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COMMENTARY

Decoding the Human Genetic and Immunological Basis of COVID-19 mRNA Vaccine-Induced Myocarditis

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More than 10 billion doses of COVID-19 vaccines have been administered worldwide in the span of 18 months, providing an unprecedented opportunity to study and understand immunological responses and clinical reactions to vaccines. While severe adverse reactions to live-attenuated viral or bacterial vaccines have been successfully deciphered since the 1950s, with the discovery of a wide range of underlying inborn errors of immunity [1, 2], there is currently no

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molecular, cellular, and immunological explanation for life-threatening reactions to any other type of vaccine. COVID-19 mRNA vaccines are very effective at preventing hypoxemic COVID-19 pneumonia. For example, their efficacy for preventing invasive mechanical ventilation and in-hospital death has been estimated at 90% (95% CI = 88–91%) [3]. COVID-19 mRNA vaccines are also well tolerated by most people, with either no side effects or mild local/systemic reactions, such as pain at the injection site, fever, or chills in the days following vaccination [4]. However, rare but serious adverse events have been observed, including anaphylaxis, myocarditis, Guillain-Barré syndrome, transverse myelitis, Bell's palsy, and multisystem inflammatory syndrome [4–7]. These adverse events have a combined prevalence of about 90 per million doses administered [4]. It is unknown whether they are triggered by the adjuvant (lipid nanoparticles for the mRNA vaccines), the vaccine antigen (the perfusion-stabilized spike protein translated by the human cells), the core components of the vaccine (the nucleoside-modified mRNA), or a combination thereof. Some possible mechanisms have been suggested [8–10], but the underlying immunopathology and, hence, the risk factors predisposing a minority of vaccinees to experience any of these severe reactions remain unknown.

Myocarditis (with or without pericarditis) following vaccination with COVID-19 mRNA vaccines is the serious adverse event most closely monitored by national agencies and vaccine producers [11]. Myocarditis is an inflammation of the heart muscle. Before the emergence of COVID-19, the estimated global incidence of acute myocarditis, regardless of its etiology, was 1–10 cases per 100,000 individuals per year [8]. Vaccine-induced myocarditis typically presents as chest pain within 10 days of vaccination. The diagnosis is confirmed by an abnormal electrocardiogram and echocardiogram and/or magnetic resonance imaging results and the presence of high troponin levels in the blood. Vaccine-induced myocarditis is usually milder than acute myocarditis following viral infection, with only a few deaths reported (overall survival rate of > 99%), versus an estimated 4–5% risk of death or need for heart transplantation in the first year after viral-induced myocarditis [8]. In most cases, vaccine-induced myocarditis is treated with nonsteroidal anti-inflammatory drugs and resolves within a few days [11]. Studies around the world have shown that the frequency of myocarditis is approximately 1 per 100,000 doses of COVID-19 mRNA vaccines [12–14]. The risk is higher after the second dose, when the second dose is given less than six weeks after the first dose [15]. It is more frequent in male subjects between the ages of 12 and 30 years [12–14]. Another potential reported risk factor is intense physical activity just before or after vaccination, although it is harder to assess the risk of vaccine-induced myocarditis posed by exercise quantitatively. However, these risk factors alone cannot account for the rarity of these cases or shed light on the mechanism involved.

In this article of JoCI, Nishibayashi et al. report the first case of vaccine-induced myocarditis in monochorionic diamniotic twins [5]. The 13-year-old male twins developed myocarditis one day after receiving their second dose of the Pfizer-BioNTech BNT162b2 vaccine. The authors also noted that only one other vaccine-induced case was diagnosed at their hospital, which showed that the overall frequency of vaccine-induced myocarditis diagnosed at their hospital was similar to what has been observed around the world [5]. This case report suggests the hypothesis that only a very small fraction of vaccinated individuals develop post-vaccine myocarditis because these individuals carry rare germline genetic variants predisposing to myocarditis. Three additional arguments support the formulation of this hypothesis: (i) Rare inborn errors of immunity have been associated with rare adverse events following vaccination with live-attenuated vaccines [1]. Such inborn errors are the most frequent etiology of adverse events following administration of the bacille Calmette-Guérin (BCG) or oral poliovirus vaccines [1]. (ii) Rare variants of genes encoding sarcomeric proteins and associated with cardiomyopathy have been reported to increase the risk of acute myocarditis after viral infection [16, 17]. (iii) Human leukocyte antigen (HLA) alleles have been associated with adverse events following the oral administration or injection of drugs or vaccines (including inactivated or recombinant vaccines) [18–21]. For example, HLA-C*07:01 has been shown to be associated with clozapine-induced myocarditis in patients with schizophrenia [22]. Another HLA class I allele, HLA-A*03:01, has been associated with a higher frequency of side effects, such as fever and chills, following the administration of COVID-19 mRNA vaccines [23].

