Supplemental Figures

Figure S1: Distribution of standardized residuals for continuous anti-EBNA-1 titers in the QIMR sample after generalized linear model (GLM) analysis with box effect, row effect, and column effect as fixed factors while also controlling sex, age, age x sex, age^2 and age^2 x sex. Here the Res_con refer to the residual value of anti-EBNA-1 titres, while Frequency refer to the number of samples.

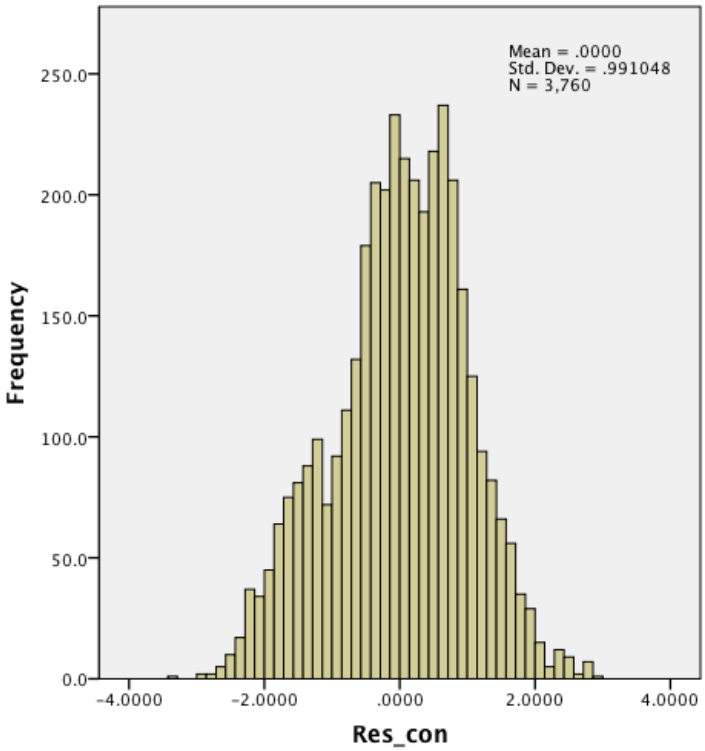


Figure S2: Manhattan Plot for QIMR Twin Families EBNA-1 GWAS (QTFEGWAS) a) using all samples (N = 3,599). b) only parents (N = 1,243). c) only children (N = 2,356).d) only children with positive anti-EBNA-1 IgG titres (N = 1,488)

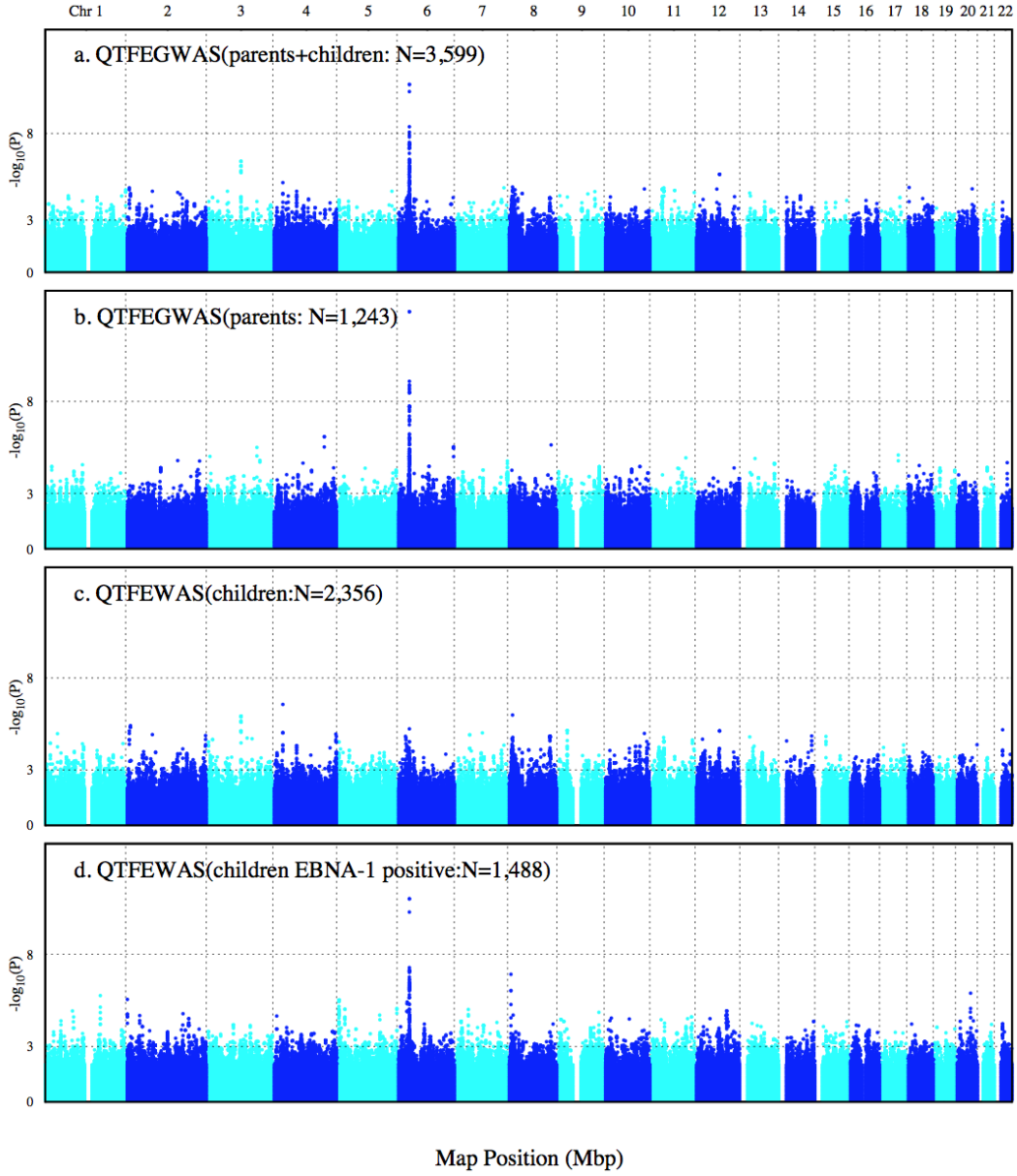


Figure S3: QQ plot for QTFEGWAS using a) both parents and children (N = 3,599). b) only parents (N = 1,243). c) only children (N = 2,356). d) only children with positive anti-EBNA-1 IgG titres (N = 1,488) e)QQ plot for EGMA (effective N = 5,555). f) QQ plot for MGMA excluding HLA region (chr6: 25Mb-35Mb) (effective N = 20,786).

