SUPPLEMENTAL INFORMATION

Individual Study Methods and Cohort Descriptions

Supplemental Methods

Additional human replication findings

Pleiotropy analysis

Supplemental Tables

Table S1: Population Characteristics of Each Cohort

Table S2: Erythrocyte trait definitions
Table S3: Replication of established loci

Table S4: Ethnic-specific results

Table S5: Replication of novel findings in the Gutenberg Health Study (cohorts GHS1 and

GHS2), the Genes and Blood-Clotting (GBC) Study, the NEO study, and the

JUPITER trial (Replication data only)

Table S6: Replication of novel findings in the Gutenberg Health Study (cohorts GHS1 and

GHS2), the Genes and Blood-Clotting (GBC) Study, the NEO study, and the

JUPITER trial (Discovery and Replication data combined)

Table S7: Fine mapping of novel and established loci identified in European ancestry

meta-analysis by MANTRA trans-ethnic analysis.

Table S8: ENCODE analysis of functional elements for the MCH chromosome 8 region

(RBPMS)

Table S9: Mouse QTL validation of MANTRA transethnic findings (summary, organized

by trait)

Table S10: Correlation matrix red blood cell traits

Supplemental Figures

-log P value plots and varLD plots

Supplemental References

Acknowledgements

Individual Study Methods and Cohort Descriptions

The cohorts contributing to this study were general population samples. All participants provided written informed consent and studies were approved by their local Research Ethics Committees and/or Institutional Review Boards. Summary demographic characteristics are listed in **Table S2**. References for ascertainment methods and erythrocyte trait measurement for each participating study are given below.

European Ancestry Cohorts

Age, Gene/Environment Susceptibility-Reykjavik Study (AGES)^{1,2}

Atherosclerosis Risk in Communities Study (ARIC)^{2,3}

Austrian Stroke Prevention Study (ASPS) 4

Baltimore Longitudinal Study of Aging (BLSA)⁵

Coronary Artery Risk Development in Young Adults (CARDIA)⁶

Cardiovascular Health Study (CHS)^{2,7}

Framingham Heart Study (FHS)^{2,8}

Johns Hopkins Genetic Study of Atherosclerosis Risk (GeneSTAR)9-11

Health, Aging, and Body Composition (HealthABC)9,12

Invecchiare in Chianti Study (InCHIANTI)⁵

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER/PHASE)¹³

Rotterdam Study I (RS-I)^{2,14}

Rotterdam Study II (RS-II)14

Rotterdam Study III (RS-III)14

East-Asian Ancestry Cohorts

The BioBank Japan Project (RIKEN)^{15,16}

Asian Genetic Epidemiology Network (AGEN)^{17,18}

African-American Ancestry Cohorts

Atherosclerosis Risk in Communities Study (ARIC)3,12,19

Jackson Heart Study (JHS)^{12,19,20}

Coronary Artery Risk Development in Young Adults (CARDIA)^{6,12,19}

Cardiovascular Health Study (CHS)⁷

Johns Hopkins Genetic Study of Atherosclerosis Risk (GeneSTAR) 9-11

Health, Aging, and Body Composition (HealthABC)^{9,12}
Women's Health Initiative (WHI)^{12,19,21}

Replication CohortsGutenberg Health Study (GHS)²²

Genes and Blood-Clotting Study (GBC)²³

Netherlands Epidemiology of Obesity Study (NEO)²⁴

JUPITER Trial²⁵

HealthyAging in Neighborhoods of Diversity across the Life Span (HANDLS)^{9,12}

Supplemental Methods and Results

Additional Human Replication Findings

The discovery and replication results were meta-analysed separately for the EUR and AFR cohorts in METAL and with RE2, and as a further step, the combined METAL results were further meta-analysed with the EAS discovery data using METAL, MANTRA and RE2 methods. (**Table S5**).

In both the replication and discovery samples, we verified the allele directions in the original input files to address the question whether allele flipping could account for the *RBPMS* finding for MCH. In our results rs2979489 only became genome-wide significant in the trans-ethnic meta-analysis; the individual ethnic-specific results were not significant. We checked the allele frequencies in several 1000G panels. In all cases A was the most common allele and G the rarest, as is the case in our HapMap analyses.

Pleiotropy analysis

To further relate these findings in the rbpms gene family back to the human association data, we evaluated *RBPMS* in WBC traits and *RBPMS2* in our RBC analyses and WBC traits. The purpose of this analysis was to explore possible pleiotropy which might suggest effects on an earlier hematopoietic progenitor cell.

Variants in the *RBPMS* and *RBPMS2* gene regions (+/- 50kb from exon borders) showed no association with WBC traits in a trans-ethnic analysis of the same cohorts. Further, there was no evidence of association with erythrocyte traits in the *RBPMS2* region. Therefore, while there may be evidence of a functional class effect of the rbpms genes in the zebrafish experimental data, the human association data suggest that genetic variation in the *RBPMS* locus specifically influences erythrocyte traits in humans and that *RBPMS* is likely the true causal gene underlying this association.

Supplemental Figures

Figure S1

-log P value plots and varLD plots

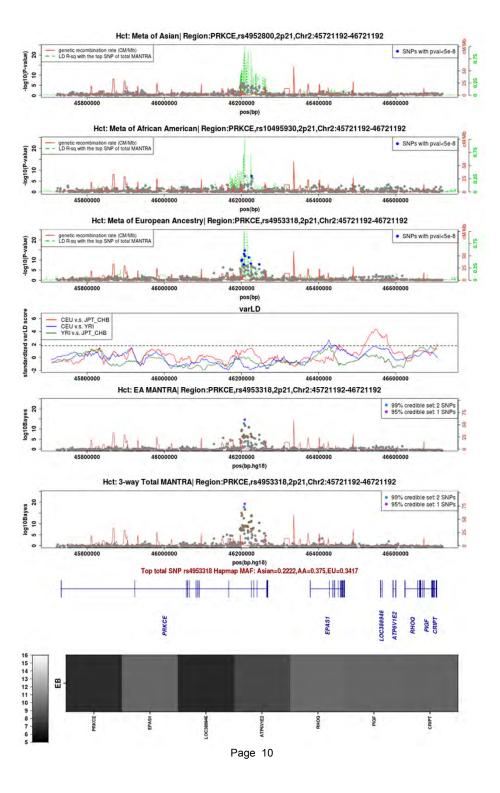
Regional association plots for loci identified by our trans-ethnic analysis. For each trait-locus identified in the MANTRA analyses, including the novel and previously known loci, we have plotted the individual ethnicity-specific meta-analysis (METAL) results, the trans-ethnic fixed effects meta-analysis (METAL) and the Bayesian meta-analysis (MANTRA) results with SNPs colored according to the credible interval set for that region. Also shown for each region is the pair-wise LD correlation (varLD) and RNA expression of genes within the locus in erythroblast cell lines).²⁷

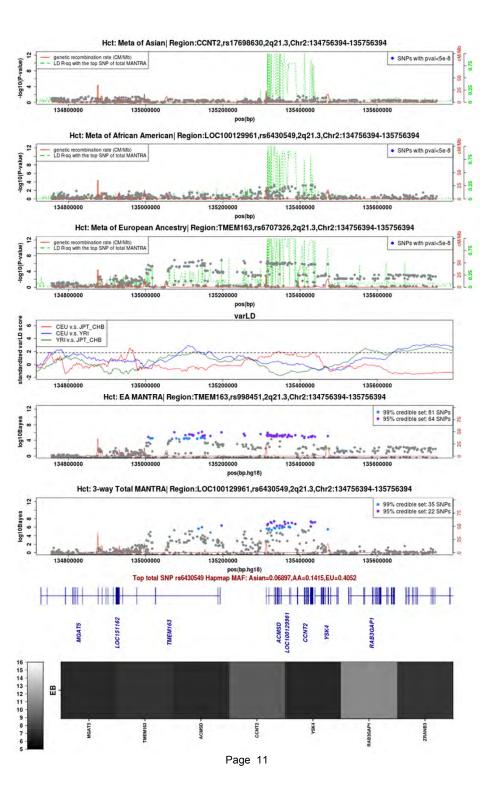
trait	Region	chr	cyto	Index SNP	Total_gene	Page
Hct	1	2	2p21	rs4953318	PRKCE	10
Hct	2	2	2q21	rs6430549	ACMSD	11
Hct	3	4	4q12	rs218237	KIT	12
Hct	4	4	4q21	rs1398018	SHROOM3	13
Hct	5	6	6p22	rs1800562	HFE	14
Hct	6	6	6q23	rs9399137	HBS1L	15
Hct	7	7	7q22	rs2075672	ACTL6B	16
Hct	8	7	7q31	rs2299433	MET	17
Hct	9	7	7q36	rs10224210	PRKAG2	18
Hct	10	9	9q34	rs495828	ABO	19
Hct	11	10	10q21	rs16926246	HK1	20
Hct	12	12	12q24	rs3184504	SH2B3	21
Hct	13	15	15q24	rs4886755	NRG4	22
Hct	14	17	17q21	rs241030	CRHR1	23
Hct	15	22	22q12	rs2413450	TMPRSS6	24
Hct	16	22	22q13	rs5765524	FBLN1	25
1100	10		22910	1007 00024	I DEINI	20
Hb	1	2	2p21	rs4953318	PRKCE	27
Hb	2	3	3q29	rs12632706	TFRC	28
Hb	3	4	4q12	rs170117	KIT	29
Hb	4	6	6p22	rs1800562	HFE	30
Hb	5	6	6p21	rs412657	NOTCH4	31
Hb	6	7	7q22	rs1617640	EPO	32
Hb	7	7	7q31	rs2299433	MET	33
Hb	8	7	7q36	rs10480299	PRKAG2	34
Hb	9	9	9q34	rs495828	ABO	35
Hb	10	10	10q21	rs16926246	HK1	36
Hb	11	12	12q24	rs11066301	PTPN11	37
Hb	12	15	15q24	rs4886755	NRG4	38
Hb	13	16	16p13	rs2562181	MPG	39
Hb	14	17	17q21	rs241030	CRHR1	40
Hb	15	22	22q12	rs4820268	TMPRSS6	41
110	13	22	22412	134020200	TIVII TOOO	71
MCHC	1	1	1q23	rs2479868	SPTA1	43
MCHC	2	6	6p22	rs198846	HIST1H1T	44
MCHC	3	6	6q23	rs9376090	HBS1L	45
MCHC	4	8	8p11	rs4737009	ANK1	46
MCHC	5	12	12q24	rs671	NA	47
MCHC	6	16	16p13	rs7197554	C16orf35	48
MCHC	7	16	16q24	rs2608604	CDT1	49
MCHC	8	22	22q12	rs2413450	TMPRSS6	50
WOTTO	O	22	22912	132-110-100	TIMI TOOO	00
MCH	1	1	1q31	rs12127588	PTPRC	52
MCH	2	2	2p16	rs13019832	BCL11A	53
MCH	3	3	3p24	rs2060597	PLCL2	54
MCH	4	3	3p24	rs1505307	THRB	55
MCH	5	3	3q23	rs6791816	ATR	56
MCH	6	3	3q29	rs9859401	TFRC	57
	•	9	54 - 5	. 30000 101		0,

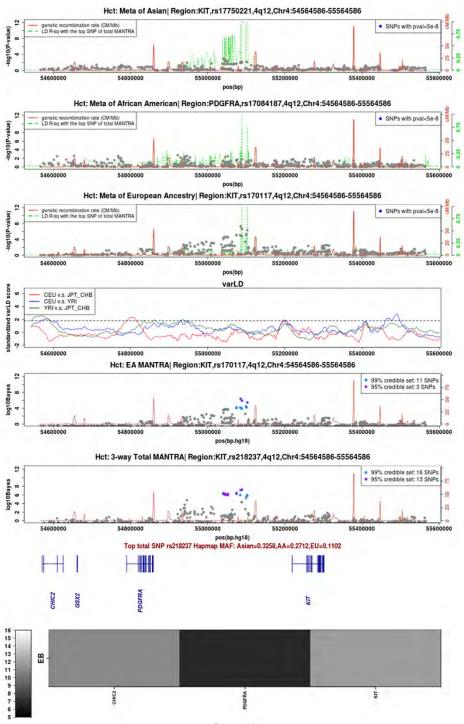
MCH	7	4	4q12	rs218237	KIT	58
MCH	8	5	5p15	rs2736100	TERT	59
MCH	9	6	6p22	rs1800562	HFE	60
MCH	10	6	6p21	rs9349205	CCND3	61
MCH	11	6	6q21	rs9400273	CCDC162P/CD164	62
MCH	12	6	6q23	rs7776054	HBS1L	63
MCH			•		CITED2/LOC655434	
	13	6	6q24	rs592423		64
MCH	14	7	7p12	rs12669559	IKZF1	65
MCH	15	7	7q22	rs12532878	MOSPD3	66
MCH	16	8	8p21	rs2076940	XPO7	67
MCH	17	8	8p12	rs2979489	RBPMS	68
MCH	18	9	9p24	rs10758656	RCL1/MIR101-2	69
MCH	19	10	10q11	rs11239550	08-mrt	70
MCH	20	10	10q11	rs17720193	NA	71
MCH	21	12	12p13	rs7309743	CCND2	72
MCH	22	12	12q24	rs2074356	NA	73
MCH	23	14	•	rs7155454	FNTB/MIR4706	74
MCH	24	15		rs7165102	C15orf44	75
MCH	25	16		rs1122794	ITFG3	76
MCH	26	17	•		ERAL1	70 77
			17q11			
MCH	27	19	•	rs8887	KIAA1881/PLIN4	78
MCH	28	19		rs2242517	GCDH	79
MCH	29	20	20q13	rs737092	RBM38	80
MCH	30	22	22q12	rs2413450	TMPRSS6	81
MCV	1	1	1q23	rs12041363	OR10R2	83
MCV	2	1	1q31	rs1036332	PTPRC/LOC100131234	84
MCV	3	1	1q44	rs3811444	TRIM58	85
MCV	4	2	2p25	rs10929547	ID2	86
MCV	5	2	2p16	rs13027161	BCL11A/MIR4432	87
MCV	6	3	3p24	rs9821630	PLCL2	88
MCV	7	3	3p24	rs1505307	THRB	89
MCV	8	3	3q23	rs6780250	ATR	90
MCV	9	3	3q29	rs3893275	ZDHHC19	91
MCV	10	4	-	rs218237	KIT	92
			4q12		TERT	
MCV	11	5	5p15	rs2736100		93
MCV	12	6	6p22	rs198833	HIST1H1T	94
MCV	13	6	6p21	rs9349205	CCND3	95
MCV	14	6	6q21	rs9374080	CD164/CCDC162P	96
MCV	15	6	6q23	rs7776054	HBS1L	97
MCV	16	6	6q24	rs592423	CITED2/LOC645434	98
MCV	17	6	6q26	rs381500	QKI	99
MCV	18	7	7p12	rs12718598	IKZF1	100
MCV	19	7	7q22	rs7385804	TFR2	101
MCV	20	8	8p21	rs10503716	XPO7	102
MCV	21	8	8p12	rs2979489	RBPMS	103
MCV	22	9	9p24	rs10758658	RCL1/MIR101-2	104
MCV	23	9	9q34	rs8176749	ABO	105
MCV	24	10	10q11	rs963029	08-mrt	106
MCV	2 4 25	12	12p13	rs11611647	CCND2	107
MCV		12			NA	107
	26 27		12q24	rs2074356		
MCV	27	14 45	14q23	rs726668	MAXMIR4706	109
MCV	28	15	15q22	rs7176565	DENND4A/MIR4511	110

MCV	29	16	16p13	rs13336641	NA	111
MCV	30	17	17q11	rs12325788	TRAF4	112
MCV	31	18	18q21	rs9949494	C18orf25	113
MCV	32	19	19p13	rs8887	KIAA1881/PLIN4	114
MCV	33	19	19p13	rs9384	GCDH	115
MCV	34	20	20q11	rs6121246	FKHL18/FOXS1	116
MCV	35	20	20q13	rs737092	RBM38	117
MCV	36	22	22q11	rs4820091	UBE2L3	118
MCV	37	22	22q12	rs5754115	FBXO7	119
MCV	38	22	22q12	rs2413450	TMPRSS6	120
MCV	39	22	22q13	rs140522	LOC440836/ODF3B	121
RBC	1	2	2p21	rs4952800	PRKCE	123
RBC	2	4	4p14	rs3860068	TMEM156	124
RBC	3	4	4q12	rs218237	KIT	125
RBC	4	6	6p21	rs9349205	CCND3	126
RBC	5	6	6q21	rs9400273	CD164/CCDC162P	127
RBC	6	6	6q23	rs9376090	HBS1L	128
RBC	7	6	6q24	rs592423	CITED2/LOC645434	129
RBC	8	7	7q22	rs2075672	ACTL6B	130
RBC	9	9	9p24	rs10758656	RCL1/MIR101-2	131
RBC	10	9	9q34	rs579459	ABO	132
RBC	11	12	12p13	rs7309743	CCND2	133
RBC	12	16	16p13	rs13339636	NA	134
RBC	13	17	17q21	rs2732706	LRRC37A	135
RBC	14	19	19p13	rs17706531	GCDH	136
RBC	15	22	22q13	rs12148	SCO2	137