These previous studies provide a strong rationale for a genetic study. Importantly, testing this hypothesis requires access to hundreds of vaccine-induced myocarditis patients and COVID-19-induced myocarditis patients of diverse ethnicities, together with healthy controls matched for ethnicity, age, and sex. Because of the rarity of these serious adverse events following mRNA vaccination, we think that the problem is best tackled by an international consortium. We initially launched the COVID Human Genetic Effort to decipher the genetic and immunological basis of the various clinical manifestations of SARS-CoV-2 infection, starting with critical COVID-19 pneumonia (www.covidhge.com). We have deciphered the pathogenesis of this condition in a significant proportion of unvaccinated and vaccinated individuals carrying inborn errors of type I interferon (IFN) immunity or autoantibodies against type I IFNs [24, 25]. We present here our efforts to leverage and expand our existing COVID HGE infrastructure to investigate the

genetic and immunological determinants of myocarditis following COVID-19 vaccination.

We will test this hypothesis by enrolling patients from around the world via our network of clinicians. We will focus on myocarditis cases that occurred within 10 days of the first, second, or booster dose of the Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273 vaccines. Given the strong enrichment of vaccine-induced myocarditis relative to viral-induced myocarditis in the population of individuals under the age of 40 years, we will prioritize the recruitment of patients in this age group. The healthy age- and sex-matched controls will be individuals who have received at least two doses of COVID-19 mRNA vaccines who experienced no adverse event or serious side effect. We will sequence the exome or full genome of cases and controls, making it possible to perform two types of genetic analyses (Fig. 1). We will first perform unbiased rare-variant gene-collapsing analyses. For each gene, we will compare the number of cases carrying one or more qualifying variants with the number of controls carrying these variants. We will use a range of variant filters based on the predicted functional impact of the variants, and the allele frequency of the variants in the population, and we will test dominant, co-dominant, and recessive models. Candidate genetic variants will be functionally tested and validated in relevant cell line systems and in cells from the patients (such as leukocytes, or human induced pluripotent stem cell-derived cardiomyocytes) where possible [16]. We will also perform an HLA-wide association study. For each HLA allele, we will test for significant enrichment in cases relative to controls. To decipher the underlying mechanism at the molecular and cellular level, we will begin by searching for the immunological basis of HLA allele associations. For example, HLA class I molecules can interact with many receptors, including T cell receptors on $CD8^+$ T cells, inhibitory and activating killer immunoglobulin-like receptors (KIRs) on natural killer cells and some T cells, and leukocyte immunoglobulin-like receptors on myeloid cells.

With this approach, we intend to identify genes and alleles predisposing individuals to vaccine-induced myocarditis. Even if our hypothesis is validated in only a few individuals, it may point to mechanistically related causes in other patients, such as auto-antibodies, as exemplified by our study of critical COVID-19 pneumonia [24]. It may also

