

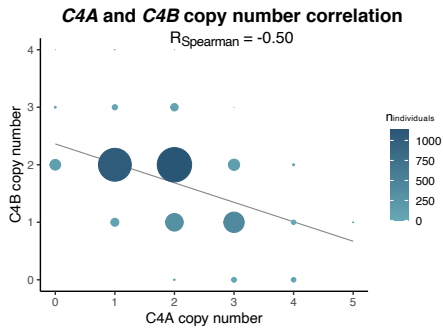
# Supplementary Figure 1

**A**

**Association of *C4* copy number with disease**  
vs. healthy controls; for each decrease in *C4* copy number

	<i>C4</i> copy number		<i>n</i> <sub>patients</sub>	<i>n</i> <sub>controls</sub>	<i>C4A</i> copy number		<i>C4B</i> copy number		<i>n</i> <sub>patients</sub>	<i>n</i> <sub>controls</sub>
	OR	p-value			OR	p-value	OR	p-value		
<b>SLE</b>	1.83	1e-20	934	1251	2.03	1e-25	1.17	0.10	913	1251
<b>pSS</b>	2.17	1e-28	905	1251	2.36	5e-33	1.33	6e-03	905	1251
<b>Myositis</b>	2.15	4e-18	451	1251	2.28	6e-20	1.56	5e-04	451	1251

**B**

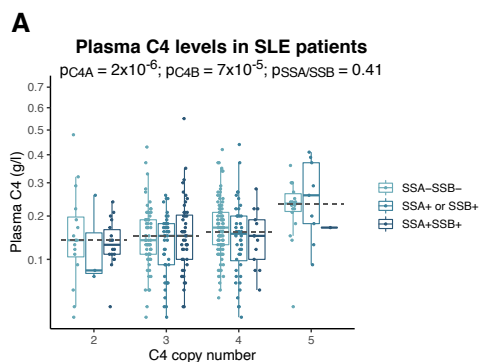


## Supplementary Figure 1 Association of *C4* copy number to three systemic inflammatory autoimmune diseases

**A** Association between each decrease in *C4* copy number and SLE, pSS and myositis as compared to healthy controls, analysed by logistic regression. Copy number of *C4A* and *C4B* were included together in additive models, whereas *C4* copy number was analysed alone. All models were adjusted for sex and PC1-PC4.

**B** Spearman correlation between *C4A* copy number and *C4B* copy number for patients ( $n_{\text{SLE}} = 913$ ,  $n_{\text{pSS}} = 905$ ,  $n_{\text{myositis}} = 451$ ) combined with healthy controls ( $n = 1,251$ ). Size of points indicate the number of individuals for each combination.

