

SUPPLEMENTARY MATERIAL

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Supplementary Table 1. Genomic control (λ) of GWAS and CMA for pulmonary function and age-related traits

	FEV1	FVC	IL-6	hsCRP	BMI	Grip strength	HbA1c	Fasting glucose
CMA	1.005	0.996	1.023	1.011	1.023	1.055	1.012	1.005
GWAS								
FEV1_IL-6_hsCRP	1.094							
FVC_IL-6_hsCRP		1.095						
FEV1_BMI	1.028							
FVC_BMI		1.034						
FEV1_Grip	1.056							
FVC_Grip		1.048						
FEV1_HbA1c	1.020							
FVC_HbA1c		1.021						
FEV1_Glucose	1.002							
FVC_Glucose		1.003						

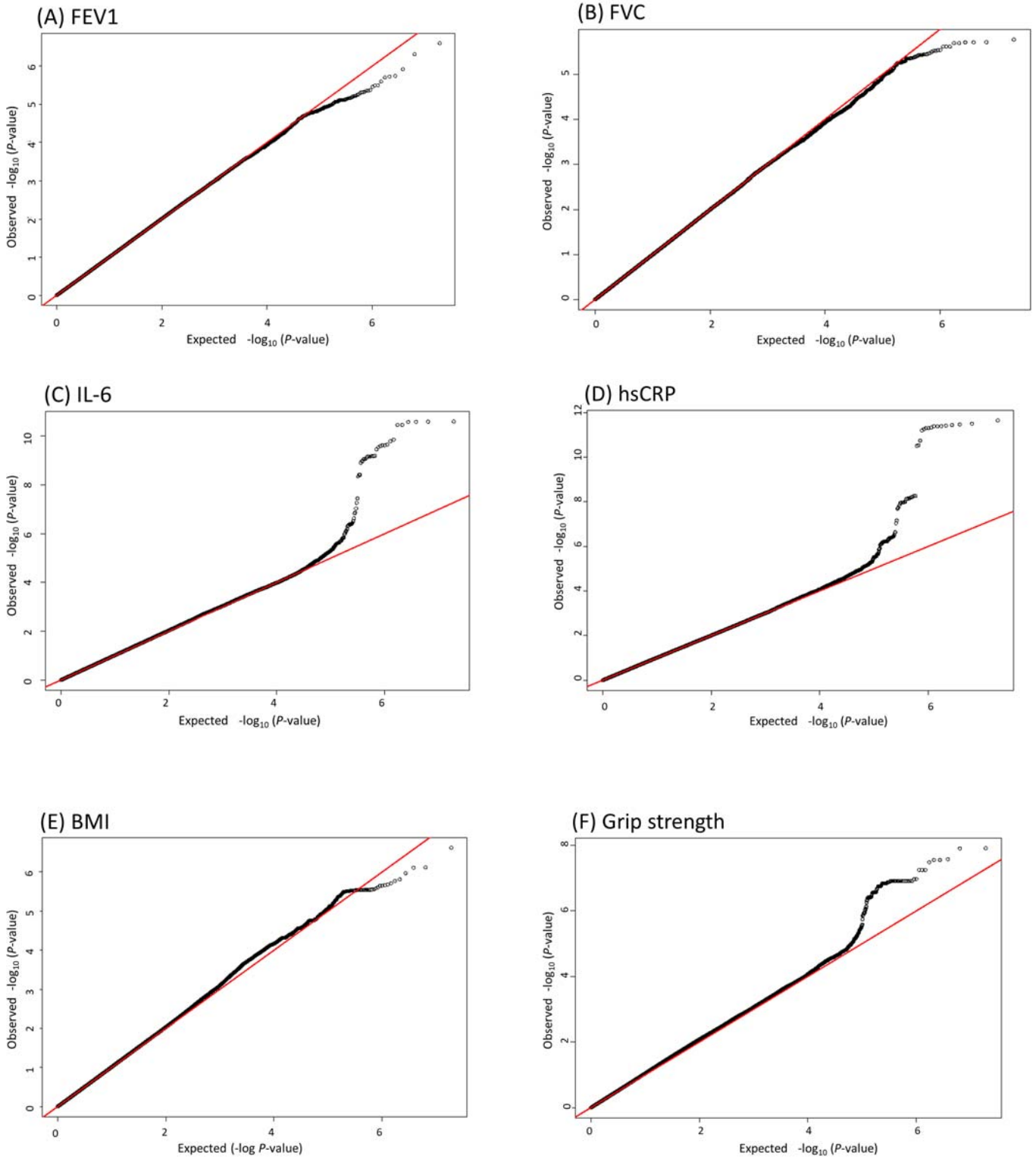
FEV1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, IL-6 = Interleukin-6; hsCRP = High-sensitivity C-reactive protein; BMI = Body mass index; Glucose = Fasting plasma glucose; Grip = Muscle (grip) strength; HbA1c = Hemoglobin A1c.

Supplementary Table 2. Tetrachoric correlations of CMA for pulmonary function and age-related traits

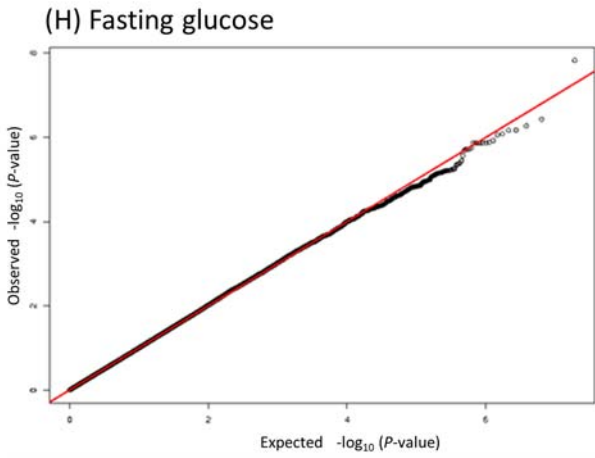
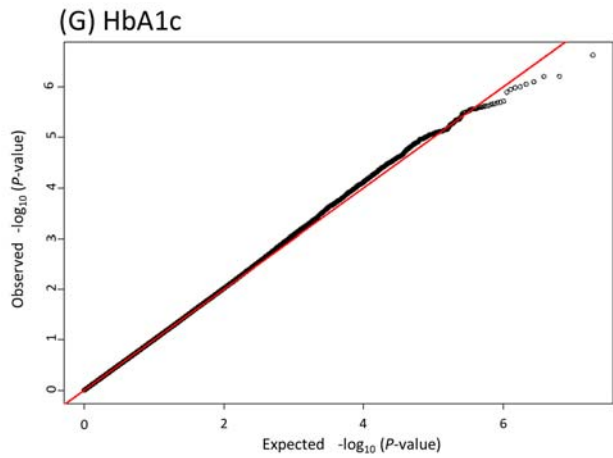
Age-related traits	FEV1	FVC
IL-6	0.012	0.016
hsCRP	0.021	0.036
IL-6 _ hsCRP	0.136	0.136
BMI	0.009	0.026
Muscle (Grip) strength	0.013	0.016
HbA1c	0.009	0.014
Glucose	0.000	0.002

FEV1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, IL-6 = Interleukin-6; hsCRP = High-sensitivity C-reactive protein; BMI = Body mass index; Glucose = Fasting plasma glucose; Grip = Muscle (grip) strength; HbA1c = Hemoglobin A1c.

Supplementary Figure 1. GWAS Q-Q plots of observed versus expected $-\log_{10}$ (P -value) for pulmonary function and age-related traits

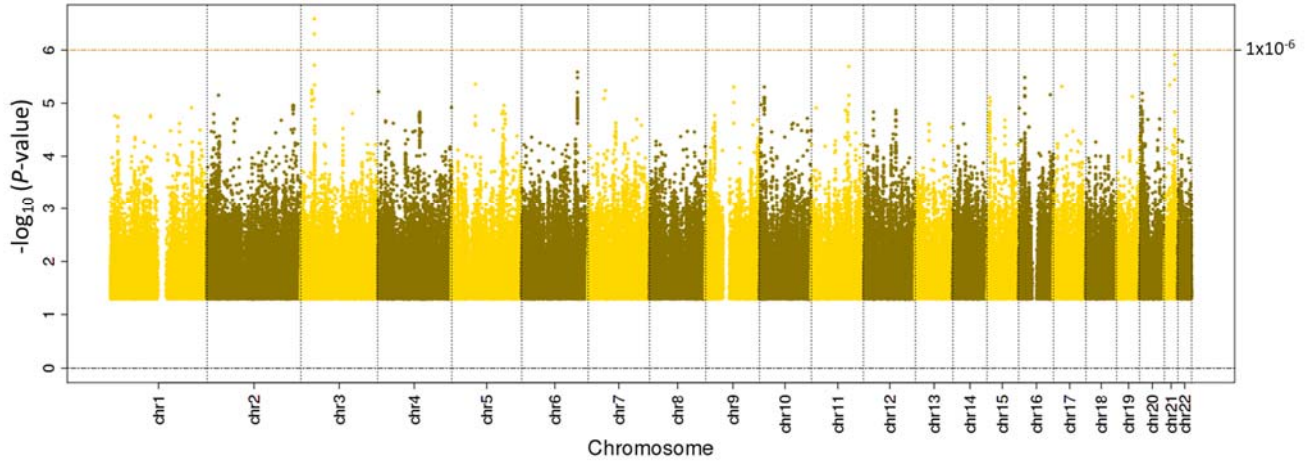


Supplementary Figure 1 (cont.)

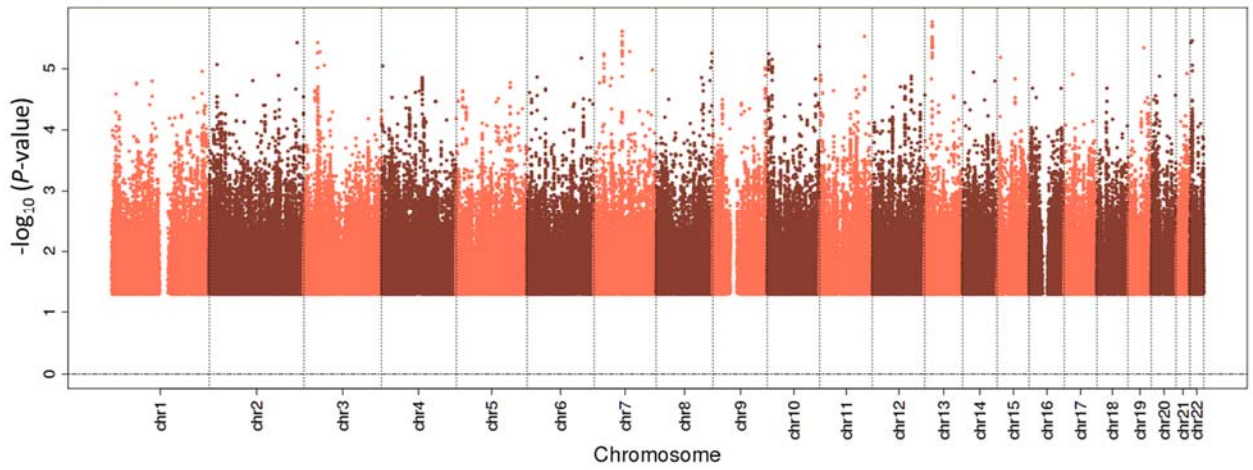


Supplementary Figure 2. Manhattan plots of GWAS for pulmonary function and age-related

