Association between interleukin 12B and interleukin 23R gene polymorphisms and systemic lupus erythematosus: a meta-analysis

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Abstract
Objective: To determine whether polymorphisms of interleukin 12B (IL12B) and IL23 receptor genes (IL23R) confer susceptibility to systemic lupus erythematosus (SLE).
Methods: A meta-analysis was conducted to analyze the associations between SLE and IL12B rs3212227 and rs17860508 and IL23R rs7517847, rs10489629, rs10889677, rs1004819, rs11209026, rs11209032, rs1343151, and rs1884444 polymorphisms using allele contrast, dominant, recessive, heterozygote, and homozygote models. Ten studies involving 1989 patients with SLE and 2394 controls were considered for the meta-analysis.
Results: The meta-analysis using the homozygote model revealed that IL23R rs10889677 was significantly associated with SLE susceptibility in the overall population (AA vs. CC) (odds ratio = 0.70, 95% confidence interval = 0.50–0.98) but not in the Asian population. Other polymorphisms of IL12B and IL23R were not significantly associated with SLE protection.
Conclusions: These findings suggest that the IL23R rs10889677 polymorphism confers SLE susceptibility to individuals of certain ethnicities. (Research Registry number: 1268)
Introduction

Systemic lupus erythematosus (SLE) is a complex, polygenic autoimmune disease with an unknown underlying cause. However, genetic factors that influence type 1 immunity are thought to play a major role in the development of disease susceptibility, as evidenced by the high prevalence of SLE among twins and within families. Various genes influence the development and progression of SLE, and genetic polymorphisms are closely associated with disease susceptibility and activity.

A previous genome-wide association study determined that polymorphisms in various genes such as STAT4, PTPN22, and ITGAM are associated with SLE, and this has been confirmed by other related studies. Signal transducer and activator of transcription (STAT)4 is a T-helper 1 (Th1) transcription factor that mediates the activity of pro-inflammatory cytokines interleukin (IL)-12 and IL-23. IL-12 links innate and adaptive immunity, is involved in the differentiation of naive T cells into Th1 cells, and induces interferon (INF)-γ production. IL-23 also induces INF-γ production via Th1 cells and activates memory T cells, while promoting tissue inflammation by inducing the expansion and survival of pathogenic Th17 cells and other IL-17-producing cells. IL-12 and IL-23 levels are increased in SLE and play important roles in disease pathogenesis, where they affect the differentiation of T cells via the shared p40 subunit and transduce their effects through binding to their respective receptors. Using ustekinumab as an antibody against these cytokines was previously shown to be effective in treating SLE.

IL-12 comprises two subunits, IL-12α and IL-12β, encoded by IL12A and IL12B, respectively, that are located on chromosome 5q31–33. IL-12 exerts its biological activity through binding the IL-12 receptor (IL-12R), which also comprises two subunits, IL-12Rβ1 and IL-12Rβ2, encoded by IL12RB1 and IL12RB2, respectively. IL-12R affects IL-12-induced signaling. Of the two subsets of IL-12, IL-12B forms IL-23 with other subsets. IL-23 is structurally and functionally similar to and shares a major signaling pathway with IL-12. IL-23 activity is mediated through binding with the IL-23R complex. IL23R is located on chromosome 1p31 and its encoded protein, IL-23R, is composed of IL-23R and IL-12Rβ subunits. The development and progression of SLE are thought to be associated with IL-12, IL-12R, IL-23, and IL-23R, and their genetic polymorphisms, which may mediate disease development. Therefore, this meta-analysis investigated the associations between polymorphisms in IL12, IL23, and genes encoding their receptors with SLE susceptibility.

Materials and Methods

Search strategy

This meta-analysis was reported according to Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines.
A literature search was conducted to identify studies examining the association between \textit{IL12}, \textit{IL12R}, \textit{IL23}, and \textit{IL23R} polymorphisms and SLE using PubMed and Embase databases (up to January 2020). The following keywords and search terms were used: “interleukin-12”, “IL-12”, “interleukin-23”, “IL-23”, “polymorphism”, “variant”, “mutation”, “genotype”, “haplotype”, and “lupus”. Additional studies that were not found in PubMed or Embase were manually searched using cited references from the included studies. In error, we did not prospectively register this trial, but we have now registered it retrospectively at Research Registry: registration number 1268. Ethical approval was waived because data was derived from previously published studies.

