Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Vaccinomics and adversomics: key elements for a personalized vaccinology

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Vaccines are one of the most important and effective tools in the prevention of infectious diseases and research about all the aspects of vaccinology are essential to increase the number of available vaccines more and more safe and effective. Despite the unquestionable value of vaccinations, vaccine hesitancy has spread worldwide compromising the success of vaccinations. Currently, the main purpose of vaccination campaigns is the immunization of whole populations with the same vaccine formulations and schedules for all individuals. A personalized vaccinology approach could improve modern vaccinology counteracting vaccine hesitancy and giving great benefits for human health. This ambitious purpose would be possible by facing and deepening the areas of vaccinomics and adversomics, two innovative areas of study investigating the role of a series of variables able to influence the immune response to vaccinations and the development of serious side effects, respectively. We reviewed the recent scientific knowledge about these innovative sciences focusing on genetic and non-genetic basis involved in the individual response to vaccines in terms of both immune response and side effects.

Keywords: Vaccination, Vaccinomics, Adversomics

Introduction

Vaccines are undoubtedly one of the most effective weapons in the prevention of infectious diseases, because of their ability to stimulate immune system in producing an effective immune response (triggered by a complex interaction among innate, humoral, and cell-mediated immunity) [1]. Currently, several effective vaccinations are available against many infectious diseases, resulting in many cases to a long-lasting immunity in the form of neutralizing antibodies and memory cells. The great value of vaccines as one of the most essential preventive tools in the fight against infectious diseases has been emphasized by the recent coronavirus disease 2019 (COVID-19) pandemic. However, on the other hands, this exceptional situation has exasperated the attitude and beliefs of certain groups of people opposed to vaccinations. This attitude is globally known as "vaccine hesitancy," defined in 2022 by the SAGE (Strategic Advisory Group of Experts on Immunization) Working Group on Vaccine Hesitancy as "a motivational state of being conflicted about, or opposed to, getting vaccinated," a definition replacing the previous one of 2014 that defined vaccine hesitancy as "the delay in acceptance or refusal of vaccines despite availability of vaccination services [2]." Many different assumptions are on the basis of this attitude, among which particular historical, political, reli-

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gious, and socio-cultural contexts [3]. In addition, in vaccine-hesitant people, some concerns arise from the fear of side effects that, often, play a leading role in this anti-vaccine sentiment. In particular, some vaccine components are believed to be potentially dangerous for human health, especially adjuvants, which are accessory components added to vaccines to increase immune response against antigens. For these reasons, the scientific research has globally focused its attention on the discovery of new molecules and compounds effective on helping antigens in immune stimulation but with high safety profiles [4]. In the arising of vaccine hesitancy, we can also probably add the complex and highly diversified response to vaccine that we can individuate among people. Actually, the intensity of humoral response to a given stimulation is extremely variable, due to genetic and non-genetic factors [5]. In recent years, in addition to the traditional methods of vaccine immunization based on the universally administration of the same vaccines to everyone, the hypothesis of synthesizing personalized vaccines has been proposed, in a perspective of precision medicine [6,7].

Personalized vaccinology is the application of personalized medicine to vaccinations [6]. Currently, the main purpose of vaccination campaigns is the immunization of whole populations with the same vaccine formulations and schedules for all individuals. This way of acting assumes that the same vaccine will be equally effective and safe for everyone, eliciting the same type of immune response with similar levels of antibodies, and similar side effects. A personalized vaccinology approach could improve modern vaccinology counteracting vaccine hesitancy and giving great benefits for human health.

This ambitious purpose would be possible by facing and deepening the areas of vaccinomics and adversomics, two innovative areas of study investigating the role of a series of variables able to influence the response to vaccinations using high-dimensional systems biology approaches to predict differences in protective and dangerous innate and adaptive immune response to vaccines [6].

More specifically, vaccinomics—a term coined in 1998 [8]—studies the ability of individual variables, divided into genetic and non-genetic variables (Fig. 1), to influence immune responses induced by vaccines, understanding the molecular immune predispositions of antibody immune re-

