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Supplemental Data

Genome-wide Trans-ethnic Meta-analysis Identifies

Seven Genetic Loci Influencing Erythrocyte Traits

and a Role for *RBPMS* in Erythropoiesis

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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 Atherosclerosis²Risk (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 ethnicspecific 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.²⁶ 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

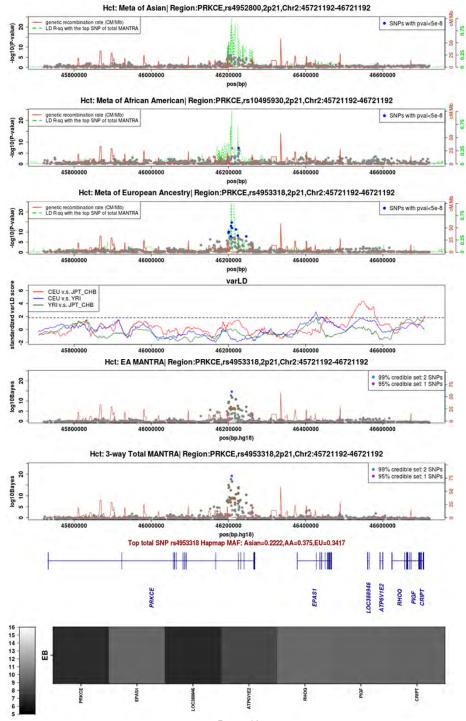
Index for Figure S1

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	10	10	10q21	rs16926246	HK1	20
Hct	12	10	12q24	rs3184504	SH2B3	20
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
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	29 30
Hb			6p22	rs412657	NOTCH4	30
	5	6 7				
Hb	6		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
MCHC	1	1	1q23	rs2479868	SPTA1	43
			-			43
MCHC MCHC	2	6 6	6p22	rs198846 rs9376090	HIST1H1T HBS1L	44 45
	3		6q23			
MCHC	4	8	8p11	rs4737009	ANK1	46
MCHC	5	12	12q24	rs671	NA Oda (of	47
MCHC	6	16	16p13	rs7197554	C16orf35	48
MCHC	7	16	16q24	rs2608604	CDT1	49
MCHC	8	22	22q12	rs2413450	TMPRSS6	50
MCH	1	1	1q31	rs12127588	PTPRC	52
MCH	2	2	2p16	rs13019832	BCL11A	53
MCH	2	2	3p24	rs2060597	PLCL2	54
MCH	3 4	3	3p24 3p24	rs1505307	THRB	55 55
MCH	4 5	3	•	rs6791816	ATR	56 56
MCH	5 6	3	3q23	rs9859401	TFRC	56 57
	U	3	3q29	139039401		57

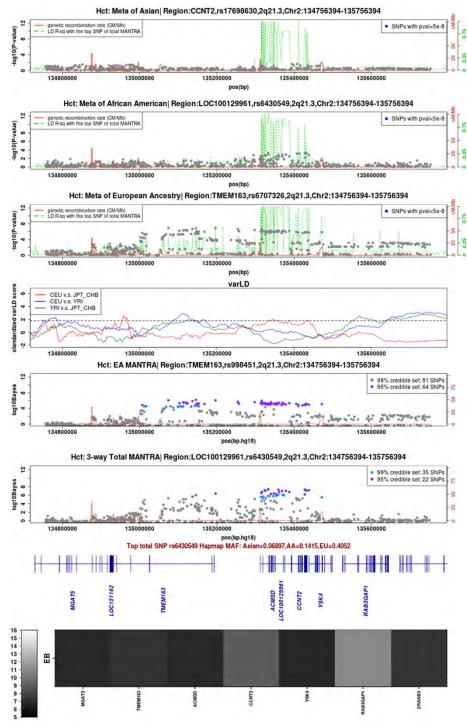
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MCH	9	6	6p22	rs1800562	HFE	60
MCH	10	6	6p21	rs9349205	CCND3	61
MCH	11	6	6q21	rs9400273	CCDC162P/CD164	62
MCH	12	6	6q23	rs7776054	HBS1L	63
MCH	13	6	6q24	rs592423	CITED2/LOC655434	64
MCH	14	7	7p12	rs12669559	IKZF1	65
		7				
MCH	15		7q22	rs12532878	MOSPD3	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	14q23	rs7155454	FNTB/MIR4706	74
MCH	24	15	15q22	rs7165102	C15orf44	75
MCH	25	16	16p13	rs1122794	ITFG3	76
MCH	26	17	17q11	rs9892942	ERAL1	70
MCH	20	19			KIAA1881/PLIN4	78
				rs8887		
MCH	28	19		rs2242517	GCDH	79
MCH	29	20	•	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		rs3893275	ZDHHC19	
			3q29			91
MCV	10	4	4q12	rs218237	KIT	92
MCV	11	5	•	rs2736100	TERT	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	102
MCV	22	9	9p24	rs10758658	RCL1/MIR101-2	103
MCV	22	9 9			ABO	104
			9q34	rs8176749		
MCV	24	10	10q11	rs963029	08-mrt	106
MCV	25	12	12p13	rs11611647	CCND2	107
MCV	26	12	12q24	rs2074356	NA	108
MCV	27	14	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

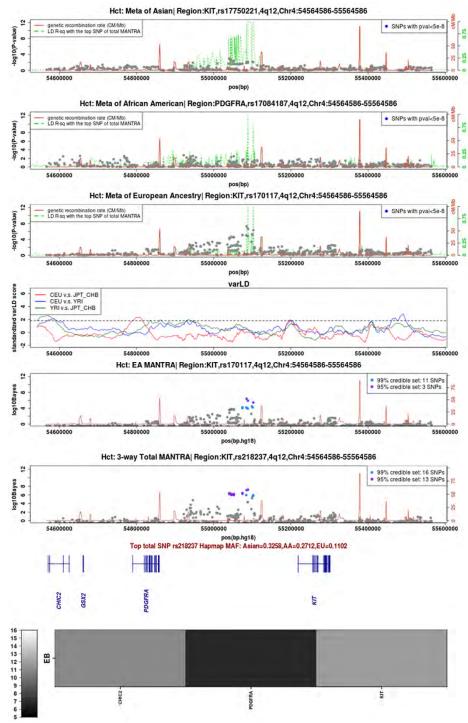
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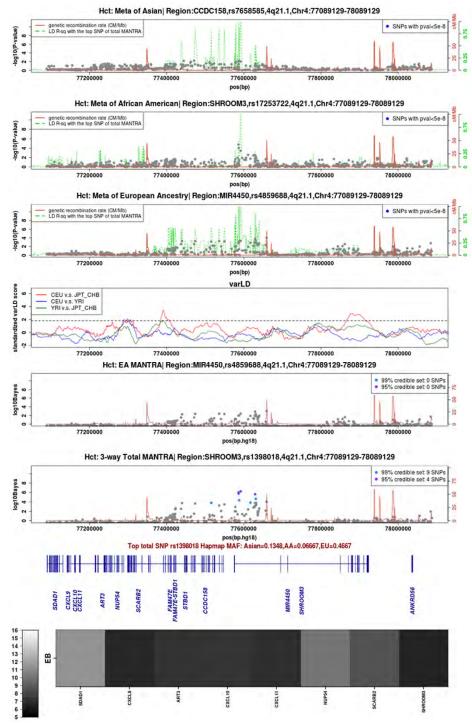




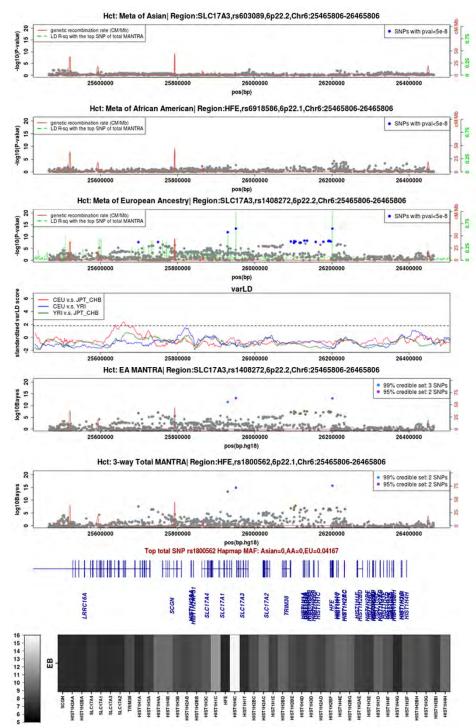
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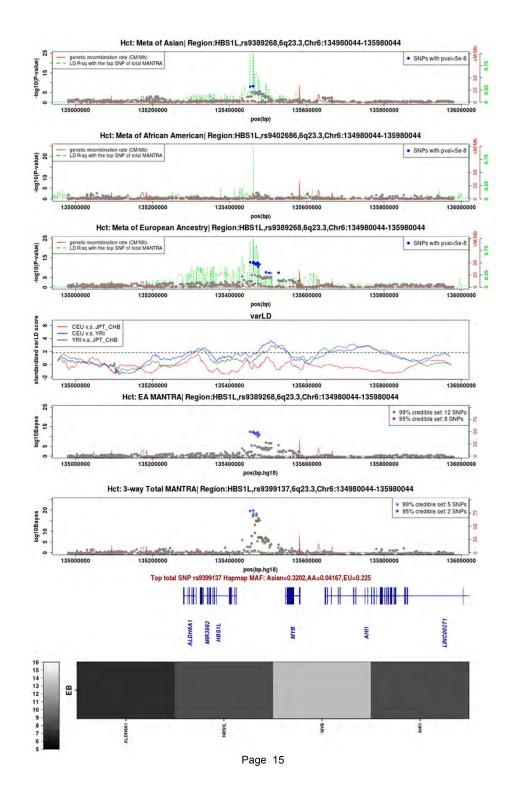
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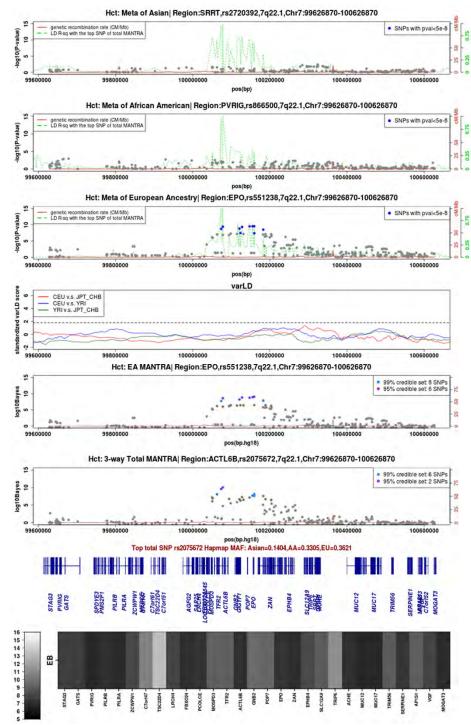


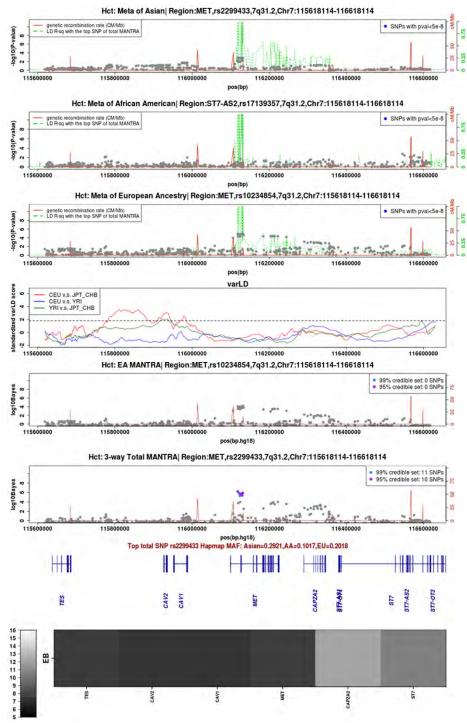




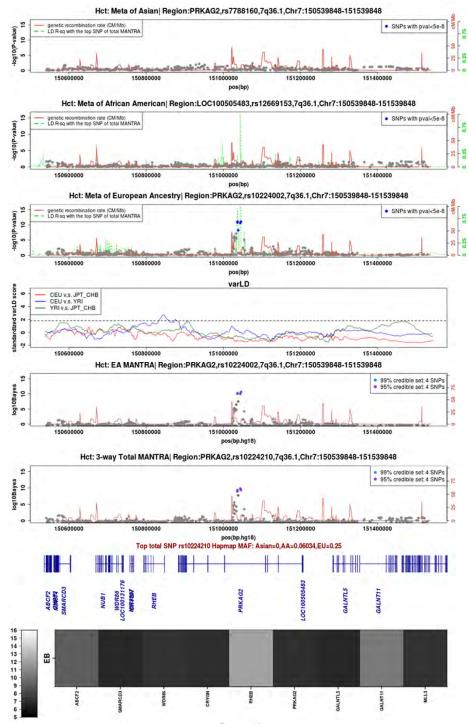




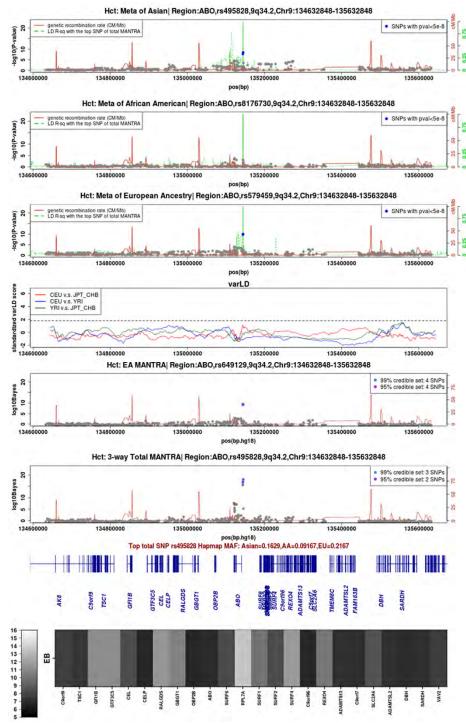




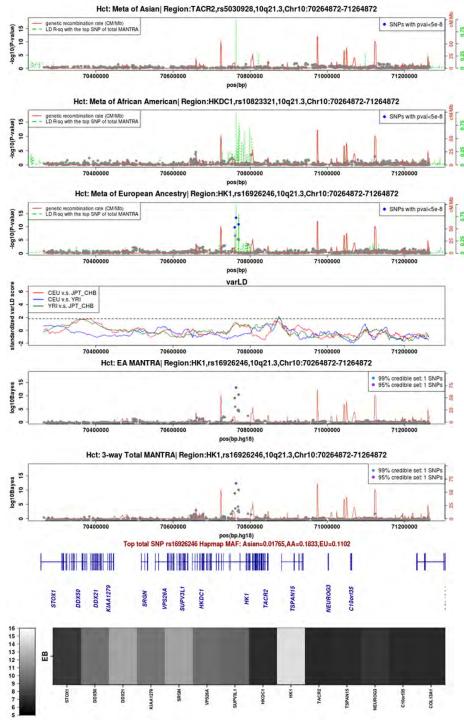
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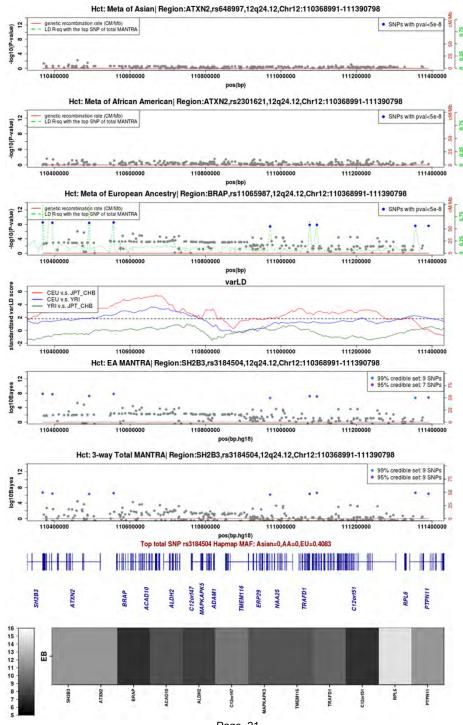
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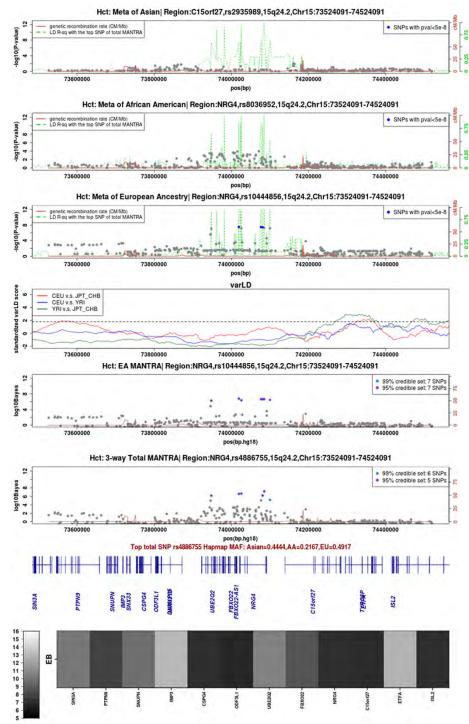
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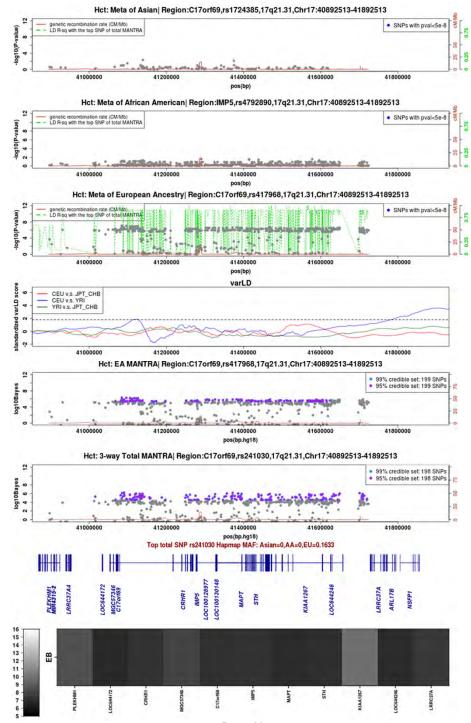




