Supplementary Information for

Genome-wide association study identifies loci influencing concentrations of liver enzymes in plasma

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Supplementary Table 1. Characteristics of participants in the genome-wide association cohorts. Results are given as mean (SD) or as % for categoric variables.

	N_{max}	Ethnic group	Age (years)	Female	BMI (kg/m^2)	Alcohol (U/week)	HT	T2D	CHD
Australian Twin	425	Caucasian	47.2 (12.5)	100	25.1 (4.6)	3.4 (4.9)	10.1	0.8	1.4
BRIGHT	1805	Caucasian	56.7 (11.1)	60.9	27.5 (3.8)	7.5 (11.1)	100	0	4.8
CoLaus	5636	Caucasian	53.2 (10.7)	52.3	25.8 (4.6)	7.0 (9.0)	19.5	6.7	3.6
Decode	12572	Caucasian	61.5 (16.8)	60.6	27.5 (5.4)	NA	26.0	8.7	26.4
Fenland	1397	Caucasian	45.0 (7.3)	56.0	27.1 (4.9)	9.9 (12.3)	28.1	0	0
FinnTwin	32	Caucasian	26.5 (1.6)	64.0	26.8 (6.1)	3.3 (3.3)	0	0	0
Framingham	2869	Caucasian	43.6 (9.8)	52.2	25.6 (4.3)	3.6 (5.0)	21.3	1.9	2.3
KORA	1809	Caucasian	62.5 (10.1)	50.6	28.1 (4.5)	15.4 (20.1)	60.7	11.0	3.5
LOLIPOP Affymetrix European	876	Caucasian	53.2 (8.2)	23.6	27.8 (4.8)	14.9 (18.0)	26.4	11.3	30.6
LOLIPOP Perlegen European	723	Caucasian	56.0 (8.9)	0	28.6 (5.3)	17.0 (19.7)	55.1	16.3	42.4
LOLIPOP Perlegen Indian Asian	588	Indian Asian	50.8 (8.2)	0	27.1 (4.0)	9.6 (15.2)	53.3	20.8	0
LOLIPOP Illumina 317 Indian Asian	2109	Indian Asian	48.1 (10.4)	0	26.8 (4.3)	7.9 (15.5)	44.0	20.1	0
LOLIPOP Illumina 610 Indian Asian	6042	Indian Asian	56.9 (10.0)	18.0	27.4 (4.3)	5.4 (11.3)	47.9	25.1	43.7
NESDA	1724	Caucasian	42.4 (12.5)	67.8	25.8 (5.2)	7.1 (9.7)	38.3	3.6	2.0
Netherland Twins Register	1721	Caucasian	45.9 (14.1)	63.4	25.2 (4.0)	8.1 (7.1)	0	6.3	0
NFBC1966	4562	Caucasian	31.2 (0.4)	53.5	24.6 (4.2)	1.2 (2.2)	19.5	0.6	0
PROCARDIS	1230	Caucasian	60.3 (7.1)	17%	28.2 (4.1)	6.5(8.5)	45.5	11.8	100
Rotterdam Study 1	4312	Caucasian	69.9 (9.0)	61.3	26.3 (3.7)	1.3 (1.8)	56.2	10.6	8.3
SardiNIA	4301	Caucasian	43.5 (17.6)	56.2	25.3 (4.8)	17.1 (15.9)	25.2	2.2	2.6
SHIP	4101	Caucasian	49.7 (16.2)	50.7	27.3 (4.7)	3.3 (3.6)	52.8	6.8	8.2
TwinsUK	2255	Caucasian	46.6 (12.3)	100	25.0 (4.7)	5.0 (7.0)	22.0	1.0	8.0

BMI: Body mass index
HT: Hypertension – Physician diagnosis on treatment, or blood pressure >140/85mmHg
CHD: Myocardial infarction, coronary revascularisation or significant coronary stenosis
T2D: Type-2 diabetes – Physician diagnosis on treatment, or fasting glucose >7mmol/L

Supplementary Table 2. Liver function marker levels and genotyping methods in the genome-wide association cohorts. Marker levels are given as mean (SD).

	ALP (IU/L)	ALT (IU/L)	GGT (IU/L)	LFT method (analyser)
Australian Twin	64.9 (22.5)	15.7 (9.1)	18.3 (17.7)	Hitachi 747 analyser
BRIGHT	-	-	24 (17–36)	Hitachi analyser
CoLaus	63.4 (20.2)	27.7 (19.6)	32.2 (40.2)	Roche Diagnostics
deCODE	80.3 (35.6)	27.4 (18.6)	43.8 (55.3)	Roche Diagnostics
Fenland	74.8 (22.1)	30.9 (19.4)	35.1 (34.2)	Dade Behring Dimension RxL
FinnTwin	-	28.3 (22.8)	21.6 (25.2)	Roche Diagnostics
Framingham	72.0 (22.1)	-	16.0 (13.2)	Beckman Liquid-Stat
KORA	-	20.4 (9.6)	40.2 (57.6)	Roche Diagnostics
LOLIPOP Affymetrix European	74.1 (16.4)	29.1 (16.8)	40.0 (25.3)	Roche Diagnostics
LOLIPOP Perlegen European	74.4 (20.9)	31.8 (18.7)	47.0 (81.5)	Roche Diagnostics
LOLIPOP Perlegen Indian Asian	77.0 (18.3)	34..6 (22.3)	47.4 (61.0)	Roche Diagnostics
LOLIPOP Illumina 317 Indian Asian	80.0 (22.1)	35.6 (23.2)	51.9 (68.2)	Roche Diagnostics
LOLIPOP Illumina 610 Indian Asian	80.8 (26.1)	29.7 (18.7)	46.8 (76.2)	Roche Diagnostics
NESDA	-	23.1 (14.3)	25.0 (25.4)	Roche Diagnostics
Netherland Twins Register	-	10.3 (6.9)	32.2 (37.5)	Vitros 250 analyser
NFBC1966	35.5 (12.8)	9.4 (4.6)	22.1 (34.6)	Roche Diagnostics
PROCARDIS	76.0 (27.3)	18.8 (10.7)	29.6 (37.1)	Hitachi 747 analyser
Rotterdam Study 1	79.6 (26.9)	18.0 (11.4)	30.0 (29.2)	ELAN-Fully Selective Analyzer
SardiNIA	-	25.0 (23.1)	27.9 (39.9)	Hitachi 747 analyser
SHIP	-	28.4 (19.8)	35.2 (75.0)	Hitachi 717 & Hitachi 704 analysers
TwinsUK	27.0 (10.5)	25.0 (10.7)	23.8 (15.1)	Synchron LX20

Supplementary Table 3. Sample and SNP QC, and use of principal components in the genome-wide association cohorts

	Design	GWA platform	Call rate	Genotype calling	Imputation Software	Association software	Study specific covariates*
Australian Twin	Twins	Perlegen 600K	>95%	Perlegen	MACH2	Merlin	None, samples excluded based on PCs
BRIGHT	Case cohort	Affymetrix 500k	>95%	BRLMM	IMPUTE	SNPTEST	None, samples excluded based on PCs
CoLaus	Population	Affymetrix 500K	>90%	BRLMM	IMPUTE	QUICKTEST	PCs
deCODE	Population	Illumina 300/370K	>96%	BeadStudio	IMPUTE	SNPtest	None, samples excluded based on PCs
Fenland	Population	Affymetrix 500K	>90%	BRLMM	IMPUTE	SNPTEST	PCs
FinnTwin	Twins	Illumina 317K	>95%	BeadStudio	IMPUTE	PLINK	None, samples excluded based on PCs
Framingham	Population	Affymetrix 500K	>97%	BRLMM	MACH	LME in R	PCs
KORA	Population	Affymetrix 500K	>93%	BRLMM	IMPUTE	SNPTEST	PCs
LOLIPOP Affymetrix European	Population	Affymetrix 500K	>90%	BRLMM	MACH	Mach2qtl	PCs
LOLIPOP Perlegen European	Population	Perlegen 284K	>90%	Perlegen	MACH	Mach2qtl	PCs
LOLIPOP Perlegen Indian Asian	Population	Perlegen 284K	>90%	Perlegen	MACH	Mach2qtl	PCs
LOLIPOP Illumina 317 Indian Asian	Population	Illumina 317K	>90%	BeadStudio	MACH	Mach2qtl	PCs
LOLIPOP Illumina 610 Indian Asian	Population	Illumina 610K	>90%	BeadStudio	MACH	Mach2qtl	PCs
NESDA	Case-control	Perlegen 600K	>96%	Perlegen	IMPUTE	SNPTEST	Case status & PCs
Netherland Twins Register	Twins	Perlegen 600K	>95%	Perlegen	MACH	SNPTEST	None, samples excluded based on PCs
NFBC1966	Population	Illumina 370K	>95%	BeadStudio	IMPUTE	SNPTEST	PCs
PROCARDIS	Case-control	Illumina 610K	>95%	BeadStudio	IMPUTE	STATA	Case status, Study site
Rotterdam Study 1	Population	Illumina 550K	>97.5	BeadStudio	MACH	Mach2qtl	PCs
SardiNIA	Population	Affymetrix 500K	>90%	BRLMM	MACH	Merlin	None, samples excluded based on PCs
SHIP	Population	Affymetrix 6.0	>92%	Birdseed2	IMPUTE	SNPtest	PCs
TwinsUK	Twins	Illumina 317K	>95%	Illuminus	IMPUTE	ProbABEL	None, samples excluded based on PCs

Each study excluded SNPs with MAF < 0.01 or with poor imputation quality (Rsq < 0.3 in MACH, or proper info < 0.3 in IMPUTE)
*PCs = Principal Components, calculated by EIGENSTRAT.

Supplementary Table 4. Genomic control lambda values for the genome-wide association analyses

Cohort	ALP	ALT	GGT
Australian Twins	1.007	1.011	1.003
BRIGHT			1.015
CoLaus	1.022	1.031	1.019
Decode	0.986	0.991	1.005
FinnTwin		1.042	0.993
Framingham	0.986	1.009	1.000
KORA	1.011	0.998	1.018
LOLIPOP- Affymetrix European	1.028	1.002	1.007
LOLIPOP- Perlegen European	0.995	1.006	1.002
LOLIPOP- Illumina 300 Indian Asian	1.009	1.016	1.020
LOLIPOP- Perlegen Indian Asian	1.002	1.015	1.029
LOLIPOP - Illumina 610 Indian Asian	1.018	1.017	1.018
NESDA		0.991	1.010
NetherlandsTwin Register		0.998	1.021
NFBC1966	1.024	1.010	1.022
PROCARDIS	1.004	1.016	1.015
Rotterdam Study 1		1.025	1.034
SardiNIA		1.130	1.157
SHIP		1.032	1.016
TwinsUK	1.008	1.015	1.023
Meta-analysis	1.001	1.000	1.005

Supplementary Table 5: Correlations between blood levels of liver markers, and between association test results for liver markers. Results reported as Pearson correlation co-effiecients between log transformed values of marker (unshaded boxes) or P value (shaded boxes). All correlations are significant at $P<10^{-10}$.

	GGT	**ALP**	**ALT**
ALT	0.64	0.19	-
ALP	0.28	-	0.022
GGT	-	0.064	0.189

Supplementary Table 6. Association of sentinel SNPs with liver markers in genome-wide association (GWA) and further testing.

Locus	SNPs at $P<1x10^{-7}$	Sentinel SNP	GWA N	GWA P	Futher testing N	Further testing P
ALT						
4q22	25	rs6834314	55458	$3.1x10^{-9}$		
8q24	17	rs2954021	55412	$5.3x10^{-9}$		
10q24	10	rs10883437	54714	$4.0x10^{-9}$		
22q13	57	rs738409	55305	$1.2x10^{-45}$		
ALP						
1p36.12	84	rs1976403	31742	$1.8x10^{-50}$		
2q24	17	rs16856332	32520	$1.6x10^{-9}$		
6p22	66	rs1883415	32533	$5.6x10^{-26}$		
8p23	10	rs6984305	32006	$2.1x10^{-10}$		
8q24	19	rs2954021	32591	$2.3x10^{-13}$		
9q21	3	rs10819937	32189	$2.0x10^{-8}$	11892	$3.2x10^{-3}$
9q34	89	rs579459	31870	$2.6x10^{-123}$		
10q21	160	rs7923609	32644	$5.9x10^{-23}$		
11q12	14	rs174601	31820	$1.3x10^{-8}$	11965	$1.0x10^{-2}$
11q.24	7	rs2236653	31853	$1.8x10^{-9}$		
16q22	7	rs7186908	32577	$4.8x10^{-9}$		
17p13	2	rs314253	32048	$8.4x10^{-12}$		
19q13	37	rs281377	31604	$1.1x10^{-15}$		
20p11	94	rs7267979	32600	$7.4x10^{-10}$		
GGT						
1p36.13	49	rs1497406	57592	$2.8x10^{-19}$		
1p22	42	rs12145922	57603	$3.8x10^{-11}$		
1p13	4	rs1335645	57649	$7.3x10^{-9}$		
1q21	30	rs10908458	57602	$1.7x10^{-15}$		
2p23	5	rs1260326	57623	$3.9x10^{-13}$		
2q12	69	rs13030978	57247	$1.1x10^{-11}$		
2q37	4	rs2140773	57604	$1.1x10^{-9}$		
3q26	44	rs10513686	56686	$6.1x10^{-11}$		
4q31	24	rs4547811	57567	$2.5x10^{-27}$		
5p15	6	rs6888304	56636	$1.0x10^{-8}$	11935	$9.1x10^{-3}$
5q11	4	rs4074793	54935	$3.4x10^{-10}$		
6p12	10	rs9296736	57554	$2.6x10^{-9}$		
7q11	21	rs17145750	57175	$2.9x10^{-9}$		
10q23	24	rs754466	57343	$6.4x10^{-10}$		
12q24	67	rs7310409	57452	$7.0x10^{-45}$		
14q32	44	rs944002	52414	$5.8x10^{-29}$		
15q21	29	rs339969	57552	$6.6x10^{-20}$		
15q23	5	rs8038465	57627	$1.5x10^{-8}$	11939	$7.2x10^{-3}$
16q23	2	rs4581712	56906	$2.2x10^{-8}$	11879	$1.1x10^{-2}$
17q24	1	rs9913711	57511	$9.5x10^{-8}$	11844	$6.5x10^{-4}$
18q21.31	1	rs12968116	48901	$1.8x10^{-8}$	11944	$3.6x10^{-3}$
18q21.32	41	rs4503880	48078	$3.0x10^{-12}$		
19q13	11	rs516246	53006	$7.6x10^{-10}$		
22q11.21	34	rs1076540	57657	$9.6x10^{-17}$		
22q11.23	16	rs2739330	48783	$1.7x10^{-9}$		
22q11.23	19	rs2073398	56216	$1.1x10^{-109}$		

Supplementary Table 7. Characteristics of LOLIPOP participants used for further testing of SNPs with ALP, ALT and GGT levels.

	European whites	**Indian Asians**	**Combined**
N=	5328	6811	12,139
Age (years)	52.4 (11.8)	46.4 (10.2)	49.0 (11.3)
Female sex (%)	40.6	61.6	52.4
BMI (kg/m^2)	27.4 (5.0)	27.5 (4.7)	27.5 (4.9)
Alcohol (Units / week)	12.1 (17.6)	3.1 (9.8)	7.0 (14.5)
HT (%)	20.0	18.0	18.9
T2D (%)	7.3	11.5	9.6
CHD (%)	7.6	0.3	3.5
ALP (IU/L)	76.2 (28.5)	82.0 (27.5)	79.5 (28.1)
ALT (IU/L)	28.3 (20.1)	28.6 (20.1)	28.5 (20.8)
GGT (IU/L)	43.8 (74.1)	39.0 (57.7)	41.1 (65.4)

BMI: Body Mass Index
HT: Hypertension – Physician diagnosis on treatment, or blood pressure >140/85mmHg
CHD: Myocardial infarction, coronary revascularisation or significant coronary stenosis.
T2D: Type-2 diabetes – Physician diagnosis on treatment, or fasting glucose >7mmol/L

Supplementary Table 8. Association of sentinel SNPs with the three liver markers tested. Arrow indicates direction of change for effect allele. Discovery association highlighted orange; secondary associations reaching 6x10^{-4} (P<0.05 after Bonferroni correction) highlighted yellow.

Region	SNP	Genes of interest	Alleles (R / E)	ALT	ALP	GGT
ALT						
4q22	rs6834314	*HSD17B13, MAPK10*	G / A	↑ 3.1x10^{-09}	↓ 7.8x10^{-02}	↑ 2.5x10^{-02}
8q24	rs2954021	*TRIB1*	G / A	↑ 5.2x10^{-09}	↑ 2.3x10^{-13}	↑ 8.0x10^{-06}
10q24	rs10883437	*CPN1*	A / T	↑ 4.0x10^{-09}	↑ 5.7x10^{-02}	↑ 1.9x10^{-03}
22q13	rs738409	*PNPLA3, SAMM50*	C / G	↑ 1.2x10^{-45}	↓ 2.2x10^{-01}	↓ 9.7x10^{-01}
ALP						
1p36.12	rs1976403	*ALPL, NBPF3*	A / C	↓ 6.7x10^{-01}	↑ 1.8x10^{-50}	↓ 7.0x10^{-01}
2q24	rs16856332	*ABCB11*	G / T	↓ 3.6x10^{-01}	↑ 1.6x10^{-09}	↓ 6.5x10^{-02}
6p22	rs1883415	*ALDH5A1, GPLD1*	A / C	↓ 7.0x10^{-01}	↑ 5.6x10^{-26}	↓ 9.2x10^{-01}
8p23	rs6984305	*PPP1R3B*	T / A	↑ 4.3x10^{-02}	↑ 2.1x10^{-10}	↓ 4.2x10^{-03}
8q24	rs2954021	*TRIB1*	G / A	↑ 5.2x10^{-09}	↑ 2.3x10^{-13}	↑ 8.0x10^{-06}
9q21	rs10819937	*ALDOB, C9orf125*	G / C	↓ 7.4x10^{-01}	↑ 2.0x10^{-08}	↑ 4.9x10^{-02}
9q34	rs579459	*ABO*	C / T	↓ 8.4x10^{-01}	↑ 2.6x10^{-123}	↓ 2.4x10^{-05}
10q21	rs7923609	*JMJD1C, NRBF2*	A / G	↓ 4.4x10^{-01}	↑ 5.9x10^{-23}	↑ 4.4x10^{-03}
11q12	rs174601	*C11orf10, FADS1, FADS2*	C / T	↓ 4.9x10^{-05}	↑ 1.3x10^{-08}	↓ 5.3x10^{-01}
11q.24	rs2236653	*ST3GAL4*	C / T	↑ 5.4x10^{-01}	↑ 1.8x10^{-09}	↓ 4.6x10^{-01}
16q22	rs7186908	*HPR, PMFBP1*	G / C	↓ 5.6x10^{-01}	↑ 4.8x10^{-09}	↑ 5.5x10^{-01}
17p13	rs314253	*ASGR1, DLG4*	T / C	↑ 2.9x10^{-01}	↑ 8.4x10^{-12}	↑ 2.4x10^{-01}
19q13	rs281377	*FUT2*	C / T	↓ 8.8x10^{-01}	↑ 1.1x10^{-15}	↓ 1.9x10^{-06}
20p11	rs7267979	*ABHD12,GINS1, PYGB*	A / G	↓ 3.8x10^{-02}	↑ 7.4x10^{-10}	↑ 6.9x10^{-01}
GGT						
1p36.13	rs1497406	*C1orf89, EPHA2*	A / G	↑ 2.3x10^{-06}	↑ 3.3x10^{-01}	↑ 3.3x10^{-19}
1p22	rs12145922	*CCBL2, PKN2*	C / A	↑ 4.1x10^{-03}	↑ 1.6x10^{-03}	↑ 4.3x10^{-11}
1p13	rs1335645	*CEPT1, DENND2D*	G / A	↑ 4.1x10^{-06}	↑ 7.6x10^{-01}	↑ 7.9x10^{-09}
1q21	rs10908458	*DPM3, EFNA1, PKLR*	C / T	↑ 2.2x10^{-07}	↑ 2.1x10^{-01}	↑ 1.9x10^{-15}
2p23	rs1260326	*C2orf16, GCKR*	C / T	↓ 9.0x10^{-01}	↑ 3.2x10^{-06}	↑ 4.4x10^{-13}
2q12	rs13030978	*MYO1B, STAT4*	C / T	↑ 3.1x10^{-01}	↑ 2.9x10^{-01}	↑ 1.2x10^{-11}
2q37	rs2140773	*EFHD1, LOC100129166*	C / A	↑ 7.6x10^{-06}	↓ 6.8x10^{-01}	↑ 1.2x10^{-09}
3q26	rs10513686	*SLC2A2*	G / A	↑ 1.3x10^{-03}	↑ 4.0x10^{-01}	↑ 6.8x10^{-11}
4q31	rs4547811	*ZNF827*	T / C	↑ 1.0x10^{-07}	↑ 6.7x10^{-01}	↑ 3.2x10^{-27}
5p15	rs6888304	*CDH6*	G / A	↑ 6.7x10^{-05}	↑ 1.9x10^{-01}	↑ 1.1x10^{-08}
5q11	rs4074793	*ITGA1*	A / G	↑ 4.7x10^{-04}	↑ 1.3x10^{-01}	↑ 3.7x10^{-10}
6p12	rs9296736	*C6orf142*	C / T	↑ 2.6x10^{-04}	↑ 6.8x10^{-05}	↑ 2.9x10^{-09}
7q11	rs17145750	*MLXIPL*	T / C	↓ 1.1x10^{-01}	↑ 5.5x10^{-02}	↑ 3.2x10^{-09}
10q23	rs754466	*DLG5*	A / T	↑ 1.8x10^{-02}	↑ 5.6x10^{-01}	↑ 7.0x10^{-10}
12q24	rs7310409	*HNF1A, C12orf27*	A / G	↓ 8.1x10^{-01}	↓ 8.5x10^{-08}	↑ 1.1x10^{-44}
14q32	rs944002	*C14orf73*	A / G	↑ 1.3x10^{-01}	↑ 1.1x10^{-01}	↑ 7.7x10^{-29}
15q21	rs339969	*RORA*	C / A	↑ 3.9x10^{-05}	↑ 5.7x10^{-01}	↑ 8.0x10^{-20}
15q23	rs8038465	*CD276*	C / T	↑ 1.6x10^{-02}	↑ 8.5x10^{-01}	↑ 1.6x10^{-08}
16q23	rs4581712	*DYNLRB2*	C / A	↑ 4.7x10^{-02}	↑ 9.4x10^{-01}	↑ 2.4x10^{-08}
17q24	rs9913711	*FLJ37644, SOX9*	G / C	↑ 7.8x10^{-05}	↑ 7.6x10^{-01}	↑ 1.0x10^{-07}
18q21.31	rs12968116	*ATP8B1*	T / C	↑ 2.5x10^{-02}	↑ 3.2x10^{-01}	↑ 2.0x10^{-08}
18q21.32	rs4503880	*NEDD4L*	C / T	↑ 5.3x10^{-03}	↑ 2.7x10^{-03}	↑ 3.4x10^{-12}
19q13	rs516246	*FUT2*	C / T	↑ 1.8x10^{-01}	↓ 1.3x10^{-14}	↑ 8.3x10^{-10}
22q11.21	rs1076540	*MICAL3*	T / C	↓ 9.0x10^{-01}	↓ 4.0x10^{-01}	↑ 1.1x10^{-16}
22q11.23	rs2739330	*DDT, DDTL, GSTT1, GSTT2B, MIF*	C / T	↑ 1.2x10^{-01}	↑ 1.3x10^{-02}	↑ 1.9x10^{-09}
22q11.23	rs2073398	*GGT1, GGTLC2*	C / G	↑ 7.2x10^{-01}	↑ 8.6x10^{-01}	↑ 3.5x10^{-109}

Supplementary Table 9: Summary of known biology for the candidate genes identified. Evidence: n=nearest gene, e=eQTL, c=coding variation, g=GRAIL, o=other.

Locus	SNP	Gene	Evidence	Summary
ALT				
4q22	rs6834314	*HSD17B13*	ne	Hydroxysteroid (17-beta) dehydrogenase 13. Highly expressed in liver and encodes enzyme that may be involved in metabolism androgen and steroidogenesis[1].
		MAPK10	e	Mitogen activated protein kinase-10. May be involved in cellular responses to inflammatory cytokines[2].
8q24	rs2954021	*TRIB1*	n	Tribbles homolog-1. A serine/threonine kinase-like proteins activation of NF-KB and MAP kinases[3]. TRIB1 binds JNK and P38, affects MAP kinase activity, and influences gene expression in TLR-mediated signalling pathways[4]. *TRIB1* variants strongly associated with triglyceride levels in GWA studies[5].
10q24	rs10883437	*CPN1*	n	Carboxypeptidase N, polypeptide 1 (also called kininase-1 and anaphylatoxin inactivator). Encodes the catalytic subunit of a plasma metallo-protease that regulates peptides such as kinins and anaphylatoxins[6]. Mutations in this gene are associated with angioedema and chronic urticaria[7].
22q13	rs738409	*PNPLA3*	nc	Patatin-like phospholipase domain containing 3 (also called Adiponutrin). A membrane bound triacylglycerol lipase present in adipocytes[8]. Involved in energy utilisation / storage by adipocytes. Also strongly expressed in liver. Genetic variants in *PNPLA3* are associated with hepatic fat[9] and susceptibility to alcoholic liver disease[10].
		SAMM50	c	SAMM50 is a component of the sorting and assembly machinery (SAM) complex of the outer mitochondrial membrane. The SAM complex has a role in integrating beta-barrel proteins into the outer mitochondrial membrane[11].
ALP				
1p36.12	rs1976403	*ALPL*	o	Alkaline phosphatase, liver/bone/kidney isoform. A glycosylated enzyme that is widely expressed, and primarily membrane bound. ALPL is the primary source of circulating ALP in plasma[12].
		NBPF3	nce	Neuroblastoma breakpoint family, member 3. The *NBPF* gene family are located primarily on regions of segmental duplications on chromosome 1. The proteins encoded are composed of repetitive elements and are of unknown function[13]. Genetic variation in *NBPF* genes associated with mental retardation[14], autism[15], schizophrenia[16] and several cancers, including neuroblastoma[17] and sarcoma[18].
2q24	rs16856332	*ABCB11*	ng	ATP-binding cassette transporter subfamily B, member 11, also called BSEP (Bile Salt Export Pump). ABCB11 is responsible for the transport of taurocholate and other cholate conjugates from hepatocytes to bile. In humans. ABCB11 activity is the major determinant of bile formation and bile flow[19]. Mutations in *ABCB11* cause progressive familial intrahepatic cholestasis type 2 (PFIC2) and are associated with increased risk of hepatocellular carcinoma[20, 21].
6p22	rs1883415	*ALDH5A1*	e	Aldehyde dehydrogenase 5 family, member A1. A mitochondrial succinic semialdehyde dehydrogenase involved in metabolism of the neurotransmitter GABA[22]. Mutations cause 4-hydroxybutyricaciduria, and lead to accumulation of GABA and related molecules with neuromodulatory properties, and a wide spectrum of neurological and psychiatric dysfunction[23].

		GPLD1	nc	Glycosylphosphatidylinositol phospholipase D1. GPLD1 is synthesised in liver and circulates in serum as a component of ApoA1 and ApoA4 containing HDL cholesterol particles[24]. Glycosylphosphatidylinositol phospholipases release proteins from glycosylphosphatidylinositol (GPI) anchors at the cell surface and thus influence cell surface binding of plasma proteins such as ALP, endoplasmic trafficking, and immune responses to pathogens[25]. Glycosylphosphatidylinositol phospholipases may also cleave GPIs to produce second messengers that mediate responses to insulin and other hormones[26].
8p23	rs6984305	*PPP1R3B*	ne	Glycogen-targeting subunit for phosphatase PP1. Facilitates interaction of PP1 with enzymes of glycogen metabolism and regulates PP1 activity[27]. Suppresses the rate at which PP1 dephosphorylates (inactivates) glycogen phosphorylase, enhances activation of glycogen synthase, and therefore limits glycogen breakdown. Its activity is inhibited by PYGL, resulting in inhibition of the glycogen synthase and glycogen phosphorylase phosphatase activities of PP1[28]. Overexpression of *PPP1R3B* increases basal and insulin-stimulated glycogen synthesis in hepatocytes[29].
8q24	rs2954021	*TRIB1*	n	Tribbles homolog-1. A serine/threonine kinase-like protein activating NF-KB[30] and MAP kinases[31]. May influence gene expression in TLR-mediated and other signalling pathways[32].
9q21	rs10819937	*ALDOB*	o	Fructose-1,6-bisphosphate aldolase B. Glycolytic enzyme that catalyzes the reversible conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate[33]. Strongly expressed in adult liver, kidney and intestine. Mutations in *ALDOB* cause hereditary fructose intolerance, characterised by hypoglycaemia, hepatomegaly and liver dysfunction after fructose ingestion[34, 35].
		C9orf125	n	Chromosome 9 open reading frame 125. Unknown function.
9q34	rs579459	*ABO*	n	ABO blood group (transferase A, alpha 1-3-N-acetylgalactosaminyltransferase; transferase B, alpha 1-3-galactosyltransferase). Encodes a glycosyltransferase which converts the H antigen (a cell surface carbohydrate sequence) into the A or B antigen[36]. *ABO* variants strongly associated with several phenotypes, including pancreatic[37] and gastric carcinoma[38] and auto-immune disease, and with ALP in GWA studies[39].
10q21	rs7923609	*JMJD1C*	nce	Jumonji domain containing 1C (also called thyroid receptor interacting protein 8, *TRIP8*). Member of large family of jumonji proteins which have histone demethylase activity[40]. Jumonji proteins play a central role in epigenetic modification of DNA binding and chromatin structure, thereby regulating gene expression, including hormone-dependent transcriptional activation[41].
		NRBF2	e	Nuclear receptor binding factor 2. May modulate transcriptional activation by nuclear receptors including PPARs, RARs and RXRs[42].
11q12	rs174601	*C11orf10*	e	Chromosome 11 open reading frame 10. Unknown function
		FADS1 / FADS2	*e / ne*	*FADS1*: Fatty acid desaturase-1; *FADS2*: Fatty acid desaturase-2. FADS1 and FADS2 are components of a lipid metabolic pathway, strongly expressed in liver, which catalyzes the synthesis of highly unsaturated fatty acids (HUFA) such as arachidonic acid from omega-3 and omega-6 polyunsaturated fatty acids[43]. HUFA play pivotal roles in many processes including atherosclerosis, inflammation, neurologic development and membrane fluidity[44].
11q.24	rs2236653	*ST3GAL4*	n	ST3 beta-galactoside alpha-2,3-sialyltransferase 4. Contributes to the incorporation of sialic acid residues into the terminal carbohydrate groups of circulating glycoproteins and glycolipids[45]. Subsequent time-dependent loss of sialic acid initiates programmed removal of circulating erythrocytes, platelets and plasma glycoproteins by exposing β-galactose residues, enabling

				recognition and phagocytosis by asialoglycoprotein receptors[46, 47].
16q22	rs7186908	*HPR*	e	Haptoglobin-related protein. Plasma protein which circulates in association with Apolipoprotein-A1, and which binds free plasma haemoglobin. May also play a role in innate immunity[48].
		PMFBP1	n	Polyamine modulated factor 1 binding protein 1. Function unknown.
17p13	rs314253	*ASGR1*	o	Asialoglycoprotein receptor 1. Cell surface receptor strongly expressed in liver. Binds plasma glycoproteins from which the terminal sialic acid residues on surface carbohydrate moieties have been removed; the receptor-liganed complex is then internalised by endocytosis[46, 47].
		DLG4	n	Discs, large homolog 4. Member of the membrane-associated guanylate kinase (MAGUK) family; may be involved in ion channel and other signalling processes[49].
19q13	rs281377	*FUT2*	nc	Fucosyltransferase 2. Encodes alpha(1,2)fucosyltransferase, the enzyme responsible for the synthesis of H antigen, the precursor of ABO antigen in body fluids and on the intestinal mucosa[50]. Individuals homozygous for nonfunctional *FUT2* alleles fail to present ABO antigens in secretions ("nonsecretors") and on epithelial cells[51]. Variants in *FUT2* are associated with vitamin B_{12} levels in GWA[52], and with susceptibility to intestinal infections such as Norovirus[53].
20p11	rs7267979	*ABHD12*	ne	Abhydrolase domain containing 12. Membrane protein with predicted monoacylglycerol lipase activity. Expressed in liver, kidney, brain, and elsewhere[54]. Function uncertain; proposed to involved in endocannabinoid signalling[55].
		GINS1	ce	GINS complex subunit 1. An essential subunit of the GINS complex, which plays an essential role in the initiation of DNA replication, and progression of DNA replication forks[56].
		PYGB	o	Phosphorylase glycogen brain. A glycogen phosphorylase found predominantly in the brain, which catalyses the rate-determining step in glycogen degradation[57].
GGT				
1p36.13	rs1497406	*C1orf89*	e	Hypothetical protein of unknown function. Homologous with GTPases involved in mitochondrial trafficking[58].
		EPHA2	ne	Ephrin receptor A2. Membrane-bound tyrosine kinase, undergoes juxtacrine activation by Ephrin-A ligands presented on apposed cell surfaces[59]. Integral role in developmental events, angiogenesis and a wide range of malignancies[60]. Mutations and common variants associated with cortical cataract[61].
1p22	rs12145922	*CCBL2*	e	Cysteine conjugate-beta lyase 2. Encodes an aminotransferase that catalyzes transamination of L-kynurenine (an L-tryptophan metabolite) to form kynurenic acid[62]. Kynurenine pathway metabolites may be involved in neuronal signalling, and have been linked to epilepsy[63], schizophrenia[64] and neurodegenerative disease[65].
		PKN2	n	Protein kinase N2. Cytoplasmic serine-threonine protein kinase, activated by lipids, particularly cardiolipin, other phospholipids and unsaturated fatty acids[66]. Variants in *PKN2* may be linked with diabetes[67].
1p13	rs1335645	*CEPT1*	ne	Choline/ethanolamine phosphotransferase-1. Encodes an enzyme which catalyses synthesis of phosphatidylcholines[68].
		DENND2D	e	DENN/MADD domain containing 2D. Unknown function.
1q21	rs10908458	*DPM3*	n	Dolichyl-phosphate mannosyltransferase polypeptide 3. Subunit of dolichyl-phosphate mannosyltransferase complex which synthesises dolichol-phosphate mannose, a donor of mannosyl residues for post-translational modification of proteins in the endoplasmic reticulum[69].

