Identification of susceptibility loci for adverse events following COVID-19 vaccination in the Japanese population: A web-based genome-wide association study.

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Abstract
The novel coronavirus disease 2019 (COVID-19) pandemic has spread rapidly worldwide. To prevent the spread of COVID-19, mRNA-based vaccines made by Pfizer/BioNTech (BNT162b1) and Moderna (mRNA-1273) have been widely used worldwide, including in Japan. Various adverse events after COVID-19 mRNA vaccinations have been reported, with differences observed among individuals. However, the analysis on the genetic background for susceptibility to side effects has been limited. In the present work, we performed genome-wide association studies (GWAS) for self-reported adverse events of COVID-19 mRNA vaccination in 4,545 Japanese individuals and identified 14 associated loci. Among these, 6p21 was associated with 37.5°C or higher fever, 38°C or higher fever, and muscle pain. Our results may enable one to prepare for and manage side effects by knowing their susceptibility to the occurrence of adverse events. Furthermore, we obtained valuable data that can lead to the understanding of the mechanism of action of COVID-19 mRNA vaccines.

Introduction
The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly since its emergence in December 2019 and has affected hundreds of millions of people worldwide¹. The development and spread of safe and efficacious vaccines are now expected to be key for controlling the COVID-19 pandemic. According to the World Health Organization, several vaccines have been developed worldwide to prevent the spread of COVID-19². The mRNA-based vaccines made by Pfizer/BioNTech (BNT162b1) and Moderna (mRNA-1273) are among the most widely used in Japan as well as in other parts of the world. As of November 29, 2021, the Japanese government estimates that 97.2 million people have been fully vaccinated (received two doses of either vaccine) in Japan, representing 76.7% of the country’s population³.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
The most common side effects reported after COVID-19 mRNA vaccination are injection site reactions, fatigue, headache, and myalgia. These side effects are reported to be mild to moderate and last for a couple of days. Other local and systemic side effects that occur following vaccination include swelling, chills, joint pain, fever, redness, itching, nausea, diarrhea, abdominal pain, rash outside the injection site, and vomiting. Serious side effects, such as mild allergic reactions and anaphylaxis, are rare but have been reported. Side effects are a sign of a common immune response to the vaccine and are reported to vary between age, sex, and ethnicity. Interestingly, an elevated risk for myocarditis following COVID-19 mRNA vaccines was observed in males aged 12–29 years. HLA alleles were also reported to be associated with adverse events following COVID-19 mRNA vaccination. However, so far, the mechanism of the development of side effects is not clear, and there is still a lack of reports from other ethnicities.

One crucial challenge is to elucidate the factors that induce adverse events in response to the COVID-19 vaccine to understand the detailed mechanism of action. Here, we hypothesize that the individual differences in responses to the COVID-19 vaccine may be explained, in part, by genetic differences. Therefore, to clarify the possible mechanisms by which host genetic variation might affect the COVID-19 vaccine treatment response, a genome-wide association study (GWAS) was performed in the Japanese population.

Materials and methods

Study subjects

The data were obtained through Japanese direct-to-consumer (DTC) genetic testing services “Genequest ALL” and “Euglena MyHealth”, which are provided by Genequest Inc. (Tokyo, Japan) and Euglena Co., Ltd. (Tokyo, Japan), respectively. We asked subjects who were aged ≥ 18 years and who gave consent to participate in the study to answer internet-based questionnaires about COVID-19 vaccine adverse events. All participants provided written informed consent for the general use of their genetic data for research purposes. Prior to participating in this study, information on the study’s aim was sent to the participants and an additional study-specific agreement was obtained by opt-in. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Genequest Inc. (IRB no. 2021-0633-4) and Tohoku University Graduate School of Medicine (IRB no. 2021-1-469).

DNA sampling, genotyping, quality control, and genotype imputation

Saliva samples were collected, stabilized, and transported using an Oragene DNA Collection Kit (DNA Genotek Inc., Ottawa, Ontario, Canada) or GeneFix Saliva DNA Collection (Cell Projects Ltd, Harrietsham, Kent, UK). Genotype analysis was performed using: Illumina Infinium Global Screening Array v1+ Custom BeadChip (Illumina, San Diego, CA, USA), which contains 704,589 markers; Infinium Global Screening Array-24 v3.0+ Custom BeadChip, which contains 655,471 markers; HumanCore-12+ Custom BeadChip, which contains 302,073 markers; HumanCore-24+ Custom BeadChip, which contains 309,725 markers; or InfiniumCore-24+ Custom BeadChip, which contains 308,500 markers. Because the analyzed single nucleotide polymorphism (SNP) sets were
very different among the genotyping chips used, the subjects were divided into two groups depending on the type of genotyping chips: those analyzed by the two former chips (595,105 common markers) and those analyzed by the three later chips (289,930 common markers). These were referred to as populations A and B, respectively. We then applied the quality control and association analysis procedures separately for each cohort.

