specific analyses, 4 genetic loci associated with faster development of HZ were identified in the European ancestry subgroup (1 in RA subjects, 3 in PsO subjects). *CD83* represents a possible gene contributing to HZ risk, as a nearby variant, rs112817503, was significantly associated with HZ risk. *CD83* is a marker of dendritic cell (DC) maturation; VZV infects mature monocyte-derived DCs and impairs their functions by down-regulating cell-surface immune molecules, including CD83, CD80, and CD86 (33). Similarly, human cytomegalovirus (HCMV), a member of the herpesvirus family, can infect monocyte-derived DCs. HCMV impairs the ability of the DCs to present antigens to T cells and thereby impairs the subsequent proliferation of T cells through multiple mechanisms, some of which involve release of soluble CD83 from DC membranes (34). Tofacitinib lowers CD80 and CD86 expression in DCs in vitro (35), suggesting that JAK inhibition could interact with a variant near CD83 to decrease presentation of virus in infected cells. The precise molecular mechanisms for these tofacitinib-related effects are not known, but may be due to inhibition of IFNα. The *CD83* association was driven by the data from the European subgroup, and remained significant in the trans-ethnic GWAS meta-analysis.

The *PMEPA1* locus was associated with faster HZ development in European subjects with RA. The variant near *PMEPA1* (i.e., *TMEPA1*) may also influence viral presentation, as HCMV reduces *CD83* expression via TGFβ1 signaling (36), which is inhibited by *PMEPA1* (37).

The *VWF* locus was associated with faster HZ development in European subjects with PsO. The *VWF* gene encodes the protein von Willebrand factor (vWF), which functions as both an antihemophilic factor carrier and a platelet-vessel wall mediator in the blood coagulation system. The levels of vWF rise in multiple types of infections (38,39). In a candidate gene study, *VWF* genetic variants were associated with human herpes simplex encephalitis, a rare complication following infection with herpes simplex virus type 1, which usually remains latent in neurons (40). Thus, the *VWF* gene may have roles in multiple infections; however, the mechanisms of vWF in HZ have not been directly studied. The *VWF* locus variant (rs200638456) is in moderate linkage disequilibrium (r^2 = 0.64 in the European population) with an eQTL variant of CD9 (rs12099542) (41); thus, CD9 could also be a candidate causal gene for this association.

Within ancestry-specific GWAS, no significant associations in the Hispanic and East Asian subgroups were identified, likely because the numbers of subjects in these ethnicity groups were small, and therefore this study had low power to detect differences.

It was hypothesized that combining ethnicity subgroups via meta-analysis would increase the power to detect genetic factors for HZ risk; indeed, 4 additional loci were identified from the trans-ancestry and trans-population meta-analysis, including a variant near the *IL17RB* gene prevalent in East Asian populations.

IL17RB encodes a cytokine receptor that specifically binds to IL-25 (IL-17E) and IL-17B, in which IL-17B is thought to be an antagonist of IL-25 binding (32). IL-25 induces Th2-type cytokine production in IL17RB-positive cells (32), and in a case report, genetic amplification of IL-25 led to an overactive Th2 response with a phenotype of recurrent varicella (42). In this analysis, the *IL17RB* locus variant was also associated with lowered proportions of Th17/Treg cells in healthy Japanese individuals. Somewhat surprisingly, the *IL17RB* locus variant was not significantly associated with increased expression of IL17RB and did not show a significant effect on Th2 cell proportions, as might have been predicted from its known biologic effects. This may have been due to the small sample size and low power, or because we tested these effects in immune cells from healthy subjects and not under conditions of disease or tofacitinib exposure. These data suggest a potential mechanism by which the *IL17RB* variant contributes to HZ risk in Japanese individuals, as the imbalance of T cell subtypes may lead to a reduced threshold for VZV reactivation.