				Mutations in *DPM3* cause congenital disorders of glycosylation, with defective surface expression of GPI-anchored proteins, and multisystem abnormalities[70].
		EFNA1	ce	Ephrin-A1. Agonist of EPHA tyrosine kinase receptors. Anchored to cell membrane by a glycosylphosphatidylinositol linkage, and acts in juxtacrine manner[71]. Involved in developmental events, angiogenesis and oncogeneisis[72, 73].
		PKLR	o	Pyruvate kinase, liver and RBC. The protein encoded by this gene is a pyruvate kinase that catalyzes the transphosphorylation of phohsphoenolpyruvate into pyruvate and ATP, which is the rate-limiting step of glycolysis[74]. Mutations in PKLR cause hereditary nonspherocytic hemolytic anemia[75].
2p23	rs1260326	*C2orf16*	e	Hypothetical protein C2orf16. Unknown function.
		GCKR	nc	Glucokinase (hexokinase 4) regulator. Regulatory protein: inhibits hepatic and pancreatic glucokinase[76]. Mutations in *GCKR* underlie maturity-onset diabetes of the young (MODY)[77]; common variants are associated with triglyeride[78], glucose[79] and CRP[80] levels and risk of non-alcoholic fatty liver disease[81] and T2D[82].
2q12	rs13030978	*MYO1B*	ne	Myosin-1B. Widely expressed myosin-I isoform that concentrates on endosomal and ruffling membranes. May play a role in membrane trafficking and dynamics, including the traffic of protein cargo in multivesicular endosomes[83].
		STAT4	e	Signal transducer and activator of transcription 4. Encodes a member of the STAT family of transcription factors mediating responses to cytokines and growth factors[84].
2q37	rs2140773	*EFHD1*	ne	EF-hand domain-containing protein 1. The EF hand domain is a helix-loop-helix structural domain found in a large family of calcium-binding proteins[85]. *EFHD1* expression is increased expression during neuronal differentiation[86], but is of unknown function.
		LOC100129166	c	Hypothetical protein
3q26	rs10513686	*SLC2A2*	nc	Solute carrier family 2 (facilitated glucose transporter), member 2. Mediates bidirectional transport of glucose across cell membrane of hepatocytes[87]. Also responsible for uptake of glucose by pancreatic beta cells, and may comprise part of the glucose-sensing mechanism of the beta cell[88]. Participates in transport of glucose in the small intestine and kidney[89]. Mutations in *SLC2A2* underlie MODY[REF]; common variants are associated with levels of glucose[79], cholesterol[78], triglycerides[78] and pacreatic beta cell function[79], and with risk of T2D[82].
4q31	rs4547811	*ZNF827*	n	Zinc finger protein 827. Expressed in liver and other tissues[REF]. Unknown function.
5p15	rs6888304	*CDH6*	n	Cadherin-6. Transmembrane membrane protein which acts as a calcium dependent cell-cell adhesion glycoprotein[90]. Cadherins mediate cell-cell binding and the maintenance of orderly structures such as epithelium[91]. Strong transcriptional expression of this gene has been observed in hepatocellular and renal carcinoma cell lines[92]. Haepatic *CDH6* is also upregulated after Hepatitis B infection[93].
5q11	rs4074793	*ITGA1*	n	Integrin, alpha 1. Subunit of integrin receptors, which selectively recognizes cell-adhesion sites provided by collagens, fibronectins and laminin[94]. Involved in cell-cell adhesion[95], inflammation[96] and fibrosis[97]. Also involved in the early remodeling of osteoarthritic cartilage[98]. *ITGA1*-null mice show severe cartilage degradation and synovial hyperplasia[99]. Common variants associated with bone-mineral density[100].
6p12	rs9296736	*C6orf142*	ne	Hypothetical protein C6orf142. Unknown function.
7q11	rs17145750	*MLXIPL*	nce	MLX interacting protein-like. Transcription factor of the Myc/Max/Mad superfamily strongly expressed in liver[101]. Binds and activates, in a glucose-dependent manner, carbohydrate response

				elements (ChoRE) in the promoters of triglyceride synthesis genes[102]. Common variants in *MLXIPL* are associated with triglyceride levels in GWA studies[103].Kooner et al.
10q23	rs754466	*DLG5*	n	Discs, large homolog 5. Encodes a member of the membrane-associated guanylate kinase (MAGUK) superfamily, which function as scaffolding molecules at sites of cell-cell contact[104]. DLG5 localizes to the plasma membrane and cytoplasm, interacts with components of adherens junctions and the cytoskeleton, and may function in the transmission of extracellular signals to the cytoskeleton and regulation of NFkB activation or caspase activation. Genetic variants in *DLG5* have been associated with inflammatory bowel disease in some studies[105].
12q24	rs7310409	*C12orf27*	e	Hypothetical protein C12orf27. Unknown function.
		HNF1A	nc	Hepatic transcription factor. Key regulator of transcription of several liver-specific genes. Mutations in *HNF1A* are a cause of maturity onset diabetes of the young type 3 (MODY3)[106] and hepatic adenomas[107]. Common variants in *HNF1A* associated with risk of T2D[82], and with levels of glucose[79], CRP[80], and lipids[78].
14q32	rs944002	*C14orf73*	nc	Hypothetical protein C14orf73. Strongly expressed in liver, but unknown function[REF]. Sequence homology with SEC6, a protein that interacts with the actin cytoskeleton and vesicle transport machinery, and which is involved in targeting exocytic vesicles to docking sites on the plasma membrane[108].
15q21	rs339969	*RORA*	n	RAR-related orphan receptor A. Member of the NR1 subfamily of nuclear hormone receptors, regulating expression of numerous metabolic and inflammatory genes including including *NF-κB*, apolipoproteins *AI*, *APOA5*, *CIII*, *CYP7A1* and *PPARgamma*[109-111]. *RORA* is widely expressed, particularly neuronal and liver tissues[112]. The staggerer (*Rora*$^{sg/sg}$) mutant mouse shows extensive cerebellar neurodegeneration and abnormal innate immunity characterized by an increased susceptibility to systemic LPS treatmen[113-115].
15q23	rs8038465	*CD276*	ne	CD276 molecule (also called B7H3). Ubiquitously expressed, including liver[116]. Regulates immune responses, including induction of cytotoxic T-cells, interferon gamma production and NK cell activity[117].
16q23	rs4581712	*DYNLRB2*	n	Dynein, light chain, roadblock-type 2. May be involved in assembly and motor function of dynein, which plays a central role in cell division and intracellular transport[118]. May also influence TGF-beta signalling[119].
17q24	rs9913711	*FLJ37644*	e	Hypothetical gene.
		SOX9	n	SRY (sex determining region Y)-box 9. Transcriptional regulator with an important role in sex and skeletal development[120]. Expressed in the genital ridge, in chondrocytes and in other tissues[121]. Involved in differentiation of Sertoli cells, enhancer expression of *COL2A1*, required for cartilage formation, and influences BMP2 and Indian hedgehog (IHH) signaling pathways in osteogenic cells[122, 123]. Mutations lead to the skeletal malformation syndrome campomelic dysplasia, and may be accompanied by sex reversal[124].
18q21.31	rs12968116	*ATP8B1*	ncg	ATPase, class I, type 8B, member 1. An ATPase that transports aminophospholipids from the outer to the inner leaflet of membranes, and maintains asymmetric distribution of phospholipids in the canicular membrane[125]. Involved in transport of bile acids into the canaliculus, and uptake of bile acids from intestinal lumen[126]. Mutations in *ATP8B1* result in progressive familial intrahepatic cholestasis type 1, and are associated with raised GGT[127].
18q21.32	rs4503880	*NEDD4L*	n	Neural precursor cell expressed, developmentally down-regulated 4-like. Encodes a ubiquitin-protein ligase which inhibits TGF-beta signalling, and promotes internalization of various plasma

				membrane proteins channels, including epithelial sodium channel. Variants in *NEDD4L* are associated with salt sensitivity and raised blood pressure[128].
19q13	rs516246	*FUT2*	nc	Fucosyltransferase 2. Encodes alpha(1,2)fucosyltransferase, the enzyme responsible for the synthesis of H antigen, the precursor of ABO antigen in body fluids and on the intestinal mucosa[50]. Individuals homozygous for nonfunctional *FUT2* alleles fail to present ABO antigens in secretions (“nonsecretors”) and on epithelial cells[51]. Variants in *FUT2* are associated with vitamin B_{12} levels in GWA[52], and with susceptibility to intestinal infections such as Norovirus[53].
22q11.21	rs1076540	*MICAL3*	ne	Microtubule associated monoxygenase, calponin and LIM domain containing 3. MICAL molecules are associated with the cytoskeleton and influences F-actin disassembly and cytoskeletal remodelling[129]. Members of the MICAL family play a key role in a number of processes dependent on F-actin, including endocytosis and semaphorin mediated axon guidance[130].
22q11.23	rs2739330	*DDT / DDTL*	*e / e*	*DDT*: D-dopachrome tautomerase. *DDTL*: D-dopachrome tautomerase-like. Converts D-dopachrome to 5,6-dihydroxindole[131]. May act synergistically with MIF to promote angiogenic factors such as VEGF[132].
		GSTT1 / GSTT2B	*e / n*	*GSTT1*: Glutathione S-transferase theta 1; *GSTT2B*: Glutathione S-transferase theta 2B. The glutathione S-transferases conjugate reduced glutathione to a wide number of exogenous and endogenous chemicals, and are key enzymes in eliminating carcinogens and harmful macromolecules[133]. *GSTT1*, *GSTT2* and *GSTT2B* are highly homologous and located in close proximity[134].
		MIF	e	Macrophage inhibitory factor. Pleiotropic cytokine with a broad range of pro-inflammatory actions, and produced involved by a variety of cell types. In addition influences cell proliferation, angiogenesis and neoplasia[132].
22q11.23	rs2073398	*GGT1*	ne	Gamma-glutamyltransferase 1. GGT is a transmembrane protein, widely expressed, and found at highest levels in liver, kidney, salivary glands and other tissues involved in absorption and secretion[135]. GGT cleaves extracellular glutathione (GSH) to generate cysteine, the rate-limiting precursor for synthesis of intracellular GSH[136]; GGT is thus an essential component of cellular antioxidant defense mechanisms. GGT also acts to conserve glutathione from luminal spaces such as renal tubules[135]. *GGT*(-/-) mice show intracellular GSH deficiency, growth retardation, reduced hepatic fat and glycogen, impaired oxidative phosphorylation and die prematurely[137].
		GGTLC2	e	A light chain-only GGT which contain a region corresponding to the GGT1 light chain, but which lack the heavy chain region and thus circulates in plasma rather than being membrane bound[135].

Supplementary Table 10: Coding SNPs in LD at r^2>0.5 (HapMap[138] or 1000G CEU[139]) with sentinel SNPs identified in the liver marker genome-wide association study. $\mathbf{P_{pheno}}$ is for the association of coding SNP with phenotype; P_{hetero} is for comparison of effect size on phenotype between sentinel SNP and coding SNP; r^2 is LD between sentinel and coding SNP (HapMap CEU or 1000G data). Genes with coding SNPs in r^2>0.5 and with phenotype $P_{hetero}>1.2\times10^{-3}$ (ie P<0.05 after correction for 42 tests) represent good candidates for mediators of the liver marker association observed and are highlighted yellow. Genes failing these parameters are highlighted grey. Coding SNPs identified through 1000G and not genotyped or imputed in the GWA study are highlighted green; association with phenotype and P_{hetero} are not available (NA).

Region	**Sentinel SNP**	**Coding SNP**	**Source**	**r^2**	**Alleles (Ref / Effect)**	**EAF**	**N**	**P_{pheno}**	**P_{hetero}**	**Gene**	**Amino acid change**	**Amino acid**
ALT												
22q13	rs738409	rs738409	HapMap	1.00	C / G	0.23	55305	1.2×10^{-45}	1.00	*PNPLA3*	I148M	Ile-Met
22q13	rs738409	rs3761472	HapMap	0.54	A / G	0.19	55437	3.7×10^{-29}	0.06	*SAMM50*	D110G	Asp-Gly
ALP												
1p36.12	rs1976403	rs1827293	HapMap	0.85	G / A	0.52	31891	9.9×10^{-31}	3.9×10^{-3}	*NBPF3*	Y114C	Tyr-Cys
1p36.12	rs1976403	rs12043777	1000G	0.53	C / G	0.38	NA	NA	NA	*NBPF3*	D444E	Asp-Glu
6p22	rs1883415	rs2760118	HapMap	0.71	C / T	0.32	12095	1.3×10^{-2}	1.8×10^{-4}	*ALDH5A1*	H180Y	His-Tyr
6p22	rs1883415	rs1126617	HapMap	1.00	C / T	0.33	32572	2.8×10^{-25}	0.83	*GPLD1*	V30I	Val-Ile
10q21	rs7923609	rs1935	HapMap	1.00	C / G	0.50	32602	1.1×10^{-18}	0.65	*JMJD1C*	E2298D	Glu-Asp
19q13	rs281377	rs601338	HapMap	0.78	A / G	0.46	32294	1.4×10^{-14}	0.52	*FUT2*	W154X	Trp-AMB
19q13	rs281377	rs602662	HapMap	0.53	A / G	0.39	32454	1.9×10^{-13}	0.48	*FUT2*	G258S	Gly-Ser
20p11	rs7267979	rs6076347	HapMap	0.76	A / G	0.48	32644	5.0×10^{-5}	0.24	*GINS1*	V97I	Val-Ile
GGT												
1q21	rs10908458	rs4745	HapMap	0.69	T / A	0.48	26670	1.8×10^{-4}	0.41	*EFNA1*	D159V	Asp-Val
2p23	rs1260326	rs1260326	HapMap	1.00	C / T	0.38	57623	4.4×10^{-13}	1.00	*GCKR*	P446L	Pro-leu
2q37	rs2140773	rs4072149	HapMap	0.66	T / C	0.50	57459	4.7×10^{-8}	0.29	*LOC100129166*	W29R	Trp-Arg
3q26	rs10513686	rs5400	HapMap	1.00	G / A	0.14	57682	2.4×10^{-10}	0.95	*SLC2A2*	T110I	Thr-Ile
7q11	rs17145750	rs35332062	1000G	0.94	G / A	0.14	NA	NA	NA	*MLXIPL*	A358V	Ala-Val
7q11	rs17145750	rs3812316	1000G	0.94	C / G	0.14	NA	NA	NA	*MLXIPL*	Q241H	Gln-His
12q24	rs7310409	rs1169288	HapMap	0.62	C / A	0.72	54604	1.4×10^{-42}	0.43	*HNF1A*	I27L	Ile-Leu
12q24	rs7310409	rs2464196	HapMap	0.56	A / G	0.72	57559	8.3×10^{-38}	0.52	*HNF1A*	S487N	Ser-Asp
14q32	rs944002	rs10131298	HapMap	0.86	A / T	0.84	27588	1.8×10^{-23}	0.14	*C14orf73*	L185H	Leu-His
14q32	rs944002	rs2297067	HapMap	1.00	C / T	0.19	52449	1.9×10^{-28}	0.85	*C14orf73*	R77W	Arg-Trp
14q32	rs944002	rs2297066	1000G	1.00	C / G	0.22	NA	NA	NA	*C14orf73*	E93D	Asp-Glu
18q21.31	rs12968116	rs12968116	HapMap	1.00	T / C	0.88	48901	2.0×10^{-8}	1.00	*ATP8B1*	R952Q	Arg-Gln
19q13	rs516246	rs601338	HapMap	1.00	G / A	0.54	57331	4.5×10^{-8}	0.65	*FUT2*	W154X	Trp-AMB
19q13	rs516246	rs602662	HapMap	0.76	G / A	0.61	57441	3.7×10^{-8}	0.72	*FUT2*	G258S	Gly-Ser

Supplementary Table 11: Relationship between sentinel SNPs in the liver marker GWA study, and expression of cis genes (±1MB) in liver. Results filtered at $P<3\text{x}10^{-5}$ for association of sentinel SNP with transcript expression (P<0.05 after Bonferroni correction for 1814 SNP-transcript associations). Genes with $r^2>0.5$ and $P_{\text{hetero}}>1.2\text{x}10^{-3}$ (ie P<0.05 after correction for 42 tests) represent good candidates for mediators of the liver marker association observed and are highlighted yellow. Genes failing these parameters are highlighted grey.

Locus	Sentinel SNP	Transcript	Gene	Direction	$P_{\text{SS-expression}}$	$P_{\text{SS-pheno}}$	Transcript SNP	$P_{\text{TS- expression}}$	$P_{\text{TS-pheno}}$	r^2	Expression P_{hetero}	Phenotype P_{hetero}
ALT												
4q22	rs6834314	NM_138980	*MAPK10*	↑	1.9E-06	3.1E-09	rs6834314	1.9E-06	3.1E-09	1.00	1.00	1.00
10q24	rs10883437	NM_018294	*CWF19L1*	↓	2.0E-06	4.0E-09	rs12784396	5.4E-32	2.7E-08	0.24	2.1E-06	0.81
ALP												
6p22	rs1883415	NM_001080	*ALDH5A1*	↓	1.9E-17	5.6E-26	rs1883415	1.9E-17	5.6E-26	1.00	1.00	1.00
8p23	rs6984305	NM_024607	*PPP1R3B*	↑	3.3E-11	2.1E-10	rs4240624	1.1E-16	5.4E-10	0.74	0.08	0.90
11q12	rs174601	NM_013402	*FADS1*	↓	9.0E-11	1.3E-08	rs174549	2.1E-17	5.9E-08	0.67	0.34	0.78
11q12	rs174601	NM_004265	*FADS2*	↓	1.9E-05	1.3E-08	rs968567	8.7E-09	1.3E-03	0.55	0.85	0.59
20p11	rs7267979	NM_015600	*ABHD12*	↓	2.8E-110	7.4E-10	rs3761117	1.6E-111	2.7E-09	0.95	0.88	0.80
GGT												
1p36.13	rs1497406	NM_030907	*C1orf89*	↓	1.4E-12	3.3E-19	rs1008529	6.9E-17	3.1E-11	0.52	0.22	0.20
1p36.13	rs1497406	NM_004431	*EPHA2*	↓	6.7E-22	3.3E-19	rs7538216	5.5E-23	9.8E-17	0.95	0.84	0.75
2p23	rs1260326	AL117421	*IFT172*	↓	1.0E-29	4.4E-13	rs6547626	3.8E-88	1.5E-06	0.41	8.2E-09	0.08
2p23	rs1260326	NM_032266	*C2orf16*	↓	7.3E-06	4.4E-13	rs1260326	7.3E-06	4.4E-13	1.00	1.00	1.00
2q37	rs2140773	NM_025202	*EFHD1*	↑	4.0E-82	1.2E-09	rs13395911	1.7E-84	2.7E-09	0.97	0.84	0.97
5q11	rs4074793	NM_181501	*ITGA1*	↓	1.7E-09	3.7E-10	rs1047483	3.6E-14	0.97	0.00	0.16	1.3E-11
6p12	rs9296736	NM_138569	*C6orf142*	↓	1.6E-118	2.9E-09	rs9349693	5.1E-123	6.8E-09	0.97	0.96	0.90
12q24	rs7310409	NM_178513	*C12orf27*	↓	2.7E-05	1.1E-44	rs7310409	2.7E-05	1.1E-44	1.00	1.00	1.00
15q23	rs8038465	NM_025240	*CD276*	↑	1.2E-07	1.6E-08	rs6495075	7.8E-08	2.5E-04	0.98	0.98	0.01
17q24	rs9913711	AK056229	*FLJ37644*	↓	2.3E-13	1.0E-07	rs9913936	1.3E-13	3.8E-07	0.98	0.95	0.79
22q11.23	rs2739330	NM_000853	*GSTT1*	↓	1.0E-34	1.9E-09	rs4822450	1.0E-70	4.4E-08	0.41	0.09	0.03
22q11.23	rs2739330	NM_002415	*MIF*	↑	2.2E-35	1.9E-09	rs5760098	1.4E-75	2.0E-05	0.55	0.02	0.63
22q11.23	rs2739330	NM_001355	*DDT*	↑	5.4E-70	1.9E-09	rs5760098	8.8E-138	2.0E-05	0.55	0.07	0.63
22q11.23	rs2739330	NM_000854	*GSTT2*	↑	7.2E-48	1.9E-09	rs5760101	8.0E-120	4.3E-04	0.55	1.2E-03	0.52

Sentinel SNP: top ranking SNP associated with liver marker levels in the genome-wide association study; **Transcript SNP**: the cis-SNP most closely associated with expression of the respective transcript in the expression study. **Direction**: direction of change in transcript expression for the allele associated with raised liver marker levels. $\mathbf{P_{SS\text{- }expression}}$: P value for association of sentinel SNP with transcript expression; $\mathbf{P_{TS\text{- }expression}}$: P value for association of transcript SNP with transcript expression. $\mathbf{P_{SS\text{-}pheno}}$: P value for association of sentinel SNP with liver marker; $\mathbf{P_{TS\text{-}pheno}}$: P value for association of transcript SNP with liver marker. **Expression** $\mathbf{P_{hetero}}$ is for the comparison of effect sizes on transcript expression between the sentinel and transcript SNPs; **Phenotype** $\mathbf{P_{hetero}}$ is for the comparison of effect sizes on liver marker levels between the sentinel and transcript SNPs. LD between sentinel and coding SNPs given as $\mathbf{r^2}$, and calculated from HapMap CEU population.

Supplementary Table 12: Relationship between sentinel SNPs identified in the liver marker GWA study, and expression of cis genes (±1MB) in peripheral blood leucocytes (deCODE)[140]. Results filtered at $P<7x10^{-5}$ for association of sentinel SNP with transcript expression (P<0.05 after Bonferroni correction for 675 SNP-transcript associations tested). Genes with $r^2>0.5$ and $P_{hetero}>1.2x10^{-3}$ (ie P<0.05 after correction for 42 tests) represent good candidates for mediators of the liver marker association observed and are highlighted yellow. Genes failing these parameters are highlighted grey.

Locus	Sentinel SNP	Transcript	Gene	Direction	$P_{SS\text{-}expression}$	$P_{SS\text{-}pheno}$	Transcript SNP	$P_{TS\text{-}expression}$	$P_{TS\text{-}pheno}$	r^2	Expression P_{hetero}	Phenotype P_{hetero}
ALT												
4q22	rs6834314	NM_178135	*HSD17B13*	↓	1.2E-39	3.1E-09	rs13102451	1.2E-39	1.5E-07	1.00	1.00	0.95
10q24	rs10883437	NM_018294	*CWF19L1*	↓	2.5E-05	4.0E-09	rs11597086	9.8E-22	1.3E-08	0.34	6.2E-04	0.97
ALP												
11q12	rs174601	NM_013402	*FADS1*	↑	1.7E-13	1.3E-08	rs968567	1.7E-21	1.3E-03	0.31	0.02	0.51
11q12	rs174601	NM_004265	*FADS2*	↑	8.2E-80	1.3E-08	rs968567	5.1E-195	1.3E-03	0.31	3.4E-12	0.51
11q12	rs174601	NM_014206	*C11orf10*	↑	3.3E-05	1.3E-08	rs174538	8.7E-06	2.4E-07	0.76	0.87	0.66
16q22	rs7186908	NM_005143	*HP*	↓	2.7E-18	4.8E-09	rs12325142	1.3E-61	1.3E-06	0.39	0.005	0.23
17p13	rs314253	NM_015362	*C17orf81*	↑	6.3E-07	8.4E-12	rs2074217	7.8E-35	1.1E-03	0.11	2.5E-06	0.94
17p13	rs314253	NM_080913	*ASGR2*	↑	3.3E-05	8.4E-12	rs314239	1.1E-28	5.7E-02	0.06	6.3E-06	8.1E-04
GGT												
1p36.13	rs1497406	NM_030907	*C1orf89*	↓	1.1E-13	3.3E-19	rs1007887	1.2E-16	1.1E-16	0.90	0.47	0.80
1p13	rs1335645	NM_024901	*DENND2D*	↑	2.3E-07	7.9E-09	rs1043096	2.2E-07	8.5E-09	1.00	0.99	0.98
2p23	rs1260326	AL117421	*IFT172*	↓	1.4E-57	4.4E-13	rs1260341	1.0E-256	5.9E-07	0.50	6.5E-11	0.26
10q23	rs754466	NM_004747	*DLG5*	↑	1.9E-05	7.0E-10	rs1248631	8.4E-62	7.1E-01	0.07	5.1E-12	2.2E-04
22q11.23	rs2739330	NM_000853	*GSTT1*	↓	4.7E-83	1.9E-09	rs407257	4.8E-185	1.5E-07	0.73	1.2E-08	0.87
22q11.23	rs2739330	NM_000854	*GSTT2 GSTT2B*	↑	2.9E-05	1.9E-09	rs9624364	5.7E-29	3.4E-03	0.07	0	0.64
22q11.23	rs2739330	NM_001355	*DDT, DDTL*	↓	1.4E-44	1.9E-09	rs5760147	2.7E-51	5.5E-09	0.93	0.18	0.98
22q11.23	rs2073398	NM_013421	*GGT1, GGTLC2*	↓	2.7E-12	3.5E-109	rs5751901	1.9E-12	8.2E-101	0.96	0.90	0.17

Abbreviations are as for Supplementary Table 11.

Supplementary Table 13: Relationship between sentinel SNPs identified in the liver marker GWA study, and expression of cis genes (±1MB) in adipose tissue (deCODE)[140] Results filtered at $P<7\times10^{-5}$ for association of sentinel SNP with transcript expression (P<0.05 after Bonferroni correction for 675 SNP-transcript associations). Genes with $r^2>0.5$ and $P_{hetero}>1.2\times10^{-3}$ (ie P<0.05 after correction for 42 tests) are good candidates for mediators of the liver marker association and are highlighted yellow. Genes failing these parameters are highlighted grey.

