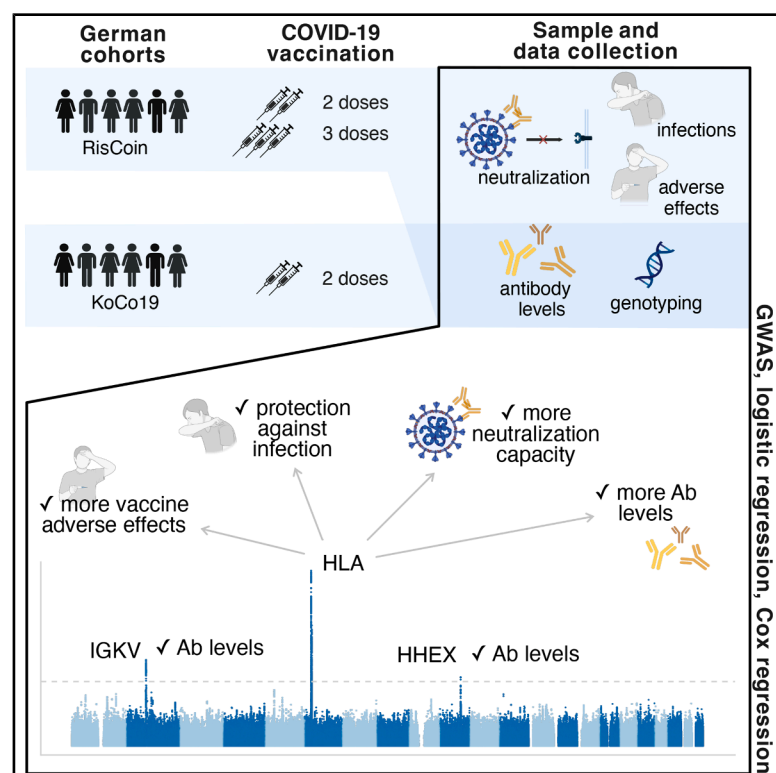


Genetic variation in HLA, IGKV, and HHEX loci influences mRNA vaccine-induced humoral protection against COVID-19

Graphical abstract



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In brief

Puzek, Wratil, et al. show that the variation in vaccine-induced protection against COVID-19 links to three genomic loci, including the HLA. The HLA association extends to neutralizing capacity and antibody level variation after a booster dose, as well as to increased vaccine side effects and reduced infections.

Highlights

- IGKV, HHEX, and HLA associate with antibody levels after two COVID-19 vaccinations
- HLA further associates with neutralizing capacity after two and three vaccine doses
- HLA class I links to more vaccine adverse effects and less infection



Article

Genetic variation in HLA, IGKV, and HHEX loci influences mRNA vaccine-induced humoral protection against COVID-19

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SUMMARY

Humoral immune responses to COVID-19 vaccination vary widely across individuals, yet the genetic determinants of functional antibody protection beyond binding antibodies after two immunizations remain poorly understood. We performed genome-wide association studies on antigen-specific antibody concentrations and live-virus neutralization activities after two and three vaccine doses in two German cohorts of SARS-CoV-2 infection-naïve individuals (RisCoin study $n = 2,877$; KoCo19 study $n = 1,654$). We found the HLA locus to be associated with differential live-virus neutralizing and anti-SARS-CoV-2 spike antibodies after both the second and third vaccinations. Consistent with its effect on third-dose neutralization, the HLA was additionally associated with a reduced incidence of breakthrough infection. We further replicated an association with antibody concentrations at the IGKV locus and discovered an association at the HHEX locus, implicating pathways linked to memory B-cell biology. Together, these findings reveal host genetic factors shaping neutralizing immunity and vaccine-induced protection against infection, with implications for personalized vaccination strategies.

INTRODUCTION

In response to the coronavirus disease 2019 (COVID-19) caused by the emergence of severe acute respiratory syndrome coronavirus

2 (SARS-CoV-2), effective vaccines were developed and rolled out swiftly. After immunization with these COVID-19 vaccines, both cellular and humoral immune responses are evoked.^{1–5} The latter consists of anti-SARS-CoV-2 spike binding and virus-neutralizing



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antibodies. Vaccine-induced humoral immunity to SARS-CoV-2 is largely dependent on virus-neutralizing antibodies, the titers of which were shown to correlate with protection from symptomatic and, especially, severe disease.⁶ Among COVID-19-vaccinated individuals, there is, however, a notable variability in the levels and quality of these antibodies,^{7–11} affecting their susceptibility to infection and their likelihood of experiencing severe disease. This variation was attributed to a range of factors, including environmental influences and genetic differences.^{12–16} Obtaining a more profound understanding of the inter-individual variability of the humoral immune response after COVID-19 vaccination is key to comprehending and predicting immunity to COVID-19.

There is a growing number of studies pointing to genetic effects that influence vaccination-induced anti-SARS-CoV-2 spike antibody response.^{14–16} Multiple studies report associations in the human leukocyte antigen (HLA) class I and II loci, with specific alleles reported differing across studies. Previous analyses focused on genetic determinants solely influencing anti-spike binding antibodies (antibody concentration or binary serostatus). There is, nevertheless, a lack of research on genetic factors influencing antibody-mediated live-virus neutralizing capacities induced by COVID-19 vaccination, which are, indeed, a more accurate correlate of protection from a SARS-CoV-2 infection and severe disease.^{6,17,18} Furthermore, genetic data on humoral immune responses after COVID-19 vaccination were, thus far, limited to the effects of two immunizations. Nowadays, a large proportion of the population has, however, received at least three COVID-19 vaccinations with a significant impact on the longevity and the breadth of the induced immune response.^{10,19,20}

Here, we performed genome-wide association studies (GWASs) on humoral immune responses in SARS-CoV-2 infection-naïve individuals from two German cohorts that were longitudinally sampled after the second and third COVID-19 vaccinations. Genetic associations not only to anti-spike antibody concentrations but also to live-virus neutralization activities were examined. These analyses revealed that variants at the HLA, IGKV, and HHEX loci influence humoral protection against COVID-19. By addressing underexplored aspects of protective

immunity and identifying an additional association signal in the HHEX locus, our findings add to the understanding of genetic contributions to the observed variability in COVID-19 vaccine responses. Our research might, thus, be important to identify vulnerable individuals as well as adapt and personalize future COVID-19 and broader mRNA vaccination campaigns.

RESULTS

Cohort characteristics

To explore genetic contributions to antibody level variability after two COVID-19 vaccinations, we used data obtained from two cohorts of adult, SARS-CoV-2 infection-naïve COVID-19 vaccinees from Germany, one consisting of healthcare workers (RisCoin)^{21,22} and the other from individuals recruited from the general population of Munich, Bavaria (KoCo19)^{23,24} (Figure 1A). In the sera obtained from both cohorts, we measured SARS-CoV-2-specific anti-spike as well as anti-nucleocapsid antibody concentrations, and in the specimens from the RisCoin cohort we, additionally, assessed live-virus neutralization activity against virus variant omicron BA.1. Only those participants were included into the data evaluation who serologically and anamnistically had no prior SARS-CoV-2 infection at the time of sampling. After applying stringent criteria for our data evaluation (see STAR Methods), the first cohort (RisCoin) included 2,877 individuals who were sampled at a median of 8 months after receiving the second, and 1,225 participants 2 months after the third vaccination with mRNA vaccines. All individuals received two primary doses of BNT162b2 (Comirnaty, BioNTech/Pfizer), followed by booster doses of either BNT162b2 (67%) or mRNA-1273 (33%; Spikevax, Moderna). The second cohort (KoCo19) consisted of 1,654 individuals sampled 2 months after the second COVID-19 vaccination, namely, BNT162b2 (67%), mRNA-1273 (8.7%), or ChAdOx1 (24%; Vaxzevria, AstraZeneca) as the first vaccine dose, and BNT162b2 (78%), mRNA-1273 (13%), or ChAdOx1 (8.4%) as the second vaccine dose. The cohort characteristics are summarized in Table S1.

