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Association of *MBL2* gene polymorphisms with sepsis in children and adult

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ABSTRACT

Sepsis is a syndrome characterized by systemic inflammatory response caused by infection or toxin, with high morbidity and mortality. Different infection microflora and environment have great influence on the occurrence, development and prognosis of sepsis, but individual genetic factors also play an extremely important role. It was reported that the polymorphisms of *mannose-binding lectin* 2 gene were closely relevant to the occurrence and development of sepsis, but the conclusions in different studies were inconsistent. Therefore, we performed this reviews on the relevance of *mannose-binding lectin* 2 gene polymorphisms and sepsis.

1. Introduction

The incidence and mortality of sepsis are very high. Although the total mortality rate is decreasing, the total number of deaths is still increasing[1]. Therefore, more studies of risk factors of sepsis should be carried out to predict the occurrence and development of sepsis earlier, thus early intervention could be implemented to high-risk patients, which can effectively reduce the morbidity and mortality of sepsis. Studies have shown that genetic factors, especially single nucleotide polymorphisms, are able to affect individual susceptibility and severity of sepsis[2]. *Mannose-binding lectin 2* (*MBL2*) gene mutation can lead to low serum *MBL* level and functional impairment, which is associated with the risk of

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sepsis[3,4]. The mutations at codon 54, 52 and 57 of exon 1 of *MBL2* structure gene can block the formation of *MBL2* peptide oligomer, reduce the binding force between *MBL2* and ligand, then degrade *MBL2* more easily, resulting in a low level of serum *MBL2*. However, current studies on the association between *MBL2* gene polymorphism and risk of sepsis are still inconsistent. The relationship between *MBL2* gene polymorphism and sepsis risk in adults and children is summarized as follows.

2. The association of *MBL2* gene polymorphism with sepsis in children

2.1. A/O polymorphism

Compared with wild type, three alleles in *MBL2* gene and one allele in promoter can cause the decrease of serum *MBL2* level independently. If serum *MBL2* is deficient, the host will mishandle apoptotic cells, which leads to sepsis. The further transformation of sepsis into severe sepsis or septic shock is also related to the mutation of *MBL2* allele. Three single-point mutations in the *MBL2* gene (B, C and D variant, together with the O variant) result in low *MBL* level. The wild-type is referred to as A variant. A/O or O/O individuals are often considered to be *MBL2* deficient. In the study of Fidler KJ *et al*[5], the presence of *MBL2* variant A/O allele significantly increased the severity of the systemic response to infection in 50 infected patients (local infections 2/15, sepsis 10/19, septic shock 12/16). The results showed that *MBL2* level was closely correlated with genotypes, and *MBL2* exon polymorphisms were associated with low *MBL* level, which significantly increased the risk of sepsis infection and septic shock to children treated in intensive care unit. In the year of 2008, Dzwonek AB *et al*[6] performed *MBL* phenotypic analysis on 120 newborn samples and their genotypes on the third day after birth (A/O, A/A and O/O). The results showed that *MBL2* genotypes were not significantly associated with the risk of sepsis. Hartz A, *et al*[7] recently conducted a large-scale study, and 6 878 infants with very low birth weight were collected and genotyped for *MBL2*, and classified plasma level as normal (A/A), low (A/O or O/O). But no association was found between genotypic *MBL2* level and the risk of blood culture or clinically confirmed sepsis in the entire group with very low birth weight, but in the subgroup with infants born between 32 and 36 weeks of gestation. O/O *MBL* level appeared to be associated with the risk of gram-negative sepsis.

2.2. $^{+}$54A/B polymorphism

Codon 54 and 57 are the two most widely studied loci for *MBL2* gene polymorphisms, which can reduce the expression of *MBL2*[8,9]. Ozkan H *et al*[10] collected 93 full-term and premature infants, including 53 sepsis cases (3 with premature sepsis, 33 with delayed sepsis and 17 with very late sepsis), and compared them with normal genotype, and the results showed that AB and BB genotype infants were more likely to be diagnosed with neonatal sepsis. In addition, the presence of B allele was associated with an increased risk of neonatal sepsis. In the study of Koroglu OA *et al*[11], a total of 99 premature infants are collected in intensive care units, and codon 54 and 57 polymorphisms of the *MBL2* gene were genotyped. The results showed that premature infants with *MBL2* polymorphisms were more likely to develop early sepsis in the first week after birth. However, *MBL* gene polymorphism was not associated with late sepsis. The study did not measure serum *MBL* level, but speculated that *MBL* gene polymorphisms were associated with the early and late stages of sepsis, suggesting that *MBL* levels were associated with gestational age and increased with the growth of term infants and premature infants.

