

Effect of *HLA-DRB1* alleles and genetic variants on the development of neutralizing antibodies to interferon beta in the BEYOND and BENEFIT trials: Supplement

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Supplementary Table e-1: Quality control (QC) of genotyping data. QC of genotyped data was conducted in two separate iterations. The first QC took place following genotyping using PLINK, a second, refined round of QC before imputation using PLINK2 v1.90b3s. QC of imputed probabilities was conducted in QCTOOL v1.4 (<http://www.well.ox.ac.uk/~gav/qctool/>).

Samples were removed according to the following criteria:		Variants were removed according to the following criteria:	
Individual genotyping rate	< 98 %	Variant call rate	< 98 %
Gender mismatches		Minor allele frequency	< 1 %
Cryptic relatedness (PI-HAT)	> 0.05	HWE test <i>p</i> -value (first round)	< 10 ⁻⁶
Removal of genetic outlier via EIGENSTRAT/SMARTPCA	> 6 SD	HWE test <i>p</i> -value (second round, after removal of individuals)	< 10 ⁻⁷
Significant deviation of autosomal heterozygosity from the mean		Variants on non-autosomal chromosomes	
		Ambivalent SNPs (A/T and G/C)	
		Variants not present in the 1000 Genomes Phase 3 reference panel	
		IMPUTE2 info metric	< 0.8

Supplementary Table e-2: Ethnicities of samples. Based on genotype data, samples of non-Caucasian ancestry clustered together with samples of Caucasian ancestry (Supplementary Figure e-1).

Ethnicity	Number of samples
Caucasian	926
Hispanic	7
Asian	1
Black	1
Other	4
Unknown	2

Supplementary Table e-3: Additional characteristics of BEYOND and BENEFIT patients included in the analyses. For all median values, the median absolute deviation is indicated in brackets.

Measurement	With SNP data	With HLA data
Median NAb AUC during the first two years (Years*NU/mL), EP3 (including NAb-negative patients)	0 (0)	0 (0)
Median maximum NAb titer during the first two years (NU/ml), EP4 (including NAb-negative patients)	0 (0)	0 (0)
Minimal maximum NAb titer in any individual (NU/ml), including NAb-negative patients	0	0
Median time to the presence of a positive NAb titer, if NAbS were developed (months), EP5	6 (0)	6 (0)
Spearman correlation of mean NAb titer to NAb positivity	0.949	0.952
Spearman correlation of mean NAb titer to NAb AUC	0.997	0.999
Spearman correlation of mean NAb titer to max. NAb titer	0.998	0.999
Spearman correlation of mean NAb titer to the time of a positive NAb titer	-0.347	-0.368

Supplementary Table e-4: Characteristics of NAb-positive patients having developed NAb within two years (secondary analysis set). NAb-positive patients were defined as having a titer >20 NU/mL during the first two years of either study. Only a subset of patients had *HLA* data available. For all median values, the median absolute deviation is indicated in brackets.

Measurement	With SNP data	With <i>HLA</i> data
Number of samples	353	247
Study: BEYOND (n (%))	289 (81.9)	246 (99.6)
Sex: Female (n (%))	246 (69.7)	168 (68.0)
Median age (years)	38 (10.4)	39 (10.4)
Median disease duration (years)	2.5 (3.7)	3.4 (4)
Median EDSS	2 (1.5)	2 (1.5)
Median cumulative newly active lesions during the studies	2 (3)	2 (3)
Interferon β -1b dose: 250 μ g (n (%))	202 (57.2)	121 (49.0)
Median duration of treatment (years)	2.7 (0.6)	2.6 (0.5)
Minimum duration of treatment with interferon β -1b (years)	0.5	1.5
Median total dose of interferon β -1b (mg)	187.2 (84.5)	184.2 (90.1)
Presence of NAb (n (%)), EP1	353 (100)	247 (100)
Median mean NAb titer (NU/ml), EP2	55 (69.7)	58.5 (76.0)
Median NAb AUC during the first two years (Years*NU/mL), EP3	1013.5 (1272.1)	1016.5 (1285.4)
Median maximum NAb titer during the first two years (NU/ml), EP4	102 (112.7)	118 (136.4)
Minimal maximum NAb titer in any individual (NU/ml)	20	20
Median time to the presence of a positive NAb titer, if NAb were developed (months), EP5	6 (0)	6 (0)
Spearman correlation of mean NAb titer to NAb AUC	0.978	0.985
Spearman correlation of mean NAb titer to max. NAb titer	0.981	0.984
Spearman correlation of mean NAb titer to the time of a positive NAb titer	-0.3	-0.323

Supplementary Table e-5: Summary statistics for the association analysis of NAb AUC with candidate markers (linear regression). Significance thresholds and abbreviations are as described in the legend of Table 2; SE = standard error.

Chr.	Gene	Allele / Variant	Freq. (%)	n	Effect	SE	Published effect	p-value	p-value (1-sided)
6	<i>HLA-DRB1</i>	*04:01	11.9	678	0.41	0.13	>0	1.2×10⁻⁰³	6.0×10⁻⁰⁴
6	<i>HLA-DRB1</i>	*04:08	2.1	678	0.78	0.33	>0	1.7×10 ⁻⁰²	8.6×10 ⁻⁰³
6	<i>HLA-DRB1</i>	*07:01	9.5	678	0.24	0.07	>0	1.5×10⁻⁰³	7.7×10⁻⁰⁴
6	<i>HLA-DRB1</i>	*15	25.5	678	-0.12	0.05	>0	1.6×10 ⁻⁰²	9.9×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*15:01	24.0	678	-0.12	0.05	>0	1.5×10 ⁻⁰²	9.9×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*16:01	2.6	678	0.22	0.19	>0	2.7×10 ⁻⁰¹	1.3×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*03:01	2.9	678	-0.08	0.06	<0	2.3×10 ⁻⁰¹	1.1×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:04	0.4	678	-0.12	0.15	<0	4.1×10 ⁻⁰¹	2.0×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:01	1.2	678	-0.18	0.08	<0	3.6×10 ⁻⁰²	1.8×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*11:04	6.9	678	-0.2.0	0.13	<0	1.2×10 ⁻⁰¹	5.8×10 ⁻⁰²
8	intergenic	rs4961252_G	40.6	941	-0.07	0.04	>0	9.6×10 ⁻⁰²	9.5×10 ⁻⁰¹
6	intergenic	rs9272105_A	49.0	941	-0.08	0.04	<0	2.0×10 ⁻⁰²	9.8×10 ⁻⁰³

Supplementary Table e-6: Summary statistics for the association analysis of maximum NAb titer with candidate markers (linear regression). Significance thresholds and abbreviations are as described in the legend of Table 2; SE = standard error.