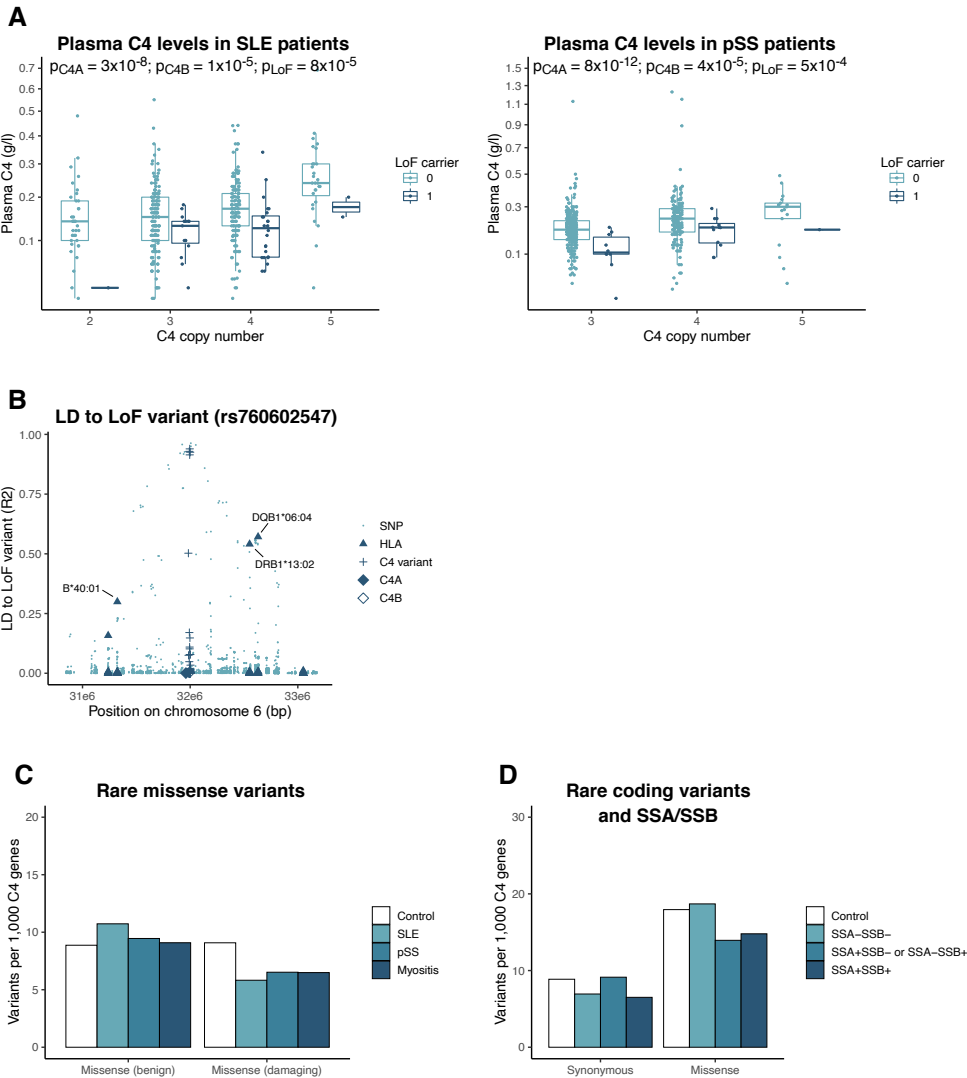
## Supplementary Figure 2



### Supplementary Figure 2 Plasma C4 level in SLE patients stratified for *C4* copy number and anti-SSA/SSB autoantibody status

**A** Plasma levels of C4 among SLE patients. Sqrt-transformed plasma C4 levels analysed by ANOVA and adjusted for sex, age at sampling and cohort ( $n = 411$ ). Note that copy numbers of *C4A* and *C4B* are included in the additive model, whereas plot shows total *C4* copy number for simplicity. Dashed line indicate median C4 concentration at each *C4* copy number level.

