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The link between genetic variation and variability in vaccine responses: Systematic review and meta-analyses

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ABSTRACT

Although immune response to vaccines can be influenced by several parameters, human genetic variations are thought to strongly influence the variability in vaccine responsiveness. Systematic reviews and meta-analyses are needed to clarify the genetic contribution to this variability, which may affect the efficacy of existing vaccines. We performed a systematic literature search to identify all studies describing the associations of allelic variants or single nucleotide polymorphisms in immune response genes with vaccine responses until July 2013. The studies fulfilling inclusion criteria were meta-analyzed.

Thirteen studies (11,686 subjects) evaluated the associations of human leukocyte antigen (HLA) and other immunity gene variations with the responses to single vaccines, including MMR-II (measles and rubella virus), HepB (hepatitis virus), influenza virus, and MenC (serogroup C meningococcus) vaccines. Seven HLA genetic variants were included in the meta-analyses. The pooled ORs showed that DRB1*07 (2.46 [95% CI = 1.60–3.77]; *P* for heterogeneity = 0.117; I^2 = 49.1%), DQA1*02:01 (2.21 [95% CI = 1.22–4.00]; *P* for heterogeneity = 0.995; I^2 = 0.0%), DQB1*02:01 (2.03 [95% CI = 1.35–3.07]; *P* for heterogeneity = 0.449; I^2 = 0.0%), and DQB1*03:03 (3.31 [95% CI = 1.12–9.78]; *P* for heterogeneity = 0.188; I^2 = 42.4%) were associated with a significant decrease of antibody responses to MMR-II, HepB, and influenza vaccines. The pooled ORs showed that DRB1*13 (0.52 [95% CI = 0.32–0.84]; *P* for heterogeneity = 0.001; I^2 = 85.1%) and DRB1*13:01 (0.19 [95% CI = 0.06–0.58]; *P* for heterogeneity = 0.367; I^2 = 0.0%) were associated with a significant increase of antibody responses to the above vaccines.

While our findings reinforce the concept that individuals with a particular HLA allelic composition are more likely to respond efficiently to vaccines, future studies should be encouraged to further elucidate the link between genetic variation and variability of the human immune response to vaccines.

1. Introduction

Vaccines are the most powerful measures to prevent the burden of infectious diseases, and represent the greatest successes in the history of public health [1], especially for microbial pathogens that are unable to evade the host immune detection and/or do not exhibit extensive variability [2]. Although the list of vaccine-preventable diseases is far from being complete [3], there is no doubt, to date, that vaccines play a great role in diminishing mortality and morbidity from major global infections, including diphtheria, pertussis, tetanus, measles, mumps, rubella, hepatitis B, and others [4].

Immune responses to vaccines are known to be influenced by several parameters, but host genetic variations are recognized as main culprits for variable vaccine responsiveness among vaccine recipients [5]. Even with standard immunization schedules, for example, 5–10% and 2–10% of healthy individuals fail to respond to hepatitis B or measles vaccine, respectively [6,7]. Although the genetic control of both humoral and cellular immune responses to vaccines remains largely unknown [8,9], immunogenetics studies revealed that single nucleotide polymorphisms (SNPs) in human leukocyte antigen (HLA) class I and class II, cytokine, cytokine receptor, and innate immune response (e.g., toll-like receptor) genes may in part account for the inter-individual variability with respect to the markers of vaccine-induced protective immunity, including neutralizing antibodies [10].

Abbreviations: IFN, interferon; IL, interleukin; HepB, hepatitis B; HBsAg, surface antigen of hepatitis B virus; HLA, human leukocyte antigen; MMR, measles–mumps–rubella; OR, odds ratio; CI, confidence interval; RR, relative risk; SNP, single nucleotide polymorphism; TLR, toll-like receptor.

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Therefore, while a meta-analysis of studies evaluating the effect of HLA on immunological response to hepatitis B vaccine suggested that specific HLA class II alleles are associated with antibody response to hepatitis B vaccine [11], a multivariate analysis study corroborated the importance of a multigenic control of both humoral and cellular immune responses to measles vaccine [12]. Thus, if HLA gene variants influence adaptive immune responses, variations in early innate immune responses, perhaps through activation of natural killer cells and secretion of type I interferons and other cytokines, could also contribute to variability in the individual responsiveness to multiple vaccines. This review represents an attempt to synthesize the current knowledge on the association of allelic variants or SNPs within immune response gene regions with vaccine responses in humans, while meta-analyses were used to provide summary estimates of the effects of human genetic variations on these responses.

2. Methods

2.1. Literature search and selection criteria

Database searches were conducted by two independent investigators (RA and PDG) to identify potentially relevant articles from MEDLINE, SCOPUS and ISI Web of Science, which were published in all languages up to July 2013. The search strategy was based on combinations of the following terms: ((*pharmacogenetics*[*MeSh*] *OR pharmacogen* OR genetic association OR genetic susceptibility OR immunogenetics*) *AND* (*vaccine*[*MeSh*] *OR vaccin OR vaccina* OR vaccine* OR vaccini* OR vaccino* OR vaccinu**)) *OR vaccinom**. The search was completed by reviewing all references cited in the articles retrieved.

