Supplementary appendix to:

Genetic architecture of adaptive immune responses and adverse reactions to inactivated COVID-19 vaccine

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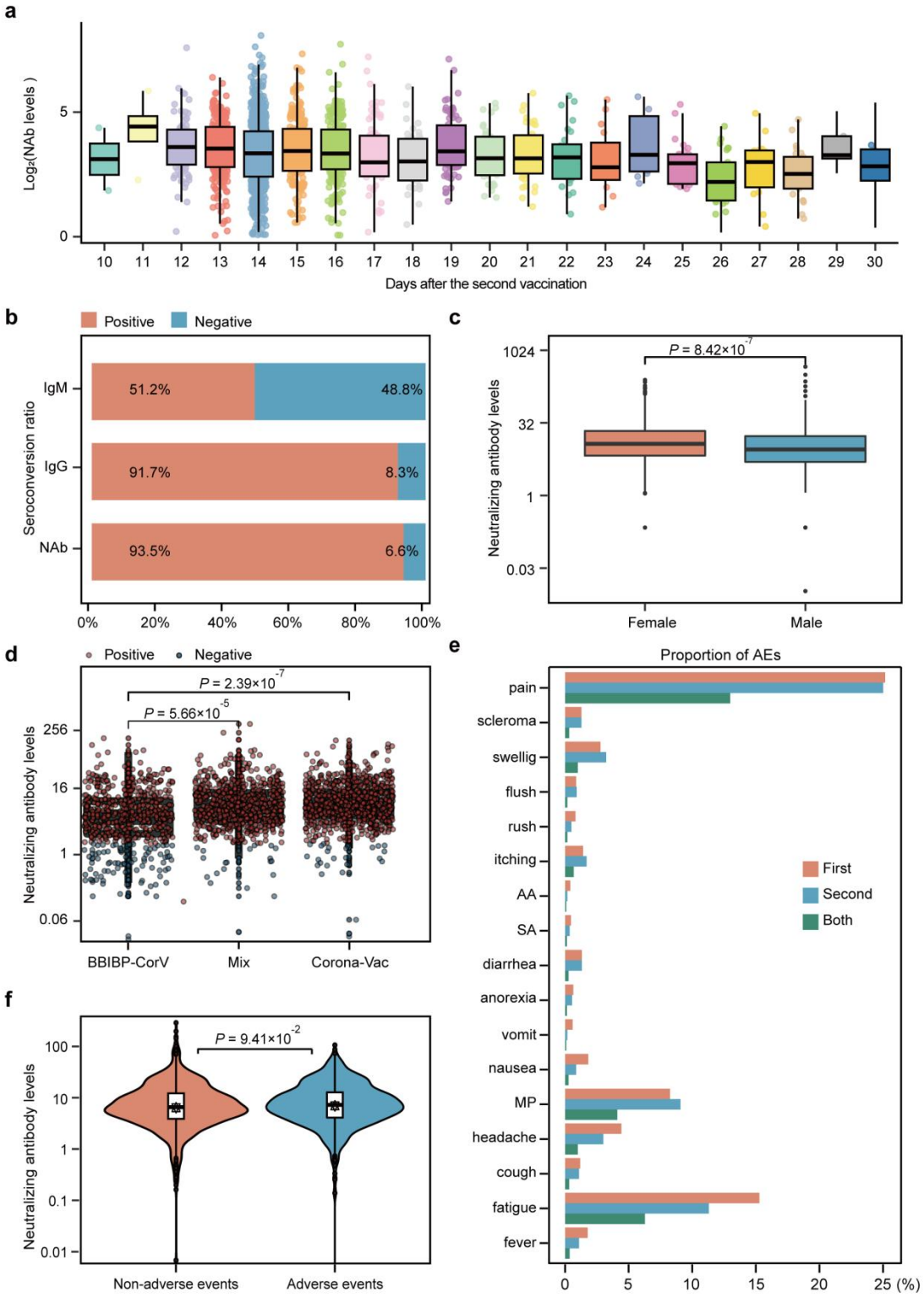
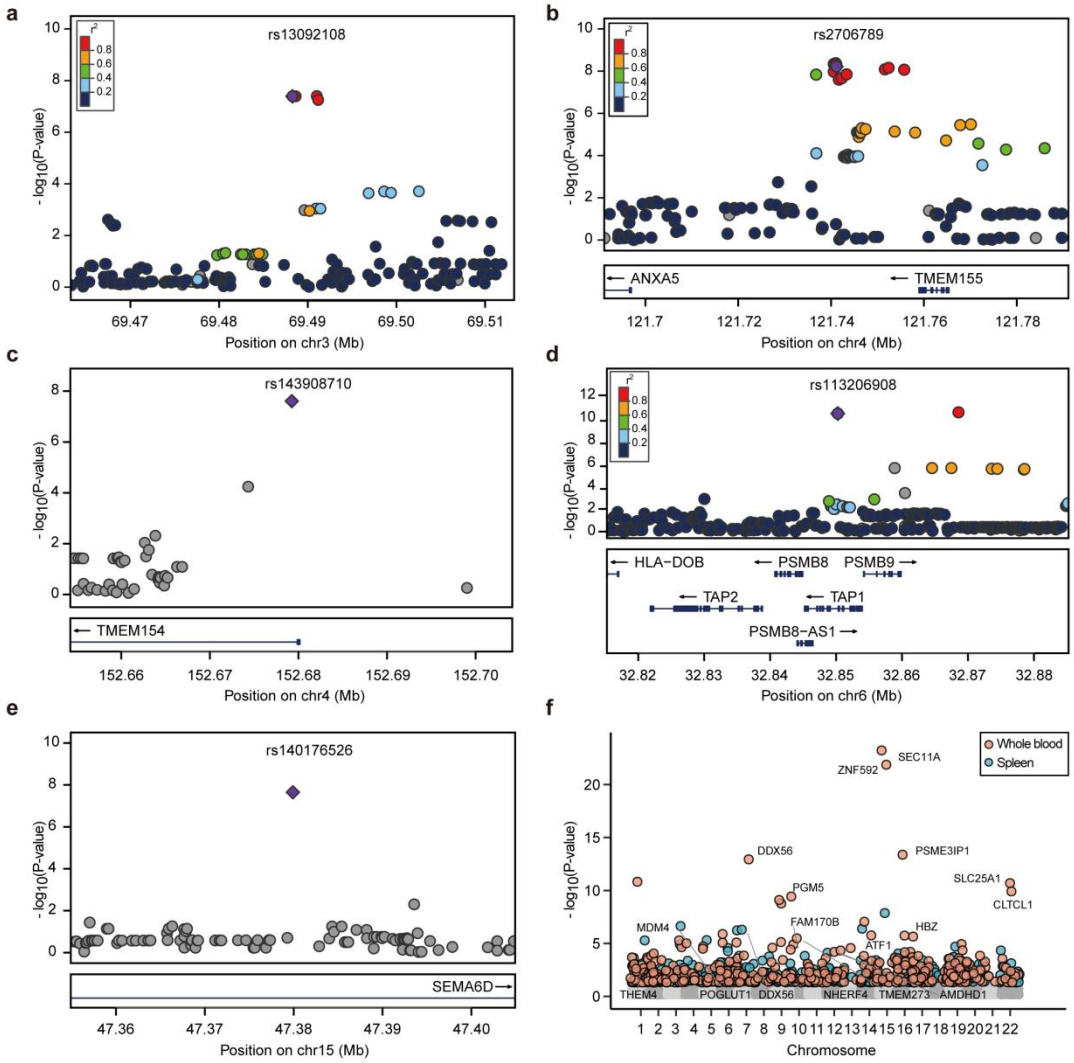


