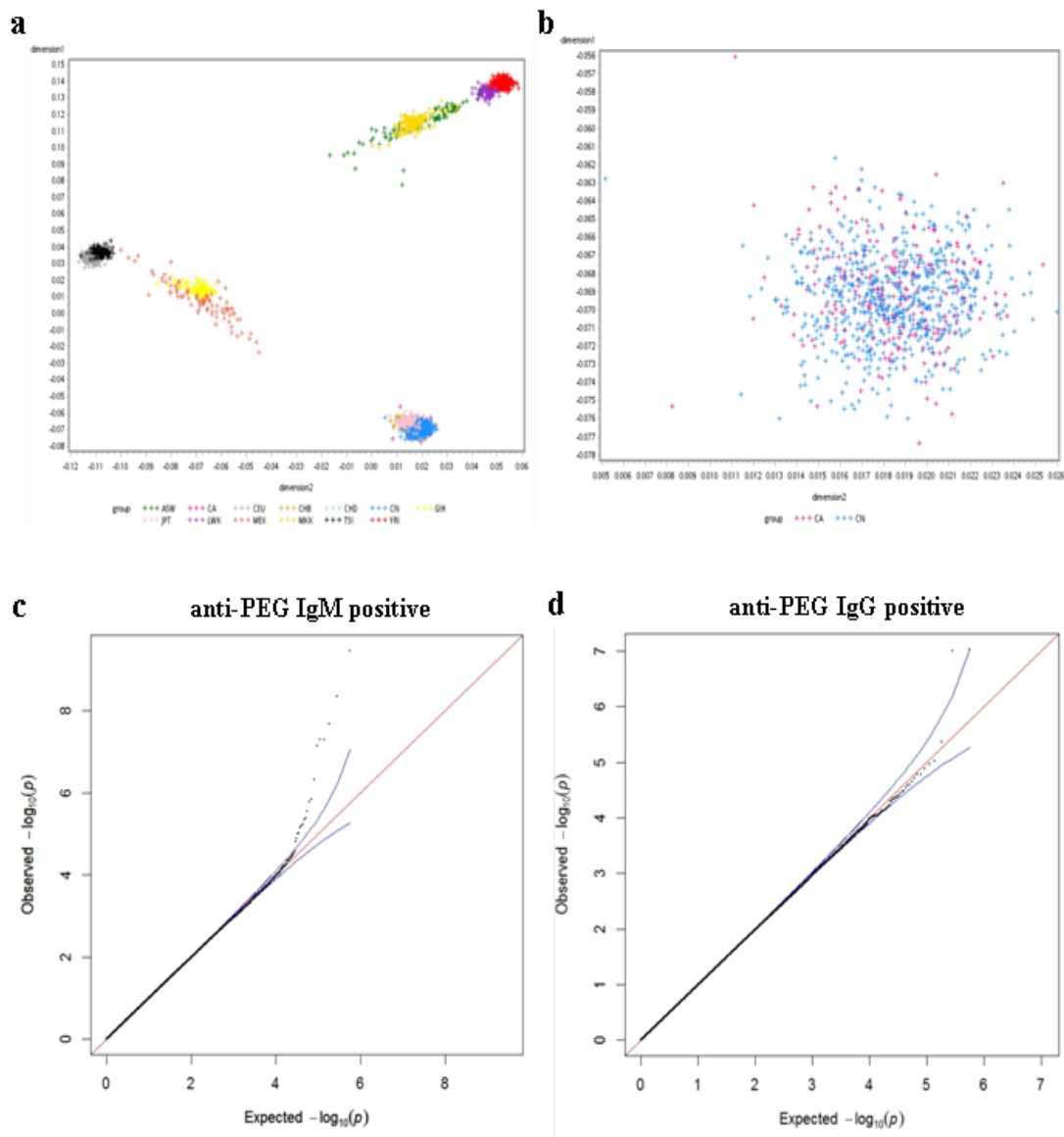


Description of Supplementary Files

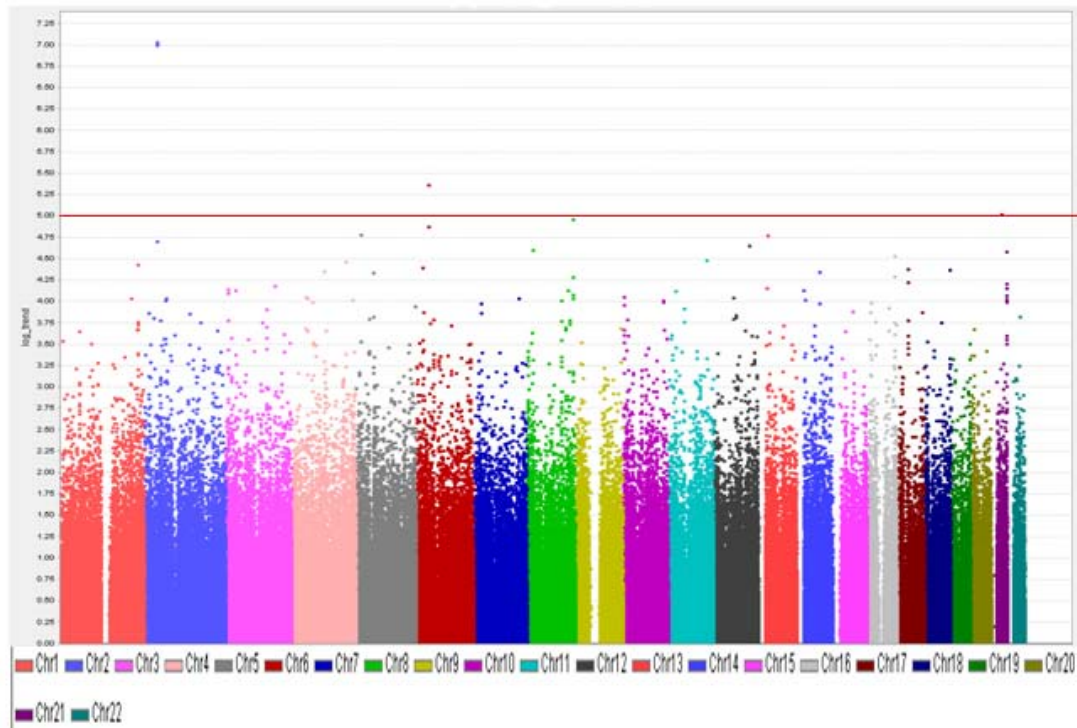
File Name: Supplementary Information

Description: Supplementary Figures and Supplementary Tables

File Name: Peer Review File

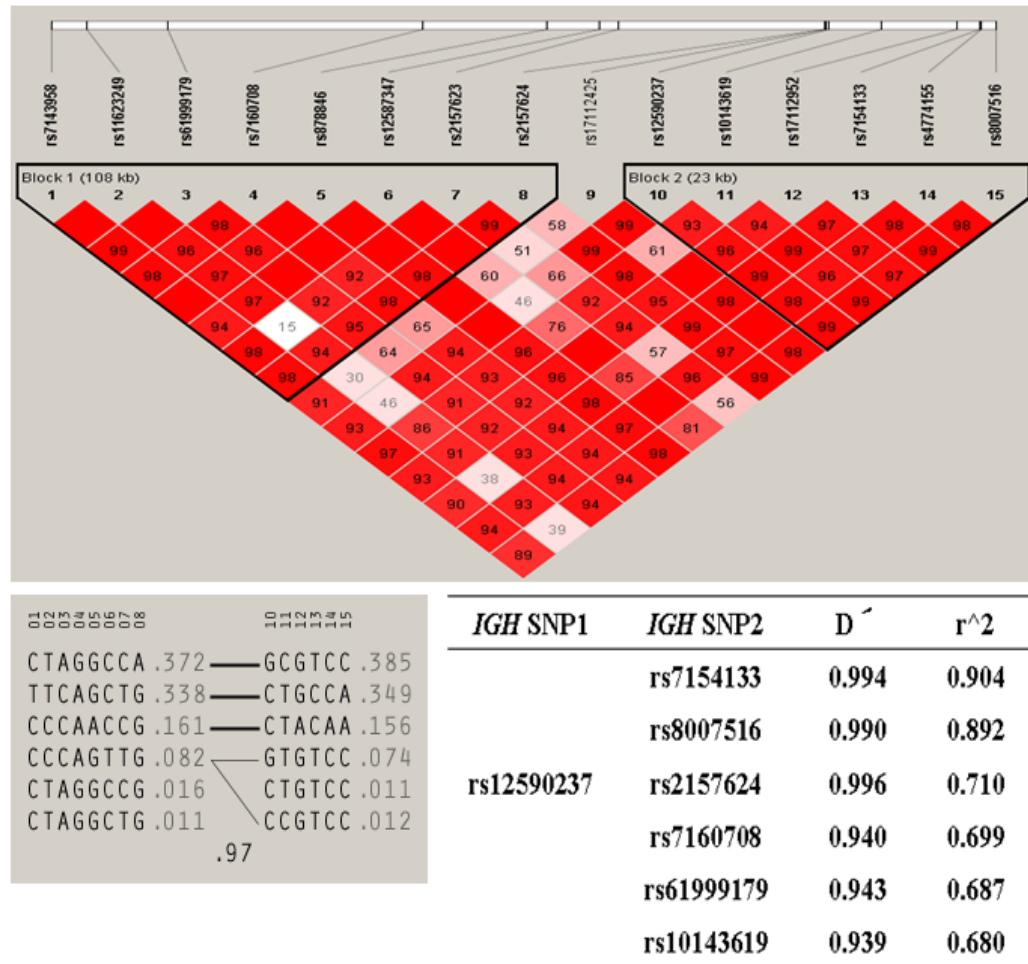


Supplementary Figure 1| Principal components analysis and quantile-quantile plot (Q-Q plot) for the trend test. (a,b) The EIGENSTRAT 2.0 was used to conduct principal components analysis (PCA) of the GWAS samples with HapMap populations (a) and the GWAS samples only (b) for population stratification. (c,d) Q-Q plot of the P values in Cochran-Armitage trend test. The lambda value is 1.049 for anti-PEG IgM and 1.027 for anti-PEG IgG.



8
9 **Supplementary Figure 2| Manhattan plots for genome-wide SNPs associated**
10 **with anti-PEG IgG responses.** Results of genome-wide association analysis ($-\log_{10}$
11 P) shown in chromosomal order for 557,394 SNPs tested for association in initial
12 samples of 140 cases (anti-PEG IgG positive) and 492 controls (double negative for
13 IgM and IgG). The x axis represents each of the SNPs used in the primary scan. The y
14 axis represents the $-\log_{10} P$ value of the trend test. Horizontal lines indicate $-\log_{10} P$
15 = 5.

a



b

SNP		P value for rs12590237	P value for linked_snp
rs61999179		1.00E-04	6.97E-01
rs7160708		6.87E-04	8.48E-01
