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# Evaluation of a Genetic Risk Score for Diagnosis of Psoriatic Arthritis

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## Abstract

**Background:** Diagnosis of psoriatic arthritis (PsA) can be challenging, resulting in delays that contribute to irreversible joint damage, reduced quality of life, and increased mortality.

**Objective:** Use genetic markers to develop and evaluate a PsA genetic risk score (GRS) for its ability to discriminate between psoriasis (PsO) only and PsO with PsA among a psoriatic cohort with full genome-wide genotype data.

**Methods:** Genome-wide single-nucleotide polymorphism genotyping was performed on 724 psoriatic patients. A set of 11 candidate risk genes previously shown to be preferentially associated with PsO or PsA were selected. To evaluate the cumulative effects of these risk loci, a PsA GRS was developed using an unweighted risk allele count (cGRS) and a weighted (wGRS) approach. Additional analyses included only human leukocyte antigen (HLA) risk alleles.

**Results:** The discriminative power attributable to each GRS was evaluated by calculating the areas under the receiver operator characteristic curve (AUROC). The AUROC for the wGRS is 56.2% versus 54.1% for the cGRS, and the AUROC for the HLA-only wGRS model was 56.9% versus 55.7% for the HLA-only cGRS.

**Conclusion:** The AUROC of 56.9% for HLA-only wGRS indicates that this approach has the greatest power in discriminating PsA from PsO among these models. Given that an AUROC of 56.9% is quite modest, this study suggests that using a small number of well-validated genetic loci

provides limited predictive power for PsA, and that future approaches may benefit from using a larger number of genetic loci.

## Background

Psoriasis (PsO) is a chronic, immune-mediated skin disease with global prevalence of 0.2% to 6.5%.[1] Up to 30% of psoriasis patients evaluated cross-sectionally in dermatology clinics have psoriatic arthritis (PsA),[2,3] a chronic inflammatory musculoskeletal disease that can involve the peripheral joints, axial skeleton, entheses, inflammation of whole digits, skin, and nails.[4] Given the insidious nature of these symptoms as well as the heterogeneity in the clinical presentation of PsA, diagnosis can be challenging, resulting in delays that contribute to progressive joint damage, irreversible deformity, reduced quality of life, and increased mortality.[5–7]

To prevent such outcomes, a variety of screening instruments have been developed to facilitate early PsA diagnosis and treatment, including the Psoriasis Epidemiology Screening Tool (PEST),[8] Psoriatic Arthritis Screening and Evaluation (PASE),[9] Toronto Psoriatic Arthritis Screen (ToPAS),[10] and Early Arthritis for Psoriatic Patients (EARP).[11] Validation studies have shown that these tools can accurately identify PsA in certain populations,[12–17] but comparative analyses have found that the sensitivities and specificities of these screening tools are not as high as initially thought. For example, certain instruments may miss key manifestations of PsA, such as axial forms,[18] or misidentify other musculoskeletal diseases as PsA.[19] Considering these limitations, there is a need for more objective diagnostic discriminators for PsA.

Genetic markers offer an objective approach to PsA diagnosis. The rationale behind this is the published observation that while both PsO and PsA have strong genetic associations, specific genetic markers such as *HLA-C\*06:02* and *HLA- B\*44:02*, and single-nucleotide polymorphisms (SNPs) near *TNFRSF9* and *LCE3C/B* significantly favor PsO over PsA while *HLA-B\*27:05, HLA-B\*39:01, HLA-B\*08:01,* and SNPs near *IL23 R* and *TNFAIP3* significantly favor PsA over PsO.[2,20] These genetic markers have significantly different frequencies between patients with PsA and PsO with odds ratios (ORs) of up to 3.77 in PsA versus PsO.

Such observations can be translated into a genetic risk score (GRS) based on a patient's specific genetic markers, such as a PsO GRS as published by Chen et al[21] or a PsA GRS as published by FitzGerald et al.[20] The objective of this study is to use the genetic markers listed above as well as others identified in the literature to develop and evaluate a PsA GRS for its ability to discriminate between PsO only and PsO with PsA among a psoriatic cohort with full genome-wide genotype data.