Chr.	Gene	Allele / Variant	Freq. (%)	n	Effect	SE	Published effect	p-value	p-value (1-sided)
6	<i>HLA-DRB1</i>	*04:01	11.9	678	0.38	0.13	>0	2.8×10⁻⁰³	1.4×10⁻⁰³
6	<i>HLA-DRB1</i>	*04:08	2.1	678	0.74	0.33	>0	2.3×10 ⁻⁰²	1.2×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*07:01	9.5	678	0.25	0.07	>0	7.3×10⁻⁰⁴	3.7×10⁻⁰⁴
6	<i>HLA-DRB1</i>	*15	25.5	678	-0.11	0.05	>0	2.4×10 ⁻⁰²	9.9×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*15:01	24.0	678	-0.12	0.05	>0	1.9×10 ⁻⁰²	9.9×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*16:01	2.6	678	0.20	0.19	>0	3.0×10 ⁻⁰¹	1.5×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*03:01	2.9	678	-0.08	0.06	<0	2.0×10 ⁻⁰¹	1.0×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:04	0.4	678	-0.09	0.15	<0	5.5×10 ⁻⁰¹	2.8×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:01	1.2	678	-0.18	0.08	<0	3.1×10 ⁻⁰²	1.6×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*11:04	6.9	678	-0.20	0.13	<0	1.1×10 ⁻⁰¹	5.7×10 ⁻⁰²
8	intergenic	rs4961252_G	40.6	941	-0.07	0.04	>0	7.8×10 ⁻⁰²	9.6×10 ⁻⁰¹
6	intergenic	rs9272105_A	49.0	941	-0.09	0.04	<0	1.4×10 ⁻⁰²	6.9×10 ⁻⁰³

Supplementary Table e-7: Summary statistics for the association analysis of mean NAb titer with candidate markers **in NAb-positive patients** (linear regression). Significance thresholds and abbreviations are as described in the legend of Table 2; SE = standard error.

Chr.	Gene	Allele / Variant	Freq. (%)	n	Effect	SE	Published effect	p-value	p-value (1-sided)
6	<i>HLA-DRB1</i>	*04:01	11.3	247	0	0.21	>0	9.9×10 ⁻⁰¹	5.0×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:08	1.8	247	1.58	0.60	>0	9.4×10 ⁻⁰³	4.7×10 ⁻⁰³
6	<i>HLA-DRB1</i>	*07:01	11.9	247	0.32	0.14	>0	2.7×10 ⁻⁰²	1.4×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*15	22.1	247	-0.06	0.11	>0	5.7×10 ⁻⁰¹	7.2×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*15:01	20.6	247	-0.11	0.11	>0	3.3×10 ⁻⁰¹	8.4×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*16:01	1.8	247	0.25	0.43	>0	5.7×10 ⁻⁰¹	2.8×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*03:01	5.1	247	-0.15	0.14	<0	2.8×10 ⁻⁰¹	1.4×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:04	0.6	247	0.35	0.36	<0	3.4×10 ⁻⁰¹	8.3×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:01	1.4	247	-0.31	0.21	<0	1.5×10 ⁻⁰¹	7.3×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*11:04	5.3	247	-0.21	0.30	<0	4.7×10 ⁻⁰¹	2.4×10 ⁻⁰¹
8	intergenic	rs4961252_G	38.8	353	-0.16	0.09	>0	6.4×10 ⁻⁰²	9.7×10 ⁻⁰¹
6	intergenic	rs9272105_A	46.6	353	-0.16	0.07	<0	2.9×10 ⁻⁰²	1.4×10 ⁻⁰²

Supplementary Table e-8: Summary statistics for the association analysis of NAb AUC with candidate markers **in NAb-positive patients** (linear regression). Significance thresholds and abbreviations are as described in the legend of Table 2; SE = standard error.

Chr.	Gene	Allele / Variant	Freq. (%)	n	Effect	SE	Published effect	p-value	p-value (1-sided)
6	<i>HLA-DRB1</i>	*04:01	11.3	247	0.07	0.21	>0	7.4×10 ⁻⁰¹	3.7×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:08	1.8	247	1.58	0.60	>0	9.3×10 ⁻⁰³	4.6×10 ⁻⁰³
6	<i>HLA-DRB1</i>	*07:01	11.9	247	0.22	0.15	>0	1.2×10 ⁻⁰¹	6.2×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*15	22.1	247	-0.09	0.11	>0	4.4×10 ⁻⁰¹	7.8×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*15:01	20.6	247	-0.13	0.11	>0	2.4×10 ⁻⁰¹	8.8×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*16:01	1.8	247	0.08	0.44	>0	8.6×10 ⁻⁰¹	4.3×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*03:01	5.1	247	-0.14	0.14	<0	3.1×10 ⁻⁰¹	1.5×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:04	0.6	247	0.26	0.36	<0	4.8×10 ⁻⁰¹	7.6×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:01	1.4	247	-0.33	0.21	<0	1.2×10 ⁻⁰¹	6.0×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*11:04	5.3	247	-0.23	0.30	<0	4.4×10 ⁻⁰¹	2.2×10 ⁻⁰¹
8	intergenic	rs4961252_G	38.8	353	-0.17	0.09	>0	4.9×10 ⁻⁰²	9.8×10 ⁻⁰¹
6	intergenic	rs9272105_A	46.6	353	-0.13	0.07	<0	7.9×10 ⁻⁰²	4.0×10 ⁻⁰²

Supplementary Table e-9: Summary statistics for the association analysis of maximum NAb titer with candidate markers **in NAb-positive patients** (linear regression). Significance thresholds and abbreviations are as described in the legend of Table 2; SE = standard error.