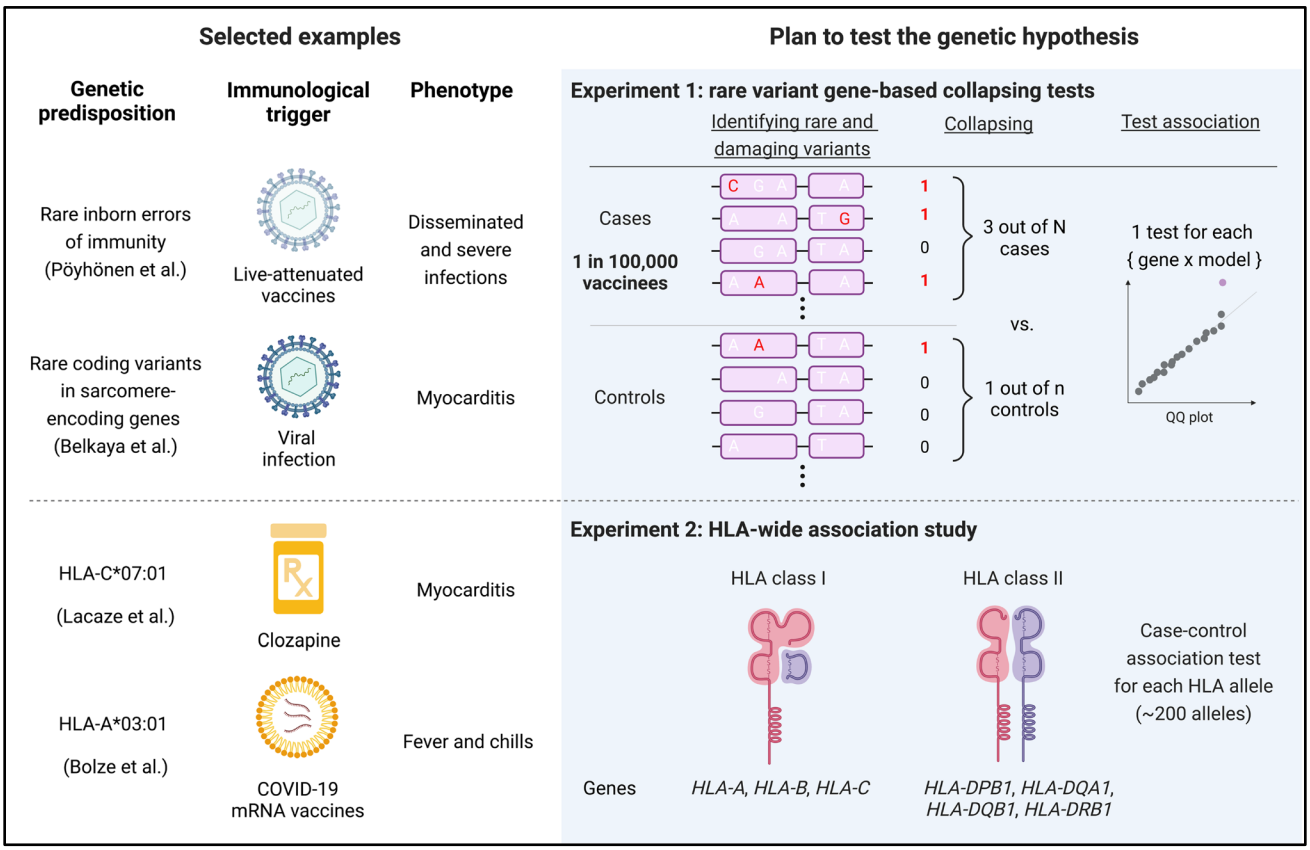

Fig. 1 Decoding the human genetic and immunological basis of COVID-19 mRNA vaccine-induced myocarditis. Left panel: examples of germline genetic variants conferring a predisposition to adverse events following a spectrum of immunological triggers. Right panel: schematic diagram of the two main genetic analyses that will be performed. Cases are patients with COVID-19 mRNA vaccine-induced myocarditis. Created with BioRender.com

help increase our understanding of the pathogenesis of acute myocarditis in general. One advantage of studying vaccine-induced myocarditis rather than acute myocarditis generally is that the immunological trigger (antigen and exposure timeline) is known with certainty and is the same for all cases. This increases the likelihood of detecting genetic homogeneity. It is also the first time that mRNA vaccines have been administered so widely, providing the first opportunity to study their rare adverse events, the pathogenesis of which may be common to other yet-to-be-developed mRNA vaccines.

The success of a genetic study to understand the cause of mRNA vaccine-induced myocarditis or other rare adverse events is dependent on the patients and families who consent to participate. The article by Nishibayashi et al. in JoCI highlights the importance of reporting cases of rare and atypical responses to mRNA vaccines, particularly familial cases such as monochorionic diamniotic twins [5]. The authors also discussed the necessity to create an international registry of patients with vaccine-induced myocarditis [5]. We hope that the article from Nishibayashi et al. and this commentary will inspire other teams of clinicians and scientists around the world to publish case reports of mRNA vaccine-induced myocarditis and refer their patients to an international consortium such as the COVID Human Genetic Effort to disentangle this mystery.

Consortium COVID human genetic effort

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Declarations

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References

1. Pöyhönen L, Bustamante J, Casanova J-L, Jouanguy E, Zhang Q. Life-threatening infections due to live-attenuated vaccines: early manifestations of inborn errors of immunity. J Clin Immunol. 2019;39:376–90.