\textbf{Inclusion and exclusion criteria}

Studies in this meta-analysis included the following: 1) case–control studies that determined the distributions of \textit{IL12}, \textit{IL12R}, \textit{IL23}, and \textit{IL23R} polymorphisms and susceptibility to SLE, and 2) detailed data reported for case and control groups, or alternatively results that could be calculated from the data provided. Studies were excluded based on the following: 1) overlapping data, 2) inability to determine the number of null and wild-type genotypes or alleles, and 3) review articles or abstract-only publications. No restrictions were placed on language, ethnicity, or geographic area.

\textbf{Data extraction}

We extracted the author, year of publication, country of residence of study participants, the number of cases and controls, Hardy–Weinberg equilibrium (HWE) \textit{p}-value, and allele and genotype frequencies of \textit{IL12}, \textit{IL12R}, \textit{IL23}, and \textit{IL23R} polymorphisms from each study. All data were carefully extracted by two authors.

\textbf{Quality assessment}

Two authors independently assessed the methodological quality of all included studies using the Newcastle–Ottawa Quality Assessment Scale (NOS), which is designed to appraise the quality of cohort studies. \textsuperscript{10} A study with a NOS score of more than 6 was considered a high-quality study. When discrepancies were found, other authors participated with a full discussion for consensus.

\textbf{Statistical analyses}

The allele-counting method\textsuperscript{11} was used to determine allele frequencies in the promoter regions of \textit{IL12}, \textit{IL12R}, \textit{IL23}, and \textit{IL23R} from two or more studies on polymorphisms at the same position. The meta-analysis was also based on allele contrast, and dominant, recessive, heterozygote, and homozygote models. The heterogeneity of the included studies was estimated using Cochran’s Q test and \( I^2 \) statistics. When Q test findings were statistically significant (\( p < 0.05 \) or \( I^2 > 50\% \)), the random effects model was used; otherwise, the fixed effects model was used.\textsuperscript{12} Subgroup analysis according to White or Asian ethnicity was performed to explore potential sources of heterogeneity. Asian is the most common population worldwide and is mainly scattered throughout Southeast Asia, East Asia, and South America.\textsuperscript{13,14} The White population originated from Europe, Western Asia, and South Asia. Forest plots were generated to visualize the overall effects, and funnel plots were generated and visually inspected for asymmetry to determine if there was any publication bias. The meta-analysis was performed using Cochrane Collaboration RevMan 5.3 software (The Cochrane
Collaboration, Copenhagen, Denmark). The HWE \( p \)-value was estimated using Pearson’s chi-square test. The odds ratio (OR) and 95% confidence interval (CI) were used to determine whether there was any evidence of an association between the respective polymorphisms and SLE susceptibility.

**Trial sequential analysis**

Trial sequential analysis (TSA) for significant single nucleotide polymorphisms (SNPs) was conducted based on previous guidelines\(^{15}\) using TSA software version 0.9.5.10 Beta. The required sample size was calculated and constructed with a significance of 5% for type I error and 30% significance for type II error, and was within TSA monitoring boundaries.\(^{16}\)

**Results**

**Selection and characteristics of studies**

A flow chart of the study selection process is shown in Figure 1. Ten studies met the

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**Figure 1.** Flow chart of the study selection procedure.
inclusion criteria, including more than two on the same locus polymorphism, and these were limited to promoter regions associated with \textit{IL12B} and \textit{IL23R}. Four studies on \textit{IL12B} (including 728 patients with SLE and 846 controls combined) and six studies on \textit{IL23} (including 1261 patients with SLE and 1548 controls combined) were included in the meta-analysis. Three studies each on the rs3212227 and rs17860508 polymorphisms of \textit{IL12B} were included, together with four on rs7517847, three on rs10489629 and rs10889677, and two on rs1004819, rs11209026, rs11209032, rs1343151, and rs1884444 polymorphisms of \textit{IL23R}. Details of the \textit{IL12B} and \textit{IL23R} polymorphism studies are summarized in Table 1. According to our NOS quality check, all these studies exhibited a high methodological quality because the mean score was 7.4.

