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Hypomethylation of CYP2E1 and DUSP22 Promoters Associated With Disease Activity and Erosive Disease Among Rheumatoid Arthritis Patients

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Objective. Epigenetic modifications have previously been associated with rheumatoid arthritis (RA). In this study, we aimed to determine whether differential DNA methylation in peripheral blood cell subpopulations is associated with any of 4 clinical outcomes among RA patients.

Methods. Peripheral blood samples were obtained from 63 patients in the University of California, San Francisco RA cohort (all satisfied the American College of Rheumatology classification criteria; 57 were seropositive for rheumatoid factor and/or anti– cyclic citrullinated protein). Fluorescence-activated cell sorting was used to separate the cells into 4 immune cell subpopulations (CD14+ monocytes, CD19+ B cells, CD4+ naive T cells, and CD4+ memory T cells) per individual, and 229 genome-wide DNA methylation profiles were generated using Illumina HumanMethylation450 BeadChips. Differentially methylated positions and regions associated with the Clinical Disease Activity Index score, erosive disease, RA Articular Damage score, Sharp score, medication at time of blood draw, smoking status, and disease duration were identified using robust regression models and empirical Bayes variance estimators.

Results. Differential methylation of CpG sites associated with clinical outcomes was observed in all 4 cell types. Hypomethylated regions in the CYP2E1 and DUSP22 gene promoters were associated with active and erosive disease, respectively. Pathway analyses suggested that the biologic mechanisms underlying each clinical outcome are cell type–specific. Evidence of independent effects on DNA methylation from smoking, medication use, and disease duration were also identified.

Conclusion. Methylation signatures specific to RA clinical outcomes may have utility as biomarkers or predictors of exposure, disease progression, and disease severity.

Rheumatoid arthritis (RA) is the most common systemic autoimmune disease, with a global prevalence of ~1% (1). Although the precise model of pathogenesis is not known, it is thought to involve the activation of both innate and adaptive immune responses as well as the destruction of cartilage and subchondral bone by resident synoviocytes, leading to joint damage and disability. The cause of RA is complex, with contributions from both genetic and nongenetic risk factors.

The strongest genetic risk factors for RA are variants of the HLA-DRB1 gene. The shared epitope (SE) alleles encoding the QKRAA and QRRRA amino acid sequences at positions 70–74 explain much of the genetic predisposition to RA (2). Recently, a large study demonstrated that the association between the major histocompatibility complex (MHC) and RA is best explained by 5 amino acids: 3 in HLA-DRB1 and 1 each in HLA-B and HLA-DPB1, of which 2 are the same as those of the shared epitope (3). Of the 16 resulting DRB1 haplotypes, valine/lysine/alanine at positions 11/71/74 is the most strongly
associated with RA, and it corresponds to the DRB1*04:01 allele (3), a well-documented association (3,4).

DNA methylation is an epigenetic modification that results from the addition of a methyl group to a cytosine DNA base in the context of cytosine–phosphate–guanine dinucleotide (CpG), and has been shown to modulate gene expression as well as determinants of higher-order DNA structure (5,6). Methylation profiles can be maintained across cell division cycles and between generations and may contribute to the “missing heritability” suggested by current genome-wide association study findings (7). In addition, DNA methylation states can be altered by a number of environmental exposures, such as tobacco smoke, air pollutants, paternal and maternal lifestyle factors, and antibiotic use (8). Thus, DNA methylation profiles may link genetic and environmental signals and serve as the intermediate between those risk factors and disease susceptibility.

A growing body of epidemiologic evidence supports an association between RA and DNA methylation. Genome-wide and candidate gene studies in RA patients and healthy controls have demonstrated disease-associated methylation differences in peripheral blood mononuclear cells (PBMCs), purified T cells and B cells, and fibroblast-like synoviocytes (9–12). Interestingly, treatment with methotrexate is able to revert RA-associated global hypomethylation in T cells and monocytes and restore regulatory T cell function through reactivation of the FOXP3 upstream enhancer (13,14). One proof-of-concept study of DNA methylation at first diagnosis identified 6 CpG sites associated with response to disease-modifying antirheumatic drugs (DMARDs) in patients with early RA (15). However, studies to date have typically been limited to case–control comparisons and have not identified methylation differences specific to RA case subgroups or clinical outcomes.

