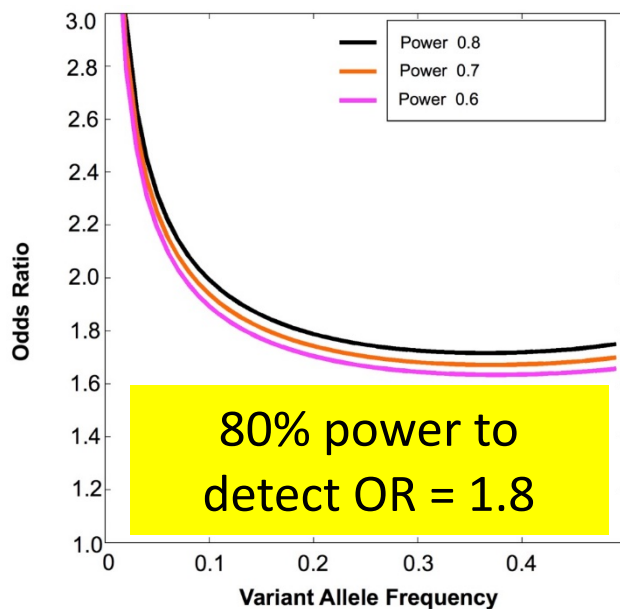
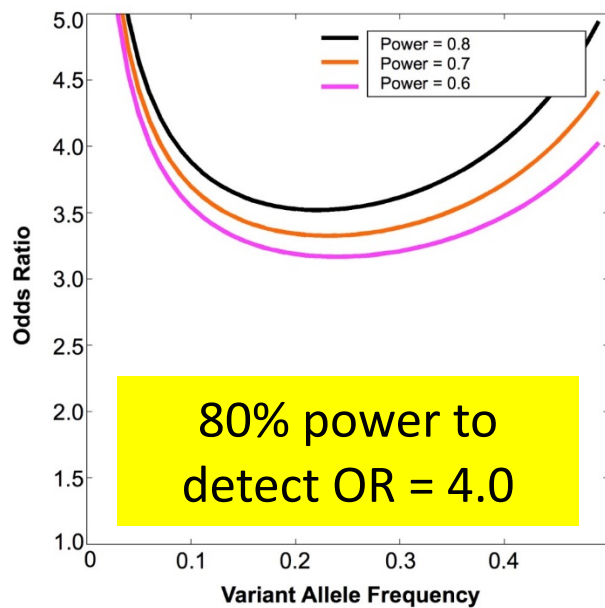


Supplementary Material

1 Supplementary Figures and Tables

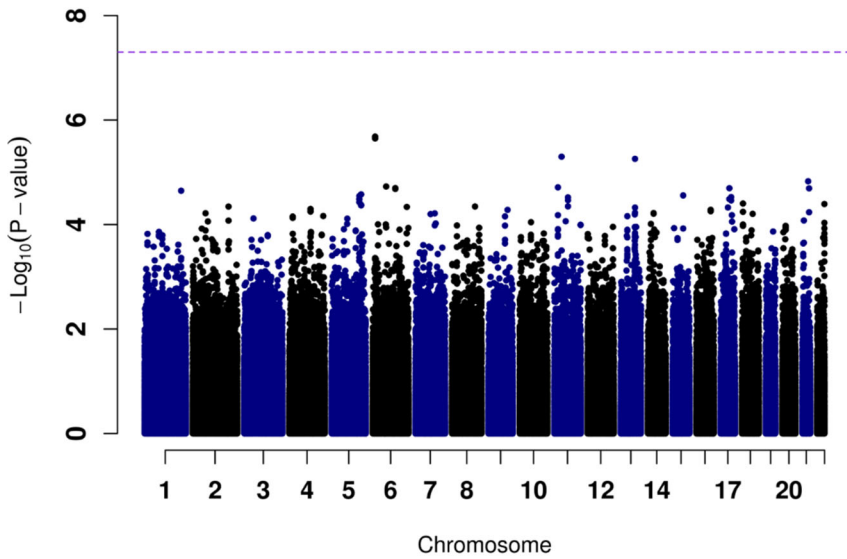
1.1 Supplementary Figures

Supplementary Figure S1 GWAS power calculations to identify clinically relevant effects in **(A)** SPL versus no lymphopenia and **(B)** SPL or MPL versus no lymphopenia.



