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Influence of genetic factors on the susceptibility to HBV infection, its clinical pictures, and responsiveness to HBV vaccination

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Summary

The association of genetic factors with hepatitis B virus (HBV) infection susceptibility, its different manifestations, and the different responses to hepatitis B antigen vaccination have been described by several authors. With regard to HLA class I molecules, association with HLA-B was especially observed. HLA-B35 and -B8 correlated with chronic active hepatitis (CAH) and with hepatitis B carriers. Correlation between HBV infection and HLA class II (loci DR and DQ) was also indicated, but results are not clear regarding the clinical pictures of the disease nor vaccination response. HLA class III (fourth complement component – C4, third complement component – C3, and properdin factor – BF) are associated with various manifestations of this disease. The gammaglobulin phenotype Gm(1, 2, 3, 10, 21) was more frequent in CAH. However, in only three publications was the impact of HLA on the efficacy of interferon therapy taken into account.

Key words: **HBV • genetics • HLA • C3 • C4 • BF • Gm • Inv**

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Hepatitis B virus (HBV) infection is one of the most common in the world²² and children are at high risk of being infected. For newborns and infants the risk of chronic infection reaches about 90%, for preschool and school children about 40%, while for adults only 5%⁴⁴. Asymptomatic and symptomatic carriers are the source of horizontally transmitted infections. Due to the importance of this problem, many authors have investigated the relationships between the lack of virus elimination, the various clinical pictures of disease, and genetic factors since the 1970's. Genes from the HLA region were especially taken into account. HLA class I was typed first. Giani et al.¹² and Hillis et al.¹⁴ found a significantly higher frequency of HLA-Bw35 in hepatitis B carriers. Such a correlation was also noted in chronic active hepatitis (CAH) by Hillis et al.¹⁴, Mota et al.³⁰, and Penner et al.³¹. A higher HLA-B8 frequency was only noted in CAH by Majsky et al.²⁶ and by Matej et al.²⁷, and in hepatitis B carriers by Jagielski and Sotnik¹⁸. It was not possible to find any regularity for HLA class I on the basis of other authors' data^{5, 33}.

HLA class II typing (loci DR and DQ) in HBV infection has been investigated since 1983. Van Hattum et al.³⁸ showed that patients with a DQw1 deficit were predisposed to CAH development, whereas Yang et al.⁴⁵ indicated a high HLA-DR3 frequency in such patients. In subsequent publications DR6 gene (DRB1*1301 and *1302 allele) was taken into consideration. The presence of these alleles in HBV-infected persons probably protects them from chronicity (a higher frequency in subjects with HBV clearance, a lower frequency in individuals with chronic infection)^{15, 37}. Higher frequencies of these alleles were also noted in individuals with acute hepatitis⁶. These findings confirmed the protective role of the alleles, because acute hepatitis very rarely transforms into chronic hepatitis. According to Cortina et al.⁶, a lack of DR4 (DRB1*04) can be connected with carrying hepatitis B. Thio et al.³⁶ marked out a haplotype connected with HLA-DR5 (in haplotype DQA1*0501-DQB1*0301-DRB1*1102) and McDermott et al.²⁹ a haplotype connected with HLA-DR7 (in haplotype DQA1*0201-DQB1*02-DRB1*0701) as responsible for predisposition to chronic persistent hepatitis. These results were confirmed by Almarri and Batchelor² regarding the allele DRB1*0701 and by Akcam et al.¹ regarding DQB1*02, while the results of Vegnente et al.⁴¹ and Diepolder et al.¹⁰ (DR7 and DR2) were the opposite. Vaughan et al.⁴⁰ tested the relationship between HLA and glomerulonephritis (GL) HBV(+) in children. They found a higher DQB1*0303 frequency in this group than in children with CAH. Bhimma et al.⁴ found a significantly higher frequency of DQB1*0603

in black children with HBV-associated membranous nephropathy than in healthy controls.

