

Association Between the IL6 -174G/C Polymorphism and the Risk of Necrotizing Enterocolitis in Preterm Infants

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) is one of the most serious gastrointestinal disorders affecting preterm infants and remains an important cause of neonatal morbidity and mortality. In addition to established clinical and environmental risk factors, genetic variation in inflammatory pathways may contribute to individual susceptibility to NEC. Interleukin-6 (IL-6) is a key proinflammatory cytokine involved in the regulation of inflammatory responses and has been implicated in the pathophysiology of NEC. Genetic variation in the IL6 promoter may contribute to interindividual differences in inflammatory responses.

Objective: To investigate the association between the IL6 -174G/C polymorphism (rs1800795) and the risk of necrotizing enterocolitis in preterm infants.

Methods: This comparative molecular genetic study included 157 newborns, comprising 85 preterm infants with NEC and 72 preterm infants without NEC who constituted the control group. The mean gestational age was 31.3 ± 2.0 weeks in the NEC group and 31.6 ± 1.8 weeks in the control group. The groups were comparable with respect to gestational age, birth weight, and sex distribution. The IL6 -174G/C polymorphism was analyzed using polymerase chain reaction followed by restriction fragment analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess associations between alleles and genotypes and NEC risk. Hardy-Weinberg equilibrium was assessed in the control group.

Results: The G allele was associated with higher odds of NEC compared with the C allele (OR, 2.276; 95% CI, 1.392–3.721; $P < .001$). The GG genotype was associated with higher odds of NEC compared with the combined CC+CG genotypes (OR, 2.381; 95% CI, 1.251–4.532; $P = .008$). In contrast, the CC genotype was associated with lower odds of NEC compared with the combined CG+GG genotypes (OR, 0.183; 95% CI, 0.049–0.677; $P = .005$). The CG genotype was not significantly associated with NEC compared with the combined CC+GG

genotypes (OR, 0.714; 95% CI, 0.377–1.351; $P = .299$). The significant associations remained after Bonferroni correction.

In the control group ($n = 72$), the observed genotype distribution was CC, 12 (16.67%); CG, 33 (45.83%); and GG, 27 (37.50%). The genotype distribution did not significantly deviate from Hardy-Weinberg equilibrium ($\chi^2 = 0.125$, $P = .723$).

Conclusions: The IL6 -174G/C polymorphism was significantly associated with NEC susceptibility in this cohort of preterm infants. The G allele and GG genotype were associated with higher odds of NEC, whereas the C allele and CC genotype were associated with lower odds. These findings suggest that IL6 -174G/C may represent a potential genetic marker for NEC risk stratification. Larger multicenter studies and functional investigations are required to validate these findings and clarify their biological significance.

Keywords: Necrotizing Enterocolitis, Interleukin-6, IL6 -174G/C, rs1800795, Genetic Polymorphism, Preterm Infants, Genetic Susceptibility

OBJECTIVE

The objective of this study was to investigate the association between the IL6 -174G/C polymorphism (rs1800795) and the risk of necrotizing enterocolitis in preterm infants.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a severe inflammatory gastrointestinal disease that predominantly affects preterm infants and remains an important cause of morbidity and mortality in neonatal intensive care. Survivors may develop substantial long-term complications, including intestinal failure, feeding difficulties, and adverse neurodevelopmental outcomes [1].

The pathogenesis of NEC is multifactorial and involves interactions among intestinal immaturity, impaired epithelial barrier function, abnormal microbial colonization, dysregulated innate immune responses, and excessive inflammatory signaling. Cytokines are important mediators of this process. In particular, interleukin-6 (IL-6) has been investigated as both a marker and mediator of intestinal inflammation in NEC.

Maheshwari et al. [2] demonstrated alterations in inflammatory cytokines, including IL-6, in extremely low-birth-weight infants with NEC, supporting the involvement of inflammatory

pathways in disease development.

Genetic variation in inflammatory pathways may contribute to differences in individual susceptibility to NEC [3]. Previous studies have identified associations between polymorphisms in genes involved in innate immunity and inflammatory signaling and the development or severity of NEC. However, genetic studies of NEC remain relatively limited, and the results have not always been consistent across populations [4-6].

The IL6 -174G/C polymorphism (rs1800795) is located in the promoter region of the IL6 gene. Fishman et al. [7] demonstrated that genetic variation in the IL6 promoter can influence IL-6 transcription and plasma IL-6 concentrations, providing a biological rationale for investigation of this polymorphism in inflammatory diseases.

The distribution and clinical significance of IL6 -174G/C vary among populations. Meta-analytic studies have reported associations between this polymorphism and susceptibility to several inflammatory diseases, although considerable population-specific heterogeneity has been observed.

Evidence directly linking IL6 -174G/C to NEC remains limited. Franklin et al. [4] investigated immune-modulating single-nucleotide polymorphisms in neonates and reported an association between IL6 rs1800795 and NEC among Caucasian preterm infants [8-10]. Their findings provide an important rationale for further investigation of this polymorphism in independent populations.