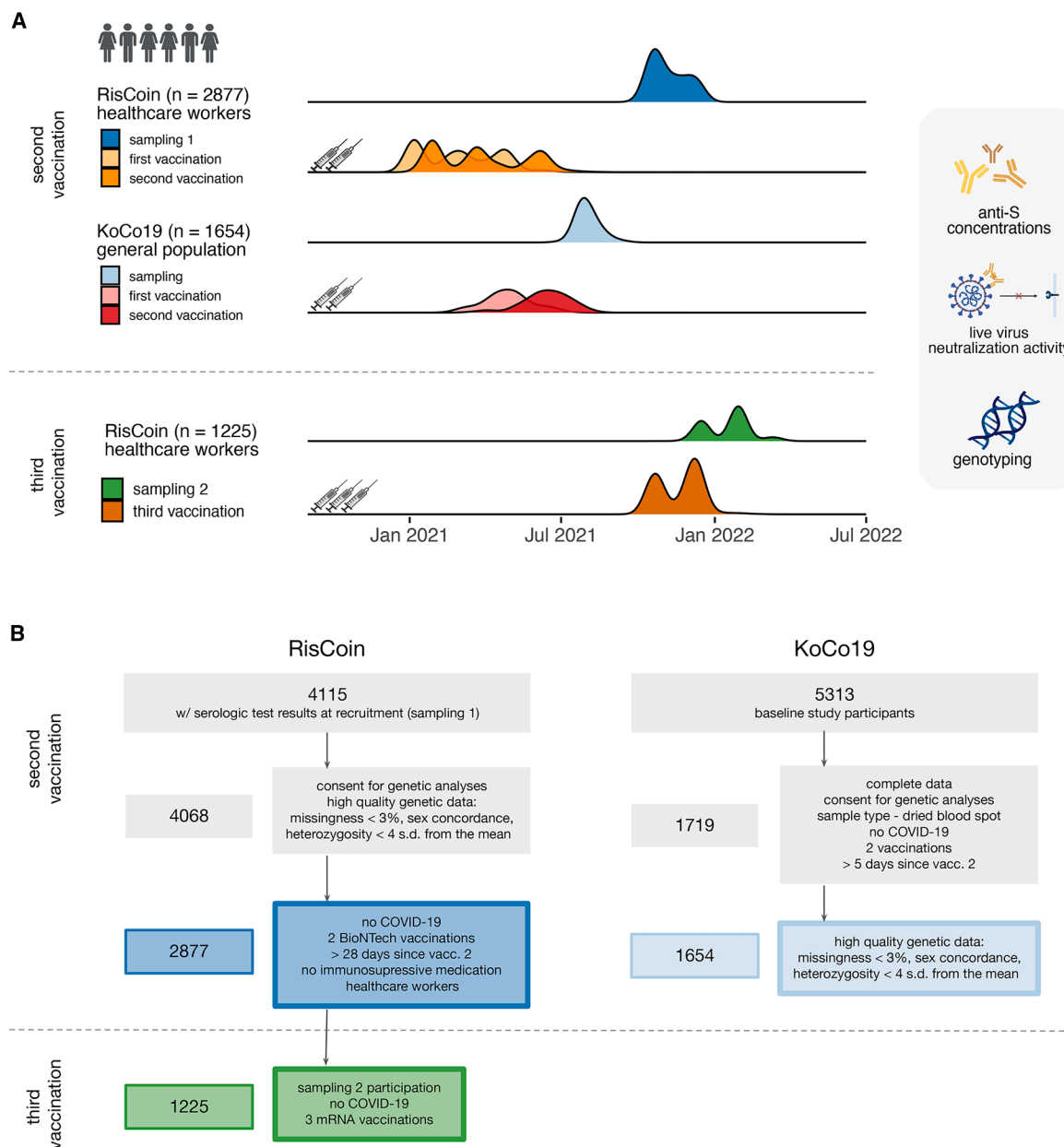


Figure 1. Study timeline and individual selection

(A) Study overview. After the second COVID-19 vaccination, analyses included 2,877 individuals from the RisCoin study and 1,654 individuals from the KoCo19 study. COVID-19 vaccinations were administered from January to July 2021 and subsequent blood sampling was performed from August 2021 to February 2022. Samples were used to determine anti-SARS-CoV-2 spike antibody concentrations and—in case of the RisCoin cohort—live virus neutralization activities as well as to obtain genotype data. After the third COVID-19 vaccination, analyses included 1,225 individuals from the RisCoin study. Blood sampling was performed from December 2021 to May 2022. Multiple peaks in the RisCoin vaccination tracks correspond to the waves of vaccinations of healthcare workers.

(B) Flow diagram of participant selection for genetic analyses in RisCoin and KoCo19 study.

Variation in HLA, IGKV, and HHX loci associated with anti-spike antibody concentrations after two COVID-19 vaccinations

To identify possible genetic factors associated with altered humoral immune responses after two COVID-19 vaccinations, we first ran GWASs on both studies individually, using a linear mixed model implemented in GEMMA.²⁵ These analyses were per-

formed with inverse-normal transformed antibody level phenotypes and included age, gender, and days since the second vaccination, the first five principal components of genetic data, and the genetic relatedness matrix as covariates, as well as vaccine type for the KoCo19 cohort. In both of the individual analyses, we found a genome-wide significant signal (p value $< 5 \times 10^{-8}$) in the HLA region (Figure S1; Table 1). Next, we

Table 1. Summary statistics of the lead variants in four independent loci identified in the GWAS meta-analysis of anti-spike antibody concentrations after two COVID-19 vaccinations

Variant	Chromosome	Position	Effect allele	EAf	KoCo19 beta	RisCoin beta	Meta-analysis beta	KoCo19 (p value)	RisCoin (p value)	Meta-analysis (p value)
rs111357016	2	89281528	A	0.067	0.40	0.31	0.35	4.3e−07	8.3e−05	1.9e−10
rs56388903	6	29795720	G	0.847	−0.23	−0.31	−0.26	7.9e−09	2.0e−13	1.6e−20
rs6905975	6	32626139	G	0.543	0.12	0.18	0.16	6.5e−05	3.6e−11	2.4e−14
rs2488075	10	94490174	C	0.490	0.08	0.12	0.10	9.1e−03	2.7e−07	1.6e−08

Genetic effect estimates and association *p* values are shown per cohort and for the meta-analysis. Position is given with respect to hg19/GRCh37 genomic build. EAF, effect allele frequency.

performed a meta-analysis of GWAS by combining the two individual studies in METAL,²⁶ weighing the effects using the inverse of the standard errors. Independent signals were identified via a stepwise model selection procedure in gcta-cojo.²⁷ In the meta-analysis, we identified four independent genome-wide significant signals across three chromosomes (Table 1; Figure 2A) and observed no *p* value inflation ($\lambda = 1.00$, Figure 2A, inset). The results included three previously reported signals within the HLA and immunoglobulin kappa variable cluster (IGKV) regions and an additional genetic signal on chromosome 10 (Table 1). The closest gene to the lead variant of the signal on chromosome 10 is hematopoietically expressed homeobox (HHEX) (Figure 2B), a transcription factor involved in a plethora of biological processes including development and hematopoiesis.²⁹ For all four lead variants, we observed concordance of direction and magnitude of effect computed in the individual analyses across the two independent cohorts (Table 1). To detect whether the genetic variants exert different effects on antibody levels at different timepoints after vaccination in the RisCoin cohort, or across different vaccination types in the RisCoin and KoCo19 cohorts, we conducted a gene-by-environment interaction analysis in GEMMA²⁵ and, at current sample size, found no evidence of an interaction (*p* value <0.05) between genetic effects and interval since vaccination or vaccine type.

To evaluate the robustness of the HHEX signal beyond our two independent cohorts, we assessed the data on the genetics of seroconversion after COVID-19 vaccination in over 200,000 British individuals from the UK Biobank.¹⁶ We found that the lead variant from our study (rs2488075) is nominally significant with a concordant direction of effect (*p* value = 0.003, beta = 0.02). Moreover, we find that the structure of the genetic signal, effect sizes, and *p* values are concordant in the whole locus (ρ [effect sizes] = 0.63, ρ [p values] = 0.64) (Figure S2). These data support the role of HHEX as a genetic modifier of humoral immunity following COVID-19 vaccination.

To prioritize genetic variants and identify effector genes in the HHEX locus, we performed statistical fine-mapping and colocalization analysis. Statistical fine mapping using susier^{30,31} identified 1 credible set of 6 variants, with overall low posterior inclusion probabilities, in line with the moderate signal strength of the association analysis (Figure 2B). Colocalization analysis was performed across all tissues in the expression quantitative trait loci (eQTL) Catalog³² using the coloc³³ package. We found significant evidence for colocalization, based on posterior prob-

ability for shared genetic signals (PP4) larger than 0.8, between the HHEX locus discovered in our study and eQTL signals for the HHEX gene across six different tissues (Figure 2C). Importantly, those included four immune cell types (i.e., Th17, Th1, NK-cells, and neutrophils), among which the highest PP4 of 0.95 was observed for Th1 cells (Figure 2D). Carrying the effect allele C of the lead GWAS variant rs2488075 was associated with decreased expression of HHEX in Th1 cells in Schmiel et al.³⁴ and with increased antibody levels in our study. Taken together, these results suggest that the genetic effect of the chromosome 10 locus that we discovered on anti-spike antibody concentrations after two COVID-19 vaccinations is mediated by HHEX gene expression.

