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ORIGINAL ARTICLE

Gene interaction analysis of psoriasis in Chinese Han population

Qiongqiong Xu[1,2,3,4,5] | Xiaodong Zheng[1,2,3,4,5] | Yiwen Mao[1,2,3,4,5] | Weiwei Chen[1,2,3,4,5] | Shirui Chen[1,2,3,4,5] | Hui Zhang[1,2,3,4,5] | Qi Zhen[1,2,3,4,5] | Bao Li[1,2,3,4,5] | Liang Yong[1,2,3,4,5] | Huiyao Ge[1,2,3,4,5] | Yafen Yu[1,2,3,4,5] | Ruixue Zhang[1,2,3,4,5] | Lu Cao[1,2,3,4,5] | Hui Cheng[1,2,3,4,5] | Wenjun Wang[1,2,3,4,5] | Liangdan Sun[1,2,3,4,5]

[1]Department of Dermatology, First Affiliated Hospital, Anhui Medical University, Hefei, China

[2]Institute of Dermatology, Anhui Medical University, Hefei, China

[3]Key Laboratory of Dermatology, Anhui Medical University, Ministry of Education, Hefei, China

[4]Anhui Medical University, Anhui Provincial Institute of Translational Medicine, Hefei, China

[5]Anhui Medical University, Inflammation and Immune Mediated Diseases Laboratory of Anhui Province, Hefei, China

Correspondence
Liangdan Sun, Department of Dermatology, First Affiliated Hospital, Anhui Medical University, Hefei 230032, China.
Email: ahmusld@163.com

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Abstract

Background/aims: Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by excessive proliferation of keratinocytes. It has a strong genetic predisposition; gene-gene interactions are important genetic models for common diseases. In this study, we explore pair-wise interactions among SNPs contributing to psoriasis susceptibility.

Methods: We first performed gene interactions with exome-sequencing, next, we analyzed gene interactions combining the exome sequencing data with the targeted sequencing data. After we sequenced *HLA* region, we analyzed gene interactions including *HLA* regions and non-*HLA* regions.

Results: We found interactions between *HLA* regions were significant. We observed significant interactions between *HLA-C*06:02* and rs118179173 (snp31443520; $p = 8.21 \times 10^{-20}$, OR = 0.22) and between *HLA-C*06:02* and *HLA-B:AA67* ($p = 1.22 \times 10^{-12}$, OR = 0.45).

Conclusion: This study provides evidence that *HLA* is the most important susceptibility region on the risk of psoriasis and interactions that occur in this region are still significant.

KEYWORDS

gene-interactions, *HLA*, psoriasis

Qiongqiong Xu, Xiaodong Zheng, Yiwen Mao equally contributed.

1 | INTRODUCTION

Psoriasis is a complex skin disease characterized by epidermal hyper-proliferation, vascular remodeling, and inflammation, the joints are frequently involved in pain and stiffness. Approximately 125 million people are affected worldwide (Armstrong & Read, 2020), the prevalence of psoriasis in China is about 0.47% (Ding et al., 2012). It is more common in adults than children, and there is no difference between male and female. Psoriasis is multifactorial in most cases, the exact etiology is unknown. Earlier family linkage studies and twin studies confirm the genetic susceptibility of psoriasis (Brandrup, 1978; Myers et al., 2005), the risk of psoriasis in monozygotic twin pairs are 2–3.5 times than dizygotic twin pairs (Lønnberg et al., 2016), subsequently, the development of genome-wide association studies (GWAS) laid the genetic foundation of psoriasis. Abnormal proliferation of keratinocytes and infiltration of immune cell means it is a disorder of the immune system, some pro-inflammatory cytokines have been demonstrated to be related to psoriasis, including interleukin-23 (IL-23; Li et al., 2018), IL-17 as well as tumor necrosis factor α (TNF-α; Cordiali-Fei et al., 2014; Girolomoni et al., 2012). Besides, environmental play an important role in the pathogenesis of psoriasis, like drugs, trauma, infection, stress, smoking, cold, and humidity (Gudjonsson et al., 2003; Patel & Weinberg, 2008; Raychaudhuri & Gross, 2000).

