

The Efficacy of Genetic Testing for Early Detection of Psoriatic Arthritis in Patients with Psoriasis

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Abstract

Background: Improved understanding of the genetic architecture of psoriatic disease (PsD) and reduction in genotyping costs provide an opportunity to assess the application of genetic testing for psoriatic arthritis (PsA) diagnosis. The study aimed to assess the performance of a multi-marker genetic kit in classifying patients as PsD and PsA and to assess whether the performance has improved by combining genetic and clinical data.

Methods: 328 patients with psoriasis and musculoskeletal symptoms (78 PsA and 250 psoriasis alone) who were referred to rheumatology for suspected PsA and 341 non-psoriatic controls were analyzed. A custom multi-SNP genetic assay, including 41 variants based on large scale association genome-wide association studies in PsA, was genotyped. Machine-learning methods were used to identify the optimal classification model by area under the receiver operating curve (AUC).

Results: The performance of all three classifiers to distinguish PsD from non-psoriatic controls was moderate with similar AUC (range 0.64 to 0.69). Logistic regression had the highest AUC and showed moderate specificity (61.9%) and specificity (67.9%). The ability of the models to correctly classify PsA among all psoriasis patients was suboptimal with AUC ranging from 0.55 to 0.60 with low sensitivity (1.3% to 34.6%) and moderate to high specificity (69.2% to 99.6%). The combination of genetic and clinical data resulted in an improvement in the performance of the models (AUC 0.65 to 0.69), however, the information contributed by the genetic markers was only marginal.

Conclusions: Genetic testing has marginal effect on correctly classifying PsA among psoriasis patients in clinical setting.

Background

Psoriatic arthritis(PsA) affects up to a third of patients with psoriasis thus, efforts to improve early detection of the disease focus on patients with psoriasis(1). Delays in diagnosis remain a major gap in care in PsA. Studies have shown that 79% of the patients with PsA were diagnosed more than 3 months of symptoms onset(2) and that the wait time to rheumatology referral was substantially longer than for other rheumatic conditions, such as rheumatoid arthritis and lupus(3). These gaps in care contribute to poor disease outcomes, such as the development of joint damage, disability and low quality of life.

One of the major factors that contributes to the delayed diagnosis of PsA is the lack of an objective laboratory test to aid in the diagnosis in early stages of the disease. The presentation of PsA can be non-specific and subtle, furthermore, it can co-exist with non-inflammatory musculoskeletal conditions, such as osteoarthritis, which can result in misdiagnosis and delays in referral to rheumatology care among non-specialists(4, 5).

To date, strategies to improve early diagnosis of PsA are directed towards screening patients with psoriasis for musculoskeletal symptoms. Recent efforts focused on screening questionnaires, however,

these tools suffer from low sensitivity and specificity. Since a considerable proportion of the psoriasis patients with musculoskeletal complaints, do not have PsA, but rather have other non-inflammatory rheumatic conditions, such as osteoarthritis(6), a simple, scalable tool is needed that can help dermatologists and family physicians triage these patients and prioritize rheumatology referral of potential PsA cases(7).

Both psoriasis and PsA have a strong genetic component as evident by substantial heritability (40–90%) and familial aggregation(8, 9). This heritability is influenced by specific loci that determine the individual's susceptibility to develop these conditions. Indeed, several large genome wide association studies (GWAS) identified over 60 risk loci for psoriasis which encode for proteins involved in the innate immune system, antigen presentation and acquired or adaptive immune response(10). Despite the smaller number of studies, several GWASs and candidate-gene studies identified specific genetic variants associated with PsA. While some of these genes overlap with those of psoriasis, others could differentiate patients with PsA from those with psoriasis without arthritis (PsC)(11–21). The strongest and most reproducible risk loci for PsA are located within the MHC region, particularly *HLA-B* and *HLA-C* genes. Additional suggested PsA-specific loci outside of the MHC region include *5q31*, *IL-23R*, *PTPN22*, *TNFAIP3*, *FBXL-19*, *ZNF816*, *IFNG* and *IL-13*(11–21). The improved understanding of the complex genetic architecture of PsA along with the reduction in the costs of genotyping provide an opportunity to assess the application of genetic testing for PsA diagnosis in clinical setting. Currently, there is limited information about the utility of genetic testing in optimizing triage of psoriasis patients with musculoskeletal symptoms and improving early detection of PsA.