Chr.	Gene	Allele / Variant	Freq. (%)	n	Effect	SE	Published effect	p-value	p-value (1-sided)
6	<i>HLA-DRB1</i>	*04:01	11.3	247	-0.03	0.21	>0	9.0×10 ⁻⁰¹	5.5×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:08	1.8	247	1.57	0.60	>0	9.9×10 ⁻⁰³	4.9×10 ⁻⁰³
6	<i>HLA-DRB1</i>	*07:01	11.9	247	0.33	0.14	>0	2.2×10 ⁻⁰²	1.1×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*15	22.1	247	-0.03	0.11	>0	7.6×10 ⁻⁰¹	6.2×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*15:01	20.6	247	-0.09	0.11	>0	4.1×10 ⁻⁰¹	7.9×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*16:01	1.8	247	0.05	0.44	>0	9.0×10 ⁻⁰¹	4.5×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*03:01	5.1	247	-0.14	0.14	<0	3.0×10 ⁻⁰¹	1.5×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:04	0.6	247	0.43	0.36	<0	2.4×10 ⁻⁰¹	8.8×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:01	1.4	247	-0.33	0.21	<0	1.2×10 ⁻⁰¹	5.8×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*11:04	5.3	247	-0.19	0.30	<0	5.3×10 ⁻⁰¹	2.6×10 ⁻⁰¹
8	intergenic	rs4961252_G	38.8	353	-0.18	0.09	>0	4.3×10 ⁻⁰²	9.8×10 ⁻⁰¹
6	intergenic	rs9272105_A	46.6	353	-0.18	0.07	<0	1.6×10 ⁻⁰²	7.8×10 ⁻⁰³

Supplementary Table e-10: Summary statistics for the association analysis of time to first NAb presence with candidate markers **in NAb-positive patients** (Cox proportional hazard model). Because of genomic inflation ($\lambda = 1.095$), p-values were adjusted using genomic control. Significance thresholds and abbreviations are as described in the legend of Table 2; SE = standard error.

Chr.	Gene	Allele / Variant	Freq. (%)	n	Effect	SE	Published effect	p-value	p-value (1-sided)
6	<i>HLA-DRB1</i>	*04:01	11.3	247/247	0.17	0.21	<0	4.2×10 ⁻⁰¹	7.9×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:08	1.8	247/247	1.03	0.59	<0	8.3×10 ⁻⁰²	9.6×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*07:01	11.9	247/247	-0.11	0.15	<0	4.5×10 ⁻⁰¹	2.2×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*15	22.1	247/247	-0.18	0.10	<0	7.5×10 ⁻⁰²	3.7×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*15:01	20.6	247/247	-0.15	0.10	<0	1.4×10 ⁻⁰¹	6.8×10 ⁻⁰²
6	<i>HLA-DRB1</i>	*16:01	1.8	247/247	-0.29	0.43	<0	5.0×10 ⁻⁰¹	2.5×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*03:01	5.1	247/247	0.13	0.13	>0	3.3×10 ⁻⁰¹	1.6×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*04:04	0.6	247/247	-0.40	0.36	>0	2.6×10 ⁻⁰¹	8.7×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:01	1.4	247/247	-0.11	0.22	>0	6.0×10 ⁻⁰¹	7.0×10 ⁻⁰¹
6	<i>HLA-DRB1</i>	*11:04	5.3	247/247	0.12	0.28	>0	6.6×10 ⁻⁰¹	3.3×10 ⁻⁰¹
8	intergenic	rs4961252_G	38.8	353/353	-0.10	0.09	<0	2.9×10 ⁻⁰¹	1.4×10 ⁻⁰¹
6	intergenic	rs9272105_A	46.6	353/353	0.15	0.07	>0	4.4×10 ⁻⁰²	2.2×10 ⁻⁰²

Supplementary Table e-11: Summary statistics of genome-wide significant variants for the association analysis of EP1-EP4 in all patients. Significance threshold $\alpha=5\times 10^{-8}$; abbreviations are as described in the legend of Table 2; SE = standard error (EP2-4 are quantitative).

EP	Chr.	Gene	Variant	Freq. (%)	n	OR / Effect	CI / SE	p-value	λ
EP1	6	intergenic	rs522308_T	25.0	941	2.60	2.05-3.29	2.30×10^{-15}	1.025
EP2	6	intergenic	rs2454138_A	22.0	941	0.41	0.05	5.29×10^{-19}	1.015
EP3	6	intergenic	rs2454138_A	22.0	941	0.41	0.05	8.44×10^{-19}	1.015
EP4	6	intergenic	rs2454138_A	22.0	941	0.41	0.05	1.00×10^{-18}	1.014