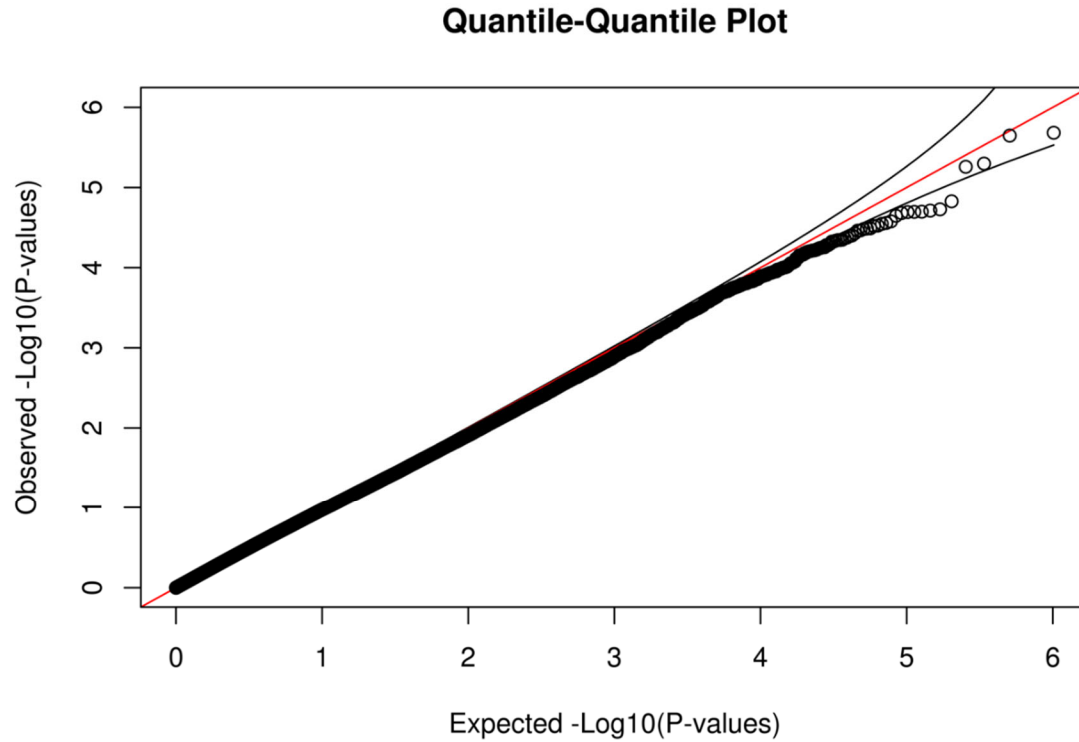
GWAS, genome-wide association study; MPL, moderate prolonged lymphopenia; OR, odds ratio; SPL, severe prolonged lymphopenia.

Supplementary Figure 2. Manhattan plot of p values for ~1 million SNPs (minor allele frequency ≥ 0.05) in a GWAS of SPL ($n = 42$) versus no lymphopenia ($n = 1,052$).



