Diagnostic and Prognostic Value of Genetics in Undifferentiated Peripheral Inflammatory Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** To evaluate the diagnostic and prognostic utility of genetic testing in undifferentiated peripheral inflammatory arthritis (UPIA).

Methods. A systematic literature search was performed in Medline, Embase, the Cochrane Library, and abstracts presented at the 2007 and 2008 meetings of the American College of Rheumatology and the European League Against Rheumatism. The target studies were those evaluating diagnostic or prognostic value of genetic markers specifically in UPIA. Two reviewers independently screened titles and abstracts and reviewed included articles in detail. All data were collected using ad hoc standard forms, permitting the calculation of positive and negative likelihood ratios of each genetic marker for diagnoses of different rheumatic diseases and for the development of relevant outcomes.

Results. Of the 3109 articles retrieved, 26 original studies fulfilled criteria of the systematic review. The most frequent diagnosis tested was rheumatoid arthritis, followed by inflammatory polyarthritis, and spondyloarthropathies. The main prognostic outcome evaluated was development of erosions, followed by median Larsen score, remission, Health Assessment Questionnaire (HAQ) score, and persistent synovitis. In total, 122 genetic markers were tested. No genetic marker had a high likelihood ratio for the diagnosis of a specific rheumatic disease. The shared epitope was associated with poor prognosis (erosions, HAQ > 1, mortality, and persistent synovitis). Other genes did not predict outcome in undifferentiated arthritis. Other outcomes for persistent disease or disability were not studied in depth.

Conclusion. In isolation, no studied genetic marker is very informative of a future diagnosis in patients with UPIA. The shared epitope has a slight association with poor prognosis of UPIA. (J Rheumatol 2011;38 Suppl 87:38–44; doi:10.3899/jrheum.101073)

Key Indexing Terms:
UNDIFFERENTIATED ARTHRITIS GENETICS DIAGNOSIS
PROGNOSIS SYSTEMATIC REVIEW

Presentation with new-onset peripheral inflammatory arthritis is notably common in early arthritis clinics. Some of these patients will be diagnosed with a specific disease, such as rheumatoid arthritis (RA) or psoriatic arthritis (PsA), while in others arthritis will remain undifferentiated for varied periods of time, some indefinitely[1,2]. Predictors of the development of persistent arthritis in patients presenting with early arthritis have been addressed in a wide number of studies. The genetic component of arthritis is largely undefined; however, it likely determines important clinical aspects of the disease, such as clinical presentation, pattern of disease progression, severity, and response to therapies[3]. Given that current clinical prediction models have insufficient power to provide patients with individualized treatments, identification of genetic factors that may be involved in the pathogenesis and prognosis of undifferentiated arthritis can open up new prospects[4,5]. We aimed to study the diagnostic and predictive value of genetic markers in undifferentiated peripheral inflammatory arthritis (UPIA).

MATERIALS AND METHODS

We sought to answer our research question by performing a systematic review as part of the multinational 3e (Evidence, Expertise, Exchange) Initiative in Rheumatology[6] to develop recommendations for the investigation and followup of UPIA.

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Supported by an unrestricted educational grant from Abbott. Abbott had no role in the design, literature search, data collection, data analysis, data interpretation, or writing of this report. Dr. Bombardier holds a Pfizer Chair and Canada Research Chair in Knowledge Transfer for Musculoskeletal Care.

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Systematic literature search. Two systematic literature searches for articles published between 1950 and January 16, 2009, were carried out in Medline, Embase, and the Cochrane Library. Comprehensive search strategies combined MeSH (medical subject heading) terms and free text for "undifferentiated arthritis," "genetics," and either "diagnostic studies" or "prognostic studies." Searches were limited to humans, adults, and to articles published in English (the full search strategy used in Ovid for Medline, Embase, and the Cochrane Library is available online at http://www.3eupia.com).

We also searched abstracts presented at the 2007 and 2008 annual scientific meetings of the American College of Rheumatology and the European League Against Rheumatism, and the reference lists of all relevant studies, letters, and review articles.