## Methods

The study population included a total of 724 patients who provided written informed consent with approval from the Committee on Human Research at the University of California, San Francisco. Genetic material was obtained via saliva samples and genotyped using the Affymetrix UK Biobank array. Clinical information was collected via a patient survey in addition to a physician questionnaire, which allowed for categorization of the patients into 3 groups: physician-confirmed PsA diagnosis (n = 140, 25.8% of the study population), possible PsA diagnosis (patients with joint symptoms but no physician-confirmed diagnosis of PsA, n = 181, 25.0%), and no PsA diagnosis (psoriasis with no history of joint symptoms, n = 403, 74.2%). The group of patients with possible PsA diagnoses were excluded such that subsequent analyses only included those patients in the confirmed PsA (cases) and PsO only (controls) groups, for a total of 543 patients.

A set of candidate risk genes shown to be associated with PsO or PsA in previous large cohort or genome-wide association studies were selected (Table 1).[2,20] All ORs are given in the same direction from published studies except for genes *HLA-C\*06:02, HLA-B\*44:02, TNFRSF9,* and *LCE3C/B* that are given as reciprocals to represent these genes associated risk of PsA versus PsO.

To evaluate the cumulative effects of these 11 risk loci, a PsA GRS was developed using both an unweighted risk allele count (cGRS) and a weighted (wGRS) approach, which involved multiplication of each patient's number of risk alleles by the OR for that gene and then subtracting the products of the 4 genes associated with risk of PsO from the 7 genes associated with risk of PsA. The hypothesis of this approach is that a higher cGRS or wGRS favors PsA, while a lower cGRS or wGRS favors PsO.

Following this initial analysis, an alternative approach was evaluated by including only the 5 human leukocyte antigen (HLA) risk alleles in an HLA-only cGRS and HLA-only wGRS. *HLA* genes are unique in that they code for cell surface antigen proteins responsible for major functions of the immune system. The role of *HLA* genes in PsA risk is well-documented,[20,21,22] suggesting that an HLA-only PsA GRS could capture a significant proportion of the genetic contribution to developing this disease.

In both sets of analyses, means with standard deviations (SDs), quartile distributions with ORs relative to the first quartile, and areas under the receiver operator characteristic curves (AUROCs) were calculated using Microsoft Excel (version 16.16.9). Values of *P* were calculated using Mann-Whitney tests.

## Results

Results are presented for both the 11 risk loci analysis (Figures 1–3) and HLA-only approach (Figures 4–6). For each figure, results are shown for the unweighted (cGRS) and weighted (wGRS) analyses.

Figure 1A illustrates the distribution of the 11 risk loci cGRS in both cases and controls, and Figure 1B shows distribution of the wGRS. The mean number of cGRS risk alleles was 1.14

(SD 2.1) in the cases and 0.84 (SD 2.0) in the controls, with a *P* value of .139. Additionally, the mean wGRS in the cases was 0.83 (SD 3.3) and the mean number of risk alleles in the controls was 0.09 (SD 3.4), with a *P* value of .028. To estimate the total amount of risk captured by each GRS, ORs were calculated according to cGRS and wGRS quartiles (Figure 2A and B). There was a significant increase in PsA ORs with increasing cGRS and wGRS quartiles, both using the first quartiles as reference groups. Next, the discriminative power attributable to each GRS was evaluated by calculating the AUROCs for the case–control data (Figure 3A and B). The AUROC for cGRS is 54.1% (confidence interval: 48.5%−59.7%) versus 56.2% (CI: 50.6%−61.8%) for wGRS.

For the HLA-only analyses, Figure 4A shows the distribution of the HLA-only cGRS in both cases and controls, and Figure 4B shows HLA-only wGRS. The mean number of HLAonly cGRS risk alleles in the cases was 0.15 (SD 0.8) and 0.31 (SD 0.8) in the controls, with a *P* value of .028. The mean HLA-only wGRS in the cases was 0.69 (SD 2.3), while the mean number of risk alleles in the HLA-only wGRS controls was 1.3 (SD 2.5), with a *P* value of .009. The quartile analyses (Figure 5A and B) show increasing PsA ORs for the second and third HLA-only quartiles in both unweighted and unweighted models, but with a small decrease from both third to fourth quartiles. Furthermore, Figure 6A and B presents the AUROCs, where the AUROC for the HLA-only wGRS model was 56.9% (CI: 51.3% −62.5%), while the AUROC for HLAonly cGRS approach was 55.7% (CI: 50.0%−61.3%). Lastly, Figure 7 illustrates the distribution of HLA alleles in cases as compared to controls.

