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Association of High-Mobility Group Box 1 (HMGB1) Gene Polymorphisms with Susceptibility and Better Survival Prognosis in Chinese Han Neonatal Necrotizing Enterocolitis

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Statistical Analysis C
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Background: High-mobility group box 1 (HMGB1) plays a crucial role in a variety of diseases, including neonatal necrotizing enterocolitis (NEC). The purpose of this study was to investigate the association of *HMGB1* gene single-nucleotide polymorphisms (SNPs) with susceptibility and survival prognosis in Chinese Han neonates with NEC.

Material/Methods: The *HMGB1* gene rs1360485, rs1045411, and rs2249825 site SNPs were genotyped in all participants. The mRNA expression of serum *HMGB1* was examined using quantitative reverse transcription-polymerase chain reaction. The correlation of the *HMGB1* rs1360485 SNP with NEC neonatal survival prognosis was evaluated by univariate analysis and logistic multivariate regression analysis.

Results: The TC and CC genotype and C allele distribution frequencies of the rs1360485 SNP were lower in the NEC group, and the differences were statistically significant (all $P<0.05$). Individuals carrying the TC and CC genotype or C allele had a low risk of being affected by NEC. However, the genotype and allele distributions of rs1045411 and rs2249825 were not significantly different between the patient and control groups ($P>0.05$). NEC neonates with *HMGB1* gene rs1360485 site mutations had lower mRNA levels of serum *HMGB1* than those with rs1360485 site wild-type, and the rs1360485 genotypes TC and CC could independently predict better survival outcomes in NEC neonates.

Conclusions: This study demonstrated that the rs1360485 SNP of the *HMGB1* gene is associated with susceptibility of NEC in neonates, and the rs1360485 genotypes TC and CC may affect *HMGB1* expression and are associated with the survival prognosis of neonates with NEC.

Keywords: Disease Susceptibility • HMGB Proteins • Necrotizing Enterocolitis • Polymorphism, Single Nucleotide • Prognosis

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Background

Necrotizing enterocolitis (NEC) is a severe intestinal inflammatory disease that mainly affects preterm infants and remains a major cause of neonatal morbidity and mortality [1,2]. NEC is often associated with premature birth, ischemia, formula feeding, antibiotics, and some risk factors that predict intestinal mucosal damage or intestinal abnormalities [3]. However, the presence of these risk factors does not necessarily lead to an increased incidence or severity in neonates with NEC [3], since NEC occurs only in certain newborns even with exposure to similar environmental conditions or interference. Although the etiology of NEC is complex, and the exact pathogenesis of the disease remains unclear, an underlying genetic predisposition to NEC has been increasingly recognized in recent years [1,4]. Therefore, studying candidate genes associated with the development and progression of NEC may help explain the molecular mechanism of NEC.

High-mobility group box 1 (HMGB1) protein is a nuclear protein ubiquitously present in almost all cell types [5]. In addition to having intracellular functions, HMGB1 can be released extracellularly as an advanced inflammatory mediator, which can be actively secreted by activated macrophages, monocytes, and natural killer cells and passively released by necrotic cells [6,7]. It has been reported that HMGB1 could stimulate the production of pro-inflammatory cytokines, and that these cytokines are hypothetical mediators of NEC-associated intestinal inflammation [8]. Several studies have revealed that HMGB1 is significantly increased in neonates with NEC [9-11], participates in the development of NEC, and plays a crucial role in the pathological mechanism of NEC. For example, a study demonstrated that HMGB1 is upregulated in the progression of NEC, and that the inhibition of HMGB1 attenuates intestinal inflammation in NEC [12]. The increased expression of HMGB1 in the intestine plays an important role in human NEC [13]. Zamora et al found that the inhibition of HMGB1 expression can limit intestinal damage in experimental NEC [8].