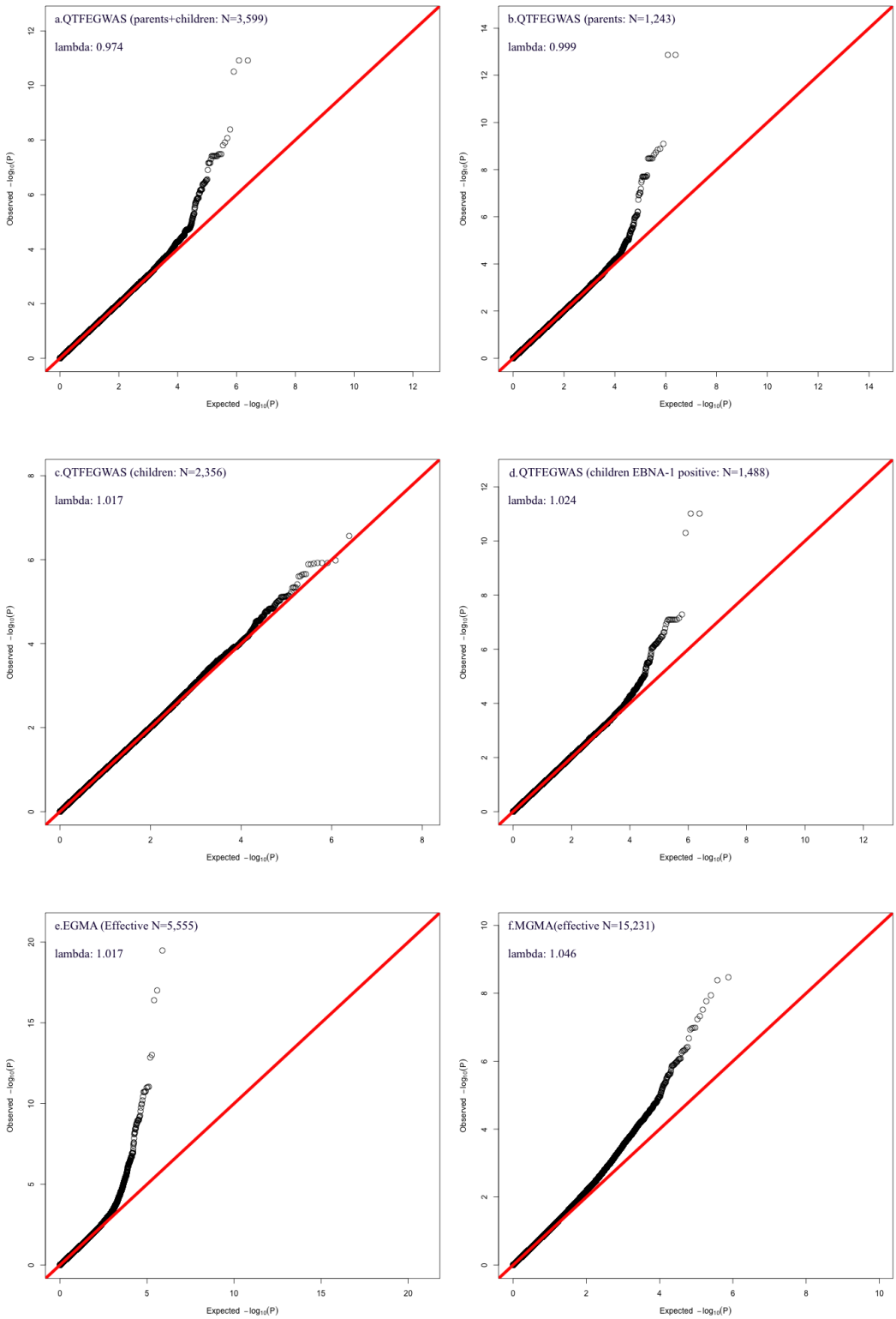


Figure S4: Manhattan plot for Meta-Analysis of EBNA-1 IgG GWAS fixed effect (EGMA): QIMR Twin Families EBNA-1 GWAS (QTFEGWAS) (N = 3,599) and Mexican-American families EBNA-1 GWAS (MAFEGWAS) (N = 1,956).

