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

Brunella Posteraro, Roberta Pastorino, Paolo Di Giannantonio, Carolina Ianuale, Rosarita Amore, Walter Ricciardi*, Stefania Boccia

Institute of Public Health, Section of Hygiene, Università Cattolica del Sacro Cuore, Rome 00168, Italy

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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.

* Corresponding author. Tel.: +39 6 35006224/+39 6 35506224; fax: +39 6 35006224/+39 6 35506224.
E-mail address: wricciardi@rm.unicatt.it (W. Ricciardi).

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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 ≥ 7 were classified as high-quality studies, whereas studies with overall scores of 4 to 6 and ≤ 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%), ≤ 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

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Table 1
Characteristics of the 34 studies included in the systematic review.

Study [Ref. no.]	Location	Age (ys = years, ms = months)	Type of vaccine (no. of doses)	No. of total subjects	No. of subjects (category) by the indicated vaccine response			Main locus(i)/gene(s) studied
					Antibody	Cytokine	Lymphoproliferative	
Hayney [17]	USA	5 to 13 ys	MMR-II (1)	146	81 (NR) 65 (HR)	–	–	HLA-DRB1
Poland [18]	USA	5 to 13 ys	MMR-II (1)	242	72 (NR) 170 (R)	–	–	HLA-DRB1|HLA-DQA1|HLA-DQB1|HLA-DPA1|HLA-DPB1
St Sauver [19]	USA	5 to 13 ys	MMR-II (1)	242	72 (NR) 170 (R)	–	–	HLA-A|HLA-B|HLA-DRB1|HLA-DQA1|HLA-DQB1|HLA-DPA|HLA-DPB
Dhiman [20]	USA	5 to 13 ys	MMR-II (1)	242	72 (NR) 170 (R)	–	–	TAP2|TAP1|HLA-DMB|HLA-DMA
Jacobson [21]	USA	5 to 13 ys	MMR-II (1)	242	72 (NR) 170 (R)	–	–	HLA-A|HLA-B
Ovsyannikova [22]	USA	5 to 13 ys	MMR-II (1)	170	93 (HR) 77 (R)	–	–	HLA-A|HLA-B|HLA-DRB1|HLA-DQA1|HLA-DQB1|HLA-DPA1|HLA-DPB1
Clifford [46]	Australia	12 to 14 ms	MMR-II (1)	137	137	137		TLR3|RIG-I
Ovsyannikova [23]	USA	12 to 18 ys	MMR-II (2)	346	346	–	346	HLA-A|HLA-C|HLA-B
Dhiman [24]	USA	12 to 18 ys	MMR-II (2)	339	339	–	–	SLAM|CD46
Dhiman [25]	USA	12 to 18 ys	MMR-II (2)	118	118	118	118	IL2|IL4|IL10|IL12A|IL12B|IFNG
Ovsyannikova [26]	USA	14 to 17 ys	MMR-II (2)	106	–	106	–	HLA-A|HLA-C|HLA-B|HLA-DRB1|HLA-DQB1|HLA-DPB1
Ovsyannikova [27]	USA	11 to 19 ys	MMR-II (2)	738	738	–	–	HLA-A|HLA-C|HLA-B|HLA-DRB1|HLA-DQB1|HLA-DPA1|HLA-DPB1
Ovsyannikova [28]	USA	11 to 19 ys	MMR-II (2)	714	–	714	–	RARB|TLR3|RARG|DDX58|TRIM22|RARA|VISA|TRIM5|TOP2B|TLR4|VDR|CASP8
Ovsyannikova [29]	USA	11 to 19 ys	MMR-II (2)	714	714	–	–	RARB|RIG-I|TRIM5|TRIM22
Ovsyannikova [30]	USA	11 to 22 ys	MMR-II (2)	745	745	745	–	CD46|SLAM|CD209
Haralambieva [31]	USA	11 to 22 ys	MMR-II (2)	764	764	–	–	IL4|IL7R|IL18|IFNA1|IL6ST|TNF|IL6|IFNA8|IFNA10|IL1R2|CSF2RB|IL12B|IL1RN
Davila [47]	Indonesia	5 to 76 ys	HepB (2)	715	277 (NR) 438 (R)	–	–	TGFB2|FOXP1|IL65T|BTNL2|HLA-B|HLA-DRA|HLA-DQB1|LY6H|TNFSF15|MBL2|KLRF1|TGFB3|CCL15|LILRB4