# Supplementary Figure 3



## Supplementary Figure 3 Plasma levels and LD plot of common LoF variant, and analysis of rare coding *C4* variants

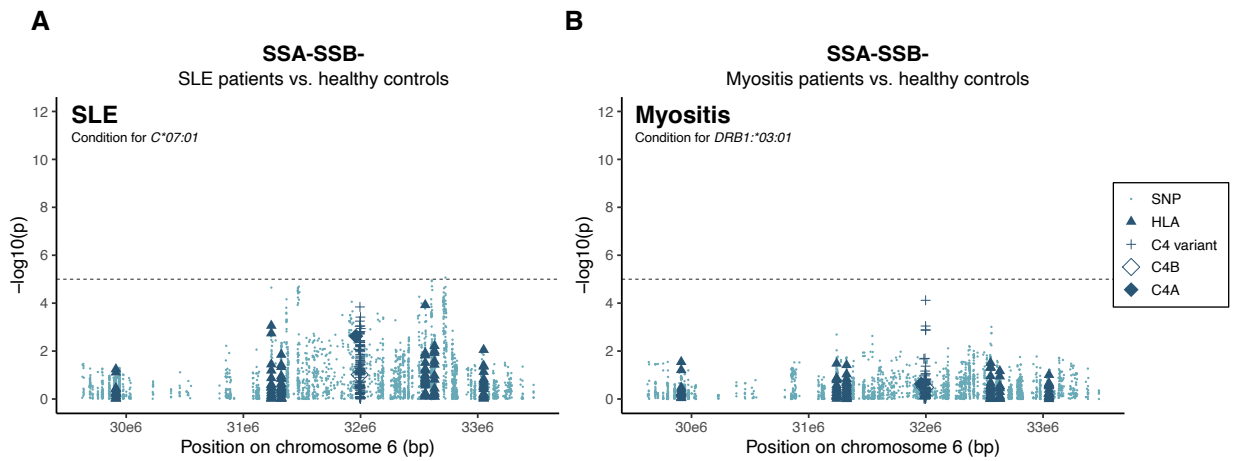
**A** Plasma C4 levels for carriers (1) and non-carriers (0) of the LoF variant rs760602547 among SLE patients (left panel) and pSS patients (right panel), stratified for *C4* copy number. Sqrt-transformed plasma C4 levels were analysed by ANOVA and adjusted for sex, age at sampling (SLE patients only) and cohort ( $n_{SLE} = 407$ ;  $n_{pSS} = 471$ ). Note that copy numbers of *C4A* and *C4B* are included in the additive model, whereas plot shows total *C4* copy number for simplicity.