Locus	Sentinel SNP	Transcript	Gene	Direction	$P_{SS\text{-}expression}$	$P_{SS\text{-}pheno}$	Transcript SNP	$P_{TS\text{-}expression}$	$P_{TS\text{-}pheno}$	r^2	Expression P_{hetero}	Phenotype P_{hetero}
ALT												
4q22	rs6834314	NM_178135	*HSD17B13*	↓	2.1E-12	3.1E-09	rs6531968	1.1E-37	1.9E-05	0.23	0.003	0.04
10q24	rs10883437	NM_018294	*CWF19L1*	↓	1.7E-15	4.0E-09	rs11597086	1.1E-69	1.3E-08	0.34	2.2E-06	0.97
ALP												
6p22	rs1883415	NM_001080	*ALDH5A1*	↓	2.8E-07	5.6E-26	rs13218564	4.3E-09	5.1E-01	0.39	0.73	2.2E-11
6p22	rs1883415	NM_177483	*GPLD1*	↓	5.9E-07	5.6E-26	rs2744576	4.2E-10	7.7E-01	0.33	0.50	4.7E-13
9q21	rs10819937	NM_000035	*ALDOB*	↓	2.3E-25	2.0E-08	rs2183745	9.9E-60	2.4E-08	0.39	0.06	0.16
9q21	rs10819937	NM_003452	*ZNF189*	↓	2.0E-19	2.0E-08	rs504023	9.4E-27	2.4E-01	0.05	0.35	1.6E-04
9q21	rs10819937	NM_019051	*MRPL50*	↓	2.5E-06	2.0E-08	rs10819924	1.1E-31	5.0E-01	0.01	3.5E-07	0.007
9q21	rs10819937	NM_032342	*C9orf125*	↓	7.6E-16	2.0E-08	rs2183745	7.8E-32	2.4E-08	0.39	0.20	0.16
10q21	rs7923609	NM_004241	*JMJD1C*	↓	1.0E-08	5.9E-23	rs1935	4.5E-09	1.1E-18	1.00	0.92	0.65
10q21	rs7923609	NM_030759	*NRBF2*	↓	2.4E-15	5.9E-23	rs10822163	1.7E-15	3.4E-22	0.86	0.79	0.85
11q12	rs174601	NM_014206	*C11orf10*	↑	9.3E-08	1.3E-08	rs174538	1.7E-12	2.4E-07	0.76	0.26	0.66
16q22	rs7186908	NM_001361	*DHODH*	↑	3.2E-06	4.8E-09	rs3213422	2.3E-20	6.9E-05	0.16	0.07	0.07
16q22	rs7186908	NM_005143	*HP*	↓	8.4E-10	4.8E-09	rs7197453	2.4E-14	1.8E-06	0.39	0.94	0.23
16q22	rs7186908	NM_020995	*HPR*	↓	5.9E-07	4.8E-09	rs7184169	7.2E-08	3.1E-07	0.75	0.88	0.33
17p13	rs314253	NM_015362	*C17orf81*	↑	1.3E-06	8.4E-12	rs222851	9.7E-26	2.3E-06	0.10	5.1E-04	0.09
19q13	rs281377	NM_182575	*IZUMO1*	↓	1.0E-08	1.1E-15	rs8104897	8.6E-18	1.5E-09	0.33	0.12	0.26
GGT												
1p36.13	rs1497406	NM_030907	*C1orf89*	↓	2.6E-26	3.3E-19	rs1008529	2.8E-42	3.1E-11	0.44	0.004	0.34
1p13	rs1335645	NM_178454	*TMEM77*	↑	7.2E-06	7.9E-09	rs3795823	6.0E-88	7.7E-03	0.06	8.6E-10	0.004
1q21	rs10908458	NM_182685	*EFNA1*	↑	9.0E-07	1.9E-15	rs4276913	2.7E-08	3.3E-12	0.84	0.57	0.68
2p23	rs1260326	AL117421	*IFT172*	↓	1.5E-50	4.4E-13	rs1260341	7.2E-241	5.9E-07	0.50	9.0E-10	0.26
2q12	rs13030978	NM_003151	*STAT4*	↓	3.1E-42	1.2E-11	rs13025919	3.3E-45	1.4E-10	0.93	0.78	0.49
6p12	rs9296736	NM_138569	*C6orf142*	↓	1.9E-13	2.9E-09	rs4715439	4.0E-16	1.8E-07	0.79	0.19	0.44
7q11	rs17145750	Contig39451	*VPS37D*	↓	1.8E-05	3.2E-09	rs10479665	5.9E-12	2.5E-01	0.00	0.002	3.5E-08
7q11	rs17145750	NM_032951	*MLXIPL*	↓	5.9E-21	3.2E-09	rs11974409	8.6E-24	5.0E-09	0.68	0.54	0.34
17q24	rs9913711	AK056229	*FLJ37644*	↓	5.9E-06	1.0E-07	rs9913936	1.5E-06	3.8E-07	0.92	0.78	0.85
22q11.23	rs2739330	NM_000853	*GSTT1*	↓	5.2E-84	1.9E-09	rs407257	2.1E-164	1.5E-07	0.73	8.5E-06	0.87
22q11.23	rs2739330	NM_000854	*GSTT2*	↑	3.1E-12	1.9E-09	rs368588	8.3E-43	5.6E-01	0.04	0.0E+00	0.20
22q11.23	rs2739330	NM_001355	*DDT DDTL*	↓	2.1E-18	1.9E-09	rs5760147	2.1E-24	5.5E-09	0.93	0.20	0.98
22q11.23	rs2739330	NM_002415	*MIF*	↑	9.5E-06	1.9E-09	rs5751749	8.4E-07	5.3E-01	0.01	0.02	0.05
22q11.23	rs2739330	NM_030807	*SLC2A11*	↓	8.9E-11	1.9E-09	rs17004046	8.5E-21	3.8E-02	0.13	2.2E-04	0.05

Abbreviations are as for Supplementary Table 11.

Supplementary Table 14: Relationship between sentinel SNPs in the liver marker GWA study, and expression of cis genes (±1MB) in peripheral blood leucocytes (University of Michigan)[141]. Results filtered at $P<2x10^{-5}$ for association of sentinel SNP with transcript expression ($P<0.05$ after Bonferroni correction for 2892 SNP-transcript associations). Genes with $r^2>0.5$ and $P_{hetero}>1.2x10^{-3}$ (ie $P<0.05$ after correction for 42 tests) represent good candidates for mediators of the liver marker association observed and are highlighted yellow. Genes failing these parameters are highlighted grey.

Locus	Sentinel SNP	Transcript	Gene	Direction	$P_{SS\text{-}expression}$	$P_{SS\text{-}pheno}$	Transcript SNP	$P_{TS\text{-}expression}$	$P_{TS\text{-}pheno}$	r^2	Expression P_{hetero}	Phenotype P_{hetero}
ALP												
1p36.12	rs1976403	223638_at	*NBPF3*	↑	4.8E-21	1.8E-50	rs1827293	1.3E-27	9.9E-31	0.85	0.44	0.004
6p22	rs1883415	203608_at	*ALDH5A1*	↓	5.4E-11	5.6E-26	rs1126617	9.9E-12	2.8E-25	1.00	0.95	0.83
6p22	rs1883415	228542_at	*MRS2L*	↓	1.6E-07	5.6E-26	rs3827640	1.2E-19	7.9E-02	0.13	0.01	1.0E-09
10q21	rs7923609	228793_at	*JMJD1C*	↓	5.1E-09	5.9E-23	rs9804238	1.1E-15	3.2E-09	0.44	1.0E-22	0.31
10q21	rs7923609	223650_s_at	*NRBF2*	↑	1.6E-08	5.9E-23	rs10822163	1.7E-08	3.4E-22	0.87	0.87	0.85
10q21	rs7923609	235016_at	*REEP3*	↑	4.0E-10	5.9E-23	rs2565185	4.3E-29	1.3E-08	0.25	5.1E-36	0.55
11q12	rs174601	218213_s_at	*C11orf10*	↑	7.2E-10	1.3E-08	rs174538	1.2E-11	2.4E-07	0.76	0.98	0.66
11q12	rs174601	208962_s_at	*FADS1*	↓	2.4E-15	1.3E-08	rs174601	2.4E-15	1.3E-08	1.00	1.00	1.00
11q12	rs174601	202218_s_at	*FADS2*	↑	1.0E-06	1.3E-08	rs174541	1.0E-08	1.1E-07	0.76	0.79	0.59
17p13	rs314253	223286_at	*C17orf81*	↑	3.2E-06	8.4E-12	rs402514	3.5E-36	4.5E-07	0.11	4.9E-08	0.17
20p11	rs7267979	228124_at	*ABHD12*	↓	2.1E-33	7.4E-10	rs2257991	1.2E-33	2.0E-09	1.00	0.97	0.95
20p11	rs7267979	206102_at	*GINS1*	↓	5.5E-15	7.4E-10	rs2500406	7.6E-17	3.0E-06	0.63	0.57	0.87
20p11	rs7267979	201481_s_at	*PYGB*	↓	1.5E-07	7.4E-10	rs2500403	1.6E-11	3.5E-03	0.24	0.05	0.41
GGT												
1p22	rs12145922	209472_at	*CCBL2*	↑	2.1E-21	4.3E-11	rs10801690	7.0E-35	1.9E-07	0.52	0.03	0.36
1p13	rs1335645	219375_at	*CEPT1*	↓	1.9E-06	7.9E-09	rs817582	3.1E-07	1.2E-05	0.72	0.75	0.11
2p23	rs1260326	209429_x_at	*EIF2B4*	↓	1.6E-06	4.4E-13	rs2272417	7.4E-07	1.5E-05	0.36	0.96	0.07
2p23	rs1260326	217765_at	*NRBP1*	↑	7.9E-06	4.4E-13	rs7586601	2.4E-09	9.7E-06	0.54	0.32	0.07
2q12	rs13030978	212364_at	*MYO1B*	↓	2.0E-20	1.2E-11	rs13025919	2.2E-23	1.4E-10	0.93	0.98	0.49
12q24	rs7310409	219022_at	*C12orf43*	↓	4.3E-07	1.1E-44	rs1169303	1.3E-07	1.6E-27	0.33	0.93	0.01
22q11.21	rs1076540	212715_s_at	*MICAL3*	↑	5.2E-10	1.1E-16	rs9617648	1.9E-16	6.8E-12	0.83	0.16	0.39
22q11.23	rs2739330	203815_at	*GSTT1*	↓	4.5E-25	1.9E-09	rs407257	1.0E-31	1.5E-07	0.73	0.04	0.87
22q11.23	rs2073398	207131_x_at	*GGT1*	↓	2.7E-17	3.5E-109	rs5760492	1.8E-17	1.8E-108	1.00	0.75	0.89

Abbreviations are as for Supplementary Table 11.

Supplementary Table 15: Candidate genes identified by GRAIL[142] using Pubmed 2006 or 2010 datasets. P values are corrected for multiple testing.

			Pubmed 2006		Pubmed 2010	
Region	**SNP**	**Position**	**Candidate**	**P**	**Candidate**	**P**
ALT						
4q22	rs6834314	88432832	*HSD17B13*	0.61	*HSD17B13*	0.78
8q24	rs2954021	126551259	*TRIB1*	0.36	*TRIB1*	0.28
10q24	rs10883437	101785351	*DNMBP*	0.11	*DNMBP*	0.67
22q13	rs738409	42656060	*PARVB*	0.33	***PNPLA3***	0.02
ALP						
1p36.12	rs1976403	21639040	*NBPF3*	0.53	*NBPF3*	0.17
2q24	rs16856332	169548820	***ABCB11***	0.02	***ABCB11***	0.007
6p22	rs1883415	24599454	*ALDH5A1*	0.87	*ALDH5A1*	0.62
8p23	rs6984305	9215678	*PPP1R3B*	0.86	*PPP1R3B*	0.78
8q24	rs2954021	126551259	*TRIB1*	0.36	*TRIB1*	0.28
9q21	rs10819937	103263054	*ALDOB*	0.94	*ALDOB*	0.50
9q34	rs579459	135143989	*ABO*	0.14	***ABO***	0.002
10q21	rs7923609	64803828	*NRBF2*	0.82	*REEP3*	0.43
11q12	rs174601	61379716	*FADS2*	0.93	*FADS1*	0.66
11q.24	rs2236653	125788995	*ST3GAL4*	0.11	*ST3GAL4*	0.29
16q22	rs7186908	70777874	*HP*	0.37	*HP*	0.31
17p13	rs314253	7032374	*ASGR1*	0.57	*ASGR1*	0.46
19q13	rs281377	53898415	*FUT2*	0.25	***FGF21***	0.04
20p11	rs7267979	25246087	*MYLK2*	0.86	*MYLK2*	0.58
GGT						
1p36.13	rs1497406	16377907	*EPHA2*	0.46	*EPHA2*	0.52
1p22	rs12145922	88918822	*PKN2*	0.99	*PKN2*	0.97
1p13	rs1335645	111485799	*TMEM77*	1.00	*DENND2D*	0.91
1q21	rs10908458	153393572	*PKLR*	0.80	*PKLR*	0.57
2p23	rs1260326	27584444	*GCKR*	0.16	***GCKR***	0.01
2q12	rs13030978	191825483	*MYO1B*	0.53	*MYO1B*	0.53
2q37	rs2140773	233221419	*EFHD1*	0.88	*EFHD1*	0.98
3q26	rs10513686	172208236	*SLC2A2*	0.28	*SLC2A2*	0.10
4q31	rs4547811	147014071	*ZNF827*	0.53	*ZNF827*	0.94
5p15	rs6888304	31056278	*CDH6*	0.76	*CDH6*	0.49
5q11	rs4074793	52228882	*ITGA1*	0.58	*ITGA1*	0.53
6p12	rs9296736	54032656	*C6orf142*	0.59	*C6orf142*	0.84
7q11	rs17145750	72664314	*MLXIPL*	0.08	***MLXIPL***	0.0004
10q23	rs754466	79350440	*DLG5*	0.79	*DLG5*	0.09
12q24	rs7310409	119909244	*HNF1A*	0.51	*HNF1A*	0.35
14q32	rs944002	102642568	*CDC42BPB*	0.24	*CDC42BPB*	0.65
15q21	rs339969	58670573	*RORA*	0.39	*RORA*	0.25
15q23	rs8038465	71765390	*NPTN*	0.74	*NPTN*	0.37
16q23	rs4581712	79055102	*CDYL2*	0.71	*CDYL2*	0.83
17q24	rs9913711	67609756	*SOX9*	0.71	*SOX9*	0.65
18q21.31	rs12968116	53473500	***ATP8B1***	0.01	***ATP8B1***	0.02
18q21.32	rs4503880	54235034	*ALPK2*	0.59	*ALPK2*	0.98
19q13	rs516246	53897984	*FUT2*	0.25	***FGF21***	0.04
22q11.21	rs1076540	16819958	*MICAL3*	0.62	*MICAL3*	0.67
22q11.23	rs2739330	22625286	*GSTT1*	0.57	*GSTT1*	0.44
22q11.23	rs2073398	23329104	*C22orf36*	0.80	***C22orf36***	0.02

Supplementary Table 16. Associations reported from GWA studies that are in proximity (+/- 1MB) to a sentinel SNP from the liver marker GWA, based on NHGRI extract September 2010.

Region	LFT SNP	Position	NHGRI SNP	Position	Distance (kb)	r^2	Disease/Trait	Reference
1p36.12	rs1976403	21639040	rs4654748	21658655	19.6	0.576	Folate pathway vitamin levels	Tanaka et al. Am J Hum Genet 2009
1p36.12	rs1976403	21639040	rs1780324	21694344	55.3	0.66	Plasma levels of liver enzymes (ALP)	Yuan et al. Am J Hum Genet 2008
1p36.12	rs1976403	21639040	rs1697421	21695879	56.8	0.511	Serum phosphorus concentrations	Kestenbaum et al. J Am Soc Nephrol 2010
1p36.12	rs1976403	21639040	rs7524102	22571034	932.0	0	Bone mineral density (spine)	Rivadeneira et al. Nat Genet 2009
1p36.12	rs1976403	21639040	rs7524102	22571034	932.0	0	Bone mineral density (hip)	Styrkarsdottir et al. N Engl J Med 2008
1p36.12	rs1976403	21639040	rs6696981	22575445	936.4	0.005	Bone mineral density (spine)	Styrkarsdottir et al. Nat Genet 2008
1p13	rs1335645	111485799	rs494453	111993645	507.8	0	Osteoporosis	Hsu et al. PLoS Genet 2010
1q21	rs10908458	153393572	rs4537545	152685503	708.1	0.01	C-reactive protein	Elliott et al. JAMA 2009
1q21	rs10908458	153393572	rs4129267	152692888	700.7	0.007	Protein quantitative trait loci	Melzer et al. PLoS Genet 2008
1q21	rs10908458	153393572	rs13376333	153080977	312.6	0	Atrial fibrillation	Ellinor et al. Nat Genet 2010
2p23	rs1260326	27584444	rs1260326	27584444	0.0	1	Triglycerides	Kathiresan et al. Nat Genetics 2008
2p23	rs1260326	27584444	rs1260326	27584444	0.0	1	Two hour glucose challenge	Saxena et al. Nat Genetics 2010
2p23	rs1260326	27584444	rs1260326	27584444	0.0	1	Other metabolic traits (Triglycerides)	Sabatti et al. Nat Genetics 2008
2p23	rs1260326	27584444	rs1260326	27584444	0.0	1	Waist circumference	Chambers et al. Nat Genetics 2008
2p23	rs1260326	27584444	rs1260326	27584444	0.0	1	Chronic kidney disease	Kottgen et al. Nat Genet 2010
2p23	rs1260326	27584444	rs780094	27594741	10.3	0.932	Fasting insulin	Dupuis et al. Nat Genet 2010
2p23	rs1260326	27584444	rs780094	27594741	10.3	0.932	Fasting plasma glucose	Dupuis et al. Nat Genet 2010
2p23	rs1260326	27584444	rs780094	27594741	10.3	0.932	HOMA IR	Dupuis et al. Nat Genet 2010
2p23	rs1260326	27584444	rs780094	27594741	10.3	0.932	Serum uric acid	Kolz et al. PLoS Genet 2009
2p23	rs1260326	27584444	rs780094	27594741	10.3	0.932	Triglycerides	Aulchenko et al. Nat Genet 2009
2p23	rs1260326	27584444	rs780094	27594741	10.3	0.932	C-reactive protein	Ridker et al. Am J Hum Genet 2008
2q24	rs16856332	169548820	rs1402837	169465600	83.2	0	Glycated hemoglobin levels	Pare et al. PLoS Genet 2008
2q24	rs16856332	169548820	rs560887	169471394	77.4	0	HOMA B	Dupuis et al. Nat Genet 2010
2q24	rs16856332	169548820	rs560887	169471394	77.4	0	Fasting plasma glucose	Dupuis et al. Nat Genet 2010
2q24	rs16856332	169548820	rs2544390	169913092	364.3	0.019	Hematological and biochemical traits	Kamatani et al. Nat Genet 2010
2q12	rs13030978	191825483	rs3821236	191611003	214.5	0	Systemic sclerosis	Radstake et al. Nat Genet 2010
2q12	rs13030978	191825483	rs7574865	191672878	152.6	0.009	Systemic lupus erythematosus	Han et al. Nat Genet 2009
2q37	rs2140773	233221419	rs7571816	232785308	436.1	0.004	Height	Okada et al. Hum Mol Genet 2010
2q37	rs2140773	233221419	rs6717918	232863354	358.1	0.002	Height	Estrada et al. Hum Mol Genet 2009
2q37	rs2140773	233221419	rs10210302	233823578	602.2	0.033	Crohn's disease	WTCCC et al. Nature 2007
2q37	rs2140773	233221419	rs3828309	233845149	623.7	0.045	Crohn's disease	Barrett et al. Nat Genet 2008
2q37	rs2140773	233221419	rs2241880	233848107	626.7	0.031	Crohn's disease	Rioux et al. Nat Genet 2007
3q26	rs10513686	172208236	rs11920090	172200215	8.0	1	Fasting glucose-related traits	Dupuis et al. Nat Genet 2010
4q22	rs6834314	88432832	rs1471403	88994267	561.4	0.006	Bone mineral density (spine)	Rivadeneira et al. Nat Genet 2009
4q22	rs6834314	88432832	rs2231142	89271347	838.5	0.001	Serum uric acid	Kolz et al. PLoS Genet 2009
7q11	rs17145750	72664314	rs13238203	71767603	896.7	0	Triglycerides	Kathiresan et al. Nature 2010
7q11	rs17145750	72664314	rs2240466	72494205	170.1	0.813	Triglycerides	Aulchenko et al. Nat Genet 2008

Region	LFT SNP	Position	NHGRI SNP	Position	Distance (kb)	r^2	Disease/Trait	Reference
7q11	rs17145750	72664314	rs714052	72502805	161.5	0.856	Triglycerides	Kathiresan et al. Nat Genet 2008
7q11	rs17145750	72664314	rs17145738	72620810	43.5	0.855	Triglycerides	Willer et al. Nat Genet 2008
7q11	rs17145750	72664314	rs3812316	72658273	6.0	NA	Triglycerides	Kooner et al. Nat Genet 2008
8p23	rs6984305	9215678	rs9987289	9220768	5.1	0.667	HDL	Kathiresan et al. Nature 2010
8q24	rs2954021	126551259	rs17321515	126555591	4.3	0.776	Triglycerides	Willer et al. Nat Genetics 2008
8q24	rs2954021	126551259	rs2954029	126560154	8.9	0.813	Triglycerides	Kathiresan et al. Nat Genet 2008
8q24	rs2954021	126551259	rs6987702	126573908	22.6	0.032	Total Cholesterol	Aulchenko et al. Nat Genet 2008
8q24	rs2954021	126551259	rs1551398	126609233	58.0	0.082	Crohn's disease	Barrett et al. Nat Genet 2008
9q34	rs579459	135143989	rs8176746	135121143	22.8	0.025	Hematological and biochemical traits	Kamatani et al. Nat Genet 2010
9q34	rs579459	135143989	rs657152	135129086	14.9	0.461	Plasma levels of liver enzymes (ALP)	Yuan et al. Am J Hum Genet 2008
9q34	rs579459	135143989	rs657152	135129086	14.9	0.461	Serum Phytosterol Levels	Teupser et al. Circ Cardiovasc Genet 2010
9q34	rs579459	135143989	rs505922	135139050	4.9	0.379	Venous thromboembolism	Tregouet et al. Blood 2009
9q34	rs579459	135143989	rs505922	135139050	4.9	0.379	Protein quantitative trait loci (TNFA)	Melzer et al. PLoS Genet 2008
9q34	rs579459	135143989	rs505922	135139050	4.9	0.379	Pancreatic cancer	Amundadottir et al. Nat Genet 2009
9q34	rs579459	135143989	rs507666	135139220	4.8	*NA*	Soluble ICAM-1	Pare et al. PLoS Genet 2008
9q34	rs579459	135143989	rs651007	135143696	0.3	0.949	Plasma E-selectin levels	Qi et al. Hum Mol Genet 2010
9q34	rs579459	135143989	rs579459	135143989	0.0	1	Serum soluble E-selectin	Paterson et al. Arterioscler Thromb Vasc Biol 2009
9q34	rs579459	135143989	rs579459	135143989	0.0	1	Soluble levels of adhesion molecules	Barbalic et al. Hum Mol Genet 2010
9q34	rs579459	135143989	rs649129	135144125	0.1	1	Soluble levels of adhesion molecules	Barbalic et al. Hum Mol Genet 2010
9q34	rs579459	135143989	rs495828	135144688	0.7	1	Angiotensin-converting enzyme activity	Chung et al. Pharmacogenomics 2010
9q34	rs579459	135143989	rs4962153	135313575	169.6	0.198	Plasma levels of liver enzymes (ALP)	Yuan et al. Am J Hum Genet 2008
9q34	rs579459	135143989	rs3025343	135468176	324.2	0	Smoking behavior	The Tobacco and Genetics Consortium. Nat Genet 2010
10q21	rs7923609	64803828	rs10995190	63948688	855.1	0	Breast cancer	Turnbull et al. Nat Genet 2010
10q21	rs7923609	64803828	rs10995271	64108492	695.3	0.001	Crohn's disease	Barrett et al. Nat Genet 2008
10q21	rs7923609	64803828	rs224136	64140681	663.1	0.001	Crohn's disease	Rioux et al. Nat Genet 2007
10q21	rs7923609	64803828	rs10761731	64697616	106.2	0.836	Triglycerides	Kathiresan et al. Nature 2010
10q21	rs7923609	64803828	rs12355784	64791571	12.3	0.967	Plasma levels of liver enzymes (ALP)	Yuan et al. Am J Hum Genet 2008
10q21	rs7923609	64803828	rs2393967	64803162	0.7	0.6	Mean platelet volume	Soranzo et al. Nat Genet 2009
10q21	rs7923609	64803828	rs2893923	64931190	127.4	0.547	Platelet aggregation	Johnson et al. Nat Genet 2010
10q21	rs7923609	64803828	rs10761779	64944933	141.1	0.967	Plasma levels of liver enzymes (ALP)	Yuan et al. Am J Hum Genet 2008
10q24	rs10883437	101785351	rs10883365	101277754	507.6	0.009	Crohn's disease	Parkes et al. Nat Genet 2007
10q24	rs10883437	101785351	rs11190140	101281583	503.8	0.009	Ulcerative colitis	McGovern et al. Nat Genet 2010
11q12	rs174601	61379716	rs174548	61327924	51.8	0.681	Serum metabolites	Gieger et al. PLoS Genet 2008
11q12	rs174601	61379716	rs174550	61328054	51.7	0.863	Fasting plasma glucose	Dupuis et al. Nat Genet 2010
11q12	rs174601	61379716	rs174550	61328054	51.7	0.863	HOMA B	Dupuis et al. Nat Genet 2010
11q12	rs174601	61379716	rs174570	61353788	25.9	0.303	Total cholesterol	Aulchenko et al. Nat Genet 2008
11q12	rs174601	61379716	rs174570	61353788	25.9	0.303	LDL cholesterol	Aulchenko et al. Nat Genet 2008
11q12	rs174601	61379716	rs1000778	61411881	32.2	0.245	Sphingolipid Concentrations	Hicks et al. PLoS Genet 2009
12q24	rs7310409	119909244	rs2014355	119659907	249.3	0.004	Serum metabolites	Illig et al. Nat Genet 2009

Region	LFT SNP	Position	NHGRI SNP	Position	Distance (kb)	r^2	Disease/Trait	Reference
10q24	rs10883437	101785351	rs11190140	101281583	503.8	0.009	Crohn's disease	Barrett et al. Nat Genet 2008
11q12	rs174601	61379716	rs17824933	60517188	862.5	0.016	Multiple sclerosis	De Jager et al. Nat Genet 2009
11q12	rs174601	61379716	rs174546	61326406	53.3	0.863	Triglycerides	Kathiresan et al. Nature 2010
11q12	rs174601	61379716	rs3136441	61326406	53.3	0	Blood lipid traits	Teslovich et al. Nature 2010
11q12	rs174601	61379716	rs174547	61327359	52.4	0.863	Serum metabolites	Illig et al. Nat Genet 2009
11q12	rs174601	61379716	rs174547	61327359	52.4	0.863	HDL cholesterol	Kathiresan et al. Nat Genet 2008
12q24	rs7310409	119909244	rs2650000	119873345	35.9	0.604	LDL cholesterol	Kathiresan et al. Nat Genet 2008
12q24	rs7310409	119909244	rs2650000	119873345	35.9	0.604	Other metabolic traits (C-reactive protein)	Sabatti et al. Nat Genet 2008
12q24	rs7310409	119909244	rs1169288	119901033	8.2	0.617	Total cholesterol	Kathiresan et al. Nature 2010
12q24	rs7310409	119909244	rs7310409	119909244	0.0	1	C-reactive protein	Ridker et al. Am J Hum Genet 2008
12q24	rs7310409	119909244	rs1169310	119923816	14.6	0.719	C-reactive protein	Reiner et al. Am J Hum Genet 2008
12q24	rs7310409	119909244	rs1169313	119927053	17.8	0.719	Plasma levels of liver enzymes (GGT)	Yuan et al. Am J Hum Genet 2008
12q24	rs7310409	119909244	rs7957197	119945069	35.8	0.114	Type 2 diabetes	Voight et al. Nat Genet 2010
12q24	rs7310409	119909244	rs7961894	120849966	940.7	0.007	Mean platelet volume	Soranzo et al. Nat Genet 2009
15q21	rs339969	58670573	rs2412710	59551119	880.5	0.003	Blood lipid traits	Teslovich et al. Nature 2010
15q23	rs8038465	71765390	rs3825942	72006635	241.2	0.129	Glaucoma (exfoliation)	Thorleifsson et al. Science 2007
16q22	rs7186908	70777874	rs2000999	70665594	112.3	0.02	Total cholesterol	Kathiresan et al. Nature 2010
16q22	rs7186908	70777874	rs7193343	71586661	808.8	0.014	Atrial fibrillation	Gudbjartsson et al. Nat Genet 2009
16q22	rs7186908	70777874	rs2106261	71609121	831.2	0.008	Atrial fibrillation	Benjamin et al. Nat Genet 2009
16q23	rs4581712	79055102	rs1424233	78240252	814.9	0.06	Obesity	Meyre et al. Nat Genet 2009
16q23	rs4581712	79055102	rs6564851	79822098	767.0	0.005	Plasma carotenoid and tocopherol levels	Ferrucci et al. Am J Hum Genet 2009
17q24	rs9913711	67609756	rs1859962	66620348	989.4	0.003	Prostate cancer	Gudmundsson et al. Nat Genet 2008
19q13	rs281377	53898415	rs492602	53898229	0.186	0.788	Plasma level of vitamin B12	Hazra et al. Nat Genet 2008
19q13	rs281377	53898415	rs492602	53898229	0.186	0.788	Total Cholesterol	Teslovich et al. Nature 2010
19q13	rs281377	53898415	rs602662	53898797	0.382	0.591	Folate pathway vitamin levels	Tanaka et al. Am J Hum Genet 2009
19q13	rs281377	53898415	rs504963	53900677	2.262	0.609	Crohn's disease	McGovern et al. Hum Mol Genet 2010
19q13	rs281377	53898415	rs2280401	54691821	793.406	0	Hematological and biochemical traits	Kamatani et al. Nat Genet 2010
22q13	rs738409	42656060	rs5759167	41830156	825.9	0.01	Prostate cancer	Eeles et al. Nat Genet 2009

Supplementary Table 17. Association of the sentinel SNPs from the 42 liver marker loci with other clinical phenotypes in published genome-wide association studies. Results are as -log10(P value) in the GWA study, signed according to the direction of change associated with the liver GWA effect allele. Associations reaching P<0.0012 (corresponding to P<0.05 after Bonferroni correction) are highlighted. P values are for the number of loci observed to be associated with each phenotype, compared to that expected under the null hypothesis. Phenotype abbreviations used and study references are described below.

