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Cumulative Evidence on Associations between Genetic Variants and Autoimmune Hepatitis

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Abstract

Genetic factors play a critical role in autoimmune hepatitis (AIH), and numerous studies have been conducted to identify variants associated with the risk of AIH. However, our knowledge of these genetic risk factors is still limited. In this study, we aim to provide a comprehensive synopsis of the genetic architecture of this disease. A systematic search was conducted to identify published studies on the associations between genetic variants and the risk of AIH. Meta-analyses were conducted to calculate the pooled odds ratio (OR) and 95% confidence interval (CI). Then, the cumulative evidence was evaluated for significant associations according to the Venice criteria and false-positive report probability. Finally, functional annotations and pathway analyses were conducted to identify potential pathogenic loci and related pathways. In total, 62 studies involving 11,068 cases and 45,482 controls were included to assess the association between 75 genetic variants and the risk of AIH. Among them, 24 variants were associated with the risk of AIH, and there is strong cumulative evidence supporting these associations. Importantly, HLA DRB1*0301 (OR: 3.023, 95% CI: 2.443 - 1.678, $P = 2.81 \times 10^{-24}$) and DRB3*0101 (OR: 3.667, 95% CI: 2.649 - 5.075, $P = 4.69 \times 10^{-15}$) are newly identified genome-wide significant risk loci. In addition, the rs3184504 variant (OR: 1.305, 95% CI: 1.122 - 1.516, P = 0.001) in the SH2B3 gene is a potential functional mutation. GO pathway analysis suggests that these genes are enriched in antigen processing and presentation, response to interferon-gamma, and immune response-

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regulating signaling pathways. This study comprehensively summarizes the genetic architecture of AIH and provides cumulative evidence. We have identified two new loci that exceed genome-wide significance. The findings from this study will offer new insights into the pathogenesis of AIH.

Keywords

Autoimmune Hepatitis, Genetic Architecture, Cumulative Evidence, Functional Annotations, HLA

1. Introduction

Autoimmune hepatitis (AIH) is a rare, chronic inflammatory liver disease with an unknown cause [1]. The clinical presentation ranges from asymptomatic elevation of liver enzymes to acute liver failure [2]. Women are the primary affected population, with a sex ratio of 3.6:1 [1]. The prevalence of AIH is increasing worldwide, and a meta-analysis has reported a prevalence of 12.99, 19.44, and 22.80 per 100,000 people in Asia, Europe, and the USA, respectively [3]. Similar annual incidence rates were found for all regions, with rates of 1.31, 1.37, and 1.00 per 100,000 people in Asia, Europe, and the USA, respectively [3].

Genetic factors play an important role in AIH [2]. AIH also presents with various clinical features and therapeutic effects as a result of genetic predisposition differences. Therefore, understanding the genetic architecture of AIH would help develop strategies for the prevention and treatment of AIH. Over the past decade, multiple genetic associations with AIH have been described in various ethnic groups [4]-[6].

However, the susceptibility of AIH has not been fully explained. AIH is a rare disease, and the number of cases in most observational studies is less than 100 [5]-[7]. As a result, they may have insufficient statistical power to establish a true association. To our knowledge, Xiong Ma *et al.* conducted the largest genome-wide meta-analysis to identify susceptibility loci for AIH with 1622 Chinese patients and 10,466 population controls from two independent cohorts [4].

Meta-analysis is a statistical technique used to extract and combine data to produce a summary result of the included studies. This method is valuable for increasing the sample size of observational studies and the associated statistical power [8]. In the present study, we aim to provide a comprehensive overview of the current understanding of the genetic architecture of AIH, drawing on published literature. Firstly, we conducted a systematic review and meta-analysis to comprehensively assess the connections between genetic variants and AIH. We then assessed the levels of cumulative evidence for significant associations ($P < 0.05$) by combining the Venice criteria and false positive report probability (FPRP) tests. Finally, we conducted functional annotations and pathway analyses for the potential pathogenic loci.

2. Methods

The methodology for the meta-analysis followed the guidelines proposed by the Human Genome Epidemiology Network for a systematic review of genetic association studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9] [10]. The protocol has been registered in the International Prospective Register of Systematic Reviews (ID: CRD42021282146).