rs12590237	rs2157624	1.07E-03	8.07E-01
rs10143619		7.05E-04	7.28E-01
rs7154133		3.74E-02	6.13E-01
rs8007516		1.01E-02	3.05E-01

Supplementary Figure 3| The LD structure and logistic regression analyses in *IGH* loci. (a) LD patterns, D' value and r^2 among the genome-wide associated SNPs in *IGH* region. (b) The P -values for the rs12590237 and the linked SNPs in logistic regression models conditioned on rs12590237. No significant effects of the linked SNPs were found in logistic regression models conditioned on rs12590237.

22 **Supplementary Table 1. Quality control of participant data.**

23

Number at start of QC	628,132 SNPs
SNPs excluded during QC steps:	
Call rate in cases or controls <95%	12,546 SNPs
Overall MAF < 5%	42,876 SNPs
HWE for control ($P < 10^{-4}$) with polymorphic in control	4,832 SNPs
Number at end of QC	557,394 SNPs

24 HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency;
 25 QC, quality control

26
 27
 28
 29
 30
 31
 32
 33
 34
 35
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50

51 **Supplementary Table 2. Validated SNPs (n=16) with $P_{trend} < 10^{-5}$ in the discovery**
52 **stage of GWAS for anti-PEG IgM.**

Chr.	SNP	Position	Gene	Allele format	Risk Allele	RAF controls	RAF cases	P	Risk allele OR (95%CI)
1	rs78378504	242715847	no gene	AG	A	0.043	0.113	4.18E-06	2.819 (1.789-4.442)