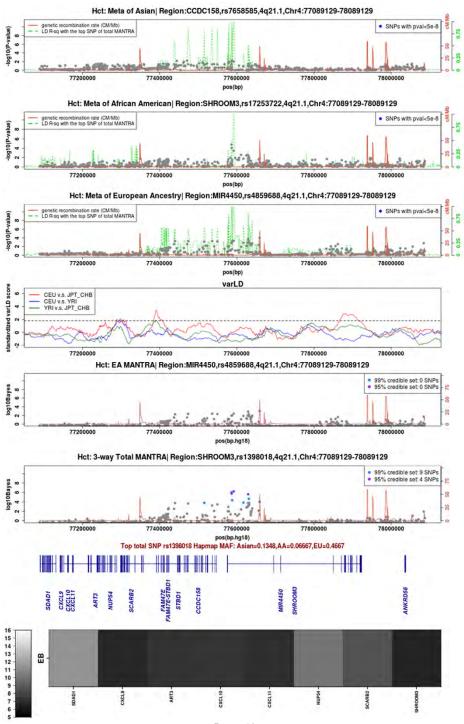
HCT



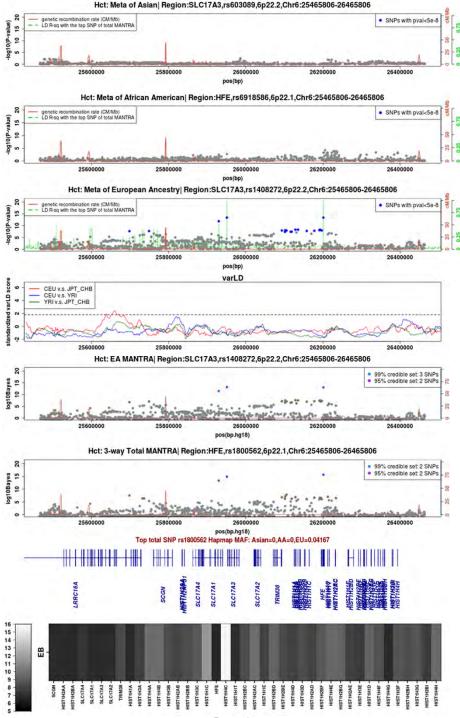




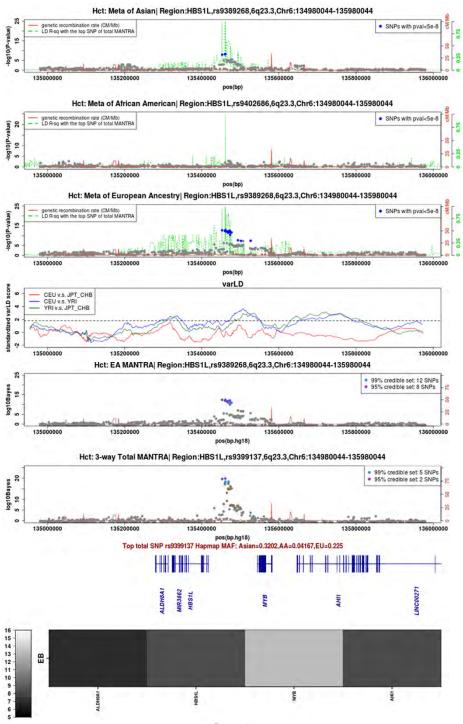
Page 12



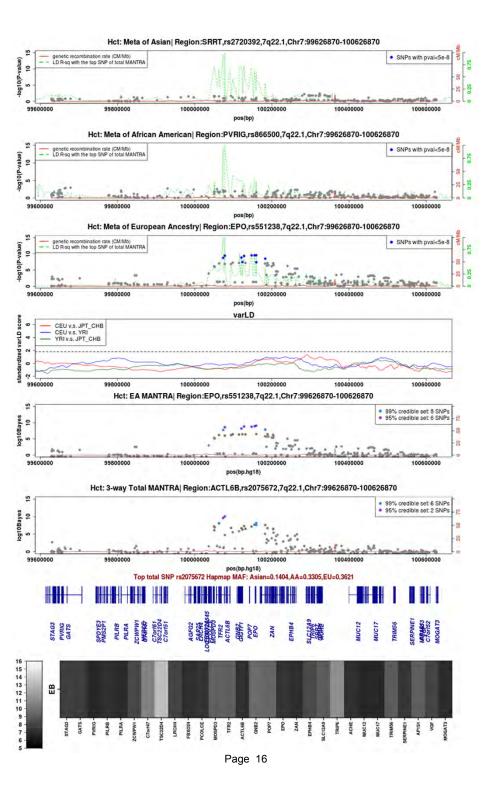
Page 13

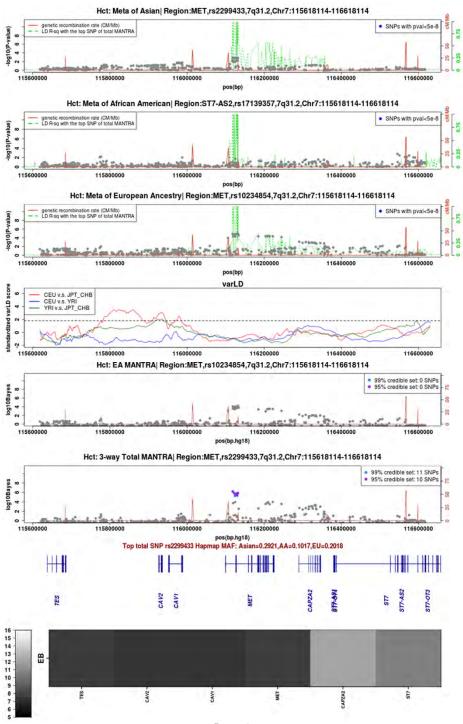


Page 14

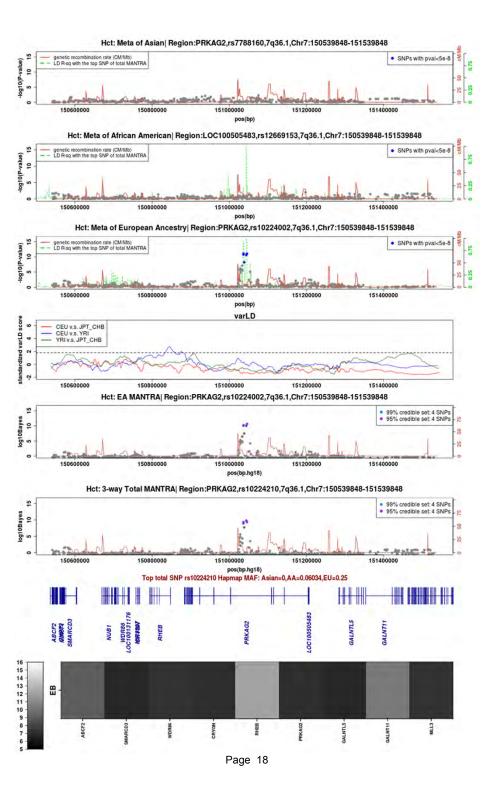


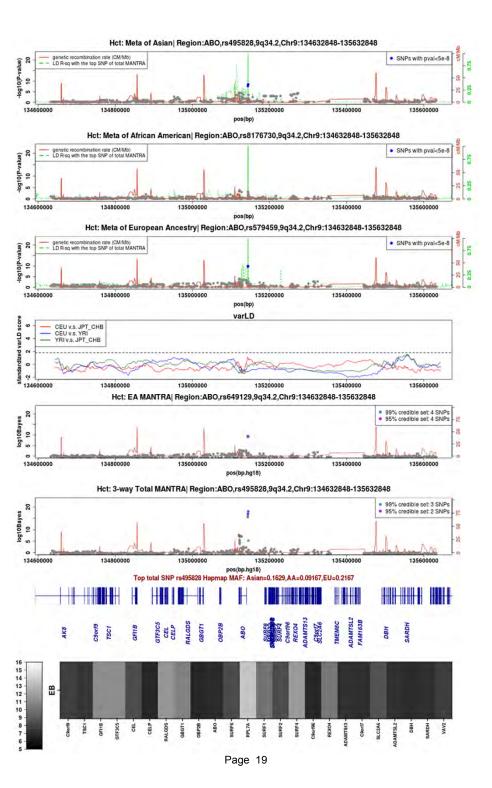
Page 15

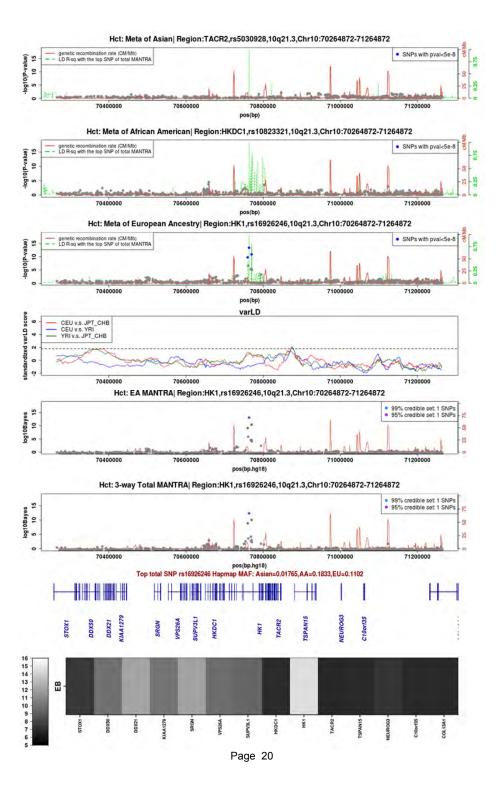


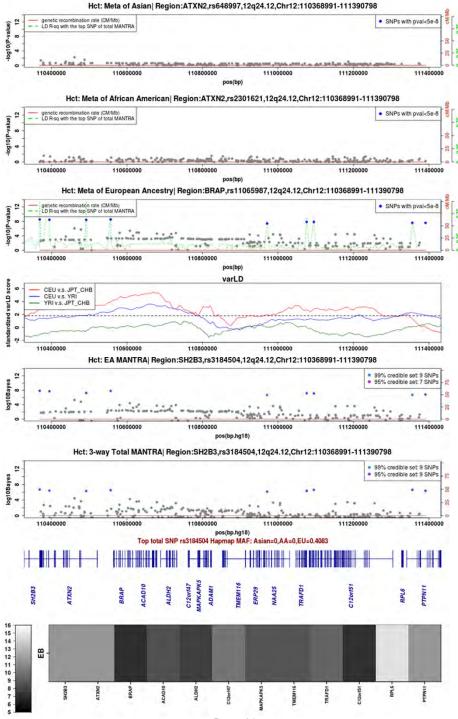


Page 17

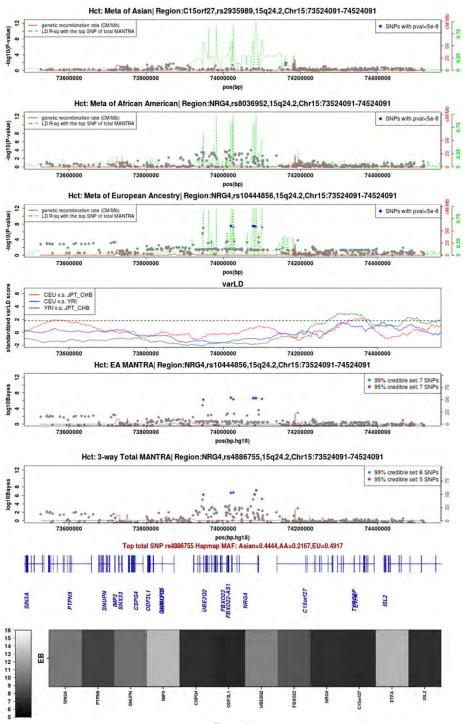




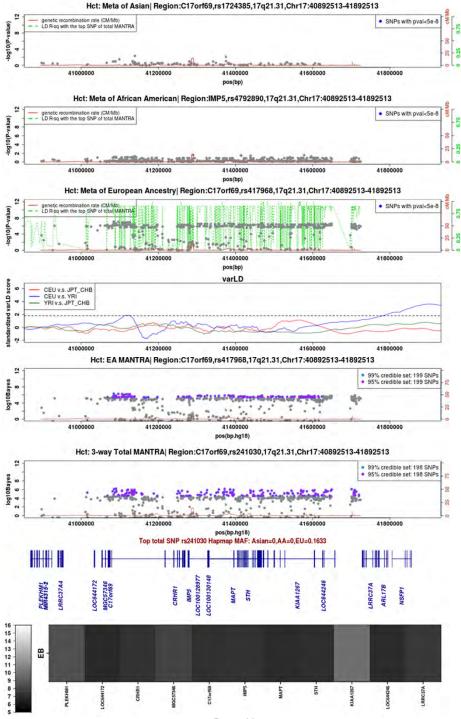




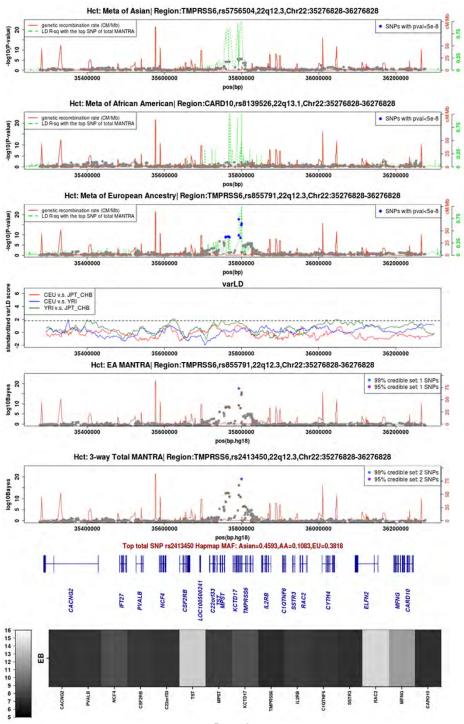
Page 21



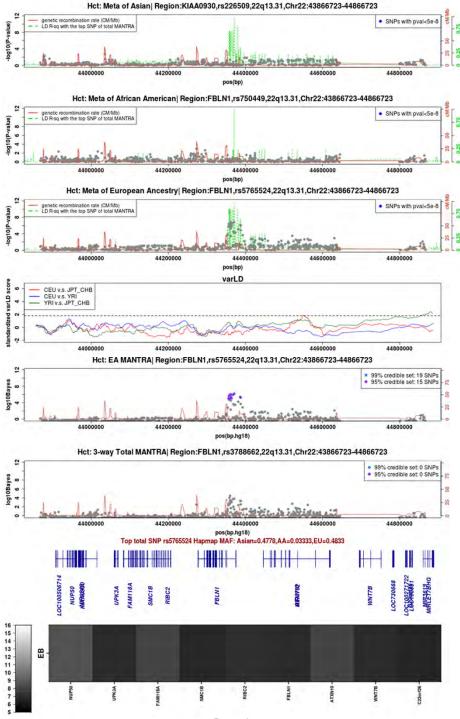
Page 22



Page 23

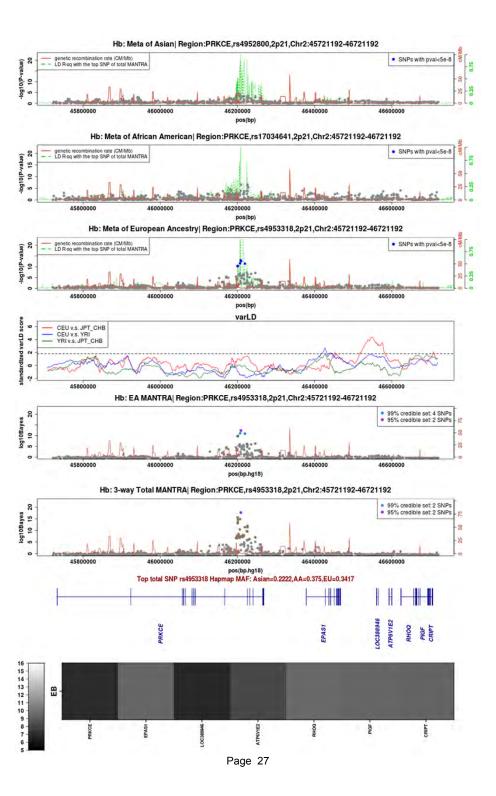


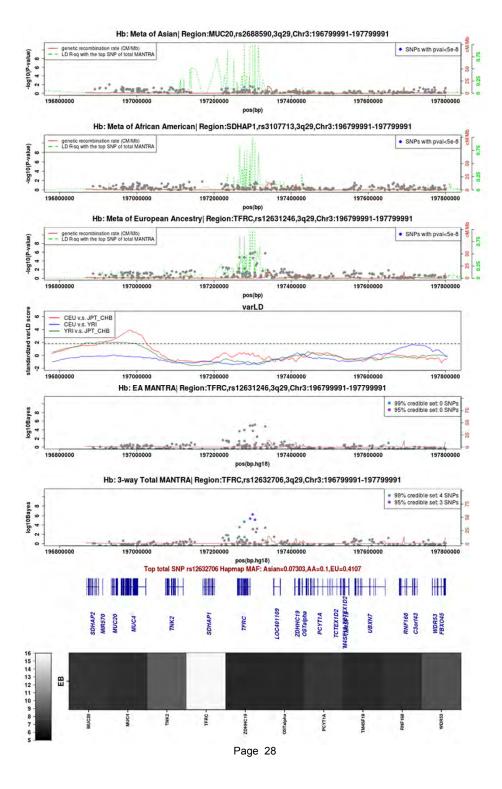
Page 24

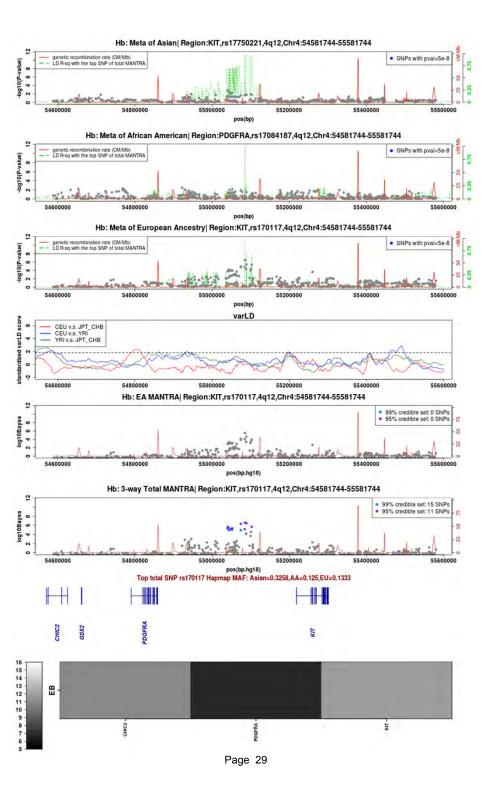


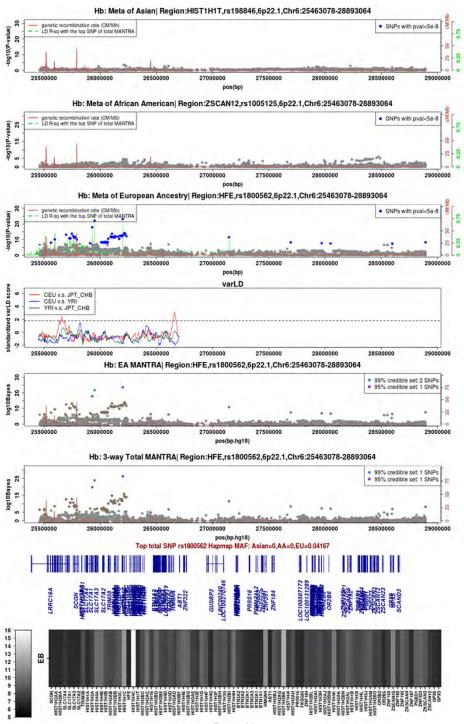
Page 25

Hb

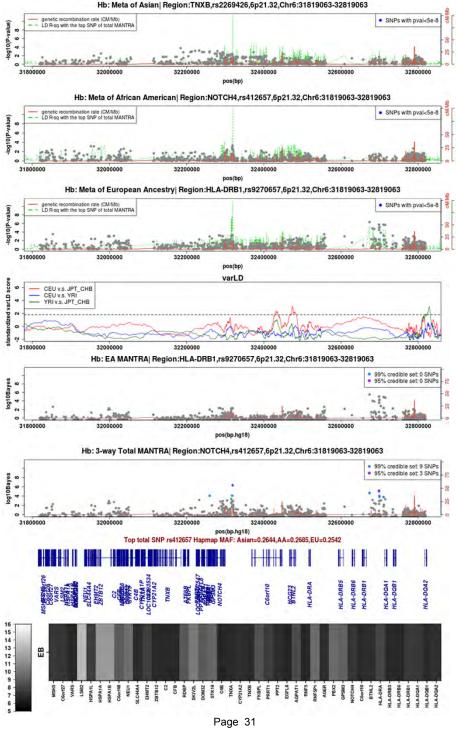


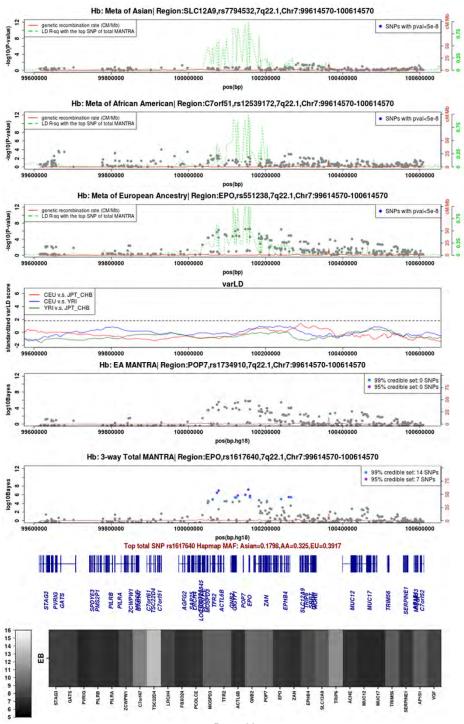




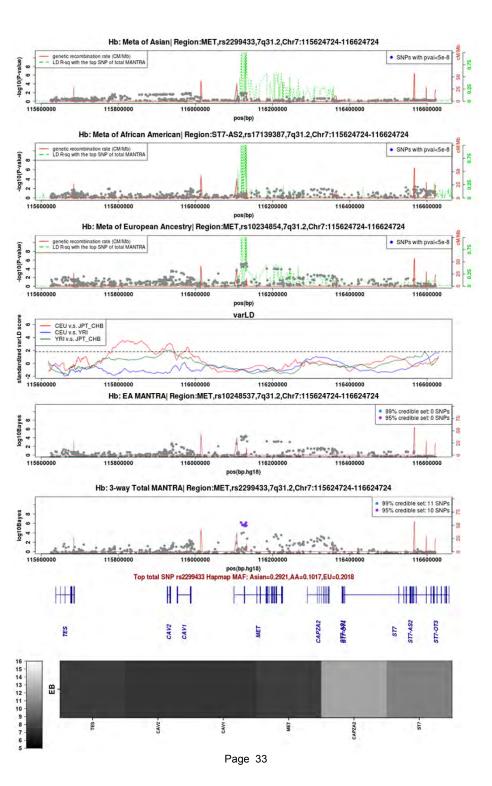


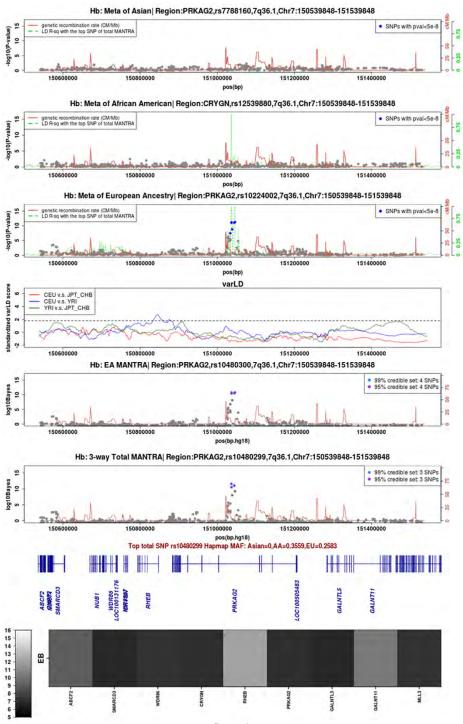
Page 30



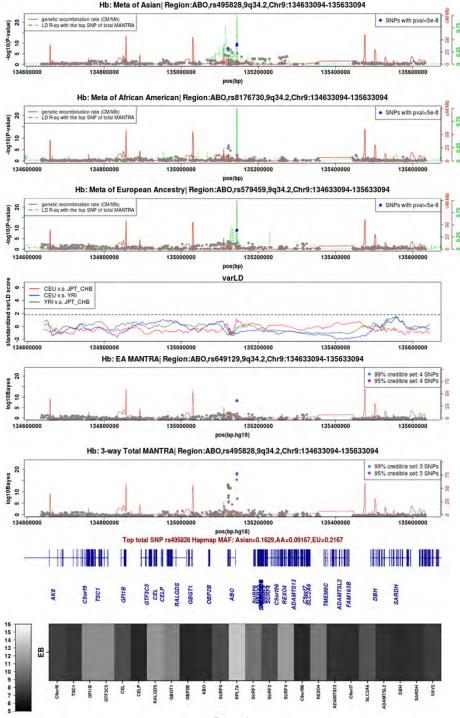


Page 32

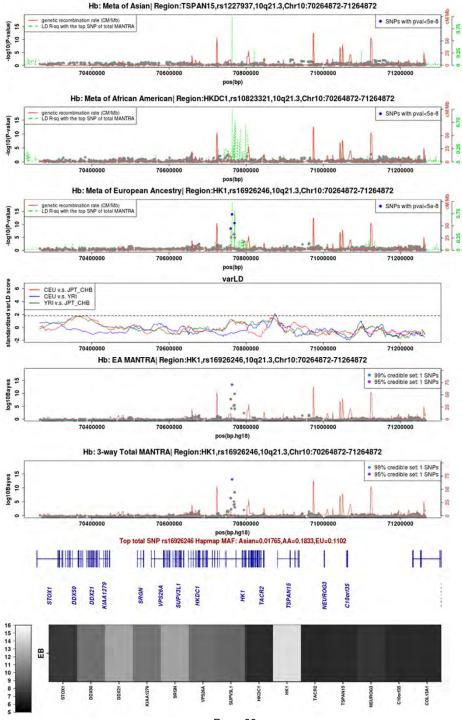




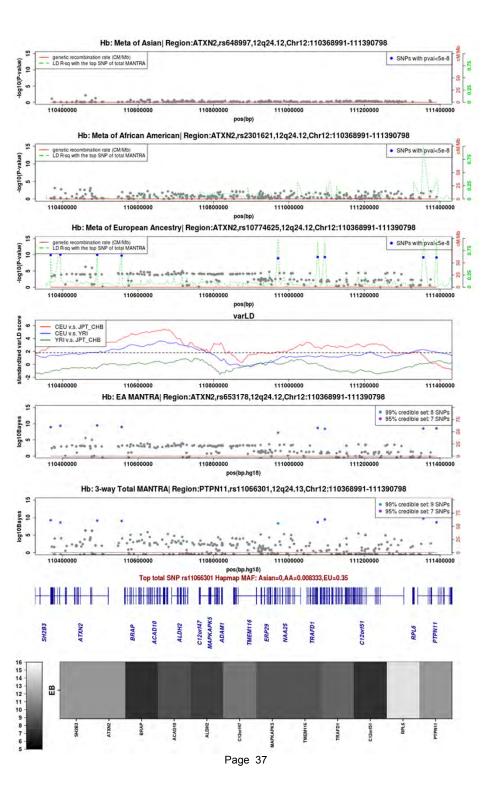
Page 34

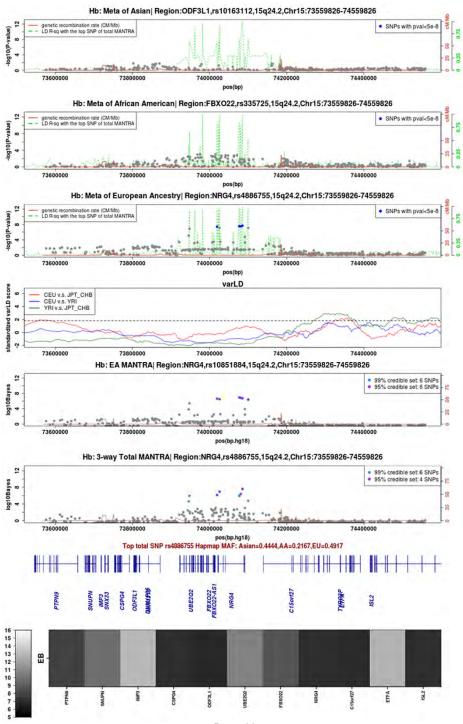


Page 35

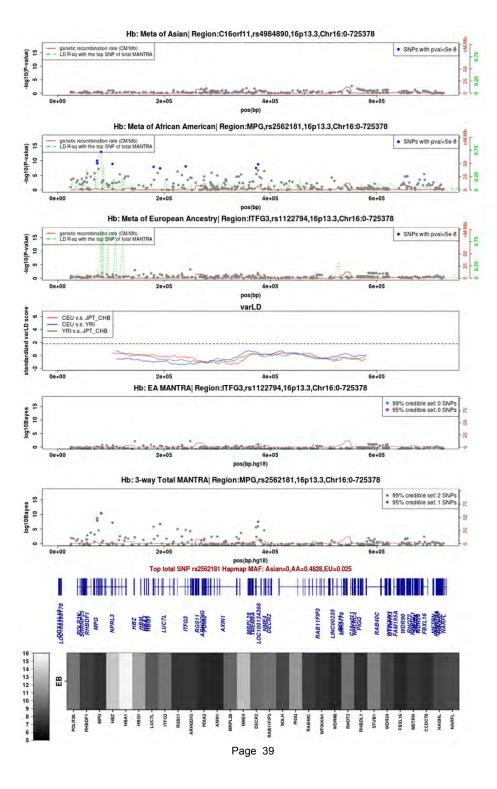


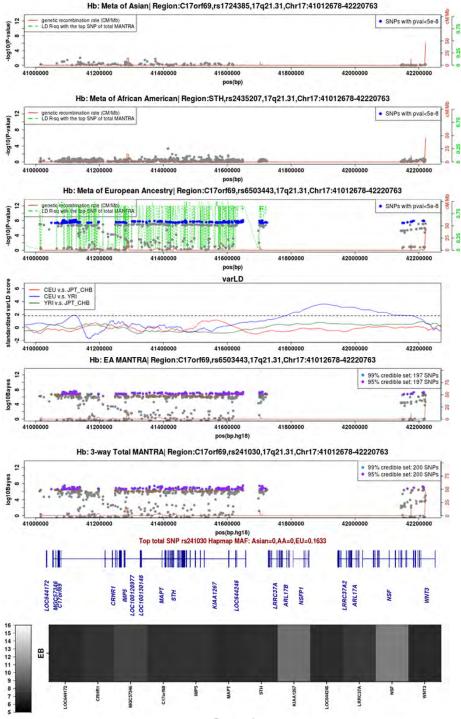
Page 36



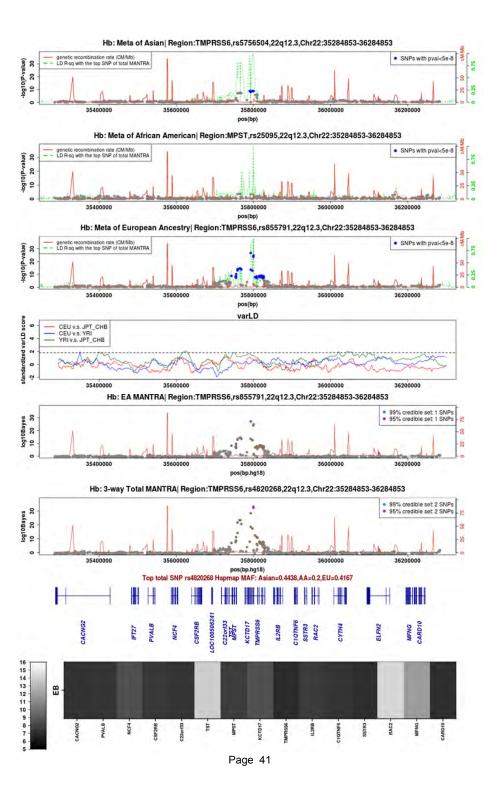


Page 38

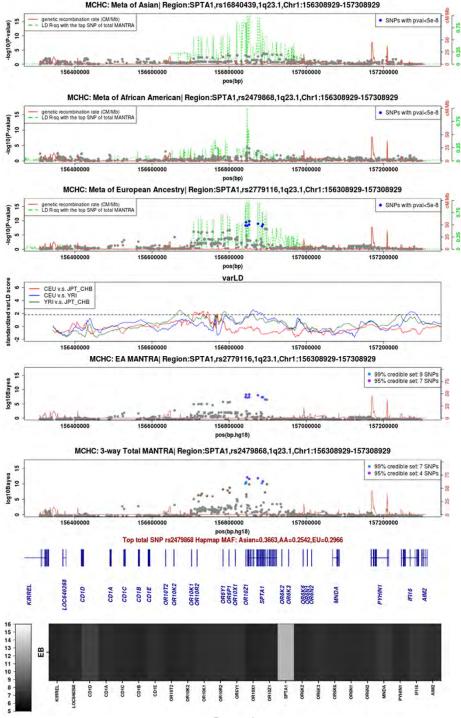




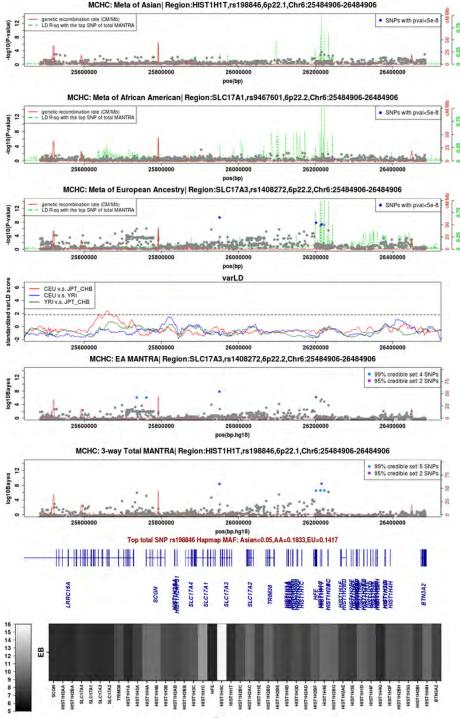
Page 40



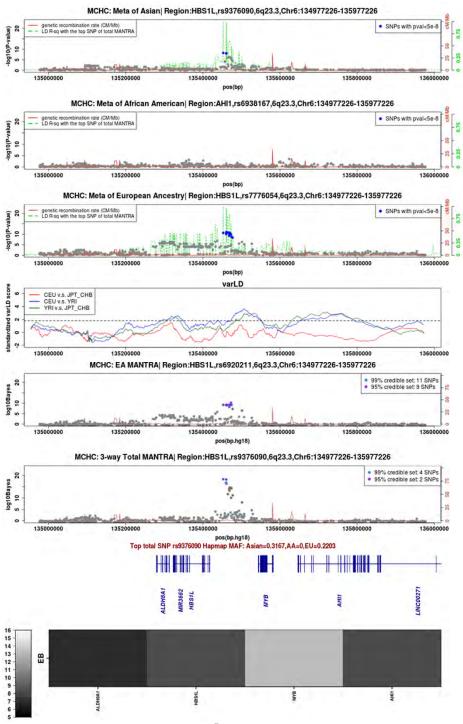
MCHC



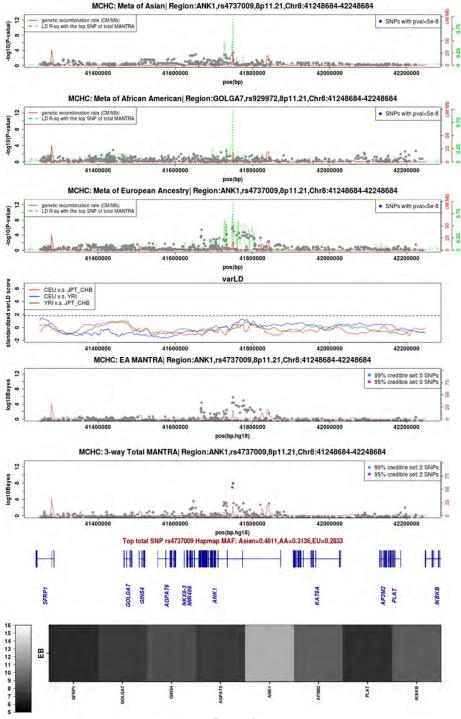
Page 43



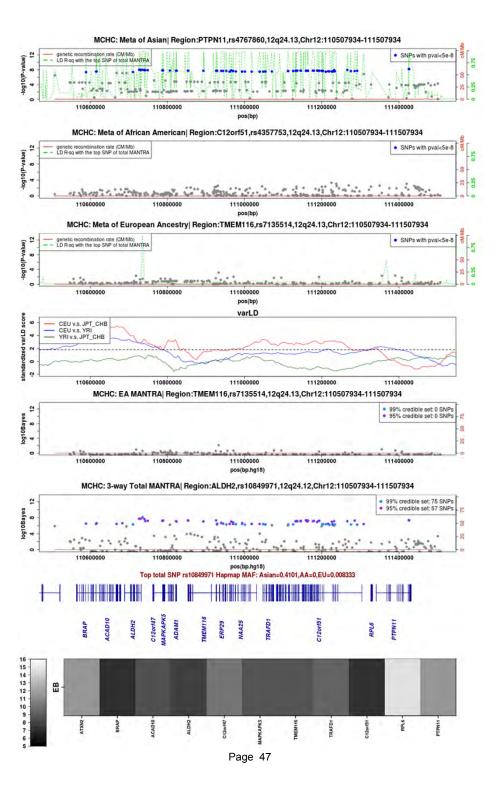
Page 44

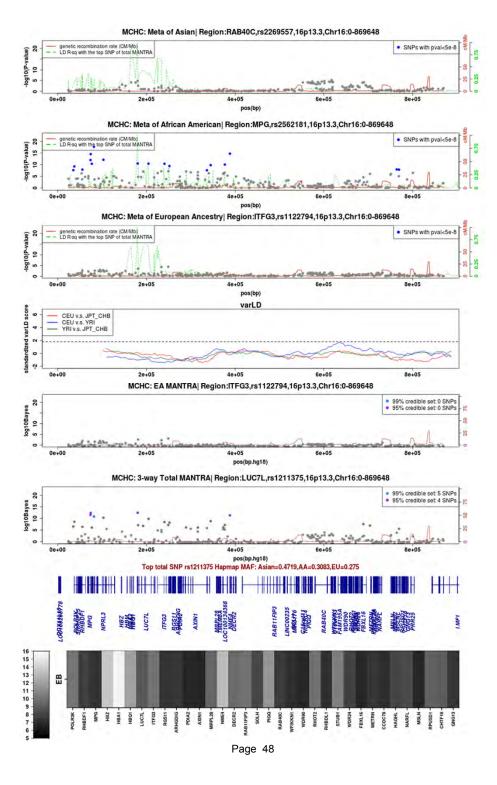


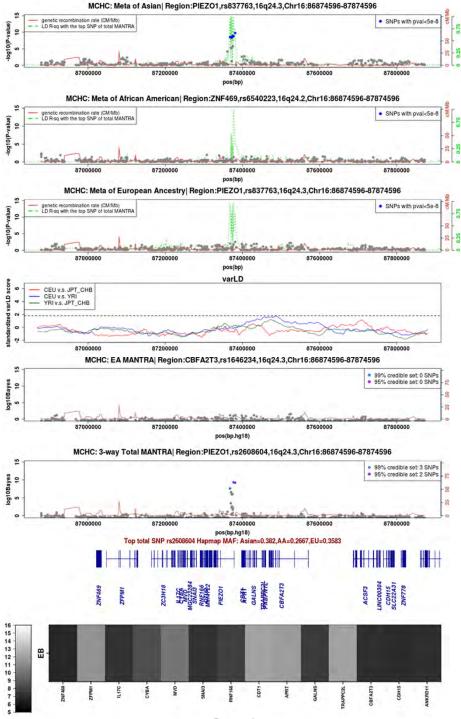
Page 45



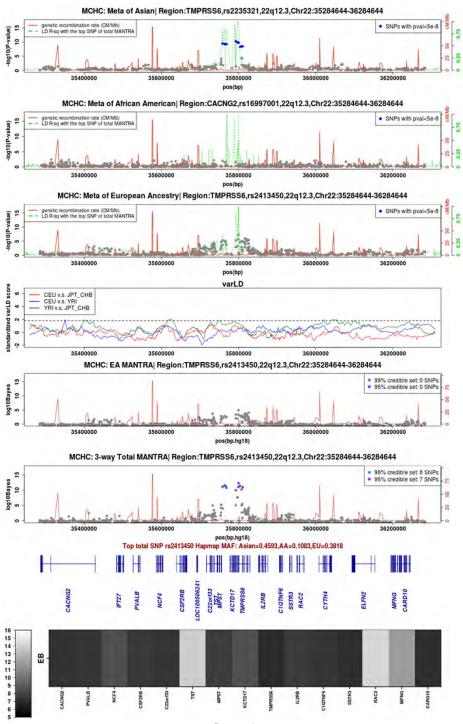
Page 46





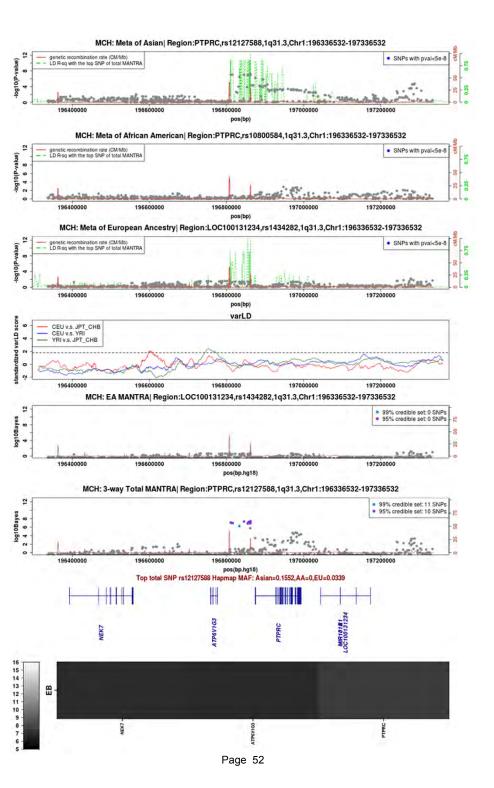


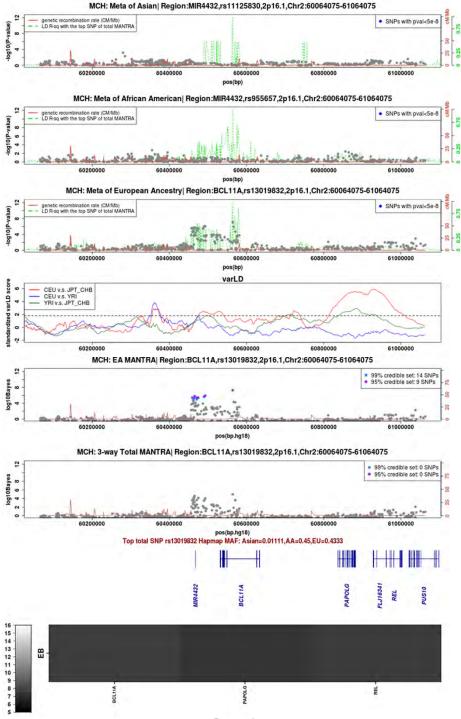
Page 49



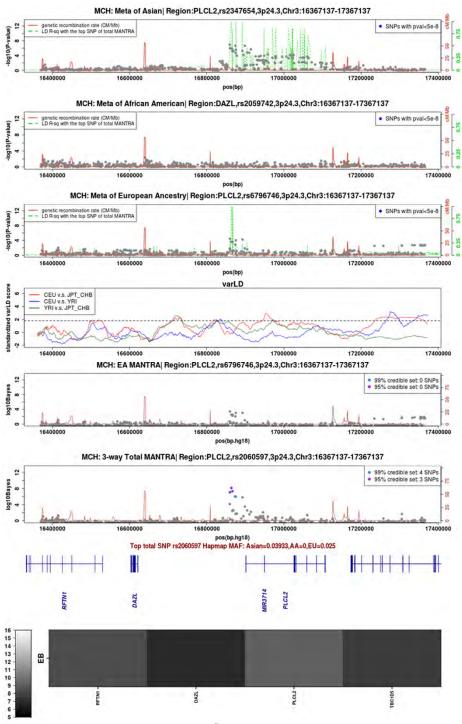
Page 50

MCH

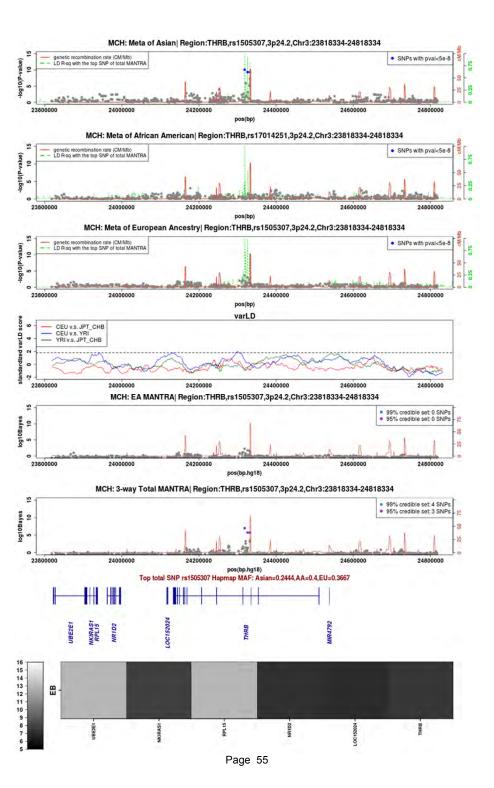


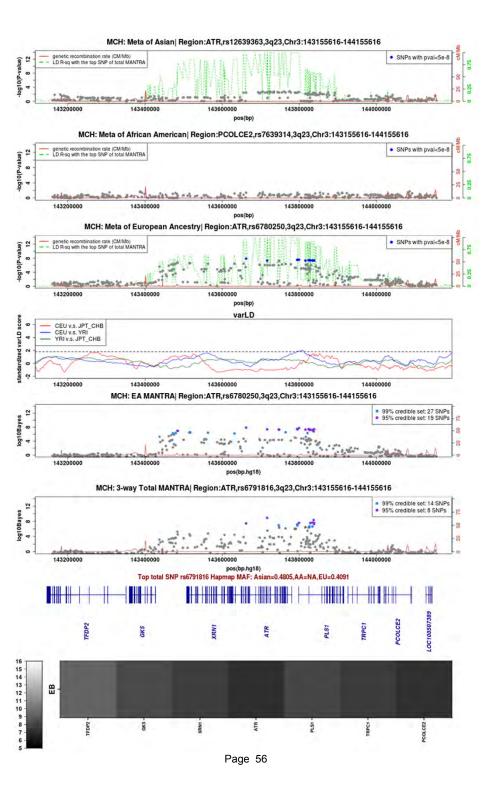


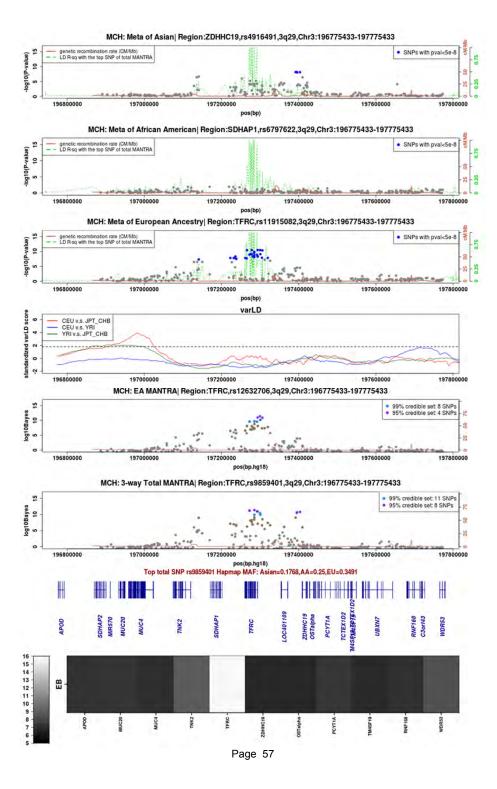
Page 53

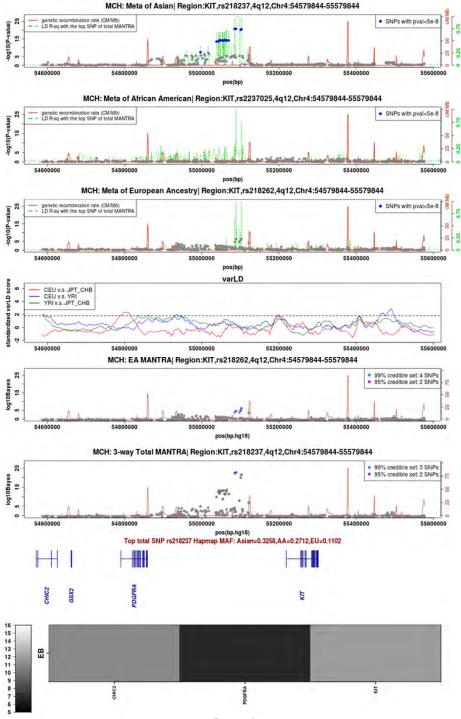


Page 54

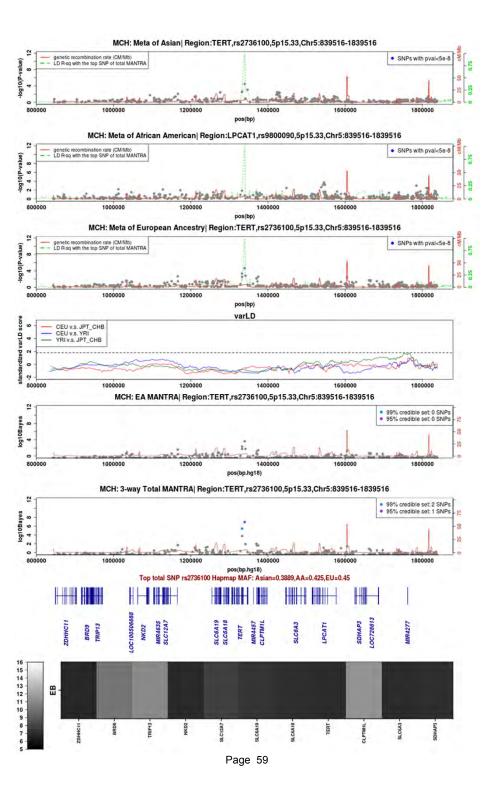


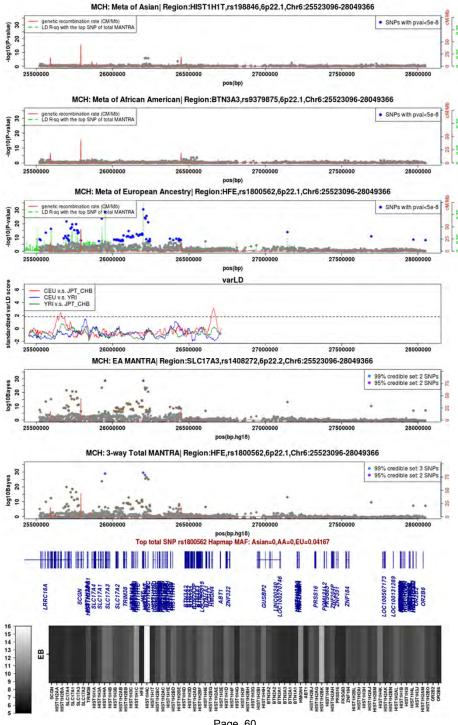




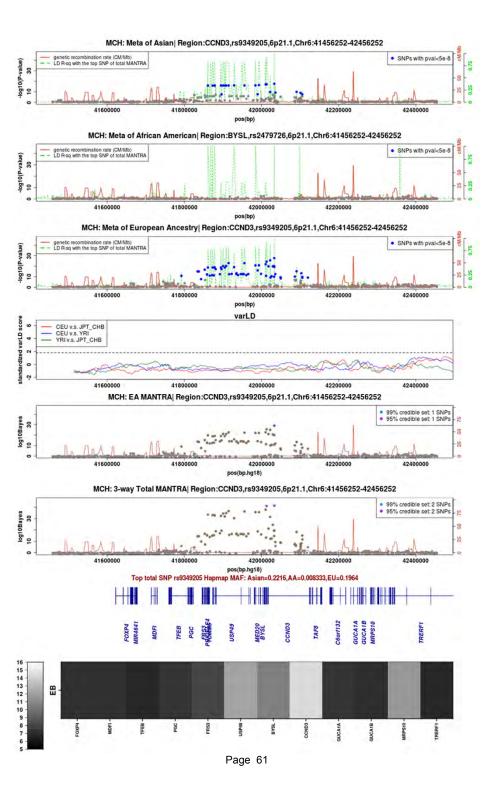


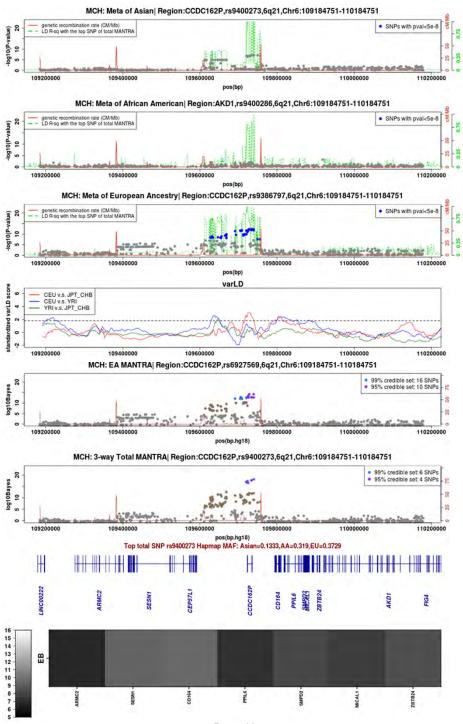
Page 58



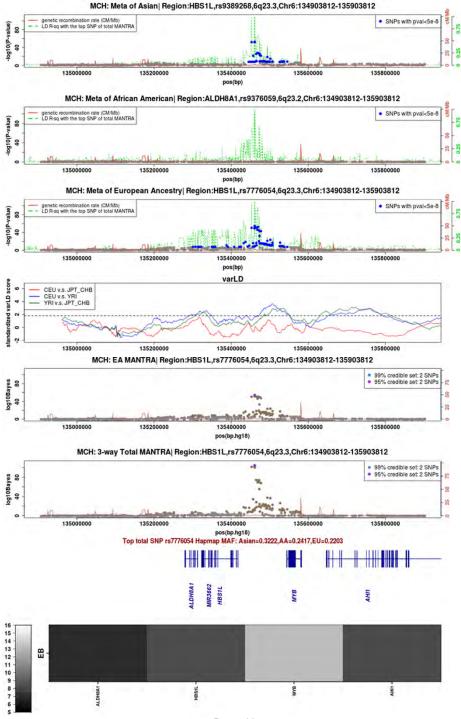


Page 60

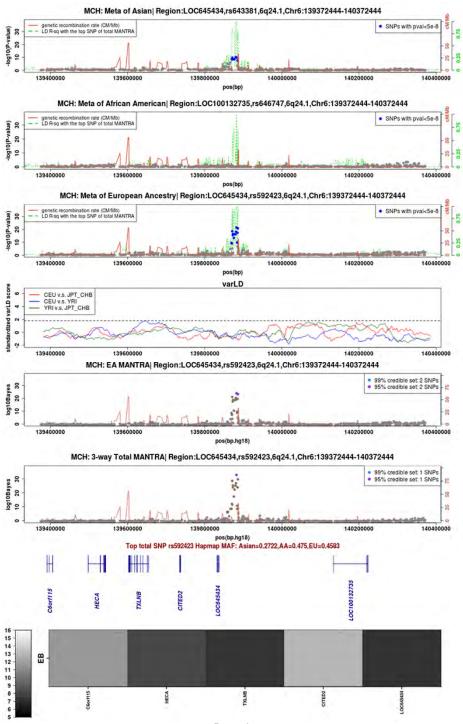




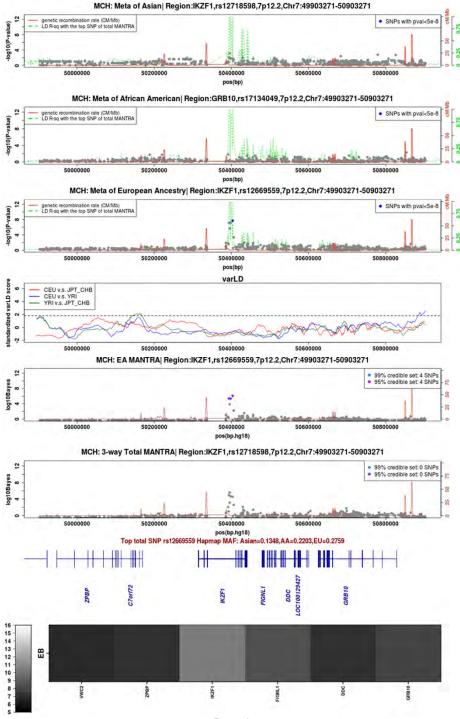
Page 62



