1 **Personalized Health and the Coronavirus Vaccines -- Do Individual Genetics Matter?**

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26   **Abstract**

27   This article assesses the role of recipient genetics to COVID-19 vaccine responses. Vaccines
28   represent preventative interventions suitable to an immunogenetic perspective to predict how
29   human variability will influence their safety and efficacy. The genetic polymorphism among
30   individuals within any population can make possible that the immunity elicited by a vaccine is
31   variable in length and strength. The same immune challenge (either virus or vaccine) could
32   provoke partial, complete or even failed protection for some individuals treated under the same
33   conditions. We review genetic variants and mechanistic relationships among chemokines,
34   chemokine receptors, interleukins, interferons, interferon receptors, toll-like receptors,
35   histocompatibility antigens, various immunoglobulins and major histocompatibility complex
36   antigens. These are the targets for variation among macrophages, dendritic cells, Natural Killer
37   cells, T- and B- lymphocytes, and complement. The acute nature of vaccine reactogenicity is
38   reminiscent of the time course of adverse drug reaction mediated by the immune system. The
39   variety of technology platforms (mRNA, viral vectors) utilized currently to produce vaccines
40   against SARS-CoV-2 infections may each also trigger genetically distinct immune reactogenic
41   profiles. With biobanking of recipient genomic DNA and serum immunoprofiling, global COVID-
42   19 vaccinations could launch a new era of research and clinical translation in personalized
43   health.

44   **Keywords:** COVID-19, immunogenetics, vaccines, reactogenicity, HLA, human polymorphism
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Introduction

The SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), the virus causing COVID-19 (Corona Virus Disease 2019) is the new entity in an ecosystem of several airborne respiratory viruses such as Influenza virus, Rhinovirus and Respiratory Syncytial Virus among others. Being hosts of this diverse virome is the reality of our daily life[21,48]. At an unprecedented speed, studies to develop COVID-19 vaccines were conducted, propelled by the current coronavirus crisis worldwide. Three vaccines were recently given an emergency use of approval (EUA) by the U.S. Food and Drug Administration (FDA) due to their favorable balance of reactogenicity and immunogenicity profile as well as no serious safety concerns observed to date. The vaccine candidates approved by the FDA are the Pfizer/ BioNTech SE (BNT162b2) Moderna (mRNA-1273) and the Johnson and Johnson (Ad26.COV2.S) with ~95% ,~94.5% and 65% of effectiveness in protection, respectively.

COVID-19 vaccines from Novavax,(NVX-CoV2373) and AstraZeneca (ChAdOx1), among others are under final Phase III trials, or have been already approved in other countries[1,6]. According to the World Health Organization (WHO), there are up to fifty-one vaccines in clinical trials, and many more in a pre-clinical stage of assessment[14]. Although the mRNA-based coronavirus vaccines, approved by the FDA, appear to be safe and help trigger an immune response in most of the individuals who have been enrolled so far in the trials, there are still a few who might face some adverse reactions or even a failure in protection. However, this might also raise the question of whether everyone will actually benefit from this or any other future COVID-19 vaccine under development

The key behind any vaccine effectiveness relies on its capacity to induce both neutralizing antibodies and T-cells response that can fight any pathogen in this case the SARS-CoV-2 virus . Unlike the passive immunization, the success of a vaccine-induced immunization is influenced by several individual parameters that regulate our immune response[51,15,16].Studies have demonstrated that 5-10% and 2-10% of healthy individuals that went through standard immunization of Hepatitis B and Measles failed to produce an immune response[55,48] exemplifying the singularity of our very own immune system response to vaccination. A multifactorial hypothesis needs to be postulated, and one of the elements that need to be included as part of the equation are the host genetics variations since they have been reported to be one of the main factors for the variable vaccine responsiveness[51].

The genetic variability among individuals within any given population can make possible that the immunity elicited to a determine vaccine is variable, meaning that the same viral insult or challenge (either in the form of a vaccine or the virus itself) will result in many different responses. Thus, the response heterogeneity could provoke that a vaccine can either elicit partial, complete or even fail to protect individuals treated under the same conditions. We know that approximately, 5 to 10% of vaccines fail to induce long-term antibody protective levels[46], a phenomenon that has been associated to the role of genetic factor in vaccine response. In this article we will review and explore advances in our understanding of SARS-CoV-2 and our

88 body's response to infection, with emphasis on genomics features, as well as how these
89 findings can impact the development of effective vaccines against COVID-19.