In this study, we assessed DNA methylation signals associated with 4 RA clinical outcomes, history of smoking, medication use, and disease duration. Such signatures may be useful as biomarkers or predictors of exposure, disease progression, or response to treatment.

PATIENTS AND METHODS

Study participants. Participants included 63 women of European ancestry from the RA cohort at the University of California, San Francisco (UCSF), all of whom met the American College of Rheumatology (ACR) 1987 criteria for RA (Table 1) (16). All participants provided a peripheral blood sample for genotyping, cell sorting, and DNA methylation profiling. The following clinical outcomes were determined for each RA patient: the Clinical Disease Activity Index (CDAI) score, presence of erosive disease, total Rheumatoid Arthritis Articular Damage (RAAD) score, and modified Sharp score for all joints (17,18). The CDAI is a sum of the tender joint count, swollen joint count, patient’s global assessment of disease activity, and physician’s global assessment of disease activity. It was treated as a dichotomized variable based on the presence of active disease (CDAI score >2.8) or remission (CDAI score ≤2.8), in accordance with the ACR recommendations (19). The European League Against Rheumatism (EULAR) criteria were used to classify erosive disease (20). According to the EULAR classification, erosive disease is defined as cortical breaks in at least 3 separate joints of the hands and feet as observed on radiographs, and this was treated as a binary variable (20). The modified Sharp score is a more detailed measure of radiographic damage, where each hand, wrist, and foot joint is scored for erosions and for joint space narrowing (18). The RAAD score is computed by evaluating 35 large and small joints using a goniometer and scoring them on a 3-point scale, and it may therefore capture aspects of joint failure not reflected on radiography-based scores (21).

Study approval. Written informed consent was obtained from all participants prior to inclusion in this study. Research was conducted in compliance with the Declaration of Helsinki, Institutional Review Board approval was obtained at UCSF, where the study subjects were recruited.

Genotyping and methylation assessment. Single-nucleotide polymorphism (SNP) genotyping and DNA methylation profiling were performed as previously described (22). Briefly, study participants were genotyped using Illumina HumanOmniExpress, HumanOmniExpressExome, or Human660W-Quad microarrays, and principal components analysis was performed using EigenStrat to characterize genetic ancestry and account for any heterogeneity in our study population (23). PBMCs were isolated from whole blood, and the following cell subpopulations were identified by fluorescence-activated cell sorting: monocytes (CD45+CD14+), B cells (CD45+CD14–CD3–CD19+), naïve CD4+ T cells (CD45+CD14–CD3–CD19–CD4+CD27–CD45RA+), as well as memory CD4+ T cells (CD45+CD14–CD3–CD19–CD4+CD27+CD45RA–). A total of 229 epigenome-wide DNA methylation profiles were generated using the Illumina Infinium HumanMethylation450 BeadChip, and β values (the ratio of methylated probe intensity to total intensities) were reported per CpG site.

Extensive quality control measures were performed, including background signal subtraction, all sample mean

| Table 1. Characteristics of the study participants at the time of blood draw* |
|---------------------------------|------------------|
| Scenepositive, no. (%)          | Anti-CCP or RF   |
| Anti-CCP                         | 57 (90.5)        |
| Anti-CCP                         | 53 (89.8)        |
| RF                              | 46 (75.4)        |
| Age, mean ± SD                  | 56.4 ± 14.8      |
| Ever smoked, no. (%)            | 33 (52.4)        |
| Disease duration, mean ± SD years | 14.0 ± 10.5     |
| Active disease (CDAI >2.8), no. (%) | 45 (76.2)        |
| Erosive disease, no. (%)        | 39 (63.9)        |
| RAAD score, mean ± SD           | 10.1 ± 13.0      |
| Sharp score, mean ± SD          | 47.2 ± 74.0      |
| Current DMARD or anti-TNF therapy, no. (%) | 52 (82.5)        |

* Anti-CCP = anti-cyclic citrullinated peptide; RF = rheumatoid factor; CDAI = Clinical Disease Activity Index; RAAD = Rheumatoid Arthritis Articular Damage; DMARD = disease-modifying antirheumatic drug; anti-TNF = anti-tumor necrosis factor.
normalization, and beta-mixture quantile normalization (24–26). Samples with low detection rates ($P > 0.05$) in more than 20% of sites were removed from analysis. The following sites were also removed from analysis: CpG sites with low detection rates ($P > 0.05$) in more than 20% of samples, non-CpG “rs” SNP probes, cross-reactive probes, and European-specific polymorphic CpGs (27). In total, we retained 428,232 CpG sites in 229 samples (58 CD14+ monocyte samples, 57 CD19+ B cell samples, 56 CD4+ naive Tcell samples, and 58 CD4+ memory Tcell samples).

