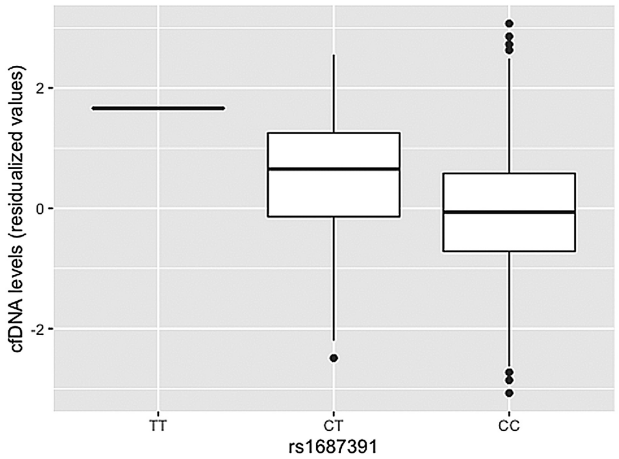
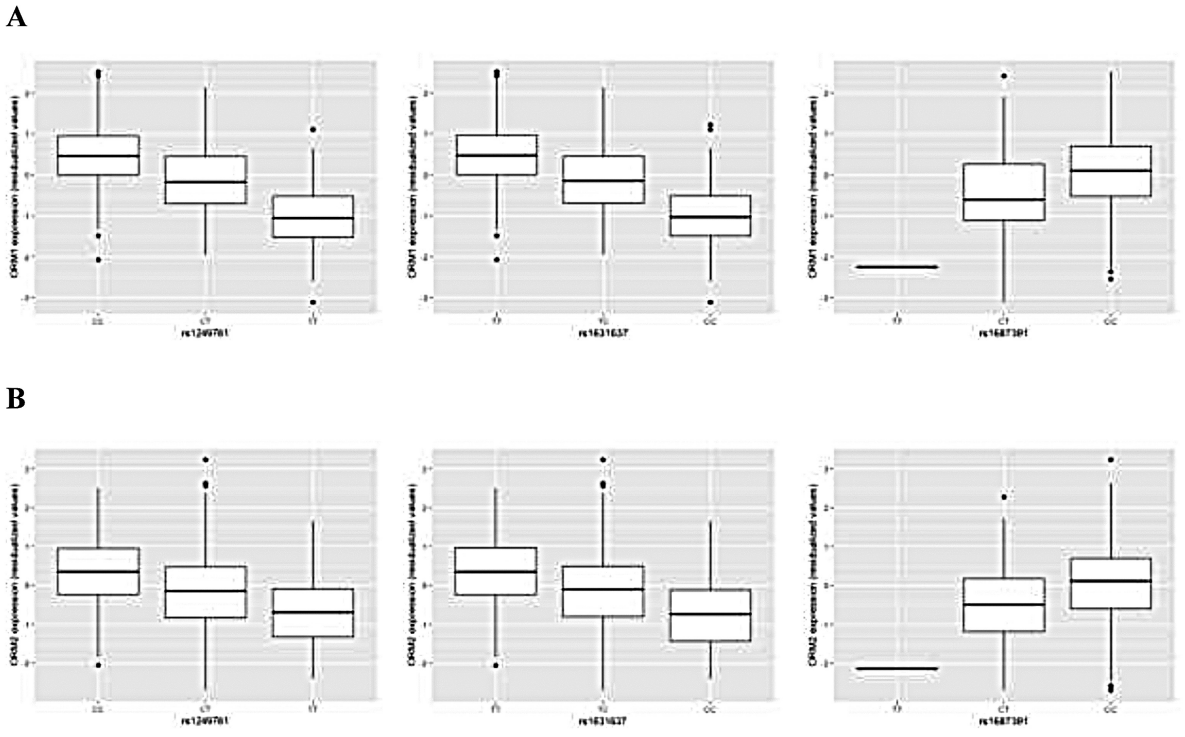
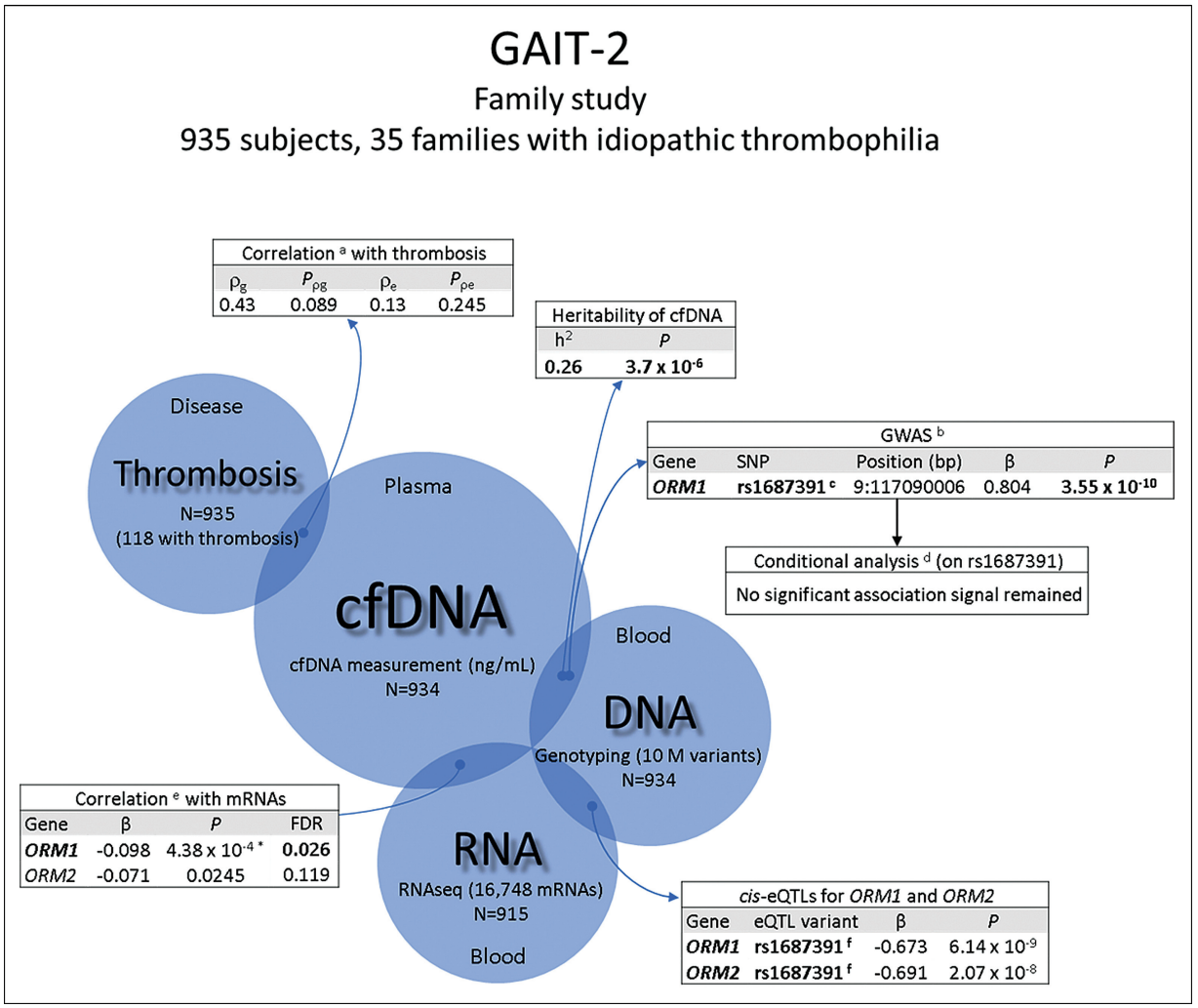