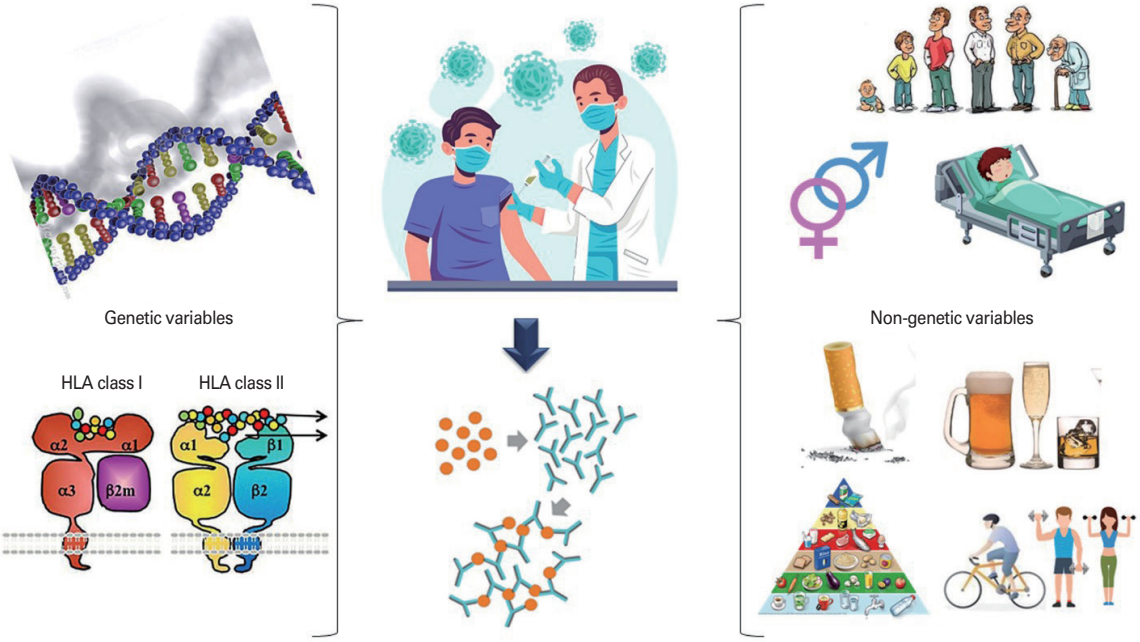

Fig. 1. Individual factors involved in the immune response to vaccines. These images were taken from the following links: (1) https://saluteplus.it/wp-content/uploads/2016/07/doppia-elica-del-dna-12883785.jpg; (2) https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_article/public/cgov_image/media_image/2022-01/fimmu-07-00030-g001.jpg?itok=G9nUVYi3; (3) https://www.asst-mantova.it/documents/338413/0/vaccino.jpg/3ccf56ce-a4f4-9491-495d-8b1b822fdf27?t=1641914154873; (4) https://www.issalute.it/images/foto_contributi/240x240/antigeni2.jpg; (5) https://www.mr-loto.it/wp-content/uploads/2016/06/sei-eta-uomo.jpg; (6) https://www.laleggepertutti.it/wp-content/uploads/2017/03/medico-ospedale-paziente-malato-clinica.jpg; (7) https://www.donnesulweb.it/wp-content/uploads/2013/05/sigaretta_spenta.jpg; (8) https://www.mark-up.it/wp-content/uploads/sites/3/2016/05/istock_000006395094large-1.jpg; (9) https://www.sge-ssn.ch/media/LMP_IT1.png; and (10) https://www.riabilimed.it/wp-content/uploads/2017/05/cosa-sintende-attivita-fisica-742img1.jpg.

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sponses to vaccines, with the possible development of early biomarkers of vaccine response, identification of who and how should get vaccinated, and increasing safety and public confidence in vaccines [9]. If this field of study was deepened over time, this would allow the implementation of personalized vaccination plans with the achievement of both economic (no more vaccine doses would be used than those necessary for immunization) and individual health benefits (the immune system would not be subjected to unnecessary "stress"). This would improve current vaccination programs that, nowadays, do not consider these inter-individual differences in vaccine efficacy, so that all individuals are vaccinated with the same number of doses, although in some cases seroconversion could be achieved with fewer doses.

Differently from vaccinomics, adversomics, a term introduced by Poland [10], deals with how individual characteristics can lead to side effects, even serious ones, following vaccination. The study of adversomics, compared to vaccinomics, has certainly been less investigated and therefore needs to be strengthened above all to dispel false myths that lead to an increase in vaccine hesitancy. People often wrongly underestimate the effectiveness of vaccines and the dangers of some pathogens, as the corresponding diseases are frequently no longer evident to the majority of population [11]. All these aspects lead to the false belief that vaccines are no longer necessary and that the risks deriving from their administration are unacceptable. Therefore, it is evident how important it is to deepen both vaccinomics and adversomics fields in order to solve multiple problems and arrive to a personalized vaccinology laying its basis on the evaluation of individual's genetic background, gender, and other factors that may have an impact on immunogenicity, efficacy, and vaccine safety.

Vaccinomics: Factors Influencing the Immune Response to Vaccines

Genetic variables

Some alleles and polymorphisms can certainly exert a role on the induction of post-vaccine immune responses. For definition, an allele is "one of two or more versions of DNA sequence (a single base or a segment of bases) at a given genomic location." Each individual inherits two alleles, one from each parent, for any given genomic location where such variation exists. If the two alleles are the same, the individual is homozygous for that allele while if the alleles are different, the individual is heterozygous [12]. Among polymorphisms, the most studied in vaccinomics are certainly the single nucleotide polymorphisms (SNPs). SNPs are single nucleotide variations (alleles) occurring in a population with a frequency of at least 1% [13]. They can be localized within coding or non-coding sequences [14], resulting in different effects. In fact, if the SNP is located within the coding region there may be a modification of the amino acid sequence of the codified protein (missense SNP), the genesis of a stop codon (nonsense SNP), or simply no effect (synonymous SNP). SNPs within the non-coding region can influence the binding between DNA and a transcription factor (with a lower or higher expression of the corresponding protein), the binding between messenger RNA (mRNA) and microRNA (with changes in post-transcriptional gene silencing) and mRNA degradation, RNA splicing, or RNA sequence of non-coding RNA [15].

Some SNPs fall within genes associated with immune responses to specific pathogens. A variety of alleles and polymorphisms that seem to modulate the immune response induced by different vaccinations have been identified (Table 1).

Genetic variables in hepatitis B vaccine response

Historically, one of the first vaccinomics focus was to study the inter-individual differences in immune response after vaccine against hepatitis B virus (HBV). Hepatitis B is an infection spread worldwide. More than 350 million people are thought to be infected with HBV globally [16], and this infection is the cause of nearly 1 million deaths each year [17]. In fact, chronic HBV infection is a fundamental cause of cirrhosis, liver failure, and hepatocellular carcinoma [18]. For these reasons, HBV vaccine is given to all infants at birth, children up to age 18 years, and to adults at high risk, and seroconversion after 3 vaccine doses is high [19]. Despite this, there is a share of non-responder people, ranging from 4% to 10% of vaccinated people [20]. The causes of this non-response to vaccination are probably linked to inter-individual factors, which in some cases appear to be associated with latent autoimmunity [21]. Considering the heritability of immune response to HBV vaccine, as showed by a twin study where a high percentage (77%) of the immune response to HBV vaccination heritability was detected [22], the involvement of genetic factors such as some alleles or polymorphisms seems to be highly plausible. In this context, a preponderant role is played by some human leukocyte antigen (HLA) genes, which help immune system distinguish the body's own proteins from foreign ones belonging to viruses and bacteria. In a study by Höhler et al. [23] in 2002, the most important HLA locus for predicting re-