**Statistical analysis.** Using the Lumi R package (28,29), methylation β values were transformed to M values in order to better approximate the homoscedasticity assumption in most statistical analyses. For each RA clinical outcome, robust linear regression models were fitted to each CpG site to assess for association with methylation, adjusting for age, history of smoking, genetic ancestry, DMARD treatment (methotrexate, hydroxychloroquine, leflunomide), anti-tumor necrosis factor treatment (anti-TNF; adalimumab, certolizumab, or golimumab), and disease duration at the time of blood draw. Regression models were fitted separately for each cell type. A robust empirical Bayes procedure as implemented in the Limma R package was used to smooth over genomic distance, generating candidate regions of differential methylation associated with each RA clinical outcome in cell type, using the following significance thresholds: Bonferroni-adjusted $P < 0.05$. Statistical significance thresholds were varied in order to capture DNA methylation differences that were smaller in magnitude but consistent across multiple RA clinical outcomes or across multiple cell types. Second, to identify DNA methylation profiles shared among RA clinical outcomes regardless of cell type, 4 CpG sets were defined as the differentially methylated CpG sites associated with each RA clinical outcome in any cell type at the same thresholds of statistical significance. The pairwise overlap between CpG sets was computed as a count (total number of CpG sites shared between 2 CpG sets) and as a shared percentage (proportion of CpG sites in one CpG set that were also found in a second CpG set).

**RESULTS**

**Disease activity.** Genome-wide analyses comparing cases with active disease (CDAI $>2.8$; categorized as low/minimal, moderate, and high/severe disease activity) to cases with disease in remission (CDAI $\leq2.8$) identified 27 CpG sites (14 hypermethylated and 13 hypomethylated) associated with active disease (Bonferroni-adjusted $P < 0.05$), independently of any history of smoking, medication use, and disease duration (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). We identified 1 statistically significant DMR containing 11 CpG sites on chromosome 10 (Figure 1A). This region is hypomethylated in cases with active disease compared to those with disease in remission in both CD14+ monocytes and naive CD4+ T cells, and it is located in the 5’ region of cytochrome P450 2E1 (CYP2E1).

**Erosive disease.** Genome-wide assessment of differential methylation associated with erosive disease identified 84 CpG sites (10 hypermethylated and 74 hypomethylated; Bonferroni-adjusted $P < 0.05$) that were independent of any history of smoking, medication use, and disease duration (Supplementary Figure 2 and Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). Most of these sites (74%) were identified in CD19+ B cells. DMR analyses identified a hypomethylated region on chromosome 6 containing 10 CpG sites that was associated with erosive disease in all 4 cell types (Figure 1B). This region overlaps with the transcription start site of dual-specificity phosphatase 22 (*DUSP22*).

**RAAD score.** A dose-dependent association between RAAD scores and methylation levels was identified for 89 CpG sites genome-wide (15 hypermethylated and 74 hypomethylated; Bonferroni-adjusted $P < 0.05$), independently of any history of smoking, medication use, and disease duration (Supplementary Figure 3 and Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). Most of these CpG sites were differentially methylated only in CD14+ monocytes, with 1 CpG (cg06355652) hypomethylated in both CD14+ monocytes and naive CD4+ T cells, DMR analyses did not yield significant associations with RAAD scores.

**Modified Sharp score.** A total of 168 CpG sites (139 hypermethylated and 29 hypomethylated) demonstrated a dose-dependent association with the modified
Sharp score (Bonferroni-adjusted \( P < 0.05 \)), independently of any history of smoking, medication use, and disease duration (Supplementary Figure 4 and Supplementary Table 4, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). Six CpG sites were differentially methylated in the same direction across multiple cell types. No regions of differential methylation were associated with the modified Sharp score after correcting for multiple hypothesis testing.