2.3. Other polymorphisms

In recent years, it has been found that there are six polymorphic loci in the *MBL* structure gene, as well as three mutation sites in the promoter region and in the exon of the *MBL2* gene, respectively, which are H/L at $^{-}$550 position of the promoter region, respectively. X/Y and P/Q at position 221 and 54, 52 and 57 codon of exon. Among these, the gene polymorphisms at the three loci of H/L, X/Y and P/Q have significantly reduced the serum level of functional *MBL2*[12,13]. In addition, heterozygous polymorphism reduced the number of functional *MBL* by 5-10 times[14]. In the study of Xue H[15], they sequenced H/L (rs11003125), X/Y (rs7096206) and P/Q (rs7095891) directly, and it was confirmed that the genotype frequencies of X/Y and P/Q polymorphisms were in line with the Hardy-Weinberg equilibrium, but the H/L genotype frequencies did not conform to the equilibrium, and the genotype distribution in infants was not calculated. In addition, in order to further understand the effect of the X/Y, P/Q genotype on the serum *MBL2* level of Chinese newborns of Han nationality, the serum *MBL2* concentration was measured. When compared with $^{+}$4PQ genotype, no significant difference in median *MBL* level of 4PQ genotype was observed. However, it was not possible to compare the levels of *MBL* with other genotypes in infants with only one 4QQ genotype, but the $^{-}$221Y/X genotype of *MBL2* was positively correlated with neonatal sepsis (Table 1).

Table 1

Studies showing of *MBL2* gene polymorphism with sepsis in children.

Ethnicity	Case	Control	Polymorphism	References
Caucasian	2 765	4 113	A/O	[7]
Caucasian	87	313	A/O	[16]
Caucasian	87	47	A/O	[16]
Caucasian	42	85	A/O ($^{-}$221Y/X)	[17]
Caucasian	41	145	A/O ($^{-}$221Y/X)	[18]
Caucasian	38	82	A/O	[6]
Caucasian	10	38	A/O	[19]
Caucasian	35	15	A/O	[5]
Caucasian	50	306	A/O	[20]
Caucasian	53	40	54 A/B	[10]
Caucasian	42	60	54 A/B	[11]
Asian	48	96	221 YX, P/Q	[15]

3. The association of *MBL2* gene polymorphism with sepsis in adult

3.1. A/O polymorphism

Molle I *et al*[21] performed a retrospective study to investigate the association between *MBL2* gene mutation (AO/OO, AA) and the risk of severe infection in multiple myeloma patients receiving autologous transplantation. The study found that patients with variant *MBL2* were at higher risk of infection than those with homozygote *MBL2*. The risk of sepsis in wild type *MBL2* homozygotes was significantly reduced. Moreto A *et al*[22] found significant higher number of fungal infections in patients with *MBL2* variants. And there was no difference in the incidence of gram-negative bacteria in patients with wild-type *MBL2* genotypes compared to those with variant *MBL2*. Bronkhorst MW *et al*[23] collected 219 patients with severe trauma, and there were 139 cases with systemic inflammatory response syndrome, 79 cases with sepsis and 37 cases with septic shock. The results showed that the genotype of exon 1 AO of *MBL2* was related to the increased positive rate of wound culture. In addition, the incidence of systemic inflammatory response syndrome, sepsis or septic shock in *MBL2* AO or OO genotype patients was higher than that in wild type AA genotype patients, but the difference was not statistically significant. Other studies have found no significant association between A/O polymorphism and the risk of sepsis[24].