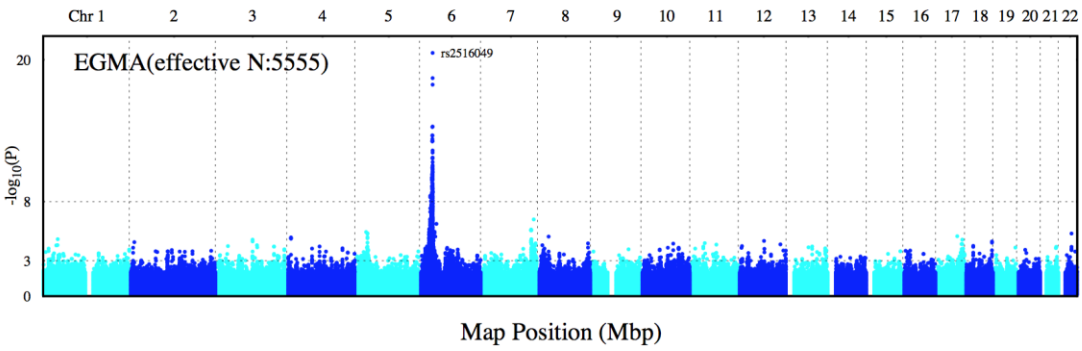
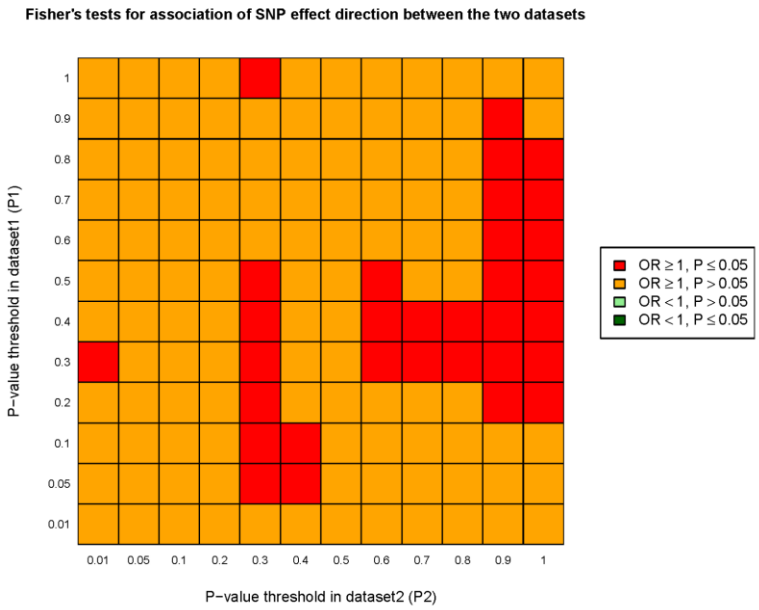


Figure S5: Heatmap for SECA results including/ excluding HLA region using EBNA-1 GWAS Meta analysis (EGMA) as the discovery sample (dataset1), and the MS GWAS Meta analysis (MGMA) as the target sample (dataset2).

a. Including HLA region. $P_{\text{FTsig-permuted}}$= 0.026 (95% CI: 0.018-0.038)



b. Excluding HLA region. $P_{\text{FTsig-permuted}}$=0.049 (95% CI: 0.037-0.064)

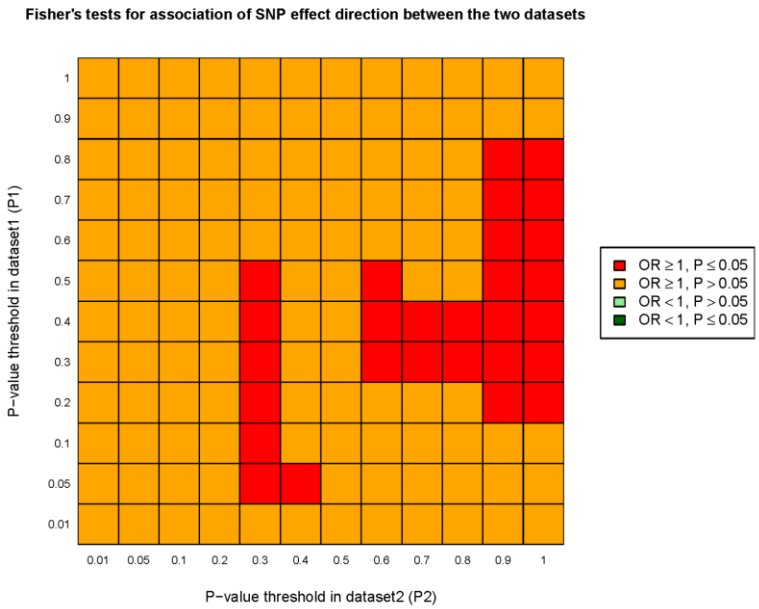
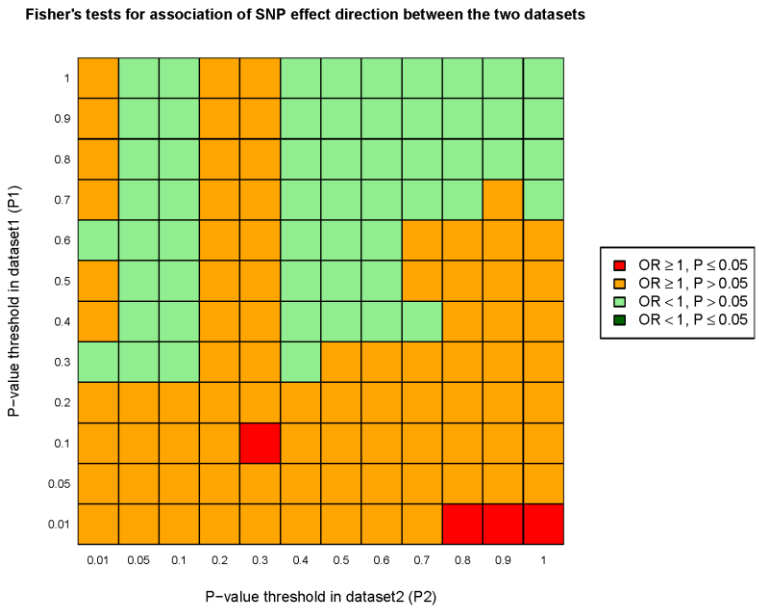


Figure S6: Heatmap for SECA results including/ excluding HLA region using the MS GWAS Meta analysis (MGMA) as the discovery sample (dataset1), and the EBNA-1 GWAS Meta analysis (EGMA) as the target sample (dataset2).

a. Including HLA region. $P_{\text{FTsig-permuted}}$ = 0.173 (95% CI: 0.151-0.197)



b. Excluding the HLA region. $P_{\text{FTsig-permuted}}$= 0.157 (95% CI: 0.136-0.181)