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Table 1 (*Continued*)

Study [Ref. no.]	Location	Age (ys = years, ms = months)	Type of vaccine (no. of doses)	No. of total subjects	No. of subjects (category) by the indicated vaccine response			Main locus(i)/gene(s) studied
					Antibody	Cytokine	Lymphoproliferative	
Hatae [42]	Japan	21 to 65 ys	HepB (3)	364	30 (NR) 214 (R)	–	–	HLA-A|HLA-C|HLA-B|HLA-DR|HLA-DQ
Mineta [43]	Japan	21 to 25 ys	HepB (3)	339	339	–	–	HLA-A|HLA-B|HLA-DRB1|HLA-DQA1|HLA-DQB1|HLA-DPA1|HLA-DPB1
Höhler [34]	Germany	–	HepB (3)	244	135 (NR) 109 (R)	–	–	HLA-DRB1
Langö-Warensjö [35]	Sweden	30 to 50 ys	HepB (3)	122	53 (NR) 69 (R)	–	–	HLA-DRB1|HLA-DQA1|HLA-DQB1|HLA-DPB1
McDermott [36]	UK	19 to 67 ys	HepB (3)	86	29 (NR) 57 (R)	–	–	HLA-DRB1|HLA-DQB1
Martinetti [37]	Italy	7 ms	HepB (3)	92	16 (NR) 76 (R)	–	–	HLA-C4A|HLA-DRB1
Höhler [38]	Germany	>18 ys	HepB (3)	215	73 (NR) 53 (R)	–	–	HLA-C4A|HLA-DRB1
Lindemann [39]	Germany	17 to 58 ys	HepB (3)	156	–	156	156	GNB3|HLA-DRB1|HLA-DQB1
Yucesoy [32]	USA	19 to 52 ys	HepB (3)	92	92	–	92	IL1B
Wang [33]	USA	13 to 18 ys	HepB (3)	174	79 (NR) 95 (R)	–	–	HLA-DRB1|HLA-DQB1|IL4|IL2|IL12B
Amirzargar [48]	Iran	mean (NR), 31 ys; mean (R), 27 ys	HepB (3)	58	12 (NR) 46 (R)	–	–	HLA-DRB1|HLA-DQB1|HLA-DQA1
Wang [49]	China	4 to 7 ys	HepB (3)	301	86 (NR) 215 (R)	–	–	IL1B|IL2|IL4|IL10|IL12B|IL13|TNFA|TLR2
Wu [44]	Taiwan	15 to 18 ys	HepB (3)	681	171 (NR) 510 (R)	–	–	HLA-DPB1
Hennig [50]	Gambia	1 to 23 ys	HepB (≤3 to 4)	662	32 (NR) 630 (R)	–	–	IFNG|CD58|CD163|MAPK8|IL10RA|ITGAL
Hsu [45]	Taiwan	1 to 62 ys	HepB (6)	1296	33 (NR) 586 (R)	–	–	HLA-B|HLA-DR|HLA-DQ
Gelder [40]	UK	34 to 83 ys	Influenza	73	32 (NR) 41 (R)	–	–	HLA-DRB1|HLA-DRB3|HLA-DRB4|HLA-DRB5|HLA-DQB1
Moore [41]	UK	11 to 21 ys 6 to 12 ys	MenC	897	425 (NR) 472 (R)	–	–	CD44|TLR3

Note: MMR-II: measles–mumps–rubella vaccine; HepB: hepatitis B vaccine; MenC: serogroup C meningococcal vaccine; NR: nonresponders; HR: hyperresponders; R: responders; –: data not available.