2.1. Literature Search Strategy and Study Eligibility

A comprehensive literature search of related studies was conducted using the PubMed, Embase database, and Web of Science (published on or before April 15, 2023), with the following keywords: "liver inflammatory disease OR autoimmune hepatitis OR autoimmune liver disease" AND "Genetic OR SNP OR polymorphism OR genotype OR variant OR allele OR mutation OR insertion OR deletion OR copy number OR genome-wide association study OR GWAS". The title, abstract, or full text of the studies were reviewed as necessary to identify all relevant articles. In addition, reference lists of all the included studies, reviews, and meta-analyses were manually screened for any additional potential studies.

Inclusion criteria: 1) original articles published in English; 2) observational studies; 3) investigating associations between genetic variants and risk of AIH; 4) providing risk estimates [including odds ratio (OR) and relative risk (RR)] and 95% confidence intervals (CIs) or data to calculate them. Exclusion criteria: 1) participants complicated with other liver diseases; 2) reviews, abstracts, case reports, and letters. Two investigators (DG and YW) independently assessed the eligibility of each publication, and disagreement was discussed with the principal author (MZ).

2.2. Data Extraction, Preparation, and Management

Two authors (DG and MZ) independently extracted the data using a predesigned collection sheet including PMID, first author, publishing year, study design, sample size of cases and controls, source of population, ethnicity, variants, gene, major and minor alleles, genotype and allele counts, risk estimates and corresponding 95% CIs, or P value (for studies using multiple adjusted models, the most fully adjusted estimates were extracted).

2.3. Meta-Analyses

Meta-analyses were performed to calculate the pooled OR and 95% CIs under an additive genetic model. The statistical heterogeneity among the studies was assessed using the Cochran Q statistic ($P < 0.10$ was considered statistically significant) and I^2 statistic ($I^2 \leq 25\%$ represented mild heterogeneity, 25% - 50% represented moderate heterogeneity, and ≥ 50% represented large heterogeneity) [11]. A random-effects model was used when $I^2 \geq 50\%$, while a fixed-effects model was

used when I^2 < 50%. For variants associated with AIH, sensitivity analyses were conducted by excluding the initial published or initial positive study. Furthermore, we assessed potential publication bias using Begg's test [12] and small-study bias using Egger's test [13].

2.4. Assessment of Cumulative Evidence

Associations with P < 0.05 in the primary meta-analyses were evaluated using the Venice criteria to assess the epidemiological credibility, and the detailed methods were described in our previous research [14]. Finally, epidemiological credibility was categorized as strong, moderate, or weak, based on the grade level of A, B, or C in three criteria: the amount of evidence, replication, and protection from bias. Furthermore, FPRP was calculated for these associations [15]. Specifically, FPRP values < 0.05, 0.20 - 0.05, and >0.20 were considered as strong, moderate, and weak evidence of a true association, respectively. We would upgrade the cumulative evidence if the FPRP result was strong, whereas downgrade the cumulative evidence if the FPRP result was weak.

2.5. Functional Annotation

To provide biological insights into the significant variants identified by meta-analysis, we mapped these SNPs to genes and conducted functional annotation with the Encyclopedia of DNA Elements (ENCODE) tool HaploReg v4.1 [16]. To identify tissues most relevant to the significant genes, GTEx tissue enrichment analysis was conducted based on 54 tissue types available from GTEx (version 8) through functional mapping and annotation of genome-wide association studies (FUMA) GENE2FUNC process [17]. In addition, we assessed the enrichment of the significant mapped genes in Gene Ontology (GO) biological processes using the WebGestalt tool [18]. We adopted the Benjamin-Hochberg procedure to correct for multiple testing and considered a false discovery rate (FDR) corrected P < 0.05 as a statistical difference.

2.6. Statistical Analysis

Statistical analysis was conducted using Stata version 15 (StataCorp, College Station, TX), and a two-tailed P < 0.05 was considered statistically different unless otherwise specified.

3. Results

3.1. Characteristics of the Included Studies

In total, we screened 1213 publications after duplicates excluded in the literature search, and the selection process is presented in **Figure 1**. After screening, a total of 62 publications involving 11,068 cases and 45,482 controls were included for quantitative analysis. Among these articles, 57 were candidate-gene association studies (including 56 case-control studies and 1 cohort study), and 5 were

GWASs. Thirty-three articles investigated the association between human leukocyte antigen (HLA) genes and the risk of AIH, while 34 articles examined the relationship between non-HLA genes and the risk of AIH.