Next, we confirmed that the IGKV signal (lead variant rs111357016, GRCh37: chr2:89281528) (Figure 2E) is a replication of the results reported by Sonehara et al.¹⁶ (lead variant rs139861548, GRCh37: chr2:89246954) identified in the analysis of British individuals from the UK Biobank. The lead variant previously reported was not represented in our dataset, so we used a variant in high LD (0.78, 1000 Genomes EUR superpopulation³⁵) as a proxy for the reported result. Conditioning on either the lead variant in our study or the proxy of the lead variant in Sonehara et al. in gcta-cojo,²⁷ we observed a substantial reduction of signal in the whole region (Figure S3), indicating that our result is an independent replication of the contribution of the IGKV genetic variation to anti-spike antibody level concentrations in a different population. Additionally, we could reproduce the high colocalization of the GWAS signal with eQTL signal for gene IGKV1-13 in GTEx³⁶ whole blood data (PP4 = 0.94). Taken together, we provided robust evidence for the role of the germline immunoglobulin gene variability in antibody concentrations after two COVID-19 vaccinations and the possible role of immunoglobulin gene expression levels as a mediating factor.

To fine-map the discovered associations in the HLA region, we imputed HLA allele, amino acid and coding variation using the T1DGC HLA reference panel²⁸ and repeated the association analyses for the individual studies as per Sakaue et al.³⁷ Meta-analysis of the association runs on the imputed datasets found HLA-A*03:01 as the lead allele signal in the HLA class I region and HLA-DQB1*05 as the lead allele signal in the HLA class II region (Figure 2F). Lead HLA-, amino acid, and single-nucleotide polymorphism (SNP) signals are listed in Table 2. To understand potential functional consequences of variation in amino acid sequences of the HLA complexes, we located the lead amino acid

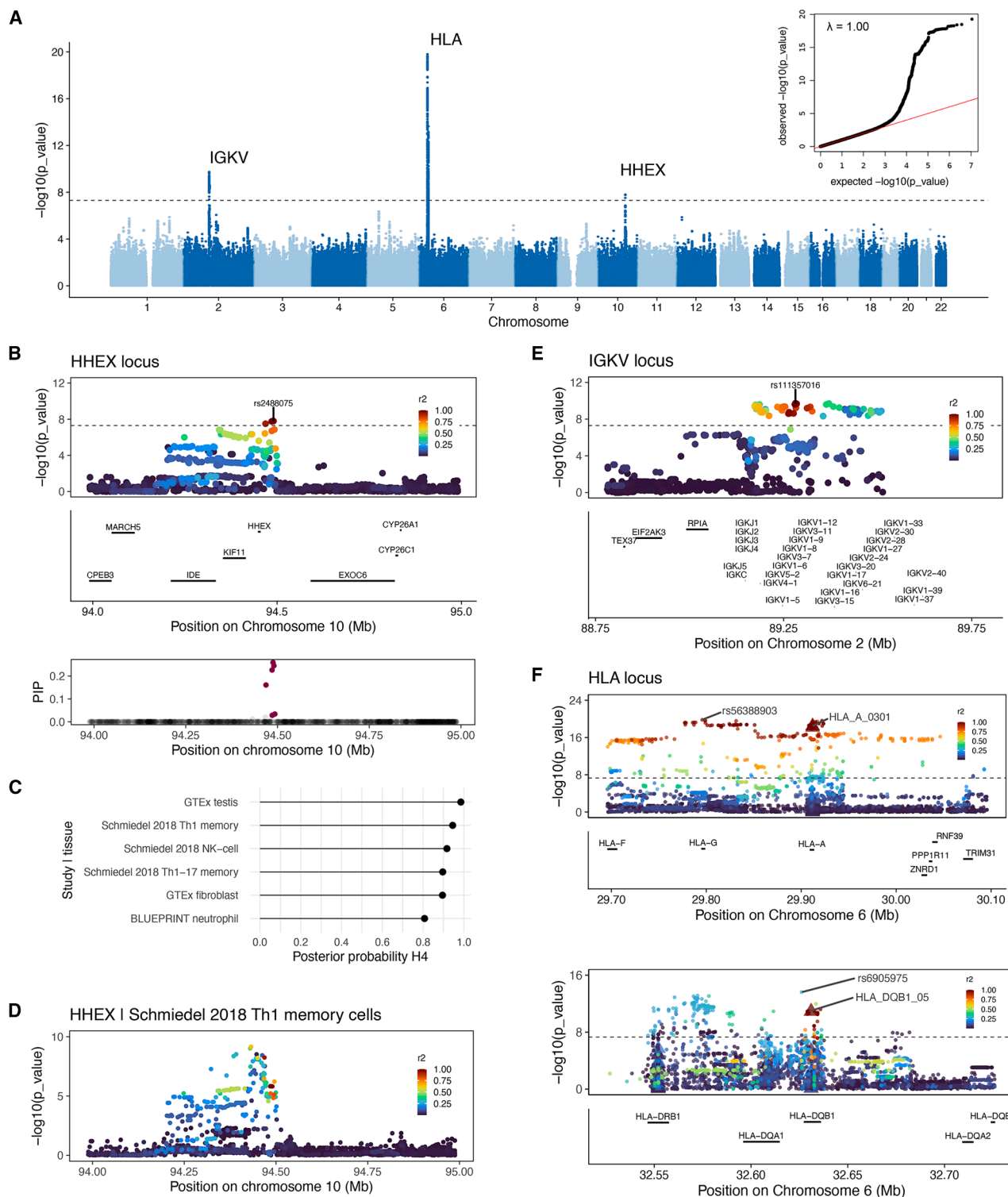


Figure 2. Genetic variation in HLA, IGKV, and HHEX loci is associated with differential anti-spike antibody concentrations after two COVID-19 vaccinations

(A) Manhattan plot showing the results of the meta-analysis of GWAS for anti-spike antibody concentrations after two COVID-19 vaccinations in infection-naïve individuals across RisCoin and KoCo19 cohorts. Meta-analysis p value per variant is shown on the y axis, plotted against the genomic positions of the variants. Genome-wide significant results are annotated with the locus name. The inset shows a qq-plot of observed versus expected association p values. Inflation factor lambda is noted.

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Table 2. Summary statistics of the lead HLA allele, amino acid, and SNP variation in the GWAS meta-analysis of anti-spike antibody concentrations after two COVID-19 vaccinations

Region	Variant	Variant type	Position	Effect allele	EA	RisCoin beta	KoCo19 beta	Meta-analysis beta	RisCoin (p value)	KoCo19 (p value)	Meta-analysis (p value)
HLA class I	HLA-A*03:01	HLA allele	29911991	P	0.15	0.30	0.22	0.26	8.0e−13	3.5e−8	3.2e−19
HLA class I	HLA-A AA 161	amino acid	29911255	Asp	0.15	0.30	0.22	0.25	2.1e−12	3.1e−8	6.7e−19
HLA class I	rs56388903	SNP	29795720	G	0.847	−0.31	−0.23	−0.26	2.0e−13	7.9e−9	1.6e−20
HLA class II	HLA-DQB1*05	HLA allele	32631061	P	0.18	−0.19	−0.18	−0.17	1.0e−8	1.9e−4	2.0e−11
HLA class II	HLA-DRB1 AA 96 His or Tyr	amino acid	32629935	P	0.28	−0.19	−0.12	−0.16	1.3e−9	1.9e−4	3.0e−12
HLA class II	rs6905975	SNP	32626139	G	0.543	0.18	0.12	0.16	3.6e−11	6.5e−5	2.4e−14

Genetic effect estimates and association *p* values are shown per cohort and for the meta-analysis. Position on chromosome six is given with respect to the hg19/GRCh37 genomic build. Multi allelic variation is encoded as P, presence; A, absence. Biallelic amino acid variation is encoded with three-letter amino acid codes. Amino acid variant names indicate the variable position in the translated protein, and the amino acid considered in the analysis in case of multiallelic variation. EAF, effect allele frequency.

signal from our study in a publicly available 3D structure of an HLA-A*02-SARS-CoV-2 peptide complex.³⁸ Corroborating other studies,^{15,16} we found that the amino acid, that was the lead signal in the HLA class I region in the association analysis, is located in the peptide binding groove of the HLA complex (Figure S4). This suggests that the differential production of spike-specific antibodies in carriers versus non-carriers is due to differential peptide binding affinity and consequently dissimilar CD8⁺ T cell activation.