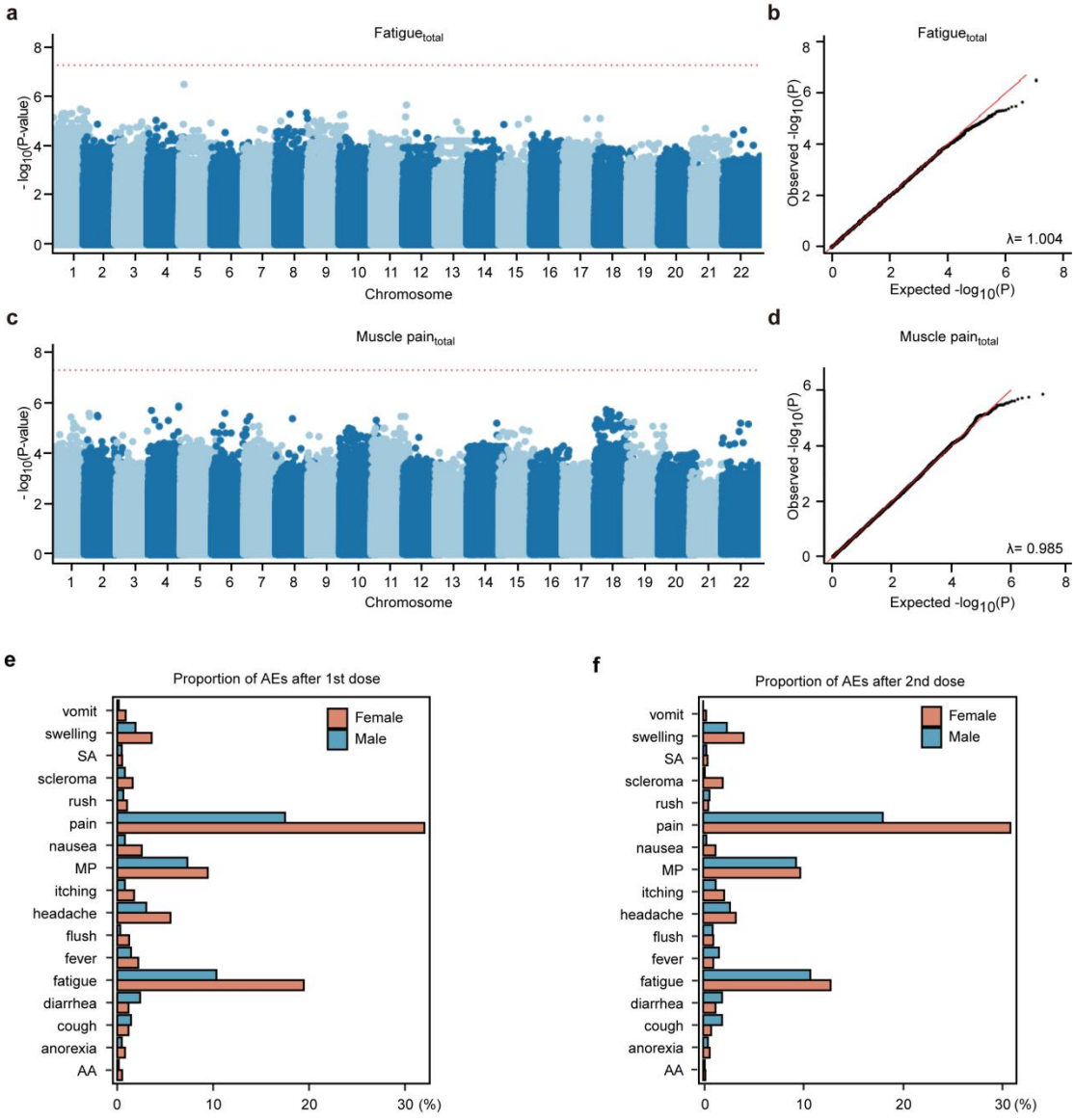
Supplementary Figure 1. Characteristics of immune responses among cohort individuals. **a**, Distribution of neutralizing antibody (NAb) levels measured from Day 10 to Day 30 after the second vaccine dose. **b**, Percentage of antibody seropositivity among participants. **c**, Comparison of NAb levels between males and females ($P < 0.05$, t-test). **d**, Comparison of NAb levels among participants vaccinated with different vaccine regimens ($P < 0.05$, t-test). BBIBP-CorV