\textbf{Association between IL12B polymorphisms and SLE}

The rs3212227 and rs17860508 polymorphisms were not found to be significantly associated with SLE using allele contrast and all genotype models (Table 2). All included studies on rs17860508 were conducted in White subjects; however, the studies on rs3212227 included two White and one Asian subject. Subgroup analysis of rs3212227 was conducted for the White populations and no significant association was found with SLE susceptibility (Table 2).

\textbf{Association between IL23R polymorphisms and SLE}

Of the eight promoter region polymorphisms of \textit{IL23R} included in the meta-analysis, seven (rs7517847, rs10489629, rs1004819, rs11209026, rs11209032, rs1343151, and rs1884444) were not significantly associated with SLE susceptibility using allele contrast and all genotype models (Table 3). In the homozygote model of rs10889677, the AA genotype was significantly associated with low SLE susceptibility \((p=0.04;\) Figure 2). However, allele contrast and other genotype models were not significantly associated with SLE susceptibility. Three of the four studies on rs7517847 were conducted on White populations, and two of the three studies on rs10889677 were conducted on Asian populations. Subgroup analyses revealed no significant associations between the polymorphisms and SLE susceptibility (Table 3).

\textbf{Heterogeneity and publication bias}

In some analyses of \textit{IL12B} rs3212227 and rs17860508, and of \textit{IL23R} rs7517847, rs10489629, rs11209032, and rs1343151, heterogeneity existed between studies, and the random effects model was used. In the analysis of \textit{IL23R} rs10889677, the fixed effects model was used in all genetic models for the overall population. Because our analysis included up to four studies per locus, the tests for investigating funnel plot asymmetry, which are typically performed when at least five studies are included in the meta-analysis\cite{note1}, were not carried out because they would be unable to differentiate asymmetry from chance.

\textbf{TSA of significant SNPs}

In the homozygote model of rs10889677, the required sample size is 820 samples, and the cumulative z-curve crossed the trial sequential monitoring boundary before reaching the required sample size, suggesting that our conclusions are robust with sufficient evidence.

\textbf{Discussion}

In this meta-analysis, we addressed the association between \textit{IL12B} and \textit{IL23R} polymorphisms and SLE susceptibility.
We found no associations between \textit{IL12B} polymorphisms (rs3212227, rs17860508, and rs17860508) and SLE. However, among \textit{IL23R} polymorphisms (rs7517847, rs10489629, rs1004819, rs11209026, rs11209032, rs1343151, and rs1884444), the homozygote model of rs10889677 was significantly associated with SLE susceptibility.
the overall population but not in the Asian population. Other polymorphisms of IL23R were not significantly associated with SLE susceptibility.

IL-12B is a Th1 cell cytokine whose gene expression is increased in patients with SLE.\textsuperscript{18} IL12B encodes the common subunit (p40) of both IL-12 and IL-23, and its polymorphisms modulate the secretion and activity of IL-12.\textsuperscript{19} IL-12p40 levels are elevated in the presence of disease, and IL-12 plus free p40/IL-12 ratios correlate with disease severity.\textsuperscript{20} The rs3212227 polymorphism was shown to be associated with psoriatic arthritis and Behçet’s disease in meta-analyses,\textsuperscript{21,22} while previous studies reported associations between the rs17860508 polymorphism with rheumatoid arthritis and ankylosing spondylitis.\textsuperscript{23,24} However, the current meta-analysis found