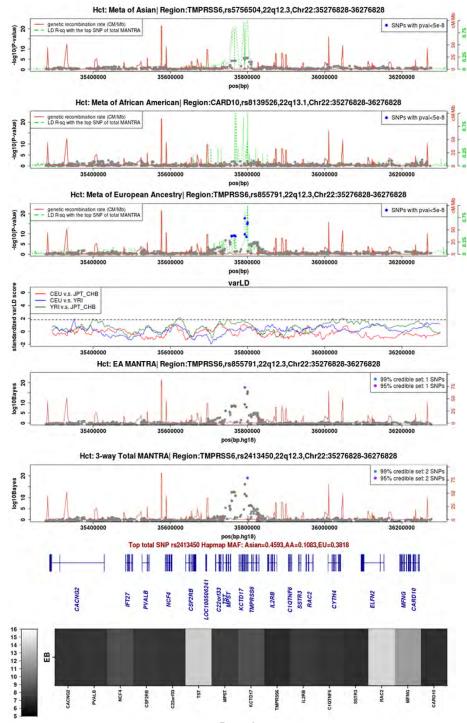
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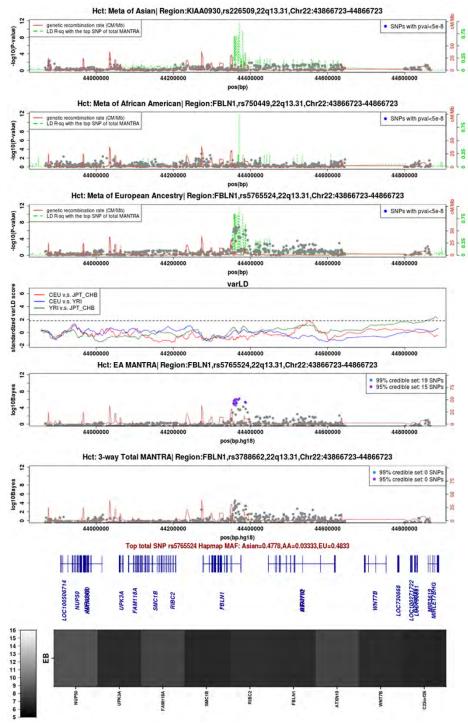






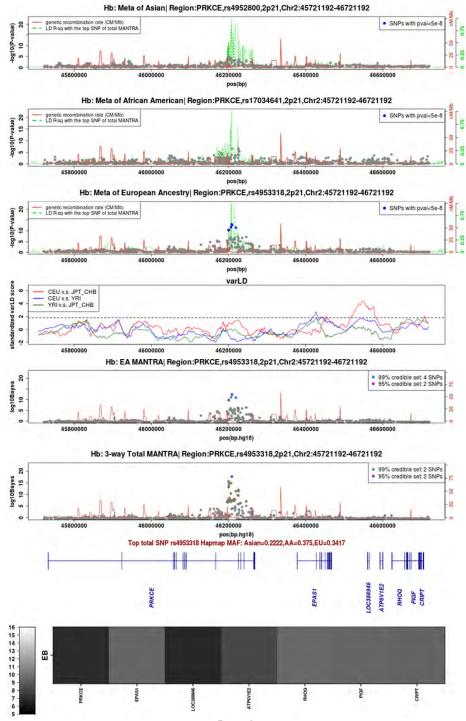


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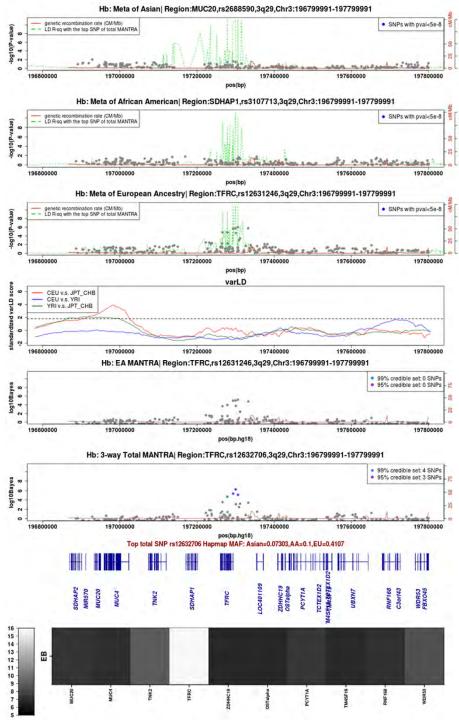


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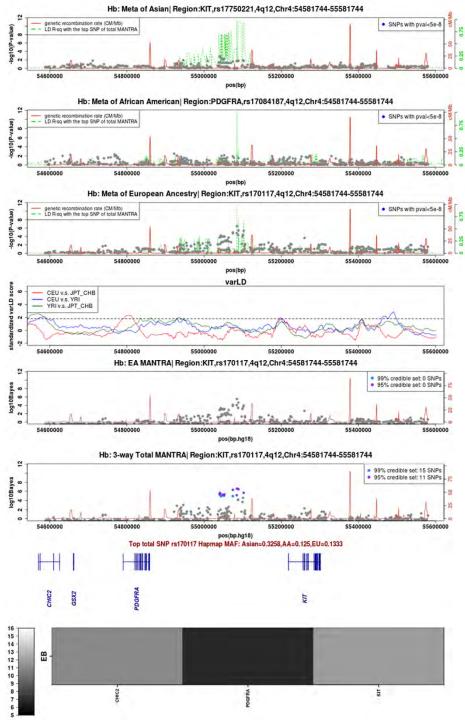
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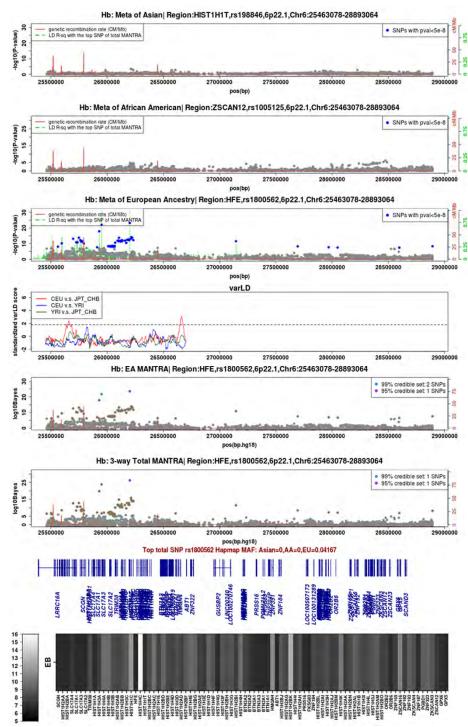




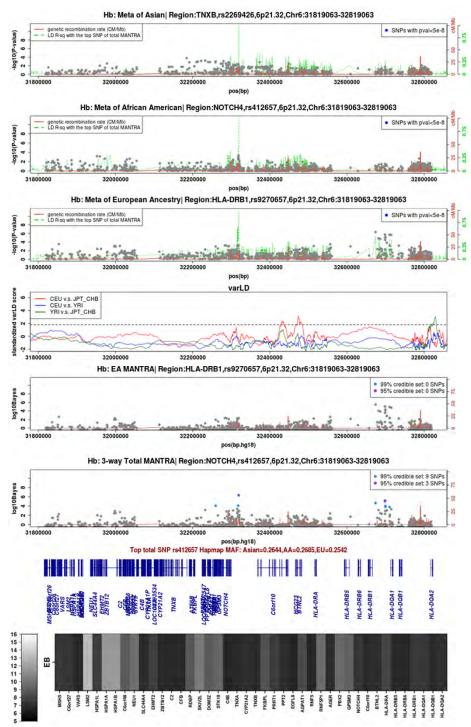




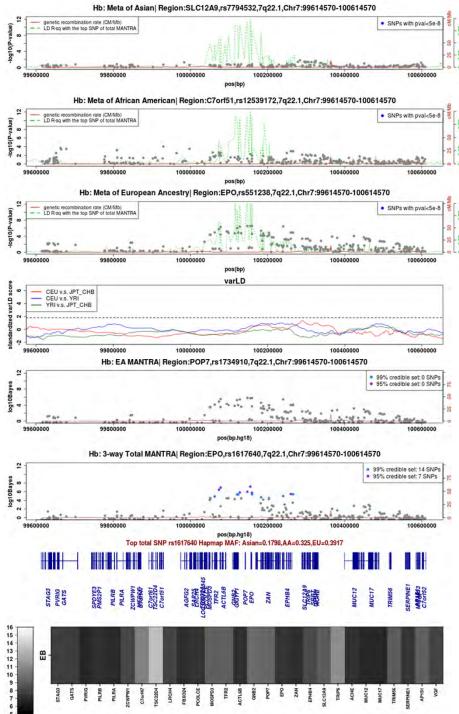


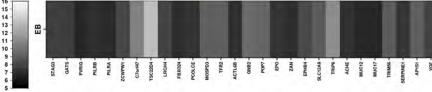


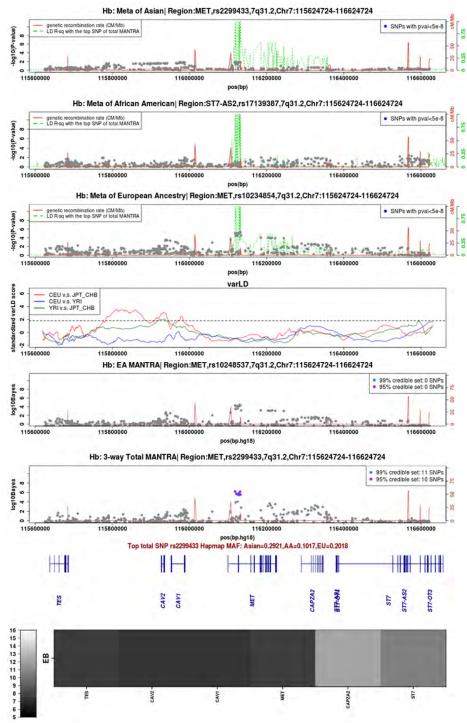




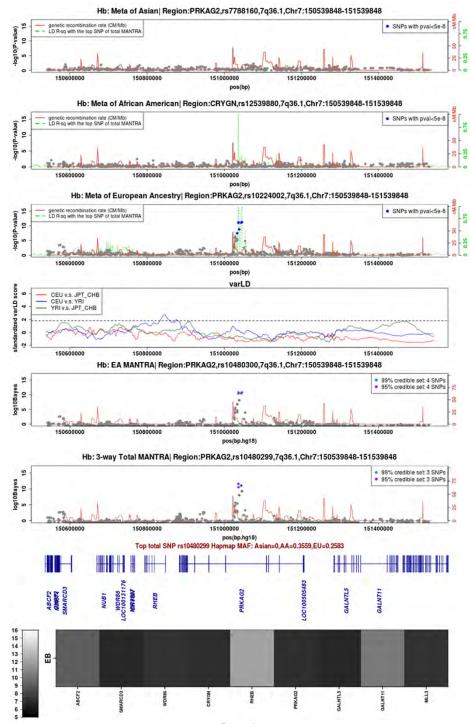
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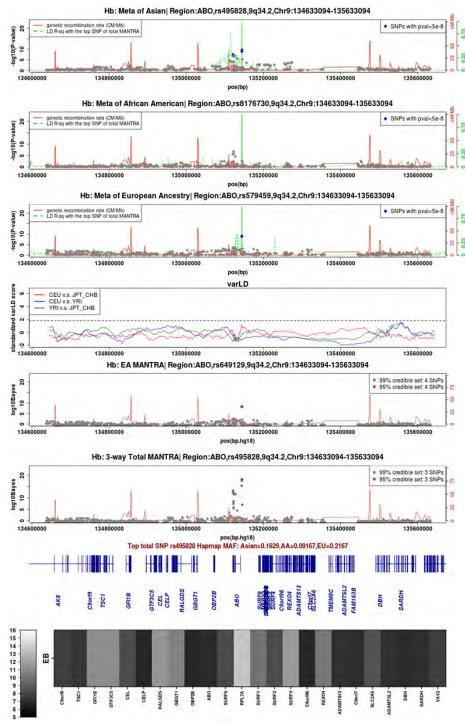




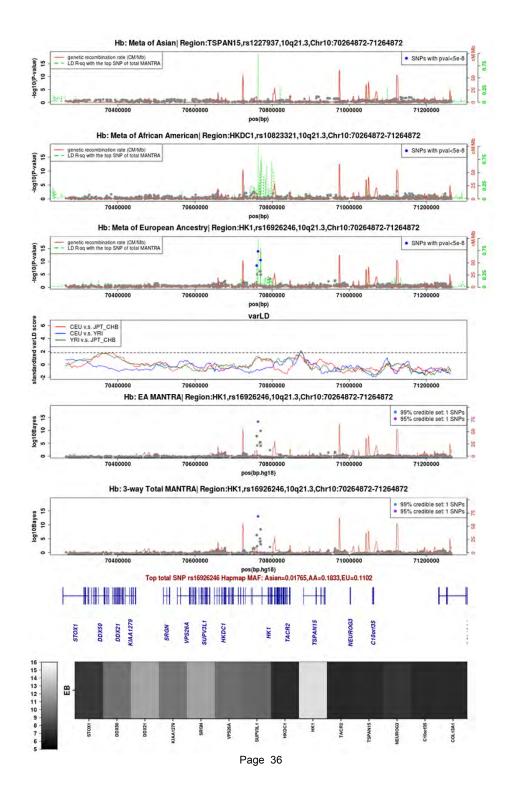
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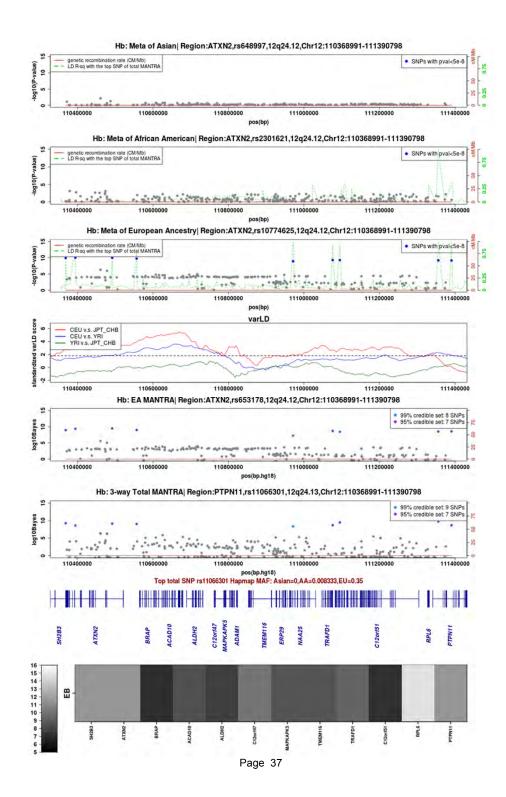


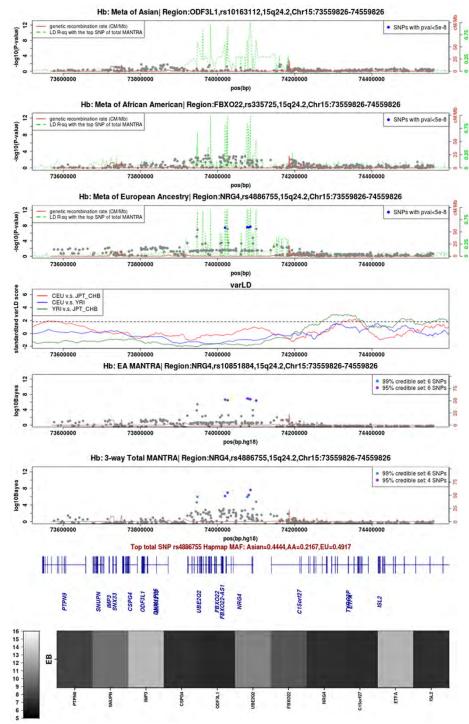
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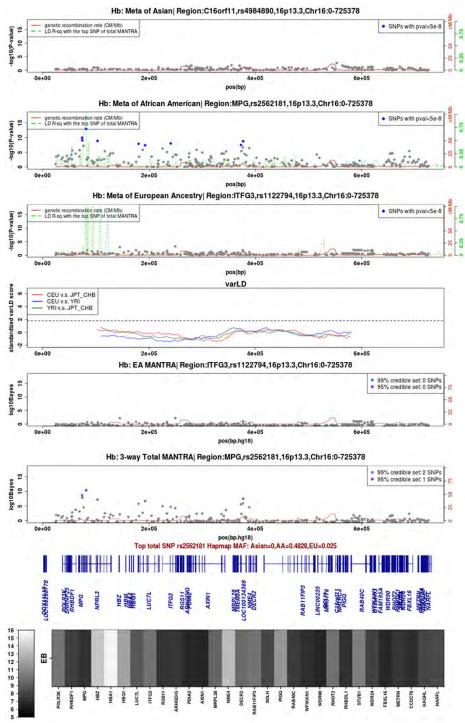
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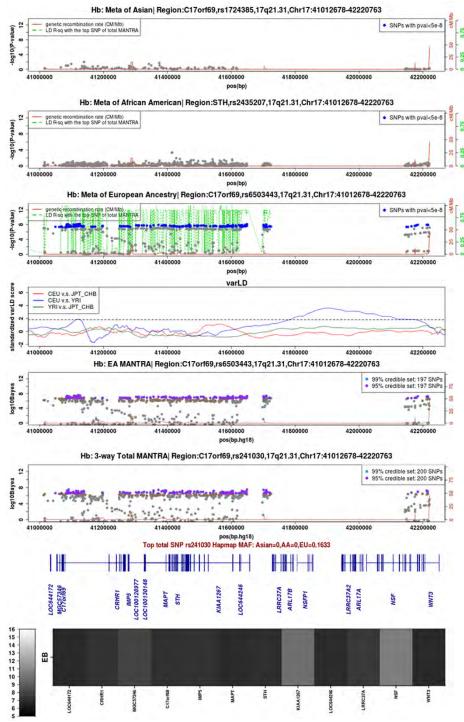




