Insights into the genetic architecture of haematological traits from deep phenotyping and whole-genome sequencing for two Mediterranean isolated populations

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Supplementary Tables

Supplementary Table 1. Variable transformations, outlier exclusions and covariates used for phenotype preparation for genome-wide association analysis

Trait	Short name	Outlier exclusion	Transformation	Covariates sex	age	age^2
white blood cell count	wbc	4SD*	none	yes	yes	no
red blood cell count	rbc	4SD	none	yes	yes	yes
haemoglobin	hgb	4SD	none	yes	yes	yes
hematocrit	hct	4SD	none	yes	yes	yes
mean corpuscular volume	mcv	none	rbin	yes	yes	yes
mean corpuscular hemoglobin	mch	none	rbin	yes	yes	yes
mean corpuscular hemoglobin concentration	mchc	4SD	none	yes	yes	no
platelet count	plt	4SD	none	yes	yes	no
red cell distribution width	rdw	none	rbin	yes	yes	no
platelet distribution width	pdw	none	ln	yes	no	no
mean platelet volume	mpv	4SD	none	yes	yes	no
plateletcrit	pct	4SD	none	yes	yes	no
large platelet distribution ratio	lpcr	4SD	none	yes	no	no
granulocyte count	gran	4SD	ln	yes	yes	yes
lymphocyte count	lym	<0.5	ln	yes	yes	yes
neutrophil count	neut	<0.23	ln	yes	yes	yes
mixed cell count	mid/mxd	>1.1	none	yes	yes	yes

* values that were more than 4 standard deviations (SD) larger or smaller than the mean

Supplementary Table 2. Functional annotation of previously unreported variants that were significantly associated with haematological traits and the rest of variants in the corresponding credible sets.

Credible set	rsID	Chr	Position	Nearest gene	Distance	Function	CADD	RDB	minChrState	commonChrState	Enhancer
Pomak - WBC	-	2	81484692	-	-	-	-	-	-	-	-
	-	2	81745516	-	-	-	-	-	-	-	-
	-	2	81759339	-	-	-	-	-	-	-	-
	-	2	81954850	-	-	-	-	-	-	-	-
	-	2	82175950	-	-	-	-	-	-	-	-
	-	2	82474919	-	-	-	-	-	-	-	-
	-	2	82654646	-	-	-	-	-	-	-	-
	-	2	82697	-	-	-	-	-	-	-	-
	rs7394178	2	82835859	AC098817.3	16594	intergenic	0.322	0.41041	5	15	-
	rs190806297	2	83537814	AC010744.1	14311	intergenic	6.931	0.32023	9	15	-
	rs140340075	2	83662388	-	-	-	-	0.66931	-	-	-
	rs188113595	2	83930989	AC104395.1	52435	intergenic	1.752	0.13454	14	15	-
	-	2	84150305	-	-	-	-	-	-	-	-
	-	2	84159599	-	-	-	-	-	-	-	-
	-	2	84341799	-	-	-	-	-	-	-	-
	-	2	84464726	-	-	-	-	-	-	-	-
	-	2	84535445	-	-	-	-	-	-	-	-
	-	2	82642216	-	-	-	-	-	-	-	-
	-	2	82318904	-	-	-	-	-	-	-	-
	-	2	82307777	-	-	-	-	-	-	-	-
Pomak - RDW	rs145221983	9	110885694	LPAR1	0	intronic	-	0.96117	-	-	-
	-	9	111255116	-	-	-	-	-	-	-	-
	-	9	111297888	-	-	-	-	-	-	-	-
	-	9	111369858	-	-	-	-	-	-	-	-
	-	9	111775585	-	-	-	-	-	-	-	-
	rs182113470	9	111881162	UGCG	15603	intergenic	9.204	0.18412	5	15	-
	-	9	112005782	-	-	-	-	-	-	-	-
	-	9	112103327	-	-	-	-	-	-	-	-
	rs138523839	9	112122739	SUSD1	0	intronic	-	0.52984	-	-	-
	-	9	112317999	-	-	-	-	-	-	-	-