### Table 2. Association between IL12B polymorphisms and SLE. (a) Overall and (b) White.

| Test of association | Test of heterogeneity |
|---------------------|-----------------------|
| OR | 95% CI | P-value | Model | P-value | I² (%) |
| (a) rs3212227 | | | | | |
| C vs. A | 0.97 | 0.79–1.20 | 0.80 | F | 0.31 | 14 |
| Dominant model | 1.35 | 0.46–3.99 | 0.59 | R | 0.09 | 59 |
| Recessive model | 1.10 | 0.84–1.44 | 0.49 | F | 0.21 | 37 |
| AC vs. AA | 0.87 | 0.65–1.15 | 0.33 | F | 0.19 | 39 |
| AC vs. CC | 0.70 | 0.42–1.17 | 0.18 | F | 0.71 | 0 |
| CC vs. AA | 1.01 | 0.62–1.67 | 0.96 | F | 0.26 | 26 |
| rs17860508 | | | | | |
| 2 vs. 1 | 1.11 | 0.56–2.20 | 0.77 | R | <0.00001 | 92 |
| Dominant model | 0.68 | 0.39–1.18 | 0.18 | R | 0.08 | 60 |
| Recessive model | 1.00 | 0.35–2.84 | 0.99 | R | <0.00001 | 92 |
| 12 vs. 11 | 0.84 | 0.30–2.35 | 0.75 | R | <0.00001 | 90 |
| 12 vs. 22 | 0.78 | 0.55–1.12 | 0.19 | F | 0.22 | 35 |
| 22 vs. 11 | 0.70 | 0.22–2.26 | 0.55 | R | <0.00001 | 91 |
| (b) rs3212227 | | | | | |
| C vs. A | 1.10 | 0.84–1.44 | 0.48 | F | 0.83 | 0 |
| Dominant model | 3.35 | 0.11–106.55 | 0.49 | R | 0.02 | 81 |
| Recessive model | 0.94 | 0.68–1.29 | 0.70 | F | 0.99 | 0 |
| AC vs. AA | 1.01 | 0.73–1.42 | 0.93 | F | 0.19 | 0 |
| AC vs. CC | 0.65 | 0.29–1.44 | 0.28 | F | 0.44 | 0 |
| CC vs. AA | 1.58 | 0.72–3.47 | 0.25 | F | 0.48 | 0 |

OR: odds ratio; CI: confidence interval; R: random effects model; F: fixed effects model; NA: not applicable; IL12B, interleukin 12B; SLE, systemic lupus erythematosus.
Table 3. Association between IL23R polymorphisms and SLE. (a) Overall, (b) White, and (c) Asian.