Table 1. Genetic variables involved in the immune response to vaccines

Vaccine	Genetic variables	Effects	References
HBV vaccine	HLA-DRB1*0301, HLA-DRB1*0701	Little or no antibody production	Höhler et al. [23] (2002)
	HLA-DRB1*01, HLA-DRB1*11, HLA-DRB1*15	Rapid post-vaccination antibody production	Omersel et al. [9] (2020)
	Null alleles of C4A gene	Poor response	Omersel et al. [9] (2020)
	IL-1β (rs1143633 "A" and rs1143627 "G"; IL-13 (rs1295686); IL-4 (rs2243248)	No response	Omersel et al. [9] (2020)
	IL-4 receptor (rs1805015) and TLR-2 (rs3804100)	Good vaccine response	Omersel et al. [9] (2020)
	DRB1*0405, DQB1*0401, DPB1*0501	Low post-vaccination antibody production	Nishida et al. [24] (2018)
	HLA-DBQ1 (rs32734227 and rs32734289)	Little or no response	Davila et al. [25] (2010)
	HLA-DRB1 (rs477515)	Vaccination non-response	Pan et al. [26] (2013)
	HLA-DPB1 (rs770370)	Vaccination non-response	Roh et al. [27] (2016)
	HLA-DP (rs9277535 and rs3077)	Strong response	Okada et al. [28] (2017)
	IL-4 (rs2243250 and rs2227284)	Low antibody titer	Roh et al. [29] (2017)
	DTX1 allele "G" (rs2384077) and the minor allele "C" (rs10744794)	Higher immune response	Xie et al. [30] (2016)
	CXCR5 (rs497916, rs3922, rs676925) and CXCL13 (rs355687)	Good response	Duan et al. [31] (2014)
	IRG1 (rs17470171 and rs17385627)	Good response	Liu et al. [32] (2017)
	IL-17 (rs4711998 GG)	Lower frequency in non-responders	Borzooy et al. [33] (2016)
MMR vaccine	TNF-α (rs1799964) and IL-6 (rs2069849)	Low levels antibodies	Dhiman et al. [41] (2008)
	IL-2 receptor subunit α (rs2228149); IL-1B (rs1143634)	Poor response	Dhiman et al. [41] (2008)
	HLA alleles B*3503	Good antibody response	Ovsyannikova et al. [42] (2011), [37] (2012)
	DQA1*0201, DRB1*0701, DQB1*0303, A*2705, A*5701, DPA1 *0201, DPB1*0301, DPB1*1301	Poor production of antibodies	Ovsyannikova et al. [42] (2011), [37] (2012)
	TLR2 (rs33804100)	Good response	Ovsyannikova et al. [43] (2011)
	TLR4 (rs5030710)	Poor response	Ovsyannikova et al. [43] (2011)
	TLR3 (rs5743305)	Rubella-specific granulocyte-macrophage colony-stimulating factor production	Ovsyannikova et al. [45] (2010)
	IFN B1 (rs7873167, rs3885423, rs1364613, and rs1364612); IL2RA (rs12722713 and rs12722698); IL2RB (rs228937); IL-6 (rs2069824); TNF receptor superfamily member 1A (rs4149650)	Poor response	Omersel et al. [9] (2020)
	WT1 (rs4986811, rs5030172, rs5030157, rs5030166)	Low secretion of rubella-specific-IL-6	Voigt et al. [44] (2018)
Influenza vaccine	HLA AA genotype (rs41547618) and TT genotype (rs17885382)	Low levels of antibodies	Zhong et al. [48] (2022)
	HLA (rs41542812, rs17885382, rs2068205, rs41547618, rs6905837, rs9270299—CCTGCA)	No response	Zhong et al. [48] (2022)
	TLR8-129 G/C genotype GT (rs3764879); TLR7-1817 G/T (rs5741880)	Good antibody response	Tsang et al. [49] (2023)
	ZBTB46 TT genotype (rs2281929); IQGAP2 GG genotype (rs2455230)	Low responsiveness	Wen et al. [50] (2021)
	LEPR (rs6673591 GA+AA genotype)	Low response (males)	Li et al. [51] (2021)
	PPARG (rs17793951 AG+GG genotype)	Low response (females)	Li et al. [51] (2021)
	LEPR (rs1327118, rs7602, rs1137101, rs1938589, rs6673591, rs1137100, and rs13306523)	Good immune response	Li et al. [51] (2021)
	PPARG (rs796313 and rs17793951)	Low responsiveness	Li et al. [51] (2021)
COVID-19 vaccine	HLA-DRB1* 07:01 allele and the HLA-DRB1*07:01–DQA1 *02:01–DQB1*02:02 haplotype	Higher antibody titer	Gutiérrez-Bautista et al. [52] (2022)
	TNFSF5 allele T (rs1883832)	Lower levels of anti-spike IgA	Speletas et al. [53] (2022)
	ALDH2 (rs671)	Attenuated immunogenicity	Matsumoto et al. [54] (2022)

HBV, hepatitis B virus; HLA, human leukocyte antigen; IL, interleukin; TLR, toll-like receptor; CXCR, C-X-C chemokine receptor; IRG1, immune-responsive gene 1; MMR, Measles-Mumps-Rubella; TNF-α, tumor necrosis factor-α; IFN-ɣ, interferon-gamma; ZBTB46, zinc finger and BTB domain containing 46; IQGAP2, IQ motif containing GTPase activating protein 2; LEPR, leptin receptor; PPARG, peroxisome proliferator activated receptor gamma; COVID-19, coronavirus disease 2019; ALDH2, aldehyde dehydrogenase 2.