-	9	112319793	-	-	-	-	-	-	-	-
rs77635713	9	106600661	RP11-308N19.1	0	ncRNA_intronic	11.43	0.13454	9	15	-
rs74462705	9	106627773	RP11-308N19.4	0	ncRNA_intronic	0.253	0.00545	5	15	-
rs111665332	9	106919659	ZNF462	0	intronic	-	0.13454	-	-	-
-	9	107190792	-	-	-	-	-	-	-	-
-	9	107196770	-	-	-	-	-	-	-	-
rs117587268	9	107332803	-	-	-	-	0.58955	-	-	-
-	9	107571052	-	-	-	-	-	-	-	-
-	9	108623836	-	-	-	-	-	-	-	-
-	9	108880384	-	-	-	-	-	-	-	-
-	9	109419994	-	-	-	-	-	-	-	-
-	9	109533768	-	-	-	-	-	-	-	-
-	9	109549645	-	-	-	-	-	-	-	-
rs138963580	9	109592925	PALM2	47862	intergenic	1.102	0.13454	5	15	-
-	9	109723269	-	-	-	-	-	-	-	-
-	9	109725304	-	-	-	-	-	-	-	-
rs141803223	9	109874774	PALM2	0	intronic	-	0.00167	-	-	-
-	9	110077259	-	-	-	-	-	-	-	-
-	9	110120344	-	-	-	-	-	-	-	-
-	9	110234106	-	-	-	-	-	-	-	-
-	9	110495617	-	-	-	-	-	-	-	-
rs189173017	9	110453573	SVEP1	0	intronic	4.766	0.15676	4	15	-
rs201551854	9	110423173	SVEP1	0	intronic	-	1.0	-	-	-
-	9	111362114	-	-	-	-	-	-	-	-
-	9	111383838	-	-	-	-	-	-	-	-
-	9	111199635	-	-	-	-	-	-	-	-
-	9	107250353	-	-	-	-	-	-	-	-
-	9	85709292	-	-	-	-	-	-	-	-
-	9	85967943	-	-	-	-	-	-	-	-
-	9	86306598	-	-	-	-	-	-	-	-
-	9	96719475	-	-	-	-	-	-	-	-

		968687								
-	9	42	-	-	-	-	-	-	-	-
		969587								
-	9	74	-	-	-	-	-	-	-	-
		970864								
-	9	31	-	-	-	-	-	-	-	-
		972899								
-	9	04	-	-	-	-	-	-	-	-
		973044								
-	9	95	-	-	-	-	-	-	-	-
		974949								
-	9	30	-	-	-	-	-	-	-	-
		976359								
-	9	38	-	-	-	-	-	-	-	-
		976940								
-	9	03	-	-	-	-	-	-	-	-
		979516								
-	9	78	-	-	-	-	-	-	-	-
		982485								
-	9	33	-	-	-	-	-	-	-	-
		100892								
-	9	323	-	-	-	-	-	-	-	-
		101096								
-	9	088	-	-	-	-	-	-	-	-
		101404								
-	9	065	-	-	-	-	-	-	-	-
		101924								
-	9	769	-	-	-	-	-	-	-	-
		102174								
-	9	037	-	-	-	-	-	-	-	-
		102216								
-	9	094	-	-	-	-	-	-	-	-
		102423								
-	9	847	-	-	-	-	-	-	-	-
		102561								
-	9	755	-	-	-	-	-	-	-	-
		102562								
-	9	060	-	-	-	-	-	-	-	-
		102636								
-	9	296	-	-	-	-	-	-	-	-
		102937								
-	9	004	-	-	-	-	-	-	-	-
		103166								
-	9	715	-	-	-	-	-	-	-	-
		103457								
-	9	924	-	-	-	-	-	-	-	-
		103469								
-	9	106	-	-	-	-	-	-	-	-
		103479								
-	9	069	-	-	-	-	-	-	-	-
		103682								
-	9	658	-	-	-	-	-	-	-	-
		103776								
-	9	239	-	-	-	-	-	-	-	-
		103832								
-	9	805	-	-	-	-	-	-	-	-
		103884								
-	9	030	-	-	-	-	-	-	-	-
		103929								
-	9	450	-	-	-	-	-	-	-	-
		103938								
-	9	082	-	-	-	-	-	-	-	-