Study selection. Selection criteria were predefined by protocol, as agreed on by the review group plus the remaining investigators in the 3e Initiative. To be selected for systematic review a study had to include (1) population of adults with UPIA; (2) investigation of a genetic marker such as genes, polymorphisms, or alleles; and (3) outcome of a specific diagnosis (RA, PsA, spondyloarthritis, systemic lupus erythematosus, etc.) or a specific prognosis, with reference to disease progression in terms of radiographic damage (erosive disease or radiographic scores), persistence of arthritis, remission, disability, etc. Selection for diagnosis-related review required data on specificity and sensitivity of a marker for a specific diagnosis. Selection for prognosis-related review required clinical trial, cohort, or case-control study design.

Two reviewers (LS, IC) independently screened titles and abstracts of citations identified by the search strategy. On a limited number of articles for which the 2 reviewers disagreed, a third reviewer (LC) decided if the article should be included for the review. Selected articles were then reviewed in detail reading the complete article. A number of articles were excluded after this second step. Articles that did not fulfil all inclusion criteria or that had insufficient data for analysis were excluded.

Data extraction and quality assessment. Publication details, number of included patients and their characteristics, definition of comparator groups, genetic markers studied, duration of followup, and data on relevant outcomes were extracted from all included articles using ad hoc standard forms. Data unavailable directly from the article were calculated from the raw data in the text when possible.

The assessment of study quality of diagnostic studies was based on an ad hoc checklist: (1) Was the "gold standard" appropriate? (2) Does the study show a correct spectrum of patients? (3) Is the test adequately described? (4) Was there adequate blinding of the assessment of test results? (5) Was the decision to conduct the gold standard independent of outcome of the test problem? and (6) Is it possible to calculate likelihood ratios (LR) from the tables? In the absence of a good diagnostic quality scale, we decided to sum all responses of "yes" to questions above, and rate the impression as "good" or "poor." The checklist was based on common sources of bias in diagnostic studies[7]. The Newcastle-Ottawa Quality Scale (NOS) was used to assess the quality of prognostic studies, either cohorts or case-control studies[8].

Data analysis. We aggregated weighted data for the description of the study populations. Also, we calculated sensitivity, specificity, and positive and negative LR of each genetic marker for the different diagnoses if these were not available in the original report. We also estimated their confidence intervals. For the prognosis review we calculated the odds ratio (OR) and relative risk (RR) for each outcome when it was possible to extract the raw data from the article; otherwise, we directly extracted the measures of association. All analyses and confidence intervals were performed with Stata 10 (Stata Corp., College Station, TX, USA).

RESULTS

Details of our systematic literature search are available online at http://www.3eupia.com (Supplementary Figure 1A and B). The systematic search strategy related to diagnosis retrieved 1444 articles, of which 225 were duplicated in Medline and Embase, plus 121 abstracts presented at meetings. After title and abstract screening, 44 articles were selected for full article review, of which 18 fulfilled inclusion criteria. The excluded articles and the reason for the exclusion are detailed in a supplementary table available online (http://www.3eupia.com). No meeting abstract or hand-searched report was included.

The systematic search strategy related to prognosis identified 1665 references and 121 meeting abstracts. After review of titles and abstracts and removal of the 159 duplicates across databases, 40 full-text articles were retrieved for further evaluation and 15 articles were retained for our analysis. A summary of the 25 excluded articles and the reason for the exclusion are detailed in a supplementary table available online (http://www.3eupia.com). Similarly, no meeting abstract or hand-searched report was included in this review.

Diagnostic value of genetics. Eighteen articles were included in the review of diagnostic utility[9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]. Details on the quality of the studies plus a description of the population included are available online (http://www.3eupia.com) as supplementary data. Included studies yielded 5335 patients, with a mean weighted age of 53 years (range 35–56) of whom 64% (range 37–82) were women. As expected, RA was the most frequently tested diagnosis as an outcome since it was tested in 12 studies[12,13,14,15,16,17,18,21,22,23,24,25]. Ten studies tested the utility of genetic markers to diagnose inflammatory arthritis in general[9,10,11,15,18,19,20,21,25,26], 2 studied spondyloarthritis[12,21], and 2 PsA and reactive arthritis[12,25]. More than 100 genetic markers were tested across the 18 articles. Among the different markers, the shared epitope (SE) was the most commonly tested. Table 1 shows the utility of the presence of SE for diagnosis of RA from the 8 included studies where it was tested. The largest LR (6.75) came from the study with poorest quality and the smallest sample size[24].

Table 2 summarizes utility of other markers for diagnosis of RA. The gene with the highest positive LR (LR+) was the mannose-binding lectin (MBL) polymorphism B/D, although with a very low sensitivity. All other LR+ were < 4 and negative LR (LR–) were > 0.03. So no gene demonstrated a high utility for diagnosis of RA.