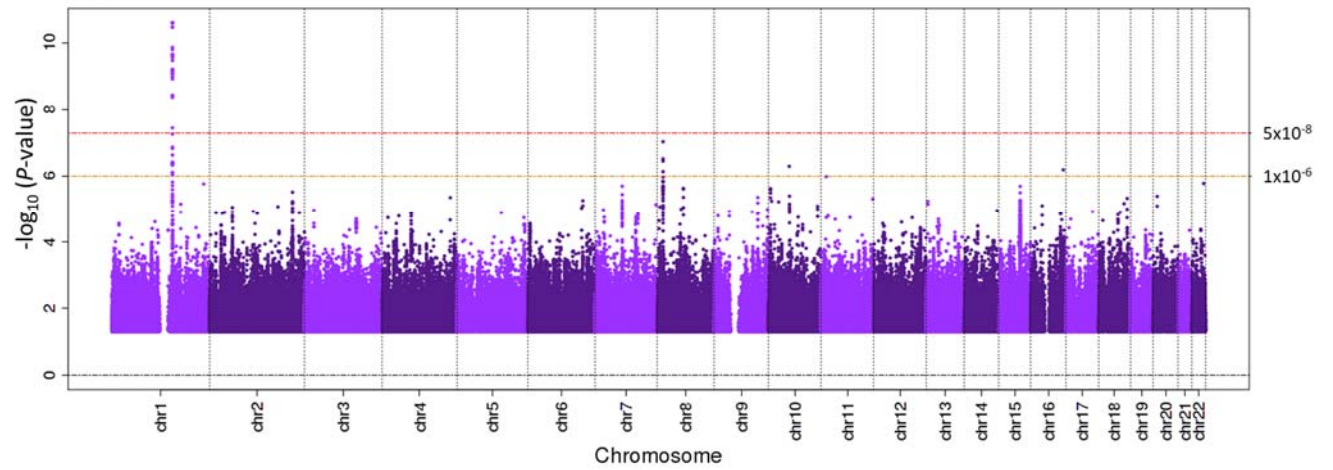
(A) FEV1



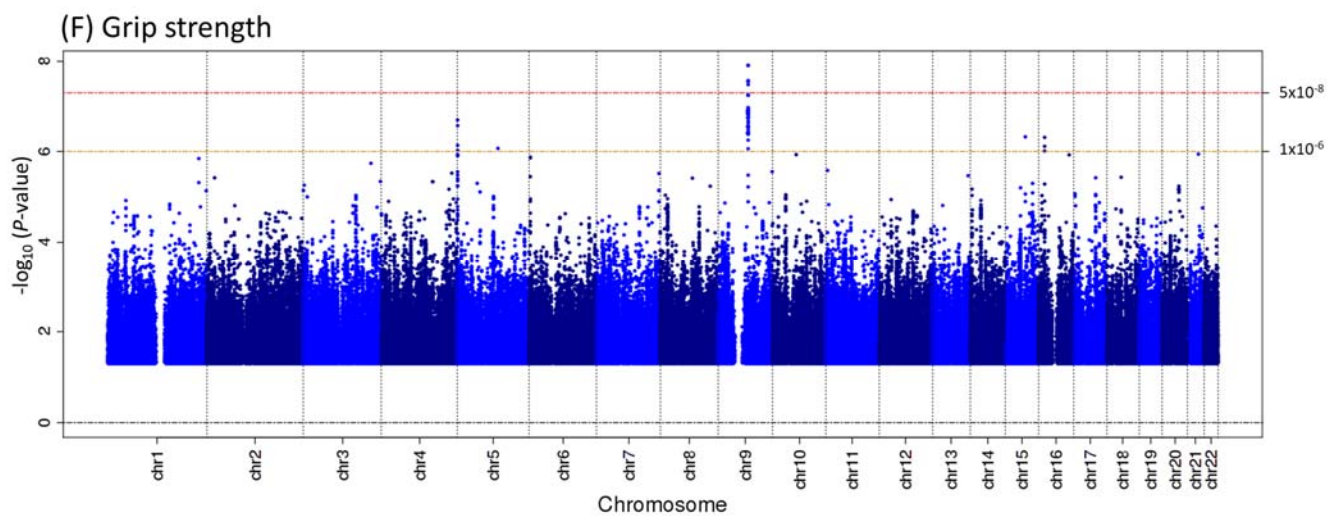
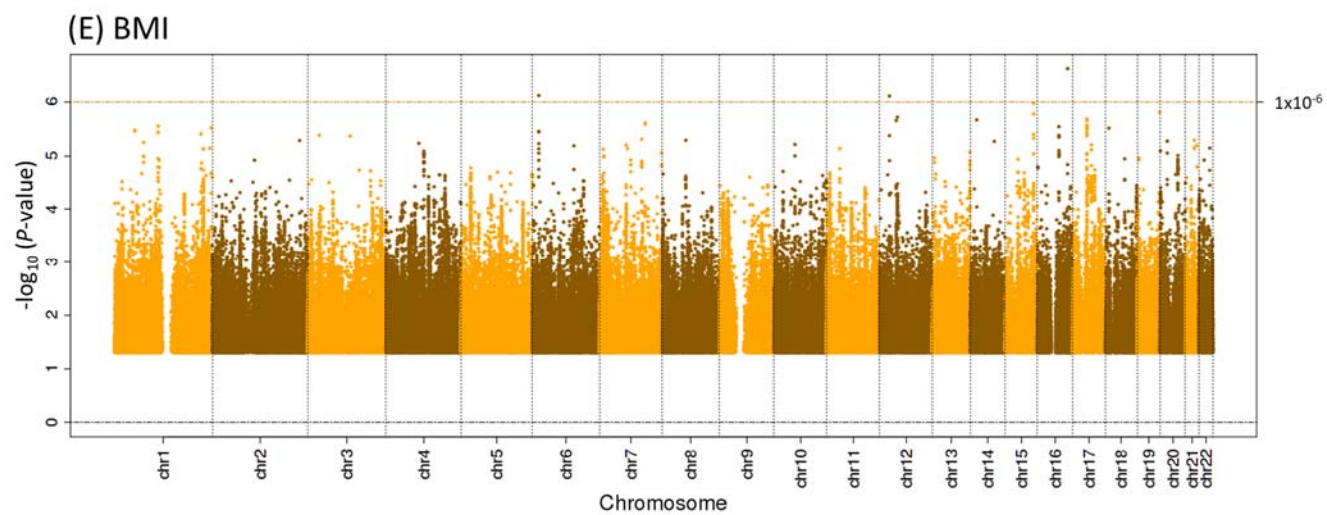
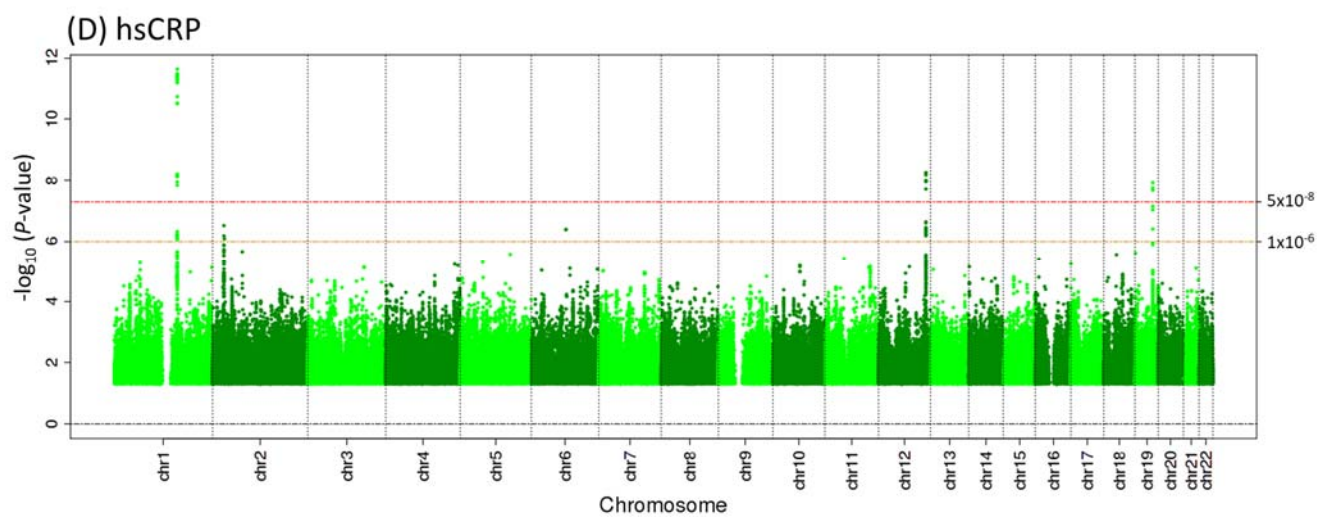
(B) FVC



(C) IL-6

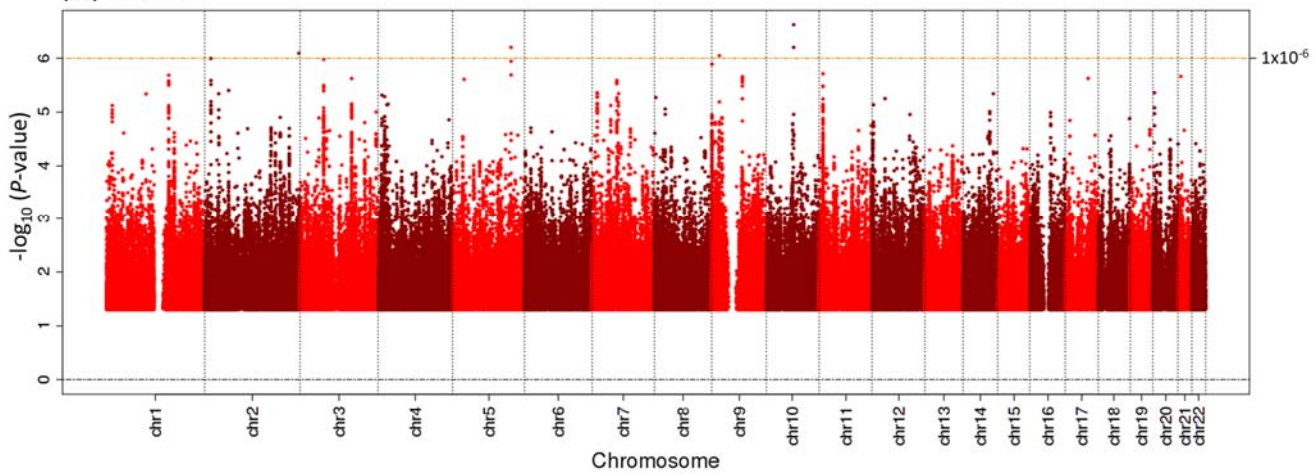


Supplementary Figure 2 (cont.)

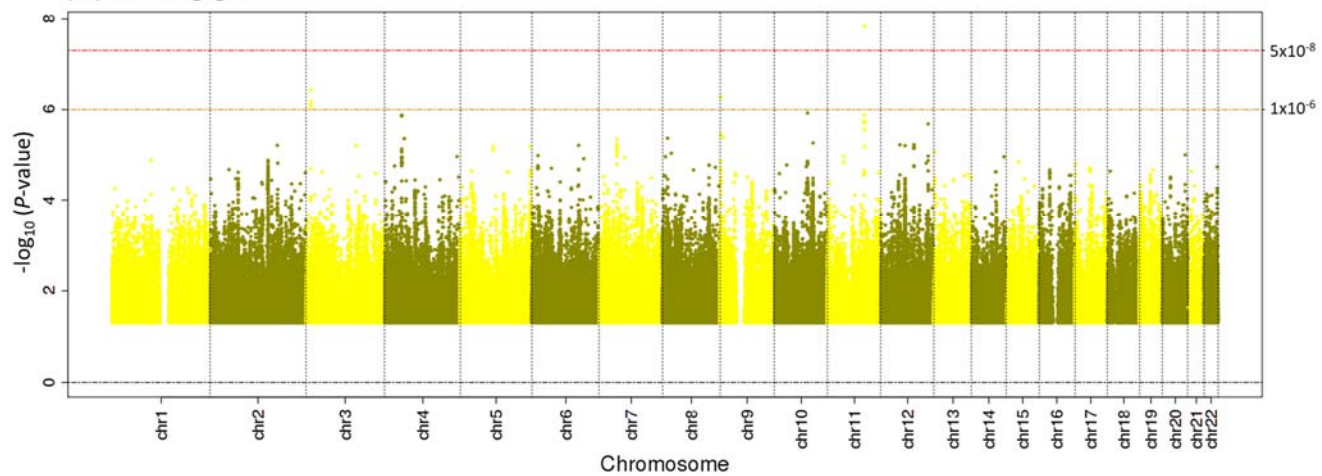


Supplementary Figure 2 (cont.)

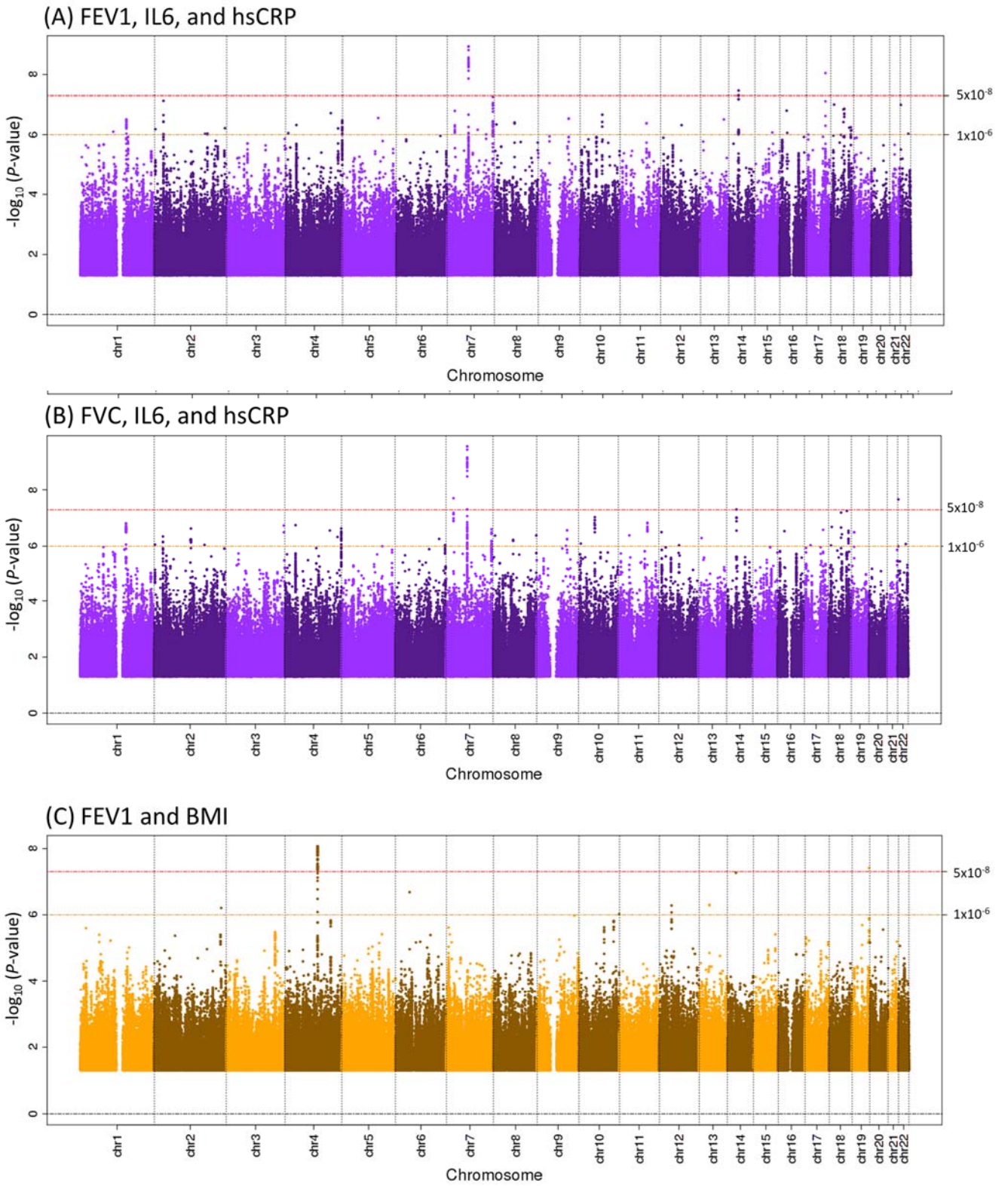
(G) HbA1c



(H) Fasting glucose

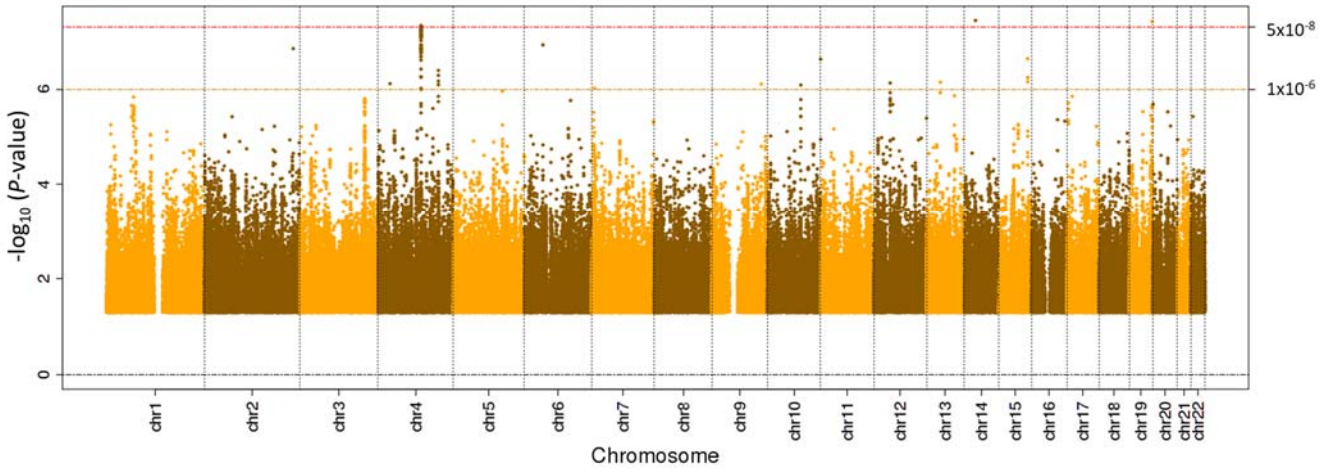


Supplementary Figure 3. Manhattan plot of CMA for pulmonary function and age-related traits