In addition, IL17RB is an expression marker that can be used to define invariant natural killer T (iNKT) cell heterogeneity (43). Studies have shown that iNKT cells produce Th1, Th2, or Th17 cytokines when challenged (43). The role of IL17RB and the JAK-dependent cytokine IL-15 in the development and ratio of iNKT cells has been characterized in mice: CD4+IL17RB+ iNKT cells produce large amounts of Th2 and moderate amounts of Th17 cytokines, whereas CD4+IL17RB– iNKT cells produce the anti-viral Th1 cytokine IFNγ (43). CD4+IL17RB– iNKT cells express the IL-15 receptor CD122, and require the presence of the JAK-dependent cytokine IL-15 for development (43). In mice hypomorphic for IL-15 signaling, levels of Th1-producing iNKT cells decrease, while levels of Th2-producing iNKT cells increase (43). Deficient iNKT cells are characterized by low production of IFNγ; however, the functions of normal T cells and NK cells have been linked to disseminated HZ in response to vaccination in 2 case reports, despite an otherwise intact immune system (44,45). These IL-25 and iNKT studies and the association near the *IL17RB* gene suggest that the ratio of iNKT cell subsets at baseline may be important for HZ risk when combined with inhibition of IL-15 signaling by tofacitinib.

Based on the significant loci identified in this analysis, we observed that genetic risks related to HZ are population- and ethnicity-dependent. The *CD83* variant was prevalent in European subjects; overall, its association with HZ was driven by the genetic effects observed in European subjects in the PsO population. The *IL17RB* variant was most prevalent in East Asian subjects; overall, its association with HZ was driven by the genetic effects observed in East Asian subjects in the RA population. This implies that genetic risk variants from different ethnicities may interact with disease conditions and tofacitinib exposure, jointly contributing to VZV reactivation. The *IL17RB* locus variant had an allele frequency of 8–17% in East Asian subjects, which was higher than the allele frequencies of all of the other HZ-associated variants (<7% across populations) in this analysis. The common alleles from the *IL17RB* variant compared with other low-frequency variants in other ethnicities may explain the higher HZ rate observed in tofacitinib-treated East Asian individuals. Notably, the *IL17RB* variant did not show association with HZ in Asian subjects with PsO. This may have been because sample sizes were small or there were differences in HZ-modifying risk factors between the PsO and RA populations. The functional mechanisms of the associations between the *GPR141, TOX3*, and *ACSF3/CDH15* loci and HZ events also warrant further investigation.

This genetic and functional study is fundamentally limited by the relatively small sample sizes of the Hispanic and East Asian populations, as well as the assessment of multiple different subgroups (i.e., ethnicity and disease). Furthermore, we showed that the trans-ancestry association findings are sensitive to the MAF threshold used. When we restricted the meta-analysis to variants with an MAF of >2% in all ethnic groups, only 2 loci retained genome-wide significance (*CD83* and *ACSF3*), and 1 locus had suggestive genome-wide significance (*TOX3*). These results highlight the importance of validating the current findings in large-scale studies. An additional limitation is that data on prior HZ vaccination,

which might have lowered the risk of VZV reactivation, were not collected in this study.

Overall, this analysis identified multiple genetic factors associated with HZ risk in tofacitinib-treated subjects with RA or PsO. The findings provide novel insights into the molecular mechanisms contributing to VZV reactivation during tofacitinib treatment, which can be further validated in additional JAK inhibitor clinical studies or by genetic analysis of larger cohorts of East Asian subjects characterized by VZV response.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bing had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bing, Hirose, Kochi, Fujio, Valdez, Vincent, Clark.

Acquisition of data. Bing, Zhou, Tsuchida, Sumitomo, Zhang, Valdez.

Analysis and interpretation of data. Bing, Zhou, Chen, Hirose, Kochi, Tsuchida, Ishigaki, Zhang, Valdez, Martin, Clark.

ROLE OF THE STUDY SPONSOR

This study was sponsored by Pfizer Inc. Pfizer Inc. was involved in the study design, data collection, and data analysis. The studies of the CD4+ T cell subsets were supported by funding from Pfizer Inc. and Takeda Pharmaceutical Co., Ltd., and a grant from RIKEN. Medical writing support, under the guidance of the authors, was provided by Christina Viegelmann, PhD, and Sarah Piggott, MChem (CMC Connect, McCann Health Medical Communications) and was funded by Pfizer Inc. New York, in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med 2015;163:461–4). All authors, including those employed by the sponsor, were involved in data interpretation, revised the manuscript critically for intellectual content, and made the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer Inc.

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