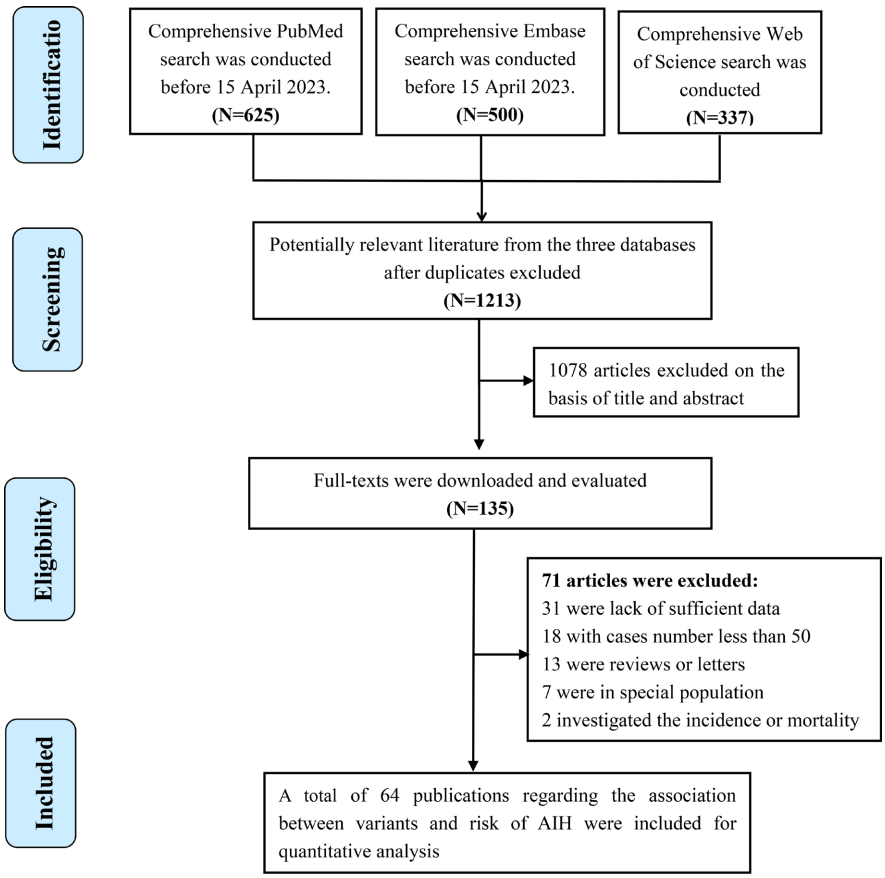

Figure 1. Flowchart of literature selection in the meta-analysis.

3.2. Results of the Meta-Analysis

In total, we performed meta-analyses to investigate the association between 75 variants in 11 genes or loci and the risk of AIH. Among these variants, 17 in the *HLA* gene and 7 in non-HLA genes were associated with AIH (**Table 1** and **Table 2**). However, no association was found between 51 variants and AIH.

Seventeen variants in the HLA gene were found to be associated with the risk of AIH. Among them, 7 associations were graded as strong, 4 were graded as moderate, and 6 were graded as weak (**Table 1**). In particular, strong evidence suggested that rs2187668 (OR: 2.695, 95% CI: 2.418 - 3.004, $P = 1.10 \times 10^{-71}$), DRB1*0405 (OR: 3.223, 95% CI: 2.602 - 3.993, $P = 8.20 \times 10^{-27}$), DRB1*0301 (OR: 3.023, 95% CI: 2.443 - 1.678, $P = 2.81 \times 10^{-24}$), DRB3*0101 (OR: 3.667, 95% CI: 2.649 - 5.075, $P = 4.69 \times 10^{-15}$), and DQB1*0201 (OR: 2.554, 95% CI: 1.863 - 3.503, $P = 5.88 \times 10^{-9}$) were associated with AIH at genome-wide significance level ($P < 5.0 \times 10^{-8}$). Importantly, DRB1*0301 and DRB3*0101 were the newly identified genome-wide significant risk loci (**Table 1**).

Table 1. Variants in *HLA* gene associated with risk of autoimmune hepatitis in meta-analysis.