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sponse to HBV vaccine has been shown to be HLA-DRB1*. In fact, extensive studies have identified the HLA-DRB1*0301 and HLA-DRB1*0701 alleles as the cause of little or no antibody production following anti-HBV vaccination, while the HLA-DRB1*01, HLA-DRB1*11, and HLA-DRB1*15 alleles induce rapid post-vaccination antibody production, as it has been well reported by Omersel et al. [9] in 2020. Other alleles identified as HLA alleles responsible for low post-vaccination antibody production are DRB1*0405, DQB1*0401, and DPB1*0501 [24]. In addition, genome-wide association studies have allowed to identify other SNPs that were involved in a variation of the normal response to anti-HBV vaccine. For example, in a study by Davila et al. [25] in 2010, two different SNPs in HLA-DBQ1 (rs32734227 and rs32734289) were identified as markers of little or no response to anti-HBV vaccination. SNPs responsible for HBV vaccination non-response were also identified in HLA-DRB1 (rs477515) [26] and HLA-DPB1 (rs770370) [27]. Instead, a strong response to HBV vaccine was traced to two SNPs in HLA-DP (rs9277535 and rs3077) [28]. Responses to HBV vaccination also appear to be modulated by other genes. In fact, Omersel et al. [9] in 2020 highlighted: (1) null alleles of the complement component C4A Gene, which are associated with poor response to HBV vaccine; (2) the interleukin (IL)-1β haplotype rs1143633 (A) and rs1143627 (G) and SNPs in genes encoding IL-13 (rs1295686) and IL-4 (rs2243248), which are associated with no response to HBV vaccine; (3) SNPs encoding the IL-4 receptor (rs1805015) and toll-like receptor (TLR)-2 (rs3804100), which lead to a good vaccine response. Other studies, such as that of Roh et al. [29] in 2017, demonstrated how IL-4 gene SNPs (rs2243250 and rs2227284) showed strong association with low antibody titer, while Xie et al. [30] in 2016 underlined that the minor allele "G" of rs2384077 and the minor allele "C" of rs10744794 in the first intron of the DTX1 gene are associated with a stronger immune response to HBV vaccine. Moreover, genetic association analysis revealed that SNPs in CXCR5 (rs497916, rs3922, rs676925) and in CXCL13 (rs355687) are associated with HBV-vaccine response [31], as well as the SNPs rs17470171 and rs17385627 in the IRG1 (immune-responsive gene 1) gene are associated with the immune response to HBV vaccination [32]. Finally, Borzooy et al. [33] in 2016 demonstrated that the IL-17 rs4711998 GG genotype had a significantly lower frequency in non-responders to HBV vaccination. Therefore, from what has been said, it is noted that multiple alleles and polymorphisms are involved in the response to anti-HBV vaccination.

Genetic variables in MMR vaccine response

Measles-mumps-rubella (MMR) vaccine is an immunological preparation against measles, mumps, and rubella. Measles is still responsible for more than 100,000 deaths each year due to complications that can occur following infection, such as pneumonia and encephalitis [34]. Mumps affects at least 500,000 people each year [35] while the World Health Organization estimates that around 100,000 cases of congenital rubella syndrome occur every year [36]. An effective and safe vaccine against these three viral diseases is available. There are various studies on MMR vaccine, which demonstrated that inter-individual variations in cell-mediated and humoral immune responses to this vaccine are due to genes involved in immune response to a good 30%, including the HLA [37,38].

There is a correlation between the change in antibody titer after measles vaccination and heredity [39], and this phenomenon is often due to a combination of multiple genes [40]. A correlation between genes encoding cytokines and their receptors and a variability in the response to measles vaccination has been demonstrated. Specifically, the SNPs rs1799964 in tumor necrosis factor-α (TNF-α) gene and rs2069849 in IL-6 gene have been associated with low levels of post-vaccination measles antibodies [41]. Even in a study conducted on HLA alleles, some SNPs such as the B*3503 allele, responsible for a good antibody response to measles vaccination, and DQA1*0201 and DRB1*0701, associated with a poor production of antibodies, have been identified [42]. SNPs in the TLR family also influence the immune response to measles vaccine, e.g., the SNP rs3804100 in TLR2 is associated with a good response to vaccination, while the SNP rs5030710 in TLR4 is associated with a poor response [43]. With regard to mumps, the allele DQB1*0303, involved in a poor antibody response, was identified [42]. Moreover, two SNPs always associated with poor response to vaccination, one of them in IL-2 receptor subunit α (rs2228149), and the other one in IL-1B (rs1143634) were recognized [41]. Concerning rubella, both alleles and SNPs influencing the immune response to vaccination have been identified. Some alleles such as A*2705, A*5701, DPA1*0201, DPB1*0301, and DPB1*1301 are associated with a poor response to vaccination [42]. Omersel et al. [9] in 2020 have summarized all the polymorphisms involved in an insufficient response to rubella vaccination. Specifically, these are the rs7873167, rs3885423, rs1364613, and rs1364612 in interferon B1; rs12722713 and rs12722698 in IL2RA; rs228937 in IL2RB; rs2069824 in IL-6; rs4149650 in TNF receptor superfamily member 1A; rs4986811, rs5030172, rs5030157, rs5030166 in the tumor suppressor gene WT1, that are shown to be associated with a low

secretion of rubella-specific-IL-6 from peripheral blood mononuclear cells post MMR-vaccination [44]. Conversely, a polymorphism in TLR3 (rs5743305) was associated with rubella-specific granulocyte-macrophage colony-stimulating factor production [45].