Genetic variation in the HLA region associated with altered live-virus neutralization activity against SARS-CoV-2 omicron after two COVID-19 vaccinations

We next assessed whether genetic variation was associated with differential antibody-mediated live-virus neutralization activity against SARS-CoV-2 Omicron BA.1 in the sera of individuals who received two vaccine doses in the RisCoin cohort (Figure 3A). In line with results from previous studies,^{10,11} we found a limited predictive value of anti-spike antibody concentrations for live-virus neutralization activities. Indeed, more than a third of participants showed neutralization activity below the

threshold of detection (i.e., below a serum dilution of 1:10) while having detectable anti-spike antibody concentrations. In participants, for whom both live-virus neutralization activities and anti-spike antibody concentrations were quantifiable above the assays' thresholds, the measurements showed a modest yet highly statistically significant correlation ($\rho = 0.43$, p value $< 1 \times 10^{-16}$) (Figure 3B). These results warranted investigation of the genetics of the live-virus neutralization activity. Our linear mixed-model association analysis included age, gender, days since vaccination, the first five principal components of genetic data and the genetic relatedness matrix as covariates. The neutralization activity phenotype was inverse-normal transformed. Our GWAS identified two independent, genome-wide significant signals (p value $< 5 \times 10^{-8}$) on chromosome 6, in the HLA class I and class II regions (Figures 3C and 3D). Interestingly, discovered lead allele signals, i.e., HLA-A*03:01 and HLA-DQB1*05, were the same as those found in the anti-SARS-CoV-2 spike antibody level analysis (discussed earlier). These results suggest that the genetic determinants are shared between the two phenotypes, despite a limited concordance at the phenotype level.

(B) Regional association plot (top) of the HHEX locus showing the results of a GWAS meta-analysis of anti-spike antibody concentrations after two COVID-19 vaccinations. Posterior inclusion probability (PIP) values from statistical fine-mapping analysis are shown against the variant position (bottom). Six credible set variants were identified (colored in magenta).

(C) Colocalization analyses were performed across all tissues in the eQTL catalog. Posterior probability for shared genetic signals (PP4) is shown on the x axis for six tissues, in which PP4 was higher than 0.8.

(D) Regional association plot depicts the eQTL signal for HHEX gene expression measured in Th1 cells. Linkage disequilibrium estimates (r^2) are shown with respect to the lead GWAS variant rs2488075.

(E) Regional association plot of the IGKV locus showing the results of a GWAS meta-analysis of anti-spike antibody concentrations after two COVID-19 vaccinations.

(F) Regional association plot of the HLA class I and II loci depicting the results of a GWAS meta-analysis of anti-spike antibody concentrations after two COVID-19 vaccinations. Analyses were conducted using SNP and HLA allele variation imputed using the T1DGC panel.²⁸ SNPs are represented by circles and HLA alleles by triangles. Lead SNP and HLA allele signals per locus are labeled.

In (B) and (D)–(F), the color indicates the linkage disequilibrium estimate (r^2) to the lead variant or HLA allele and coordinates of the genes in the locus are shown in the lower images. In all images, the dashed line represents the genome-wide significance threshold (5×10^{-8}) and variant positions were shown with respect to hg19/GRCh37 genome build.

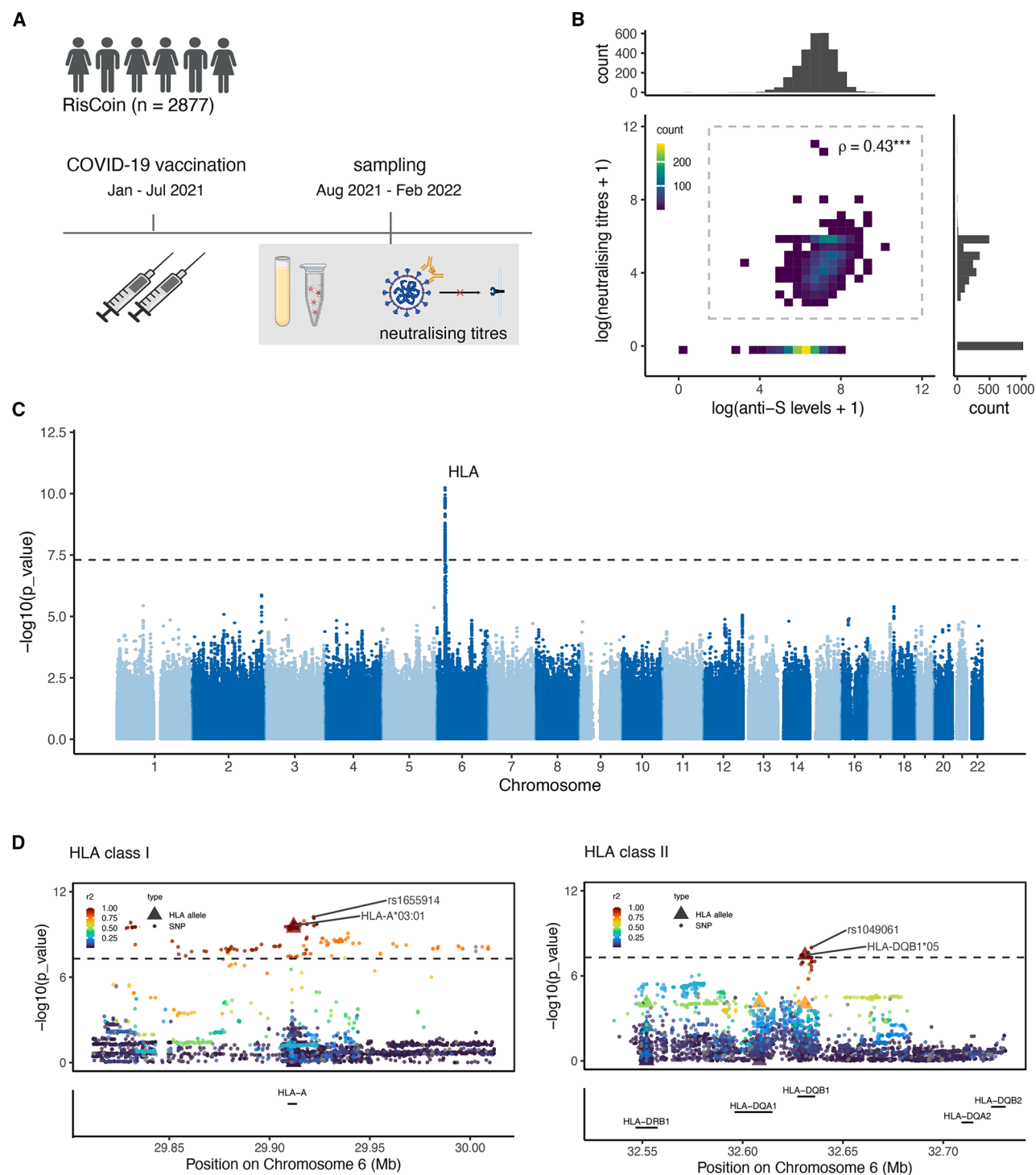


Figure 3. Genetic variation in HLA class I and II regions is associated with differential live-virus neutralization activities after two COVID-19 vaccinations

(A) Cohort overview. We ran GWAS on the live-virus neutralization activity against SARS-CoV-2 Omicron BA.1 from 2,877 infection-naïve individuals in the RisCoin cohort, collected at median 227 days post second COVID-19 vaccination.

(B) Correlation of anti-spike antibody concentrations and live-virus neutralization activities (Spearman $\rho = 0.43$, p value $< 1 \times 10^{-16}$). The color scale indicates the number of individuals in each bin.

(C) Manhattan plot showing the results of the GWAS of live-virus neutralization activity. Genome-wide significant results are annotated with the locus name.