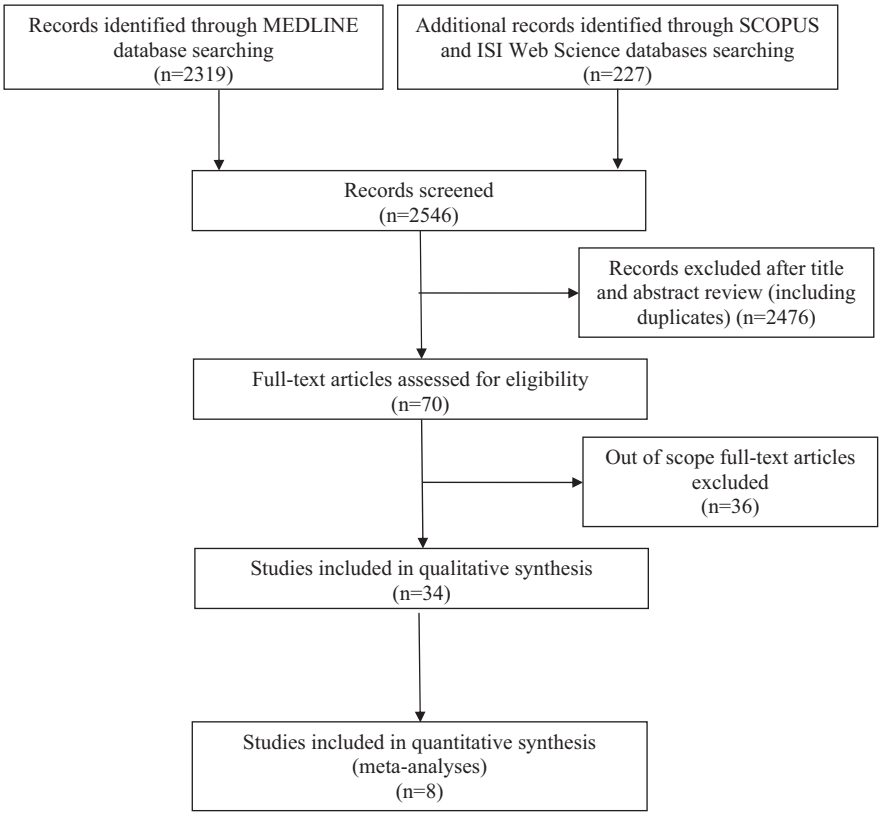

Fig. 1. Flow diagram of article selection process.

evaluated the effects of associations between vaccine responses and variants of HLA and other genes within the major histocompatibility complex (MHC) region, whereas 15 studies also reported data on vaccine responses associated with polymorphisms of other immune response genes, including those that code for interleukin (IL), tumor necrosis factor-alpha (TNF-α), alpha and gamma interferons (IFN-α and IFN-γ), signaling lymphocyte activation molecule (SLAM), complement regulatory protein (i.e., CD46), and others. Based on the specified criteria for the study quality assessment, we scored 25 studies as high-quality studies, 7 as medium-quality studies, and 2 as low-quality studies (data not shown).