Genetic variables in influenza vaccine response

Influenza viruses infect large numbers of hosts, have high mutation rates, and reassort frequently. As a result, their ability to adapt to new hosts and escape the immune system seems limitless. For this reason, influenza remains a major threat to public health, with 290,000–650,000 deaths every year [46]. To reduce the risk of infection, a safe and effective vaccination is available, which manages to protect 40%–60% of the overall population during the season when the vaccine strains well match the circulating ones [47]. However, flu vaccine is not universally protective; in fact, there are individuals who fail to have an appropriate antibody titer following vaccination. A role in this failure is also played by genetic variants. In a study by Zhong et al. [48] in 2022, it was shown that SNPs in HLA genes influenced the antibody response to the trivalent influenza vaccine. More specifically, it has been demonstrated that the AA genotype of the SNPs rs41547618 is correlated with low levels of Hemagglutination inhibiting antibody (HAI) that are specific for the A/H1N1 strain, while the TT genotype of the SNPs rs17885382 is correlated with low levels of HAI antibodies for the A/H3N2 strain.

In addition, an HLA haplotype consisting of rs41542812—rs17885382—rs2068205—rs41547618—rs6905837—rs9270299—CCTGCA is correlated with non-responsiveness to influenza vaccine [48]. A study about the administration of the trivalent inactivated flu vaccine (TIV) to 550 children showed a correlation between a low probability of a good antibody response and genotype GT for SNPs rs3764879 in TLR8-129G/C and for SNPs rs5741880 in TLR7-1817G/T [49]. In a study by Wen et al. [50] in 2021, the TT genotype of zinc finger and BTB domain containing 46 (ZBTB46) rs2281929 and the GG genotype of IQ motif containing GTPase activating protein 2 (IQGAP2) rs2455230 were associated with a higher risk of low responsiveness to trivalent inactivated vaccine. It is also possible that there is a correlation between SNPs, low responsiveness to flu vaccine, and gender. In fact, it has been shown that the leptin receptor (LEPR) rs6673591 GA+AA genotype is correlated with low responsiveness to influenza in males, whereas the peroxisome proliferator activated receptor gamma (PPARG) rs17793951 AG+GG genotype is associated with low responsiveness only in females [51]. Also, in the study by Li et al. [51] in 2021, it was also highlighted that the CAAAAAC haplotype, composed of LEPR rs1327118, rs7602, rs1137101, rs1938589, rs6673591, rs1137100, and rs13306523, is correlated with a good immune response after vaccination with influenza vaccine, whereas haplotype TG comprised of PPARG rs796313 and rs17793951 is correlated with a low responsiveness.

Genetic variables in COVID-19 vaccine response

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a pandemic of acute respiratory disease, named COVID-19, which have threatened and still threatens human health and public safety. Vaccination is certainly one of the most effective weapons at our disposal to counter this pandemic. Also, in the case of anti-SARS-CoV-2 vaccination, an inter-individual difference in immune response was noted, and studies were conducted on the influence of some genes or polymorphisms on the post anti-SARS-CoV-2 vaccination efficacy. For example, a possible association between the HLA-DRB1*07:01 allele and the HLA-DRB1*07:01–DQA1*02:01–DQB1*02:02 haplotype and a higher antibody titer, 30 days after the administration of the second dose of mRNA-1273, has been demonstrated [52]. Instead, in a study by Speletas et al. [53] in 2022, the contribution of the SNPs rs1883832 affecting the Kozak sequence of the TNF superfamily member 5 (TNFSF5) gene, encoding CD40 ligand, on the antibody response to mRNA and adenoviral vector COVID-19 vaccines was investigated. The results showed that the allele T of the rs1883832 polymorphism is significantly associated with lower levels of anti-spike immunoglobulin A (IgA), especially in those vaccinated with mRNA vaccine (BNT162b2). Also, the rs671 polymorphism in the aldehyde dehydrogenase 2 (ALDH2) gene, which results from missense mutations in the coding region, has also been associated with attenuated immunogenicity of COVID-19 mRNA vaccines [54].

Non-genetic variables in vaccinomics

In the context of vaccinomics, it is equally important to evaluate the possible non-genetic individual variables capable of influencing the response to vaccinations. All these factors can be divided into endogenous (age, gender, comorbidities) and exogenous factors. Among the latter, the most important ones are behavioral (smoking habit, alcohol consumption, physical activity), and nutritional factors (body mass index [BMI], micronutrients) [55].

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Endogenous factors

Among endogenous factors, age is certainly able to influence individual response to vaccinations, especially in infants and the elderly. For example, infants have a lower capacity to produce antibodies, less strong cell-mediated immune responses, as well as the response to T-independent polysaccharide antigens [56]. An immature immune system, such as that of an infant, shows suboptimal interaction between antigen-presenting cells and T lymphocytes, which causes lower functionality of CD4+ and CD8+ cells, polarization toward T helper 2 cells and the induction of memory B lymphocytes, rather than antibody-secreting plasma cells [57]. In addition, passive acquisition of maternal antibodies, may interfere with the response to vaccination [58]. A meta-analysis of 20 studies about measles vaccine immune response, showed that the number of infants who seroconvert after a dose of measles vaccination, ranged from 50% (if the vaccine is given at 4 months) up to 85% (if given at 8 months) [59], highlighting how greater maturation of the immune system results in a better performing response. In the elderly, on the other hand, a natural decrease in the immune response, called immunosenescence, has been shown to occur [55]. This phenomenon leads to a decrease in T-cell-derived antibodies and B-lymphocyte generation with advancing age [60]. Immunosenescence may thus explain both lower efficiencies in response to any bacterial or viral pathogens and a lower post-vaccination antibody response, which is also less durable in some cases [61]. The main signs of innate immune dysfunction commonly observed in the elderly also include altered cytokine secretion, decreased NK-cell activity, reduced expression of TLRs and a chronic inflammatory state known as "inflamm-aging" [55]. As evidence for this, different studies, conducted following the administration of different types of vaccine preparation (diphteria, influenza, hepatitis A, hepatitis B, pneumococcal, tetanus, tick-borne encephalitis, SARS-CoV-2), have shown that there is a negative correlation between old age and antibody production [62,63].