1	rs75966753	242720432	no gene	CA	C	0.047	0.122	1.47E-06	2.807 (1.817-4.338)
1	rs76254089	242765102	no gene	TC	T	0.045	0.113	6.46E-06	2.716 (1.737-4.246)
3	rs75133071	105951670	no gene	AG	G	0.783	0.897	2.84E-06	2.416 (1.657-3.521)
5	rs76793186	52411735	no gene	GT	G	0.056	0.130	5.92E-06	2.506 (1.660-3.785)
7	rs740209	97653811	no gene	GT	T	0.571	0.706	6.93E-06	1.805 (1.390-2.344)
13	rs76900511	90874497	no gene	GT	T	0.631	0.767	4.50E-06	1.923 (1.454-2.541)
14	rs61999179	106909084	<i>IGH</i>	AC	A	0.357	0.517	4.91E-07	1.925 (1.503-2.466)
14	rs7160708	106944848	<i>IGH</i>	GA	G	0.356	0.528	5.14E-08	2.025 (1.582-2.592)
14	rs2157624	107001253	<i>IGH</i>	AG	A	0.335	0.503	7.33E-08	2.008 (1.567-2.572)
14	rs12590237	107001719	<i>IGH</i>	GC	G	0.410	0.611	3.46E-10	2.269 (1.767-2.912)
14	rs10143619	107009038	<i>IGH</i>	CT	C	0.353	0.523	5.02E-08	2.007 (1.568-2.569)
14	rs7154133	107022978	<i>IGH</i>	TC	T	0.435	0.622	4.52E-09	2.143 (1.669-2.751)
14	rs8007516	107025099	<i>IGH</i>	CA	C	0.438	0.617	2.12E-08	2.068 (1.610-2.656)
19	rs7252042	33720811	no gene	TC	T	0.154	0.257	9.81E-06	1.900 (1.415-2.551)
19	rs17694094	33723705	no gene	GT	G	0.164	0.277	1.68E-06	1.957 (1.468-2.609)

53 Chr. = chromosome; Gene = Gene the SNPs located; RAF = risk allele frequency.

54 Controls = double negative for anti-PEG IgM and IgG; Cases = anti-PEG IgM.

55 95% CI = 95% confidence interval; OR = odds ratio for risk-allele.