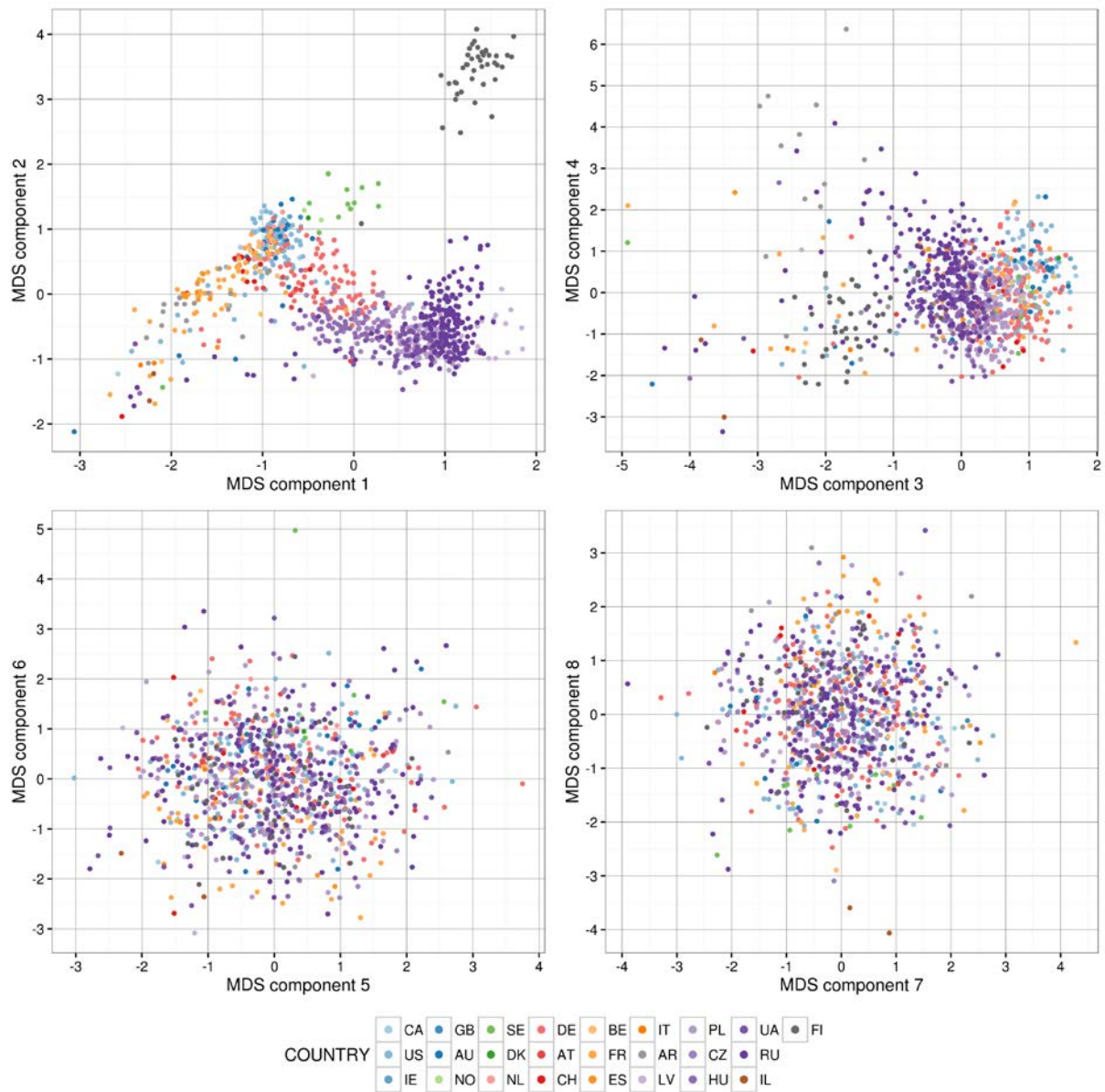
Supplementary Table e-12: Significant single-tissue eQTLs of variant rs522308 in whole blood, GTEx Analysis Release V7.

SNP	Gene	Effect	p-value
rs522308	HLA-DQA2	1	2.00×10^{-54}
rs522308	HLA-DRB6	0.72	1.10×10^{-32}
rs522308	HLA-DQB2	0.62	4.50×10^{-21}
rs522308	HLA-DRB1	-0.21	3.30×10^{-16}
rs522308	HLA-DQB1	-0.44	5.70×10^{-16}
rs522308	HLA-DQA1	-0.23	1.90×10^{-11}
rs522308	HLA-DQB1-AS1	-0.24	4.80×10^{-07}
rs522308	HLA-DRB9	0.31	6.40×10^{-07}

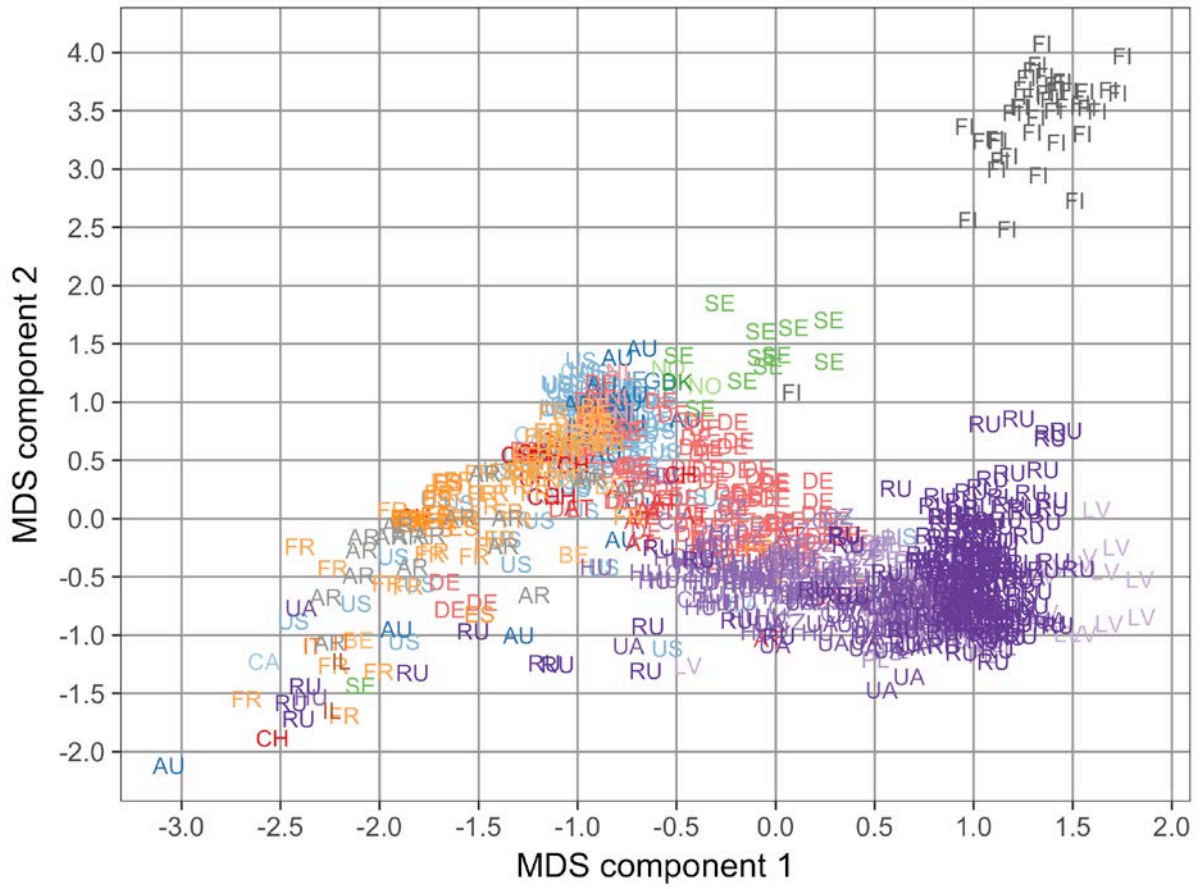
Supplementary Figure e-1: Population substructure analysis. The plot shows scaled MDS components of the genetic similarity matrix. MDS components were calculated in PLINK2 v1.90b3.27 using the eigendecomposition-based algorithm. IBS/IBD computation was conducted using the command `--genome` after filtering of genotyped variants (MAF ≥ 0.05 , HWE p -value $\geq 10^{-3}$, removal of the extended MHC region (chromosome 6, 25-35 Mbp) and a typical inversion site on chromosome 8 (7-13 Mbp)), and pruning (command `--indep-pairwise 200 100 0.2`). Country codes: CA = Canada, GB = Great Britain, SE = Sweden, DE = Germany, BE = Belgium, IT = Italy, PL = Poland, UA = Ukraine, FI = Finland, US = United States, AU = Australia, DK = Denmark, AT = Austria, FR = France, AR = Argentina, CZ = Czech Republic, RU = Russia, IE = Ireland, NO = Norway, NL = Netherlands, CH = Switzerland, ES = Spain, LV = Latvia, HU = Hungary, IL = Israel.