Gender exerts also some influence, as much in the onset of autoimmune disease and responses to infectious diseases as in response to vaccination. In fact, at a young age, females have a more active immune system and higher levels of circulating antibodies than males. This difference is secondary both to a different hormonal set-up, as estrogens exert an immunostimulatory action [64] while androgens are immunosuppressive [65], and to the presence of some genes involved in the adaptive and innate immune response. These genes, located on the X chromosome [66] such as FoxP3, CD40L, and TLR7 [67], somehow, may escape the inactivation of the female second X chromosome with their overexpression. In general, women have higher responses to vaccination against Dengue, *Haemophilus influenzae b*, hepatitis A and B, herpes simplex, inactivated polio vaccine (IPV), MMR, rabies, smallpox, TIV, yellow fever [6,55]. Conversely, the situation changes in menopause (naturally or following surgery), when there is a deficit in antibody production, as confirmed by our previous study [68], probably due to a reduced number of total lymphocytes [69].

Another important intrinsic host factors that can affect immune system function, including response to vaccination, is the presence of comorbidities. In children, the most common diseases that can affect immune responses are undoubtedly celiac disease and diabetes mellitus. For example, children with celiac disease have lower antibody responses to HBV and hepatitis A virus (HAV) vaccination, and definitely lower seroconversion rates than healthy children [70]. Regarding diabetes mellitus, children affected by this disease have a lower response to vaccination against HBV, pneumococcal polysaccharide vaccine (PPV23), and MMR [71]. In the elderly, on the other hand, the diseases that most influence the response to vaccination are cardiovascular diseases (CVDs), chronic obstructive pulmonary diseases (COPDs), and chronic kidney diseases, especially end-stage renal diseases [72]. CVDs are mediated by chronic inflammation and characterized by immunological alterations that could impact the immune response to vaccination. Evidence for this came from a study by Frasca and Blomberg [73] in 2014 in which it was shown that elderly people with congestive heart failure showed a lower response to influenza vaccination than healthy elderly people. COPDs is also caused by chronic inflammatory processes, which can affect the ability to breathe to the point of leading to a drastic reduction in lung function. Patients with these diseases show milder humoral immune responses following influenza vaccination compared to healthy subjects [74], probably due to T cell exhaustion, which is characteristic of chronic inflammatory stages [75]. Several studies have been conducted on endoplasmic reticulum storage diseases, which have shown that there are some immunological alterations able to affect innate and adaptive immunity, making dysfunctional the immune response. These include complement system, neutrophils, monocytes, macrophages, and lymphocytes, but especially dendritic cells, which seem to be the ones most involved in the lack of response to vaccination [76]. In addition,

altered iron metabolism is also associated with these pathologies, leading to impaired immunoreactivity [77]. In any case, patients with chronic renal failure on hemodialysis showed lower antibody responses following vaccination against diphtheria, HBV, and tetanus [78].

People affected by diabetes are at higher risk to get infections, probably due to a chronic inflammation caused by high blood glucose levels and production of pro-inflammatory mediators [79]. This chronic inflammation, often related to overweight and obesity present in these patients, may cause immune dysfunction and could explain the increased incidence of some infections such as COVID-19 in people with diabetes [80]. Furthermore, a recent systematic review showed a decreased antibody response to COVID-19 vaccination in people with diabetes compared to healthy controls [81].

Another intrinsic factor to consider is the concomitant use of drugs. For example, chemotherapy is able to impair vaccine-induced immune responses. It has been shown that patients who underwent recent chemotherapy are about two times less responsive to influenza vaccination [82]. Furthermore, an impaired immune response to COVID-19 vaccination has been shown due to any form of cancer therapy, chemotherapy, or steroid treatment [83]. Some evidences indicate that vaccine schedule adjustments to ongoing chemotherapy modifying the timing of vaccination may not contribute to vaccine efficacy; therefore, they are no necessary [84].

Behavioral factors

A key role in the antibody response, both to natural infections and vaccinations, is also played by behavioral factors. A relevant importance is exerted by cigarette smoking, which compromises the overall immune response and the ability to form memory cells, necessary for lasting immunity, causing lower vaccine-induced immunoglobulin G (IgG) antibody levels [85]. Many studies have shown that smoking can negatively affect the response to HBV and influenza vaccinations, leading to more rapid disappearance of post-vaccination antibodies in smokers than in non-smokers [86], and increases the risk to develop low-avid antibodies following human papillomavirus vaccination [87]. In our previous study [7], it was demonstrated an inverse relationship between years of smoking and post vaccination against SARS-CoV-2 antibody titer.

Alcohol consumption also influences immune responses and therefore that to vaccinations. There is clear evidence of the immunosuppressive capacity of chronic alcohol abuse, which causes a greater susceptibility to bacterial and viral infections, as well as a lower response to anti-SARS-CoV-2 vaccines and lower seroconversion rates after vaccination with PPV23 to serotypes 3, 4, 7F, 8, and 19F [88]. However, at the same time, a moderate alcohol consumption seems to exert positive effects, which could improve immune responses to vaccinations, due to a higher frequency of antigen-specific T cells and antibodies in moderate drinkers [7,89]. In any case, a positive effect is shown by some compounds contained in alcoholic beverages, such as resveratrol and B vitamins which manifests a powerful anti-inflammatory effect, and helps to modulate innate and adaptive immunity. Their positive role could be due to the stimulation of macrophages, T cells, and natural killer cells activation and the cooperation to the inhibitory regulation of CD4+ CD25+ T cells [90].