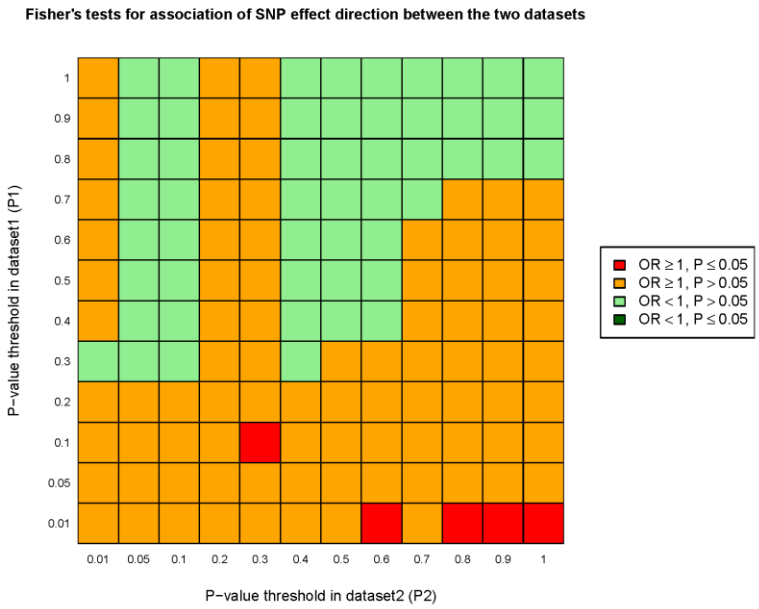
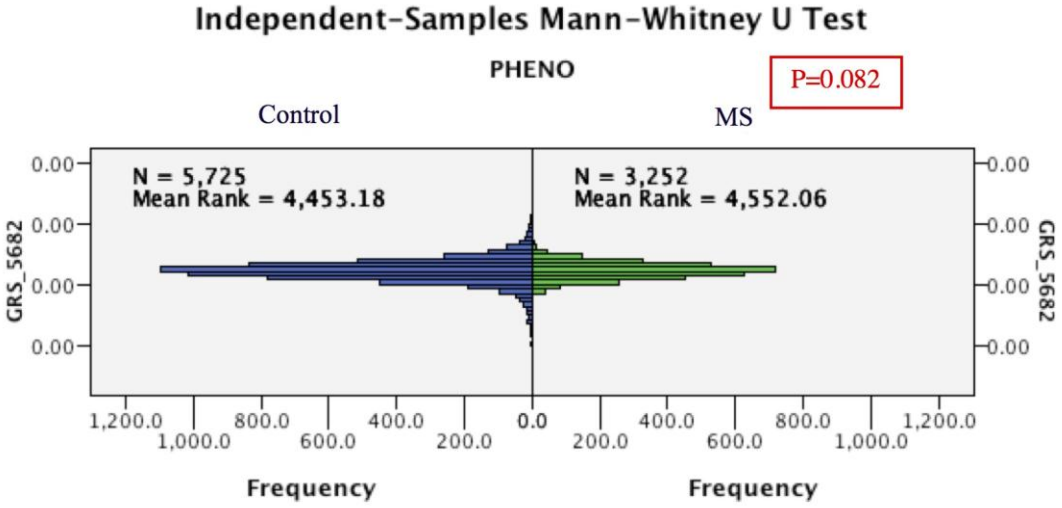


Figure S7: Genetic Risk Score (GRS) results using the EBNA-1 GWAS meta analysis (EGMA) as the discovery sample, and dbGaP and ANZgene (MS cases) as target samples. a) The EBNA-1 constructed GRS values (5,682 SNPs with $P_{EGMA} \leq 0.05$) are higher in MS than controls and this difference is significant using an independent sample t-test (p=0.007) and marginally significant using a nonparametric test (p=0.082). b) Using the enriched SNP set (597 SNPs with $P_{EGMA} \leq 0.05$ and $P_{MGMA} \leq 0.1$) for which the correlation of SNP effects is strongest, the result is more significant whether using an independent sample t test (p=0.003) or nonparametric test (p=0.002). Below are the plot results for the nonparametric test. The mean rank value was used to compare which was higher.

a.



b.

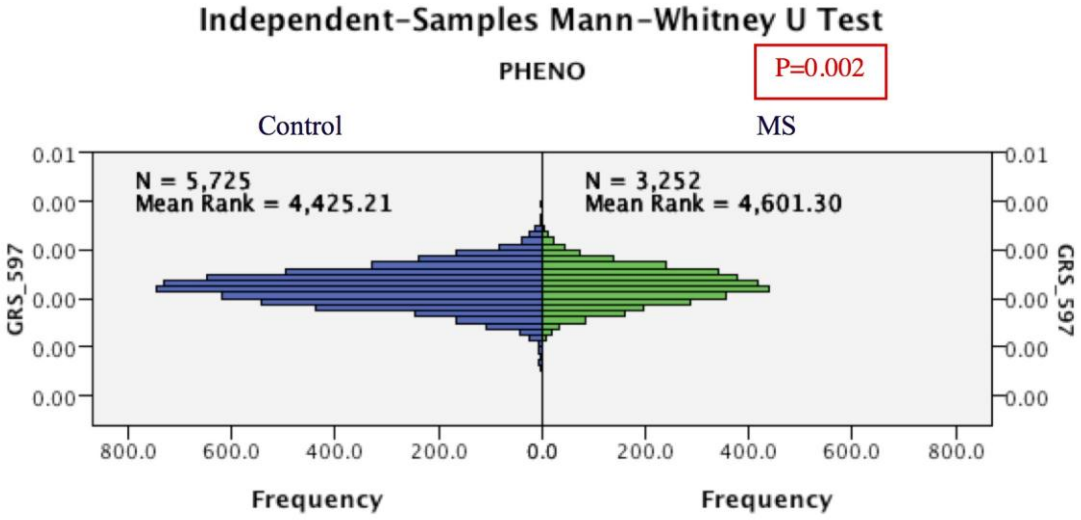


Figure S8: Genetic risk score (GRS) results using the MS GWAS meta-analysis (MGMA) as the discovery sample, and the QIMR Twin Families EBNA-1 GWAS as a target sample. The MS constructed GRS values (5,770 SNPs with $P_{MGMA} \leq 0.05$) do not correlate with the anti-EBNA-1 titres in QIMR Twin Families EBNA-1 GWAS, whether using Pearson correlation (P = 0.752, r = -0.013) or Spearman's correlation (P = 0.453, r = -0.030); indicating that MS case status itself does not predict anti-EBNA-1 titres. Below is the scatter plot for the correlation. Here the GRS_5770 refers to the constructed GRS values using 5,770 SNPs, while the Res_EBNA1 refers to the residuals of anti-EBNA-1 titres in QIMR Twin Families.

