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Supplemental Data

Common Variants of Large Effect in F12, KNG1, and HRG Are Associated with Activated Partial Thromboplastin Time

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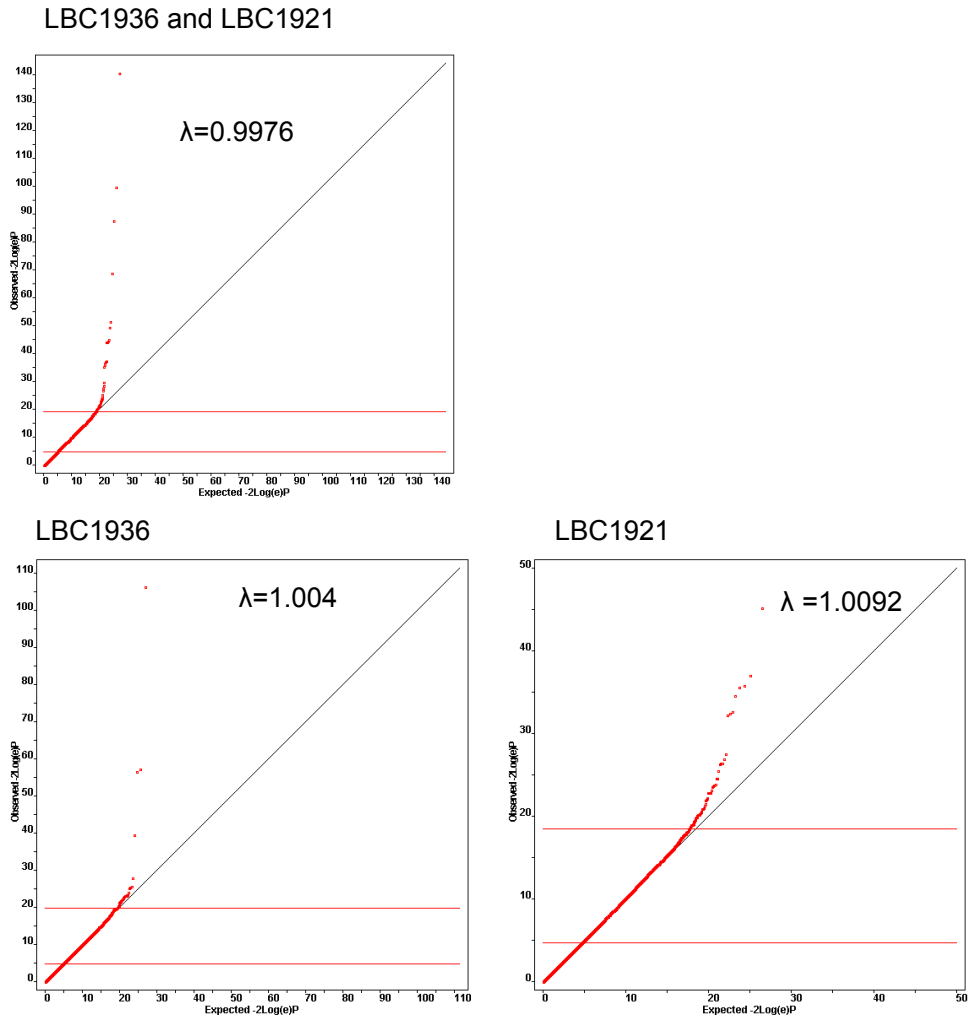
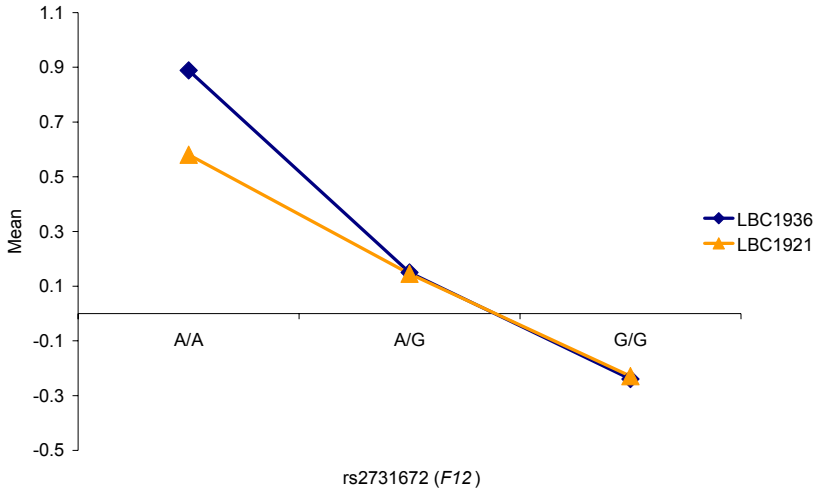
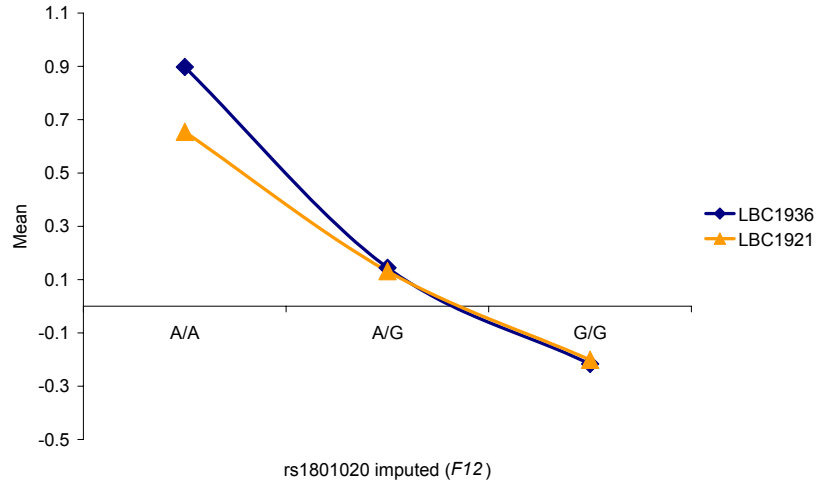


