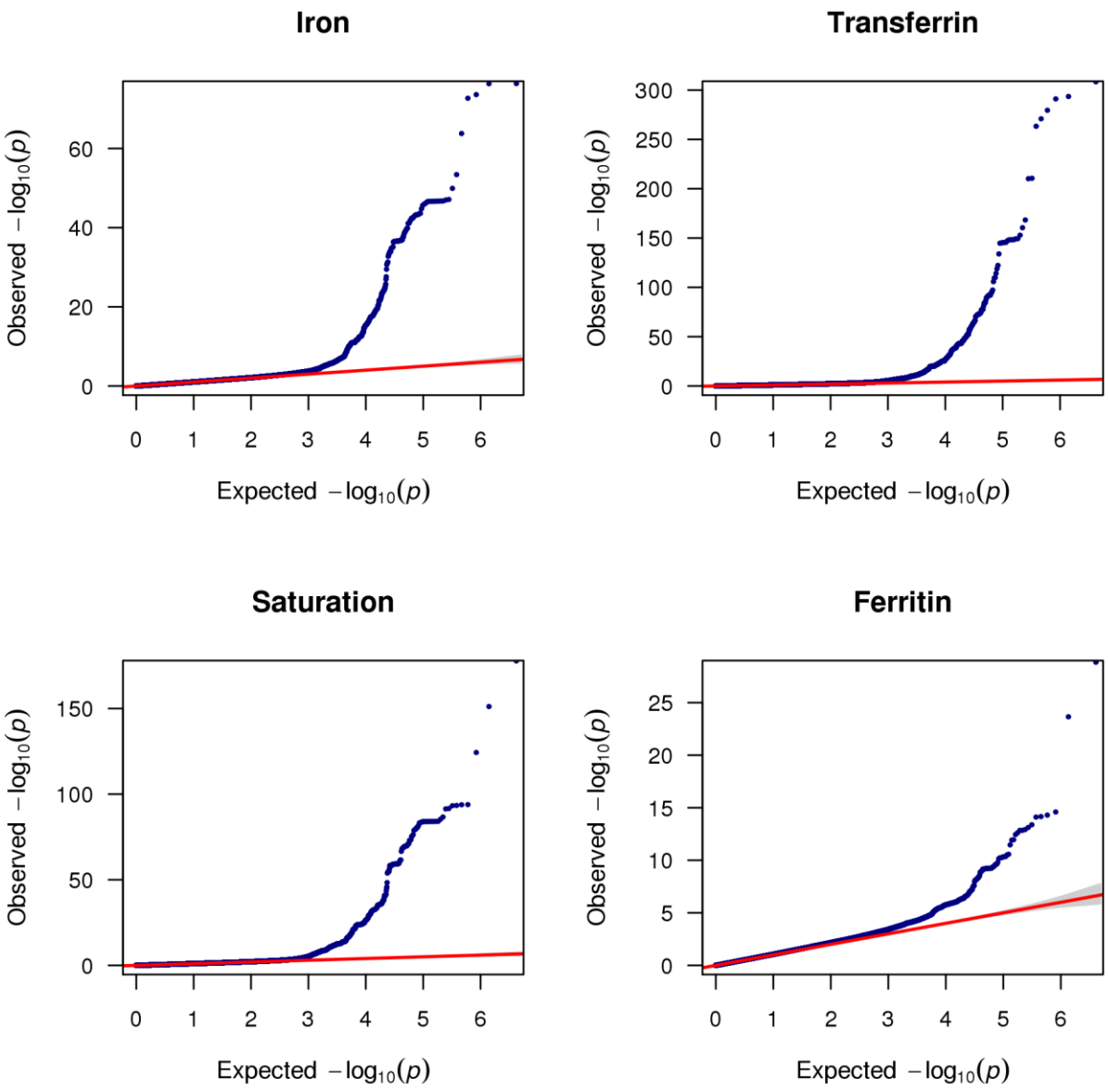
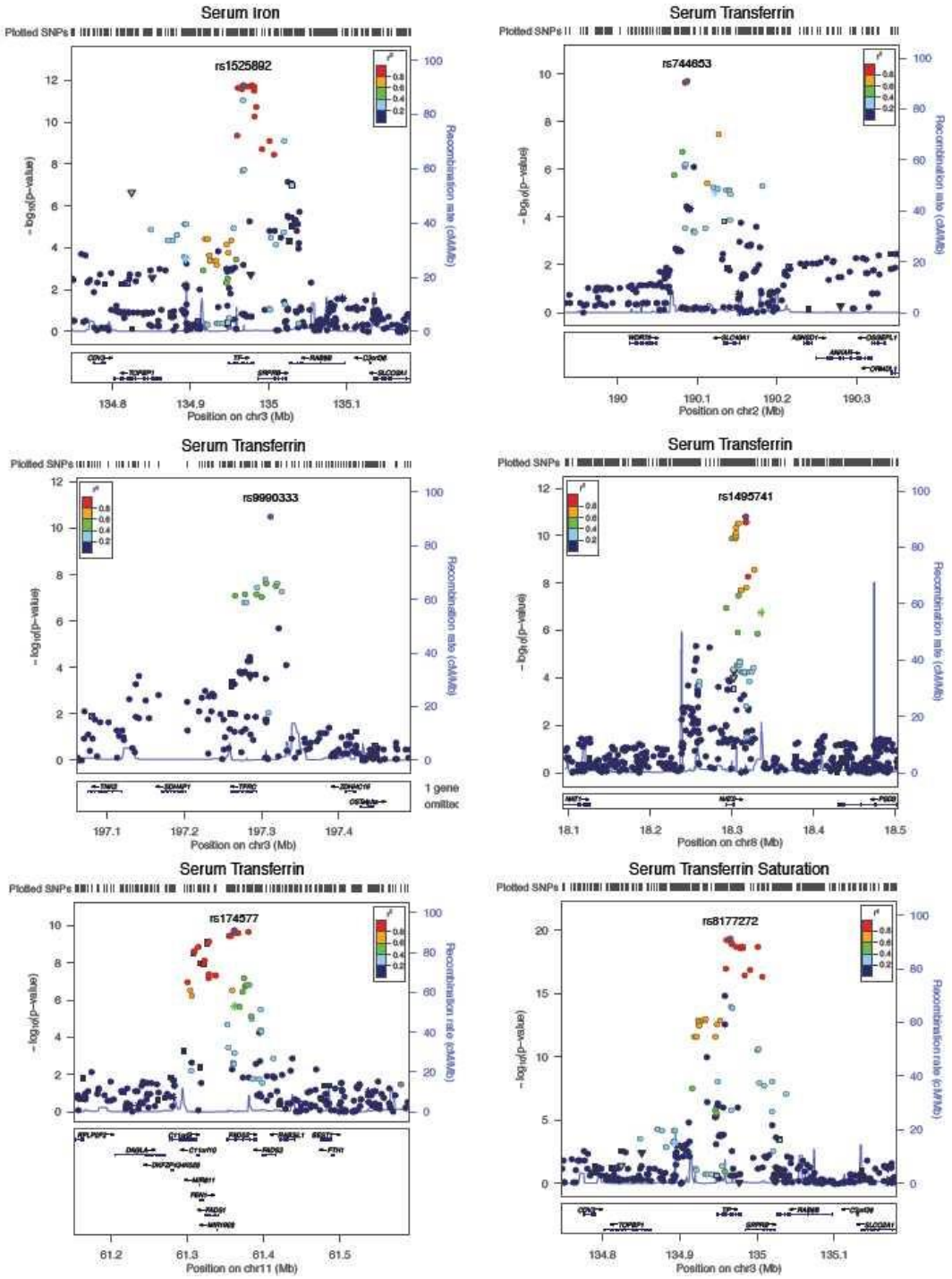


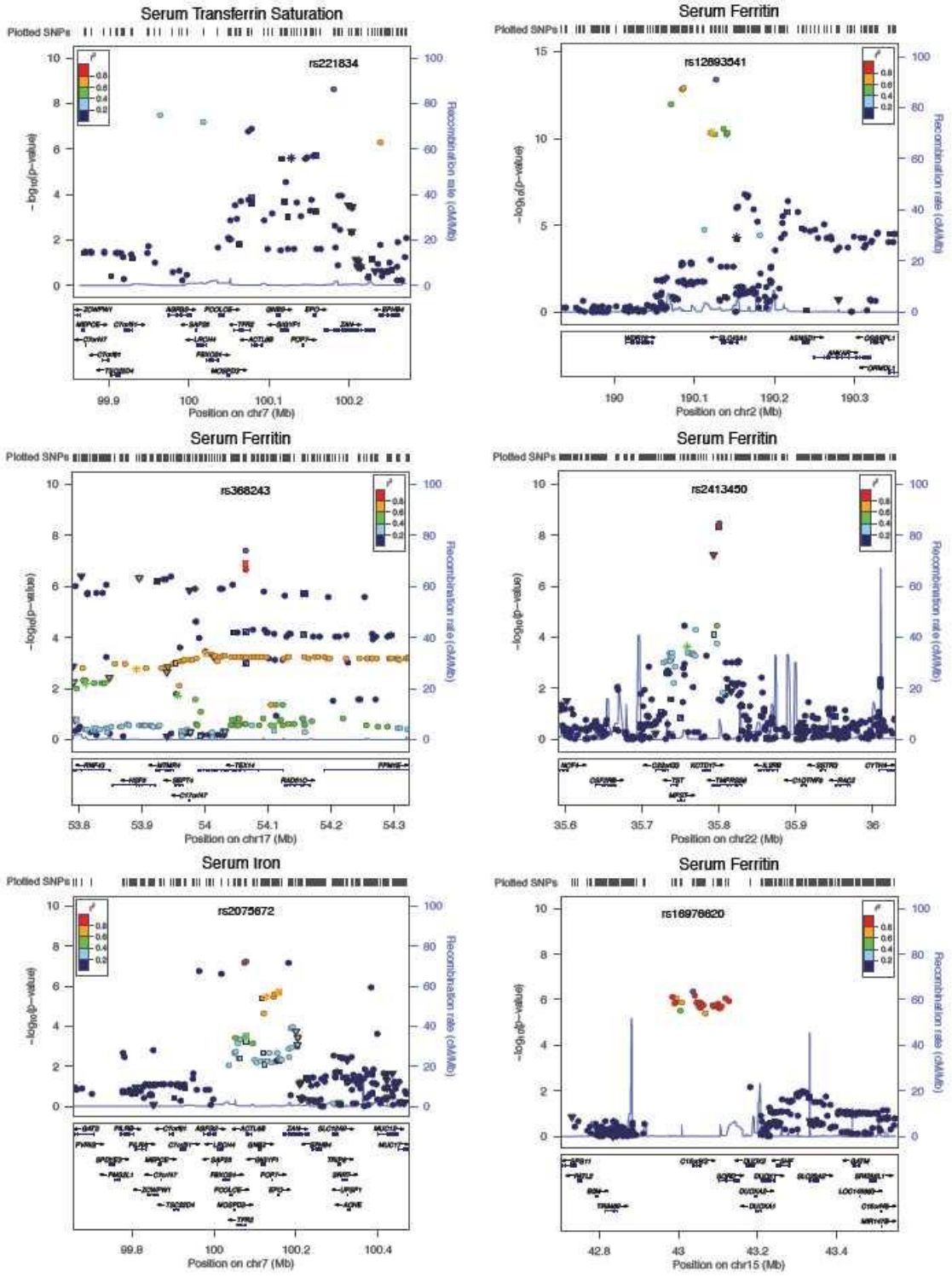
Supplementary Figure 1. Q-Q plots for iron, transferrin, saturation and ferritin in the Discovery meta-analysis. The genomic inflation factors (λ) are 1.035, 1.092, 1.051 and 1.067 for serum iron, transferrin, transferrin saturation and ferritin, respectively.

Supplementary Figure 2.

DISCOVERY.

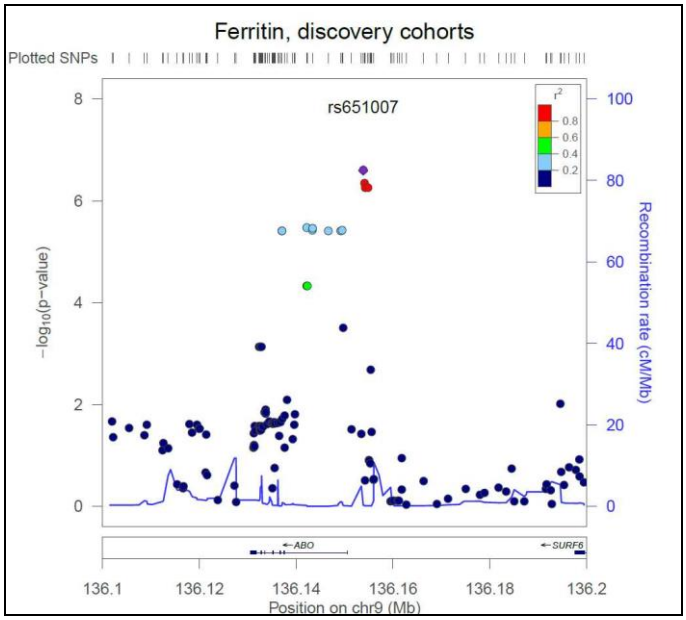


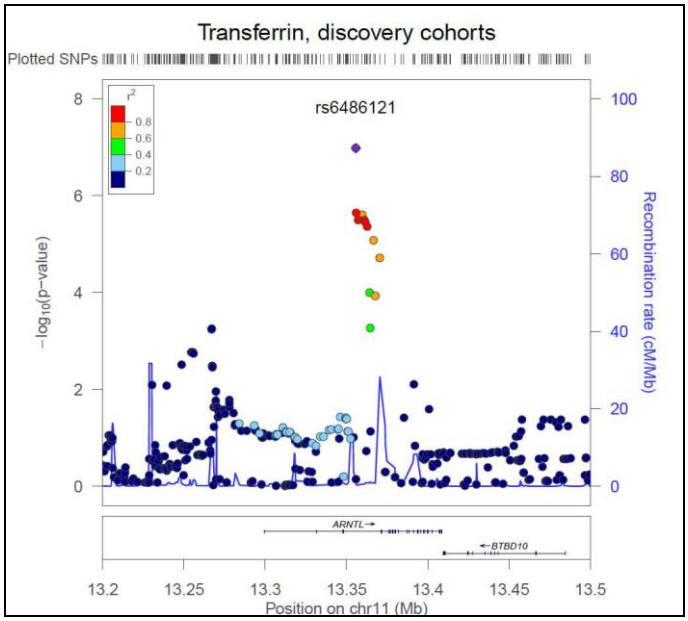
Supplementary Figure 2 (continued).



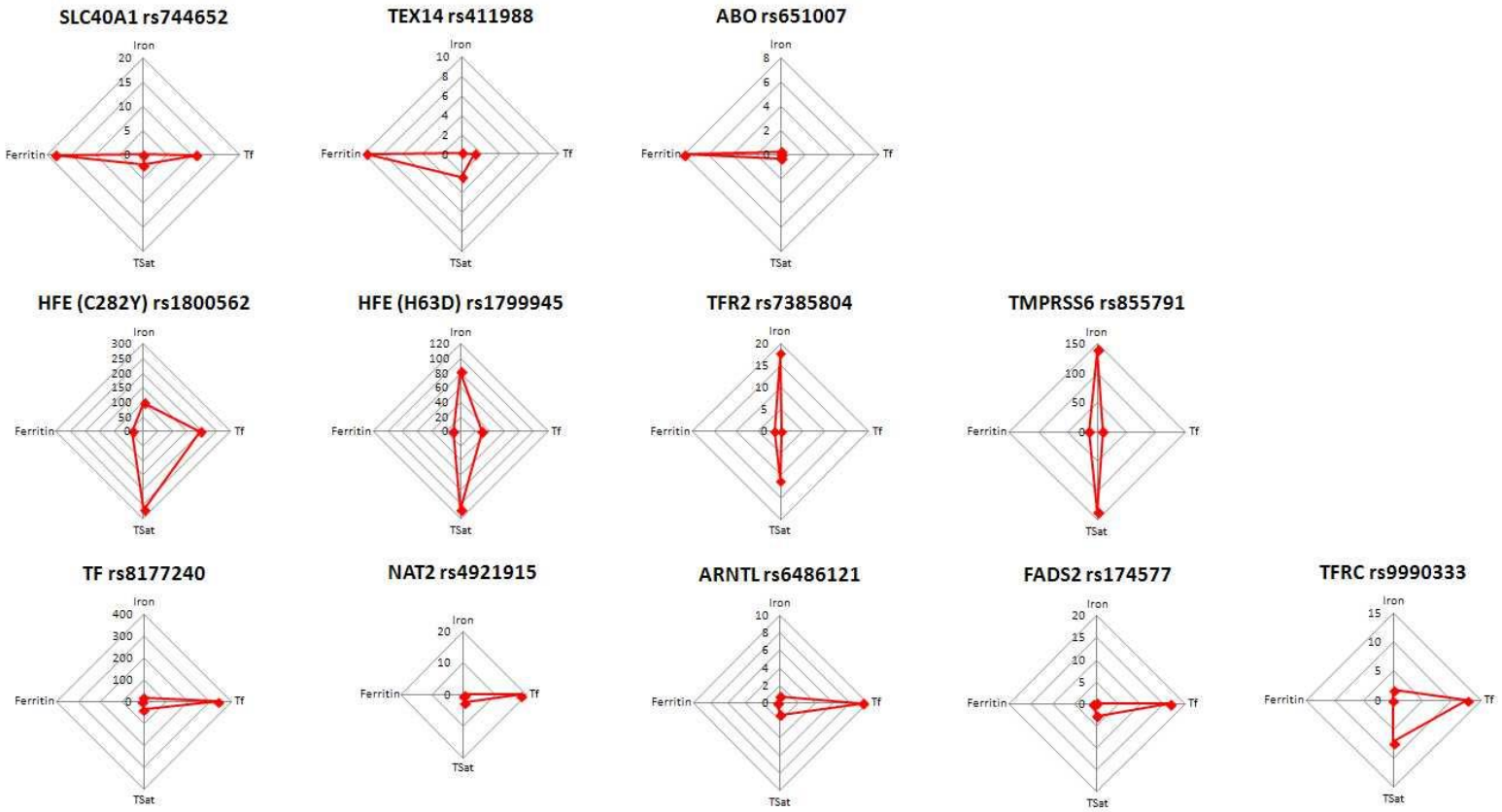
Supplementary Figure 2 (continued).