90

91 **Understanding the Immune System**

92 To understand the host-pathogen relationship it is necessary to appreciate how our immune
93 system functions and the evasion strategies those pathogens have developed. The immune
94 system possesses two arms that coexist and complement each other: the innate immune
95 system and the adaptive immune system. The innate immune system is the first line of defense
96 against invading microbial pathogens. The activation of innate immune system relies on a large
97 family of pattern recognition receptors (PRRs) existing within the immune cells, which detect
98 distinct conserved structures on pathogens termed (PAMPs). Toll-like receptors (TLRs) are the
99 prototype of PRRs and are expressed within a number of immune cells such as macrophages
100 (MO), dendritic cells (DCs) and natural killer cells (NK). The innate immunity is unspecific, rapid,
101 short, and lacks memory. By contrast, the activation and priming of adaptive system relies on
102 specific recognition of antigenic epitopes a process that develops more slowly but retains
103 memory and capacity to develop anamnestic recall for effector cells. Nevertheless SARS-Cov-2
104 is effective evading the innate immune response associated the type 1 and 2 IFN therefore
105 delaying the priming and activation of the adaptative immune response risking a severe COVID-
106 19 illness[31,32,50,60]. This deviation may be linked to some immunosuppressive phenotypes that
107 inhibit a proper antigen presentation[30].

108 The protagonists of the adaptive immunity are lymphocyte B and T (B-cells and T-cells)
109 although ultimately the cells that carry out the clearance and destruction of microbial agents are
110 the cells of innate immunity. The messengers among all cells of innate and adaptive immunity
111 belong to a large family of proteins called cytokines. The complement system is another
112 component of the immune system, which enhances the ability of phagocytic cells and antibodies
113 secreted by B-cells to uptake and destroys of pathogens. Thus, complement system participates
114 in both arms of the immune systems. ***Table 1*** lists some of these potential candidates of clinical
115 relevance. Individual variation in the genes that are involved in the HLA recognition between T-
116 cells and antigen presenting cells or in the complement cascade may alter the host response to
117 pathogens. Understanding the role and the importance of the adaptative immune response in
118 the clearance of the SARS-CoV-2 virus and its immune memory generated is crucial for the
119 success of all COVID-19 vaccines.

120

121 **BOX 1: Toll Like Receptors (TLR).** Human TLRs comprise 10 members (TLR1-TLR10), which
122 localize to the cell surface or to intracellular compartment such as endosome. Each TLR recognize
     distinct or overlapping PAMPs such as lipids, nucleic acid or lipoprotein. Upon TLRs recognize
123 PAMPs, TLRs recruit adaptor proteins such as MyD88 and TRIF, which initiate a complex signal
     transduction pathway that culminate in the activation of the nuclear factor-κB (NF-κB), IRF or MAP
124 kinases to regulate the expression of cytokines, chemokines and Type-I interferon (IFN-I) that protect
125 the host from microbial infection

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BOX 2: Complement System. The complement system is formed by a large number of serum proteins that remain in circulation in inactive form (zymogen form). The complement system can be activated through different pathways, which although differ in the molecules that promote the initiation, converge to generate the same set of effector molecules. The classical way of complement activation is effective at late phase of infection in the presence of antibodies and thereby is part of host's defense during adaptive immunity.

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Importance of Macrophages and Dendritic cells in the Immune Response

Dendritic cells (DCs) and macrophages (MO) are phagocytic cells also known as polymorphonuclear leukocytes. DCs are the prototype of sentinels' cells. They are the first cells responsible to sense and capture microbes and process microbial antigens to effectively present these antigens to naïve T-cell within to lymphoid tissues. During their migration to lymphoid tissues DCs undergo extensive stimulus-dependent irreversible differentiation, a process that is called "maturation'. The maturation influences the type of the immune response, e.g., T-helper type-1 (Th1) vs. Th2 types that elicit the CD4+ T cell responses[22,57]. Thus, DCs allow a link between innate and adaptive immunity and play key roles in the antigen-specific T-cell mediated immunity. This seems to be critical for some COVID-19 vaccines, as a strong cell-mediated immune response (Th1-biased CD4+ and CD8+) elicited by Pfizer/ BioNTech SE (BNT162b2) has been reported in clinical trials[8].