For diagnosis of other diseases there were fewer data. El-Gabalawy, *et al*[21] studied the value of different genetic markers for diagnosis of spondyloarthritis, finding a very low utility, with LR+ as follows: HLA-B8 1.14; HLA-B27 2.62; HLA-B60 2.32; HLA-DR*0101 1.02; HLA-DR*0301 0.99; HLA-DR*0401 1.03; HLA-DQ*0301 0.97; and HLA-DQ*0302 1.80. Two other studies[10,12] tested the utility of HLA-B27 for different diseases. In Kvien, *et al*[10] LR+ for HLA-B27 was 1.6 for Chlamydia-induced arthritis; 6.3 for enterobacterial reactive arthritis; 0.24 for sarcoid arthritis, and 0.24 for noninflammatory joint disease. In a study

Table 1. Utility of the presence of the shared epitope for the diagnosis of rheumatoid arthritis. Results are presented as estimated values (95% CI).

Study	Sensitivity	Specificity	LR+	LR–
Morel[24]	0.50 (0.25, 0.75)	0.93 (0.76, 0.99)	6.75 (1.63, 27.94)	0.54 (0.32, 0.89)
Vos[17]	0.08 (0.05, 0.13)	0.98 (0.96, 0.99)	3.82 (1.76, 8.27)	0.94 (0.89, 0.98)
El-Gabalawy[21]	0.57 (0.47, 0.67)	0.64 (0.59, 0.69)	1.58 (1.26, 1.97)	0.67 (0.52, 0.85)
van der Helm-van Mil[16]	0.63 (0.55, 0.70)	0.59 (0.54, 0.64)	1.49 (1.25, 1.76)	0.65 (0.52, 0.80)
Jacobsen[23]	0.32 (0.20, 0.47)	0.78 (0.52, 0.94)	1.44 (0.55, 3.73)	0.87 (0.64, 1.19)
Goeb[13]	0.40 (0.32, 0.48)	0.72 (0.63, 0.79)	1.40 (0.99, 1.96)	0.84 (0.71, 0.99)
Gough[22]	0.64 (0.55, 0.73)	0.53 (0.48, 0.58)	1.38 (1.16, 1.63)	0.67 (0.51, 0.86)
Thomson[15]	0.60 (0.55, 0.65)	0.49 (0.45, 0.54)	1.18 (1.05, 1.32)	0.81 (0.70, 0.94)

LR: likelihood ratio.

Table 2. Utility of genetic markers for the diagnosis of rheumatoid arthritis. Results are presented as estimated values (95% CI).