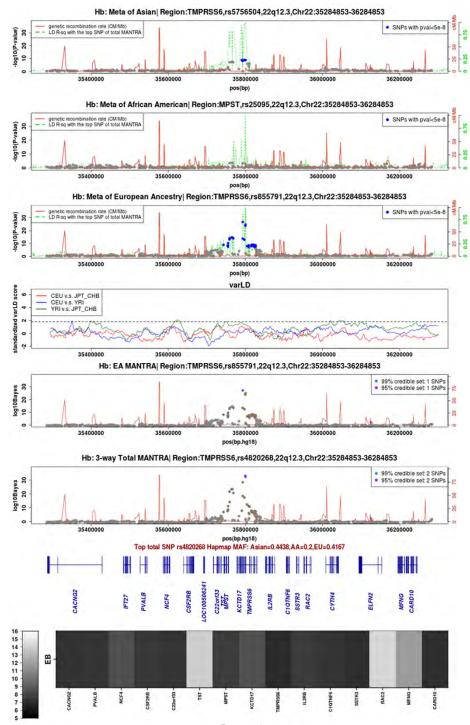




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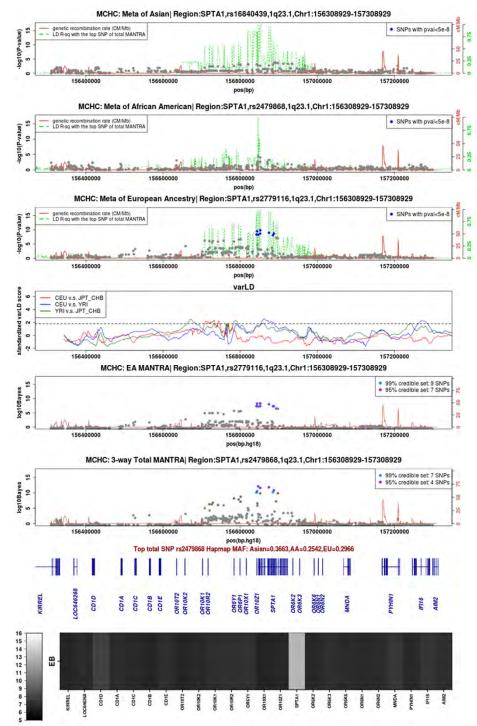




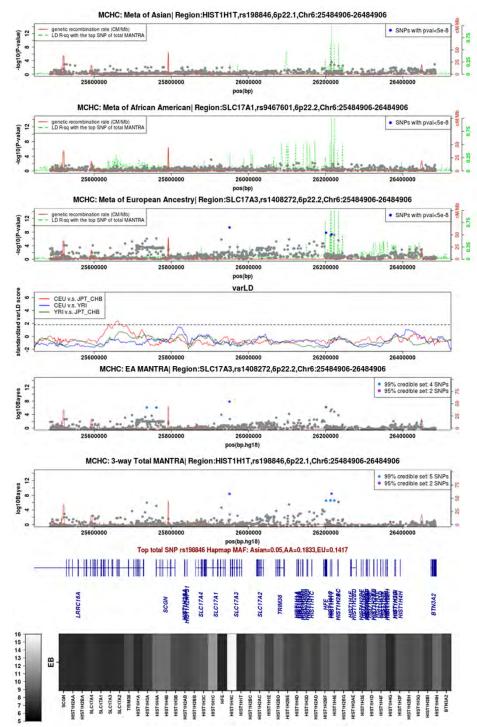


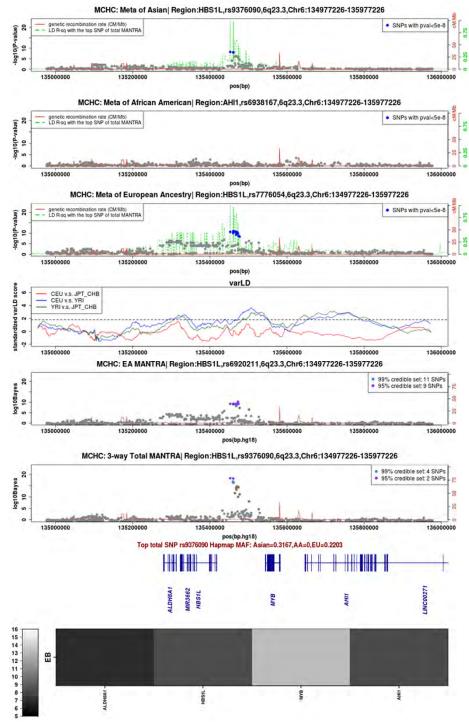


MCHC

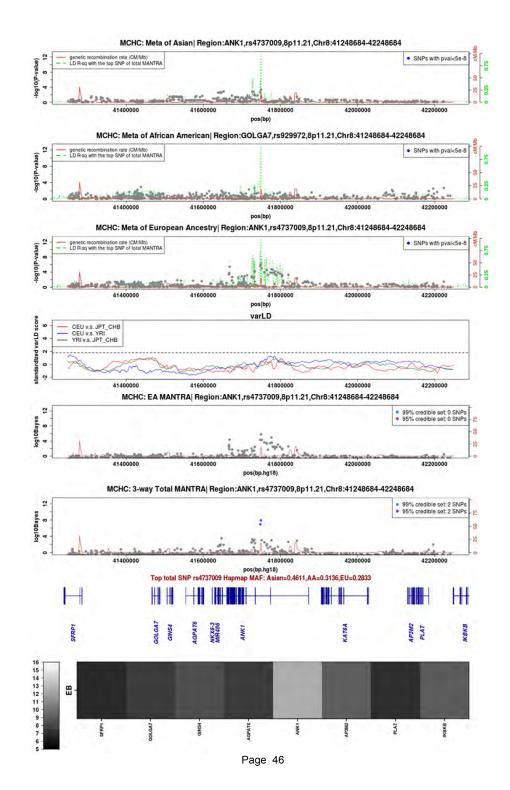


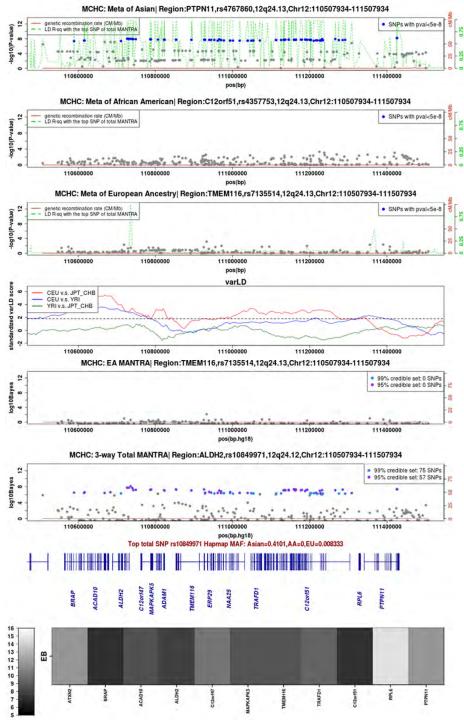




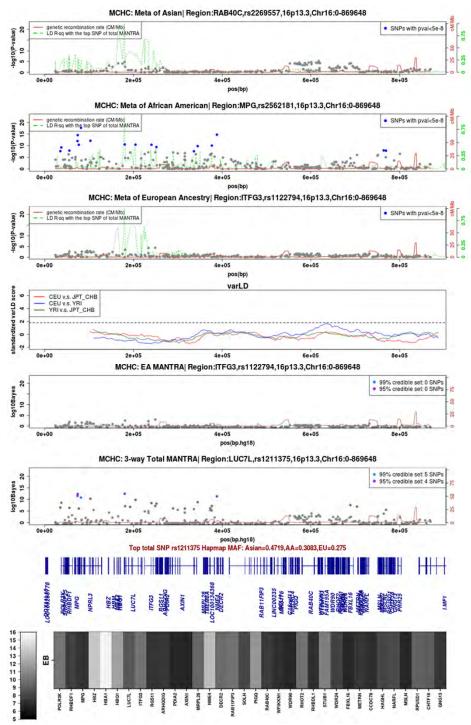




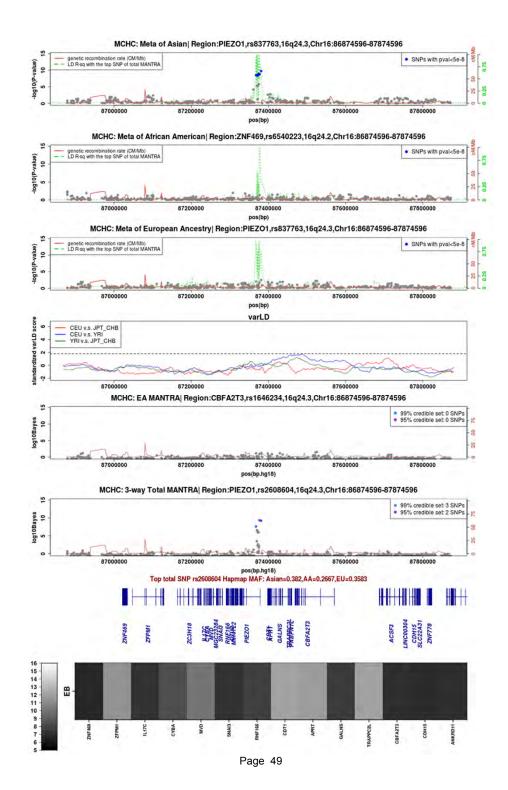


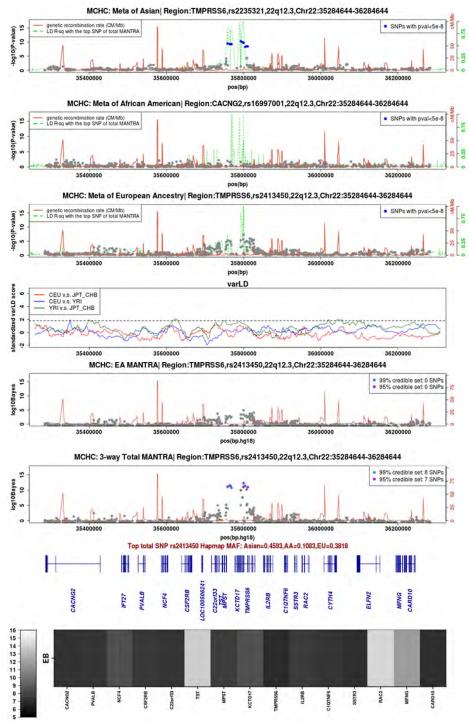






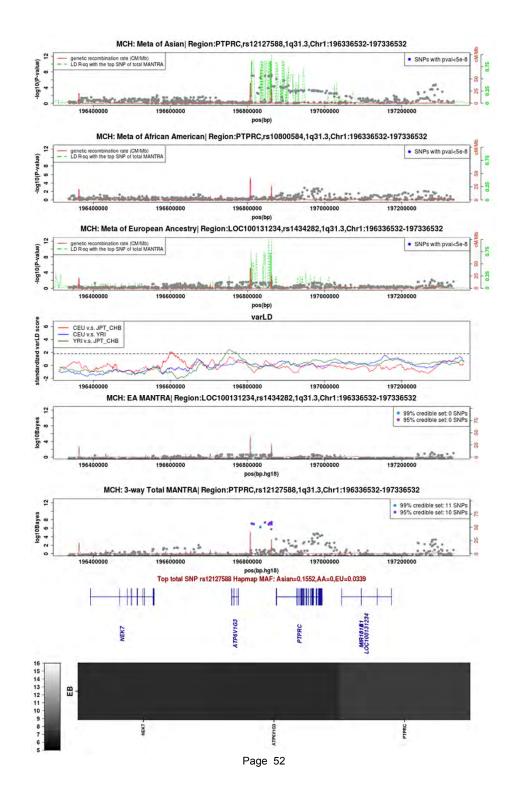
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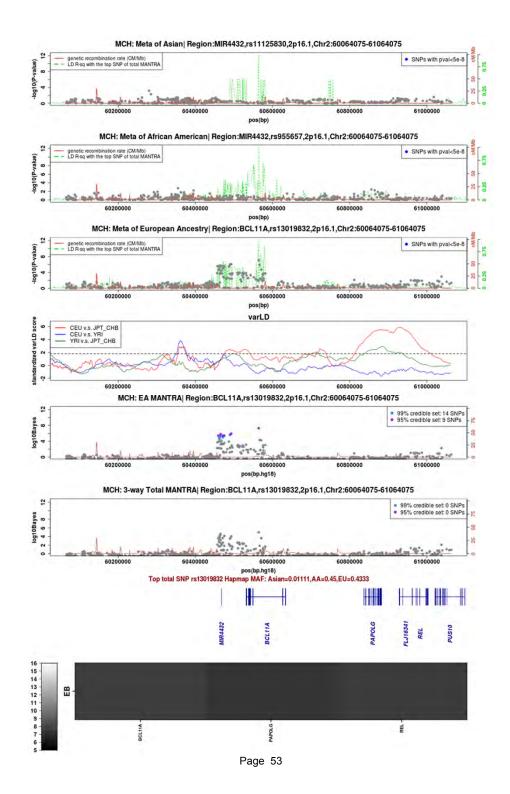


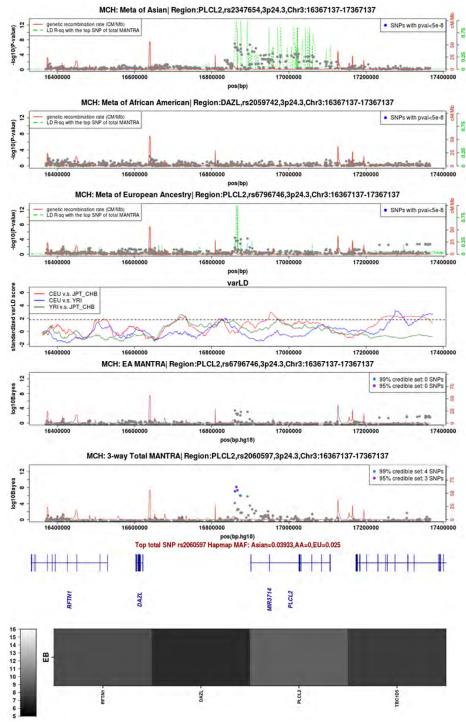


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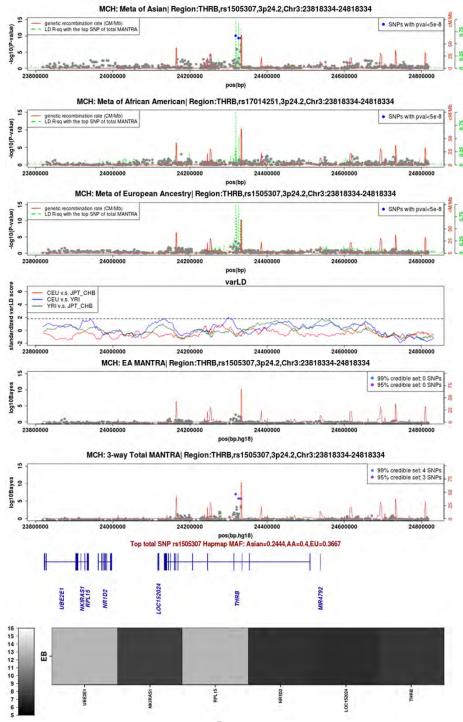
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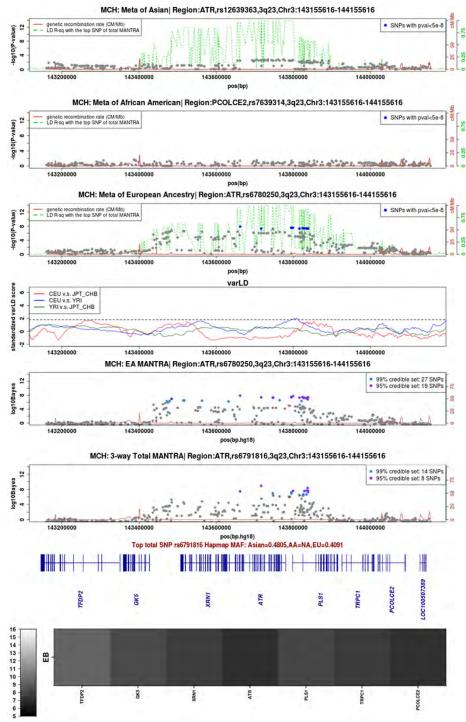