It is now well established that heredity is an important part of the etiology of psoriasis. Major histocompatibility complex (MHC) region more precisely the *HLA-C*, it accounts for about 35%–50% of disease heritability, is regarded as the most important genetic component of psoriasis, subsequently GWAS identified 86 susceptibility genes associated with psoriasis in total (Hwang et al., 2017). Most association studies detect SNPs independently rather than considering interactions between them, it ignores the complex interactions that often occur in biological systems. There are some gene interaction studies in autoimmune diseases, including rheumatoid arthritis (Liu et al., 2011), systemic lupus erythematosus (Zhang et al., 2016), ankylosing spondylitis (Evans et al., 2011). For psoriasis, researches on the interaction between some susceptibility genes are also being carried out in different populations (Strange et al., 2010; Vasilopoulos et al., 2011). Various algorithms have been proposed to detect the interactions between genes (Niel et al., 2015), In our study, we performed gene interactions using multifactor dimensionality reduction (MDR).

In the last decade, our group has identified eight independent susceptibility loci of psoriasis in *HLA* region (Zhou et al., 2016) and more than 30 susceptibility genes in non-*HLA* regions in Chinese population using GWAS (Cheng et al., 2014; Tang et al., 2014; Zhang et al., 2009; Zuo et al., 2015), based on the previous GWAS data, we performed gene-gene interactions for psoriasis. The aim of this study is to further explain the genetic mechanism of psoriasis by identifying interacting SNPs and genes.

2 | MATERIALS AND METHODS

2.1 | Samples

Firstly, 781 psoriasis cases and 676 controls were used to discover gene-gene interactions among SNPs in exome-sequencing, and a second cohort was 9946 cases and 9906 controls in targeted sequencing (Tang et al., 2014), thus we analyzed the gene interactions with the two combined datasets, next, we further identified interactions in *HLA* regions and those susceptibility genes in non-*HLA* regions in 10,689 controls and 9946 patients selected from above cohorts (Zhou et al., 2016). All samples were Chinese Han people. Diagnoses of disease, inclusion and exclusion criteria, collection of specimen, and information have been described previously. The study was approved by the institutional ethics committee of each hospital and was conducted according to the principles of the Declaration of Helsinki.

2.2 | Experimental process

Genomic DNAs of the peripheral blood mononuclear cells (PBMCs) was extracted using Flexi Gene DNA Kit (Qiagen), then we used NanoDrop-2000 to dilute DNA to standard experimental concentration, for the whole genome genotype concentration is 50 ng/μl, the range of A260/A280 is 1.8–2.0, select samples that meet the criteria for the next step of genotyping. Next, SNP genotyping was performed on the Illumina HiSeq 2000 platform to generate 90-bp paired-end reads. Locus-specific polymerase chain reaction (PCR) was performed and PCR reaction products were purified by AgencourtAMpure SPRI XP bead. Genomic DNA for each individual was hybridized with the NimbleGen 2.1M-probe sequence capture array (Albert et al., 2007) to enrich exonic DNA in each library. Samples were aligned to the NCBI human genome reference assembly (build 36.3) using BWA (Burrows-Wheeler Aligner; Li & Durbin, 2010), using the Genome Analysis Toolkit (GATK v1.6; McKenna et al., 2010) to perform realignment around known indels. All aligned read data were subjected to CountCovariates (GATK) on the basis of known SNVs (dbSNP135), and base quality was then recalibrated (Table Recalibration in GATK).

2.3 | Statistical analysis and quality control

The variants with $p < 0.05$ in the exome sequencing dataset, the combined datasets of exome sequencing and

targeted sequencing as well as the 8 variants reported in the *HLA* sequencing analysis included in this study. We used PLINK 1.07 to test SNP × SNP interactions for case-control population-based samples. Then we could obtain odds ratio for interaction (OR), chi-square statistic (STAT), asymptotic *p*-value (*p*). The multifactor dimensionality reduction (MDR, V2.0 Beta 2) was used to calculate the interactions between variants according to reported method (Ritchie et al., 2001). Interactions were selected if $p < 5 \times 10^{-2}$. Bonferroni correction was used to define the statistical significance with $p < 2.84 \times 10^{-8}$ ($0.05/1326^2$).

