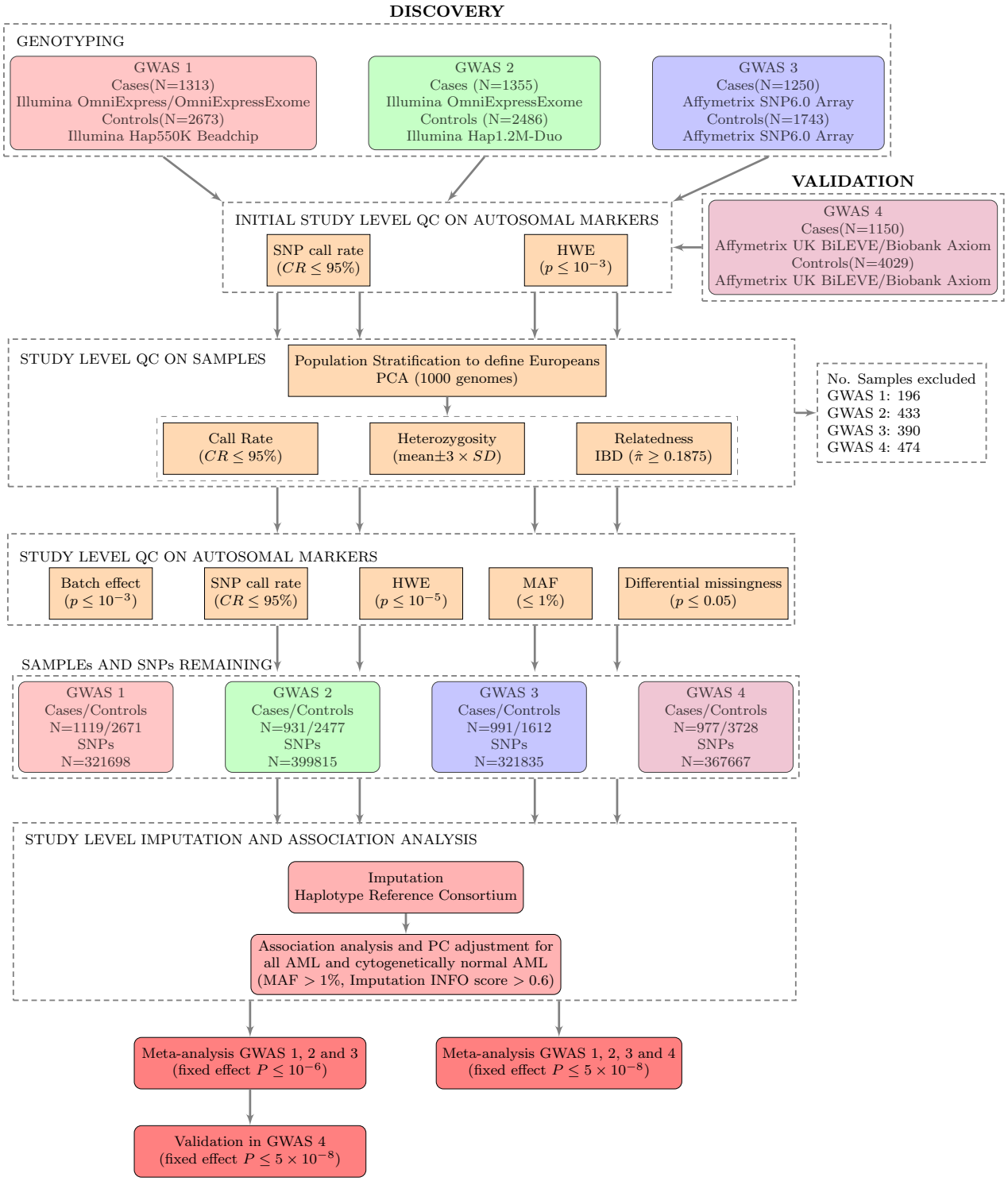
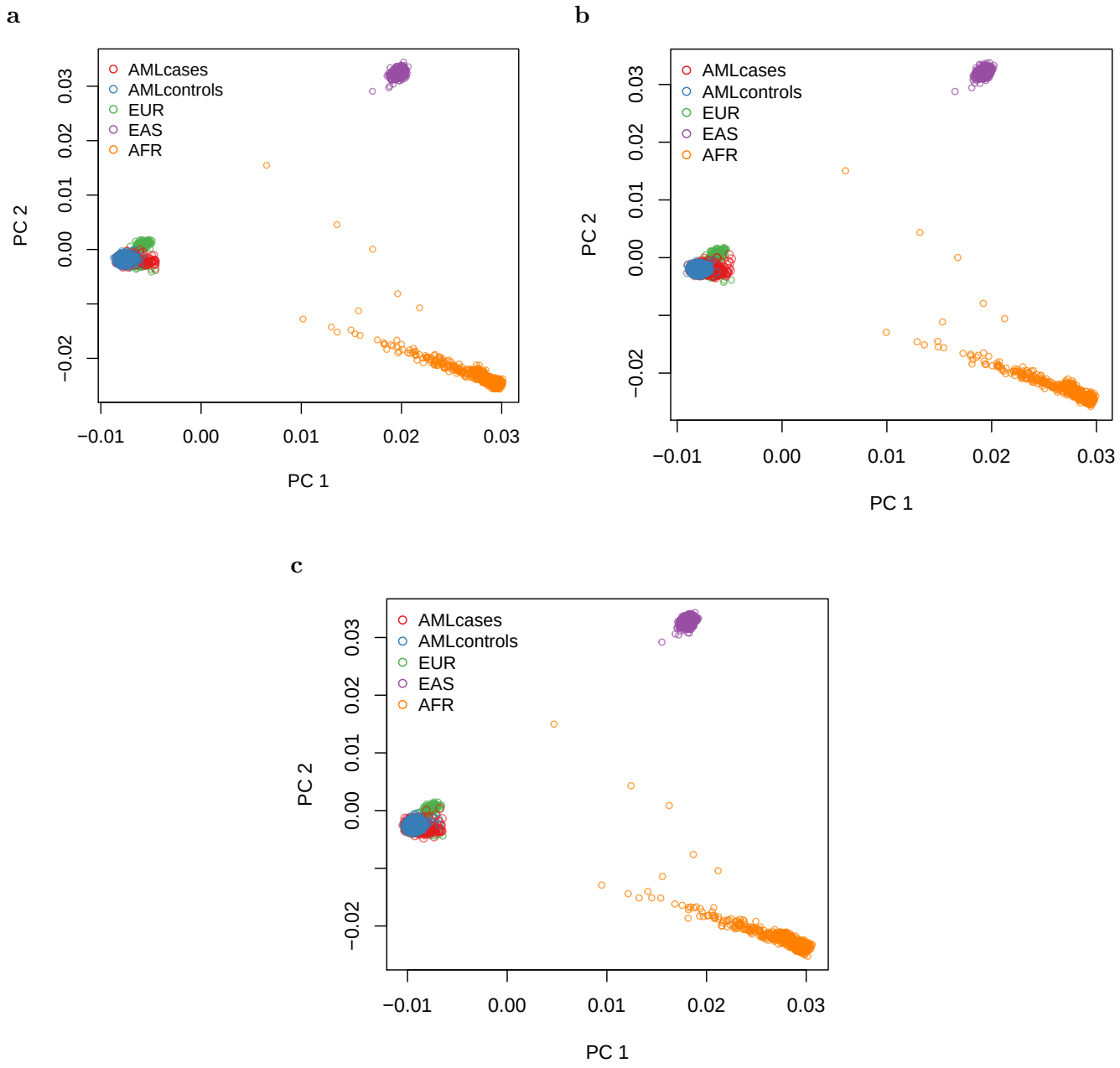
# Genome-wide association study identifies susceptibility loci for acute myeloid leukemia

