



# Complement genes contribute sex-biased vulnerability in diverse disorders

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## Supplementary Material for

### Complement genes contribute sex-biased vulnerability in diverse illnesses

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1 **Supplementary Note 1 - Fine mapping of an independent association signal in the MHC class II**  
2 **region**

3  
4  
5 **Linkage disequilibrium of *C4* variation to other variants in the MHC genomic region differs by**  
6 **ancestry**

7  
8 The linkage-disequilibrium (LD) relationships of *C4* variation to other genetic variation in the MHC  
9 region differ greatly between European-ancestry and African American cohorts, and are in general far  
10 stronger among Europeans. For example, **Extended Data Fig. 4d, e** shows the LD-correlation ( $r^2$ ) of  
11 SNPs across the MHC region to an estimate of *C4* composite risk (the composite estimate of *C4*-derived  
12 SLE risk derived from the genotype-group risk measurements in **Fig. 2a**). (Other *C4* features, such as  
13 total *C4* gene copy number, also exhibit strikingly different correlations with genetic markers between  
14 the two populations.) Most notably, LD in European ancestry is widespread across the extended MHC  
15 genomic region (**Extended Data Fig. 4d**) – and particularly strong in the nearby MHC class II region  
16 (32-33 Mb) – while strong LD in African Americans is localized primarily to a much-smaller region  
17 immediately flanking the *C4* genes (**Extended Data Fig. 4e**).

18  
19 A direct comparison of the two population-specific LD patterns confirms that nearly all variants with  
20 LD to *C4* variation have greater linkage in the European-ancestry cohort than in the African American  
21 cohort (**Extended Data Fig. 4f**).

22  
23  
24 **Initial (*C4*-naïve) association analysis produces divergent association results in the MHC genomic**  
25 **region for European-ancestry and African American cohorts**

26  
27 In unconditional (*C4*-naïve) association analysis of SLE for each variant in the MHC region, there is  
28 little correlation between results from European-ancestry and African American cohorts<sup>3,5</sup> (**Extended**  
29 **Data Fig. 4g, h**). In particular, a SNP's level of association in one population offers very little  
30 predictive information about its level of association to SLE in the other population (**Extended Data Fig.**  
31 **4g**). This could in principle result from multiple population-specific variants or even population-  
32 specific biology – but more-parsimonious explanations are both strongly preferred, and more strongly  
33 constrained and testable by available data.

34  
35 Of course, *C4* alleles have both allele-frequency and LD differences between these populations  
36 (**Extended Data Table 1**) and therefore could be a potential contributor to the population differences  
37 visible in **Extended Data Fig. 4g, h**. To evaluate this possibility, the variants in **Extended Data Fig.**  
38 **4g, h** are colored orange in proportion to their European-ancestry LD ( $r^2$ ) to *C4* composite risk,  
39 revealing that SNPs with European-specific associations tend to have strong LD to *C4* in Europeans.  
40 This highlights the strong effect that *C4* alleles would be likely to have in shaping the relative  
41 association strengths of genetic markers throughout the MHC genomic region.

42  
43  
44 **Controlling for *C4* composite risk aligns the residual association signal in the MHC genomic**  
45 **region across ancestries**

46  
47 If, beginning with the European-ancestry cohort, we now consider SNPs, not in a naïve association  
48 analysis, but in a joint association analysis together with *C4* (i.e. with *C4* composite risk as a covariate),  
49 then the association statistics for variants in the two cohorts begin to align with each other more strongly  
50 (**Extended Data Fig. 4i**, which should be compared to **Extended Data Fig. 4g**). Further adjusting the  
51 association statistics for the African American cohort analysis to account for *C4* changes the overall  
52 pattern more modestly (**Extended Data Fig. 4j, k**); this likely reflects reduced LD to *C4* alleles among  
53 African Americans. The genetic signal for SLE in both populations (in this *C4*-adjusted analysis) now

54 converges onto two variants (rs2105898 and rs9271513, separated by 975 bp) which are in strong  
55 ( $r^2 > 0.9$ ) LD across both populations and can be considered as a haplotype. rs2105898 is used as an  
56 index SNP in further analyses in the following sections and as such is highlighted in **Extended Data**  
57 **Fig. 4j, k**, with variants colored purple in proportion to their European-ancestry LD ( $r^2$ ) with rs2105898.  
58 Population-specific *HLA* alleles (*DRB1*\*15:01 and *DRB1*\*15:03) have been proposed as potential  
59 explanations for the apparently divergent association signals across European-ancestry and African  
60 American populations<sup>3,5</sup>; in **Extended Data Fig. 4j**, these alleles are shown with grey triangles.

