Short Communication

Genetic Variability in SARS-CoV-2 Vaccine Response: Association of rs3824949 in *TRIM5* With Antibody Titers in a Japanese Cohort

§Satomi Nagaya*[1], §Nguyen Hoang Thao Giang*[1], J. Luis Espinoza*[2], Koichi Yamaguchi*[1,3], Kota Goto*[4], Hisanori Horiuchi*[4], †Eriko Morishita*[1,5]

†Correspondence: Department of Clinical Laboratory Science, Division of Health Sciences, Graduate School of Medical Science, Kanazawa University, 5-11-80 Kodatsuno, Kanazawa, Ishikawa 920-0942, Japan
Tel: +81-76-265-2606; Fax: +81-76-265-2606;
E-mail: eriko86@staff.kanazawa-u.ac.jp
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§These authors contributed equally to this work
*1 Department of Clinical Laboratory Science, Division of Health Sciences, Graduate School of Medical Science, Kanazawa University, 5-11-80 Kodatsuno, Kanazawa, Ishikawa 920-0942, Japan
*2 Faculty of Health Sciences, Kanazawa University, 5-11-80 Kodatsuno, Kanazawa, Ishikawa 920-0942, Japan
*3 Department of Medical Technology, Faculty of Health Sciences, Tsukuba International University, 6-20 Manabe, Tsuchiura, Ibaraki 300-0051, Japan
*4 Department of Molecular and Cellular Biology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan
*5 Department of Hematology, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8640, Japan

ABSTRACT

Individual immune responses to SARS-CoV-2 vaccination vary considerably; however, the genetic factors influencing antibody production remain incompletely understood. This study investigated the association between genetic polymorphisms and anti-SARS-CoV-2 antibody levels in 405 healthy Japanese individuals three weeks after their first dose of an mRNA vaccine. We focused on three genetic polymorphisms previously associated with antibody responses in humans. The GG genotype of rs3824949 in *TRIM5* was significantly associated with higher antibody titers ($P = 0.0009$), whereas rs4792800 in *TNFRSF13B* and rs1611350 in *HLA-F-AS1* showed no significant associations. Stepwise regression analysis confirmed that rs3824949 remained an independent predictor after adjusting for age, lymphocyte count, and platelet count. Given the role of *TRIM5* in innate immunity, our findings suggest that rs3824949 may enhance immune responses to SARS-CoV-2 mRNA vaccination, highlighting the role of host genetics in individual variability in vaccine responses. By identifying a genetic factor that significantly influences antibody responses, this study lays the groundwork for personalized vaccine strategies tailored to individual genetic backgrounds. Moreover, these findings may have broader implications beyond SARS-CoV-2, informing the design and optimization of future mRNA vaccines targeting other infectious diseases or cancers. Our work highlights the potential of precision vaccinology and emphasizes the need to include ethnically diverse populations in immunogenetic research. These insights contribute to a more equitable and effective global vaccination strategy, particularly in the era of rapidly advancing mRNA vaccine technologies.

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Key Words
COVID-19, gene association studies, immune response; SARS-CoV-2 vaccine, tripartite motif-containing 5α (TRIM5α)

I. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in millions of deaths worldwide and represents one of the most extensively documented diseases in modern medical history [1]. To prevent COVID-19, various vaccines were authorized between late 2020 and early 2021, with mRNA vaccines becoming the most widely administered [2]. Substantial interindividual variation in antibody production has been reported following mRNA vaccination, with notable differences observed across racial and geographic populations [3)4)]. Factors such as age, sex, underlying health conditions, and vaccine type have been proposed as contributors, along with host genetic factors, including polymorphisms in immune-related genes [3)5)-7)]. For instance, a study conducted in Germany reported that individuals with the GG genotype of the *IFITM3* polymorphism rs34481144 exhibited lower antibody responses to the BNT162b2 (Pfizer-BioNTech) mRNA vaccine compared to those carrying the A allele [8]. In the United Kingdom, the HLA-DQB1*06:04 allele has also been associated with increased antibody production following SARS-CoV-2 vaccination [9]. These findings have drawn global attention to the influence of genetic background on vaccine-induced immune responses. Numerous human genetic polymorphisms have been shown to affect humoral responses to vaccines targeting common pathogens. These include rs3824949 in tripartite motif-containing 5 (*TRIM5*), which has been associated with anti-rubella antibody responses [10]; rs4792800 in tumor necrosis factor receptor superfamily member 13B (*TNFRSF13B*), linked to IgG levels in healthy individuals [11]; and rs1611350 in human leukocyte antigen-F antisense RNA 1 (*HLA-F-AS1*), associated with variability in immune responses, including IgM, IgG, and IgG1 levels, following vaccination [12]. TRIM5α plays a pivotal role in innate immunity by restricting retroviruses such as human immunodeficiency virus (HIV) [13]. *TNFRSF13B* encodes a protein in the tumor necrosis factor (TNF) receptor superfamily that supports humoral immunity. *HLA-F-AS1* modulates immune responses through interactions with microRNAs.

Given the known racial differences in immune responses, this study investigated the association between three genetic polymorphisms and immune responses to SARS-CoV-2 vaccination in the Japanese population. Anti-SARS-CoV-2 antibody titers were measured in 405 healthy Japanese individuals three weeks after receiving the first dose of an mRNA vaccine, and polymorphisms in *TRIM5*, *TNFRSF13B*, and *HLA-F-AS1* were genotyped in 272 of these participants. In addition, potential associations between antibody titers and various complete blood count (CBC) parameters obtained at the same time point were evaluated. Interindividual variability in vaccine responses remains a major challenge across numerous diseases. By identifying host genetic factors in a Japanese cohort, this study contributes to precision vaccinology and highlights the importance of ethnicity-specific research. Although this study focuses on SARS-CoV-2 mRNA vaccines, the genetic mechanisms identified may also be relevant to other mRNA-based vaccines, highlighting TRIM5α as a potential universal modulator of vaccine-induced immunity.

II. Materials and methods

Ethical Approval and Informed Consent

All participants, including university employees and students, were recruited from Kanazawa University. All procedures involving human participants were conducted in accordance with the Declaration of Helsinki and institutional guidelines. The study protocol was approved by the Ethics Committee of Kanazawa University (No. 1025-6, August 22, 2022) and Tohoku University (No. 2021-1-1125, March 23, 2022). Written informed consent was obtained from all the participants prior to their inclusion in the study.

Study Population and Study Design

This study included 405 Japanese individuals who received the Moderna mRNA SARS-CoV-2 vaccine. All participants were employees or students from a single institution and were vaccinated as part of a mass vaccination program. International students were excluded from the study. Blood samples were collected approximately three weeks after the first dose, with a median of 21 days (interquartile range [IQR], 19–22), during the period from July 29 to August 20, 2021. Antibody levels and complete blood counts (CBC) were assessed concurrently. Baseline (pre-vaccination) blood samples were not available for analysis.

Blood Sample Collection, Anti-SARS-CoV-2 Antibody Titers, and CBC Measurement

A total of 2 mL of blood was collected in an EDTA-2K tube for CBC analysis using the XE-2000 hematology analyzer (Sysmex Corporation, Kobe, Japan). An additional 9 mL of blood was drawn into a serum separation tube, centrifuged, and the serum was stored at −80℃ until analysis. Measurement of serum antibody titers was outsourced to Sysmex Corporation. Serum levels of anti-

SARS-CoV-2 spike IgG (S-IgG) antibody titers were measured using the HISCL-5000 system with the HISCL™ SARS-CoV-2 S-IgG reagent. S-IgG antibody titers were converted from SU/mL to the World Health Organization (WHO) International Standard BAU/mL (NIBSC code 20/136) using the manufacturer's formula ($y = 5.93x + 0.21$), calibrated against the WHO standard. Nucleocapsid IgG (N-IgG) antibody titers were measured using the HISCL™ SARS-CoV-2 N-IgG reagent, with a cutoff of 10 SU/mL used to confirm prior infection. As reported in the external validation by Noda et al. [14], the performance of the assay was validated using serum samples from 60 individuals with confirmed SARS-CoV-2 infection and 500 pre-pandemic negative controls, yielding an exceptionally high area under the curve (AUC) of 0.9998 and demonstrating excellent stability and reproducibility. These validation samples were not part of the present cohort and were collected and analyzed under independent approvals (NCGM-G-003472-02; NCC 2020-026).