Supplementary Fig. S1 Plasma levels of cfDNA versus rs1687391 in GAIT-2. Box plot showing the association of plasma levels of cfDNA (plate-normalized cfDNA values are represented on the *y*-axis) with the genotype of the lead SNP rs1687391 (*x*-axis) identified in the GWAS for cfDNA levels in GAIT-2. The effect of the minor rs1687391-T allele on increasing the plasma levels of cfDNA is shown. cfDNA, cell-free DNA; SNP, single nucleotide polymorphism.



Supplementary Fig. S2 Box plots of *ORM1* and *ORM2* expression levels versus genotypes of most relevant *cis*-eQTL variants identified in whole blood. Box plots illustrating *ORM1* **(A)** and *ORM2* **(B)** residual expression levels (*y*-axis) as a function of the genotypes of their strongest *cis*-eQTLs (*x*-axis). From left to right, rs1249761, the lead *cis*-eQTL of *ORM1* (rs1249761-C, $\beta = 0.73$; $p = 8.17 \times 10^{-65}$) is also an eQTL of *ORM2* (rs1249761-C, $\beta = 0.53$; $p = 1.18 \times 10^{-28}$); rs1631637, the lead *cis*-eQTL of *ORM2* (rs1631637-T; $\beta = 0.53$; $p = 4.36 \times 10^{-31}$) is also an eQTL of *ORM1* (rs1631637-T; $\beta = 0.69$; $p = 2.42 \times 10^{-63}$); rs1687391, the lead SNP in our GWAS for cfDNA levels is a *cis*-eQTL for *ORM1* (rs1687391-T; $\beta = -0.673$; $p = 6.14 \times 10^{-9}$) and for *ORM2* (rs1687391-T; $\beta = -0.691$; $p = 2.07 \times 10^{-8}$). cfDNA, cell-free DNA; eQTL, expression quantitative trait loci; SNP, single nucleotide polymorphism.