3.1. Association between vaccine specific antibody responses and genetic variations

Several allelic variants or SNPs were found to be statistically significantly associated with vaccine specific antibody responses across the 34 studies included in the systematic review. Supplementary Table 1 summarizes these associations and provides the calculated ORs (or RRs) for 8 studies [18,21,33,34,38,40,42,48]. The HLA-A*01 (OR 1.64 [95% CI = 1.01–2.69]), HLA-B*13 (8.56 [1.50–48.78]), HLA-B*08 (2.36 [1.32–4.23]), HLA-DPA1*02:01 (1.71 [1.02–2.85]), HLA-DQA1*02:01 (2.21 [1.10–4.46]), HLA-DQA1*05:01 (1.73 [1.11–2.71]), HLA-DQB1*02:01 (1.90 [1.22–2.97]), and HLA-DRB1*03 (2.48 [1.40–4.37]) alleles were associated with anti-measles antibody serum negativity [18,21], whereas the HLA-B*07 (0.33 [0.15–0.71]) and HLA-B*51 (0.19 [0.04–0.91]) alleles were associated with anti-measles antibody serum positivity [21]. In addition, the HLA-DRB1*13 allele and the SLAM (rs12076998), IL2 (rs2069762 and rs2069763), IL18 (rs1946519), IFNA1 (rs28383797), and IL1R2 (rs4851531) SNPs were associated with high anti-measles antibody serum levels [17,24,25,31]. With regard to antibody response to rubella, the HLA-B*27:05 and HLA-DPA1*02:01 alleles and the RARB (rs4416353 and rs6793694), RIG-I (DDX58) (rs10813831), and TRIM22 (rs2179) SNPs were associated with a low-level response [27,28], whereas the HLA-DPB1*04:01 allele and the RIG-I (rs669260) and TRIM5 (rs3824949) SNPs were associated with a high-level response [27,28]. With regard to HepB vaccine response, the HLA-DQA1*03:01 (5.90 [1.73–20.11]), HLA-DQB1*04:01 (2.94 [1.34–6.44]), HLA-DQB1*02:01 (2.94 [1.04–8.30]), HLA-DRB1*07 (5.18 [2.18–12.29]), HLA-DRB1*07:01 (7.49 [2.51–22.28]), and C4AQ0 (3.60 [1.44–9.00]) alleles were associated with anti-HBsAg antibody serum negativity [33,38,42,48], whereas 2 alleles, HLA-DRB1*13 (OR 0.10 [95% CI = 0.03–0.33]) and HLA-DRB1*13:01 (0.14 [0.04–0.51]), were associated with anti-HBsAg antibody serum positivity [34,38]. In addition, the HLA-B*07, HLA-B*46, HLA-DPA1*01:03, HLA-DPB1*02:02, HLA-DPB1*03:01:01, HLA-DPB1*04:01:01, HLA-DPB1*04:02, HLA-DPB1*13:01, HLA-DQA1*01:03, HLA-DQA1*05:03, HLA-DQB1*03:01, HLA-DQB1*06:02, HLA-DQB1*06:03, HLA-DRB1*01, HLA-DRB1*01:01, HLA-DRB1*08:03:02, HLA-DRB1*14:03, and HLA-DRB1*15 alleles [34,35,39,43,44] and the HLA-DRA (rs2395177 and rs5000563), IL1B (+3953 minor variant), IFNG (rs2069727), IL10RA (rs2508450), ITGAL (rs2230433 and rs4243232), and MAPK8 (rs10857565) SNPs were associated with high anti-HBsAg antibody serum levels [32,47,50]. With regard to influenza vaccine, the HLA-DQB1*03:03 (OR 20.40 [95% CI = 1.10–376.80]) and HLA-DRB1*07 (4.00 [1.30–12.20]) alleles and the HLA-DRB3*0X (0.36 [0.10–0.88]) and HLA-DRB1*13 (0.18 [0.05–0.69]) alleles were associated with negative or positive influenza-specific antibody responses, respectively [40]. Lastly, the CD44 (rs996076 and rs11033013) and TLR3 (rs3775291) SNPs were associated with high-level antibody responses to serogroup C meningococcus [41].