A: MDS components 1-8. **B:** MDS components 1 and 2, labeled by country codes.

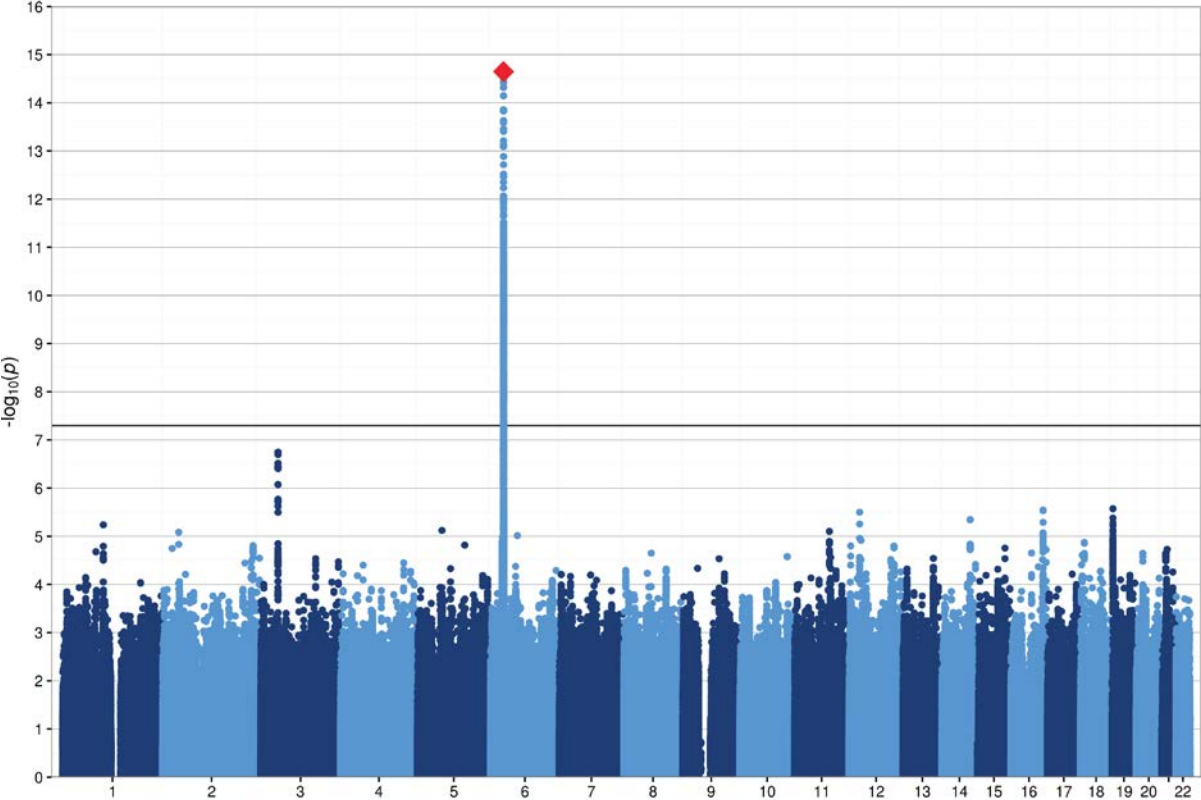
A



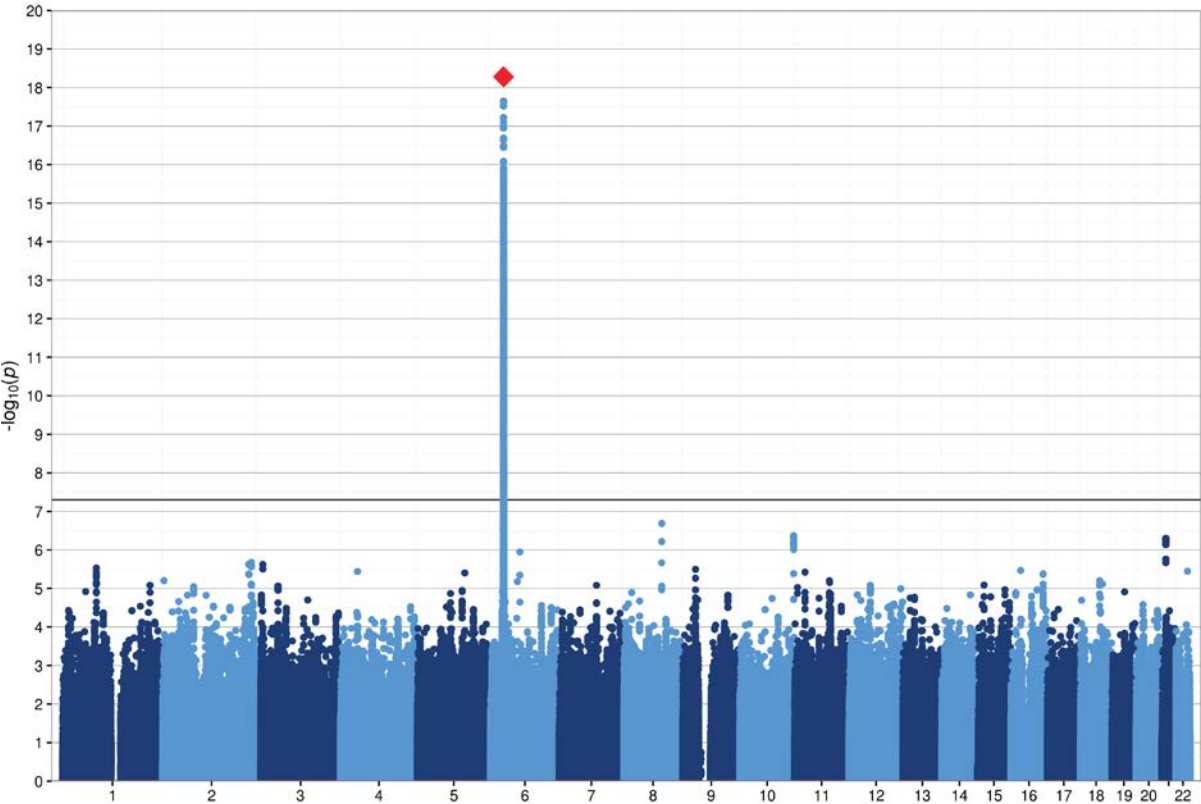
B



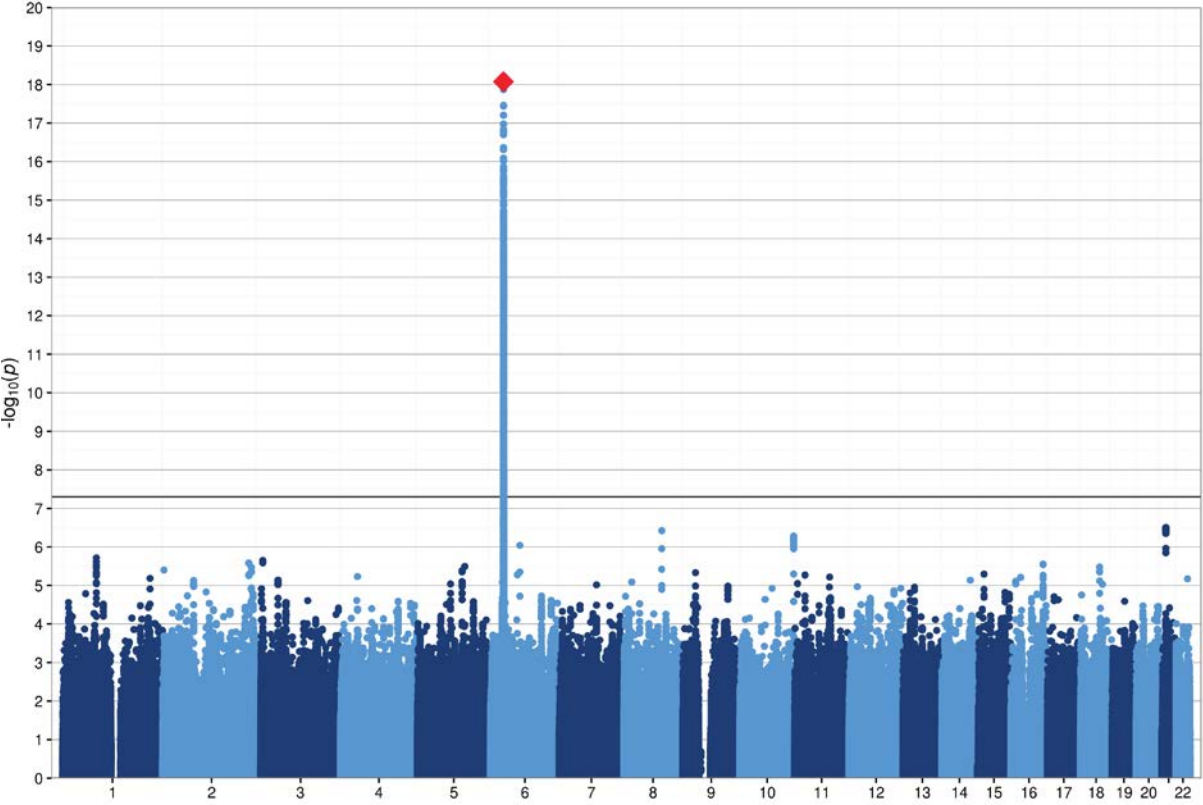
Supplementary Figure e-2: Manhattan plot of GWAS of EP1 in all patients, showing the strength of evidence for association with NAb presence. The gray line marks the genome-wide significance