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ORIGINAL REPORT

Cytokine Genetic Variations and Fatigue Among Patients With Breast Cancer

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ABSTRACT

Purpose
Fatigue is a common adverse effect of cancer treatment and may persist for years after treatment completion. However, risk factors for post-treatment fatigue have not been determined. On the basis of studies suggesting an inflammatory basis for fatigue, this study tested the hypothesis that expression-regulating polymorphisms in proinflammatory cytokine genes would predict post-treatment fatigue in breast cancer survivors.

Patients and Methods
Women diagnosed with early-stage breast cancer (n = 171) completed questionnaires to assess fatigue and other behavioral symptoms (ie, depressive symptoms, memory complaints, sleep disturbance) and provided blood for genotyping within 3 months after primary treatment. Genomic DNA was extracted from peripheral-blood leukocytes and assayed for single nucleotide polymorphisms (SNPs) in the promoter regions of three cytokine genes: *ILB* −511 C>T (rs16944), *IL6* −174 G>C (rs1800795), and *TNF* −308 G>A (rs1800629). An additive genetic risk score was computed by summing the number of high-expression alleles (zero, one, or two) across all three polymorphisms.

Results
The genetic risk index was significantly associated with fatigue; as the number of high-expression alleles increased, so did self-reported fatigue severity ($P = .002$). Analyses of individual SNPs showed that *TNF* −308 and *IL6* −174 were independently associated with fatigue ($P = .032$). The genetic risk index was also associated with depressive symptoms ($P = .007$) and memory complaints ($P = .016$).

Conclusion
These findings further implicate inflammatory processes as contributors to cancer-related fatigue and suggest a new strategy for identifying and treating patients at risk for this symptom based on genetic variants in proinflammatory cytokine genes.

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INTRODUCTION

Fatigue is one the most common adverse effects of cancer treatment[1] and may persist for months or years after treatment completion, causing significant impairment in quality of life[2,3] and possibly presaging shorter survival.[4] Basic research on neural-immune signaling has demonstrated that proinflammatory cytokines signal the CNS to trigger fatigue and other behavioral changes,[5,6] leading investigators to hypothesize that cancer-related fatigue may be related to activation of the proinflammatory cytokine network.[7] Indeed, a growing number of studies have documented an association between fatigue and circulating markers of inflammation in patients with cancer during and after treatment.[8-16]

There is considerable variability in the experience of fatigue that cannot be explained by objective characteristics of the disease and/or its treatment.[17-19] This suggests that host factors may play an important role in fatigue severity and persistence. However, biologic risk factors that increase vulnerability to fatigue and other cancer-related behavioral disturbances have not been determined. Given links between fatigue and markers of proinflammatory cytokine activity, genetic factors that influence cytokine gene expression are plausible risk factors for cancer-related fatigue.[20] Single nucleotide polymorphisms (SNPs) that influence quantitative gene expression have been identified in the promoter regions of several genes that encode proinflammatory cytokines[21] and examined individually in relation to breast cancer susceptibility and

prognosis,[22-24] as well as treatment-related toxicities.[25] There is preliminary evidence that SNPs in proinflammatory cytokine genes may also be associated with cancer-related fatigue. In a study of patients with cancer undergoing radiation therapy, polymorphisms in *TNF* and *IL6* were associated with elevated fatigue,[26,27] and SNPs in these genes were also associated with elevated fatigue in a small sample of patients with prostate cancer undergoing androgen-deprivation therapy.[28] We found an association between polymorphisms in *ILB* and *IL6* and fatigue in a small sample of long-term survivors of breast cancer[29]; these SNPs were also associated with cellular expression of cytokines in this sample. Furthermore, cytokine genes have also been linked with fatigue in survivors of lung cancer.[30] However, work in this area is still limited, with some contradictory results.[31] In addition, few studies have examined links between cytokine genetic variants and other common cancer-related behavioral symptoms, such as depressive symptoms, sleep disturbance, and cognitive complaints.[1]