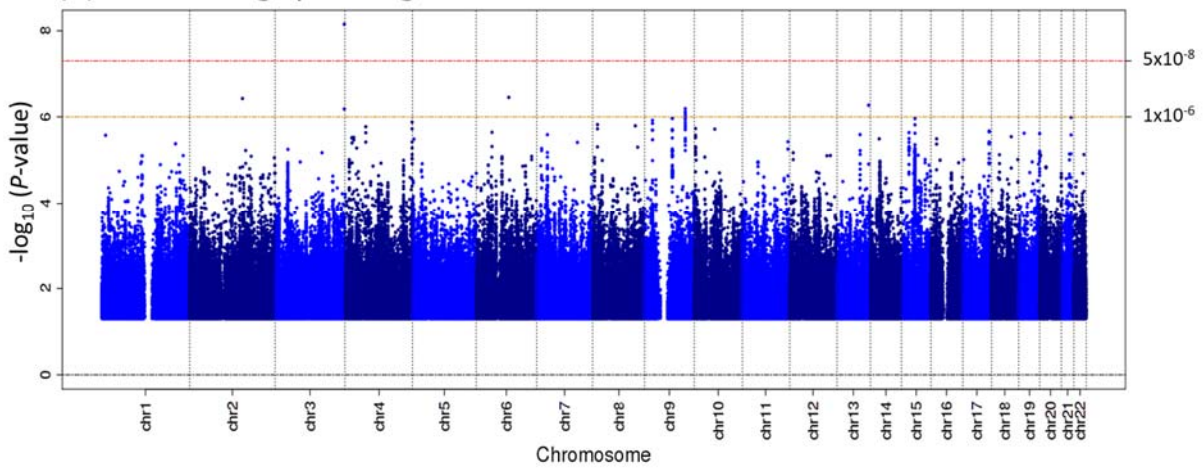


Supplementary Figure 3 (cont.)

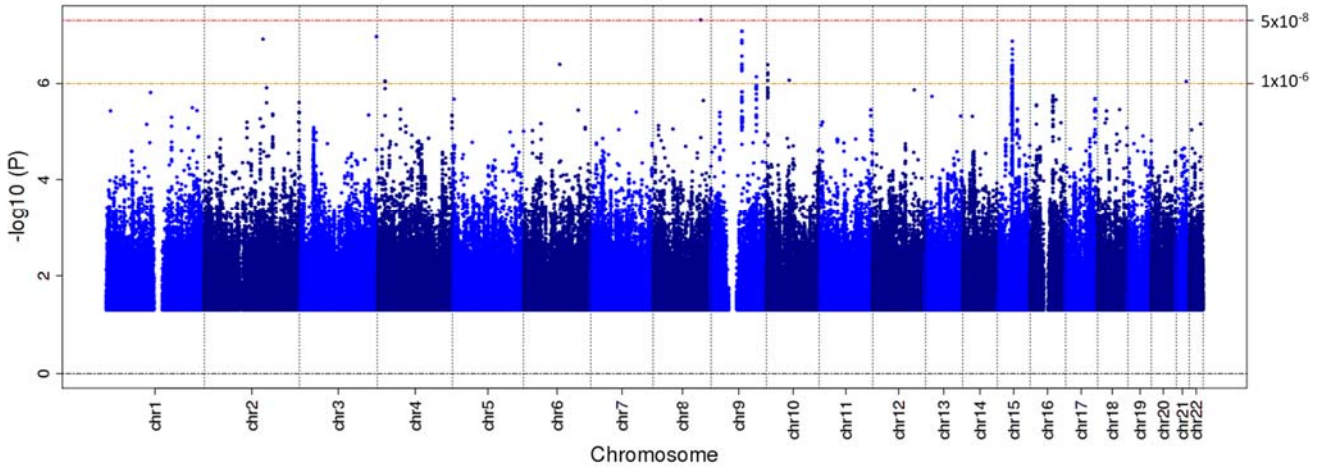
(D) FVC and BMI



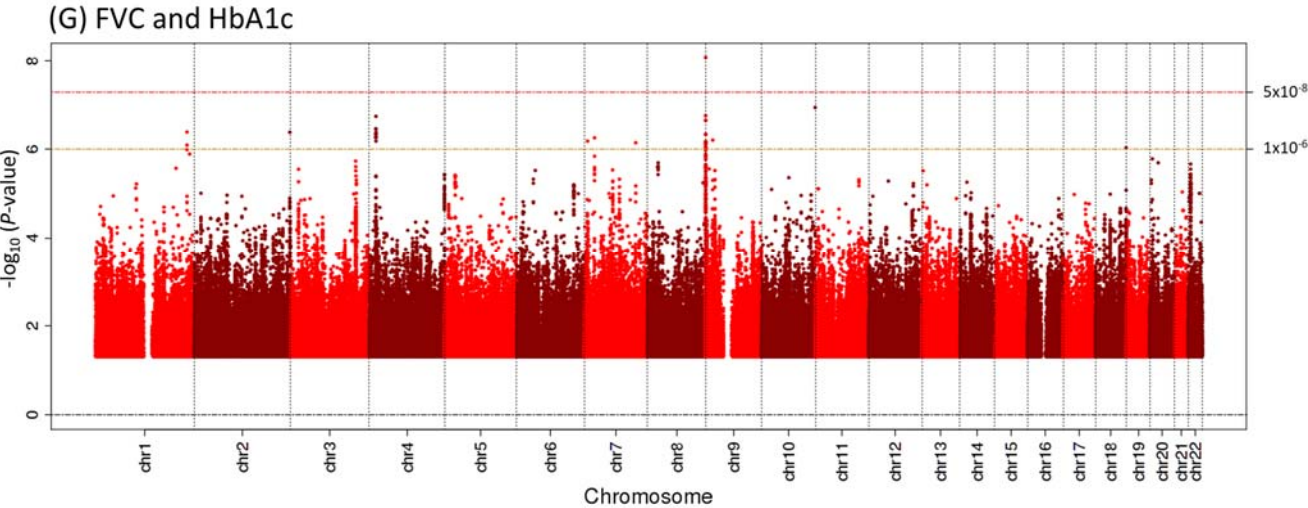
(E) FEV1 and grip strength



(F) FVC and grip strength

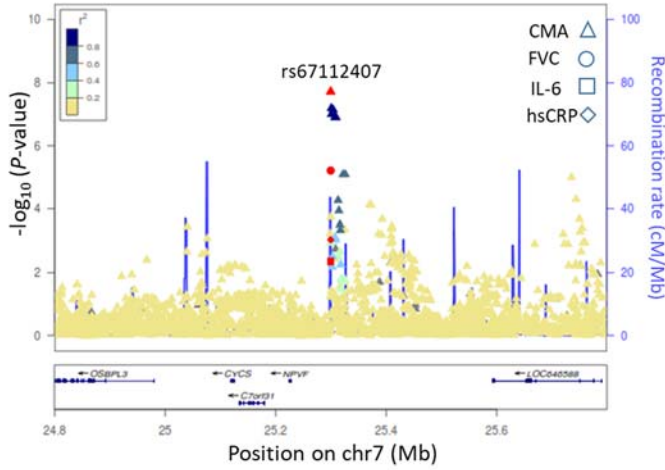


Supplementary Figure 3 (cont.)

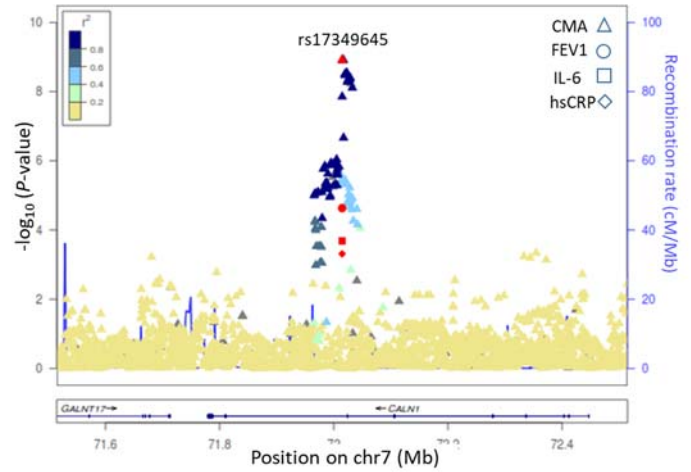


Supplementary Figure 4. Locuszoom plots of CMA for sex-combined associated variants with pulmonary function and inflammatory markers (A, B, C, D, E, F, G, H), BMI (I, J, K, L, M, N), grip strength (O, P), and HbA1c (Q)