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Genetic variation in HLA class I region associated with differential live-virus neutralization activities and anti-spike antibody concentrations after three COVID-19 vaccinations

We next investigated whether genetic contribution to live-virus neutralization and anti-spike antibody concentrations change after receiving a third COVID-19 vaccination. To this end, we ran a GWAS on the RisCoin cohort including data from 1,225 individuals who had previously received a third COVID-19 vaccination and were SARS-CoV-2 infection-naïve (Figure 4A). The median time since the third booster vaccination was 56 days. After the third immunization, the correlation of anti-spike antibody concentrations and neutralization activity against Omicron increased compared with that calculated post-second vaccination ($p = 0.53$) (Figure 4B). Our linear mixed-model association analysis included age, gender, days since vaccination, vaccine type, the first five principal components of genetic data, and the genetic relatedness matrix as covariates. Values for anti-spike antibody concentrations and live-virus neutralization activity were inverse-normal transformed. For both phenotypes, we observed one independent genome-wide significant signal (p value $< 5 \times 10^{-8}$) (Figure 4C), an association in HLA class I region (Figure 4D). The lead allele of this signal, HLA-A*03:01, was identical to that observed for both phenotypes post second vaccination. Of note, the HLA class II signal, HLA-DQB1*05, that we discovered after the second immunization diminished (anti-spike antibody concentrations GWAS p value = 4.3×10^{-3}) (Figure 4E) albeit showing an effect size ($\beta = -0.15$) comparable to the effect after second vaccination ($\beta = -0.17$). Beyond previously reported associations with post-second vaccination response, our findings demonstrate that the HLA locus influences protective humoral immunity as measured by live-virus neutralization activity and anti-spike antibody concentrations after the third vaccination.

Carrying the HLA-A*03:01 allele was associated with decreased incidence of breakthrough infections and increased incidence of self-reported severe vaccination adverse effects

In the RisCoin cohort, self-reported adverse effects of the COVID-19 vaccinations as well as the incidence of SARS-CoV-2 breakthrough infections were assessed utilizing questionnaires and a weekly questionnaire via smartphone app.³⁹ Severe adverse effects were defined as symptoms after the third immunization causing impairment in everyday life, leading to a doctor's visit or sick leave, for example, and were reported by 203 of 3,126 participants with complete data. Furthermore, out of the 476 individuals with three mRNA vaccinations, who attended the final sampling round, 310 individuals experienced a SARS-CoV-2 breakthrough infection (Figure 5A, STAR Methods). We tested whether individual genotypes could predict the incidence of self-reported severe adverse effects or breakthrough infection after receiving three vaccine doses using logistic and Cox proportional hazards regres-

sion, respectively. In this analysis, as predictors, we used age, gender, and the genotypes at the lead HLA allele signals identified in the GWAS of anti-spike antibody concentrations in the independent KoCo19 cohort (Tables 1 and 2). We found no significant effect of gender, while age showed a negligible protective effect against a breakthrough infection (hazard ratio = 0.98, 95% confidence interval [0.97, 0.99]). Importantly, we found that carrying two copies of HLA-A*03:01 was associated with a decreased risk of experiencing a breakthrough infection (hazard ratio = 0.36, 95% confidence interval [0.13, 0.98]), and carrying one copy with an increased risk of experiencing more self-reported severe adverse effects after the third vaccination (odds ratio = 2.22, 95% confidence interval [1.65, 2.98]) (Figure 5B). In a study of over 17,000 individuals,⁴⁰ who self-reported adverse effects after a COVID-19 vaccination across similar categories (no to moderate difficulties, or severe to extreme difficulties with daily routine), the same allele, HLA-A*03:01, was implicated in the genetic analysis. Carrying the same allele was also previously associated with reduced breakthrough infection rates in a cohort of 113 individuals,⁴¹ a finding that we have now confirmed in a larger sample. Thus, our results corroborate previous findings of other studies and demonstrate that beyond neutralizing titers at the third vaccination, the HLA association extends to clinical protection.

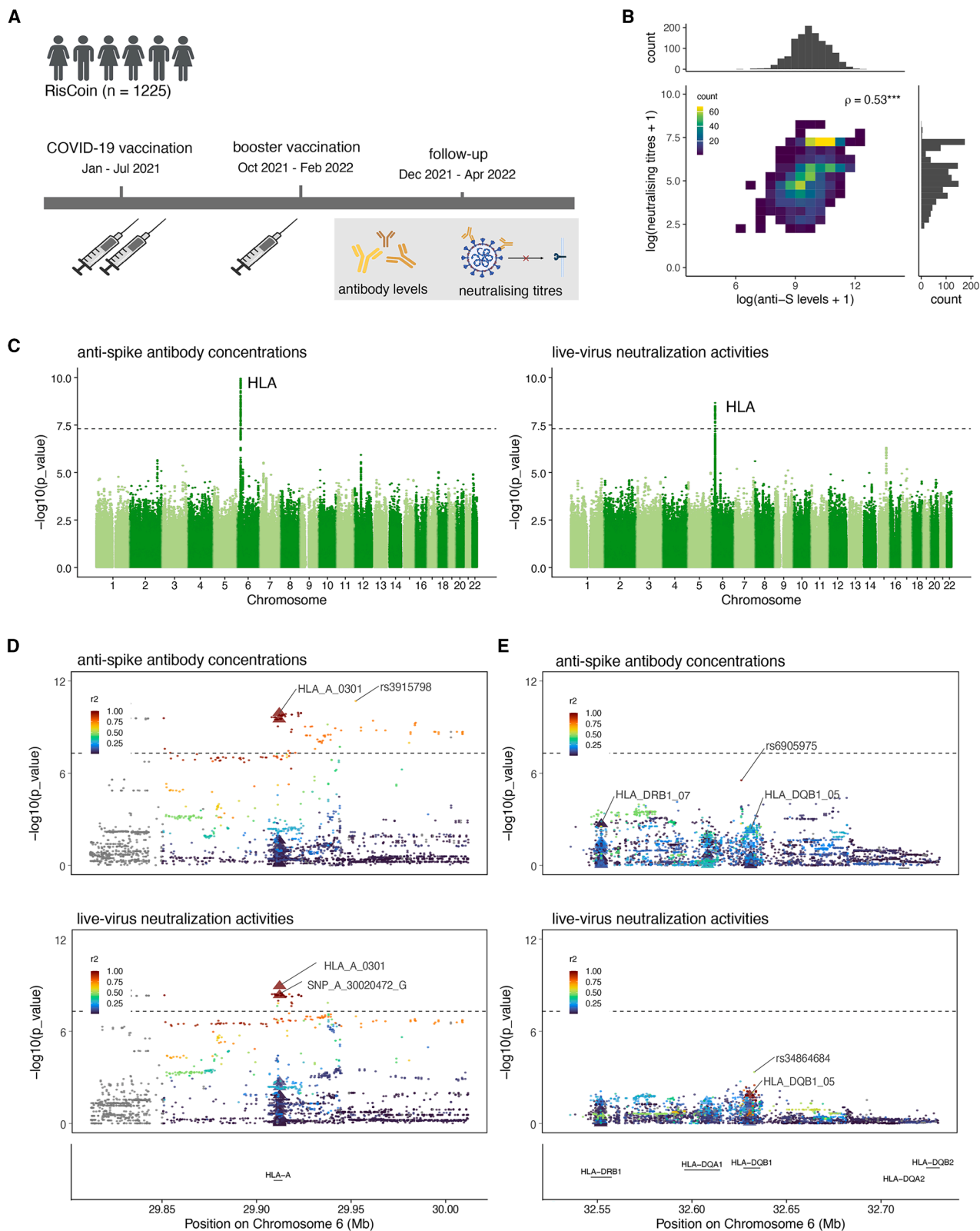
DISCUSSION

The genetic contribution to the neutralizing activity of vaccine-induced antibodies and the humoral response after the third vaccination has been unclear. In two large cohorts of predominantly mRNA vaccinees, we quantify neutralizing antibody titers, anti-spike antibody concentrations, and the third-dose protection in an infection-naïve population. We show that variants at the HLA, IGKV, and HHEX loci influence immunity against COVID-19 up to 9 months after vaccination. While we replicated and expanded the well-established contribution of HLA, we also identified an additional signal, potentially because of our late sampling time point, underscoring the context specificity of genetic effects on vaccine responses. Our findings at IGKV add to growing evidence that germline immunoglobulin variation shapes vaccine-induced antibody profiles, paralleling historical insights from HLA. Altogether, these results may inform design and optimization of mRNA vaccines beyond COVID-19, including for other infectious diseases and cancer.

The association between the HHEX locus and anti-SARS-CoV-2 spike antibody concentrations is, as our findings suggest, likely mediated through differential gene expression levels of the transcription factor HHEX. Of importance, HHEX was recently described as a key player in memory B cell development.⁴² Given that anti-spike specific memory B cells were reported to be good correlates of anti-spike antibody levels several months after COVID-19 vaccination,^{43,44} we speculate that HHEX could have an influence on antibody levels via modulation of the memory B

(D) Regional association plot of the HLA class I (left) and II (right) loci depicting the results of a GWAS conducted using SNP, amino acid and HLA allele variation imputed using the T1DGC panel.²⁸ The color indicates the linkage disequilibrium estimate (r^2) to the lead variant. SNPs are represented by circles and HLA alleles by triangles. Coordinates of the genes in the locus are shown in the lower image. Lead SNP and HLA allele signals per locus are labeled.