**B** LD ( $R^2$ ) between the loss-of-function (LoF) variant rs760602547 in *C4A* and *HLA* alleles, *C4* variants and SNPs in the *HLA* region.

**C** Number of *C4* genes carrying a rare (present among  $< 0.5\%$  of individuals) missense variant in each disease cohort. Effect of variants have been predicted using PolyPhen as benign ( $n_{variants} = 51$ ) or possibly/probably deleterious ( $n_{variants} = 49$ ). The number of variants in each disease group has been adjusted for total *C4* copy number in order to account for lower copy number of *C4* among patients with systemic inflammatory autoimmune diseases.

**D** Same as (C), but for SLE, pSS and myositis patients combined and grouped on anti-SSA/SSB status ( $n_{missense} = 100$ ,  $n_{synonymous} = 44$ ).

## Supplementary Figure 4



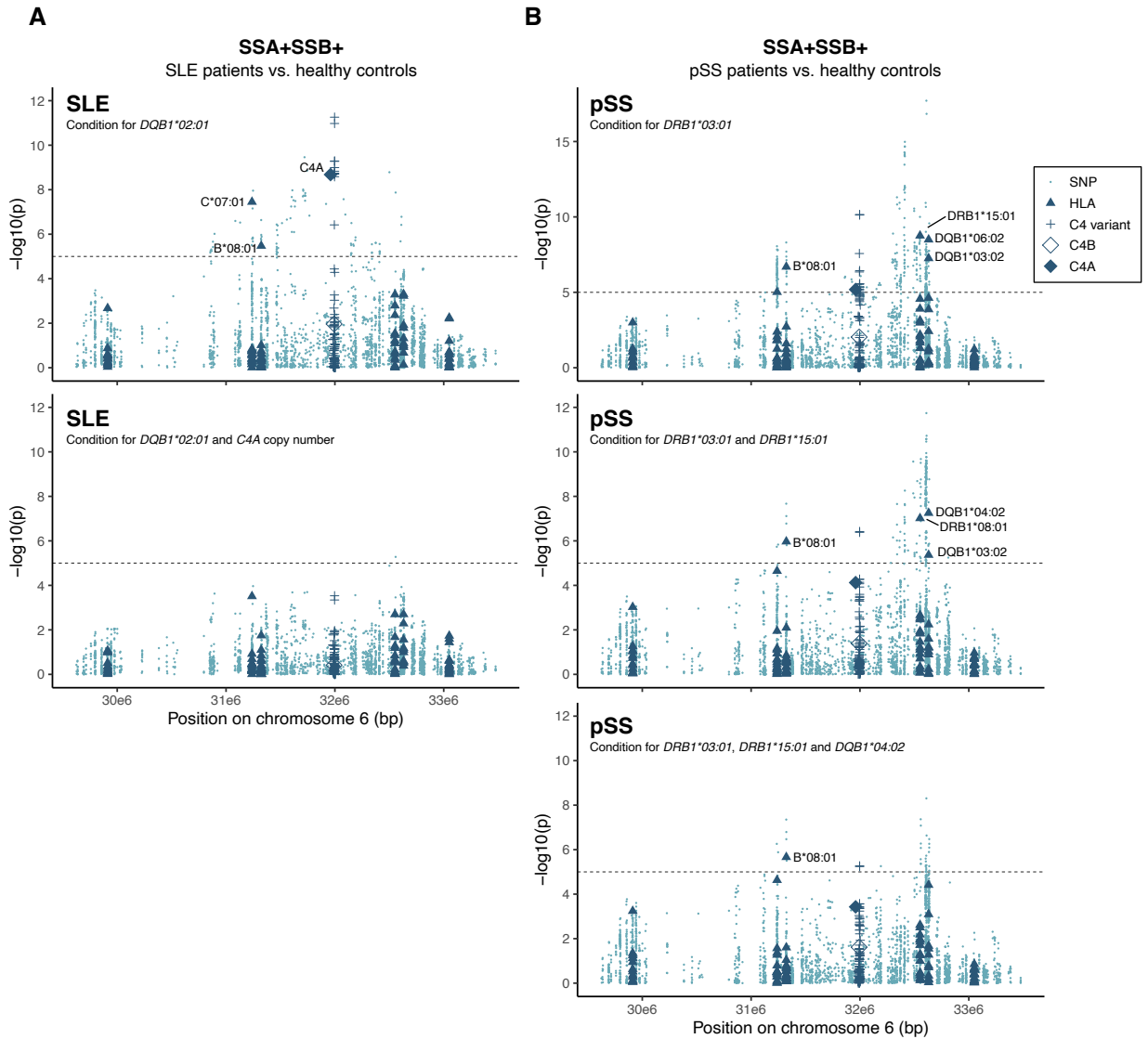
### Supplementary Figure 4 Conditional analysis of variants in *HLA* region for in anti-SSA/SSB-negative patients

**A** Conditional analysis of variants in *HLA* region to patients with SLE ( $n = 544$ ) without any autoantibodies against SSA/SSB as compared to healthy controls ( $n = 1,251$ ).