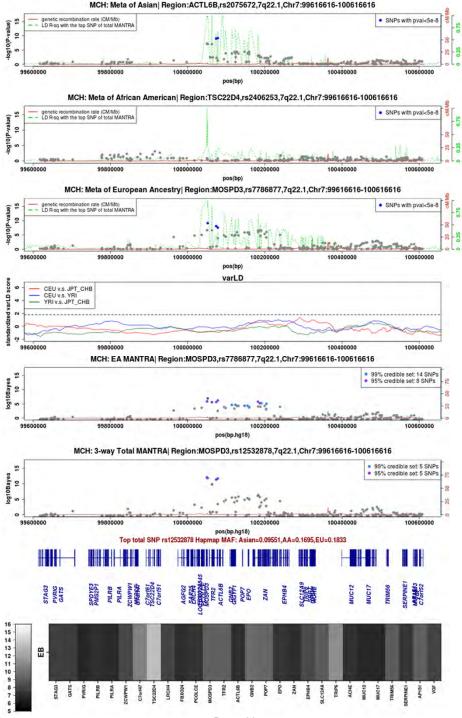
Page 63



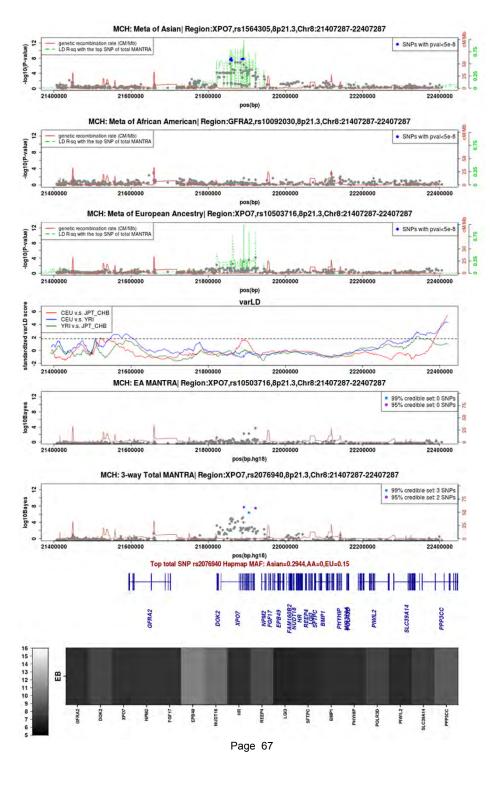
Page 64

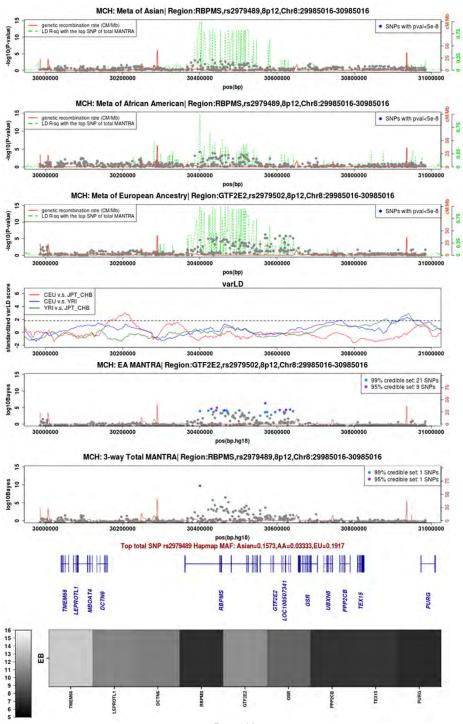


Page 65

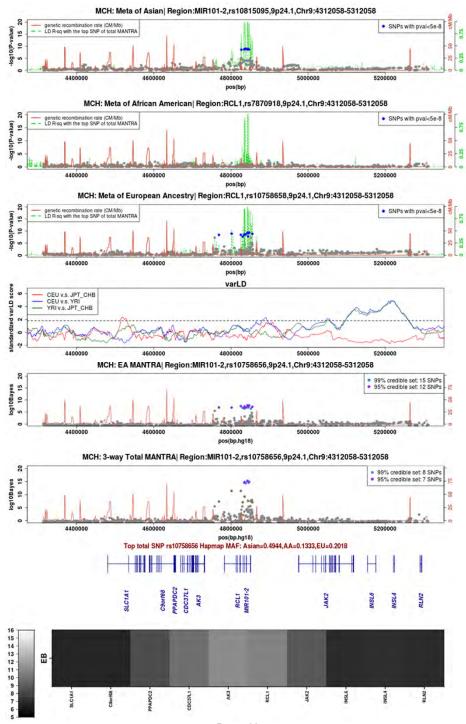


Page 66

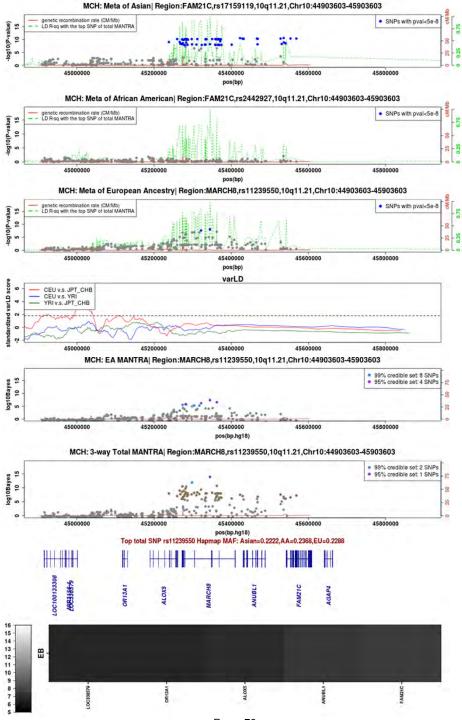




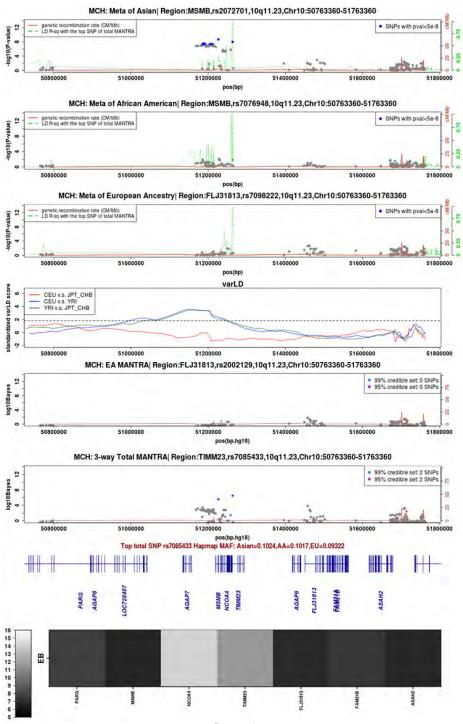
Page 68



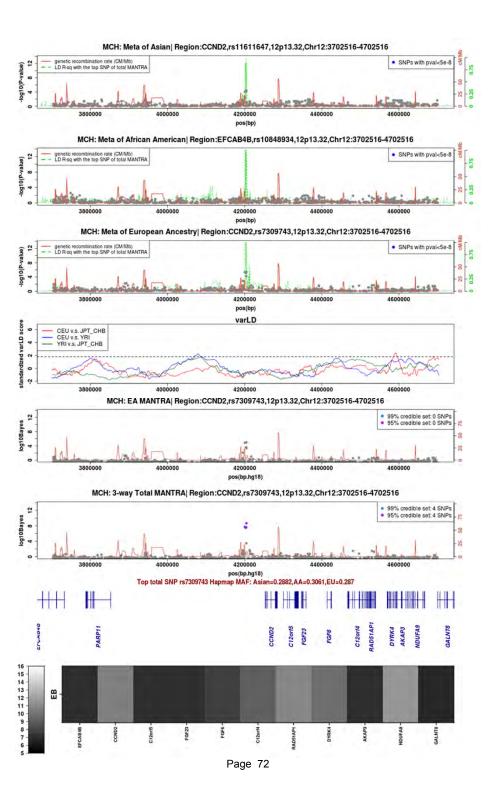
Page 69

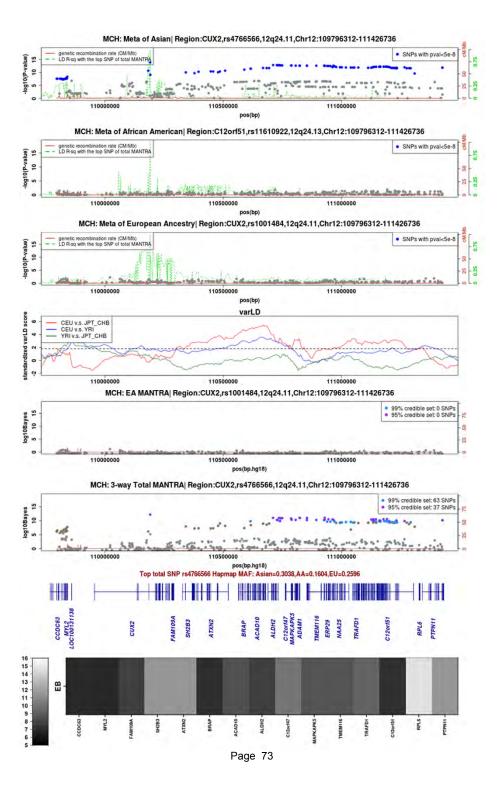


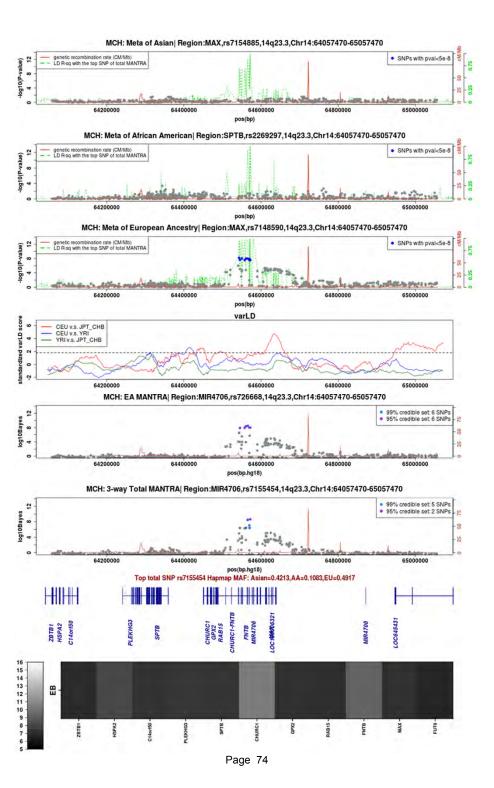
Page 70

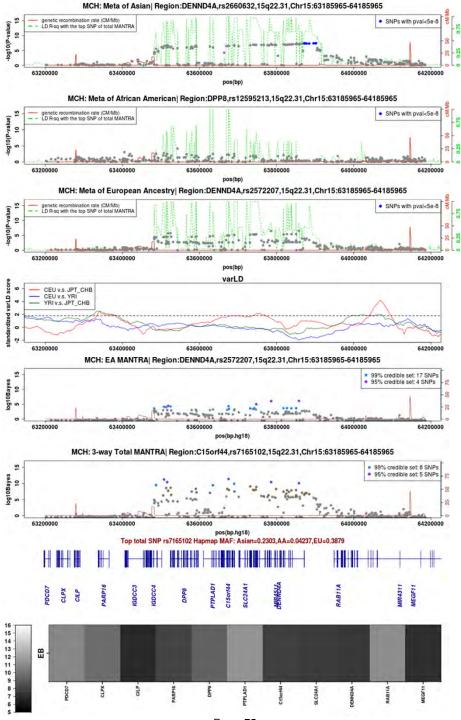


Page 71

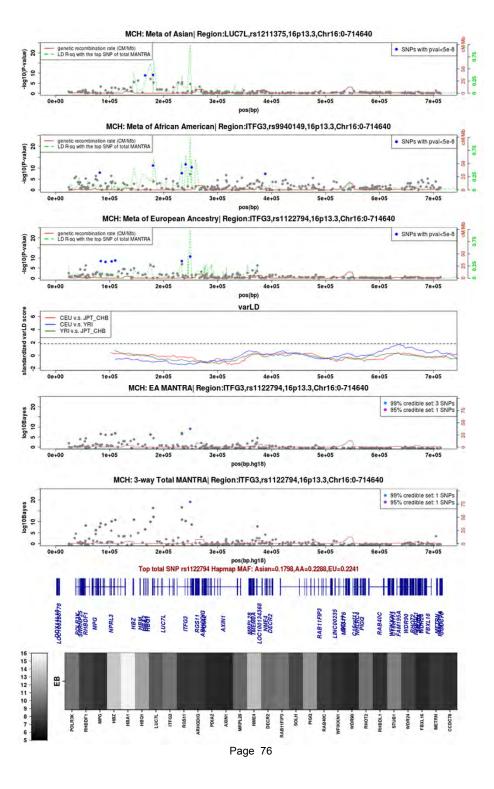


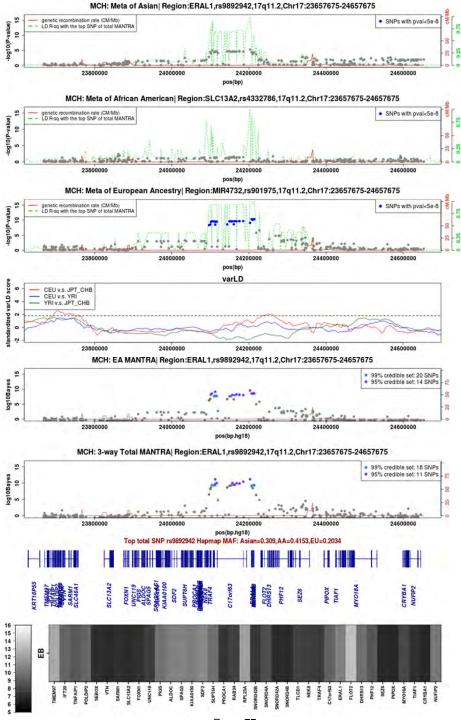




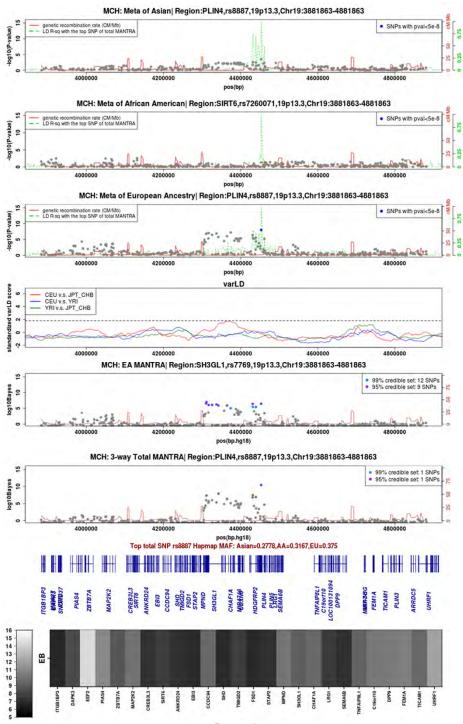


Page 75

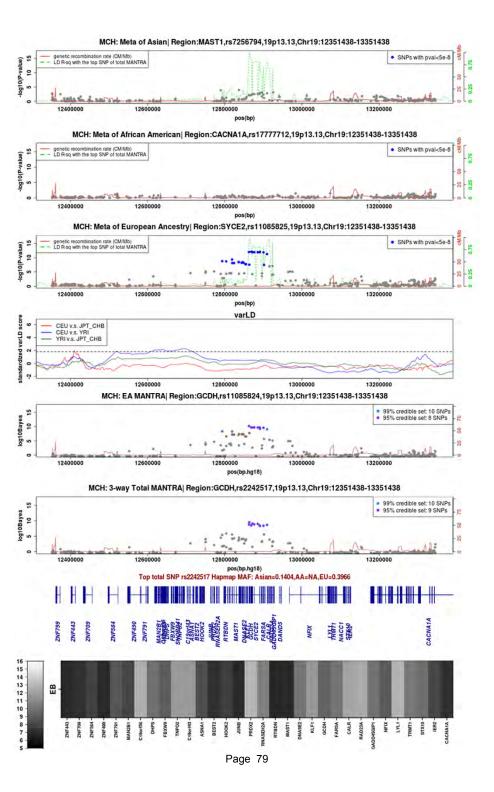


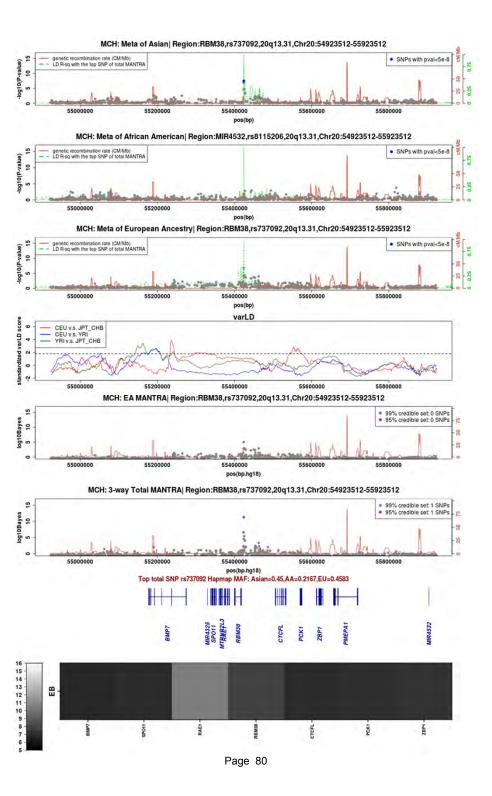


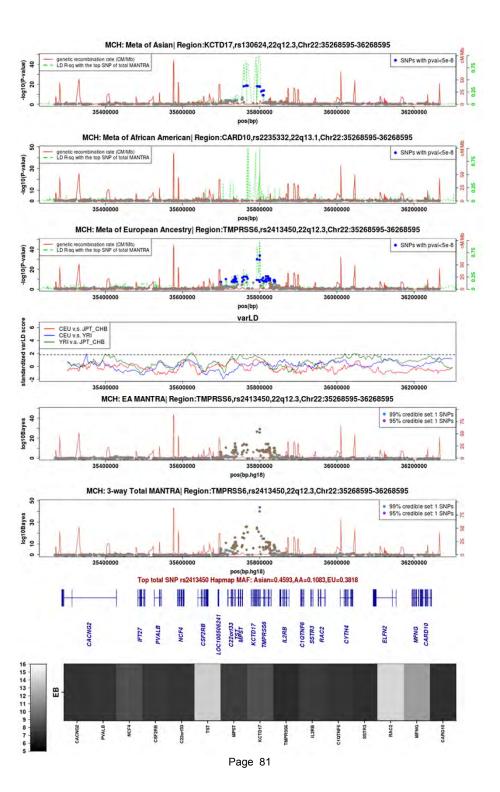
Page 77



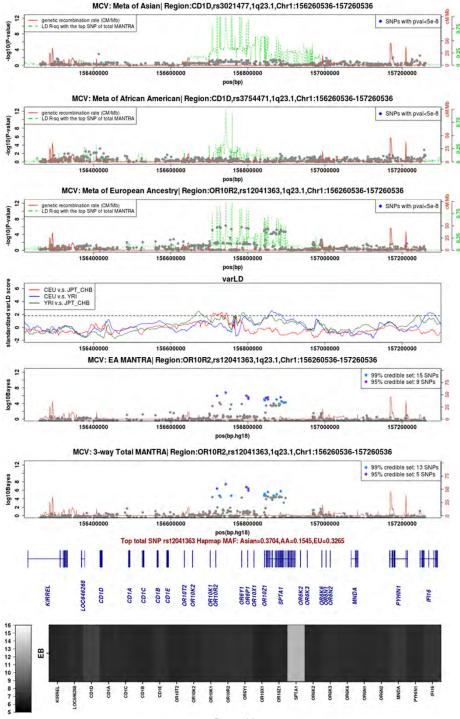
Page 78



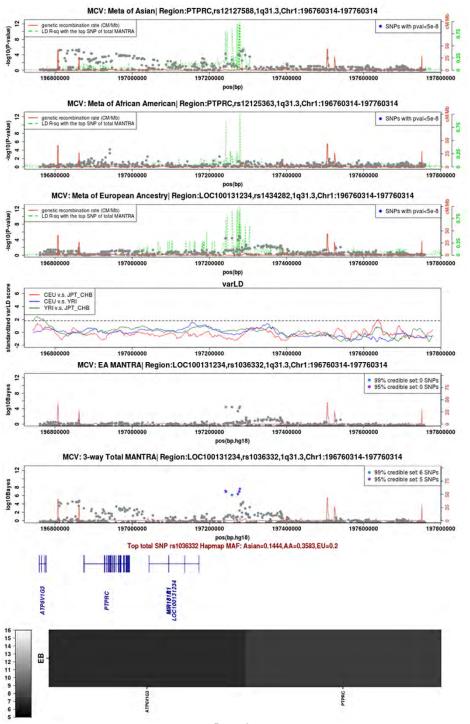




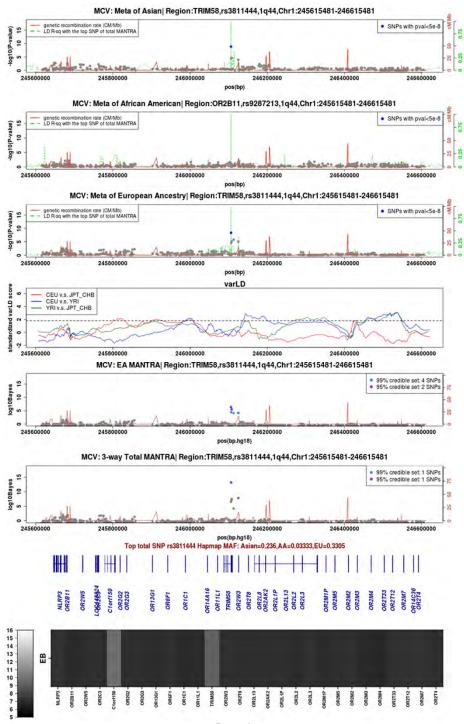
MCV



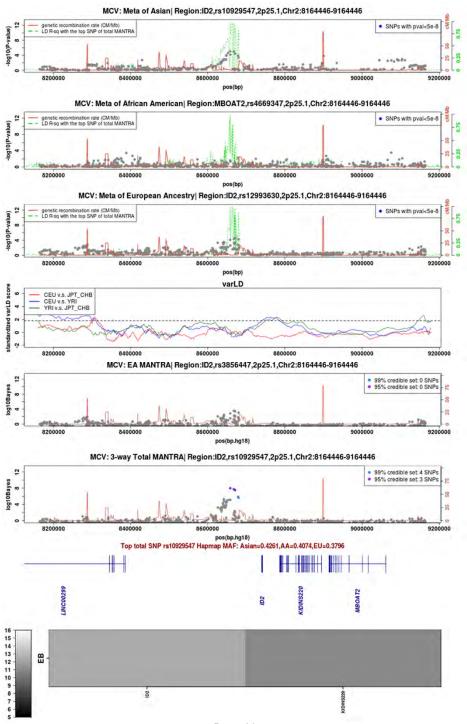
Page 83



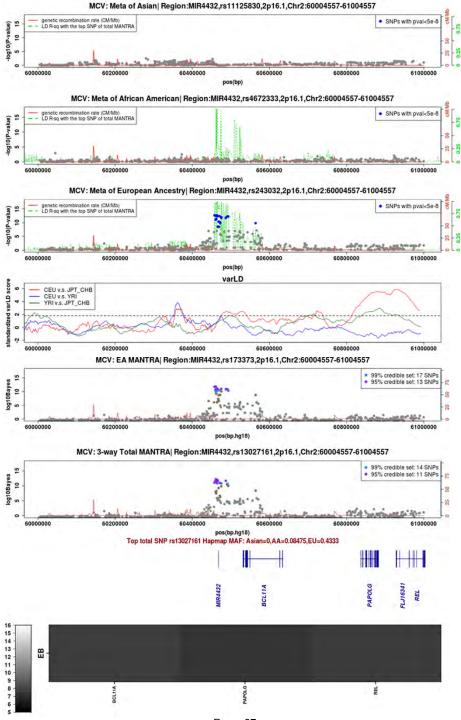
Page 84



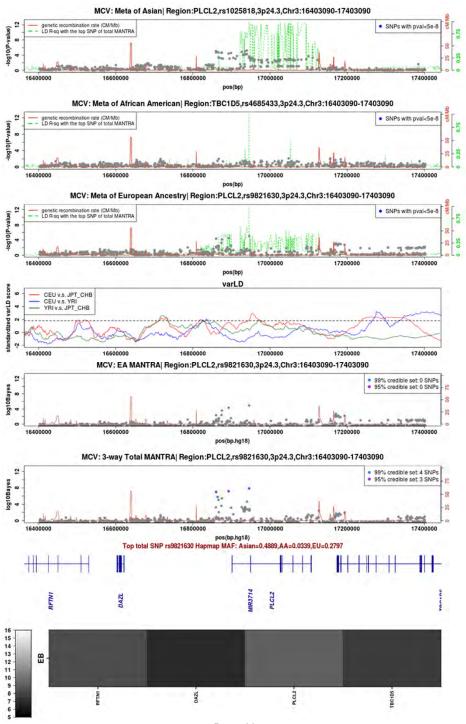
Page 85



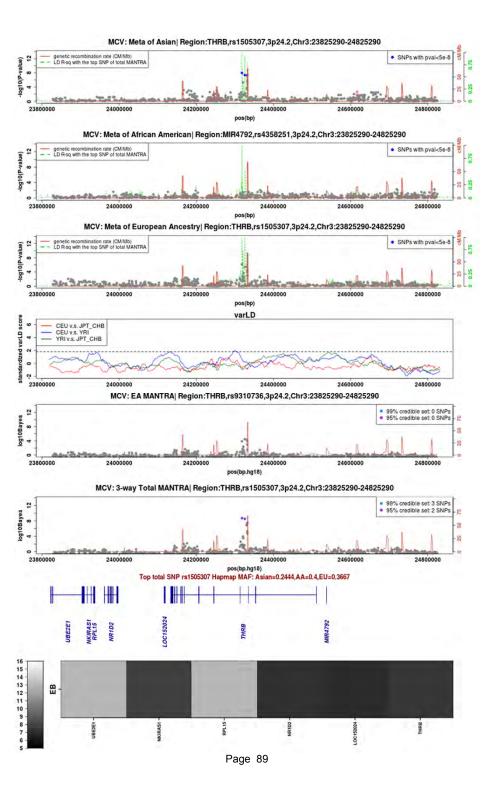
Page 86

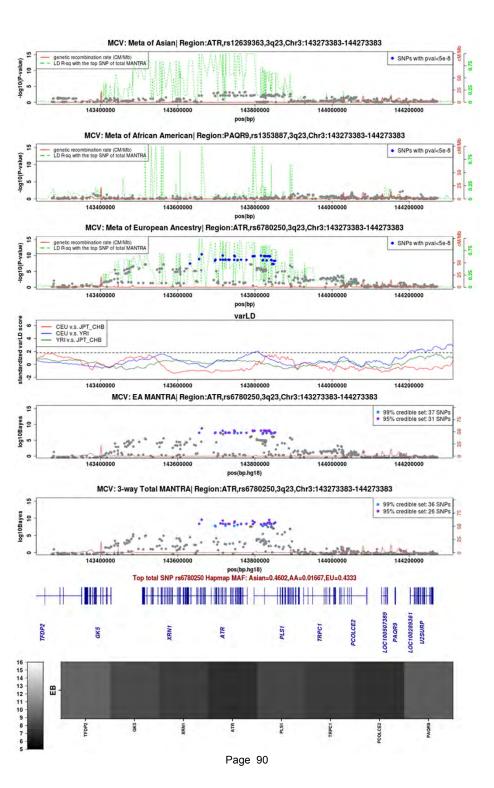


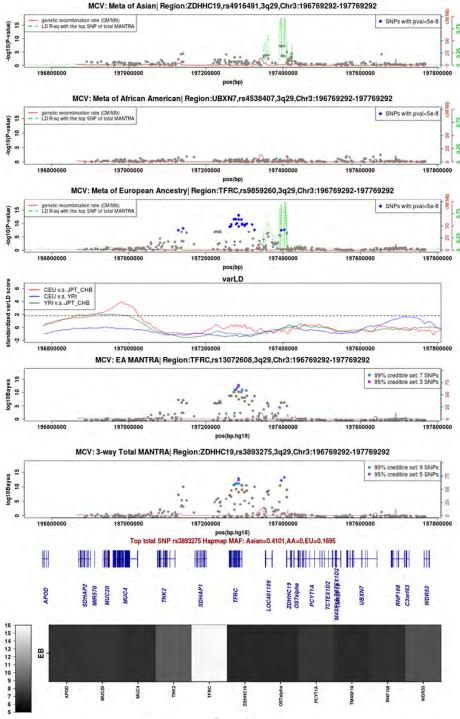
Page 87



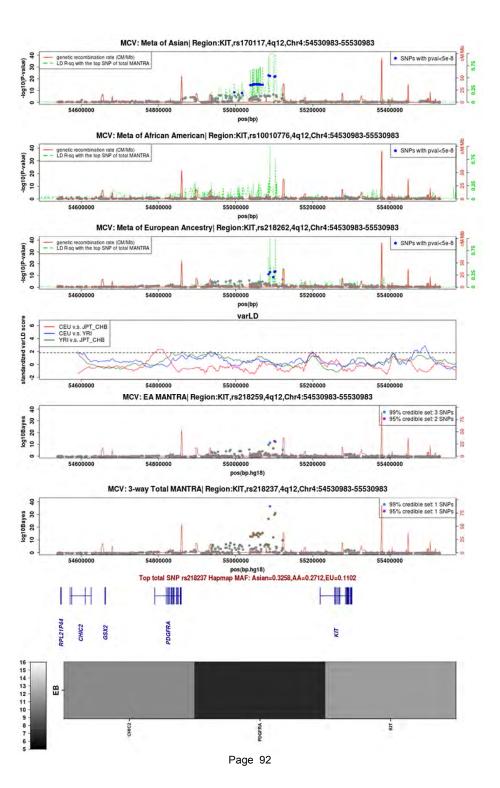
Page 88

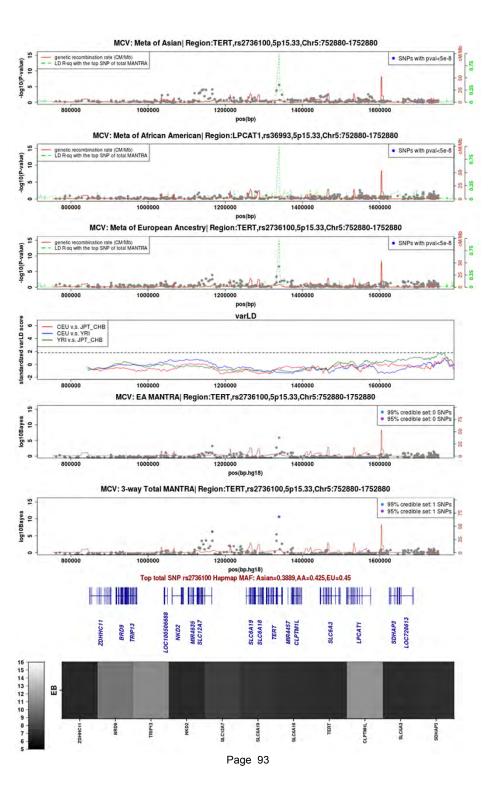


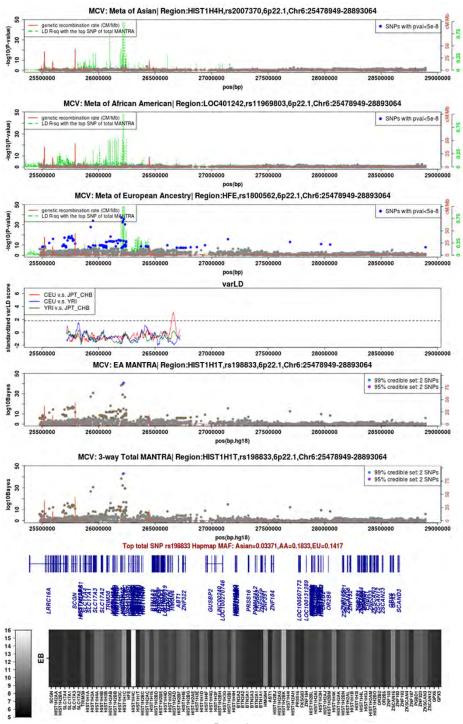




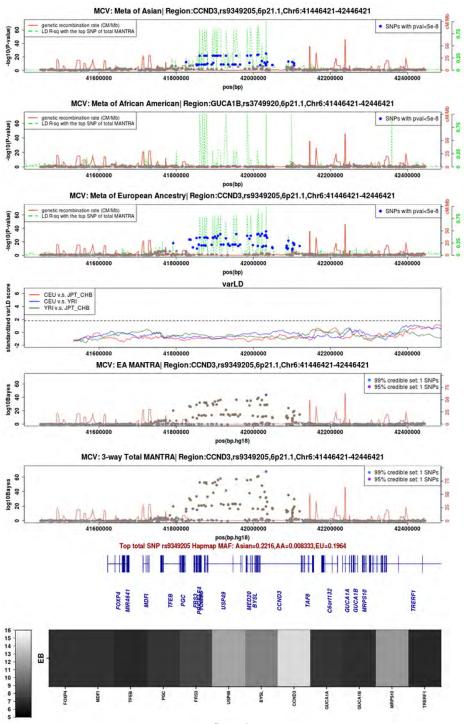
Page 91



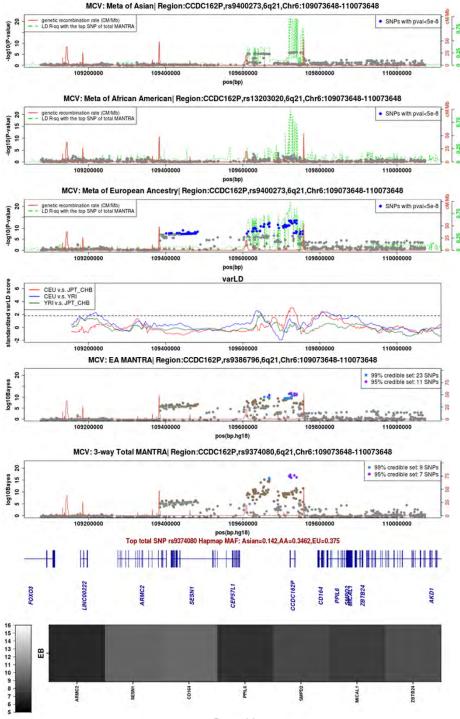




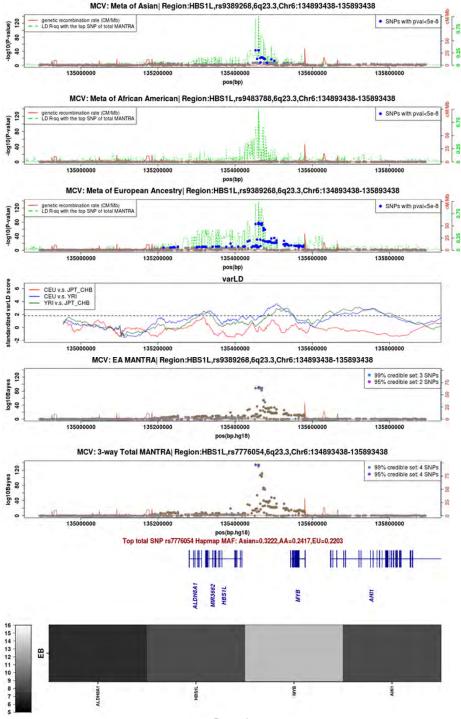
Page 94



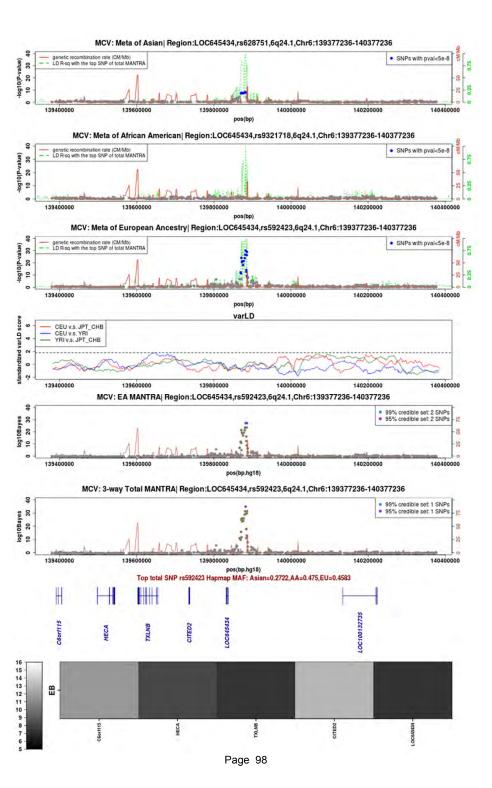
Page 95

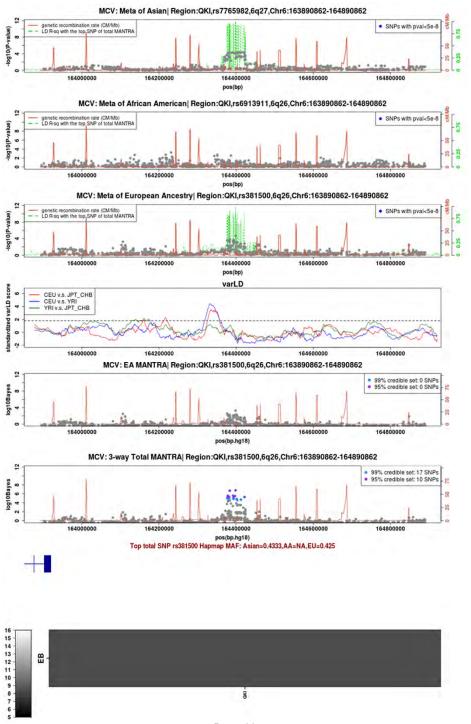


Page 96

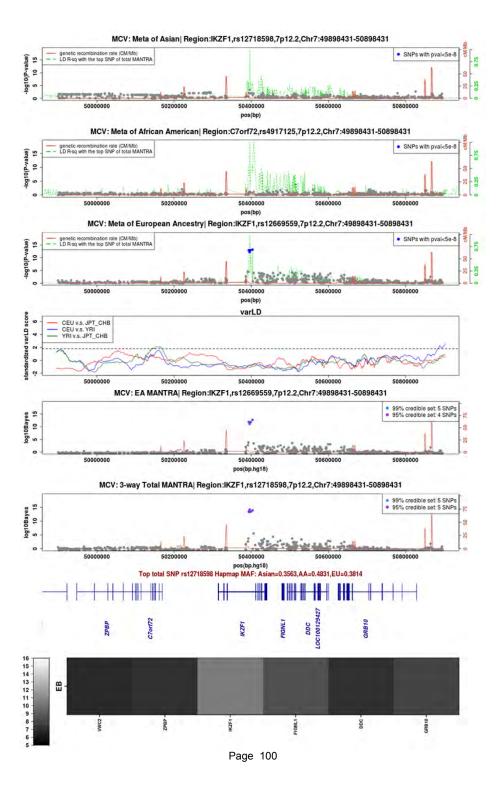


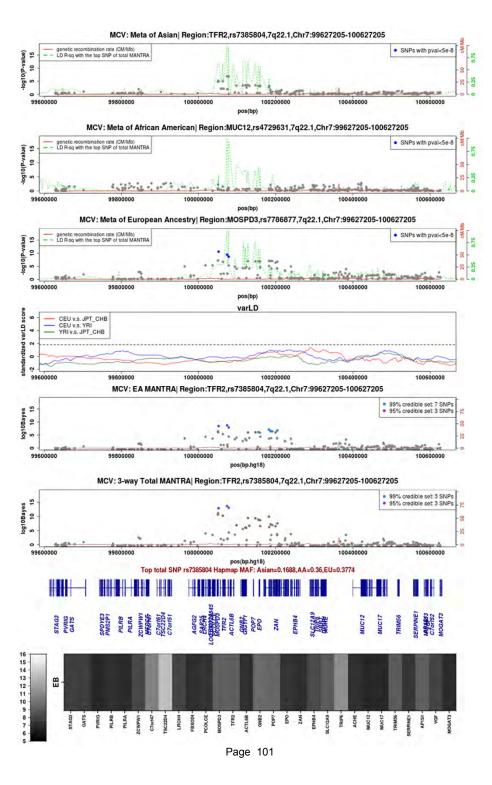
Page 97

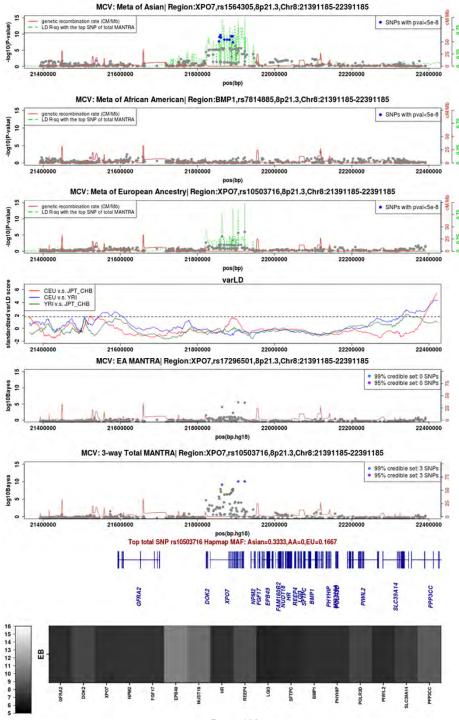




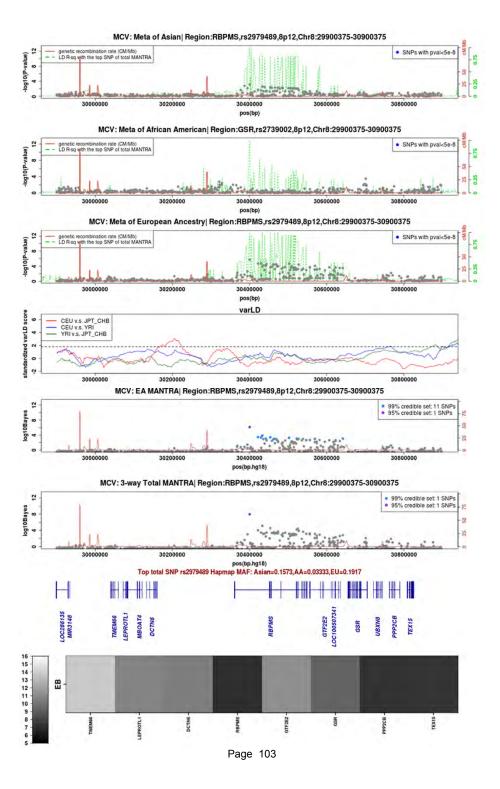
Page 99

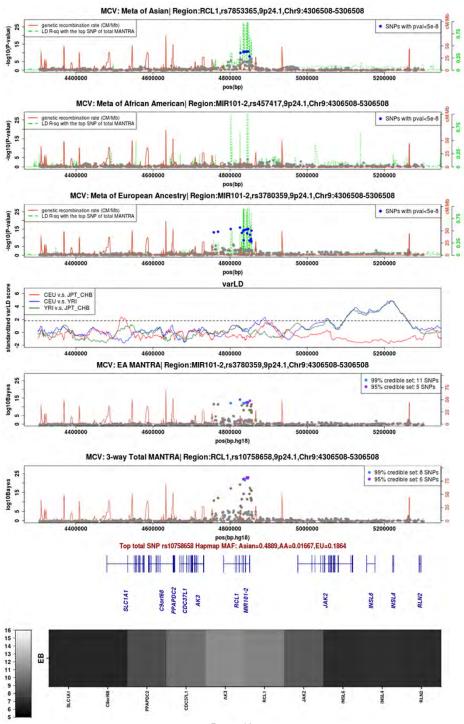




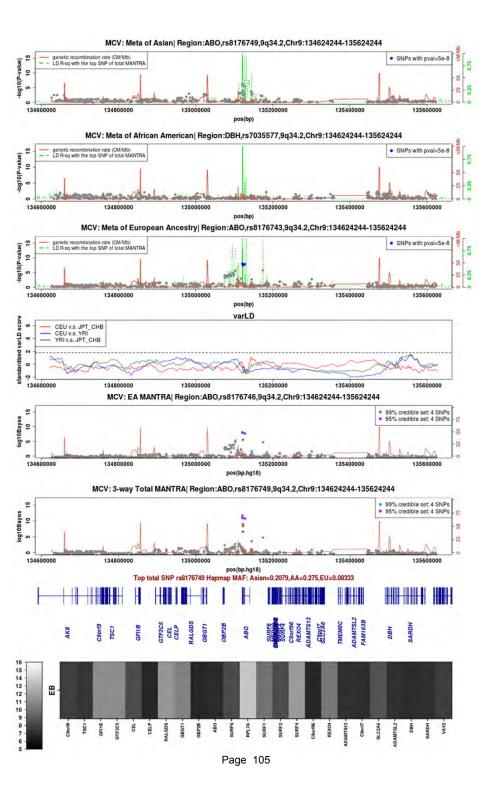


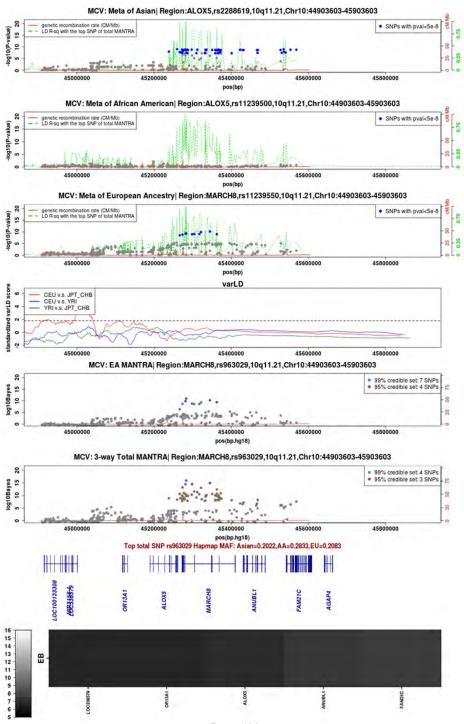
Page 102



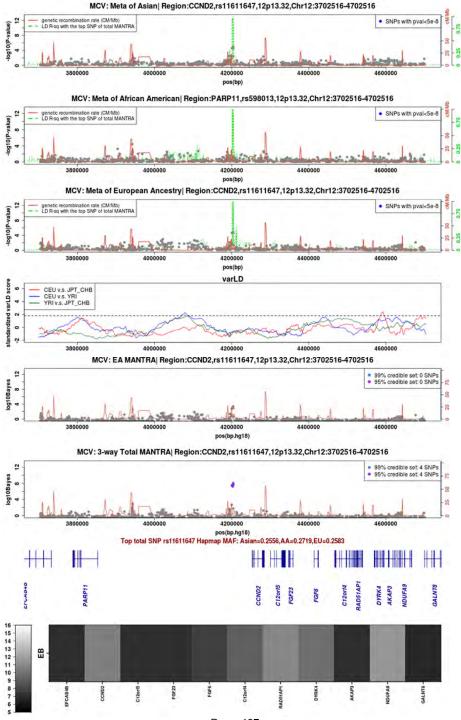


Page 104

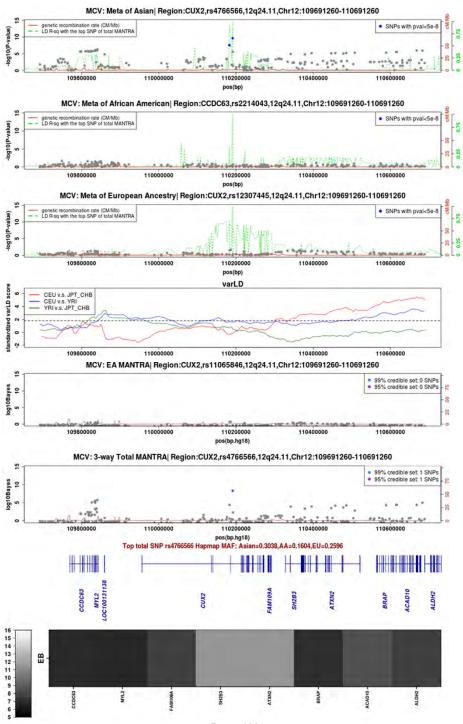




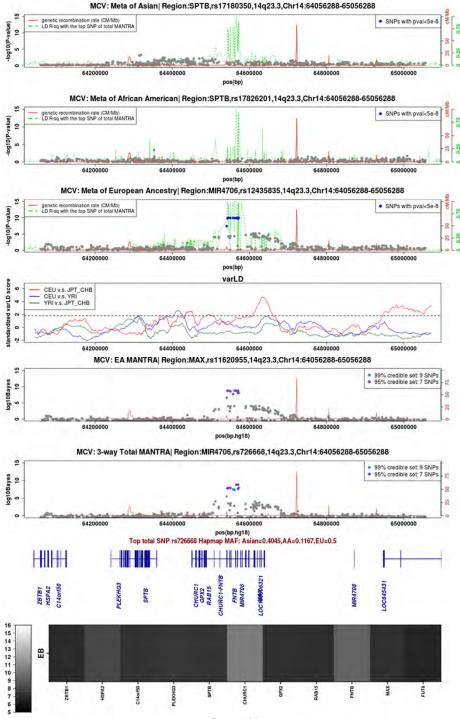
Page 106



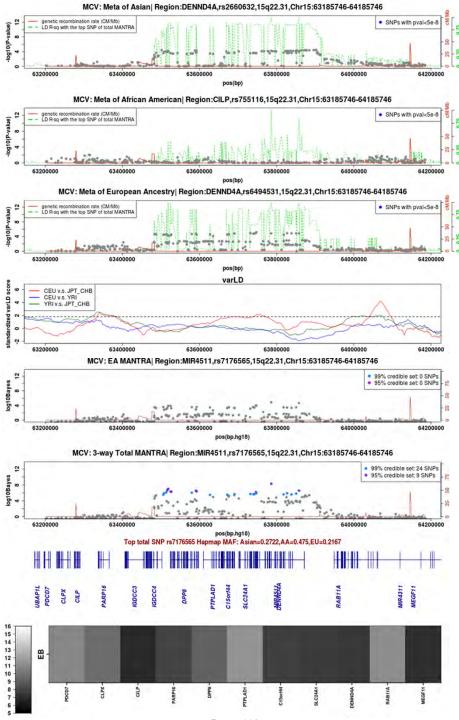
Page 107



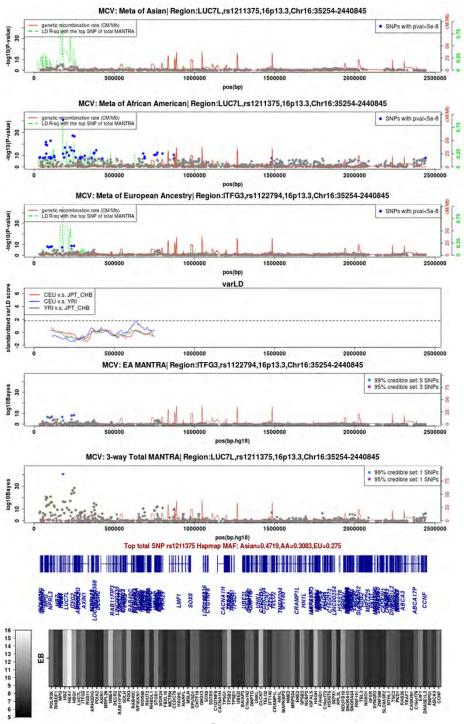
Page 108



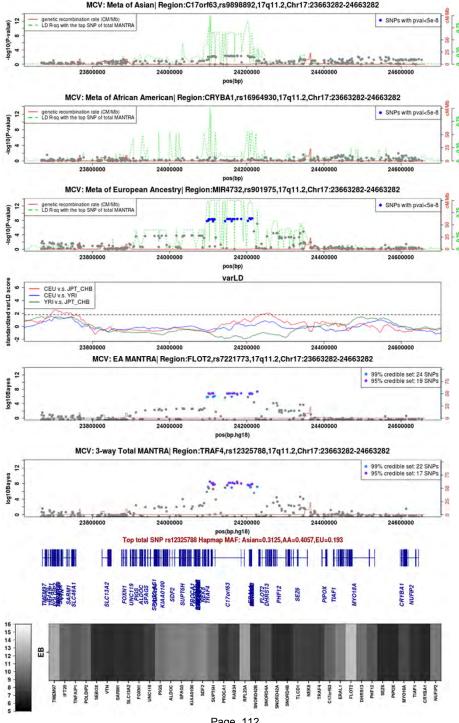
Page 109



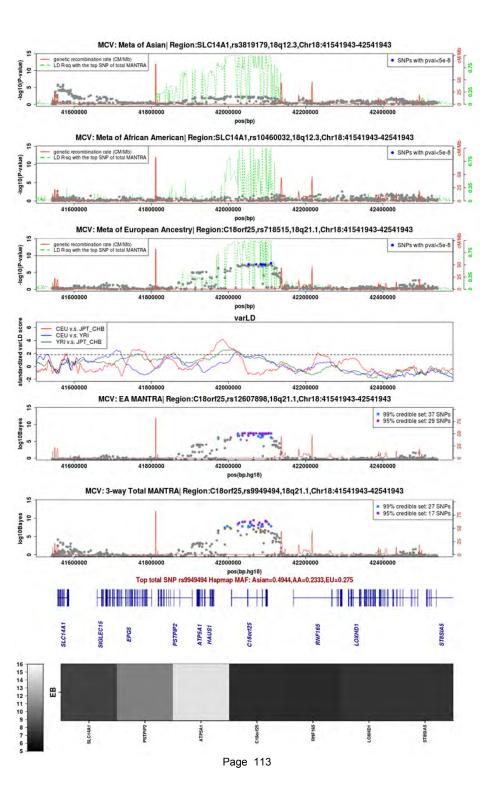
Page 110

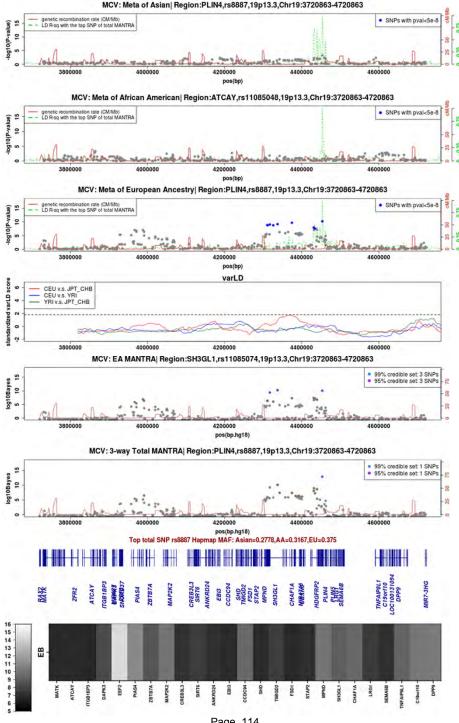


Page 111

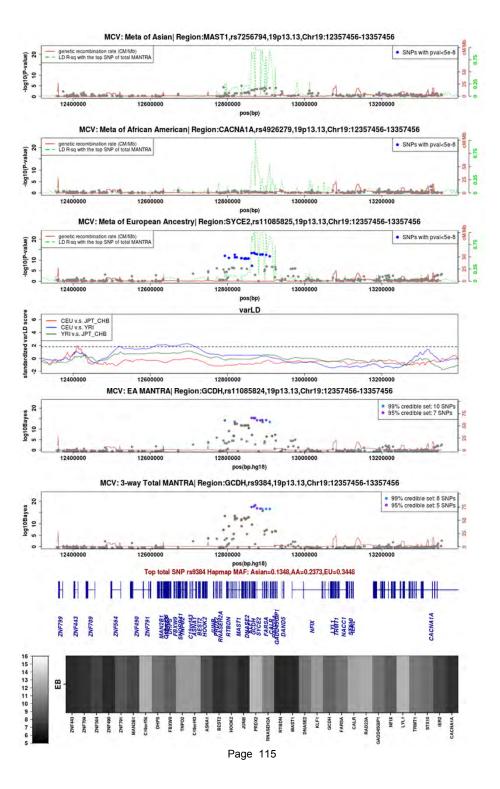


