Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants

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Psoriasis is a complex disease of skin with a prevalence of about 2%. We conducted the largest meta-analysis of genome-wide association studies (GWAS) for psoriasis to date, including data from eight different Caucasian cohorts, with a combined effective sample size >39,000 individuals. We identified 16 additional psoriasis susceptibility loci achieving genome-wide significance, increasing the number of identified loci to 63 for European-origin individuals. Functional analysis highlighted the roles of interferon signalling and the NFκB cascade, and we showed that the psoriasis signals are enriched in regulatory elements from different T cells (CD8+ T-cells and CD4+ T-cells including Th0, Th1 and Th17). The identified loci explain ~28% of the genetic heritability and generate a discriminatory genetic risk score (AUC = 0.76 in our sample) that is significantly correlated with age at onset (p = 2 × 10−89). This study provides a comprehensive layout for the genetic architecture of common variants for psoriasis.

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Psoriasis is a chronic and complex multi-genic immune-mediated skin disease, affecting around 2% of European-origin individuals. Previous association studies of psoriasis have identified over 60 psoriasis susceptibility loci, 47 of which are associated with the risk of psoriasis in European-origin populations. These findings have greatly advanced the understanding of disease mechanisms and associated pathways. Thus, the IL23R, IL12B, IL23A and TRAF3IP2 loci suggest a prominent role of the IL23 signalling pathway and promotion of T<sub>H</sub>17 responses; whereas the TNFAIP3, NFKBIA, NFKBIZ, TNIP1 and RELA loci suggest dysregulation of the NFκB pathway in disease pathogenesis. Interestingly, seven (44%) of the new loci were identified using only GWAS data sets (Supplementary Table 3), as the Immunochip data does not provide good genotype coverage of these regions. Moreover, only two new loci were identified in the 186 non-contiguous regions that underwent dense genotyping in the Immunochip platform. As shown for other complex traits, we found that the minor allele frequencies (MAFs) of the associated signals are negatively correlated (p = -0.57; p = 2 × 10<sup>-8</sup>) with the risk allele effect sizes of the disease loci (Fig. 2a; Supplementary Table 4). Among the novel loci, rs76959677 has the largest effect size (OR = 7.9; p = 2 × 10<sup>-8</sup>) among the new loci (Table 1). Altogether, the 63 loci account for over 28% of the estimated heritability, as compared to 26% using only known loci. Our estimations are very similar to those obtained using other approaches, as shown in Supplementary Table 5. To evaluate whether the susceptibility loci could be used to discriminate between affected and unaffected individuals in our sample, we used the effect sizes and imputed dosages from our cohorts to compute genetic risk scores (GRS), and associated them with the disease status. Figure 2b shows receiver operating curves (ROC) plotting the true positive rate versus false positive rate under different GRS thresholds. The area under the curve (AUC) is 0.76, suggesting GRS has discriminative power for predicting disease status among individuals in these cohorts. Age-at-onset has emerged as a key clinical and stratification feature for psoriasis. To examine the correlation between age-at-onset and the GRS, we analysed 6,251 psoriatic patients for whom this information was available. Our results show that the GRS is inversely correlated with age-at-onset ( Spearman ρ = -0.25; p = 2 × 10<sup>-8</sup>); mean age-at-onset was 34.9 years for psoriatic patients in the lowest fifth percentile of GRS, compared to 20.4 in those in the highest fifth percentile (Fig. 2c). This correlation remains significant after removing the MHC signal from the calculation (ρ = -0.08; p = 2 × 10<sup>-11</sup>).

Functional interpretation of GWAS data. To evaluate the underlying disease mechanisms responsible for these genetic signals, we applied a recently-developed algorithm termed minimum distance-based enrichment analysis for genetic association (MEAGA) to simultaneously query biological functions and pathways, as well as protein-protein interactions, for enrichment among genes mapping to the identified psoriasis loci. We found 87 significantly enriched functions/pathways (false discovery rate ≤0.1, Supplementary Table 6). As expected, many of these are immune-related functions such as lymphocyte differentiation/regulation, Type I interferon, pattern recognition and response to virus/bacteria (Fig. 3a; Supplementary Fig. 8). Among the enriched functions, ‘Regulation of IκB kinase/NF-κB cascade'
We next asked whether the observed association signals are enriched among enhancers that have been mapped to public databases. We found that the utilization of newer, less costly GWAS assays shows that the utilization of newer, less costly GWAS assays to interrogate the entire genome in follow-up samples is a cost-effective approach capable of revealing subtle genetic signals. To our knowledge, this is the first large genetic association study that is well-appreciated as components of NF-κB signalling, our results further implicate this pathway in the pathophysiology of psoriasis.