Importance of Activation and Maturation of T-cells and B-cells in Antibody Production

T and B-cells are lymphocytes involved in the adaptive immunity and are cells able to recognize and respond specifically to antigenic epitopes. The successful activation and differentiation of naïve T-cells occur only if three signals are present: 1) interaction with the antigenic peptides presented by the antigen-presenting cells by the human leukocyte antigen (HLA) molecule, 2) signaling through co-stimulatory molecules, and 3) participation of cytokines that initiate the clonal expansion[25]. Depending on nature and concentration of antigen, the type of antigen-presenting cell and its activation state, the T-cells can differentiate to CD4+ T or CD8+ T subsets. If the T cell expresses CD4, it is converted into T-helper cell (Th), which has a double function: to produce cytokines and to stimulate B cells to generate antibodies. The differentiation of CD4+ T-cells to Th1 is induced by IL-12, IL-18 and type-1 IFN-α and IFN-β secreted by DCs and MOs after being activated by intracellular pathogens. Th1 cells stimulate strong cell immunity as well as participate in the development of delayed type hypersensitivity. The differentiation of CD4+ T-cells to Th2 is generated by IL-4, IL-25, IL-33 secreted by mast cells and eosinophils. Th2 cells produce cytokines which are important for induction and development of humoral (antibody) immune responses.

Naïve T-cells that expresses CD8 develops its effector functions converting into cytotoxic T cells that are able to attack and destroy cells infected with viruses. Cytotoxic T cells also produce

165   IFN-γ and TNFα, which are important in the defense against viral infections[9].Memory T-cells
166   (Tm cells) can be either CD4 or CD8 virus-specific depending on the type of antigen
167   encountered[34]. Tm cells remain long-term after an infection has been eliminated and are quickly
168   converted into large numbers of effector T cells upon re-exposure to the specific invading
169   antigen that originated their activation and differentiation. Current COVID-19 vaccines seem to
170   have the ability to elicit both humoral and cell-mediated antiviral mechanisms, including a strong
171   IFN-γ–producing and interleukin-2–producing CD8+ cytotoxic T-cell responses[8].

172   B-cells participate in the humoral adaptive immune system and are responsible for mediating
173   the production of antigen-specific antibodies against invading pathogen. B-cells originate in the
174   bone marrow and after the encounter with the pathogen migrates to the spleen and other
175   lymphoid organs where they mature and differentiate into immunocompetent antibody producer
176   cells. Direct binding of the microbial antigen to receptors on its surface causes cell division and
177   proliferation. Some stimulated B-cells become plasma cells, which produce antibodies and
178   others become in long-life memory B-cells, which can be stimulated later and differentiate into
179   plasma cells.

180   **Human Leukocyte Antigen (HLA) Polymorphisms and Individual Vaccine Efficacy**

181   The immune system is diverse, with person to person variability, and the mosaic of human
182   leukocyte antigens (HLA) is the best example of its human polymorphism. Humans have
183   different allelic versions of the HLA genes, and certain variants at these loci encode for cell
184   receptors that can bind less reliably to some viral peptides and blunt the immune system's
185   normal defenses against the virus in vulnerable patients. Based on prior predictions, the
186   receptor binding domain (RBD) subunit appears to have no MHC class II peptides displayed in
187   ~15% of the worldwide population, ranging from 0.8% in self-reported Whites to 37% for Asians
188   (Liu et al.,2020). Notably, such a predicted uncovered population for RBD with no peptide-MHC
189   hits might be reduced to 0% (MHC class I) and 0.31% (MHC class II) by taking into account
190   some computed sets of augmentation peptides encompassing all filtered peptides from SARS-
191   CoV-2, according to computer-aided predictions[30].