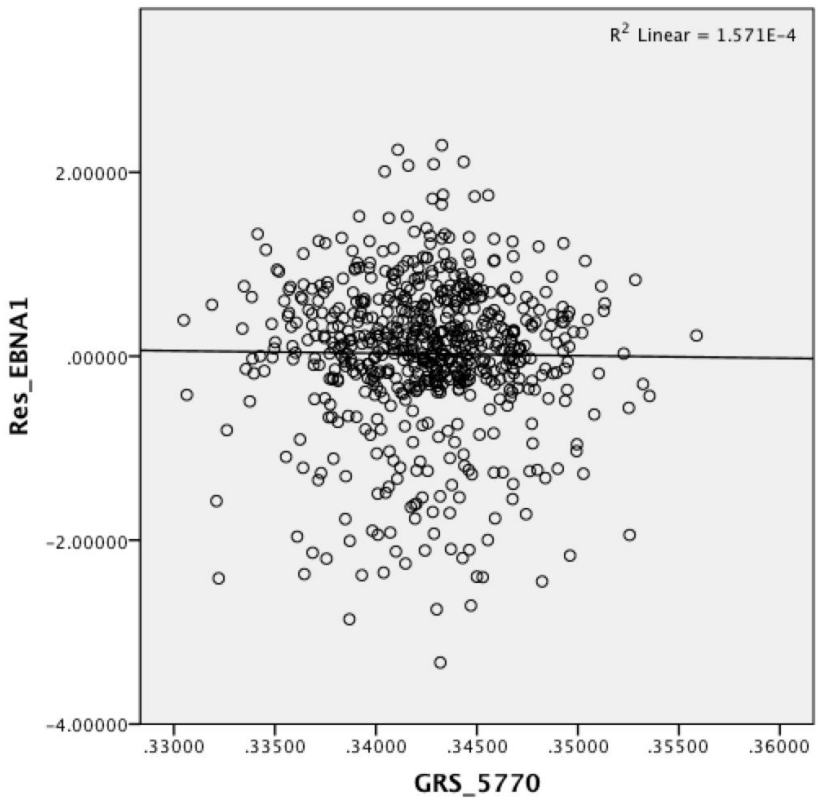
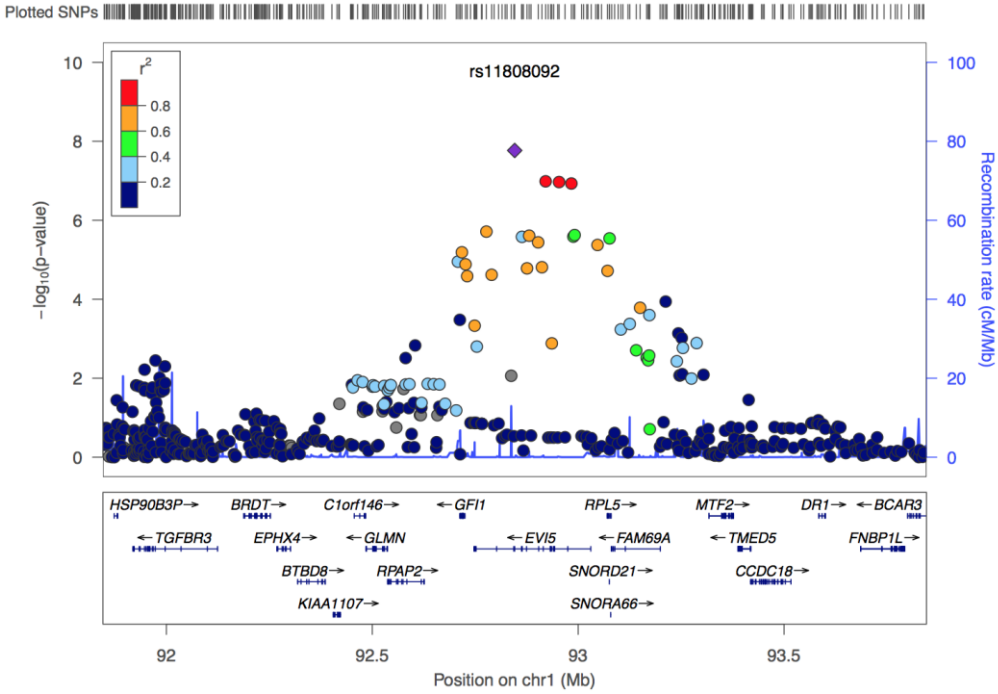
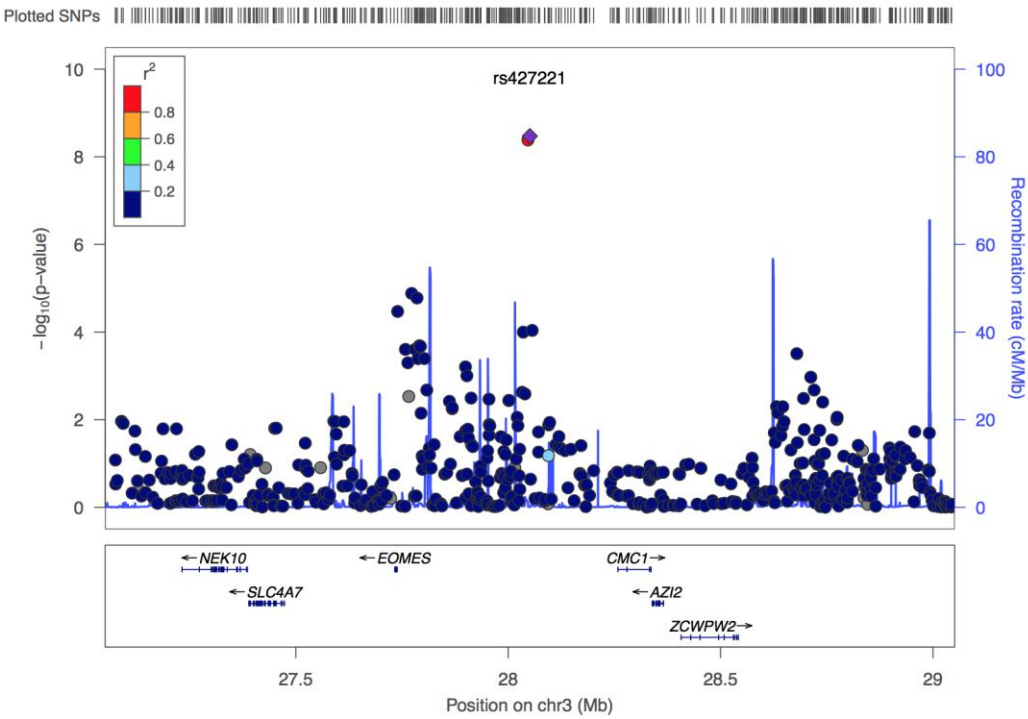