## Discussion

These results include several key findings. First, the GRS distribution and quartile analyses generally support a main hypothesis of this study: a higher GRS favors PsA while a lower score favors PsO. For example, Figure 1A shows a general trend that PsO controls have lower cGRS values while PsA cases have higher cGRS values. Similarly, Figure 2A depicts a significant increase in the ORs of PsA with increasing cGRS quartiles, demonstrating a steady rise in PsA genetic risk as the cGRS values increase. Furthermore, the average GRS among patients with PsA is greater than the average GRS among patients with PsO in all 4 models of this large cohort.

Second, the AUROC of 56.9% for HLA-only wGRS (Figure 6B) indicates that this approach has the greatest power in discriminating PsA from PsO among the 4 models. The discriminative power of the HLA alleles is further supported by Figure 7, which demonstrates the frequency of alleles that favor PsA over PsO among cases is consistently higher than among controls. These findings suggest that HLA alleles alone can capture a predictive signal, as previously reported.[2,20–22] For the 11 loci model, the wGRS also performs better than the cGRS (AUROC of 56.2% vs 54.1%). These results suggest that a weighted approach incorporating each allele's OR is a superior method compared to an unweighted GRS calculation.

Third, while HLA-only wGRS approach is the best discriminator evaluated in this study, an AUROC of 56.9% is still quite modest. Nevertheless, the value of this study is demonstrating that a small number of genetic loci can provide some limited predictive power. This is

significant because prior research has either used fewer loci to predict PsO rather than PsA,[21] used HLA alleles only but without weighting the PsA GRS with ORs,[20] or relied upon up a far greater number of alleles to detect a PsA predictive signal.[23]

## Conclusion

In this study, a PsA GRS that included a small number of highly replicated loci was found to have modest predictive power in discriminating PsA cases from PsO controls. Weighting the GRS with the OR of each allele's associated risk of PsA versus PsO proved to be a better discriminator than a simple unweighted scoring system, which agreed with prior research in this area.[21] Furthermore, a weighted model that only included HLA risk alleles was found to be the best discriminator of all the models tested, which also supports literature asserting the driving force of certain HLA risk alleles in the development of PsA.[20–22]

Future efforts are aimed in 3 directions. First, recently published data demonstrates the advantages of using large cohorts and a high number of genetic markers (ie, 200 risk alleles) to identify subtle genetic differences that better distinguish PsA from PsO.[23] Such approaches further benefit from advanced statistical techniques and machine-learning approaches to achieve up to 90% precision and 100% specificity for predicting PsA among patients with PsO.[23] Future research should focus on leveraging such innovative methods.

Second, the promise of genetic prediction models is not meant to replace thorough clinical assessment of psoriatic patients. Comprehensive evaluations are critical to understanding the role of genetic screening in diagnosing and managing PsA. It is possible that adding a GRS to screening tools like the PEST, PASE, ToPAS, EARP, and others can improve the sensitivity and specificity of these instruments. With this in mind, there is a need to continue refining genetic risk scoring for PsA so that this method can be tested and validated in rigorously designed studies with larger cohorts and in a range of practice settings.

Third, there are currently no biomarkers to predict which patients with PsO are at risk of PsA, to track the progression of PsA or to evaluate response to therapies.[24–26] Researchers have identified various potential targets, ranging from soluble biomarkers related to inflammation to microRNA associated with immune cell activity.[26] The identification of PsA-specific biomarkers is an area of ongoing research that could be combined with genetic risk scoring to provide a robust, objective approach to PsA diagnosis and monitoring.

In conclusion, prediction of PsA remains a high priority for clinicians, researchers, and patients around the world. The research community should continue developing novel approaches that combine a growing source of genetic data with clinical information and biologic indicators to optimize PsA diagnosis.