We hypothesize that genetic testing could improve the accuracy of early detection of PsA among psoriasis patients who present with musculoskeletal symptoms. The overall aim of our research is to develop a personalized model for identifying PsA and PsD using genetic data. Specifically, we aimed to 1) Assess the performance of the multi-marker genetic kit in classifying patients PsD from non-psoriatic controls and PsA from psoriasis alone; and 2) to assess whether the performance of the prediction model for PsA improved by combining genetic and clinical data.

Methods

Study population

Psoriasis patients who were referred to rheumatology for suspected PsA were prospectively recruited in a single medical academic centre in Toronto, Canada. All patients had dermatologist conformed diagnosis of psoriasis and were experiencing musculoskeletal symptoms. None of the patients had a prior diagnosis of PsA. The patients were referred from dermatology and family medicine clinics as well as from a phototherapy centre that serves as a tertiary referral center for dermatologists from the Greater Toronto Area. The control population comprised of osteoarthritis patients with no psoriasis, inflammatory arthritis or other autoimmune diseases. The study was conducted from January 2016 to December 2018.

Case definition

All participating patients and controls underwent a clinical assessment by a rheumatologist. Patients were classified as having PsA if they met the CASPAR classification criteria for PsA. Patients who were classified as not having PsA at baseline were reassessed after 1 year to determine whether they have developed PsA since the baseline visit. The rheumatologist was blinded to the genetic testing results. In addition, clinical information about the patients' demographics, psoriasis characteristics, duration and severity, family history of PsA, comorbidities, and patient reported outcomes were collected at the baseline visit.

Genetic Testing

A custom multi-SNP genetic assay was designed using the program Assay Design Suite and Typer IV (Agena Biosciences) and genotyped on a MassARRAY system (Agena Biosciences). The custom PsA panel is comprised of 41 variants in or near 19 genes based on genome-wide significance or significant associations in multiple candidate gene studies in psoriasis or PsA studies (including PsA specific variants) (22). Polymorphisms within the following genetic loci were included in the panel: *HLA-B*, *HLA-C*, *LCE3A*, *IL-23A*, *IL-23R*, *IL-12B*, *REL*, *TNIP1*, *IL-13*, *PTPN22*, *TRAF3IP2*, *TYK2*, *TNFRSF9*, 5q31, *KIR2DS2*, *TNFAIP3*, *FBXL19*, *ZNF816A*, *MICA*.

Statistical analysis

The accuracy of genetic testing for differentiating between PsA and non-PsA patients was assessed twice for each of the following outcomes: 1) diagnosis of PsA at baseline; and 2) diagnosis of PsA at 1 year. In addition, we assessed the ability of the genetic testing to distinguish between PsD and non-psoriatic controls.

First, we tested the association between each genetic marker individually and patient diagnosis using Chi Square test and reported the odds ratio (OR) and its 95% Confidence Intervals (CI). Results were reported for significance levels of $p < 0.05$ and after correcting for multiple testing ($p < 0.001$ for 41 individual tests).

We then used the entire information from the genetic assay to develop machine-learning classifiers to predict PsA and PsD diagnosis including logistic regression, naïve bayes and random forest. Age and sex were included in each of the models in addition to genetic data. The performance of the resulting classification models at distinguishing between PsA and non-PsA patients and PsD and non-psoriatic controls, was evaluated by calculating their sensitivity, specificity, precision (proportion of subtype that was accurate) and area under the receiver operator curve (AUC). We then selected a number of clinical and demographic variables to assess whether their combination with genetic data could improve the model performance. We selected clinical variables that were reported to be associated with PsA compared to psoriasis alone. The following variables were selected for testing: age, sex, race (Caucasian vs. non-Caucasian), psoriasis duration, a history of uveitis, nail psoriasis, flexural psoriasis, psoriasis area and severity index (PASI), body mass index (BMI), patient pain (visual analogue scale of 0 to10), health

assessment questionnaire disability index (HAQ-DI), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT) and high sensitivity C-Reactive Protein (hsCRP) and family history of PsA.