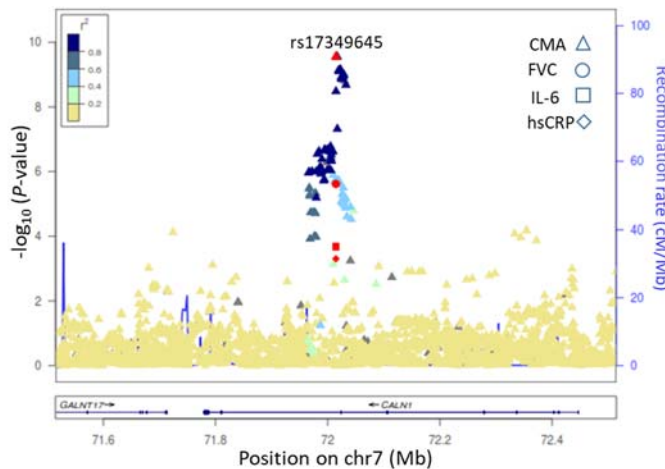
(A) FVC_IL6_hsCRP: rs67112407



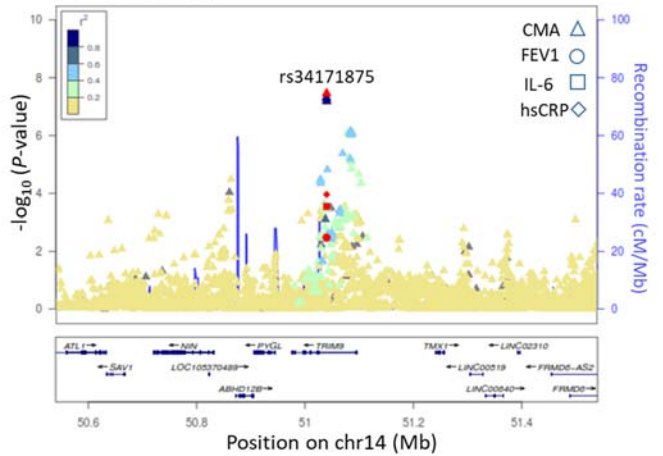
(B) FEV1_IL-6_hsCRP: rs17349645



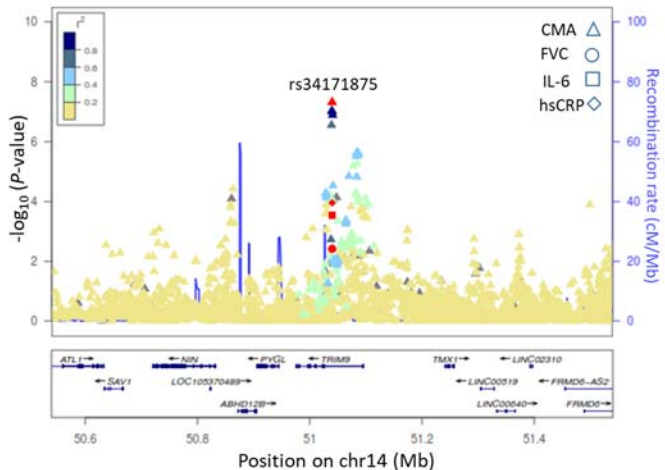
(C) FVC_IL-6_hsCRP: rs17349645



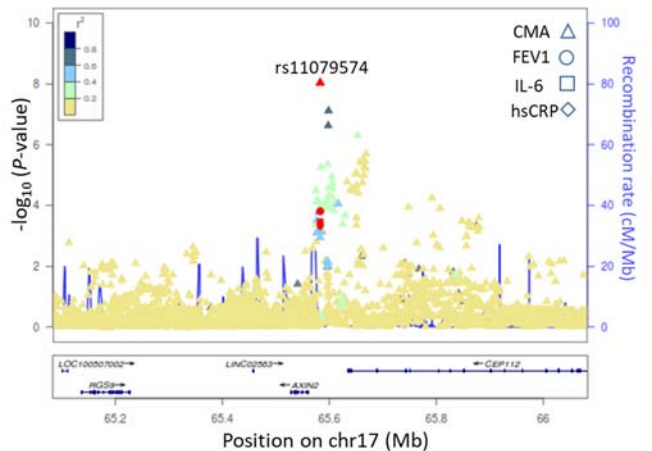
(D) FEV1_IL-6_hsCRP: rs34171875



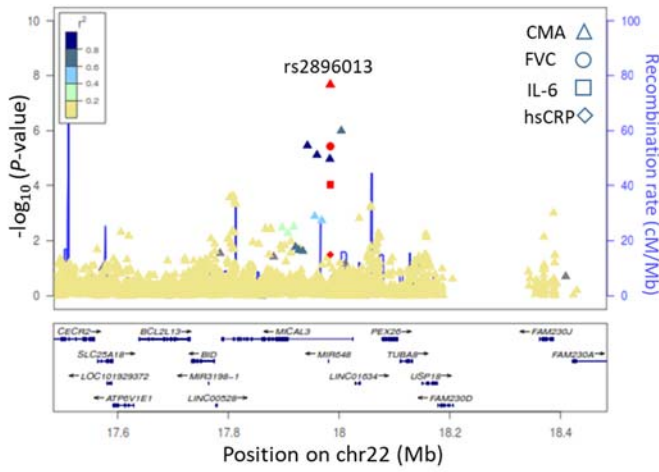
(E) FVC_IL-6_hsCRP: rs34171875



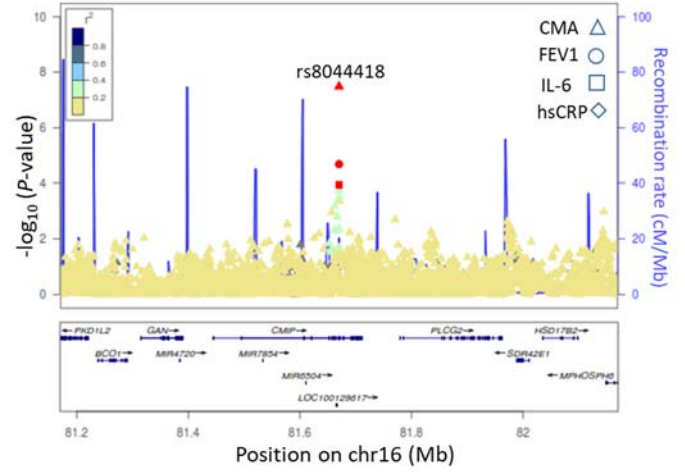
(F) FEV1_IL-6_hsCRP: rs11079574



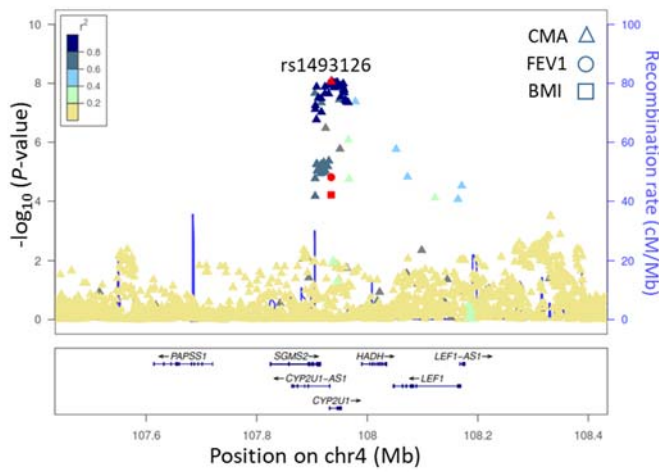
(G) FVC_IL-6_hsCRP: rs2896013



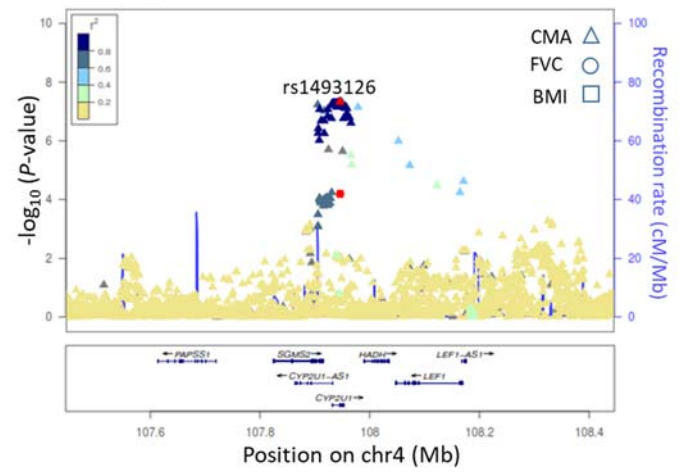
(H) FEV1_hsCRP: rs8044418



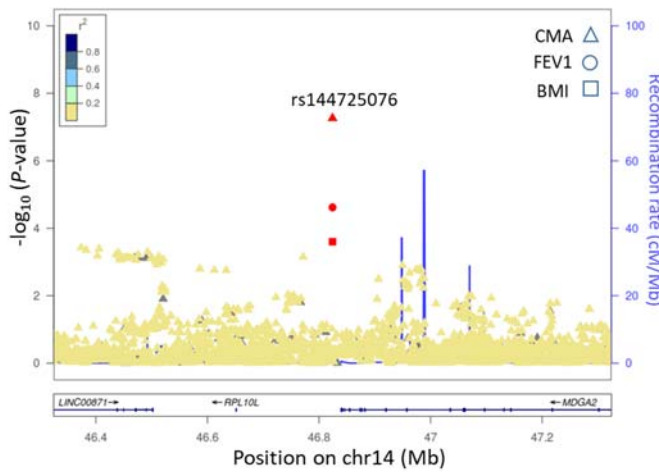
(I) FEV1_BMI: rs1493126



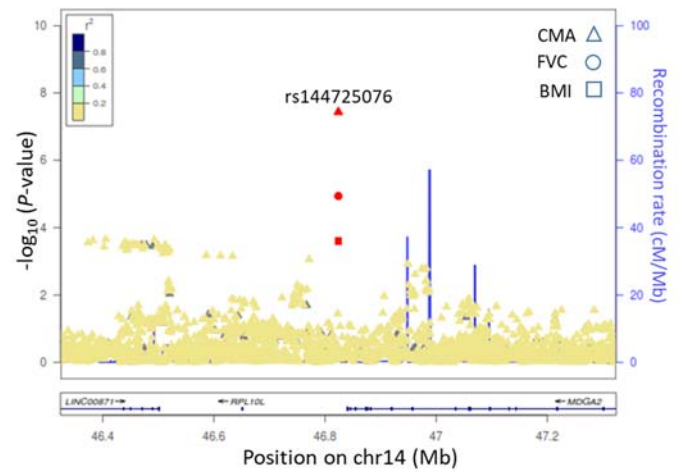
(J) FVC_BMI: rs1493126



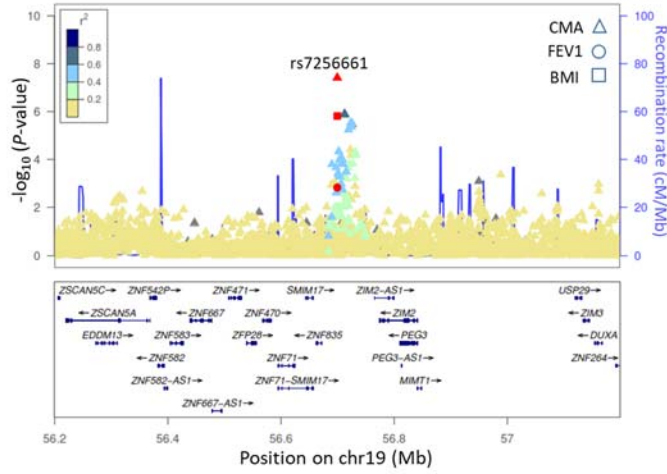
(K) FEV1_BMI: rs144725076



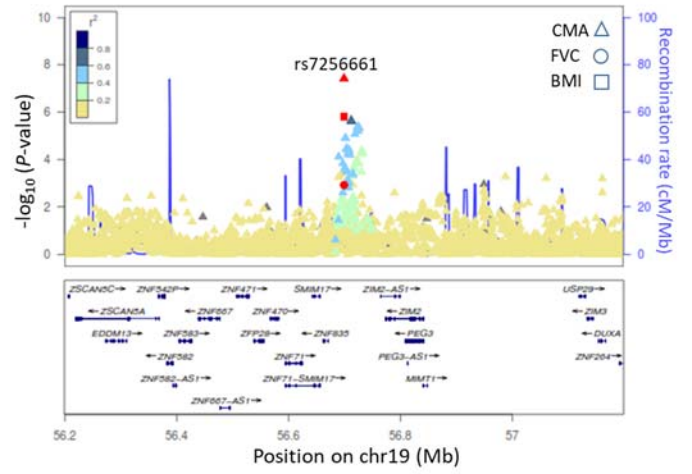
(L) FVC_BMI: rs144725076



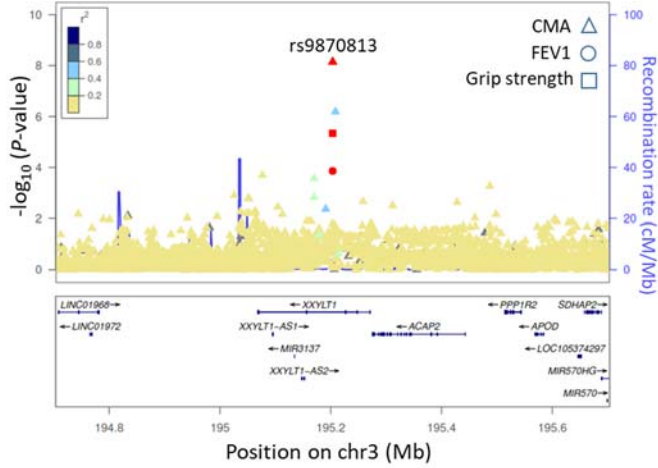
(M) FEV1_BMI: rs7256661



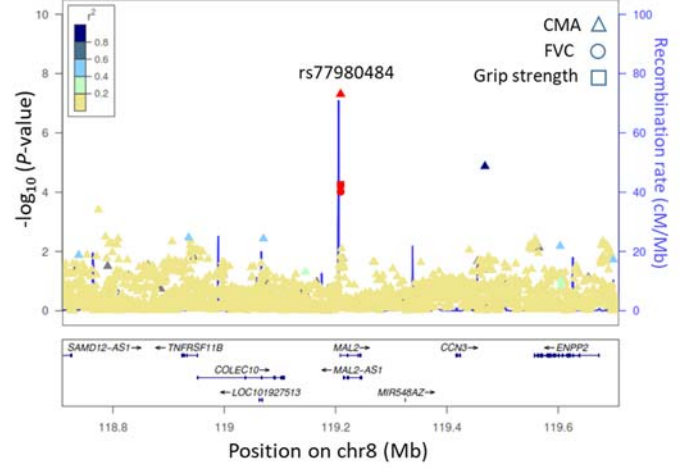
(N) FVC_BMI: rs7256661



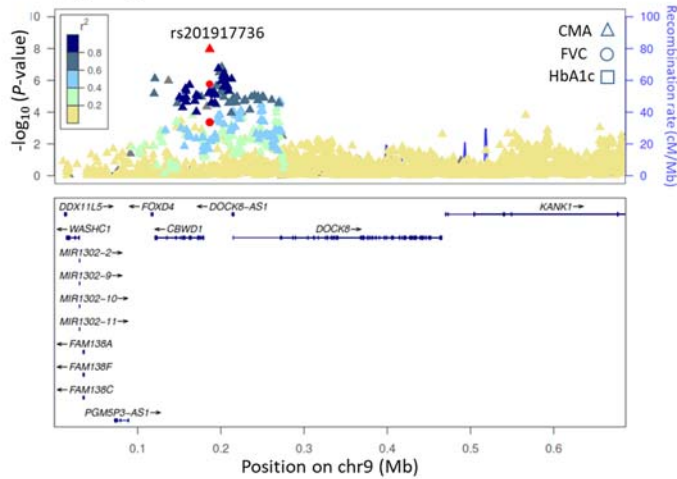
(O) FEV1_Grip strength: rs9870813



(P) FVC_Grip strength: rs77980484

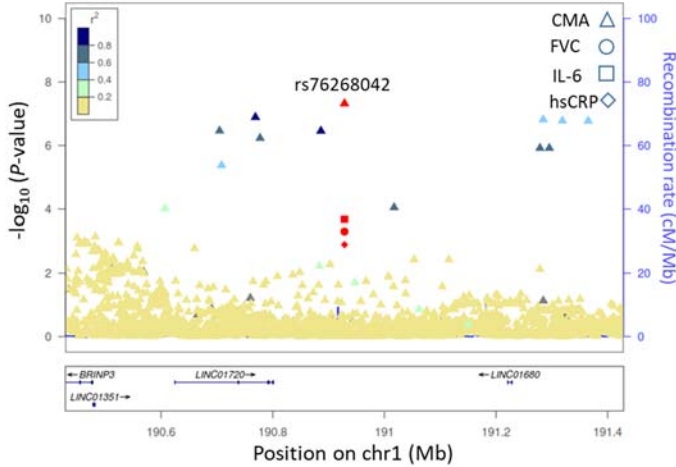


(Q) FVC_HbA1c: rs201917736

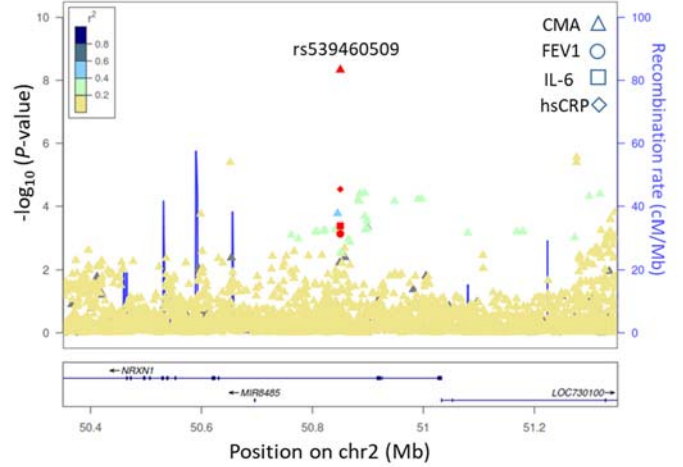


Supplementary Figure 5. Locuszoom plots of CMA for sex-specific associated variants between pulmonary function and inflammatory markers (Men: M1 – M12, Women: W1 – W11), BMI (Men: M13 – M14), grip strength (Women: W12 – W14), and HbA1c (Women: W15)