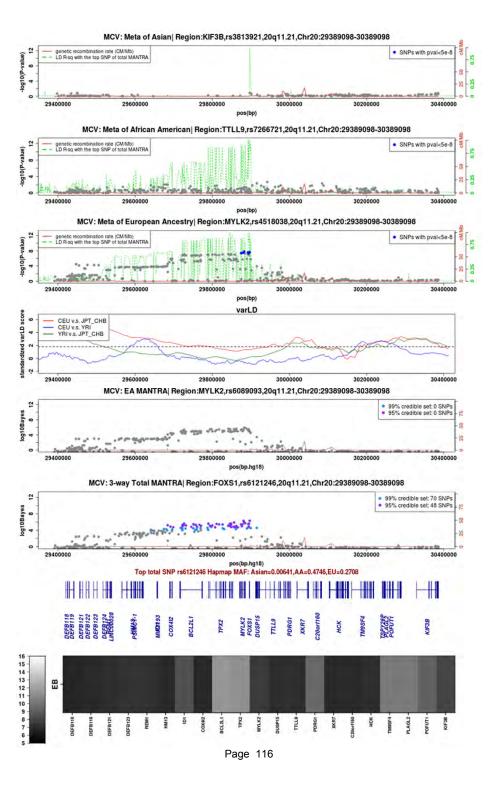
Page 112

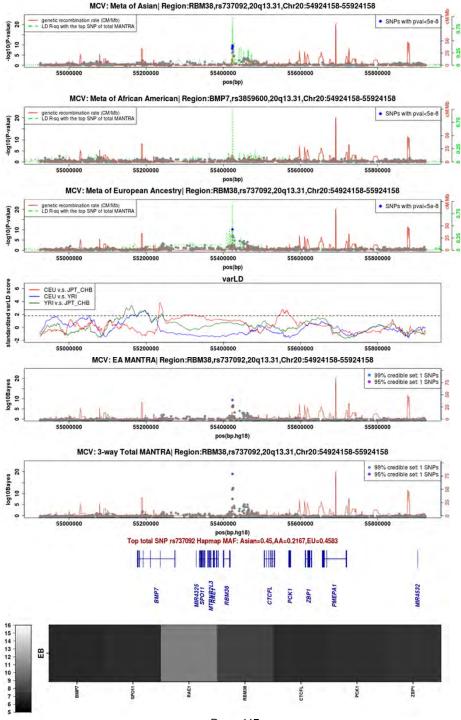




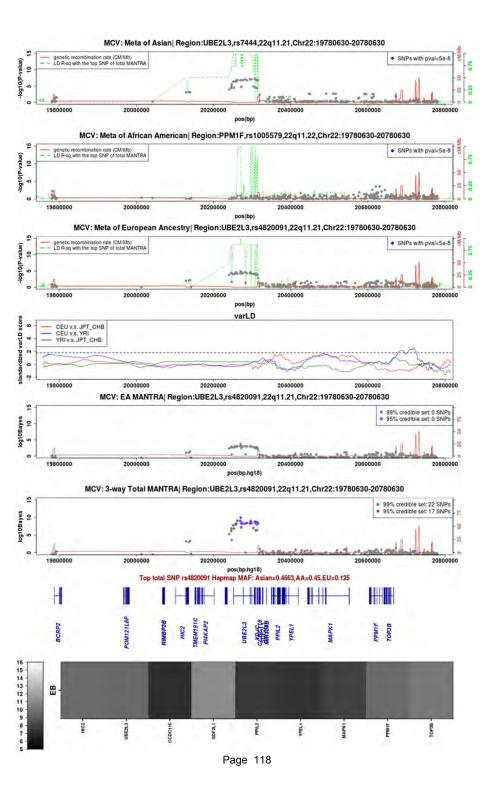
Page 114

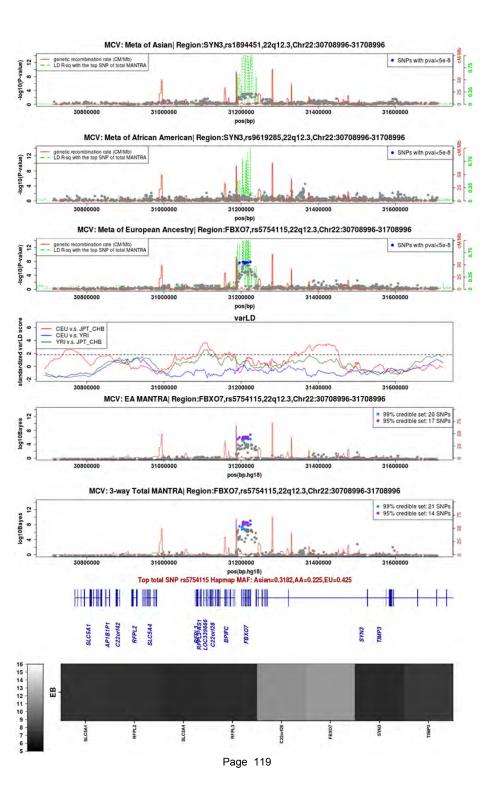


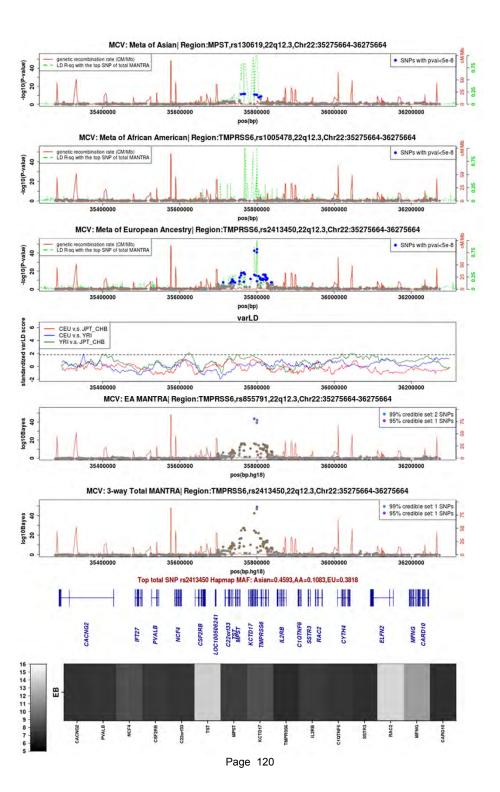


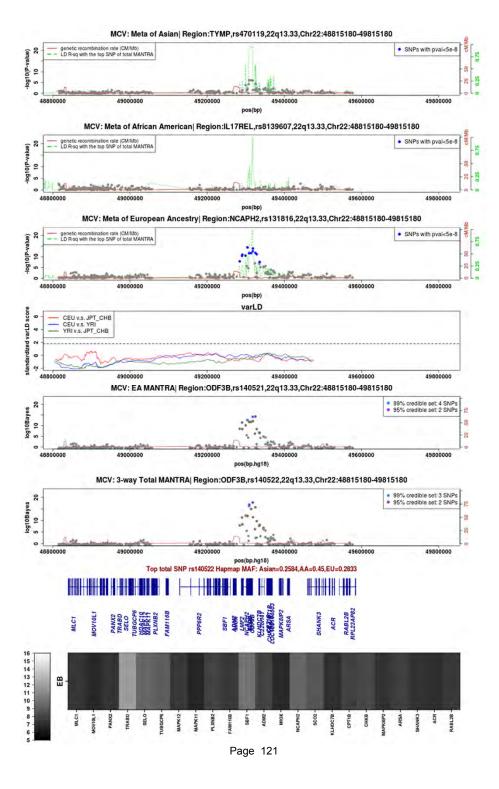


Page 117

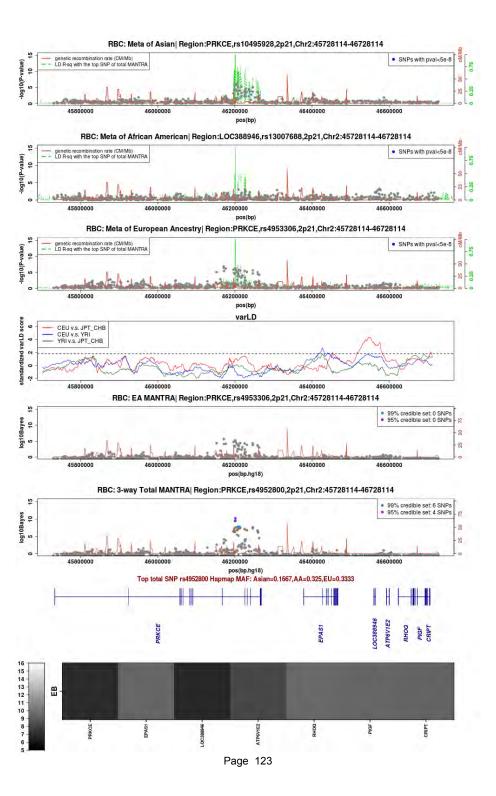


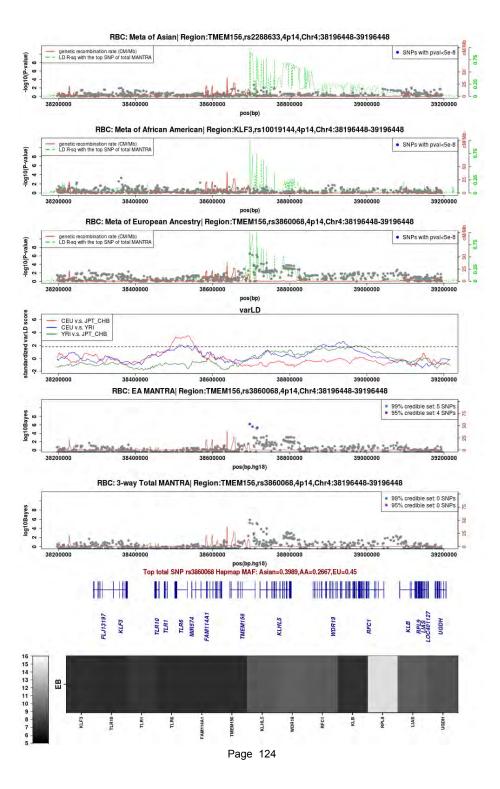


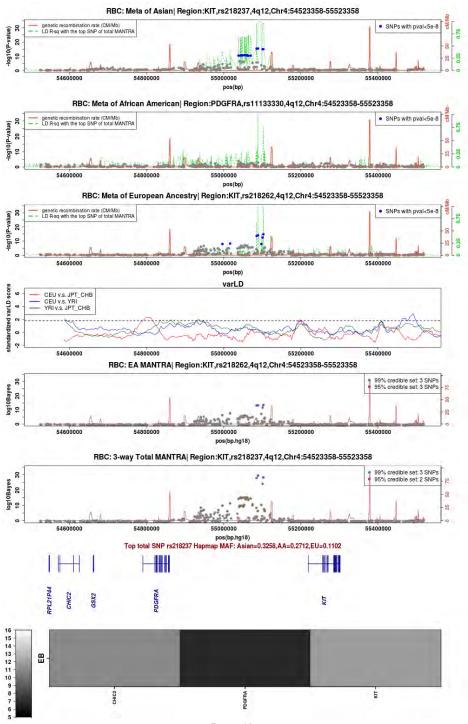




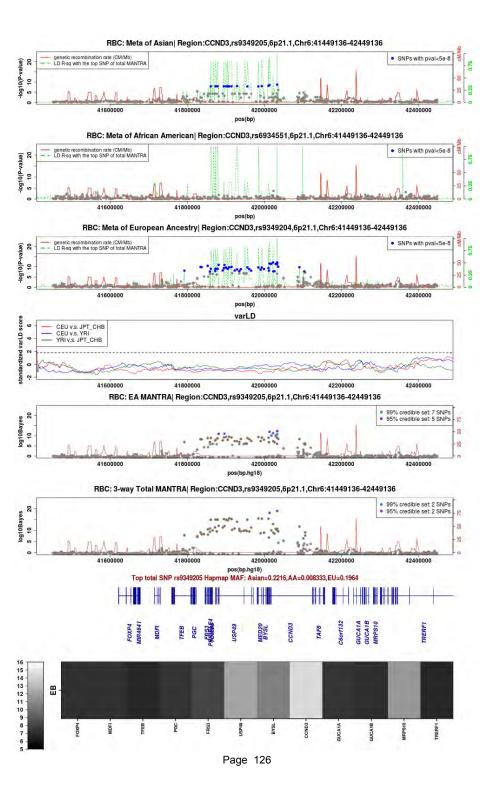
RBC

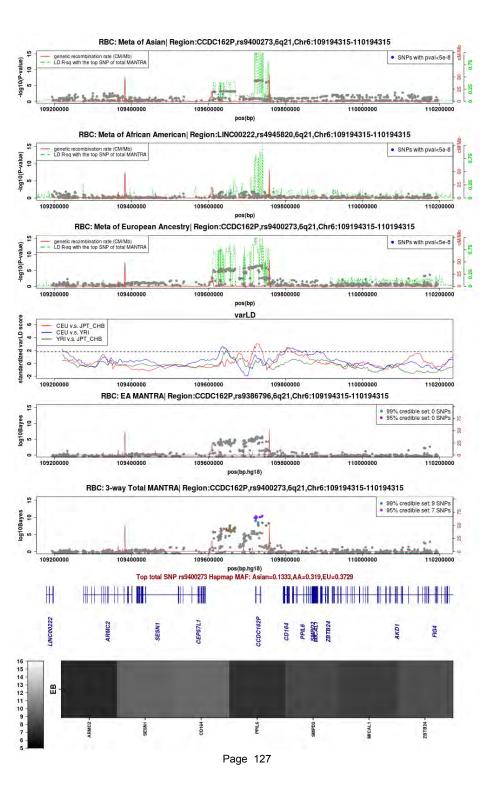


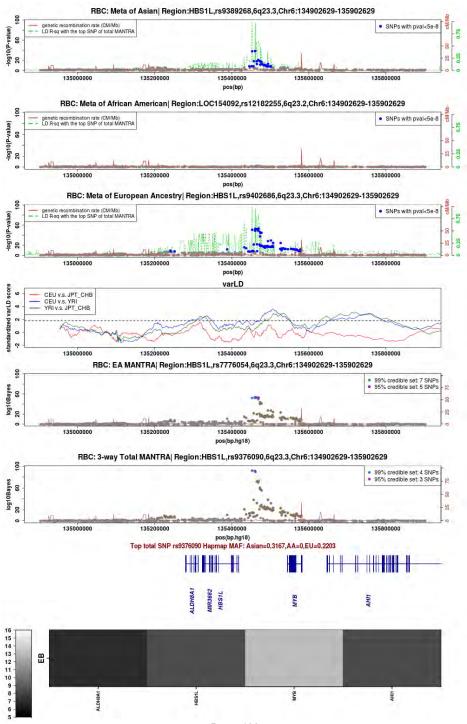




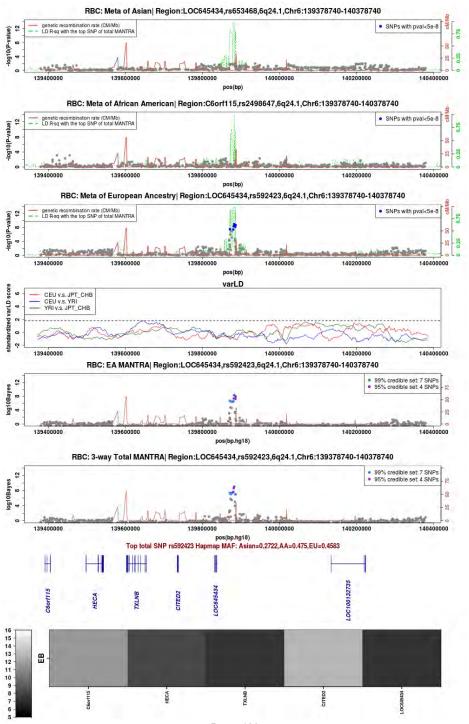
Page 125



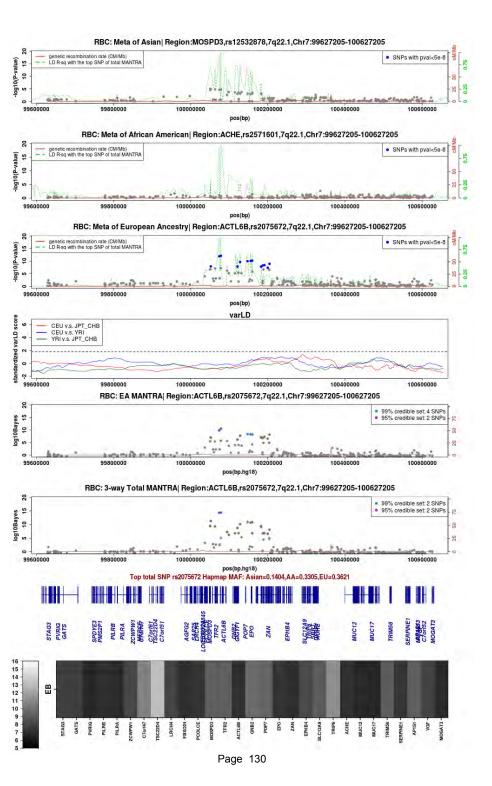


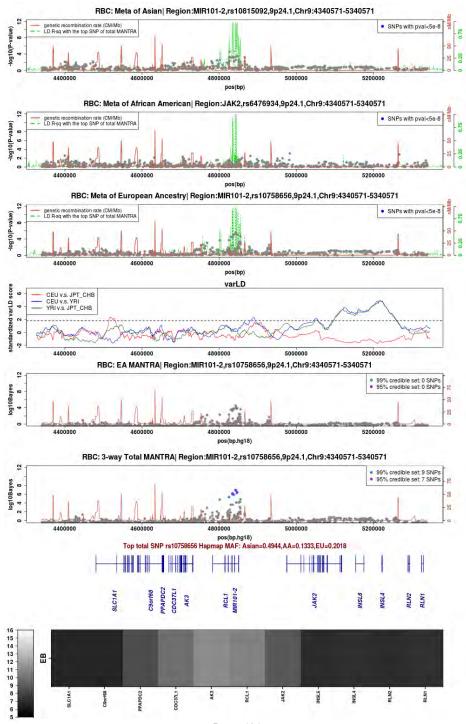


Page 128

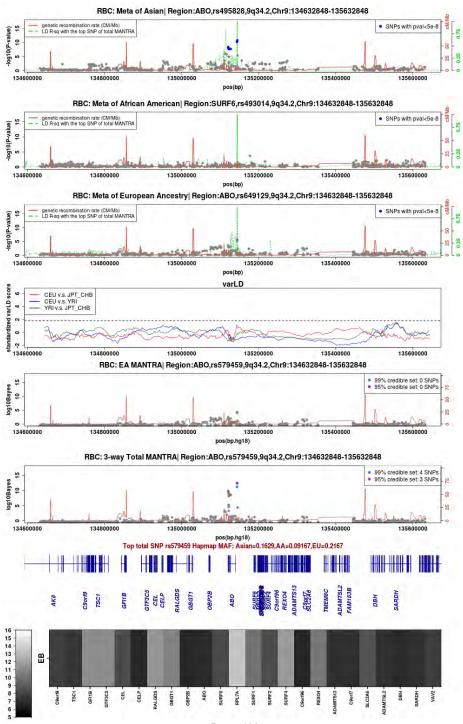


Page 129

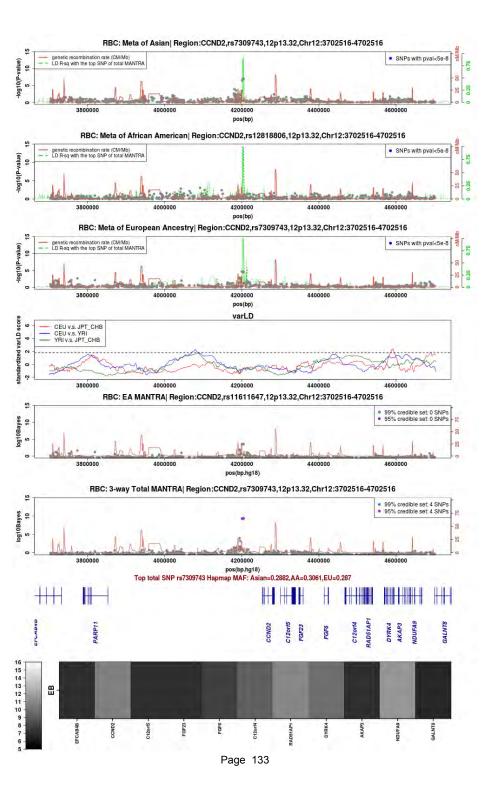


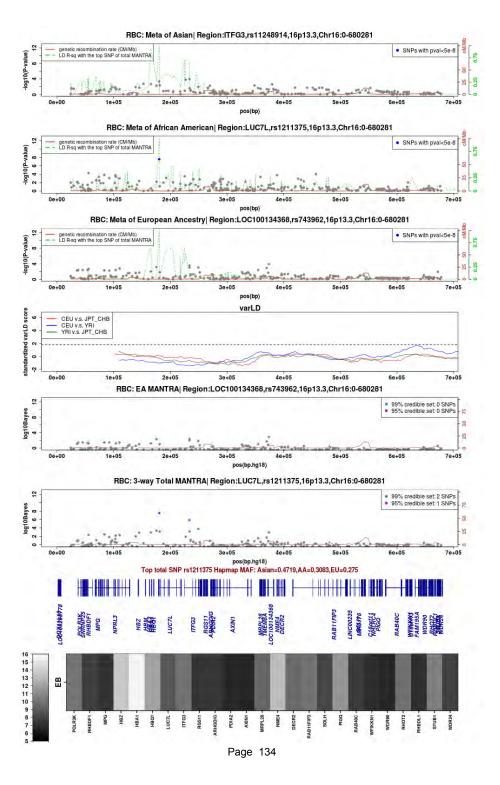


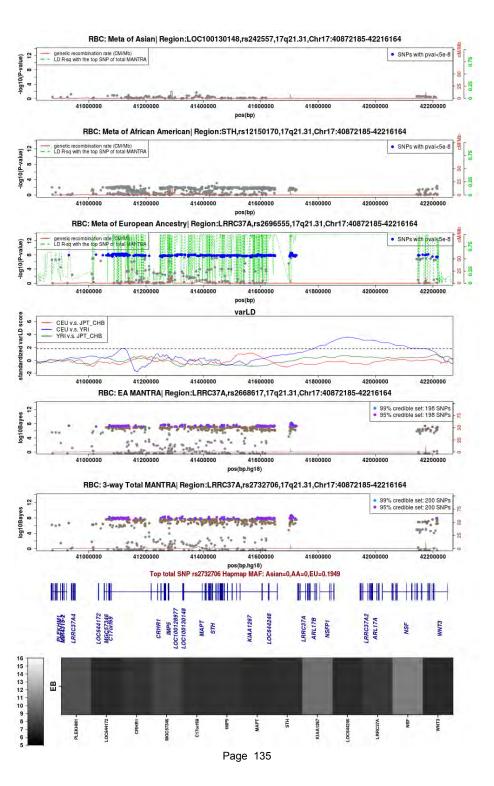
Page 131

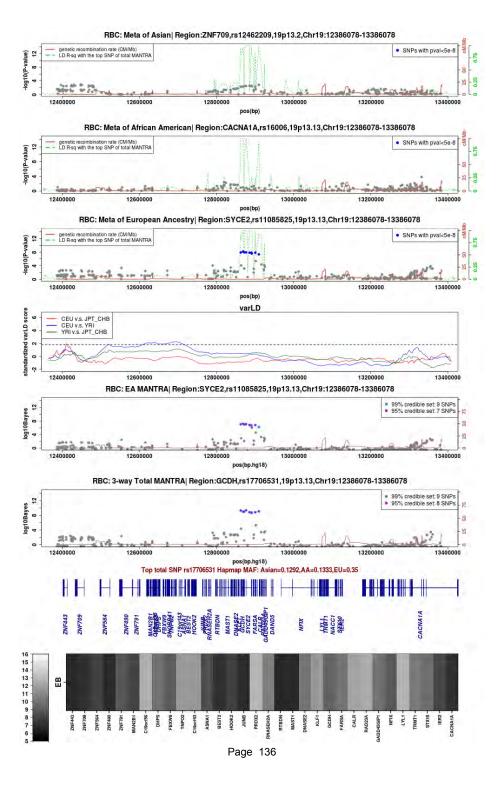


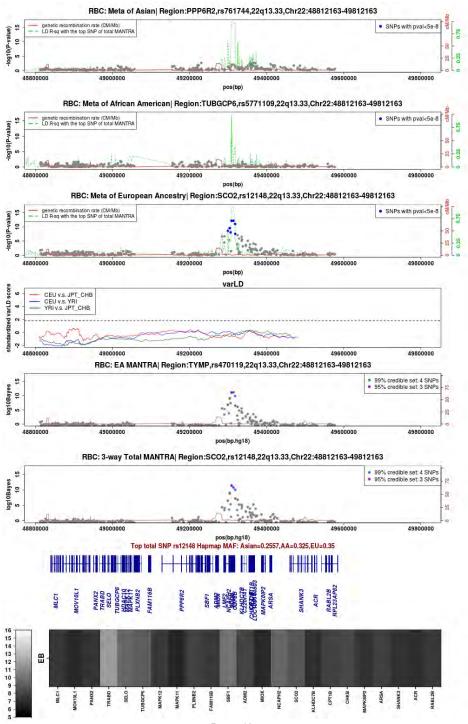
Page 132











Page 137

Supplemental References

- Harris, T. B. et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. Am.
 J. Epidemiol. 165, 1076–1087 (2007).
- Ganesh, S. K. et al. Multiple loci influence erythrocyte phenotypes in the CHARGE Consortium. Nat. Genet. 41, 1191–1198 (2009).
- 3. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. PMID: 2646917. *Am. J. Epidemiol.* **129,** 687–702 (1989).
- 4. Schmidt, R. *et al.* Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study (ASPS). *Neuroepidemiology* **13**, 308–313 (1994).
- 5. Nalls, M. A. et al. Multiple Loci Are Associated with White Blood Cell Phenotypes. PLoS Genet 7, e1002113 (2011).
- 6. Friedman, G. D. *et al.* CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J. Clin. Epidemiol.* **41,** 1105–1116 (1988).
- 7. Fried, L. P. *et al.* The Cardiovascular Health Study: design and rationale. PMID:1669507. *Ann. Epidemiol.* **1,** 263–276 (1991).
- 8. Feinleib, M., Kannel, W. B., Garrison, R. J., McNamara, P. M. & Castelli, W. P. The Framingham Offspring Study.

 Design and preliminary data. PMID: 1208363. *Prev. Med.* **4,** 518–525 (1975).
- 9. Qayyum, R. *et al.* A Meta-Analysis and Genome-Wide Association Study of Platelet Count and Mean Platelet Volume in African Americans. *PLoS Genet* **8**, e1002491 (2012).
- Vaidya, D. et al. Coronary Artery Disease Incidence Over 10 Years in Siblings of Patients with Premature
 Coronary Artery Disease. Am. J. Cardiol. 100, 1410–1415 (2007).