Comparison of DNA methylation profiles among RA clinical outcomes. In order to identify CpG sites associated with multiple RA clinical outcomes, we performed intersections of CpG sets identified from the previous analyses where each RA clinical outcome was treated separately. Methylation profiles observed in the current study were largely unique to specific RA clinical outcomes and to individual cell types (Figure 2A). The vast majority of CpG sites were associated with only 1 RA clinical outcome and were differentially methylated in only 1 cell type. Varying the statistical significance threshold did not change our findings (Supplementary Figures 5A–C, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). Pooling CpG sites across cell types for an RA outcome also did not reveal any sets of CpG sites that were differentially methylated across multiple RA clinical outcomes (Figure 2B and Supplementary Figure 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract).

Pathway analyses for RA clinical outcomes. Pathway analysis of differentially methylated genes associated with disease activity identified enrichment of 32 GO terms (FDR \( q < 0.05 \)), as summarized in Supplementary Table 5 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). Only CpG sites that were differentially methylated in naive CD4+ T cells were enriched for GO terms. The top enriched pathways suggest dysregulation of interferon-\( \gamma \) (IFN\( \gamma \)) production, negative regulation of natural killer cell–mediated cytotoxicity, and antigen presentation (Table 2).

Pathway analysis of differentially methylated genes associated with the modified Sharp score...
identified enrichment of 9 GO terms \( (FDR \, q < 0.05) \), as summarized in Supplementary Table 6 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). The results suggest that dysregulation of voltage-gated calcium-channel transport and preganglionic parasympathetic fiber development in CD14\(^+\) monocytes plays a role in the development of radiographic erosions as measured by the modified Sharp score (Table 2).

**History of smoking.** Across all regression models, a total of 154 CpG sites (44 hypermethylated and 110 hypomethylated) showed differential methylation associated with any history of smoking \( (\text{Bonferroni}-\text{adjusted} \, P < 0.05) \), independently of all other covariates (Figure 3). The results are summarized in Supplementary Table 7 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). The association between smoking and

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**Table 2.** Top GO pathways significantly enriched for associations with rheumatoid arthritis clinical outcomes

| GO accession no. | Group/term                                                                 | \( P \)          | Cell type          | No. of genes in group | Differentially methylated genes in group |
|------------------|---------------------------------------------------------------------------|------------------|--------------------|-----------------------|----------------------------------------|
| GO:0032729       | Positive regulation of IFN\( \gamma \) production                        | \( 3.55 \times 10^{-7} \) | CD4 naive          | 61                    | \( \text{WNT5A, LTA, HLA-A} \)                |
| GO:0045953       | Negative regulation of natural killer cell cytotoxicity                  | \( 7.82 \times 10^{-6} \) | CD4 naive          | 10                    | \( \text{HLA-A, TAP1} \)                      |
| GO:0002484       | Antigen presentation and presentation of endogenous peptide antigen via MHC class I via ER pathway | \( 7.08 \times 10^{-6} \) | CD4 naive          | 9                     | \( \text{HLA-A, TAP1} \)                      |
| GO:0034762       | Regulation of transmembrane transport                                    | \( 1.81 \times 10^{-5} \) | CD14               | 424                   | \( \text{CACNB2, KCN6, ANO1, CACNA1H, CACNA1G, CTTNBP2NL, NAV2, PLXNA4, NRIP1} \) |
| GO:0021783       | Preganglionic parasympathetic fiber development                          | \( 1.18 \times 10^{-5} \) | CD14               | 16                    | \( \text{CACNB2, KCN6, ANO1, CACNA1H, CACNA1G, CTTNBP2NL, NAV2, PLXNA4, NRIP1} \) |

\* GO = Gene Ontology; IFN\( \gamma \) = interferon-\( \gamma \); MHC = major histocompatibility complex; ER = endoplasmic reticulum.
DNA methylation was observed for all cell types and for all RA clinical outcomes; ~50% of associated CpG sites were present in naive CD4+ T cells. No regions of differential methylation or enrichment for GO terms were significantly associated with smoking.

