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# The Influence of Polymorphisms in the *MxA* Promoter and the *elF-2α* Regulatory Region 2 on the Natural outcome of HBV Infection

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## Abstract

Interferon(IFN) stimulates the expression of a number of genes encoding enzymes with antiviral activities, including myxovirus resistance A(*MxA*) and double-stranded RNA-dependent protein kinase(PKR). PKR is also activated by dsRNA, this leads to the phosphorylation of eukaryotic initiation factor 2a(elF-2α), which halts viral replication. We investigated whether polymorphisms in *MxA* promoter and elF-2α regulatory region 2(*elF-2α reg2*) influenced the natural outcome of hepatitis B virus(HBV) infection. A total of 243 patients with chronic HBV infection and 160 patients with self-limited HBV infection were used to genotype and identify this single-nucleotide polymorphism(SNP) by polymerase chain reaction-restriction fragment length polymorphism and sequencing, respectively. The distribution of the genotypes(GG, GT, and TT) at position -88 in the *MxA* promoter was 52.7%, 44.4%, and 2.9% in patients with chronic HBV infection and 41.3%, 43.1%, and 15.6% in patients with self-limited HBV infection, respectively. The frequencies of the TT genotype at position -88 in the *MxA* promoter were significantly higher among patients with self-limited HBV infection compared with patients with chronic HBV infection (odds ratio=6.24; 95% CI: 2.63-14.81; *P*=0.001). However, the polymorphisms both at position -123 in the *MxA* promoter and in the *elF-2α reg2* were not significantly different between the two groups (P>0.05). In conclusion, Polymorphism at position -88G/T in the *MxA* promoter influences the natural outcomes of HBV infection to some extent. This SNP of *MxA* promoter may be used as a clinical prognostic marker of HBV infection.

**Keywords:** *MxA* promoter and the *elF-2*α regulatory region 2

## Introduction

Hepatitis B virus (HBV) infection is one of the most important chronic viral diseases in the world. An estimated 400 million people worldwide are carriers of HBV, and approximately 250,000 deaths occur each year as a consequence of fulminant hepatic failure, cirrhosis, and hepatocellular carcinoma [1-2]. When HBV is acquired in adulthood, the majority of infections are cleared, with chronic infection occurring in 5% to 10% of cases [3]. However, the dynamic interaction of the host inflammatory response with HBV, and the subsequent impact of this interaction on the clinical outcome of HBV infection, are not yet fully understood, nor are the underlying mechanisms for persistence of the virus [4-5]. But it has been thought that genetic associations may also provide clues to the development of HBV infection [6-7]. Some polymorphisms have been reported to be involved in susceptibility to chronic hepatitis B, in disease severity and progression, or in disease prognosis [8-11].

Interferon (IFN) is an important cytokine for resistance to HBV infection as well as for the clinical treatment of Hepatitis B [12-13]. The antiviral mechanisms of IFN are predominately mediated through the induction of antiviral proteins [14-16]. Therefore, this study investigated the IFN-induced antiviral protein myxovirus resistance protein A (MxA) and the eukaryotic initiation factor 2α regulatory region 2 (*elF-2α reg2*). *MxA* is considered to be the strongest IFN-specific index that can directly suppress HBV replication, the SNP at the -88 and -123 positions of the *MxA* promoter can affect *MxA* mRNA expression. Protein kinase-activated *elF-2α reg2* is also an important factor in IFN signal transduction, but *elF-2α reg2* gene single nucleotide polymorphisms (SNPs) correlated with IFN treatment efficacy. To explore the relationship between genotype and HBV infection outcome, polymerase chain reaction-restriction fragment length polymorphism analysis was utilized to detect SNPs in the *MxA* promoter at positions -88 and -123 and in *elF-2α reg2* in samples from patients in Hubei area of China with self-limited HBV infection and chronic HBV infection.

| Category | Cases(n) | Gender(male/female) | Age(mean±SD) |
|---|---|---|---|
| Self-limited infection group | 160 | 106/54 | 56.4±14.0 |
| Chronic infection group | 243 | 178/65 | 54.7±14.8 |
| P Value | | 0.807 | 0.569 |