Discussion

rather than relying on following up promising signals, here we show that the utilization of newer, less costly GWAS assays to interrogate the entire genome in follow-up samples is a cost-effective approach capable of revealing subtle genetic signals. In addition, we have implemented an approach used in epidemiology studies to adjust a misclassified binary outcome. To our knowledge, this is the first large genetic association study to compare outcomes using specialist-diagnosed versus self-diagnosed.

Table 1 | Newly identified psoriasis associated loci.

| Chr | Pos | Marker | RA | NRA | RAF_case | RAF_cont | ORs | P value | Direction* |
|-----|-----|--------|----|-----|----------|----------|-----|---------|------------|
| 1   | 78450517 | rs34517439 | A  | C   | 0.13     | 0.12     | 1.18 | 4.43 × 10^-9 | + ? + + + + + + |
| 2   | 12268326 | rs10959675 | A  | G   | 0.48     | 0.46     | 1.10 | 5.6 × 10^-9 | + + + + + + + + |
| 3   | 16248575 | rs11053802 | T  | C   | 0.69     | 0.67     | 1.11 | 4.17 × 10^-9 | + + + + + + + + |
| 4   | 11569875 | rs11065787 | T  | C   | 0.47     | 0.45     | 1.08 | 1.67 × 10^-8 | + + + + + + + + |
| 5   | 19950260 | rs9513593 | G  | A   | 0.19     | 0.18     | 1.12 | 3.60 × 10^-8 | + + + + + + + + |
| 6   | 98668778 | rs142903734 | AAG | A    | 0.81     | 0.79     | 1.12 | 7.15 × 10^-9 | + + + + + + + + |
| 7   | 31637666 | rs28624578 | T  | C   | 0.85     | 0.83     | 1.13 | 9.22 × 10^-10 | + + + + + + + + |
| 8   | 73890363 | rs55823223 | A  | G   | 0.15     | 0.13     | 1.15 | 1.06 × 10^-8 | + + + + + + + + |
| 9   | 12857002 | rs5594067 | T  | G   | 0.47     | 0.45     | 1.10 | 1.19 × 10^-10 | + + + + + + + + |
| 10  | 19206417 | rs6187342 | G  | A   | 0.49     | 0.46     | 1.11 | 6.57 × 10^-13 | + + + + + + + + |

*Direction of the effect of the risk allele in the eight data sets in the order of: PsA GWAS, CASP GWAS, Kiel GWAS, Genizon GWAS, WTCCC2, Exomechip with GWAS content, PAGE Immunochip and 23andMe GWAS, proceeding from left to right. '?' means the marker is not imputed well in the corresponding cohort. NRA, Non-risk allele; OR, odds ratio; RA, risk allele; RAF, risk allele frequency.

Figure 1 | Meta-analysis results. The 'Manhattan' plot shows the negative log p values of the meta-analysis. The known loci are coloured in blue; the sixteen novel loci are in red.
reported affectation and to adjust for response misclassification. Of note, we observed that disease allele frequencies and ORs were underestimated in an independent study that defined psoriasis status based on the electronic health records. This may be because psoriatic lesions appear similar to other common skin diseases, including atopic eczema and seborrhoeic dermatitis, leading to misdiagnosis. Our results illustrate the importance of correcting misclassification of disease outcome as large-scale data-mining of phenotypes becomes more common. The disease-associated loci define a GRS that is capable of discriminating case-control status in our sample (AUC = 0.76). Similar results have been reported in the Chinese population as well as a smaller European-origin sample. In concordance with previous studies, we found that the GRS is also strongly inversely correlated with age-at-onset of psoriasis, with the MHC comprising much of this effect (Fig. 2c). The strong association between HLA-Cw6 and streptococcal infection in juvenile-onset psoriasis may explain part of this association. However, correlations between genetic risk allele load and age-at-onset are not universal in complex genetic disorders, and the relationship between GRS and age-at-onset needs to be explored on a disease-by-disease basis. While we did not find any disease-associated variants that alter protein structure in new loci, we demonstrated significant enrichment for genes involved in immune system function among the known and novel genetic signals. We also found significant enrichment of psoriasis genetic signals in active chromatin domains in Th1 and Th17 cells (Fig. 3). Among the individual candidates, FASLG encoding Fas ligand, IKBKE encoding IKK-α, CHUK encoding IKK-α, IL31 encoding the cytokine IL-31, KLRK1 encoding NKG2D, a killer cell lectin-like receptor and PTPN2 encoding T-cell protein tyrosine phosphatase, all play prominent roles in T-cell activation, signalling and/or effector function. By guiding further functional investigation into the roles of these

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**Figure 2 | Association of psoriasis susceptibility with disease risk.** (a) The effect size (odds ratio, OR) of the risk allele is plotted against the minor allele frequency of the signal among all susceptibility loci. (b) True positive rate versus false positive rate for using genetic risk score to distinguish psoriasis versus control samples. Blue line shows the averaged results among the different cohorts (grey), and the s.e. bars are also shown. (c) The median age-at-onset of psoriasis is plotted against different percentile bins (every 2%) of genetic risk scores for all loci (blue) or all loci without MHC (red).
variants in the regulation of their target genes, as well as further functional investigation of these targets, these results will serve as an important framework guiding future research into the pathogenesis and treatment of psoriasis.