The current study sought to determine whether regulatory polymorphisms in three key proinflammatory cytokine genes were associated with fatigue in women who had recently completed treatment for early-stage breast cancer. We focused on SNPs in genes encoding cytokines that have been linked at the protein level to cancer-related fatigue, including *ILB* −511 C>T (rs16944),[32,33] *IL6* −174 G>C (rs1800795),[34,35] and *TNF* −308 G>A (rs1800629).[36] We and others have found that these SNPs are associated with overexpression of cytokines.[29,34,37] The *TNF* polymorphism was of particular interest given initial findings from a subsample of these patients showing a link between fatigue and a circulating biomarker of tumor necrosis factor (TNF) activity.[38] We assessed the individual and aggregate effects of these polymorphisms to determine whether they might predict elevated fatigue in the aftermath of cancer treatment. We also explored the association between these SNPs and other behavioral symptoms, including depression, memory complaints, and sleep disturbance.

PATIENTS AND METHODS

Participants

The present data come from a larger study of cognitive functioning after cancer treatment conducted at the University of California, Los Angeles. Eligibility criteria for the parent trial were as follows: diagnosis of stage 0 to IIIA breast cancer; primary cancer treatment (ie, surgery, radiation therapy, and/or chemotherapy) completed within the past 3 months and endocrine therapy not yet started; age 21 to 65 years; and no neurologic or immune-related medical conditions or behaviors known to influence the immune system (eg, smoking, heavy drinking).[39] Participants were identified primarily through the Los Angeles County Surveillance, Epidemiology, and End Results registry, which provided rapid case ascertainment of stage-eligible patients from selected hospitals where the collaborating physicians practiced.

More than 3,000 patients identified from the Surveillance, Epidemiology, and End Results registry were sent invitation letters; we also received referral of 83 patients, independent of the registry recruitment. Four hundred thirty-nine women requested more information about the study, with 41 declining further screening and 150 deemed ineligible after screening. The most common reasons for ineligibility were as follows: initiation of endocrine therapy/beyond enrollment window (53%), demographic/medical exclusions (18%), and immune and behavioral confounders (eg, alcohol/tobacco use; 15%). Two hundred forty patients were eligible after screening, 190 completed the baseline visit with evaluable data, and 171 had specimens available for genetic analysis. The research was approved by the University of California, Los Angeles Institutional Review Board, and informed consent was obtained from all participants.

Measures

Demographic and clinical information was obtained from self-report and medical record abstraction. Fatigue was assessed using the Multidimensional Fatigue Symptom Inventory–Short Form, a 30-item questionnaire developed for use in patients with cancer that has acceptable psychometric properties and discriminates between patients with cancer and healthy controls.[40] Depressive symptoms were assessed using the Beck Depression Inventory-II,[41] and subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index.[42] Higher scores on these scales indicate more severe problems. Cognitive complaints were assessed using the Squire Memory Questionnaire.[43] We focused on memory because it is one of the key complaints of patients with breast cancer[44,45] and is also influenced by inflammatory processes.[46] For the Squire Memory Questionnaire, higher scores indicate better outcomes.

Genomic DNA was extracted from peripheral-blood leukocytes and assayed by a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA) performed on a iCycler real-time polymerase chain reaction instrument (BioRad, Hercules, CA) following manufacturers' protocols, as previously described.[47]

Statistical Analyses

Multiple regression analyses were used to examine the association between genetic risk factors and behavioral measures, controlling for demographic and medical confounders (ie, age, body mass index, race/ethnicity, and treatment with chemotherapy). Of note, we used self-reported race/ethnicity to control for this potential confounder rather than ancestry informative markers, because self-reported race has been found to be correlated with tumor characteristics.[48] To evaluate the aggregate effect of expression-regulating polymorphisms across proinflammatory cytokine genes, we created an additive genetic risk score by summing the number of high-expression alleles (zero, one, or two) across the three SNPs of interest. We then evaluated the association between each individual SNP and the behavioral measures. An additive model was used rather than a dominant or recessive model based on previous research showing a linear effect of the number of alleles on cancer-related fatigue and other aspects of quality of life.[28,29,49,50] Analyses were also conducted to determine whether chemotherapy moderated the association between the genetic risk factor and fatigue; the interaction between chemotherapy and the risk index was not significant and was dropped from further analyses. Although the primary analyses used multiple regression with fatigue as a continuous variable, logistic regression analyses were conducted to determine the risk of being classified as fatigued based on the genetic risk index. For the purpose of these analyses, women were classified as fatigued if they scored in the top third of the distribution of fatigue scores (ie, Multidimensional Fatigue Symptom Inventory score ≥ 20). All statistical tests were two-sided, and $P = .05$ was considered statistically significant. Analyses were conducted using SPSS version 15.0 (SPSS, Chicago, IL).