DISCOVERY + REPLICATION *(data from Discovery meta-analysis only, but these loci become significant in the combined data)*

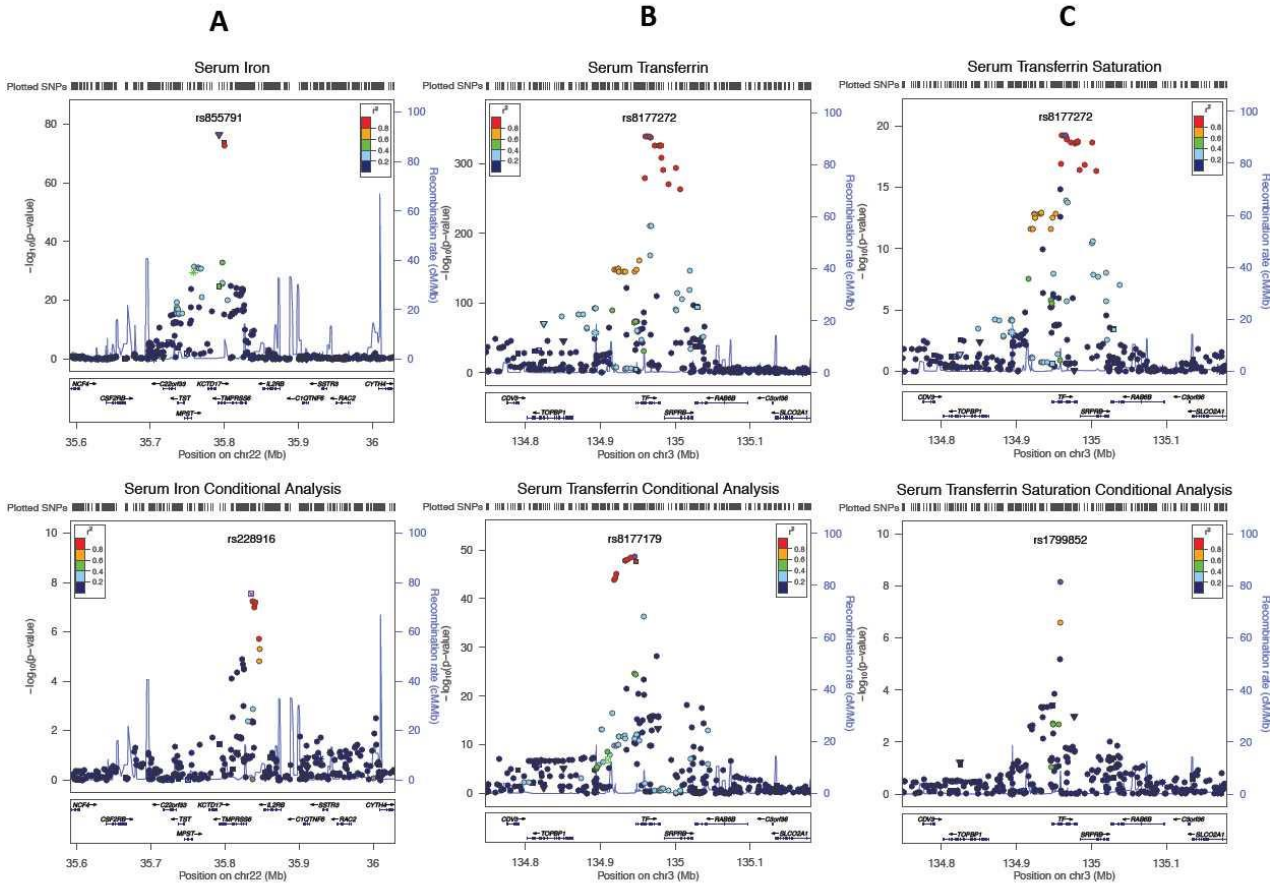




Supplementary Figure 2. Regional association plots for loci with significant results in meta-analysis of data from the Discovery cohorts or the Discovery + Replication cohorts.



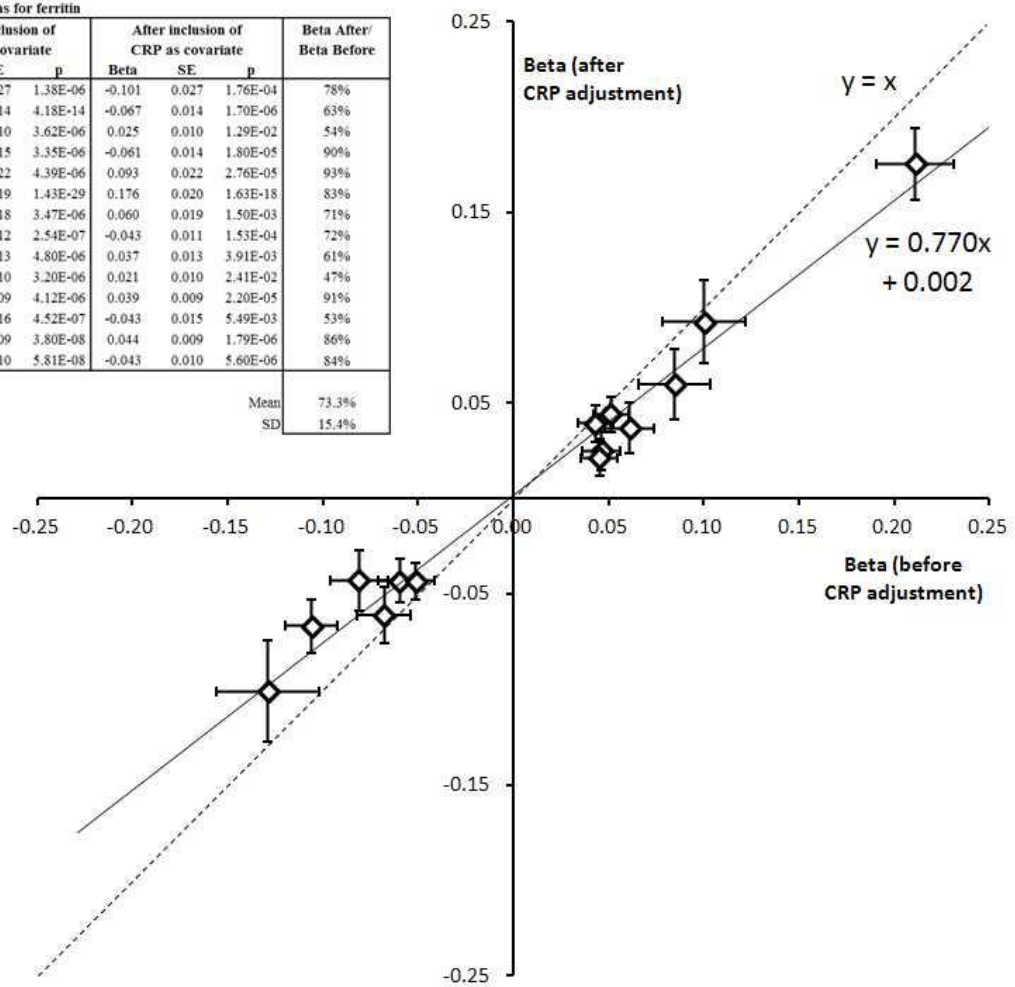
Supplementary Figure 3. Patterns of allelic effects on the four phenotypes, serum iron, transferrin, transferrin saturation and ferritin, for the most significant SNP at each locus (from the Discovery + Replication data). The top row shows loci which mainly affect ferritin, the second row shows loci which mainly affect iron and transferrin saturation, and loci in the bottom row mainly affect transferrin.



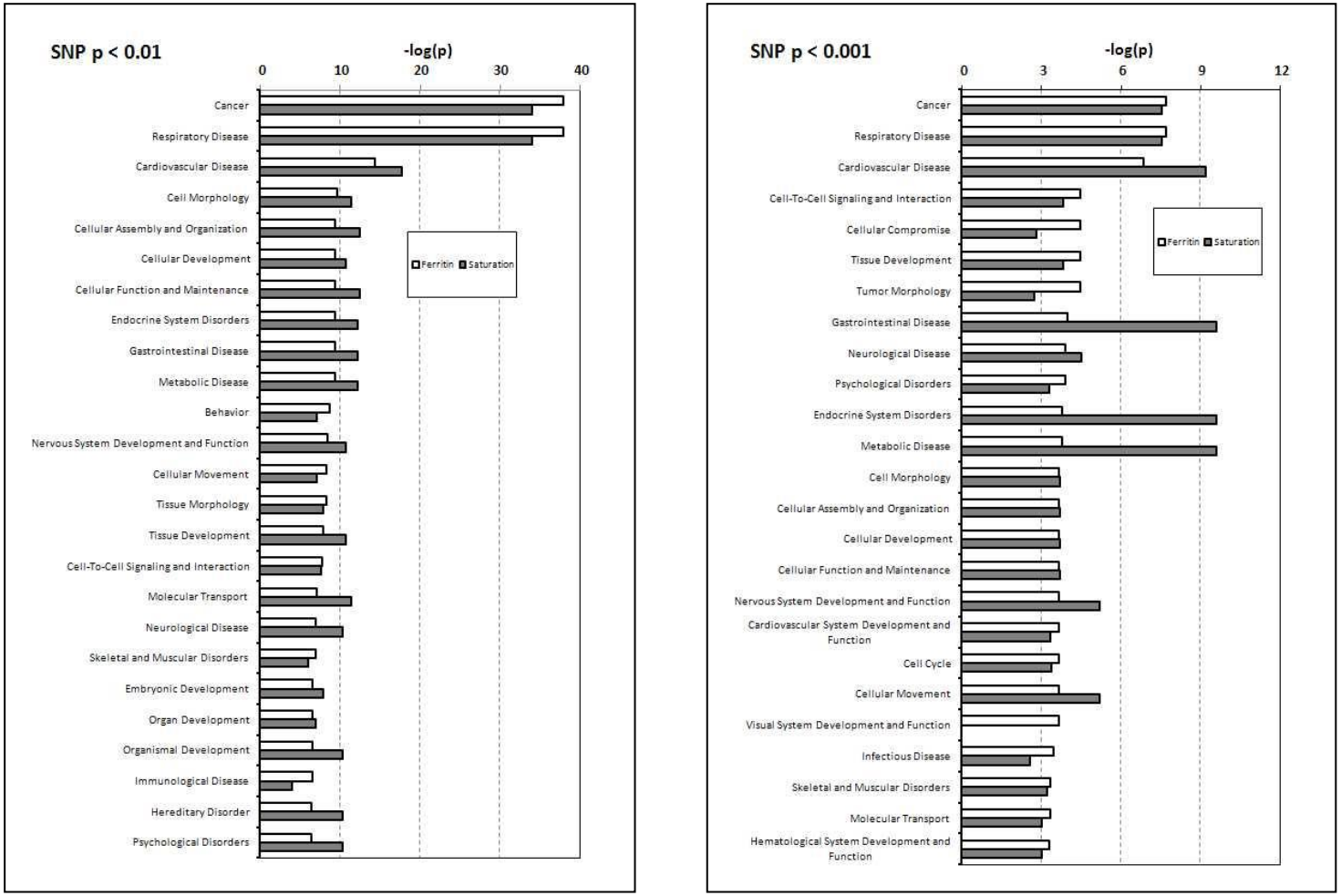
Supplementary Figure 4. Results from conditional analysis, in which original results (top panels) are compared with results obtained after including the lead SNP from the initial analysis as a covariate (bottom panels). A: serum iron at the *TMPRSS6* locus; B: serum transferrin at the *TF* locus; C: transferrin saturation at the *TF* locus.

Effects of adjustment for serum CRP on standardised betas for ferritin

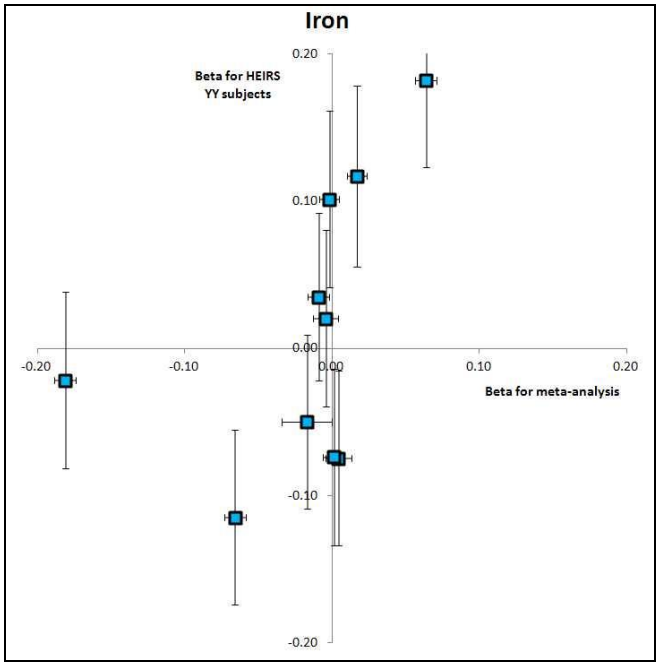
MarkerName	Chr	Gene	Before inclusion of CRP as covariate Beta	SE	p	After inclusion of CRP as covariate Beta	SE	p	Beta After/ Beta Before
rs7603193	2	*BCL11A*	-0.129	0.027	1.38E-06	-0.101	0.027	1.76E-04	78%
rs12693541	2	*SLC40A1*	-0.106	0.014	4.18E-14	-0.067	0.014	1.70E-06	63%
rs4376025	3	*CRBN-LRRN1*	0.046	0.010	3.62E-06	0.025	0.010	1.29E-02	54%
rs173780	5	*FLJ37543*	-0.068	0.015	3.35E-06	-0.061	0.014	1.80E-05	90%
rs17236666	5	*ISL1*	0.100	0.022	4.39E-06	0.093	0.022	2.76E-05	93%
rs1800562	6	*HFE*	0.211	0.019	1.43E-29	0.176	0.020	1.63E-18	83%
rs9322487	6	*RBM16-TIAM2*	0.085	0.018	3.47E-06	0.060	0.019	1.50E-03	71%
rs651007	9	*ABO*	-0.060	0.012	2.54E-07	-0.043	0.011	1.53E-04	72%
rs1752162	9	*DENND1A*	0.061	0.013	4.80E-06	0.037	0.013	3.91E-03	61%
rs7395347	11	*RAB6IP1*	0.045	0.010	3.20E-06	0.021	0.010	2.41E-02	47%
rs1050045	12	*OS9*	0.043	0.009	4.12E-06	0.039	0.009	2.20E-05	91%
rs16976620	15	*C15orf43*	-0.081	0.016	4.52E-07	-0.043	0.015	5.49E-03	53%
rs368243	17	*TEX14*	0.051	0.009	3.80E-08	0.044	0.009	1.79E-06	86%
rs855791	22	*TMPRSS6*	-0.051	0.010	5.81E-08	-0.043	0.010	5.60E-06	84%
								Mean	73.3%
								SD	15.4%

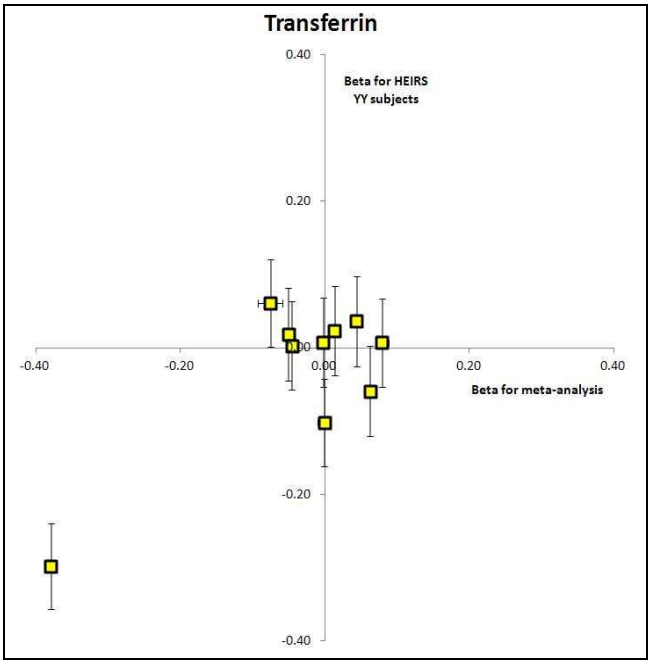


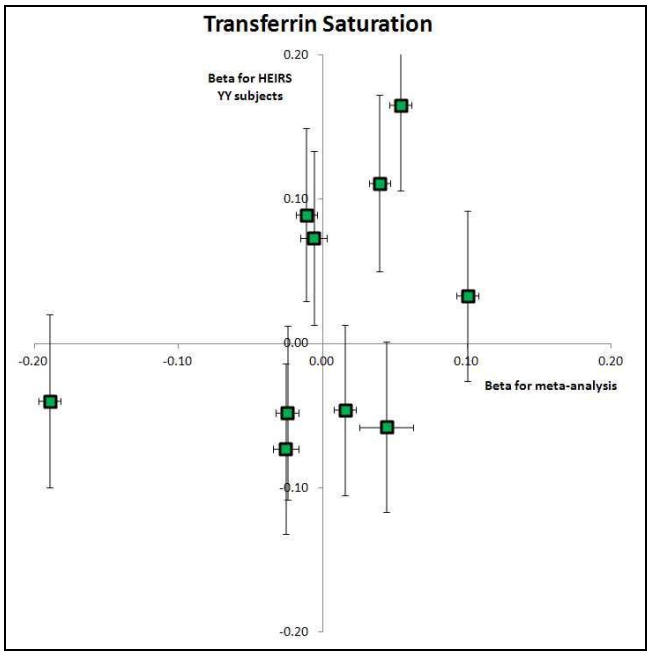
Su)wing effect sizes
(b bars show standard
er x.