61  
62 Much of the remaining trans-ancestry differences in association pattern in the MHC region appear to be  
63 explained by differences in LD patterns between populations; in **Extended Data Fig. 4l**, blueness of  
64 variants represents greater LD to rs2105898 in the European-ancestry cohort (relative to LD among  
65 African Americans) and redness represents greater LD in the African American cohort (relative to LD  
66 among European-ancestry individuals). Notably, the many variants with relatively stronger association  
67 signals among Europeans (including *DRB1*\*1501) exhibit stronger LD to rs2105898 among European-  
68 ancestry individuals, while select variants with relatively stronger association signals among African  
69 Americans (including *DRB1*\*1503) exhibit stronger LD to rs2105898 among African Americans. The  
70 strong LD this risk haplotype has with *DRB1*\*15:01 in Europeans and *DRB1*\*15:03 in African  
71 Americans may explain earlier findings of population-specific associations with *DRB1*\*15:01 in  
72 Europeans and *DRB1*\*15:03 in African Americans.

73  
74 This analysis also indicates that while much, if not all, of the European ancestry-specific association  
75 after controlling for *C4* composite risk can be accounted for by European ancestry-specific LD to  
76 rs2105898, this is not true for African Americans, who may harbor at least one additional, independent  
77 genetic effect not explained by the above analysis.

### 78 79 80 **The *C4*-independent association signal comprising rs2105898 and another linked variant defines** 81 **strong pan-tissue expression QTLs for *HLA* class II genes**

82  
83 Data from the GTEx Consortium<sup>52</sup> (v7) included 227 instances (gene/tissue pairs) in which this  
84 haplotype of two variants (rs2105898 and rs9271513) associated with elevated (*HLA-DRB1*, *-DRB5*, *-*  
85 *DQA1*, and *-DQB1*) or reduced (*HLA-DRB6*, *-DQA2*, and *-DQB2*) expression of an *HLA* class II gene  
86 with at least nominal ( $p < 10^{-4}$ ) significance. Some of the strongest associations at each gene ( $p < 10^{-8}$  to  
87  $10^{-76}$ ) were in whole blood, but expression QTLs elsewhere can also reflect the presence of blood and  
88 immune cells within those tissues<sup>53</sup>. Although eQTL analyses of *HLA* genes may be affected by read-  
89 alignment artifacts in these genes' hyperpolymorphic domains, most such observed signals are robust  
90 after adjusting for individual *HLA* alleles<sup>54</sup>.

91  
92 The haplotype with elevated expression of *HLA-DRB1*, *-DRB5*, *-DQA1*, and *-DQB1* (allele frequency 0.20  
93 among Europeans, 0.22 among African Americans) associated with increased SLE risk (odds ratio) of  
94 1.52 (95% CI: 1.44-1.61;  $p < 10^{-48}$ ) in Europeans and 1.49 (95% CI: 1.35-1.63;  $p < 10^{-16}$ ) in African  
95 Americans in analyses adjusting for *C4* effects. The risk haplotype tagged by rs2105898 tended to be on  
96 low-risk *C4* haplotypes in Europeans, a relationship that may have made both genetic influences (*C4* and  
97 the rs2105898 haplotype) harder to recognize in earlier work; controlling for either rs2105898 or *C4*  
98 (**Extended Data Fig. 3b**) greatly increased the association of SLE with the other genetic influence  
99 (**Extended Data Table 3**). Controlling for the simpler (2.3)*C4A*+*C4B* model in SNP associations with  
100 SjS (as precision of estimates of individual alleles were low due to sample size) also pointed strongly to  
101 the same haplotype, with the same allele of rs2105898 associating in the same direction but larger effect  
102 (OR: 1.96; 95% CI: 1.64-2.34;  $p < 10^{-12}$ ) as compared to SLE (**Extended Data Fig. 3d**).

### 103 104 105 **The rs2105898 haplotype affects the XL9 hotspot of active chromatin and transcription factor** 106 **binding**

107  
108 The two variants defining this short haplotype reside within the XL9 regulatory region<sup>55,56</sup>, a well-  
109 studied region of open chromatin that contains abundant chromatin marks characteristic of active  
110 enhancers and transcription factor binding sites. As characterized by HaploReg v4.1<sup>57</sup>, rs2105898 in  
111 particular lies within multiple histone marks that are associated with active enhancers (6 tissues), in the  
112 XL9 region of open chromatin (15 tissues), and under ChIP-seq binding peaks for 19 transcription  
113 factors (**Extended Data Fig. 5a**, data from the ENCODE project<sup>58,59</sup> and Roadmap Epigenomics  
114 Consortium<sup>60</sup>).