**Table 1:** Characteristics of patients with chronic HBV infection.

## Materials and Methods

### Subjects

According to epidemiological expert advice, a total of 243 patients with chronic HBV infection (the chronic infection group) and 160 cases of self-limited HBV infection (the self-limited infection group) from Renmin Hospital of Wuhan University in Hubei, China were studied (Table 1). All patients were diagnosed according to the diagnostic criteria for viral hepatitis issued by the 2000 Chinese Medical Association Infectious and Parasitic Diseases Committee that was jointly revised by the Hepatology Committee [17-18]; additionally, patients were screened for other hepatitis virus infections. Patients in the self-limited infection group were not vaccinated against HBV, and the lab results for hepatitis B surface antigen (HBsAg) negative, anti-HBs antibody (anti-HBs) positive, blood count and biochemical parameters were within the reference range, which excluded the presence of liver,

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kidney, endocrine, or cardiovascular disease. As also shown in Table 1, differences in gender and age between chronic infection group and self-limited infection group were of no significance. Informed consent was obtained from each patient before inclusion into the study. Likewise, the study conformed to the ethical guidelines of the Helsinki declaration was approved by the Renmin Hospital of Wuhan University ethics committees.

### Specimens preparation

Blood samples were collected from the patients in the two groups. Using Genomic DNA Extraction Kits ( SBS Biological Engineering Co., Ltd, Shanghai, China), we extracted whole blood genomic DNA, which was stored at -20°C until use.

### Primer design and main reagents

Gene sequences and the corresponding SNP sites for the *MxA* promoter and the *elF-2α reg2* gene were obtained from the U.S. National Center for Biotechnology Information's Gene Bank (GenBank). Primer5.0 and a reference paper [19] were used to design the necessary primers. The primers were synthesized by SBS Biological Engineering Co., Ltd. The primer sequences for the *MxA* promoter -88 and -123 positions amplified a 350 bp fragment of DNA. The sequences of the primers utilized to amplify a 563 bp fragment of the *elF-2α reg2* gene were as shown in Table 2. Taq DNA polymerase, dNTPs, and DNA molecular weight markers were purchased from Takara Biotechnology Co., Ltd (Dalian, China). *HhaI, Pst*I, and *Ssp*I restriction enzymes were purchased from Shanghai Biological Engineering Technology Services Co. Ltd., (Shanghai, China) which distributes Amersham Life Sciences (Cleveland, OH, USA) products.

### SNP analysis

The PCR amplifications were performed in a final volume of 25-μL using the following reagents: 2.5μL of 10×PCR reaction buffer (50 mmol/L KCl, 10 mmol/L Tris-HCl, pH 9.0, 1 g/L Triton X-100), 1.0 U of Taq DNA polymerase, 200μmol/L of each dNTP, 2.0 mmol/L of MgCl2, 0.4μmol/L of each primer, and 50-100 ng of template. For the amplification of the *MxA* promoter -88 and -123 positions, the conditions were as follows: denaturation at 94°C for 5 min followed by 35 cycles of denaturation at 94°C for 45 s, annealing at 57°C for 45 s, and extension at 72°C for 1 min with a final extension at 72°C for 5 min. The amplification conditions for the *elF-2α reg2* locus were as follows: denaturation at 94°C for 5 min followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 1 min with a final extension at 72°C for 7 min. PCR amplification products were assessed using agarose gel electrophoresis, ethidium bromide (EB) staining, and observation under ultraviolet light. Mixtures of 8-μL of the reaction products and 2-μL of loading buffer (300 mL/L glycerol, 0.75 g/L bromophenol blue) were run on gels with DNA molecular weight standards to enable product identification. For digestions, PCR products (10-μL), 10× buffer (2-μL), restriction enzyme (1-μL of a 2 U/μL mix), and 10 × BSA (2-μL) were mixed with deionized water for a total volume of 20-μL per reaction. Digestions were performed at 37°C for 4 h. Digestion products (12-μL) were run in 20 g/L agarose gels and visualized under UV light with reference to DNA standards to identify fragments. The three digestion sites are listed in Table2. Additionally, selected PCR products were analyzed by DNA sequencing to confirm the PCR-RFLP results.

### Statistical methods

Alleles and genotype frequencies in *MxA* promoter -88 G/T and -123 C/A sites and the elF-2a-reg2 were calculated manually in 160 patients with self-limited HBV infection and 243 patients with chronic HBV infection. The differences in distribution of the genotypes and alleles between groups and the Hardy-Weinberg equilibrium were tested using chi-square tests and Fisher's exact tests. The genotype distribution comparisons between two groups were done after adjusting genotype distribution for potential confounding factor such as age and gender using analysis of covariance (ANCOVA). The odds ratio (OR) with 95% CI was also calculated. For statistical analysis, we used SPSS 11.0 software to perform. A P value of $< 0.05$ was considered statistically significant.