Methods

Data sets. The collection of samples for the five GWAS (PsA, CASP, Kiel, Genizon and WTCCC2) and the Immunochip dataset were described previously5–7,9,18. The new Exomechip cohort, consisting of 6,463 genetically independent psoriasis cases and 6,096 unrelated controls of European Caucasian descent collected in North America and Sweden, was genotyped using the Affymetrix Axiom Biobank Plus Genotyping Array at the Affymetrix facility (Santa Clara, CA). All human subjects provided written informed consent and were enrolled according to the institutional review board (IRB) for human subject research of each institution, in adherence with the Declaration of Helsinki principles. The basic array contains 246,000 genome-wide markers, 265,000 exon coding SNPs and indels, and 95,000 eQTL pharmacogenomic and novel loss-of-function variants, which was supplemented by addition of 77,000 Helsinki principles. The basic array contains 246,000 genome-wide markers, and this is especially true for the PsA GWAS, in which all included cases have psoriatic arthritis.

Quality control. For each dataset, we removed samples with high missingness (>2%) or a high inbreeding coefficient (FIS > 0.03), and we also removed markers with low call rate (<95%), with more than two alleles, or that failed Hardy Weinberg equilibrium (p < 1 × 10⁻⁶). We identified duplicated or highly related pairs (that is, first and second degree relatives) of individuals among our data sets using independent markers outside of the known psoriasis susceptibility loci (‘null markers’3); this includes samples that were genotyped in multiple cohorts (for example, the same sample might be genotyped in both the CASP GWAS or Exomechip cohorts). When related or identical pairs were identified in different data sets, we preferentially kept the sample from the genotyping platform with the higher number of markers with genome-wide coverage (Supplementary Table 1). We used the independent (that is, ld>0.2) markers that are outside the known psoriasis loci to compute the principal components for each data set; and for the Immunochip data set, since the platform is enriched with markers from the immune-associated regions, we first conducted a meta-analysis using the CASP, Kiel, and WTCCC2 cohorts and identified independent markers which have meta-analysis P values > 0.5 as ‘null markers’ to compute the principal components. We then used principal components to remove the population outliers to ensure all analysed individuals were of European ancestry9.

23andMe cohort. The 23andMe cohort was drawn from the customer base of 23andMe, Inc., a personal genetics company. The samples from this cohort were genotyped on one of four platforms: the V1 and V2 platforms were variants of the Illumina HumanHap550 BeadChip with additional custom content; the V3 platform is a variant of the Illumina OmniExpress + BeadChip, with custom content; the V4 platform is a fully custom design, including lower redundancy subsets of V2 and V3 SNPs with coverage of low allele frequency coding variants, as well as 570,000 additional SNPs. Research participants included in the cohort provided informed consent and answered surveys online according to the 23andMe human subject protocol, which was reviewed and approved by Ethical & Independent Review Services, a private institutional review board. The ‘psoriasis’ phenotype combines self-reported psoriasis diagnoses from several sources available on the 23andMe website: (i) Medical History Survey; (ii) Roots into the future intake form; (iii) research snippet. There are three choices (yes, no, not sure) for each psoriasis-related question from each source. We merged the yes/no responses from these questions, with inconsistent responses scored as missing: cases have at least one positive response and no negative responses, and controls have at least one negative response and no positive responses. We also derived responses from two additional questions derived from the IBD Community Survey and Health Intake Form, regarding whether the individual has been diagnosed with psoriasis to define cases (when any response is a yes) and controls (when it is not a case and at least one response is control).

Imputation and association. We performed haplotype phasing21 and imputation22 for each dataset. For imputation, we used haplotypes from all populations in the 1,000 Genomes Project phase 1 (release 3) as a reference panel23. We then analysed markers with imputation quality greater than 0.7 in at least half (that is, 4) of the data sets. For each data set, we performed logistic regression using top principal components and data collection center indicator variables as covariates to correct for population stratification. We computed the inflation factor (λ) using the ‘null markers’ for the genomic control analysis (Supplementary Table 1).