Because NEC is a multifactorial disease, identification of a genetic association should not be interpreted as evidence of a single causal mechanism. Rather, genetic variants may contribute to a complex network of susceptibility factors that also includes gestational age, birth weight, feeding practices, microbial exposure, and other clinical and perinatal characteristics.

MATERIALS AND METHODS

Study Population

This comparative molecular genetic study included 157 newborns. The main group consisted of 85 preterm infants with a confirmed diagnosis of NEC, whereas the control group included 72 preterm infants without NEC.

The mean gestational age was 31.3 ± 2.0 weeks in the NEC group and 31.6 ± 1.8 weeks in the control group. No statistically significant difference in gestational age was

observed between the groups ($P > .05$). Birth weight and sex distribution were also comparable between the groups.

The diagnosis of NEC was established on the basis of clinical, laboratory, and instrumental findings according to accepted diagnostic criteria. Disease severity was assessed using the Bell classification as modified by Walsh and Kliegman.

Infants with congenital gastrointestinal malformations, chromosomal abnormalities, primary immunodeficiency, or severe concomitant disorders that could substantially affect the inflammatory response were excluded.

Molecular Genetic Analysis

Venous blood samples were used for molecular genetic analysis. Genomic DNA was isolated using standard commercial reagent kits.

The IL6 -174G/C polymorphism (rs1800795) was analyzed using polymerase chain reaction followed by restriction fragment analysis. Genotyping quality control included repeat analysis of randomly selected samples.

Statistical Analysis

Allele and genotype frequencies were compared between the NEC and control groups.

For allele-based analysis, the G allele was compared with the C allele.

For genotype-based analysis, specific genetic models were used. The GG genotype was compared with the combined CC+CG genotypes, representing a recessive model for the G allele. The CC genotype was compared with the combined CG+GG genotypes, representing a recessive model for the C allele. The CG genotype was compared with the combined CC+GG genotypes, representing an overdominant genotype comparison.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using 2×2 contingency tables.

Differences in allele and genotype frequencies were assessed using the chi-square test or Fisher exact test, as appropriate. Hardy-Weinberg equilibrium was assessed in the control group.

Statistical significance was defined as $P < .05$. Because multiple comparisons were performed, the Bonferroni correction was applied to reduce the risk of type I error.

All statistical analyses were performed using SPSS version 23.0.

RESULTS

Distribution of IL6 -174G/C Alleles and Genotypes

The distribution of IL6 -174G/C alleles and genotypes differed between preterm infants with NEC and preterm infants without NEC.

The G allele was more frequent among infants with NEC than among controls and was associated with higher odds of NEC compared with the C allele (OR, 2.276; 95% CI, 1.392–3.721; $P < .001$).

Conversely, the C allele was associated with lower odds of NEC compared with the G allele (OR, 0.439; 95% CI, 0.269–0.718; $P = .001$).

At the genotype level, the GG genotype was associated with higher odds of NEC compared with the combined CC+CG genotypes (OR, 2.381; 95% CI, 1.251–4.532; $P = .008$).

The CC genotype was associated with lower odds of NEC compared with the combined CG+GG genotypes (OR, 0.183; 95% CI, 0.049–0.677; $P = .005$).

The CG genotype was not significantly associated with NEC compared with the combined CC+GG genotypes (OR, 0.714; 95% CI, 0.377–1.351; $P = .299$).

After Bonferroni correction, the associations involving the G allele, C allele, GG genotype, and CC genotype remained statistically significant.

The genotype distribution in the control group was consistent with Hardy-Weinberg equilibrium ($\chi^2 = 0.125$, $df = 1$, $P = .723$), indicating no statistically significant deviation from the expected genotype proportions.

DISCUSSION

The present study demonstrated a significant association between the IL6 -174G/C polymorphism and susceptibility to NEC in preterm infants. The G allele was associated with higher odds of NEC compared with the C allele. At the genotype level, the GG genotype was associated with higher odds of NEC compared with the combined CC+CG genotypes, whereas the CC genotype was associated with lower odds compared with the combined CG+GG genotypes.

These findings support the hypothesis that genetic variation in inflammatory pathways may contribute to interindividual differences in susceptibility to NEC.

The biological plausibility of an association between IL6 genetic variation and NEC is supported by the established involvement of inflammatory cytokines in the pathogenesis of NEC. Prematurity is accompanied by immature intestinal barrier function and dysregulated innate immune responses. Activation of inflammatory signaling can lead to excessive production of cytokines and amplification of intestinal injury.

IL-6 is an important mediator of the inflammatory response. Increased IL-6 concentrations have been reported in infants with NEC, suggesting that IL-6-related signaling may contribute to the inflammatory cascade associated with intestinal injury.

The IL6 -174G/C polymorphism is located in the promoter region of the gene. Fishman et al. [7] demonstrated that polymorphic variation within the IL6 promoter can influence IL-6 transcription and plasma IL-6 concentrations. This provides a biological rationale for investigating rs1800795 in inflammatory disorders.

However, the functional significance of the -174G/C polymorphism is not completely consistent across different populations and experimental systems. Therefore, the association identified in the present study should not be interpreted as direct evidence that the G allele or GG genotype necessarily results in increased IL-6 production in every individual.