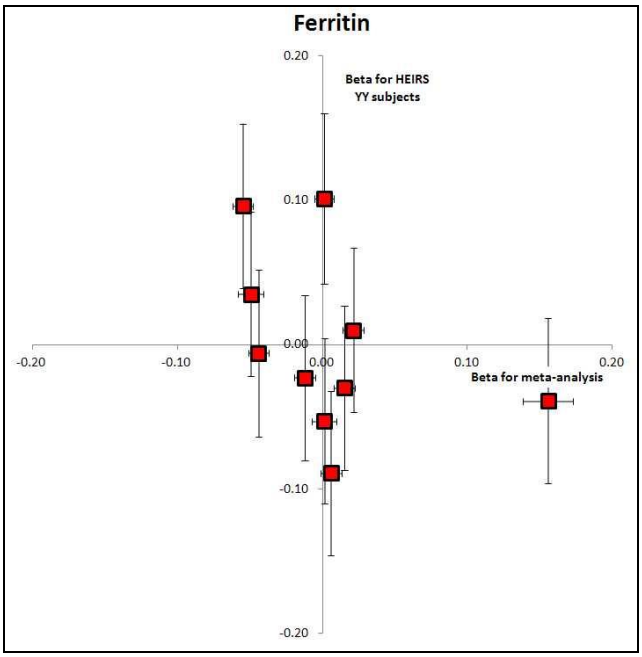


Supplementary Figure 6. Summary of disease and biological process overlap with genes identified through transferrin saturation and ferritin associations at $p < 0.01$ and $p < 0.001$, using Ingenuity Pathway Analysis.









Supplementary Figure 7. Comparison of allelic effects in Discovery + Replication meta-analysis and in C282Y homozygotes from the HEIRS study. Error bars show standard errors for betas.

Supplementary Tables

Supplementary Table 1. Cohort information and acknowledgements

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
Discovery Cohorts:			
Australia- Adult	Study participants comprised (a) adult twins, their spouses and first-degree relatives who volunteered for studies on risk factors or biomarkers for physical or psychiatric conditions; (b) people with self-reported migraine or endometriosis and unaffected relatives. These studies were approved by The Queensland Institute of Medical Research Human Research Ethics Committee and, for the studies on alcohol and nicotine genetics, also by Washington University School of Medicine Human Subjects Committee. Benyamin et al. Common variants in TMPRSS6 are associated with iron status and erythrocyte volume. Nat Genet. 2009;41:1173-5. PMID 19820699 Painter et al. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. Nat Genet. 2011;43:51-4. PMID: 21151130 Anttila et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet. 2010;42:869-73. PMID: 20802479	We acknowledge funding from the Australian National Health and Medical Research Council (NHMRC grants 241944, 389875, 389891,389892, 389938, 442915, 442981, 496739 and 552485), US National Institutes of Health (NIH grants AA07535, AA10248 and AA014041) and the Australian Research Council (ARC grant DP0770096). D.R.N. and G.W.M . are supported by the NHMRC Fellowship Scheme.	
Australia-Adolescent	Adolescent twins and their non-twin siblings who participated in studies on skin cancer risk factors at ages 12 and 14, and on cognition at age 16. These studies were approved by The Queensland Institute of Medical Research Human Research Ethics Committee, and both the participants and their parents or guardians gave informed consent. Middelberg RPS, Martin NG, Whitfield JB. A longitudinal genetic study of plasma lipids in adolescent twins. Twin Research and Human Genetics 2007;10:127-135. Powell JE, Henders AK, McRae AF, et al. The Brisbane Systems Genetics Study: genetical genomics meets complex trait genetics. PLoS One. 2012;7:e35430.	Financial support for aspects of the adolescent studies was provided by grants from the National Health and Medical Research Council of Australia, and the National Institute on Alcohol Abuse and Alcoholism (AA007535, AA014041).	
Estonian Biobank (original cohort)	The Estonian cohort comes from the population-based biobank of the Estonian Genome Project of University of Tartu (EGCUT). The project is conducted according to the Estonian Gene Research Act and all	This work was supported by the Targeted Financing from the Estonian Ministry of Science and Education [SF0180142s08];	We acknowledge EGCUT technical personnel, especially Mr V. Soo and S. Smit. Data analyzes were carried out

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	participants have signed the broad informed consent (www.biobank.ee). In total, 52 000 individuals aged 18 years or older participated in this cohort (33% men, 67% women). The population distributions of the cohort reflect those of the Estonian population (83% Estonians, 14% Russians and 3% other). General practitioners (GP) and physicians in the hospitals randomly recruited the participants. A Computer-Assisted Personal interview was conducted during 1–2 h at doctors' offices. Data on demographics, genealogy, educational and occupational history, lifestyle and anthropometric and physiological data were assessed. These studies were approved by the Research Ethics Committee of the University of Tartu. Website: http://www.biobank.ee/ Leitsalu L, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. Int J Epidemiol. 2014 Feb 11.	the US National Institute of Health [R01DK075787]; the Development Fund of the University of Tartu (grant SP1GVARENG); the European Regional Development Fund to the Centre of Excellence in Genomics (EXCEGEN; grant 3.2.0304.11-0312); and through FP7 grant 313010.	in part in the High Performance Computing Center of University of Tartu.
Kora (F3, F4)	The KORA study is a series of independent population-based epidemiological surveys of participants living in the region of Augsburg, Southern Germany. All survey participants are residents of German nationality identified through the registration office and were examined in 1994/95 (KORA S3) and 1999/2001 (KORA F4). In the KORA S3 and S4 studies 4,856 and 4,261 subjects have been examined implying response rates of 75% and 67%, respectively. 3,006 subjects participated in a 10-year follow-up examination of S3 in 2004/05 (KORA F3), and 3080 of S4 in 2006/2008 (KORA F4). Individuals for genotyping in KORA F3 and KORA F4 were randomly selected. The age range of the participants was 25 to 74 years of recruitment. Informed consent has been given by all participants. The study has been approved by the local ethics committee (Ethik-Kommission der Bayerische Landesärztekammer). Holle R, Happich M, Löwel H, Wichmann HE (2005) KORA–a research platform for population based health research. Gesundheitswesen 2005 Aug;67(Suppl 1): S19–25. Wichmann H-E, Gieger C, Illig T (2005) KORA-gen–resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 2005Aug ;67(Suppl 1): S26–30.	The KORA research platform (KORA, Cooperative Health Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.	
Val Borbera	Val Borbera: The INGI-Val Borbera population is a collection of 1,664 genotyped samples collected in the Val Borbera Valley, a geographically isolated valley located within the Appennine Mountains	The research was supported by funds from Compagnia di San Paolo, Torino, Italy; Fondazione Cariplo, Italy and	We thank the inhabitants of the VB that made this study possible, the local administrations, the Tortona and

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	in Northwest Italy1. The valley is inhabited by about 3,000 descendants from the original population, living in 7 villages along the valley and in the mountains. Participants were healthy people 18-102 years of age that had at least one grandfather living in the valley. The study plan and the informed consent form were reviewed and approved by the institutional review boards of San Raffaele Hospital in Milan. Traglia, M. et al. Heritability and demographic analyses in the large isolated population of Val Borbera suggest advantages in mapping complex traits genes. PLoS One 4, e7554 (2009).† Colonna V, et al. Small effective population size and genetic homogeneity in the Val Borbera isolate. Eur J Hum Genet. 2):89-94. 2013	Ministry of Health, Ricerca Finalizzata 2008 and CCM 2010, PRIN 2009 and Telethon, Italy to DT. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	Genova archdiocese and the ASL-22, Novi Ligure (Al) for support. We also thank Fiammetta Viganò for technical help, Corrado Masciullo and Massimiliano Cocca for building the analysis platform.
NBS (Nijmegen Biomedical Study)	The Nijmegen Biomedical Study (NBS; http://www.nijmegenbiomedischestudie.nl) is a population-based survey conducted by the Department for Health Evidence and the Department of Laboratory Medicine of the Radboud University Medical Centre, Nijmegen, The Netherlands. The study has been described before (1). Briefly, in 2002, 22,451 age and sex-stratified randomly selected adult inhabitants of Nijmegen, a city located in the eastern part of the Netherlands, received an invitation to fill out a postal questionnaire (QN) including questions about lifestyle, health status, and medical history, and to donate a blood sample for DNA isolation and biochemical studies. A total of 9350 (43%) persons filled out the QN, of which 6468 (69%) donated blood samples. A second, third and fourth questionnaire were sent out in 2005, 2008 and 2012, respectively. Approval to conduct the NBS was obtained from the Radboud University Medical Centre Institutional Review Board. All participants gave written informed consent for participation in the NBS. For this study we used the subset of 1980 NBS participants that was selected to serve as controls in GWAS (2). 1. Hoogendoorn EH, Hermus AR, de Vegt F, Ross HA, Verbeek AL, Kiemeney LA, Swinkels DW, Sweep FC, den Heijer M. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. Clin Chem 2006;52:104-11. 2. Kiemeney LA, Thorlacius S, Sulem P, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet	This work was sponsored by the Stichting Nationale Computerfaciliteiten (National Computing Facilities Foundation, NCF) for the use of supercomputer facilities, with financial support from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Netherlands Organization for Scientific Research, NWO).	The Nijmegen Biomedical Study is a population-based survey conducted at the Department for Health Evidence, and the Department of Laboratory Medicine of the Radboud University Medical Centre. Principal investigators of the Nijmegen Biomedical Study are Lambertus A. Kiemeney, Martin den Heijer, André L.M. Verbeek, Dorine W. Swinkels and Barbara Franke.

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	2008;40:1307-12.		
Cambridge	The UK Blood Services (UKBS) Common Controls Panel 1 and 2 (UKBS - CC1 and UKBS - CC2) is a national collection of 3,000 DNA samples from the 12 health regions of Great Britain established in 2005 - 2006 by a partnership between NHS Blood and Transplant (NHSBT) of England, the Scottish National Blood Transfusion Service and the Welsh Blood Service. The Common Controls collection was established for use as the shared controls in the WTCCC Genome - Wide Association Studies (WGAS), and was approved by the Peterborough & Fenland Local Research Ethics Committee Wellcome Trust Case Control Consortium. Genome - wide association study of 14, 000 cases of seven common diseases and 3,000 shared controls. Nature 447 , 661 - 78 (2007).	Research in the Ouwehand laboratory is supported by program grants from the National Institute for Health Research (NIHR) to WHO and the British Heart Foundation (to AR) under numbers RP-PG-0310-1002 and RG/09/12/28096.	
Micros/EURAC	The MICROS study is part of the genomic health care program 'GenNova' and was carried out in three villages of the Val Venosta, South Tyrol (Italy), in 2001-2003. It comprised members of the populations of Stelvio, Vallelunga and Martello. A detailed description of the MICROS study is available elsewhere (Pattaro et al. 2007). Briefly, study participants were volunteers from three isolated villages located in the Italian Alps, in a German-speaking region bordering with Austria and Switzerland. Owing to geographical, historical and political reasons, the entire region experienced a prolonged period of isolation from surrounding populations. Information on the participant's health status was collected through a standardized questionnaire. Laboratory data were obtained from standard blood analyses. The study participants are connected among each other in a unique genealogy for the three villages. The study was approved by the Landesethikkomitee (ethics committee) of the autonomous province of Bolzano. Pattaro C, Marroni F, Riegler A, Mascalzoni D, Pichler I, Volpato CB, Dal Cero U, De Grandi A, Egger C, Eisendle A, Fuchsberger C, Gögele M, Pedrotti S, Pinggera GK, Stefanov SA, Vogl FD, Wiedermann CJ, Meitinger T, Pramstaller PP. The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. BMC Med Genet. 2007 Jun 5;8:29.	The study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano and the South Tyrolean Sparkasse Foundation.	For the MICROS study, we thank the primary care practitioners Raffaela Stocker, Stefan Waldner, Toni Pizzecco, Josef Plangger, Ugo Marcadent and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project.
ERF/Rotterdam	The Erasmus Rucphen Family study is part of the Genetic Research in Isolated Populations (GRIP) program. It is a cross-sectional population-based study that includes over 3000 participants descending from 22	ERF: The genotyping for the ERF study was supported by EUROSPAN (European Special Populations Research Network)	

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	couples who lived in the Rucphen region in the southwest Netherlands and had at least 6 children baptized in the community church between 1850 and 1900 . All living descendants of these pairs (as well as their spouses), ascertained on the basis of municipal and baptismal records, were traced and invited to participate (n = 3000). Selection of the study participants was not based on any disease. The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam approved the study and informed consent was obtained from all participants. Aulchenko YS, Heutink P, Mackay I, et al. Linkage disequilibrium in young genetically isolated Dutch population. Eur J Hum Genet 2004;12:527-34. PMID:15054401	and the European Commission FP6 STRP grant (018947; LSHG-CT-2006-01947). The ERF study was further supported by grants from the Netherlands Organisation for Scientific Research, Erasmus MC, the Centre for Medical Systems Biology (CMSB) and the Netherlands Brain Foundation (HersenStichting Nederland). We are grateful to all participating individuals and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, Jeannette Vergeer for the supervision of the laboratory work and P. Snijders for his help in data collection.	
Busselton Health Study	Residents of the town of Busselton in the southwest of Western Australia have been involved in a series of health surveys since 1966.a The population is predominantly of European origin. In 1994/95 there was a follow-up study involving a subset of those who had attended any of the previous surveys. Cases of asthma were defined as those who reported doctor-diagnosed asthma at any survey that they attended from 1966 to 1994 (answer 'Yes' to 'Has your doctor ever told you that you had asthma?').b Controls are those who have consistently answered 'No' to 'Has your doctor ever told you that you had asthma?' at all previous surveys that they have attended from 1996 to 1994. For the GWA study, a case control sample of unrelated individuals was selected. After QC a total of 1,207 subjects were retained in the GWAS analyses. Ethical approval was obtained through the Human Research Ethics Office, University of Western Australia Website: http://www.busseltonhealthstudy.com/ James AL, Knuiman MW, Divitini ML et al. Changes in the prevalence of asthma in adults since 1966: the Busselton Health Study. Eur Respir J 2009	The Busselton Health Study (BHS) acknowledges the generous support for the 1994/5 follow-up study from Healthway, Western Australia and the numerous Busselton community volunteers who assisted with data collection and the study participants from the Shire of Busselton. The Busselton Health Study is supported by The Great Wine Estates of the Margaret River region of Western Australia.	
Replication Cohorts:			
Estonian Biobank (replication cohort)	The Estonian cohort comes from the population-based biobank of the Estonian Genome Project of University of Tartu (EGCUT). The project is conducted according to the Estonian Gene Research Act and all participants have signed the broad informed consent	This work was supported by the Targeted Financing from the Estonian Ministry of Science and Education [SF0180142s08]; the US National Institute of Health	We acknowledge EGCUT technical personnel, especially Mr V. Soo and S. Smit. Data analyzes were carried out in part in the High Performance

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	(www.biobank.ee). In total, 52 000 individuals aged 18 years or older participated in this cohort (33% men, 67% women). The population distributions of the cohort reflect those of the Estonian population (83% Estonians, 14% Russians and 3% other). General practitioners (GP) and physicians in the hospitals randomly recruited the participants. A Computer-Assisted Personal interview was conducted during 1–2 h at doctors' offices. Data on demographics, genealogy, educational and occupational history, lifestyle and anthropometric and physiological data were assessed. These studies were approved by the Research Ethics Committee of the University of Tartu. Website: http://www.biobank.ee/ Leitsalu L, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. Int J Epidemiol. 2014 Feb 11.	[R01DK075787]; the Development Fund of the University of Tartu (grant SP1GVARENG); the European Regional Development Fund to the Centre of Excellence in Genomics (EXCEGEN; grant 3.2.0304.11-0312); and through FP7 grant 313010.	Computing Center of University of Tartu.
InCHIANTI	The InCHIANTI study is a population-based epidemiological study aimed at evaluating the factors that influence mobility in the older population living in the Chianti region in Tuscany, Italy. The details of the study have been previously reported[1]. Briefly, 1616 residents were selected from the population registry of Greve in Chianti (a rural area: 11,709 residents with 19.3% of the population greater than 65 years of age), and Bagno a Ripoli (Antella village near Florence; 4,704 inhabitants, with 20.3% greater than 65 years of age). The participation rate was 90% (n=1453), and the subjects ranged between 21-102 years of age. Overnight fasted blood samples were for genomic DNA extraction, and measurement of iron-related traits. Illumina Infinium HumanHap 550K SNP arrays were used for genotyping [2]. The study protocol was approved by the Italian National Institute of Research and Care of Aging Institutional Review, and Medstar Research Institute (Baltimore, MD). 1. Ferrucci, L., et al., Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. J Am Geriatr Soc, 2000. 48(12): p. 1618-25. PMID: 11129752 2. Melzer, D., et al., A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet, 2008. 4(5): p. e1000072. PMID: 18464913	The InCHIANTI study baseline (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).	
SardiNIA	The SardiNIA study is a longitudinal study which recruited and phenotyped 6,148 individuals, males and females, aged 14–102 y, from a cluster of four towns in the Lanusei Valley [Pilia et al Plos Genetic	We thank the many individuals who generously participated in this study. We are also grateful for the important	