represented 2 doses of Sinopharm BIBP COVID-19 vaccine; Mix represented 1 dose of Sinopharm BIBP COVID-19 vaccine and 1 dose of Sinovac-CoronaVac vaccine; Corona-Vac represented 2 doses of Sinovac-CoronaVac vaccine. **e**, Proportion of participants reporting specific adverse reactions following vaccination. **f**, Comparison of NAb levels grouped by reported adverse reactions ($P < 0.05$, t-test). AA: Acute allergy; SA: Skin and mucosa abnormity; MP: Muscle pain.



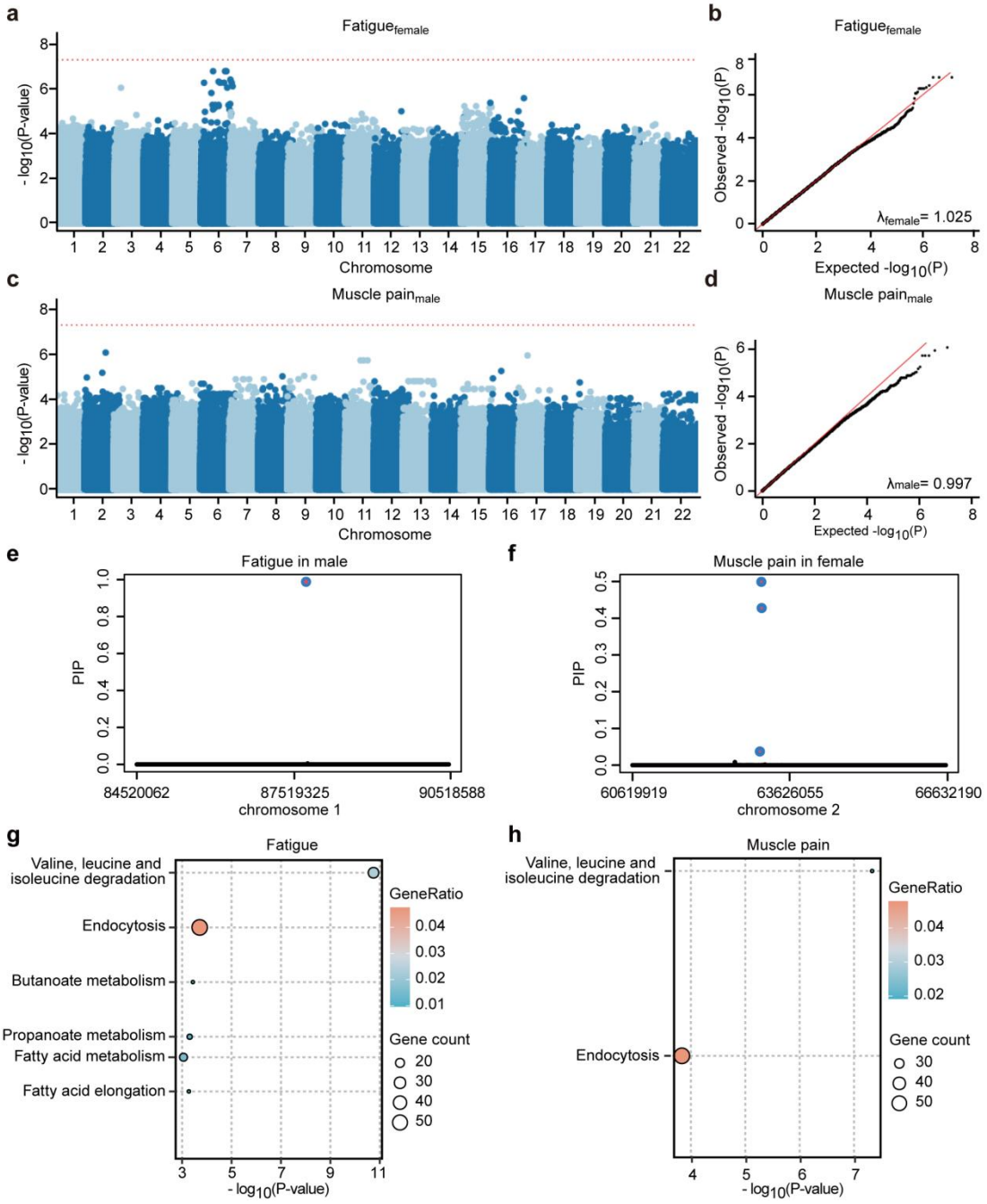
Supplementary Figure 2. Fine-mapping of candidate causal variants linked to neutralizing antibody responses.

a-**e,** Regional fine-mapping plots depicting genomic loci on chromosomes 3, 4, 6, and 15 that were identified through GWAS. SNP positions are plotted along the *x*-axis, and their corresponding association strength (-$\log_{10}$*P*-value) with NAb levels on the *y*-axis. SNPs are colored by linkage disequilibrium (r^2) relative to the lead SNP (purple diamond). **f,** Manhattan plot presenting genes identified by transcriptome-wide association studies (TWAS) and genes significantly expressed in relation to NAb responses (represented as colorful points). Each dot corresponds to an individual gene. The *x*-axis indicates the physical position (chromosomal localization) of the gene, and the *y*-axis represents the -$\log_{10}$ of *P* value for the association between the gene and NAb. Genes that are significantly expressed in different tissues are highlighted in distinct colors: blue for the spleen and red for whole blood.