## Results

### Analysis of *MxA* promoter gene polymorphism

Consistent with expectations, the *MxA* promoter PCR products were 350 bp in size. Products of individual digestions with *Hha*I (digestion of the *MxA* promoter -88 G/T position) and *Pst*I (digestion of the *MxA* promoter -123 C/A position) are in Figures 1 and 2. DNA

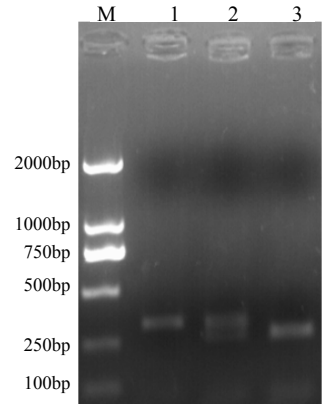


**Figure 1:** Results of the *MxA* promoter -88 G/T position gene typing. Lane M: DNA molecular weight maker; Lane 1: TT genotype; Lane 2: GT genotype; Lane 3: GG genotype.

| Digestion sites | PCR Primer sequences (direction 5'to3') | Restriction enzymes | Digestion products (bp) | Genotypes |
|---|---|---|---|---|
| *MxA* promoter-88 G/T | F:TGAAGACCCCCAATTACCAA R: CTCTCGTTCGCCTCTTTCAC | Hha I | 259 | GG |
| | | | 310 | TT |
| | | | 310, 259 | GT |
| *MxA* promoter -123 C/A | F:TGAAGACCCCCAATTACCAA R: CTCTCGTTCGCCTCTTTCAC | Pst I | 225, 125 | CC |
| | | | 350 | AA |
| | | | 350, 225, 125 | CA |
| *elF-2α reg2* A/G | F:TGCTTGCTAGTTTGTTTCCCAC R:GCCATGTACATCACAGGTTTACTG | Ssp I | 476 | AA |
| | | | 563 | GG |
| | | | 563, 476 | AG |

**Table 2:** DNA products size and genotypes of the three digestion sites in the *MxA* promoter and elF-2α.

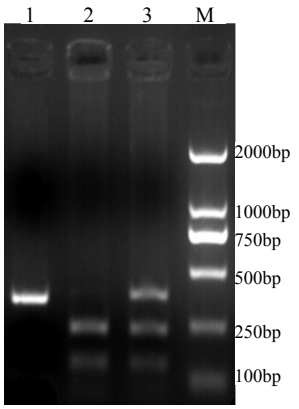


**Figure 2:** Results of the *MxA* promoter -123 C/A position gene typing. Lane M: DNA molecular weight maker; Lane 1: AA genotype; Lane 2: CC genotype; Lane 3: CA genotype.

| | Self-limited patients (n, %) | Chronic HBV patients (n, % ) | OR | 95% CI | P |
|---|---|---|---|---|---|
| *MxA*-88 alleles | | | | | |
| G | 201 (62.8 ) | 364 (74.9 ) | 0.57 | 0.42~0.77 | 0.001 |
| T | 119 (37.2 ) | 122 (25.1 ) | | | |
| *MxA*-88 genotypes | | | | | |
| GG | 66 (41.3 ) | 128 (52.7 ) | 0.63 | 0.42~0.94 | 0.025 |
| GT | 69 (43.1 ) | 108 (44.4 ) | 0.95 | 0.63~1.42 | 0.765 |
| TT | 25 (15.6 ) | 7 (2.9 ) | 6.24 | 2.63~14.81 | 0.001 |
| *MxA*-123 alleles | | | | | |
| C | 262 (81.9 ) | 387 (79.6 ) | 1.15 | 0.81~1.66 | 0.380 |
| A | 58 (18.1 ) | 99 (20.4 ) | | | |
| *MxA*-123 genotypes | | | | | |
| CC | 110 (68.7 ) | 156 (64.2 ) | 1.23 | 0.80~1.88 | 0.346 |
| CA | 42 (26.3 ) | 75 (30.9 ) | 0.80 | 0.51~1.24 | 0.324 |
| AA | 8 (5.0 ) | 12 (4.9 ) | 1.01 | 0.40~2.54 | 0.990 |
| *elF-2α reg2* alleles | | | | | |
| A | 286 (89.4 ) | 417 (85.8 ) | 1.39 | 0.90~2.16 | 0.178 |
| G | 34 (10.6 ) | 69 (14.2 ) | | | |
| *elF-2α reg2* genotypes | | | | | |
| AA | 130 (81.3 ) | 186 (76.5 ) | 1.33 | 0.81~2.18 | 0.259 |
| AG | 26 (16.2 ) | 45 (18.5 ) | 0.85 | 0.50~1.45 | 0.653 |
| GG | 4 (2.5 ) | 12 (5.0 ) | 0.49 | 0.16~1.56 | 0.241 |