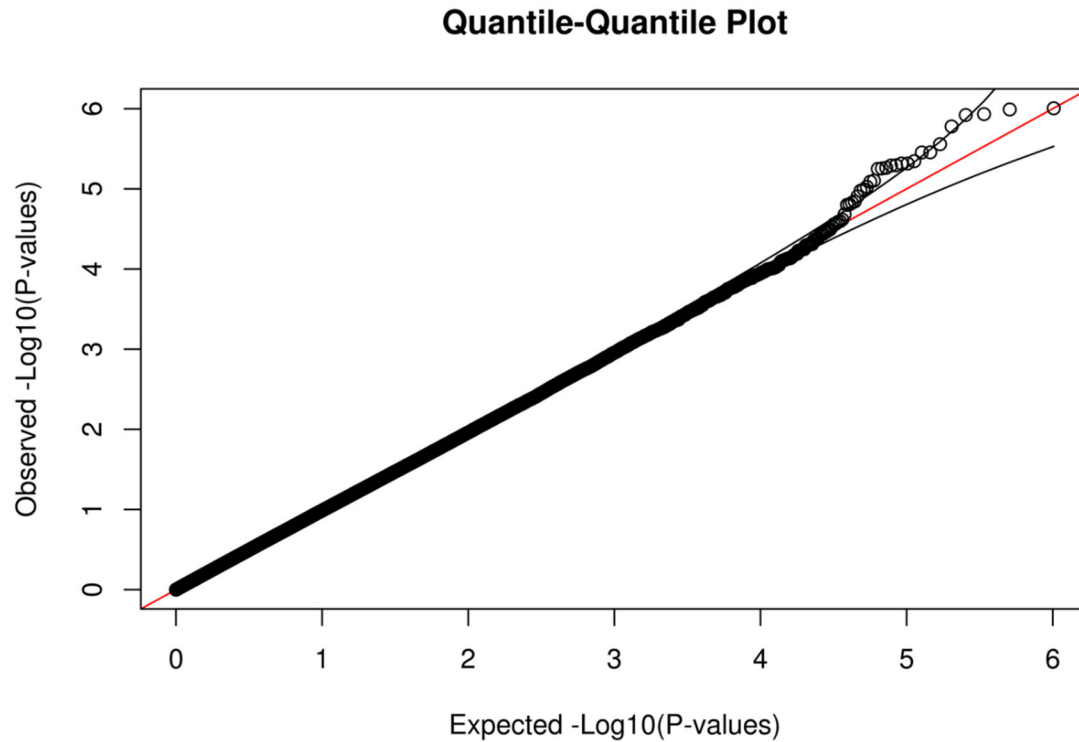
GWAS, genome-wide association study; SNP, single nucleotide polymorphism; SPL, severe prolonged lymphopenia.

Supplementary Figure 3. Quantile-quantile plot of observed versus expected p values for ~1 million SNPs (minor allele frequency ≥ 0.05) in a GWAS of SPL ($n = 42$) versus no lymphopenia ($n = 1,052$).



GWAS, genome-wide association study; SNP, single nucleotide polymorphism; SPL, severe prolonged lymphopenia.

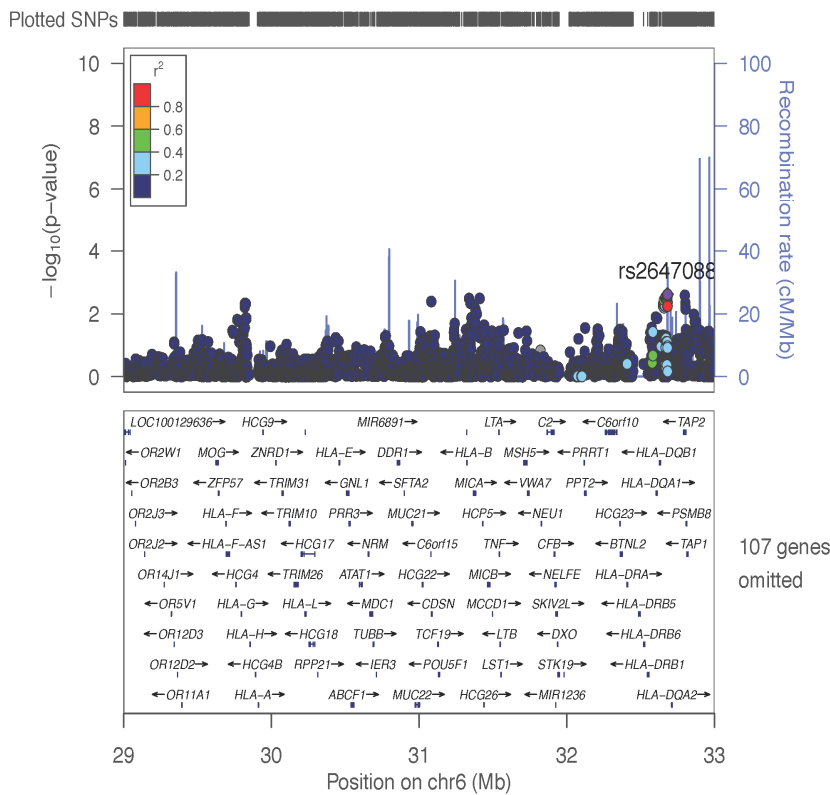
Supplementary Figure 4. Quantile-quantile plot of observed versus expected p values for ~1 million SNPs (minor allele frequency ≥ 0.05) in a GWAS of SPL or MPL ($n = 206$) versus no lymphopenia ($n = 1,052$).