**DMARD treatment.** Results from regression modeling demonstrated evidence of association between DMARD treatment and DNA methylation for 285 CpG sites (250 hypermethylated and 35 hypomethylated; Bonferroni-adjusted $P < 0.05$), independently of all other covariates (Figure 3). The results are summarized in Supplementary Table 8 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). DNA methylation levels were the most affected in memory CD4+ T cells (74%), which also showed enrichment for “homophilic cell adhesion via plasma membrane adhesion molecules” (GO term 0007156; $P = 1.53 \times 10^{-8}$).

**Disease duration.** Associations between disease duration and DNA methylation were observed for 718 CpG sites (188 hypermethylated and 530 hypomethylated; Bonferroni-adjusted $P < 0.05$), which was independent of all other covariates (Figure 3). The results are summarized in Supplementary Table 10 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40408/abstract). DNA methylation levels were the most affected in memory CD4+ T cells (74%), which also showed enrichment for “homophilic cell adhesion via plasma membrane adhesion molecules” (GO term 0007156; $P = 2.80 \times 10^{-8}$).

**DISCUSSION**

In this study of DNA methylation in sorted immune cell types, we identified methylation profiles associated with clinical outcomes of RA. Our findings indicate that the profiles were highly specific for each clinical outcome and for individual cell types. We also found that medication use and disease duration at the time of blood draw were significantly associated with DNA methylation in specific cell types.

We identified a region of 11 hypomethylated CpG sites near the transcription start site of *CYP2E1* associated with active disease, as indicated by the CDAI score. A multivariate hidden Markov model trained on histone modifications observed in chromatin immunoprecipitation sequencing experiments performed on 2 blood samples predicts this region to be a promoter, suggesting that CYP2E1 expression is elevated in the monocytes and naive T cells of patients with active disease (35,36). CYP2E1 is a member of the cytochrome P450 enzyme family and is responsible for the metabolism of exogenous substrates such as nicotine, ethanol, acetaminophen, and aspartame (37). Expression of *CYP2E1* is induced by lipopolysaccharide and interleukin-4 (IL-4) in human astrocytes and hepatocytes and is regulated by the oxidative stress pathway in monocytes, implying some immune function (38,39). Interestingly, alcohol consumption has been linked to impaired priming of CD4+ T cells by dendritic cells and to the production of autoantibodies against CYP2E1 (40,41). While the identified DMR reflects the independent association between active disease and DNA methylation after accounting for any history of smoking and current medication use, we were unable to investigate other environmental or dietary exposures, such as alcohol consumption, that might contribute to the methylation of the CYP2E1 promoter.
We also identified a region of 10 hypomethylated CpGs near the transcription start site of DUSP22 that was associated with erosive disease. This region overlaps with an active promoter chromatin state in blood tissues and was differentially methylated in all 4 cell types we examined (36). DUSP22 is a protein phosphatase involved in MAPK signaling, and it appears to lie at the intersection of several immune signaling pathways, including those mediated through the T cell antigen receptor, IL-6 leukemia-inhibiting factor, and the estrogen receptor (42,43). A study of the DUSP22-knockout mouse showed autoimmune tendencies: splenic T cells had stronger responses to anti-CD3 stimulation, serum levels of proinflammatory cytokines and autoantibodies were higher, and symptoms in an experimental autoimmune encephalomyelitis mouse model developed faster and were more severe (44). Hypomethylation observed among RA cases with erosive disease in the current study should lead to increased messenger RNA (mRNA) expression of DUSP22. Further studies are needed to confirm the relationship between methylation and expression and to understand the dynamics between mRNA expression and protein levels in order to understand how DUSP22 might contribute to erosive disease.

Examination of the differentially methylated CpG sites using Gene Ontology identified cellular processes underlying disease activity and severity. Disease activity was related to differential methylation of CpG sites in genes involved in the IFN signaling and antigen-presentation pathways; the finding that these effects were observed only in naive CD4+ T cells suggests that this population is biased toward Th1 differentiation. In addition, pathway analysis of the CpG sites associated with the modified Sharp score showed dysregulation of transmembrane transport and preganglionic parasympathetic fiber development in CD14+ monocytes. Previous studies of cardiovascular autonomic nervous system function in RA patients led to the hypothesis that the equilibrium between the opposing effects of the sympathetic and parasympathetic nervous systems has been disrupted (45). Our results support this theory and further highlight the role played by the autonomic nervous system as a modulator of immune function and a possible target for future RA therapies.