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3.2. Association between vaccine specific cytokine responses and genetic variations

Several allelic variants or SNPs were found to be statistically significantly associated with cytokine responses to MMR-II vaccine. As shown in Supplementary Table 2, the majority were SNPs within the CD46 gene [30]. In particular, these SNPs affected the serum levels of secreted IL-6 (rs2796267 and rs2724384), IFN-α (rs2724384, rs41318019, and rs11118516), IFN-γ (rs2796267), IFN-λ1 (rs2724382), and TNF-α (rs2724384, rs7144, rs2796268, and rs2724382), in response to measles virus. In addition, the IFNG (rs1861494) and IL2RA (rs706781) SNPs and the IL4RA (rs2234898) and IL12Ap30 (rs582537) SNPs were associated, respectively, with high IL-10 or IL-12 serum levels, in response to measles virus [25]. With regard to rubella virus response, 14 allelic variants (HLA-A*02:01, HLA-A*24:02, HLA-A*68:01, HLA-DQB1*05:01, and HLA-DRB1*01:01) [26] or SNPs within the genes DDX58 (rs10813821, rs9650702, and rs626214), TRIM22 (rs12285602 and rs7948996), TLR3 (rs6822014 and rs3775296), RARG (rs3741434), and RARB (rs12636426) [29] affected the serum levels of secreted IFN-γ. In addition, 10 allelic variants (HLA-A*02:01, HLA-A*68:01, HLA-B*49:01, HLA-DRB1*13:02) [26] or SNPs within the genes RARB (rs1881706, rs1286729, rs1286733, and rs17526942), RXRA (rs3118536), and VISA (rs7262903) affected the serum levels of secreted IL-10 [29], in response to rubella virus. Interestingly, among the DDX58 SNPs, 4 (rs592515, rs6476363, rs4633144, and rs3824456) and 2 (rs10813831 and rs9650702) affected, respectively, the serum levels of secreted TNF-α or GM-CSF [29].

3.3. Association between vaccine specific lymphoproliferative responses and genetic variations

A total of 11 statistically significant associations were found between genetic variants and measles, rubella, or hepatitis B virus-induced lymphoproliferation. As shown in Supplementary Table 3, the HLA-B*35:03 and HLA-CW*35:03 alleles were associated with high lymphoproliferative responses to rubella virus antigens [23], whereas 7 SNPs within the IL2 (rs2069762 and rs2069763), IL10 (rs1800890, rs1800871, and rs1800872), IL12RB (rs3790567 and rs372889) genes [25] were associated with low lymphoproliferative responses to measles virus antigens. The other 2 SNPs, GNB3 (825 T) and IL1B (+3953 minor variant), were associated with high lymphoproliferative responses to HBsAg antigen [32,39].

3.4. Association between HLA allelic variants and antibody response to multiple vaccines

Seven HLA genetic variants, which have been assessed in at least two studies [18,33,34,38,40,42,48], were included in the meta-analyses, including 2 two-digit numbering of DRB1 alleles (DRB1*07 and DRB1*13) and 5 four-digit numbering of DRB1 (DRB1*13:01), DQA1 (DQA1*02:01 and DQA1*03:01), and DQB1 (DQB1*02:01 and DQB1*03:03) alleles (Fig. 2). Significant heterogeneity were observed in 2 alleles (DRB1*13 and DQA1*03:01). 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.

4. Discussion

Despite the plethora of studies aimed at deciphering the immunogenetic basis of vaccine responses in humans, the literature in this field is somewhat sporadic given the magnitude of different vaccines, immune response measures, and vaccine-related genetic polymorphisms. To this context, using stringent study selection and data extraction criteria (e.g., healthy participants enrolled; genetic association estimates by using P values corrected for multiple testing) when possible, we summarized the published data of 34 studies describing the associations of 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. While HLA-DRB1 (e.g., DRB1*13:01) and HLA-DQB1 allelic variants were shown to be associated with antibody response to HepB in a very recent meta-analysis study [11], our purpose here was to identify common genetic variations affecting the immune responses not only to the HepB but also to the other aforementioned vaccines.