Variant	Datasets	Cases/ Controls	Risk estimates		Heterogeneity		Venice criteria grade	FPRP	Cumulative evidence of association
			OR (95%CI)	P	I^2	P			
rs2187668	3	1177/18024	2.695 (2.418, 3.004)	1.10×10^{-71}	12.00%	0.321	AAA	<0.002	Strong
DRB1*0405	6	607/1939	3.223 (2.602, 3.993)	8.20×10^{-27}	0.00%	0.738	BAA	<0.003	Strong
DRB1*0301	13	1216/2945	3.023 (2.443, 3.742)	2.81×10^{-24}	11.70%	0.328	AAA	<0.005	Strong
DRB3*0101	3	291/381	3.667 (2.649, 5.075)	4.69×10^{-15}	0.00%	0.8	BAA	<0.008	Strong
DQB1*0201	4	285/554	2.554 (1.863, 3.503)	5.88×10^{-9}	0.00%	0.857	BAA	<0.013	Strong
DRB1*0401	5	613/1763	2.651 (1.808, 3.885)	5.82×10^{-7}	0.00%	0.623	BAA	<0.016	Strong
DRB1*1302	4	511/1648	0.434 (0.297, 0.635)	1.65×10^{-5}	0.00%	0.499	BAA	0.001	Strong
DRB1*1301	5	490/1454	3.869 (1.779, 8.414)	6.40×10^{-4}	43.70%	0.131	BBA	0.106	Moderate
DQ4	3	108/1152	2.483 (1.434, 4.299)	0.001	0.00%	0.442	BAC	0.091	Moderate
B*07	3	245/520	0.466 (0.290, 0.747)	0.002	23.50%	0.27	BAA	0.07	Moderate
DQB1*0602	3	199/452	0.435 (0.250, 0.757)	0.003	0.00%	0.987	BAC	0.165	Moderate
DRB1*01	4	267/457	0.477 (0.279, 0.818)	0.007	0.00%	0.429	BAC	0.239	Weak
DRB1*0406	4	516/1728	0.499 (0.296, 0.842)	0.009	0.00%	0.602	BAA	0.26	Weak
DQA1*0102	3	255/379	0.473 (0.252, 0.886)	0.019	61.40%	0.075	BCC	0.461	Weak
DRB1*15	6	426/875	0.597 (0.379, 0.940)	0.026	51.90%	0.065	BBC	0.609	Weak
DR7	4	338/1369	0.627 (0.415, 0.949)	0.027	0.00%	0.705	BAC	0.573	Weak
B*08	7	435/1975	2.570 (1.049, 6.293)	0.039	91.80%	<0.001	BCC	0.717	Weak

FPRP, false positive report probability.

Table 2. Variants non-*HLA* gene associated with risk of autoimmune hepatitis in meta-analysis.

Gene	Variant	Allele*	RAF	Datasets	Cases/ Controls	Risk estimates		Heterogeneity		Venice criteria grade	FPRP	Cumulative evidence of association
						OR (95%CI)	P	I2	P			
CARD10	rs6000782	C/A	0.05	2	1100/17539	1.590 (1.327, 1.905)	4.88×10^{-7}	12.00%	0.286	AAA	<0.001	Strong
TNF-α	rs1800629	A/G	0.14	3	183/750	1.889 (1.375, 2.595)	8.53×10^{-5}	16.20%	0.303	BAC	0.003	Moderate
SH2B3	rs3184504	C/T	0.53	2	1100/17539	1.305 (1.122, 1.516)	0.001	46.30%	0.172	AAA	0.065	Strong
PTPN22	rs2488457	A, C/G	0.76	3	393/784	0.748 (0.617, 0.906)	0.003	0.00%	0.672	BAA	0.296	Weak
STAT4	rs7574865	T/G	0.23	3	2032/11058	1.489 (1.124, 1.972)	0.005	81.20%	0.005	AAA	0.167	Strong
CTLA-4	rs231775	C/T	0.6	7	1106/1645	1.177 (1.041, 1.331)	0.009	3.00%	0.403	AAC	0.223	Weak
CTLA-4	exon 1	-	-	3	286/236	1.312 (1.007, 1.710)	0.044	0.00%	0.612	BAA	0.769	Weak

*Risk/Other allele. AIH, autoimmune hepatitis, FPRP, false positive report probability.