3.2. $^{+}$54A/B polymorphism

The mutation frequency of *MBL2* gene was significantly different among different ethnic groups, except the frequency of Cys52 point mutation which was lower in the study population. The frequency of Asp54 mutation was 0.19 in England and 0.11 in Han nationality in Hong Kong. The frequency of Asp54 mutation was rare among Africans. The frequency of Glu57 mutation was 0.29 in African Gambians and 0.02 in Caucasians[25]. The *MBL2* gene rs1800450 polymorphism (codon 54A/B, G230A) was genotype (GG, GA, AA, G, A) in Chinese Han patients with sepsis, and the HWE test was performed, the results showed that the allele could significantly increase the risk of sepsis, the GA genotype was closely related to the pathogenesis of sepsis, while the AA genotype had no significant correlation with the occurrence of sepsis according to the studies of Liu L *et al*[26]. A total of 266 patients with sepsis and 398 healthy subjects were included, the association of three single nucleotide polymorphisms of *MBL2* gene (54, $^{-}$550, $^{+}$4) with sepsis in Korean was detected, the results showed that single nucleotide polymorphism was not associated with the occurrence of sepsis, but the homozygosity of promoter 54 (A/A) and promoter $^{-}$550 (H/H) was related to the severity of sepsis, but not to the outcome of sepsis, Huh JW *et al*[27].

3.3. Other polymorphisms

Based on the *MBL2* gene polymorphism in Korean patients, 41 patients with persistent *Staphylococcus aureus* bacteremia and 46 patients with a bacteremia recovery were compared. Six mononuclear polymorphic loci of *MBL2* were selected(2550G/C, 2221C/G, 4C/T, 54GGC/GAC, 57GGA/GAA), including alleles A/B, A/C and A/D of exon 1, and alleles H/L, X/Y and P/Q of promoter region, respectively. In addition, the level of *MBL2* in serum was measured. The high *MBL* genotype group was HYPA/HYPA, HYPA/LXPA, HYPA/LYPA, HYPA/LYQA, LYPA/LXPA, LYPA/LYQA, LYQA/LXPA, and the median of serum *MBL* concentration was 1 773 ng/mL. The median of serum *MBL* concentration was 686 ng/mL with LXPA/LYPB, LYPB/LYPB, and the median of serum *MBL* concentration was 286 ng/mL in low yield group with HYPA/LYPB, HYPA/HYPB, LXPA/LXPA, LXPA/LYPB, LYPA/LYPB. Low *MBL* genotype was significantly higher in patients with persistent bacteremia than in normal controls, and that was an important risk factor for persistent bacteremia[28]. In the latest comprehensive Meta-analysis, *MBL*'s A/O polymorphism was significantly associated with sepsis, but there was no association between $^{-}$221 Y/X and $^{-}$550 H/L[13] (Table 2).

Table 2

The association of *MBL2* gene polymorphism with sepsis in adult.

Ethnicity	Case	Control	Polymorphism	References
Caucasian	140	250	A/O ($^{-}$221Y/X)	[24]
Caucasian	197	75	A/O ($^{-}$221Y/X)	[29]
Caucasian	170	236	A/O($^{-}$221Y/X, 550H/L)	[30]
Caucasian	174	353	A/O	[4]
Caucasian	11	102	A/O	[21]
Caucasian	376	689	A/O ($^{-}$221Y/X)	[31]
Caucasian	145	400	A/O ($^{-}$221Y/X)	[32]
Caucasian	39	28	A/O	[33]
Caucasian	57	114	A/O ($^{-}$221Y/X)	[34]
Caucasian	59	84	A/O ($^{-}$221Y/X)	[35]
Caucasian	143	47	A/O ($^{-}$221Y/X)	[36]
Caucasian	164	52	A/O ($^{-}$221Y/X)	[37]
Caucasian	116	103	A/O ($^{-}$221Y/X)	[23]
Caucasian	152	196	A/O ($^{-}$221Y/X)	[38]
Caucasian	31	41	A/O	[22]
Caucasian	496	477	A/O ($^{-}$221Y/X)	[39]
Asian	7	106	54A/B	[40]
Asian	266	396	54A/B (550HL)	[27]
Caucasian	28	53	54A/B(221Y/X, 550HL)	[41]
Asian	41	46	54A/B(221Y/X, 550HL)	[28]
Asian	107	134	54A/B	[26]

In recent years, the researches on *MBL2* gene polymorphisms and sepsis have been increasing in the world. However, at present, there are some limitations in this field, such as the small number of samples increased the possibility of false positive and false negative association, and the subjects were from different geographical regions and races, the composition of the control population was different, the basic diseases were different, the research methods were not consistent, and the binding degree of *MBL2* level to various pathogenic microorganisms was different. In particular, children with different age groups have different factors. Sepsis is an extremely

complex disease affected by a variety of genetic and environmental factors. Therefore, further research is needed to achieve early diagnosis and accurate treatment of sepsis.

Conflict of interest statement

The authors report no conflict of interest.

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