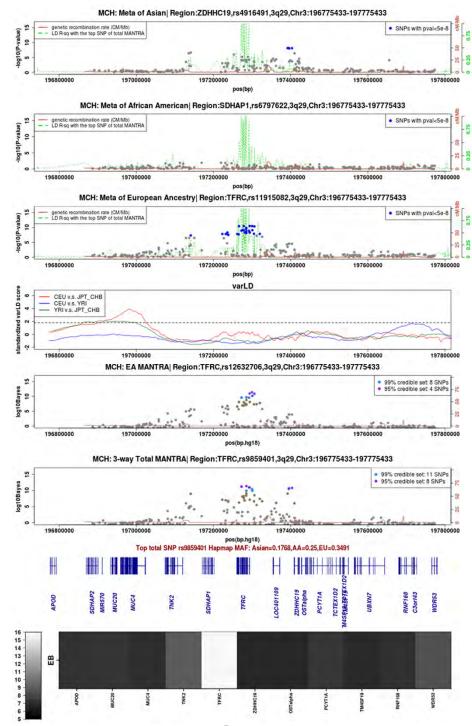




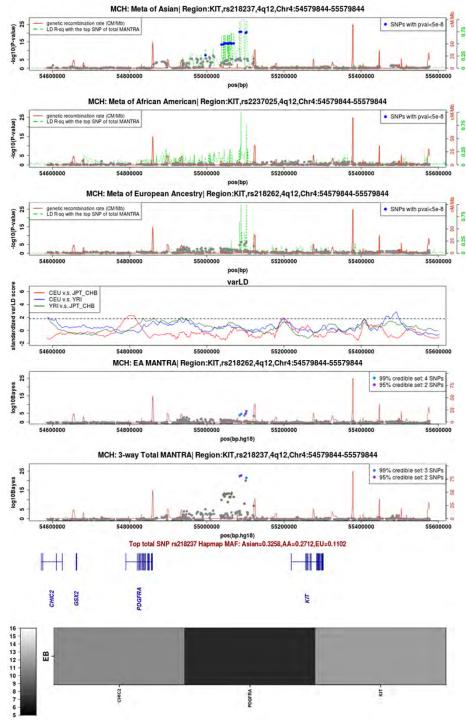
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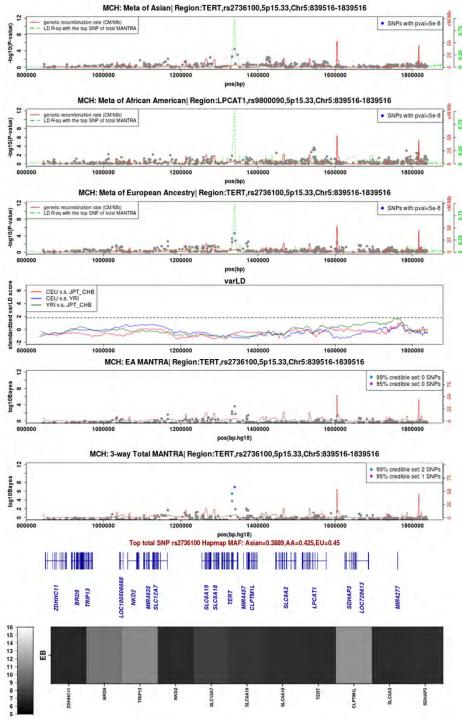




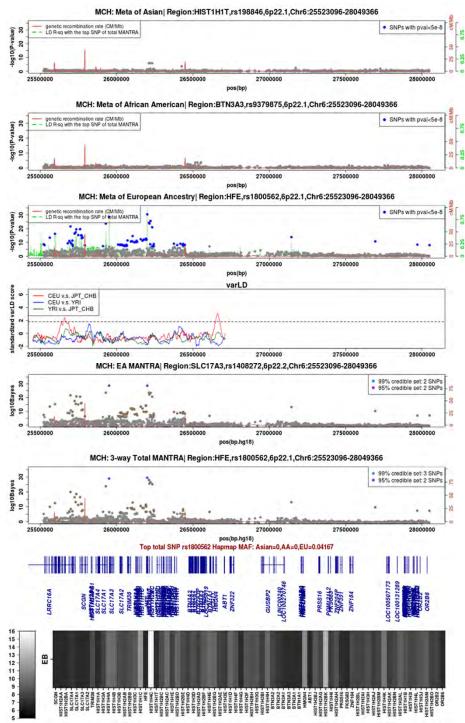
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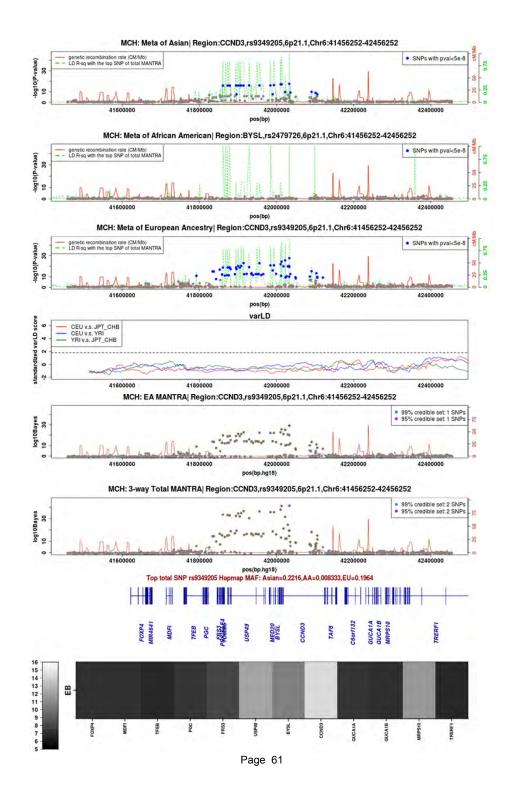
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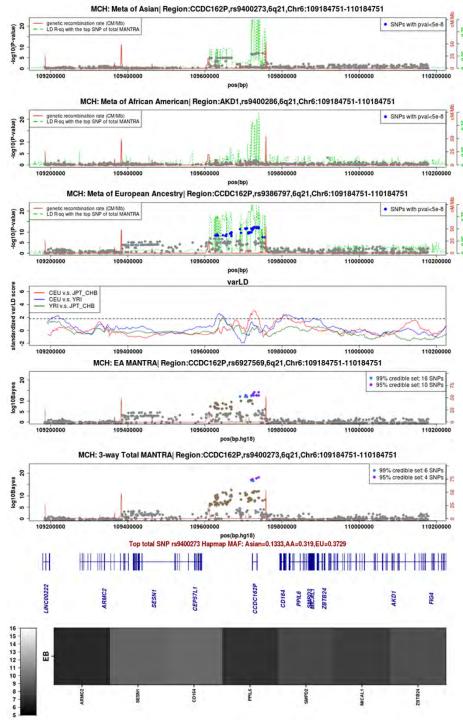


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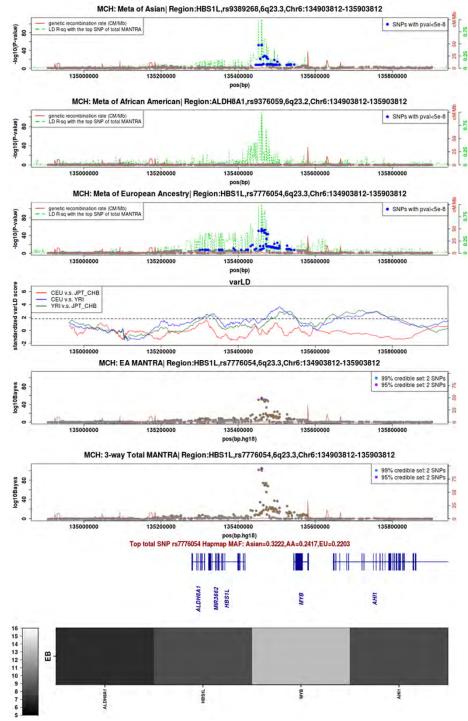


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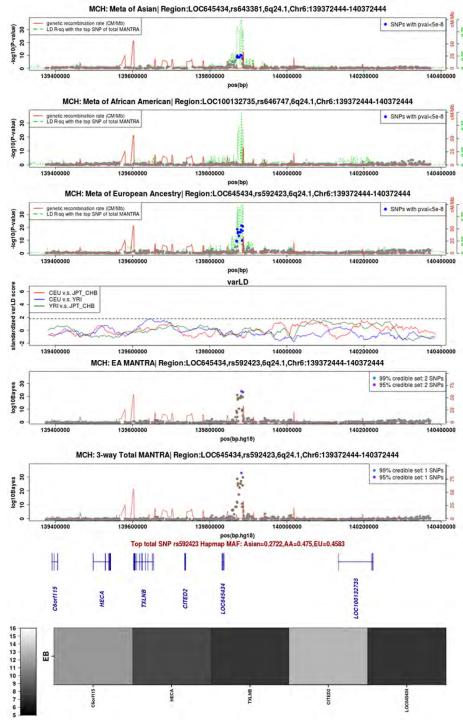




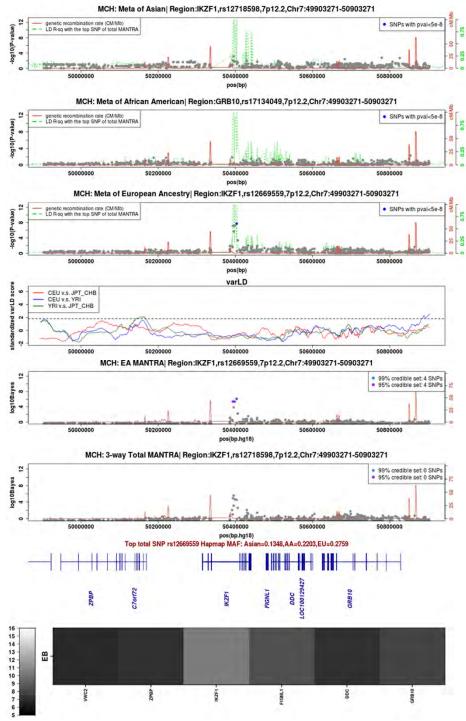
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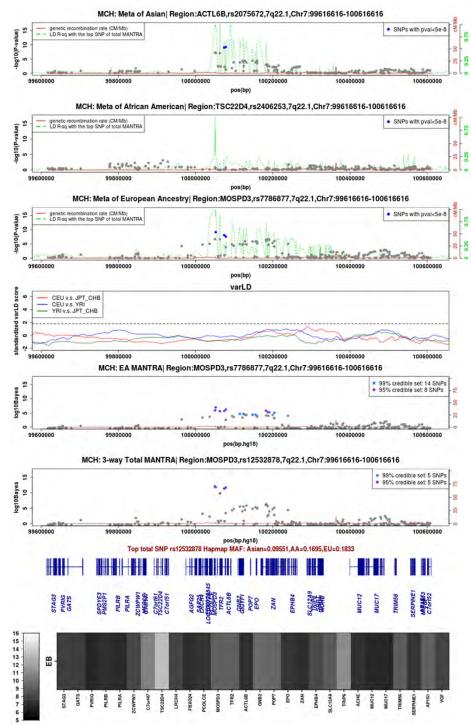