Supplementary Figure 3. GWAS analysis of vaccine-associated adverse events following inactivated COVID-19 vaccination.

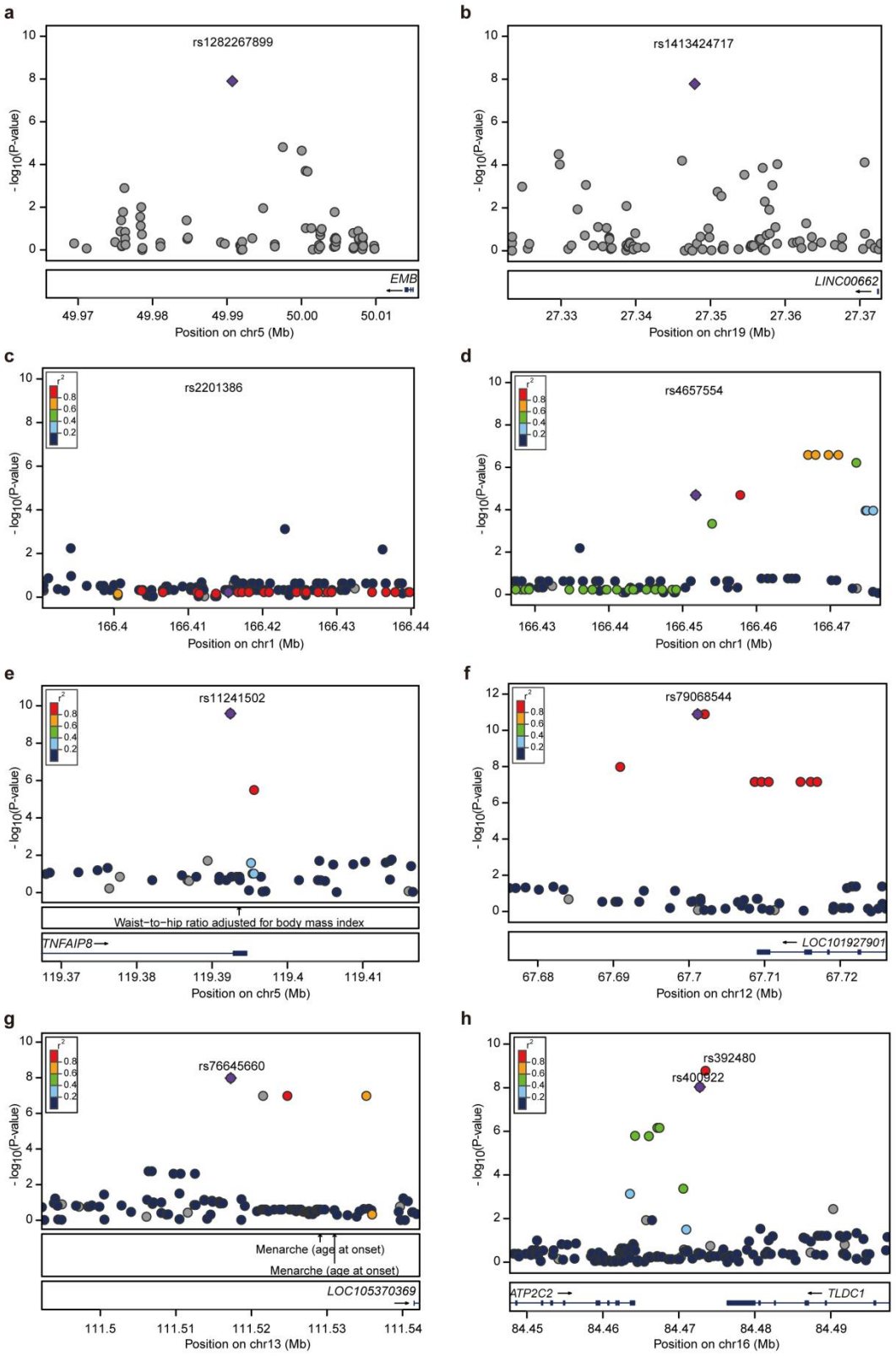
a, Manhattan plot displaying genome-wide association results for vaccine-associated fatigue following the second vaccine dose. The red horizontal line indicates genome-wide significance ($P < 5 \times 10^{-8}$). **b**, Quantile-quantile (QQ) plot illustrating observed versus expected *P*-values for GWAS of fatigue. **c**, Manhattan plot displaying genome-wide association results for vaccine-associated muscle pain following the second vaccine dose. The red horizontal line indicates genome-wide significance ($P < 5 \times 10^{-8}$). **d**, QQ plot illustrating observed versus expected *P*-values for GWAS of muscle pain. **e-f**, Proportion of males and females reporting adverse events following each vaccination (SA: skin and mucosal abnormity; MP: muscle pain; AA: acute allergy).