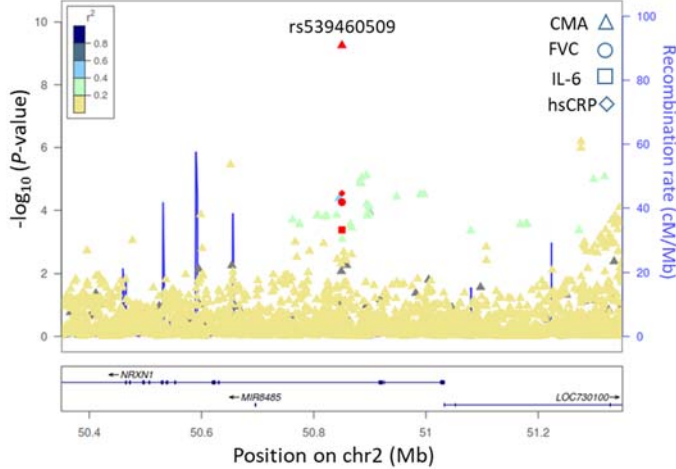
(M1) Men FVC_IL6_hsCRP: rs76268042



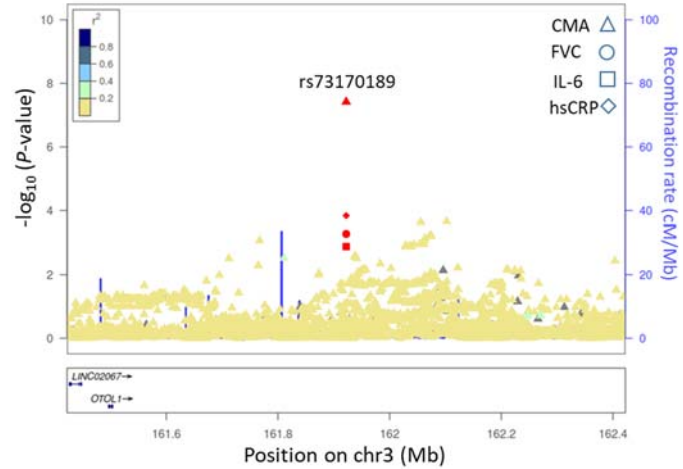
(M2) Men FEV1_IL6_hsCRP: rs539460509



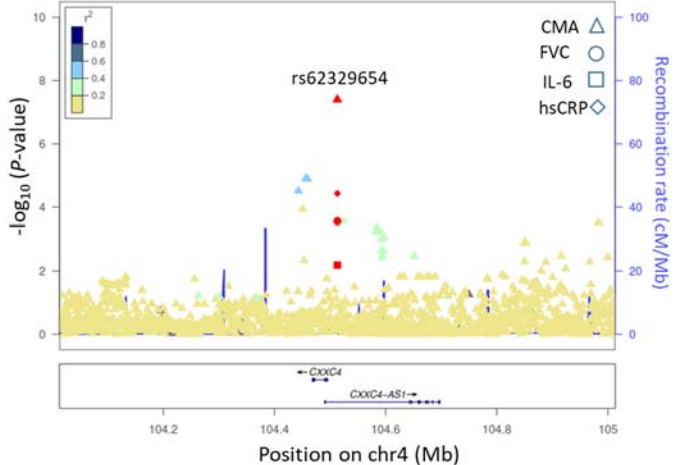
(M3) Men FVC_IL6_hsCRP: rs539460509



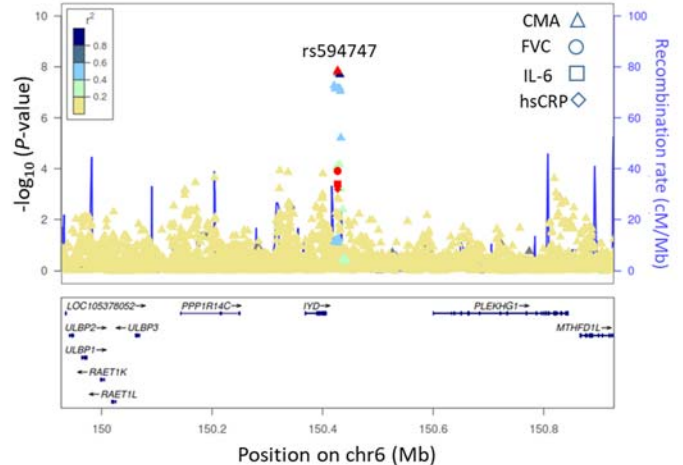
(M4) Men FVC_IL6_hsCRP: rs73170189



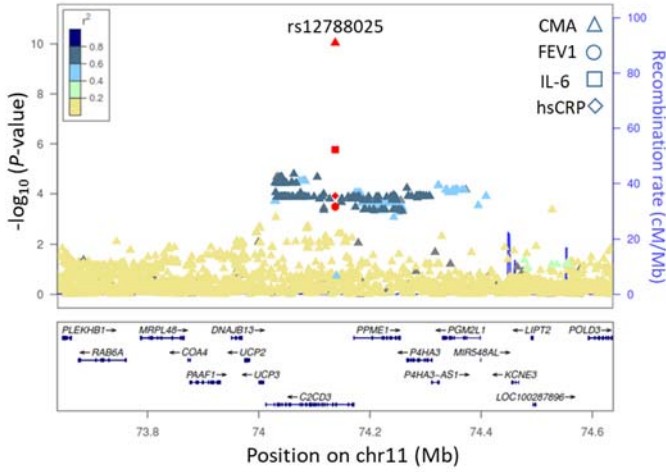
(M5) Men FVC_IL6_hsCRP: rs62329654



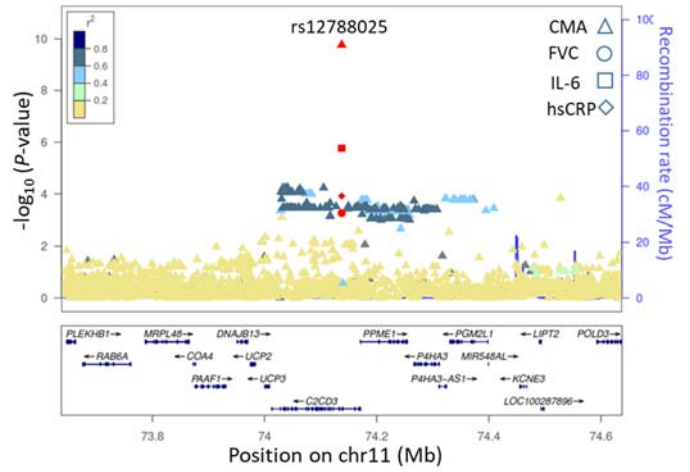
(M6) Men FVC_IL6_hsCRP: rs594747



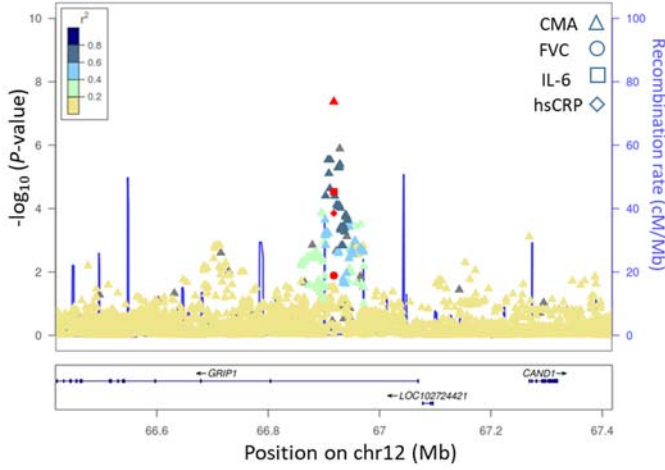
(M7) Men FEV1_IL6_hsCRP: rs12788025



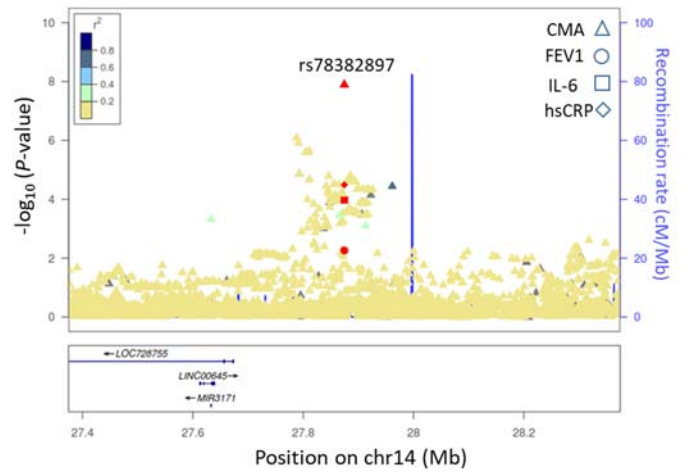
(M8) Men FVC_IL6_hsCRP: rs12788025



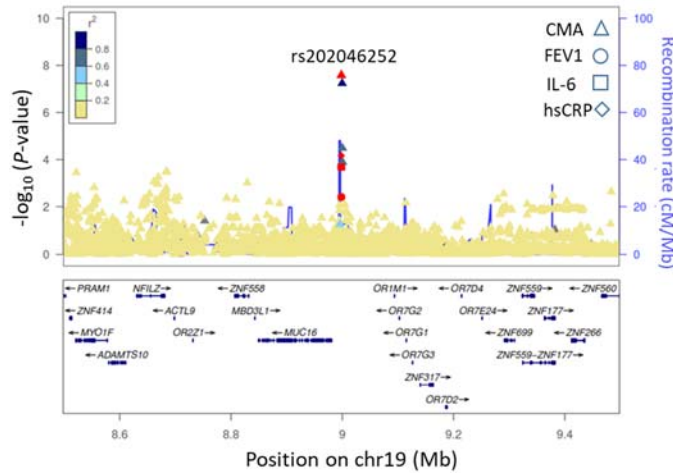
(M9) Men FVC_IL-6_hsCRP: rs58387290



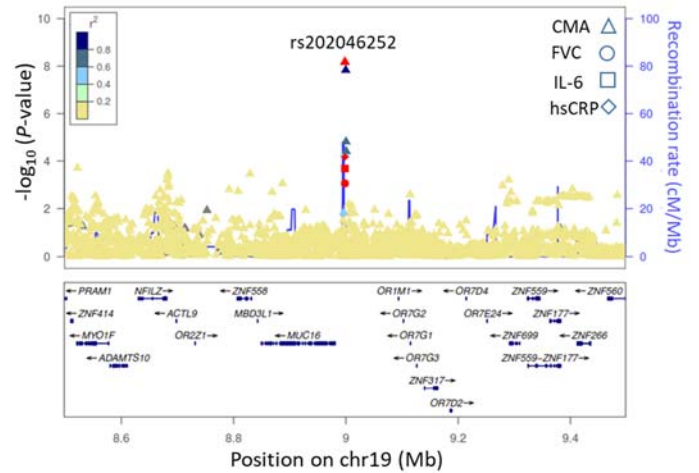
(M10) Men FEV1_IL6_hsCRP: rs78382897



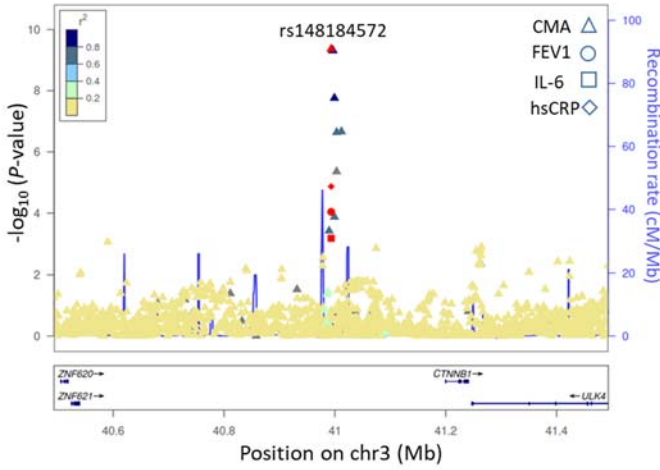
(M11) Men FEV1_IL6_hsCRP: rs202046252



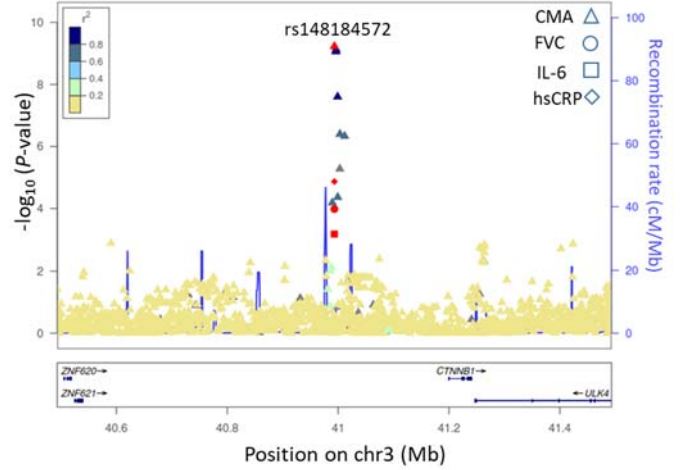
(M12) Men FVC_IL6_hsCRP: rs202046252