## Acknowledgments

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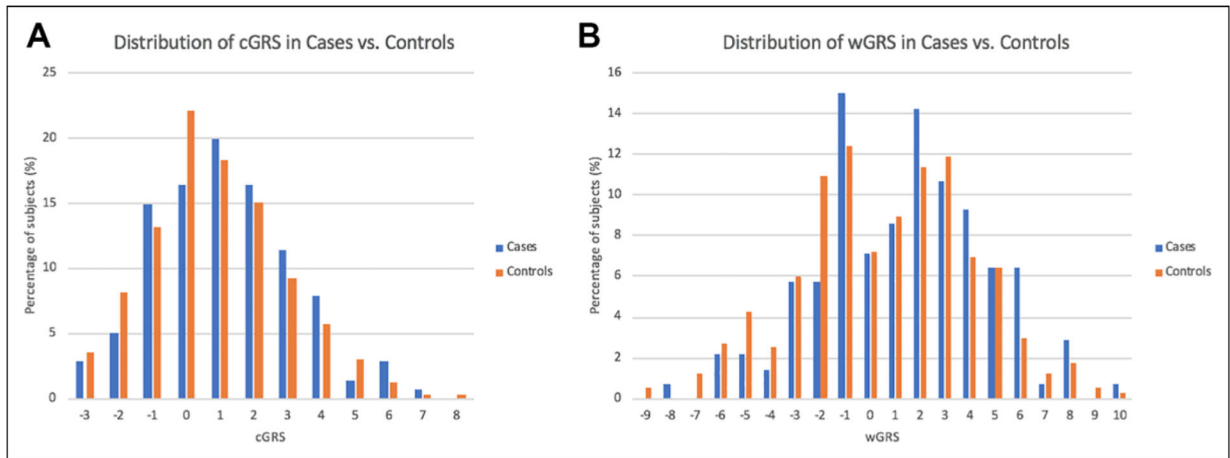
**Figure 1.**
A, Distribution of cGRS in cases (confirmed PsA) versus controls (PsO only). B, Distribution of wGRS in cases (confirmed PsA) versus controls (PsO only). cGRS indicates count genetic risk score; wGRS, weighted genetic risk score; PsA, psoriatic arthritis; PsO, psoriasis.
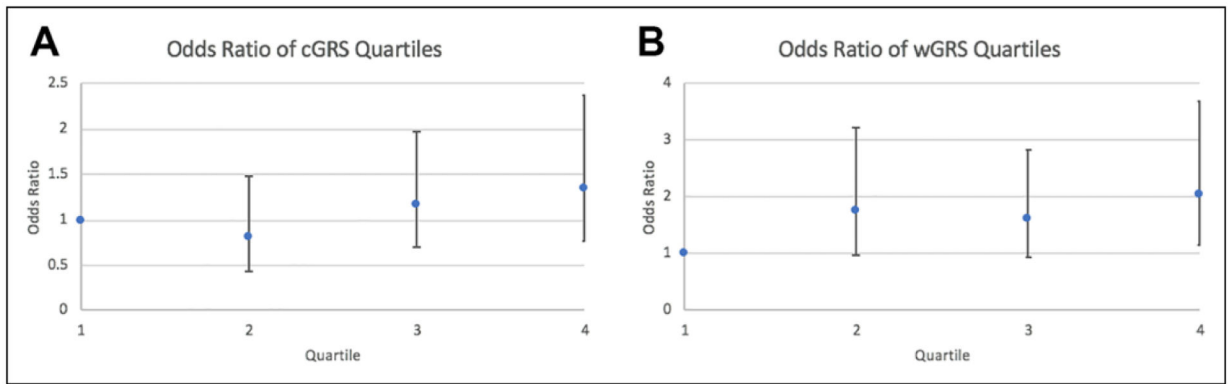
**Figure 2.**
A, Odds ratios of cGRS quartiles relative to first quartile, vertical bars represent 95% confidence intervals. B, Odds ratios of wGRS quartiles relative to first quartile, vertical bars represent 95% confidence intervals. cGRS indicates count genetic risk score; wGRS, weighted genetic risk score.