Lin et al

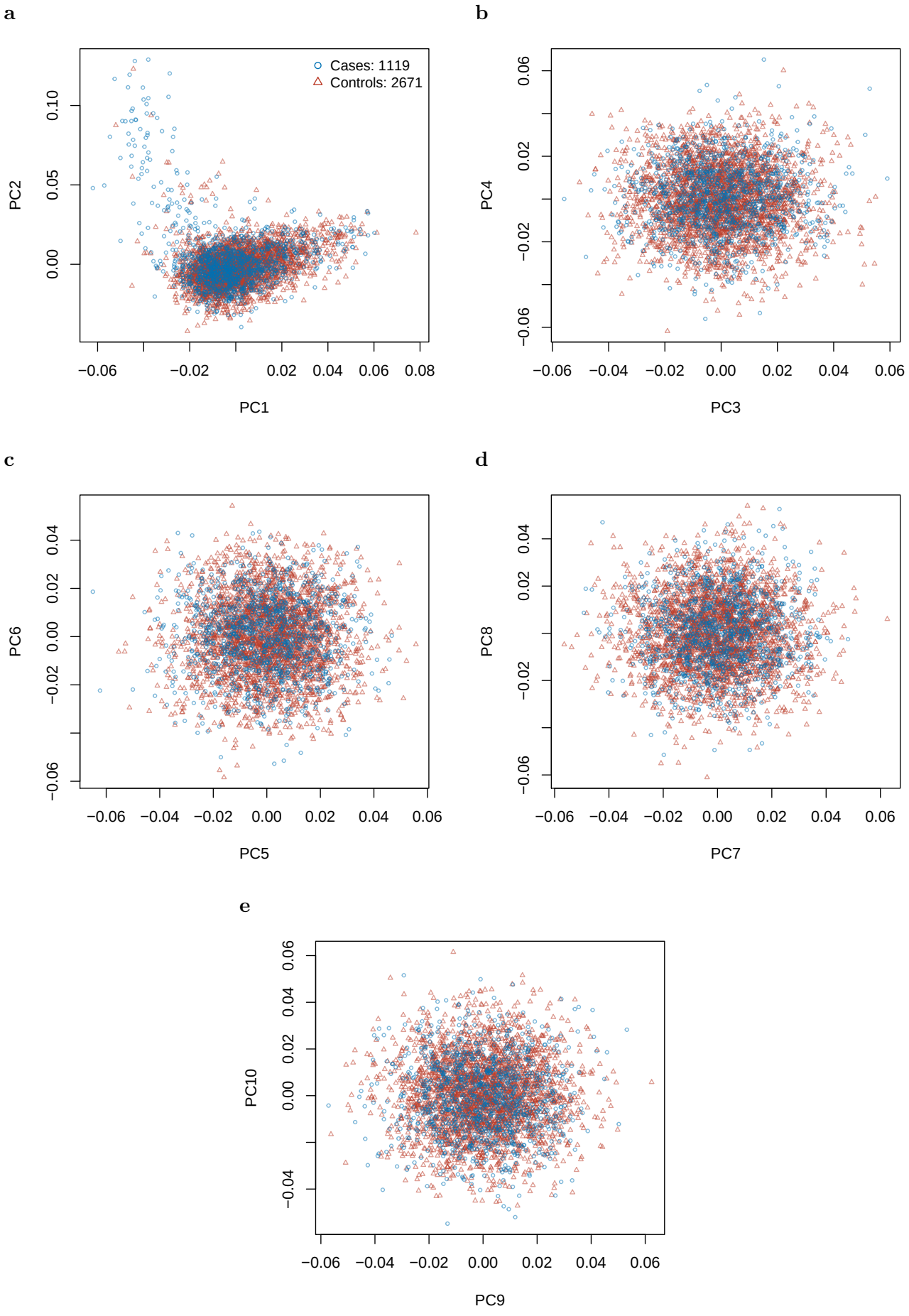
# Supplementary Figures



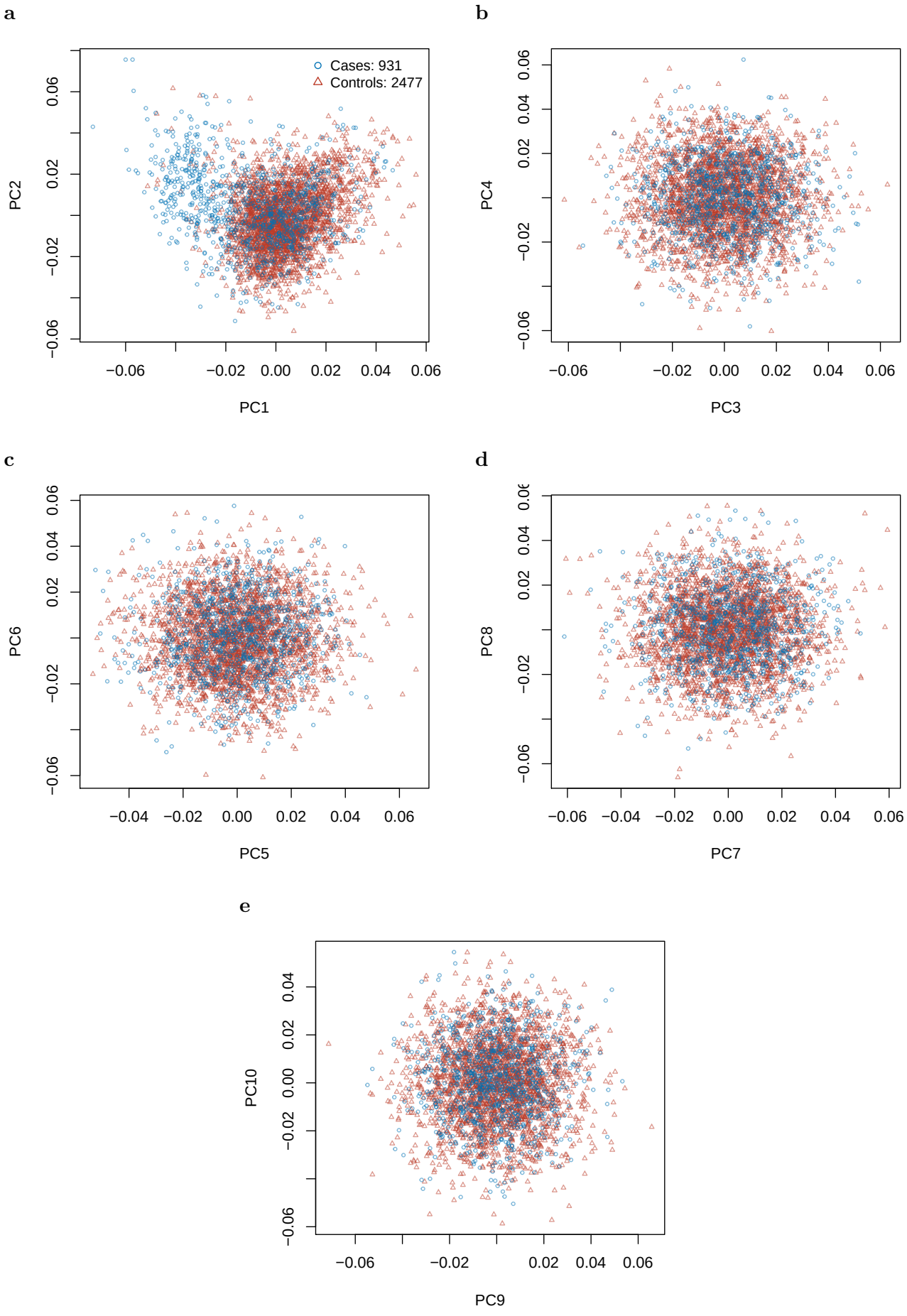

Supplementary Figure 1: **Details of data analysis workflow and quality control filters applied to each AML GWAS.** SNPs with a call rate $< 98\%$ or showing significant deviation from Hardy-Weinberg ($P \leq 10^{-3}$) were excluded. SNPs that showed significant differences ($P < 10^{-3}$) between genotype batches and with significant differences ($P < 0.05$) in missingness between cases and controls were also excluded. Samples were excluded due to low call rate ($< 95\%$), ancestry (principal components analysis), relatedness ($\pi \geq 0.1875$) or heterozygosity (mean $\pm 3\times$SD). Imputed SNPs with information score $< 0.6$ or MAF $< 0.01$ were excluded.



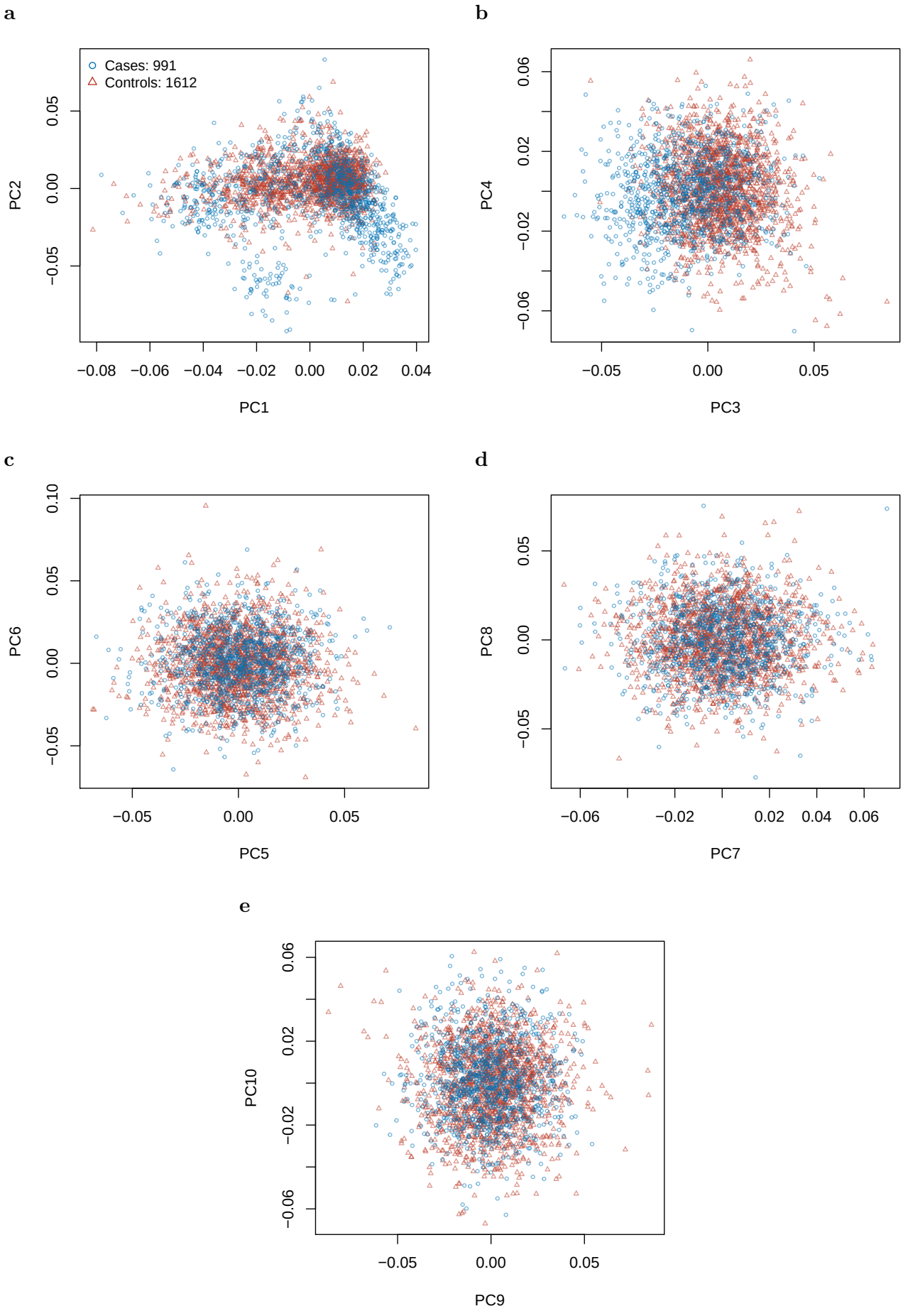

Supplementary Figure 2: **Principal component analysis (PCA) plots of ethnicity structure in a GWAS 1 b GWAS 2 c GWAS 3.** The first two principal components are shown here. European (EUR), East Asian (EAS) and African (AFR) individuals from 1000 genomes project are plotted in green, purple and orange, respectively. AML cases are plotted in red and controls are plotted in blue. PC1, principal component 1; PC2, principal component 2.