In (C) and (D), association p value per variant is shown on the y axis, plotted against the positions of the variants on hg19/GRCh37 genomic build, and the dashed line represents the genome-wide significance threshold (5×10^{-8}).



(legend on next page)

cell compartment. Therefore, detection of the HHEX locus may be attributable to our late sampling time point in the RisCoin cohort, i.e., by median 8 months after the second vaccination, although we were limited in power to detect interactions between genetic effects and the interval post vaccination. It might have also become apparent because we measured continuous antibody levels rather than a binary serostatus. Either the late sampling time point or the continuous measurement, or their combination, could explain why the association between HHEX locus and anti-SARS-CoV-2 spike antibody concentrations was not observed previously and adds to our understanding of protection against COVID-19.

Our results regarding the IGKV locus confirm previous reports on the influence of germline variation in the Ig gene on antigen-specific antibody concentrations.¹⁶ Our findings support the hypothesis that the antibody repertoire is constrained by inborn Ig variability.^{45–47} Individuals carrying specific genetic Ig variants may, thus, be predisposed to produce fewer antibodies after exposure to specific antigens. Narrowing down on the exact genetic variants mediating the effect is currently limited because of the complexity of the IGKV locus, which would require additional sequencing data to resolve. Especially, developing genotype imputation panels for the Ig loci would potentially help overcome this limitation and, thereby, add to the existing evidence for the role of germline Ig variation in antibody repertoire and disease susceptibility.^{45–47}

Lead HLA allele signals associated with anti-SARS-CoV-2 antibody responses differ across previously published studies.¹⁴ In our analyses, HLA-A*03:01 was positively associated with SARS-CoV-2-specific humoral immune responses, whereas HLA-DQB1*05 showed a negative association. In line with previous reports, we suggest that the binding affinity of spike-derived peptides differs between the different HLA-A types. Consequently, HLA-A-dependent CD8⁺ T cell activation and downstream immune functions may be affected, ultimately influencing anti-spike antibody production and quality. Interestingly, regarding HLA class II alleles, it was shown *in vitro* that anti-spike memory B cell and overall CD4⁺ T cell responses differ between HLA-DQB1*06 carriers and non-carriers, adding evidence to the proposed mechanism behind the association between HLA variation and antibody concentrations after COVID-19 vaccination.¹⁵ We discovered that HLA loci are not only associated with anti-SARS-CoV-2 spike antibody concentrations after the second COVID-19 vaccination but also with those after the third dose and, moreover, with live-virus neutralization activities against Omicron BA.1. While an independent replication cohort for these two phenotypes is lacking, the HLA association observed with post-second vaccination anti-

spike antibody levels, in our cohort and others, does provide additional support for this finding. These results highlight the importance of the discovered HLA loci for influencing antibody responses to SARS-CoV-2, even after repeated exposure to the spike antigen, and neutralizing immunity, which was shown to be a strong correlate of protection against symptomatic and severe disease.^{6,17,18,48,49} Participants of our study who were homozygous for HLA-A*03:01 were, indeed, significantly protected from breakthrough infection, in line with reports from others.⁴¹ Collectively, our findings indicate the potential relevance of the HLA locus for future personalized immunization approaches.

In conclusion, our study identified genetic determinants of humoral immunity to SARS-CoV-2 after the second and third COVID-19 vaccinations. This study provides relevant context for investigating the genetics of neutralizing immunity and humoral immune responses after the third immunization. HLA loci that we showed to be associated with the functional correlate of protection against SARS-CoV-2 but also the other discovered loci may in future be helpful to identify and protect vulnerable individuals and provide them access to personalized vaccination strategies. Some of the genetic variants identified here may not only be important for shaping immunity to SARS-CoV-2, but they may also play a more general role in modulating vaccine-induced immunity to other pathogens.

Limitations of the study

Despite elucidating the role of HLA, IGKV, and HHEX loci on immunity against COVID-19, our study has some limitations. First, the loci highlighted here and elsewhere warrant experimental validation to confirm roles in antibody production and persistence and to assess generalizability across vaccine platforms and antigens. Also, our study primarily reflects the genetic effects on humoral protection following vaccination with mRNA-based vaccines. Interaction analyses provided no evidence that genetic variants exert differential effects on antibody levels or neutralizing capacity across vaccine types, although such differences may be too small to detect at the current sample size. We also acknowledge that the lack of ancestral diversity within our study populations limits the broader applicability of our findings. Population-specific effects have been proposed as a potential source of the heterogeneity observed across previous reports, and cross-ancestry meta-analysis has been suggested as a means of formally addressing this issue.¹⁴ Another limitation is that we only assessed live-virus neutralization activities against Omicron BA.1 and not against other, more recent SARS-CoV-2 variants. There is, however,

Figure 4. Genetic variation in HLA class I region associates with neutralization activities and anti-spike antibody concentrations after the third COVID-19 vaccination

(A) Cohort overview. We ran GWAS on the live-virus neutralization activity against SARS-CoV-2 Omicron BA.1 and anti-spike antibody concentrations from 1,225 infection-naïve individuals in the RisCoin cohort, collected at median 56 days post third COVID-19 vaccination.
(B) Correlation of anti-spike antibody concentrations and live-virus neutralization activities (Spearman $\rho = 0.53$, p value $< 1 \times 10^{-16}$).
(C) Manhattan plot showing the results of the GWAS of anti-spike antibody concentrations (left) and live-virus neutralization activity (right). Genome-wide significant results are annotated with the locus name.
(D and E) Regional association plot of the HLA class I (D) and II (E) loci, for the anti-spike antibody concentrations (top) and neutralization activities GWAS (bottom), conducted using SNP, amino acid, and HLA allele variation imputed using the T1DGC panel.²⁸ The color indicates the linkage disequilibrium estimate (r^2) to the lead variant. SNPs are represented by circles and HLA alleles by triangles. Coordinates of the genes in the locus are shown in the lower image. Lead SNP and HLA allele signals per locus are labeled, and additionally HLA-DQB1*05 is labeled in (E) (top).
In (C)–(E), association p value per variant is shown on the y axis, plotted against the positions of the variants on the hg19/GRCh37 genomic build, and the dashed line represents the genome-wide significance threshold (5×10^{-8})