**B** Conditional analysis of variants in *HLA* region to patients with myositis ( $n = 247$ ) without any autoantibodies against SSA/SSB as compared to healthy controls ( $n = 1,251$ ).

(A and B) *HLA* alleles for 6 genes (from left: *HLA-A*, *-C*, *-B*, *-DRB1*, *-DQB1* and *-DPB1*), *C4A/C4B* copy number, and variants in *C4* present in more than 1% of individuals were included in the analysis. Analysed by logistic regression adjusted for sex and PC1-PC4. Dashed line represents Bonferroni-corrected significance threshold ( $p = 1 \times 10^{-5}$ ).

# Supplementary Figure 5



## Supplementary Figure 5 Conditional analysis of variants in *HLA* region for in anti-SSA/SSB-positive patients

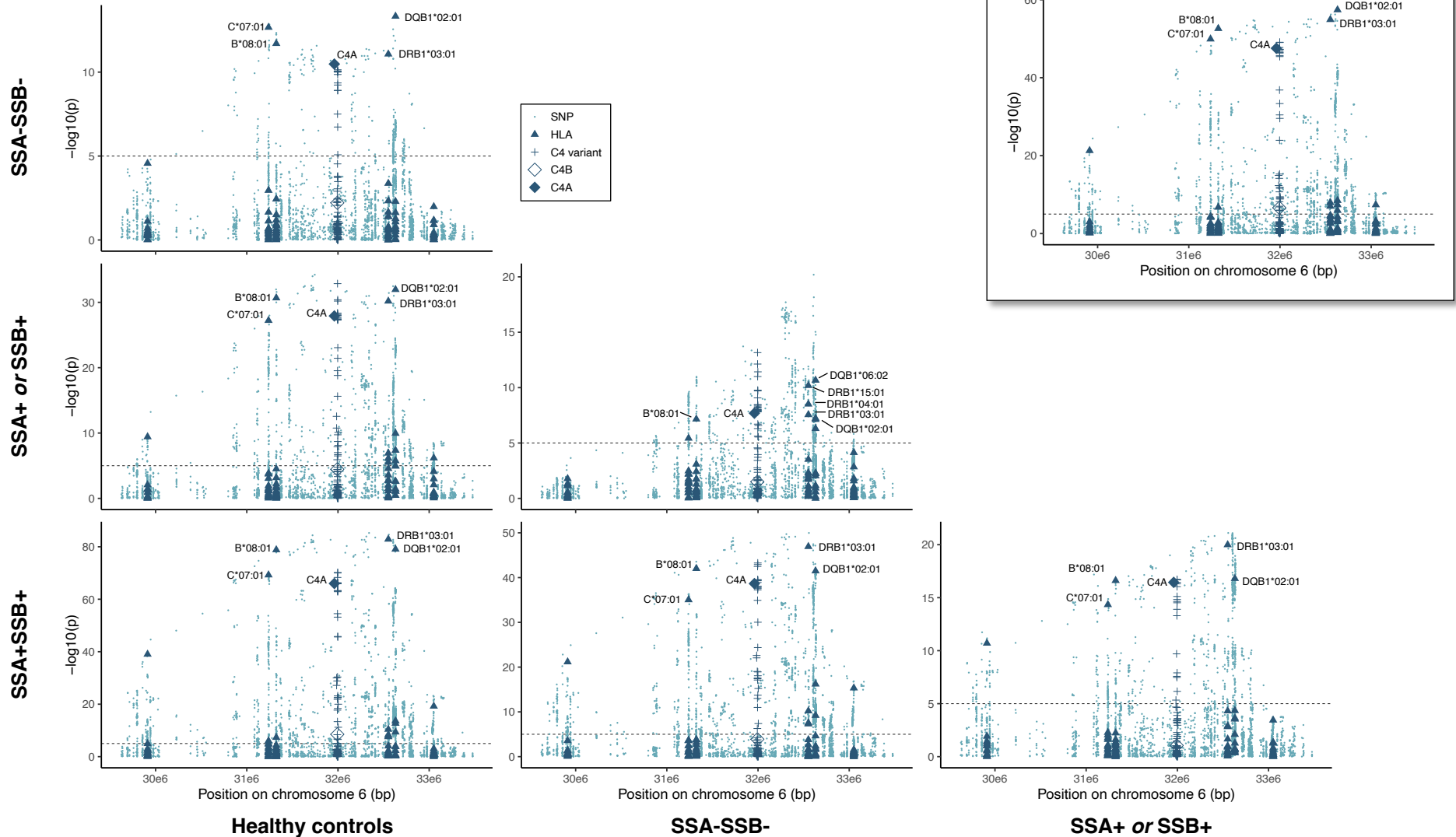
**A** Conditional analysis of variants in *HLA* region in patients with SLE (n = 168) with autoantibodies against both SSA and SSB as compared to healthy controls (n = 1,251).