Region	SNP	Alcohol intake	BMI	Systolic BP	Diastolic BP	Total chol	LDL chol	HDL chol	Triglycerides	Glucose	Insulin	HOMA-B	HOMA-IR	CRP	T2D
	N (max)	28188	32530	69738	69743	100184	95454	99900	97598	46186	38238	36466	37037	16015	22570
ALT															
4q22	rs6834314	0.84	0.10	0.57	1.52	-0.59	0.18	0.77	-2.69	-0.12	0.01	-0.33	-0.05	1.25	0.86
8q24	rs2954021	-0.66	-0.63	0.35	-0.19	30.84	26.48	-15.95	46.14	-0.29	0.08	0.03	-0.01	0.14	-0.05
10q24	rs10883437	0.84	0.23	-0.02	0.12	-1.72	-1.17	-2.23	0.27	0.11	0.13	-0.24	0.12	0.26	0.24
22q13	rs738409	-0.33	-1.06	-0.19	0.28	-3.85	-2.10	-2.36	-0.05	0.73	0.55	0.07	0.86	-1.04	1.16
ALP															
1p36.12	rs1976403	0.12	0.11	0.11	0.45	-0.16	-0.19	0.09	-0.11	-0.15	-1.30	-1.34	-1.53	-0.03	0.28
2q24	rs16856332	1.14	-0.09	0.92	0.39	-0.85	-0.20	-0.43	-0.23	0.77	-0.38	-1.67	-0.40	-0.35	0.00
6p22	rs1883415	0.07	-0.24	0.11	0.12	-0.58	-0.43	-0.37	-0.30	-2.27	-1.64	-0.35	-1.77	0.92	0.49
8p23	rs6984305	-0.59	0.14	0.34	0.24	-19.23	-12.79	-14.89	0.97	5.98	3.69	0.19	3.49	-2.93	0.31
8q24	rs2954021	-0.66	-0.63	0.35	-0.19	30.84	26.48	-15.95	46.14	-0.29	0.08	0.03	-0.01	0.14	-0.05
9q21	rs10819937	0.65	-0.36	-0.56	-0.66	0.37	0.32	-0.36	0.79	0.09	0.37	0.21	0.59	0.32	-0.03
9q34	rs579459	0.14	0.21	0.72	2.99	-19.31	-21.29	-1.04	1.74	-2.34	-0.23	0.97	-0.28	-0.88	-0.47
10q21	rs7923609	-0.15	-1.69	-1.11	-2.34	2.61	2.45	3.57	-8.25	-0.67	-2.06	-0.87	-2.42	-1.11	0.11
11q12	rs174601	0.09	0.14	0.00	1.95	-17.37	-16.79	-18.57	20.34	-6.04	0.88	3.87	0.27	0.31	-1.6
11q.24	rs2236653	0.09	-1.04	-0.63	-0.24	0.28	0.09	0.83	-0.17	-0.44	-0.33	-0.54	-0.50	-0.80	0.58
16q22	rs7186908	-0.06	0.20	-0.21	-0.29	-0.75	-0.40	0.97	0.19	-0.78	-0.43	0.11	-0.62	0.65	0.89
17p13	rs314253	0.88	-0.24	-0.20	-0.09	-4.53	-4.62	0.00	-0.83	-0.14	-0.24	-0.06	-0.06	-0.12	0.50
19q13	rs281377	-3.02	0.60	-0.24	-0.24	-6.64	-3.68	-0.09	-3.13	0.02	0.34	0.42	0.43	-0.69	0.35
20p11	rs7267979	-0.79	0.05	2.33	2.13	-2.22	-3.47	0.08	0.51	3.47	-0.61	-1.99	-0.15	0.01	0.70
GGT															
1p36.13	rs1497406	0.03	-0.32	1.45	1.73	2.84	1.60	0.47	0.97	0.13	-0.10	-0.19	-0.07	0.66	-0.02
1p22	rs12145922	0.20	-1.22	-1.42	-1.09	1.57	2.10	0.04	0.26	-0.13	-1.01	-0.89	-1.06	1.20	-1.63
1p13	rs1335645	-0.52	-0.18	-0.22	-0.20	-0.14	0.07	-0.41	-0.21	0.66	0.52	0.11	0.25	-0.23	-0.06
1q21	rs10908458	0.00	-0.07	0.55	0.49	-2.02	-2.33	0.10	-0.22	-0.68	0.09	0.37	0.05	0.54	-0.07
2p23	rs1260326	-1.83	-1.01	0.52	0.12	22.01	3.20	-1.46	117.56	-12.37	-3.92	-0.48	-6.04	4.04	-0.34
2q12	rs13030978	-0.39	0.19	0.10	0.57	-0.45	-1.55	-0.02	0.83	-0.12	-0.72	-0.53	-0.44	-0.62	1.87
2q37	rs2140773	-0.09	0.40	0.46	0.47	-0.32	-0.11	-0.04	-1.70	0.47	-0.03	-0.17	0.05	0.31	-0.60
3q26	rs10513686	0.17	-0.35	0.34	0.33	1.73	1.89	-0.31	2.14	-5.66	0.58	3.75	0.00	1.09	-1.55

4q31	rs4547811	-0.20	-0.13	-0.48	-0.13	0.42	0.36	-0.12	-0.13	-0.78	-0.11	0.24	0.00	0.24	-0.32
5p15	rs6888304	0.34	-0.35	-0.31	-0.03	0.10	-0.29	0.87	-0.23	-0.61	0.87	1.03	0.78	-0.07	-0.21
5q11	rs4074793	-1.13	0.28	-0.33	-1.46	2.89	3.35	0.09	-0.10	0.78	0.16	0.02	0.30	0.02	0.06
6p12	rs9296736	-0.11	0.47	0.21	-0.18	-1.27	-1.30	-0.37	-0.41	-0.21	0.05	0.45	0.03	0.13	0.01
7q11	rs17145750	0.12	0.28	0.19	0.90	1.73	-0.13	-4.79	57.78	-0.14	-0.61	-0.43	-0.39	2.32	-0.42
10q23	rs754466	-0.15	0.15	1.28	0.75	-0.35	-0.03	0.29	-0.40	-0.44	-0.65	0.02	-0.50	0.05	-0.65
12q24	rs7310409	0.34	0.26	-0.02	0.05	-8.90	-9.07	-1.39	-0.09	-0.07	1.19	1.20	0.93	30.29	-2.31
14q32	rs944002	-0.63	0.01	-0.62	-0.27	0.12	0.20	-0.42	0.11	1.61	-0.27	-0.70	-0.10	-0.81	0.24
15q21	rs339969	0.74	1.41	0.11	-0.07	-1.25	-1.30	1.05	0.04	-0.16	0.24	0.12	0.04	1.38	0.70
15q23	rs8038465	0.30	0.39	-0.13	0.02	0.93	0.10	0.19	0.66	-0.07	0.04	0.12	0.06	-0.41	-0.27
16q23	rs4581712	-0.01	0.38	-0.37	-0.07	-0.33	-0.35	0.02	0.19	0.59	-0.01	-0.03	0.23	0.87	0.31
17q24	rs9913711	0.88	0.04	-0.20	-0.30	-0.26	0.08	-0.21	-1.15	-0.33	0.38	0.02	0.21	0.01	-0.12
18q21.31	rs12968116	0.54	0.70	0.17	-0.35	-1.67	-1.27	-0.04	-0.89	0.17	0.11	0.04	0.24	1.34	1.48
18q21.32	rs4503880	0.01	-1.16	-1.13	-0.52	-0.21	-0.47	-0.04	-0.44	-0.81	-0.46	-0.27	-0.61	-1.01	0.74
19q13	rs516246	1.90	-0.94	0.20	0.21	9.45	7.32	-0.30	5.13	-0.40	-0.36	-0.48	-0.61	0.68	-0.59
22q11.21	rs1076540	-0.08	0.33	-0.37	-0.79	-0.45	-0.72	0.33	0.64	0.15	-0.29	-0.13	-0.17	0.66	0.05
22q11.23	rs2739330	-1.45	0.04	0.03	-0.53	-0.14	-0.63	0.79	1.12	0.32	-0.43	-0.49	-0.35	-0.24	-1.56
22q11.23	rs2073398	-0.38	-0.81	-0.11	-0.15	-1.36	-0.46	-1.24	-0.46	0.74	-0.18	-1.28	-0.40	-0.76	1.28
N at P<0.0012		**1**	**0**	**0**	**0**	**9**	**10**	**5**	**6**	**5**	**2**	**2**	**2**	**2**	**0**
P=		**0.05**	**0.95**	**0.95**	**0.95**	**$<10^{-15}$**	**$<10^{-15}$**	**1.9×10^{-9}**	**1.4×10^{-11}**	**1.9×10^{-9}**	**1.2×10^{-3}**	**1.2×10^{-3}**	**1.2×10^{-3}**	**1.2×10^{-3}**	**0.95**

Abbreviations / references:

Alcohol: Alcohol intake[143]
BMI: Body mass index[144]
BP: Blood pressure[145]
Chol: Cholesterol[78]
CRP: C-reactive protein[80]
Glucose[79]
Insulin[79]
HOMA-IR: Homeostasis model assessment of insulin resistance[79]
HOMA-B: Homeostasis model assessment of beta cell function[79]
T2D: Type-2 diabetes[82]
Triglycerides[78]

Supplementary Table 18. Associations with liver markers and proportion of population variance explained, amongst the 8,112 participants of the LIFELINES.[14] Effect: % (95%CI) change in phenotype per allele copy. Direction: concordant (+) or discordant (-) direction of effect compared with results from the GWA study. # indicates proxy SNP for the sentinel SNP in the GWA study.

Region	SNP	Genes	Effect (%)	P	Direction	r2
ALT						
4q22	rs6832102#	*HSD17B13, MAPK10*	1.8 (0.2 to 3.5)	2.8E-02	+	0.000
8q24	rs2954021	*TRIB1*	1.4 (-0.1 to 2.9)	7.1E-02	+	0.000
10q24	rs4919416#	*CPN1*	1.4 (-0.6 to 3.4)	1.7E-01	+	0.000
22q13	rs738409	*PNPLA3, SAMM50*	5.0 (2.2 to 7.8)	3.1E-04	+	0.002
ALP						
1p36.12	rs1976403	*ALPL, NBPF3*	3.8 (2.9 to 4.6)	1.5E-18	+	0.008
2q24	rs16856332	*ABCB11*	0.9 (-1.4 to 3.2)	4.4E-01	+	0.000
6p22	rs1126617#	*ALDH5A1, GPLD1*	3.4 (2.5 to 4.3)	1.8E-14	+	0.007
8p23	rs6984305	*PPP1R3B*	1.9 (0.3 to 3.5)	1.6E-02	+	0.001
8q24	rs2954021	*TRIB1*	0.7 (-0.2 to 1.5)	1.3E-01	+	0.000
9q21	rs10819937	*ALDOB, C9orf125*	1.3 (0.1 to 2.5)	3.0E-02	+	0.001
9q34	rs579459	*ABO*	7.8 (6.7 to 8.9)	2.7E-48	+	0.024
10q21	rs7923609	*JMJD1C, NRBF2*	2.6 (1.8 to 3.5)	1.6E-09	+	0.004
11q12	rs174601	*C11orf10, FADS1, FADS2*	2.1 (0.7 to 3.6)	4.0E-03	+	0.001
11q.24	rs2236653	*ST3GAL4*	1.3 (0.1 to 2.4)	3.2E-02	+	0.001
16q22	rs7186908	*HPR, PMFBP1*	0.8 (-0.3 to 1.8)	1.4E-01	+	0.000
17p13	rs314253	*ASGR1, DLG4*	2.3 (0.9 to 3.6)	7.4E-04	+	0.001
19q13	rs601338#	*FUT2*	2.7 (1.8 to 3.7)	1.4E-08	+	0.004
20p11	rs7267979	*ABHD12, GINS1, PYGB*	1.1 (0.3 to 1.9)	1.0E-02	+	0.001
GGT						
1p36.13	rs1497406	*C1orf89, EPHA2*	3.8 (2.2 to 5.5)	3.7E-06	+	0.003
1p22	rs12145922	*CCBL2, PKN2*	1.5 (-0.2 to 3.2)	8.1E-02	+	0.000
1p13	rs1043096#	*CEPT1, DENND2D*	2.5 (-0.2 to 5.3)	6.5E-02	+	0.000
1q21	rs10908458	*DPM3, EFNA1, PKLR*	1.8 (0.0 to 3.7)	5.1E-02	+	0.001
2p23	rs1260326	*C2orf16, GCKR*	1.9 (0.3 to 3.6)	2.3E-02	+	0.001
2q12	rs13030978	*MYO1B, STAT4*	4.3 (2.4 to 6.3)	6.1E-06	+	0.003
2q37	rs4973550#	*EFHD1, LOC100129166*	1.5 (-1.0 to 3.9)	2.4E-01	+	0.000
3q26	rs10513686	*SLC2A2*	4.1 (1.4 to 6.9)	2.6E-03	+	0.001
4q31	rs4547811	*ZNF827*	4.3 (2.2 to 6.4)	4.2E-05	+	0.002
5p15	rs6888304	*CDH6*	0.5 (-1.6 to 2.7)	6.5E-01	+	0.000
5q11	rs4074793	*ITGA1*	5.8 (2.7 to 9.0)	2.2E-04	+	0.002
6p12	rs9296736	*C6orf142*	0.4 (-1.5 to 2.5)	6.6E-01	+	0.000
7q11	rs13233571#	*MLXIPL*	3.9 (1.5 to 6.3)	1.3E-03	+	0.001
10q23	rs754466	*DLG5*	2.0 (-0.1 to 4.0)	6.1E-02	+	0.000
12q24	rs7310409	*HNF1A, C12orf27*	5.5 (3.8 to 7.2)	6.0E-11	+	0.004
14q32	rs944002	*C14orf73*	7.5 (3.7 to 11.4)	8.5E-05	+	0.001
15q21	rs339969	*RORA*	2.2 (0.5 to 3.8)	9.2E-03	+	0.001
15q23	rs8038465	*CD276*	3.1 (1.5 to 4.7)	1.6E-04	+	0.001
16q23	rs4581712	*DYNLRB2*	0.9 (-1.0 to 2.7)	3.6E-01	+	0.000
17q24	rs9913711	*FLJ37644, SOX9*	-0.1 (-2.0 to 1.9)	9.4E-01	-	0.000
18q21.31	rs12968116	*ATP8B1*	3.6 (0.8 to 6.5)	1.2E-02	+	0.001
18q21.32	rs4503880	*NEDD4L*	3.1 (-0.8 to 7.2)	1.2E-01	+	0.000
19q13	rs601338#	*FUT2*	1.1 (-0.7 to 2.9)	2.4E-01	+	0.000
22q11.21	rs1076540	*MICAL3*	2.6 (0.6 to 4.6)	1.1E-02	+	0.001
22q11.23	rs2739330	*DDT, DDTL, GSTT1, GSTT2B, MIF*	0.4 (-1.8 to 2.6)	7.4E-01	+	0.000
22q11.23	rs2330795#	*GGT1, GGTLC2*	8.1 (6.2 to 10.0)	8.8E-18	+	0.007

Supplementary Table 19. Association of SNP scores with liver markers amongst the 8,112 participants of the LIFELINES study.[14] Results provided as: i. proportion of population variation explained (r^2); ii. mean (SD) level of liver marker amongst participants in each quartile of SNP score, and iii. odds ratio for raised liver marker (>upper limit of normal) associated with SNP score in quartile 2-4, compared to quartile 1 (reference) SNP score.

			Mean (SD) levels of liver marker by quartile of SNP score				**Odds ratio (95%CI) for raised liver marker by quartile of SNP score**		
Phenotype	**SNP score#**	**r^2**	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Quartile 2**	**Quartile 3**	**Quartile 4**
ALT	ALT SNPs	0.001	23.1 (14.7)	23.5 (19.7)	24.0 (14.3)	24.7 (17.8)	0.89 (0.69 to 1.16)	1.10 (0.86 to 1.41)	1.42 (1.12 to 1.79)
ALT	All SNPs	0.001	23.4 (18.1)	23.5 (17.6)	24.1 (15.3)	24.3 (15.9)	0.98 (0.76 to 1.26)	1.24 (0.97 to 1.58)	1.31 (1.03 to 1.66)
ALP	ALP SNPs	0.035	59.1 (18.3)	61.8 (17.2)	63.5 (17.9)	66.9 (19.1)	0.90 (0.37 to 2.23)	1.92 (0.89 to 4.14)	2.43 (1.16 to 5.09)
ALP	All SNPs	0.012	60.4 (16.9)	62.4 (17.4)	63.4 (19.1)	65.1 (19.5)	1.56 (0.68 to 3.62)	1.89 (0.84 to 4.26)	2.47 (1.13 to 5.38)
GGT	GGT SNPs	0.019	23.6 (20.8)	25.6 (22.9)	26.6 (23.0)	29.5 (29.9)	1.36 (1.04 to 1.78)	1.39 (1.07 to 1.82)	1.84 (1.43 to 2.37)
GGT	All SNPs	0.011	24.4 (21.7)	25.0 (19.1)	26.8 (28.5)	29.2 (27.2)	1.00 (0.77 to 1.31)	1.18 (0.92 to 1.53)	1.53 (1.20 to 1.96)

[#] SNP scores determined as the sum of effect alleles for the SNPs associated with respective phenotype [ALT, ALP, GGT] at $P<1x10^{-8}$ in the GWA study, or the sum of effect allele for SNPs at all 42 loci identified [All SNPs]. Mean values of SNP scores (quartile 1 to quartile 4 respectively) were i. ALP SNPs: 9.9, 11.9, 13.2, 15,2; ii. ALT SNPs: 2.6, 3.5, 4.2, 5.2; iii. GGT SNPs: 20.8, 23.2, 24.9, 27.3; and iv. All SNPs: 35.8, 39.3, 41.7, 45.2.

Supplementary Table 20. Associations with hepatic steatosis assessed by CT in 9,610 people (GOLD study).[13] Lower attenuation indicates greater steatosis. Effect is change in liver attenuation per copy of allele associated with raised liver markers in the GWA study (Table 1).

Region	SNP	Trait	Effect	SE	P
ALT					
4q22	rs6834314	*HSD17B13, MAPK10*	-0.001	0.019	0.95
8q24	rs2954021	*TRIB1*	-0.044	0.017	0.01
10q24	rs10883437	*CPN1*	-0.002	0.018	0.92
22q13	rs738409	*PNPLA3, SAMM50*	-0.261	0.021	4.3E-34
ALP					
1p36.12	rs1976403	*ALPL, NBPF3*	0.014	0.019	0.47
2q24	rs16856332	*ABCB11*	-0.055	0.051	0.28
6p22	rs1883415	*ALDH5A1, GPLD1*	-0.008	0.018	0.68
8p23	rs6984305	*PPP1R3B*	0.232	0.031	7.9E-14
8q24	rs2954021	*TRIB1*	-0.044	0.017	0.01
9q21	rs10819937	*ALDOB, C9orf125*	0.009	0.026	0.73
9q34	rs579459	*ABO*	0.009	0.023	0.68
10q21	rs7923609	*JMJD1C, NRBF2*	-0.018	0.017	0.30
11q12	rs174601	*C11orf10, FADS1, FADS2*	-0.006	0.019	0.75
11q.24	rs2236653	*ST3GAL4*	-0.029	0.018	0.11
16q22	rs7186908	*HPR, PMFBP1*	0.013	0.021	0.56
17p13	rs314253	*ASGR1, DLG4*	0.015	0.019	0.41
19q13	rs281377	*FUT2*	0.028	0.021	0.19
20p11	rs7267979	*ABHD12,GINS1, PYGB*	0.005	0.018	0.77
GGT					
1p36.13	rs1497406	*C1orf89, EPHA2*	-0.001	0.018	0.95
1p22	rs12145922	*CCBL2, PKN2*	0.026	0.018	0.14
1p13	rs1335645	*CEPT1, DENND2D*	-0.044	0.027	0.11
1q21	rs10908458	*DPM3, EFNA1, PKLR*	-0.007	0.018	0.71
2p23	rs1260326	*C2orf16, GCKR*	0.064	0.018	3.6E-04
2q12	rs13030978	*MYO1B, STAT4*	0.030	0.019	0.12
2q37	rs2140773	*EFHD1, LOC100129166*	0.003	0.018	0.86
3q26	rs10513686	*SLC2A2*	0.007	0.028	0.81
4q31	rs4547811	*ZNF827*	0.029	0.024	0.23
5p15	rs6888304	*CDH6*	0.004	0.021	0.85
5q11	rs4074793	*ITGA1*	-0.055	0.036	0.12
6p12	rs9296736	*C6orf142*	0.001	0.019	0.94
7q11	rs17145750	*MLXIPL*	0.012	0.026	0.63
10q23	rs754466	*DLG5*	0.034	0.022	0.12
12q24	rs7310409	*HNF1A, C12orf27*	0.049	0.018	6.3E-03
14q32	rs944002	*C14orf73*			
15q21	rs339969	*RORA*	-0.015	0.019	0.43
15q23	rs8038465	*CD276*	0.008	0.018	0.66
16q23	rs4581712	*DYNLRB2*	-0.009	0.020	0.63
17q24	rs9913711	*FLJ37644, SOX9*	0.037	0.019	0.05
18q21.31	rs12968116	*ATP8B1*	-0.023	0.024	0.35
18q21.32	rs4503880	*NEDD4L*	-0.002	0.022	0.92
19q13	rs516246	*FUT2*	-0.021	0.020	0.30
22q11.21	rs1076540	*MICAL3*	0.025	0.021	0.23
22q11.23	rs2739330	*DDT, DDTL, GSTT1, GSTT2B, MIF*	-0.005	0.019	0.78

22q11.23	rs2073398	*GGT1, GGTLC2*	0.001	0.022	0.97

Supplementary Figure 1. Regional plots for genetic loci associated with ALT in the genome-wide association study.

Figure 1.1 Locus 4q22

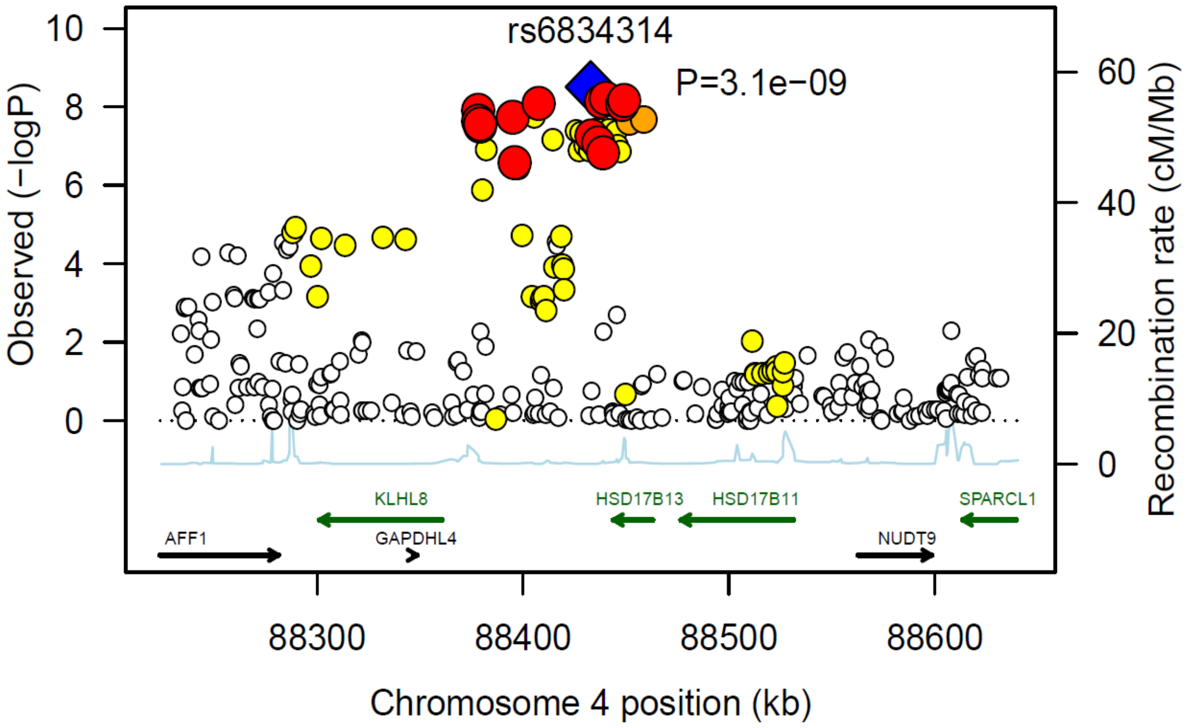


Figure 1.2 Locus 8q24

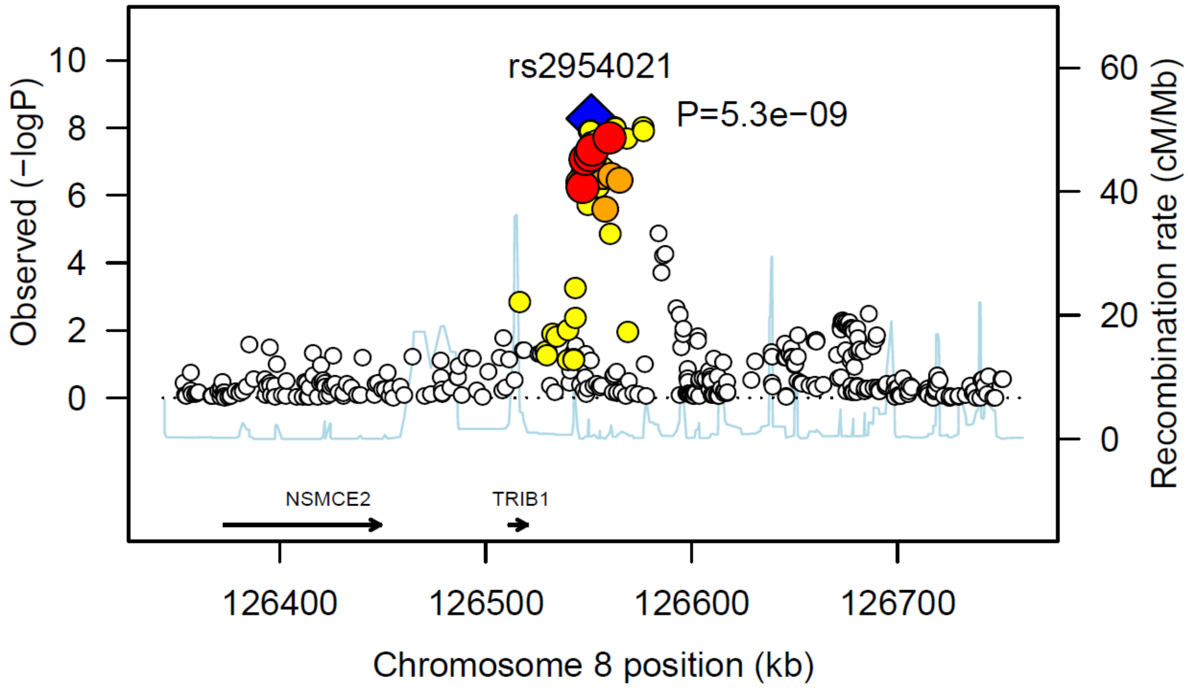


Figure 1.3 Locus 10q24

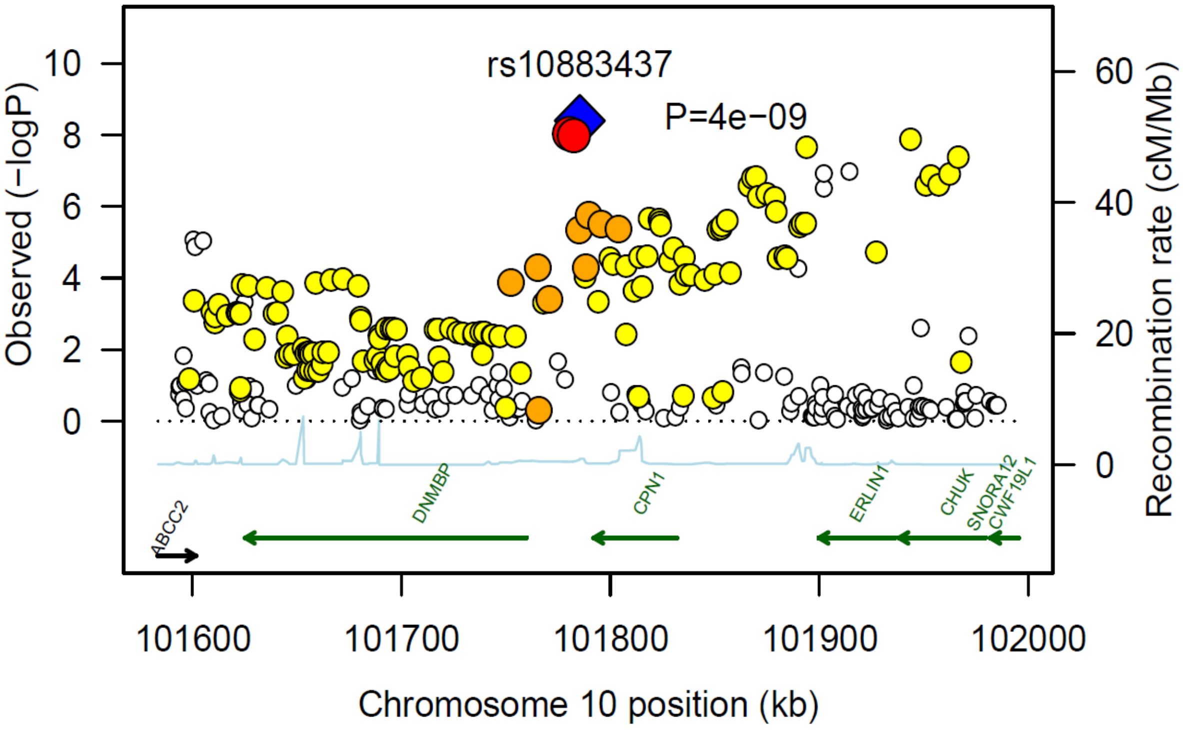
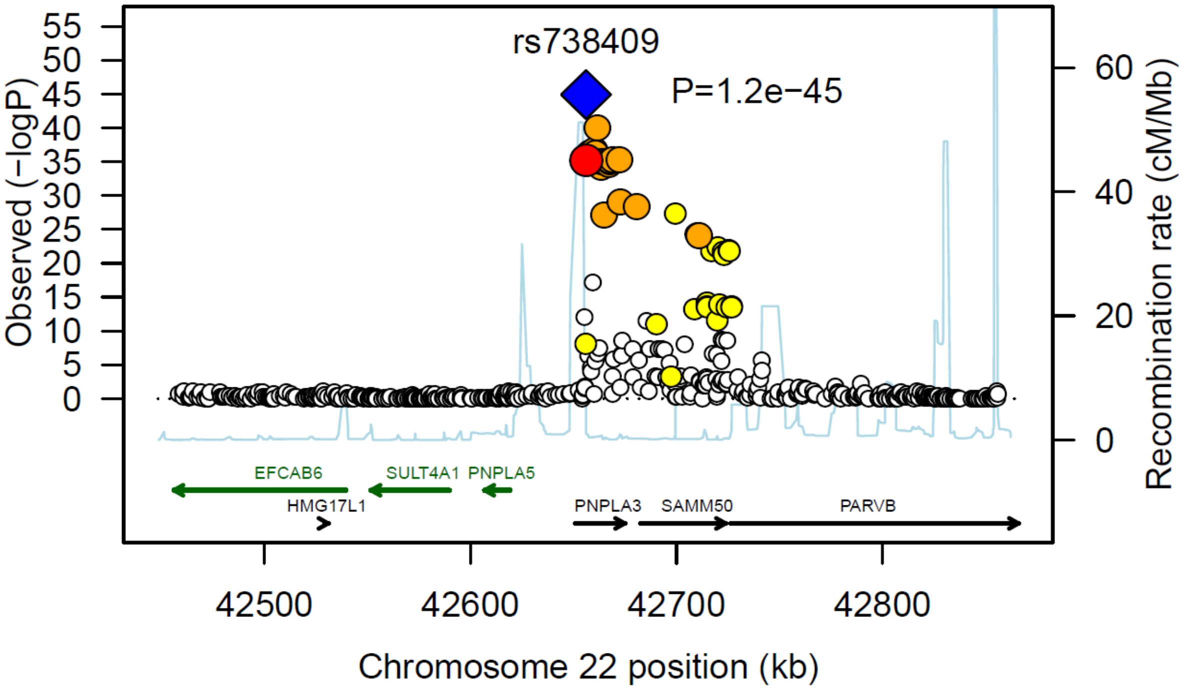


Figure 1.4 Locus 22q13



Supplementary Figure 2. Regional plots for genetic loci associated with ALP in the genome-wide association study.