The associations between genetic variants in non-HLA genes and AIH are presented in **Table** 2. Among the 16 associations, 7 showed statistical differences ($P < 0.05$). Furthermore, 3 associations were graded as strong, 1 as moderate, and 2 as weak based on cumulative evidence. Rs6000782 in *CARD1*0 and rs1800629 in *TNF-α* were with an OR > 1.5.

3.3. Heterogeneity, Sensitivity Analysis, and Bias

In total, 37 (49.3%) associations revealed mild heterogeneity, 11 (14.7%) associations revealed moderate heterogeneity and 27 (36.0%) associations revealed large heterogeneity (**Table 1** and **Table 2**). Sensitivity analyses were performed for significant associations, and the results (16 associations, 66.7%) were stable when a single or first positive study was excluded. In addition, publication bias was found in 2 (8.3%) associations.

3.4. Functional Annotation and Pathway Analysis of Significant Variants

Functional annotation was conducted using HeploReg V4.1 for 7 variants associated with AIH (**Table 3**). Of these variants, rs3184504 is a missense variant, rs2187668, rs7574865, and rs2488457 are intronic variants. In addition, GO pathway analysis across these significant mapped genes revealed enrichment in antigen processing and presentation, response to interferon-gamma, and immune response-regulating signaling pathway (FDR < 0.05) (**Table 4**). However, GTEx tissue enrichment analysis suggested that no significant tissue enrichment is observed for the mapped genes associated with AIH.

Table 3. Functional annotation for variants associated with autoimmune hepatitis through HeploReg V4.1.

SNP	chr: pos (hg38)	Alt/Ref	EUR freq	Promoter histone marks[a]	Enhancer histone marks[b]	DNAse[c]	Proteins bound[d]	Motifs changed[e]	GENCODE genes	dbSNP func annot
rs2187668	6:32638107	T/C	0.10	5 tissues	BLD	4 tissues	POL2, POL24H8		HLA-DQA1	intronic
rs231775	2:203866178	C/T	0.60	BLD, GI	BLD, THYM			SIX5, Znf143	CTLA4	
rs1800629	6:31575254	A/G	0.14	7 tissues	12 tissues	BLD, BLD, BLD		ATF3, CCNT2, SP1	TNF	
rs7574865	2:191099907	G/T	0.77		BLD			Foxj2, Foxp1	STAT4	intronic
rs2488457	1:113872746	A, C/G	0.76	BLD, THYM, GI	10 tissues	11 tissues	STAT3		RP5-1073O3.5	intronic
rs3184504	12:111446804	C/T	0.53		19 tissues	4 tissues		HES1, Mtf1	SH2B3	missense
rs6000782	22:37532179	C/A	0.05					4 altered motifs	CARD10	

[a]Evidence of local H3K4Me1 and H3K27Ac modification (cell lines/types: if >3, only the number is included). [b]Evidence of local H3K4Me3 modification (cell lines/types: if >3, only the number is included). [c]Evidence of chromatin hypersensitivity to DNase (cell lines/types: if >3, only the number is included). [d]ChIP-seq experiments indicate an alteration in the binding of transcription factor (if >3, only the number is included). [e]Evidence of alteration in the regulatory motif (if >3, only the number is included).

Table 4. GO pathway analysis across the significant mapped genes.

Gene Set	Description	Enrichment Ratio	P	FDR
GO:0019882	antigen processing and presentation	38.490	2.07×10^{-6}	0.001
GO:0034341	response to interferon-gamma	34.280	3.28×10^{-6}	0.001
GO:0002764	immune response-regulating signaling pathway	16.963	4.17×10^{-6}	0.001

4. Discussion and Conclusions

In the current study, we conducted a comprehensive evaluation of the associations between genetic variants and AIH risk using data from 62 articles, which included a total of 11,068 cases and 45,482 controls. We conducted meta-analyses to evaluate 75 variants in 11 genes or loci and their association with the risk of AIH. Our findings revealed that 24 variants were significantly linked to the risk of AIH. Importantly, we have identified two newly genome-wide significant risk loci (DRB1*0301, DRB3*0101), which may provide novel insights into the pathogenesis of AIH. Cumulative evidence suggests 10 strong associations for AIH, including the missense mutation rs3184504 in *SH2B3*. Furthermore, GO pathway analysis suggested that these genes are enriched in antigen processing and presentation, response to interferon-gamma, and immune response-regulating signaling pathways.