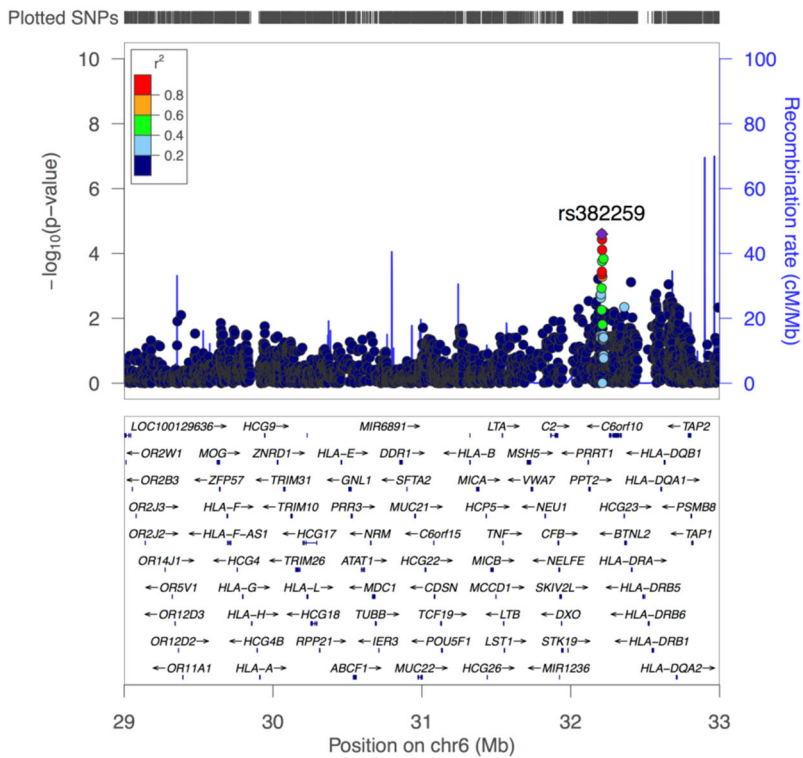
GWAS, genome-wide association study; MPL, moderate prolonged lymphopenia; SNP, single nucleotide polymorphism; SPL, severe prolonged lymphopenia.

Supplementary Figure 5. Nonsignificant peaks in the major histocompatibility complex for **(A)** SPL ($n = 42$) versus no lymphopenia ($n = 1,052$) and **(B)** SPL or MPL ($n = 206$) versus no lymphopenia ($n = 1,052$).