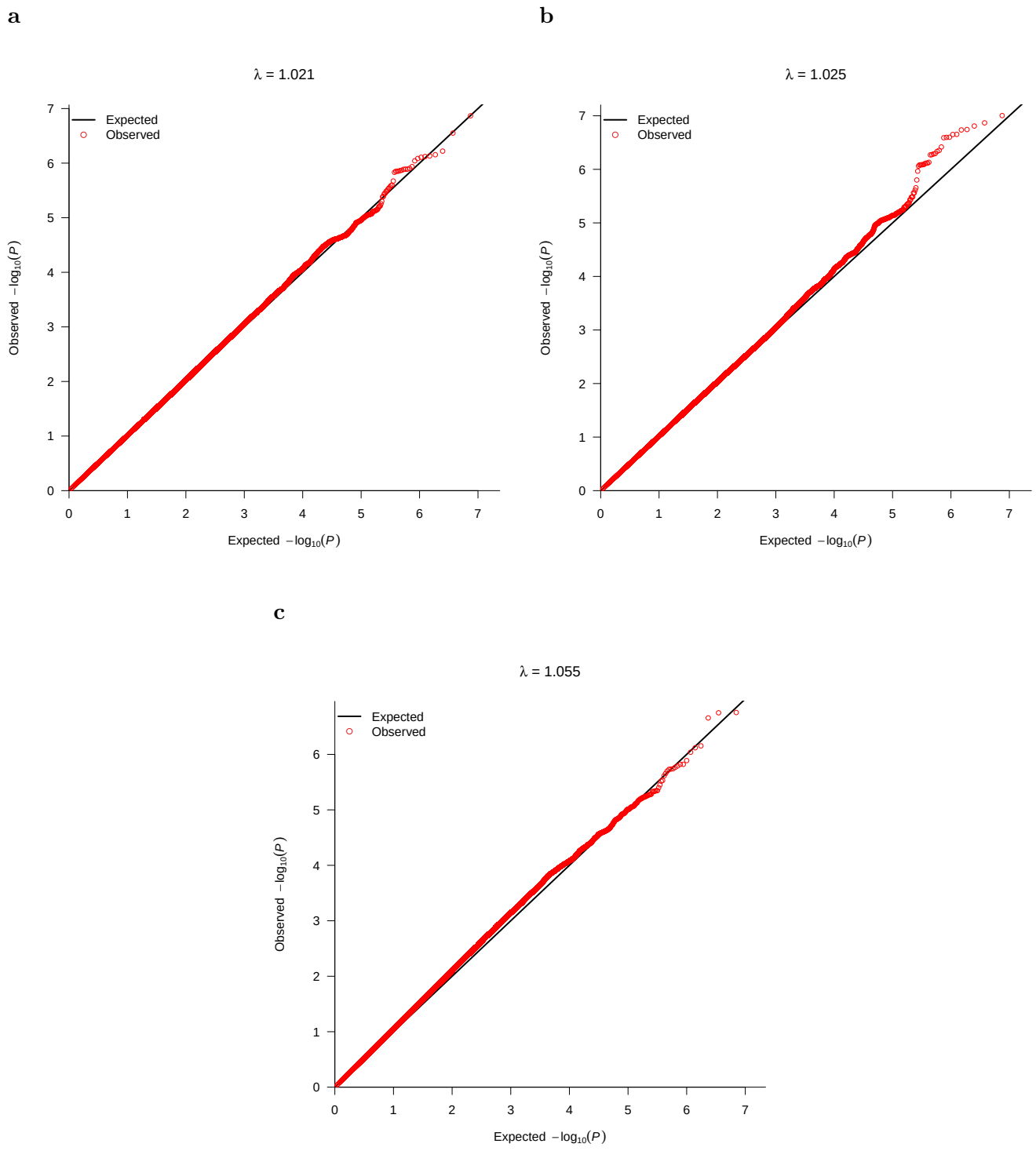

Supplementary Figure 3: PCA in GWAS 1. a PC1 and PC2. b PC3 and PC4. c PC5 and PC6. d PC7 and PC8. e PC9 and PC10.



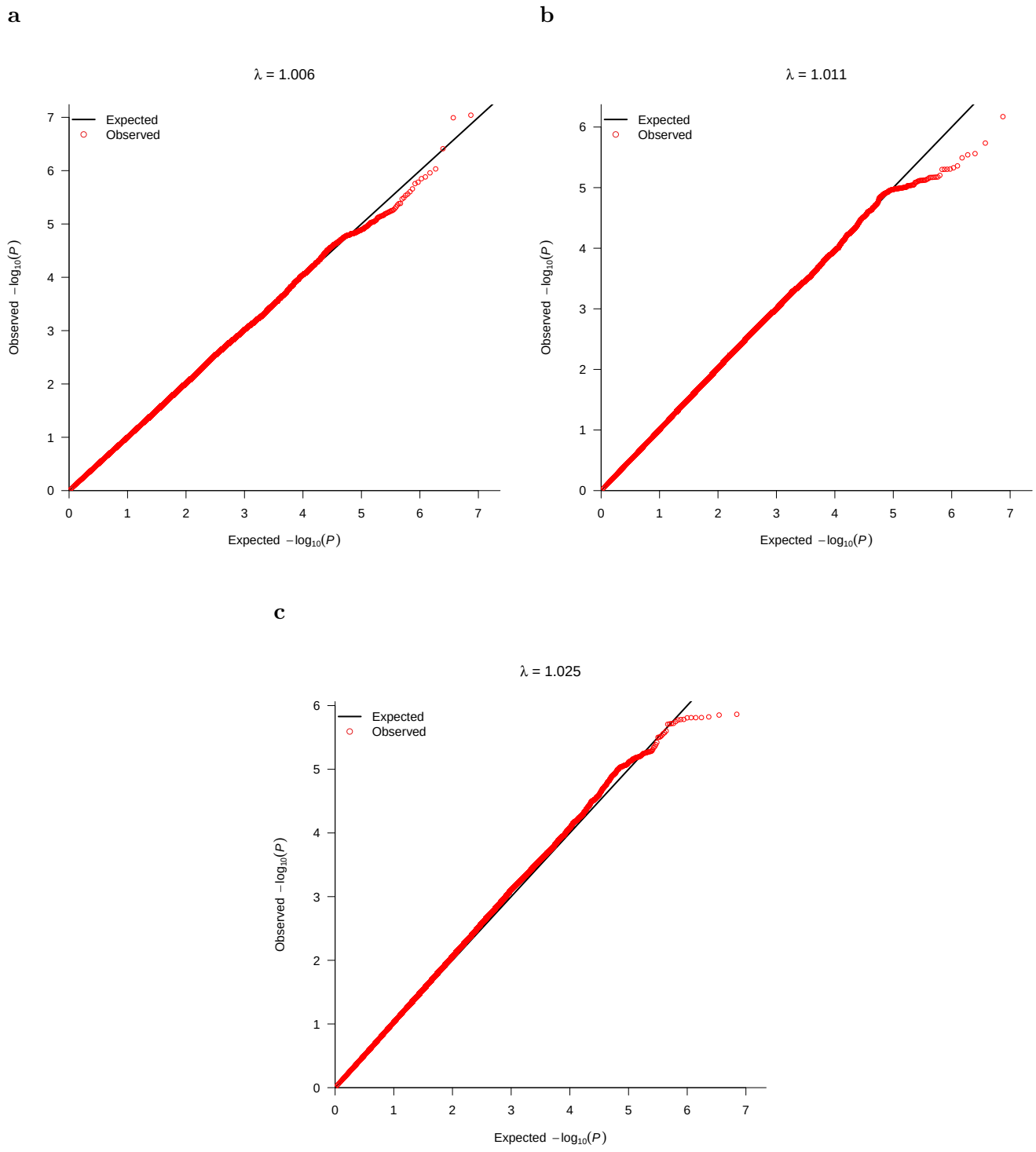

Supplementary Figure 4: PCA in GWAS 2. a PC1 and PC2. b PC3 and PC4. c PC5 and PC6. d PC7 and PC8. e PC9 and PC10.




Supplementary Figure 5: PCA in GWAS 3. a PC1 and PC2. b PC3 and PC4. c PC5 and PC6. d PC7 and PC8. e PC9 and PC10.