**B** Conditional analysis of variants in *HLA* region in patients with pSS (n = 368) with autoantibodies against both SSA and SSB as compared to healthy controls (n = 1,251).

(A and B) *HLA* alleles for 6 genes (from left: *HLA-A*, *-C*, *-B*, *-DRB1*, *-DQB1* and *-DPB1*), *C4A/C4B* copy number, and variants in *C4* present in more than 1% of individuals were included in the analysis. Analysed by logistic regression adjusted for sex and PC1-PC4. Dashed line represent Bonferroni-corrected significance threshold ( $p = 1 \times 10^{-5}$ ).

# Supplementary Figure 6 (continued on next page)

## SIAD (systemic inflammatory autoimmune disease)



Supplementary Figure 6 (continued on next page) LocusZoom of *C4* copy number and *HLA* for SSA/SSB subgroups of SIAD patients and healthy controls

Association of *C4A/C4B* copy number, *C4* variants, *HLA* alleles and SNPs present among > 1% of individuals, subgrouping patients on anti-SSA/SSB autoantibody status.

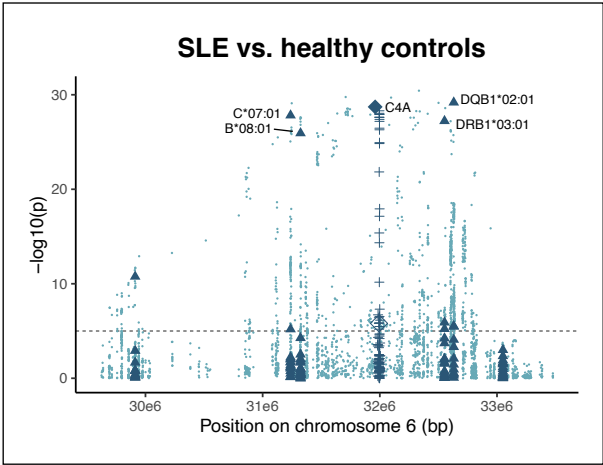
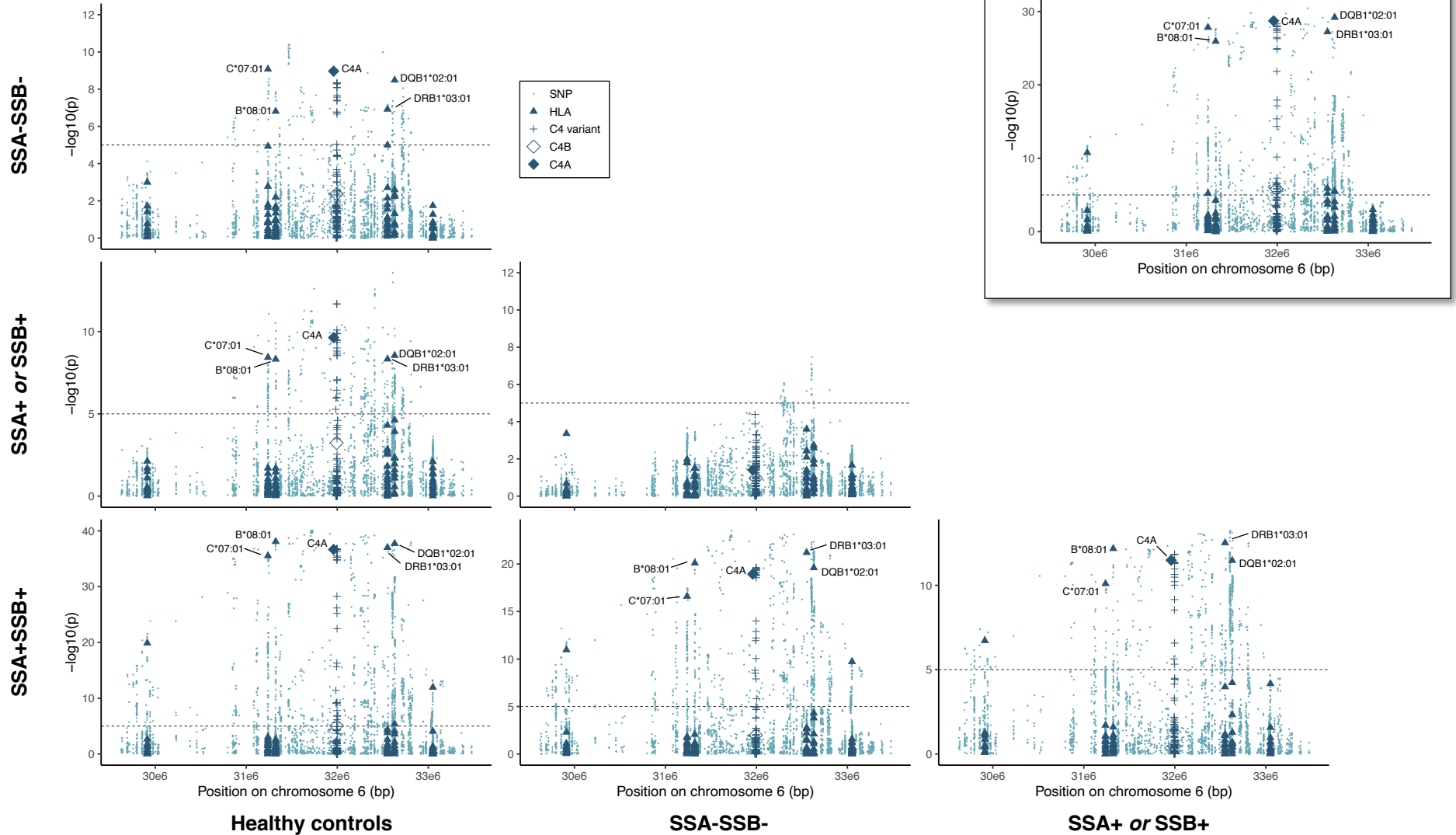
*HLA* alleles for 6 genes (from left: *HLA-A*, *-C*, *-B*, *-DRB1*, *-DQB1* and *-DPB1*), *C4A/C4B* copy number, and variants in *C4* present in more than 1% of individuals were included in the analysis.