(A)



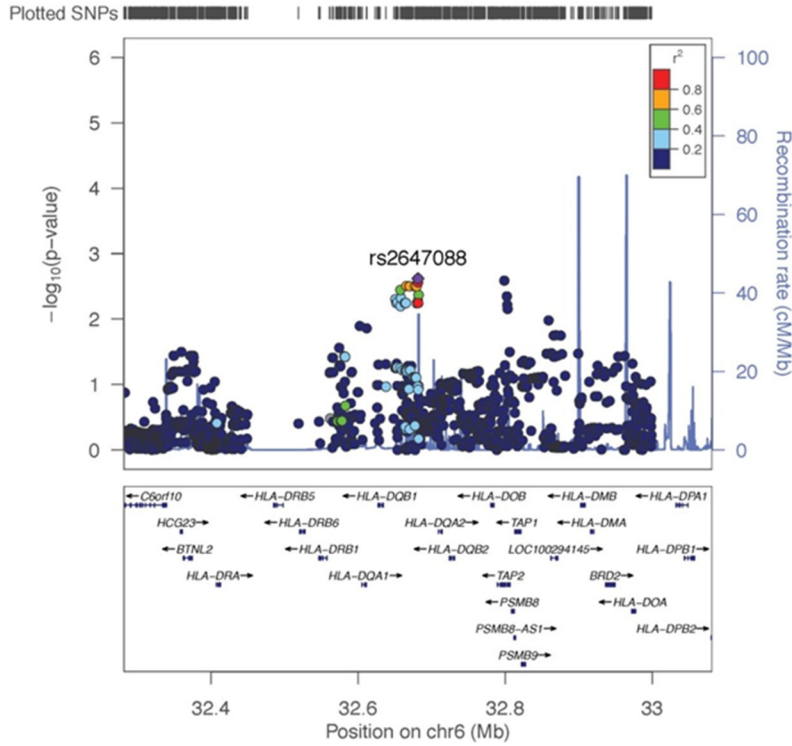
(B)



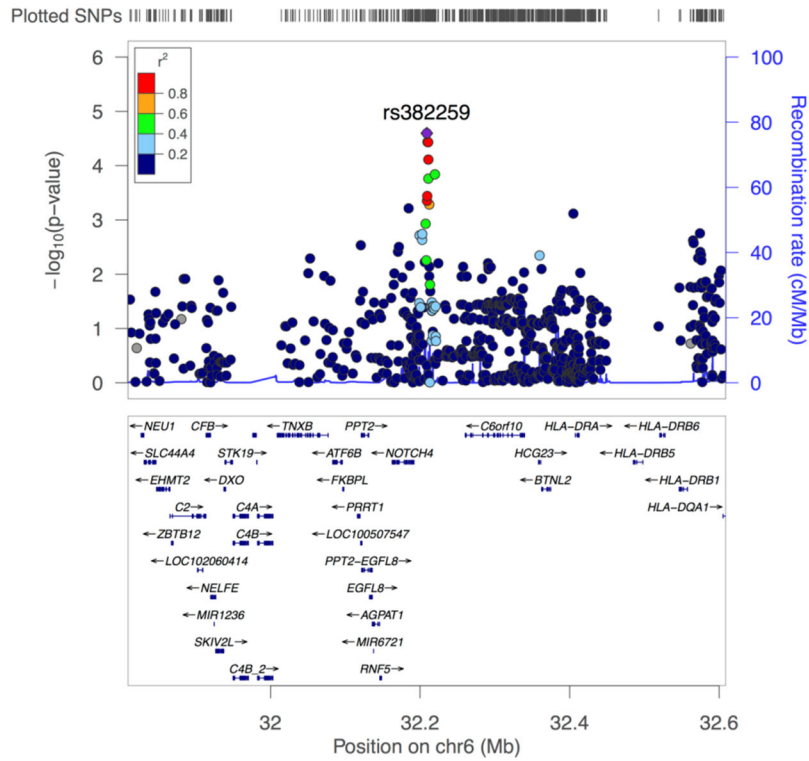
MPL, moderate prolonged lymphopenia; SPL, severe prolonged lymphopenia.

Supplementary Figure 6. Regional association plot of p values for SNPs in the major histocompatibility complex gene region on chromosome 6 (29Mb-33Mb) from a GWAS of MS cases with **(A)** SPL versus no lymphopenia (total $n = 1,094$)^a and **(B)** SPL or MPL versus no lymphopenia (total $n = 1,258$)^b.