Supplementary Fig. S3 Design and results of the study of cfDNA in GAIT-2. Design of an integrated genetic and transcriptomic analysis with 935 subjects from a family study of idiopathic thrombophilia (GAIT-2). cfDNA levels were measured in plasma as a marker of NETs, with the aim to identify genes that control the interindividual variability of cfDNA. Our results show evidence of the role of *ORM1* in regulating cfDNA levels in plasma, which might contribute to the susceptibility to thrombosis. cfDNA, cell-free DNA; NET, neutrophil extracellular trap. [a]Genetic and environmental correlations of cfDNA with thrombosis (including venous thrombosis, arterial thrombosis and both) in the GAIT-2 sample. A $P \leq 0.05$ was considered as significant. P_g: coefficient of genetic correlation between cfDNA and thrombosis; P_{rg}: *P* value of the genetic correlation coefficient; re: coefficient of environmental correlation between cfDNA and thrombosis; P_{re}: *P* value of the environmental correlation coefficient; *P* value ≤ 0.05 was considered as statistically significant. h^2: Heritability. [b]Genome-wide association study for cfDNA levels. A genome-wide $P \leq 5 \times 10^{-8}$ was considered statistically significant. [c]Lead SNP in the GWAS. β: Effect size of one copy of the minor allele. [d]Conditional analysis on the lead SNP rs1687391. [e]Linear associations of cfDNA levels with gene expression levels. *Significant *P* values at a FDR < 0.05. [f]The lead SNP rs1687391 is a significant cis-eQTL for both *ORM1* and *ORM2* after Bonferroni correction, considering significance at $P < 0.05/28{,}133$.

Supplementary Table S1 Genetic and environmental correlations of cfDNA levels with thrombosis in GAIT-2

Disease	ρ_g	$p_{\rho g}$	ρ_e	$p_{\rho e}$	*n* (%)[a]
Thrombosis	0.43	0.089	0.13	0.246	118 (12.62)
• VT	0.41	0.135	0.15	0.142	85 (9.09)
• AT	0.58	0.186	−0.09	0.571	47 (5.02)

Note: ρ_g: genetic correlation coefficient; $p_{\rho g}$: *p*-value of the genetic correlation coefficient; ρ_e: environmental correlation coefficient; $p_{\rho e}$: *p*-value of the environmental correlation coefficient; $p \leq 0.05$ was considered statistically significant. Thrombosis included 71 patients with VT (venous thrombosis), 33 patients with AT (arterial thrombosis), and 14 patients with both VT and AT.
[a]Total number of individuals in GAIT-2 affected with the disease. The percentage of individuals of the total sample ($n = 935$) is shown in brackets.

Supplementary Table S7 *cis*-eQTL variants overlapping with SNPs of the associated locus with cfDNA levels on chromosome 9