level and the red diamond the top SNP rs522308. Genomic inflation $\lambda = 1.025$.



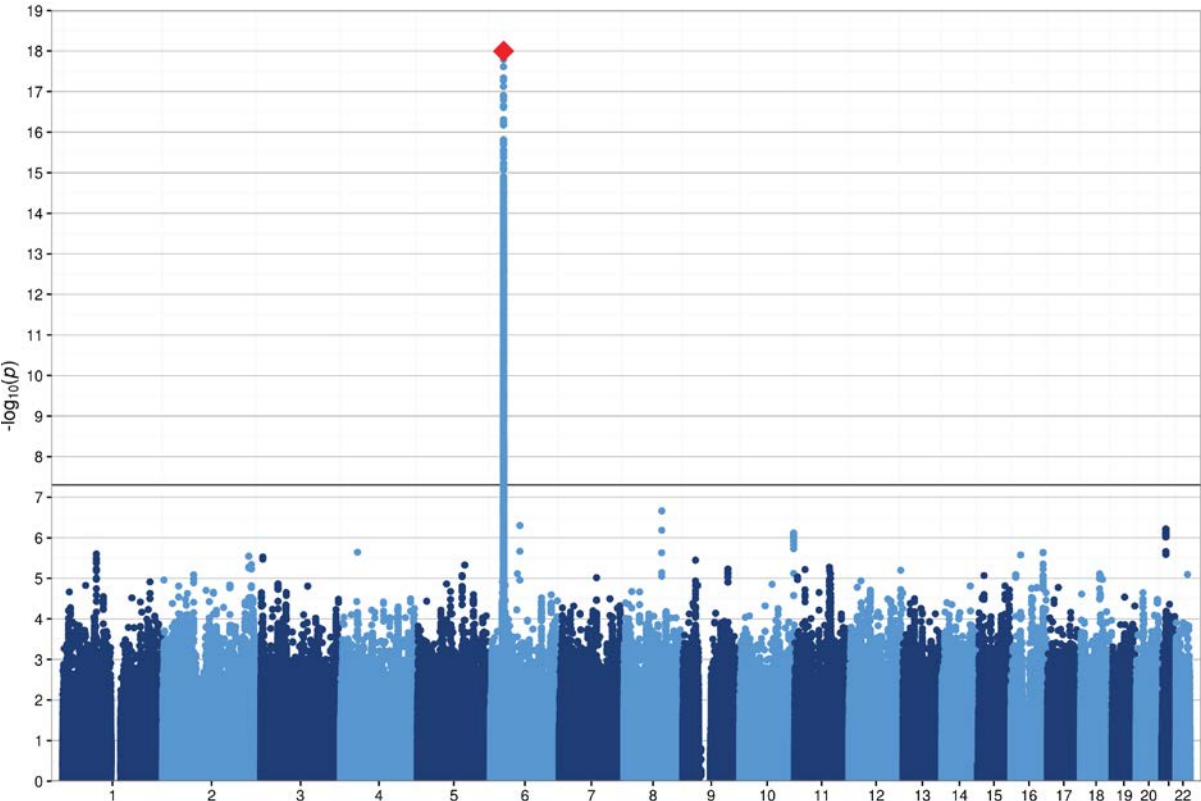
Supplementary Figure e-3: Manhattan plot of GWAS of EP2 in all patients, showing the strength of evidence for association with mean NAb titer. The gray line marks the genome-wide significance level and the red diamond the top SNP rs2454138. Genomic inflation $\lambda = 1.015$.