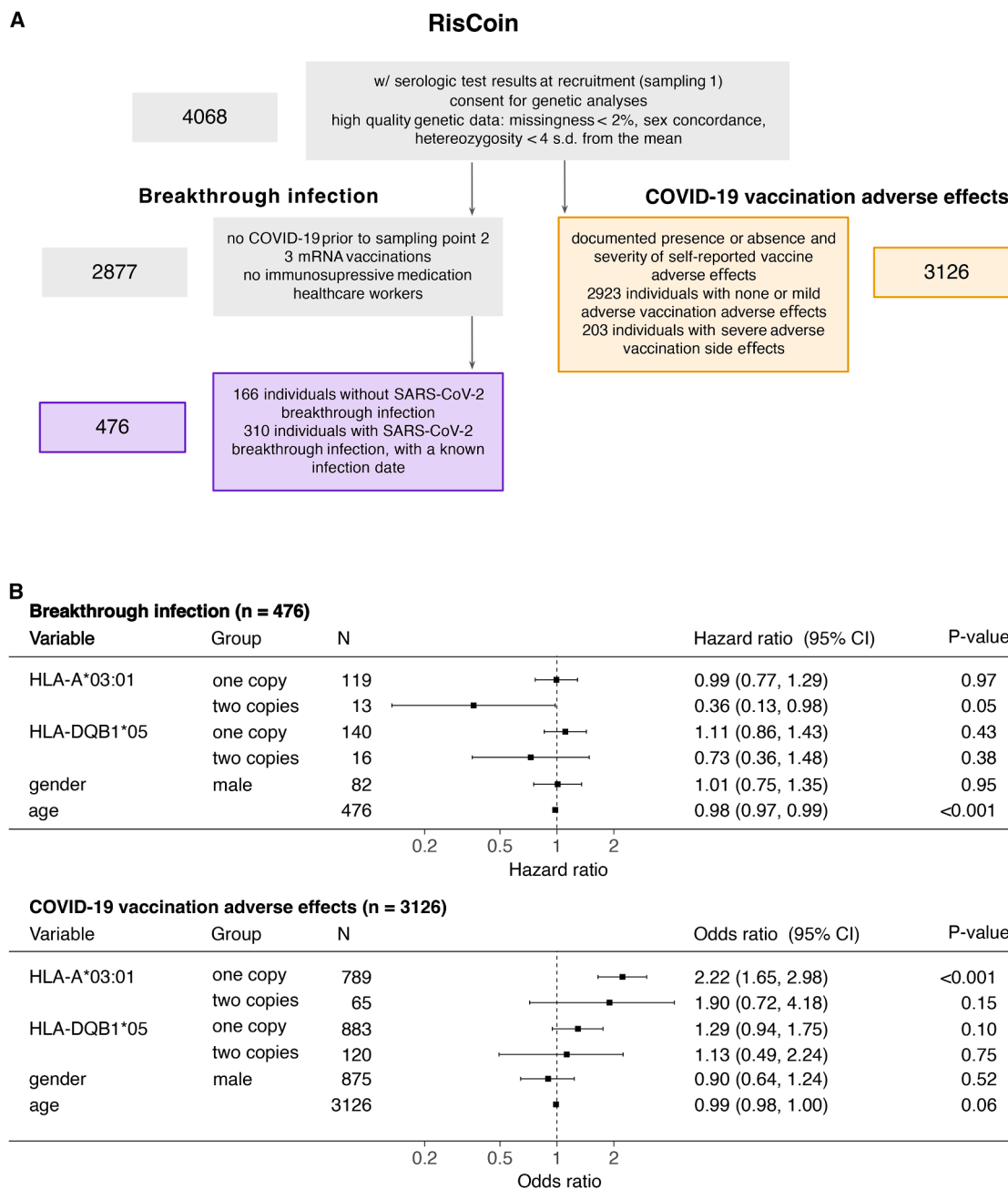


Figure 5. Carrying HLA class I variation is associated with decreased incidence of breakthrough infection and increased incidence of self-reported severe adverse effects after COVID-19 vaccination

(A) Flow diagram of RisCoin participant selection for genetic analyses of vaccination adverse effects and breakthrough infection after COVID-19 vaccination. (B) Annotated forest plot indicating Cox proportional hazards regression results for breakthrough infection incidence (top) and logistic regression results for self-reported severe adverse effect incidence (bottom) in the RisCoin cohort. From left to right, the plot shows the variable of interest, the group of interest, the number of individuals per variable level, visual and numeric indication of regression results. The results shown are relative to a reference group, defined as individuals with zero copies of the variant of interest, or as females when gender is the variable considered. Boxes indicate hazard ratio estimates for breakthrough infection, and odds ratio estimates for self-reported severe adverse effects incidence. Whiskers indicate the 95% CI. CI, confidence interval.

evidence that vaccination-induced neutralization titers correlate strongly between different virus variants.^{10,11} We, thus, hypothesize that the associations between the HLA loci and live-virus neutralization activity against Omicron BA.1 also apply to other

SARS-CoV-2 variants, especially to those of the predominant Omicron clade. Finally, by leveraging a cohort of healthcare workers vaccinated on standardized schedules, we could characterize the protection up to 9 months post-vaccination as well as

post-third-dose responses. Nonetheless, power at the third dose was limited with considerably smaller number of participants in the post-third-dose subset compared after the second, and additional loci may emerge with larger sample sizes. Extending genetics to fourth and later boosters would be highly informative as well but would require new data. However, recruiting infection-naïve individuals after ≥ 3 immunizations became impractical following Omicron, when breakthrough infections were widespread in the general population from Spring 2022 onwards.^{50,51} Consequently, our study may remain one of very few opportunities to assess genetic determinants of post-booster and neutralizing immunity against COVID-19 independent of the effects of a previous infection.

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to the lead contact, Sarah Kim-Hellmuth (sarah.kimhellmuth@helmholtz-munich.de).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Single-study GWAS summary statistics are deposited in the GWAS Catalog (study IDs: GCST90726556, GCST90726557, GCST90726558, GCST90726559, and GCST90726560). Meta-analysis and HLA GWAS summary statistics are deposited at <https://github.com/kimhellmuthlab/COVID-19-vacc-gwas>.
- All original code has been deposited at Zenodo at <https://doi.org/10.5281/zenodo.21409919> and is publicly available as of the date of publication.
- To protect participant privacy and remain within the scope of consent obtained, individual-level genotyping data are not made publicly available.
- Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization and supervision, S.K.-H., S.K., and M.H.; RisCoin study design and funding acquisition, A.C., B.K., H.P.T., K.A., O.T.K., S.K., and V.H.; KoCo19-SEPAN study design and funding acquisition, M.H., E.Z., and C.G.; data generation and curation, P.R.W., C.J., T.G.L.T., R.R.-A., I.C.S., G.L., M.S., A.Z., N.C., A.W., and J.R.; formal analysis and visualization, B.P.; writing, B.P., P.R.W., and S.K.-H. All authors contributed to editing the manuscript and approved the final version.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used Claude (Anthropic) to review the formatting and language of the article. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Bacterial and virus strains		
SARS-CoV-2, Omicron BA.1	Wratil et al. ¹⁰	GISAID EPI ISL: 7808190
Biological samples		
Human serum samples, RisCoin cohort	Koletzko et al. ²¹	N/A
Human dried blood spot samples, KoCo19 cohort	Le Gleut et al. ²⁴	N/A
Critical commercial assays		
Elecsys Anti-SARS-CoV-2	Roche	Cat#09203095190
Elecsys Anti-SARS-CoV-2 S	Roche	Cat#09289267190
Illumina GSA-24 v3.0	Illumina	Cat#20030772
Deposited data		
Single-study GWAS summary statistics	This paper; GWAS Catalog	GCST90726556- GCST90726560
Meta-analysis and HLA GWAS summary statistics and analysis code	This paper	https://doi.org/10.5281/zenodo.21409919
Haplotype Reference Consortium panel (release 1.1)	McCarthy et al. ⁵²	https://doi.org/10.1038/ng.3643 ; accessed via https://imputationserver.helmholtz-munich.de/
T1DGC HLA reference panel (SNP2HLA)	Rich ²⁸	https://doi.org/10.58020/63vn-7d44
1000 Genomes Project reference data	Auton et al. ³⁵	https://www.internationalgenome.org/data/
eQTL Catalog gene expression summary statistics	Kerimov et al. ³²	https://www.ebi.ac.uk/eqtl/Data_access/
GTEx whole blood eQTL summary statistics	GTEx Consortium ³⁶	https://gtexportal.org/home/downloads/adult-gtex
UK Biobank COVID-19 vaccine seroconversion GWAS	Sonehara et al. ¹⁶	https://doi.org/10.1016/j.xgen.2025.100783 ; obtained directly from the authors
Software and algorithms		
PLINK	Purcell et al. ⁵³	https://www.cog-genomics.org/plink/
Helmholtz Munich Imputation Server	Rayner et al. ⁵⁴	https://imputationserver.helmholtz-munich.de/
SNP2HLA	Jia et al. ⁵⁵	https://software.broadinstitute.org/mpg/snp2hla/
GEMMA	Zhou and Stephens ²⁵	https://github.com/genetics-statistics/GEMMA
METAL	Willer et al. ²⁶	https://genome.sph.umich.edu/wiki/METAL
GCTA-COJO	Yang et al. ²⁷	https://yanglab.westlake.edu.cn/software/gcta/
susieR	Wang et al. ³⁰ ; Zou et al. ³¹	https://github.com/stephenslab/susieR
coloc	Giambartolomei et al. ³³	https://github.com/chr1swallace/coloc
R package survival (coxph)	Therneau ⁵⁶	https://cran.r-project.org/package=survival
R package stats (glm)	R Core Team ⁵⁷	https://www.r-project.org
Biorender	N/A	https://www.biorender.com/
R package ggplot2 (ggplot)	Wickham ⁵⁸	https://ggplot2.tidyverse.org/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The RisCoin study was approved by the ethics committee of the Faculty of Medicine at the Ludwig Maximilian University of Munich (study-No.: 21–0839). The KoCo19 study protocol was approved by the ethics committee of the Faculty of Medicine at the Ludwig Maximilian University of Munich, Germany (study-No.: 20–275), prior to study initiation. Informed consent was obtained from all study participants prior to study inclusion.