A small role in the response to vaccinations may also be played by physical activity. In fact, it is well-known that it plays a protective role against various respiratory infections, also lowering the mortality rates for bacterial and viral infections by at least 50% [91]. So presumably, physical activity would also be expected to play a role in vaccination response, as would appear in a study by Eskola et al. [92] in 1978, in which the antibody responses to tetanus vaccination were higher in runners vaccinated after completing a marathon than in control groups. It seems that a stimulating effect towards the response to the TIV vaccine, at least in individuals older than 62 years, can also occur with simple vigorous exercise three or more times per week [93]. Edwards and Booy [94] have shown that a chronic exercise or high levels of physical activity seems to be related to vaccination responses in older adults. Moreover, physical training showed a positive effect on antibody titers after SARS-CoV-2 vaccination [95].

Nutritional factors

Among the nutritional factors an importance in the response to vaccination is exerted by the BMI. In fact, a high BMI can influence the antibody response after vaccination in terms of decreased antibody production. Indeed, the cytotoxic responses of CD8+ T-cells, CD4+ T-helper T-cells, memory T-cells and antibodies after vaccination are impaired in those who are obese in terms of BMI [96]. Many studies confirm the above regarding post-vaccination antibody responses against HAV and HBV, as reported by Zimmerman and Curtis [55] in 2019, while for TIV vaccination, a high BMI is correlated with a greater decrease in antibodies 12 months after administration [97].

In addition to BMI, an important nutritional factor for vacci-

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nation response is represented by the intake of micronutrients. These are vitamins and minerals needed by the body, but in small quantities, yet their impact on health is enormous, and a lack of any of them can cause serious conditions, some potentially fatal. This is because they perform a vital function for the body, such as the production of enzymes, hormones, and so forth. Vitamin A, for example, significantly affecting the regulation of innate and adaptive immunity [98], cell integrity, cytokine production, innate immune cell activation, antigen presentation, and lymphocyte trafficking to mucosal surfaces [99], it is also expected to have effects on vaccination response. Some studies have been conducted on the simultaneous administration of vitamin A and anti-measles vaccine, showing that there was an increase in the geometric mean of antibody titers if administered at 18 months, 6 years, and 8 years of age [100]. However, in a study by Church et al. [101] in 2019, vitamin A administration did not in any way improve the efficacy of oral polio vaccine in Zimbabwean infants. Vitamin D is a steroid hormone produced in human skin from 7-dehydrocholesterol following exposure to solar ultraviolet B (range, 280–315 nm) [102], or that it can be obtained through the ingestion of dairy products or fish liver oil [103]. The activity of this hormone is regulated by vitamin D nuclear receptors which, once bound to the vitamin, translocate to the nucleus to bind the DNA vitamin D receptor element, allowing to regulate the expression of several genes involved in immune responses such as beta-defensin and cathelicidins. Furthermore, vitamin D levels may affect the expression of TLRs, which are implicated in antimicrobial responses [104]. For the above, circulating vitamin D levels have been associated with good immune responses to natural infections and vaccinations [105]. In a study by Sadarangani et al. [106] in 2015 it has been reported that adult mice vaccinated with inactivated vaccines (IPV, *Haemophilus influenzae* type b oligosaccharide conjugated to diphtheria toxoid vaccine and HBV) co-administered with 1,25-(OH)2D3 have developed specific IgA and IgG. In a recent our paper, we have demonstrated that circulating levels of vitamin D are significantly and directly related to the mRNA COVID-19 vaccination immune response [7]. However, the actual ability of vitamin D to influence the response to vaccination is still a matter of debate, as many studies show conflicting results.

Adversomics

Adversomics is concerned with using omics sciences for investigating the mechanisms underlying the individual differences in the development of side effects after a vaccination at genetic and molecular levels [10]. Obviously, this requires a better understanding of harmful response genesis and its underlying mechanisms. Side effects or harmful responses following vaccination are rare but possible, despite vaccines are pharmaceutical products subjected to strictest safety protocols. The problem is that these side effects often arise in the post-marketing phase, so the development in the field of adversomics may in the future make safer vaccine preparations and reduce vaccine hesitancy. This science is certainly younger than vaccinomics, but using the same tools it has already made it possible to detect the existence of an association between specific alleles or SNPs and an unfavorable post-vaccination immune response.

Adversomics of HBV vaccine

While a number of genetic elements about HBV vaccine responses and efficacy are currently known, very little is known about the prediction of side effects to the HBV vaccine. HBV vaccine is in general a safe and well tolerated product [107]. However, following the start of massive HBV vaccination campaigns worldwide, some evidences about the onset of several autoimmune diseases, such as multiple sclerosis, optic neuritis, vasculitis, rheumatoid arthritis, and systemic lupus erythematosus occurred after the HBV administration have been reported [108]. Particularly, multiple sclerosis and other demyelinating diseases have been investigated, but the majority of these studies have indicated no increased risk to develop this disease after HBV vaccination [109]. However, concerns about risks after HBV vaccine administration have not been completely removed yet. Actually, a theoretical base for the development of an HBV-vaccine-induced autoimmunity through various pathways has been scientifically demonstrated [110]. Some animal and human studies have shown the onset of a temporary autoimmunity in terms of levels of auto-antibodies [111,112] and T-regulatory cells after HBV vaccination [113]. However, even if no significant difference in the levels of auto-antibodies was detected between responders and non-responders among HBV-vaccinated children [114], non-responder children showed higher levels of anti-smooth-muscle antibodies (30% versus 2%, respectively). These anti-smooth-muscle antibody-positive non-responders were all characterized by the presence of the haplotype HLA-C4AQ0, DRB1*0301, and DQB1*02, which on the one hand has been associated with poor HBV response [115] and on the other one is a well-known factor pre-