Supplementary Figure 4. Sex-stratified analysis of adverse events following inactivated COVID-19 vaccination.

a, Manhattan plot displaying genome-wide association results for vaccine-associated fatigue in females following the second vaccine dose. The red horizontal line indicates genome-wide significance ($P < 5 \times 10^{-8}$). **b**, Quantile-quantile (QQ) plot illustrating observed versus expected *P*-values for GWAS of fatigue in females. **c**, Manhattan plot displaying genome-wide association results for vaccine-associated muscle pain in males following the second vaccine dose. The red horizontal line indicates genome-wide significance ($P < 5 \times 10^{-8}$). **d**, QQ plot illustrating observed versus expected *P*-values for GWAS of muscle pain in males. **e-f**, Ideograms of fine-mapped variants associated with vaccine-associated fatigue on chromosomes 1 (panel **e**) and 2 (panel **f**). Likely causal variants are indicated in red; the 95% credible sets (CS) are shaded in blue. **g-h**,

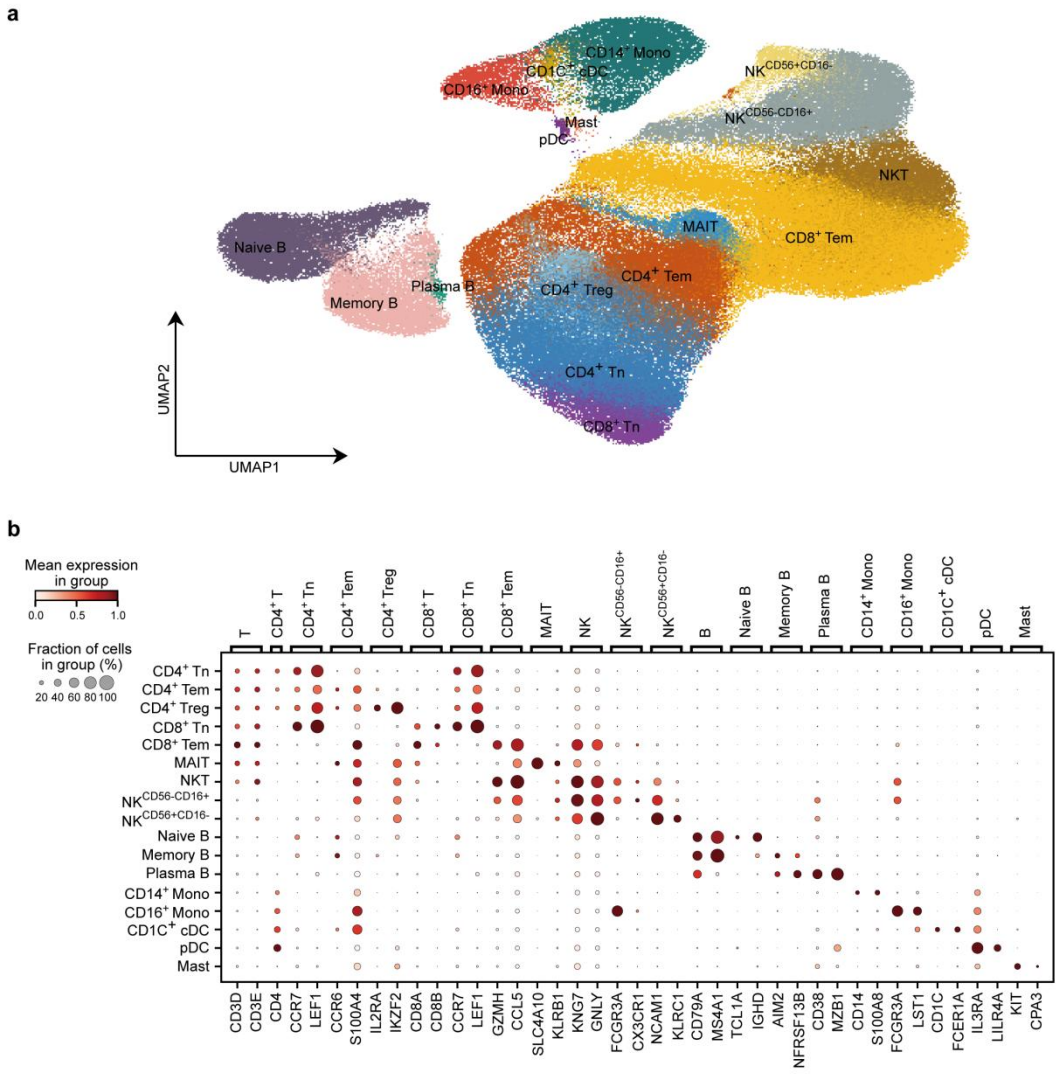
Bubble plot for KEGG pathway enrichment analysis of TWAS-significant genes associated with fatigue (in males) and muscle pain (in females) associated by vaccine. The bubble size represents the number of genes in each pathway, while the color indicates the gene ratio. The adjusted p-values are displayed along the *x*-axis, and the pathway names are shown on the *y*-axis.