- 11. Becker DM, Segal J, Vaidya D & et al. SEx differences in platelet reactivity and response to low-dose aspirin therapy. *JAMA* **295**, 1420–1427 (2006).
- 12. Reiner, A. P. *et al.* Genome-Wide Association Study of White Blood Cell Count in 16,388 African Americans: the Continental Origins and Genetic Epidemiology Network (COGENT). *PLoS Genet* **7**, e1002108 (2011).
- 13. Shepherd, J. *et al.* The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am. J. Cardiol.* **84,** 1192–1197 (1999).

- 14. Hofman, A. *et al.* The Rotterdam Study: 2016 objectives and design update. *Eur. J. Epidemiol.* **30,** 661–708 (2015).
- 15. Nakamura, Y. The BioBank Japan Project. Clin. Adv. Hematol. Oncol. HO 5, 696–697 (2007).
- 16. Okada, Y. *et al.* Identification of Nine Novel Loci Associated with White Blood Cell Subtypes in a Japanese Population. *PLoS Genet* **7**, e1002067 (2011).
- 17. Liao, W.-L. *et al.* Gene polymorphisms of adiponectin and leptin receptor are associated with early onset of type 2 diabetes mellitus in the Taiwanese population. *Int. J. Obes.* **36,** 790–796 (2012).
- 18. Jo, J. *et al.* Prediction of Colorectal Cancer Risk Using a Genetic Risk Score: The Korean Cancer Prevention Study-II (KCPS-II). *Genomics Inform.* **10**, 175–183 (2012).
- 19. Chen, Z. et al. Genome-wide association analysis of red blood cell traits in African Americans: the COGENT Network. *Hum. Mol. Genet.* **22**, 2529–2538 (2013).
- 20. Taylor, H. A. *et al.* Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn. Dis.* **15**, S6–4–17 (2005).
- 21. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control. Clin. Trials* **19,** 61–109 (1998).
- 22. Wild, D. P. S. et al. Die Gutenberg Gesundheitsstudie. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **55**, 824–830 (2012).
- 23. Desch, K. C. *et al.* Linkage analysis identifies a locus for plasma von Willebrand factor undetected by genomewide association. *Proc. Natl. Acad. Sci. U. S. A.* **110,** 588–593 (2013).
- 24. Mutsert, R. de *et al.* The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur. J. Epidemiol.* **28**, 513–523 (2013).
- 25. Ridker, P. M. Rosuvastatin in the Primary Prevention of Cardiovascular Disease Among Patients With Low Levels of Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein Rationale and Design of the JUPITER Trial. *Circulation* **108**, 2292–2297 (2003).