HLA is known to be the most significant genetic factor associated with AIH onset. Associations of HLA alleles with disease predisposition, clinical phenotype, response to therapy, and outcome have been extensively studied [1]. Our study further confirmed the significance of the *HLA* gene in the pathogenesis of AIH. Strong evidence suggests that 5 variants (DRB1*0301, rs2187668, DQB1*0201, DRB1*0405, DRB3*010) are associated with AIH at a genome-wide significance level, of which DRB1*0301 and DRB3*0101 are novel. In this gene locus, DRB1*0301 was the most studied variant, and this novel allele was found to be associated with a 3.023-fold risk of AIH. However, DRB1*0301 has been identified as a protective genetic locus for primary sclerosing cholangitis and primary biliary cholangitis [19]. Another novel variant, DRB3*0101, which encodes the serologically defined DR52a antigen, was more strongly associated with AIH than the DRB1*0301 allele. Doherty *et al.* reported that susceptibility associated with DRB3*0101 had a dose-related effect [20]. In addition, the *HLA* has been reported to be associated with many autoimmune diseases, such as primary biliary cholangitis [21], rheumatoid arthritis [22], multiple sclerosis [23], and autoimmune neurological syndromes [24].

AIH also has non-HLA genetic associations, but ORs for the risk of AIH are significantly lower than those for HLA alleles. In the current study, rs3184504 in *SH2B3* was found to be associated with a higher risk of AIH with strong cumulative evidence. This SNP was also identified as a risk factor for other autoimmune diseases, including primary sclerosing cholangitis [25], rheumatoid arthritis, or

celiac disease [26] [27]. This encodes a missense variant in exon 3 of the *SH2B3* gene, which is situated in the 12q24 region. It was the first reported genetic AIH locus outside the *HLA* [28]. The risk allele A of rs3184504 leads to the substitution of the basic polar arginine with the nonpolar tryptophan at position 262 (R262W) in the pleckstrin homology domain of the *SH2B3* protein [28]. Expression quantitative trait locus (eQTL) analyses suggest that the A allele of rs3184504 is associated with higher expression levels of several genes involved in interferon-γ production, indicating that the risk allele leads to an increased adaptive immune response. Conversely, the protective allele C of rs3184504 is associated with higher expression of genes involved in toll-like receptor signaling [29].

Furthermore, the GO pathway analysis suggested that these susceptibility genes are enriched in antigen processing and presentation, response to interferon-gamma, and immune response-regulating signaling pathways. The pathogenesis of AIH is not fully understood. Dysfunctional genetic variants or deficient levels of gene products may disrupt immune homeostasis, thereby affecting the proliferation and survival of autoreactive T and B cells, regulating cytokine production, and modulating inflammatory and immune responses [30].

Several limitations should be considered. Firstly, in addition to HLA alleles, haplotypes also influence susceptibility to AIH, which we did not consider in our analysis. Secondly, the functional SNP rs3184504 was found to be associated with AIH in two independent datasets, but we were unable to perform a sensitivity analysis. Therefore, the results may be unstable and warrant further investigation. Thirdly, although strong evidence suggested that 10 variants were associated with AIH, whether they are causal variants needs to be further determined. Finally, we found large heterogeneity in 27 (36.0%) associations, and the results should be interpreted with caution.

In summary, this study systematically evaluated published research that investigated the relationships between genetic variants and the risk of AIH. The study found strong evidence of an association with AIH for 10 genetic variants in 4 genes. Importantly, DRB1*0301 and DRB3*0101 are newly identified genome-wide significant loci and rs3184504 in *SH2B3* is a missense mutation. These findings could enhance the current understanding of the genetic architecture of this rare disease.

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Availability of Data and Material

All data generated or analyzed in this study are included in the submitted manuscript and its supplemental information file.

Authors' Contributions

All authors contributed significantly to this work. G.D. and Z.M. designed the research study; D.G., Y.W., and Z.M. collected the data; M.Z. and L.G. analyzed the data; D.G. wrote the first draft of the manuscript. All authors reviewed, edited, and approved the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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