For quality control analysis, we filtered out SNP markers. The parameters were as follows: call rate per SNP < 0.95; Hardy–Weinberg equilibrium exact test p-value < 1 × 10⁻⁶; minor allele frequency < 0.01; SNPs not in autosomes. We also excluded subjects according to the following parameters: inconsistent sex information between the genotype and questionnaire; call rate per subject < 0.95; close relationship pairs determined using the identity-by-descent method (PI_HAT > 0.1875); and estimated non-Japanese ancestry. Quality control analyses were carried out using PLINK¹²,¹³ (version 1.90b3.42) and Eigensoft¹⁴ (version 6.1.3).

Genome-wide genotype imputation was performed using a pre-phasing/imputation stepwise approach implemented in EAGLE²¹⁵ (version 2.4) / Minimac³¹⁶ (version 2.0.1). The imputation reference panel was 1000 Genome Phase ³⁷ (version 5). We excluded variants with low imputation quality (R² < 0.3) and low minor allele frequency (<0.05) from further analysis. Finally, we used the dosage data for the common 5,930,410 variants for the GWAS in populations A and B.

**Adverse events measurement**

We provided internet-based questionnaires about the COVID-19 vaccine to the study subjects. First, they were asked about the manufacturer name of the COVID-19 vaccine they were shot. Next, they answered the local or systemic reactions they had after the first and/or second COVID-19 vaccination. The questionnaire provided 51 options for adverse events that are reported to occur with a frequency of 0.1% or more in Japanese subjects¹⁸. Detailed information about the questionnaires is provided in Table S1.

**Genome-wide association and meta-analysis**

The association between genotype dosage and the occurrence of COVID-19 vaccine adverse events was examined using a logistic regression model under the assumption of additive genetic effects. For each population, GWAS was performed with adjustment for age and sex using PLINK (version 2.00a3).

We combined the statistical data from both populations using a fixed-effects model and the inverse-variance weighting method with METAL software¹⁹ (version 2011-03-25). Variants achieving genome-wide significance (p < 5.0 × 10⁻⁸) in the meta-analysis were considered to be associated with the occurrence of COVID-19 vaccine adverse events.

**Results and Discussion**

**Study subjects and occurrence of COVID-19 vaccine adverse events**

The data was analyzed independently in the two groups established according to genotyping chips (population A and B), because the analyzed SNP sets were very different between the chips. The
characteristics of the subjects are presented in Table 1. The population vaccinated with mRNA-1273 vaccine was older and had a greater prevalence of females, when compared to the population vaccinated with BNT162b1. This difference may be a result of the Japanese vaccination circumstance where the BNT162b1 vaccine was approved at first and administered to vaccination priority targets, such as elderly people and health care workers. The occurrence of each adverse event following the COVID-19 vaccine is shown in Table S2. The occurrence of systemic reactions was more prevalent after the 2\textsuperscript{nd} vaccination dose than after the 1\textsuperscript{st} vaccination (44% and 71% in BNT162b1, 57% and 96% in mRNA-1273, for 1\textsuperscript{st} and 2\textsuperscript{nd} doses, respectively). This is consistent with previous reports\textsuperscript{8,20}. Compared to the report from the Japanese Ministry of Health, Labour, and Welfare\textsuperscript{18}, most of the adverse events had occurrences with a range of difference of < 5%; 88% and 82% for BNT162b1 vaccine, and 79% and 62% for mRNA-1273 vaccine, for 1\textsuperscript{st} and 2\textsuperscript{nd} dose, respectively (Table S2).