3 | RESULTS

3.1 | The optimal *p*-value for psoriasis

The identified variants only explained a small part of genetic risk, GWAS threshold is conventionally using a *p*-value of 5×10^{-8} to avoid issues of false-positive findings due to multiple testing, many genes influence psoriasis but do not reach a significant level (5×10^{-8}), here, we used polygenic risk score (PRS) analysis to identify high-risk loci for psoriasis. PRSice 2.1.11 (https://github.com/choishingwan/PRSice) was used to calculate the *p* value. Exome sequencing including 1457 participants (859 males and 598 females) was observed. We chose more than 70 psoriasis susceptibility genes reportedly from human genome (HG19), locating upstream and downstream 500K loci, totally 30923 variants. When the *p*-value was 0.05, the model was optimal, and the polygenic risk score of the phenotype was 0.77, and the *p*-value was 1.1×10^{-87} (Figure 1).

3.2 | Interactions in exome and targeted sequencing data

We performed the interactions of variants with $p < 5 \times 10^{-2}$ in exome sequencing data with 781 psoriasis cases and 676 controls, due to the genetic complexity of *HLA* region, single nucleotide variants (SNVs) within this region were excluded, 1326 genes was selected (Tang et al., 2014). The interaction between *C1orf186* and *TNFRSF1B* showed the most significance (chr1_12

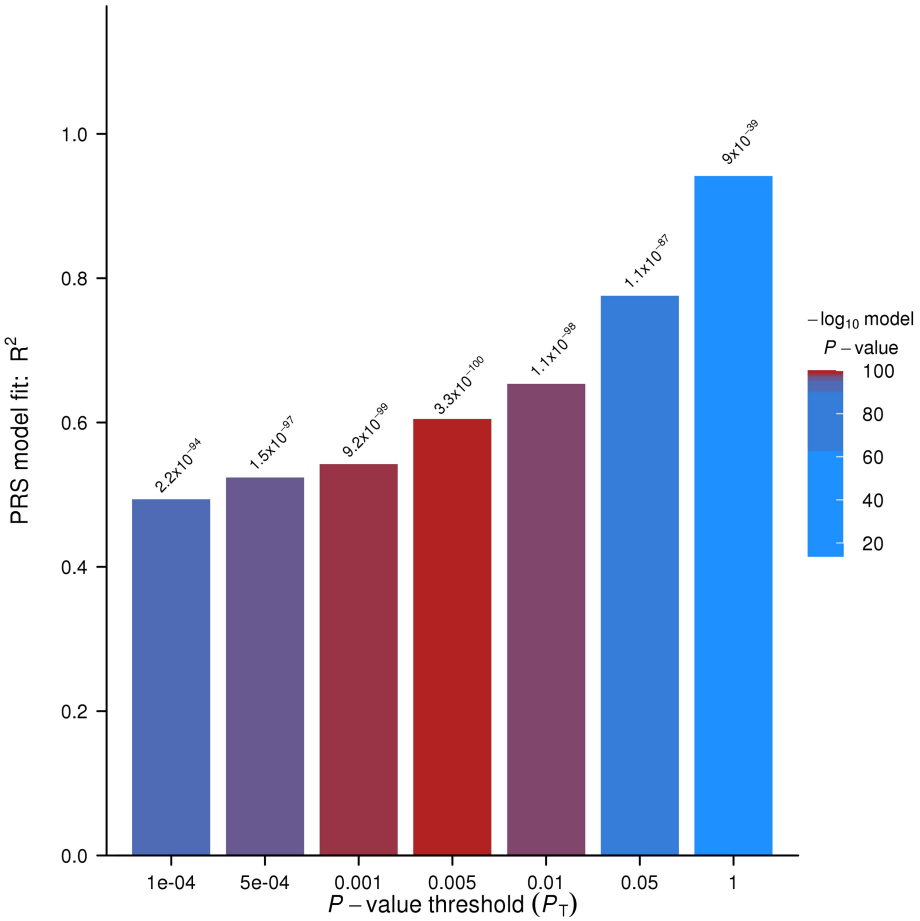

FIGURE 1 The optimal *p*-value for psoriasis using polygenic risk score (PRS) analysis