The following inclusive criteria were established and reviewed by two independent investigators (BP and RP): (1) studies reporting the association between human genetic variants and responses (i.e., antibody, cytokine, or lymphoproliferation) to vaccines; (2) any observational study in any geographic location; (3) participants included healthy subjects of all ages, who had been immunized with currently licensed vaccines; and (4) odds ratios (ORs), in case-control studies, and relative risks (RRs), in cohort studies, reported with their respective 95% confidence intervals (CIs) (or, if 95% CIs were not available, the each study's data were sufficient to calculate them). Exclusion criteria included: (1) duplicate publications; (2) studies with less than 10 participants; (3) studies conducted on twins or family groups; (4) studies conducted on experimental (e.g., HIV-1) or (small) pox virus vaccines; (5) genome-wide association studies or studies using large custom-designed SNP genotyping arrays; and (6) reviews, not original papers. When more than one paper focusing on the same genetic variant(s) and vaccine(s) was published by the same author with the same study population, the paper with more study subjects was included in the systematic review.

2.2. Data extraction and quality assessment

Data were extracted independently by two investigators (PDG and CI), using a standardized form. Any discrepancy was resolved by consensus. The following information was collected from each study: first author; publication year; location of the study; study subjects; type(s) of vaccine; number of vaccine-responsive subjects and non-vaccinated controls; type(s) of vaccine response; type of allelic variant(s) and/or polymorphism(s) within immune response genes. To allow appropriate comparison of all studies, subjects were classified as vaccine responders (or hyperresponders) and nonresponders, if they provided, respectively, a virus/bacterium-specific positive (i.e., above a defined cut-off value) or a negative (i.e., below a defined cut-off value) response after a whole immunization schedule. If vaccine responses were quantitatively determined, they were defined as high-level or low-level responses when the values of serum antibody or cytokine concentrations or lymphoproliferation index ratios were above or below their respective median or mean values in the study population, or the values in the SNP heterozygote subjects increased or decreased compared to values in the SNP homozygote (reference) subjects. In addition, the HLA allele designations reported in the original studies were updated to reflect the 2010 nomenclature update (see http://hla.alleles.org.nomenclature/nomenc_updates.html).

Two investigators (BP and RP) independently examined the quality of each included study, by using an adapted 10-point scoring system which relies on both epidemiologic and genetic issues [13]. Five domains were used to assess representativeness of vaccinated subjects, ascertainment of vaccine response(s), ascertainment of control groups, genotypic examination, and association assessment. Studies with an overall score of $\geq$7 were classified as high-quality studies, whereas studies with overall scores of 4 to 6 and $\leq$3 were classified as medium-quality or low-quality studies, respectively. Any disagreement was resolved by discussion or by consulting the review supervisor (SB).

2.3. Statistical analysis

All statistical analyses were performed using STATA version 12.0 software. Heterogeneity was assessed by means of χ^2 (Q) and inconsistency (I^2) tests. I^2 values were quantified with the lying between 0% and 100%, where values less than 40% suggest that homogeneity is good for the reliability of meta-analysis [14]. A random effects model was used to take into account the heterogeneity between studies [15]. Pooled ORs with the corresponding 95% CIs were calculated. A P value of <0.05 was considered statistically significant.

The systematic review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

3. Results

Of 2546 potentially relevant articles identified, 70 studies were assessed for eligibility. According to the inclusion and exclusion criteria, 34 studies were ultimately included in this systematic review (Fig. 1). The main characteristics of the 34 included studies are shown in Table 1. Of these studies, 17 were from USA [17–33], 8 from European [34–41], 2 from Japan [42,43], 2 from Taiwan [44,45], 1 from Australia [46], 1 from Indonesia [47], 1 from Iran [48], 1 from China [49], and 1 from Gambia [50]. All studies covered 11,686 subjects (more than 70% were Caucasians and aged 0–25 years of age), who had been immunized with 1 dose (12.2%) or 2 doses (39.2%) of measles–mumps–rubella (MMR-II) vaccine, with 2 doses (6.1%), 3 doses (23.2%), $\leq$3 to 4 doses (5.7%), or 6 (5.3%) doses of hepatitis B (HepB) vaccine, with 1 dose of influenza vaccine (0.6%), and with 1 dose (7.7%) of serogroup C meningococcal (MenC) vaccine.

Of the 34 studies selected, 26 studies (9272 subjects) measured only the antibody responses [17–22,33–38,40–42,45,47–50] and 2 studies (820 subjects) only the cytokine responses [26,28], whereas 1 study (118 subjects) measured all antibody, cytokine, and lymphoproliferative responses [25], 2 studies (882 subjects) both antibody and cytokine responses [30,46], 2 studies (438 subjects) both antibody and lymphoproliferative responses [23,32], and 1 study (156 subjects) both cytokine and lymphoproliferative responses [39] Among them, the majority (19 studies) only