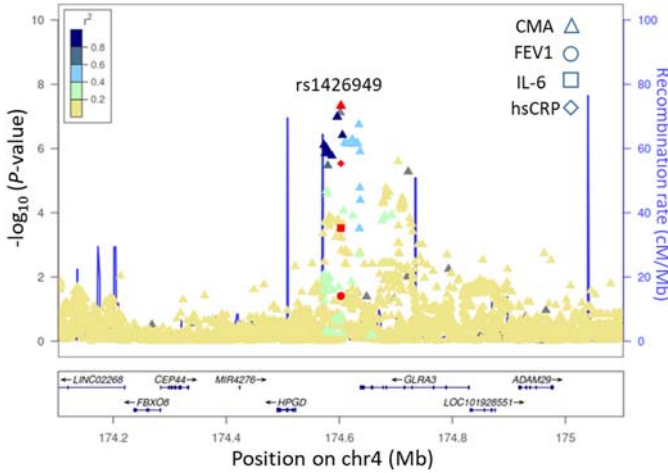
(W1) Women FEV1_IL-6_hsCRP: rs148184572



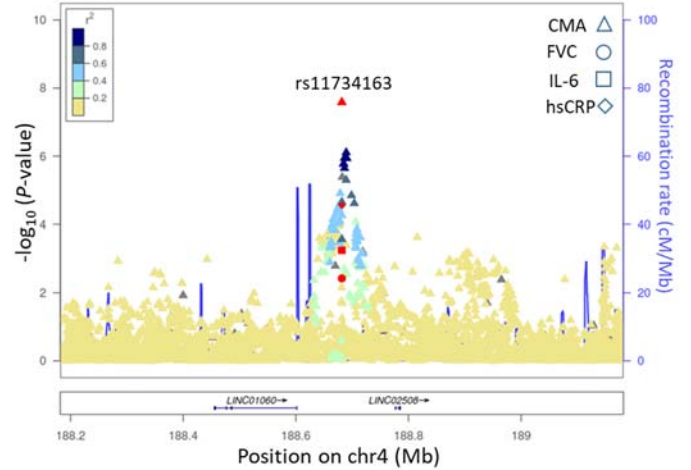
(W2) Women FVC_IL-6_hsCRP: rs148184572



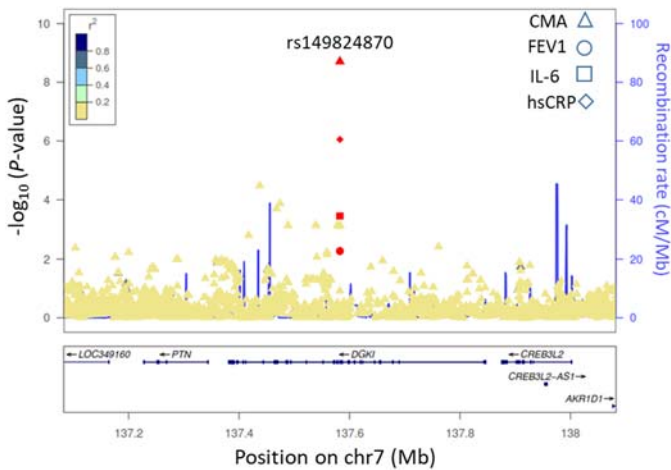
(W3) Women FEV1_IL-6_hsCRP: rs1426949



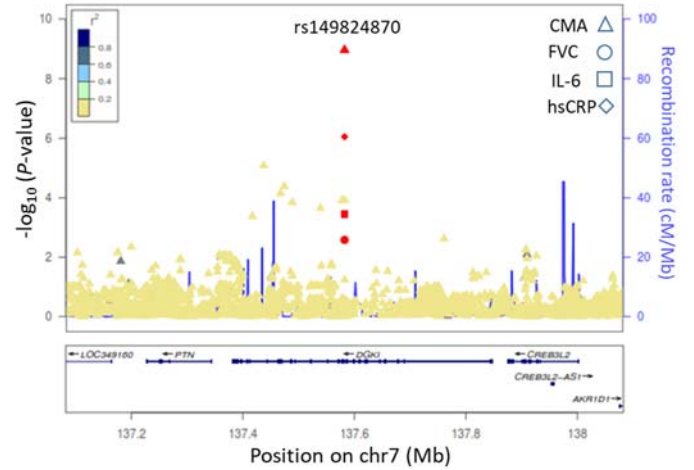
(W4) Women FVC_IL-6_hsCRP: rs11734163

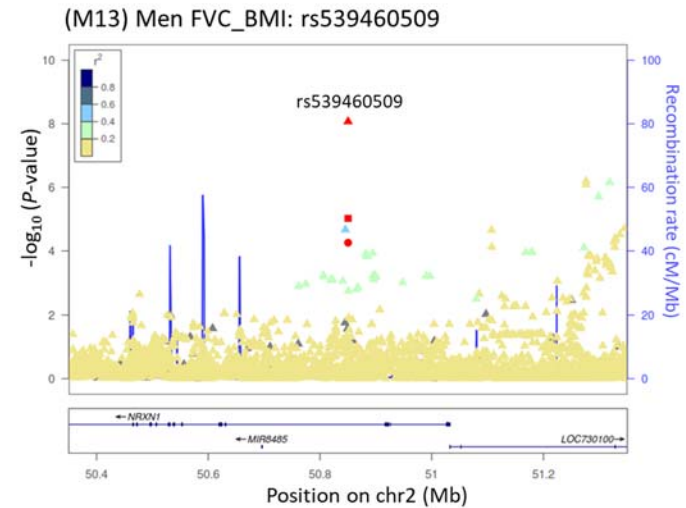
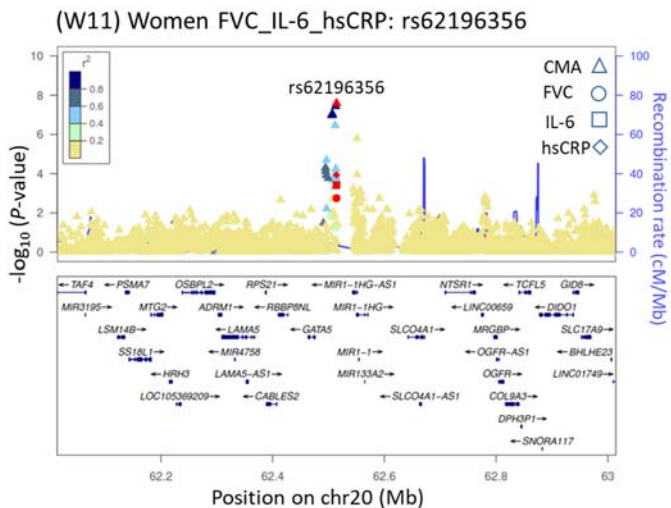
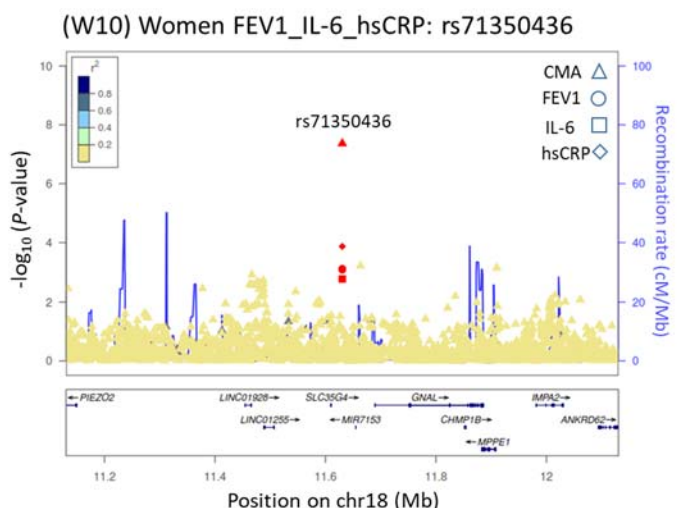
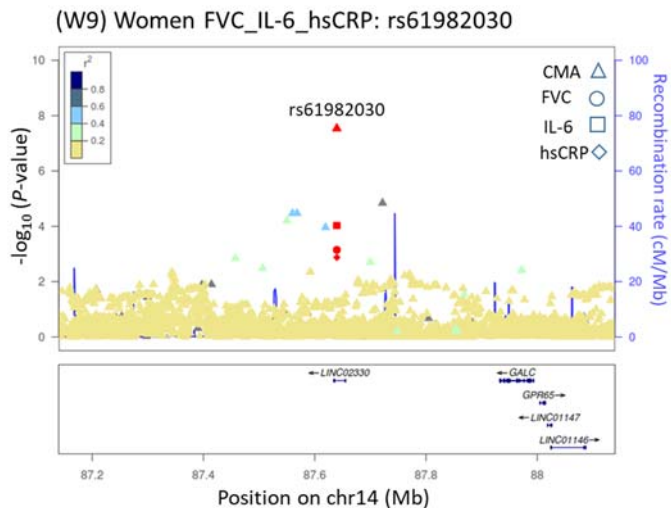
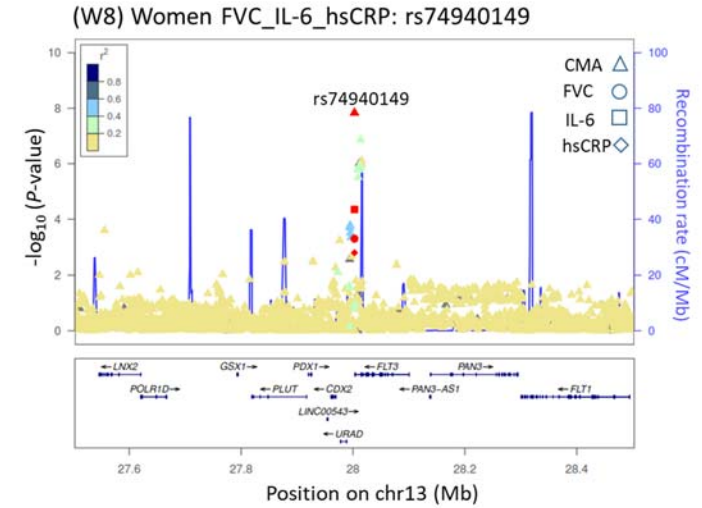
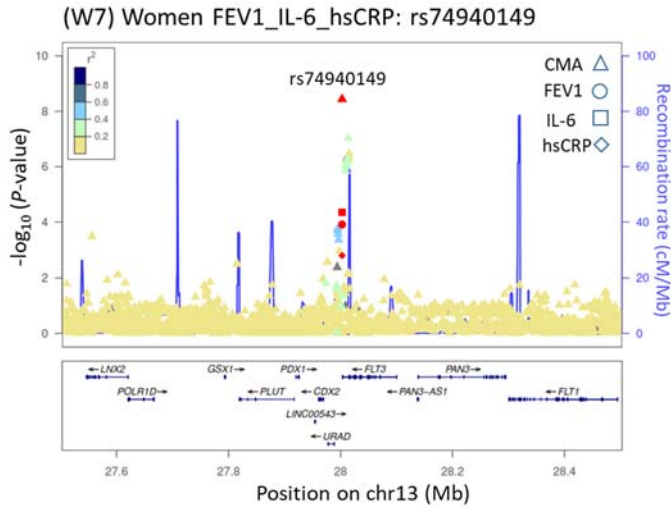


(W5) Women FEV1_IL-6_hsCRP: rs149824870

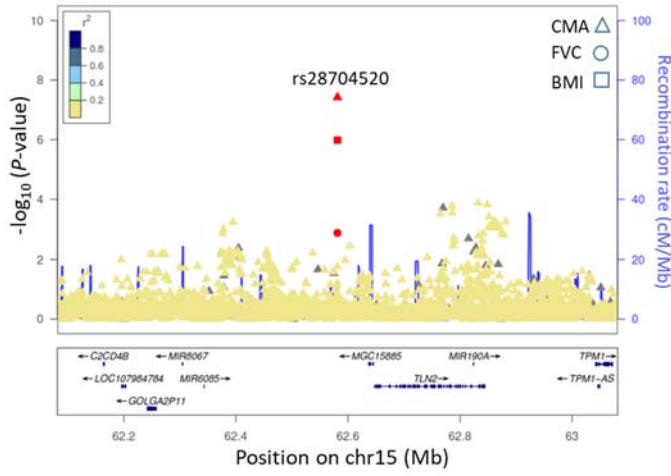


(W6) Women FVC_IL-6_hsCRP: rs149824870

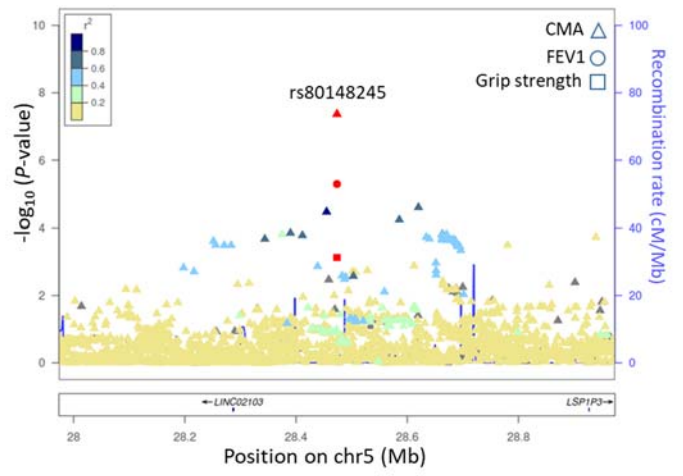




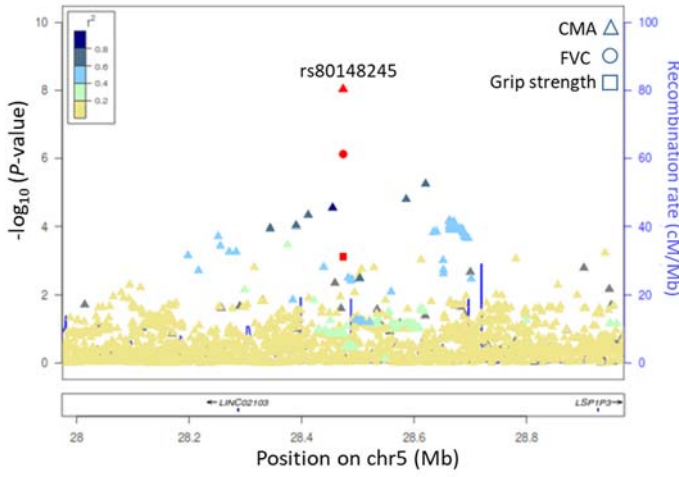
(M14) Men FVC_BMI: rs28704520



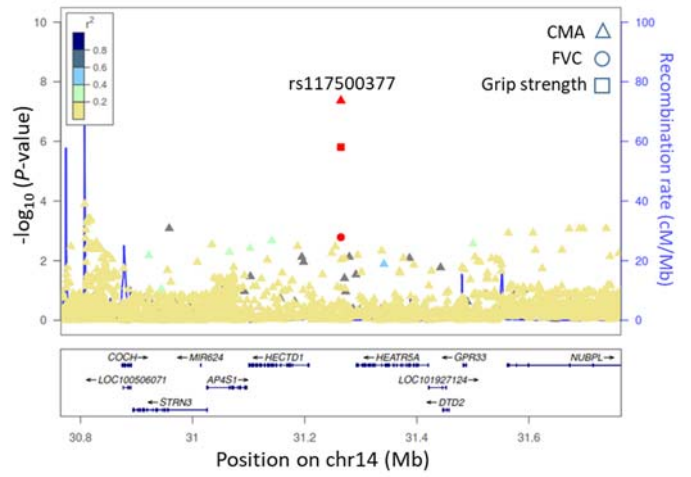
(W12) Women FEV1_Grip strength: rs80148245



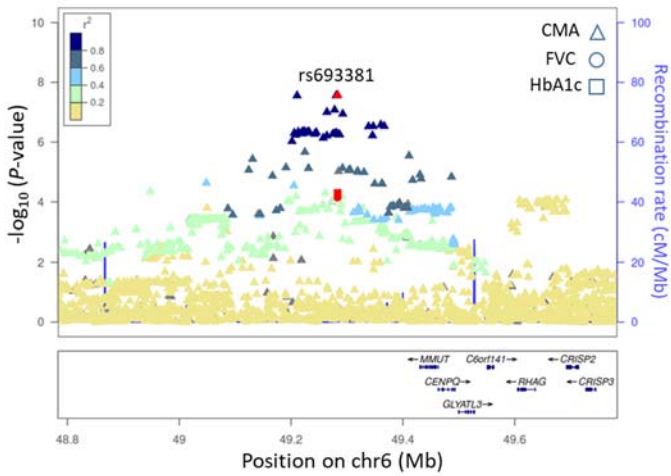
(W13) Women FVC_Grip strength: rs80148245