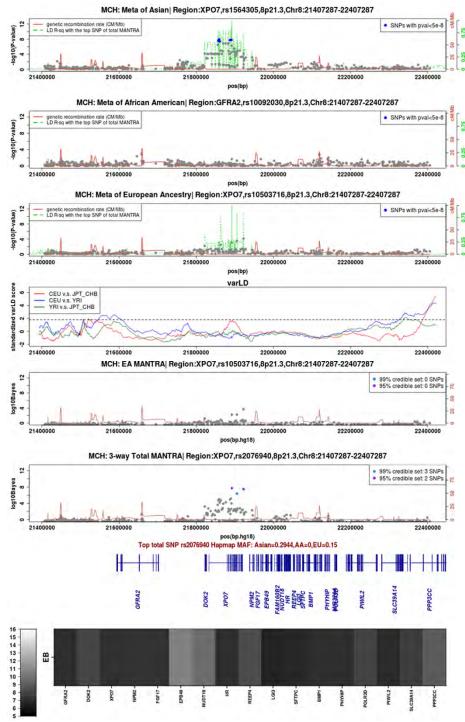




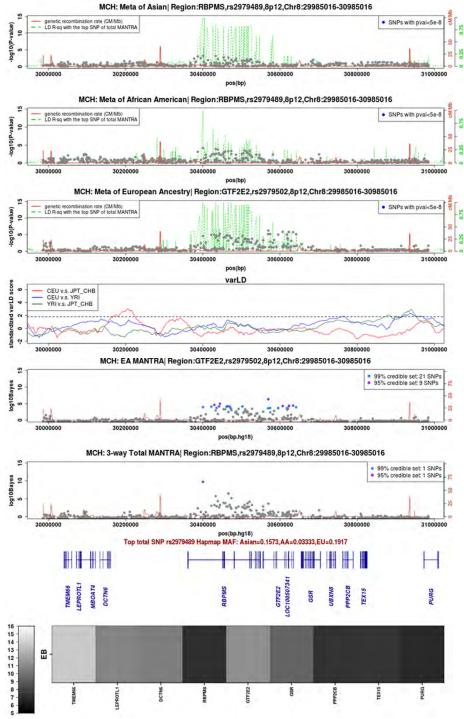




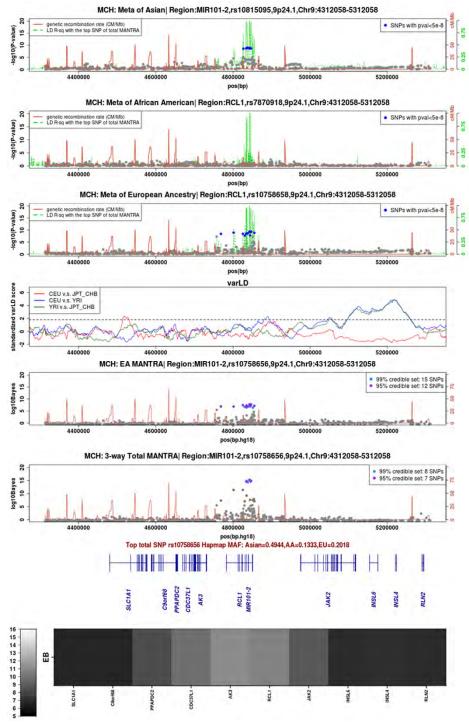




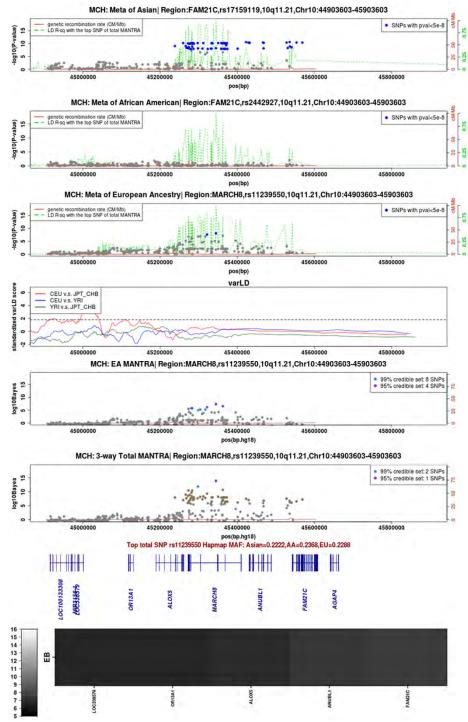




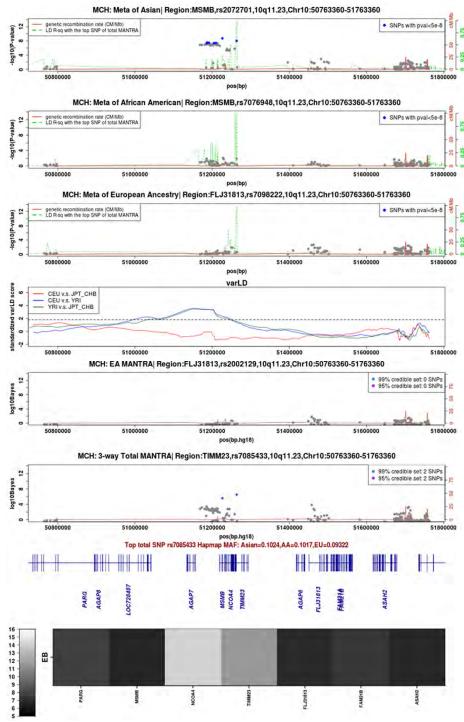




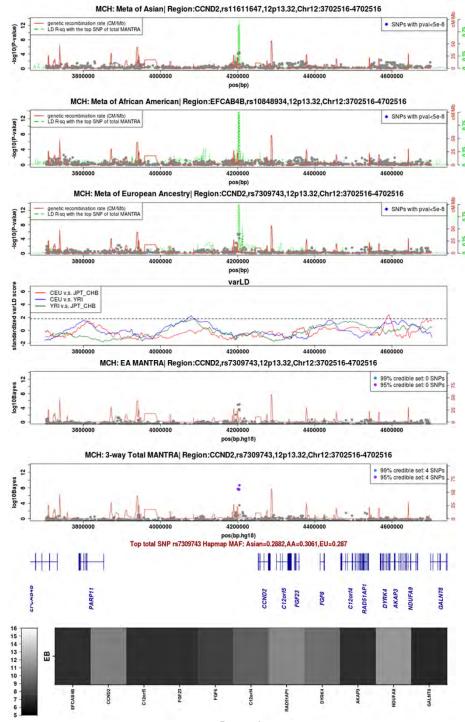




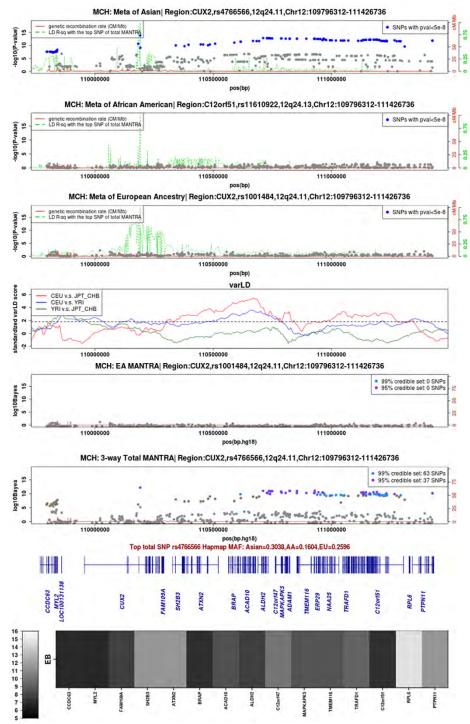




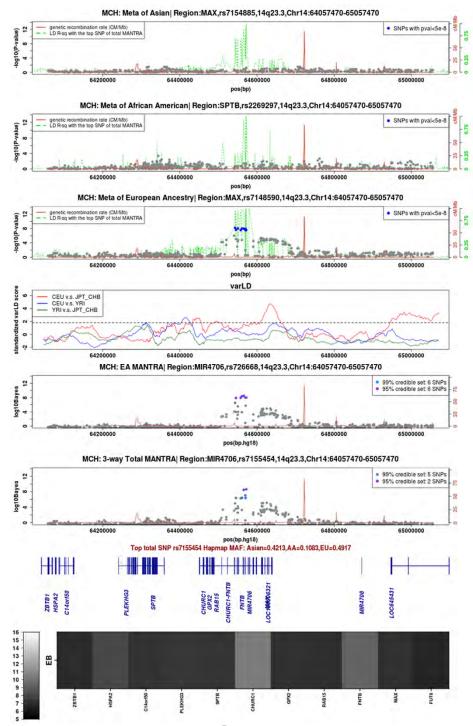




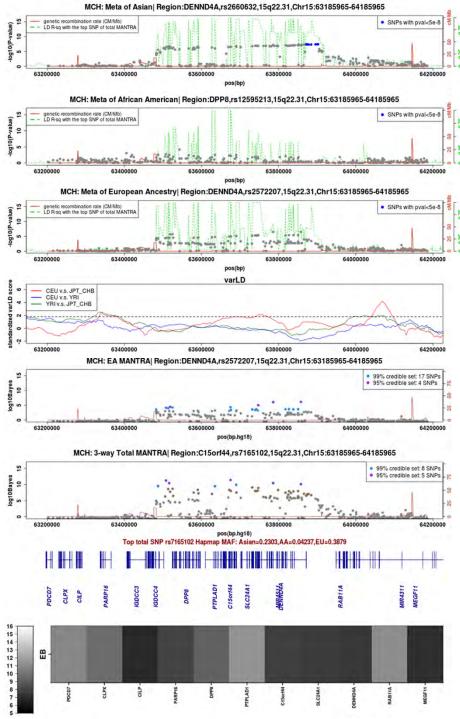
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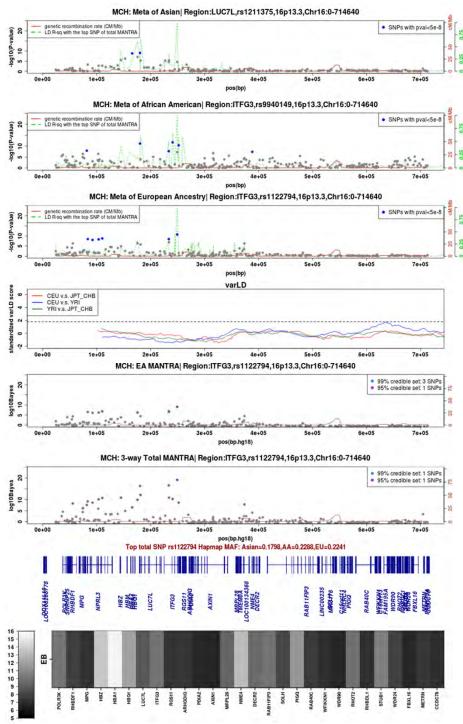
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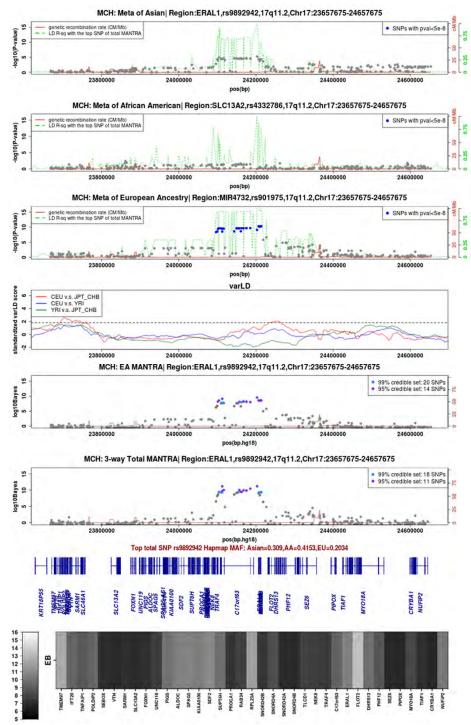
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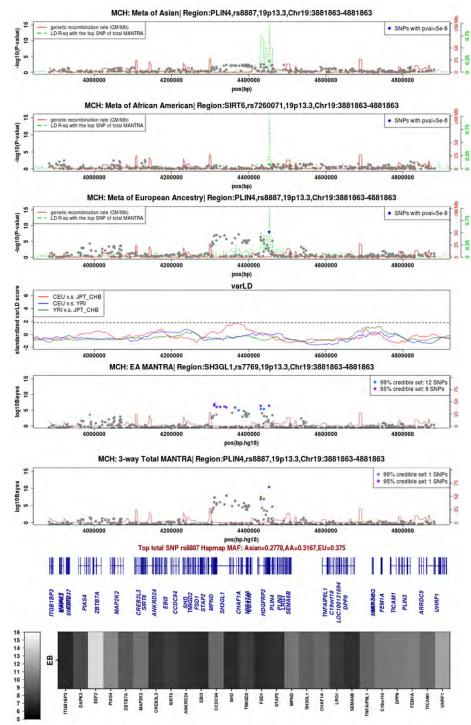




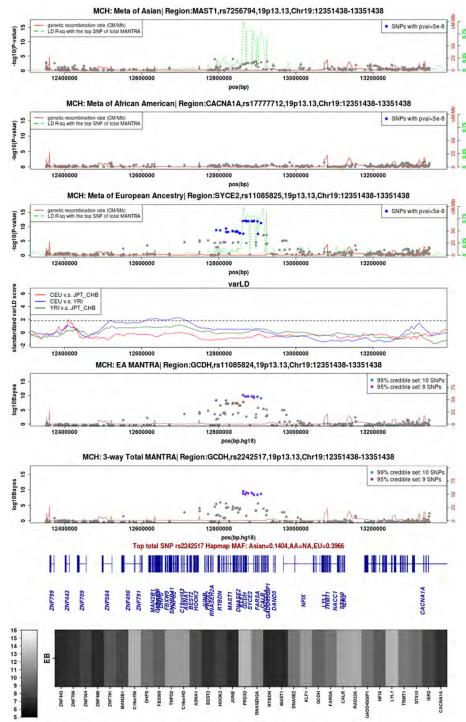




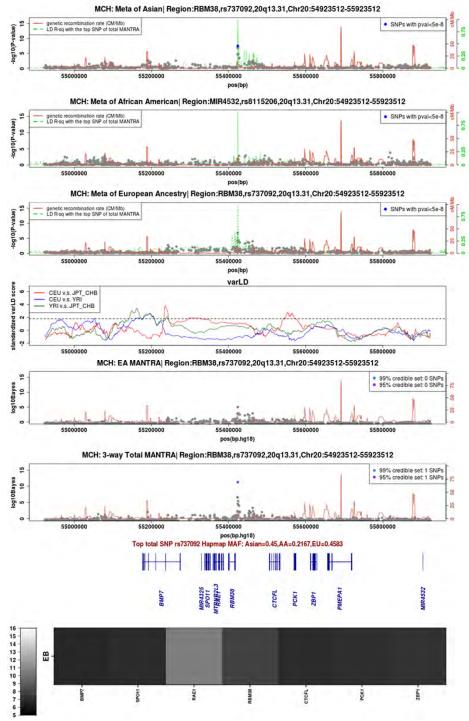




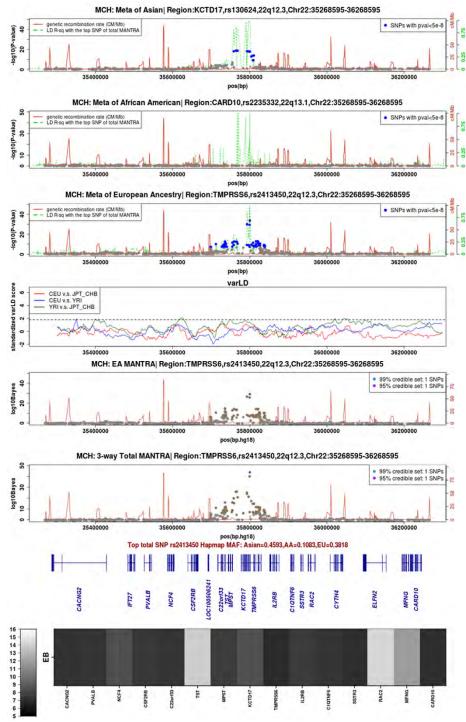






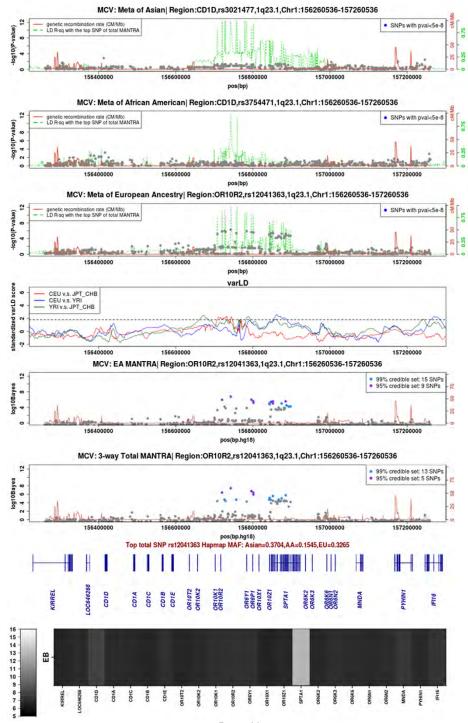




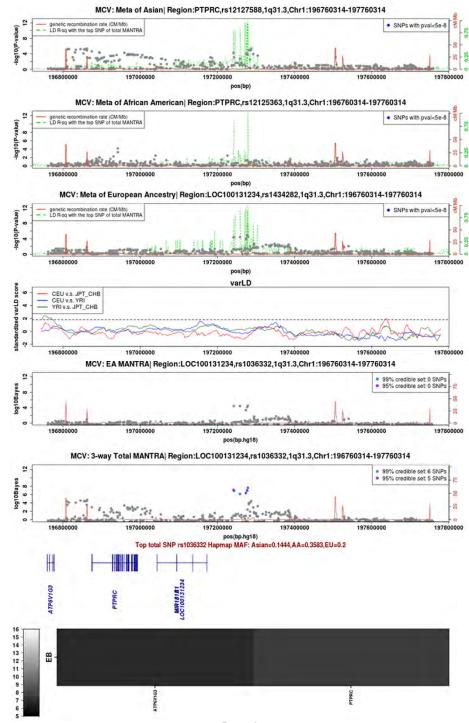


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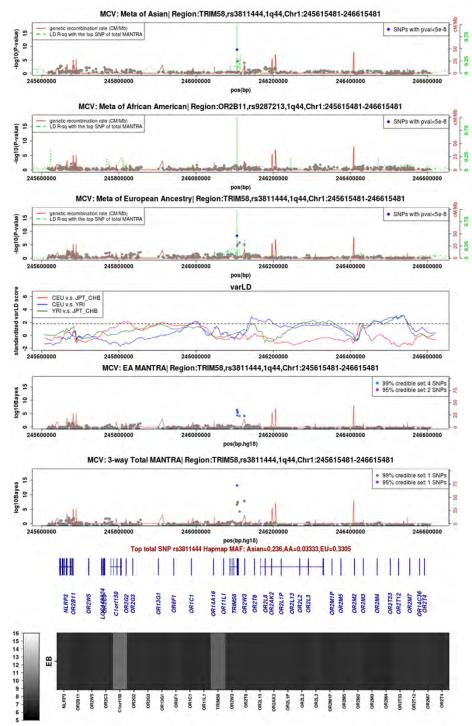
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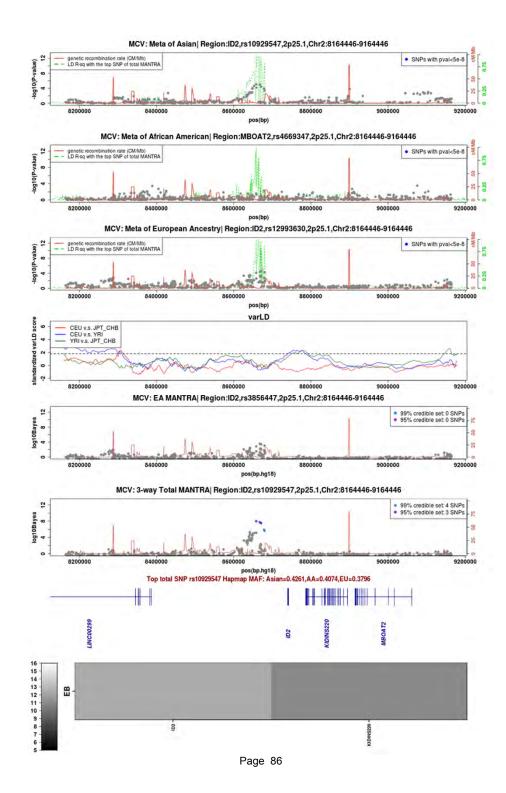
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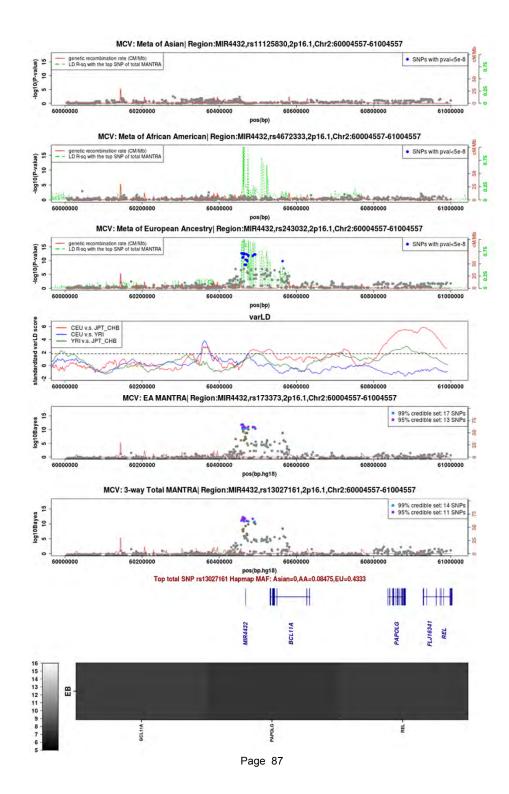