Study and Markers	Sensitivity	Specificity	LR+	LR–
Jacobsen[23]				
MBL polymorphism B/D	0.06 (0.02, 0.16)	0.99 (0.96, 0.99)	5.36 (1.11, 25.80)	0.95 (0.88, 1.02)
MBL polymorphism B/B	0.02 (0.00, 0.10)	0.99 (0.96, 0.99)	1.79 (0.19, 16.83)	0.99 (0.95, 1.03)
MBL polymorphism A/D	0.14 (0.06, 0.26)	0.90 (0.86, 0.93)	1.44 (0.66, 3.14)	0.95 (0.84, 1.07)
MBL polymorphism A/C	0.06 (0.02, 0.16)	0.96 (0.92, 0.97)	1.24 (0.36, 4.18)	0.99 (0.92, 1.06)
MBL polymorphism A/B	0.22 (0.12, 0.35)	0.80 (0.75, 0.84)	1.09 (0.61, 1.93)	0.98 (0.83, 1.14)
MBL polymorphism A/A	0.48 (0.35, 0.61)	0.37 (0.32, 0.43)	0.77 (0.57, 1.03)	1.39 (1.02, 1.90)
MBL polymorphism D/D	0.0 (0.00, 0.07)	1.0 (0.98, 1.0)	0.0	1.0 (0.99, 1.01)
MBL polymorphism B/C	0.02 (0.00, 0.10)	1.0 (0.98, 1.0)		0.98 (0.94, 1.02)
Nasrallah[25]				
HLA-B27	0.23 (0.11, 0.40)	0.86 (0.80, 0.90)	1.65 (0.78, 3.48)	0.89 (0.73, 1.09)
El-Gabalawy[21]				
HLA-B27	0.16 (0.10, 0.25)	0.89 (0.85, 0.91)	1.42 (0.83, 2.42)	0.95 (0.86, 1.04)
Hülsemann[12]				
HLA-B27	0.10 (0.04, 0.23)	0.68 (0.60, 0.75)	0.32 (0.12, 0.83)	1.32 (1.14, 1.53)
Goeb[13]				
PTPTN22 rs2476601	0.76 (0.68, 0.82)	0.21 (0.14, 0.30)	0.96 (0.83, 1.09)	1.15 (0.72, 0.85)
Feitsma[14]	0.21 (0.15, 0.28)	0.77 (0.72, 0.82)	0.93 (0.62, 1.38)	1.02 (0.92, 1.14)
PTPTN22 rs2476601				
El-Gabalawy[21]				
HLA-DR0401	0.29 (0.20, 0.38)	0.92 (0.88, 0.94)	3.40 (2.14, 5.40)	0.78 (0.68, 0.89)
HLA-B60	0.13 (0.08, 0.21)	0.92 (0.89, 0.95)	1.75 (0.94, 3.27)	0.94 (0.86, 1.02)
HLA-DQ0302	0.28 (0.20, 0.37)	0.82 (0.77, 0.85)	1.51 (1.02, 2.23)	0.89 (0.77, 1.01)
HLA-DR0301	0.23 (0.16, 0.33)	0.83 (0.79, 0.86)	1.37 (0.90, 2.09)	0.92 (0.82, 1.04)
HLA-B8	0.20 (0.14, 0.29)	0.85 (0.80, 0.88)	1.35 (0.85, 2.14)	0.94 (0.84, 1.04)
HLA-DQ0301	0.43 (0.33, 0.53)	0.61 (0.55, 0.65)	1.09 (0.83, 1.41)	0.94 (0.78, 1.14)

LR: likelihood ratio.

by Hülsemann and Zeidler[12] LR+ values were 0.32 for RA, 1.79 for reactive arthritis, 0 for polymyalgia rheumatica, 4.12 for ankylosing spondylitis, and 0.50 for PsA.

Prognostic value of genetics. Fifteen articles were included in the review of the predictive utility[20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]. Included studies yielded 5172 patients, with mean weighted age of 54 years (range 42–59), of whom 66% (range 62%–87%) were women. The most frequently tested prognostic outcome was development of erosions, tested in 12 studies[20,21,22,23,26,27,28,29,30,32,33,34], followed by median Larsen score[26,27,33], remission[24,34], Health Assessment Questionnaire (HAQ) score[27,33], and persistent synovitis[22,32]. Other outcomes were tested in single studies, including parameters of radiographic damage (Larsen score in highest tertile[28] and severe radiographic damage[32]), disability (from cutoffs of HAQ score[27,32,33]), or mortality (general and cardiovascular mortality[31]). Table 3 shows the utility of different genetic markers to predict development of erosions. Again, the SE was the most frequently tested marker. Table 4 summarizes the different association measures of SE with several prognostic outcomes.

DISCUSSION

Our systematic review summarizes and evaluates available

Table 3. Utility of different genetic markers for predicting the development of erosions. Results are presented as estimated values (95% CI).