**Table 1.** Characteristics of the subjects included in the present study

|                    | population A |                    | population B |                    |
|--------------------|--------------|--------------------|--------------|--------------------|
|                    | BNT162b1 vaccine | mRNA-1273 vaccine | BNT162b1 vaccine | mRNA-1273 vaccine |
| N                  | 2395         | 2017               | 1184         | 1028               |
| female (%)         | 47.06        | 47.00              | 40.96        | 41.53              |
| Age (mean ± SD)    | 52.43 ± 11.48| 53.70 ± 11.37      | 45.61 ± 11.26| 46.08 ± 11.34      |
|                    | 629          | 537                | 62.9         | 42.08              |
|                    | 11.26        | 11.34              | 11.77        | 10.53              |

SD, standard deviation

**Incidence of COVID-19 vaccine adverse events with respect to sex and age differences**

Previous studies\textsuperscript{7,20} reported that women and younger people have a higher risk of experiencing adverse events after COVID-19 vaccination. Consistent with these studies, the present study also showed a higher risk for females (\(p\)-value < 0.05; 51% and 63% in BNT162b1, 39% and 53% in mRNA-1273, for 1\textsuperscript{st} and 2\textsuperscript{nd} doses, respectively) and younger people (\(p\)-value < 0.05; 51% and 63% in BNT162b1, 31% and 41% in mRNA-1273, for 1\textsuperscript{st} and 2\textsuperscript{nd} doses, respectively) (Table S3, S4).

**GWAS for COVID-19 vaccine adverse events**

We performed GWAS for each population and performed a meta-analysis of adverse events. We identified 14 loci associated with adverse events in response to COVID-19 vaccine at the genome-wide significance level (\(p\)-value < \(5 \times 10^{-8}\)), for 1\textsuperscript{st} or 2\textsuperscript{nd} dose of BNT162b1 or mRNA-1273 vaccine (Table 2, Table S5). The associations between rs9266082 and higher fever, and rs13279405 and chest pain were found with \(p\)-value < 0.05, for both BNT162b1 and mRNA-1273 vaccines. However, the other SNPs were differentially associated with BNT162b1 and mRNA-1273 vaccines. Two hypothesis could explain this fact: the genetic susceptibility to adverse events may differ between the two COVID-19 mRNA vaccines; or the populations may have differential statistical power because of differential sample size and adverse event occurrence. In these associated loci, 6p21 (rs551634406, rs183300, rs9266082, rs375726766, rs3135408) was associated with 37.5 °C or higher fever, 38 °C or
higher fever, and muscle pain.

The annotations of the associated SNPs are shown in Tables 321,22. The occurrence of adverse events in response to COVID-19 vaccines was previously reported to differ among ethnicities. The prevalence of fatigue as a reaction to BNT162b2 vaccine was 59% and 69%, and fever was 16% and 38%, in European and Japanese populations, respectively8,18,20. The prevalence of fatigue as a reaction to mRNA-1273 vaccine was 68% and 80%, and fever was 17% and 77%, in European and Japanese populations, respectively8,18,20. In our study, the allele frequencies for eight out of the 14 SNPs (rs10744866, rs146922515, rs551634406, rs183300, rs375726766, rs13279405, rs34086990, rs3135408) differed by more than 10% between European and Japanese populations, suggesting the possibility that the difference in genetic backgrounds may influence the occurrence of adverse events in response to COVID-19 vaccines. These loci, especially 6p21, were associated with the expression of many genes according to GTEx22. These genes were suggested to influence the mechanism of action of the COVID-19 vaccine. HLA genes’ (HLA-B, C, DPA1) mRNA expression differed among the genotypes of the associated loci. HLA alleles were also reported to be associated with adverse events following COVID-19 mRNA vaccination10. In fact, HLA genes have been reported to be associated with the occurrence of adverse events after administration of various vaccines23 and drugs24. Regarding other genes, increased NOTCH4 expression in circulating regulatory T cells in COVID-19 patients was associated with disease severity and predicted mortality25. The expression of RPS18 was previously found to be increased in isolated T-cells on stimulation with the live influenza virus26. A SNP in the BAK1 and A haplotype of MICB was associated with dengue hemorrhagic fever caused by dengue virus27,28. A SNP in PSORS1C1 was associated with allopurinol-induced severe adverse reactions29,30. SNPs in HSP70, TAPBP, and WDR46 were found to be associated with aspirin-exacerbated respiratory disease31–33.