	rs14427		103944		1500			0.18			
	4933	9	315	SMC2	00	intergenic	-	412	-	-	-
	rs18675		103979		1150			0.18			
	2055	9	368	SMC2	00	intergenic	-	412	-	-	-
			104080								
	-	9	610	-	-	-	-	-	-	-	-
			104189								
	-	9	862	-	-	-	-	-	-	-	-
			104219								
	-	9	362	-	-	-	-	-	-	-	-
			104223								
	-	9	472	-	-	-	-	-	-	-	-
	rs19956		104786				8.5	0.18			
	2704	9	394	ABCA1	0	intronic	26	412	4	4	-
			105164								
	-	9	953	-	-	-	-	-	-	-	-
	rs20134		105477					0.48			
	3203	9	274	FSD1L	0	intronic	-	029	-	-	+
	rs18828		105670				1.1	0.13			
	0004	9	420	TAL2	7333	intergenic	77	454	5	15	+
	rs18686		105725				1.8	0.54			
	8542	9	513	TMEM38B	0	intronic	76	97	4	15	+
			105756								
	-	9	160	-	-	-	-	-	-	-	-
			105801								
	-	9	547	-	-	-	-	-	-	-	-
			106070								
	-	9	662	-	-	-	-	-	-	-	-
Poma	rs73183	2	584783					0.88			
k -	273	0	56	APCDD1L	0	intronic	-	155	-	-	-
PDW		2	586546								
	-	0	96	-	-	-	-	-	-	-	-
		2	586576								
	-	0	72	-	-	-	-	-	-	-	-
		2	587901								
	-	0	84	-	-	-	-	-	-	-	-
	rs19071	2	586852	STX16-			7.5				
	1845	0	86	NPEPL1	0	intronic	62	1.0	4	5	-
	rs11711	2	587963		1248		2.4	0.58			
	2030	0	10	PIEZO1P2	7	intergenic	91	955	5	14	-
		2	587049								
	-	0	21	-	-	-	-	-	-	-	-
Man		1	101913								
olis -	-	5	651	-	-	-	-	-	-	-	-
RBC		1	101904								
	-	5	736	-	-	-	-	-	-	-	-

Chr: chromosome
Position: position on hg19
NearestGene: The nearest Gene of the SNP based on ANNOVAR annotations.
Distance: Distance to the nearest gene. SNPs which are locating in the gene body or 1kb up- or down-stream of TSS or TES have 0.
Function: Functional consequence of the SNP on the gene obtained from ANNOVAR.
CADD: CADD score which is computed based on 63 annotations.
RDB: RegulomeDB probability score (ranging from 0 to 1). 1 is the highest score that the SNP has the most biological evidence to be regulatory element.
minChrState: The minimum 15-core chromatin state across 127 tissue/cell type.
commonChrState: The most common 15-core chromatin state across 127 tissue/cell types.
Enhancer: Overlap with enhancer histone site, active in blood.

79 **Supplementary Table 3. Results of the credible sets in the latest GWAS of blood traits.**

						Astle et al. 2016 [PMID: 27863252]				HELIC [this study]			
Trait	**rsID**	**Chr**	**Position (b37)**	**REF**	**ALT**	**ALT_FREQ**	**Beta**	**SE**	**P**	**ALT_FREQ**	**Beta**	**SE**	**P**
Pomak													
white blood cell count	rs551751343*	2	81711816	C	T	0.0005	0.05	0.13	0.688	0.004	1.72	0.29	4.14E-09
	rs73941786	2	83062983	A	C	0.0046	-0.07	0.03	0.017	0.004	1.72	0.29	4.14E-09
	rs190806297*	2	83764938	G	A	0.0006	-0.20	0.11	0.066	0.004	1.72	0.29	4.14E-09
	rs140340075*	2	83889512	A	C	0.0003	-0.01	0.16	0.929	0.004	1.72	0.29	4.14E-09
	rs188113595*	2	84158113	C	T	0.0005	-0.12	0.11	0.280	0.004	1.72	0.29	4.14E-09
	rs548781149*	2	84386723	C	T	0.0003	0.23	0.18	0.203	0.004	1.72	0.29	4.14E-09
	rs531231069	2	82869328	T	C	0.0010	-0.10	0.08	0.188	0.005	1.45	0.26	2.52E-08
red cell distribution width	rs182113470	9	114643442	A	G	0.0015	0.09	0.06	0.167	0.002	-2.64	0.39	3.92E-11
	rs138523839	9	114885019	A	G	0.0014	-0.01	0.06	0.833	0.002	-2.64	0.39	3.92E-11
	rs77635713	9	109362942	C	T	0.0121	-0.01	0.02	0.680	0.003	-2.47	0.37	1.01E-10
	rs74462705	9	109390054	G	A	0.0122	0.00	0.02	0.870	0.003	-2.47	0.37	1.01E-10
	rs117587268	9	110095084	C	G	0.0011	0.02	0.06	0.792	0.003	-2.26	0.35	2.30E-10
	rs773501657	9	111386116	G	A	0.0003	-0.21	0.14	0.144	0.003	-2.05	0.32	3.06E-10
	rs538815382	9	112182274	G	A	0.0002	-0.27	0.15	0.067	0.003	-2.05	0.32	3.06E-10
	rs141803223	9	112637054	A	G	0.0004	-0.01	0.10	0.914	0.003	-2.05	0.32	3.06E-10
	rs189173017*	9	113215853	A	G	0.0045	0.01	0.03	0.588	0.004	-1.89	0.30	8.42E-10
	rs369702397	9	114124394	A	G	0.0012	0.05	0.06	0.372	0.004	-1.94	0.32	2.31E-09
	rs545561131	9	114146118	C	T	0.0012	0.06	0.06	0.342	0.004	-1.94	0.32	2.31E-09
	rs562693440	9	113961915	C	A	0.0015	0.00	0.06	0.977	0.004	-1.83	0.30	2.88E-09
	rs565079224	9	110012634	G	A	0.0130	-0.03	0.02	0.127	0.004	-1.76	0.29	3.20E-09
	rs569248438	9	100713960	C	T	0.0011	0.02	0.06	0.737	0.002	-2.36	0.39	3.89E-09
	rs568091454	9	104687051	G	A	0.0019	0.03	0.05	0.565	0.002	-2.36	0.39	3.89E-09
	rs530417185	9	104936319	T	C	0.0016	0.02	0.05	0.749	0.002	-2.36	0.39	3.89E-09
	rs555777146	9	105398578	T	C	0.0021	0.04	0.05	0.424	0.002	-2.36	0.39	3.89E-09

