

Heritability and association with distinct genetic loci of erythropoietin levels in the general population

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Supplementary Table S1. Participants' characteristics by sex.

	Men (N = 527)	Women (N = 582)	p-Value
Age (years)	47.12 ± 17.78	47.69 ± 17.19	0.588
BMI (kg/m ²)	25.92 ± 4.21	24.14 ± 4.62	<1x10 ⁻⁴
Hemoglobin (g/L)	147.50 ± 10.18	134 ± 9.61	<1x10 ⁻⁴
Hematocrit (%)	43.78 ± 2.92	40.5 ± 2.73	<1x10 ⁻⁴
RBC count (millions/mm ³)	4.89 ± 0.39	4.48 ± 0.34	<1x10 ⁻⁴
MCV (fL)	89.68 ± 4.06	90.5 ± 4.23	0.001
MCH (pg)	30.22 ± 1.40	30.1 ± 1.55	0.178
MCHC (g/L)	337.10 ± 8.62	331.6 ± 9.25	<1x10 ⁻⁴
RDW (%)	13.21 ± 0.69	13.29 ± 1.03	0.133
Epo (IU/L)	8.08 ± 3.63	8.41 ± 3.79	0.140
eGFR (ml/min/1.73 m ²)	98.05 ± 18.69	94.69 ± 17.32	0.002
Currently smoking (%)	28.6	20.4	0.001

All participants were of European descent up to their grand-parents. Index cases of families were randomly selected from the general population, and family members were phenotyped on separate occasions. N, number of samples; BMI, body mass index; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; Epo, erythropoietin (n = 471 for men and 535 for women); eGFR estimated glomerular filtration rate. Data are shown as mean ± SD. P-values were calculated by unpaired t-tests for continuous variables and a chi-square test for the dichotomous variable (smoking).

Supplementary Table S2. GWAS summary statistics for plasma Epo levels.

Chr	Position	SNP	N	effect allele	other allele	MAF	p-Value	BETA	SE	R ²	Gene(s)
15	68211497	rs413451	872	T	C	0.46675	1.05x10 ⁻⁷	0.2672	0.04982	0.03208	<i>MAP2K5-SKOR1-PIAS1</i>
6	135419688	rs9402685	872	C	T	0.22537	1.46x10 ⁻⁴	0.2285	0.0599	0.01649	<i>HBS1L-MYB</i>
7	100320221	rs7789679	872	A	G	0.06896	0.1706	0.1422	0.1037	0.002162	<i>EPO</i>

Chr, chromosome; SNP, single-nucleotide polymorphism; N, number of samples; MAF, minor allele frequency; SE, standard error; R², variance explained.

Supplementary Table S3. Candidate gene analysis.

Gene	Score	Gene	Score
<i>ACO1</i>	8.37x10 ⁻¹	<i>FAM132B</i>	NA
<i>ACO2</i>	5.89x10 ⁻¹	<i>FKBP8</i>	1.39x10 ⁻²
<i>APBA3</i>	1.06x10 ⁻¹	<i>HAMP</i>	6.87x10 ⁻¹
<i>ARNT</i>	7.07x10 ⁻¹	<i>HIF1AN</i>	6.81x10 ⁻¹
<i>ATF3</i>	1.39x10 ⁻¹	<i>HIF3A</i>	1.82x10 ⁻²
<i>ATF4</i>	7.27x10 ⁻¹	<i>IRP1</i>	8.37x10 ⁻¹
<i>BCL11A</i>	5.34x10 ⁻¹	<i>IRP2</i>	8.47x10 ⁻¹
<i>CDKN1B</i>	9.41x10 ⁻¹	<i>MAGEA9</i>	NA
<i>DCTN4</i>	6.93x10 ⁻¹	<i>MAGEA11</i>	NA
<i>EGLN1</i>	8.73x10 ⁻¹	<i>MIR125B1</i>	9.95x10 ⁻¹
<i>EGLN2</i>	9.90x10 ⁻¹	<i>MIR125B2</i>	8.35x10 ⁻¹
<i>EGLN3</i>	2.69x10 ⁻¹	OS9	1.47x10^{-3*}
<i>EPAS1</i>	8.26x10 ⁻¹	<i>USF1</i>	3.92x10 ⁻¹
<i>EPOR</i>	7.09x10 ⁻¹	<i>USF2</i>	5.90x10 ⁻¹
<i>ESR1</i>	7.81x10 ⁻¹	<i>VHL</i>	2.65x10 ⁻¹
<i>ESR2</i>	3.09x10 ⁻¹		
<i>ETV4</i>	9.14x10 ⁻¹		
<i>ETV5</i>	3.63x10 ⁻¹		

The score shows the PASCAL p-value for the given gene. NA, gene not available. *Statistically significant after Bonferroni correction.