We used RWeka package in R for the machine learning and statistical analysis.

Results

A total of 328 patients with psoriasis who were referred for a suspected diagnosis of PsA due to musculoskeletal symptoms were enrolled in the study. Of those, 78 patients were classified as PsA by the rheumatologist at the initial visit (PsA-baseline) and the remaining 250 patients were deemed not to have PsA (cutaneous psoriasis (PsC)). 17 additional patients have developed PsA within 1 year after the baseline visit, resulting in 95 patients with PsA at 1 year (PsA-1 year). Patients who were lost to follow up were assumed not to have PsA at 1 year. In addition, DNA from 341 non-psoriatic controls was analyzed. The patient characteristics are shown in Table 1.

Table 1
Characteristics of the patients with PsA and PsC

Variable	All	PsA (N = 78)	PsC (N = 250)
Age (years)	49.2 (14.5)	45.8 (13.5)	50.3 (14.7)
Sex: Female (%)	194 (59.2%)	38 (48.7%)	156 (62.4%)
Race: Caucasian (%)	253 (77.1%)	53 (67.9%)	200 (80%)
Psoriasis duration (Years)	17.1 (14.4)	15 (10.9)	17.8 (15.3)
Family Hx of PsA (%)	21 (6.4%)	5 (6.4%)	16 (6.4%)
BMI (kg/m ²)	29.1 (7)	28.6 (5.9)	29.3 (7.2)
PASI	4.7 (5.8)	5.6 (7.3)	4.4 (5.3)
Psoriatic nail lesions (%)	115 (35.1%)	35 (44.9%)	80 (32%)
Flexural psoriasis	23 (7%)	12 (15.6%)	11 (4.4%)
Uveitis (%)	9 (2.7%)	3 (3.9%)	6 (2.4%)
Patient pain (0–10)	4.1 (2.6)	5.1 (2.6)	3.7 (2.5)
HAQ	0.4 (0.5)	0.6 (0.6)	0.4 (0.4)
FACIT	34.2 (10.9)	32.9 (11.4)	34.7 (10.8)
hsCRP (mg/L)	4.9 (9.1)	7.8 (13.1)	4 (7.2)

Genetic-based classifiers for PsD vs. controls

The association between the tested SNPs and PsD vs. controls is shown in Fig. 1 and supplementary Table 1.

The frequencies of the following 17 SNPs located in 8 genes were associated with PsD compared with controls: IL-23R (rs11209026), PTPN22 (rs2476601), REL (rs13017599), 5q31 (rs715285), HLA-C (rs887466, rs3869115, rs1050414, rs12189871, rs12191877, rs13214872, rs2894207, rs4406273), HLA-B (rs6457374, rs3131382, rs3129944), MICA (rs67841474) and TYK2 (rs34536443). After correction for multiple testing the variants in PTPN22, REL, HLA-C and HLA-B remained significantly associated with PsD vs. controls ($p < 0.001$). Next, we used all 41 genetic SNPs to develop classifiers to predict PsD diagnosis. The performance of the following three machine learning methods: logistic regression, naïve bayes and random forest are shown in Table 2. Overall, the performance of all three classifiers was moderate with similar AUC (range 0.64 to 0.69). Logistic regression had the highest AUC and showed moderate specificity (61.9%) and specificity (67.9%).