							GWAS data			*cis*-eQTL data for *ORM1*			*cis*-eQTL data for *ORM2*		
eQTL variant	Position (bp)[a]	eQTL Location	eQTL type	Alleles[b]	Minor Allele	MAF[c]	p[d]	β[e]	Var[f]	Distance from TSS (bp)	β[e]	p[g]	Distance from TSS (bp)	β[e]	p[g]
rs1687391[h]	117090006	*ORM1*	Intergenic	C/T	T	0.057	3.54×10^{-10}	0.804	0.0495	4,670	−0.673	6.14×10^{-9}	−2,143	−0.691	2.07×10^{-8}
rs10982163[h]	117091033	*ORM2*	Intergenic	G/T/A	T	0.059	9.77×10^{-10}	0.764	0.0473	5,697	−0.658	5.32×10^{-9}	−1,116	−0.697	6.14×10^{-9}
rs10982164[h]	117091067	*ORM2*	Intergenic	G/A	A	0.058	9.8×10^{-10}	0.764	0.0472	5,731	−0.658	5.26×10^{-9}	−1,082	−0.697	6.0×10^{-9}
rs112164771[h]	117091002	*ORM2*	Intergenic	C/T/A	T	0.059	1.25×10^{-9}	0.759	0.0469	5,666	−0.661	4.3×10^{-9}	−1,147	−0.690	8.16×10^{-9}
rs1687390	117089888	*ORM1*	Intergenic	G/A	A	0.063	3.59×10^{-9}	0.711	0.0442	4,552	−0.649	1.76×10^{-9}	−2,261	−0.712	5.29×10^{-10}
rs7040440[i]	117091074	*ORM2*	Intergenic	C/T/G	T	0.068	3.97×10^{-9}	0.679	0.0427	5,738	−0.538	2.17×10^{-7}	−1,075	−0.560	4.04×10^{-7}
rs146077223[h]	117089921	*ORM1*	Intergenic	G/T	T	0.063	7.98×10^{-9}	0.697	0.0425	4,585	−0.643	2.70×10^{-9}	−2,228	−0.706	7.77×10^{-10}
rs3762056[h]	117090434	*ORM2*	Intergenic	C/T	T	0.063	8.10×10^{-9}	0.696	0.0425	5,098	−0.640	2.99×10^{-9}	−1,715	−0.707	7.2×10^{-10}
rs10982154[h]	117087212	*ORM1*	Intron	T/A	A	0.063	9.67×10^{-9}	0.693	0.0419	1,876	−0.647	2.05×10^{-9}	−4,937	−0.704	8.79×10^{-10}
rs10982155[h]	117087254	*ORM1*	Intron	C/T	T	0.063	9.68×10^{-9}	0.693	0.0419	1,918	−0.647	2.07×10^{-9}	−4,895	−0.704	8.79×10^{-10}
rs145835687	117087745	*ORM1*	Intron	G/A/T	A	0.063	9.84×10^{-9}	0.692	0.0419	2,409	−0.645	2.25×10^{-9}	−4,404	−0.703	9.0×10^{-10}
rs10982156[h]	117088064	*ORM1*	Intron	T/A	A	0.063	1.0×10^{-8}	0.691	0.0418	2,728	−0.643	2.38×10^{-9}	−4,085	−0.702	9.25×10^{-10}
rs3762055[i]	117090575	*ORM2*	Intergenic	T/C	C	0.063	1.09×10^{-8}	0.686	0.0416	5,239	−0.633	3.72×10^{-9}	−1,574	−0.695	1.12×10^{-9}
rs116994374[i]	117084672	*ORM1*	Intergenic	G/A	A	0.062	1.73×10^{-8}	0.693	0.0395	−664	−0.688	3.58×10^{-10}	−7,477	−0.793	1.03×10^{-11}
rs113354603[i]	117086241	*ORM1*	Intron	G/A	A	0.066	1.76×10^{-8}	0.665	0.0391	905	−0.561	1.16×10^{-7}	−5,908	−0.632	1.99×10^{-8}
rs188924106	117084722	*ORM1*	Intergenic	G/A	A	0.062	2.06×10^{-8}	0.689	0.0392	−614	−0.684	4.6×10^{-10}	−7,427	−0.795	8.53×10^{-12}
rs150611042[h]	117083803	*ORM1*	Intergenic	C/A/T	A	0.063	3.07×10^{-8}	0.679	0.0379	−1,533	−0.675	7.25×10^{-10}	−8,346	−0.779	2.20×10^{-11}
rs140041983[h]	117084971	*ORM1*	Intergenic	C/G/T	G	0.054	1.15×10^{-7}	0.700	0.0357	−365	−0.713	1.35×10^{-9}	−7,178	−0.830	3.05×10^{-11}
rs7851482[h]	117078286	*COL27A1*	Intergenic	T/G	G	0.398	1.64×10^{-6}	−0.260	0.0232	−7,050	0.623	1.26×10^{-43}	−13,863	0.504	7.24×10^{-25}
rs11787950[h]	117072382	*COL27A1*	Intron	G/A	A	0.471	1.80×10^{-6}	−0.248	0.0249	−12,954	0.571	7.88×10^{-39}	−19,767	0.491	3.22×10^{-25}
rs1249756[h]	117073006	*COL27A1*	3′UTR	C/T	T	0.372	4.17×10^{-6}	−0.234	0.0241	−12,330	0.677	2.98×10^{-59}	−19,143	0.521	8.75×10^{-30}
rs9299216[h]	117078173	*COL27A1*	Intergenic	A/T	T	0.351	4.22×10^{-6}	−0.244	0.0236	−7,163	0.727	2.49×10^{-62}	−13,976	0.556	9.9×10^{-31}
rs1631637[h]	117076684	*COL27A1*	Intergenic	T/C	C	0.349	4.97×10^{-6}	−0.229	0.0236	−8,652	0.692	2.42×10^{-63}	−15,465	0.528	4.36×10^{-31}
rs1766082[h]	117077326	*COL27A1*	Intergenic	G/T	T	0.347	5.30×10^{-6}	−0.231	0.0233	−8,010	0.701	9.65×10^{-64}	−14,823	0.529	1.34×10^{-30}
rs1249760[h]	117070767	*COL27A1*	Intron	C/A/T	A	0.341	6.6×10^{-6}	−0.236	0.0223	−14,569	0.724	3.98×10^{-64}	−21,382	0.541	4.0×10^{-30}
rs1249761[h]	117069223	*COL27A1*	Intron	C/T	T	0.338	7.98×10^{-6}	−0.234	0.0226	−16,113	0.730	8.17×10^{-65}	−22,926	0.530	1.18×10^{-28}
rs2787334[h]	117078838	*COL27A1*	Intergenic	C/T/G	T	0.395	2.60×10^{-5}	−0.228	0.0170	−6,498	0.641	4.08×10^{-45}	−13,311	0.492	3.72×10^{-23}
rs1000744[h]	117072656	*COL27A1*	Intron	C/A	A	0.454	5.30×10^{-5}	−0.223	0.0200	−12,680	0.657	8.88×10^{-45}	−19,493	0.420	3.65×10^{-16}
rs111548718[i]	117067888	*COL27A1*	Intron	G/C/A	C	0.113	5.60×10^{-5}	0.349	0.0223	−17,448	−0.742	1.26×10^{-22}	−24,261	−0.602	1.59×10^{-13}