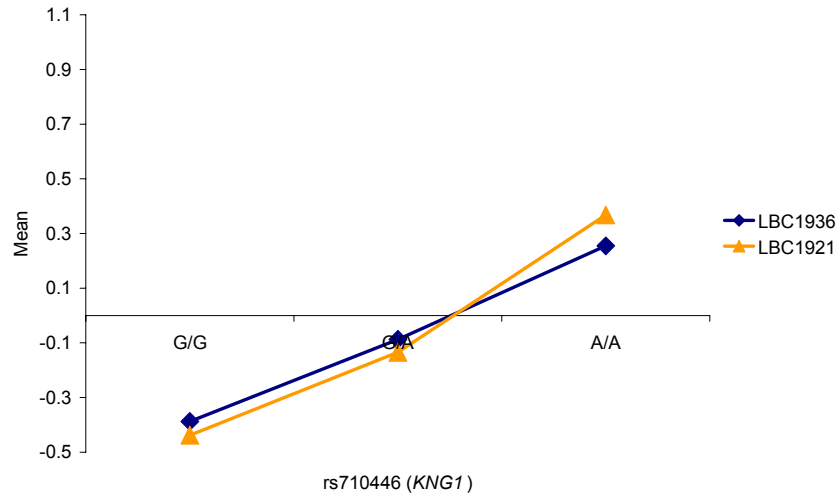
Figure S1.
Q-Q plots of the genome-wide association study *P*-values for activated partial thromboplastin time (aPTT) in Lothian Birth Cohorts together, and separately: Lothian Birth Cohort 1936 (LBC1936) (n = 989), and Lothian Birth Cohort 1921 (LBC1921) (n = 488). Y axis is the observed -2Log(P), while the X axis is the expected -2Log(P) values. The lower red line denotes the 90th percentile, while the upper one indicates the point where the *P*-values lift from the expected line. The lambda values suggest no inflation of association signals in accordance with random expectation.



rs2731672 (*F12*)



rs1801020 imputed (*F12*)



rs710446 (*KNG1*)