56 P = Trend P derived from a one-degree-of-freedom of Armitage trend test.

57

58

59

60

61

62

63

64

65

66

67

68

69

70

71 **Supplementary Table 3. GWAS and replication results in the SNPs ($P_{trend} < 10^{-5}$**
72 **in GWAS) for anti-PEG IgG.**

Chr.	SNP	Position	Gene	Allele format	Risk allele	Stage	RAF controls	RAF cases	Trend P
2	rs2373305	38029531	no gene	TC	T	GWAS	0.321	0.496	9.22E-08
						Replication	0.369	0.404	2.32E-01
2	rs11899949	38049069	no gene	AG	A	GWAS	0.310	0.482	9.89E-08
						Replication	0.359	0.380	4.44E-01
6	rs77137655	35510259	no gene	AG	A	GWAS	0.059	0.139	4.26E-06
						Replication	0.084	0.073	5.00E-01
21	rs79714376	29197039	no gene	CT	C	GWAS	0.048	0.125	9.39E-06
						Replication	0.084	0.070	3.98E-01

73 Gene = Genes containing the SNP; RAF controls = risk allele frequency in control.

74 RAF cases = risk allele frequency in case.

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99 **Supplementary Table 4. Heterogeneity test between GWAS and replication groups**
100 **for analyses of anti-PEG IgM.**

Chr.	SNP	A1	A2	Heterogeneity Q test	I^2	Trend- <i>P</i> GWAS	Trend- <i>P</i> Replicate	Trend- <i>P</i> Combined
14	rs61999179	A	C	0.9758	0	4.91E-07	4.50E-08	2.13E-14
14	rs7160708	G	A	0.9723	0	5.14E-08	1.79E-09	5.37E-17
14	rs2157624	A	G	0.9448	0	7.33E-08	2.12E-09	1.71E-16
14	rs12590237	G	C	0.8795	0	3.46E-10	5.34E-13	2.23E-22
14	rs10143619	C	T	0.9516	0	5.02E-08	2.41E-09	1.13E-16
14	rs7154133	T	C	0.5886	0	4.52E-09	4.77E-13	2.36E-21
14	rs8007516	C	A	0.5109	0	2.12E-08	1.09E-12	2.60E-20

101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127

128 **Supplementary Table 5. Prevalence of anti-PEG antibodies in GWAS and**
129 **replication samples.**

	Number of IgM positive only	Number of IgG positive only	Number of double positive	Number of double negative	Total
GWAS	177 (20%)	140 (15.8%)	76 (8.6%)	492 (55.6%)	885
Replication	211 (19.2%)	192 (17.5%)	101 (9.2%)	596 (54.2%)	1100

130

131

132

133

134

135

136

137

138

139

140

141

142

143

144

145

146

147

148

149

150

151

152

153

154

155

156

157

158

159

160

161 **Supplementary Table 6. Sample population characteristics with age and sex.**

	Age group (years) --- GWAS stage							
	Total	20-29	30-39	40-49	50-59	60-69	70-79	≥ 80
	885 (100%)	120 (14%)	121 (14%)	157 (18%)	142 (16%)	173 (20%)	116 (13%)	56 (6%)
Male	449 (51%)	68 (57%)	57 (47%)	84 (54%)	65 (46%)	77 (45%)	69 (59%)	29 (52%)
Female	436 (49%)	52 (43%)	64 (53%)	73 (46%)	77 (54%)	96 (55%)	47 (41%)	27 (48%)
	Age group (years) --- Replication stage							
	Total	20-29	30-39	40-49	50-59	60-69	70-79	≥ 80
	1100 (100%)	152 (14%)	157 (14%)	219 (20%)	212 (19%)	182 (17%)	149 (14%)	29 (3%)
Male	539 (49%)	82 (54%)	65 (41%)	109 (50%)	109 (51%)	88 (48%)	75 (50%)	11 (38%)
Female	561 (51%)	70 (46%)	92 (59%)	110 (50%)	103 (49%)	94 (52%)	74 (50%)	18 (62%)

162

163

164