**Table 3:** Comparisons of three polymorphisms between patients in self-limited and chronic HBV infection.

sequencing has the same results with the RFLP. All polymorphism results of patients with *MxA* promoter -88 G/T and -123 C/A genotypes are presented in Table 2. Overall, the GG, GT, and TT genotypes at the -88 position of the *MxA* promoter were detected in 48.1% (194/403), 43.9% (177/403), and 8.0% (32/403) of the samples, respectively. At the -123 position of the *MxA* promoter, the CC, CA, and AA genotypes were detected in 66.0% (266/403), 29.0 % (117/403) and 5.0% (20/403) of samples, respectively. The genotype distributions of *MxA* promoter -88 G/T and -123 C/A in both present populations followed the Hardy-Weinberg equilibrium. Compared to patients with chronic HBV infection, the -88 position of the *MxA* promoter in patients with self-limited HBV infection carried the GG genotype ($P$=0.025) or G allele ($P$=0.001) with a lower frequency and the TT genotype ($P$=0.001) or T allele ($P$=0.001) with a higher frequency (OR=6.24, 95% CI: 2.63-14.81). The influences of gender and age were also of no significance when analysis of covariance (ANCOVA) was used after adjusting genotype distribution according to age and gender(Table 4). The frequencies of *MxA* promoter position -123 genotypes and alleles were not significantly different between the two groups. Furthermore, we performed the haplotype analysis for evaluating the haplotype frequencies of SNPs located at *MxA* promoter -88 G/T and -123 C/A, trying to derive haplotypes specifically correlated with the natural outcome of HBV infection. The results are summarized in Table 5. The haplotypes of the *MxA* promoter -88 G/T and -123 C/A show a significant different distribution between the patients with chronic HBV infection and the patients with self-limited HBV infection.

### Analysis of elF-2α *reg2* gene polymorphism

The *elF-2α reg2* gene PCR products were 563 bp in size, consistent with the expected amplified DNA fragment size of the primers designed in this study. PCR products were digested with SspI; the electrophoresis results are shown in Figure 3. The DNA sequencing and the RFLP detected the same *elF-2α reg2* genotypes. The *elF-2α reg2* AA, AG, and GG genotypes were detected in 78.4% (316/403), 17.6% (71/403), and 4.0% (16/403) of patients, respectively. The genotype distributions of *elF-2α reg2* in both present populations followed the Hardy-Weinberg equilibrium. Genotypes and alleles frequencies were not statistically significant between the two groups (Table 3).

## Discussion

Epidemiological data indicate that host genetic factors significantly

| Genotype | Self-limited patients | | Chronic HBV patients | |
|---|---|---|---|---|
| | Gender (male/female) | Age (mean±SD) | Gender (male/female) | Age (mean±SD) |
| GG | 42/24 | 57.6±13.4 | 98/30 | 55.9±13.1 |
| GT | 46/23 | 55.2±14.7 | 75/33 | 53.3±16.6 |
| TT | 18/7 | 56.5±13.9 | 5/2 | 53.9±13.8 |

**Table 4:** Gender and age in different genotype of *MxA* promoter -88 G/T between patients in self-limited and chronic HBV infection.

| Genes | Haplotypes | Self-limited patients (n=320, %) | Chronic HBV patients (n=486, %) | P |
|---|---|---|---|---|
| *MxA* promoter -88, 123 | GC | 191(59.7) | 346 (71.2) | 0.012 |
| | TC | 39 (12.2) | 41 (8.4) | |
| | GA | 10 (3.1) | 18 (3.7) | |
| | TA | 80 (25.0) | 81 (16.7) | |

**Table 5:** Haplotype analysis of SNPs located at *MxA* promoter -88 G/T and -123 C/A.

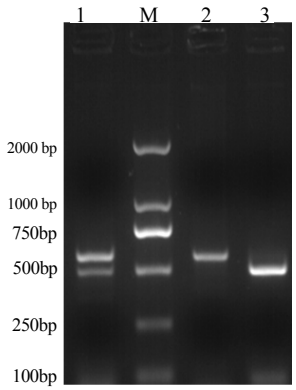


**Figure 3:** Results of the *elF-2α reg2* position gene typing. Lane M: DNA molecular weight maker; Lane 1: AG genotype; Lane 2: GG genotype; Lane 3: AA genotype.