- 26. Keller, M. F. *et al.* Trans-ethnic meta-analysis of white blood cell phenotypes. *Hum. Mol. Genet.* ddu401 (2014). doi:10.1093/hmg/ddu401
- 27. Watkins, N. A. *et al.* A HaemAtlas: characterizing gene expression in differentiated human blood cells. *Blood* **113**, e1–e9 (2009).

Acknowledgements

Funding for Age, Gene/ Environment Susceptibility Reykjavik Study (AGES)was made possible by NIA/NIH contract AG000932-2 (2009) Characterization of Normal Genomic Variability. The Age, Gene/ Environment Susceptibility Reykjavik Study is funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association) and the Althingi (the Icelandic Parliament).

Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

Cardiovascular Health Study: This CHS research was supported by NHLBI contracts

HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080,

N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295,

R01HL087652, R01HL105756, R01HL103612, and R01HL120393 with additional contribution

from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support

was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of

principal CHS investigators and institutions can be found at CHS-NHLBI.org.

The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The National Heart, Lung, and Blood Institute's Framingham Heart Study is a joint project of the National Institutes of Health and Boston University School of Medicine and was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contract No. N01-HC-25195) and its contract with Affymetrix for genotyping services (contract No. N02-HL-6-4278). Analyses reflect the efforts and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. A portion of this research was conducted using the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at the Boston University School of Medicine and Boston Medical Center. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

The Health ABC Study was supported in part by the Intramural Research Program of the NIH, National Institute on Aging, NIA contracts N01AG62101, N01AG62103 and N01AG 62106. The GWAS was funded by NIA grant 1R01AG032098- 01A1 to Wake Forest University Health Sciences and genotyp- ing services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal con- tract from the National

Institutes of Health to The Johns Hopkins University (contract number HHSN268200782096C).