Figure 2.1 Locus 1p36.12

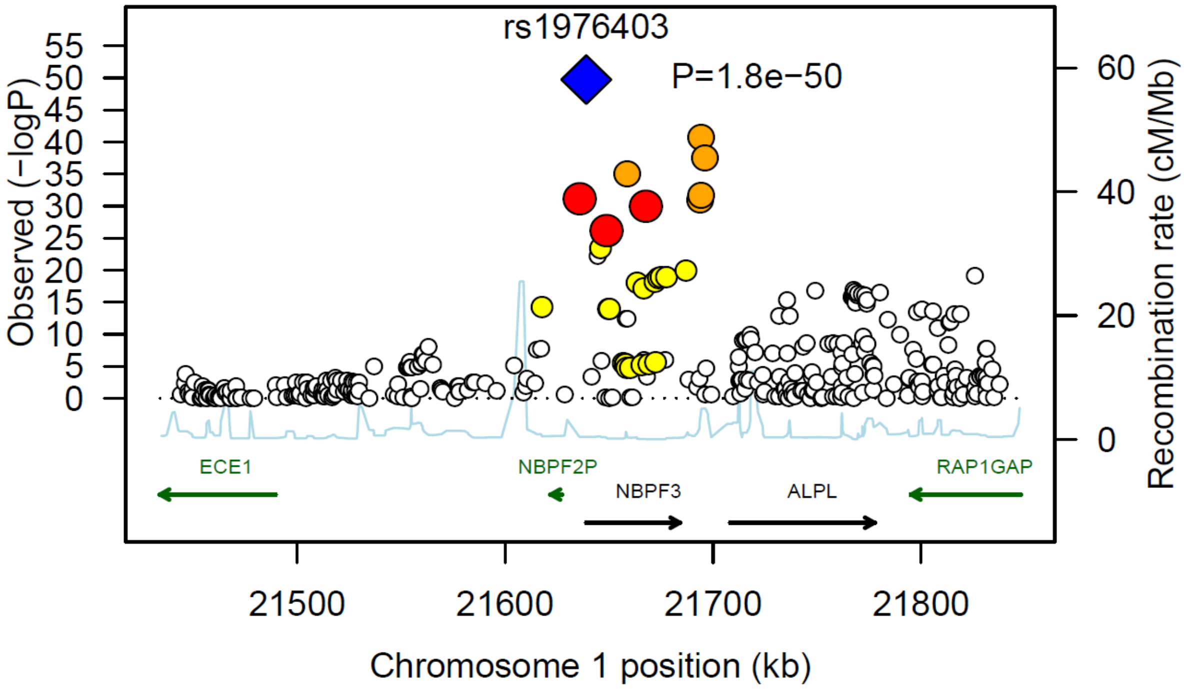


Figure 2.2 Locus 2q24

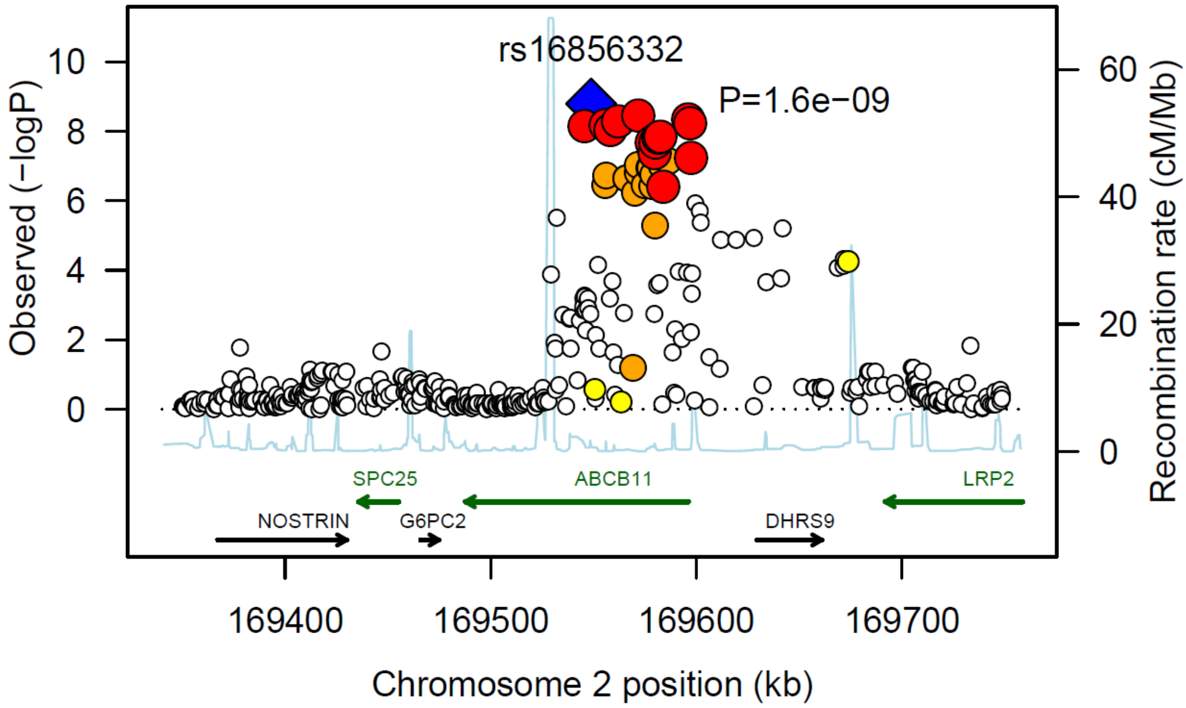


Figure 2.3 Locus 6p22

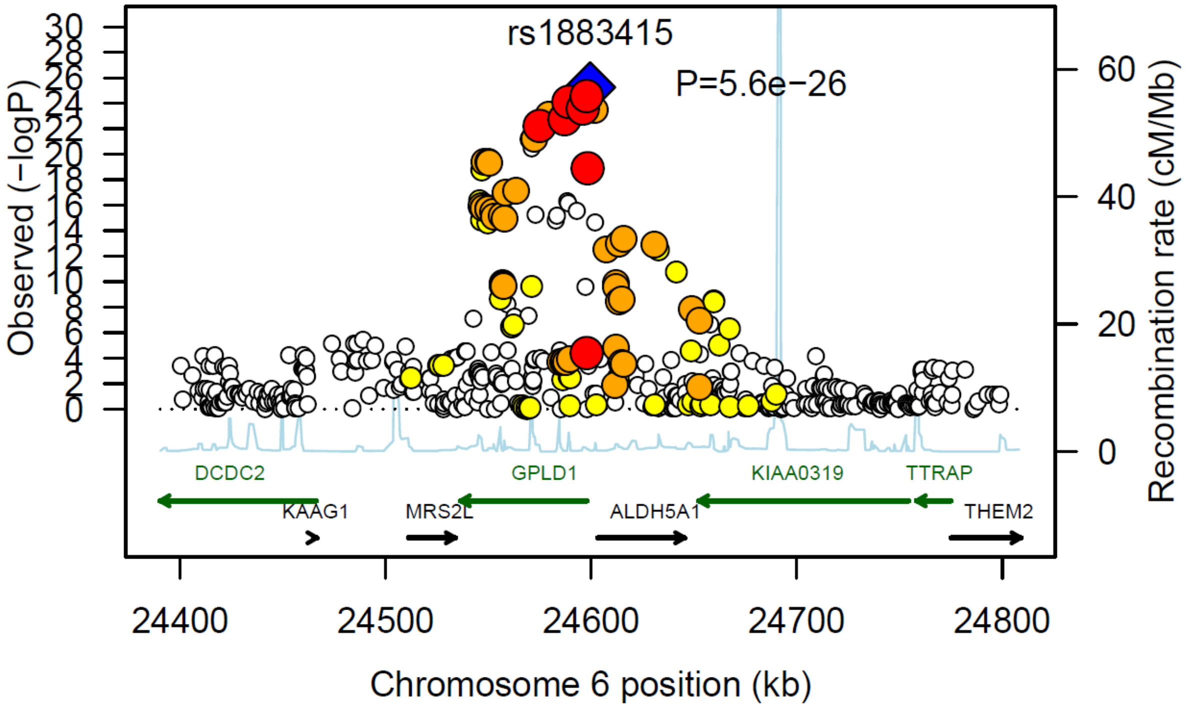


Figure 2.4 Locus 8p23

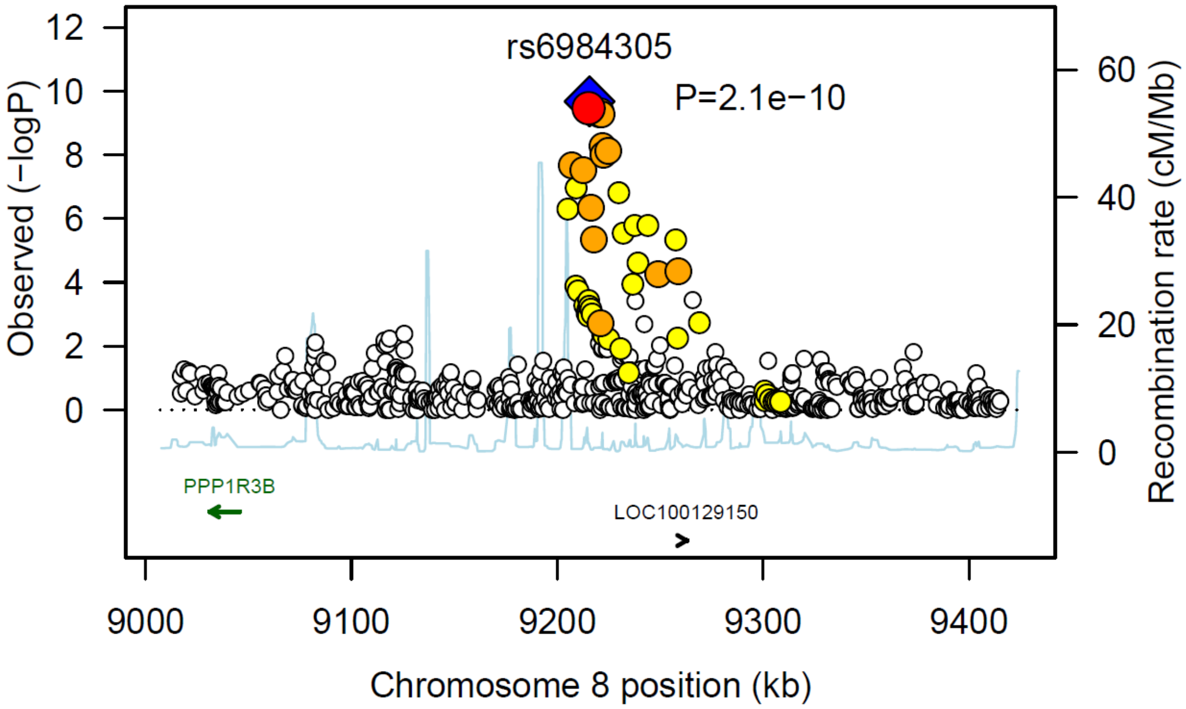


Figure 2.5 Locus 8q24

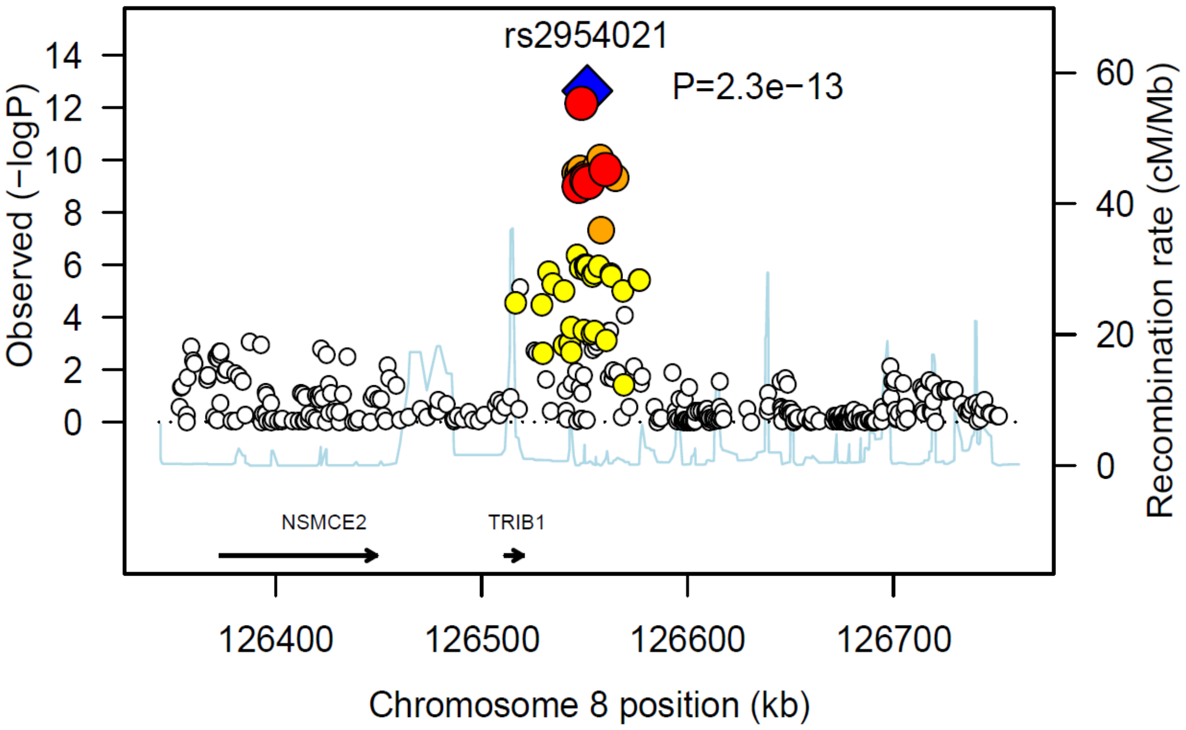


Figure 2.6 Locus 9q21

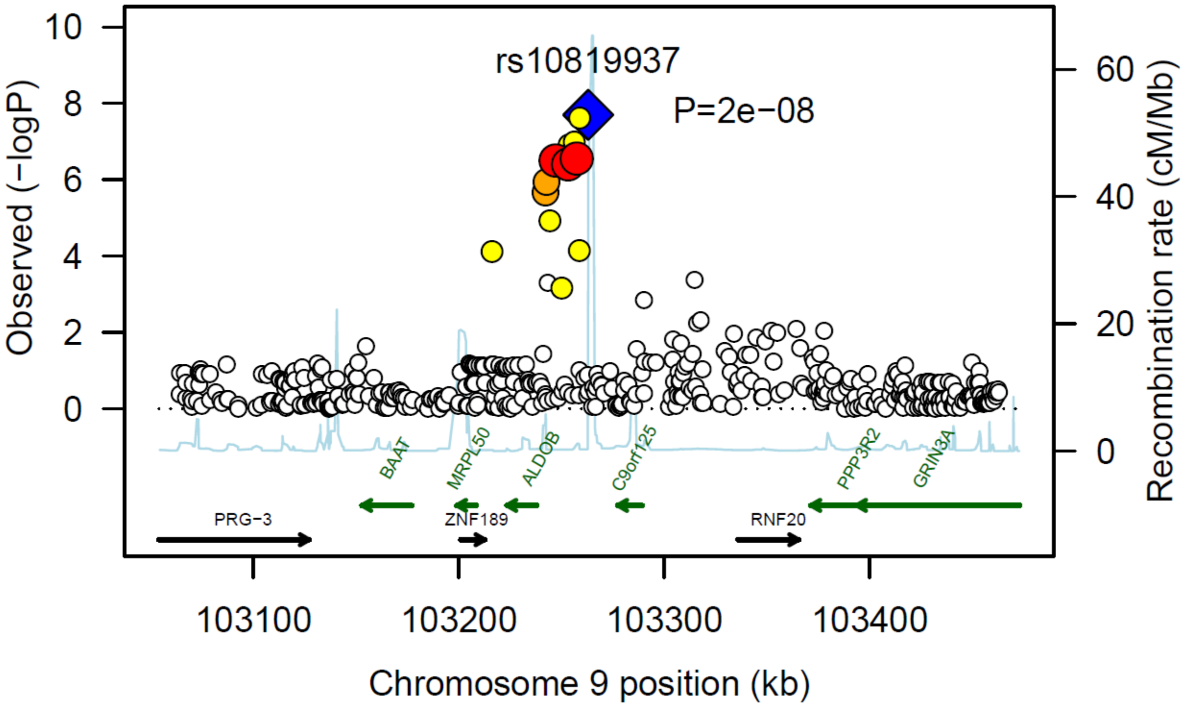


Figure 2.7 Locus 9q34

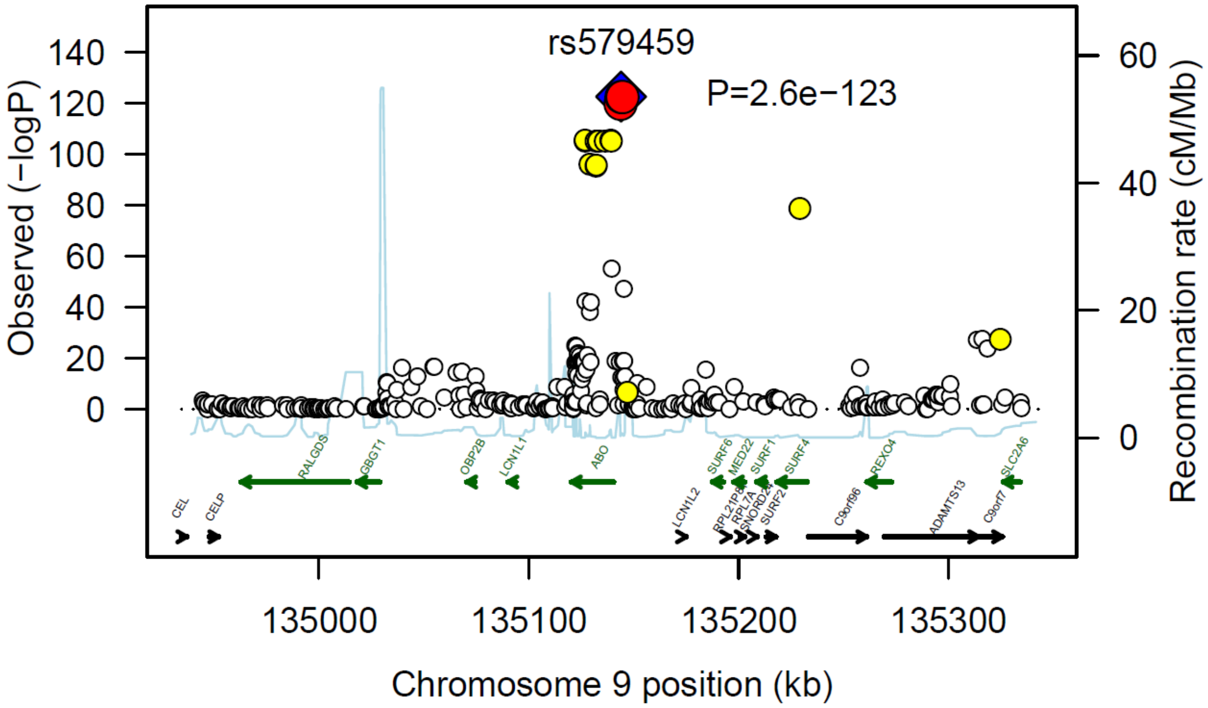


Figure 2.8 Locus 10q21

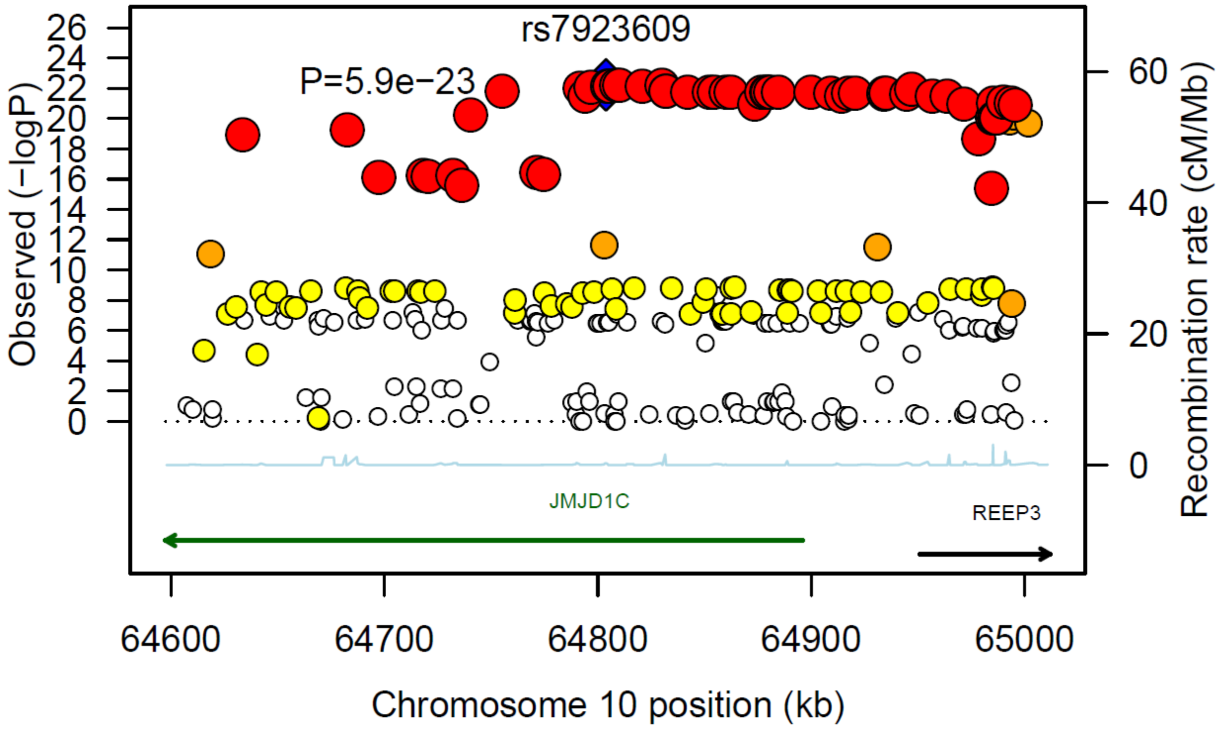


Figure 2.9 Locus 11q12

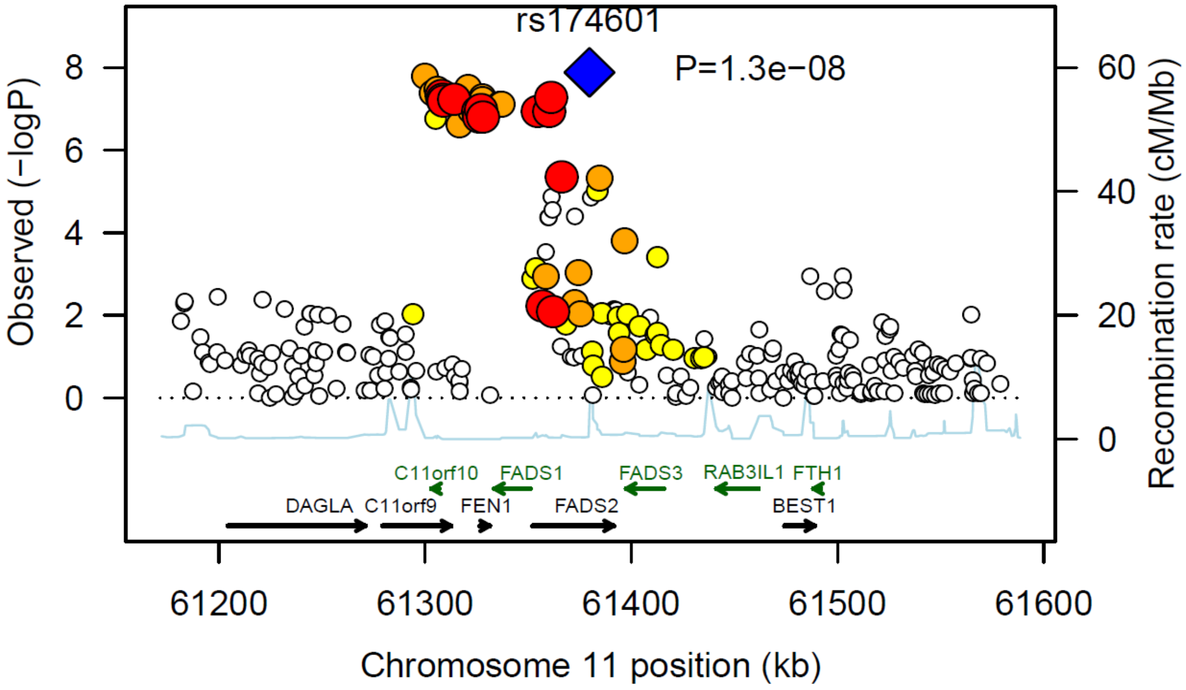


Figure 2.10 Locus 11q24

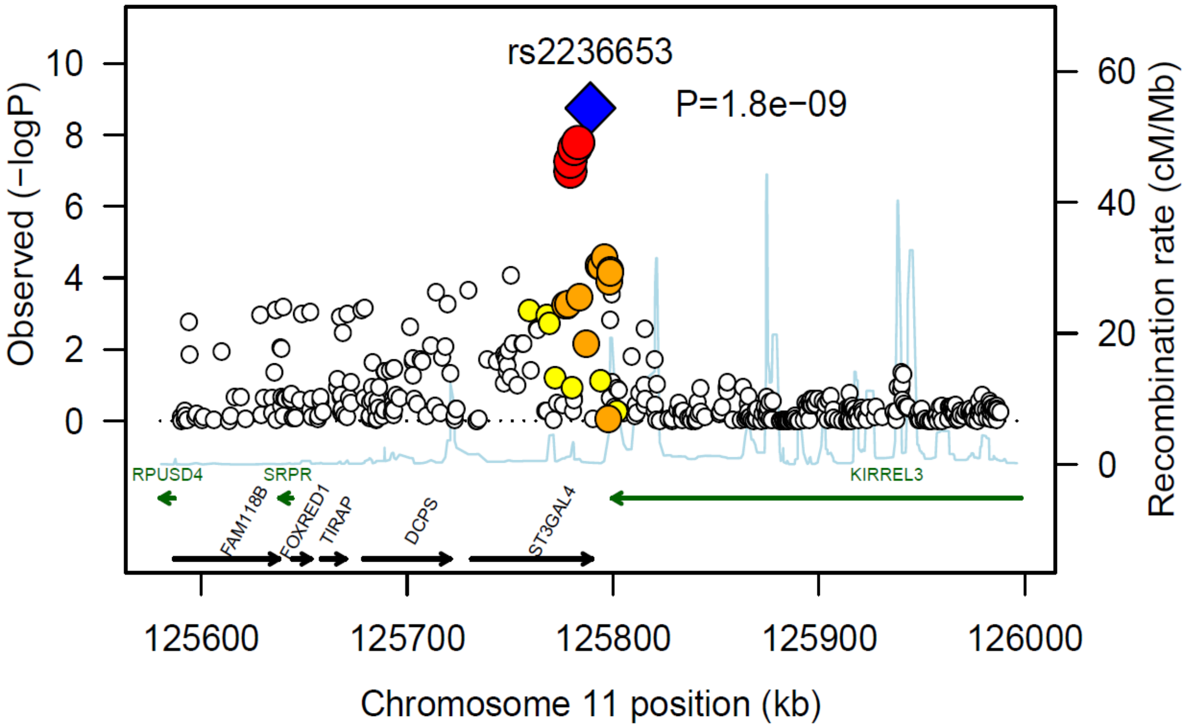


Figure 2.11 Locus 16q22

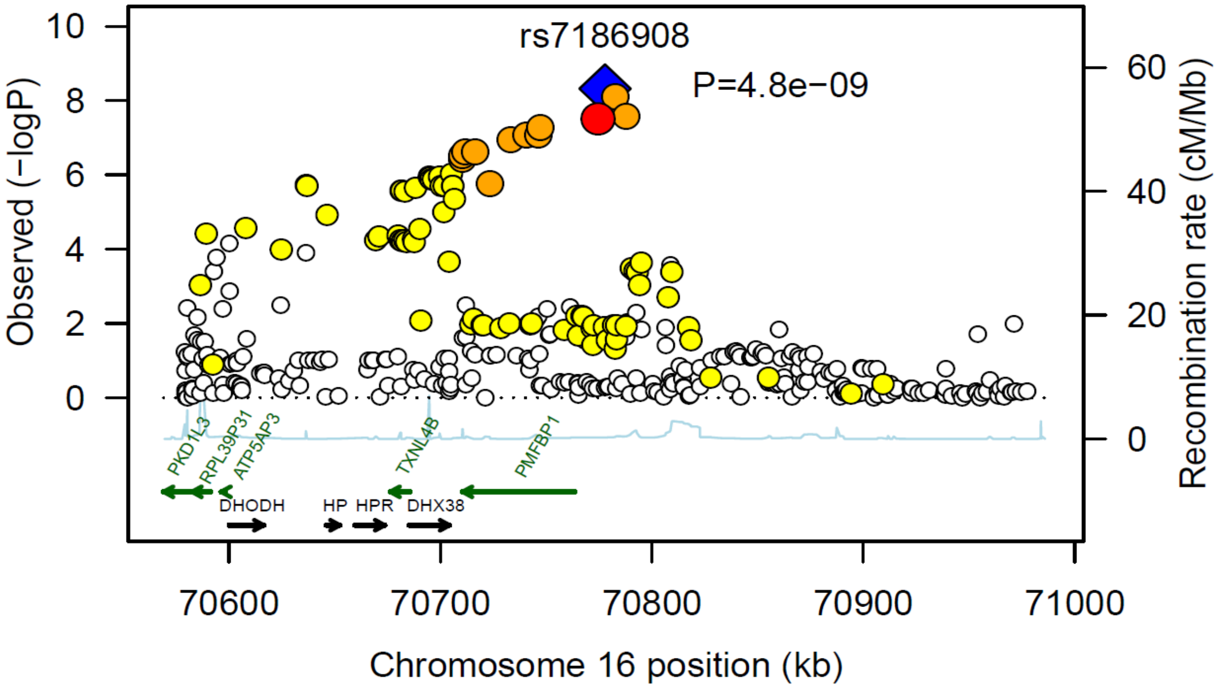


Figure 2.12 Locus 17p13

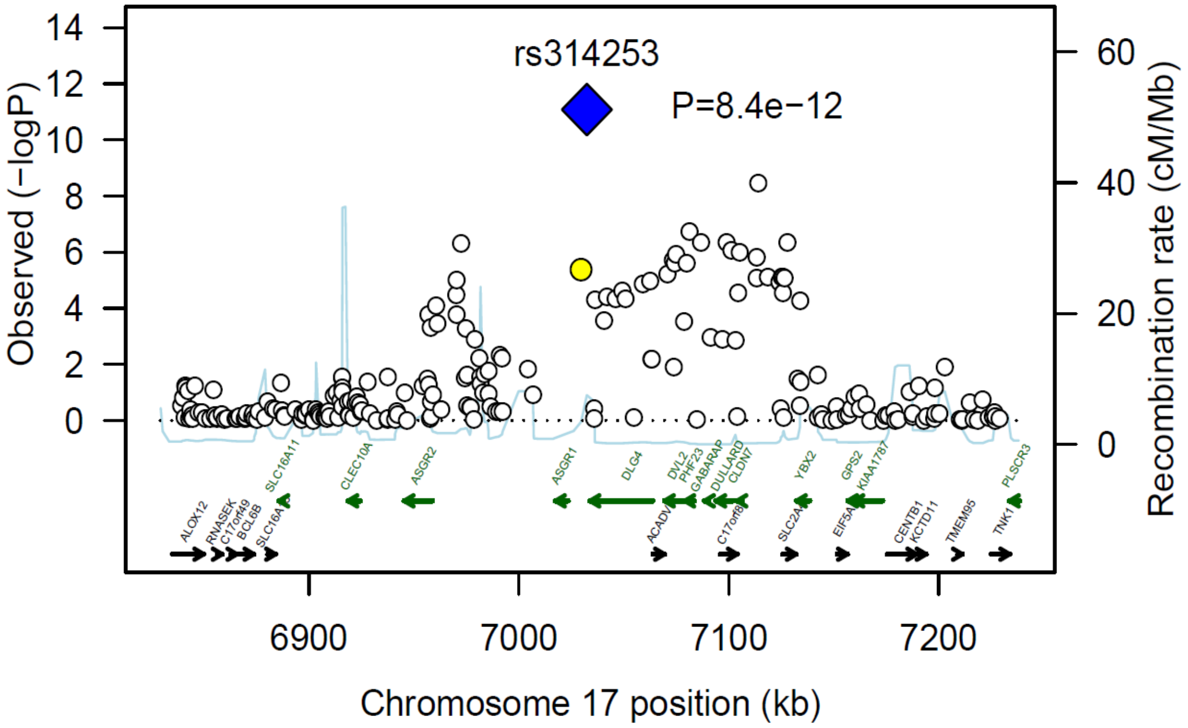


Figure 2.13 Locus 19q13

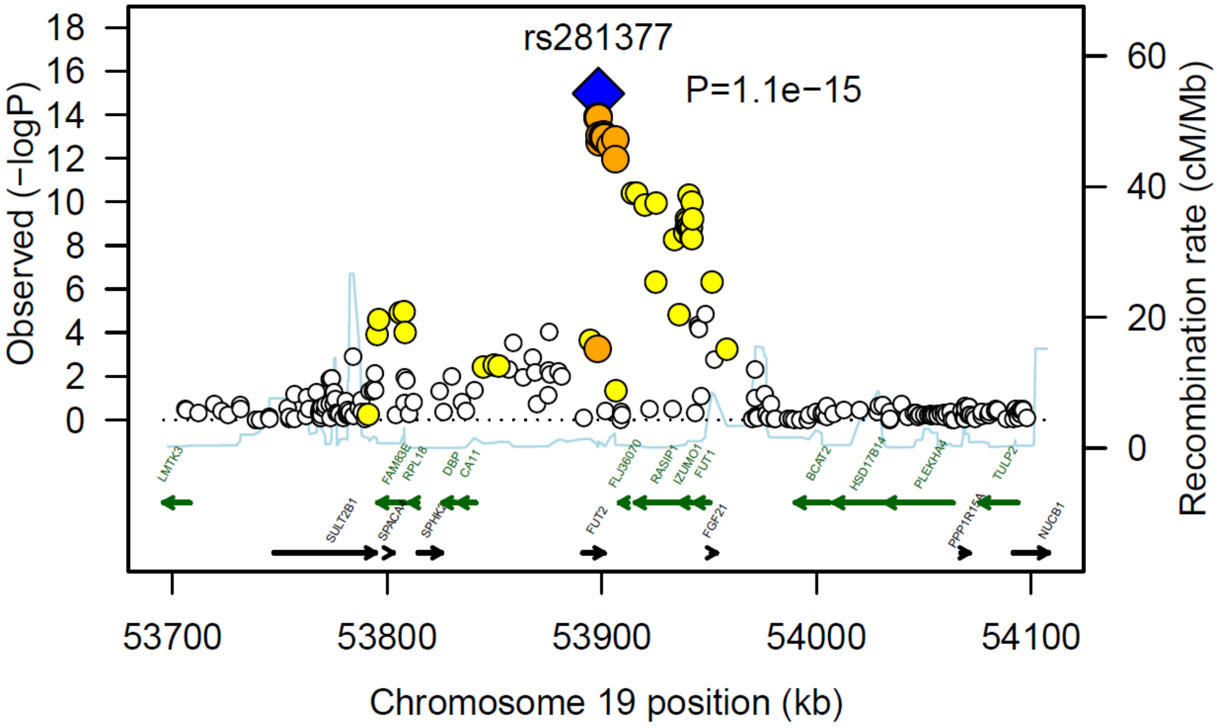
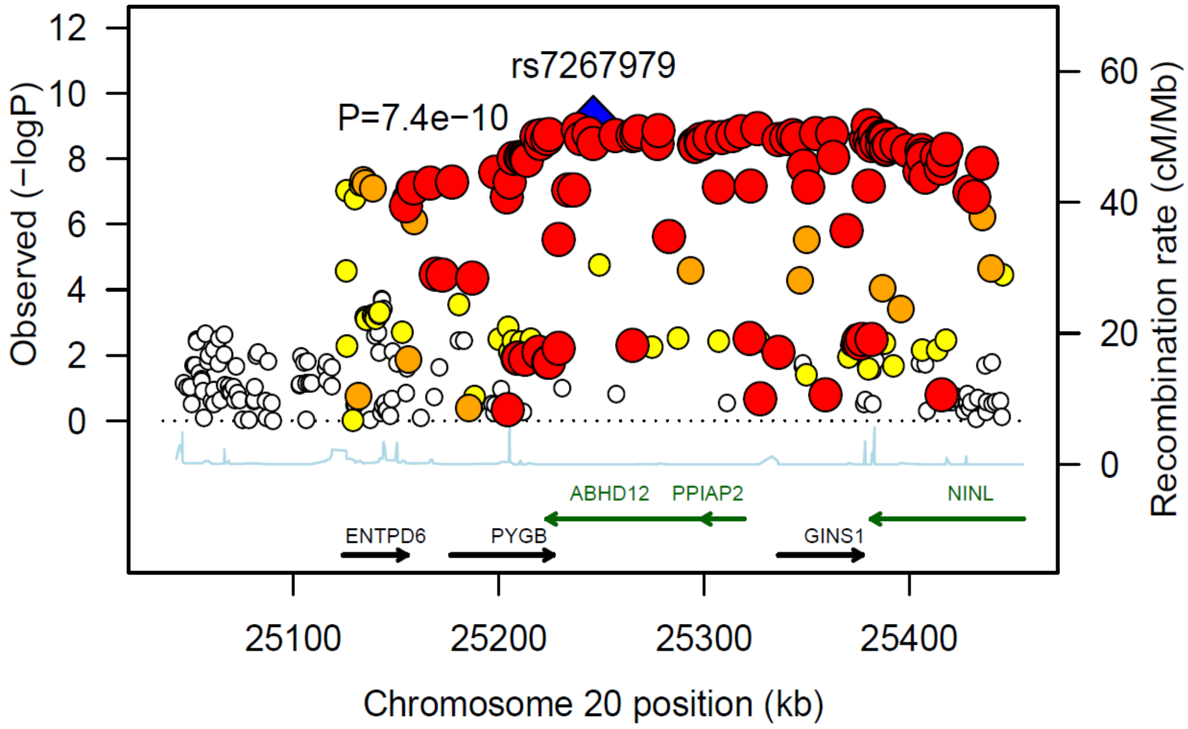


Figure 2.14 Locus 20p11



Supplementary Figure 3. Regional plots for genetic loci associated with GGT in the genome-wide association study.