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	2006], located in the central east coast of the Sardinia island, Italy. During physical examination of each individual, a blood sample was collected and divided into two aliquots. One aliquot was used for DNA extraction and the other to characterize several blood phenotypes. During the study, we genotyped, by common GWAS arrays (Affymtrix 10K, Affymetrix 500K and Affymetrix 6.0), 4,694 individuals selected from the whole sample to represent the largest available families, regardless of their phenotypic values. Genotyping protocol and quality checks for the genotyping arrays were described previously [Naitza et al Plos Genet 2012]. The quality controlled 731,209 autosomal markers were used to estimate genotypes for additional 1,594,772 polymorphic SNPs assessed in the CEU HapMap population (release 22) by genotype imputation. The SardiNIA study was approved by both the IRB at the National Institute on Ageing and the local Italian Ethical Committee "Azienda Unita' Sanitaria Locale (U.S.L.) N 4, Lanusei.	computing resources made available for imputation and analysis by the CRS4 HP Computing Cluster in Pula (Cagliari, Italy), and in particular to Lidia Leoni, Luca Carta e Michele Muggiri. This work was supported by the Intramural Research Program of the National Institute on Aging (NIA), National Institutes of Health (NIH). The SardiNIA ("Progenia") team was supported by Contract NO1-AG-1–2109 from the NIA.	
CoLAUS	The CoLaus study is a population-based cohort study in Lausanne, Switzerland and has been described previously [Firmann M, BMC Cardiovascular Disorders, 2008, PMID 18366642]. Briefly, the baseline study was conducted between 2003 and 2006, recruiting over 6,000 subjects. The following inclusion criteria were applied: a) voluntary participation in the examination, including blood sample, b) aged 35-75 years, and c) Caucasian origin defined as having both parents and grand-parents Caucasian (determined by birth place). A follow-up visit took place from 2009-2012, hence 5 years after the baseline study, (n=5,228, 78% follow-up) and similar measurements were repeated. The Institutional Review Board of the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne and the Cantonal Ethics Committee (Commission Cantonale d'éthique de la recherche sur l'être humain) approved the study protocol for both the baseline and follow-up studies and signed informed consent was obtained from participants.	The CoLaus study was supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, Switzerland, and the Swiss National Science Foundation (grant no: 33CSCO-122661, 33CS30-139468). ZK was supported by the Leenaards Foundation and the Swiss National Science Foundation (31003A-143914).	The authors thank Peter Vollenweider, Vincent Mooser and Dawn Waterworth, Co-PIs of the CoLaus study. Special thanks to Murielle Bochud, Yolande Barreau, Mathieu Firmann, Vladimir Mayor, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection.
PREVEND	The PREVEND Study is a prospective, observational cohort study, focussed to assess the impact of elevated urinary albumin loss in non-diabetic subjects on future cardiovascular and renal disease. PREVEND is an acronym for Prevention of REnal and Vascular ENd-stage Disease. This study started with a population survey on the prevalence of micro-albuminuria and generation of a study cohort of the general population. The goal is to monitor this cohort for the long-term development of cardiac-, renal- and peripheral vascular end-stage disease. For that purpose the participants receive questionnaires on	This work was supported by the following grants: PREVEND genetics is supported by the Dutch Kidney Foundation (Grant E033), the National Institutes of Health (grant LM010098), The Netherlands Organization for Scientific Research (NWO-Groot 175.010.2007.006, NWO VENI grant 916.761.70, ZonMW 90.700.441), and	

Cohort Name	Cohort description, ethical approvals and references	Acknowledgements Financial support	Acknowledgements Other
	events and are seen every three/four years for a survey on cardiac-, renal- and peripheral vascular morbidity. 'The PREVEND study was approved by the medical ethics committee of the University Medical Center Groningen and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent. Website: http://www.prevend.org/index.php	the Dutch Inter University Cardiology Institute Netherlands. N. Verweij is supported by the Netherlands Heart Foundation (grant NHS2010B280).	
FENLAND	The Fenland study is a population based cohort in Eastern England (UK) designed to analyse gene-lifestyle interactions on intermediate quantitative traits related to obesity and type 2 diabetes risk. It combines detailed measurement of the lifestyle exposures with accurate metabolic and anthropometric phenotyping. More than 10,000 men and women born between 1950 and 1975 have been recruited since 2004 and is still ongoing. Exclusion criteria were people suffering from a psychotic illness, pregnant and lactating females, people unable to walk unaided, individuals with diagnosed diabetes or a prognosis of less than 1 year. GWAS data is currently available on 1,500 randomly selected participants. The study was approved by Cambridge Local Research Ethics Committee (NHS). De Lucia Rolfe E, Am J Clin Nutr, 2010, PMID 21248185	The Fenland Study is funded by the Medical Research Council (MC_UU_12015/1 and MC_UU_12015/8); the Support Funding programme; Camstrad; and the British Heart Foundation (PG/07/108/23369). Clara Podmore is funded by the Wellcome Trust (097451/Z/11/Z).	We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for assistance with recruitment. We thank the Fenland Study Investigators, Fenland Study Co-ordination team and the Epidemiology Field, Data and Laboratory teams. Biochemical assays were performed by the National Institute for Health Research, Cambridge Biomedical Research Centre, Core Biochemistry Assay Laboratory, and the Cambridge University Hospitals NHS Foundation Trust, Department of Clinical Biochemistry.
INTERACT	The InterAct study is a case-cohort study of incident cases of type 2 diabetes (T2D) from eight of the ten countries involved in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts [Langenberg C, Diabetologia 2011 PMID 21717116]. In brief, 12,403 verfied incident cases of T2D occured between 1991 and 2007 among the participants eligible for inclusion in InterAct, and a centre-stratified subcohort of 16,154 individuals was defined for comparative analysis. As part of EPIC, standardised information had been collected on participants, including information on lifestyles exposures, diet, physical activity, standard anthropometric data and biomarker measurements on stored blood samples. The study was approved by the Internal Review Board of the International Agency for Research on Cancer, in addition to the local ethics committees in the participating countries.	InterAct was funded by the EU Integrated Project LSHM-CT-2006-037197.	We thank all EPIC participants and staff for their contribution to the study.

Supplementary Table 2. Cohort, phenotype and method information.

					Cohort Statistics, Means ± SD							Laboratory Methods		
Cohort	**Cohort Full Name**	**Sex**	**N**	**References (for Cohort)**	**Age (Years)**	**Iron (µmol/l)**	**Transferrin (g/l)**	**TIBC (µmol/l)**	**Saturation (Percent)**	**Ferritin (µg/l)**	**Log Ferritin**	**Method for serum iron**	**Method for serum transferrin (or total iron binding capacity)**	**Method for ferritin**
Discovery Cohorts:														
Australia-Adult	QIMR Berghofer Adult	M	3432 (1868 families)	PMID 19820699; 21151130; 20802479.	47.5 ± 12.3	21.2 ± 6.4	2.7 ± 0.35		32.1 ± 10.5	257.3 ± 190.3	2.30 ± 0.34	Colorimetric, Ferrozine, Roche 917 or Modular P analyser	Immunoturbidimetric, Roche 917 or Modular P analyser	Latex particle immunoturbidimetry, Roche 917 or Modular P analyser
		F	5716 (3204 families)		46.0 ± 12.8	18.5 ± 6.7	2.9 ± 0.47		26.7 ± 10.4	99.1 ± 108.6	1.82 ± 0.41			
Australia-Adolescent	QIMR Berghofer Adolescent	M	1230 (741 families)	PMID 17539372; 22563384.	14.6 ± 2.0	17.3 ± 5.5	2.9 ± 0.36		24.0 ± 8.22	60.3 ± 44.9	1.70 ± 0.23	Colorimetric, Ferrozine, Roche 917 or Modular P analyser	Immunoturbidimetric, Roche 917 or Modular P analyser	Latex particle immunoturbidimetry, Roche 917 or Modular P analyser
		F	1314 (760 families)		14.9 ± 2.3	16.3 ± 5.4	3.0 ± 0.38		22.3 ± 7.7	43.7 ± 30.4	1.56 ± 0.26			
Estonia (original)	Estonian Genome Project	M	440	PMID: 24518929	37.3 ± 15.4	19.4 ± 7.7	2.7 ± 0.44		29.9 ± 12.5	143.6 ± 163.4	1.99 ± 0.39	Colorimetric method	Electro-chemiluminescence immunoassay (ECLIA)	Immunoturbidimetry
		F	453		37.5 ± 15.7	16.9 ± 7.4	2.9 ± 0.58		24.0 ± 11.7	50.1 ± 51.9	1.51 ± 0.44			
Val Borbera	Val Borbera Study	M	733		54.4 ± 18.4	17.7 ± 6.3	2.4 ± 0.4		29.6 ± 11.4	109.4 ± 112.2	1.9 ± 0.4	Standard methods	Standard methods	Standard methods
		F	926		54.8 ± 18.7	16.4 ± 5.8	2.5 ± 0.5		26.9 ± 10.5	108.2 ± 112.1	1.8 ± 0.4			
NBS	Nijmegen Biomedical Study	M	889		66.3 ± 7.1	18.3 ± 5.8		58.1 ± 8.7	32.0 ± 11.0	209.9 ± 191.1	2.19 ± 0.36	Colorimetric measurement using ascorbate/FerroZine reagents(Roche Diagnostics) on an Abbott Aeroset analyzer.	Unsaturated iron binding capacity was measured by adding a known quantity of Fe3+ to the serum samples, reducing it with ascorbate to Fe2+ and measuring it with FerroZine as described for total serum iron (Roche reagents on an Aeroset). TIBC was calculated by adding serum iron and unsaturated iron-binding capacity.	Serum ferritin concentration was determined by a chemiluminescent microparticle immunoassay on the Abbott Architect calibrated against the ferritin assay on the Immulite 2000 of Diagnostic Products Corporation.
		F	902		56.6 ± 10.8	16.3 ± 5.5		60.6 ± 9.7	27.5 ± 10.0	105.8 ± 89.1	1.87 ± 0.39			
Cambridge	UK Blood Services (UKBS)	M	1198	PMID: 17554300	45.1 ± 11.9	N/A	N/A		N/A	34.7 ± 27.1	3.29 ± 0.73	N/A	N/A	Ferritin concentrations from plasma collected

					Cohort Statistics, Means ± SD							Laboratory Methods		
Cohort	**Cohort Full Name**	**Sex**	**N**	**References (for Cohort)**	**Age (Years)**	**Iron (µmol/l)**	**Transferrin (g/l)**	**TIBC (µmol/l)**	**Saturation (Percent)**	**Ferritin (µg/l)**	**Log Ferritin**	**Method for serum iron**	**Method for serum transferrin (or total iron binding capacity)**	**Method for ferritin**
	Common Controls panel	F	1221		42.1 ± 12.7	N/A	N/A		N/A	19.4 ± 16.0	2.69 ± 0.76			from a blood donation pack (containing anitcoagulant) were measured by a two-site sandwich immunoassay using direct chemiluminometric technology.
Micros/ EURAC		M	528		45.5 ± 15.8	20.3 ± 7.3	2.60 ± 0.34		31.8 ± 12.4	170.1 ± 143.0	2.08 ± 0.41	Photometry	PEG-Enhanced Immunoturbidimetry	Microparticle enzyme immunoassay (MEIA), AxSym, Abbott, USA
		F	690		46.0 ± 16.7	18.0 ± 7.4	2.79 ± 0.48		26.4 ± 11.2	53.3 ± 54.2	1.53 ± 0.43			
ERF/ Rotterdam		M	342	PMID: 15054401; 16877869	54.6 ± 14.1	21.3 ± 7.0			36.1 ± 13.4	229.8 ± 186.0	5.16 ± 0.77	Serum iron was measured by the Ferrozine method, using Roche/Hitachi 747 - 400 Kit(Roche).	Transferrin saturation (%) was calculated as serum iron levels divided by serum total iron binding capacity.	Serum ferritin levels were measured by a two-site chemiluminescencent immunometric assay using the Immulite 2000 (Diagnostics Products Corporation).
		F	529		52.8 ± 15.1	18.8 ± 6.5			31.0 ± 11.9	105.7 ± 163.3	4.23 ± 0.92			
KORA F3	Kooperative Gesundheitsforschung in der Region Augsburg	M	809	PMID: 16032513; 16032514	63.0 ± 10.1	17.5 ± 5.5	2.45 ± 0.33		28.9 ± 9.5	289.8 ± 245.6	2.33 ± 0.35	Colorimetric assay, (Cobas®, Roche)	Immunonephelometry, (Behring Nephelometer®, Siemens)	Electrochemiluminescence immunoassay (ECLIA) Cobas, Roche
		F	825		62.1 ± 10.1	16.1 ± 5.2	2.57 ± 0.36		25.4 ± 8.7	141.0 ± 120.4	2.00 ± 0.39			
KORA F4	Kooperative Gesundheitsforschung in der Region Augsburg	M	882	PMID: 16032513; 16032514	61.2 ± 8.9	22.2 ± 6.9	2.52 ± 0.36		35.7 ± 12.4	282.7 ± 255.9	2.31 ± 0.37	Colorimetric assay, (Cobas®, Roche)	Immunonephelometry, (Behring Nephelometer®, Siemens)	Electrochemiluminescence immunoassay (ECLIA) Cobas, Roche
		F	927		60.6 ± 8.8	20.2 ± 6.5	2.55 ± 0.35		32.2 ± 11.1	133.5 ± 132.6	1.97 ± 0.40			
BHS	Busselton Health Study	M	397		54.0 ± 15.4	18.6 ± 5.7	2.59 ± 0.21		29.5 ± 10.0	234.6 ± 397.0	2.20 ± 0.37	Colorimetric	Immunoturbidimetric	Electrochemiluminescence
		F	480		55.5 ± 14.9	17.1 ± 5.8	2.69 ± 0.50		26.6 ± 11.4	98.6 ± 95.7	1.81 ±0.43			
Replication Cohorts:														
Estonia (replication)	Estonian Genome	M	547	PMID: 24518929	54.4 ± 16.1	19.0 ± 6.6	2.7 ± 0.40		31.9 ± 11.5	181.9 ± 189.4	2.11 ± 0.37	Colorimetric method	Electro-chemiluminescence immunoassay	Immunoturbidimetry

					Cohort Statistics, Means ± SD							Laboratory Methods		
Cohort	**Cohort Full Name**	**Sex**	**N**	**References (for Cohort)**	**Age (Years)**	**Iron (µmol/l)**	**Transferrin (g/l)**	**TIBC (µmol/l)**	**Saturation (Percent)**	**Ferritin (µg/l)**	**Log Ferritin**	**Method for serum iron**	**Method for serum transferrin (or total iron binding capacity)**	**Method for ferritin**
	Project	F	470		53.4 ± 15.9	17.3 ± 6.5	2.8 ± 0.51		29.0 ± 12.7	88.9 ± 96.2	1.74 ± 0.45			
InCHIANTI	InCHIANTI study	M	536	PMID: 19880490	67.1 ± 15.3	15.4 ± 5.0	1.23 ± 0.5			185.2 ± 180	4.28 ± 1.0	Colorimetric assay (Roche Diagnostics, Mannheim, Germany)	Chemiluminescent immunoassay (Abbott Diagnostics and Nichols Institute Diagnostics).	Chemiluminescent immunoassay (Abbot Diagnostics).
		F	670		69.1 ± 15.6	14.5 ± 4.4	1.25 ± 0.43			105.1 ± 94.5	4.26 ± 0.95			
SardiNIA	SardiNIA study on aging	M	2051	PMID: 16934002	43.7 ± 18.1	17.3 ± 6.4	2.96 ± 0.57					Express 560 Plus chemistry analyzer (Bayer)	Express 560 Plus chemistry analyzer (Bayer)	-
		F	2643		43.1 ± 17.3	14.8 ± 6.0	3.15 ± 0.65							
CoLAUS	Cohorte Lausanne	M	2550	PMID: 18366642	52.9 ± 10.8	18.3 ± 6.1	2.33 ± 0.33		35.69 ± 12.35	256.9 ± 219.2	2.28 ± 0.35	Timed-endpoint method (SYNCHRON® System)	Turbidimetric method (SYNCHRON® system, Beckman Coulter)	Immunoturbidimetric method (Ferritin Tina-quant fourth generation, Roche Diagnostics, measured on Modular P).
		F	2869		52.9 ± 10.8	18.3 ± 6.1	2.33 ± 0.33		35.69 ± 12.35	256.9 ± 219.2	2.28 ± 0.35			
PREVEND	Prevention of Renal and Vascular Endstage Disease	M	1875		50.9 ± 12.8	16.5 ± 5.5	2.54 ± 0.37		26.30 ± 8.99	180.2 ± 166.1	2.12 ± 0.35	Colorimetric assay, Roche Modular P	Immunoturbidimetric assay,Roche Modular P	Sandwich immunoassay, Roche Modular E
		F	1769		48.2 ± 12.0	15.0 ± 5.6	2.64 ± 0.43		23.30 ± 9.51	87.0 ± 96.9	1.75 ± 0.43			
FENLAND	Fenland Study	M	615	PMID: 21248185	44.5 ± 7.4	20.0 ± 6.4	2.53 ± 0.37		34.78 ± 12.03	n/a	n/a	Colorimetric assay (Siemens Healthcare Diagnostics®) on a Siemens Dimension® RxL analyser.	Immunoturbidimetric assay (Siemens Healthcare Diagnostics®) on a Siemens Dimension® RxL analyser.	
		F	787		45.4 ± 7.2	17.6 ± 6.8	2.65 ± 0.45		29.48 ± 12.68	n/a	n/a			
INTERACT (cases)	InterAct (cases)	M	2087	PMID: 21717116	54.7 ± 8.0	18.5 ± 6.2	2.76 ± 0.40		27.37 ± 10.03	249.6 ± 219.7	2.24 ± 0.39	Colorimetric assay (Roche Diagnostics, Mannheim, Germany), on a Roche Hitachi Modular P analyser.	Immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany), on a Roche Hitachi Modular P analyser.	Electrochemiluminescence immunoassay (ECLIA) with a sandwich principle (Roche Diagnostics, Mannheim, Germany), on a Roche Hitachi Modular E analyser.
		F	2251		55.6 ± 8.3	16.1 ± 5.6	2.89 ± 0.45		22.91 ± 8.68	124.0 ± 121.6	1.89 ± 0.46			
INTERACT (subcohort)	InterAct (sub-cohort)	M	1816		52.2 ± 9.2	18.3 ± 6.0	2.72 ± 0.38		27.32 ± 9.38	186.1 ± 171.7	2.12 ± 0.39			
		F	3140		51.7 ± 9.6	16.5 ± 5.9	2.82 ± 0.44		23.91 ± 9.34	80.4 ± 90.1	1.71 ± 0.43			