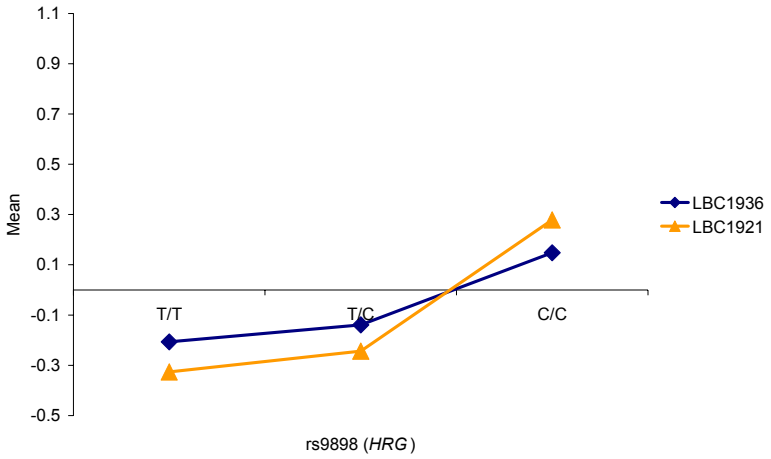


Figure S2.
The genotype means of four genome-wide significant SNPs associated with activated partial thromboplastin time (aPTT): rs2731672 (*F12*), rs1801020 (imputed *F12*), rs710446 (*KNG1*), and rs9898 (*HRG*). On the x-axis are the three genotypes, the y-axis represents aPTT, as a standardised variable having been adjusted for age and sex.

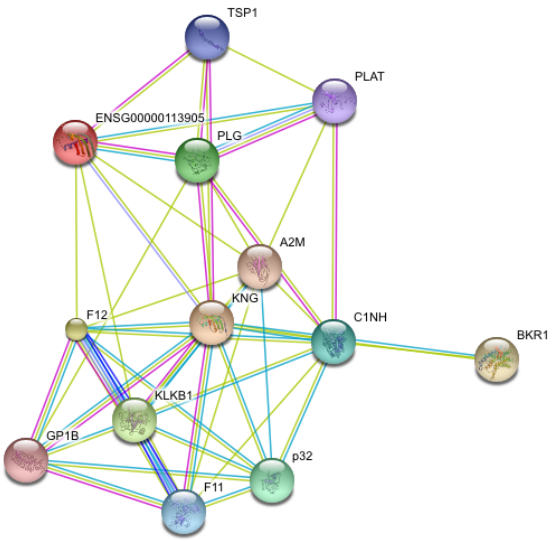


Figure S3. Pathway Analysis of *F12*, *KNG* and *HRG*
This pathway analysis was performed using String DB (Jensen et al. 2009). The three most significant genes revealed by this association analysis were entered in this database, and were found to be related to each other in annotated PubMed databases. Expanding this network reveals other members of the coagulation cascade. A2M is alpha-2-macroglobulin. BKR1 is B1 bradykinin receptor. C1NH is Plasma protease C1 inhibitor precursor. ENSG00000113905 is Histidine-rich glycoprotein precursor. F11 is Coagulation factor XI precursor. F12 is Coagulation factor XII precursor. GP1B is Platelet glycoprotein Ib alpha chain precursor. KLKB1 is Plasma kallikrein precursor. KNG is Kininogen-1 precursor. PLAT is Tissue-type plasminogen activator precursor. PLG is plasminogen. P32 is Complement component 1 Q subcomponent-binding protein, mitochondrial precursor. TSP1 is Thrombospondin-1 precursor. Green lines indicate neighbourhood connections in the genome, red lines indicate gene fusion, blue lines indicate occurrence (protein conservation/homology between organisms), black lines indicate co-expression connections, purple lines indicate expression interactions, turquoise lines indicates database evidence and khaki lines indicate text mining evidence. SNPs in and surrounding these genes were checked for association to aPTT. SNPs within *F11* show a significant association with aPTT, as described in the text.