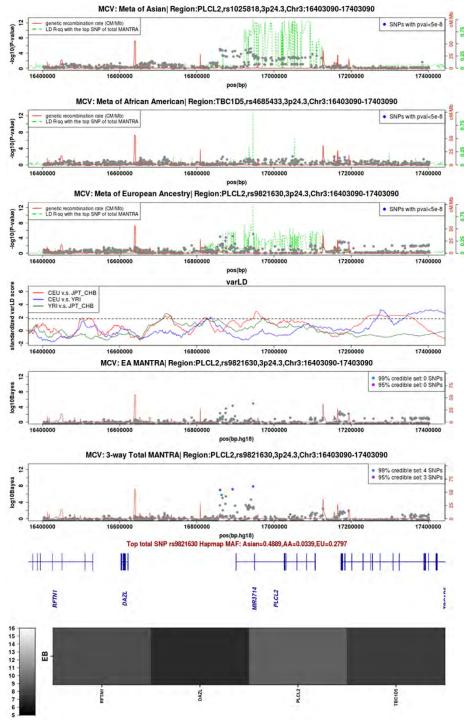




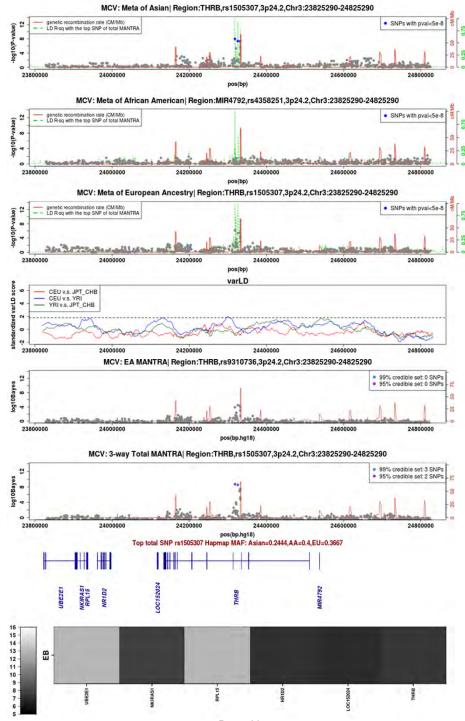




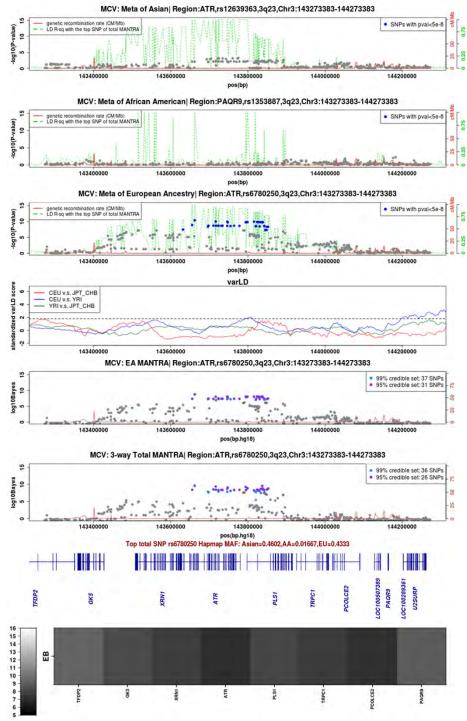




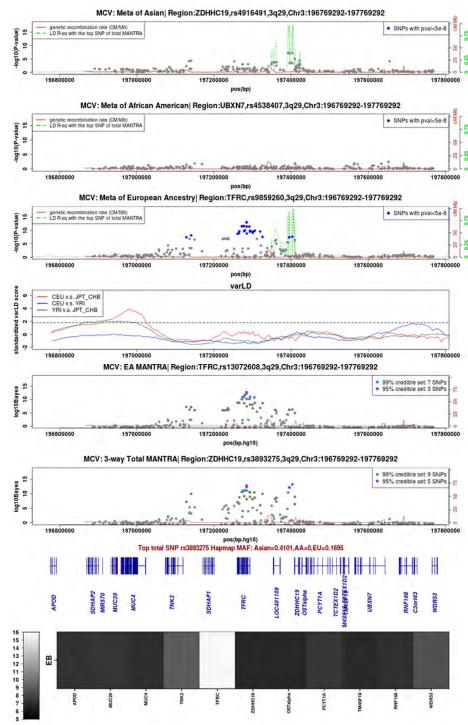
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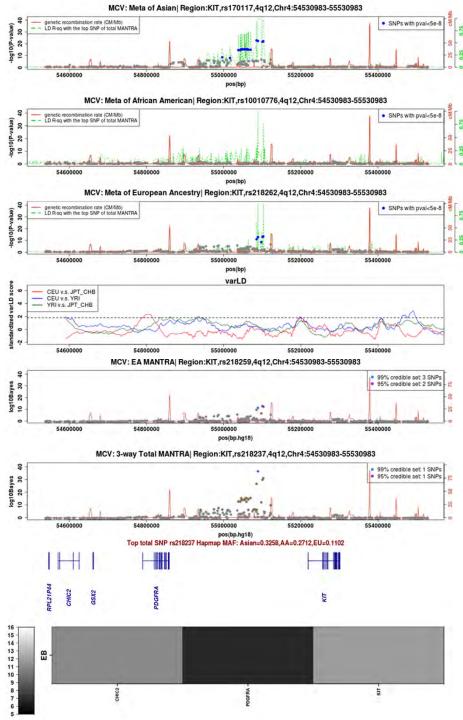
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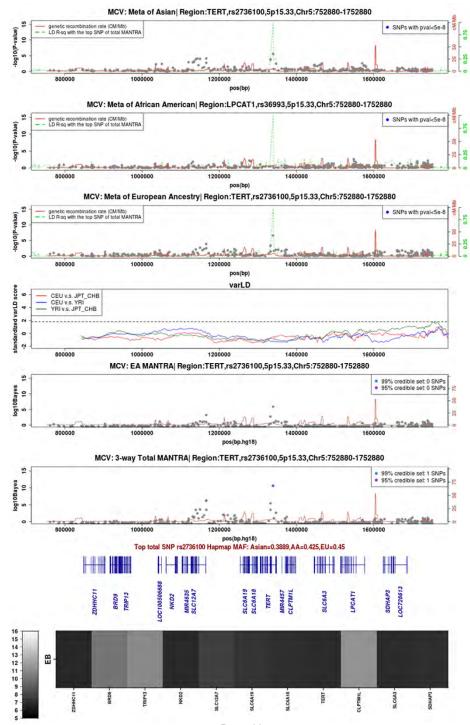
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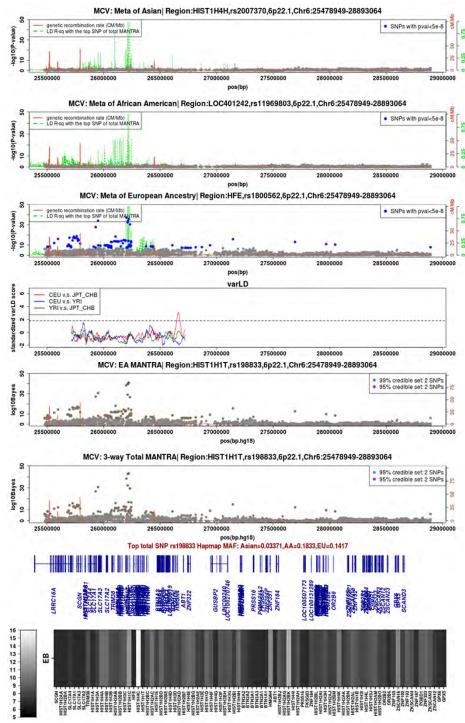




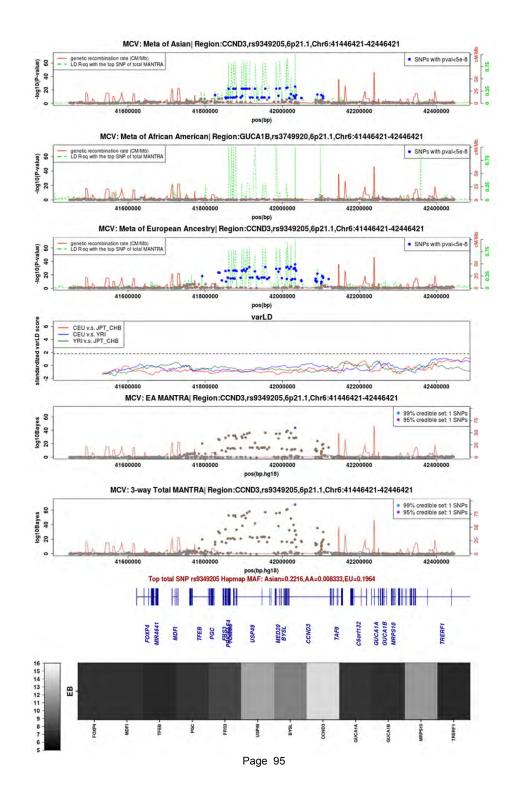


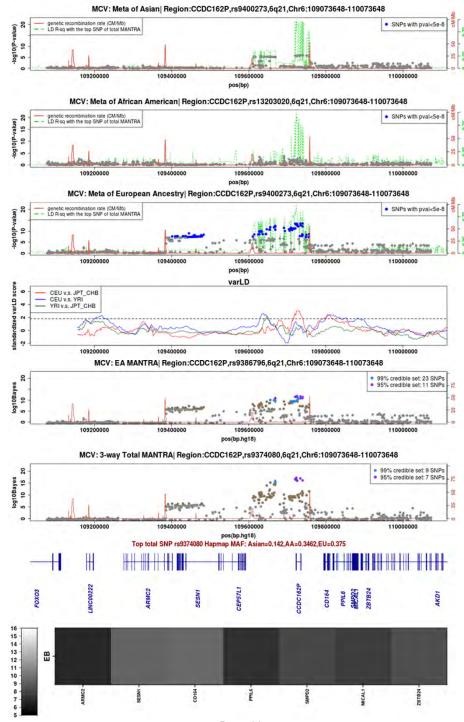




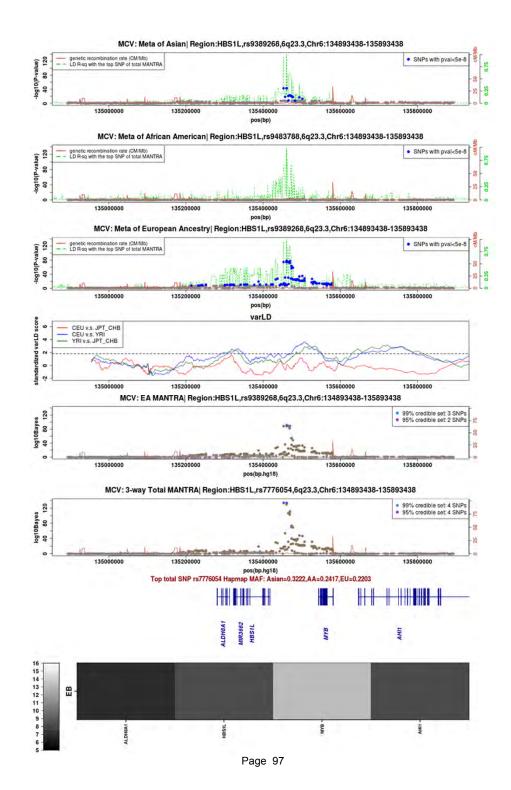


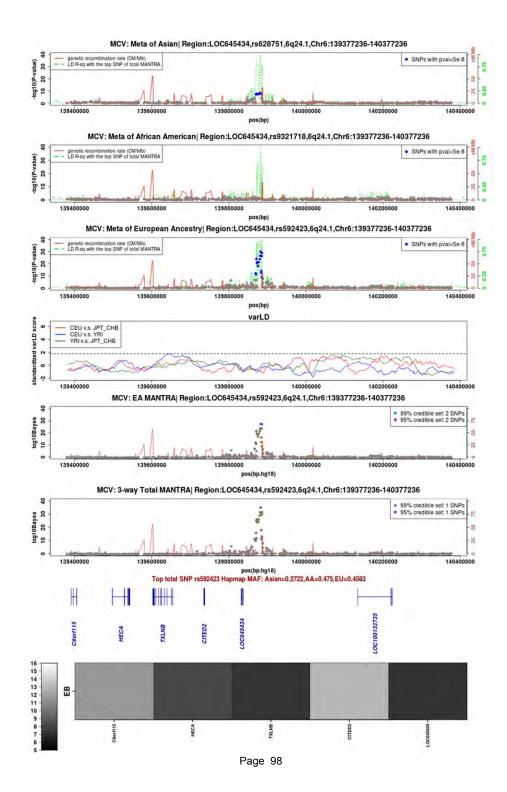
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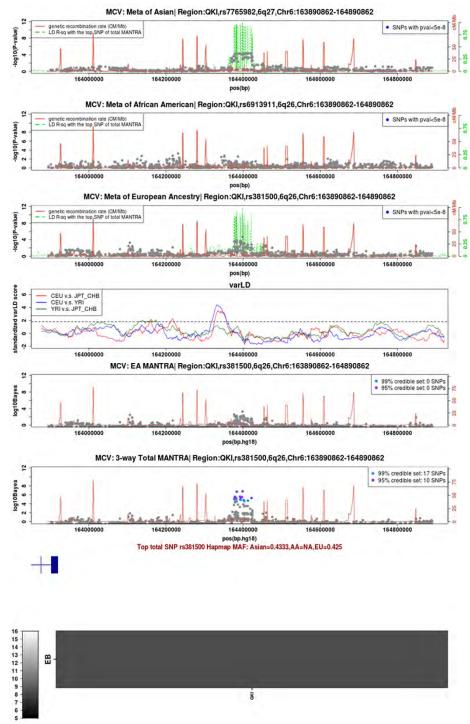




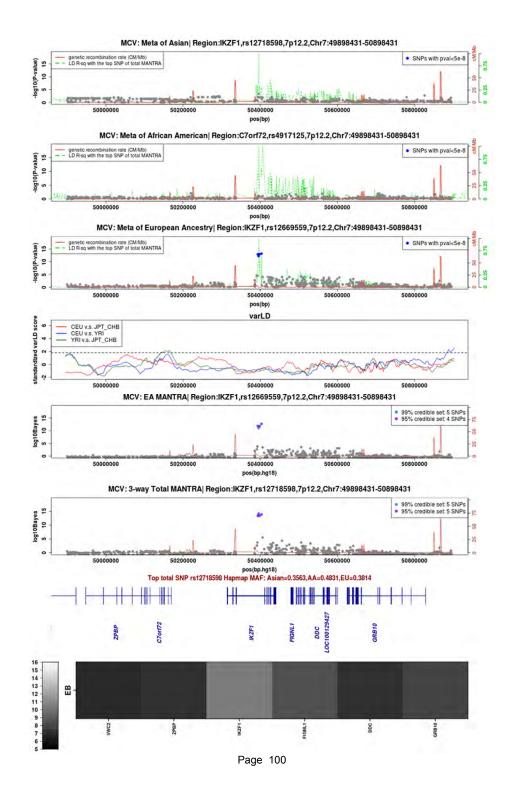
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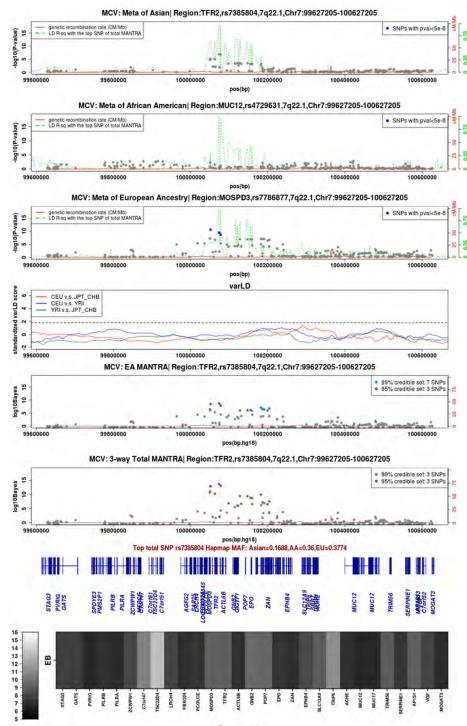




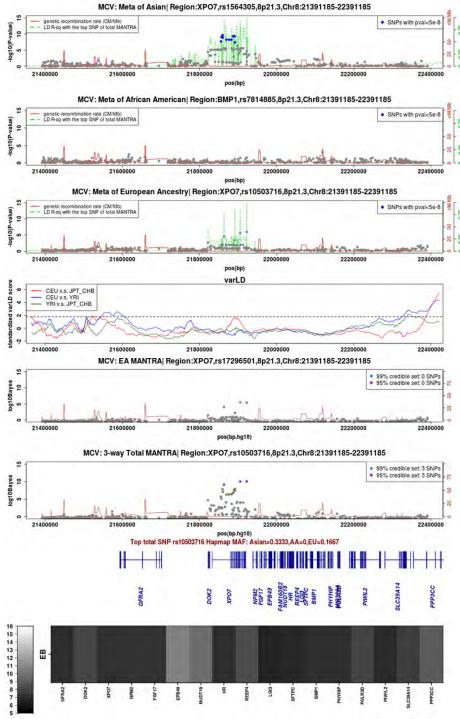




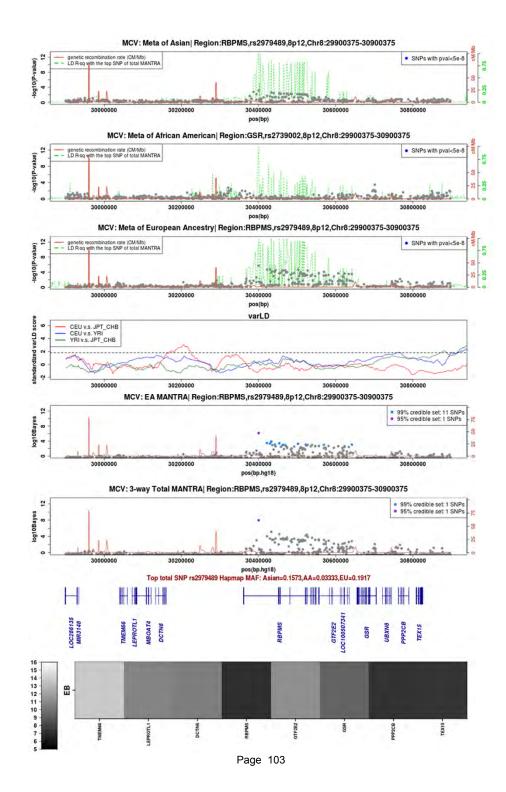


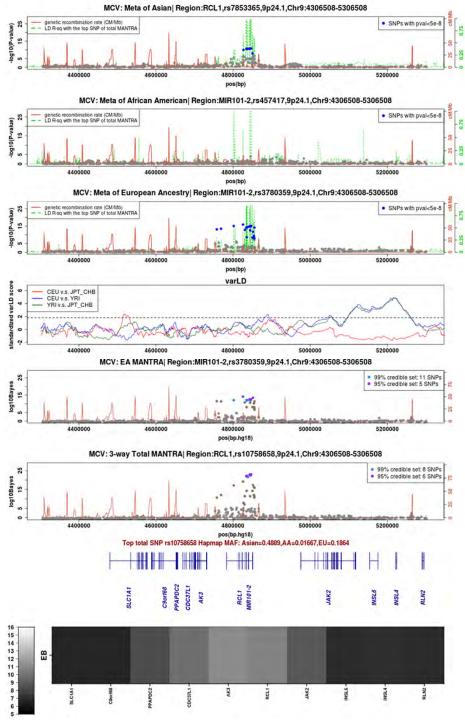




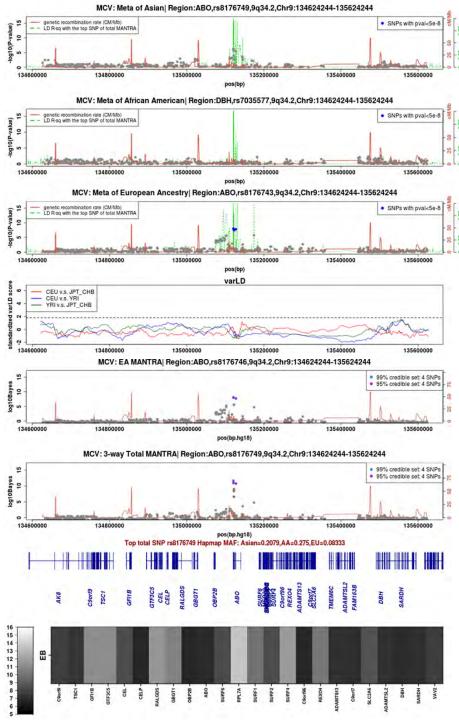


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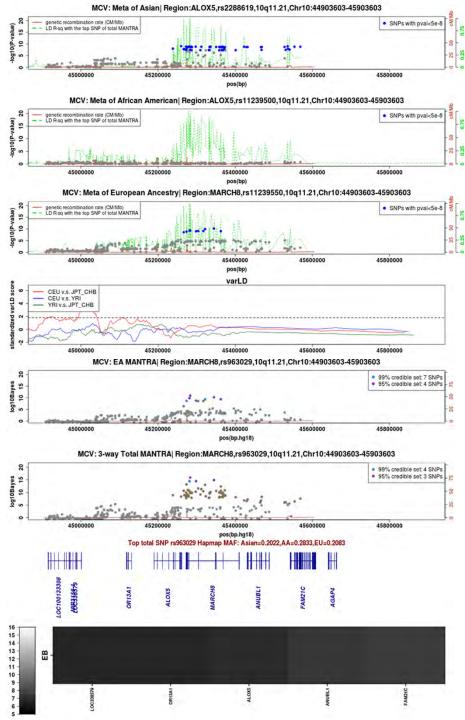