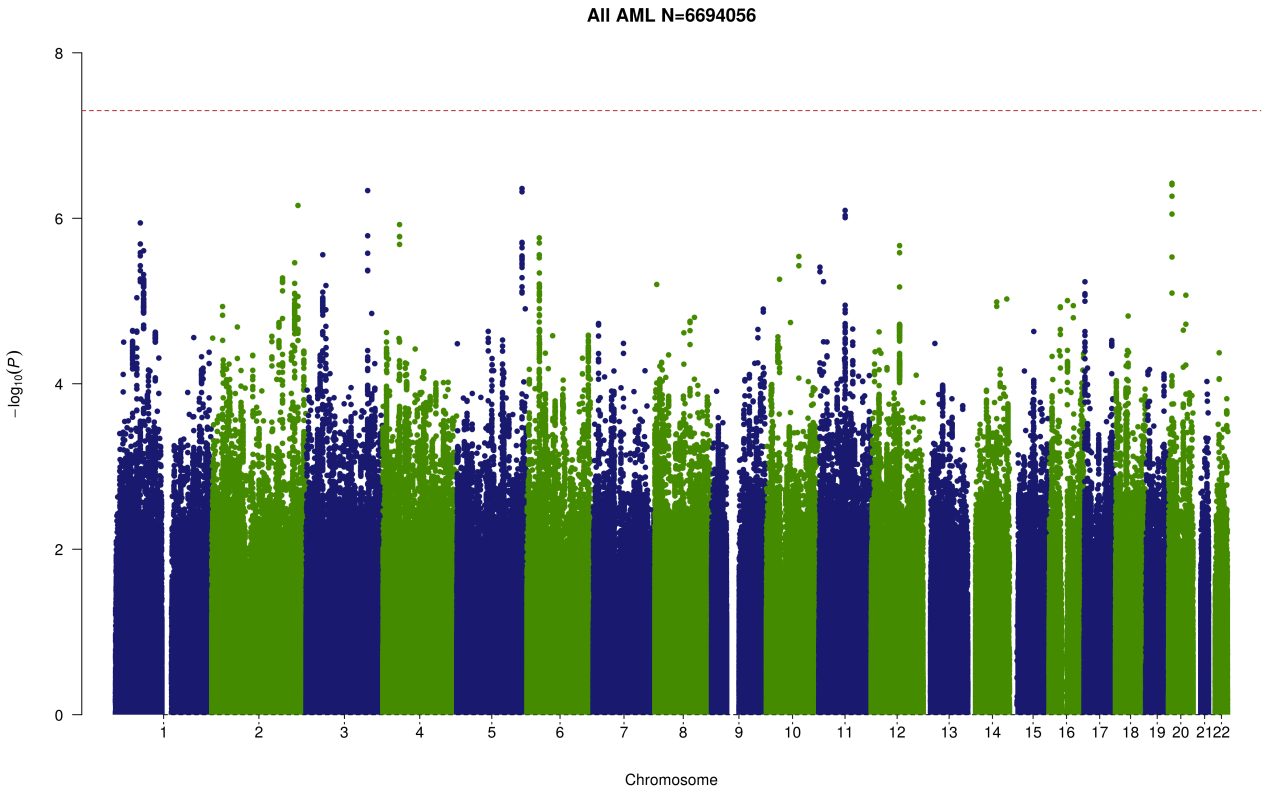



Supplementary Figure 6: **Quantile-Quantile plots of observed P values versus expected P values from association results for all AML in a GWAS 1 b GWAS 2 c GWAS 3.** For each GWAS, association tests were performed for all AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association P values (observed versus expected) on imputed genotype data (MAF $> 0.01$, INFO $> 0.6$) are plotted for all AML cases. All statistical tests were two-sided and no adjustments were made for multiple comparisons.

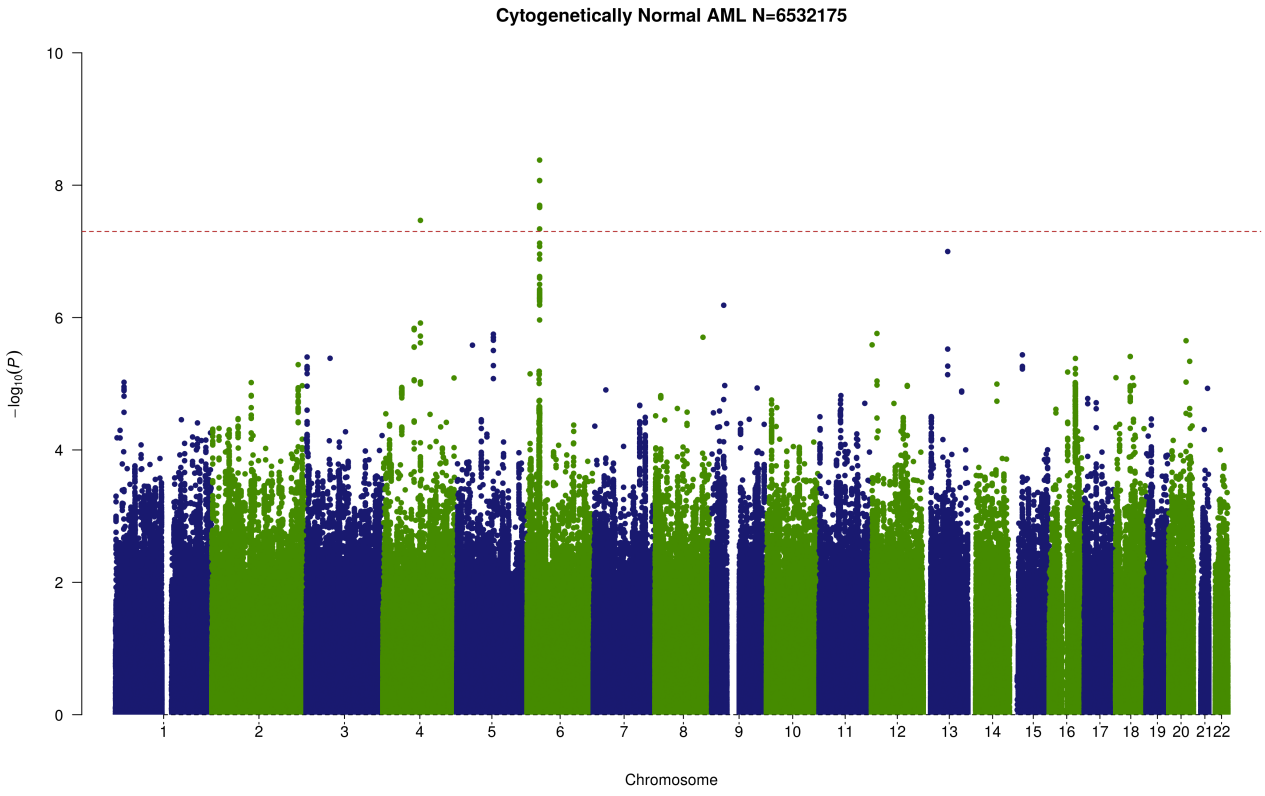



Supplementary Figure 7: **Quantile-Quantile plots of observed P values versus expected P values from association results for cytogenetically normal AML in a GWAS 1 b GWAS 2 c GWAS 3.** For each GWAS, association tests were performed for cytogenetically normal AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association P values (observed versus expected) on imputed genotype data (MAF $> 0.01$, INFO $> 0.6$) are plotted for cytogenetically normal AML cases. All statistical tests were two-sided and no adjustments were made for multiple comparisons.