192   Following a genomic combinatorial approach, MIT's OptiVax and EvalVax programs evaluate a
193   host of possible combinations of common alleles (e.g., HLA haplotypes) in each ancestry group
194   to find the most likely combo in order to design a vaccine with better coverage in every single
195   population. The two algorithms work in tandem in a feedback loop, but EvalVax takes relevant
196   population data from different individuals across the three main ancestry groups to feed the
197   beam search that OptiVax conducts over peptide-receptor pairs (i.e., by mapping the immune
198   response to the unique biochemistry of each population by genetic ancestral status), and
199   therefore ensure population coverage[30].

200   Significant differences among HLA alleles can define the susceptibility for a disease or the
201   effectiveness of a vaccine. Studies have been conducted to investigate the HLA genetic
202   variation and the immune response towards the SARS-CoV-2 *(Figure 1)*. These studies have
203   demonstrate that HLA-B*15:03 have a high capacity for presenting peptides suggesting that this
204   allele may be widely protective and could enable a cross-protective T-cell bases immunity,

205 whereas the HLA-B* 46:01 was found to bind to fewer peptides of the SARS-CoV-2, suggesting
206 that persons who hold this allele may produce a weak immune response therefore developing
207 severe symptoms (20). The HLA-B*46:01 was previously predicted as a susceptibility marker of
208 the SARS-CoV and associated to its severity in Asian populations[29]. These findings provide a
209 means of identifying individuals at risk of developing life-threatening COVID-19 and ensuring
210 their enrolment in vaccine trial.

211 Different genetic factors or risk loci, mostly related to key host antiviral defense mechanisms
212 and mediators of inflammation, have been reported since the beginning of the pandemic[42,11].
213 Among them, a gene cluster on chromosome 3 inherited from Neanderthals has been identified
214 as a potential predictor a COVID-19 severity[11]. Likewise, some novel GWAS significant hits on
215 chr12q24.13 (rs10735079, $p=1.6·10^{-8}$) in a gene cluster encoding antiviral restriction enzyme
216 activators (*OAS1-3*); on chr19p13.2-3 (rs2109069, $p=2.3·10^{-12}$ and rs2109069, $p=3.9·10^{-12}$) near
217 the gene encoding tyrosine kinase 2 (*TYK2*) and within the gene encoding dipeptidyl peptidase
218 9 (*DPP9*), respectively, as well as on chr21q22.1 (rs2236757, $p=5·10^{-8}$) in the interferon
219 receptor gene (*IFNAR2*) and the monocyte/macrophage chemotactic receptor (*CCR2*), have
220 also been postulated as potential predictors of critical illness caused by COVID-19[41].

221 Notably, a significant number of patients with severe COVID-19 carried rare genetic variants in
222 13 genes known to be critical in the body's defense against influenza virus, and more than 3.5%
223 were completely missing a functioning gene to produce any detectable type I interferons (IFNs)
224 in response to SARS-CoV-2[39]. A recent report by Bastard and co-workers from the COVID
225 Human Genetic Effort found that neutralizing autoantibodies against type I IFNs might underlie
226 critical COVID-19 by impairing the binding to their receptors and the activation of the
227 downstream responsive pathway (IFN-stimulated genes)[3,12]. Indeed, B cell autoimmune
228 phenocopy of inborn errors of type I IFN immunity seems to account for life-threatening COVID-
229 19 events (e.g., pneumonia) in up to 12.5% patients, mostly men. Consequently, adaptive
230 autoimmunity might be able to impair innate and intrinsic antiviral immunity in these patients.

231 Mutations in the ACE2 and the TMPRSS2, the primary and the second host proteins involved in
232 the SARS-CoV-2 infection have been identified. They identified 33 ACE2 variations in
233 approximately 7,000 Italian persons, with one of the variations (N720D) being adjacent to the
234 TMPRSS2 cleavage site and three other mutations: W69C, L351V and P389H were estimated
235 to cause conformational changes altering the interactions with the receptor binding domains
236 (RBD) of the S glycoprotein[5]. Recent reports of mutations in the spike S-protein of the SARS-
237 CoV-2 virus, and the corresponding receptor binding domains (RBD). New SARS-CoV-2 genetic
238 variants have been identified. The first mutation described was identified in the early months of
239 the pandemic and was a mutation located in the 614 amino acid position of the Spike protein[15].
240 Three other variants have been identified, one in South Africa designated B.1.351 or
241 501Y.V2[15,16,32], one in the United Kingdom, designated as B.1.1.7 or 501Y.V1.[15,16] and one in
242 Brazil designated as P-1[16].The B.1.1.7 variant has caused concern since it demonstrate to be
243 more transmissible[15,16,60]. Although these significant mutations in the spike protein have not
244 proven to affect critically the efficacy of the vaccine, is possible that further mutations can
245 enhance the capacity of the virus to evade the immune system therefore reducing the
246 effectiveness of the vaccines.