Supplementary Figure 5. Fine-mapping candidate causal variants associated with Th1 cell responses and B cell memory.

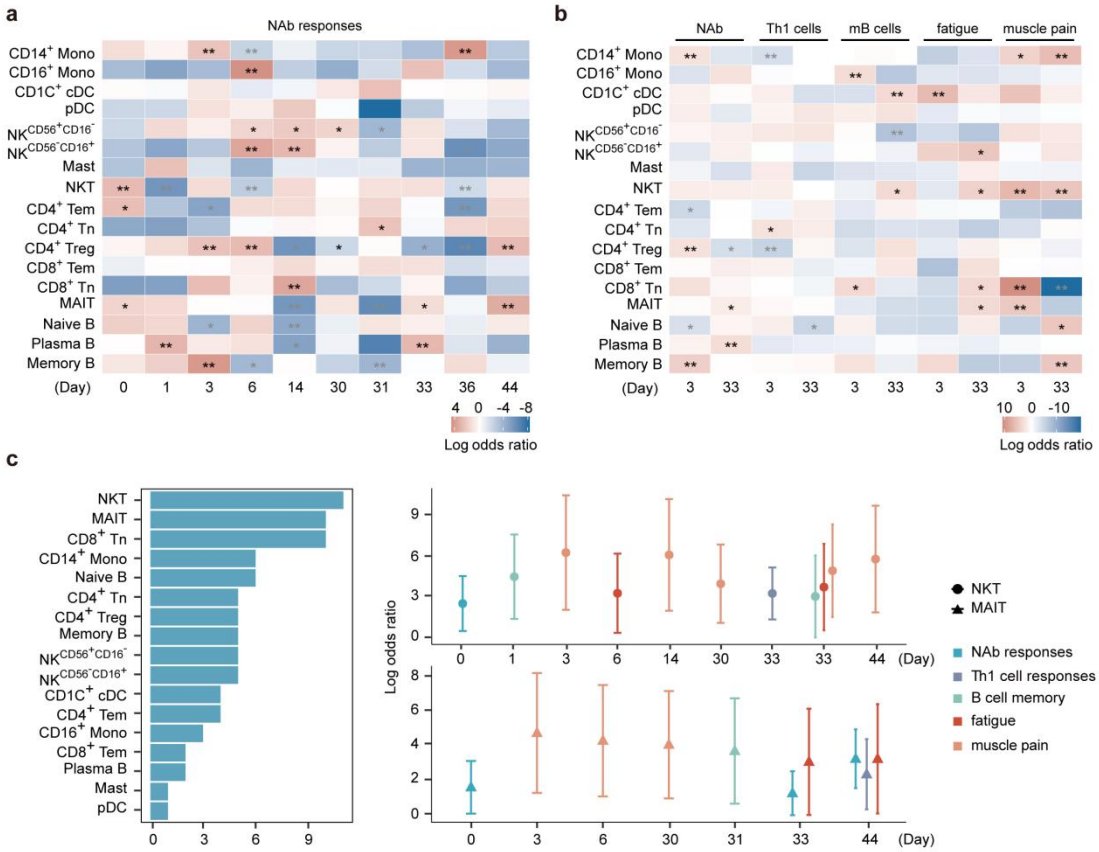
Regional fine-mapping plots for loci on chromosomes 5 (**a**) and 19 (**b**) associated with B cell memory. SNPs are plotted on the *x*-axis according to their position, and the significance of the association between each SNP and B cell memory (-$\log_{10}$ *P*-value) are plotted on the *y*-axis.