Figure S9: Regional plots for the significant non-HLA loci in the joint EBNA-1 and MS meta analysis.

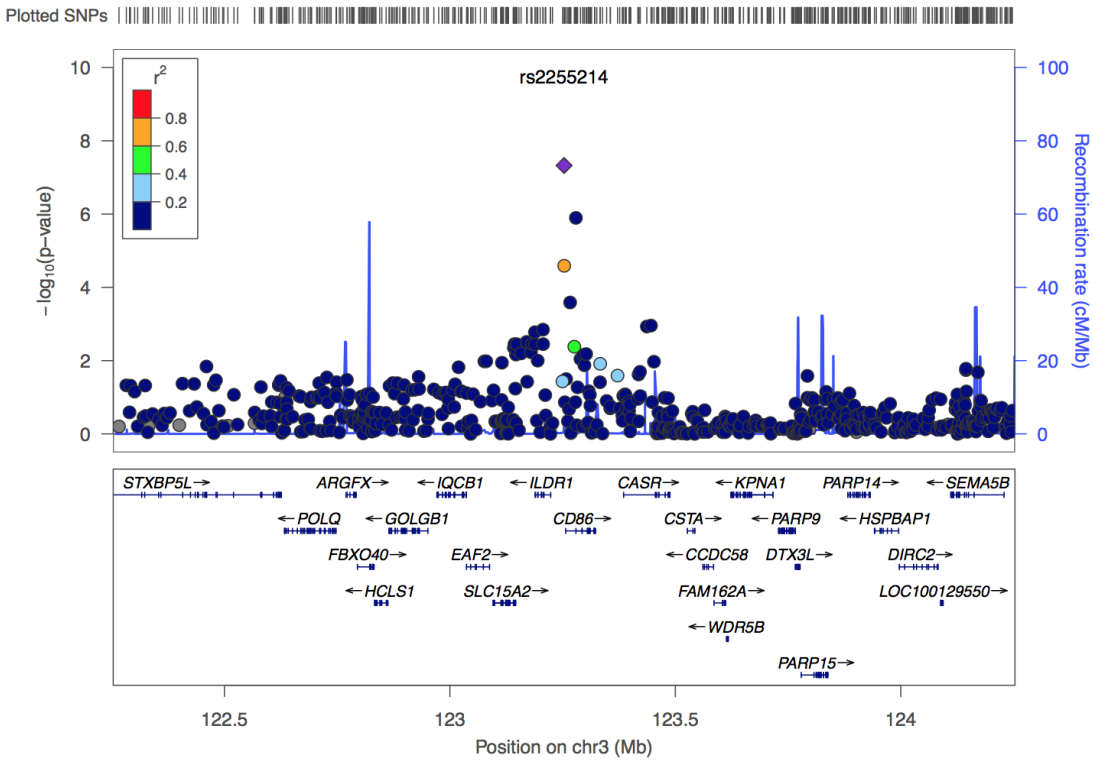
a. Regional plots for the significant loci (1p22.1). The top significant SNP is rs11808092 in the gene *EVI5*.



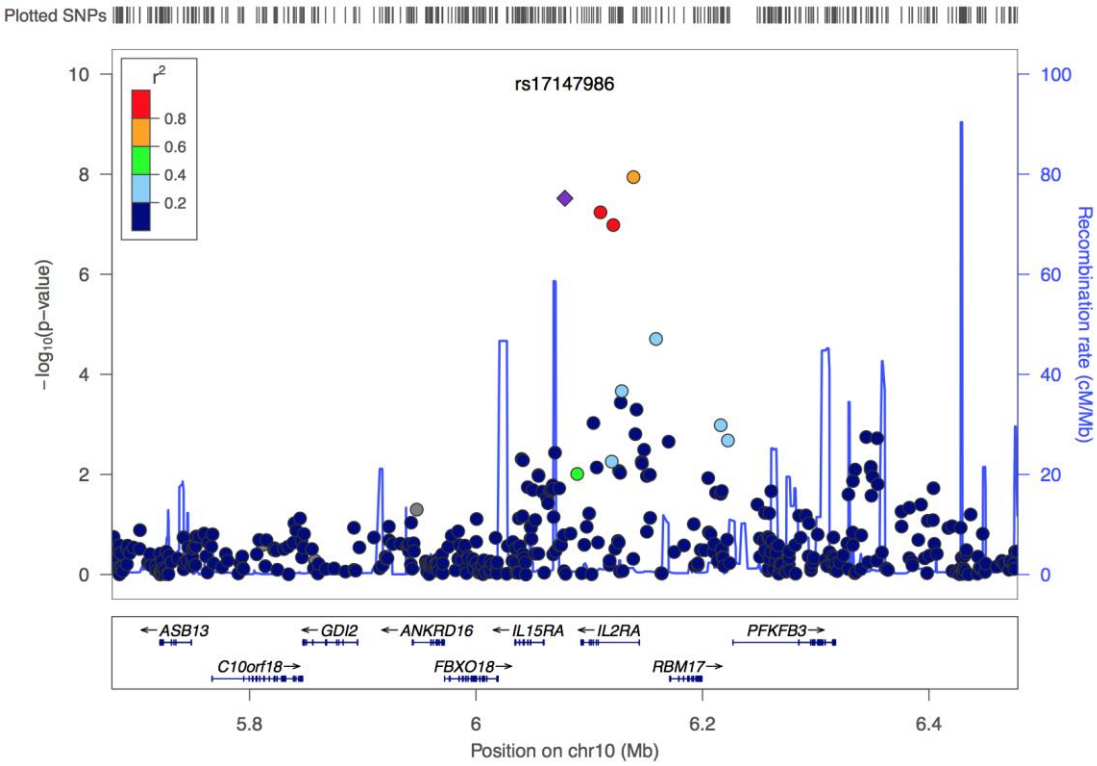
b. Regional plot for the significant loci (3p24.1). The top significant SNP is rs427221.



c. Regional plot for the significant loci (3q13.33). The top significant SNP is rs2255214.



d. Regional plot for the significant loci (10p15.1). Significant SNP rs17147986 is used as reference.