Extraction of Cell-Free DNA and Genotyping of Genetic Polymorphisms

Cell-free DNA was extracted from serum samples using the FitAmp Plasma/Serum DNA Isolation Kit (Epigentek Group Inc., Farmingdale, NY, USA). Genetic polymorphisms were analyzed using TaqMan® SNP Genotyping Assays (Thermo Fisher Scientific, Inc., Waltham, MA, USA) with the QuantStudio® 3 Real-Time PCR System (Thermo Fisher Scientific, Inc.). Genotyping was specifically conducted for rs3824949 (Assay ID: C_1452185_20), rs4792800 (Assay ID: C_27968962_10), and rs1611350 (Assay ID: C_26543570_10). These assays were developed and validated by the manufacturer under stringent quality control measures to ensure high accuracy and reproducibility, thereby enhancing the reliability of the genotyping results in this study.

Statistical Analysis

Statistical analyses were performed using StatFlex (version 7; Artec Co., Ltd., Osaka, Japan). Variables with |skewness| ≥ 1.0 or |kurtosis| ≥ 3.0 underwent power transformation. Normality was assessed using the Kolmogorov–Smirnov test (P-value > 0.05 = normal; **Supplementary Table 1**). Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median and IQR. For three-group comparisons of non-normal antibody levels, the Kruskal–Wallis test was used; significant results were followed by Dunn's test with Bonferroni correction for pairwise comparisons. Multiple regression was conducted in three steps to identify independent determinants of antibody titers: first, age and CBC parameters (platelet and lymphocyte counts) were included based on preliminary associations; second, genotype (rs3824949) was added to assess its independent effect; finally, a genotype-only model was evaluated. Statistical significance was set at P-value < 0.05.

Table 1 Cross-tabulation analysis of genetic variant genotypes and anti-SARS-CoV-2 antibody levels

rs3824949 (*TRIM5*)		GG	GC	CC	H-value	*P*-value
	n (%)	105 (38.6)	92 (33.8)	75 (27.6)		
Ab titer (BAU/mL)	Median	444	380	336	13.061	0.0015
	IQR	300–664	264–608	198–412		
rs4792800 (*TNFRSF13B*)		**AA**	**AG**	**GG**	**H-value**	***P*-value**
	n (%)	114 (41.9)	118 (43.4)	40 (14.7)		
Ab titer (BAU/mL)	Median	381	378	368	0.580	0.7482
	IQR	268–571	267–597	232–509		
rs1611350 (*HLA-F-AS1*)		**TT**	**TC**	**CC**	**H-value**	***P*-value**
	n (%)	93 (34.2)	141 (51.8)	38 (14.0)		
Ab titer (BAU/mL)	Median	375	376	387	0.255	0.8803
	IQR	260–543	258–591	272–519		

Data are presented as the number of subjects (n), median antibody titers, and interquartile ranges (IQR) for each genotype of the genetic polymorphisms. Only rs3824949 (*TRIM5*) showed a significant association between genotype and anti-SARS-CoV-2 antibody levels.

Abbreviation: Ab titer, antibody titer; *HLA-F-AS1*, human leukocyte antigen-F antisense RNA 1; IQR, interquartile range; *TNFRSF13B*, tumor necrosis factor receptor superfamily member 13B; *TRIM5*, tripartite motif-containing 5.