Supplementary Table 3. Genotyping, imputation and quality control procedures

Cohort	Sample QCs	Genotyping			Imputation					Statistical Analysis	Covariates
		Platforms	Exclusion Criteria	N Clean SNPs	N imputed SNPs	Exclusion Criteria	N Clean SNPs	Imputation Method	Reference panel		
Australia- Adult	ethnic outliers; duplicates; Mendelian error; Sex mismatch;	HumanCNV370-Quadv3;HumanCNV370-Quadv3;Human610-Quad;Human317K;Human610-Quad;Human610-Quad;Human610-Quad	MAF<1%; Call Rate<99; P HWE<10-6; genecall<0.7	312,937-531,042	2543887	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2377358	Mach	HAPMAP II CEU Panel (Release 22, NCBI Build36, dbSNP b126)	Merlin	Age, 5 PCs
Australia-Adolescent	ethnic outliers; duplicates; Mendelian error; Sex mismatch;	HumanCNV370-Quadv3;HumanCNV370-Quadv3;Human610-Quad;Human317K;Human610-Quad;Human610-Quad;Human610-Quad	MAF<1%; Call Rate<99; P HWE<10-6; genecall<0.7	312,937-531,042	2543887	MAF<1%; Call Rate<99; P HWE<10-6;Rsq<0.3	2374850	Mach	HAPMAP II CEU Panel (Release 22, NCBI Build36, dbSNP b126)	Merlin	Age, 5 PCs
Estonia (original)	ethnic outliers; duplicates; Sex mismatch;	Illumina HumanCNV370	MAF<1%; Call Rate<95%; P HWE<10-6	320,955	2548513	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2198922	IMPUTE v0.5	HapMap II , CEU, Build 36	SNPTEST (v2.1)	Age, sex, 5 PCs
KORA F3	call rate 93%	Affymetrix 500K	call rate < 95%, pHWE < 5x10-6, maf < 0.01	379,392	2549999	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2471287	Impute v1.0.0	Hap Map 2	SNPTEST v2.1.1, method expected	age, (separate analysis for males and females)
KORA F4	call rate 93%	Affymetrix 6.0	call rate 93%, hapmap snps only	651,596	2543887	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2424291	MACH v1.0.15	Hap Map 2	mach2QTL	age, (separate analysis for males and females)
Val Borbera	Mendelian error; Sex mismatch	Illumina 370 Quad-CNV array, v3	MAF<1%; Call Rate<90; P HWE<10-4	332,887	2471497	MAF<1%; Call Rate<90; P HWE<10-4;Rsq<0.3	2423712	MACH	HapMap release 22 build 36	R, GenABEL, ProbABEL (mmscore function was used to account for relatedness)	Age, 5 PCs
NBS/Nijmegen		Illumina HumanHap370CNV-Duo BeadChip			2542995	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2366475	IMPUTE v0.5	CEU HapMap Phase II (version 22, build 36)	SNPTEST (v2.1)	

Cambridge	call rate 90%	Affymetrix v6.0 and Illumina 1.2M SNP arrays	MAF<1%; Call Rate<90; P HWE<10-6	2492005	2622175	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2497685	IMPUTE v2	NCBI build 36	SNPTEST	
Micros/EURAC		Illumina 300k (HumHap300v2)			2543887	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2377883	MACH version 1.0.16	HapMap II , CEU, Build 36	regression using linear mixed models based on genomic kinship with ProbABEL v. 0.0-6	
ERF/Rotterdam	Mendelian error; Sex mismatch	Illumina 318K, Illumina 370K and Affymetrix 250K	MAF<1%; Call Rate<98; P HWE<10-6	450,877	2543887	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2395264	MACH	HapMap II , CEU, Build 36	regression using linear mixed models based on genomic kinship with ProbABEL v. 0.0-6	age
BHS-WA					2543887	MAF<1%; Call Rate<99; P HWE<10-6; Rsq<0.30	2416309	MACH	HapMap r22 b36	ProbABEL	
Estonia (replication)	ethnic outliers; duplicates; Sex mismatch;	Illumina OmniExpress	MAF<1%; Call Rate<95%; P HWE<10-6	647,357	2543887	none	2543887	IMPUTE2	HapMap II , CEU, Build 36	SNPTEST (v2.1)	Age, sex, 5 PCs
InCHIANTI	call rate < 97%, sex mismatch, heterozygosity > 0.3, missing data	Illumina 550K	MAF<1% call rate<99, HWE<10-6	498,838	2557230	None	2557230	MACH	HapMap release 22 build 36	Merlin-offline	age, sex, center
SardiNIA	call rate >95%	Affymetrix 10K, 500K, 6.0	MAF>5% (10K, 500K) or >1% (6.0); HWE <10-6 ; call rate >90% (10K,. 500K) or >95% (6.0); >2% Mendelian Inheritance Errors; >2% discrepancies for SNPs present in different arrays	731209	2561960	rsqr<0.3, MAF <1%, Excess Mendelian Errors	2353985	MACH	HapMap r22 b36	Merlin (--fastassoc)	age, age-squared, sex
CoLAUS	1) ethnic outliers; 2) related individuals and duplicates; 3) Missing body weight and height	Affymetrix GeneChip Human Mapping 500k	MAF<1%; call rate <70%; HWE <10-7	390,631	2557249	None	2557249	IMPUTE	HapMap r21 b35	Matlab	age, sex and the first 5 ancestry PCs

PREVEND	1) callrate <95%, 2) Duplicates, sex mismatches, 3) Samples were excluded when for they diverged from the mean with at least 3 standard for the first 5 principal components.	Illumina Cyto SNP12 v2	MAF<1%, call rate <95%, HWE <10-5	232571	2442175	maf<0.01, info<0.1	2289008	Beagle	HapMap r22 b36	Plink 1.07	Age, Sex, first 5 PCs
FENLAND	ethnic outliers; duplicates and relatedness check; Sex mismatch check; heterozygosity check; call-rate>=95%	Affymetrix SNP5.0	MAF<1%, call rate <90%, HWE <10-6	369,945	2252514	NA	2622459	IMPUTE2	HapMap2	SNPTEST2	age, sex, 4 PCs
INTERACT (cases and subcohort)	call-rate>=95%; ethnic outliers; duplicates and relatedness check; Sex mismatch check; heterozygosity check; sequenom identity fail; missing data	Illumina 660w quad chip	leftover fails; failed to map 1000G(v3);call rate <95%, HWE <10-6;	564371	30505916	MAF=0; Impute-info<0.3	21023929	IMPUTE2	1,000 Genomes haplotypes -- Phase I integrated variant set release (v3) _no singleton	SNPTEST2	age, sex, centre, 5 PCs
INTERACT (others)	as above										

Supplementary Table 4. Initial meta-analysis; lead SNP at loci showing suggestive results ($p < 5 \times 10^{-6}$) from meta-analysis of the Discovery datasets. Statistical tests and numbers of subjects are as described in the paper.

CHR	SNP	BP(B37)	BP (B36)	A1	A2	Freq1	Effect	StdErr	P.value	Nearby gene(s)
Iron										
2	rs12693541	190,418,690	190,126,935	t	c	0.871	-0.106	0.014	4.18E-14	*SLC40A1*
2	rs6726348	239,084,119	238,748,858	t	c	0.444	0.047	0.010	3.12E-06	*ILKAP*
3	rs7638018	133,495,461	134,978,151	a	g	0.667	-0.074	0.010	1.87E-12	*TF*
5	rs17236666	50,940,708	50,976,465	t	c	0.950	0.100	0.022	4.39E-06	*ISL1*
5	rs173780	60,903,201	60,938,958	a	g	0.135	-0.068	0.015	3.35E-06	*FLJ37543*
6	rs1800562	26,093,141	26,201,120	a	g	0.067	0.372	0.020	3.96E-77	*HFE*
6	rs4715597	56,103,037	56,210,996	c	g	0.294	0.056	0.011	4.66E-07	*COL21A1*
6	rs6920211	135,431,318	135,473,011	t	c	0.758	-0.054	0.012	3.14E-06	*HBS1L, MYB*
7	rs2075672	100,240,296	100,078,232	a	g	0.379	-0.056	0.010	5.95E-08	*TFR2*
8	rs604302	37,004,569	37,123,727	t	c	0.200	0.058	0.012	3.07E-06	*FKSG2*
9	rs1752162	126,551,037	125,590,858	t	c	0.146	0.061	0.013	4.80E-06	*DENND1A*
12	rs1050045	58,115,271	56,401,538	t	c	0.559	0.043	0.009	4.12E-06	*OS9*
15	rs16976620	45,249,892	43,037,184	a	g	0.098	-0.081	0.016	4.52E-07	*C15orf43*
15	rs7172337	61,767,743	59,555,035	t	c	0.728	-0.052	0.011	2.63E-06	*RORA*
17	rs7209063	1,892,031	1,838,781	c	g	0.487	0.048	0.010	3.61E-06	*RTN4RL1*
17	rs2007993	56,590,643	53,945,642	t	c	0.785	0.057	0.011	4.18E-07	*MTMR4*
20	rs6067410	48,973,912	48,407,319	a	t	0.456	-0.047	0.010	3.93E-06	*LOC284751*
22	rs855791	37,462,936	35,792,882	a	g	0.446	-0.187	0.010	4.31E-77	*TMPRSS6*
Transferrin										
1	rs946526	46,487,168	46,259,755	t	c	0.042	-0.122	0.026	2.98E-06	*MAST2*
2	rs11680788	33,059,096	32,912,600	t	c	0.046	-0.115	0.025	4.57E-06	*TTC27*
2	rs744653	190,378,750	190,086,995	t	c	0.854	0.092	0.014	2.00E-10	*WDR75, SLC40A1*
3	rs8177240	133,477,701	134,960,391	t	g	0.671	-0.423	0.011	< E-340	*TF*
3	rs9990333	195,827,205	197,311,602	t	c	0.460	-0.067	0.010	3.01E-11	*TFRC*
4	rs1865383	73,110,424	73,329,288	t	g	0.316	-0.052	0.011	2.17E-06	*NPFFR2, ADAMTS3*
5	rs10055024	11,149,808	11,202,808	t	c	0.386	0.051	0.010	8.98E-07	*CTNND2*

CHR	SNP	BP(B37)	BP (B36)	A1	A2	Freq1	Effect	StdErr	P.value	Nearby gene(s)
6	rs1800562	26,093,141	26,201,120	a	g	0.066	-0.550	0.021	1.26E-153	*HFE*
7	rs4291160	11,974,451	11,940,976	t	g	0.754	-0.055	0.012	3.68E-06	*TMEM106B*
8	rs1495741	18,272,881	18,317,161	a	g	0.782	0.083	0.012	1.57E-11	*NAT2*
8	rs1354342	107,200,980	107,270,156	a	g	0.051	0.126	0.024	1.28E-07	*ZFPM2, OXR1*
9	rs2165554	119,479,774	118,519,595	t	c	0.392	-0.048	0.011	4.19E-06	*ASTN2*
11	rs6486121	13,355,770	13,312,346	t	c	0.627	-0.056	0.011	1.04E-07	*ARNTL*
11	rs174577	61,604,814	61,361,390	a	c	0.333	0.068	0.011	1.90E-10	*FADS2*
12	rs12371237	29,831,076	29,722,343	a	c	0.336	-0.050	0.011	3.48E-06	*TMTC1*
12	rs2374503	106,034,829	104,558,959	c	g	0.421	-0.048	0.010	2.95E-06	*LOC387882*
19	rs12978009	17,113,634	16,974,634	a	g	0.179	-0.064	0.014	3.17E-06	*CPAMD8*
22	rs2275901	19,135,603	17,515,603	a	g	0.239	0.060	0.013	1.77E-06	*GSCL*
Saturation										
3	rs8177272	133,482,870	134,965,560	a	g	0.331	-0.097	0.011	5.52E-20	*TF*
3	rs2061336	164,591,618	166,074,312	a	g	0.913	-0.093	0.018	1.99E-07	*SI*
3	rs9990333	195,827,205	197,311,602	t	c	0.460	0.049	0.010	7.37E-07	*TFRC*
6	rs1800562	26,093,141	26,201,120	a	g	0.067	0.577	0.020	1.52E-178	*HFE*
6	rs2841000	56,077,917	56,185,876	t	c	0.701	-0.051	0.011	2.78E-06	*COL21A1*
6	rs9389269	135,427,159	135,468,852	t	c	0.727	-0.055	0.011	9.78E-07	*HBS1L, MYB*
7	rs11765024	100,125,975	99,963,911	a	g	0.897	-0.091	0.017	3.32E-08	*AGFG2 (TFR2, EPO)*
7	rs221834	100,343,175	100,181,111	c	g	0.928	-0.123	0.021	2.38E-09	*ZAN (TFR2, EPO)*
8	rs604302	37,004,569	37,123,727	t	c	0.200	0.058	0.012	3.26E-06	*FKSG2*
12	rs11046313	22,274,788	22,166,055	a	c	0.286	-0.056	0.011	6.86E-07	*CMAS, ST8SIA1*
17	rs4790859	1,897,820	1,844,570	a	g	0.474	0.048	0.010	2.29E-06	*RTN4RL1*
22	rs855791	37,462,936	35,792,882	a	g	0.446	-0.192	0.010	3.50E-80	*TMPRSS6*
Ferritin										
2	rs7603193	60,478,727	60,332,231	t	c	0.033	-0.129	0.027	1.38E-06	*BCL11A*
2	rs12693541	190,418,690	190,126,935	t	c	0.871	-0.106	0.014	4.18E-14	*SLC40A1*
3	rs4376025	3,419,984	3,394,984	t	c	0.680	0.046	0.010	3.62E-06	*CRBN, LRRN1*
5	rs17236666	50,940,708	50,976,465	t	c	0.950	0.100	0.022	4.39E-06	*ISL1*
5	rs173780	60,903,201	60,938,958	a	g	0.135	-0.068	0.015	3.35E-06	*FLJ37543*
6	rs1800562	26,093,141	26,201,120	a	g	0.068	0.211	0.019	1.43E-29	*HFE*
6	rs9322487	155,255,431	155,297,123	a	g	0.080	0.085	0.018	3.47E-06	*RBM16, TIAM2*
9	rs1752162	126,551,037	125,590,858	t	c	0.146	0.061	0.013	4.80E-06	*DENND1A*

CHR	SNP	BP(B37)	BP (B36)	A1	A2	Freq1	Effect	StdErr	P.value	Nearby gene(s)
9	rs651007	136,153,875	135,143,696	t	c	0.203	-0.060	0.012	2.54E-07	*ABO*
11	rs7395347	9,152,463	9,109,039	t	c	0.341	0.045	0.010	3.20E-06	*SCUBE2, RAB6IP1*
12	rs1050045	58,115,271	56,401,538	t	c	0.559	0.043	0.009	4.12E-06	*OS9*
15	rs16976620	45,249,892	43,037,184	a	g	0.098	-0.081	0.016	4.52E-07	*C15orf43*
17	rs368243	56,708,979	54,063,978	t	c	0.440	0.051	0.009	3.80E-08	*TEX14*
22	rs2413450	37,470,224	35,800,170	t	c	0.463	-0.056	0.010	3.57E-09	*TMPRSS6*

Supplementary Table 5. List of additional genes significantly associated with iron status ($p < 3.0 \times 10^{-6}$, based on ~17,000 genes), from the gene-based analyses of the discovery dataset, performed using VEGAS statistical package, http://gump.qimr.edu.au/VEGAS/ .

Phenotype	Chr	Gene	N of SNPs	Region Start	Region Stop	Test statistic	Gene-based P-value	Best SNP	Top SNP P-value
Iron	6	*FKSG83*	103	27,400,556	27,401,720	834.0128	3.00E-06	rs2235233	5.51E-06
Iron	7	*TFR2*	26	100,055,974	100,077,109	329.942	1.00E-06	rs2075672	5.95E-08
Saturation	7	*TFR2*	26	100,055,974	100,077,109	326.6695	1.00E-06	rs11761260	6.45E-08
Saturation	7	*EPO*	32	100,156,358	100,159,259	411.2104	1.00E-06	rs221834	2.38E-09 [1]
Ferritin	15	*C15orf43-SORD*	27	43,036,194	43,058,713	621.26896	1.00E-06	rs16976620	4.52E-07

[1] The VEGAS output associated this SNP with the EPO region, but rs221834 is within ZAN and the regional plot (Supplementary Figure 3) shows allelic associations across a region ≈ 200 kb which includes *TFR2* and *EPO*.

Supplementary Table 6. Effects of omitting subjects with low ferritin on allelic effects on serum iron, transferrin, transferrin saturation and ferritin. The lead SNPs at loci which were significant ($p < 5 \times 10^{-8}$) or suggestive (p between 5×10^{-8} and 5×10^{-6}) for one or more phenotypes in the initial analysis of the entire Discovery dataset are listed, and effects and p-values are omitted for each phenotype where results were neither significant nor suggestive.