The PROSPER study was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Prof. Dr. J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

The InChianti Study was supported as a 'targeted project' (ICS 110.1RS97.71) by the Italian Ministry of Health, by the US Na- tional Institute on Aging (contracts N01-AG-916413, N01-AG-821336, 263 MD 9164 13 and 263 MD 821336) and in part by the Intramural Research Program, National Institute on Aging, National Institutes of Health, USA.

The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters, MSc, and Carolina Medina-Gomez, MSc, for their help in creating the GWAS database, and Karol Estrada, PhD, Yurii Aulchenko, PhD, and Carolina Medina-Gomez, MSc, for the creation and analysis of imputed data. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and

Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

Funding for COGENT was obtained through the Broad Institute (N01-HC- 65226) to create this genotype/phenotype database for wide dissemination to the biomedical research community.

Coronary Artery Risk in Young Adults (CARDIA): University of Alabama at Birmingham (N01-HC- 48047), University of Minnesota (N01-HC-48048), North- western University (N01-HC-48049), Kaiser Foundation Research Institute (N01-HC-48050), University of Alabama at Birmingham (N01-HC-95095), Tufts-New England Medical Center (N01-HC-45204), Wake Forest University (N01-HC-45205), Harbor-UCLA Research and Education Institute (N01- HC-05187), University of California, Irvine (N01-HC-45134 and N01-HC-95100).

Jackson Heart Study (JHS): Contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities. .

Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS): This research was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (intra-mural project # Z01-AG000513 and human subjects protocol # 2009-149).

Health ABC: This research was supported by NIA contracts N01AG62101, N01AG62103 and N01AG62106. The GWAS was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University (contract number HHSN268200782096C). This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

GeneSTAR: This research was supported by the National Heart, Lung, and Blood Institute (NHLBI) through the PROGENI (U01 HL72518) and STAMPEED (R01 HL087698-01) consortia. Additional support was provided by grants from the NIH/National In- stitute of Nursing Research (R01 NR08153) and the NIH/National Center for Research Resources (M01-RR000052) to the Johns Hopkins General Clinical Research Center.