	rs559968830	9	105699286	G	A	0.0006	0.15	0.10	0.118	0.002	-2.36	0.39	3.89E-09
	rs575509433	9	106444940	T	C	0.0005	0.00	0.09	0.957	0.002	-2.36	0.39	3.89E-09
	rs562943353	9	106646311	A	G	0.0016	0.00	0.05	0.980	0.002	-2.36	0.39	3.89E-09
	rs569604024	9	106691731	A	G	0.0006	0.04	0.09	0.605	0.002	-2.36	0.39	3.89E-09
	rs144274933	9	106706596	C	T	0.0007	0.02	0.07	0.822	0.002	-2.36	0.39	3.89E-09
	rs186752055	9	106741649	A	G	0.0008	0.02	0.06	0.753	0.002	-2.36	0.39	3.89E-09
	rs574569400	9	106842891	G	A	0.0008	0.02	0.06	0.729	0.002	-2.36	0.39	3.89E-09
	rs562332781	9	106952143	G	A	0.0008	-0.01	0.06	0.895	0.002	-2.36	0.39	3.89E-09
	rs540673651	9	106985753	C	T	0.0008	0.00	0.07	0.959	0.002	-2.36	0.39	3.89E-09
	rs199562704	9	107548675	C	T	0.0003	-0.13	0.15	0.384	0.002	-2.36	0.39	3.89E-09
	rs560612431	9	107927234	A	T	0.0022	-0.10	0.04	0.026	0.002	-2.36	0.39	3.89E-09
	rs188280004	9	108432701	A	G	0.0006	-0.08	0.11	0.429	0.002	-2.36	0.39	3.89E-09
	rs186868542	9	108487794	G	T	0.0025	-0.02	0.04	0.542	0.002	-2.36	0.39	3.89E-09
platelet distribution width	rs73183273*	20	57053412	C	G	0.0106	-0.02	0.02	0.360	0.007	1.44	0.23	8.88E-10
	rs574441315	20	57232728	G	C	0.0025	0.04	0.04	0.408	0.009	1.24	0.21	4.06E-09
	rs190711845	20	57260342	A	G	0.0029	0.01	0.04	0.885	0.009	1.24	0.21	4.06E-09
	rs117112030	20	57371365	A	T	0.0034	0.02	0.03	0.594	0.009	1.20	0.20	5.24E-09

Chr: chromosome; Pos: position (b37); REF: reference allele; ALT: effect allele; ALT_FREQ: allele frequency of the effect allele; SE: standard error; P: p-value

The markers that have reached nominal significance threshold in previous GWAS are highlighted in bold. The star (*) denotes the lead variant in each region.