III. Results

Genetic Polymorphisms and Anti-SARS-CoV-2 Antibody Titers

Among the 405 healthy Japanese individuals included in this study, 169 (41.7%) were men and 236 (58.3%) were women, with a median age of 27 (21–45) years (**Supplementary Table 1**). A questionnaire survey conducted at the time of blood collection revealed that none of the participants reported a history of symptomatic SARS-CoV-2 infection during the sample collection period, and no individuals tested positive for SARS-CoV-2 N-IgG. Based on these findings, the immune response due to prior SARS-CoV-2 infection was considered to be minimal in this cohort. We then investigated the association of anti-SARS-CoV-2 antibody titers with genetic variants in genes that were reportedly associated with humoral immune responses to other vaccines. Cell-free DNA samples for these genotyping studies were available in 272 subjects, of whom 96 (35.3%) and 146 (64.7%) were men and women, respectively, with a median age of 23 (21–34) years. The genotype frequencies of the three genetic polymorphisms tested were as follows (**Figure 1A**): rs3824949 (GG = 38.6%, CC = 27.6%, and GC = 33.8%), rs4792800 (AA = 41.9%, GG = 14.7%, and AG = 43.4%), and rs1611350 (TT = 34.2%, CC = 14.0%, and TC = 51.8%). The genotype distribution was consistent with available data on the Japanese population from the HapMap Project and the 1000 Genomes Project. Individuals carrying the GG genotype of the rs3824949 polymorphism had significantly higher antibody levels than those with the CC genotype ($P = 0.0015$; **Table 1**, **Figure 1B**). Specifically, subjects with the GG genotype had the highest levels of antibody titers at 444 (300–664) BAU/mL, followed by the GC genotype at 380 (264–608) BAU/mL and the CC genotype at 336 (198–412) BAU/mL. Meanwhile, rs4792800 and rs1611350 were not associated with the levels of antibodies against SARS-CoV-2 (**Table 1**, **Figures 1C, 1D**).

Stratification of Anti-SARS-CoV-2 Antibody Titers and Their Associations with Age, Sex, and CBC Parameters

Participants were classified into three groups based on antibody titer levels measured three weeks after the first vaccine dose: a high antibody titer group (≥ 550 BAU/mL, n = 112), a moderate antibody titer group (200–549 BAU/mL, n = 227), and a low antibody titer group (< 200 BAU/mL, n = 66). Comparison of demographic factors and CBC parameters among the three groups revealed that younger age was significantly associated with higher antibody titers ($P = 0.00145$). In contrast, no significant difference in antibody titers was observed between men and women. Additionally, higher platelet and lymphocyte counts were significantly correlated with higher antibody titers ($P = 0.01481$ and $P = 0.00750$, respectively; Supplementary **Table 2**).

Next, the Kruskal–Wallis test was performed to conduct multiple comparisons by stratifying age, platelet counts, and lymphocyte counts into five groups. The results indicated that only age and lymphocyte count were significantly associated with anti-SARS-CoV-2 antibody titers ($P = 0.0366$ and $P = 0.0010$, respectively; **Supplementary Table 3**). The group with a platelet count of $\geq 350 \times 10^3/\mu L$ exhibited a clear tendency toward higher antibody titers; however, the difference was not statistically significant due to the limited sample size. Based on these findings, a post hoc analysis using Dunn' s test was conducted to further evaluate intergroup differences (**Figure 1E–1G**). The analysis revealed that individuals with lymphocyte counts of 2,500–2,900/μL had significantly higher antibody titers than those in the ≤ 1,500/μL, 1,500–1,999/μL, and 2,000–2,499/μL groups ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively). In contrast, no significant differences in antibody titers were observed in the ≥ 3,000/μL group compared to other groups, likely due to limited sample size and insufficient statistical power. These findings suggest that an increase in lymphocyte count may contribute to an enhanced antibody response (**Figure 1G**).