Supplemental Tables

Table S1: (a) Descriptive data for QIMR Twin Families (N = 3,760 individuals). MZ

Groups		Sex		Age (years)	
		Female	Male	Mean	Std. Deviation
Parents	Fathers	0	661	47.54	5.22
	Mothers	725	0	45.31	4.53
Children	MZ	473	466	15.48	1.61
	DZ	465	467	15.5	1.6
	Siblings	270	233	15.26	2.87
	Total	1933	1827	26.84	15.31

represents monozygotic twins. DZ represents dizygotic twins.

Table S1: (b) The number of complete pairs and single twins.

Twins	Zygosity		
	MZ	DZ	Total
Single Twin	24	55	79
Twin Pair	333	563	896

Table S2: Top 45 significant SNPs within the HLA region in EBNA-1 GWAS Meta-Analysis (EGMA)(effective sample size: 5,555) and related P-values for these SNPs in MS GWAS Meta-Analysis (MGMA)(effective sample size: 17,698) (fixed effect). Of these, 40 SNPs are in complete LD ($r^2 = 1$) and showed the same direction of effect; these are in weak LD ($r^2 = 0.089$) with the other 5 SNPs ($r^2 = 1$ for these five SNPs) which showed opposite direction of effect. E(A) represents the effect allele. Effect(EGMA) represents the beta value for each SNP in EGMA. P(EGMA) represents the p-value for SNPs in EGMA. P(QTFE) represent the p-value for QTFEGWAS(parents+children). P(MAFE) represents the p-value for MAFEGWAS. OR(MS) represents the OR value for each related SNP in MGMA. P(MS) represents the p-value for each related SNP in MGMA.

SNP	CHR	POS	E(A)	O(A)	Effect(EGMA)	P(EGMA)	P(QTFE)	P(MAFE)	OR(MS)	P(MS)
rs2516049	6	32678378	T	C	0.204	3.32E-20	4.11E-09	6.43E-14	1.321	4.49E-20
rs9268853	6	32537621	T	C	0.188	9.81E-18	3.30E-08	6.18E-12	1.415	4.59E-30
rs2395185	6	32541145	G	T	0.184	3.97E-17	6.95E-08	9.76E-12	1.413	1.02E-29
rs204999	6	32217957	A	G	0.180	9.78E-14	7.03E-05	1.14E-13	1.133	1.01E-04
rs3891175	6	32742445	C	T	0.194	1.41E-13	5.25E-06	2.89E-11	1.139	1.31E-04
rs3130284	6	32248465	T	C	0.186	9.15E-12	3.24E-05	5.81E-11	1.166	1.37E-05
rs3096697	6	32242488	G	A	0.186	9.68E-12	3.33E-05	6.07E-11	1.159	5.25E-04
rs2395182	6	32521295	T	G	-0.169	1.04E-11	5.22E-06	2.47E-07	0.426	3.68E-163
rs3134608	6	32225949	T	G	0.184	1.70E-11	2.17E-05	3.94E-10	1.151	7.05E-05
rs3132965	6	32254975	A	G	0.183	1.93E-11	3.35E-05	2.92E-10	1.168	1.08E-05
rs3134945	6	32254470	C	A	0.183	1.93E-11	3.24E-05	2.92E-10	1.167	1.14E-05
rs3134947	6	32253183	C	T	0.183	1.93E-11	3.24E-05	2.92E-10	1.166	1.29E-05
rs5020946	6	32558067	G	T	0.143	3.75E-11	7.68E-06	2.01E-07	1.556	7.95E-54
rs443198	6	32298384	A	G	0.141	6.37E-11	6.94E-08	1.61E-04	1.297	3.33E-17
rs3129888	6	32519704	A	G	-0.163	1.04E-10	5.22E-06	3.78E-06	0.430	1.34E-161
rs3129882	6	32517508	A	G	-0.134	1.14E-10	3.15E-07	1.42E-04	0.624	7.88E-65
rs2073045	6	32447526	G	A	0.139	1.79E-10	3.71E-05	1.48E-07	1.403	4.44E-19
rs204993	6	32263559	A	G	0.151	2.98E-10	2.18E-06	1.74E-05	1.260	2.70E-12