There are multiple variants in *HMGB1*, and it has been shown that single-nucleotide polymorphisms (SNPs) in the *HMGB1* gene play critical roles in the pathogenesis of various diseases. For example, SNPs at the rs1045411 and rs2249825 loci of the *HMGB1* gene were related to susceptibility and prognosis in Chinese Han patients with sepsis [14]. The SNP at the rs2249825 locus of *HMGB1* has been reported to be associated with susceptibility and inflammatory response to pneumonia [15]. Lin et al revealed the relationship of rs1360485 and rs1045411 haplotypes with oral squamous cell carcinoma risk and their synergistic effect on its pathogenesis [16]. In addition, studies have shown that SNPs of the *HMGB1* gene may affect its gene expression [17,18]. Moreover, *HMGB1* is known to play a vital role in the progression of NEC. However, the relationship between *HMGB1* gene SNPs and NEC is still unknown. Consequently, this study explored the association of the *HMGB1* gene rs1045411, rs2249825, and rs1360485 SNPs with the occurrence of NEC in neonates and further evaluated the correlation of *HMGB1* gene SNPs with disease survival prognosis.

Material and Methods

Patients and Sample Collection

A total of 258 neonates who were admitted to Weifang People's Hospital from 2011 to 2018 with NEC were recruited as a case group. The inclusion criteria were (1) Han ethnicity, (2) gestational age <37 weeks, and (3) NEC was diagnosed according to the criteria originally defined by Bell et al, and subsequently modified by Walsh and Kliegman [19]. Exclusion criteria were (1) congenital intestinal malformations, (2) congenital genetic metabolic diseases, and (3) combined NEC-unrelated gastrointestinal inflammation or infectious diseases. The neonates with NEC included 154 boys and 104 girls, with a gestational age of 34.1±2.2 weeks and a birth weight of 2267±381 g. According to NEC staging criteria [20], they were divided into stage II (161 cases) and stage III (97 cases). In addition, 180 newborns matched with the NEC case group in terms of gestational age, birth weight, and sex were enrolled as a control group during the same period, and the inclusion criteria were (1) Han ethnicity, (2) gestational age <37 weeks, (3) no NEC, and (4) no severe underlying diseases. The control group consisted of 98 boys and 82 girls, with a gestational age of 34.6±2.3 weeks and a birth weight of 2332±408 g. Our study was approved by the Ethics Committee of Weifang People's Hospital (approval number: 110239), and we obtained informed consent from the guardians of the subjects for the use of serum samples and subsequent analyses. No consanguinity was found among the participants.

An amount of 2 mL of peripheral venous blood was collected from each participant and anticoagulated with 5% ethylene diamine tetra acetic acid. Genomic DNA (gDNA) was extracted with the Takara Genomic DNA extraction kit (Beijing Boiteke Corporation, Beijing, China) and then stored at -20°C for genotyping. In addition, 2-mL samples of blood from the NEC neonates and control newborns were collected without anticoagulant; the blood was separated by centrifugation to obtain the serum and stored at -80°C for further use.

Determination of SNPs

The sequences of *HMGB1* SNP sites rs1045411, rs2249825, and rs1360485 were amplified by polymerase chain reaction (PCR) using gDNA as a template. The primer fragments used for amplification were designed by Primer Premier 5.0 and synthesized by Shanghai Sangon Biotech Co., Ltd. (**Table 1**). The

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Table 1. Primer sequences of the *HMGB1* gene rs1045411, rs2249825, and rs1360485 polymorphisms.

Variations		Primer sequences
rs1045411	For.	5'-ATGGAAGTGGGAGGCAATTTAG-3'
	Rev.	5'-CATTTTAAAAGTTGGCCCAATT-3'
rs2249825	For.	5'-TGTCTGATTTTACGGAGGTTGAT-3'
	Rev.	5'-GTTTGCACAAAAAATGCATATGAT-3'
rs1360485	For.	5'-GAGACCAACCTGGGCAACAT-3'
	Rev.	5'-ACACTTGCCACAACTTGGGA-3'

PCR process was as follows: 95°C for 10 min; 35 cycles of 95°C for 30 s, 60°C for 3 s, and 72°C for 4 s; final extension for 10 min at 72°C; and storing at 4°C. The resulting PCR products were purified and sent to Shanghai Biotech Bioengineering Technology Co., Ltd. for sequencing.