### 115 116 117 **rs2105898 disrupts a binding site for the ZNF143 transcription factor**

118  
119 We identified transcription factors whose binding motif is significantly affected by rs2105898. The  
120 strongest hit (ZNF143) is also among the transcription factors that have been determined by ChIP-seq  
121 analysis (from the ENCODE project) to bind to DNA sequence at rs2105898 (**Extended Data Fig. 5b**).  
122 ZNF143 is a widely expressed zinc-finger transcription factor that has been found to anchor chromatin  
123 interactions that connect distal regulatory elements with gene promoters<sup>61</sup>.

124  
125 Two databases (HaploReg, CIS-BP TF<sup>62</sup>) evaluate ZNF143 as having low or no binding to the minor  
126 (reference) allele of rs2105898 and very high affinity to the major (alternate) allele of rs2105898:

#### 127 128 **CIS-BP (log score)**

129 Reference (T) allele: 4.459

130 Alternate (G) allele: 13.273

131

#### 132 **HaploReg (log score)**

133 Reference (T) allele: -0.4

134 Alternate (G) allele: 11.5

135

136 ZNF143 is a recently identified component of complexes that maintain topologically associated domains  
137 (TADs) in concert with CTCF and cohesin (SMC1, SMC3, RAD21, STAG1/2), both of which also have  
138 numerous ChIP-seq peaks overlapping rs2105898. Specifically, ZNF143 has been found to directly  
139 bind and regulate promoter interaction with distal enhancers, congruous with the observation of  
140 numerous RNA polymerase ChIP-seq peaks at rs2105898 but with nearest promoter being 14.5kb away  
141 (*HLA-DQA1*, downstream). Furthermore, as this region lies in the genomic neighborhood of many  
142 genes for which rs2105898 is a multi-tissue eQTL (*HLA-DRB1*, *-DRB5*, *-DRB6* upstream and *-DQA1*, *-*  
143 *DQA2*, *-DQB1*, and *-DQB2* downstream) it seems plausible that by regulating ZNF143 binding,  
144 rs2105898 alters the interaction between this enhancer region and the promoters of the numerous  
145 proximal *HLA* class II genes. We also note that there have been other findings on the *DRB1*\*15:01  
146 haplotype in European-ancestry individuals (among whom *DRB1*\*15:01 is in high LD with rs2105898)  
147 including hypomethylation<sup>63</sup> that could in principle reflect the effect of this haplotype.

148

149

### 150 **rs2105898 is in strong LD with index SNPs for other autoimmune disorders**

151

152 rs2105898 also has high LD to the most strongly associated SNPs for other autoimmune phenotypes in  
153 the NHGRI-EBI GWAS catalog<sup>64</sup>. Of these associations, the strongest is to the peak SNP for multiple  
154 sclerosis oligoclonal band status ( $r^2=0.88, D'=0.98$ ). Also in high LD to rs2105898 is a shared peak SNP  
155 for associations to broad multiple sclerosis, immunoglobulin A production, ulcerative colitis, and  
156 Crohn's disease (all  $r^2=0.49, D'=0.98$ ).

157 **Supplementary Note 2 - Sex bias of C4 and C3 gene expression across human tissues**  
158

159 We analyzed expression levels of C4 and C3 across 46 human tissues for which the GTEx project<sup>35</sup> has  
160 analyzed (by RNA-seq) tissues from both men and women in the most recent release at time of writing  
161 (v8). Specifically, for each tissue we applied a non-parametric unsigned Mann-Whitney rank-sum test  
162 to compare transcripts per million (TPM) measurements between men and women and calculated  
163 Bonferroni-corrected p-values. For C4, the TPM values for C4A and C4B were summed (per sample).  
164

165 At a cutoff of  $\alpha = 0.01$ , results for brain, blood, liver and lymphoblastoid cells were insignificant; the  
166 only two tissues with significant sex differences for C4 expression were “Adipose - Subcutaneous”  
167 (higher in men) and “Breast - Mammary Tissue” (higher in women). For C3, three tissues showed  
168 higher expression in women: “Breast - Mammary Tissue”, “Skin - Not Sun Exposed (Suprapubic)”, and  
169 “Skin - Sun Exposed (Lower leg)”. These differences may well reflect sexual dimorphism in cell-type  
170 composition; for example, breast tissue undergoes monthly remodeling with infiltrating immune cells in  
171 women<sup>65</sup>. More broadly, breast tissue and subcutaneous fat distribution<sup>66</sup> are highly dimorphic between  
172 men and women. Though we cannot formally exclude the possibility that these tissues contribute to the  
173 sex difference protein concentrations we observed in CSF (and earlier studies have also observed in  
174 plasma), we note all cases except for “Adipose - Subcutaneous” involve higher detected expression  
175 levels in women and thus have the opposite sign of the observed difference in CSF/plasma protein  
176 concentration.

177 **Supplementary Note 3 - Full list of collaborators from the Schizophrenia Working Group of the**  
 178 **Psychiatric Genomics Consortium**

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