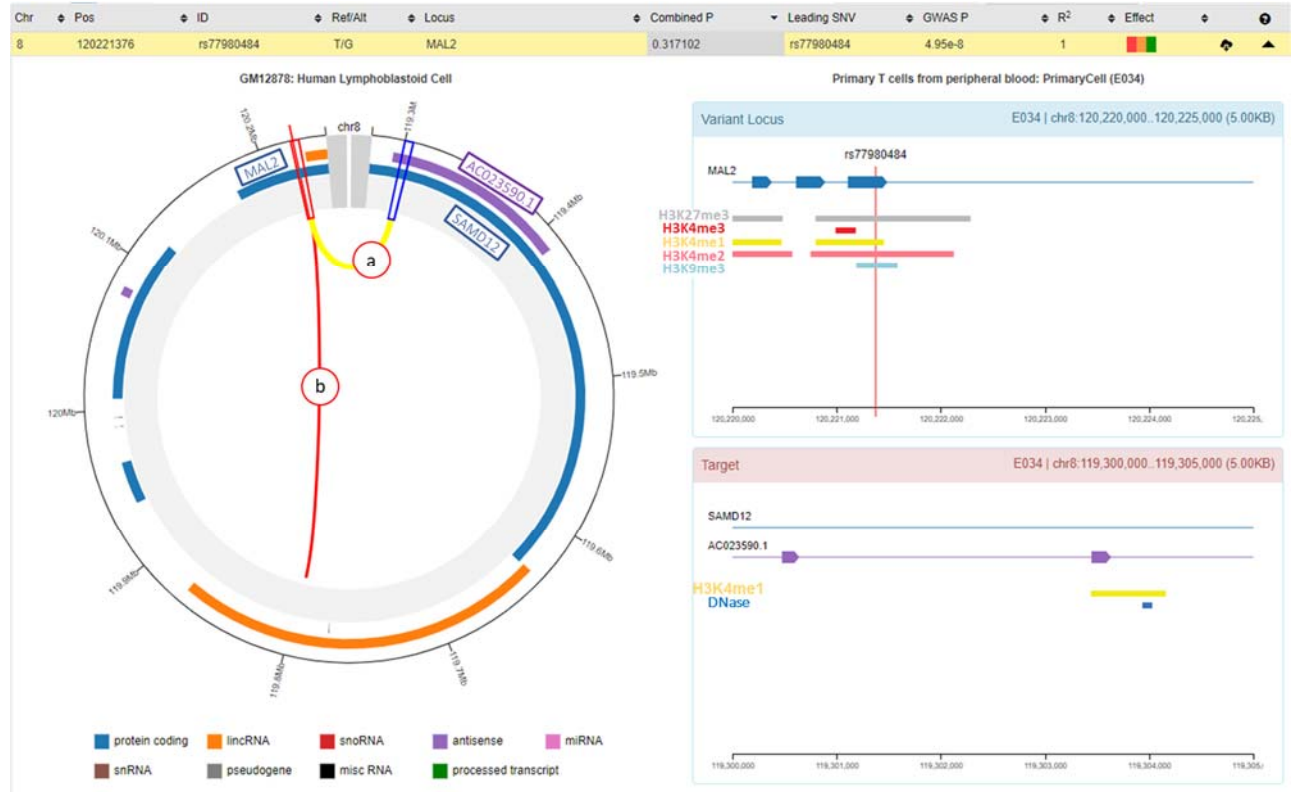
(W14) Women FVC_Grip strength: rs117500377



(W15) Women FVC_HbA1c: rs693381

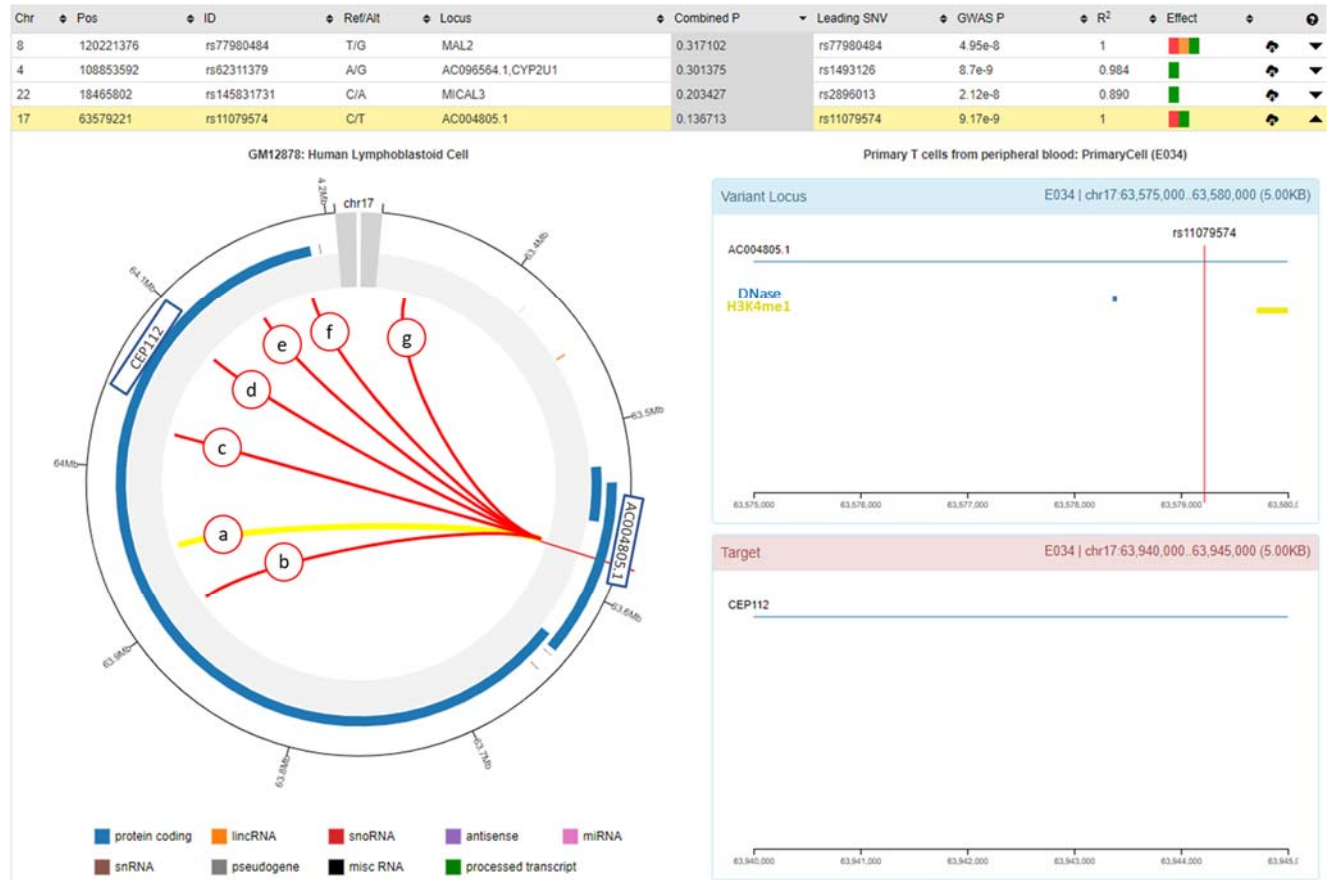


Supplementary Figure 6. GWAS4D regulatory features of rs77980484 (8q24.12) on T-cells from peripheral blood



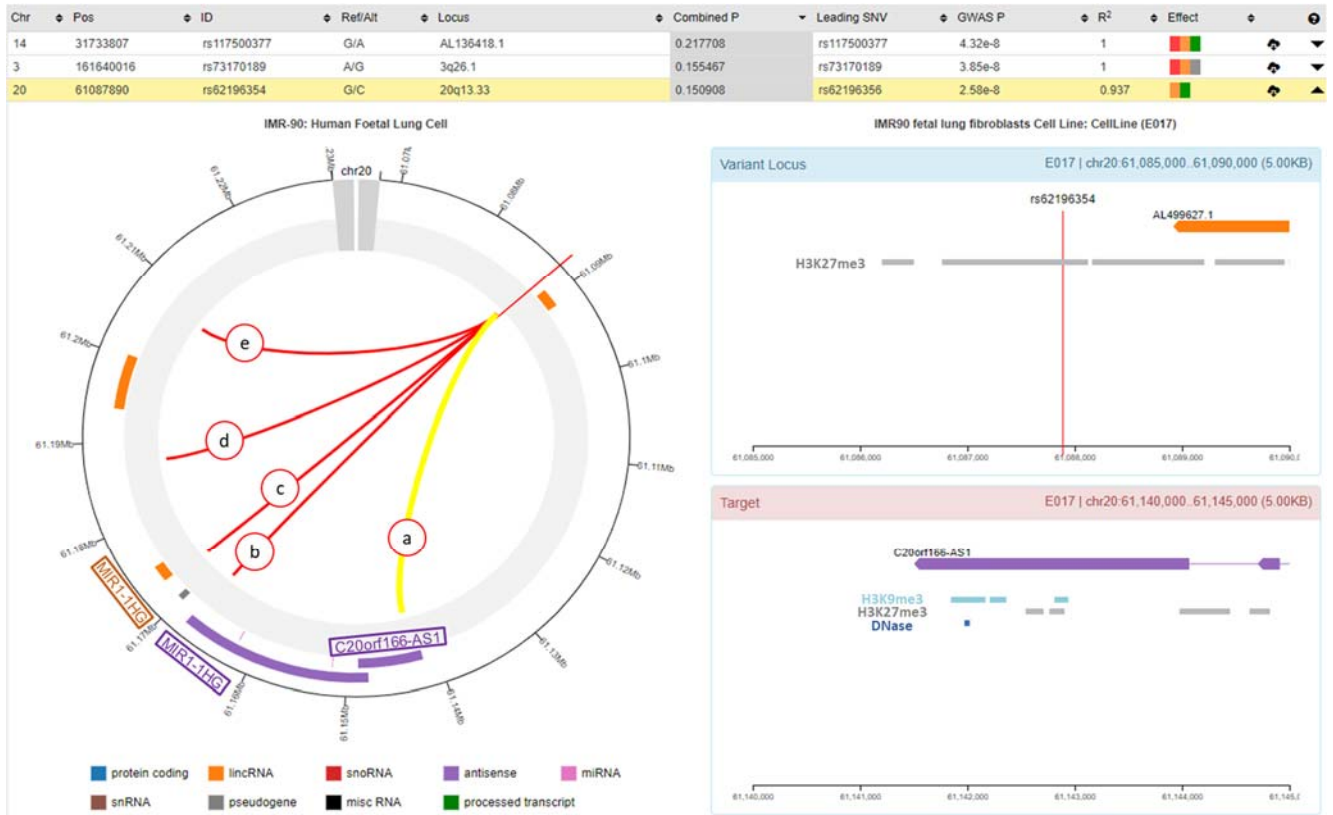
Notes: Chr = chromosome; Pos = Position (GRCh37, hg19); ID = prioritized regulatory variant; Ref/Alt = Reference and alternative alleles; Combined p = Combined regulatory probability; Leading SNP = The most significant SNP; GWAS p = correlated meta-analysis p -value; r^2 = square correlation coefficient between ID SNP and leading SNP (see Supplementary Table 11). The prioritized SNP rs77980484, residing on the *MAL* locus, indicated regulatory features on primary T-cells from peripheral blood. The uniform processes of Hi-C data at 5kb resolution are represented at spatiotemporal level (left graphic). Significant Hi-C interactions (internal lines) were detected between *MAL* intronic- rs77980484 with (a) *SAMD12* / *AC023590.1* (1.69) and (b) lincRNA *SAMD12-AS1* (1.60). rs77980484 is located in the histone acetyltransferase activity (H3) regions. *SAMD12* is located in H3 regions and DNase hypersensitivity site (for "a", right-bottom graphic).

Supplementary Figure 7. GWAS4D regulatory features of rs11079574 (17q23-q24.1) on T-cells from peripheral blood



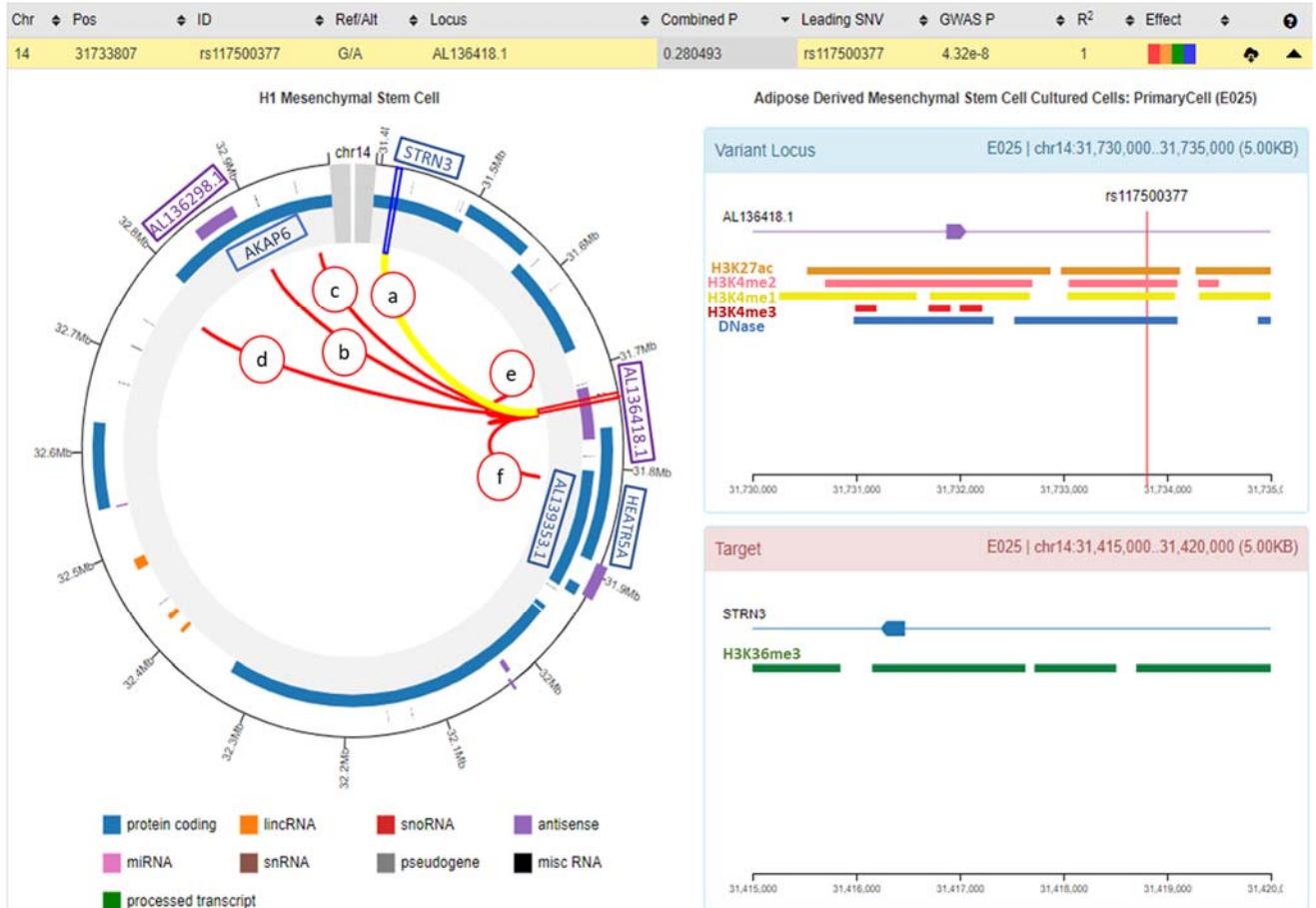
Notes: Chr = chromosome; Pos = Position (GRCh37, hg19); ID = prioritized regulatory variant; Ref/Alt = Reference and alternative alleles; Combined p = Combined regulatory probability; Leading SNP = The most significant SNP; GWAS p = correlated meta-analysis p -value; r^2 = square correlation coefficient between ID SNP and leading SNP (see [Supplementary Table 11](#)). The prioritized SNP rs11079574, residing on *AC004805* gene, indicated regulatory features on primary T-cells from peripheral blood. The uniform processes of Hi-C data at 5kb resolution are represented at spatiotemporal level (left graphic). Significant Hi-C interactions (internal lines) were detected between rs11079574 with (a-f) *CEP112* (1.32 - 1.56) and (g) 63,34 Mb (1.35). rs11079574 is located in the histone acetyltransferase activity (H3) region and DNase hypersensitivity site.