247 The rare vaccine-elicited disease enhancement could be an example of this kind of immunity
248 errors when already vaccinated subjects encounter circulating SARS-CoV-2 viruses. Such an
249 event invariably involves antibody-mediated immune "aberrant" mechanisms from direct
250 antibody-dependent enhancement (ADE) to immune complex formation by antibodies, albeit
251 accompanied by various coordinated cellular responses such as Th2 T-cell skewing. It is similar
252 to the clinical course of COVID-19 patients, in whom severe COVID-19 disease is associated
253 with the development of abnormal anti-SARS-CoV-2 serum antibodies, with titers correlating
254 directly with the severity of disease[34,44]. Like the risk of some idiosyncratic systemic adverse
255 events, a genetic trigger might certainly be involved in these episodes of vaccine-elicited
256 disease worsening. However, ADE is usually linked to viruses attacking macrophages such as
257 dengue and zika viruses.

258
259 **Population Diversity and Relationships to Vaccine Efficacy**

260 BNT162b2 and mRNA-1273 COVID-19 vaccines are based on messenger RNA (mRNA)
261 technology. mRNA vaccines consist of a single-stranded RNA encoding key virus proteins. In
262 the case of SARS-CoV-2 vaccine mRNA contains the transcript for proteins that help virus to
263 infect cells. Once injected, cells receive mRNA and use it as a template to make viral proteins.
264 These proteins trigger T- and B-cells, which activate, and B-cells produce antibodies. If a person
265 gets exposed to SARS-CoV-2 the T- cells as well as the antibodies will recognize the proteins
266 on the virus, which helps the immune system to detect and destroy the virus before it causes
267 illness. A safe and effective mRNA vaccine for COVID-19 is the first of its kind with an
268 authorization granted since such a technology has yet to be used for an approved vaccine.

269 Using machine learning (ML)-assisted *in silico* prediction modeling, researchers from the
270 Massachusetts Institute of Technology suggested that COVID-19 vaccines developed by
271 Moderna, Pfizer, AstraZeneca and others, may not protect individuals of non-European genetic
272 backgrounds (e.g., African or Asian descent) as well as they are expected to do for white
273 people[30,33]. According to these authors, individuals of mostly African or Asian ancestry seemed
274 to have on average a slightly increased risk of vaccine ineffectiveness. It is likely a consequence
275 of the lack of sufficiently diverse set of viral particles within the vaccine preparation to stimulate
276 the immune response at the same level across all individuals from different populations. Indeed,
277 depending on their genetic makeup, current vaccines could leave gaps in population coverage.
278 However, recently released data and publications on the BNT162b2 and AZD1222 vaccine
279 clinical trials suggest a certain degree of diversity. For BNT162b2, 26% participants self-
280 identified as Hispanics were enrolled whereas participants from Brazil, South Africa and UK
281 populations were enrolled in the AZD1222 trial[7,2].

282 Concerning the development of novel vaccines for the prevention of COVID-19, the NIH-Wide
283 Strategic Plan for COVID-19 Research stated on page 19, Objective 4.1, that it is paramount to
284 make efforts for ensuring the participation of a broad range of populations in clinical testing,
285 including high-risk groups as a major priority. Accordingly, efficacy studies are designed to also
286 include more genetically diverse underserved populations along with older individuals, people

287 with comorbidities, and other high-risk groups, as earlier described in the NIAID Strategic Plan
288 for COVID-19 Research ("NIH-Strategic Plan",2020).