(A)

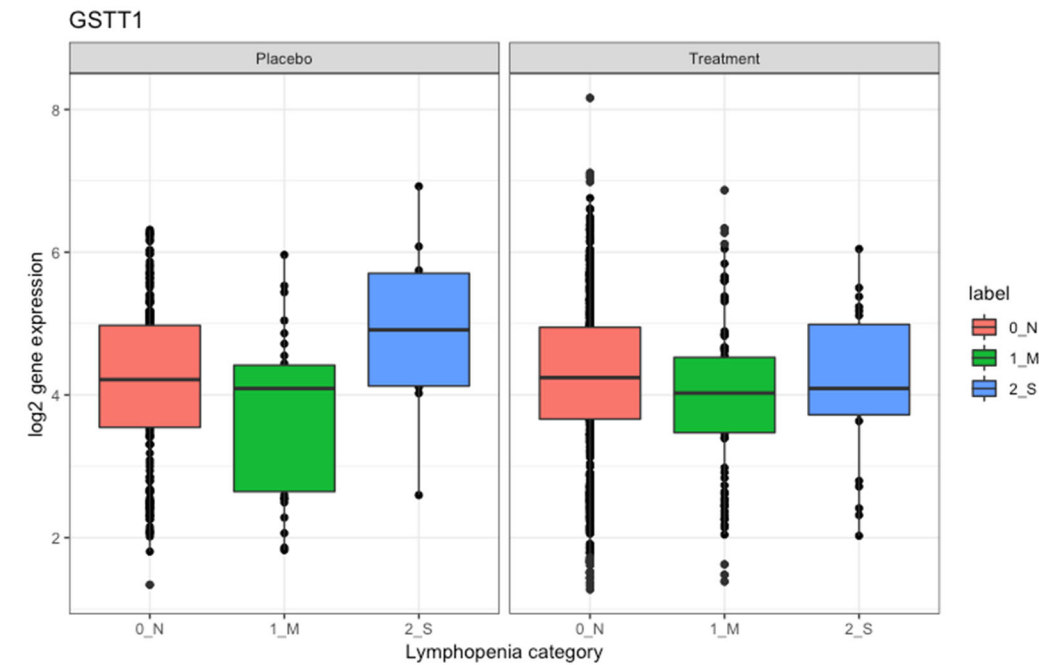


(B)