Stepwise Regression Analysis of Determinants of Anti-SARS-CoV-2 Antibody Titers

To identify factors influencing antibody titers, a multiple regression analysis was performed in three steps (**Table 2**). Covariates were selected based on preliminary statistical analyses (**Supplementary Table 2**), and age, lymphocyte counts, and platelet counts were included as significant predictors. In step 1, a model including age, lymphocyte counts, and platelet counts yielded an R^2 of 0.0321. Among these variables, age (Std. $\beta = -0.1233$, $P = 0.01237$) and lymphocyte counts (Std. $\beta = 0.1414$, $P = 0.00470$) were significantly associated with antibody titers, indicating that lower age and higher lymphocyte counts were correlated with antibody levels. In contrast, platelet counts showed no significant association ($P = 0.39735$). In Step 2, the addition of genotype (rs3824949) increased the model's R^2 to 0.0840 ($\Delta R^2 = 0.0519$), denoting that rs3824949 contributes to the variation in antibody titers. In this model, rs3824949 remained a significant predictor (Std. $\beta = 0.1859$, $P = 0.00175$), while age also remained significant (Std. $\beta = -0.1439$, $P =$

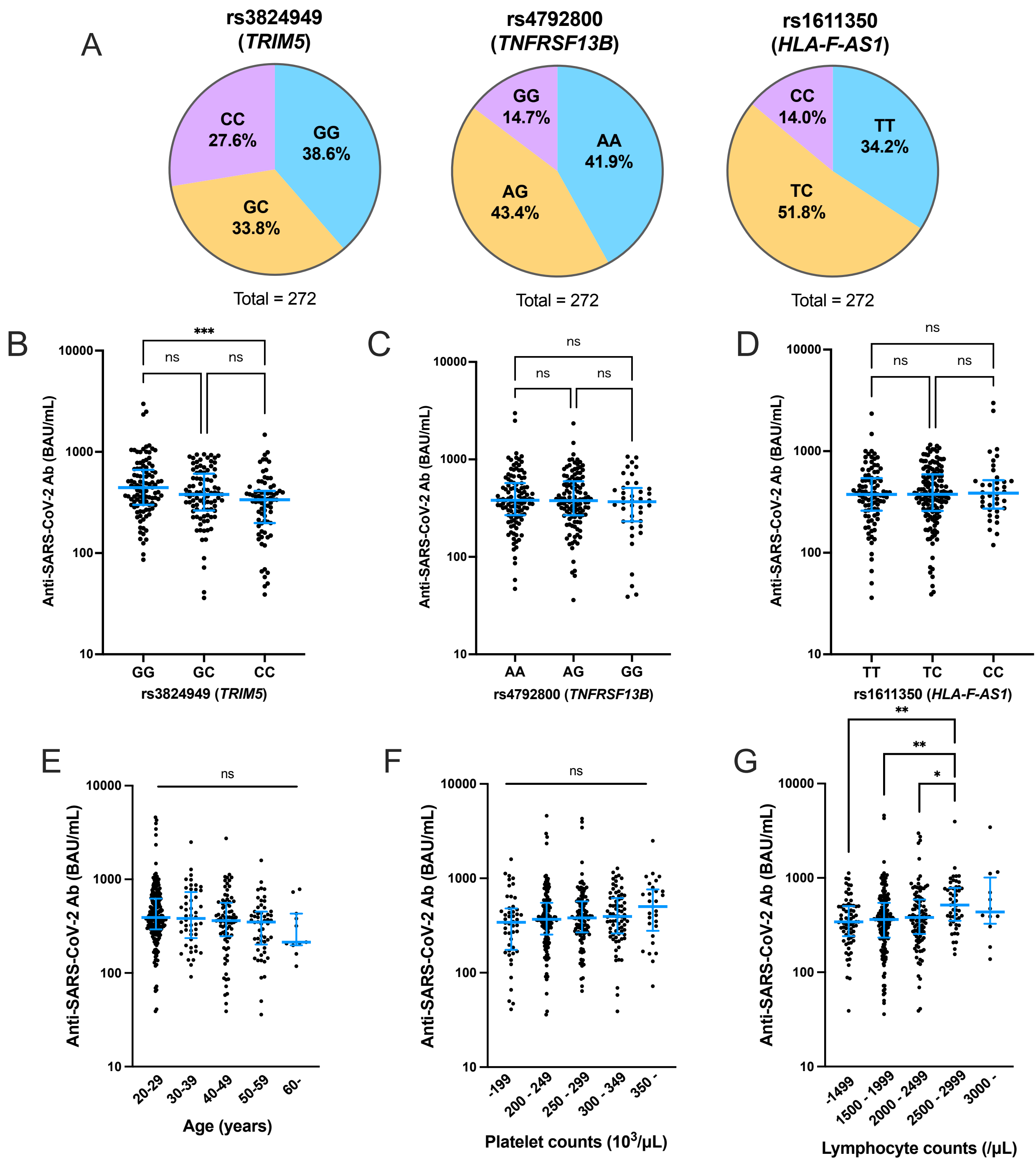

Figure 1 Distribution of genetic polymorphisms and anti-SARS-CoV-2 antibody titers by genotype and blood cell counts in Japanese individuals

The distribution of genetic polymorphisms (A) and the comparison of anti-SARS-CoV-2 antibody titers among different genotypes and complete blood cell counts are presented. The Kruskal–Wallis test was applied to compare three groups based on anti-SARS-CoV-2 antibody levels, and if a significant difference was detected, Dunn's test with Bonferroni correction was used for pairwise comparisons. All graphs display the median and interquartile range (IQR). (B) Levels of antibody titers in relation to the rs3824949 (*TRIM5*) genotypes (GG, GC, CC). The GG genotype is related to higher levels of antibody titers compared with the CC genotype (***P = 0.0009, Dunn's test with Bonferroni correction). (C) Levels of antibody titers in relation to the rs4792800 (*TNFRSF13B*) genotypes (AA, AG, GG). No