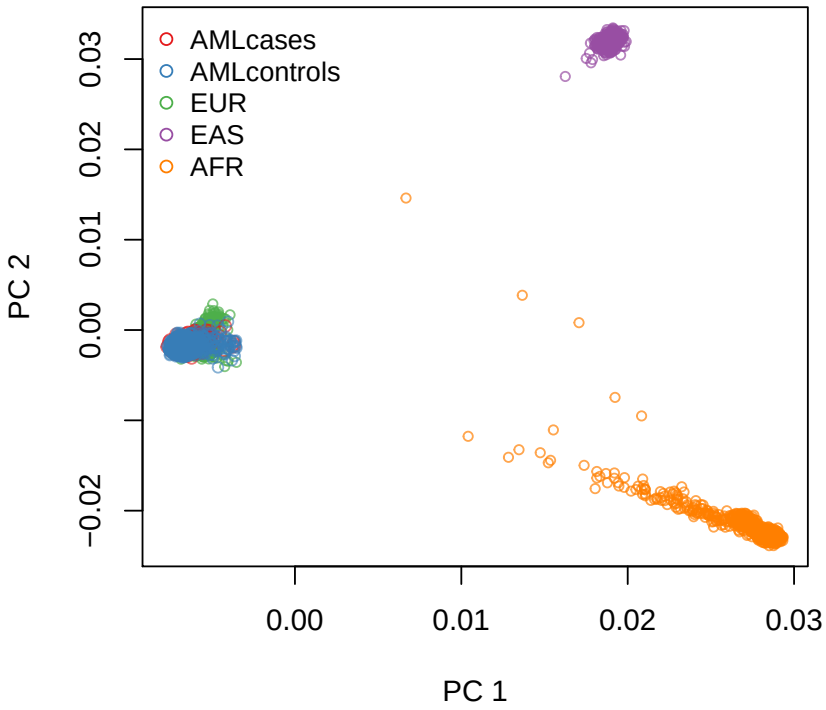
**a**



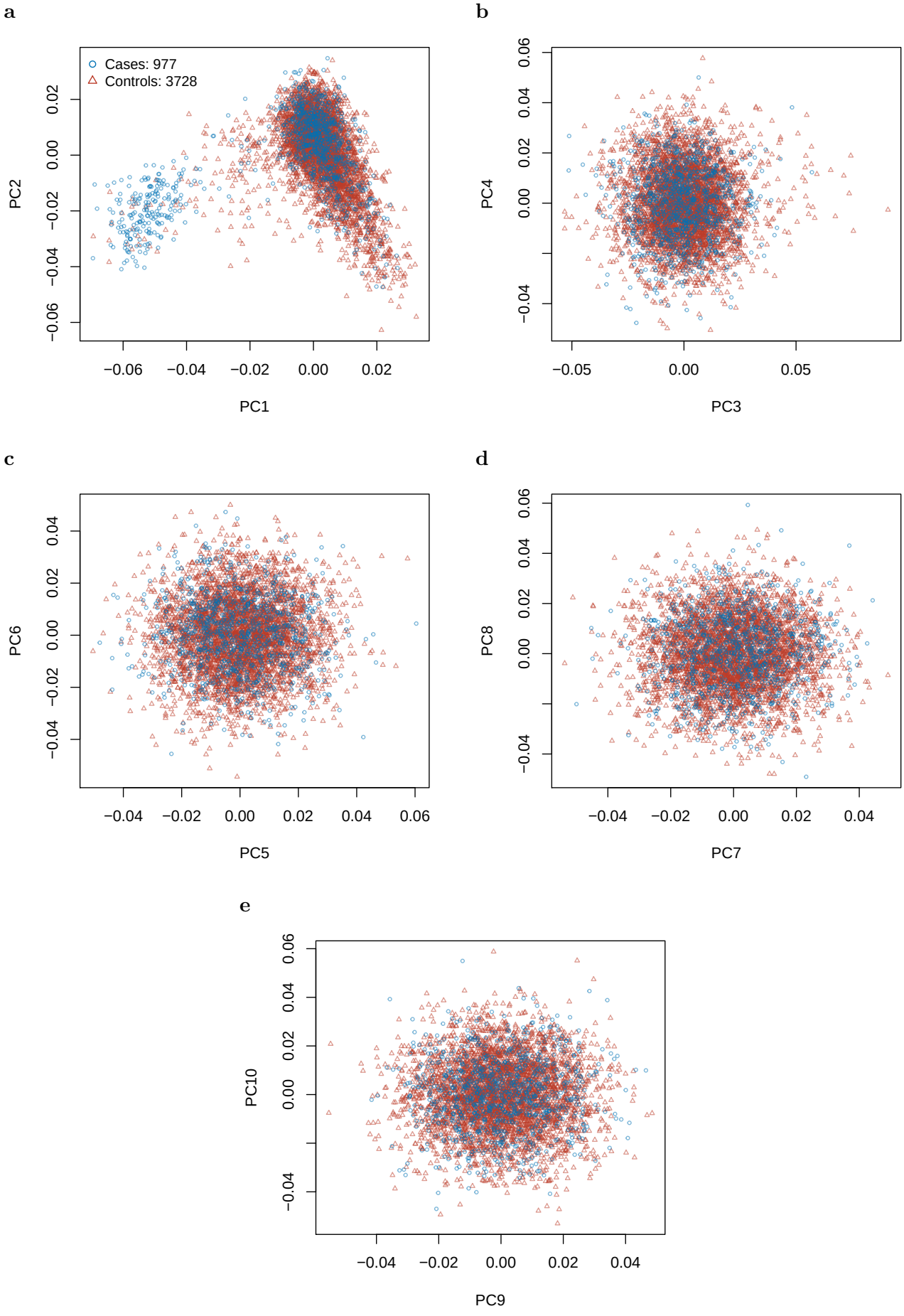

**b**



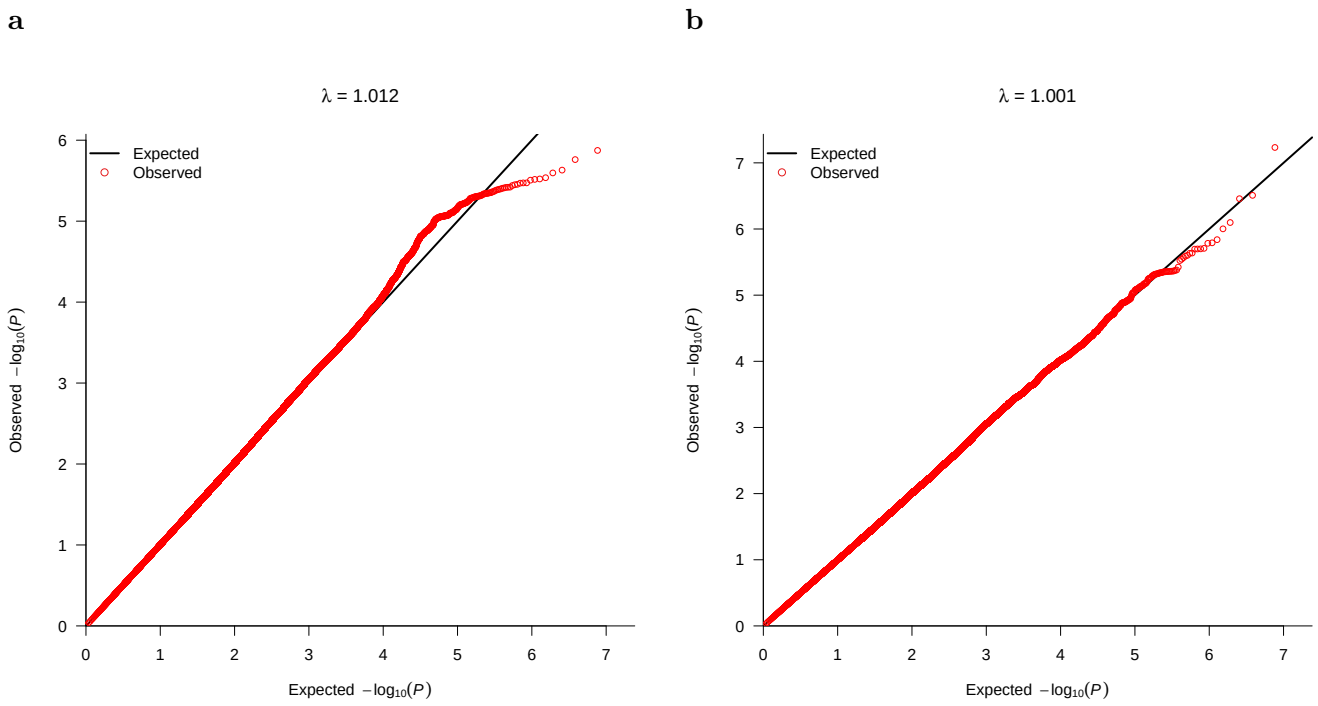

Supplementary Figure 8: **Manhattan plot from meta-analysis of 3 genome-wide association studies for all AML a and cytogenetically normal AML b**. For each GWAS, association tests were performed for all AML cases and cytogenetically normal AML assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to GWAS 1, GWAS 2 and GWAS 3, in fixed effects models using PLINK. Manhattan plots show negative $log_{10}$ (fixed effects meta P values, Y-axis) over 22 autosomal chromosomes. All statistical tests were two-sided and no adjustments were made for multiple comparisons. Horizontal red line denotes the threshold for statistical significance in a genome-wide association study ($P < 5.0 \times 10^{-8}$).



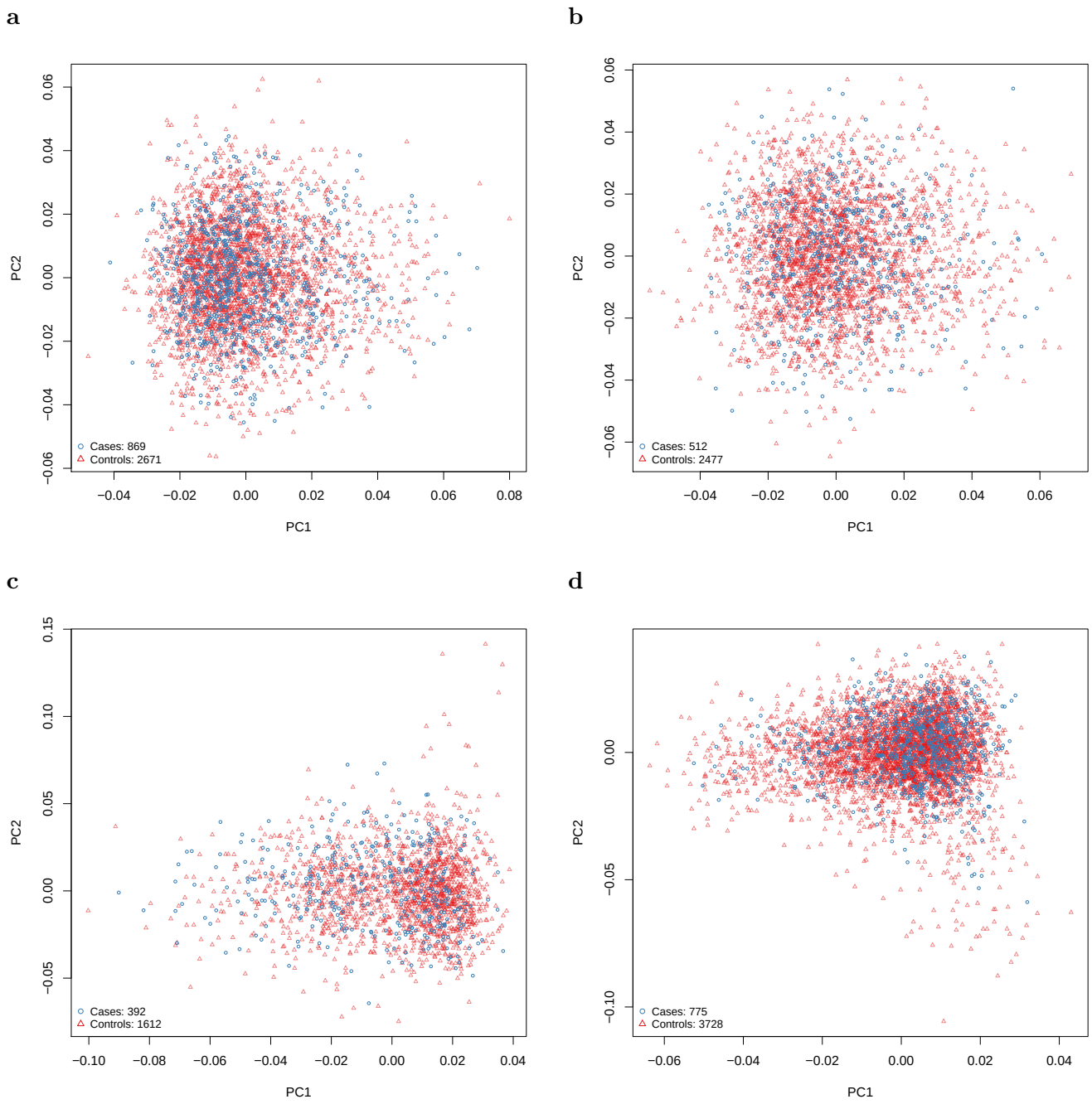

Supplementary Figure 9: **Principal component analysis (PCA) plots of ethnicity structure in GWAS 4.** The first two principal components are shown here. European (EUR), East Asian (EAS) and African (AFR) individuals from 1000 genomes project are plotted in green, purple and orange, respectively. AML cases are plotted in red and controls are plotted in blue. PC1, principal component 1; PC2, principal component 2.