RNA Extraction and Quantitative Reverse Transcription PCR

RNA was extracted from serum using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). A PrimeScript RT reagent kit (TaKaRa, Japan) was used to synthesize cDNA from the obtained RNA.

Serum *HMGB1* mRNA expression was examined using quantitative reverse transcription (qRT)-PCR, which was carried out using the SYBR Green I Master Mix kit (Invitrogen, Carlsbad, CA, USA) and 7300 Real-Time PCR system (Applied Biosystems, USA). All procedures were performed following the manufacturer's instructions. GAPDH was used as an internal reference gene for the reaction, and thermocycling conditions were as follows: 95°C for 3 min; denaturation at 95°C for 30 s, annealing at 58°C for 20 s, and extension at 72°C for 20 s, for a total of 40 cycles. Primers sequences were as follows:
HMGB1 forward, 5'-GCTCAGAGAGGTGGAAGAC-3';
HMGB1 reverse, 5'-CCAATGGATAAGCCAGGAT-3';
GAPDH forward, 5'-TTGGTATCGTGGAAGGACTCA-3'; and
GAPDH reverse, 5'-TGTCATCATATTTGGCAGGTTT-3'.
HMGB1 mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to GAPDH.

Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was analyzed for each SNP in the case and control groups to evaluate the quality of the study samples. The distribution differences of genotypes and alleles between the 2 groups were compared by the chi-squared test. The correlation of *HMGB1* gene SNPs with neonatal NEC susceptibility was evaluated by odds ratios (OR) and 95% confidence interval (95% CI). Differences of *HMGB1* mRNA expression levels among NEC neonates with different *HMGB1* rs1360485 genotypes were compared using one-way ANOVA. The correlation between the *HMGB1* rs1360485 locus SNP and survival prognosis of neonates was assessed by the chi-squared test and logistic multivariate regression analysis.

Results

HWE test results

As shown in **Table 2**, the genotype distributions of the *HMGB1* gene rs1045411, rs2249825, and rs1360485 SNPs were in accordance with the HWE in the case and control groups (all $P>0.05$), revealing the representativeness of our study population.

Genetic association of *HMGB1* gene SNPs with NEC susceptibility

The present study used the OR and 95% CI to reflect the association of *HMGB1* gene SNPs with neonatal NEC susceptibility to evaluate the influence of genotype and allele frequencies on the onset of NEC. As shown in **Table 2**, no significant difference was observed for the rs1045411 SNP between the case and control groups. The GG, GA, and AA genotype frequencies were 66.7%, 28.3%, 5.0% in the NEC case group, and 67.8%, 28.3%, 3.9% in the control group, respectively. The G and A allele frequencies were 80.8% and 19.2% in the NEC case group and 81.9% and 18.1% in the control group, respectively, but none of the distribution differences were significant (all $P>0.05$). Additionally, no significant difference in the rs2249825 SNP of the *HMGB1* gene was found between the NEC case and control groups. The CC, CG, and GG genotype frequencies were 72.1%, 24.8%, and 3.1% in the NEC case group and 73.9%, 22.8%, and 3.3% in the control group, respectively. The C and G allele frequencies were 84.5% and 15.5% in the NEC case group and 85.3% and 14.7% in the control group, respectively, but none of the distribution differences were significant (all $P>0.05$). The results demonstrated that there might be a lack of association between the *HMGB1* gene rs1045411 and rs2249825 SNPs and neonatal NEC susceptibility in the Chinese Han neonates.