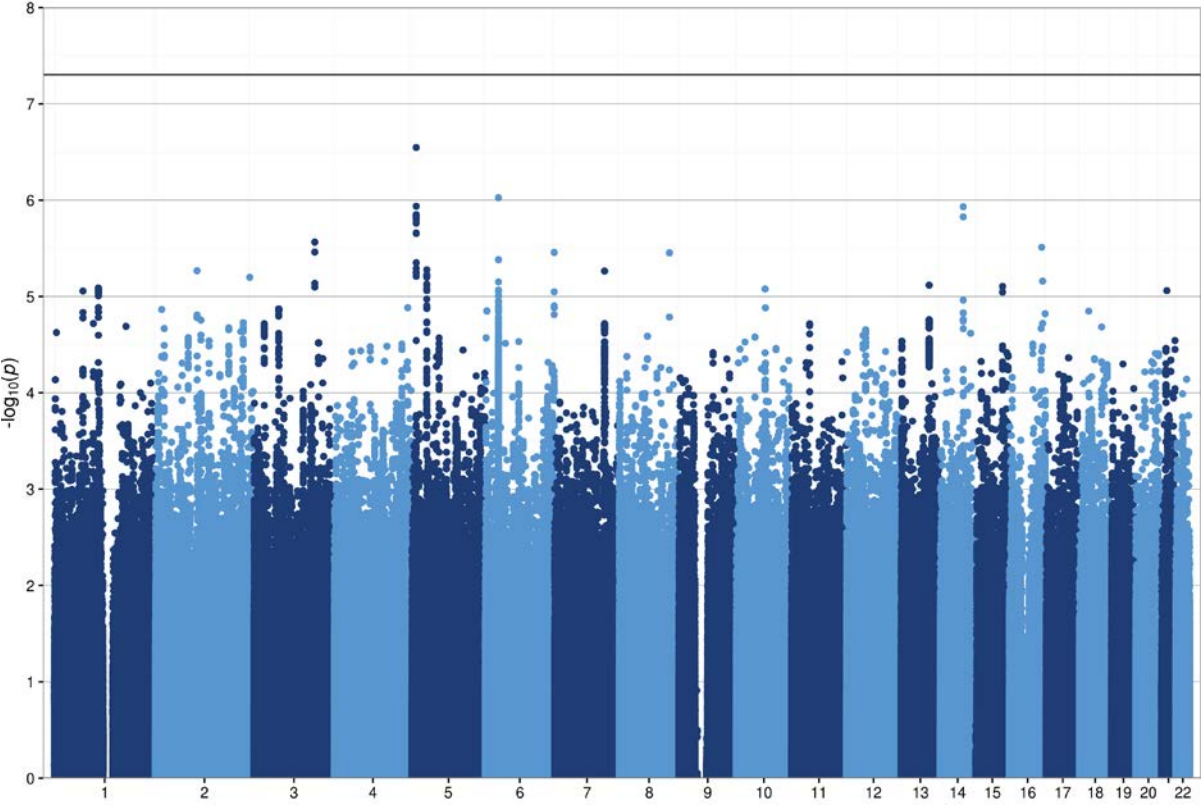
Supplementary Figure e-4: Manhattan plot of GWAS of EP3 in all patients, showing the strength of evidence for association with NAb AUC. The gray line marks the genome-wide significance level and the red diamond the top SNP rs2454138. Genomic inflation $\lambda = 1.015$.



