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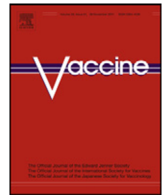

Brief report

IL4R and *IL13* polymorphic variants and development of antibodies to surface antigen of hepatitis B virus in hemodialysis patients in response to HBV vaccination or infection☆

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ABSTRACT

We searched for an association between the interleukin 4 receptor gene (*IL4R*) rs1805015 and interleukin 13 gene (*IL13*) rs20541 polymorphisms and the development of antibodies to hepatitis B surface antigen (anti-HBs) in the case of hepatitis B virus (HBV) vaccination or infection in hemodialysis (HD) patients. HD patients who failed to respond to HBV vaccination did not differ in genotype frequencies of *IL4R* (TT 72.7%, CT 22.6%, CC 4.7%) and *IL13* (CC 59.0%, CT 34.2%, TT 6.8%) from vaccine responders (*IL4R* TT 68.0%, CT 27.3%, CC 4.7%; *IL13* CC 55.0%, CT 38.5%, TT 6.5%). HD patients who did not develop anti-HBs despite HBV infection also did not differ in genotype frequencies of *IL4R* (TT 67.8%, CT 26.8%, CC 5.4%) and *IL13* (CC 60.7%, CT 33.9%, TT 5.4%) from HD patients who developed an anti-HBs response (*IL4R* TT 65.4%, CT 30.8%, CC 3.8%; *IL13* CC 60.5%, CT 34.6%, TT 4.9%). In HD patients, neither the *IL4R* nor *IL13* polymorphism is associated with anti-HBs development irrespective of whether an immunization is provoked by HBV vaccination or HBV infection.

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1. Introduction

Several genotypes have been recognized as factors involved in the development of antibodies to hepatitis B virus surface antigen (anti-HBs) in the case of hepatitis B vaccination or natural hepatitis B virus (HBV) transmission [1–10]. We focused on specific polymorphisms of the interleukin 4 receptor gene (*IL4R*) and interleukin 13 gene (*IL13*). Through their involvement in the Th1/Th2 system, polymorphisms in *IL4R* and *IL13* may constitute a common etiologic pathway in anti-HBs development [11]. Th1/Th2 and cytokine profiles of hemodialysis (HD) patients are altered compared to those of healthy subjects [12].

Our aim was to search for an association between SNP rs1805015 in exon 11 of *IL4R* (Ser503Pro) located on chromosome 16p11 and SNP rs20541 in exon 4 of *IL13* (Gln144Arg) located on chromosome 5q31.1 and the development of anti-HBs in the case of HBV vaccination or HBV infection in Caucasian HD patients.

2. Materials and methods

2.1. Patients and controls

Patients enrolled to the study had to fulfill the following criteria:

- Treatment with HD due to end-stage renal disease,
- No signs and symptoms of acute infection with blood-borne viruses within 6 months before enrollment,
- Determined panel of HBV seromarkers sufficient for a classification of a patient to:

Abbreviations: ALT, alanine aminotransferase; ANCA, anti-neutrophil cytoplasmic antibodies; anti-HBc, antibodies to core antigen of hepatitis B virus; anti-HBs, antibodies to surface antigen of hepatitis B virus; anti-HCV, antibodies to hepatitis C virus; AST, aspartate aminotransferase; CI, confidence interval; CKD, chronic kidney disease; CMIA, chemiluminescent microparticle immunoassay; DNA, deoxyribonucleic acid; GGT, gamma-glutamyltranspeptidase; HBsAg, surface antigen of hepatitis B virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; HRM, high-resolution melting curve analysis; Ig, immunoglobulin; *IL13*, interleukin 13 gene; *IL4R*, interleukin 4 receptor gene; MEIA, microparticle enzyme immunoassay; NA, not applicable; OR, odds ratio; RNA, ribonucleic acid; RRT, renal replacement therapy; SNP, single nucleotide polymorphism; Th, Thelper lymphocytes.

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- ◦ HBV vaccinated group (I) without (subgroup Ia) or with (subgroup Ib) developed anti-HBs,
- ◦ HBV infected group (II) without (subgroup IIa) or with (subgroup IIb) developed anti-HBs.

Only patients with no history of acute hepatitis B, showing negative all tests for both the surface antigen of HBV (HBsAg) and antibodies to the core antigen of HBV (anti-HBc), were included into group I. Patients that were never vaccinated for hepatitis B with consistently maintained anti-HBc positivity, also showing isolated anti-HBc positivity (both HBsAg and anti-HBs negative but anti-HBc positive), were considered as HBV infected in the past (group II).

Group I included 824 patients who were vaccinated against hepatitis B with recombinant DNA yeast-derived vaccines, composed of the S protein of HBsAg (Engerix B, GlaxoSmithKline Biologicals, Belgium; Hepavax – Gene, BIOMED SA, Poland; Euvax B, LG Chemical, South Korea) according to the rules established for HD patients [13]. When an anti-HBs titer was <10 IU/L, assumed to be non-protective, vaccination was repeated. Group II consisted of 241 HD patients. In group I there were 190 patients who did not develop an anti-HBs titer > 10 IU/L (subgroup Ia) despite repeat vaccination, whereas in group II 56 patients had anti-HBs titer ≤ 10 IU/L (subgroup IIa). Patients of groups I and II who developed anti-HBs > 10 IU/L were included into subgroups Ib and IIb, respectively.