253062 × chr1_206239574, $p = 2.77 \times 10^{-5}$, OR = 7.22). Besides, interaction between *COL5A3* and *SLC9A4* was also notable; interactions with $p < 0.01$ were shown in Table S1. Then we enlarged the sample size with the targeted sequencing data of 1326 selected genes in 9946 psoriasis patients and 9906 controls. We analyzed gene-gene interactions with these two combined datasets. More than 20,000 interactions were identified with $p < 0.05$ (Table S2). The significant interactions were between *MIR548AZ* and *TYK2* (chr14_64897018 × chr19_10464687, $p = 2.34 \times 10^{-5}$, OR = 0.56; chr14_64897018 × chr19_10472933, $p = 2.35 \times 10^{-5}$, OR = 0.57; chr14_64896783 × chr19_10472933, $p = 8.59 \times 10^{-5}$, OR = 0.59; chr14_64896783 × chr19_10464687, $p = 9.56 \times 10^{-5}$, OR = 0.58); *CARD14* and *TNP2* ($p = 2.34 \times 10^{-5}$, OR = 3.95); *NDST2* and *UBLCP1* ($p = 2.85 \times 10^{-5}$, OR = 0.3); *TAF1L* and *TARBP1* ($p = 8.06 \times 10^{-5}$, OR = 7.78); *IL12B* and *SUOX* ($p = 9.63 \times 10^{-5}$, OR = 0.2; Table 1).

3.3 | Interactions in *HLA* and non-*HLA* regions

Then we explored interactions adding *HLA* region. Datasets are obtained from the entire 5-Mb *MHC* region in 20,635 individuals of Chinese Han population (including 10,689 controls and 9946 patients with psoriasis selected from the exome and targeted sequencing). MHC sequencing identified eight independent variants, including HLA-C*07:04, HLA-C*06:02, rs118179173 (snp31443520), HLA-B amino acid9 (HLA-B:AA9), HLA-B:AA67, HLA-B:AA116, HLA-DPB1*05:01, and BTNL2:AA281 (snp32472030; Zhou et al., 2016). The strong interactions with these 3 sequencing datasets were located in *HLA* regions between *HLA-C*06:02* and snp31443520 (rs118179173; $p = 8.21 \times 10^{-20}$, OR = 0.22) and between *HLA-C*06:02* and *HLA-B:AA67* ($p = 1.22 \times 10^{-12}$, OR = 0.45; Table 2, Table S3).

Previously reported interactions have also been confirmed, interactions between the *ERAP1* and *HLA-C* was obvious (chr5_96139250 × *HLA-C*06:02, $p = 3.61 \times 10^{-7}$, OR = 0.74;chr5_96117300 × *HLA-C*06:02, $p = 1.68 \times 10^{-6}$, OR = 0.75; chr5_96118852 × *HLA-C*06:02, $p = 3.43 \times 10^{-5}$, OR = 0.78; chr5_96125910 × *HLA-C*06:02, $p = 3.81 \times 10^{-5}$, OR = 0.78; chr5_96124447 × *HLA-C*06:02, $p = 6.44 \times 10^{-5}$, OR = 0.79; chr5_96121994 × *HLA-C*06:02, $p = 6.50 \times 10^{-5}$, OR = 0.79; chr5_96121715 ×*HLA-C*06:02, $p = 6.96 \times 10^{-5}$, OR = 0.79; Interactions between them were shown in Table 3). Besides, We also observed significant interactions between *HLA* and *IL12B* (chr5_158750013 × *HLA-C*06:02, $p = 0.009494$).

4 | DISCUSSION

In recent years, the exploring of gene-gene interaction is an important supplement to the genetic mechanism of psoriasis and enriches the genetic pattern of psoriasis in Chinese Han population. Based on GWAS data, this study further explores interactions between susceptibility genes of psoriasis. With a large sample size, we have identified significant genetic interacting signals within the *HLA* complex as expected, more than 60% of the interactions SNP are located at 6p21. We observed significant interactions between *HLA-C*06:02* and rs118179173 (snp31443520; $p = 8.21 \times 10^{-20}$, OR = 0.22) and between *HLA-C*06:02* and *HLA-B:AA67* ($p = 1.22 \times 10^{-12}$, OR = 0.45). Previous reported interactions have also been confirmed, including interactions between *HLA* and *ERAP1* (Strange et al., 2010), *HLA* and *IL12B* (Zheng et al., 2011).