Marker Information					Iron							
					Before excluding subjects with low ferritin				After excluding subjects with low ferritin			
SNP	CHR	BP (build36)	A1	A2	Freq	Effect	StdErr	P.value	Freq	Effect	StdErr	P.value
rs946526	1	46,259,755	t	c								
rs7603193	2	60,332,231	t	c								
rs744653	2	190,086,995	t	c								
rs4376025	3	3,394,984	t	c								
rs8177240	3	134,960,391	t	g	0.669	-0.073	0.011	2.37E-12	0.669	-0.067	0.012	8.84E-09
rs2061336	3	166,074,312	a	g								
rs9990333	3	197,311,602	t	c								
rs4547769	4	73,299,023	a	g								
rs17236666	5	50,976,465	t	c								
rs1800562	6	26,201,120	a	g	0.067	0.372	0.020	3.96E-77	0.068	0.376	0.022	1.87E-66
rs4895441	6	135,468,266	a	g								
rs2075672	7	100,078,232	a	g	0.379	-0.056	0.010	5.95E-08	0.375	-0.068	0.011	2.41E-09
rs1495741	8	18,317,161	a	g								
rs604302	8	37,123,727	t	c	0.200	0.058	0.012	3.07E-06	0.202	0.042	0.014	0.0020
rs1354342	8	107,270,156	a	g								
rs1752162	9	125,590,858	t	c								
rs651007	9	135,143,696	t	c								
rs7395347	11	9,109,039	t	c								
rs6486121	11	13,312,346	t	c								
rs174577	11	61,361,390	a	c								
rs11046313	12	22,166,055	a	c								
rs12371237	12	29,722,343	a	c								
rs2374503	12	104,558,959	c	g								
rs16976620	15	43,037,184	a	g								
rs7172337	15	59,555,035	t	c	0.728	-0.052	0.011	2.63E-06	0.726	-0.042	0.012	0.00071
rs4790859	17	1,844,570	a	g								
rs411988	17	54,064,033	a	g								
rs12978009	19	16,974,634	a	g								
rs6067410	20	48,407,319	a	t	0.456	-0.047	0.010	3.93E-06	0.457	-0.048	0.011	2.28E-05
rs2275901	22	17,515,603	a	g								
rs855791	22	35,792,882	a	g	0.446	-0.187	0.010	4.31E-77	0.445	-0.185	0.011	8.15E-61

Supplementary Table 6 (continued)

Marker Information					Transferrin							
					Before excluding subjects with low ferritin				After excluding subjects with low ferritin			
SNP	CHR	BP (build36)	A1	A2	Freq	Effect	StdErr	P.value	Freq	Effect	StdErr	P.value
rs946526	1	46,259,755	t	c	0.042	-0.122	0.026	2.98E-06	0.043	-0.091	0.030	0.0022
rs7603193	2	60,332,231	t	c								
rs744653	2	190,086,995	t	c	0.854	0.092	0.014	2.00E-10	0.855	0.082	0.016	1.92E-07
rs4376025	3	3,394,984	t	c								
rs8177240	3	134,960,391	t	g	0.671	-0.423	0.011	0	0.671	-0.408	0.012	1.86E-258
rs2061336	3	166,074,312	a	g								
rs9990333	3	197,311,602	t	c	0.460	-0.067	0.010	3.01E-11	0.460	-0.047	0.011	2.57E-05
rs4547769	4	73,299,023	a	g	0.332	-0.050	0.011	2.25E-06	0.333	-0.026	0.012	0.025
rs17236666	5	50,976,465	t	c								
rs1800562	6	26,201,120	a	g	0.066	-0.550	0.021	1.26E-153	0.067	-0.437	0.022	2.14E-86
rs4895441	6	135,468,266	a	g								
rs2075672	7	100,078,232	a	g								
rs1495741	8	18,317,161	a	g	0.782	0.083	0.012	1.57E-11	0.781	0.078	0.013	4.04E-09
rs604302	8	37,123,727	t	c								
rs1354342	8	107,270,156	a	g	0.051	0.126	0.024	1.28E-07	0.050	0.094	0.026	0.00039
rs1752162	9	125,590,858	t	c								
rs651007	9	135,143,696	t	c								
rs7395347	11	9,109,039	t	c								
rs6486121	11	13,312,346	t	c	0.627	-0.056	0.011	1.04E-07	0.634	-0.044	0.012	0.00015
rs174577	11	61,361,390	a	c	0.333	0.068	0.011	1.90E-10	0.332	0.065	0.012	3.59E-08
rs11046313	12	22,166,055	a	c								
rs12371237	12	29,722,343	a	c	0.336	-0.050	0.011	3.48E-06	0.340	-0.042	0.012	0.00036
rs2374503	12	104,558,959	c	g	0.421	-0.048	0.010	2.95E-06	0.425	-0.034	0.011	0.0022
rs16976620	15	43,037,184	a	g								
rs7172337	15	59,555,035	t	c								
rs4790859	17	1,844,570	a	g								
rs411988	17	54,064,033	a	g								
rs12978009	19	16,974,634	a	g	0.179	-0.064	0.014	3.17E-06	0.178	-0.053	0.015	0.00041
rs6067410	20	48,407,319	a	t								
rs2275901	22	17,515,603	a	g	0.239	0.060	0.013	1.77E-06	0.238	0.053	0.014	0.00016
rs855791	22	35,792,882	a	g								

Supplementary Table 6 (continued)

Marker Information					Saturation							
					Before excluding subjects with low ferritin				After excluding subjects with low ferritin			
SNP	CHR	BP (build36)	A1	A2	Freq	Effect	StdErr	P.value	Freq	Effect	StdErr	P.value
rs946526	1	46,259,755	t	c								
rs7603193	2	60,332,231	t	c								
rs744653	2	190,086,995	t	c								
rs4376025	3	3,394,984	t	c								
rs8177240	3	134,960,391	t	g	0.669	0.097	0.011	5.85E-20	0.669	0.039	0.012	0.00087
rs2061336	3	166,074,312	a	g	0.913	-0.093	0.018	1.99E-07	0.911	-0.076	0.020	0.00010
rs9990333	3	197,311,602	t	c	0.460	0.049	0.010	7.37E-07	0.459	0.032	0.011	0.0029
rs4547769	4	73,299,023	a	g								
rs17236666	5	50,976,465	t	c								
rs1800562	6	26,201,120	a	g	0.067	0.577	0.020	1.52E-178	0.068	0.495	0.022	9.93E-113
rs4895441	6	135,468,266	a	g	0.727	-0.055	0.011	1.02E-06	0.729	-0.042	0.012	0.00065
rs2075672	7	100,078,232	a	g	0.379	-0.055	0.010	1.39E-07	0.375	-0.063	0.011	3.50E-08
rs1495741	8	18,317,161	a	g								
rs604302	8	37,123,727	t	c	0.200	0.058	0.012	3.26E-06	0.203	0.047	0.014	0.00055
rs1354342	8	107,270,156	a	g								
rs1752162	9	125,590,858	t	c								
rs651007	9	135,143,696	t	c								
rs7395347	11	9,109,039	t	c								
rs6486121	11	13,312,346	t	c								
rs174577	11	61,361,390	a	c								
rs11046313	12	22,166,055	a	c	0.286	-0.056	0.011	6.86E-07	0.291	-0.045	0.013	0.00034
rs12371237	12	29,722,343	a	c								
rs2374503	12	104,558,959	c	g								
rs16976620	15	43,037,184	a	g								
rs7172337	15	59,555,035	t	c								
rs4790859	17	1,844,570	a	g	0.474	0.048	0.010	2.29E-06	0.473	0.032	0.011	0.0052
rs411988	17	54,064,033	a	g								
rs12978009	19	16,974,634	a	g								
rs6067410	20	48,407,319	a	t								
rs2275901	22	17,515,603	a	g								
rs855791	22	35,792,882	a	g	0.446	-0.192	0.010	3.50E-80	0.445	-0.181	0.011	5.23E-58

Supplementary Table 6 (continued)

Marker Information					Ferritin							
					Before excluding subjects with low ferritin				After excluding subjects with low ferritin			
SNP	CHR	BP (build36)	A1	A2	Freq	Effect	StdErr	P.value	Freq	Effect	StdErr	P.value
rs946526	1	46,259,755	t	c								
rs7603193	2	60,332,231	t	c	0.033	-0.129	0.027	1.38E-06	0.033	-0.097	0.030	0.0011
rs744653	2	190,086,995	t	c	0.855	-0.098	0.013	1.20E-13	0.855	-0.092	0.015	3.55E-10
rs4376025	3	3,394,984	t	c	0.680	0.046	0.010	3.62E-06	0.680	0.028	0.011	0.012
rs8177240	3	134,960,391	t	g								
rs2061336	3	166,074,312	a	g								
rs9990333	3	197,311,602	t	c								
rs4547769	4	73,299,023	a	g								
rs17236666	5	50,976,465	t	c	0.950	0.100	0.022	4.39E-06	0.951	0.074	0.025	0.0028
rs1800562	6	26,201,120	a	g	0.068	0.211	0.019	1.43E-29	0.069	0.265	0.021	2.73E-38
rs4895441	6	135,468,266	a	g								
rs2075672	7	100,078,232	a	g								
rs1495741	8	18,317,161	a	g								
rs604302	8	37,123,727	t	c								
rs1354342	8	107,270,156	a	g								
rs1752162	9	125,590,858	t	c	0.146	0.061	0.013	4.80E-06	0.148	0.044	0.015	0.0032
rs651007	9	135,143,696	t	c	0.203	-0.060	0.012	2.54E-07	0.200	-0.068	0.013	1.65E-07
rs7395347	11	9,109,039	t	c	0.341	0.045	0.010	3.20E-06	0.344	0.043	0.011	6.45E-05
rs6486121	11	13,312,346	t	c								
rs174577	11	61,361,390	a	c								
rs11046313	12	22,166,055	a	c								
rs12371237	12	29,722,343	a	c								
rs2374503	12	104,558,959	c	g								
rs16976620	15	43,037,184	a	g	0.098	-0.081	0.016	4.52E-07	0.096	-0.054	0.018	0.0029
rs7172337	15	59,555,035	t	c								
rs4790859	17	1,844,570	a	g								
rs411988	17	54,064,033	a	g	0.564	-0.049	0.009	1.28E-07	0.564	-0.040	0.010	0.00012
rs12978009	19	16,974,634	a	g								
rs6067410	20	48,407,319	a	t								
rs2275901	22	17,515,603	a	g								
rs855791	22	35,792,882	a	g	0.445	-0.051	0.010	5.81E-08	0.444	-0.062	0.011	3.83E-09

Supplementary Table 7.(a) Summary of published data on gene expression at loci containing significant SNP associations or significant results from gene-based test, from eQTL.chicago.edu/cgi-bin/gbrowse/eqtl/,accessed 2014-02-18; (b) significant expression results from meta-analysis of data for peripheral blood cells, http://genenetwork.nl/bloodeqtlbrowser/, accessed 2014-02-18; (c) significant results for gene expression in macrophages or monocytes.

(a)

Chr (Mbp)	Candidate Gene	Summary of published eQTL data[1]
2 (190)	*SLC40A1*	No reported eQTLs
3 (133)	*TF*	Multiple eQTLs for *SRPRB* in LCLs or monocytes, but not for *TF*
3 (195)	*TFRC*	rs9990333 is an eQTL for LOC440993
6 (26)	*HFE*	rs198853 is an eQTL for *HFE* in liver
7 (100)	*TFR2*	Region contains eQTLs for *TFR2* (rs10247962, rs1052897, rs4729598, rs4729600, rs7457868)
8 (18)	*NAT2*	No reported eQTLs
9 (136)	*ABO*	No reported eQTLs
11 (13)	*ARNTL*	Multiple eQTLs for *ARNTL* in LCLs or monocytes
11 (61)	*FADS2*	rs174577 is an eQTL for *FADS2, CPSF7, NXF1*
15	*C15orf43*	Region contains multiple eQTLsf or *SORD* in LCLs or monocytes
17 (56)	*TEX14*	Region contains multiple eQTLs for *RAD51C* and *TRIM37* in LCLs or monocytes
22 (37)	*TMPRSS6*	Region contains eQTL for *TMPRSS6* in liver

(b)

SNP	Candidate gene	Probe	Probe Chr.	Probe Chr. position	Gene name	Expression P-value	False discovery rate
CIS EFFECTS							
rs744653	*SLC40A1*	730164	2	190,133,988	*SLC40A1*	1.31E-10	0
rs8177240	*TF*	4480224	3	135,022,061	*SRPRB*	1.36E-91	0
rs8177179	*TF*	4480224	3	135,022,061	*SRPRB*	3.01E-34	0
rs1799852	*TF*	4480224	3	135,022,061	*SRPRB*	5.08E-05	0.02
rs9990333	*TFRC*	2940435	3	197,260,777	*TFRC*	8.84E-06	0
rs1800562	*HFE(C282Y)*	3930377	6	26,093,147	*TRIM38*	6.09E-06	0
rs1800562	*HFE(C282Y)*	6200669	6	26,266,387	*HIST1H2AC,HIST1H2BD,HIST1H4A*	1.24E-05	0.01
rs1800562	*HFE(C282Y)*	290730	6	26,279,307	*HIST1H2AC,HIST1H2BD,HIST1H4A*	9.88E-07	0
rs1800562	*HFE(C282Y)*	2970019	6	26,393,396	*HIST1H4H*	1.41E-08	0
rs1799945	*HFE(H63D)*	3930377	6	26,093,147	*TRIM38*	4.18E-17	0
rs1799945	*HFE(H63D)*	7210333	6	26,335,240	-	1.00E-22	0
rs7385804	*TFR2*	580133	7	100,050,486	*MOSPD3*	2.29E-14	0
rs7385804	*TFR2*	3850703	7	100,050,557	*MOSPD3*	5.70E-09	0
rs7385804	*TFR2*	1260730	7	100,238,327	*EPHB4*	2.72E-34	0
rs7385804	*TFR2*	110450	7	100,302,456	*SLC12A9*	1.29E-05	0.01
rs4921915	*NAT2*				No reported cis-eQTL effect	-	-
rs651007	*ABO*	4490687	9	135,018,261	*GBGT1*	6.35E-06	0
rs651007	*ABO*	2600452	9	135,187,879	*SURF6*	8.04E-07	0

SNP	Candidate gene	Probe	Probe Chr.	Probe Chr. position	Gene name	Expression P-value	False discovery rate
rs6486121	*ARNTL*				No reported cis-eQTL effect	-	-
rs174577	*FADS2*	630445	11	61,313,884	*C11orf10*	5.51E-54	0
rs174577	*FADS2*	2360020	11	61,324,012	*FADS1*	4.45E-33	0
rs174577	*FADS2*	380224	11	61,390,508	*FADS2*	8.44E-15	0
rs411988	*TEX14*	4670458	17	53,952,688	*SEPT4*	1.36E-07	0
rs411988	*TEX14*	5910215	17	54,127,426	*RAD51C*	3.13E-33	0
rs411988	*TEX14*	7610129	17	54,129,167	*RAD51C*	4.17E-50	0
rs411988	*TEX14*	510544	17	54,154,786	*RAD51C*	4.05E-41	0
rs228916	*TMPRSS6*				No reported cis-eQTL effect	-	-
rs855791	*TMPRSS6*				No reported cis-eQTL effect	-	-
TRANS EFFECTS							
rs1800562	*HFE(C282Y)*	2940446	20	36,199,898	*TGM2*	4.97E-08	0.01
rs1800562	*HFE(C282Y)*	4180768	X	55,052,299	*ALAS2*	5.53E-10	0
rs1800562	*HFE(C282Y)*	1230376	X	55,056,672	*ALAS2*	1.53E-11	0
rs1799945	*HFE(H63D)*	4180768	X	55,052,299	*ALAS2*	3.24E-09	0
rs1799945	*HFE(H63D)*	1230376	X	55,056,672	*ALAS2*	6.82E-10	0
rs855791	*TMPRSS6(V736A)*	4180768	X	55,052,299	*ALAS2*	1.54E-10	0
rs855791	*TMPRSS6(V736A)*	1230376	X	55,056,672	*ALAS2*	4.23E-10	0

(c) Macrophage and monocyte data, significant associations with gene expression.

Chr (SNP)	Candidate Gene	Other cells (monocytes, macrophages)
9 (rs651007)	*ABO*	rs651007 affects expression at *SNORD36A* (in macrophages p=0.0066; in monocytes p=0.030)
11 (rs6486121)	*ARNTL*	rs6486121 affects expression at *ARNT L*in monocytes (p=0.0033) but not in macrophages (p=0.297)
11 (rs174577)	*FADS2*	rs174577 affects expression at *RAB3IL1* in macrophages (p=0.049;) but not in monocytes (p=0.550)

Supplementary Table 8. Associations with (a) erythrocyte or (b) lipid phenotypes at loci associated with iron phenotypes in this study; and associations with iron phenotypes at loci previously reported to affect (c) erythrocyte or (d) lipid phenotypes.

p(Fe), p(Tf), p(Sat) and p(Ferri) are p-values for allelic association for serum iron, transferrin, transferrin saturation and (log-transformed) ferritin, respectively. For the erythrocyte and lipid phenotypes: HB = haemoglobin, MCH = mean cell haemoglobin, MCHC = mean cell haemoglobin concentration, MCV = mean cell volume, PCV = packed cell volume, RBC = red blood cell count; TC = total cholesterol, HDL = high-density-lipoprotein cholesterol, LDL = high-density-lipoprotein cholesterol, TG = (log-transformed) triglycerides.

(a) Associations with erythrocyte phenotypes at loci found to be significant in this study for iron phenotypes. Erythrocyte data are from van der Harst et al, Nature 2012;492:369-75; empty cells had no results reported.

Lead SNPs at GW-significant loci for iron phenotypes					**Hemoglobin**			**RBC**			**MCH**			**MCV**		
SNP	**chr:bp(Build37)**	**LOCUS**	**A1**	**A2**	**Beta**	**SE**	**p**	**Beta**	**SE**	**p**	**Beta**	**SE**	**p**	**Beta**	**SE**	**p**
rs744653	chr2:190378750	*WDR75-SLC40A1*														
rs8177240	chr3:133477701	*TF*														
rs9990333	chr3:195827205	*TFRC*	t	c							-0.060	0.010	1.33E-10	-0.138	0.025	1.06E-08
rs1799945	chr6:26091179	*HFE (H63D)*	c	g	-0.094	0.009	3.60E-26				-0.217	0.015	4.01E-47	-0.463	0.040	2.35E-33
rs1800562	chr6:26093141	*HFE (C282Y)*	a	g	0.110	0.016	5.57E-13				0.425	0.028	6.50E-56	0.943	0.072	1.25E-42
rs7385804	chr7:100235970	*TFR2*	a	c				-0.020	0.002	1.58E-17	0.084	0.011	3.12E-16	0.216	0.029	1.79E-15
rs4921915	chr8:18272466	*NAT2*														
rs651007	chr9:136153875	*ABO*	t	c	-0.053	0.008	3.82E-14	-0.021	0.003	1.61E-14						
rs6486121	chr11:13355770	*ARNTL*														
rs174577	chr11:61604814	*FADS2*														
rs411988	chr17:56709034	*TEX14*														
rs855791	chr22:37462936	*TMPRSS6 (V736A)*	a	g	-0.079	0.006	4.65E-40				-0.193	0.011	1.01E-69	-0.426	0.029	2.40E-54

(b) Associations with lipid phenotypes at loci found to be significant in this study for iron phenotypes. Lipid data from Willer et al., Nature Genetics 2013;45:1274-83, at http://www.sph.umich.edu/csg/abecasis/public/lipids2013/, accessed 2013-12-05.