289 The genetic variability among individuals within any given population can make possible that the
290 immunity elicited to a determine vaccine is variable, meaning that the same viral insult or
291 challenge (either in the form of a vaccine or the virus itself) will result in many different
292 responses. Thus, the response heterogeneity could provoke that a vaccine can either elicit
293 partial, complete or even fail to protect individuals treated under the same conditions. We know
294 that approximately, 5 to 10% of vaccines fail to induce long-term antibody protective levels[48], a
295 phenomenon that has been associated to the role of genetic factor in vaccine response. For
296 example, twins' studies have revealed variations of 89%, 39% and 46% in the IgG antibody
297 titters elicited by individuals vaccinated against measles, mumps and rubella vaccines[59].
298 Moreover, high heritability (40-70%) has been also observed in oral polio, tetanus, diphtheria
299 and hepatitis B vaccines (Newport et al.,2004). Since these variations have been observed in
300 vaccines that have been used worldwide for dozens of years, we can expect to see them in the
301 vaccines against SARS-CoV-2 in development. Based on immunogenicity findings from
302 conducted clinical trials, higher doses of the COVID-19 vaccine might actually be necessary to
303 elicit optimal protection in those with lower antigen-binding IgG and virus-neutralizing responses
304 due to a weakened immune system[8].

305 We still do not know how long immunity last, or whether these vaccines can only prevent the
306 illness or also prevent the infection. To these questions are also added the fact that is the first
307 time that mRNA vaccines could be authorized and there are no previous experiences on how to
308 produce it, preserve it and distribute it on huge scale a vaccine of this type without affecting their
309 stability.
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311 **Reactogenic Triggers from Vaccine Delivery Vectors**
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313 The variety of technology platforms (mRNA, viral vectors) utilized currently to produce vaccines
314 against SARS-CoV-2 infections may each also trigger genetically distinct immune reactogenic
315 profiles against chemical or genetic components of the vector.
316
317 Lipid nanoparticles (LNPs) are the vectors used for RNA delivery of BNT162b2 and mRNA-1273
318 vaccines[36]. Ionizable lipids, phospholipids, cholesterol and lipid-anchored polyethylene glycol
319 (PEG) are the most commonly used components for LNP formulations[58]. LNPs has been
320 advanced significantly with the development of new, ionizable lipids and lipid-like materials
321 which maintain a neutral or mildly cationic surface charge at physiological pH, thereby reducing
322 nonspecific lipid–protein interactions and facilitating oligonucleotide release in the cytosol[19].
323 Phospholipids play a structural role in LNPs, supporting the formation and disruption of the lipid
324 bilayer to facilitate endosomal escape. Cholesterol serves as a stabilizing element in LNPs and
325 plays a crucial role in the transfection of cells. Lipid-anchored PEGs deposit on the LNP surface,
326 where they act as barriers stabilizing the LNP sterically and reduce nonspecific protein binding.
327 The PEG in the LNP coating is suspected to have led to reactogenic sequelae and anaphylaxis
328 in some individuals[11,20].
329
330 Replication-incompetent adenoviral vectors have been under investigation as a platform to carry
331 a variety of transgenes, and express them as a basis for vaccine development[27]. A replication-

incompetent adenoviral vector based on human adenovirus type 26 (Ad26) is the basis of the ChAdOx1, Ad26.COV2.S, and Gam-COVID-Vac vaccines. Little is known about the mechanisms of immunity to the vector. However, neutralizing antibodies and cellular responses are induced after Ad26 vector administration to humans and non-human species. Vector specific neutralizing antibodies can specifically inhibit vector entry. A strategy to avoid reactogenicity is to construct vaccines with initial and booster immunizations in different adenovirus vectors (e.g. rAd26 followed by rAd5) to minimize cross reactivity. This approach has been successfully implemented for the Gam-COVID-Vac vaccine[56]. Individuals will have heterogeneous levels of reactogenicity to the vector depending on prior adenovirus exposure and also recipient immunogenetics[28].

There is precedent for variability in immune responses to exogenous chemicals manifested as cutaneous necrolyzing reactions. This immunogenetic link is best exemplified by the association between hypersensitivity to anticonvulsant drugs and HLA antigens (Fan et al 2017). Dermal hypersensitivity reactions associated with carbamazepine can occur in up to 10% of patients, and may also involve the eye. Conditions such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life threatening. The mechanism may be a reaction of CD8 or CD14 T cells, which produces tissue injury.