disposing for autoimmune diseases [116]. For this reason, HBV vaccine non-responders positive for the haplotype HLA-C4AQ0, DRB1*0301, and DQB1*02 might be more at risk to develop autoimmune diseases [114]. Furthermore, Miller and Whitehair [117] in 2005 demonstrated that the presence of some HLA-DRB1 alleles (*01:01, *03:01, *04:01, *13:01, *15:01), identified as HBV vaccine response modulators [23,115] would be able to cause the activation of CD8+ T cells by HLA-HBV surface antigens with the production of high levels of interferon-gamma (IFN-γ) and TNF-α and promotion of autoimmune disorders. Therefore, it has been hypothesized that HBV-non responsive infants could be at risk to develop autoimmune disease later in life, and possible markers of this latent autoimmunity could be SNPs in the genes codifying for IL-18 and IFN-γ [21]. This association between HBV-nonresponse and autoimmunity has been also confirmed by a recent study that showed high expression levels of pro-inflammatory genes (i.e., IFN pathways) in non-responders compared to vaccine responders before HBV vaccination [118]. Recently, it has also been possible to identify SNPs of immunoregulatory genes, such as cytotoxic T lymphocyte-associated protein 4 (CTLA4), CD28, and tumor necrosis factor ligand superfamily member 4 (TNFSF4) related to side effects induced by anti-COVID-19 vaccination. Indeed, rs3181096 and rs3181098 of CD28, rs733618 and rs3087243 of CTLA4, and rs1234314 of TNFSF4 are associated with mild side effects induced by mRNA or adenoviral vector anti-COVID-19 vaccines [119]. In a study by Bolze et al. [120] in 2022, on the other hand, the association between severe difficulties with daily routine after vaccination and HLA-A*03:01 was evaluated. This association was statistically significant only for those who received the Pfizer-Biontech vaccine, in which the HLA-A*03:01 was associated with a 2-fold increase in risk of self-reported severe difficulties with daily routine following due to chills, fever, fatigue, and generally feeling unwell.

Adversomics of MMR vaccine

Some adverse events as fever have been reported with the administration of live-attenuated vaccines, such as MMR. Differently from evidences about genetic predisposition to MMR efficacy, studies about MMR adversomic are very poor. One comprehensive review was carried out by Feenstra et al. [121] in 2014 who, through a series of Genome-wide association studies, compared the genetic profile of children with febrile seizures occurred after MMR vaccine administration to children with vaccine-unrelated febrile seizures, and to controls without a history of febrile seizures. Specifically, two distinct SNPs were associated with MMR-related febrile seizures and located in two genes were identified: interferon-induced protein 44 like (IFI44L) (rs273259) and CD46 (rs1318653) [121]. Interestingly, both genes were associated with the efficacy of seroconversion after MMR vaccine administration [122]. Moreover, the authors found that three different loci were associated with febrile seizures in general. These genetic elements differed between controls and children with MMR-vaccine-related seizures, and between controls and children with MMR-vaccine-unrelated seizures, but not between the two groups of children that experienced MMR-vaccine-related and MMR-vaccine-unrelated seizures. The alleles in the interested loci were rs6432860 in the sodium voltage-gated channel alpha subunit 1 (SCN1A), rs3769955 in the SCN2A, and rs114444506 in the anoctamin 3 (ANO3) [121]. In extremely rare cases and in immunocompromised individuals, MMR vaccination can lead to a severe complication, known as measles inclusion-body encephalitis, characterized by mortality rates as high as 10% to 20% [123]. Especially T cell deficiencies, such as that in severe combined immune deficiency, have been associated with severe outcomes after MMR vaccine administration. However, these kinds of immune impartments are normally diagnosed very early, before administration of the first MMR vaccine dose. Therefore, this particularly severe outcome is very rare in clinical practice [123]. On the other hand, children affected by DiGeorge syndrome, showing a mild-to-moderate T cell lymphopenia but intact T cell function, have no severe outcomes after MMR vaccination [123]. Conversely, deficiencies of type I IFN immunity might be accompanied by more remarkably severe outcomes after MMR vaccine administration, as these immunity impairments have milder presentation and are usually diagnosed later in life. Previous literature data identified IFN-γ as one of the most important genes in both vaccine response and fever networks [124]. Some studies have described mutations in genes of the IFN networks involved in severe side effects and adverse reactions to the MMR vaccine. Specifically, severe measles infection and in some cases, death after MMR vaccine administration in healthy children without signs of immune deficiency has been associated with mutations in the following genes: signal transducer and activator of transcription 1 (STAT1) [125], STAT2 [126], interferon alpha and beta receptor subunit 1 (INFAR1) [127], INFAR2 [128], interferon regulatory factor 7 (IRF7) [129], and IRF9 [130].

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Conclusion

Vaccinations are crucial tools in the fight against infectious diseases. However, in the last decades, many concerns have arisen about vaccine efficacy and safety and more and more people are taking on anti-vaccination attitudes and, in general, vaccine hesitancy. Efficacy and safety are substantially the two most important vaccine features to improve in order to fight these negative attitudes. A more and more personalized vaccinology approach would provide the development of specific vaccines based on several factors. In some cases, we only can adjust the vaccination schedule and doses according to weight, gender, or age. In some others, we need of a deep study of a genetic predisposition to vaccine response and side effects. As a result, a new era of personalized vaccinology able to design and develop new vaccines has to be reached, in order to have the possibility to give a vaccine based on likelihood and need of response with the number of doses likely to be needed to induce a protective response to a vaccine. Moreover, the study of a genetic predisposition to potential side effects induced by vaccinations could improve the vaccination outcome avoiding the occurrence of, although rare, negative and potentially harmful effects.

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