The HLA alleles, holding in one of the most gene-dense, but most variable regions of human genome, namely the major histocompatibility complex (MHC) region [51], are essential for determining the specificity of an individual's immune response [5]. As HLA molecules are part of the structural component for immune recognition by T-lymphocytes, which in turn stimulates antibody-producing B-lymphocytes, polymorphisms in these molecules were expected to modulate antibody responses to vaccination [10]. While MHC class II molecules, encoded in humans by the polymorphic genes HLA-DR, HLA-DQ, and HLA-DP, bind to different peptides, the MHC class I polymorphic forms also behave differently; some forms are almost always loaded with peptides (e.g., most HLA-B alleles in humans), whereas only a proportion of other variants are loaded (30–70% for HLA-A and HLA-C) [52]. In essence, HLA polymorphisms are clustered inside pockets, which form the peptide binding groove and restrict peptide binding against foreign antigens, like the vaccine virus. Consequently, the HLA–peptide complexes generated in response to vaccination or infection could influence the secretion of a specific pattern of cytokines and hence the outcome of the immune response to vaccination [5].

By means of meta-analyses, we showed that four HLA alleles, such as DRB1*07, DQA1*02:01, DQB1*02:01, and DQB1*03:03, were significantly associated with the absence of antibody response to the MMR-II, HepB, or influenza vaccines, whereas two HLA alleles, such as DRB1*13 and DRB1*13:01, were significantly associated with positive antibody responses to the MMR-II, HepB, or influenza vaccines. Thus, while the products of the HLA-DRB1*07 allele might be less efficient at processing and presentation of the vaccine virus than are other HLA alleles, it is plausible that the HLA-DRB1*13 (and HLA-DRB1*13:01) allele may function more globally in a pathway common to the processing and presentation of many viral antigens. Yet, some following limitations of our analyses should be considered: (1) only few studies, involving relatively small number of participants, were included in our meta-analysis of each risk HLA allelic variant; (2) linkage disequilibrium of HLA genes or interactions between MHC genes and unlinked genes outside the complex MHC [51] would have resulted in false-positive vaccine associations; (3) HLA allele distribution may be influenced by interactions between different alleles, so the multicenter evaluations and haplotypes analysis are needed in future studies; and (4) the potential for selection bias of the single study's participants. Nonetheless, our findings reinforce the concept that individuals with a particular HLA allelic composition are more likely to respond efficiently to vaccines [5].

However, the quality (and durability) of vaccine-induced protective immunity is dependent on cell-mediated immunity [10], as well as it is the activation of the innate immune system that

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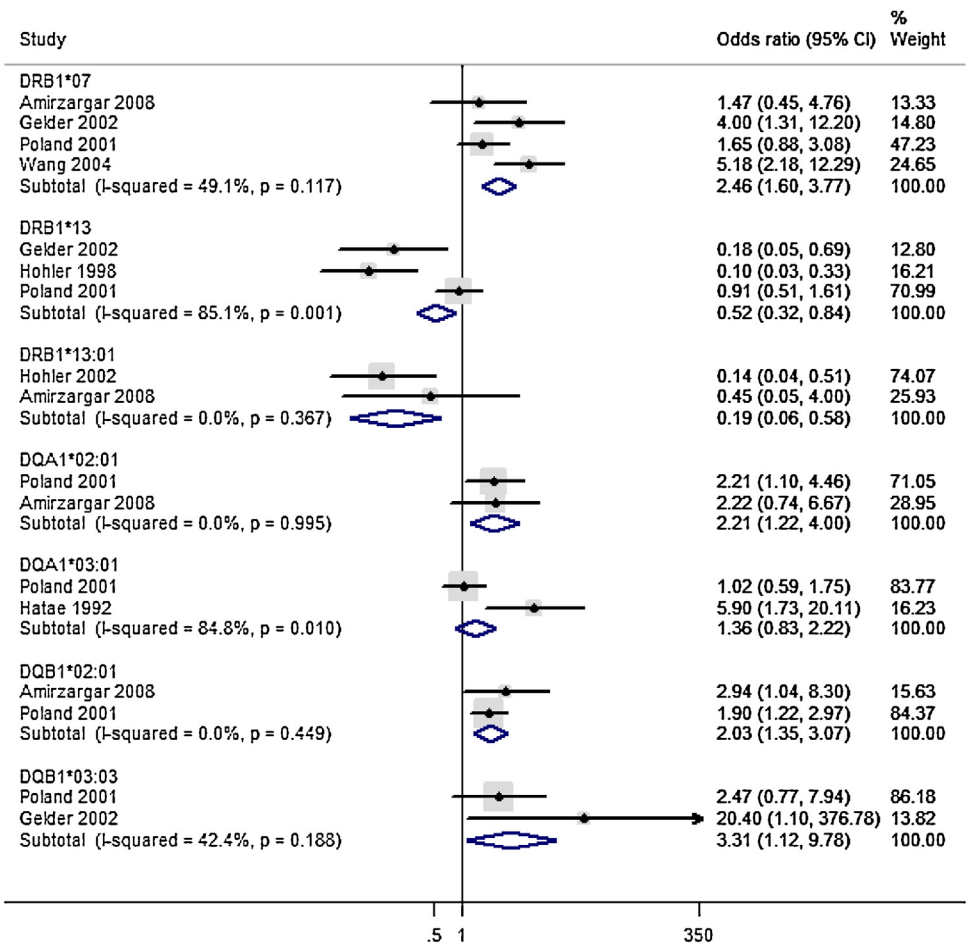