Study	Sensitivity	Specificity	LR+	LR–
Jacobsen[23]				
MBL polymorphism B/B	0.06 (0.01, 0.28)	0.97 (0.86, 0.99)	2.25 (0.15, 33.76)	0.96 (0.84, 1.10)
MBL polymorphism B/D	0.13 (0.03, 0.36)	0.92 (0.80, 0.97)	1.63 (0.30, 0.82)	0.95 (0.77, 1.16)
MBL polymorphism A/A	0.44 (0.23, 0.67)	0.63 (0.51, 0.74)	1.18 (0.62, 2.25)	0.89 (0.56, 1.43)
MBL polymorphism A/D	0.19 (0.06, 0.43)	0.84 (0.70, 0.92)	1.18 (0.35, 4.01)	0.97 (0.74, 1.26)
MBL polymorphism A/B	0.13 (0.03, 0.36)	0.77 (0.63, 0.86)	0.53 (0.13, 2.15)	1.14 (0.90, 1.46)
MBL polymorphism A/C	0.06 (0.01, 0.28)	0.92 (0.79, 0.97)	0.79 (0.09, 7.05)	1.02 (0.87, 0.119)
MBL polymorphism B/C	0.0 (0.00, 0.19)	0.97 (0.85, 0.99)	0.0	1.03 (0.97, 1.09)
Barton[28]				
TNF-α –1031C	0.22 (0.18, 0.27)	0.82 (0.78, 0.85)	1.26 (0.96, 1.64)	0.94 (0.88, 1.01)
TNF-α –238A	0.06 (0.04, 0.09)	0.95 (0.92, 0.96)	1.26 (0.73, 2.15)	0.99 (0.95, 1.02)
TNF-α +851G	0.06 (0.04, 0.09)	0.95 (0.92, 0.96)	1.16 (0.67, 2.00)	0.99 (0.96, 1.02)
TNF-α –238G	0.89 (0.85, 0.92)	0.13 (0.10, 0.17)	1.03 (0.98, 1.08)	0.83 (0.58, 1.19)
TNF-α +489A	0.10 (0.07, 0.13)	0.90 (0.87, 0.92)	1.02 (0.68, 1.52)	1.0 (0.65, 1.60)
TNF-α +1304A	0.90 (0.87, 0.93)	0.11 (0.08, 0.14)	1.01 (0.96, 1.05)	0.89 (0.60, 1.33)
TNF-α +489G	0.90 (0.86, 0.92)	0.10 (0.08, 0.13)	1.0 (0.96, 1.05)	0.98 (0.66, 1.46)
TNF-α +851A	0.94 (0.91, 0.96)	0.06 (0.04, 0.08)	1.0 (0.96, 1.03)	1.01 (0.60, 1.69)
TNF-α +1304G	0.09 (0.06, 0.11)	0.91 (0.88, 0.93)	0.94 (0.61, 1.45)	1.01 (0.96, 1.04)
TNF-α –1031T	0.77 (0.72, 0.80)	0.18 (0.15, 0.21)	0.93 (0.87, 0.99)	1.32 (1.01, 1.70)
TNF-α –308A	0.14 (0.10, 0.17)	0.81 (0.77, 0.84)	0.72 (0.53, 0.98)	1.07 (1.01, 1.13)
Emery[30]				
3AHVR	0.84 (0.65, 0.94)	0.38 (0.21, 0.57)	1.34 (0.94, 1.91)	0.43 (0.15, 1.20)
Jacobsen[23]				
DR4	0.25 (0.10, 0.49)	0.68 (0.54, 0.79)	0.78 (0.30, 2.00)	1.10 (0.78, 1.55)

LR: likelihood ratio; MBL: mannose-binding lectin.

Table 4. Utility of the shared epitope (SE) for predicting different outcomes. Results are presented as raw estimate.

Outcome	n	Study	Utility Measure
Erosions	49	Emery (3AHVR)[30]	OR 3.15
	211	El-Gabalawy (any SE)[21]	OR 2.80
	177	Gough (any SE)[22]	RR 4.28
	532	Harrison (DR4)[32]	RR 2.60
Severity of radiographic damage	532	Harrison (DR4)[32]	RR 2.60
Mortality	1022	Farragher (DR4)[31]	HR 2.63
Cardiovascular mortality	1022	Farragher (DR4)[31]	HR 4.04
HAQ > 1	532	Harrison (2 copies SE)[32]	RR 1.60
Persistent synovitis	177	Gough (2 copies SE)[22]	RR 3.25

HR: hazard ratio; OR: odds ratio; RR: risk ratio; HAQ: Health Assessment Questionnaire.

published evidence on utility of genetic markers for diagnosing and establishing prognosis of UPIA. Our results may only be generalized in the context of undifferentiated arthritis, either early or late in the diagnostic process. UPIA is a diagnosis by exclusion, and thus the search for studies that focused on the utility of tests in this particular population in which previous tests had not been conclusive is a difficult one. There is no established definition of UPIA, and no common terminology, which is reflected by the heterogeneous selection criteria of the included studies. On top of the difficulty of search and selection, we detected high heterogeneity in the reporting of the studies, which was generally poor, probably reflecting the poor design of many studies, with low sample sizes or improperly distributed samples, unclear choice of controls, or lack of significant data. Thus, almost all LR had to be calculated as almost no study reported them, some diagnostic studies did not even report sensitivity or specificity, and few provided confidence intervals.