Table 2
The performance of genetic markers to classify patients with PsD vs. Controls

Method	TP	TN	FP	FN	Accuracy	Sensitivity	Specificity	AUC
Logistic regression	231	203	125	110	0.65	67.7%	61.9%	0.69
Random Forest	106	284	44	235	0.58	31.1%	86.6%	0.64
Naïve Bayes	247	167	161	94	0.62	72.4%	50.9%	0.67

AUC – Area under the receiver operating curve; FN- false negative; FP – false positive; TN – true negative; TP – true positive

Genetic-based classifiers for PsA vs. Psoriasis

In the comparison between PsA and PsC at baseline the following three SNPs were more frequent in patients with PsA: *LCE3A* (rs10888503, $p = 0.004$, OR 1.73), *IL-23R* (rs4655683, $p = 0.049$, OR 1.46) and *TNIP1* (rs146571698, $p = 0.038$, OR 2.12). None of them remained significantly associated with PsA after correcting for multiple testing. We then analyzed the ability of the multi-marker panel to correctly classify patients with PsA at baseline from those with PsC (Table 3).

Overall the classifiers showed low sensitivity (range 1.3–32%) and high specificity (range 76–99.6%) with modest AUROC of 0.55 to 0.60. The results were not substantially changed when the outcome was considered to be PsA-1-year (AUROC 0.52 to 0.56, data not shown). Lastly, we evaluate the changed in specificity and sensitivity when modifying the logistic regression model cut-off level. Using a cut-off level of 0.3 instead of the default level of 0.5, the sensitivity increased from 24.4–34.6% and the specificity reduced from 88.4–69% and with a cut-off level of 0.7 the sensitivity reduced to 7.7% and specificity increased to 98%.

Table 3
The performance of genetic markers to classify patients with PsA vs. PsC

Method	TP	TN	FP	FN	Accuracy	Sensitivity	Specificity	AUC
Logistic regression	19	221	29	59	0.73	24.4%	88.4%	0.56
Cut-off								
- 0.3	27	173	77	51	0.61	34.6%	69.2%	0.56
- 0.7	6	245	5	72	0.77	7.7%	98%	0.56
Random Forest	1	249	1	77	0.76	1.3%	99.6%	0.55
Naïve Bayes	25	190	60	53	0.66	32.1%	76%	0.60
AUC – Area under the receiver operating curve; FN- false negative; FP – false positive; TN – true negative; TP – true positive								

The performance combined clinical- and genetic-based classifiers for PsA

Since the performance of the genetic-based classifiers was suboptimal, we evaluated whether combining clinical and genetic data could improve their performance in classifying patients as having PsA vs. PsC. The results are shown in Table 4. The combination of genetic and clinical data has improved the performance of the models with an AUC ranging from 0.65 to 0.69. Logistic regression had the highest AUC (0.69) and showed reasonable specificity (81.2%) with low sensitivity (47.4%). Using a lower cut-off level of 0.3 the sensitivity increased to 57.6% and the specificity reduced to 80%. To find irrelevant and redundant features, we also applied gain ratio attribute evaluator and ranker search method to score these genetic and clinical variables. The variables that contributed most information to the model were: rs146571698(*TNIP1*), HAQ and hsCRP. The results were not substantially changed when the outcome was considered to be PsA-1-year (AUC 0.65 to 0.69, data not shown).

Table 4

The performance of machine learning methods to classify patients with PsA vs. PsC using genetic and clinical variables

Method	TP	TN	FN	FP	Accuracy	Sensitivity	Specificity	MCC	AUC
Logistic regression	27	220	51	30	0.75	47.4%	81.1%	0.25	0.69
Cut-off									
- 0.3	19	236	59	14	0.78	57.6%	80%	0.27	0.69
- 0.7	41	196	37	54	0.72	43.2%	84.1%	0.29	0.69
Random Forest	3	250	75	0	0.77	100%	76.9%	0.17	0.68
Naïve Bayes	28	214	50	36	0.74	43.8%	81.1%	0.23	0.65
AUC – Area under the receiver operating curve; FN- false negative; FP – false positive; TN – true negative; TP – true positive;MCC- Matthews correlation coefficient									

Discussion

Our study evaluated the performance of a multi-marker genetic kit in classifying patients PsD and PsA in a real-world setting. The results of our study suggest that despite the association of several genetic markers with PsD and PsA, the overall ability of a multi-marker genetic test to correctly classify patients with PsD and those with PsA, is modest is only modest. In particular, the low sensitivity of the genetic test suggests that it is not useful as a screening tool among psoriasis patients referred to rheumatology for suspected PsA.