Much of the differential methylation observed for RA clinical outcomes was present in CD14+ monocytes and naive CD4+ T cells, which further highlights the role of these immune subpopulations in RA pathogenesis and disease progression. Treatment of normal synovial fibroblasts with an inhibitor of DNA methylation was able to reproduce the hypomethylation and activated phenotype observed in RA synovial fibroblasts (46). A previous study of RA patients reported higher frequencies of CD14+CD16+ circulating monocytes in patients with active disease, and response to drug therapy was correlated with changes in these frequencies (47,48). These circulating monocytes can migrate into the synovial joint, where they can recruit lymphocytes to the inflamed joint and drive the polarization of CD4+ helper T cells (49). Furthermore, activated T cells from the peripheral immune system are able to stimulate the differentiation of monocytes into osteoclasts, thereby contributing to bone damage and production of radiographic lesions (50). Thus, the interactions between monocytes and T cells in both peripheral blood and synovial joints may prove interesting for therapeutics that target disease activity and progression.

RA is a heterogeneous disease with symptom presentations and prognoses that differ between patients. Therefore, it may be important to consider various measures of disease activity and severity in order to identify the different biologic mechanisms that underlie disease heterogeneity. We analyzed 4 RA clinical outcome measures: disease activity as measured by the CDAI score, erosive disease, the RAAD score, and the modified Sharp score. Each of these 4 measures captures different aspects of RA disease progression and is associated with different risk factors and prognoses. By analyzing each measure separately, we were able to investigate the association between RA disease heterogeneity and DNA methylation and to identify profiles specific to each clinical outcome. We found that DNA methylation profiles were highly specific to each clinical outcome measure, suggesting that different biologic processes drive different measures of disease activity and severity. These results can help in the development of new therapies targeted toward specific manifestations and thus aid in the generation of patient-specific treatment plans.

Our previous analysis in the same RA patient population identified predominantly hypomethylated candidate CpG sites in naive and memory CD4+ T cells from the patients as compared to healthy controls (22). Comparison of the results from the current study of clinical phenotypes with the previous RA case-control study did not reveal significant overlap of differential methylation. These findings suggest that DNA methylation changes relevant to disease susceptibility in RA are largely distinct from those that contribute to disease severity and phenotypic expression.

The strengths of our study include the large sample size and selection of female RA cases to minimize confounding by sex. By sorting PBMCs before performing DNA methylation profiling, we were able to avoid major confounding by cell-type heterogeneity and to analyze cell-specific effects for each RA clinical outcome. Using
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with specific DNA methylation profiles and that these
sures of RA disease activity and severity are associated
local biologic processes that drive joint damage.
chips, and imputation or pyrosequencing must be per-
DNA methylation profiling was performed on microarray
ability to extrapolate our results beyond this population.
progression. Our RA patient sample consisted
temporality of these DNA methylation differences relative
to disease progression. Our RA patient sample consisted
nature, which limited our ability to determine causality or
timepoint of these DNA methylation differences relative
to disease progression. Our RA patient sample consisted

In summary, we have shown that different mea-
sures of RA disease activity and severity are associated
with specific DNA methylation profiles and that these
methylation differences are also highly cell type specific.
Our results further support the premise that genetic,
as well as epigenetic, variations may drive clinical hetero-
genity in RA.

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. Criswell 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. Mok, Rhead, Holingue, Barcellos, Criswell.

Acquisition of data. Shao, H. L. Quach, D. Quach, Sinclair, Graf, Imboden, Link, Harrison, Chernitskiy, Barcellos, Criswell.

Analysis and interpretation of data. Mok, Rhead, Holingue, Barcellos, Criswell.

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The American College of Rheumatology is Launching an Open Access Journal and Seeking an Editor-in-Chief

DOI 10.1002/art.40510

The American College of Rheumatology is excited to announce that a third official journal of the College is scheduled to be launched in January 2019. This journal will be entirely open access. More details will be coming soon, as will the call for applications for the position of Editor-in-Chief. ACR/ARHP members who have current or past experience on the editorial board of Arthritis & Rheumatology or Arthritis Care & Research (Associate Editor level or higher) are invited to apply.