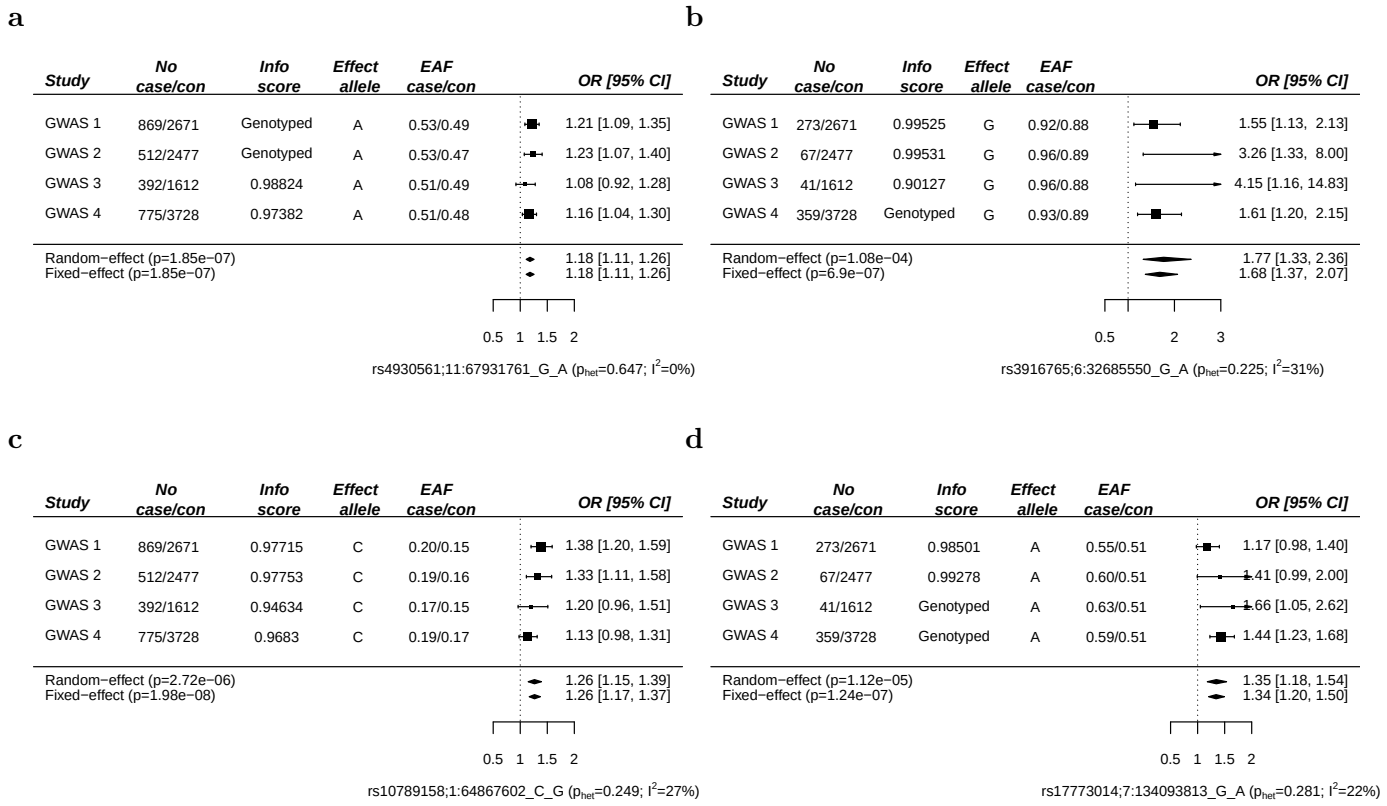

Supplementary Figure 10: PCA in GWAS 4. a PC1 and PC2. b PC3 and PC4. c PC5 and PC6. d PC7 and PC8. e PC9 and PC10.



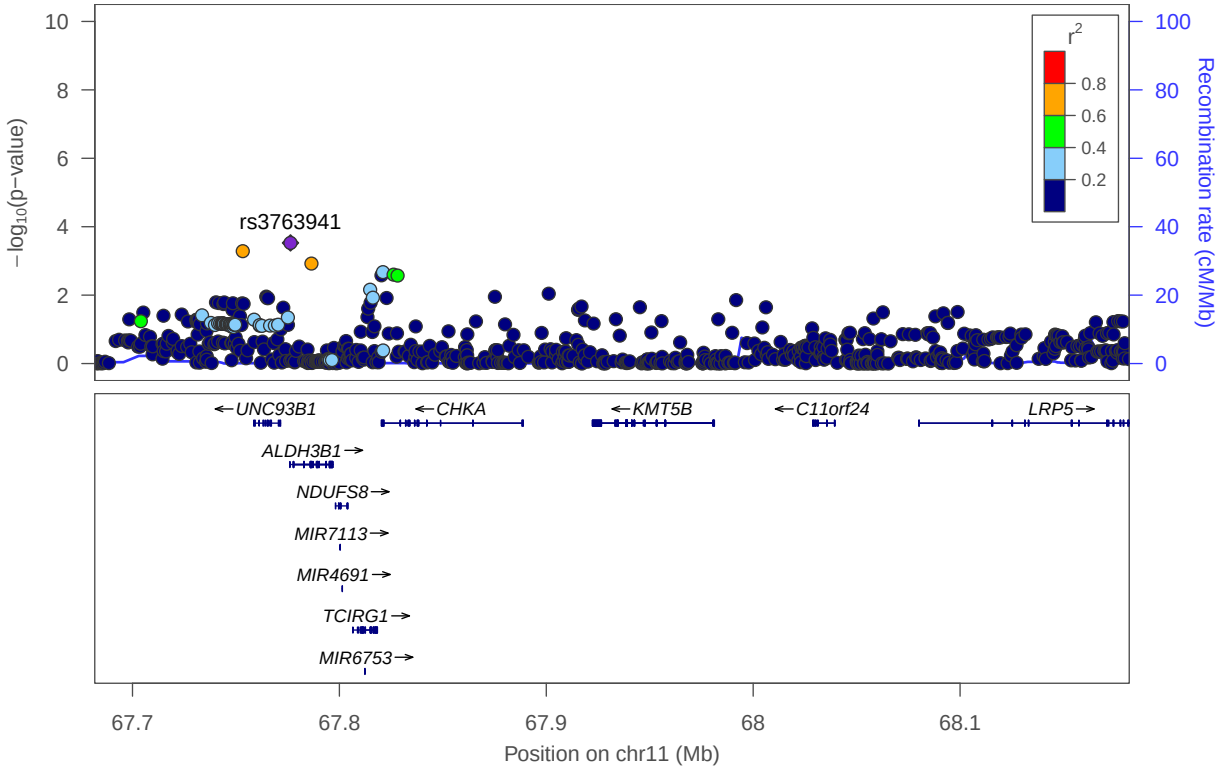

Supplementary Figure 11: **Quantile-Quantile plots of observed P values versus expected P values from association results for all AML a and cytogenetically normal AML b in GWAS 4.** For each GWAS, association tests were performed for all AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association P values (observed versus expected) on imputed genotype data (MAF $> 0.01$, INFO $> 0.6$) are plotted. All statistical tests were two-sided and no adjustments were made for multiple comparisons.