RESULTS

Demographics and medical and behavioral characteristics of participants are listed in Table 1. Study participants were predominantly white, married, and well educated. The majority had been treated with radiation therapy, and approximately half had received chemotherapy. Fatigue was elevated in this group relative to comparison samples of healthy individuals, consistent with previous research on survivors of breast cancer after treatment.[51]

Genotype frequencies were consistent with those previously observed in the Single Nucleotide Polymorphism Database and fell at Hardy-Weinberg equilibrium (departure χ^2 tests all $P > .23$). Figure 1A shows the distribution of patients at each level of the additive genetic risk score. The majority of patients had between three and five high-frequency alleles across the three SNPs.

Table 1. Demographics and Clinical Characteristics of Participants

Characteristic	No. of Patients (N = 171)	%
Age, years		
Mean	51.5	
Range	31-66	
Race/ethnicity		
White	136	80
Other	35	20
Married/committed relationship	132	77
Education status		
High school/some college	26	15
Associate degree/college graduate	93	54
Graduate degree	52	30
Annual household income*		
≤ $60,000	22	13
$60,000-$100,000	44	26
≥ $100,000	102	61
Cancer treatment		
Radiation	124	73
Chemotherapy	91	53
Time since treatment, months		
Mean	1.16	
SD	1.05	
Behavioral symptoms		
Fatigue (MFSI-SF total score)		
Mean	11.2	
SD	19.1	
Depressive symptoms (BDI-II)		
Mean	8.8	
SD	6.8	
Sleep disturbance (PSQI)		
Mean	8.3	
SD	4.1	
Cognitive complaints (SMQ)		
Mean	−9.8	
SD	16.7	

Abbreviations: BDI-II, Beck Depression Inventory-II; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SMQ, Squire Memory Questionnaire.
*Data missing for three patients.