With the limitations expressed above, our results showed that, to date, evidence of the diagnostic and predictive utility of the genetic markers is very scarce in patients with an unclear diagnosis in arthritis clinics. Among the different genetic markers tested, only the SE may have a role in predicting a future diagnosis of RA and poor prognosis. However, its utility in the diagnosis of RA is quite poor, since the only relevant positive LR came from the study

with the poorest quality and the smallest sample size. Although in recent decades extensive evidence has been published showing associations between the SE encoding alleles and susceptibility to RA[35,36,37,38,39,40,41,42,43,44,45], very few studies have included populations with undifferentiated arthritis. The majority have included patients previously diagnosed with RA. This may explain why in our review the evidence of such association was quite poor.

We also found that, in isolation, no other genetic marker was informative of a future diagnosis in patients with UPIA. Apart from the SE, the most useful marker for diagnosing RA in patients with UPIA was the MBL polymorphism B/D, but it had very limited utility. Besides MBL polymorphisms, a large number of previously studied genetic markers for susceptibility to RA such as protein tyrosine phosphatase non-receptor type 22, peptidyl arginine deiminase-4, Fc receptor-like 3, or SLC22A4 were not confirmed in our review. To date, these genetic markers have not been studied in depth in patients with UPIA.

We also did not find useful genetic markers for diagnosis of other rheumatic diseases such as spondyloarthritis or PsA. Since our search was focused on peripheral arthritis, it did not retrieve studies on the rheumatic diseases with typically axial manifestations. That may be the reason why very few studies included in our review assessed the utility of HLA-B27 for UPIA, a marker classically associated with axial manifestations of arthritis.

With regard to the prognostic value of genetic markers in UPIA, the SE was again the most frequently studied marker. In our review, it proved to be associated with a poor prognosis of arthritis in terms of development of erosions, mortality, HAQ > 1, and persistent synovitis. The influence of SE on severity of arthritis has been extensively investigated, although the majority of those studies were focused on RA. Homozigosity for the SE is associated with a higher risk for the development of RA and with more severe radiologic destruction[46,47]. A French study found an increasing risk of erosions with an increasing number of copies of the SE. However, this effect was not significant until after 2 years from symptom start[48]. The SE may be particularly associated with erosions at sites such as the wrist and with periodontal bone destruction[49].

Our review has found other markers associated with development of erosions in UPIA, namely some MBL polymorphisms. MBL gene polymorphisms have been associated with disease activity, physical disability, and radiographic progression in early RA[50,51]. MBL is a liver-derived component of the innate immune system that may bind to various sugar motives and thereby activate complement through MBL-associated serine proteases[52,53]. Some studies have found that low levels of MBL are associated with erosive disease[23,54], whereas others have not[29]. Two of those studies included patients with UPIA and were, therefore, included in our review. Jacobsen, *et al*[23] found that some variant alleles of MBL appear to be weak susceptibility markers for RA, and patients with early polyarthritis who were homozygous for MBL structural variant alleles have a higher risk of developing early erosive RA. On the other hand, Barton, *et al*[29] found that polymorphisms within the MBL gene are not associated with the presence or extent of erosions at 5 years in patients with RA or undifferentiated inflammatory polyarthritis. Further studies are needed to confirm or discard this association. More recent studies have found that increased serum levels of MBL are associated with increased risk of developing RA[55] and ischemic heart disease when having RA[56].

Some tumor necrosis factor-α (TNF-α) gene polymorphisms have been related to susceptibility and radiographic damage in RA[57]. Nevertheless, in the only study included in our review that assessed utility of these polymorphisms in patients with UPIA from the NOAR cohort, Barton, *et al*[28] did not find an association of TNF-α genes with severity of arthritis as assessed by erosive outcome at 5 years. This is another genetic association of RA that may not be extrapolated to undifferentiated peripheral arthritis.

In conclusion, we found that, in isolation, no studied genetic marker is very informative of a future diagnosis in patients presenting with UPIA. Perhaps a combination of different genetic markers may better predict the development of a specific disease. We found that, among all markers, the SE may have a slight association with poor prognosis in patients with UPIA, in terms of development of erosions, mortality, disability, and persistent synovitis. Other genes do not predict outcome in undifferentiated arthritis, and other outcomes have not been studied in depth. Further studies on the utility of genetic markers are needed, especially in populations of undifferentiated polyarthritis. To date, and supported by a moderate level of evidence, no genetic marker may be recommended in these patients.

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