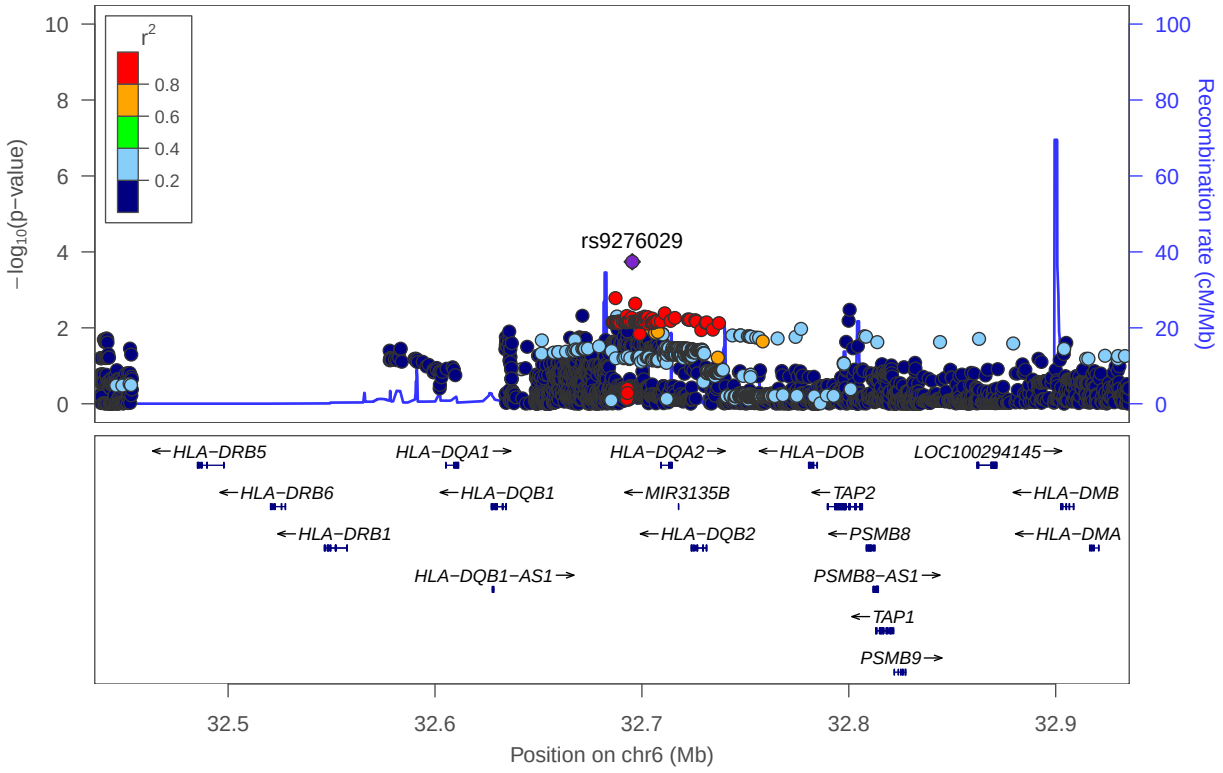

Supplementary Figure 12: **PCA showing PC1 and PC2 restricted to CEU cases and controls of UK origin for a GWAS 1, b GWAS 2 and d GWAS 4 and restricted to CEU cases of German origin for c GWAS 3.**



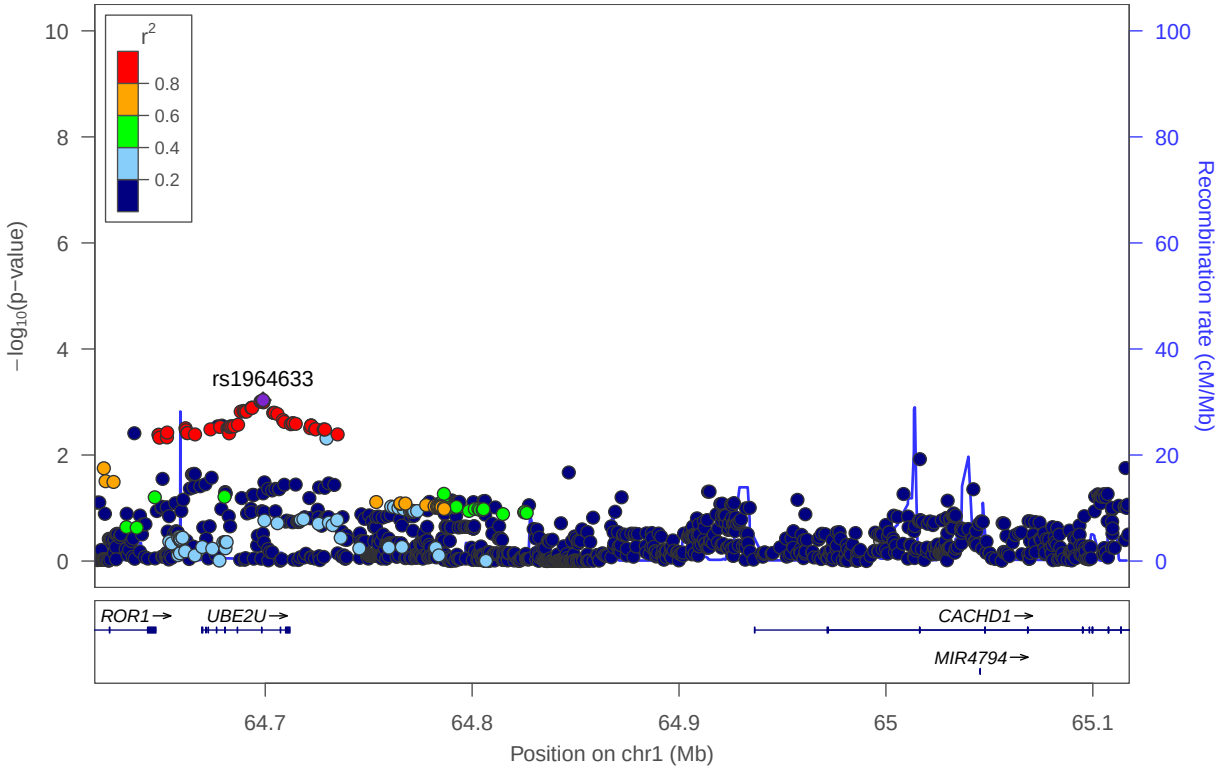

Supplementary Figure 13: **Forest plots for 4 new loci associated with acute myeloid leukemia restricted to CEU cases of UK (GWAS 1, 2 and 4) or German (GWAS 3) origin.** Study cohorts, sample sizes (case and controls (con)), imputation (info) score, effect allele, effect allele frequencies (EAF) and estimated odds ratios (OR) for rs4930561 a, rs3916765 b, rs10789158 c and rs17773014 d. The vertical line corresponds to the null hypothesis (OR=1). The horizontal lines and square brackets indicate 95% confidence intervals (95% CI). Areas of the boxes are proportional to the weight of the study. Diamonds represent combined estimates for fixed-effect and random-effect analysis. Cochrans $Q$ statistic was used to test for heterogeneity such that $P_{HET} > 0.05$ indicates the presence of non-significant heterogeneity. The heterogeneity index, $I^2$ (0-100) was also measured which quantifies the proportion of the total variation due to heterogeneity. All statistical tests were two-sided and no adjustments were made for multiple comparisons.



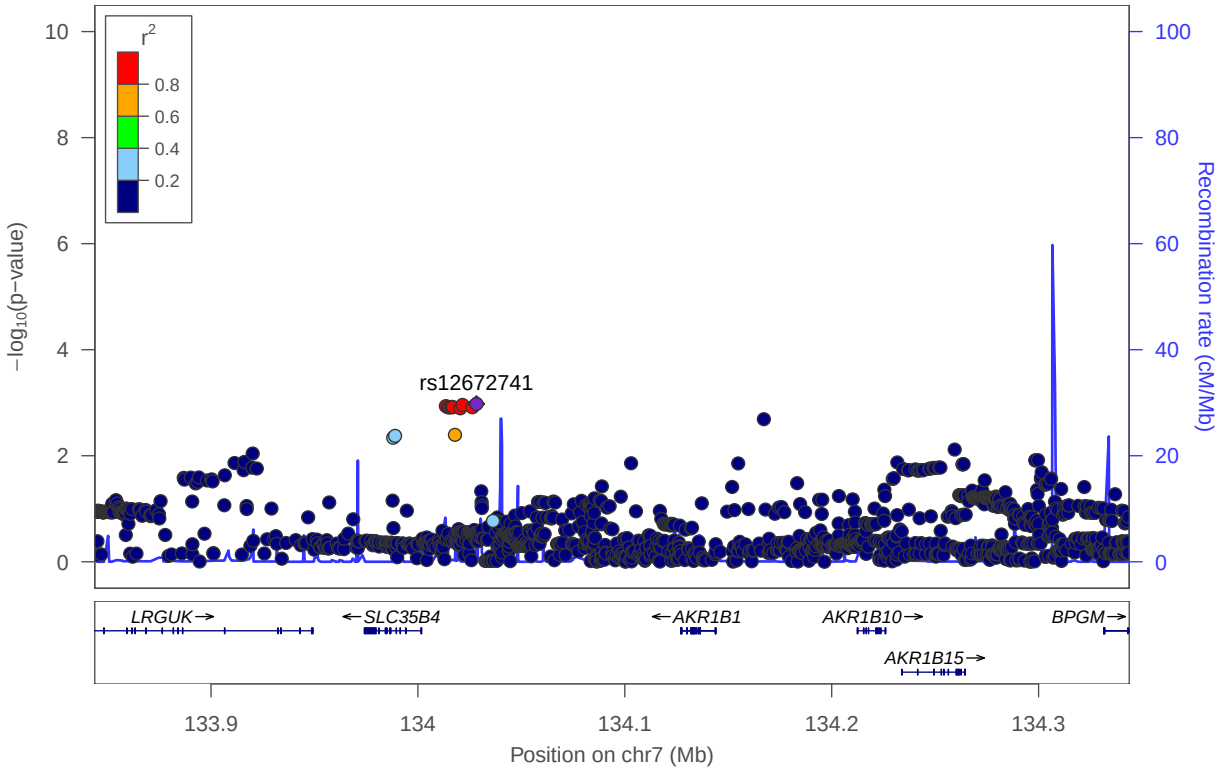

Supplementary Figure 14: **Regional association and linkage disequilibrium plots for association analysis conditioning on the top variant at the chromosome 11q13 susceptibility locus for AML.** Regional association plot showing the chromosome 11q13 AML susceptibility locus conditioning on rs4930561. For each GWAS, association tests were performed for all AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to all four GWAS, in fixed effects models using PLINK. SNP coordinates based on genomic build b37/h19 are shown on the x-axis and $-log_{10}$ (P values) on the y-axis. SNPs are coloured according to their linkage disequilibrium (pairwise $r^2$) with the lead SNP (annotated) based on the 1000 Genomes European panel. Reference genes in the region are shown in the lower panel, with arrows indicating transcript direction, dense blocks representing exons and horizontal lines representing introns. All statistical tests were two-sided and no adjustments were made for multiple comparisons.