Figure 3.1 Locus 1p36.13

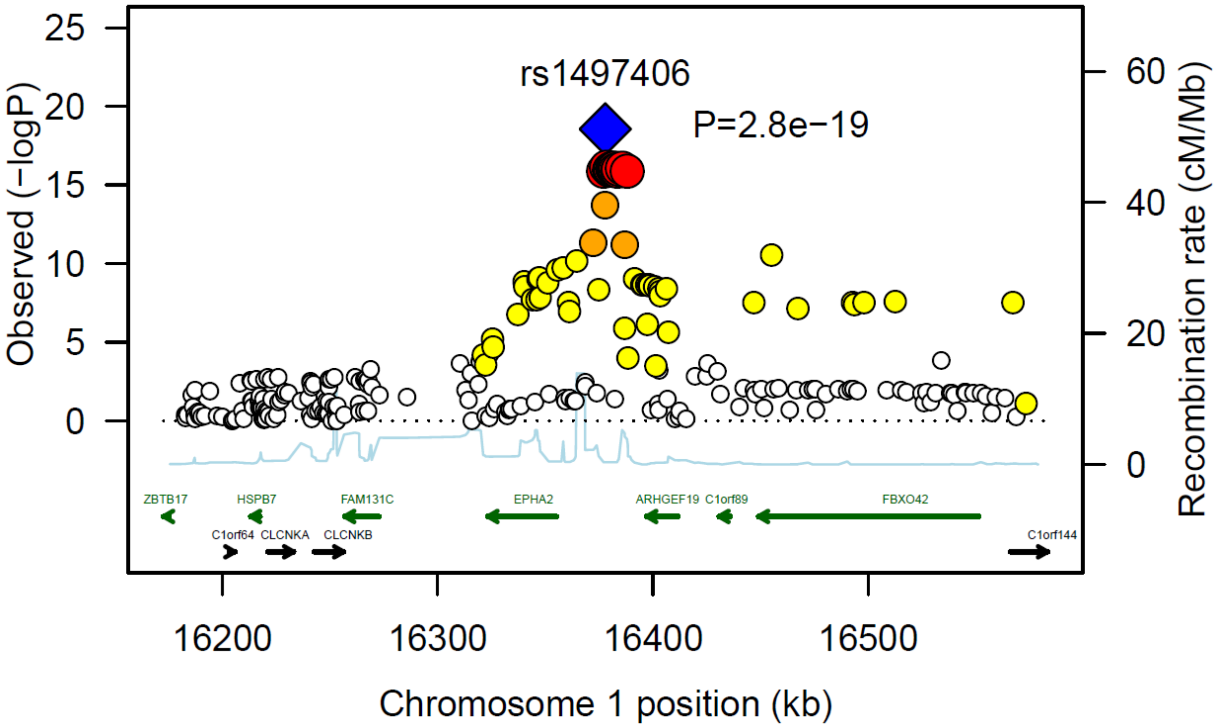


Figure 3.2 Locus 1p22

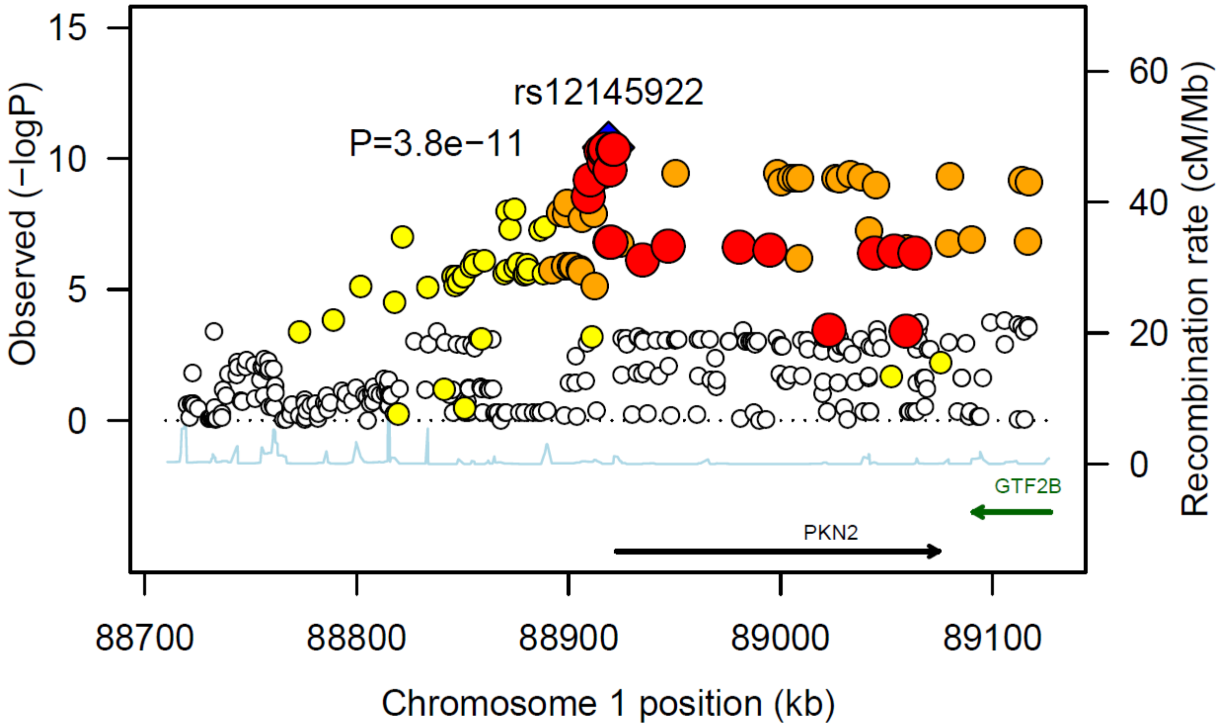


Figure 3.3 Locus 1p13

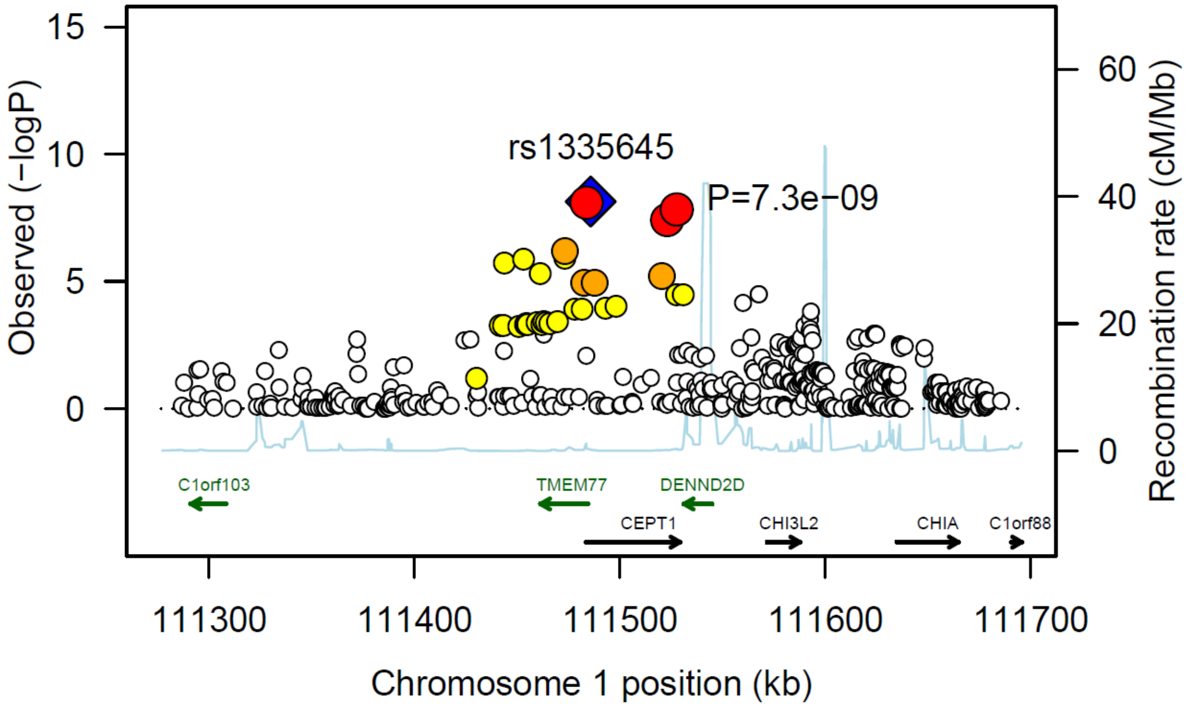


Figure 3.4 Locus 1q21

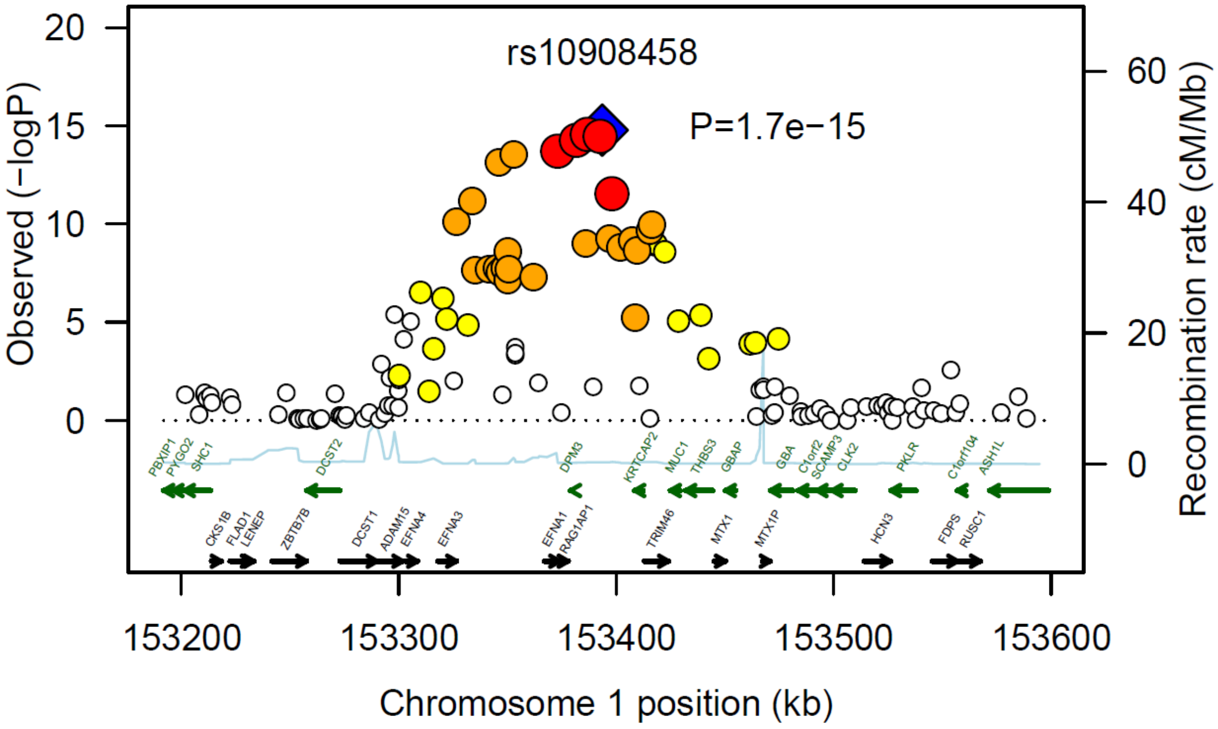


Figure 3.5 Locus 2p23

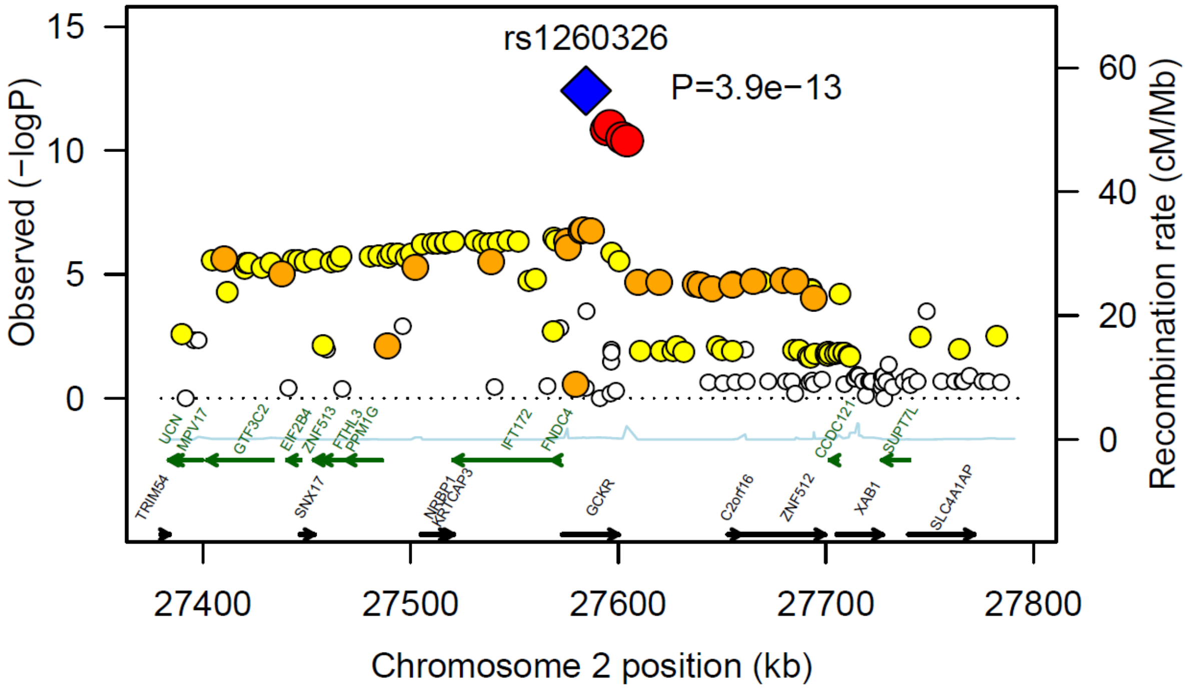


Figure 3.6 Locus 2q12

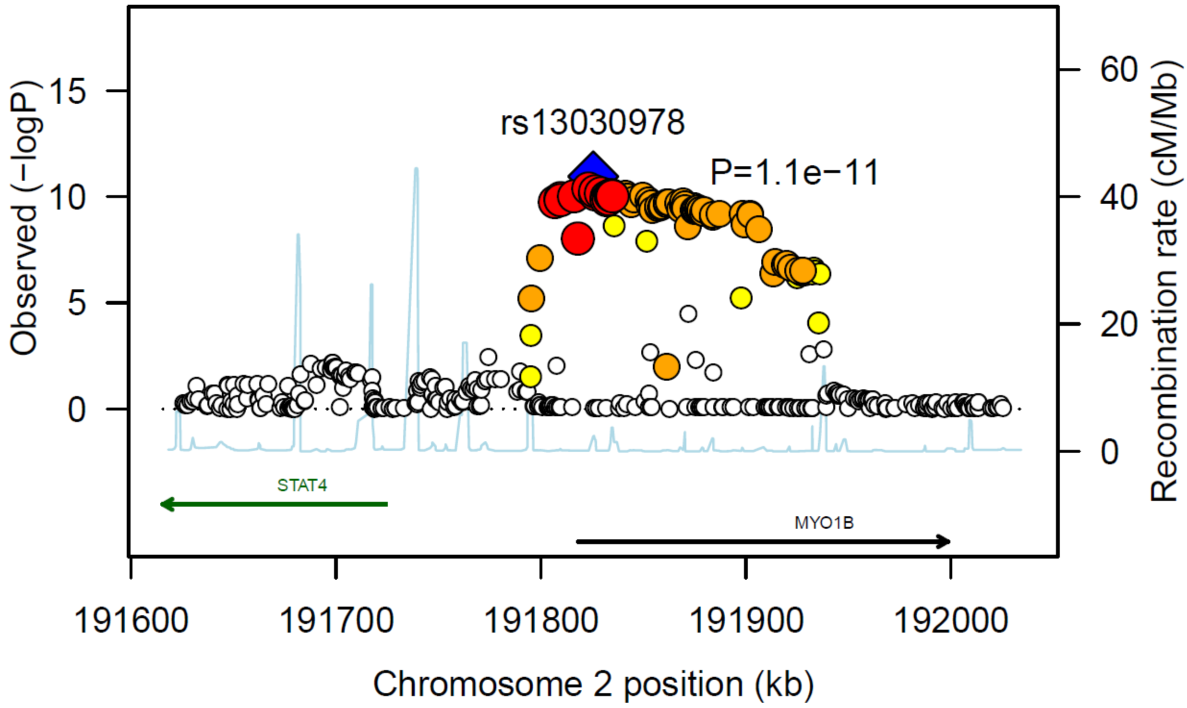


Figure 3.7 Locus 2q37

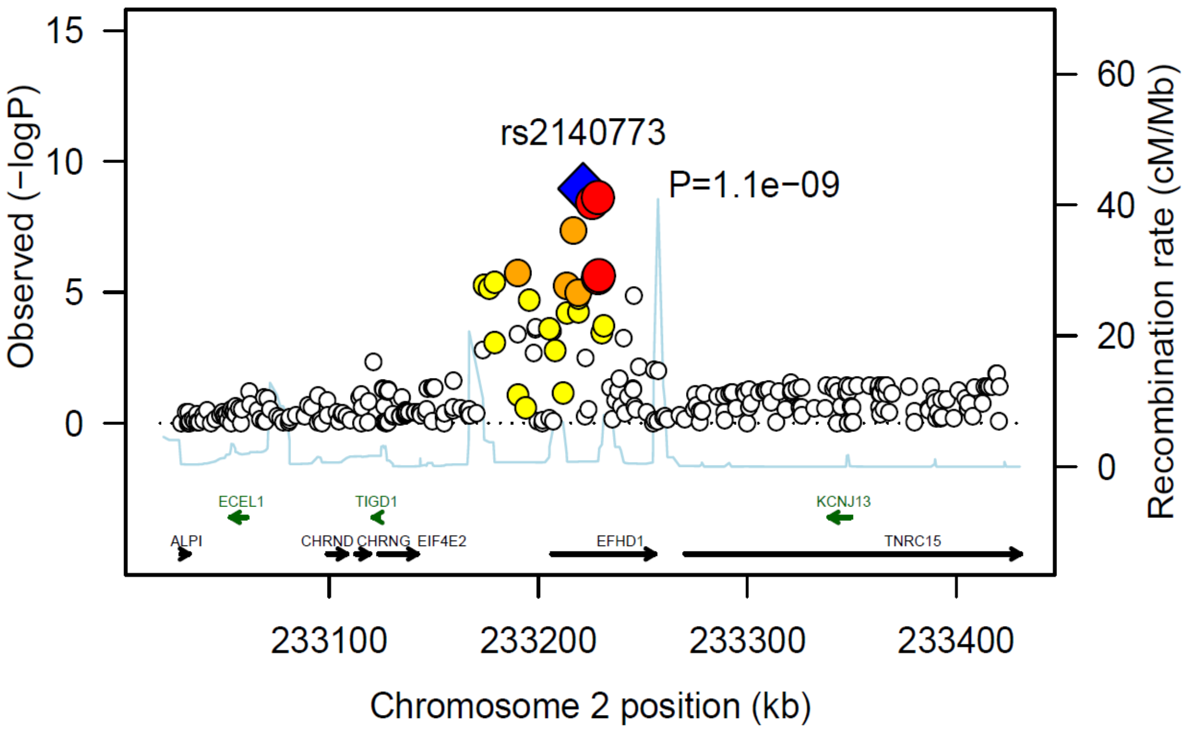


Figure 3.8 Locus 3q26

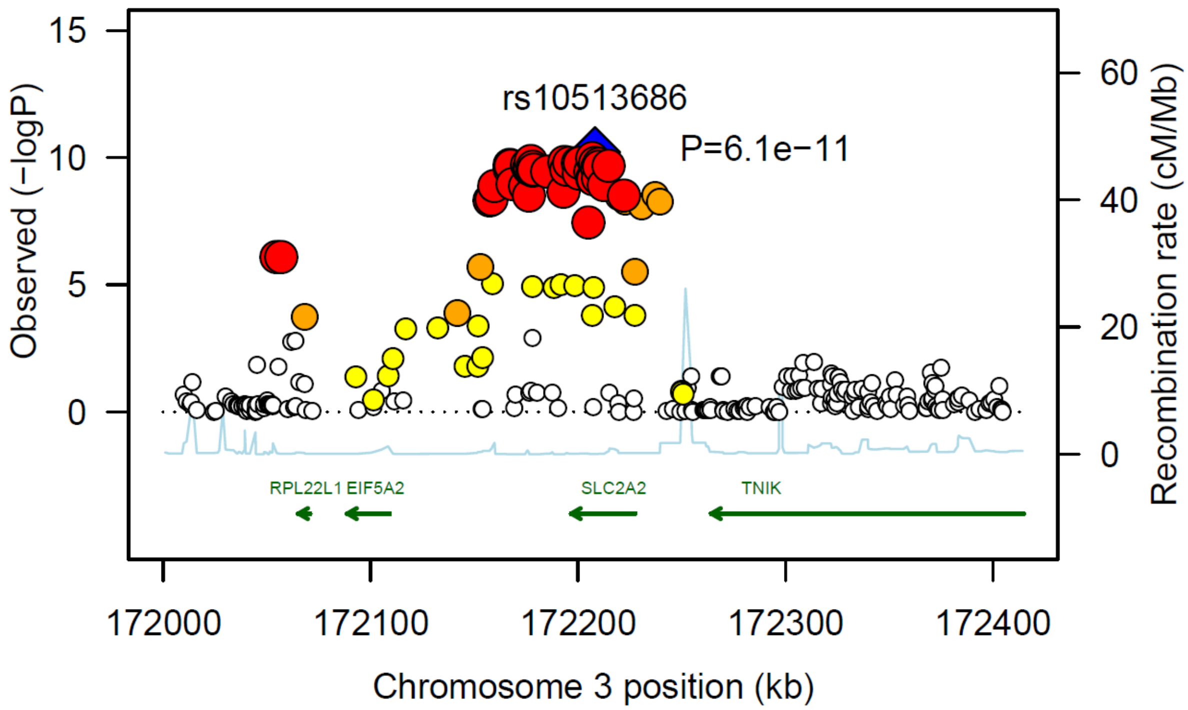


Figure 3.9 Locus 4q31

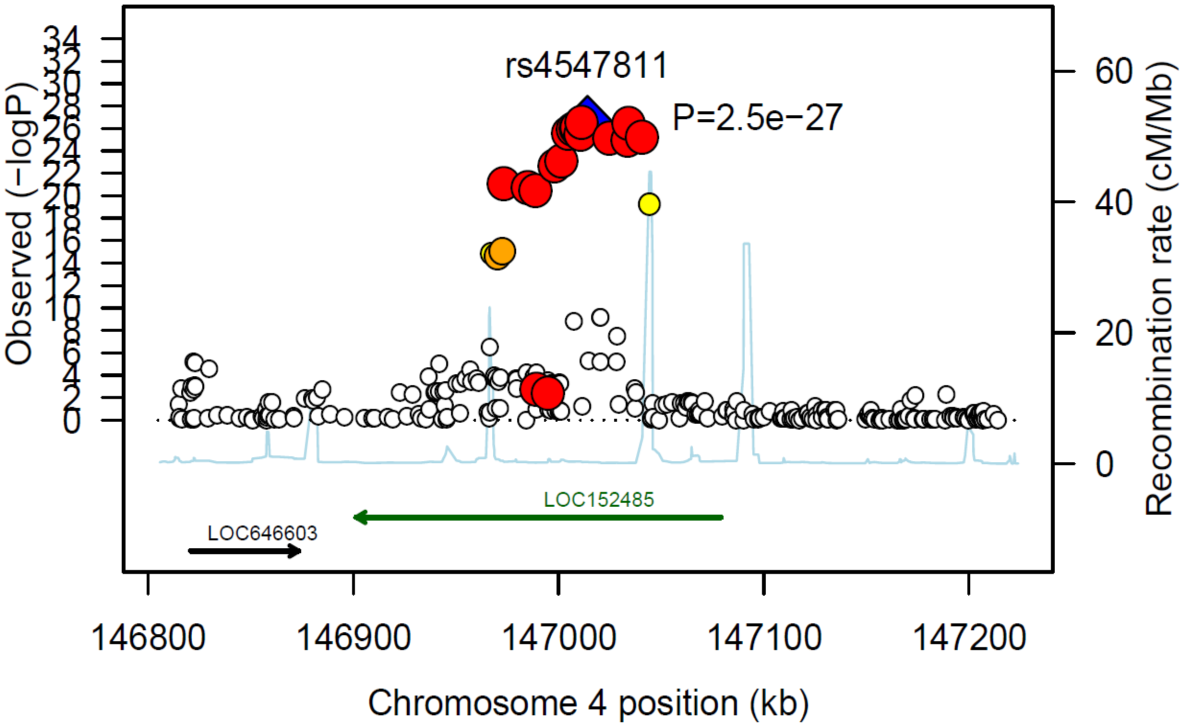


Figure 3.10 Locus 5p15

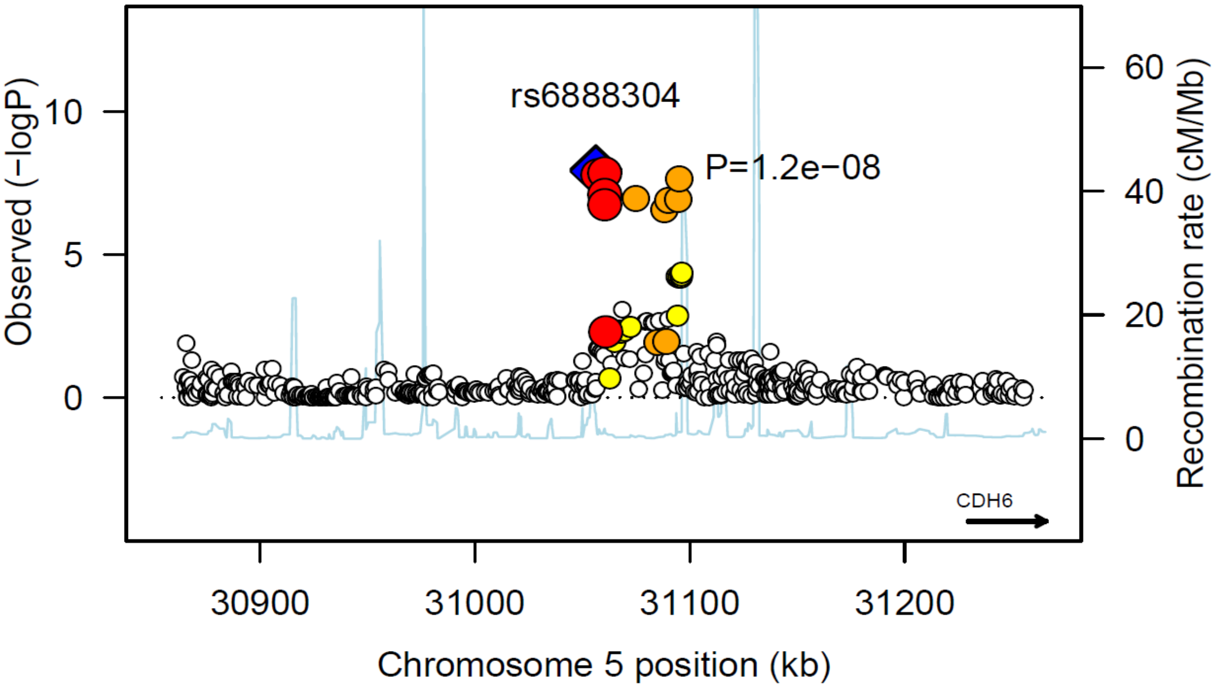


Figure 3.11 Locus 5q11

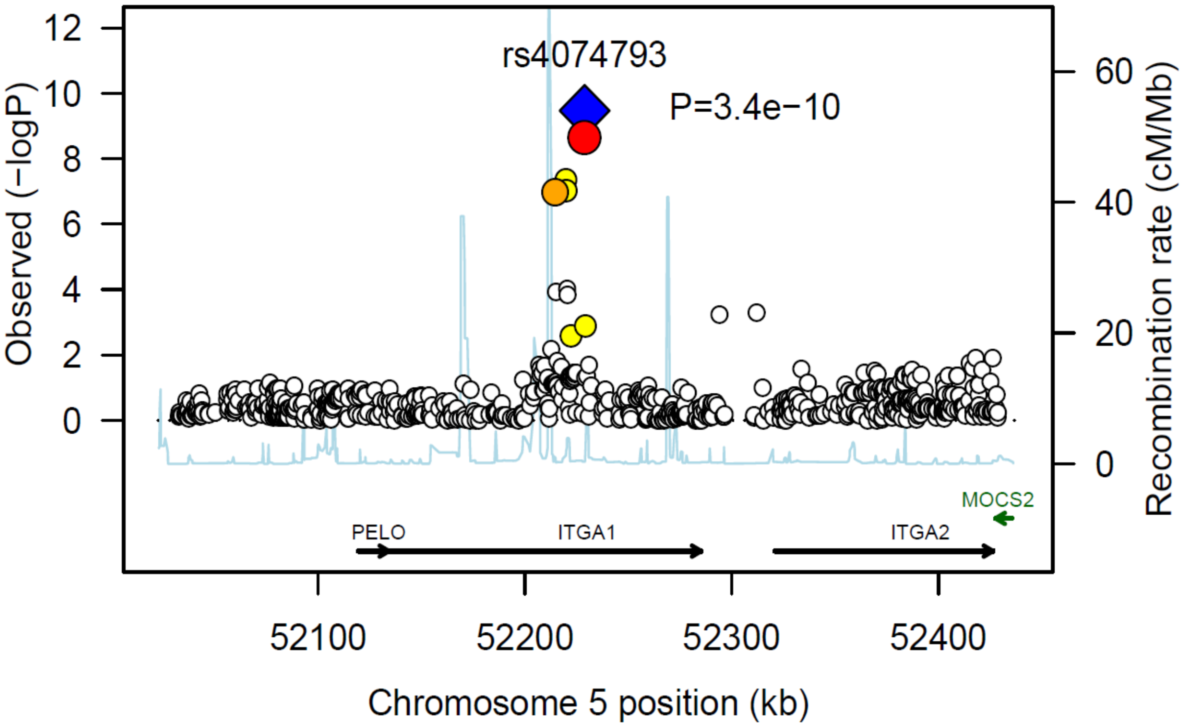


Figure 3.12 Locus 6p12

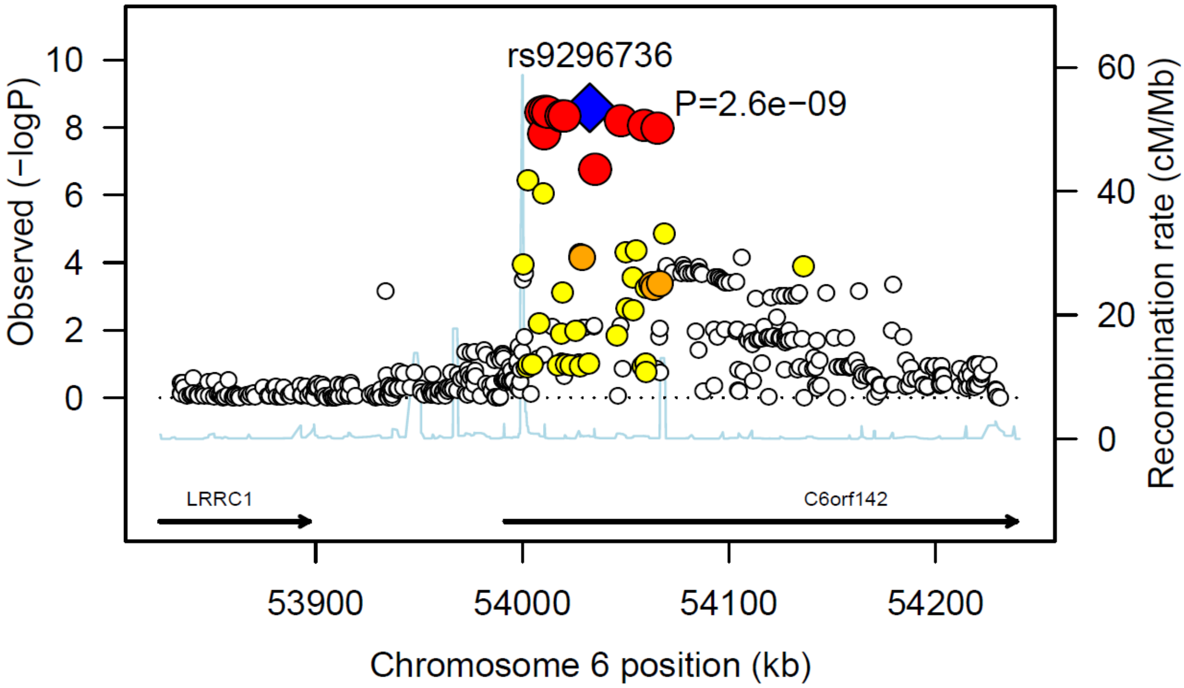


Figure 3.13 Locus 7q11

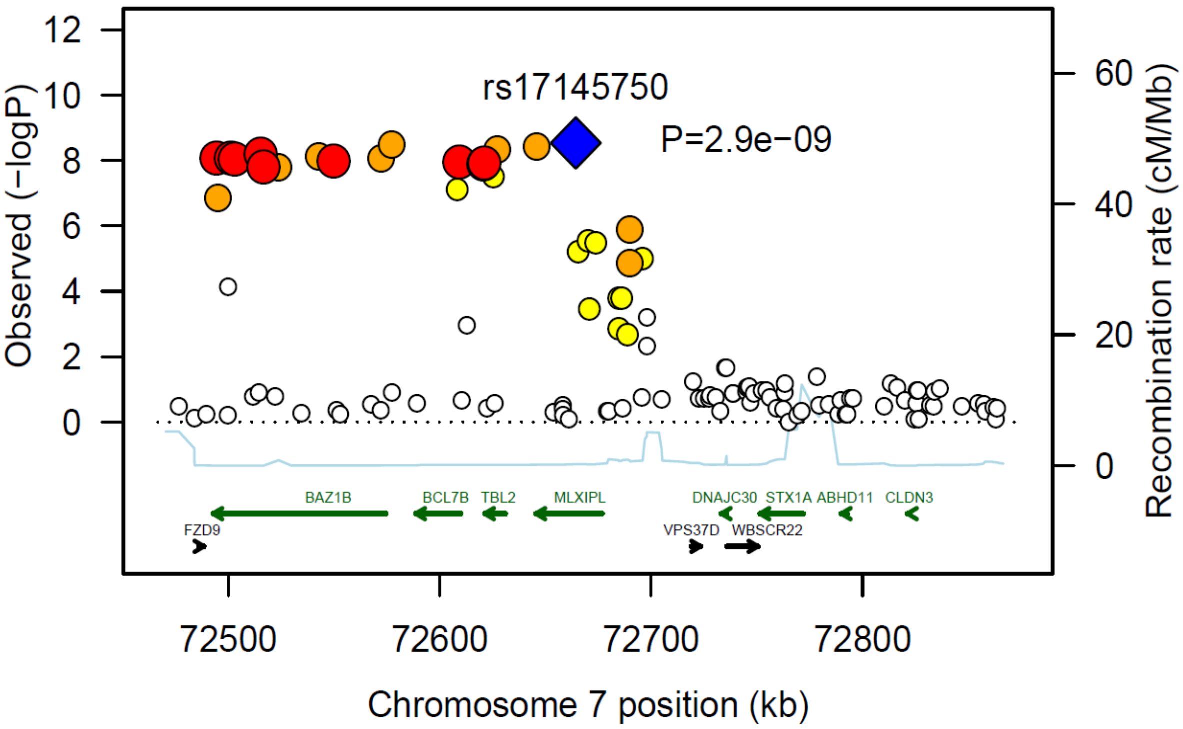


Figure 3.14 Locus 10q23

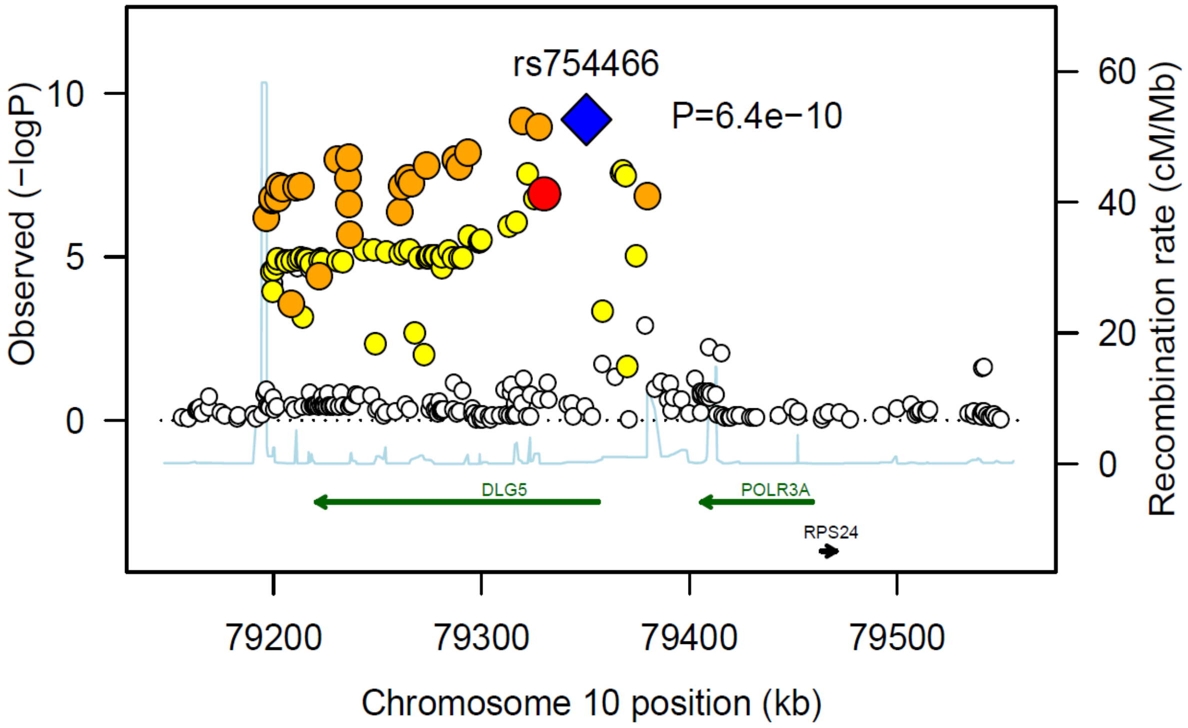


Figure 3.15 Locus 12q24

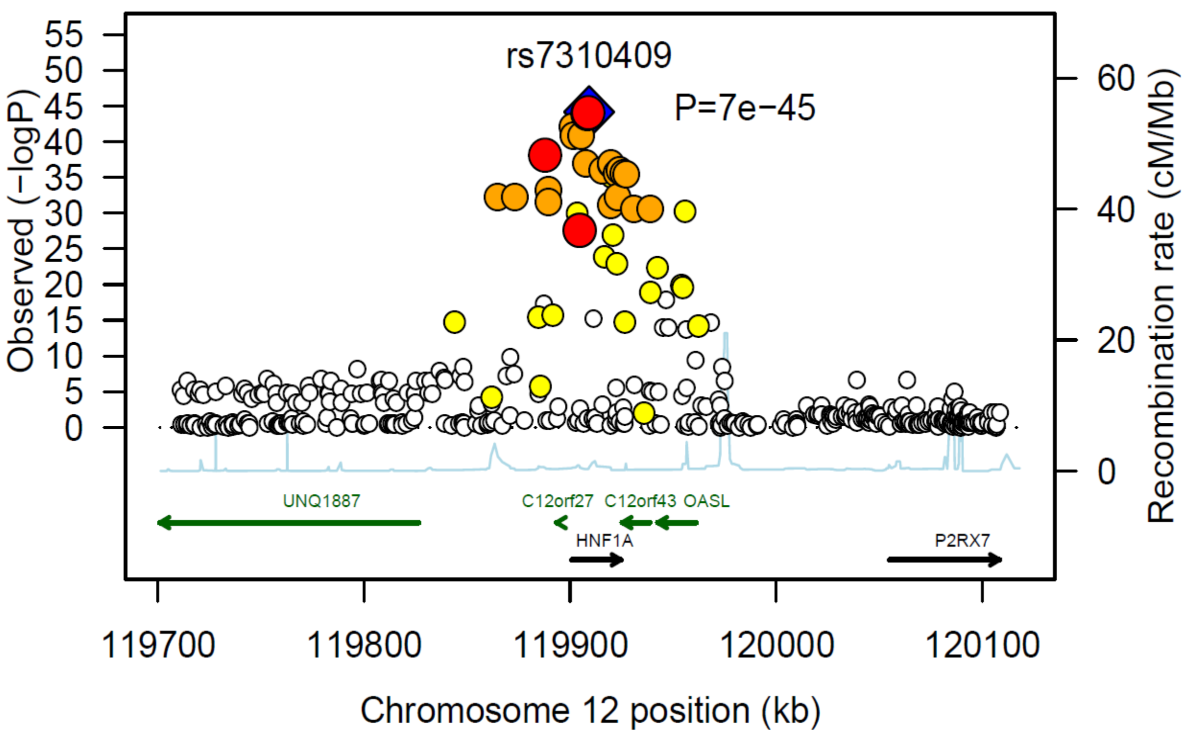


Figure 3.16 Locus 14q32

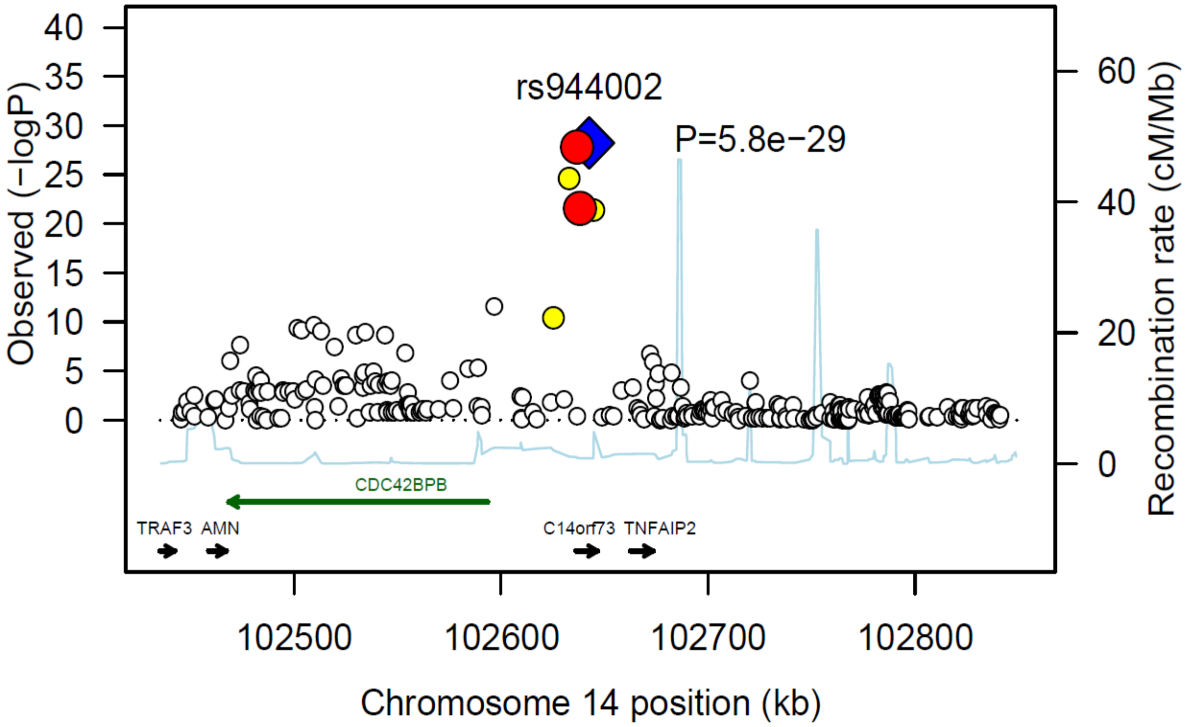


Figure 3.17 Locus 15q21

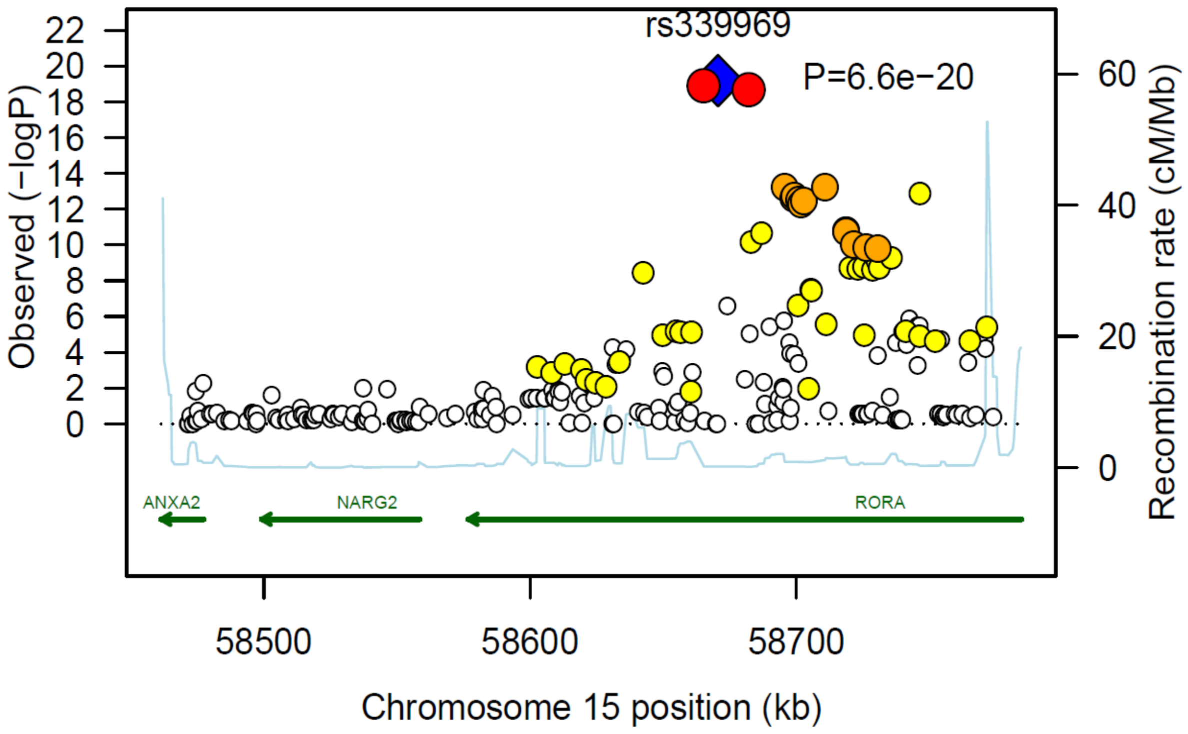


Figure 3.18 Locus 15q23

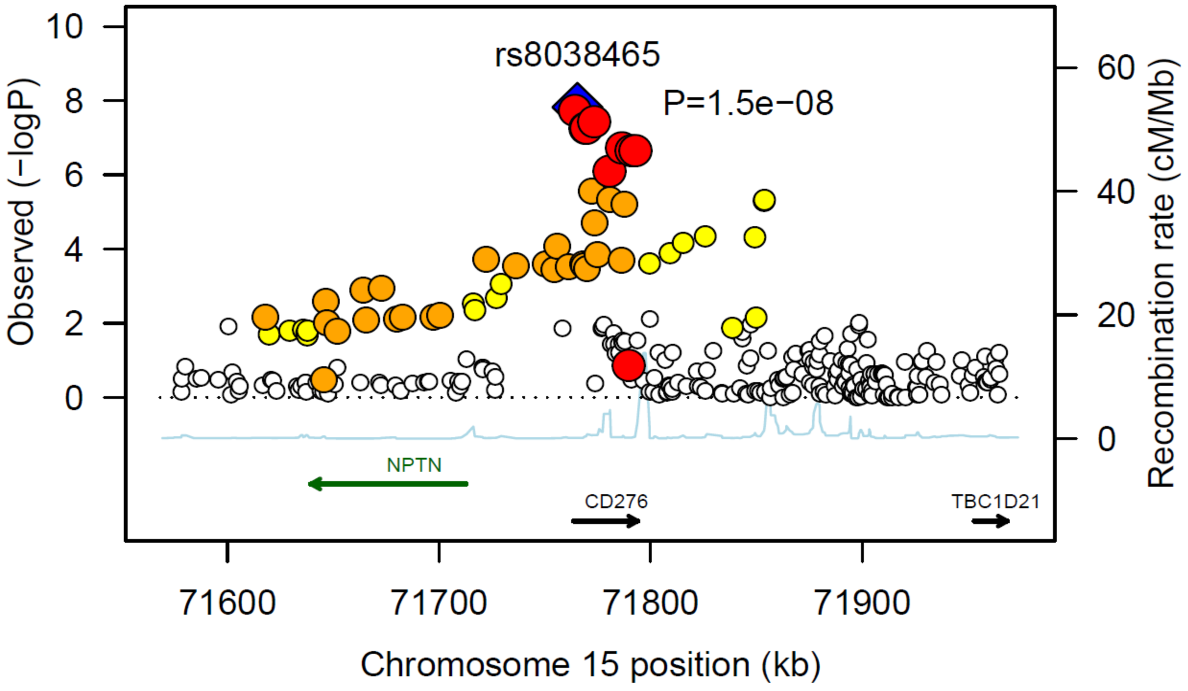


Figure 3.19 Locus 16q23

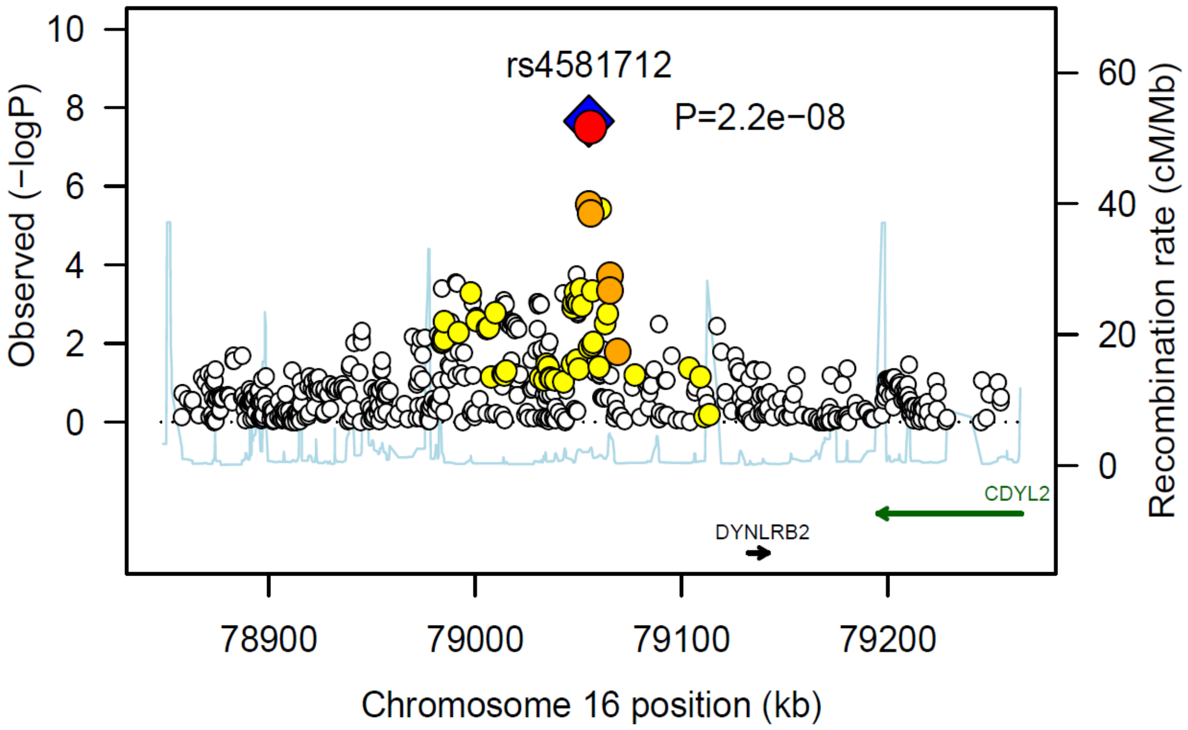


Figure 3.20 Locus 17q24

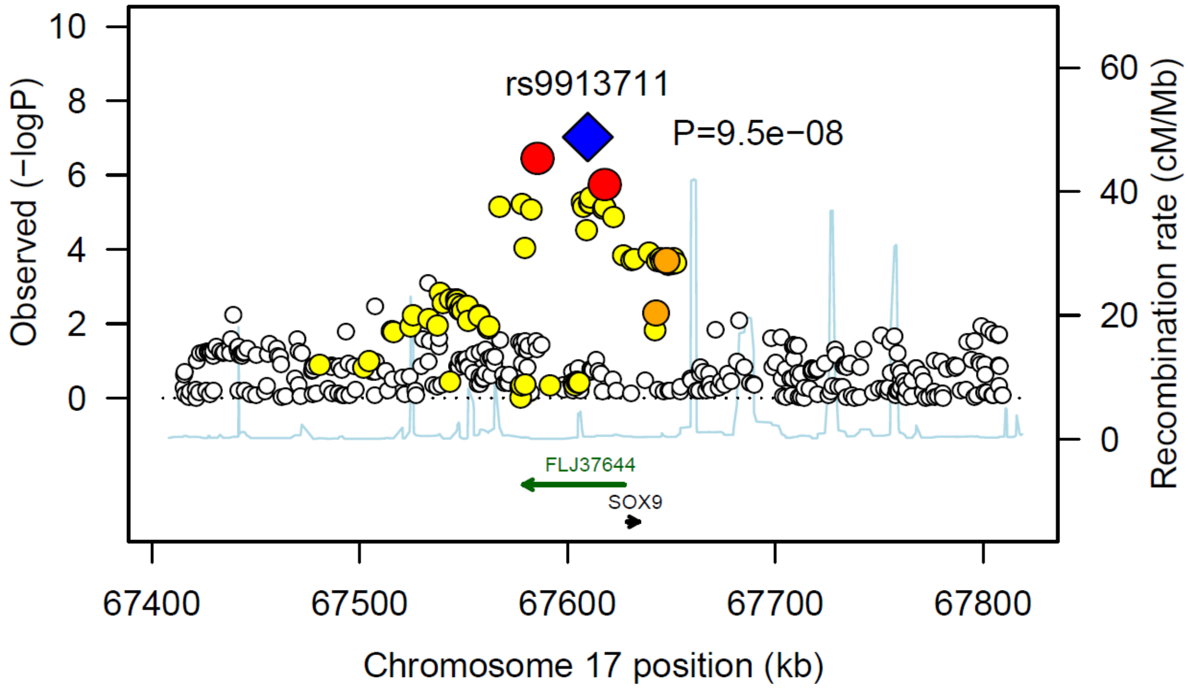


Figure 3.21 Locus 18q21.31

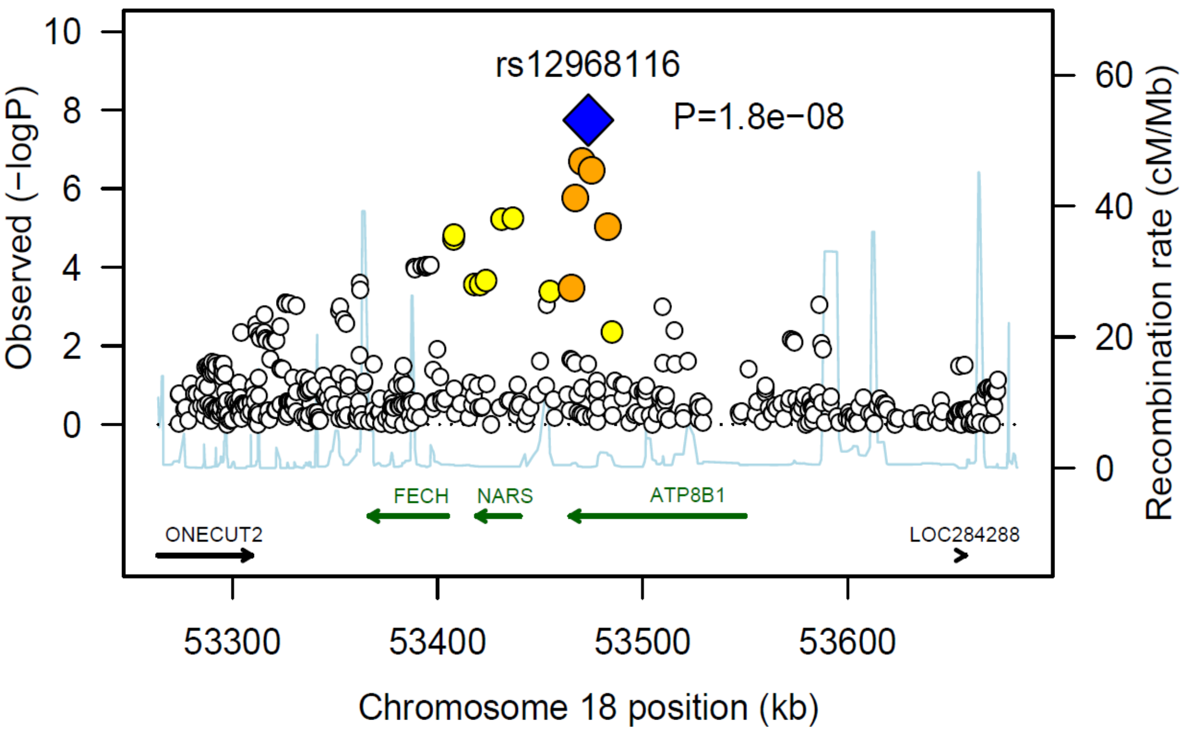


Figure 3.22 Locus 18q21.32

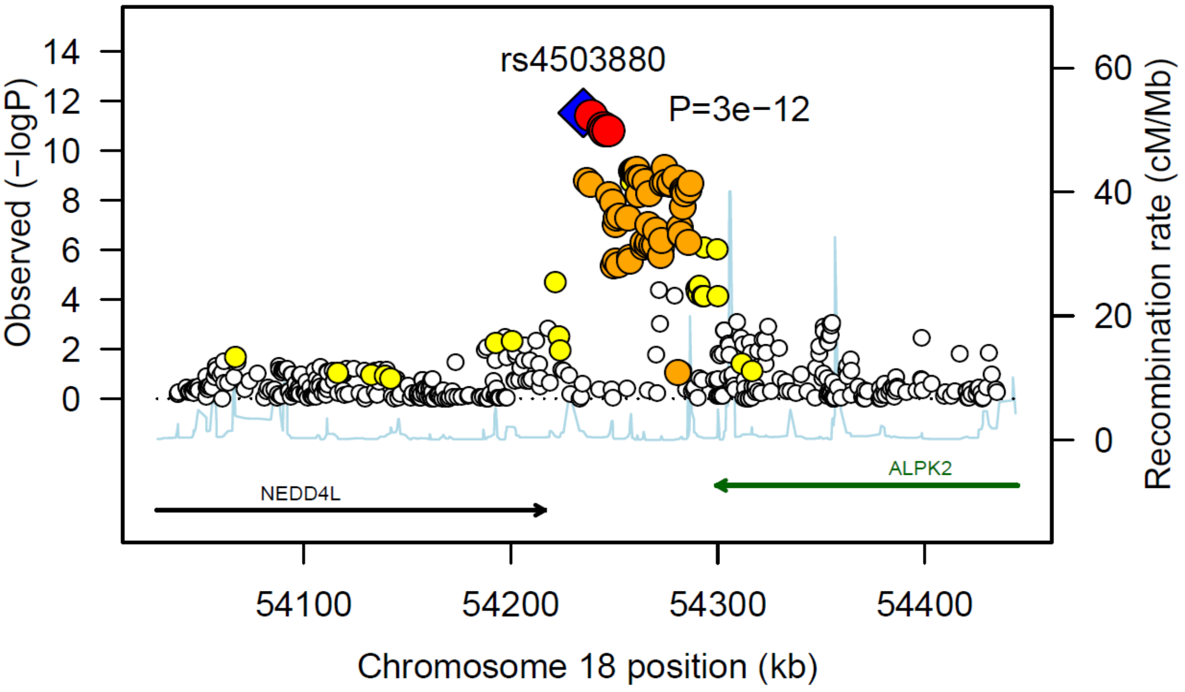


Figure 3.23 Locus 19q13

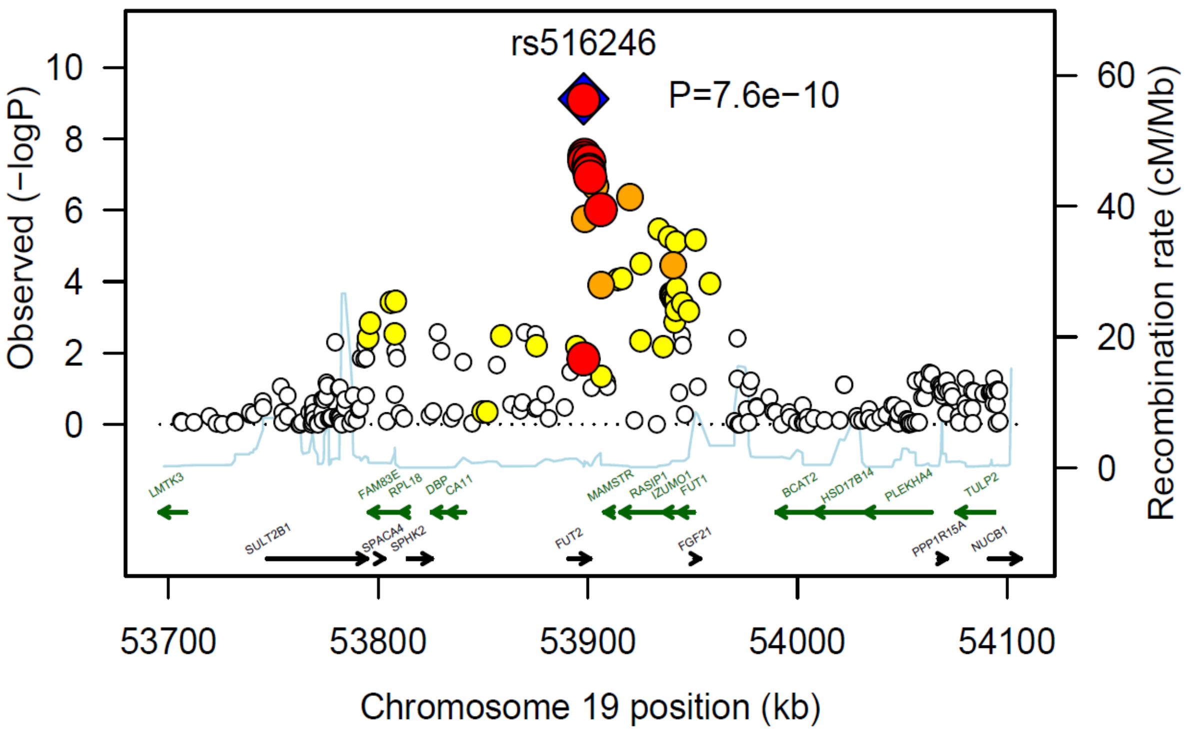


Figure 3.24 Locus 22q11.21

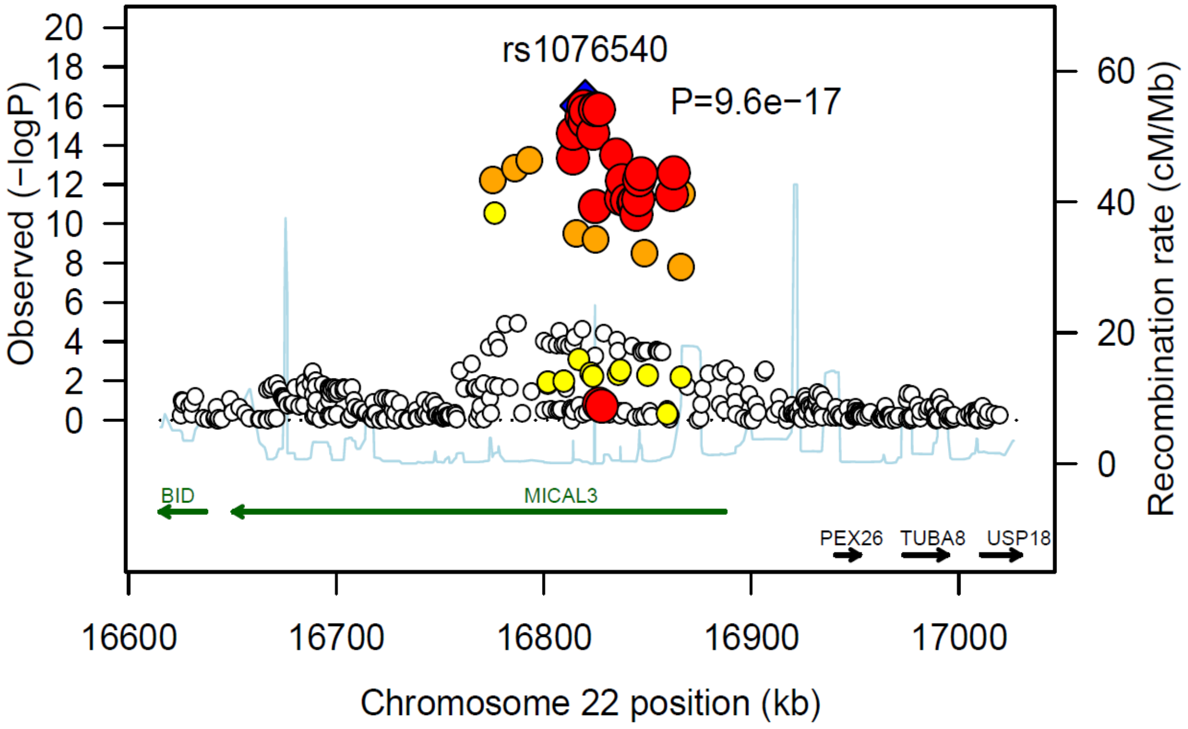


Figure 3.25 Locus 22q11.23

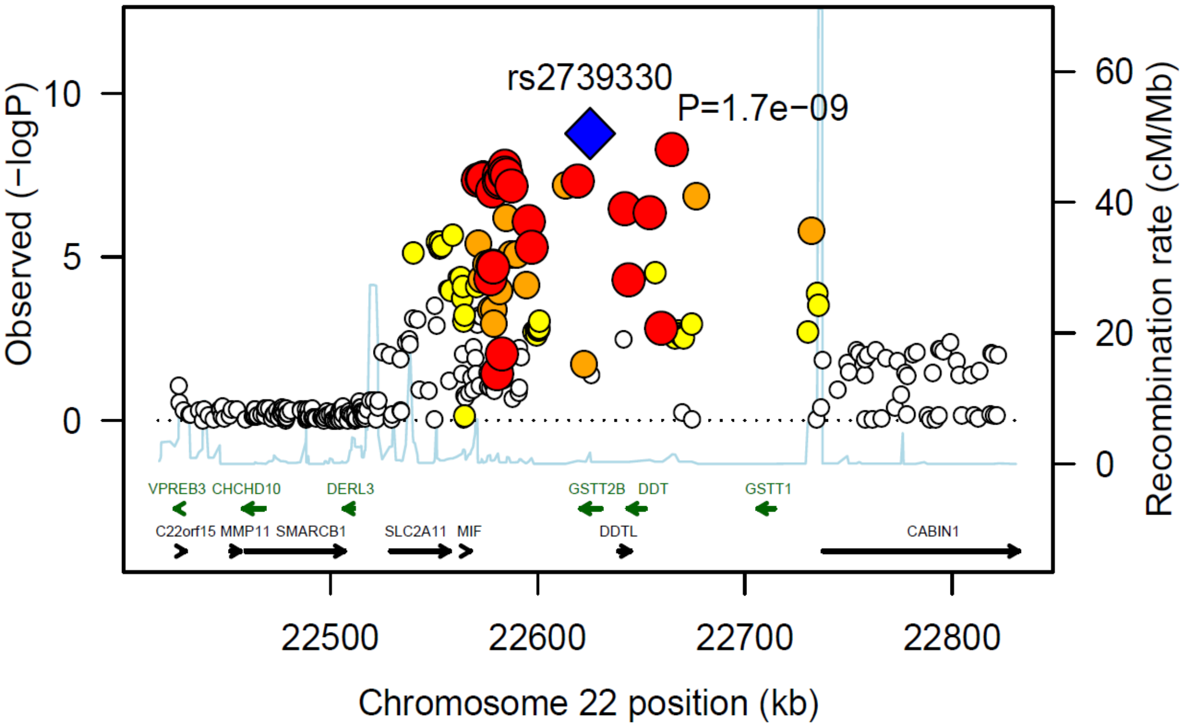
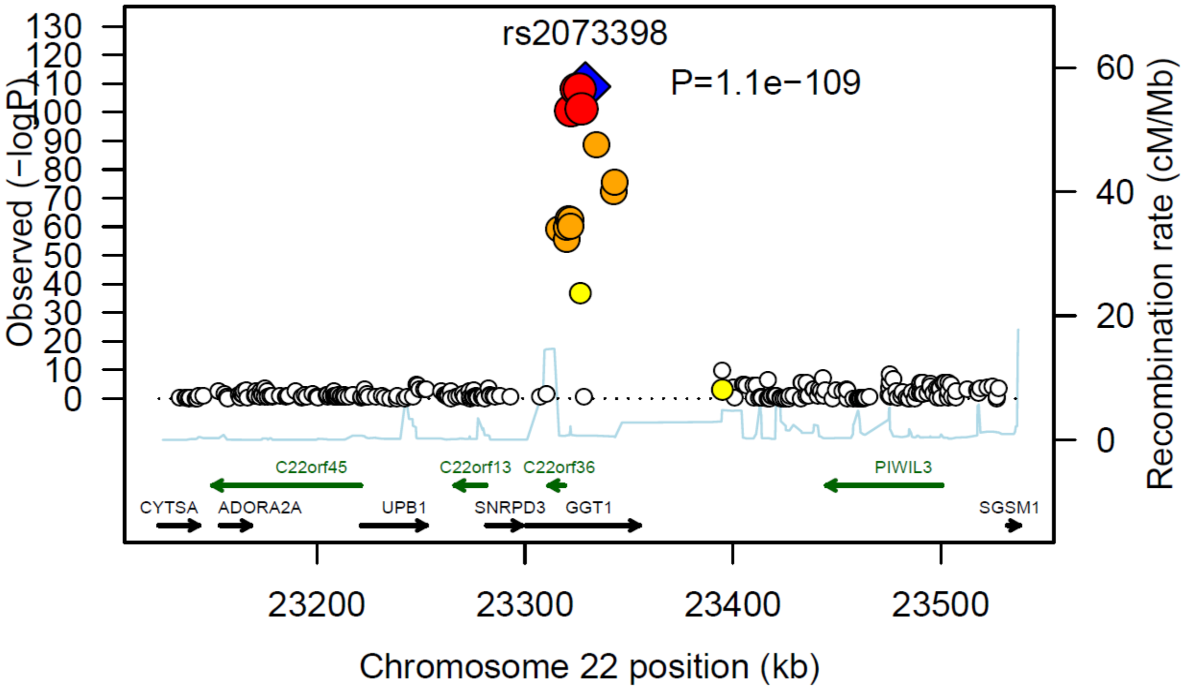
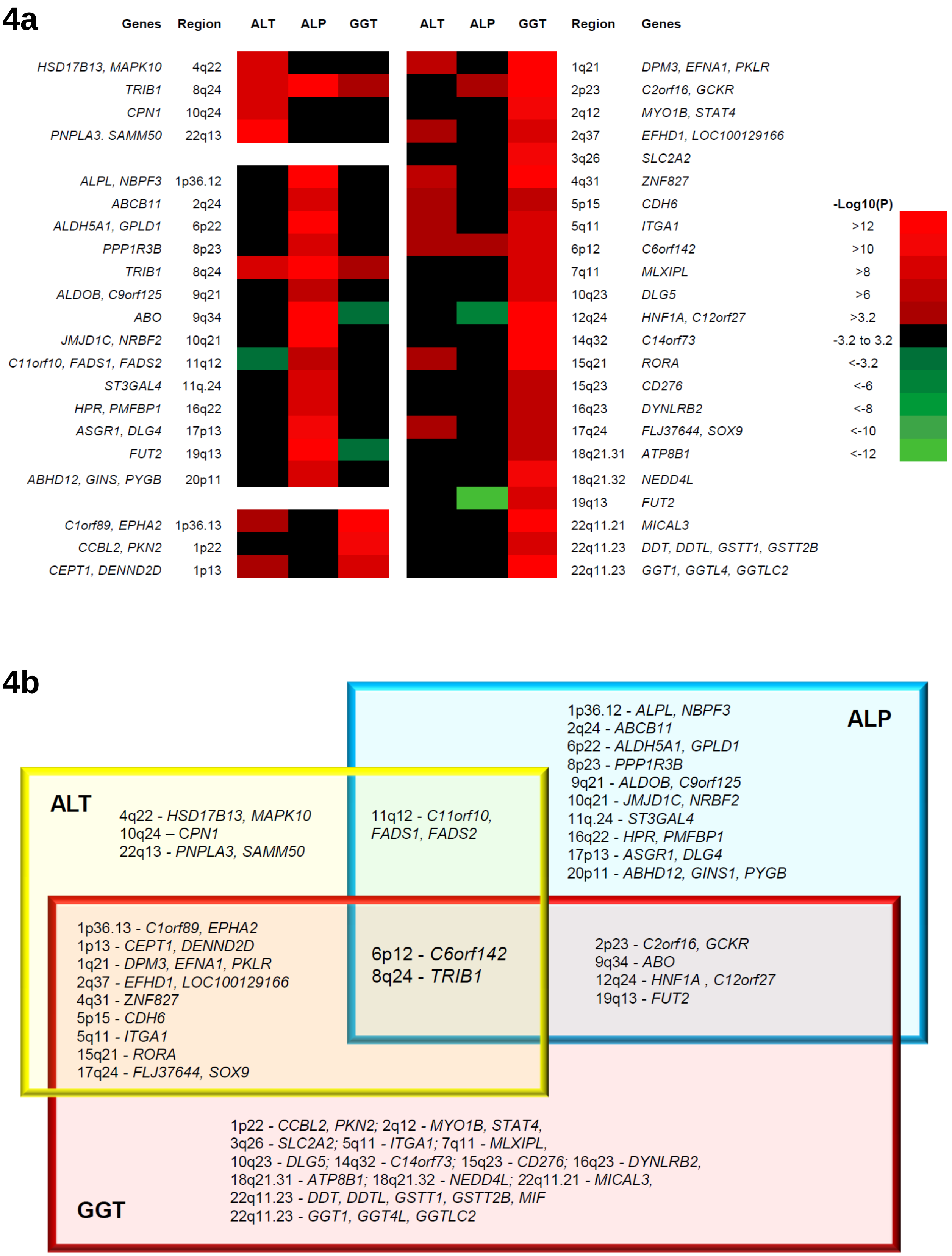


Figure 3.26 Locus 22q11.23



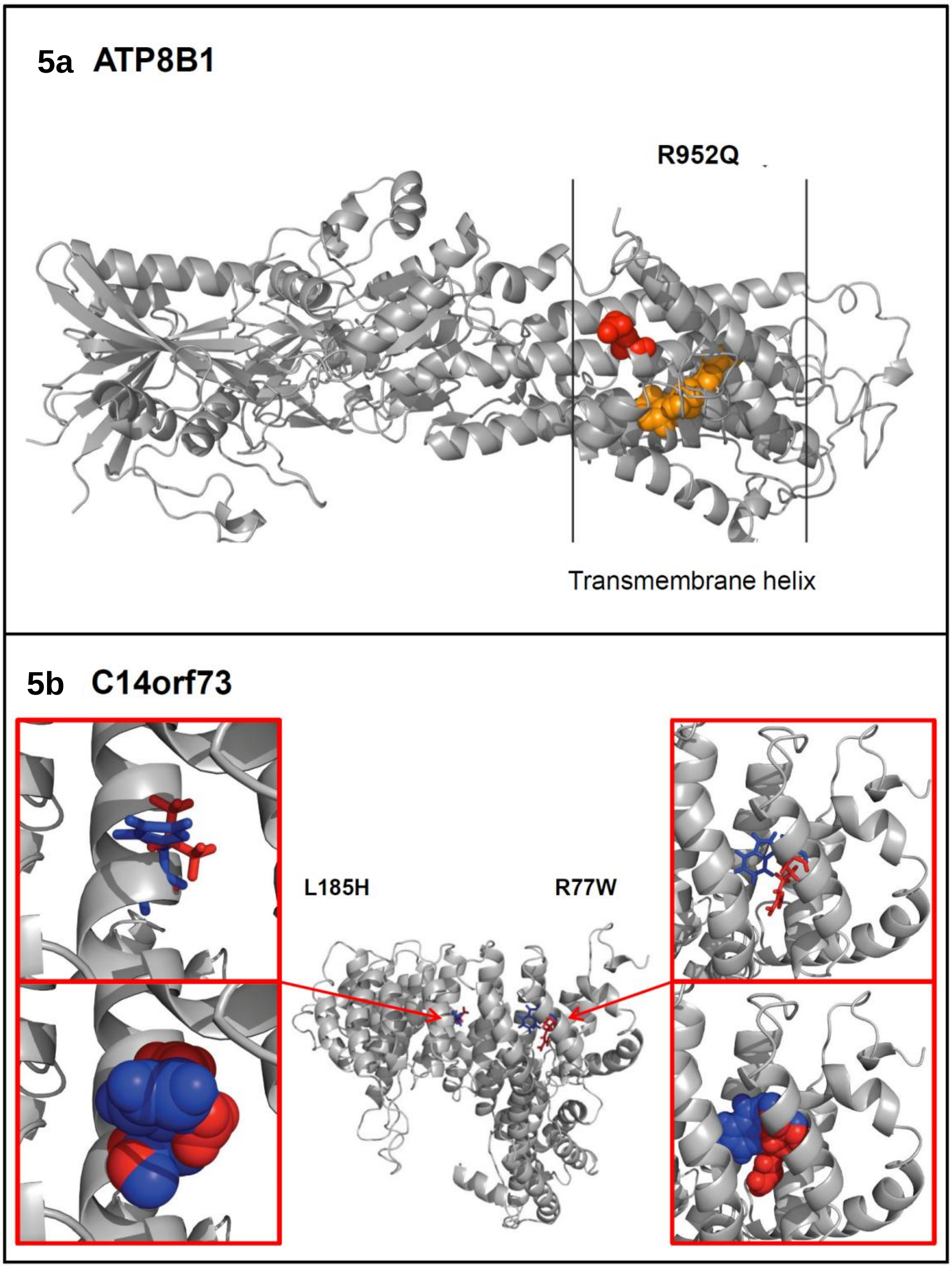
Supplementary Figure 4. Heatmap (**4a**) and venn diagram (**4b**) summarising the association of the 42 loci identified with liver markers in the genome-wide association study. In addition to associations at $P<1x10^{-8}$ with respective discovery marker, 16 loci showed secondary associations with other liver markers at $P<6x10^{-4}$ (P<0.05 after Bonferroni correction).



Supplementary Figure 5. Molecular models illustrating positions and predicted molecular changes of coding variants identified. Models generated using Phyre [106] and 3DLigandSite.[107]