significant difference in levels of antibody titers was observed across the genotypes (P = 0.7482). (D) Levels of antibody titers in relation to the rs1611350 (*HLA-F-AS1*) genotypes (TT, TC, CC) showed no significant association (P = 0.8803). (E) Age, (F) platelet counts, and (G) lymphocyte counts were classified into five groups, showing the respective anti-SARS-CoV-2 antibody titers. In the graph of (G), *P < 0.05, **P < 0.01. All graphs show the median and interquartile range (IQR).

Abbreviation: *HLA-F-AS1*, human leukocyte antigen-F antisense RNA 1; IQR, interquartile range; *TNFRSF13B*, tumor necrosis factor receptor superfamily member 13B; *TRIM5*, tripartite motif-containing 5.

Table 2 Multivariate regression analysis for anti-SARS-CoV-2 antibody titers, including age, lymphocyte counts, and platelet counts with or without genotype (rs3824949)

Model	Variable included	Unstd. Coef. β	Std. Error	Std. β	t-val	*P*-value	R^2	ΔR^2
1	(Constant)	-1941.1	880	—	—	—	0.0321	—
	Age	-4.633	1.844	-0.1233	-2.5129	0.01237		
	LYM	270.4	95.12	0.1414	2.8246	0.00470		
	PLT	98.26	116.0	0.0422	0.8473	0.39735		
2	(Constant)	-1625.1	737.2	—	—	—	0.0840	0.0519
	Age	-4.276	1.737	-0.1439	-2.4621	0.01444		
	LYM	150.9	80.62	0.1113	1.8714	0.06238		
	PLT	176.6	98.28	0.1067	1.7965	0.07355		
	rs3824949	78.59	24.86	0.1859	3.1614	0.00175		
3	(Constant)	355.2	34.42	-	-	-	0.0448	-
	rs3824949	92.93	25.09	0.2199	3.7039	0.00026		

The GG genotype of rs3824949 and age were identified as significant determinants of anti-SARS-CoV-2 antibody titers. Platelet and lymphocyte count showed weak associations. The inclusion of rs3824949 in the regression model significantly improved the explanatory power, as indicated by an increase in R^2 from 0.0321 to 0.0840 ($\Delta R^2 = 0.0519$). A genotype-only model yielded an R^2 of 0.0448, suggesting that while rs3824949 contributes independently to antibody titer variation, its explanatory power is enhanced when combined with demographic and hematological variables. Abbreviation: LYM, lymphocyte counts; PLT, platelet counts; Std. β, standardized coefficient beta; Std. Error, standard error; Unstd. Coef. β, unstandardized coefficient beta.