Limitations

This study has some limitations. Initially, we included 51 types of adverse events, but multiple test corrections were not performed. Therefore, the associated loci that we identified can include false positives, and thus, replicate studies are required. Second, our data on the adverse events was based on web-based self-reports and might have been affected by recall bias. However, the occurrence of adverse events was similar to the large-scale survey performed before in Japan18. Thus, our adverse event data is thought to have some reliability. Finally, our GWAS was based only on the Japanese population. Therefore, our results may not be directly applicable to other ethnicities.
| Reaction                                              | SNP       | CHR | Position   | EA | NEA  | EAF | BNT162b1 Vaccine | mRNA-1273 Vaccine |
|-------------------------------------------------------|-----------|-----|------------|----|------|-----|----------------|------------------|
| itching of vaccination site                           | rs10744866| 12  | 110104688 | A  | T    | 0.37| 1\textsuperscript{st} 0.89, 0.12, 0.317 | 0.55, 0.11, 2.42 × 10\textsuperscript{-8} |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 1.10, 0.11, 0.404 | 0.88, 0.11, 0.239 |
| movement disorder at the vaccination site             | rs146922515| 10  | 23658821  | CA | C    | 0.43| 1\textsuperscript{st} 1.13, 0.07, 0.0783 | 1.23, 0.09, 0.0286 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 1.03, 0.08, 0.738 | 1.80, 0.11, 3.69 × 10\textsuperscript{-8} |
| internal bleeding in vaccination site                 | rs1217097 | 8   | 64623330  | A  | G    | 0.24| 1\textsuperscript{st} 4.12, 0.24, 1.79 × 10\textsuperscript{-9} | 1.11, 0.41, 0.797 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 1.85, 0.34, 0.0699 | 0.25, 0.78, 0.0768 |
| 37.5°C or higher fever                                | rs551634406| 6   | 30965800  | (A)\textsubscript{15}TAT | A | 0.49| 1\textsuperscript{st} 0.90, 0.11, 0.354 | 0.96, 0.11, 0.703 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 0.66, 0.07, 1.09 × 10\textsuperscript{-9} | 0.84, 0.12, 0.127 |
| 37.5°C or higher fever                                | rs183300  | 6   | 33526951  | C  | T    | 0.46| 1\textsuperscript{st} 0.97, 0.11, 0.741 | 0.91, 0.10, 0.359 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 0.66, 0.06, 3.39 × 10\textsuperscript{-11} | 0.82, 0.11, 0.0736 |
| 38°C or higher fever                                  | rs9266082 | 6   | 31320022  | C  | T    | 0.39| 1\textsuperscript{st} 1.31, 0.21, 0.201 | 1.39, 0.16, 0.0448 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 1.60, 0.08, 4.59 × 10\textsuperscript{-9} | 1.13, 0.09, 0.144 |
| 38°C or higher fever                                  | rs375726766| 6   | 33335716  | C  | CA   | 0.36| 1\textsuperscript{st} 1.04, 0.23, 0.856 | 0.90, 0.18, 0.556 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 0.60, 0.09, 3.67 × 10\textsuperscript{-8} | 0.98, 0.09, 0.855 |
| peripheral coolness                                  | rs10205263| 2   | 221076324 | C  | T    | 0.090| 1\textsuperscript{st} 13.09, 0.44, 7.30 × 10\textsuperscript{-9} | 1.31, 0.93, 0.771 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 3.61, 0.41, 0.00180 | 0.37, 0.56, 0.0777 |
| dizzy                                                 | rs67053119| 8   | 51750913  | T  | A    | 0.075| 1\textsuperscript{st} 0.52, 0.63, 0.300 | 1.25, 0.63, 0.726 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 0.93, 0.38, 0.851 | 5.84, 0.32, 2.94 × 10\textsuperscript{-8} |
| chest pain                                            | rs13279405| 8   | 12986585  | T  | C    | 0.056| 1\textsuperscript{st} 17.29, 0.51, 2.69 × 10\textsuperscript{-8} | 7.87, 0.68, 0.00225 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 5.66, 0.56, 0.00210 | 4.38, 1.02, 0.146 |
| abdominal discomfort                                  | rs57177321| 11  | 33988111  | T  | C    | 0.10 | 1\textsuperscript{st} 7.63, 0.36, 2.30 × 10\textsuperscript{-8} | 0.71, 0.91, 0.705 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 1.94, 0.50, 0.182 | 0.43, 0.82, 0.301 |
| joint pain                                            | rs34086990| 8   | 81791475  | A  | AT   | 0.19 | 1\textsuperscript{st} 0.72, 0.31, 0.284 | 3.78, 0.24, 3.94 × 10\textsuperscript{-8} |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 1.07, 0.18, 0.708 | 1.34, 0.18, 0.0962 |
| muscle pain                                           | rs3135408 | 6   | 33275013  | C  | T    | 0.36 | 1\textsuperscript{st} 0.82, 0.09, 0.0392 | 0.84, 0.11, 0.111 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 0.56, 0.10, 1.13 × 10\textsuperscript{-8} | 0.88, 0.10, 0.222 |
| urticaria                                             | rs2274569 | 1   | 100435079 | C  | T    | 0.064| 1\textsuperscript{st} 3.82, 0.51, 0.00811 | 2.94, 0.79, 0.170 |
|                                                      |           |     |            |    |      |     | 2\textsuperscript{nd} 11.78, 0.45, 3.15 × 10\textsuperscript{-8} | 1.91, 1.23, 0.600 |
Loci that reached genome-wide significance after meta-analysis at the 1st or 2nd dose of BNT162b1 or mRNA-1273 vaccine. CHR, chromosome; EA, effect allele; NEA, non-effect allele; EAF, effect allele frequency; OR, odds ratio of effect allele; SE, standard error for beta of effect allele; P, p-value
Table 3. Allele frequency and expression quantitative trait locus (eQTL) genes for loci associated with COVID-19 vaccine adverse events