The risk of hypersensitivity is increased by the presence of specific *HLA* alleles. The *HLA-B*15:02* allele is strongly associated with carbamazepine-induced SJS/TEN in populations where this allele is most common, such as in Southeast Asia. According to the FDA-approved drug label for carbamazepine, testing for *HLA-B*15:02* for all patients with ancestry in populations with increased frequency of *HLA-B*15:02*, should be conducted prior to initiating carbamazepine, and the drug should not be used in patients who are carriers for *HLA-B*15:02* unless benefit outweighs risk. Carbamazepine dosing guidelines based on *HLA* genotype have been drawn by various consortia[17]. *HLA-B*15:02* is also associated with an increased risk of SJS and TEN in response to phenytoin treatment[49].

The *HLA-A*31:01* allele may also be a risk factor for SJS/TEN but is more strongly associated with other carbamazepine-induced reactions, such as DRESS and MPE. *HLA-A*31:01* is found in most populations, worldwide. *HLA-B*15:11* is another allele that has been linked with SJS/TEN. As a counterpart, *HLA-B*0702* has been associated as a protective marker to SJS[13].

Conclusion

This article has attempted to encompass the range of possible genetic polymorphism that could underlie immune response to vaccines. Public health policy on vaccinations may commonly incorporate individual characteristics of age and disease comorbidity, but rarely includes genetic polymorphisms, an addressable problem. This human genomic diversity could pinpoint individuals best served by nuanced or stratified recommendations, a paradigm of personalized health. The current COVID-19 pandemic represents an opportunity for personalized health.

The COVID-19 vaccines have been launched with a median observation time of 3 months and it is expected that observation of seroconversion will be longer lasting through the end of 2021. These seroconversion studies will unveil whether periodic "boosters shots" are required and shed some light on some clinical endpoints regarding disease protection and reduction of infectiousness. These seroprevalence studies will constitute fertile ground for population

genetics research as well during this period with global vaccination efforts to diverse populations. Immunogenetics, ancestry and other ethnicity-specific factors need to be taken seriously into account in the acceptability of foreign clinical data by regulatory agencies, given the substantial amount of critical information collected from volunteers who participated in these clinical trials of COVID-19 vaccines globally and its international development perspective[24]. The inter-ethnic differences in treatment responses are well known and have been reviewed previously[54].

The acute nature of allergic reactions to vaccination is reminiscent of the time course of adverse drug reaction mediated by the immune system. It may be that chemical features of the modified RNA or lipid coating of the vaccine is triggering these hypersensitivity reactions. Here, HLA antigens could be examined first, as these have traceable ethnogeography frequencies. There are also reactogenic features of the vaccination that would be amenable to genetic analysis. The most common side effects (fatigue, chills, myalgia, arthralgia, fever) are stronger after the second dose, and were felt by one-third to two-thirds of recipients in clinical trials. The variable reactions constitute an early sign the vaccines are prompting a variable immune response.

At a point when antibody titers have declined yet disease resistance prevails it would be appropriate to assess for the function of memory B-cells and memory T-cells that might retain information about the coronavirus for years or even decades. This will be a far more difficult task spanning the corresponding longer time interval of observation. Certainly, the realization that booster vaccinations may be necessary if antibody and immune protection wane would only elevate the relevance of the findings during that first-year post-vaccination. It is critical that vaccination efforts encompass parallel biobanking of recipient genomic DNA and serum immunoprofiling. The wonder of the novel COVID-19 vaccines could also elicit a new era of research and application of immunogenetics and personalized health.

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631   *Table 1.* List of potential relevant markers for immune response.