Analysed by logistic regression, adjusting for sex and PC1-PC4. Dashed line represent Bonferroni-corrected significance threshold ( $p = 1e-5$ ).

$n_{SIAD} = 2,290$ ;  $n_{SSA+SSB+} = 547$ ;  $n_{SSA+ or SSB+} = 606$ ;  $n_{SSA-SSB-} = 1,032$ ;  $n_{HC} = 1,251$

# Supplementary Figure 6 (...continued...)

## SLE



**Supplementary Figure 6 (...continued...) LocusZoom of *C4* copy number and *HLA* for SSA/SSB subgroups of SLE patients and healthy controls**

Association of *C4A/C4B* copy number, *C4* variants, *HLA* alleles and SNPs present among > 1% of individuals, subgrouping patients on anti-SSA/SSB autoantibody status.

*HLA* alleles for 6 genes (from left: *HLA-A*, *-C*, *-B*, *-DRB1*, *-DQB1* and *-DPB1*), *C4A/C4B* copy number, and variants in *C4* present in more than 1% of individuals were included in the analysis.

Analysed by logistic regression, adjusting for sex and PC1-PC4. Dashed line represent Bonferroni-corrected significance threshold ( $p = 1e-5$ ).

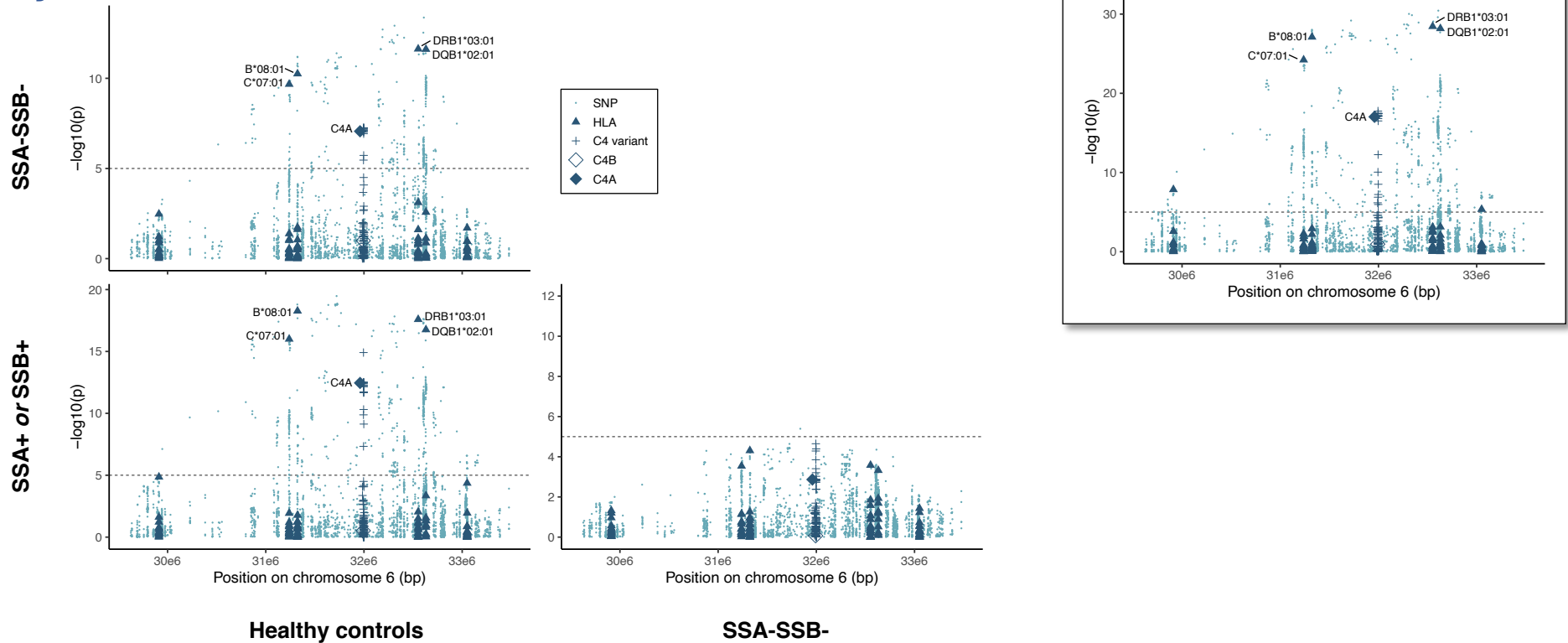
$n_{SLE} = 934$ ;  $n_{SSA+SSB+} = 168$ ;  $n_{SSA+ \text{ or } SSB+} = 207$ ;  $n_{SSA-SSB-} = 544$ ;  $n_{HC} = 1,251$ .





## Supplementary Figure 6 (...continued...)

### Myositis



#### Supplementary Figure 6 (...continued...) LocusZoom of *C4* copy number and *HLA* for SSA/SSB subgroups of myositis patients and healthy controls

Association of *C4A/C4B* copy number, *C4* variants, *HLA* alleles and SNPs present among > 1% of individuals, subgrouping patients on anti-SSA/SSB autoantibody status.

*HLA* alleles for 6 genes (from left: *HLA-A*, *-C*, *-B*, *-DRB1*, *-DQB1* and *-DPB1*), *C4A/C4B* copy number, and variants in *C4* present in more than 1% of individuals were included in the analysis. Analysed by logistic regression, adjusting for sex and PC1-PC4. Dashed line represent Bonferroni-corrected significance threshold ( $p = 1e-5$ ).

$n_{\text{Myositis}} = 451$ ;  $n_{\text{SSA+SSB+}} = 11$ ;  $n_{\text{SSA+ or SSB+}} = 106$ ;  $n_{\text{SSA-SSB-}} = 247$ ;  $n_{\text{HC}} = 1,251$ . Due to few SSA+SSB+ myositis patients, no LocusZoom has been performed for this subgroup of patients.

# Supplementary Table 1

Supplementary Table 1 Basic characteristics of study participants

	SLE	pSS	Myositis	Control
n	934	905	451	1,251
Females	805 (86%)	844 (93%)	300 (67%)	1,079 (86%)
Age at diagnosis	36 (3-85)	53 (14-90) <sup>a</sup>	52 (12-82) <sup>b</sup>	-
Age at data abstraction	52 (18-94)	62 (19-92)	62 (24-87) <sup>c</sup>	-
Age	-	-	-	54 (19-88) <sup>d</sup>