			Total cholesterol			LDL-C			HDL-C			Triglycerides		
SNP	**Build37**	**LOCUS**	**Beta**	**SE**	**p**	**Beta**	**SE**	**p**	**Beta**	**SE**	**p**	**Beta**	**SE**	**p**
rs744653	chr2:190378750	WDR75-SLC40A1	0.0086	0.0072	0.085	0.0127	0.0074	0.027	0.0127	0.0069	0.078	0.0103	0.0067	0.132
rs8177240	chr3:133477701	TF	0.0091	0.0054	0.136	0.0065	0.0055	0.468	0.0010	0.0050	0.632	0.0066	0.0050	0.301
rs9990333	chr3:195827205	TFRC	0.0043	0.0052	0.539	0.0022	0.0053	0.613	0.0022	0.0048	0.941	0.0023	0.0047	0.602
rs1800562	chr6:26093141	HFE(C282Y)	0.0565	0.0077	1.91E-12	0.0615	0.0080	8.25E-14	0.0074	0.0074	0.242	0.0130	0.0072	0.172
rs1799945	chr6:26091179	HFE(H63D)	0.0096	0.0051	0.055	0.0110	0.0053	0.020	0.0024	0.0050	0.460	0.0062	0.0048	0.098
rs7385804	chr7:100235970	TFR2	0.0041	0.0054	0.457	0.0033	0.0055	0.599	0.0053	0.0051	0.319	0.0054	0.0049	0.175
rs4921915	chr8:18272466	NAT2	0.0315	0.0044	6.71E-13	0.0222	0.0046	1.35E-06	0.0002	0.0042	0.680	0.0350	0.0041	1.33E-15
rs651007	chr9:136153875	ABO	0.0647	0.0065	5.23E-21	0.0663	0.0066	4.52E-21	0.0119	0.0061	0.087	0.0119	0.0061	0.065
rs6486121	chr11:13355770	ARNTL	0.0071	0.0036	0.110	0.0075	0.0037	0.084	0.0186	0.0035	5.52E-07	0.0169	0.0034	1.37E-06
rs174577	chr11:61604814	FADS2	0.0485	0.0037	1.05E-37	0.0523	0.0038	1.04E-40	0.0386	0.0035	9.74E-27	0.0429	0.0034	7.56E-35
rs411988	chr17:56709034	TEX14	0.0055	0.0051	0.481	0.0064	0.0052	0.270	0.0025	0.0048	0.891	0.0047	0.0047	0.359
rs855791	chr22:37462936	TMPRSS6(V736A)	0.0061	0.0037	0.078	0.0104	0.0038	0.0035	0.0029	0.0035	0.467	0.0057	0.0034	0.054

(c) Associations with iron phenotypes, at all loci reported for erythrocyte phenotypes by van der Harst et al, Nature 2012;492:369-75. For overlap with the 75 erythrocyte loci, the critical p-value is $(0.05/75)=6.67\times10^{-4}$; values below this are shown in bold type.

	Loci reported to affect erythrocyte phenotypes				From GISC discovery meta-analysis				Comments
Candidate genes	**Marker name**	**Chr**	**Position(B36)**	**Phenotype**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	
CCDC27,LRRC48	rs1175550	1	3,681,388	MCHC	0.940	0.949	0.790	0.614	
HEYL	rs3916164	1	39,842,526	MCH	0.891	0.774	0.717	0.357	
TAL1	rs741959	1	47,448,820	MCV	0.945	0.528	0.929	0.551	
OR6Y1,OR10Z1,SPTA1	rs857684	1	156,842,353	MCHC	0.999	0.420	0.956	0.599	
MIR181A1	rs7529925	1	197,273,831	RBC	0.722	0.224	0.295	0.679	
ATP2B4	rs7551442	1	201,921,744	MCHC	0.216	0.143	0.055	0.0053	
TMCC2	rs9660992	1	203,516,073	MCH	0.764	0.351	0.964	0.256	
TRIM58	rs3811444	1	246,106,074	RBC	-	-	-	-	No results for this SNP or proxies

Loci reported to affect erythrocyte phenotypes					From GISC discovery meta-analysis				Comments
Candidate genes	**Marker name**	**Chr**	**Position(B36)**	**Phenotype**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	
PRKCE	rs4953318	2	46,208,555	PCV	0.582	0.073	0.974	0.260	
BCL11A	rs243070	2	60,473,790	MCV	0.258	0.953	0.467	0.181	
ACOXL	rs10207392	2	111,566,130	MCV	0.221	0.522	0.158	0.236	
THRB	rs9310736	3	24,325,815	MCV	0.060	0.732	0.207	0.034	
RASA2	rs6776003	3	142,749,183	MCV	0.226	0.746	0.383	0.929	
XRN1	rs13061823	3	143,603,476	MCV	0.0065	0.624	0.049	0.607	
TFRC	rs11717368	3	197,318,754	MCH	0.288	**2.98E-08**	**4.68E-04**	0.262	
KIT	rs218238	4	55,089,781	RBC	0.304	0.334	0.083	0.642	
BBS7,CCNA2	rs13152701	4	122,970,511	MCV	0.335	0.240	0.468	0.042	
GMPR	rs6914805	6	16,389,166	MCH	0.812	0.956	0.742	0.168	
HFE,SLC17A3	rs1408272	6	25,950,930	MCH	**1.63E-64**	**1.24E-134**	**6.76E-152**	**2.22E-24**	
HIST1H2AM,HIST1H2BO,HIST1H3J	rs13219787	6	27,969,649	MCH	**4.61E-24**	**1.71E-61**	**2.50E-60**	**7.78E-08**	
TRIM39-RPP21	rs2097775	6	30,462,282	HB	**5.73E-06**	**2.67E-15**	**8.12E-15**	**3.60E-06**	
HLA-DQA1,HLA-DQA2	rs9272219	6	32,710,247	RBC	0.235	0.065	0.086	0.055	
CCND3	rs9349204	6	42,022,356	MCV	0.441	0.393	0.195	0.679	
VEGFA	rs9369427	6	43,919,408	HB	0.500	0.614	0.300	0.799	
CCDC162P	rs1008084	6	109,733,658	MCH	0.051	0.246	0.027	0.544	
HBS1L	rs9389269	6	135,468,852	MCV	**6.35E-06**	0.0053	**9.78E-07**	0.489	
CITED2	rs590856	6	139,886,122	MCV	0.708	0.693	0.739	0.930	
QKI	rs736661	6	164,402,826	MCH	0.191	0.016	0.046	0.681	
IKZF1	rs12718598	7	50,395,939	MCV	0.955	0.017	0.436	0.095	
ACTL6B,TFR2	rs2075672	7	100,078,232	RBC	**5.95E-08**	0.391	**1.39E-07**	0.025	
PRKAG2	rs10480300	7	151,036,938	HB	0.826	0.922	0.805	0.625	
ANK1	rs4737009	8	41,749,562	MCHC	0.029	0.317	0.167	0.458	
C8orf40	rs6987853	8	42,576,607	MCHC	0.142	0.792	0.233	0.866	
RCL1	rs2236496	9	4,834,265	MCV	0.755	0.189	0.401	0.067	
ABO	rs579459	9	135,143,989	RBC	0.476	0.224	0.168	**4.52E-07**	
MARCH8	rs901683	10	45,286,428	MCV	0.124	0.821	0.467	0.496	
HK1	rs10159477	10	70,769,894	HB	0.236	-	0.032	-	
NKX2-3	rs11190134	10	101,272,190	MCH	0.675	0.423	0.977	0.817	
AKIP1,C11orf16,NRIP3,ST5	rs11042125	11	8,894,625	HB	0.158	0.830	0.264	0.191	
SBF2	rs7936461	11	9,997,462	PCV	0.632	0.089	0.826	0.141	

Loci reported to affect erythrocyte phenotypes					From GISC discovery meta-analysis				Comments
Candidate genes	**Marker name**	**Chr**	**Position(B36)**	**Phenotype**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	
CORO1B,PTPRCAP,RPS6KB2	rs2302264	11	66,964,002	MCV	0.251	0.219	0.609	0.260	
ARHGEF17,P2RY6	rs7125949	11	72,686,732	HB	0.928	0.180	0.894	0.326	
CACNA1C	rs7312105	12	2,393,616	PCV	0.079	0.057	0.312	0.485	
CCND2	rs10849023	12	4,202,739	MCH	0.264	0.114	-	0.940	
KITLG	rs11104870	12	87,353,425	RBC	0.523	0.124	0.141	0.382	
ATXN2,SH2B3	rs3184504	12	110,368,991	HB	0.646	0.051	0.196	0.688	
ACADS,MLEC	rs3829290	12	119,610,821	MCV	0.392	0.0021	0.388	0.783	
FNTB,MAX	rs7155454	14	64,571,992	MCH	0.116	0.837	0.279	0.378	
SMOC1	rs11627546	14	69,435,677	MCV	0.020	0.547	0.038	0.229	
EIF5	rs17616316	14	102,892,515	MCH	0.239	0.512	0.226	0.206	
LIPC	rs1532085	15	56,470,658	HB	0.292	0.348	0.557	0.834	
DENND4A,PTPLAD1	rs2572207	15	63,857,747	MCV	0.623	0.856	0.442	0.551	
PPCDC,SCAMP5	rs8028632	15	73,108,315	MCV	0.979	0.117	0.651	0.019	
NRG4	rs11072566	15	74,081,026	HB	0.469	0.884	0.562	0.505	
DNAJA4,WDR61	rs2867932	15	76,378,092	MCHC	0.167	0.949	0.118	0.800	
NPRL3	rs11248850	16	103,598	MCH	0.200	0.338	0.414	0.821	
CTRL,DUS2L,EDC4,NUTF2,PSMB10	rs2271294	16	66,459,827	RBC	0.088	0.789	0.180	0.226	
PIEZO1	rs10445033	16	87,367,963	MCHC	0.977	0.655	0.543	0.470	
SPECC1	rs888424	17	19,926,019	MCH	0.594	0.295	0.350	0.042	
C17orf63,ERAL1,NEK8,TRAF4	rs2070265	17	24,099,550	MCH	0.293	0.079	0.788	0.811	
CDK12,NEUROD2	rs8182252	17	34,981,476	RBC	0.443	0.356	0.551	0.487	
SLC4A1,UBTF	rs2269906	17	39,649,863	MCHC	0.925	0.532	0.870	0.419	
ARHGAP27,ARL17B,C17orf69, CRHR1,SPPL2C,KANSL1,MAPT,STH	rs12150672	17	41,182,408	RBC	0.361	0.472	0.294	0.0051	
PGS1	rs4969184	17	73,905,008	HB	0.414	0.019	0.051	**1.84E-04**	
C18orf25	rs4890633	18	42,087,276	MCH	0.029	0.248	0.011	0.109	
AP3D1	rs2159213	19	2,087,102	HB	0.222	0.007	0.955	0.143	
MPND,SH3GL1,UBXN6	rs732716	19	4,317,219	MCV	0.067	0.344	0.078	0.245	
CALR,FARSA,SYCE2	rs741702	19	12,885,250	MCH	0.247	0.276	0.399	0.407	
NUDT19	rs3892630	19	37,873,324	MCV	0.457	0.652	0.553	0.254	
RBM38	rs737092	20	55,423,811	MCV	0.748	0.059	0.685	0.438	
ATP5O	rs2032314	21	34,276,393	PCV	0.178	0.455	0.262	0.982	

Loci reported to affect erythrocyte phenotypes					From GISC discovery meta-analysis				Comments
Candidate genes	**Marker name**	**Chr**	**Position(B36)**	**Phenotype**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	
UBE2L3,YDJC	rs5754217	22	20,269,675	MCV	0.024	0.292	0.032	0.363	
FBXO7	rs5749446	22	31,210,585	MCH	0.039	0.566	0.247	0.826	
KCTD17,TMPRSS6	rs855791	22	35,792,882	MCH	**4.31E-77**	**1.29E-04**	**3.50E-80**	**5.81E-08**	
TYMP,NCAPH2,ODF3B,SCO2	rs140522	22	49,318,132	MCV	0.423	0.604	0.951	0.0042	

(d) Associations with iron phenotypes, at all loci reported significant for lipid phenotypes by Willer et al., Nature Genetics 2013;45:1274-83. For overlap with the 149 lipid loci the critical p-value is (0.05/149)=3.36x10^{-4}; values below this are shown in bold type.

Loci reported to affect lipid phenotypes					From GISC discovery meta-analysis				Comments
Locus	**Marker name**	**Chr.**	**hg19 position (Mb)**	**Associated trait(s)**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	
ASAP3	rs1077514	1	23.77	TC	0.346	0.643	0.308	0.117	
LDLRAP1	rs12027135	1	25.78	TC,LDL	0.010	0.023	0.080	0.757	
PIGV-NR0B2	rs12748152	1	27.14	HDL,LDL,TG	0.076	0.594	0.024	0.288	
PABPC4	rs4660293	1	40.03	HDL	0.540	0.656	0.311	0.727	
PCSK9	rs2479409	1	55.50	LDL,TC	0.326	0.996	0.246	-	
ANGPTL3	rs2131925	1	63.03	TG,LDL,TC	0.176	0.524	0.142	0.836	
EVI5	rs7515577	1	93.01	TC	0.999	0.478	0.686	0.275	
SORT1	rs629301	1	109.82	LDL,TC	0.060	0.936	0.215	0.219	
ANXA9-CERS2	rs267733	1	150.96	LDL	0.789	0.126	0.339	0.832	
HDGF-PMVK	rs12145743	1	156.70	HDL	0.905	0.839	0.897	0.535	
ANGPTL1	rs4650994	1	178.52	HDL	0.479	0.096	0.866	0.242	
ZNF648	rs1689800	1	182.17	HDL	0.978	0.097	0.747	0.184	
MOSC1	rs2642442	1	220.97	TC,LDL	0.383	0.100	0.612	0.036	
GALNT2	rs4846914	1	230.30	HDL,TG	0.0064	0.574	0.016	0.279	
IRF2BP2	rs514230	1	234.86	TC,LDL	0.134	0.639	0.077	0.422	
APOB	rs1367117	2	21.26	LDL,TC	0.729	0.989	0.762	0.942	
GCKR	rs1260326	2	27.73	TG,TC	0.488	**2.71E-04**	0.026	0.482	
ABCG5/8	rs4299376	2	44.07	LDL,TC	0.038	0.739	0.038	0.378	
EHBP1	rs2710642	2	63.15	LDL	0.647	0.983	0.701	0.902	
INSIG2	rs10490626	2	118.84	LDL,TC	0.878	0.656	0.881	0.184	
LOC84931	rs2030746	2	121.31	LDL,TC	0.173	0.019	0.016	**1.96E-04**	

Loci reported to affect lipid phenotypes					From GISC discovery meta-analysis				
Locus	**Marker name**	**Chr.**	**hg19 position (Mb)**	**Associated trait(s)**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	**Comments**
RAB3GAP1	rs7570971	2	135.84	TC	0.441	0.323	0.778	0.689	
COBLL1	rs12328675	2	165.54	HDL	0.813	0.397	0.857	0.441	
ABCB11	rs2287623	2	169.83	TC	0.157	0.917	0.373	0.877	
FAM117B	rs11694172	2	203.53	TC	0.588	0.162	0.767	0.924	
CPS1	rs1047891	2	211.54	HDL	0.958	**1.38E-04**	0.174	0.645	Using rs715 as proxy, R^2=0.922
FN1	rs1250229	2	216.30	LDL	0.300	0.770	0.256	0.839	
IRS1	rs2972146	2	227.10	HDL,TG	0.122	0.148	0.341	0.718	
UGT1A1	rs11563251	2	234.68	TC,LDL	0.259	0.026	0.704	0.615	
ATG7	rs2606736	3	11.40	HDL	0.480	0.110	0.849	0.159	
RAF1	rs2290159	3	12.63	TC	0.976	0.136	0.761	0.905	
CMTM6	rs7640978	3	32.53	LDL,TC	0.062	0.044	0.0052	0.457	
SETD2	rs2290547	3	47.06	HDL	0.0095	0.959	0.032	0.742	
RBM5	rs2013208	3	50.13	HDL	0.295	0.061	0.057	0.044	
STAB1	rs13326165	3	52.53	HDL	0.164	0.747	0.333	0.763	
PXK	rs13315871	3	58.38	TC	0.643	0.716	0.452	0.301	
GSK3B	rs6805251	3	119.56	HDL	0.043	0.180	0.0038	0.235	
ACAD11	rs17404153	3	132.16	LDL,HDL	0.0012	0.974	0.0026	0.338	
MSL2L1	rs645040	3	135.93	TG	0.504	0.013	0.853	0.840	
LRPAP1	rs6831256	4	3.47	TG,TC,LDL	0.045	0.012	0.512	0.738	Using rs2699429 as proxy, R^2=0.966
C4orf52	rs10019888	4	26.06	HDL	0.778	0.108	0.328	0.842	
KLHL8	rs442177	4	88.03	TG	0.714	0.014	0.328	0.940	
FAM13A	rs3822072	4	89.74	HDL	0.806	0.346	0.930	0.132	
ADH5	rs2602836	4	100.01	HDL	0.205	0.025	0.467	0.211	
SLC39A8	rs13107325	4	103.19	HDL	0.396	0.849	0.388	-	
ARL15	rs6450176	5	53.30	HDL	0.888	-	0.754	0.615	
MAP3K1	rs9686661	5	55.86	TG	-	-	-	-	No results for this SNP or proxies
HMGCR	rs12916	5	74.66	TC,LDL	0.671	0.059	0.215	0.117	
CSNK1G3	rs4530754	5	122.86	LDL,TC	0.155	0.917	0.096	0.288	
TIMD4	rs6882076	5	156.39	TC,TG,LDL	0.131	0.776	0.312	0.170	
MYLIP	rs3757354	6	16.13	LDL,TC	0.175	0.060	0.415	-	

Loci reported to affect lipid phenotypes					From GISC discovery meta-analysis				
Locus	**Marker name**	**Chr.**	**hg19 position (Mb)**	**Associated trait(s)**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	**Comments**
HFE	rs1800562	6	26.09	LDL,TC	**3.96E-77**	**1.26E-153**	**1.52E-178**	**1.43E-29**	
HLA	rs3177928	6	32.41	TC,LDL	0.354	0.701	0.517	0.0041	
C6orf106	rs2814982	6	34.55	TC	0.238	0.900	0.172	0.607	
KCNK17	rs2758886	6	39.25	TC	0.103	0.507	0.272	0.886	
VEGFA	rs998584	6	43.76	TG,HDL	-	-	-	-	No results for this SNP or proxies
FRK	rs9488822	6	116.31	TC,LDL	0.888	0.044	0.422	0.167	
RSPO3	rs1936800	6	127.44	HDL,TG	0.232	0.329	0.140	0.043	
HBS1L	rs9376090	6	135.41	TC	**6.59E-06**	0.0075	**1.32E-06**	0.355	
CITED2	rs605066	6	139.83	HDL	0.718	0.543	0.634	0.595	
LPA	rs1564348	6	160.58	LDL,TC	0.425	0.886	0.347	0.521	
GPR146	rs1997243	7	1.08	TC	0.103	0.188	0.012	0.734	
DAGLB	rs702485	7	6.45	HDL	0.827	0.907	0.941	0.283	
SNX13	rs4142995	7	17.92	HDL	0.977	0.978	0.523	0.598	
DNAH11	rs12670798	7	21.61	TC,LDL	0.904	1.000	0.675	0.099	
MIR148A	rs4722551	7	25.99	LDL,TG,TC	0.898	0.0041	0.204	0.071	
NPC1L1	rs2072183	7	44.58	TC,LDL	-	-	-	-	No results for this SNP or proxies
IKZF1	rs4917014	7	50.31	HDL	0.203	0.178	0.145	0.273	
TYW1B	rs13238203	7	72.13	TG	0.541	0.881	0.539	0.819	
MLXIPL	rs17145738	7	72.98	TG,HDL	0.260	0.077	0.096	0.666	
MET	rs38855	7	116.36	TG	0.840	0.525	0.857	0.233	
KLF14	rs4731702	7	130.43	HDL	0.656	0.504	0.880	0.948	
TMEM176A	rs17173637	7	150.53	HDL	0.013	0.514	0.055	0.491	
PPP1R3B	rs9987289	8	9.18	HDL,TC,LDL	0.566	0.0013	0.311	-	
PINX1	rs11776767	8	10.68	TG	0.503	0.253	0.688	0.244	
NAT2	rs1495741	8	18.27	TG,TC	0.468	**1.57E-11**	0.0038	0.599	
LPL	rs12678919	8	19.84	TG,HDL	0.541	0.905	0.300	0.818	
SOX17	rs10102164	8	55.42	LDL,TC	0.036	0.852	0.107	0.651	
CYP7A1	rs2081687	8	59.39	TC,LDL	0.376	0.114	0.610	0.472	
TRPS1	rs2293889	8	116.60	HDL	0.848	0.021	0.237	0.860	
TRIB1	rs2954029	8	126.49	TG,TC,LDL,HDL	0.842	**1.12E-04**	0.143	**4.03E-05**	