Supplementary Table S7 (*Continued*)

							GWAS data			*cis*-eQTL data for *ORM1*			*cis*-eQTL data for *ORM2*		
eQTL variant	Position (bp)[a]	eQTL Location	eQTL type	Alleles[b]	Minor Allele	MAF[c]	p[d]	β[e]	Var[f]	Distance from TSS (bp)	β[e]	p[g]	Distance from TSS (bp)	β[e]	P[g]
rs1249751[h]	117065812	*COL27A1*	Intron	G/C	C	0.38	6.10×10^{-5}	−0.211	0.0188	−19,524	0.628	3.06×10^{-45}	−26,337	0.466	1.1×10^{-21}
rs2636881[h]	117080388	*ORM1*	Intergenic	A/G	G	0.245	7.60×10^{-5}	0.241	0.0176	−4,948	−0.552	2.90×10^{-25}	−11,761	−0.526	2.23×10^{-20}
rs2993412[h]	117091499	*ORM2*	Intergenic	A/C	C	0.26	2.84×10^{-4}	0.208	0.0145	6,163	−0.431	4.15×10^{-17}	−650	−0.416	2.68×10^{-14}
rs1249753[h]	117064559	*COL27A1*	Intron	C/A/T/G	A	0.415	4.45×10^{-4}	0.178	0.0145	−20,777	0.541	9.64×10^{-36}	−27,590	0.392	9.5×10^{-17}
rs10982136[i]	117058723	*COL27A1*	Intron	A/G	G	0.145	1.28×10^{-3}	0.249	0.0146	−26,613	−0.561	6.08×10^{-16}	−33,426	−0.459	6.52×10^{-10}

Abbreviations: COL27A1, collagen type XXVII α 1; eQTL, expression quantitative trait loci; eQTL location, indicates the closest gene to the eQTL variant; ORM1, orosomucoid 1; ORM2, orosomucoid 2; TSS, transcription start site.

Note: eQTL variants without footnote indicate they were not found in GTEx either directly or through a proxy.

[a]Position (bp) was based on the human GRCh37/hg19 assembly.

[b]Alleles aligned to + strand. Underlined alleles are very rare alleles in some populations, with minor allele frequency (MAF) < 0.01, not present in our sample.

[c]Minor allele frequency of the SNP.

[d]*p*-Value of the association with cfDNA levels. Genome-wide significant threshold was set at $p \leq 5 \times 10^{-8}$.

[e]Effect size of a single risk allele.

[f]Percentage of the variance in cfDNA levels that is explained by the effect of one copy of the rare allele.

[g]Nominal *p*-values of *cis*-eQTL variants. Significance was considered after Bonferroni correction at $p < 0.05/28{,}133$.

[h]Indicates the eQTL variants that were found also in GTEx as significant *cis*-eQTLs for both *ORM1* and *ORM2*.

[i]Indicates the eQTL variants that were found also in GTEx as significant *cis*-eQTLs for *ORM2* only.