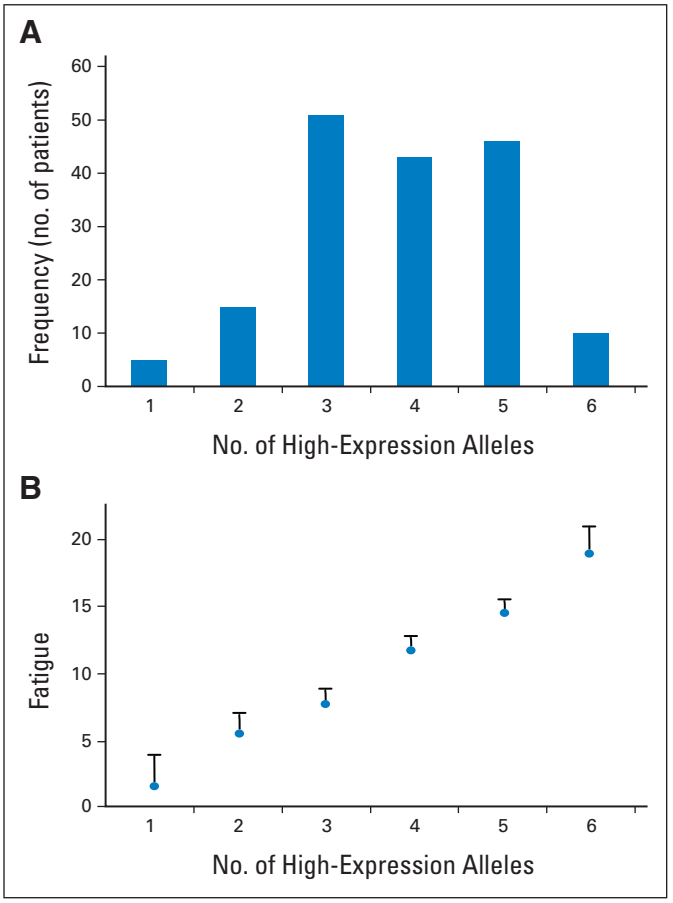

Fig 1. (A) Frequency of patients at each level of an additive genetic risk score summing the number of high-expression alleles across *TNF* −308, *IL6* −174, and *IL1B* −511. There was a linear relationship between the genetic risk score and symptoms of fatigue. (B) Predicted scores on the MFSI-SF at each level of the additive genetic risk score. There was a linear relationship between the genetic risk score and symptoms of fatigue, such that patients with more high-expression alleles reported significantly higher levels of fatigue.

Consistent with hypotheses, the genetic risk score was significantly associated with fatigue ($P = .002$), controlling for potential confounders (ie, age, body mass index, race/ethnicity, and treatment with chemotherapy). As shown in Figure 1B, there was a linear association between the number of high-expression alleles and severity of fatigue symptoms, such that women with more high-expression alleles reported significantly higher levels of fatigue. Results of the regression analysis predicting fatigue are listed in Table 2, and fatigue scores at each level of the genetic risk index are listed in Table 3. Together, the predictor variables explained approximately 16% of the variance in fatigue ($R^2 = 0.163$), a medium to large effect (effect size, $r = 0.40$).[52] Hierarchical linear regression was conducted to examine the variance specifically attributable to the genetic risk score. When this variable was entered on the last step of the regression model, the R^2 change was 0.051, indicating that the genetic risk composite accounted for approximately 5% of the variance in fatigue, a small to medium effect (effect size, $r = 0.22$). In logistic regression analyses, the genetic risk index was again a significant predictor of fatigue, controlling for covariates (odds ratio, 1.45; 95% CI, 1.05 to 2.0; $P = .025$). Each high-expression allele was associated with a 45% increase in the relative odds of severe fatigue.

To assess the contribution of each individual SNP to fatigue symptoms, regression analyses were also conducted. Results showed that both *TNF* −308 ($P = .034$) and *IL6* −174 ($P = .037$) were significantly associated with fatigue. As shown in Figure 2, fatigue levels were approximately twice as high in the *TNF* −308 GG genotype than GA and twelve times higher in GG than AA. Fatigue was also

Table 2. Linear Regression Model Predicting Fatigue

Predictor	B	95% CI	*P*
Age	−0.38	−0.73 to −0.03	.035
Body mass index	0.56	0.05 to 1.06	.031
Race/ethnicity	1.84	−5.3 to 9.0	.613
Chemotherapy	10.09	4.6 to 15.6	< .001
Genetic risk index	3.82	1.4 to 6.2	.002

NOTE. Unstandardized regression coefficients are indicated. Race/ethnicity was coded as white or other. Total $R^2 = 0.163$.

Table 3. Unadjusted (raw) and Predicted Fatigue Scores by Number of High-Expression Alleles

No. of High-Expression Alleles	Raw Fatigue Score		Predicted Fatigue Score	
	Mean	SE	Mean	SE
1	5.20	10.98	1.62	2.45
2	6.43	4.01	5.44	1.70
3	6.56	2.33	7.86	0.84
4	12.47	2.73	11.68	1.06
5	14.37	2.94	14.89	1.10
6	19.90	9.36	18.8	2.29

elevated in the *IL6* −174 GG genotype relative to GC or CC. Fatigue was more pronounced in the *ILB* −511 CC genotype, but differences failed to reach statistical significance.

We next examined the association between cytokine genetic variants and other common behavioral symptoms. The genetic risk index was significantly associated with depressive symptoms ($P = .006$) and memory complaints ($P = .016$), controlling for potential confounders (ie, age, body mass index, race/ethnicity, and treatment with chemotherapy). Women with more high-expression alleles reported significantly higher levels of depressive symptoms and memory complaints. Together, these variables explained approximately 15% of the variance in depressive symptoms ($R^2 = 0.148$) and 22% of the variance in memory problems ($R^2 = 0.218$). Examination of individual SNPs showed that the *IL6* −174 SNP was significantly associated with severity of depressive symptoms ($P = .024$), with higher levels of depressive symptoms in the GG genotype (mean score, 9.74) compared with GC (mean score, 7.66) or CC (mean score, 7.83). Memory complaints were also marginally worse in the GG genotype ($P = .089$). Depressive symptoms and memory complaints were marginally worse in the *TNF* −308 GG genotype ($P = .082$ for depression; $P = .055$ for memory). Neither the genetic risk index nor any of the individual SNPs were significantly associated with subjective sleep quality.