Loci reported to affect lipid phenotypes					From GISC discovery meta-analysis				
Locus	**Marker name**	**Chr.**	**hg19 position (Mb)**	**Associated trait(s)**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	**Comments**
PLEC1	rs11136341	8	145.04	LDL,TC	0.867	0.798	0.409	0.756	
VLDLR	rs3780181	9	2.64	TC,LDL	0.843	0.917	0.723	0.777	
TTC39B	rs581080	9	15.31	HDL,TC	0.054	0.832	0.161	0.365	
ABCA1	rs1883025	9	107.66	HDL,TC	0.989	0.495	0.812	0.264	
ABO	rs9411489	9	136.16	LDL,TC	0.358	0.188	0.110	**2.54E-07**	Using rs651007 as proxy, R^2=1.000
AKR1C4	rs1832007	10	5.25	TG	0.023	0.093	0.229	0.758	
VIM-CUBN	rs10904908	10	17.26	TC	-	-	0.093	-	
MARCH8-ALOX5	rs970548	10	46.01	HDL,TC	0.848	0.060	0.412	0.427	
JMJD1C	rs10761731	10	65.03	TG	0.030	0.592	0.116	0.731	
CYP26A1	rs2068888	10	94.84	TG	0.133	0.049	0.005	0.495	
GPAM	rs2255141	10	113.93	TC,LDL	0.390	0.852	0.404	0.373	
AMPD3	rs2923084	11	10.39	HDL	0.306	0.159	0.123	0.579	
SPTY2D1	rs10128711	11	18.63	TC	0.680	0.882	0.759	0.237	
LRP4	rs3136441	11	46.74	HDL	0.116	0.678	0.062	0.711	
OR4C46	rs11246602	11	51.51	HDL	0.984	0.566	0.704	0.251	
FADS1-2-3	rs174546	11	61.57	TG,LDL,TC,HDL	0.901	**7.43E-10**	0.023	0.051	
KAT5	rs12801636	11	65.39	HDL	0.088	0.304	0.043	0.495	
MOGAT2-DGAT2	rs499974	11	75.46	HDL	0.807	0.669	0.884	0.333	
APOA1	rs964184	11	116.65	TG,TC,HDL,LDL	0.706	0.246	0.583	0.956	
PHLDB1	rs11603023	11	118.49	TC	0.182	0.027	0.876	0.691	
UBASH3B	rs7941030	11	122.52	TC,HDL	0.844	0.0056	0.470	0.363	
ST3GAL4	rs11220462	11	126.24	LDL,TC	0.354	0.161	0.683	0.021	
PHC1-A2ML1	rs4883201	12	9.08	TC	0.591	0.049	0.411	0.811	
PDE3A	rs7134375	12	20.47	HDL	0.165	0.521	0.265	0.400	
LRP1	rs11613352	12	57.79	TG,HDL	0.512	0.239	0.262	**1.44E-04**	
MVK	rs7134594	12	110.00	HDL	0.023	0.149	0.019	0.655	
BRAP	rs11065987	12	112.07	TC,LDL	0.390	0.0052	0.043	0.185	
HNF1A	rs1169288	12	121.42	TC,LDL	0.326	0.488	0.627	0.043	
SBNO1	rs4759375	12	123.80	HDL	0.593	0.630	0.596	0.327	
ZNF664	rs4765127	12	124.46	HDL,TG	0.182	0.223	0.208	0.130	

Loci reported to affect lipid phenotypes					From GISC discovery meta-analysis				
Locus	**Marker name**	**Chr.**	**hg19 position (Mb)**	**Associated trait(s)**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	**Comments**
SCARB1	rs838880	12	125.26	HDL	0.158	0.948	0.286	0.886	
BRCA2	rs4942486	13	32.95	LDL	0.197	0.296	0.062	0.703	
NYNRIN	rs8017377	14	24.88	LDL	0.636	0.703	0.890	0.051	
ZBTB42-AKT1	rs4983559	14	105.28	HDL	0.335	0.641	0.428	0.042	
CAPN3	rs2412710	15	42.68	TG	-	-	-	-	No results for this SNP or proxies
FRMD5	rs2929282	15	44.25	TG	0.640	0.190	0.140	0.406	
LIPC	rs1532085	15	58.68	HDL,TC,TG	0.292	0.348	0.557	0.834	
LACTB	rs2652834	15	63.40	HDL	0.905	0.796	0.992	0.122	
PDXDC1	rs3198697	16	15.13	TG	0.555	0.182	0.443	0.283	
CTF1	rs11649653	16	30.92	TG	0.222	0.832	0.339	0.838	
FTO	rs1121980	16	53.81	HDL,TG	0.700	0.166	0.457	0.710	
CETP	rs3764261	16	56.99	HDL,LDL,TC,TG	0.838	0.432	0.875	0.633	
LCAT	rs16942887	16	67.93	HDL	0.081	0.628	0.285	0.904	
HPR	rs2000999	16	72.11	TC,LDL	0.189	0.011	0.958	0.025	
CMIP	rs2925979	16	81.53	HDL	0.844	0.510	0.572	0.118	
DLG4	rs314253	17	7.09	TC,LDL	0.055	0.154	0.021	0.828	
STARD3	rs11869286	17	37.81	HDL	0.029	0.068	0.210	0.866	
MPP3	rs8077889	17	41.88	TG	0.600	0.624	0.319	0.379	
OSBPL7	rs7206971	17	45.43	LDL,TC	0.240	0.059	0.712	0.362	
APOH-PRXCA	rs1801689	17	64.21	LDL	-	-	-	-	No results for this SNP or proxies
ABCA8	rs4148008	17	66.88	HDL	0.853	0.527	0.458	0.550	Using rs4148005 as proxy, R^2=1.000
PGS1	rs4129767	17	76.40	HDL	0.466	0.033	0.078	**3.21E-04**	
LIPG	rs7241918	18	47.16	HDL,TC	0.694	0.025	0.734	0.083	
MC4R	rs12967135	18	57.85	HDL	0.218	0.0075	0.012	0.148	
INSR	rs7248104	19	7.22	TG	0.249	9.56E-04	0.019	0.070	
ANGPTL4	rs7255436	19	8.43	HDL	0.771	0.022	0.896	0.029	
LDLR	rs6511720	19	11.20	LDL,TC	0.961	0.391	0.743	0.718	
ANGPTL8	rs737337	19	11.35	HDL	0.233	0.282	0.792	0.800	
CILP2	rs10401969	19	19.41	TC,TG,LDL	0.281	0.023	0.047	0.331	
PEPD	rs731839	19	33.90	TG,HDL	0.842	0.398	0.890	0.252	

Loci reported to affect lipid phenotypes					From GISC discovery meta-analysis				
Locus	**Marker name**	**Chr.**	**hg19 position (Mb)**	**Associated trait(s)**	**p(Fe)**	**p(Tf)**	**p(Sat)**	**p(Ferri)**	**Comments**
APOE	rs4420638	19	45.42	LDL,TC,HDL	-	-	-	-	No results for this SNP or proxies
FLJ36070	rs492602	19	49.21	TC	0.098	0.833	0.114	0.155	
HAS1	rs17695224	19	52.32	HDL	0.295	0.535	0.029	0.083	
LILRA3	rs386000	19	54.79	HDL	0.035	0.490	0.027	0.395	
SPTLC3	rs364585	20	12.96	LDL	0.500	0.362	0.349	-	
SNX5	rs2328223	20	17.85	LDL	0.383	**6.30E-05**	0.649	0.444	
ERGIC3	rs2277862	20	34.15	TC	0.199	0.150	0.459	0.557	
MAFB	rs2902940	20	39.09	TC,LDL	0.617	0.460	0.472	0.193	
TOP1	rs6029526	20	39.67	LDL,TC	0.813	0.064	0.188	0.871	
HNF4A	rs1800961	20	43.04	HDL,TC	-	-	-	-	No results for this SNP or proxies
PLTP	rs6065906	20	44.55	HDL,TG	0.697	0.549	0.822	0.262	
UBE2L3	rs181362	22	21.93	HDL	0.020	0.269	0.027	0.380	
MTMR3	rs5763662	22	30.38	LDL	-	0.327	-	-	
TOM1	rs138777	22	35.71	TC	0.602	0.842	0.646	0.431	
PLA2G6	rs5756931	22	38.55	TG	0.962	0.442	0.914	0.289	
PPARA	rs4253772	22	46.63	TC,LDL	0.412	0.101	0.820	0.726	

Supplementary Table 9. SNP associations in *HFE* YY subjects only. Statistical tests were performed and results for the QIMR and HEIRS data were meta-analysed as described in the paper.

Iron							HEIRS			QIMR adults			Combined		
SNP	**CHR**	**BP (B37)**	**Nearest gene**	**A1**	**A2**	**Freq1**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**
rs744653	2	190,378,750	*SLC40A1*	T	C	0.854	0.060	0.059	0.312	-0.106	0.119	0.372	0.027	0.053	0.614
rs8177240	3	133,477,701	*TF*	T	G	0.669	-0.115	0.059	0.053	-0.009	0.120	0.940	-0.094	0.053	0.077
rs9990333	3	195,827,205	*TFRC*	T	C	0.460	0.117	0.062	0.057	-0.046	0.120	0.703	0.083	0.055	0.129
rs7385804	7	100,235,970	*TFR2*	A	C	0.621	0.182	0.059	0.0020	0.161	0.119	0.174	0.178	0.053	0.00076
rs4921915	8	18,272,466	*NAT2*	A	G	0.782	-0.075	0.059	0.209	-0.177	0.118	0.135	-0.095	0.053	0.073
rs651007	9	136,153,875	*ABO*	T	C	0.202	0.020	0.060	0.735	0.019	0.121	0.877	0.020	0.054	0.710
rs6486121	11	13,355,770	*ARNTL*	T	C	0.631	-0.037	0.059	0.534	-0.136	0.119	0.256	-0.057	0.053	0.288
rs174577	11	61,604,814	*FADS2*	A	C	0.330	-0.074	0.060	0.219	0.116	0.119	0.330	-0.035	0.054	0.509
rs411988	17	56,709,034	*TEX14*	A	G	0.564	0.101	0.060	0.091	0.104	0.120	0.387	0.102	0.054	0.058
rs855791	22	37,462,936	*TMPRSS6*	A	G	0.446	-0.022	0.060	0.720	-0.304	0.115	0.008	-0.083	0.053	0.121

Transferrin							HEIRS			QIMR adults			Combined		
SNP	**CHR**	**BP (B37)**	**Nearest gene**	**A1**	**A2**	**Freq1**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**
rs744653	2	190,378,750	*SLC40A1*	T	C	0.854	0.042	0.060	0.485	0.136	0.117	0.245	0.061	0.053	0.249
rs8177240	3	133,477,701	*TF*	T	G	0.669	-0.298	0.058	2.16E-07	-0.338	0.111	0.0023	-0.306	0.051	1.93E-09
rs9990333	3	195,827,205	*TFRC*	T	C	0.460	0.018	0.063	0.777	0.134	0.117	0.253	0.044	0.055	0.430
rs7385804	7	100,235,970	*TFR2*	A	C	0.621	0.007	0.061	0.909	0.150	0.116	0.196	0.038	0.054	0.485
rs4921915	8	18,272,466	*NAT2*	A	G	0.782	0.007	0.060	0.906	-0.106	0.116	0.360	-0.017	0.053	0.751
rs651007	9	136,153,875	*ABO*	T	C	0.202	-0.012	0.060	0.093	-0.043	0.118	0.719	-0.089	0.054	0.097
rs6486121	11	13,355,770	*ARNTL*	T	C	0.631	0.003	0.060	0.958	0.123	0.115	0.285	0.029	0.053	0.588
rs174577	11	61,604,814	*FADS2*	A	C	0.330	-0.059	0.061	0.332	0.264	0.113	0.020	0.013	0.053	0.806
rs411988	17	56,709,034	*TEX14*	A	G	0.564	0.023	0.061	0.702	0.009	0.118	0.942	0.020	0.054	0.709
rs855791	22	37,462,936	*TMPRSS6*	A	G	0.446	0.036	0.061	0.554	0.303	0.112	0.007	0.096	0.053	0.072

Transferrin Saturation							HEIRS			QIMR adults			Combined		
SNP	**CHR**	**BP (B37)**	**Nearest gene**	**A1**	**A2**	**Freq1**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**

rs744653	2	190,378,750	*SLC40A1*	T	C	0.854	0.041	0.059	0.488	-0.042	0.130	0.746	0.027	0.054	0.619
rs8177240	3	133,477,701	*TF*	T	G	0.669	0.033	0.059	0.581	-0.057	0.129	0.658	0.017	0.054	0.752
rs9990333	3	195,827,205	*TFRC*	T	C	0.460	0.111	0.061	0.070	-0.106	0.129	0.413	0.071	0.055	0.198
rs7385804	7	100,235,970	*TFR2*	A	C	0.621	0.165	0.059	0.005	-0.100	0.128	0.435	0.119	0.054	0.026
rs4921915	8	18,272,466	*NAT2*	A	G	0.782	-0.073	0.059	0.217	0.008	0.130	0.954	-0.059	0.054	0.272
rs651007	9	136,153,875	*ABO*	T	C	0.202	0.073	0.060	0.220	-0.036	0.131	0.784	0.054	0.054	0.317
rs6486121	11	13,355,770	*ARNTL*	T	C	0.631	-0.046	0.059	0.437	-0.116	0.129	0.368	-0.058	0.054	0.280
rs174577	11	61,604,814	*FADS2*	A	C	0.330	-0.048	0.060	0.421	0.035	0.130	0.787	-0.034	0.054	0.536
rs411988	17	56,709,034	*TEX14*	A	G	0.564	0.089	0.060	0.137	-0.004	0.129	0.977	0.073	0.054	0.181
rs855791	22	37,462,936	*TMPRSS6*	A	G	0.446	-0.040	0.060	0.505	-0.278	0.125	0.026	-0.084	0.054	0.119

Ferritin							**HEIRS**			**QIMR adults**			**Combined**		
SNP	**CHR**	**BP (B37)**	**Nearest gene**	**A1**	**A2**	**Freq1**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**	**Effect**	**SE**	**P**
rs744653	2	190,378,750	*SLC40A1*	T	C	0.854	0.031	0.057	0.583	-0.086	0.117	0.464	0.009	0.051	0.861
rs8177240	3	133,477,701	*TF*	T	G	0.669	0.010	0.057	0.864	0.073	0.117	0.534	0.022	0.051	0.670
rs9990333	3	195,827,205	*TFRC*	T	C	0.460	0.101	0.059	0.085	-0.145	0.116	0.213	0.051	0.052	0.327
rs7385804	7	100,235,970	*TFR2*	A	C	0.621	-0.030	0.057	0.602	-0.067	0.117	0.566	-0.037	0.052	0.471
rs4921915	8	18,272,466	*NAT2*	A	G	0.782	-0.053	0.057	0.356	0.004	0.118	0.970	-0.042	0.051	0.415
rs651007	9	136,153,875	*ABO*	T	C	0.202	0.035	0.057	0.544	0.140	0.118	0.233	0.055	0.052	0.285
rs6486121	11	13,355,770	*ARNTL*	T	C	0.631	-0.089	0.057	0.116	-0.386	0.108	3.36E-04	-0.153	0.050	0.0022
rs174577	11	61,604,814	*FADS2*	A	C	0.330	-0.023	0.057	0.690	-0.077	0.117	0.512	-0.033	0.052	0.518
rs411988	17	56,709,034	*TEX14*	A	G	0.564	-0.006	0.058	0.912	0.030	0.118	0.799	0.001	0.052	0.990
rs855791	22	37,462,936	*TMPRSS6*	A	G	0.446	0.096	0.057	0.092	-0.411	0.107	0.000	-0.016	0.051	0.755

Supplementary Table 10. Associations between genetic prediction scores (from lead SNPs at significant or suggestive loci) from the population-based Discovery + Replication datasets, and the observed phenotypes in the *HFE* C282Y homozygotes from the HEIRS Study. Sex stratified regression analysis, adjusted for age, phlebotomy status and blood donation history. Note that the near-significant correlation for ferritin in men is in the opposite direction to that expected.

Trait:	**Sex**	**N**	**Beta ± SE**	**R^2 (percent of variance)**	**P-value**
Iron	Male	119	0.02 ± 0.09	0%	0.83
	Female	158	0.13 ± 0.08	1.5%	0.12
Transferrin	Male	119	0.35 ± 0.09	12%	0.0001
	Female	158	0.21 ± 0.08	4.5%	0.007
Saturation	Male	119	-0.03 ± 0.09	0%	0.74
	Female	158	0.09 ± 0.08	0.8%	0.27
Log_{10}Ferritin	Male	119	-0.17 ± 0.09	3%	0.06
	Female	158	-0.01 ± 0.08	0%	0.94