5a. ATP8B1**.** Coding variant R952Q is located in the 5th transmembrane helix of this plasma membrane protein. The variation from arginine (larger, charged), to glutamine (smaller, uncharged) is non-conservative. The variant (highlighted red) is close to residues that are functionally important in homologous calcium transporters (highlighted orange).[108]

5b. C14orf73. R77W is a non-conservative change from a polar basic amino acid to a non-polar hydrophobic amino acid. The affected residue is in an alpha helix and the amino acid change to tryptophan is likely to disrupt tertiary structure of the protein. L185H is predicted to be conservative as both residues are polar and basic. The SNP residues are shown in stick and spacefill formats with the side chains of the two different amino acids displayed.

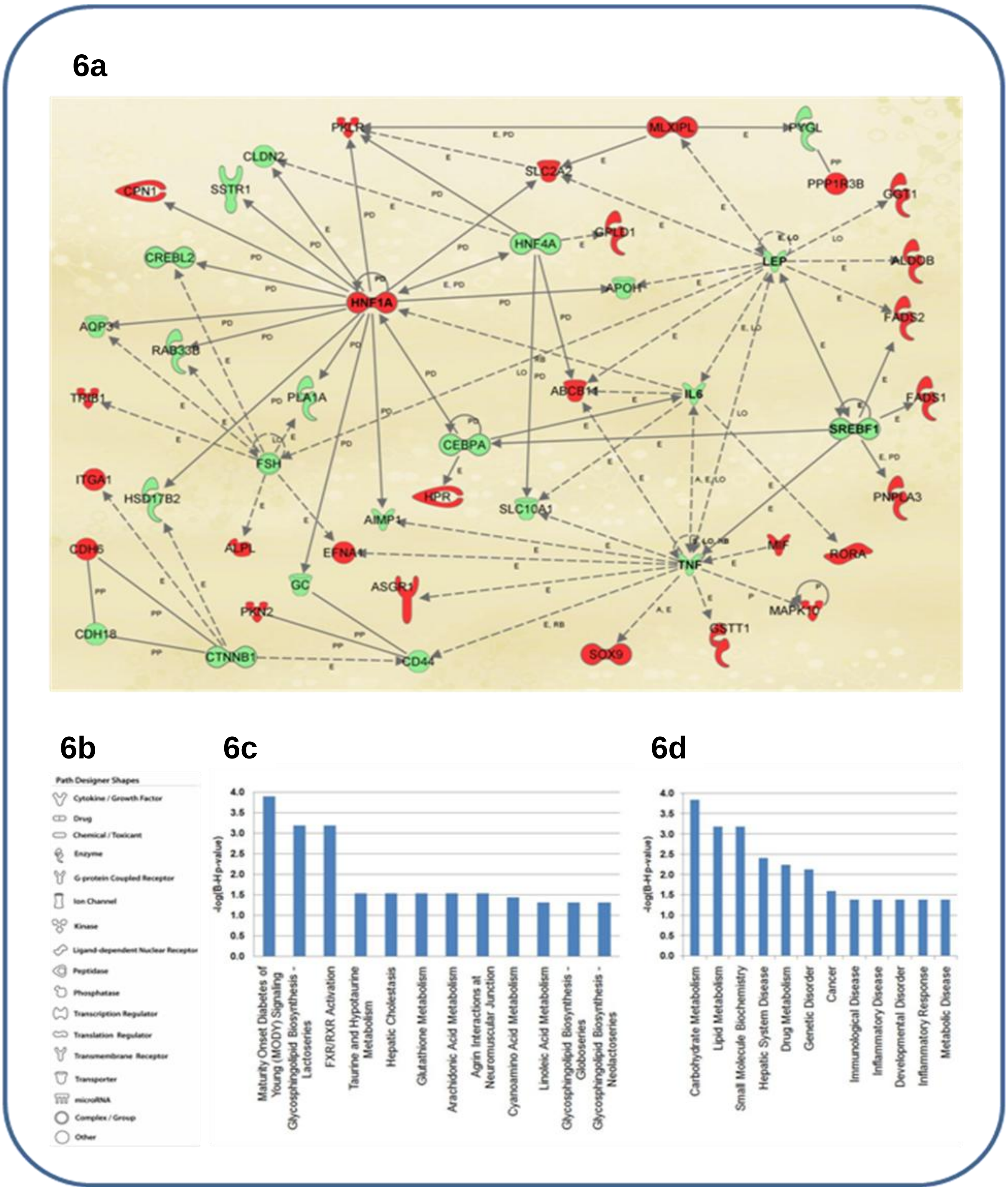


Supplementary Figure 6. Results of pathway analysis carried out for the 69 candidate genes identified at the 42 liver marker loci, using the Ingenuity Pathway Analysis tool (IPA, Ingenuity Systems, USA).

6a. Top network identified - IPA description "Lipid Metabolism, Small Molecule Biochemistry and Carbohydrate Metabolism". Candidate genes from liver marker loci are highlighted in red. Edge annotations are as follows: expression (E); protein-DNA binding (PD); protein-protein binding (PP); localisation (LO); activation (A); regulation of binding (RB); phosphorylation / dephosphorylation (P). Direct interactions are indicated by solid lines and indirect interactions by dashed lines.

6b. Symbols used to represent protein type/function.

6c and 6d: Canonical Pathways (**6c**) and Functions (**6d**) significant at P<0.05 after correction for multiple testing.



Supplementary Note

Participating cohorts

Genome-wide association was done amongst 61,089 participants from the following studies: the Australian Twin cohort (N=425) a study based on Australian twin pairs born before 1964 who participated in questionnaire- and interview-based studies on psychological and metabolic risk factors for psychiatric and cardiovascular disease; the British Genetics of Hypertension study (BRIGHT, N=1,955) comprising hypertensive probands from families with multiplex affected sibships or parent–offspring trios, of British ancestry and recruited though primary care practices; the Lausanne Cohort (CoLaus, N=5,636), a cross-sectional study of a random sample of European men and women, aged 35–75 yrs, living in Lausanne, Switzerland, deCODE genetics (N=12,572) is a population-based genomics study aiming to collate health records, genealogical