Regional fine-mapping plots for loci on chromosome 1(**c, d**), 5 (**e**), 12 (**f**), 13 (**g**) and 16 (**h**) associated with Th1 cell responses. SNPs are plotted on the *x*-axis according to their position, and the significance of the association between each SNP and Th1 responses (-$\log_{10}$ *P*-value) are plotted on the *y*-axis. Dot corlor represents the level of linkage disequilibrium, expressed as r^2 between each SNP and the lead SNP (purple diamond). The lead variant is the SNP with the strongest association signal in the region. Linkage disequilibrium (r^2) measures the non-random association of alleles at different loci, with values ranging from 0 (no association) to 1 (complete association).



Supplementary Figure 6. Single-nucleus multi-omic characterization of PBMCs before and after vaccination.

a, UMAP projection of single-nucleus ATAC-seq (snATAC-seq) and single-nucleus RNA-seq (snRNA-seq) co-assay data annotated by inferred cell-type assignments based on gene activity scores. **b**, Dot plot of canonical marker gene expression for annotated immune cell types in vaccinated adult individuals.



Supplementary Figure 7. Cell-type- and time-resolved partitioned heritability enrichment analysis for vaccine response-associated traits.

a, Partitioned heritability enrichment in immune cell subsets NAb responses. Statistical significance is indicated by asterisks (*P < 0.05; **P < 0.01). **b,** Cross-trait comparison of partitioned heritability enrichment across immune cell subsets at Day 3 after each vaccination. Traits include NAb responses (NAb), Th1 cell responses (Th1 cells), B cell memory responses (mB cells), fatigue, and muscle pain. **c,** Summary statistics of cell type-specific enrichment across vaccine-associated traits. Left panel: Frequency of significant enrichments per immune cell type and their relative rankings. Right panel: Cross-trait enrichment analysis specifically for NKT and MAIT cells at selected timepoints after vaccination.

Characteristic \ Cohort	Antibody responses (n=2,217)	Th1 cell responses (n=159)	B cell memory (n=135)	Adverse events (n=1,952)
Age				
median (IQR)	36.7 (16.0)	34.5 (15.0)	36.4 (16.0)	36.7 (16.0)
Missing, n (%)	212 (9.6)	5 (3.1)	1 (0.8)	31 (1.6)
Sex, n (%)				
Female	1,514 (68.3)	89 (56.0)	86 (66.1)	1,376 (70.5)
Male	619 (27.9)	65 (40.9)	43 (33.1)	576 (29.5)
Missing	84 (3.8)	5 (3.1)	1 (0.8)	0 (0.0)
BMI				
median (IQR)	20.5 (4.5)	22.9 (5.1)	23.3 (4.9)	22.5 (4.5)
Missing, n (%)	217 (9.8)	5 (3.1)	1 (0.8)	31 (1.6)
Brand of vaccine, n (%)				
BBIBP-CorV	590 (26.6)	33 (20.8)	40 (30.8)	496 (25.4)
Mix	692 (31.2)	34 (21.4)	52 (40.0)	630 (32.3)
Corona-Vac	851 (384)	87 (54.7)	38 (29.2)	795 (40.7)
Missing	84 (3.8)	5 (3.1)	0 (0.0)	31 (1.6)
Interval between first and second vaccine, n (%)				
1-2 weeks	1,157 (52.2)	2 (1.2)	0 (0.0)	2 (0.1)
3-4 weeks	976 (44.0)	152 (95.6)	130 (100.0)	1,917 (98.3)
Missing	84 (3.8)	5 (3.1)	0 (0.0)	31 (1.6)

Supplementary Table 1. Characteristics for participants from all cohort subsets.