affect the development and persistence of chronic HBV infection [20-21]. Further evidence indicates that host genetic factors can control the production of certain cytokines or sensitivities to cytokines to regulate the host immune response, thereby inhibiting HBV replication [22-23]. Following infection, the most important early antiviral response is induction of IFN production [24]. Normal cells generally do not spontaneously produce IFN, they have the potential for IFN synthesis [9]. Under homeostatic conditions, IFN genes are suppressed in the quiescent state; however, this suppression is lifted after viral infection, enabling IFN expression [25]. When bound to its receptor, IFN activates downstream JAK-STAT signaling pathways for the formation of two transcription factors, IFN-alpha-activated factor(AAF)and IFN-stimulated gene factor 3 (ISGF3). AAF and ISGF3 translocate into the nucleus and bind to antiviral protein gene promoters containing IFN response-stimulated elements (ISREs), which leads to IFN-induced antiviral gene expression and the generation of a variety of antiviral proteins, including protein kinases, 2 ‘, 5’-oligoadenylate synthetase, and *MxA* [26-28].

*MxA* is considered to be the strongest IFN-specific index that can directly suppress HBV replication [29]. According to GenBank, the *MxA* promoter has three similar ISRE sequences; the -88 position of the *MxA* promoter, the second ISRE sequences are similar. The similarity of the -88 region to ISRE sequences increases after the occurrence of G®T mutations. The G to T mutation can promote *MxA* mRNA expression, generating increased *MxA* protein levels that exert antiviral effects. It is hypothesized that the SNP at the -88 and -123 positions of the *MxA* promoter can affect *MxA* mRNA expression [30]. This study found that the TT genotype and T allele at *MxA* promoter position -88 were more common in patients with self-limited HBV infection compared to patients with chronic HBV infection (OR=6.24; 95% CI: 2.63-14.81). It is possible that individuals with the T allele (GT, TT) express more *MxA* protein compared to individuals with a non-T genotype (GG); increased *MxA* expression could help resolve natural HBV infections. Therefore, the GT and TT genotype at *MxA* promoter position -88 may exert a more potent anti-HBV effect compared to the GG genotype. The relationship between *MxA* promoter polymorphism at position -123 and viral infection outcomes has been less well studied. In a study concerning chronic hepatitis C infection suggested that *MxA* promoter C/A SNP at position -123 affected interferon therapy; further, these authors indicated that the -123 position SNP was highly connected with the -88 position G/T SNP [31-32]. However, in our study, it was found that the frequencies of *MxA* promoter -123 locus genotypes and alleles were not statistically different between patients with chronic HBV infection and patients with self-limited HBV infection. This result may be related to the sample size or virus genotype.

Protein kinase-activated *elF-2α reg2* is also an important factor in IFN signal transduction. King et al. studied 82 patients to evaluate the relationship between *elF-2α reg2* gene SNPs and response to IFN treatment in chronic hepatitis B patients in Taiwan; the results suggested that *elF-2α reg2* gene SNPs correlated with IFN treatment efficacy. IFN treatment efficacy in AG genotype patients with chronic hepatitis B was not satisfactory. In this study, we looked from another point of view and observed the relationship of *elF-2α reg2* gene SNPs and the natural outcome of HBV infection and found that the frequencies of different *elF-2α reg2* genotypes and alleles in patients with self-limited HBV infection and patients with chronic HBV infection were not statistically significant. These results suggest that the *elF-2α reg2* gene in HBV infection may not play a major role in viral clearance.

There are many factors that affect the outcome of HBV infection. In addition to the molecular characteristics of the virus and the biology of the host immune response against HBV and other factors, the antiviral activity of IFN depends on many genes in the signaling pathway and the various antiviral proteins produced [33-34]. Therefore, the relationship between *MxA* promoter and *elF-2α reg2* gene polymorphisms and the natural outcome of HBV infection only shows one aspect of the diverse nature of the host genetic background and its complexity in relationship to viral infection. The evaluation of the relationship between the IFN signaling pathway gene SNP and HBV infection requires the large-scale detection of SNPs. The accumulation of more data that take various factors into consideration is needed to reach a definitive conclusion. In short, because host genetic factors produce changes in the natural outcome of HBV infection, it is worth intensive future study. Compared to *elF-2α reg2* gene SNPs, the G/T polymorphism in the *MxA* promoter at position -88 is expected to become a predictor of HBV infection outcome and drug treatment responsiveness.

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