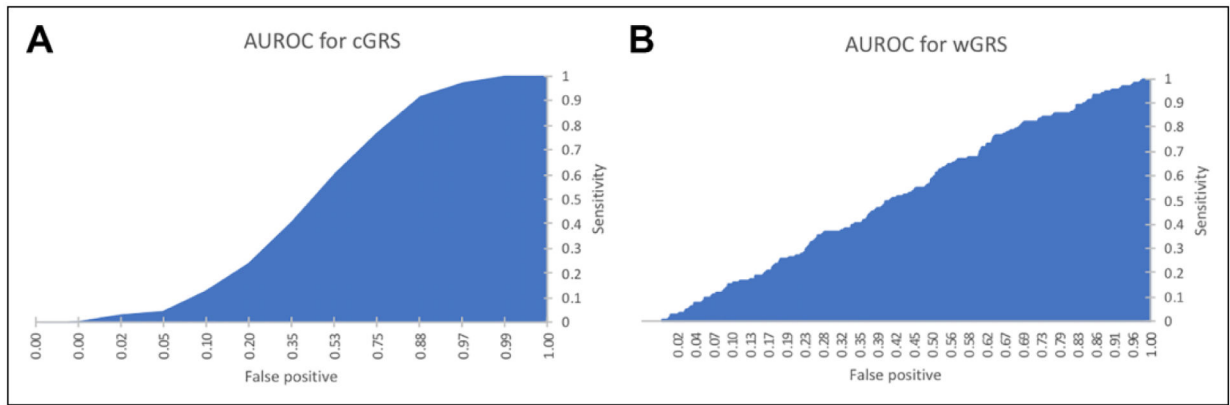
**Figure 3.**
A, Area under the receiver operating characteristic curve (AUROC) for cGRS model. B, Area under the receiver operating characteristic curve (AUROC) for wGRS model. cGRS indicates count genetic risk score; wGRS, weighted genetic risk score.
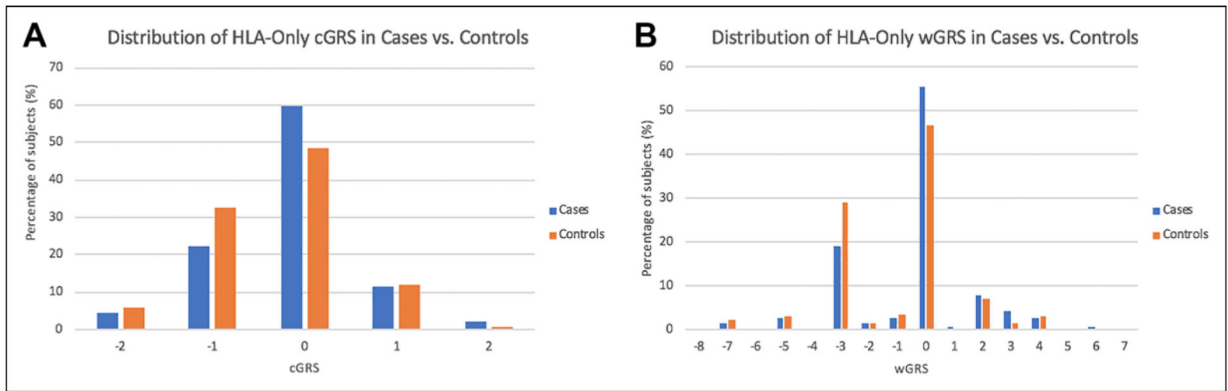
**Figure 4.**
A, Distribution of HLA-only cGRS in cases (confirmed PsA) versus controls (PsO only). B,
Distribution of HLA-only wGRS in cases (confirmed PsA) versus controls (PsO only).
cGRS indicates count genetic risk score; PsA, psoriatic arthritis; PsO, psoriasis.
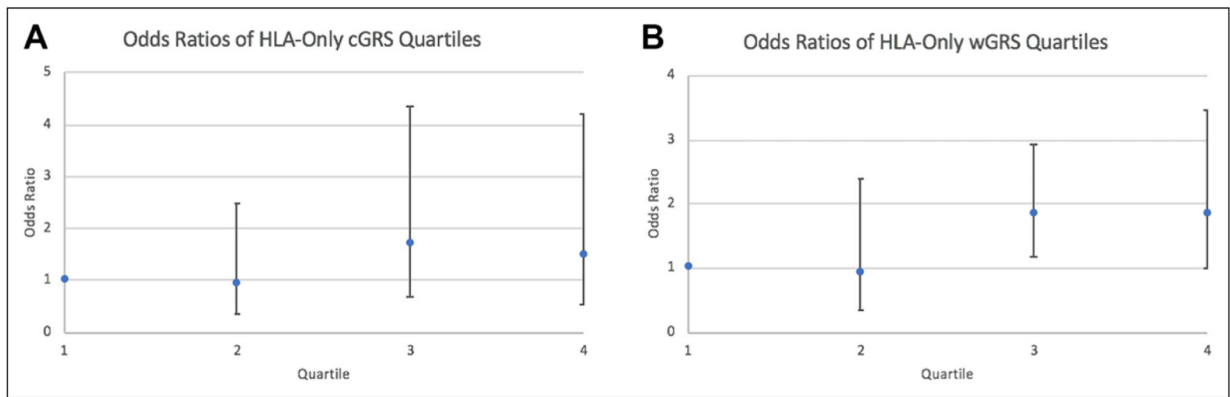