2. Gothe F, Howarth S, Duncan CJ, Hambleton S. Monogenic susceptibility to live viral vaccines. Curr Opin Immunol. 2021;72:167–75.
3. Tenforde MW, Self WH, Gaglani M, Ginde AA, Douin DJ, Talbot HK, et al. Effectiveness of mRNA vaccination in preventing COVID-19-associated invasive mechanical ventilation and death - United States, March 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71:459–65.
4. Rosenblum HG, Gee J, Liu R, Marquez PL, Zhang B, Strid P, et al. Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the Vaccine Adverse Event Reporting System and v-safe. Lancet Infect Dis. 2022;802–12. Available from: https://doi.org/10.1016/s1473-3099(22)00054-8.
5. Nishibayashi H, Kishimoto S, Sekiguchi K, Okada S, Ihara K. Myocarditis in 13-year-old monochorionic diamniotic twins after COVID-19 vaccination. J Clin Immunol. 2022. Available from: https://doi.org/10.1007/s10875-022-01360-z.
6. Toledo-Salinas C, Scheffler-Mendoza SC, Castano-Jaramillo LM, Ortega-Martell JA, Del Rio-Navarro BE, Santibáñez-Copado AM, et al. Anaphylaxis to SARS-CoV-2 vaccines in the setting of a nationwide passive epidemiological surveillance program. J Clin Immunol. 2022. Available from: https://doi.org/10.1007/s10875-022-01350-1.
7. Klein NP, Lewis N, Goddard K, Fireman B, Zerbo O, Hanson KE, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021;326:1390–9.
8. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat Rev Cardiol. 2022;19:75–7.
9. Trougakos IP, Terpos E, Alexopoulos H, Politou M, Paraskevis D, Scorilas A, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. Trends Mol Med. 2022. Available from: https://doi.org/10.1016/j.molmed.2022.04.007.
10. Ko HL, Zhuo N, Chang ZW, Santosa A, Kalimuddin S, Lim XR, et al. In vitro vaccine challenge of PBMCs from BNT162b2 anaphylaxis patients reveals HSP90α-NOD2-NLRP3 nexus. Allergy. 2022. Available from: https://doi.org/10.1111/all.15503.
11. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. JAMA. 2022;327:331–40.
12. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021;144:471–84.
13. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex. Circulation. 2022. Available from: https://doi.org/10.1161/CIRCULATIONAHA.122.059970.
14. Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med. 2022. Available from: https://doi.org/10.1016/s2213-2600(22)00059-5.
15. Le Vu S, Bertrand M, Jabagi M-J, Botton J, Weill A, Dray-Spira R, et al. Risk of myocarditis after covid-19 mRNA vaccination: impact of booster dose and dosing interval. bioRxiv. 2022. Available from: https://www.medrxiv.org/content/10.1101/2022.07.31.22278064v1.
16. Belkaya S, Kontorovich AR, Byun M, Mulero-Navarro S, Bajolle F, Cobat A, et al. Autosomal recessive cardiomyopathy presenting as acute myocarditis. J Am Coll Cardiol. 2017;69:1653–65.
17. Kontorovich AR, Patel N, Moscati A, Richter F, Peter I, Purevjav E, et al. Myopathic cardiac genotypes increase risk for myocarditis. JACC Basic Transl Sci. 2021;6:584–92.
18. Stasiak M, Zawadzka-Starczewska K, Lewiński A. Significance of HLA Haplotypes in two patients with subacute thyroiditis triggered by mRNA-based COVID-19 vaccine. Vaccines (Basel). 2022;10. Available from: https://doi.org/10.3390/vaccines10020280.
19. Whitaker JA, Ovsyannikova IG, Poland GA. Adversomics: a new paradigm for vaccine safety and design. Expert Rev Vaccines. 2015;14:935–47.
20. Mitchell LA, Tingle AJ, MacWilliam L, Horne C, Keown P, Gaur LK, et al. HLA-DR class II associations with rubella vaccine-induced joint manifestations. J Infect Dis. 1998;177:5–12.
21. Klein NP, Zerbo O, Goddard K, Wang W, Fohner AE, Wiesner A, et al. Genetic associations with a fever after measles-containing vaccines. Hum Vaccin Immunother. 2021;17:1763–9.
22. Lacaze P, Ronaldson KJ, Zhang EJ, Alfirevic A, Shah H, Newman L, et al. Genetic associations with clozapine-induced myocarditis in patients with schizophrenia. Transl Psychiatry. 2020;10:37.
23. Bolze A, Neveux I, Schiabor Barrett KM, White S, Isaksson M, Dabe S, et al. HLA-A*03:01 is associated with increased risk of fever, chills, and stronger side effects from Pfizer-BioNTech COVID-19 vaccination. Human Genetics and Genomics Advances. 2022;100084. https://doi.org/10.1016/j.xhgg.2021.100084.
24. Bastard P, Vazquez S, Liu J, Laurie MT, Wang CY, Gervais A, et al. Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs. Sci Immunol. 0:eabp8966.
25. Zhang Q, Bastard P, COVID Human Genetic Effort, Cobat A, Casanova J-L. Human genetic and immunological determinants of critical COVID-19 pneumonia. Nature. 2022;603:587–98.