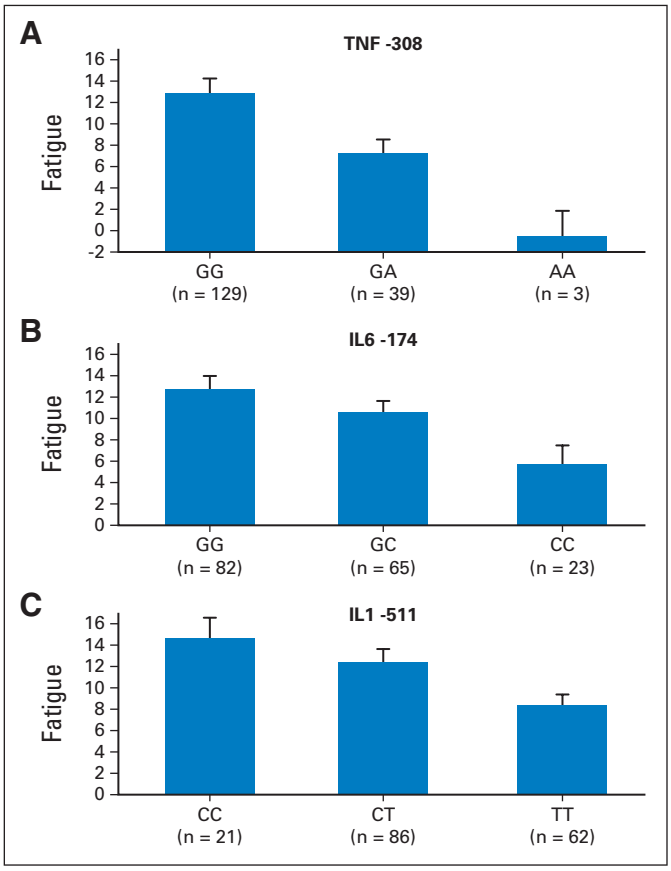

Fig 2. Associations between the three individual single nucleotide polymorphisms (SNPs) and fatigue. There was a significant association (A) between *TNF* −308 and fatigue, with higher levels of fatigue in the GG genotype, and (B) between *IL6* −174 and fatigue, with higher levels of fatigue in the GG genotype. (C) *IL1B* −511 was not significantly associated with fatigue.

DISCUSSION

Despite its prevalence, the etiology of cancer-related fatigue is still poorly understood, and risk factors for the development and persistence of fatigue have not been determined. This study sought to identify risk factors for fatigue in women recently treated for early-stage breast cancer, focusing on host genetic factors linked to inflammation. We found that an additive genetic risk index defined over three genes encoding proinflammatory cytokines (*TNF* −308, *IL6* −174, and *ILB* −511) was associated with elevated fatigue, such that women with more high-expression alleles across the three SNPs reported higher levels of fatigue. In analyses considering fatigue as a categorical variable, each high-expression allele increased the risk of more severe fatigue by 45%. At the individual SNP level, women who were homozygous for the high-expression alleles of *TNF* −308 and *IL6* −174 reported the highest levels of fatigue.

These findings build on previous research linking circulating markers of proinflammatory cytokine activity and related cytokine gene variants with cancer-related fatigue.[53] To date, most of this work has focused on circulating inflammatory markers and has generally shown a positive association with fatigue, particularly in the post-treatment period.[8,11,13,14,16] Few studies have examined cytokine gene polymorphisms in relation to cancer-related fatigue. Two longitudinal studies of patients undergoing treatment found that individual polymorphisms in *TNF* and *IL6* were linked to fatigue,[26-28] and we have previously shown an association between SNPs in *IL1* and *IL6* and fatigue in a small sample of survivors of breast cancer.[29] However, a recent study found no differences in the distribution of these polymorphisms in Norwegian survivors of breast cancer with versus without cancer-related fatigue.[31] These differences may be a result of the timing of assessment, the method for assessing and categorizing fatigue, and other differences between samples. In addition, considering the additive effects of multiple inflammation-related SNPs in the current study may have provided a more comprehensive measure of cytokine exposure, enhancing our ability to detect associations with fatigue. Overall, our findings converge with studies examining inflammatory markers and with those examining polymorphisms in proinflammatory cytokine genes to support an inflammatory basis for cancer-related fatigue.