**Figure 5.**
A, Odds ratios (ORs) of HLA-only cGRS quartiles relative to first quartile, vertical bars represent 95% confidence intervals. B, Odds ratios of HLA-only wGRS quartiles relative to first quartile, vertical bars represent 95% confidence intervals. cGRS indicates count genetic risk score.
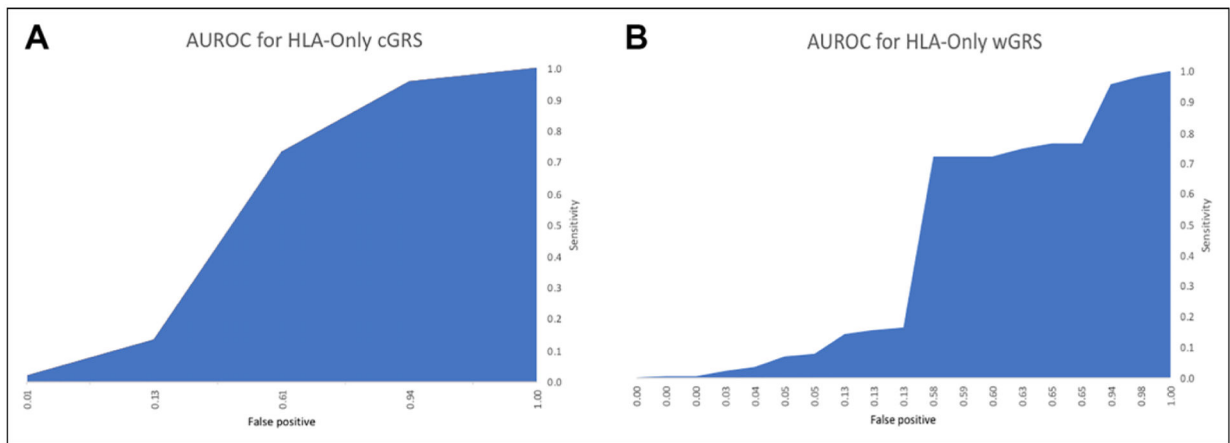
**Figure 6.**
A, Area under the receiver operating characteristic curve (AUROC) for HLA-only cGRS
model. B, Area under the receiver operating characteristic curve (AUROC) for HLA-only
wGRS model. cGRS indicates count genetic risk score; wGRS, weighted genetic risk score.
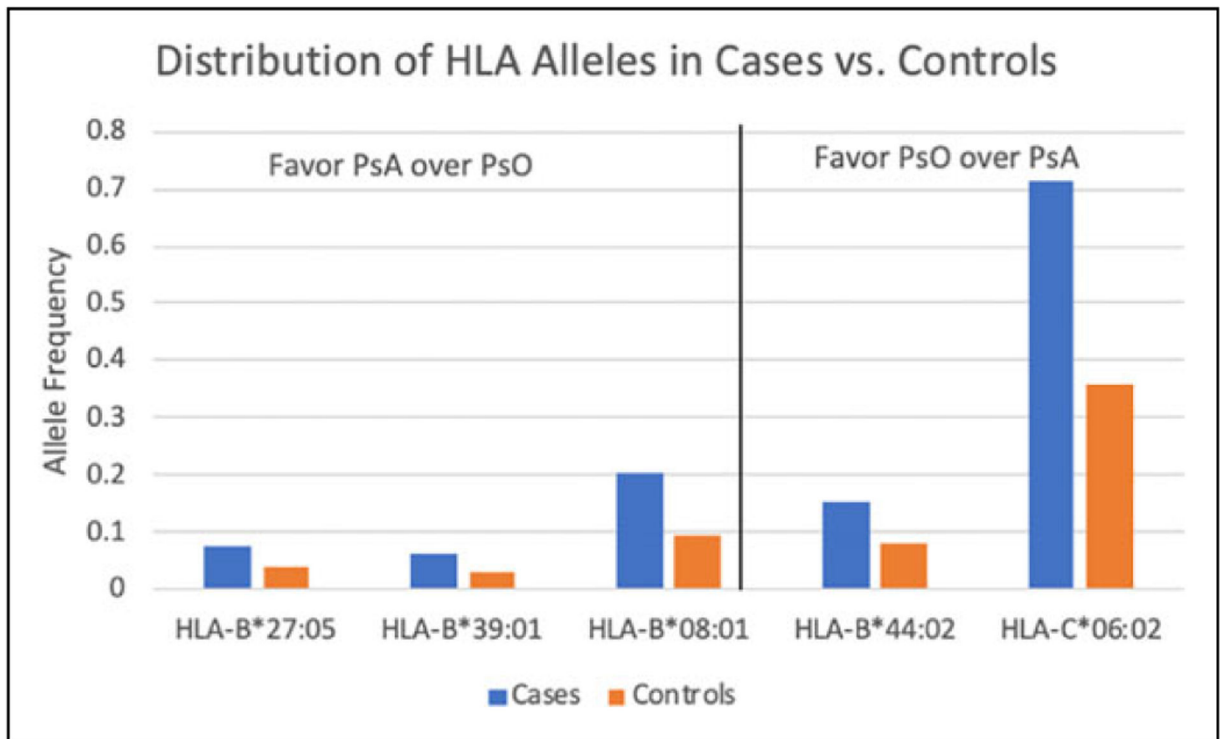
**Figure 7.**
Distribution of HLA alleles in cases (confirmed PsA) versus controls (PsO only). PSA
indicates psoriatic arthritis; PsO, psoriasis.