Table S1. Descriptive Statistics of Activated Partial Thromboplastin Time (aPTT) Measures for Participants in the Genome-wide Association Analysis in the Lothian Birth Cohort (LBC1936) and the Lothian Birth Cohort 1921 (LBC1921)

	N	Minimum	Maximum	Mean	Standard Deviation
LBC1936					
aPTT ratio (0.8-1.2)	989	0.7	1.8	0.94	0.11
aPTT level (27.0-38.0 seconds)	989	21	54	28.59	3.12
LBC1921					
aPTT ratio (0.9-1.2)	488	0.63	1.63	0.91	0.13

aPTT levels were not available for LBC1921.

Table S2. Additive Effects (in SD Units) of Genome-wide Significant SNPs ($P < 5 \times 10^{-8}$) from the Lothian Birth Cohorts of 1936 and 1921 (LBC1936 and LBC1921) on the Activated Partial Thromboplastin Time (aPTT), Separately by Gender

Gene Region	Chr	SNP	MA	MAF	N	BETA	SE	R^2	P
Males									
HRG	3	rs9898	T	0.33	707	-0.32	0.054	0.047	5.47×10^{-9}
KNG1	3	rs710446	G	0.39	709	-0.37	0.054	0.062	2.12×10^{-11}
F12	5	rs2731672	A	0.27	709	0.47	0.058	0.086	2.13 a 10^{-15}
Females									
HRG	3	rs9898	T	0.32	761	-0.20	0.053	0.018	0.00025
KNG1	3	rs710446	G	0.40	768	-0.35	0.050	0.059	8.55×10^{-12}
F12	5	rs2731672	A	0.27	768	0.44	0.052	0.086	1.15×10^{-16}

Chr is chromosome. MA is the minor allele. MAF is the minor allele frequency. N is the sample size. BETA is the regression coefficient of the trait value on the number of minor alleles. R^2 is the proportion of variance explained by each SNP. The gene name in brackets is the location of the SNP.

Table S3. Comparison of the Top SNPs' Associations in the Three Genes with Activated Partial Thromboplastin Time (aPTT) in the Lothian Birth Cohorts of 1936 and 1921 (LBC1936 and LBC1921), with and without Removing Individuals with Potentially Abnormal aPTT (N = 62 LBC1936; N = 45 LBC1921)

Exclusion	Chr	SNP	N	BETA	SE	R^2	P
Joint							
Yes	3	rs9898	1365	-0.24	0.034	0.037	1.14×10^{-12}
No	3	rs9898	1468	-0.26	0.038	0.031	1.34×10^{-11}
Yes	3	rs710446	1373	-0.33	0.033	0.069	5.32×10^{-23}
No	3	rs710446	1477	-0.36	0.037	0.060	9.52×10^{-22}
Yes	5	rs2731672	1373	0.45	0.034	0.112	2.96×10^{-37}
No	5	rs2731672	1477	0.45	0.039	0.085	2.16×10^{-30}
LBC1936							
Yes	3	rs9898	925	-0.20	0.042	0.023	3.6×10^{-6}
No	3	rs9898	987	-0.20	0.047	0.018	2.2×10^{-5}
Yes	3	rs710446	927	-0.32	0.039	0.066	1.8×10^{-15}
No	3	rs710446	989	-0.33	0.044	0.052	5.0×10^{-13}
Yes	5	rs2731672	927	0.49	0.041	0.13	7.2×10^{-30}
No	5	rs2731672	989	0.49	0.047	0.096	1.6×10^{-23}
LBC1921							
Yes	3	rs9898	440	-0.33	0.057	0.071	1.3×10^{-8}
No	3	rs9898	481	-0.36	0.063	0.064	1.7×10^{-8}
Yes	3	rs710446	446	-0.35	0.059	0.075	4.5×10^{-9}
No	3	rs710446	488	-0.43	0.065	0.081	1.5×10^{-10}
Yes	5	rs2731672	446	0.38	0.060	0.080	1.1×10^{-9}
No	5	rs2731672	488	0.39	0.067	0.066	9.2×10^{-9}

Chr is chromosome. N is the sample size. BETA is the regression coefficient of the trait value on the number of minor alleles. R^2 is the proportion of variance explained by each SNP.