Our findings are particularly relevant in comparison with the study by Franklin et al. [4], which investigated immune-modulating single-nucleotide polymorphisms in neonates and reported an association between IL6 rs1800795 and NEC among Caucasian preterm infants. Their study provides independent evidence supporting a possible role of this polymorphism in NEC susceptibility.

Although the direction of association is consistent with the findings of Franklin et al. [4], differences in effect estimates between studies may be explained by differences in population genetic background, allele frequencies, clinical characteristics, sample size, environmental exposures, and statistical models.

Previous genetic studies of NEC have also demonstrated that the disease is likely influenced by multiple interacting genetic and environmental factors. Consequently, the clinical significance of a single polymorphism should be evaluated

within the context of a broader risk profile.

The association observed in the present study may have potential implications for future risk-stratification models. However, IL6 -174G/C alone is unlikely to provide sufficient predictive accuracy for a multifactorial disease such as NEC. A clinically useful predictive model would likely require integration of genetic markers with established clinical and perinatal risk factors.

An important strength of the present study is the use of preterm infants without NEC as the control group. This approach allows the genetic association to be evaluated within a population that shares prematurity as an important baseline risk factor.

Another strength is the direct evaluation of a polymorphism previously implicated in inflammatory regulation and previously investigated in relation to NEC.

Nevertheless, several limitations should be considered. First, the sample size was relatively small, with 85 infants in the NEC group and 72 controls. Second, the study was conducted in a single population, which may limit generalizability. Third, only one IL6 polymorphism was evaluated. Finally, circulating IL-6 concentrations were not measured, and therefore the functional relationship between genotype and cytokine expression could not be directly assessed.

Further studies involving larger multicenter cohorts and ethnically diverse populations are required to validate the observed association. Functional studies combining genotyping with IL-6 expression or circulating cytokine measurements may also help clarify the biological mechanisms underlying the association.

Strengths and Limitations

The principal strength of this study is the investigation of a biologically plausible inflammatory genetic marker in a defined cohort comprising preterm infants with NEC and preterm infants without NEC.

The main limitations include the relatively small sample size, single-center design, absence of functional measurements of IL-6, and the use of term infants as controls for preterm NEC cases. The difference in gestational maturity may introduce confounding and should be considered when interpreting the association. In addition, the study evaluated only one genetic polymorphism and therefore cannot account for the full complexity of genetic susceptibility to NEC.

These limitations should be considered when interpreting the findings, and independent replication in larger cohorts is necessary.

CONCLUSIONS

The IL6 -174G/C polymorphism (rs1800795) was significantly associated with susceptibility to necrotizing enterocolitis in the studied cohort.

The G allele was associated with higher odds of NEC, whereas the C allele was associated with lower odds. The GG genotype was associated with higher odds of NEC compared with the combined CC+CG genotypes, while the CC genotype was

associated with lower odds compared with the combined CG+GG genotypes. The CG genotype was not significantly associated with NEC.

These findings indicate that IL6 -174G/C may represent a potential genetic marker for NEC risk stratification. However, the findings do not establish a causal relationship between the polymorphism and NEC.

Future multicenter studies with larger sample sizes, diverse populations, functional cytokine measurements, and analysis of additional genetic and clinical determinants are needed to determine whether IL6 -174G/C can be incorporated into clinically useful predictive models for NEC.

Table 1. Distribution of IL6 -174G/C Alleles and Genotypes in Newborns with NEC and Controls

Genetic variant	NEC group, n (%)	Control group, n (%)	Comparison/model	OR (95% CI)	P value
C allele	38 (22.35)	57 (39.58)	C vs G	0.439 (0.269–0.718)	.001
G allele	132 (77.65)	87 (60.42)	G vs C	2.276 (1.392–3.721)	<.001
CC genotype	3 (3.53)	12 (16.67)	CC vs CG+GG	0.183 (0.049–0.677)	.005
CG genotype	32 (37.65)	33 (45.83)	CG vs CC+GG	0.714 (0.377–1.351)	.299
GG genotype	50 (58.82)	27 (37.50)	GG vs CC+CG	2.381 (1.251–4.532)	.008

Abbreviations: CI: Confidence Interval; NEC: Necrotizing Entero Colitis; OR: Odds Ratio.
Note: For allele analysis, the G allele was compared with the C allele. For genotype analysis, GG was compared with CC+CG, CC was compared with CG+GG, and CG was compared with CC+GG. Hardy-Weinberg equilibrium in the control group: CC = 12 (16.67%), CG = 33 (45.83%), GG = 27 (37.50%); $\chi^2 = 0.125$, $P = .723$.

STATEMENTS

Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the appropriate institutional ethics committee. Written informed consent was obtained from the parents or legal representatives of participating infants.

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Conflict of Interest

The authors declare no conflicts of interest related to this study.

Author Contributions

All authors contributed to the study conception and design, data collection and analysis, interpretation of the results, and preparation and revision of the manuscript. All authors approved the final version of the manuscript.

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