| SNP       | associated reaction                      | location | allele frequency | eQTL genes                                      |
|-----------|-----------------------------------------|----------|------------------|-------------------------------------------------|
| rs10744866 | itching of vaccination site             | 12q24    | 0.20             | 0.37 MVK, FOXN4, KCTD10                         |
| rs146922515| movement disorder at the vaccination site| 10p12    | 0.35             | 0.43 None in GTEx                               |
| rs1217097  | internal bleeding in vaccination site   | 8q12     | 0.28             | 0.24 RP11-579E24.2, LINCO1289                    |
| rs551634406| 37.5°C or higher fever                  | 6p21     | 1.00             | 0.49 None in GTEx                               |
| rs183300   | 37.5°C or higher fever                  | 6p21     | 0.65             | 0.46 BAK1, COL11A2, DAXX, IP6K3                  |
| rs9266082  | 38°C or higher fever                    | 6p21     | 0.30             | 0.39 C4B, CCHCR1, CSNK2B, HCG22, HCG27, HLA-B, HLA-C, HSPA1B, MIBC, MIR6891, NOTCH4, POUSF1, PSORS1C1, PSORS1C2, RNF5, SFTA2, TCF19, USP8P1, VARS2, VWA7, WASF5P, Xbac-BPG181B23.7, Xbac-BPG248L24.12, Xbac-BPG299F13.17 |
| rs375726766| 38°C or higher fever                    | 6p21     | 0.60             | 0.36 None in GTEx                               |
| rs10205263 | peripheral coolness                     | 2q35     | 0.071            | 0.09 No eQTL genes                              |
| rs67053119 | dizzy                                   | 8q11     | 0.12             | 0.075 No eQTL genes                             |
| rs13279405 | chest pain                              | 8p22     | 0.24             | 0.056 No eQTL genes                             |
| rs57177321 | abdominal discomfort                    | 11p13    | 0.072            | 0.1 No eQTL genes                               |
| rs34086990 | joint pain                              | 8q21     | 0.042            | 0.19 None in GTEx                               |
| rs3135408  | muscle pain                             | 6p21     | 0.54             | 0.36 None in GTEx                               |
| rs2274569  | urticaria                               | 1p21     | 0.076            | 0.064 None in GTEx                               |

European allele frequency, allele frequency of European (non-Finnish) in gnomAD v2.1.1; Japanese allele frequency, allele frequency in this study; eQTL genes, SNPs associated with COVID-19 vaccine adverse events were associated with gene expression in GTEx (p-value <0.0005).

Conclusions

In this study, we performed GWAS for adverse events following COVID-19 vaccination. To the extent of our knowledge, this work represents the first of its kind focusing on East Asian populations. We identified 14 loci associated with adverse effects of COVID-19 vaccines, in the Japanese population. We discovered that the genetic background was in fact associated with susceptibility to adverse events following COVID-19 vaccination. Our results may enable one to prepare for and manage adverse events on the basis of their susceptibility to the occurrence of adverse events. Furthermore, we obtained valuable basic data that can be used for investigating the mechanism of action of COVID-19 vaccines.
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Author contributions

K.S. and S.T. designed the experiment. S.N., K.K., M.C., H.K., and K.T. created the questionnaire about the COVID-19 vaccine and reviewed the data. S.N. performed the statistical analyses. S.N. and K.S. wrote the manuscript. H.K. and K.T. contributed to the interpretation of the results and critically reviewed the manuscript. All authors commented on and approved the manuscript.

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Competing interests

S.N., K.K, and M.C. are employees of Genequest Inc.; K.S. and S.T. are board members of Genequest Inc.; H.K. and K.T. declare no competing interests.

Data availability

All data analyzed during this study are included in this published article and its additional files. Other data are available from the authors upon reasonable request.

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