The use of genetic testing at the point of care is part of common practice for the diagnosis of ankylosing spondylitis (AS) as testing for the presence of HLA-B*27 is part of the classification criteria for axial SpA(23) and can help with the diagnosis of this condition. However, PsA is much more genetically heterogenous and unlike AS, in which HLA-B*27 is carried by the majority of patients, in PsA no single dominant susceptibility gene has been identified(22, 24). The majority of the genetic heritability in PsA is explained by genes located in the MHC region and there are few non-MHC genes that have been specifically associated with PsA when compared with PsC(11, 12, 20). In this context, the suboptimal performance of our multi-marker genetic testing could be explained.

Patrick et al. used 200 genetic markers to develop a classifier that distinguished between PsA and PsC with good fidelity (AUC 0.82)(25). However, it should be noted that patients with PsA and PsC were recruited from different sources, thus potentially resulting in substantial differences in the two populations that may have been driven by the different genetic profiles. This may create a type of selection bias where patients who developed PsA prior to or at the time of development of psoriasis have not been included in our study that focused on patients with prevalent and often long-term psoriasis. Thus, susceptibility genes with high penetrance for PsA, such as the *HLA-B*27*, are expected to be less frequent in our study population as patients who carry these genes are expected to have already

developed PsA (immortal time bias) (26). Indeed, the prevalence of the tagging SNP for *HLA-B*27* was only 4% which was similar to the prevalence found in the general population and much lower than the reported prevalence in other PsA cohorts (~ 15%) (14, 26). However, we believe that our source population of psoriasis patients represent a more relevant population to test the performance of genetic testing in clinical setting as it represent a typical population of patients referred to rheumatology for suspected PsA. In this population, genetic factors with high penetrance for PsA may play a lesser role in disease susceptibility compared to other genes with weaker effect or to environmental risk factors.

The combination of clinical and genetic factors has improved the performance of the model classifier with AUC approaching 0.70 and a reasonable specificity, however the sensitivity of the test remained low. However, most of the information in these models was provided by non-genetic factors including patient reported outcomes and other clinical variables. The relatively lower sensitivity of these models precludes their use as screening tools.

Our study was limited in several aspects including the relatively small sample size that may have limited the performance of some of the machine learning methods. Secondly, the study population included patients with psoriasis who had musculoskeletal symptoms, thus, some of the patients that were classified as PsC at baseline may have had subclinical PsA leading to clinical misclassification thus contributing to the suboptimal performance of the model. Indeed, 17 (6.8%) out of the 250 patients with PsC have converted to PsA within 1 year, although when considering these converters, no significant differences were observed in the model performance.

Conclusions

The results of our study showed that the overall ability of multi-marker genetic testing to distinguish patients with PsA from those with PsC was only modest. This suggests that genetic testing has limited role for screening for or diagnosing PsA among patients with psoriasis in clinical setting. Studies should focus on more dynamic biomarkers that could reflect the change in relevant immunologic pathways over time.

List Of Abbreviations

AUC - area under the receiver operator curve

BMI - body mass index

FACIT - Functional Assessment of Chronic Illness Therapy – Fatigue

GWAS - genome wide association studies

HAQ-DI - health assessment questionnaire disability index

OR - odds ratio

PASI - psoriasis area and severity index

PsA – psoriatic arthritis

PsC – cutaneous psoriasis

PsD - psoriatic disease

Declarations

Ethics approval and consent to participate

The study was approved by the Women’s College Hospital Ethics Board and all patients gave their informed consent (REB#2016-0043). All participants signed an informed consent form for participation in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to terms of our research ethics board.

Competing interests

The authors declare that they have no competing interests

Authorship

LE: conception, design of the work, acquisition of data, interpretation of data; drafted the manuscript; QL: design of the work, data analysis; interpretation of the results; review of the manuscript; DJ: design of the work, data acquisition, review of the manuscript; CF: design of the work, data acquisition, review of the manuscript; JY: data acquisition, review of the manuscript; PR: conception, design of the work, acquisition of data, interpretation of data; review of the manuscript; All authors have read and approved the final manuscript.

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