rs9268516	6	32487467	C	T	0.138	5.65E-10	4.27E-05	1.71E-06	1.404	5.35E-26
rs3763316	6	32484724	C	T	0.138	6.27E-10	4.27E-05	2.05E-06	1.380	3.02E-24
rs9268494	6	32483330	A	C	0.136	7.22E-10	5.65E-05	1.71E-06	1.375	6.41E-24
rs2076524	6	32478662	A	G	0.136	1.10E-09	5.65E-05	2.64E-06	1.395	6.81E-26
rs2076525	6	32478594	T	C	0.136	1.10E-09	5.65E-05	2.64E-06	1.412	3.49E-28
rs3817962	6	32476292	C	A	0.136	1.10E-09	5.65E-05	2.57E-06	1.352	2.39E-14
rs9268474	6	32465143	T	C	0.136	1.10E-09	5.92E-05	2.64E-06	1.396	6.14E-26
rs204995	6	32262263	A	G	0.159	1.17E-09	1.57E-04	6.48E-08	1.156	3.95E-05
rs9268493	6	32483308	G	A	0.134	1.51E-09	1.48E-04	6.73E-07	1.327	4.40E-20
rs2395157	6	32456123	A	G	0.134	1.65E-09	1.12E-04	1.90E-06	1.387	5.71E-25
rs204994	6	32262976	C	T	0.160	1.66E-09	1.20E-04	1.16E-07	1.157	3.15E-05
rs3817963	6	32476065	T	C	0.134	2.01E-09	5.65E-05	6.14E-06	1.395	6.55E-26
rs3763311	6	32484154	C	T	0.133	2.12E-09	4.14E-05	9.37E-06	1.357	2.87E-14
rs9268403	6	32449451	T	C	0.133	2.77E-09	1.12E-04	3.44E-06	1.389	4.96E-25
rs3130048	6	31721718	T	C	0.148	3.52E-09	2.40E-03	1.54E-10	1.182	3.02E-07
rs176095	6	32266297	A	G	0.153	5.92E-09	1.56E-04	6.74E-07	1.154	3.84E-05
rs2267647	6	33083489	G	A	-0.124	6.51E-09	8.90E-07	1.58E-03	0.920	2.70E-03
rs2076536	6	32447326	T	C	-0.131	8.04E-09	3.53E-05	2.79E-05	0.590	1.34E-49
rs6901158	6	32313920	C	T	0.188	1.42E-08	1.31E-04	3.65E-07	1.136	2.48E-03
rs9268499	6	32483673	G	A	0.124	2.52E-08	1.48E-04	2.69E-05	1.328	3.76E-20
rs1265159	6	31248026	G	A	0.142	2.89E-08	5.36E-04	9.19E-07	1.050	1.60E-01
rs652888	6	31959213	A	G	0.151	3.05E-08	1.81E-03	5.08E-09	1.195	3.03E-06
rs4248166	6	32474399	T	C	-0.160	9.55E-10	1.86E-02	9.19E-11	1.274	2.74E-11
rs2294881	6	32475582	T	C	-0.152	3.87E-09	1.86E-02	1.11E-09	1.271	4.64E-11
rs2294882	6	32475493	T	C	-0.152	3.87E-09	1.86E-02	1.11E-09	1.240	1.70E-06
rs2294884	6	32475237	T	G	-0.151	7.19E-09	1.86E-02	2.53E-09	1.246	2.73E-07
rs10947261	6	32481210	G	T	-0.177	3.90E-08	9.95E-02	2.02E-08	1.061	2.35E-01

Table S3: The combined meta-analysis of EBNA-1 GWAS Meta-Analysis (EGMA) results(N = 5,555) and MS GWAS Meta-Analysis results(N = 17,698) (MGMA) (excluding the HLA region); only significant SNPs are listed (P_Meta < 5.0×10^{-8}). E(A) represents the effect allele. P_MGMA represents the p-value for SNPs in MGMA. P_EGMA represents the p-value for related SNPs in EGMA. P_Meta represents the meta-analysis results of the MGMA and EGMA. I^2 represents the percentage of total variation in SNP effects across MGMA and EGMA. Phet represents p-value for heterogeneity between EGMA and MGMA.

SNP	E(A)	O(A)	CHR	POS	P _MGMA	OR_MGMA	P _EGMA	Beta_EGMA	P _Meta	I^2	Phet
rs11808092	A	C	1	92845816	2.94×10^{-06}	1.149	1.25×10^{-03}	0.025	1.71×10^{-08}	0	0.605
rs669607	A	C	3	28046448	2.10×10^{-08}	0.854	0.0484	-0.041	4.12×10^{-09}	0	0.659
rs427221	T	C	3	28050989	2.28×10^{-08}	0.855	0.0382	-0.043	3.72×10^{-10}	0	0.738
rs2255214	T	G	3	123253229	4.95×10^{-07}	0.872	0.0300	-0.047	4.73×10^{-08}	36.4	0.209
rs17147986	C	A	10	6078484	2.57×10^{-08}	1.274	0.1910	0.043	3.04×10^{-08}	0	0.812
rs12722561	C	T	10	6109899	2.20×10^{-08}	1.240	0.3110	0.033	5.78×10^{-08}	0	0.553
rs2104286	T	C	10	6139051	3.52×10^{-10}	1.215	0.7450	0.009	1.15×10^{-08}	57.8	0.124

Table S4: Interaction analysis (p-value) results for two paired SNPs (MS GWAS obtained from dbGaP and ANZgene (cases = 3,252; controls = 5,725)). $P < 0.005$ were defined as significant after Bonferroni correction.

SNP	rs11808092	rs427221	rs2255214	rs2516049	rs12722561
rs11808092	NA	0.656	0.389	0.006	0.311
rs427221	0.656	NA	0.917	0.416	0.671
rs2255214	0.389	0.917	NA	0.177	0.158
rs2516049	0.006	0.416	0.177	NA	0.198
rs12722561	0.311	0.671	0.158	0.198	NA

Table S5 Detailed interaction results for rs2616049 (between *HLA-DRB1* and *HLA-DQA1*) and rs11808092 (*EVI5*) at each genotype level. The reference genotype is C/C-C/C

Genotype	Frequency (%)	OR (95% CI)	P-value
C/C-C/C	400 (4.5)	1.00 [Reference]	
C/C-C/A	318 (3.5)	0.83 (0.56, 1.20)	*0.47*
C/C-A/A	51 (0.6)	0.88 (0.42, 1.83)	*0.90*
C/T-C/C	2,046 (22.8)	1.63 (1.26, 2.13)	*0.11*
C/T-C/A	1,442 (16.1)	1.76 (1.34, 2.30)	*0.96*
C/T-A/A	238 (2.7)	**3.05 (2.10, 4.41)**	$\boldsymbol{6.73 \times 10^{-5}}$
T/T-C/C	2,350 (26.2)	**2.23 (1.71, 2.88)**	***0.04***
T/T-C/A	1,826 (20.4)	**2.68 (2.06,3.45)**	***0.01***
T/T-A/A	301 (3.4)	2.25 (1.59, 3.18)	*0.59*
Trend:			***P = 0.006***

Genotype presented as rs2616049 genotype/rs11808092 genotype.