Fig. 2. Meta-analyses of the influence of HLA alleles on antibody responses to MMR-II, HepB, and influenza vaccines.

determines the magnitude and the quality of adaptive immune response following immunization [53]. It was observed, for example, that measles vaccine induces both humoral and cell-mediated responses, but the duration of protective immunity is shorter than that of acquired immunity during infection with the wild-type virus [54]. Thus, if the HLA diversity is a major contributor to individual differences in immune responsiveness, the concept of a multigenic nature of the immune responses to complex antigens, such as certain virus or bacteria [10], is corroborated by the results of replication studies here presented. They showed that SNPs in non-HLA genes, such as the measles CD46 and SLAM receptors or the TLR3 (which specifically recognizes virally derived nucleic acids [55]) and the hyaluronan receptor CD44, were associated with measles-specific antibody and IL-6, IFN-α, TNF-α, and IFN-γ responses [30] or with the persistence of the antibody response to MenC vaccine [41]. In the last case, as CD44 variants were also implicated in the immunity induced by HepB vaccination [50], this indicates that commonalities in the mediation of responses to viral and bacterial vaccines may exist [41]. Lastly, in the largest rubella vaccine immunogenetics study reported at the time of this writing, SNPs in the genes coding for the retinoic acid (vitamin A) receptor (RARB), the retinoic acid-inducible (RIG-I) pathway (DDX58), and the antiretroviral tripartite motif-containing factor 5 (TRIM5) were shown to strongly influence the rubella humoral immunity following MMR-II vaccination [28]. As the TRIM5 nonsynonymous coding polymorphism, rs3824949, that was significantly associated with higher rubella specific-antibody response, also had an effect on human HIV-1 infection [56], it was speculated that the TRIM5 SNPs may contribute to the overall human antiviral response [28]. Unfortunately, we were unable to perform meta-analysis of the effects of these SNPs on the vaccine responsiveness, that could enhance the statistical power for interpreting the data published in the literature, which are partly object of this systematic review. Thus, the significance of most of these associations remains to be understood, as well as the functional genetic variations responsible for most of these associations.

In conclusion, our attempt to clarify the link between genetic variation and variability of the human immune response to vaccines could appear restricted, unless it consider the huge side effect to encourage further studies, that will need to be large, with well-controlled populations, in order to be adequately powered. Further studies will also examine the possibility of multigenic SNP interactions across immune response genes and additional genes that may be involved in the immunogenetics of measles, HepB, influenza, rubella, and other vaccines. Finally, the development of approaches to analyze immune responses at the single-cell and systems levels will allow to elucidate and more effectively generate vaccine-induced protective immune responses.

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None.

Ethics committee approval

This study does need ethics committee approval.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.01.057.

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