**Table 1.**

Eleven Candidate Risk Genes Used to Calculate the Psoriatic Arthritis Genetic Risk Score (PsA GRS) in Case–Control Samples.

| Candidate Risk Gene | Single-Nucleotide Polymorphism | Risk Allele Favors | Chromosome Location | Position | Alleles Risk/Nonrisk | Odds Ratio[a] |
|---|---|---|---|---|---|---|
| HLA-C*06:02 | - | PsO | 6 | - | - | 3.846 |
| HLA-B*44:02 | - | PsO | 6 | - | - | 1.667 |
| HLA-B*27:05 | - | PsA | 6 | - | - | 3.77 |
| HLA-B*39:01 | - | PsA | 6 | - | - | 2.86 |
| HLA-B*08:01 | - | PsA | 6 | - | - | 1.81 |
| TNFRSF9 | rs4908742 | PsO | 1 | 8,245,030 | A/C | 1.195 |
| LCE3C/B | rs10888503 | PsO | 1 | 152,593,549 | T/C | 1.149 |
| IL23R | rs12044149 | PsA | 1 | 67,600,686 | T/G | 1.196 |
| IL23R | rs4655683 | PsA | 1 | 67,611,613 | A/G | 1.135 |
| TNFAIP3 | rs9321623 | PsA | 6 | 137,958,265 | C/T | 1.172 |
| CSF2/P4HA2 | rs715285 | PsA | 5 | 131,485,383 | G/A | 1.18 |

Abbreviations: PsO, psoriasis; PsA, psoriatic arthritis.

[a] All odds ratios are given in the same direction from published studies except for genes HLA-C*06:02, HLA-B*44:02, TNFRSF9, and LCE3C/B that are given as reciprocals to reflect these genes associated risk of PsA versus PsO.[2,20]