HLA has strong homology and complex polymorphism, HLA-C may affect both innate and adaptive immune system, it plays an important role in antigen recognition, presentation, immune response, and regulation, the skin lesions of psoriasis are rich in activated CD^{8+} T cells (Chang et al., 1995), HLA-C participates in the immune response by presenting antigens to CD^{8+} T cells and interacting with natural killer (NK) cell receptors (Prinz, 2017). The frequency of *HLA-Cw6* alleles in Chinese patients with psoriasis is 16.18%–18.6% (Chang et al., 2003; Tsai et al., 2002), it is a major contributor to psoriasis (psoriasis susceptibility 1 [PSORS1]). *HLA-C* has been recognized as the acknowledged susceptibility gene in multiple populations (Capon et al., 2004), association studies have defined the *HLA-Cw6* allele as a factor that predisposes to early-onset disease (Das et al., 2017), moreover, patients with *HLA-Cw6* are usually earlier to develop psoriatic arthritis (Chen & Tsai, 2018), research around *HLA* accounts for the majority studies regard to gene interactions.

This study also verified previously reported gene interactions, among which the interaction between *HLA-C* and *ERAP1* is the most significant. Interactions between *HLA* and *ERAP1* also define the importance of *ERAP1* in the risk of psoriasis. In a study by Yin et al. (2013), when *ERAP1* and *HLA-C* co-exist in an individual, the interaction between them was obvious, which increases the risk of psoriasis by 20 times compared with individuals with *HLA-C* alone. *ERAP1* is an immune-functional gene that encodes a multifunctional aminopeptidase and is involved in processing *HLA* molecular antigen peptides (Kochan et al., 2011). Enzymes encoded by *ERAP1* genes can produce pro-inflammatory cytokines and chemokines, which also inhibit immune cells maturation, then induce psoriasis (Aldhamen et al., 2013). Deficiency in ERAP1

TABLE 1 Interaction analysis in exome and targeted sequencing data

SNP1	SNP2	OR	*p*	Gene 1	Gene 2
chr14_64897018	chr19_10464687	0.5653	2.34E-05	MIR548AZ	TYK2
chr16_11363025	chr17_78171944	3.954	2.34E-05	CARD14	TNP2
chr14_64897018	chr19_10472933	0.5768	2.35E-05	MIR548AZ	TYK2
chr5_158705065	chr10_75564624	0.302	2.85E-05	NDST2	UBLCP1
chr1_234565787	chr9_32633719	7.783	8.06E-05	TAF1L	TARBP1
chr14_64896783	chr19_10472933	0.594	8.95E-05	MIR548AZ	TYK2
chr14_64896783	chr19_10464687	0.5831	9.56E-05	MIR548AZ	TYK2
chr5_158750013	chr12_56398287	0.2036	9.63E-05	IL12B	SUOX

TABLE 2 Interaction analysis in exome, targeted and HLA sequencing data

Vatiant 1	Vatiant 2	OR	*p*	Gene 1	Gene 2
HLA-C*06:02	rs118179173	0.22	8.21E-20	HLA-C	HLA-B
HLA-C*06:02	HLA-B:AA67	0.45	1.22E-12	HLA-C	HLA-B
chr5_96139250	HLA-C*06:02	0.74	3.61E-07	ERAP1	HLA-C
chr5_96117300	HLA-C*06:02	0.75	1.68E-06	ERAP1	HLA-C
HLA-C*06:02	HLA-C*07:04	0.28	6.86E-06	HLA-C	HLA-C
chr5_96118852	HLA-C*06:02	0.78	3.43E-05	ERAP1	HLA-C
chr5_96125910	HLA-C*06:02	0.78	3.81E-05	ERAP1	HLA-C
snp31443520	HLA-DPB1*05:01	1.47	6.07E-05	HLA-B	HLA-DPB1
chr5_96124447	HLA-C*06:02	0.79	6.44E-05	ERAP1	HLA-C
chr5_96121994	HLA-C*06:02	0.79	6.50E-05	ERAP1	HLA-C
chr5_96121715	HLA-C*06:02	0.79	6.96E-05	ERAP1	HLA-C
chr5_96129512	HLA-C*06:02	0.80	0.0002089	ERAP1	HLA-C
chr5_96222183	HLA-C*06:02	0.80	0.0002627	ERAP2	HLA-C
HLA-C*06:02	HLA-DPB1*05:01	1.26	0.0002793	HLA-C	HLA-DPB1
chr5_96222185	HLA-C*06:02	0.81	0.0005506	ERAP2	HLA-C
chr5_96232222	HLA-C*06:02	0.82	0.0009334	ERAP2	HLA-C
chr5_96237114	HLA-C*06:02	0.82	0.0009459	ERAP2	HLA-C
chr5_96132795	HLA-C*06:02	0.77	0.0009922	ERAP1	HLA-C