Proportion of true positives among 23andMe psoriasis cases. For each of the previously identified signals from the known psoriasis loci, we compared the risk allele frequencies in cases and controls estimated from our dermatologist-diagnosed-based data9 with those estimated by the 23andMe cohort. The RAFs in cases from the dermatologist-diagnosed cohorts are systematically higher than those in the 23andMe cohort (34 out of 36 loci listed in Tsoi et al.9 manifested
RAF(case_Tsoi(2012)) higher than those estimated in RAFcase_23andMe); while the RAFs in controls are highly concordant (Supplementary Fig. 1). We hypothesized that some of the defined cases are false positives (that is, the individuals do not actually have psoriasis). Assuming the defined cases from the 23andMe cohort contain a mixture of true cases and controls, we would get:

RAF(case_Tsoi(2012)) = (q)RAF(case_Tsoi(2012)) + (1 - q)RAF(control_Tsoi(2012))

where q is the proportion of true positives. The proportion could then be estimated as:

\[
\text{Median}_{\text{controls}} \text{RAF}_{\text{controls}} - \text{RAF}_{\text{cases}} \]

We estimated that q = 0.36. Ignoring the misclassification of psoriasis phenotype, the 16,120 self-reported cases and 254,909 controls of the 23andMe cohort yield an estimated disease prevalence of 5.9%. But if we assume q = 0.36 and correct for misclassification, then we would obtain a 2.1% prevalence (Supplementary Table 1), matching the disease frequencies estimated for European-origin populations50.

**Adjustment for misclassification of 23andMe cases.** We employed Duffy’s approach to adjust odds ratios and s.e.’s for bias caused by response misclassification in logistic regression48. If \( \beta' \) and \( V(\beta') \) are the naive log OR and its variance for the misclassified case-control data, then by Duffy’s method the corrected log OR and its variance can be estimated as:

\[
\beta = \beta' \left( \frac{(q - \rho)(q - 1 + \rho)}{(q + 3q^2 - 1 - (1 + \rho)^2)} \right)
\]

\[
V(\beta) = V(\beta') \left[ \frac{q(1 - 2q) - (q - 1 + \rho)^2}{(q + 3q^2 - 1 - (1 + \rho)^2)^2} \right]
\]

and

\[
(\beta' + 1)^2 + q \left( \frac{(q - \rho)(q - 1 + \rho)}{(q + 3q^2 - 1 - (1 + \rho)^2)^2} \right)
\]

\[
(\beta' + 1 - q)^2 + q \left( \frac{(q - \rho)(q - 1 + \rho)}{(q + 3q^2 - 1 - (1 + \rho)^2)^2} \right)
\]

Parameters \( q \) and \( \rho \) are the sensitivity and specificity of the binary classification. For the 23andMe sample we assumed \( q = 1 \) (that is, all true cases were reported as such); using \( q = 0.36 \), \( \rho \) could then be estimated as \( 0.9611 \). \( V(\beta) \) was estimated to be 2.67 \( \times 10^{-6} \) using Monte Carlo simulation based on the observed RAPs for 32,240 case chromosomes from the 23andMe cohort and for 21,176 case and 45,612 control chromosomes from our previous study6. \( V(\beta) \) was assumed to be 0.001. The observed case prevalence in the sample (\( p' \)) is 0.0595. Because \( p' \) is small, deviations of our assumptions for \( q \) and \( V(\beta) \) are often small. On the other hand, the ARE for each locus was the ratio of the variance for the Duffy-corrected ORs to the log OR that would have been obtained if there had been no misclassification of disease phenotype. Because both of these OR estimators are convergent and asymptotically unbiased, the ARE for these two parameters (and their corresponding Wald chi-square test statistics) is equal to the ratio of their variances. We determined this variance ratio by simulation. We bootstrap sampled one of our largest studies with dermatologist-diagnosed phenotypes (the PAGE Immunochip study) to create 25 data sets mimicking the 23andMe study; that is, each sampled dataset had 5,803 true cases, 10,317 false cases, and 254,909 true controls. For each of 28 independent known psoriasis loci with adequate marker coverage, we performed enrichment analysis by first enumerating the number of associated loci that overlap or are in linkage disequilibrium (LD) \( (r^2 \geq 0.8) \) with markers in regulatory elements, and then comparing that with the expected number of overlaps. The expected numbers were estimated by randomly sampling markers from the meta-analysis matching the LD-block length, MAF, and the number of genes in the LD-block, and counting the number of times these null markers overlap/in LD with the regulatory elements.

**Drug databases.** We downloaded data from PharmGKB40 and Drugbank59, and searched for drugs with potential gene targets from these databases.

**Data availability.** The data of the ExomeChip cohort is available in dbGap (phs010316.v1.p1). The GWAS statistics from the 23andMe cohort can be requested by applying to the 23andMe collaboration program.

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