Women's Health Initiative (WHI): The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C...

Funding for RIKEN and the BioBank Japan Project was supported by Ministry of Education, Culture, Sports, Science and Technology, Japan.

The Gutenberg Health Study is funded through the government of Rhineland-Palatinate ("Stiftung Rheinland-Pfalz für Innovation", contract AZ 961-386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and

PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study. VG PSW are funded by the Federal Ministry of Education and Research (BMBF 01EO1503). TZ and PSW are PIs of the German Center for Cardiovascular Research. The remaining authors have nothing to declare.

The Genes and Blood Clotting Study was supported by the National Institute of Health grants R37HL039693 (K.C.D., D.G.) and RO1HL112642 (A.B.O., K.C.D.,J.Z.L., D.G.). Additionally, David Ginsburg is a Howard Hughes Medical Institute investigator.

The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank the NEO study group, Pat van Beelen, Petra Noordijk and Ingeborg de Jonge for the coordination, lab and data management of the NEO study. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze. The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. Dennis Mook-Kanamori is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023).

The JUPITER trial and the genotyping were supported by AstraZeneca.

The development of the software package MANTRA was performed by Andrew P. Morris, a Wellcome Trust Senior Research Fellow in Basic Biomedical Science (grant numbers WT098017, WT090532 and WT064890).

Professor Luanne L. Peters (LLP) is supported by NIH grants HL085480 and DK100692, and by National Cancer Institute Award P30CA034196 to the Jackson Laboratory. Santhi.K.Ganesh is supported by the Doris Duke Charitable Foundation and NIH HL122684 grants. Yukinori

Okada was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI grant numbers 15H05911, 15H05670, 15K14429, the Japan Science and Technology Agency (JST), Mochida Memorial Foundation for Medical and Pharmaceutical Research, Takeda Science Foundation, Gout Research Foundation, the Tokyo Biochemical Research Foundation, and the Japan Rheumatism Foundation. Robert J. Klein was supported by grant number U01 HG007033 from NHGRI.

The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.