The control group included 230 Caucasian blood donors from the same geographical area. All controls showed negative blood testing for HBsAg and HBV DNA as well as for seromarkers of infection with the hepatitis C virus (HCV). Polish blood donors are not obligated to test for anti-HBc [14], and so anti-HBc titers were not examined in this study. The hepatitis B vaccination rate and anti-HBs titers were not known in these healthy individuals.

Genotype analysis for *IL4R* and *IL13* was done in all HD patients and was repeated with exclusion of patients in whom causes or accelerators of chronic kidney disease (CKD) included severe immunocompromise diseases (*Supplementary Table I*). Appropriate medication, including corticosteroids and immunosuppressants, was used for treatment of these diseases. In controls, *IL4R* polymorphism was obtained in 225 subjects, and in 230 subjects we obtained the *IL13* polymorphism.

Informed consent was obtained from all study participants. The research design was approved by the Institutional Review Board of Poznań University of Medical Sciences, Poland.

2.2. IL4R and IL13 genotyping

DNA was isolated from blood lymphocytes by salt extraction. Genotyping was carried out by high-resolution melting curve analysis (HRM) on the *LightCycler* 480 system (Roche Diagnostics, Germany). HRM results were confirmed by DNA sequencing using ABI Prism™ BigDye™ Terminator Cycle Sequencing kit and ABI Prism 3730 capillary sequencer (Applied Biosystems, USA). Primer sequences and conditions for HRM analyses are presented in *Supplementary Table II*.

2.3. Laboratory methods

HBsAg and anti-HBc were determined by microparticle enzyme immunoassay (MEIA) technology (AxSYM, Abbott Laboratories, USA). MEIA was also used (ABBOTT, Germany) for the detection of anti-HBs and antibodies to HCV (anti-HCV). HBV DNA was determined using HUMAN HEPATITIS B VIRUS (Genekam Biotechnology AG, Germany; detection limit 250 copies/mL). HCV RNA was tested using COBAS AMPLICOR Hepatitis C Virus Test, version 2.0 (Roche Diagnostics Ltd., Switzerland; detection limit 100 IU/mL) or HUMAN HEPATITIS C VIRUS (Genekam Biotechnology AG, Germany; detection limit 250 copies/mL). All positive results were the subject of confirmation tests with alternative methods. The presence of HBsAg was confirmed by a neutralizing confirmatory test, such as the Elecsys HBsAg Confirmatory Test (Roche Diagnostics Corporation, USA); anti-HCV and anti-HBc – by a chemiluminescent microparticle immunoassay (CMIA) method (Abbott, Germany).

2.4. Statistical methods

Hardy–Weinberg equilibrium was tested to compare the observed genotype frequencies to the expected ones. Associations between *IL4R* and *IL13* genotypes and risk of impaired anti-HBs development were estimated by computing the odds ratios (OR) and their 95% confidence intervals (CI) and adjusted for variables differentiating respective subgroups.

An epistatic interaction between currently (*IL4R* rs1805015, *IL13* rs20541) and previously (*IL18* rs360719 [10], *IL12A* rs568408 and *IL12B* rs3212227 [8]) tested SNPs was analyzed using the logistic regression and epistasis option in the PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/).

Values of $P < 0.05$ were judged as significant.

3. Results

HD non-responders for vaccination were older, had shorter renal replacement therapy (RRT) duration and showed diabetic nephropathy, amyloidosis, or ANCA-related vasculitis more frequently compared to responders (Table 1, *Supplementary Table I*). HD patients that did not develop anti-HBs in response to HBV infection, were HBsAg positive more frequently and had higher ALT compared to patients that became anti-HBs positive (Table 1).

Agreement of the examined genotypes with Hardy–Weinberg equilibrium was shown in all HD subgroups and controls.

There were no significant differences in genotype and allele frequencies of *IL4R* and *IL13* between all groups, analyzed without (*Supplementary Tables III–VIII*) or with adjustment (Tables 2 and 3, *Supplementary Tables IX and X*). Exclusion of HD patients who suffered from immunocompromise diseases did not influence the significance of statistical analysis in respect to differences in genotype and allele frequencies (*Supplementary Tables XI–XVII*). The interaction analysis showed no significant epistatic interaction in anti-HBs development between *IL4R* and *IL13* polymorphisms as well as between polymorphic variants of *IL4R* or *IL13* and *IL18*, *IL12A*, or *IL12B* (*Supplementary Tables XVIII and XIX*).

4. Discussion

Th2 cytokines, such as IL-4, IL-5, IL-10, and IL-13, provide help to B cells and promote the production of neutralizing antibodies such as IgG1 antibodies [15,16], which are the dominant subclass in chronic carriers as well as recovered and vaccinated individuals [17]. IL-13 shares overlapping biological functions with IL-4, and mediates its effect through the IL-4R [11].

IL4R was not associated with anti-HBs development in response to hepatitis B vaccine. Therefore, our data do not confirm the results of Chen et al. [6] showing that allele C of *IL4R* (Ser503Pro) rs1805015 protects from non-response to anti-HBV vaccine. Wang et al. [2] did not show an association between *IL4R* (Gln551Arg) rs1801275 and a hepatitis B vaccine responder phenotype. Polymorphisms *IL4R* rs1801275 and *IL4R* rs1805015 are moderately conjugated (HapMap CEU data http://hapmap.ncbi.nlm.nih.gov/), and the latter, examined in this study, was also not associated with a protective immune response to the hepatitis B vaccine. We consider the results of Wang et al. [2] as compatible with our study in this respect.

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