| Polymorphism | Test of association | Test of heterogeneity |
|--------------|---------------------|-----------------------|
|              | OR 95% CI           | P-value               | Model | P-value | I² (%) |
| rs7517847    |                     |                       |       |         |        |
| G vs. T      | 0.97 0.75–1.26      | 0.83 R                | F      | 0.45    | 65     |
| Dominant model | 0.82 0.63–1.05   | 0.12 F                | F      | 0.43    | 0      |
| Recessive model | 1.15 0.80–1.65  | 0.46 R                | R      | 0.08    | 55     |
| TG vs. TT    | 0.83 0.58–1.19      | 0.31 R                | R      | 0.05    | 62     |
| TG vs. GG    | 0.79 0.60–1.03      | 0.08 F                | F      | 0.39    | 0      |
| GG vs. TT    | 1.15 0.86–1.54      | 0.33 F                | F      | 0.45    | 0      |
| rs10489629   |                     |                       |       |         |        |
| A vs. G      | 1.11 0.93–1.31      | 0.24 F                | F      | 0.19    | 39     |
| Dominant model | 0.82 0.62–1.09   | 0.17 F                | F      | 0.23    | 32     |
| Recessive model | 1.12 0.79–1.58  | 0.52 R                | R      | 0.07    | 57     |
| GA vs. GG    | 1.03 0.78–1.37      | 0.81 F                | F      | 0.64    | 0      |
| GA vs. AA    | 0.83 0.61–1.12      | 0.23 F                | F      | 0.33    | 10     |
| AA vs. GG    | 1.22 0.87–1.73      | 0.25 F                | F      | 0.17    | 44     |
| rs10889677   |                     |                       |       |         |        |
| A vs. C      | 0.88 0.76–1.01      | 0.07 F                | F      | 0.73    | 0      |
| Dominant model | 1.20 0.98–1.47   | 0.08 F                | F      | 0.15    | 47     |
| Recessive model | 1.14 0.88–1.47  | 0.31 F                | F      | 0.37    | 0      |
| CA vs. CC    | 0.96 0.73–1.25      | 0.76 F                | F      | 0.16    | 45     |
| CA vs. AA    | 1.14 0.74–1.74      | 0.55 R                | R      | 0.06    | 65     |
| AA vs. CC    | 0.70 0.50–0.98      | **0.04** F            | F      | 0.67    | 0      |
| rs1004819    |                     |                       |       |         |        |
| A vs. G      | 0.94 0.79–1.13      | 0.51 F                | F      | 0.18    | 44     |
| Dominant model | 1.27 0.84–1.91   | 0.25 F                | F      | 0.22    | 33     |
| Recessive model | 1.02 0.81–1.29  | 0.84 F                | F      | 0.30    | 8      |
| GA vs. GG    | 1.02 0.80–1.30      | 0.87 F                | F      | 0.48    | 0      |
| GA vs. AA    | 1.29 0.84–1.98      | 0.25 F                | F      | 0.34    | 0      |
| AA vs. GG    | 0.80 0.52–1.22      | 0.29 F                | F      | 0.17    | 46     |
| rs11209026   |                     |                       |       |         |        |
| A vs. G      | 0.97 0.61–1.55      | 0.91 F                | F      | 0.62    | 0      |
| Dominant model | 0.36 0.04–3.51   | 0.38 F                | F      | 0.78    | 0      |
| Recessive model | 1.09 0.67–1.77  | 0.73 F                | F      | 0.81    | 0      |
| GA vs. GG    | 0.87 0.53–1.41      | 0.57 F                | F      | 0.96    | 0      |
| GA vs. AA    | 0.33 0.03–3.45      | 0.35 F                | F      | 0.79    | 0      |
| AA vs. GG    | 2.73 0.28–26.41     | 0.39 F                | F      | 0.78    | 0      |
| rs11209032   |                     |                       |       |         |        |
| A vs. G      | 1.01 0.85–1.20      | 0.89 F                | F      | 0.10    | 64     |
| Dominant model | 1.16 0.80–1.70   | 0.43 F                | F      | 0.13    | 56     |
| Recessive model | 0.92 0.73–1.17  | 0.50 F                | F      | 0.19    | 41     |
| GA vs. GG    | 1.45 0.73–2.87      | 0.29 R                | R      | 0.004   | 88     |
| GA vs. AA    | 1.23 0.82–1.83      | 0.32 F                | F      | 0.22    | 33     |
| AA vs. GG    | 0.91 0.45–1.83      | 0.79 R                | R      | 0.09    | 66     |
| rs1343151    |                     |                       |       |         |        |
| A vs. G      | 0.88 0.44–1.78      | 0.73 R                | R      | 0.02    | 80     |
| Dominant model | 1.00 0.63–1.57   | 0.99 F                | F      | 0.37    | 0      |

(continued)
Table 3. Continued.

| Test of association | Test of heterogeneity |
|---------------------|-----------------------|
| OR                  | 95% CI                | P-value | Model | P-value | I² (%) |
|---------------------|-----------------------|
| Recessive model     | 1.10                  | 0.42–2.90 | 0.84   | R       | 0.01   | 84     |
| GA vs. GG           | 0.94                  | 0.36–2.42 | 0.90   | R       | 0.02   | 82     |
| GA vs. AA           | 1.11                  | 0.69–1.80 | 0.66   | F       | 0.78   | 0      |
| AA vs. GG           | 1.18                  | 0.72–1.93 | 0.52   | F       | 0.18   | 45     |
| rs1884444 G vs. T   | 1.06                  | 0.90–1.24 | 0.48   | F       | 0.94   | 0      |
| Dominant model      | 0.97                  | 0.71–1.32 | 0.83   | F       | 0.56   | 0      |
| Recessive model     | 0.91                  | 0.74–1.14 | 0.41   | F       | 0.50   | 0      |
| TG vs. TT           | 1.10                  | 0.87–1.38 | 0.43   | F       | 0.42   | 0      |
| TG vs. GG           | 1.00                  | 0.72–1.40 | 0.98   | F       | 0.41   | 0      |
| GG vs. TT           | 1.08                  | 0.77–1.51 | 0.65   | F       | 0.83   | 0      |
| rs7517847 G vs. T   | 0.90                  | 0.62–1.31 | 0.59   | R       | 0.02   | 75     |
| Dominant model      | 0.83                  | 0.62–1.10 | 0.19   | F       | 0.25   | 27     |
| Recessive model     | 1.23                  | 0.74–2.05 | 0.42   | R       | 0.02   | 74     |
| TG vs. TT           | 0.80                  | 0.49–1.30 | 0.36   | R       | 0.04   | 70     |
| TG vs. GG           | 0.80                  | 0.59–1.08 | 0.15   | F       | 0.23   | 33     |
| GG vs. TT           | 1.14                  | 0.82–1.59 | 0.43   | F       | 0.26   | 25     |

OR: odds ratio; CI: confidence interval; R: random effects model; F: fixed effects model; NA: not applicable.