Kacprzak-Bergman and Hałasa^{19, 20, 21} studied C4, C3, BF, Gm, and Inv polymorphism in three clinical pictures of HBV infection in children: those with CAH, with GL, and with Gianotti-Crosti syndrome (G-CS), and in healthy children. They observed a significantly higher frequency of C3F phenotype in G-CS than in healthy persons ($p > 0.01$). Moreover, C*F gene in this group was expressed 1.9-times more frequently than in patients with CAH and 1.3-times more frequently than in healthy children. BFS phenotype (properdyne system) was significantly more frequent in the GL group than in the CAH ($p > 0.025$). Phenotype C4A3B2,Q0 was found more often in children with CAH than in healthy subjects. In addition, A*4 gene was 12.6-times more frequent in G-CS than in healthy individuals and 4.85-times more frequent than in the CAH group. All infected children were characterized by a lack of A*1 and A*7 alleles. Furthermore, the Gm(1, 2, 3, 10, 21) phenotype was indicated with a higher frequency in the CAH group vs. the GL plus G-CS group ($p = 0.0173$) and healthy children ($p = 0.0073$).

The association of HLA antigens and response to interferon (IFN) therapy in children with chronic hepatitis B was investigated by Giacchino et al.¹¹. Twenty-eight children were treated with lymphoblastoid IFN- α for 12 weeks. Among them were found 13 responders, who were all characterized by the presence of HLA-B35. In adults also treated with lymphoblastoid IFN, Scully et al.³⁴ noted in 6 of 7 responders antigen HLA-DR6. Zavaglia et al.⁴⁶ used various IFNs (lymphoblastoid or recombinant) for different periods of cure. They did not find any correlation between HLA class I or class II and responsiveness.

Since 1981 the relationship between the HLA system and response to hepatitis B vaccines has also been examined. Watanabe et al.⁴² noted that the haplotype Bw54-DR4-DRw53 was more frequent in non-responders. Several authors showed, however, that low responders were characterized by higher DR7 frequency^{25, 26, 28, 32, 43}. McDermott et al.²⁹ found higher DRB1*0701 and DQB1*02 frequencies in non-responders, while Qian et al.³² found a higher DRB1*02 frequency. However, in a study by Matej et al.²⁸, no correlation between HLA class II and response to hepatitis B vaccine was found. Alper et al.³ noted that B8-DR3 homozygotes are weak responders. del Canho et al.⁸ found B8-DR3 in all 8 of their non-responders and in 2 of 8 low responders (healthy newborns). Varla-Leftherioti et al.³⁹ showed that patients with B35-DR3 were frequently (but not

significantly) found among vaccinated hemodialyzed persons without response, while de Silvestri et al.⁹ noted among such patients a correlation with the DRB1*0301-DQB1*02 haplotype. In two studies, Hsu et al.^{16, 17} showed a correlation between DR14-DR52 and weak response to vaccine. With regard to the DQ locus, Langö-Warensjö et al.²³ found lower DQB*06 gene frequency in various haplotype combinations in non-responders. Lindemann et al.²⁴ showed higher DQB1*0301 gene frequency in positive responders.

Relationships between complement system phenotypes and genes and responses to HBV antigens were also tested (C2, C3, C4, BF). In 1986, Craven et al.⁷, and later many of these same authors³ suggested

a contribution of SCO1 complotype to the low response or lack of response to hepatitis B vaccination. The association between C4 gene and the results of vaccination (non-responsiveness) was observed by Stachowski et al.³⁵, de Silvestri et al.⁹, and Hatae et al.¹³ (mainly Q0 alleles in loci A and B).

This review has shown that responses to HBV infection, HBV antigens (vaccines), and treatment are connected with genetic traits. Such correlations are still not clear, especially with regard to different populations, age, and course of disease. These investigations should be continued, especially in patients treated with IFNs, which are still the most important means of treatment. This could be useful in typing patients to this very expensive therapy.

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