Supplementary Table 5. Case-only regression analysis comparing the effects of each individual *HBB* mutation on red cell traits to the most common thalassemia mutation: IVS-I-110 (c.93-21G>A) for MANOLIS and IVS-II-745 (c.316-106C>G) for Pomak. The analyses were adjusted for age and sex.

	MANOLIS				Pomak			
Trait	**Mutation**	**Beta**	**SE**	**P-value**	**Mutation**	**Beta**	**SE**	**P-value**
Red cell distribution width	HbS c.20A>T	10.15	1.66	4.8E-8	HbO-Arab c.364G>A	5.58	0.89	4.2E-9
	IVS-I-6 c.92+6T>C	9.14	2.55	6.1E-4	IVS-I-6 c.92+6T>C	4.02	1.38	4.1E-3
	CD39 c.118C>T	0.29	1.47	0.84				
	CD8/9+G c.27dupG	-0.81	1.32	0.54				
Red blood cell count	HbS c.20A>T	-0.84	0.18	8.4E-6	HbO-Arab c.364G>A	-0.65	0.12	2.1E-7
	IVS-I-6 c.92+6T>C	-0.51	0.30	0.09	IVS-I-6 c.92+6T>C	0.05	0.19	0.79
	CD39 c.118C>T	0.13	0.16	0.42				
	CD8/9+G c.27dupG	-0.06	0.15	0.69				
Haemoglobin	HbS c.20A>T	1.09	0.39	6.4E-3	HbO-Arab c.364G>A	2.59	0.38	3.2E-10
	IVS-I-6 c.92+6T>C	0.35	0.65	0.59	IVS-I-6 c.92+6T>C	1.10	0.59	0.06
	CD39 c.118C>T	-0.09	0.35	0.79				
	CD8/9+G c.27dupG	-0.57	0.33	0.09				
Haematocrit	HbS c.20A>T	1.98	1.21	0.11	HbO-Arab c.364G>A	3.20	0.94	8.6E-4
	IVS-I-6 c.92+6T>C	1.42	2.02	0.48	IVS-I-6 c.92+6T>C	3.16	1.46	0.03
	CD39 c.118C>T	0.02	1.10	0.99				
	CD8/9+G c.27dupG	-1.86	1.03	0.07				
Mean corpuscular volume	HbS c.20A>T	14.92	1.39	6.2E-17	HbO-Arab c.364G>A	14.96	1.25	5.5E-23
	IVS-I-6 c.92+6T>C	8.93	2.32	2.5E-4	IVS-I-6 c.92+6T>C	5.16	1.94	8.8E-3
	CD39 c.118C>T	-1.33	1.26	0.30				
	CD8/9+G c.27dupG	-2.51	1.18	0.04				
	HbS c.20A>T	5.88	0.47	1.9E-20	HbO-Arab c.364G>A	7.77	0.58	1.1E-26

Mean corpuscular haemoglobin	IVS-I-6 c.92+6T>C	2.72	0.78	7.8E-4	IVS-I-6 c.92+6T>C	1.85	0.90	0.04
	CD39 c.118C>T	-0.53	0.42	0.21				
	CD8/9+G c.27dupG	-0.78	0.39	0.05				
Mean corpuscular haemoglobin concentration	HbS c.20A>T	1.11	0.34	1.8E-3	HbO-Arab c.364G>A	3.98	0.32	2.3E-24
	IVS-I-6 c.92+6T>C	-0.33	0.57	0.56	IVS-I-6 c.92+6T>C	0.47	0.49	0.34
	CD39 c.118C>T	-0.16	0.31	0.60				
	CD8/9+G c.27dupG	0.14	0.29	0.63				

Supplementary Table 6. Pathogenic HBB mutations present in 3,724 individuals from INTERVAL and their associations with red cell distribution width

Mutation	Observed in HELIC	Position b38	Minor allele count	Beta	P-value
rs63751128 c.*111A>G		5225487	1	0.76	0.45
rs33946267 (c.364G>A, p.Glu122Lys)	Pomak	5225678	1	-1.08	0.281
rs33913413 (c.316-3C>A)	MANOLIS	5225729	1	-0.88	0.380
rs11549407 (c.118C>T, p.Gln40Ter)	MANOLIS	5226774	1	-2.61	0.009

Supplementary Figures

Supplementary Figure 1. Manhattan plot showing genome-wide associations of variants with red cell distribution width in A) MANOLIS and B) Pomak. Genome-wide significant associations are highlighted in green and indicated by grey dotted lines.