0.01444). However, the effect of lymphocyte counts was attenuated ($P = 0.06238$), and platelet counts remained non-significant ($P = 0.07355$). In Step 3, a genotype-only model was constructed, yielding an R^2 of 0.0448, with rs3824949 remaining a significant predictor (Std. β = 0.2199, $P = 0.00026$), highlighting the strength of its effect. These results indicate that the rs3824949 genotype makes a significant and independent contribution to the variation in antibody titers. However, R^2 was lower compared to the model incorporating covariates (Step 2).

IV. Discussion

In this study, we confirmed the substantial inter-individual variability in SARS-CoV-2 antibody titers and categorized participants into high, moderate, and low responders. A higher frequency of the G allele of rs3824949 in the *TRIM5* gene was significantly associated with enhanced antibody response following Moderna vaccination ($P = 0.0015$). In contrast, rs4792800 in the *TNFRSF13B* and rs1611350 in the *HLA-F-AS1* showed no significant association with antibody levels. These findings suggest that host genetic factors may contribute to SARS-CoV-2 mRNA vaccination in the Japanese population.

The *TRIM5* gene encodes tripartite motif-containing protein 5 alpha, also known as RING finger protein 88, a restriction factor that targets retroviral capsids and plays a regulatory role in innate immunity [15,16]. TRIM5α has been proposed to function as a pattern recognition receptor (PRR) involved in pathogen recognition [17]. The rs3824949 polymorphism identified in this study is located in the 5' UTR, which may influence *TRIM5* gene expression [18], although the precise mechanisms by which rs3824949 affects the antibody response remain unclear. In this study, the G allele of rs3824949 was associated with enhanced immune response to SARS-CoV-2 vaccination. The allele frequency in the Japanese population (0.543) is comparable to that observed in European populations (0.442) and is similar to the global average (0.495), suggesting that the immunogenetic impact of rs3824949 may be relevant across diverse populations. This supports the generalizability of our findings and highlights the potential utility of *TRIM5* genotyping in broader vaccine response studies. Given that TRIM5α functions as a restriction factor against various viruses, its role may extend beyond mRNA vaccines to other vaccine platforms. Future studies should investigate the impact of TRIM5α across diverse vaccine modalities, including viral vector, protein-based, and inactivated vaccines, and elucidate the molecular mechanisms through which rs3824949 modulates immune responses.

As a secondary analysis, we examined demographic and CBC parameters potentially associated with antibody titers following the first dose of an anti-SARS-CoV-2 mRNA vaccine. Age, lymphocyte counts, and platelet count were independently and significantly associat-

ed with antibody titers, with higher titers observed in younger individuals and those with elevated lymphocyte and platelet counts. These findings are consistent with previous studies [8),19)-21)]. Notably, even after adjustment for these variables, the rs3824949 polymorphism remained significantly associated with higher antibody titers (**Table 2**). Furthermore, the model incorporating age, lymphocyte counts, and platelet counts exhibited greater explanatory power compared to the genotype-only model **(Table 2**; $\Delta R^2 = 0.0519$). These results suggest that the effect of rs3824949 may be mediated, at least in part, through interactions with age and hematologic parameters.