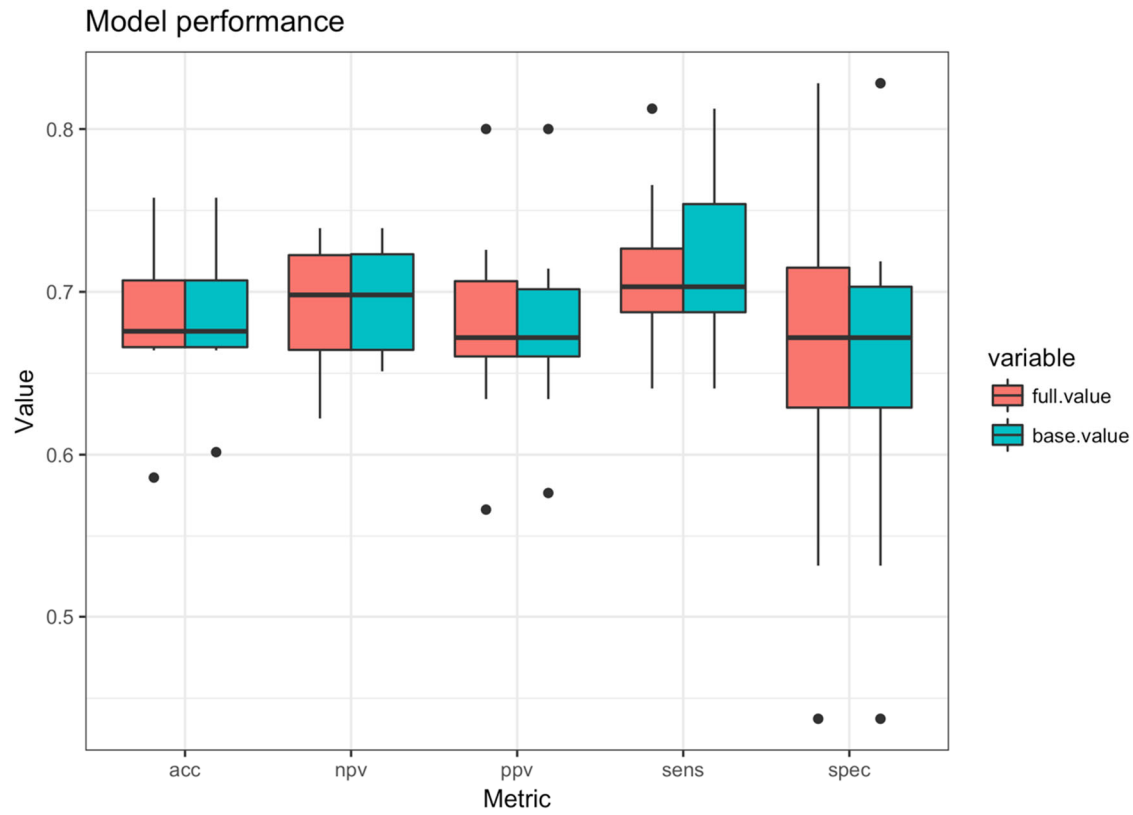
GWAS, genome-wide association study; MPL, moderate prolonged lymphopenia; SNP, single nucleotide polymorphism; SPL, severe prolonged lymphopenia. ^aOdds ratio (OR) 1.7, 95% confidence interval (CI) 1.3–2.2, $p = 2.5 \times 10^{-5}$ at rs382259 (chr6:32,209,027). ^bOR 2.1, 95% CI 1.3–3.5, $p = 2.4 \times 10^{-3}$ at rs2647088 (chr6:32,681,518).

Supplementary Figure 7. Expression of GSTT1 baseline cross-sectional association with lymphopenia severity (0_N: no lymphopenia, 1_M: moderate prolonged lymphopenia, 2_S: severe prolonged lymphopenia).



GSTT1, glutathione-S-transferase T1. Expression data for the Treatment group was collected at baseline of the DEFINE/CONFIRM trials. Expression data in the placebo group was collected at week 96 of the trials before switching to treatment in the extension study. The association with lymphopenia status was not significant ($p = 0.2$).

Supplementary Figure 8. Performance metrics comparison of the base (demographic and clinical covariates) and full (including gene expression) models (acc: accuracy; npv: negative predictive value; ppv: positive predictive value; sens: sensitivity; spec: specificity).



1.2 Supplementary Table

Table S1. Peak association regions ($p < 1e-5$) in the SPL GWAS.

SNP	Allele	p Value	OR (95% CI)	Chromosome	Region
rs9392985	A	2.3e-6	3.4 (2.0–5.6)	6	8,266,686– 8,266,858
kgp1734375	A	2.1e-6	3.4 (2.1–5.7)		
kgp4224365	G	5.0e-6	2.9 (1.8–4.6)	11	32,368,744– 32,375,669
kgp6724547	G	5.5e-6	3.8 (2.1–6.8)	13	91,979,352– 91,996,756

GWAS, genome-wide association study; OR, odd ratio; SPL, severe prolonged lymphopenia.

Table S2. Peak association regions in the SPL + MPL GWAS.

SNP	Allele	p Value	OR (95% CI)	Chromosome	Region
kgp1734375	A	2.1e-6	3.4 (2.1–5.7)	6	8,266,686– 8,266,858
kgp4224365	G	5.0e-6	2.9 (1.8–4.6)	11	32,368,744– 32,375,669
kgp6724547	G	5.5e-6	3.8 (2.1–6.8)	13	91,979,352– 91,996,756

2 Supplementary Appendix 1

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