For the rs1360485 SNP, the frequency of the TC genotype in the NEC case group was significantly lower than that of the control group (34.1% vs 41.7%), and individuals carrying the TC genotype had a lower risk of developing NEC than did TT genotype carriers (OR 0.661, 95% CI 0.443-0.947, $P<0.05$). Additionally, the CC genotype frequency was also lower in the NEC case group than in the control group (2.7% vs 6.6%), and individuals with the CC genotype had a lower risk of developing NEC than did TT genotype carriers (OR 0.377, 95% CI 0.141-0.984, $P<0.05$). Moreover, the C allele of the rs1360485 SNP was significantly lower in the NEC case group than in

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Table 2. Genotype and allele distributions of the *HMGB1* gene rs1045411, rs2249825, and rs1360485 polymorphisms in case and control groups.

Genotype/allele	Control, n=180 (%)	Case, n=258 (%)	*P* value	OR (95% CI)
rs1045411				
GG	122 (67.8)	172 (66.7)	Reference	Reference
GA	51 (28.3)	73 (28.3)	0.944	1.015 (0.663-1.555)
AA	7 (3.9)	13 (5.0)	0.568	1.317 (0.511-3.398)
G	295 (81.9)	417 (80.8)	Reference	Reference
A	65 (18.1)	99 (19.2)	0.673	1.077 (0.762-1.524)
P_{HWE}	0.569	0.160	–	–
rs2249825				
CC	133 (73.9)	186 (72.1)	Reference	Reference
CG	41 (22.8)	64 (24.8)	0.633	1.116 (0.711-1.752)
GG	6 (3.3)	8 (3.1)	0.931	0.952 (0.323-2.812)
C	307 (85.3)	436 (84.5)	Reference	Reference
G	53 (14.7)	80 (15.5)	0.751	1.063 (0.729-1.549)
P_{HWE}	0.213	0.393	–	–
rs1360485				
TT	93 (51.7)	163 (63.2)	Reference	Reference
TC	75 (41.7)	88 (34.1)	**0.041**	**0.661 (0.443-0.947)**
CC	12 (6.6)	7 (2.7)	**0.044**	**0.377 (0.141-0.984)**
T	261 (72.5)	414 (80.2)	Reference	Reference
C	99 (27.5)	102 (19.8)	**0.010**	**0.659 (0.480-0.905)**
P_{HWE}	0.547	0.226	–	–

HWE – Hardy-Weinberg equilibrium.

the control group (19.8% vs 27.5%), and individuals carrying the mutant C allele showed a lower risk of being affected by NEC than did T allele carriers (OR 0.659, 95% CI 0.480-0.905, *P*<0.05). All data demonstrated that the *HMGB1* gene rs136048 SNP was correlated with susceptibility of neonatal NEC in the Chinese Han study population.

Expression of Serum *HMGB1* in NEC Patients with Different Genotypes of *HMGB1* Gene rs1360485 Locus

We used the qRT-PCR method to detect serum *HMGB1* mRNA expression in NEC neonates. As shown in **Figure 1**, NEC patients with rs1360485 locus mutations (TC or CC) had significantly lower mRNA expression of serum *HMGB1* compared with patients with wild-type (TT) (all *P*<0.05).

Association Between Genotypes of *HMGB1* Gene rs1360485 Locus and Survival Outcomes in NEC

We analyzed the factors related with the survival prognosis of NEC (**Table 3**). NEC neonates were divided into survival (n=197) and death (n=61) groups. The results indicated that metabolic acidosis, neonatal scleroderma, intestinal perforation, diffuse peritonitis, thrombocytopenia, leukocyte disorder, and rs1360485 genotypes TC and CC were associated with survival prognosis of NEC neonates (all *P*<0.01). However, there was no association between respiratory distress syndrome and survival prognosis of NEC neonates (*P*>0.05). Further, multivariate logistic regression analysis (**Table 4**) showed that metabolic acidosis, intestinal perforation, diffuse peritonitis, thrombocytopenia, and rs1360485 genotypes TC and CC (all *P*<0.05) were independently predictive of survival outcomes in patients