The RisCoin cohort comprised 4,115 individuals, predominantly healthcare workers, as well as patients diagnosed with inflammatory bowel disease and psychiatric disorders.^{21,22} At enrollment, a questionnaire was filled out and blood samples were donated for serological assessment and genotyping. Healthcare workers who were SARS-CoV-2 infection-naïve (defined by being negative for anti-nucleocapsid antibodies and self-reporting of never having been tested positive for COVID-19 by PCR), received two doses of mRNA-based COVID-19 vaccine (BNT162b2, mRNA-1273), the second dose at least 28 days ago, took no immunosuppressive medication and had high quality genetic data were selected for genetic analyses at time point #1 ($n = 2,877$). At time point #2, blood samples were taken from participants of the same cohort shortly after the third vaccination. From these, we selected 1,225 individuals, who were still SARS-CoV-2 infection-naïve and had high quality genetic data, to analyze genetic effects on anti-spike antibody concentrations and live-virus neutralization titers produced after the third immunization (Figure 1B). Weekly questionnaire was conducted using a study app.³⁹ Age and gender information of the subgroups used in each of the analyses are reported in Tables S1 and S2.

The KoCo19 cohort comprised 5,313 individuals recruited from randomly selected households in Munich, Germany, for whom anti-SARS-CoV-2 spike and nucleocapsid antibody concentrations and questionnaire data were available at multiple time points throughout the COVID-19 pandemic.^{23,24} We analyzed the data from a sampling round that took place between July and October 2021. For genotyping, we picked 1,719 participants who had complete data and consent for genetic analyses, received their second vaccination at least 5 days before the sampling round, were SARS-CoV-2 infection-naïve as inferred from their anti-nucleocapsid status and donated a dried blood spot sample and of those selected 1,654 individuals with high quality genotype data (Figure 1B). Age and gender information of the participants is reported in Table S2.

METHOD DETAILS

Antibody detection assays

For blood samples collected in the RisCoin study, serum was extracted by centrifugation at $3,200 \times g$ for 10 min at room temperature. Using the extracted sera we performed the Elecsys Anti-SARS-CoV-2 (Roche, Basel, Switzerland, cat.: 09203095190) and the Elecsys Anti-SARS-CoV-2 S (Roche, cat.: 09289267190) on a Cobas e411 (Roche). Assays were performed in accordance with the manufacturer's instructions. Following the manufacturer's recommendations, serum specimens that gave above threshold signals in the Anti-SARS-CoV-2 S assay were diluted in sample buffer and measured again until in range signals were obtained.

For samples collected in the KoCo19 cohort, quantitative anti-spike and anti-nucleocapsid antibody measurements were performed using a self-developed protocol for extraction and measurement in dried blood as described.^{59,60} In brief, participants self-collected dried-blood spot samples (Euroimmun ZV 9701-0101). Antibodies were eluted from the dried-blood spot in 80 μ L of PBS buffer containing 5% albumin, 2.5 mM ammonium thiocyanate, and 0.5% Tween 20 at 37°C for 1 h with shaking at 300rpm. Eluates were analyzed on Cobas e801 units (Roche) using Elecsys Anti-SARS-CoV-2 (Roche) and Elecsys anti-SARS-CoV-2 S (Roche). Dried-blood spot-specific cutoffs and quantitative conversion factors were established and validated against matched plasma samples to ensure accurate serological interpretation.

Live-virus neutralization assay

As previously described, we used a nasopharyngeal swab to produce high-titer virus stocks of SARS-CoV-2 Omicron BA.1 (GISAID EPI_ISL: 7808190).^{10,61} We tested the capacity of serum specimens collected in the RisCoin study to neutralize these virus stocks as described previously.^{10,61} After normalizing the results to the respective abundance of viral RNA in the stocks, a sigmoidal dose-response curve approximation was calculated for each serum tested using Prism 10.2.1 (GraphPad Software, USA) to determine its half-maximal inhibitory concentration (IC₅₀) for live-virus neutralization of SARS-CoV-2 Omicron BA.1. We set the lower threshold for live-virus neutralization to a serum dilution of 1:10.

Genotype data QC and imputation

Genotype data was obtained using the Infinium Global Screening Array-24 v3.0 (Illumina). We excluded individuals from further analysis with more than 3% missing data, mismatch of self-reported gender and sex information inferred from genetic data, as well as heterozygosity rate of more than 4 standard deviations from the mean heterozygosity rate in the cohort. We then excluded genetic variants with missingness rate greater than 2%, and those deviating from Hardy-Weinberg equilibrium (p -value $< 1 \times 10^{-4}$). Population structure was inspected via principal component analysis and compared to reference samples from the 1kg dataset³⁵ (Figure S6). In total, 698,074 variants and 4,068 individuals passed the quality control in RisCoin and 531,943 variants and 1,850 individuals in the KoCo19 cohort. All quality control metrics were computed with PLINK 1.9.⁵³

Genotype imputation was performed on the Munich Imputation Server⁵⁴ according to the documentation,⁶² where the data was phased with EAGLE2⁶³ and imputed with Minimac4⁶⁴ against the Haplotype Reference Consortium (release 1.1) imputation panel.⁵² We selected all variants with imputation scores higher than 0.3 and MAF >0.05 for further analyses.

HLA imputation

HLA allele, amino acid and coding variation imputation was performed following the guidelines of Sakaue et al.³⁷ using the SNP2HLA⁵⁵ software according to the software documentation.⁶⁵ The imputation was done against the Type 1 Diabetes Genetics Consortium (T1DGC) European reference panel.²⁸ Prior to use, the panel was lifted over to the genomic build hg19/GRCh37 with lift-Over.⁶⁶ Variants with an imputation score >0.8 were kept for subsequent analysis.

QUANTIFICATION AND STATISTICAL ANALYSIS

Association analysis

Genome-wide association analyses per cohort were conducted in GEMMA,²⁵ using a linear mixed model (-lmm) as described in the GEMMA user manual. For each phenotype and time point, we used inverse-normal transformation of the phenotype values. Number of individuals used in each analysis is reported in Figure 1B. Age, gender, days since most recent vaccination and the first 5 genotype principal components were used as covariates in the model. Additionally, the vaccine type in KoCo19 cohort post second vaccination and in the RisCoin cohort post third vaccination were included as covariates in the model (Table S1). The relationship between the interval since vaccination and phenotype levels are shown in Figure S5. The model also utilized a genetic relatedness matrix to account for relatedness among the participants. We considered variants with p -value $< 5 \times 10^{-8}$ to be genome-wide significant. Genomic inflation was quantified by the genomic inflation factor lambda. HLA association analysis was conducted in GEMMA, with the same settings as previously used in the genome-wide analysis. We considered variants, amino acid residues and HLA alleles with p -value $< 5 \times 10^{-8}$ to be genome-wide significant. To run gene-by-environment interaction analysis in GEMMA, we employed the -gxe scheme, where the fixed effects of the variant and the environmental covariate are controlled, while testing for the interaction effect. We ran the meta-analysis in METAL,²⁶ weighting the effects using the inverse of the standard errors (SCHEME STDERR). We used gcta-cojo²⁷ to identify independent associations via a stepwise model selection procedure (-cojo-slc, p -value $< 5 \times 10^{-8}$) and perform conditional analyses (-cojo-snp). Statistical fine-mapping was done using susieR.^{30,31} Colocalization was performed with the eQTL Catalogue³² gene expression summary statistics using the coloc³³ package in R, with the function *coloc.abf*. We considered only the events with posterior probability for shared genetic signals (PP4) larger than 0.8.

Breakthrough infection and adverse effects

The RisCoin cohort participants were invited for serological assessment and to answer a questionnaire several months after the third vaccination. Data from this time point #3 and the weekly app questionnaire were used for evaluating the incidence of breakthrough infections. In the analysis, we included only individuals with exactly three mRNA vaccinations and a known SARS-CoV-2 infection date, in case they experienced a breakthrough infection. Among the 476 individuals with complete data, 310 experienced a breakthrough infection (Figure 5A; Table S2). Using the data from the initial, follow-up and weekly app questionnaires, we analyzed the incidence and severity of participants' self-reported adverse effects after the third immunization. Among the 3,126 individuals with complete data, 203 self-reported severe adverse effects with impairment in everyday life (e.g., doctor's visit, sick leave) (Figure 5A; Table S2). We applied a Cox proportional hazards model using the *coxph* function^{56,67} in R to evaluate the association of breakthrough infection incidence with the two lead HLA alleles identified in the anti-spike GWAS of the independent KoCo19 cohort. We considered the hazard ratios and the 95% confidence intervals for the variables of interest. We used logistic regression using the *glm* function⁵⁷ in R to assess the incidence of self-reported severe adverse effects after the third vaccination, with the same lead variants used in the breakthrough infection analysis as predictors. We considered the odds ratios and the 95% confidence intervals for the variables of interest. In both models, age and gender were included as covariates.