information, and genetic data of the entire Icelandic population; the Fenland study (N=1,397), an ongoing population based cohort of men and women born between 1950 and 1975 and living in Eastern England; the Finnish Twin cohort study (FinnTwin N=32) which comprised MZ twin pairs, who were a subset of clinically assessed twins recruited from a population-based longitudinal study of five consecutive birth cohorts (1975–1979) of twins, their siblings and parents, identified through the national population registry of Finland; the Framingham Heart Study is a longitudinal observational, community-based cohort initiated in 1948 to prospectively investigate cardiovascular disease and its risk factors. (N=2,869); the Monica/KORA Augsburg study (KORA, N=1,809) an independent population-based sample from the general population living in the region of Augsburg, Southern Germany; the London Life Sciences Population study (LOLIPOP, N=10,338), a population based cohort of men and women, aged 35-75 years, living in West London, UK; the Northern Finland Birth Cohort 1966 (NFBC1966, N=4,562), a prospective birth cohort of persons born in 1966 in the two northernmost provinces of Finland; the Netherlands Study of Depression and Anxiety (NESDA, N=1,724) of men and women aged 18-65 years with depression, anxiety or at increased risk of psychiatric problems in the Netherlands population; the Netherlands Twin study (N=1,721) is a longitudinal study which began in1986 and conducts longitudinal studies in cohorts of newborn, adolescent and adult twins and their family members; the Precocious coronary artery disease study (Procardis, N=1,239) is a multicenter case–control study aiming to discover novel susceptibility genes for coronary artery disease; the Rotterdam Study 1 (RS1, N=4,312), a prospective population-based cohort study investigating the determinants of chronic diseases among participants aged 55 years and older; the SardiNIA study (N=4,302) a longitudinal study of aging-related quantitative traits amongst individuals 14 years or older recruited from 4 towns in the Lanusei Valley of Sardinia; the Study of Health in Pomerania (SHIP, N=4,101) a population-based, cross-sectional study of German men and women aged 20 to 79 years; and the TwinsUK study (N=2,256), a population-based sample of British female twins, unselected for any disease or trait. Cohort characteristics are shown in **Supplementary Tables 1 & 2**.

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