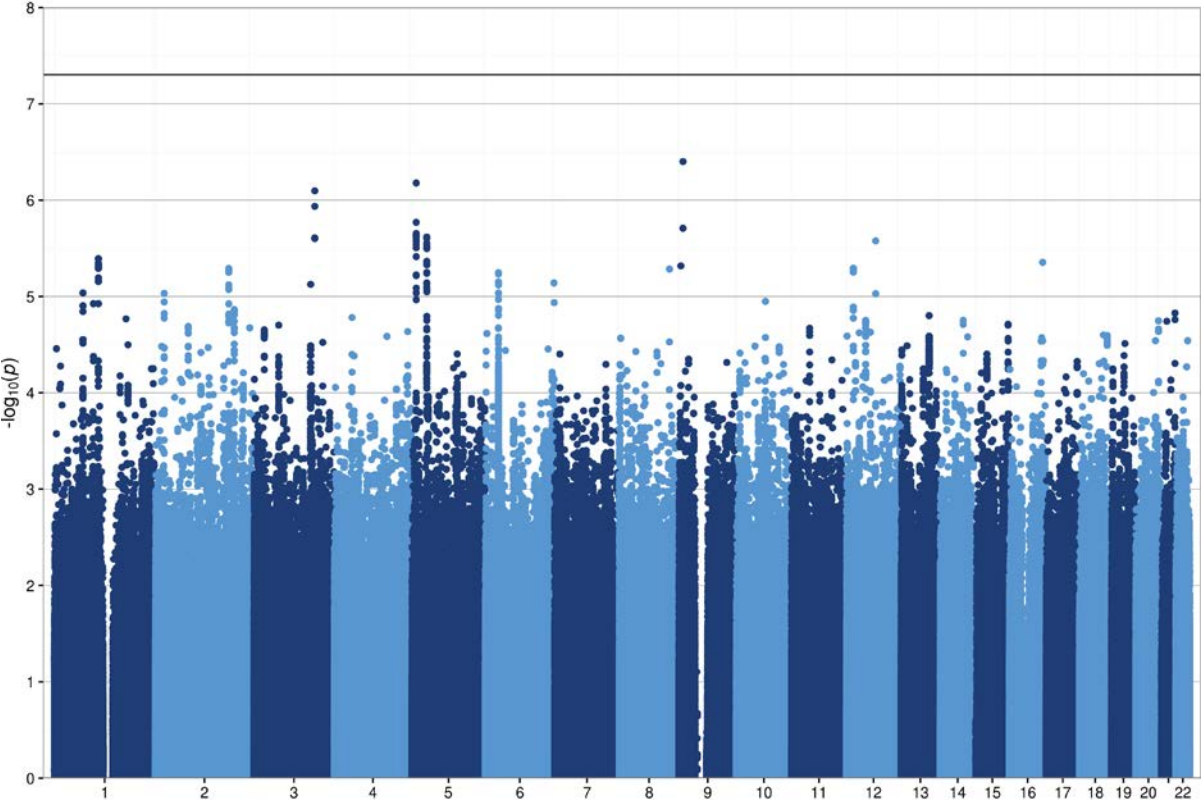
Supplementary Figure e-5: Manhattan plot of GWAS of EP4 in all patients, showing the strength of evidence for association with the maximum NAb titer. The gray line marks the genome-wide significance level and the red diamond the top SNP rs2454138. Genomic inflation $\lambda = 1.014$.



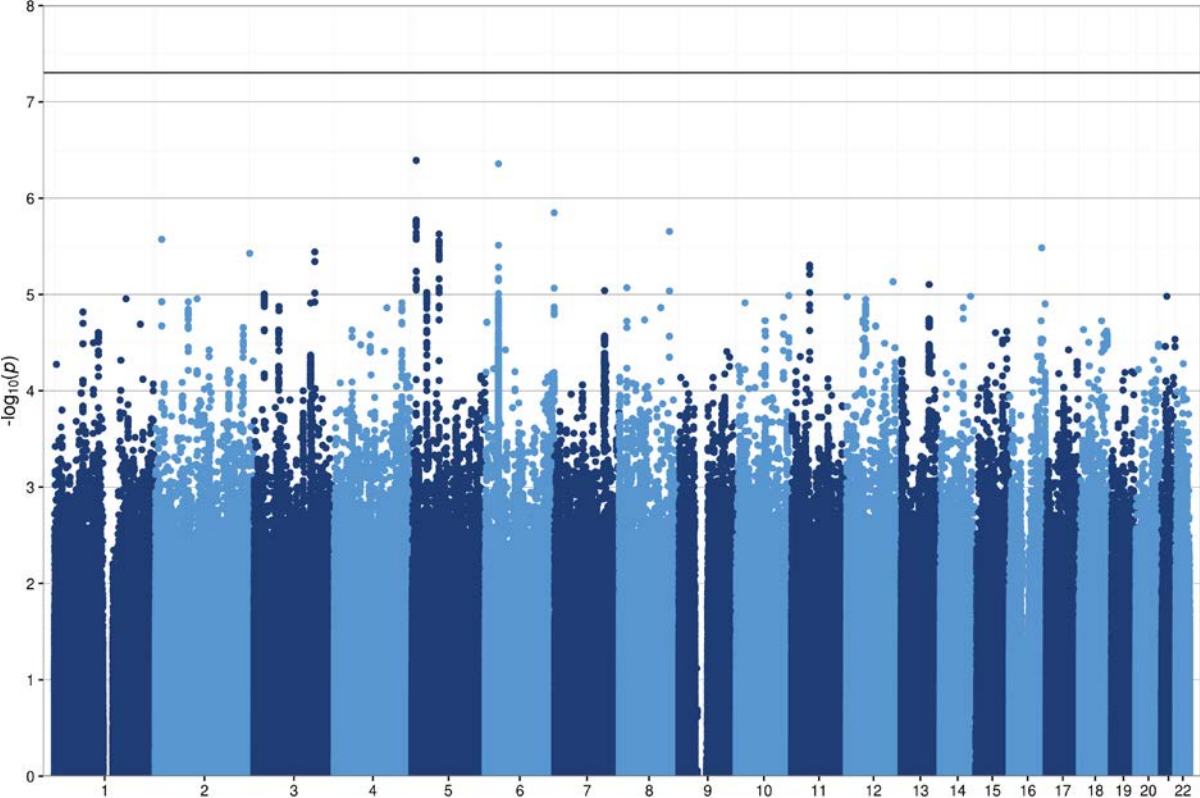
Supplementary Figure e-6: Manhattan plot of GWAS of EP2 in **NAb-positive patients**, showing the strength of evidence for association with mean NAb titer. The gray line marks the genome-wide significance level. Genomic inflation $\lambda = 1.020$.



Supplementary Figure e-7: Manhattan plot of GWAS of EP3 in **NAb-positive patients**, showing the strength of evidence for association with NAb AUC. The gray line marks the genome-wide significance level. Genomic inflation $\lambda = 1.019$.



Supplementary Figure e-8: Manhattan plot of GWAS of EP4 in **NAb-positive patients**, showing the strength of evidence for association with maximum NAb titer. The gray line marks the genome-wide significance level. Genomic inflation $\lambda = 1.017$.



Supplementary Figure e-9: Manhattan plot of GWAS of EP5 in **NAb-positive patients**, showing the strength of evidence for association with time to first NAb presence. The gray line marks the genome-wide significance level. Genomic inflation $\lambda = 0.974$.