(b) rs10889677

| Study or Subgroup | SLE | Control | Odds Ratio | 95% CI |
|-------------------|-----|---------|------------|--------|
| Chen et al.       | 262 | 309     | 1.07       | 0.72–1.59 |
| Li et al.         | 84  | 96      | 1.28       | 0.86–1.90 |
| Sanchez et al.    | 17  | 129     | 0.68       | 0.27–1.74 |
| Total             | 383 | 430     | 1.14       | 0.74–1.11 |

Total events: 534

Heterogeneity: Chi² = 0.81, df = 2 (P = 0.67), I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)

Figure 2. Odds ratios and 95% confidence intervals of individual studies and pooled data for the association between the homozygote model of IL23R rs10889677 and SLE in all study subjects. IL23R, interleukin 23 receptor; SLE, systemic lupus erythematosus.
that these two polymorphisms were not significantly associated with SLE susceptibility.

The receptor for IL-23 is mainly expressed on subsets of T cells and some lymphoid cells. IL-23R is associated with various functional proteins, such as IL-23A, IL-12RB1, STAT4, Janus kinase 2, and tyrosine kinase 2, and contributes to inflammatory processes. Additionally, IL-23R receptor antagonists have been used as targets for several diseases. Most polymorphisms in \emph{IL23R} are located in non-coding regions but still exhibit phenotypic consequences by altering mRNA splicing, affecting transcription, and reducing IL23R activity. They also affect serum cytokine concentrations and subsequently impact on dependent cytokines.

The rs10889677 polymorphism located in the 3' untranslated region of \emph{IL23R} results in the overexpression of IL-23R and affects the differentiation of CD4+ T cells into the Th17 subpopulation. Previous meta-analyses showed that rs10889677 increased the risk of inflammatory bowel disease, while the current meta-analysis found that it was significantly associated with SLE susceptibility in the homozygote model where the GG genotype increased the risk of SLE. However, polymorphisms of \emph{IL23R} at other positions (rs7517847, rs10489629, rs1004819, rs11209026, rs11209032, rs1343151, and rs1884444) were not significantly associated with SLE. Moreover, in the subgroup analysis of the Asian population, rs10889677 was not significantly associated with SLE, so further studies should be conducted of various ethnic populations, including White, to clarify the association. Because genetic polymorphisms in SLE can differ across ethnicities, and the 95% CI in this study is close to 1, it cannot be determined whether the homozygote model of rs108896677 is significantly associated with SLE susceptibility.

To the best of our knowledge, this is the first meta-analysis investigating the relationship between polymorphisms of \emph{IL12B} and \emph{IL23R} and SLE susceptibility. Although all studies included in the meta-analysis were in HWE, the results should be interpreted with caution because of the limited number of studies, which also restricted further subgroup analyses. Furthermore, as with any meta-analysis, ours has some limitations such as the presence of significant heterogeneity in some comparisons. Second, because SLE is a heterogeneous disease with various clinical features and as disease progression and individual symptoms were not analyzed in this study, it is possible that \emph{IL12B} and \emph{IL23R} polymorphisms may be associated with disease severity as well as susceptibility.

In conclusion, this meta-analysis detected no significant association between most \emph{IL12B} and \emph{IL23R} polymorphisms and SLE susceptibility, with the exception of \emph{IL23R} rs10889677. Although the GG genotype of \emph{IL23R} rs10889677 was associated with SLE in the overall population, no association was observed in the Asian population. Therefore, further studies including White populations are warranted. Because of the heterogeneity of SLE, large-scale studies assessing clinical features of SLE in individuals of various ethnicities are required.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Funding**

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Medical Research Promotion Program through Gangneung Asan Hospital funded by the Asan Foundation (grant number 20201B006).
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