Supplementary Figure 8. GWAS4D regulatory features of rs62196354 (20q13.33) on fetal lung cell lines



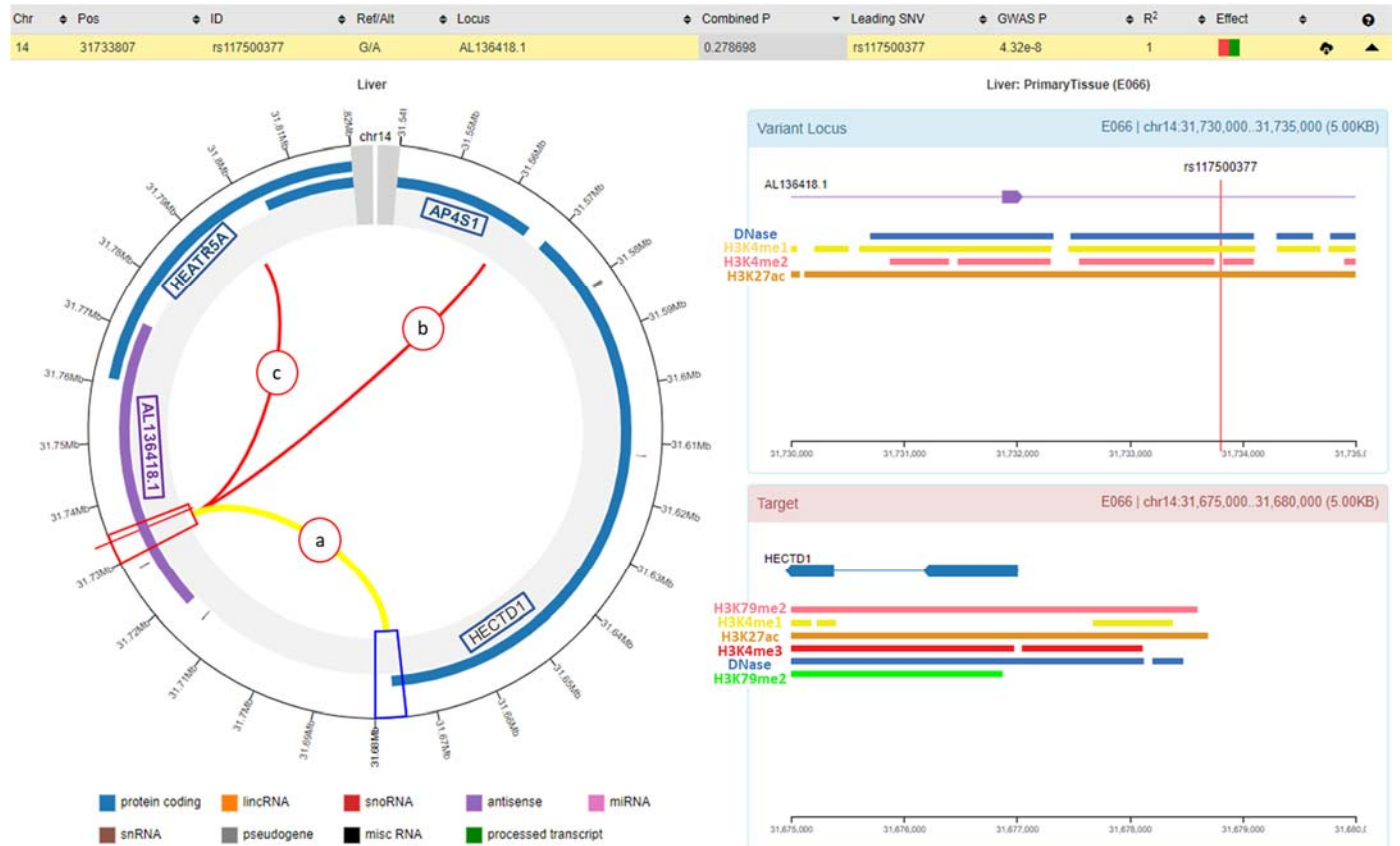
Notes: Chr = chromosome; Pos = Position (GRCh37, hg19); ID = prioritized regulatory variant; Ref/Alt = Reference and alternative alleles; Combined p = Combined regulatory probability; Leading SNP = The most significant SNP; GWAS p = correlated meta-analysis p -value; r^2 = square correlation coefficient between ID SNP and leading SNP (see [Supplementary Table 11](#)). The prioritized rs62196354 indicated regulatory features on fetal lung cell lines. The uniform processes of Hi-C data at 5kb resolution are represented at spatiotemporal level (left graphic). Significant HI-C interactions (a-e internal lines) were detected between rs62196354 with (a) *C20orf166-AS1* (2.09), (b) *MIR1-1HG* (1.97), (c) *RPL7P3 / BX640514.1* (1.53), (d) 61.19 Mb (1.47), (e) 61.2 Mb (1.68). rs62196354 is located in histone acetyltransferase activity towards (H3) region (right-top graphic). *C20orf166-AS1* is located in H3 regions and in DNase hypersensitivity site (right-bottom graphic).

Supplementary Figure 9. GWAS4D regulatory features of rs117500377 (14q12) on adipose mesenchymal stem cells



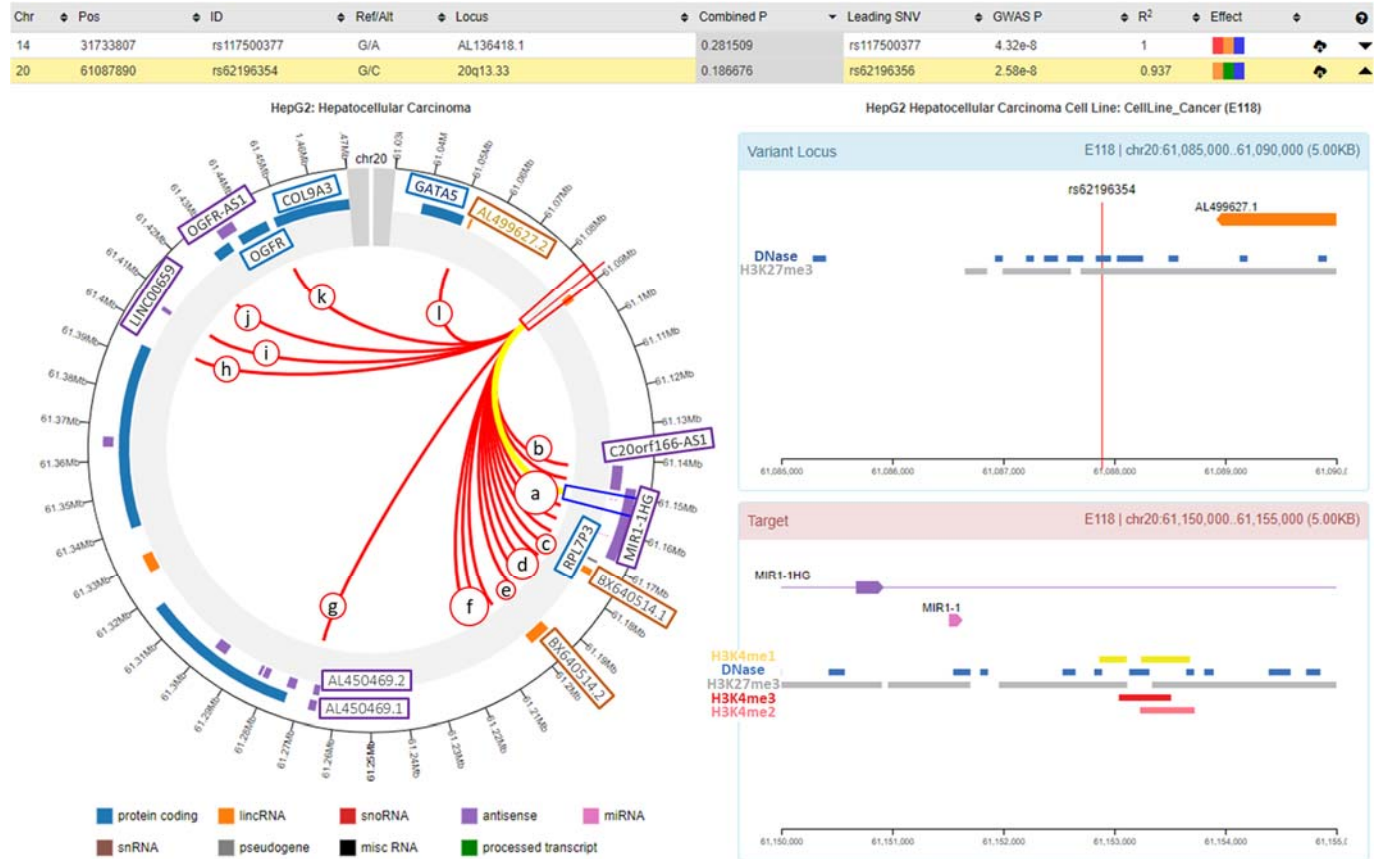
Notes: Chr = chromosome; Pos = Position (GRCh37, hg19); ID = prioritized regulatory variant; Ref/Alt = Reference and alternative alleles; Combined p = Combined regulatory probability; Leading SNP = The most significant SNP; GWAS p = correlated meta-analysis p -value; r^2 = square correlation coefficient between ID SNP and leading SNP (see [Supplementary Table 11](#)). The prioritized rs117500377, residing on antisense *AL136418.1*, indicated regulatory features on adipose derived mesenchymal stem cell. The uniform processes of Hi-C data at 5kb resolution are represented at spatiotemporal level (left graphic). Significant HI-C interactions (a-f internal lines) were detected between rs117500377 with (a) *STRN3* (score=1.99), (b, c) 32.95 Mb (scores=1.84-1.98), (d) 32.77 Mb (score=1.64), (e) 31.70 Mb (score=1.87), and (f) *HEATR5A / AL139353.1* (score=1.25). rs117500377 is located in histone acetyltransferase activity towards (H3) regions, and in DNase hypersensitivity site (right-top graphic). *STRN3* is located in H3 region (right-bottom graphic).

Supplementary Figure 10. GWAS4D regulatory features of rs117500377 (14q12) on liver



Notes: Chr = chromosome; Pos = Position (GRCh37, hg19); ID = prioritized regulatory variant; Ref/Alt = Reference and alternative alleles; Combined p = Combined regulatory probability; Leading SNP = The most significant SNP; GWAS p = correlated meta-analysis p -value; r^2 = square correlation coefficient between ID SNP and leading SNP (see Supplementary Table 11). The prioritized rs117500377, residing on antisense *AL136418.1*, indicated regulatory features on liver. Significant HI-C interactions (a-c internal lines) were detected between rs117500377 with (a) *HECTD1* (2.05), (b) *AKAP6* (1.71), (c) *HEATR5A* (1.52). rs117500377 is located in histone acetyltransferase activity towards (H3) regions and in DNase hypersensitivity site (right-top graphic). *HECTD1* is located in H3 regions and in DNase hypersensitivity site (right-bottom graphic).

Supplementary Figure 11. GWAS4D regulatory features of rs62196354 (20q13.33) on hepatocellular carcinoma cell line



Notes: Chr = chromosome; Pos = Position (GRCh37, hg19); ID = prioritized regulatory variant; Ref/Alt = Reference and alternative alleles; Combined p = Combined regulatory probability; Leading SNP = The most significant SNP; GWAS p = correlated meta-analysis p -value; r^2 = square correlation coefficient between ID SNP and leading SNP (see Supplementary Table 11). The prioritized rs62196354 indicated regulatory features on hepatocellular carcinoma cell line. The uniform processes of Hi-C data at 5kb resolution are represented at spatiotemporal level (left graphic). Significant Hi-C interactions (a-f internal lines) were detected between rs62196354 (a) *MIR1-1HG* (1.40-2.24), (b) *C20orf166-AS1* (1.81), (c) *BX640514.1/RPL7P3* (1.46), (d) 61.18 Mb (1.57-1.77), (e) *BX640514.2* (1.30), (f) 61.21 Mb (1.56 – 2.03), (g) *AL450469.1/AL450469.2* (1.59), (h) 61.40 Mb (1.37), (i) *LINC00659* (1.79), (j) 61.42 Mb (1.40), (k) *OGFR/COL9A3* (1.25), (l) *GATA5/AL499627.2* (1.37). rs62196354 is located in histone acetyltransferase activity towards (H3) region and in DNase hypersensitivity site (right-top graphic). *MIR1-1HG* is located in H3 regions and in DNase hypersensitivity site (right-bottom graphic).