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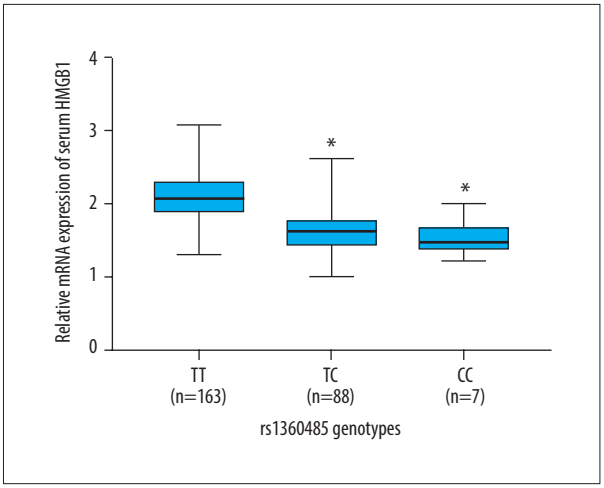

Figure 1. Expression of mRNA *HMGB1* in patients with necrotizing enterocolitis (NEC) with different genotypes of the *HMGB1* gene rs1360485 locus.

with NEC. These results suggested that rs1360485 genotypes TC and CC can independently predict better survival outcomes in patients with NEC.

Discussion

NEC is a serious gastrointestinal disease that occurs in the neonatal period and has a high mortality rate [21]. Neonates with NEC initially present with abdominal distension, intolerance to feeding, and bloody stools and often develop systemic disease involving multiple organs and shock [3,22]. Although epidemiological and other basic studies have greatly improved the understanding of NEC, its exact etiology is still unclear, and there is currently no fully effective prevention or treatment [23]. Thus, exploring the pathogenesis of NEC has become a hot spot of clinical research. HMGB1 can acts as a pleiotropic cytokine and is involved in the pathology of many diverse immune-mediated diseases [24]. When HMGB1 protein is exocrine, it can accelerate the development of NEC. Many data have indicated that inhibiting the expression of the *HMGB1* gene can improve the condition of NEC [12,13]. Therefore, *HMGB1* may exert a crucial role in NEC. Nevertheless, we did not find reports evaluating the relationship of *HMBG1* SNPs with NEC progression. The role of *HMBG1* SNPs in patients with NEC should also be assessed.

In the present study, we used the rs1360485, rs2249825, and rs1045411 SNPs in the *HMGB1* gene to evaluate the impact

Table 3. Univariate analysis for factors that were related with the survival prognosis of necrotizing enterocolitis (NEC).

Factors	Survival (n=197)	Death (n=61)	*P* value
Metabolic acidosis	15	35	<0.001
Respiratory distress syndrome	59	25	0.108
Neonatal scleredema	19	14	0.007
Intestinal perforation	9	24	<0.001
Diffuse peritonitis	29	23	<0.001
Thrombocytopenia	24	26	<0.001
Leukocyte disorder	65	33	0.003
rs1360485 genotypes TC+CC	86	9	<0.001

Table 4. Multivariate logistic regression analysis for the factors that independently predict survival outcomes in necrotizing enterocolitis (NEC) patients.

Factors	OR	95% CI	*P* value
Metabolic acidosis	18.941	6.766-53.024	<0.001
Respiratory distress syndrome	1.447	0.579-3.615	0.429
Neonatal scleredema	2.990	0.874-10.223	0.081
Intestinal perforation	21.464	5.923-77.774	<0.001
Diffuse peritonitis	6.732	2.410-18.809	<0.001
Thrombocytopenia	7.171	2.631-19.549	<0.001
Leukocyte disorder	1.424	0.589-3.443	0.433
rs1360485 genotypes TC+CC	0.306	0.111-0.844	0.022