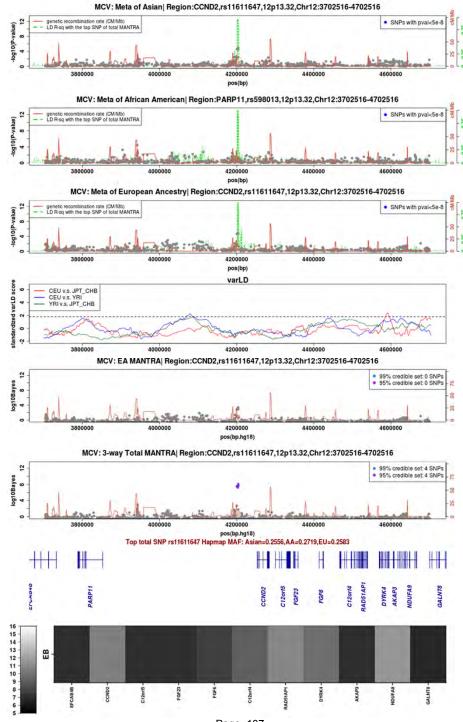




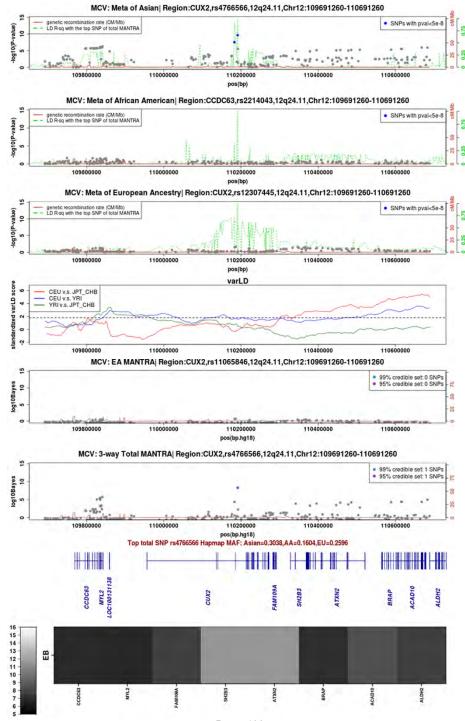




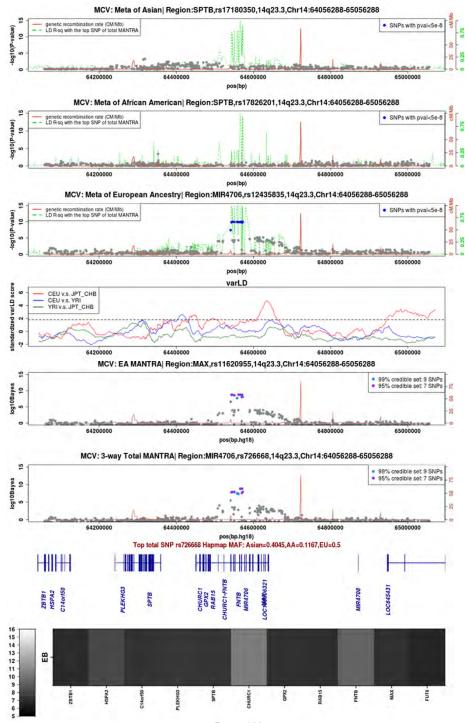




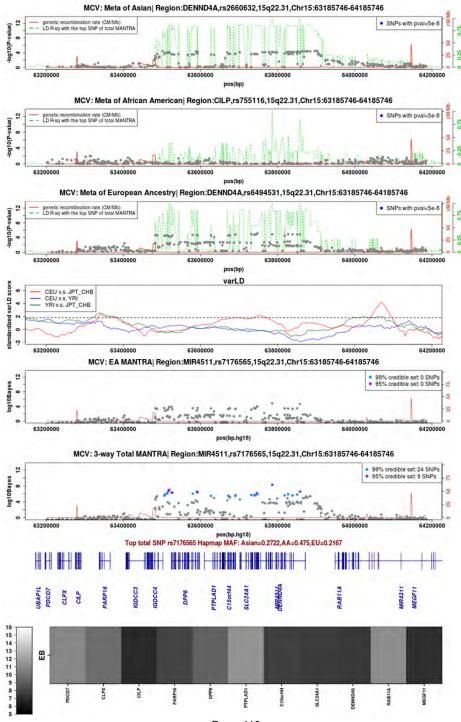
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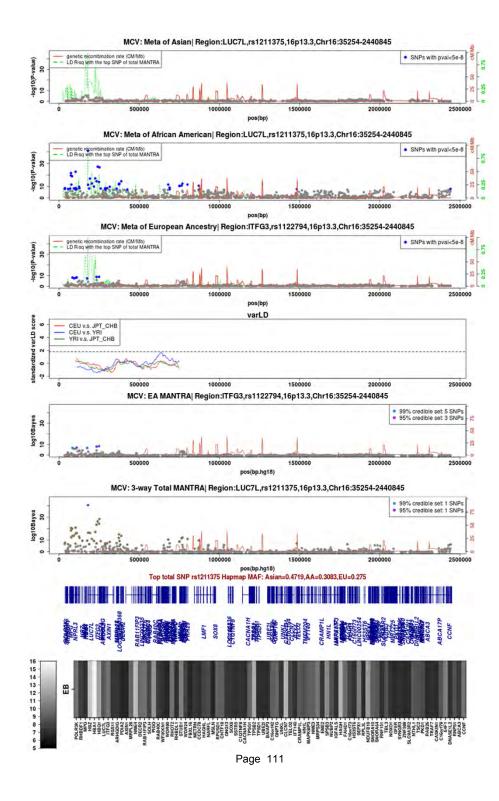
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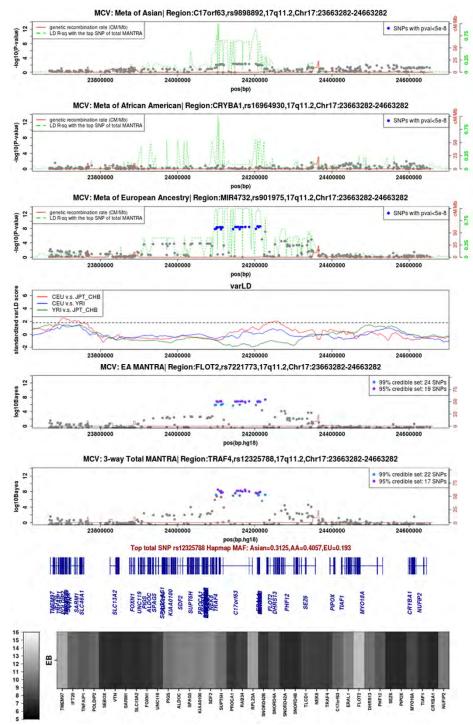




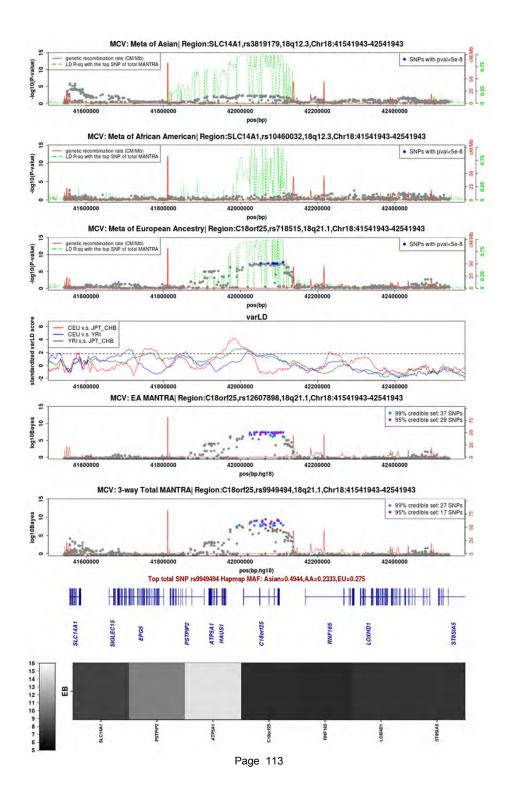


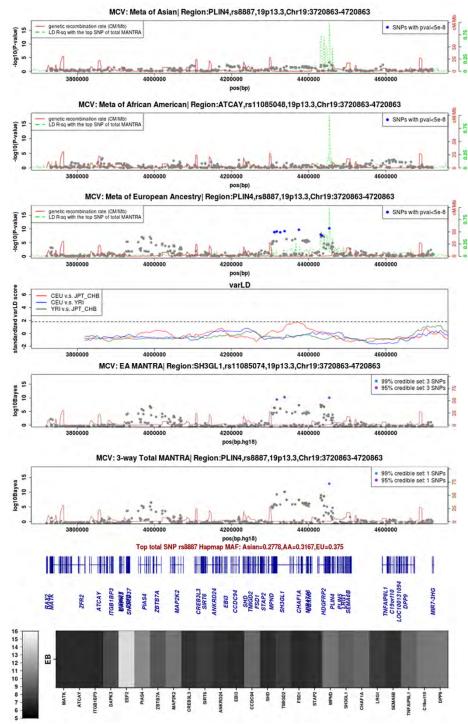
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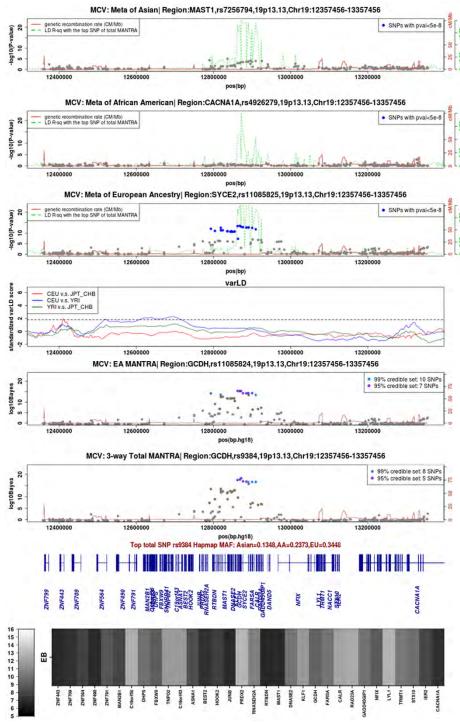




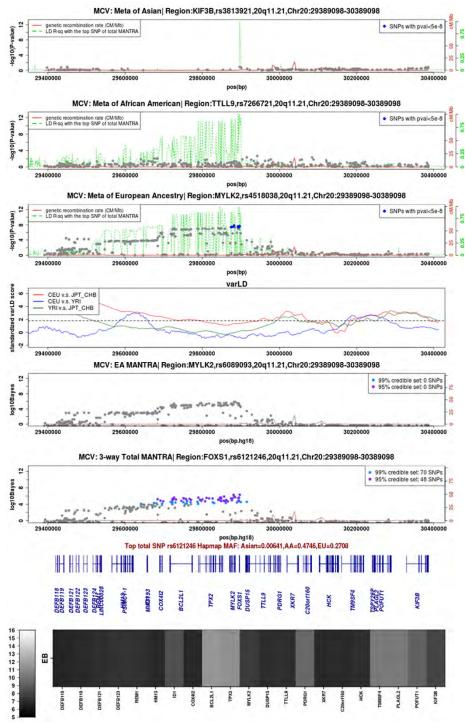




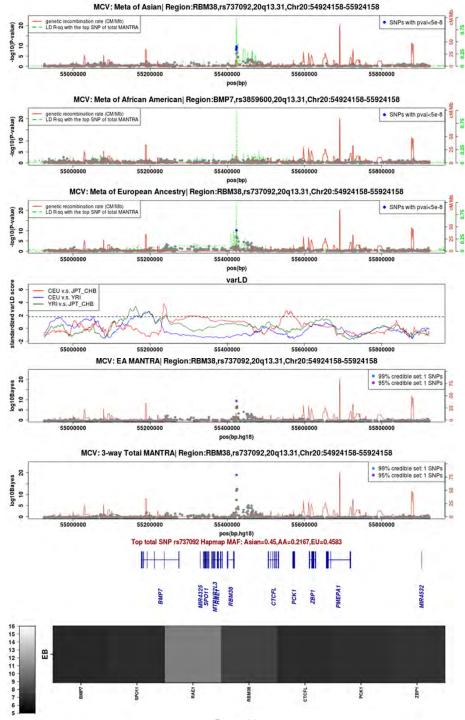




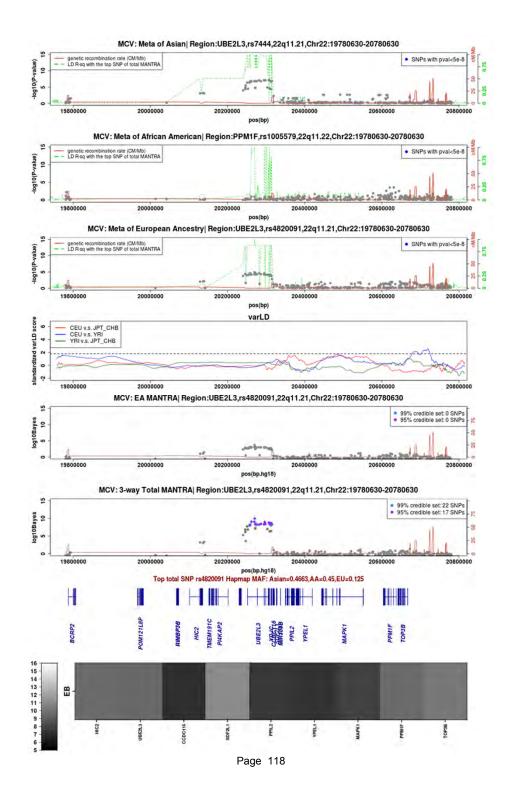
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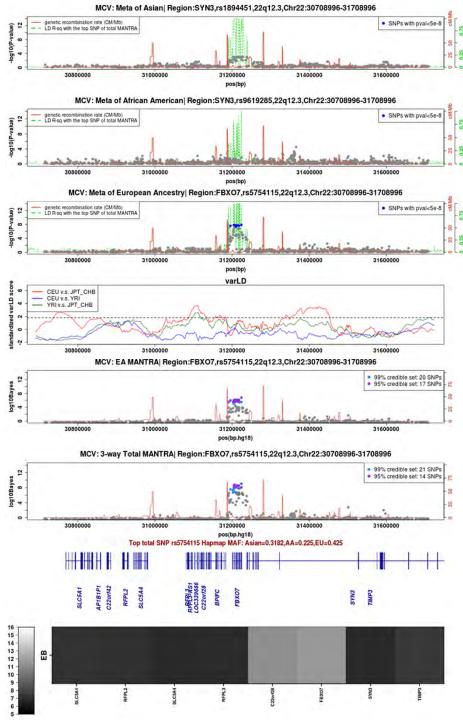


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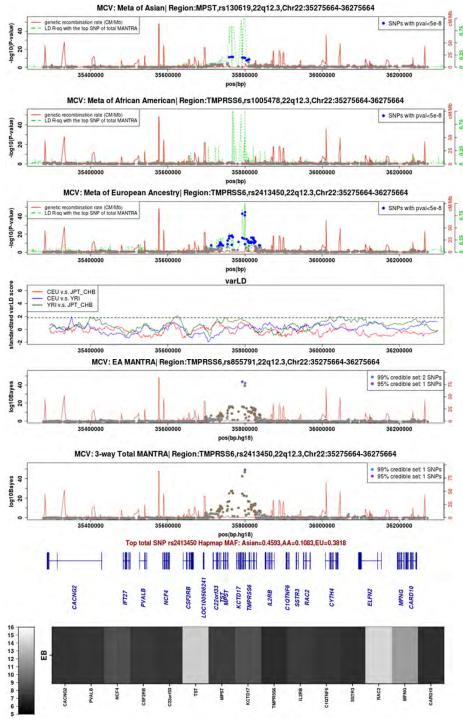