There has been more limited examination of links between inflammatory processes and other cancer-related behavioral symptoms.

In noncancer populations, depression has been associated with promoter polymorphisms in *IL6*[54] and with circulating levels of IL6 and other inflammatory markers.[55] There is also preliminary evidence of elevated IL6 in depressed patients with cancer,[56] although we have not found an association between depressive symptoms and inflammatory markers in our previous studies with fatigued survivors.[8] Memory problems have also been linked to inflammatory activity in noncancer populations[57] and, more recently, in survivors of breast cancer.[58] No previous studies have examined inflammation-related genes as predictors of depressive symptoms or memory complaints in patients with cancer, although recent findings suggest that polymorphisms in inflammation-related genes (including *TNF* −308) are associated with pain in patients with lung cancer.[50] Recent data also suggests an association between inflammation-related SNPs and sleep disturbance in patients with cancer and their family caregivers.[26,27,59] In the current study, we found that both depressive symptoms and memory problems were elevated among patients with breast cancer with high-expression alleles across the three cytokine SNPs, providing preliminary evidence that inflammation-related genetic factors may contribute to these symptoms in the cancer context. In contrast, sleep disturbance was not associated with the genetic risk index or with any of the three individual SNPs assessed, despite high levels of sleep problems in this patient group.

At this point, it is unclear whether cytokine genetic variants or circulating inflammatory markers will prove to be more useful for identifying individuals at risk for fatigue and other adverse effects of cancer treatment. Genetic factors may be particularly relevant in the acute phase of cancer diagnosis and treatment, because they may regulate the initial inflammatory response to treatment with surgery, radiation, or chemotherapy. However, proinflammatory cytokine production and signaling are also influenced by a range of nongenetic factors, which may play a more prominent role later in survivorship. For example, alterations in glucocorticoid signaling and in lymphocyte subsets may help structure the elevations in circulating inflammatory markers seen in long-term survivors with cancer-related fatigue.[9,10] In this context, circulating markers may be more strongly associated with fatigue symptoms. Longitudinal studies are needed to identify the optimal predictors of fatigue and at what point in the cancer trajectory.

This study has a number of limitations, most notably the homogeneous nature of the survivors of breast cancer who we assessed. The degree to which these findings hold for women from more diverse racial, ethnic, and socioeconomic backgrounds is an important question for future research. In addition, there is more genetic variation in *TNF*, *IL6*, and *ILB* than we assessed in this study, as well as variations in other genes that may be relevant for inflammatory signaling (eg, *IL10*[30]) or may influence fatigue via other pathways (eg, glutathione metabolic pathway[49]), which merit consideration in future research. Future studies should also include ancestry informative markers to control for the genomic component of race/ethnicity. It would also be interesting to include a comparison group with no cancer history to determine whether the association between the genetic risk score and fatigue is primarily observed in the context of cancer diagnosis and treatment (and associated physical and psychological stressors) or is also apparent in healthy individuals. Finally, results require replication in a larger sample.

Our results indicate that patients with high-expression variants of multiple cytokine genes may be at particular risk for fatigue in the immediate aftermath of cancer treatment. With further validation, the additive composite of high-expression alleles in *TNF*, *IL6*, and *ILB* could potentially be used as a simple clinical genetic biomarker of fatigue adverse effect risk in the context of primary breast cancer treatment. This genetic risk index might be helpful in identifying high-risk patients early in the cancer trajectory. Furthermore, the index might guide the development and deployment of targeted pharmacologic and behavioral interventions to combat fatigue and other debilitating adverse effects of breast cancer treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Final approval of manuscript: All authors

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