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of genotype and allele frequencies of the *HMGB1* gene locus on NEC. At first, we found a relationship between the rs1360485 SNP and NEC. Our results study indicated that the *HMGB1* gene rs1360485 SNP was correlated with susceptibility to NEC and that Chinese Han neonates carrying at least a single C allele at rs1360485 had a significantly reduced risk of being affected by NEC. In addition, we explored the serum *HMGB1* mRNA expression in NEC patients with different genotypes of the *HMGB1* gene rs1360485 SNP and found that the rs1360485 locus mutations corresponded to significantly lower serum *HMGB1* mRNA expression, compared with the wild-type homozygous genotypes. Furthermore, Tang et al found a significant correlation of the *HMGB1* gene rs1036485 SNP with the susceptibility of Chinese Han coal workers to develop pneumoconiosis, with higher serum *HMGB1* levels in the rs1360485 mutant homozygous genotype than in the wild-type heterozygous genotype [25]. Moreover, we investigated the correlation of the genotypes of the *HMGB1* gene rs1360485 locus SNP with survival outcomes in NEC. The results indicated that the rs1360485 genotypes TC and CC were associated with better survival outcomes and could independently predict survival outcomes of patients with NEC. It has been found that the rs1360485 polymorphic variant of *HMGB1* was associated with poor prognosis in patients with prostate cancer [26]. Therefore, we considered that the rs1360485 SNP of the *HMGB1* gene was associated with susceptibility and survival prognosis in Chinese Han neonates with NEC. Therefore, sufficient attention needs to be paid to the rs1360048 SNP of the *HMGB1* gene.

However, the results of our study did not find correlations between the rs1045411 and rs2249825 SNPs of the *HMGB1* gene and neonatal NEC. However, previous studies have indicated the important roles of the rs1045411 and rs2249825 SNPs of the *HMGB1* gene in other types of diseases, such as urothelial cell carcinoma [27], colorectal cancer [28], and non-small cell lung cancer [29]. Thus, the negative analysis results of SNPs rs1045411 and rs2249825 might have been limited by the small sample size in the present study, so our conclusions need to be confirmed in a larger study population in the future.

There is increasing evidence that alterations in *HMGB1* expression levels are associated with susceptibility to various diseases, and there are some individual differences in this association, mainly because of the effect of *HMGB1* gene SNPs on *HMGB1* expression levels. One study found a correlation between the rs1360485 SNP of the *HMGB1* gene and rheumatoid arthritis risk, indicating a possibility that the rs1360485 SNP alters *HMGB1* expression levels [30]. Huang et al showed that Chinese Han women carrying the rs1360485 locus variant in the *HMGB1* gene have a higher risk of developing T2 breast cancer and lymph node metastasis, which might be achieved through altering *HMGB1* expression [31]. In addition, several studies have shown that genetic mutations in the *HMGB1* gene changed *HMGB1* expression levels, which affects the survival prognosis of the disease [14,32]. Moreover, the present study found that the rs1360485 locus mutations corresponded to a significant decrease in serum *HMGB1* mRNA expression, while rs1360485 TC and CC genotypes were correlated with the survival of NEC. Therefore, we speculated that in our study, the rs1360485 SNP of the *HMGB1* gene may be associated with the susceptibility and prognosis of NEC by affecting the expression of *HMBG1*. However, the mechanism needs to be verified through further studies.

There are some limitations in this study. Our study sample was selected from the same hospital, which may have caused bias in our selection of data and reduced the statistical validity of comparing differences between the 2 groups. Also, the sample size of our study was not large enough, which may have affected the accuracy of the statistical analysis.

Conclusions

In summary, our findings indicated that the rs1360485 locus SNP of the *HMGB1* gene is associated with susceptibility to NEC in Chinese Han neonates, and individuals carrying at least 1 C allele at rs1360485 have a significantly lower risk of being affected by NEC. In addition, patients with NEC with the rs1360485 genotypes TC and CC had significantly reduced *HMGB1* expression and better survival outcomes.

Conflict of Interest

None.

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