TABLE 3 Interactions between *HLA* and *ERAP1*

SNP1	SNP2	OR	*p*	Gene 1	Gene 2
C*06:02	5_96139250	0.74	3.61E-07	*HLA-C*	*ERAP1*
C*06:02	5_96117300	0.75	1.68E-06	*HLA-C*	*ERAP1*
C*06:02	5_96118852	0.78	3.43E-05	*HLA-C*	*ERAP1*
C*06:02	5_96125910	0.78	3.81E-05	*HLA-C*	*ERAP1*
C*06:02	5_96124447	0.79	6.44E-05	*HLA-C*	*ERAP1*
C*06:02	5_96121994	0.79	6.50E-05	*HLA-C*	*ERAP1*
C*06:02	5_96121715	0.79	6.96E-05	*HLA-C*	*ERAP1*
C*06:02	5_96129512	0.80	0.0002089	*HLA-C*	*ERAP1*
C*06:02	5_96132795	0.77	0.0009922	*HLA-C*	*ERAP1*

expression was shown to result in unstable and highly immunogenic peptides presented in the context of HLA class I, which elicited potent CD^{8+} T cell and B cell responses (Hammer et al., 2007).

In addition, interactions between *MIR548AZ* and *TYK2* were references to explore more pathogenesis of psoriasis. In a study by Zhao et al. (2018), miR-548a-3p was unregulated after treating human keratinocytes with IL-22, miR-548a-3p may promote keratinocytes proliferative disorder. IL-22 is a member of the IL-10 cytokine family, Th17 cells could produce both IL-17 and IL-22 in psoriatic skin (Liang et al., 2006). IL-22 signaling is mediated by TYK2 and JAK1 (Works et al., 2014). Tyrosine kinase 2 (TYK2) belongs to the JAK family protein tyrosine kinase, by catalyzing TYK2, the downstream signaling pathway of IL-12 and IL-23 can be activated (Sohn et al., 2013). IL-23 enhances IL-22 expression during Th17 differentiation.

In a word, our study analyzed the susceptibility gene interactions of psoriasis in Chinese population and confirmed the important roles of HLA region, interactions between *HLA* and *ERAP1*, MIR548AZ, and TYK2. The results just refer to the Chinese Han population and it is worth repeating for other populations. Gene interactions provide a new perspective for understanding the genetic mechanism of psoriasis, which puts forward the ways to reveal the complex mechanisms of interactions for other common diseases.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ETHICS STATEMENT

Written informed consent was obtained from the patient. The study was approved by Ethics Committee of Anhui Medical University and was conducted according to the Principles of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Liangdan Sun, Wenjun Wang, and Hui Cheng conceived and designed the research. Xiaodong Zheng designed the structure of the manuscript. Qiongqiong Xu and Yiwen Mao wrote the manuscript. Weiwei Chen,Shirui Chen,Hui Zhang, Huiyao Ge, Ruixue Zhang, and Lu Cao were responsible for selecting samples. Qi Zhen, Bao Li, Liang Yong, and Yafen Yu analyzed the data. All authors contributed literature search, analysis of literature, and drafting of the manuscript.

ORCID

Qiongqiong Xu https://orcid.org/0000-0002-1116-4428
Ruixue Zhang https://orcid.org/0000-0002-5281-6330

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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