<sup>a</sup> Information missing for 1 individual

<sup>b</sup> Information missing for 256 individuals

<sup>c</sup> Information missing for 257 individuals

<sup>d</sup> Information missing for 182 individuals

## Supplementary Table 2

Autoantibody	SLE					pSS					Myositis				
	Positive	OR	95% CI	p	Padjusted	Positive	OR	95% CI	p	Padjusted	Positive	OR	95% CI	p	Padjusted
Antinuclear antibodies	919 (98.4%)	1.50	0.73-3.19	0.28	1.00	681 (75.6%)	2.04	1.63-2.57	6e-10	<b>6e-09</b>	178 (52.0%)	1.46	1.06-2.02	0.02	0.34
SSA	343 (37.3%)	2.01	1.65-2.47	1e-11	<b>1e-10</b>	644 (71.2%)	3.20	2.53-4.08	1e-21	<b>1e-20</b>	120 (32.4%)	1.90	1.37-2.68	2e-04	<b>3e-03</b>
- Ro52	244 (30.2%)	2.21	1.77-2.77	4e-12	<b>5e-11</b>	155 (54.4%)	3.52	2.34-5.47	6e-09	<b>6e-08</b>	101 (28.5%)	2.00	1.41-2.90	2e-04	<b>3e-03</b>
- Ro60	313 (38.7%)	1.95	1.59-2.41	4e-10	<b>4e-09</b>	273 (60.0%)	3.50	2.55-4.90	6e-14	<b>6e-13</b>	27 (7.8%)	1.54	0.87-2.84	0.15	1.00
SSB	200 (21.7%)	3.39	2.63-4.43	4e-20	<b>5e-19</b>	388 (43.0%)	2.39	1.94-2.97	1e-15	<b>1e-14</b>	11 (3.0%)	1.90	0.77-5.07	0.18	1.00
RNP	177 (25.3%)	0.92	0.72-1.16	0.48	1.00	43 (5.5%)	0.96	0.62-1.52	0.87	1.00	-	-	-	-	-
dsDNA	437 (62.0%)	0.87	0.70-1.08	0.21	1.00	29 (3.6%)	1.30	0.76-2.26	0.35	1.00	-	-	-	-	-
Sm	92 (13.0%)	1.04	0.77-1.41	0.79	1.00	9 (1.2%)	2.81	1.00-8.71	0.06	0.55	1 (0.8%)	NA	NA	NA	NA
Rheumatoid factor (RF)	125 (23.6%)	1.64	1.24-2.17	6e-04	<b>7e-03</b>	297 (48.8%)	1.81	1.42-2.33	2e-06	<b>2e-05</b>	10 (10.0%)	0.88	0.33-2.34	0.79	1.00
Lupus anticoagulant (LAC)	134 (22.6%)	0.63	0.47-0.82	8e-04	<b>1e-02</b>	-	-	-	-	-	-	-	-	-	-
Cardiolipin IgG	237 (26.0%)	0.78	0.63-0.96	0.02	0.22	-	-	-	-	-	-	-	-	-	-
Beta 2 glycoprotein 1 IgG	175 (19.9%)	0.72	0.56-0.91	6e-03	0.07	-	-	-	-	-	-	-	-	-	-
Jo-1	-	-	-	-	-	-	-	-	-	-	124 (27.7%)	1.95	1.42-2.73	6e-05	<b>9e-04</b>
U1RNP	-	-	-	-	-	-	-	-	-	-	21 (5.7%)	1.13	0.59-2.21	0.72	1.00
Mi-2	-	-	-	-	-	-	-	-	-	-	10 (2.5%)	0.63	0.26-1.52	0.30	1.00
PM/Scl	-	-	-	-	-	-	-	-	-	-	28 (7.1%)	1.82	1.00-3.47	0.06	0.86
MDA5	-	-	-	-	-	-	-	-	-	-	12 (3.8%)	1.05	0.46-2.55	0.91	1.00
SRP	-	-	-	-	-	-	-	-	-	-	19 (4.5%)	1.24	0.63-2.52	0.55	1.00
PL7	-	-	-	-	-	-	-	-	-	-	10 (2.3%)	0.97	0.39-2.46	0.94	1.00
PL12	-	-	-	-	-	-	-	-	-	-	16 (3.7%)	2.62	1.21-6.06	0.02	0.28
TIF1	-	-	-	-	-	-	-	-	-	-	19 (7.5%)	0.89	0.45-1.84	0.75	1.00

### Supplementary Table 2 Association between autoantibody status and *C4A* copy number

Association between autoantibodies and each decrease in *C4A* copy number in case-case analysis of SLE, pSS and myositis, respectively. Analysed by logistic regression, adjusting for *C4B* copy number, sex and PC1-PC4. Bonferroni correction was used for adjustment of multiple testing for each disease.

Abbreviations: SLE systemic lupus erythematosus, pSS primary Sjögren's syndrome, OR odds ratio, CI confidence interval.