In this study, lymphocyte and platelet counts measured post-vaccination were positively associated with antibody titers. However, because CBC parameters were obtained at a single time point after immunization and pre-vaccination baselines were unavailable, these findings should be interpreted as post-vaccination correlates that may reflect transient reactogenicity [22)], rather than as causal determinants of antibody responses. Notably, the association of rs3824949 with higher titers remained significant after adjustment (**Table 2**), indicating an effect at least partially independent of hematologic correlates. Platelets have been reported to modulate immune function through interactions with immune cells and may contribute to B cell activation [23)-25)]; however, we did not investigate this mechanism in the present study. Furthermore, GWAS have shown that the C allele of rs3824949 is associated with lower platelet counts ($\beta = -0.0177$, $P = 2 \times 10^{-20}$) [26)], suggesting that interindividual variation in platelet levels may be genetically modulated. However, whether platelet counts mediate the association between rs3824949 and antibody titers cannot be determined from our cross-sectional study design. Prospective longitudinal measurements before and after vaccination, along with mediation analyses, will be required to clarify the causal relationship and underlying mechanisms.

Although the COVID-19 pandemic has transitioned to endemicity, the insights from mRNA vaccine genetics remain broadly relevant. The role of TRIM5α in innate immunity suggests its potential relevance not only to current but also to future mRNA vaccines, including those targeting influenza, HIV, or Zika virus. This positions TRIM5α as a promising target for enhancing vaccine design. The observed association between rs3824949 and antibody responses further highlights the therapeutic potential of modulating TRIM5α to improve vaccine efficacy in low responders, potentially extending to mRNA-based cancer immunotherapies. As global health systems increasingly embrace personalized medicine, screening for genetic variants such as rs3824949 could facilitate risk stratification and individualized vaccination strategies. Immunization schedules tailored to genetic profiles may optimize vaccine-induced protection in high-risk or genetically susceptible populations. Future research should explore whether *TRIM5* polymorphisms influence immune responses to other vaccine platforms and their durability following booster doses or in the context of hybrid immunity. These insights may inform both vaccine development and public health strategies.

This study has several limitations. First, the positivity rate of N-IgG antibody titers measured using the HISCL™ SARS-CoV-2 N-IgG reagent reportedly declines to 26.5% more than three months after SARS-CoV-2 infection [27)]. Therefore, some participants may have experienced asymptomatic SARS-CoV-2 infections that were not detected by N-IgG testing, potentially influencing their post-vaccination immune responses [28)]. However, this effect could not be assessed in the present study. Second, since the analysis focused on antibody responses after the first vaccine dose, it remains unclear whether rs3824949 or other polymorphisms affect responses to the second or subsequent doses. Third, CBC parameters were measured only once, approximately three weeks after the first dose, without pre-vaccination baseline values. Therefore, transient post-vaccination changes cannot be distinguished from stable genotype-related differences. In addition, this cross-sectional analysis cannot determine whether platelet or lymphocyte counts mediate the association between rs3824949 and antibody responses; prospective longitudinal data are required. Finally, this study did not assess whether these genetic variations, including rs3824949, are associated with vaccine-related adverse events in the Japanese population.

In conclusion, the immune response to the Moderna vaccine in the Japanese population varied due to the genetic influence of the *TRIM5* polymorphism rs3824949, with individuals carrying the GG genotype exhibiting significantly higher antibody titers. Although the urgency of COVID-19 research has diminished, our findings address enduring questions regarding host–pathogen interactions and genetic variability in vaccine responses. By extending beyond the context of SARS-CoV-2, this study provides a foundation for optimizing mRNA vaccines across diverse populations and disease targets.

Supplementary Materials

Supplementary Tables 1, 2, and 3 provide additional data relevant to this study and are available online.

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authorship Contributions

Conceptualization: J. Luis Espinoza; Methodology: J. Luis Espinoza; Formal analysis and investigation: J. Luis Espinoza, Satomi Nagaya, Nguyen Hoang Thao Giang, Koichi Yamaguchi, and Kota Goto; Writing-original draft preparation: Satomi Nagaya, Nguyen Hoang Thao Giang, and J. Luis Espinoza; Writing-review and editing: J. Luis Espinoza, Hisanori Horiuchi, and Eriko Morishita; Funding acquisition: Hisanori Horiuchi and Eriko Morishita; Resources: Satomi Nagaya, J. Luis Espinoza, and Eriko Morishita; Supervision: Hisanori Horiuchi and Eriko Morishita.

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