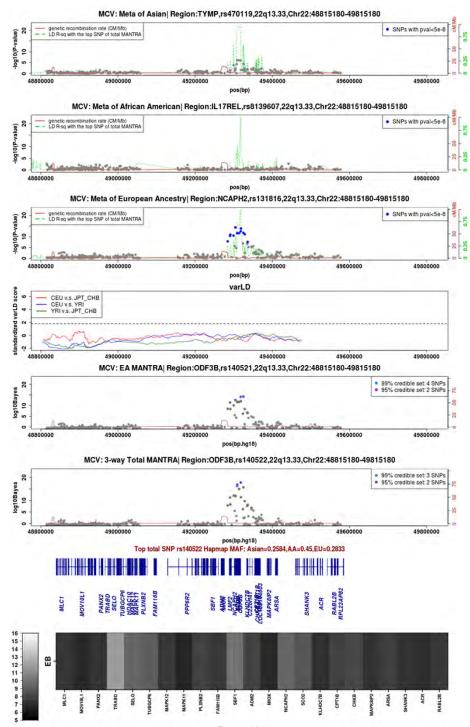






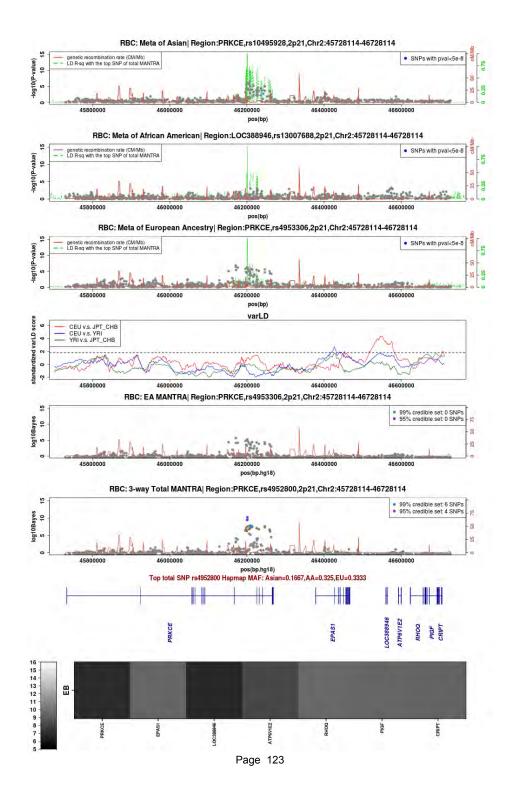


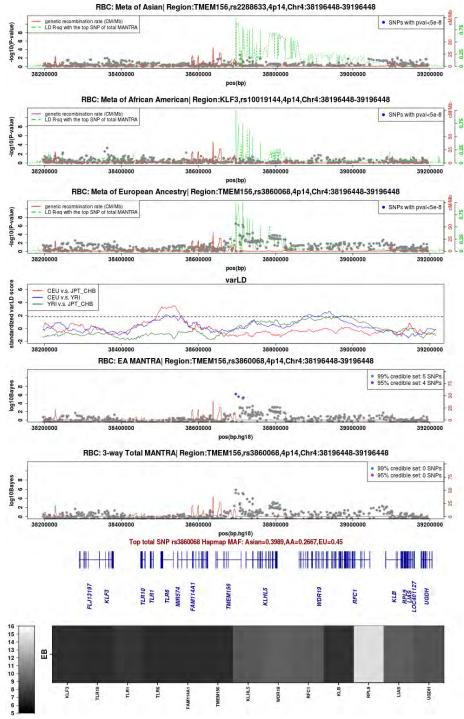




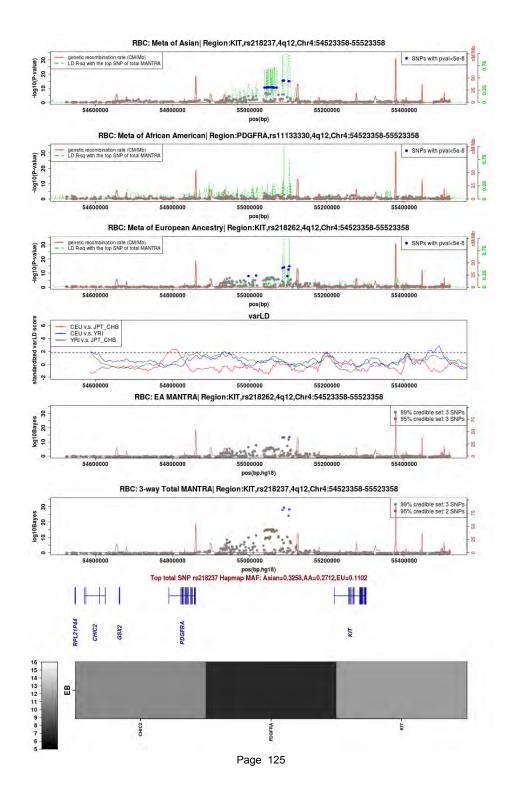
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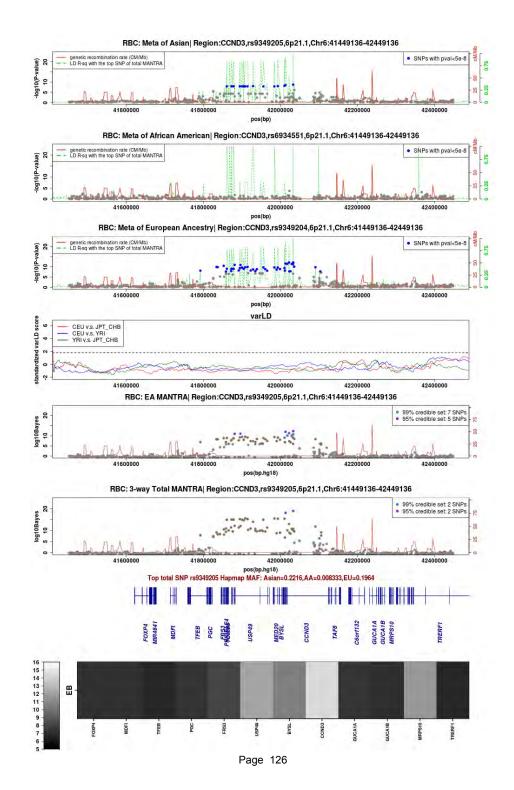
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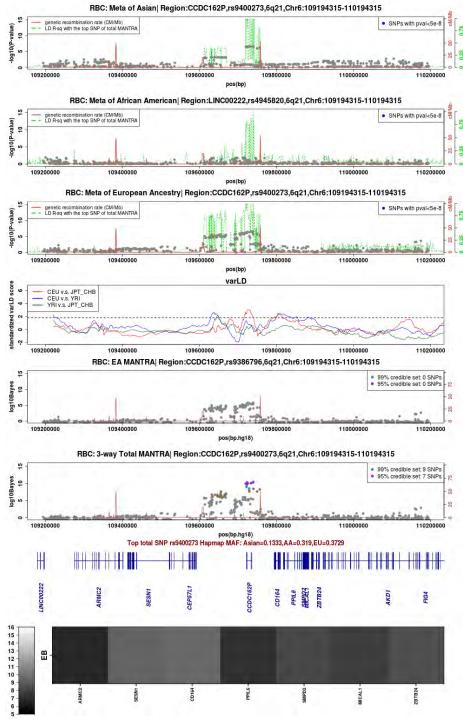




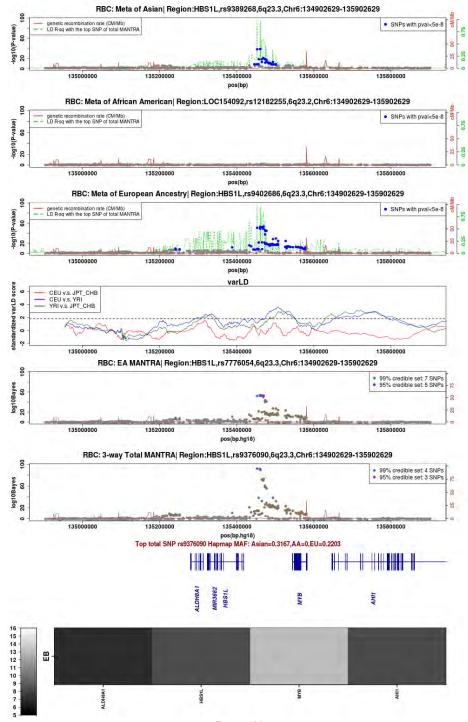




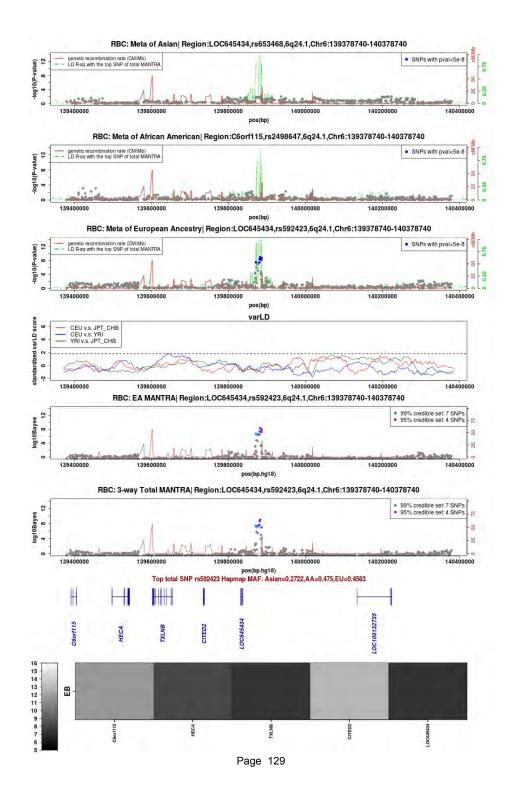


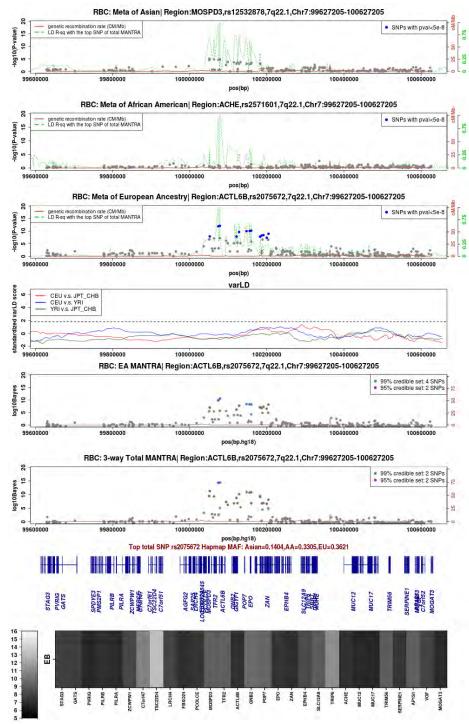


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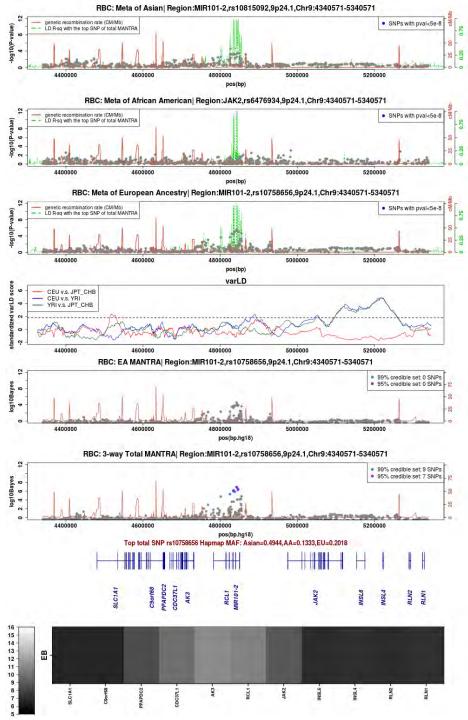


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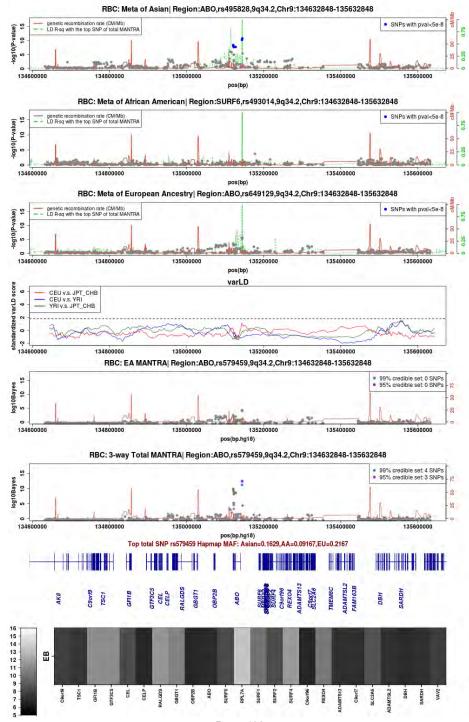




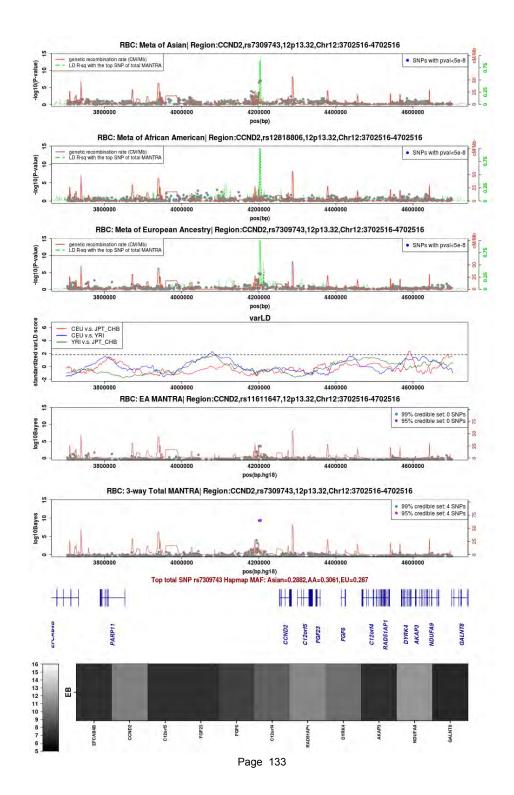
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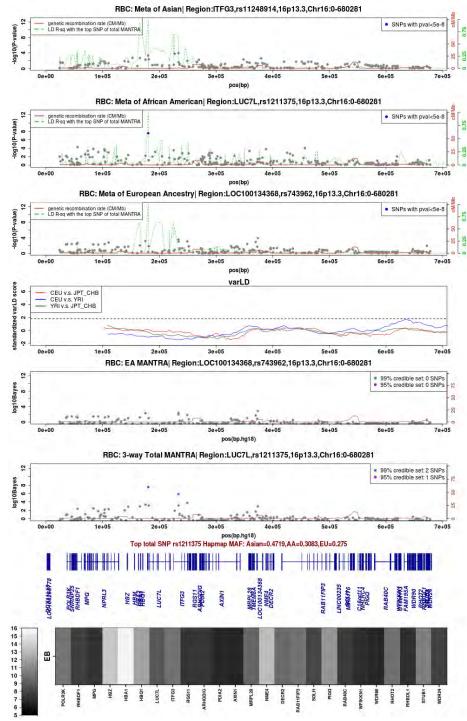




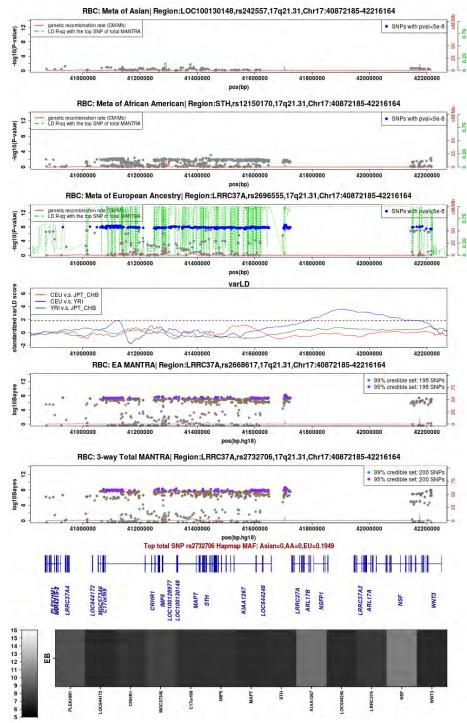


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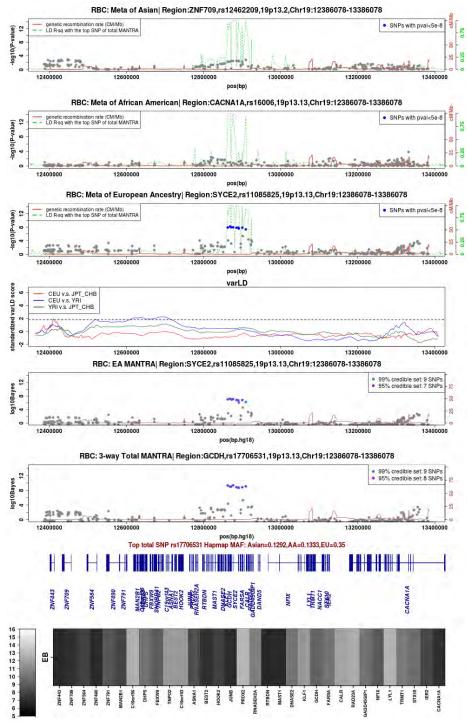




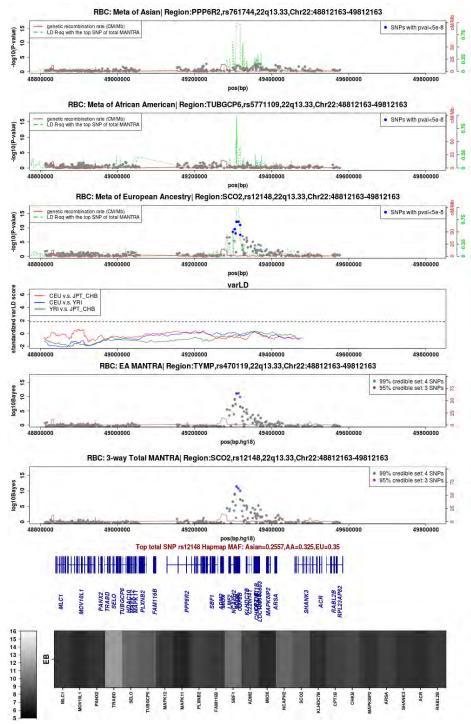
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