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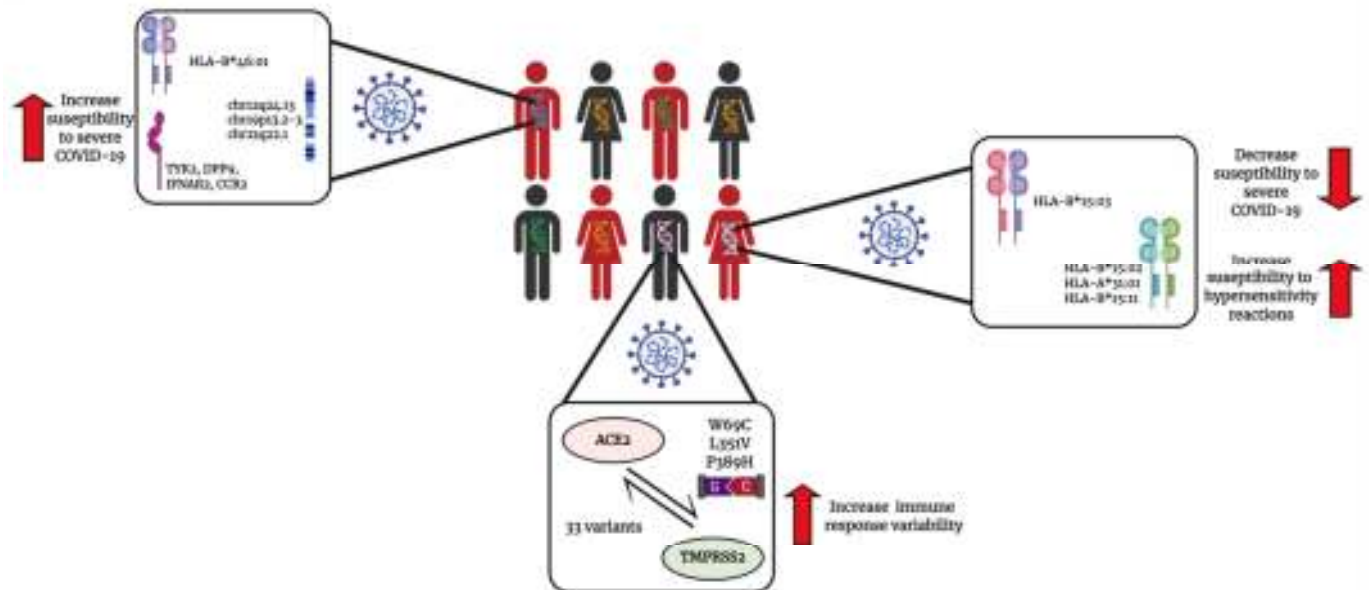| Marker	Natural Defense
BY55	natural killer cell receptor, immunoglobulin superfamily member
CCR2	chemokine C-C motif receptor 2
CCR5	chemokine C-C motif receptor 5
CCR6	chemokine C-C motif receptor 6
CD7	CD7 antigen p41
CD8A, CD8B1	CD8 antigen, alpha polypeptide and beta polypeptide 1
GNLY	granulysin
HLA-A, -C, -E, -G	major histocompatibility complex (class I, A, C, E, and G)
IFNB1	interferon, beta 1, fibroblast
IFNG	interferon gamma
INFAR1	interferon (alpha, beta, and omega) receptor 1
IFNGR2	interferon gamma receptor 2
IL-12A	interleukin 12A, natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35
IL-12B	interleukin 12B natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40
ITGB1	integrin, beta 1fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12
KIR2DL4	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 4
KLRC3	killer cell lectin-like receptor subfamily C, member 3
LGALS3BP	lectin, galactoside-binding, soluble, 3 binding protein
LILRB4	leukocyte immunoglobulin-like receptor, subfamily B with TM and ITIM domains, member 4
MICB	MHC class I polypeptide-related sequence B
PRFI	perforin 1
TCRA, TCRB	T-cell antigen receptor, alpha and beta subunits GZMA, GZMB - granzyme A and B
TNFRSF6	tumor necrosis factor receptor superfamily, member 6 (Fas)

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Figure 1.

Figure 1. The influence of the host genetics on the SARS-CoV-2 infection and COVID-19 severity suseptibility. In a population, many individuals may carry different single nucleotide polimorphisims (SNPs) in different genes. Individuals that carry specific polimorphisms near or in genes that codify for TYK2, DPP9, IFNAR2, CCR2 or carry the HLA-B*46:01 are believe to be more suseptible to develop severe COVID-19 symptoms. In contrast individuals that carry the HLA-B*15:03 are believe have a more protective phenotyoe and unlikely will develop severe COVID-19 symptoms. Individuals may have differents variants in their ACE2 and TMPRSS2 receptors, the two main receptors that the SARS-CoV-2 virus use to infect the host. These variants may increase the immune response variability between individuals therefore it may affect the efficacy of both treatments and vaccines. Hypersensitivity reactions