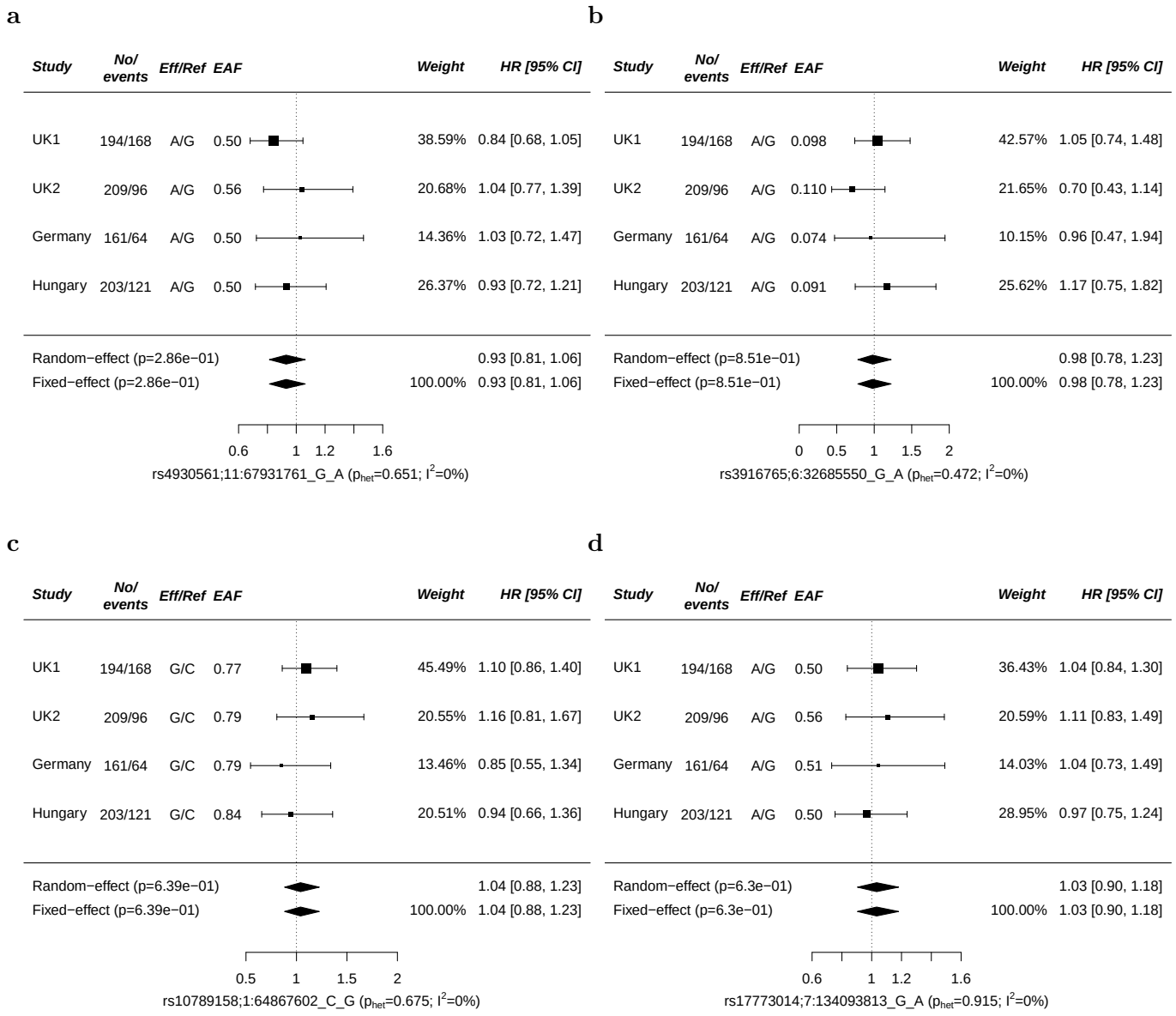

Supplementary Figure 15: **Regional association and linkage disequilibrium plots for association analysis conditioning on the top variant at the chromosome 6p21.32 susceptibility locus for cytogenetically normal AML.** Regional association plot showing the chromosome 6p21.32 AML susceptibility locus conditioning on rs3916765. For each GWAS, association tests were performed for all AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to all four GWAS, in fixed effects models using PLINK. SNP coordinates based on genomic build b37/h19 are shown on the x-axis and $-log_{10}$ (P values) on the y-axis. SNPs are coloured according to their linkage disequilibrium (pairwise $r^2$) with the lead SNP (annotated) based on the 1000 Genomes European panel. Reference genes in the region are shown in the lower panel, with arrows indicating transcript direction, dense blocks representing exons and horizontal lines representing introns. All statistical tests were two-sided and no adjustments were made for multiple comparisons.



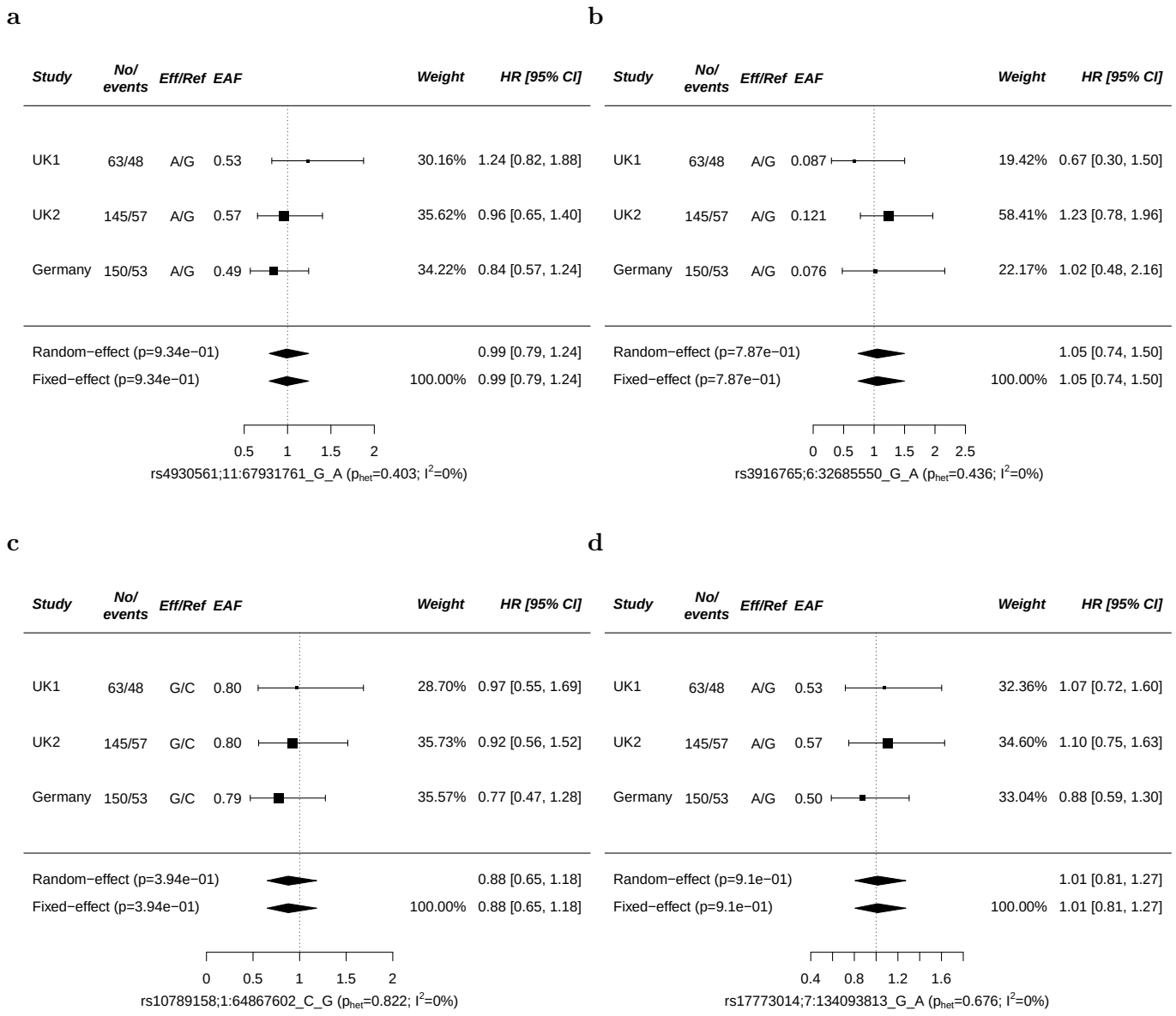

Supplementary Figure 16: **Regional association and linkage disequilibrium plots for association analysis conditioning on the top variant at the chromosome 1p31.3 susceptibility locus for AML.** Regional association plot showing the chromosome 1p31.3 AML susceptibility locus conditioning on rs10789158. For each GWAS, association tests were performed for all AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to all four GWAS, in fixed effects models using PLINK. SNP coordinates based on genomic build b37/h19 are shown on the x-axis and $-log_{10}$ (P values) on the y-axis. SNPs are coloured according to their linkage disequilibrium (pairwise $r^2$) with the lead SNP (annotated) based on the 1000 Genomes European panel. Reference genes in the region are shown in the lower panel, with arrows indicating transcript direction, dense blocks representing exons and horizontal lines representing introns. All statistical tests were two-sided and no adjustments were made for multiple comparisons.



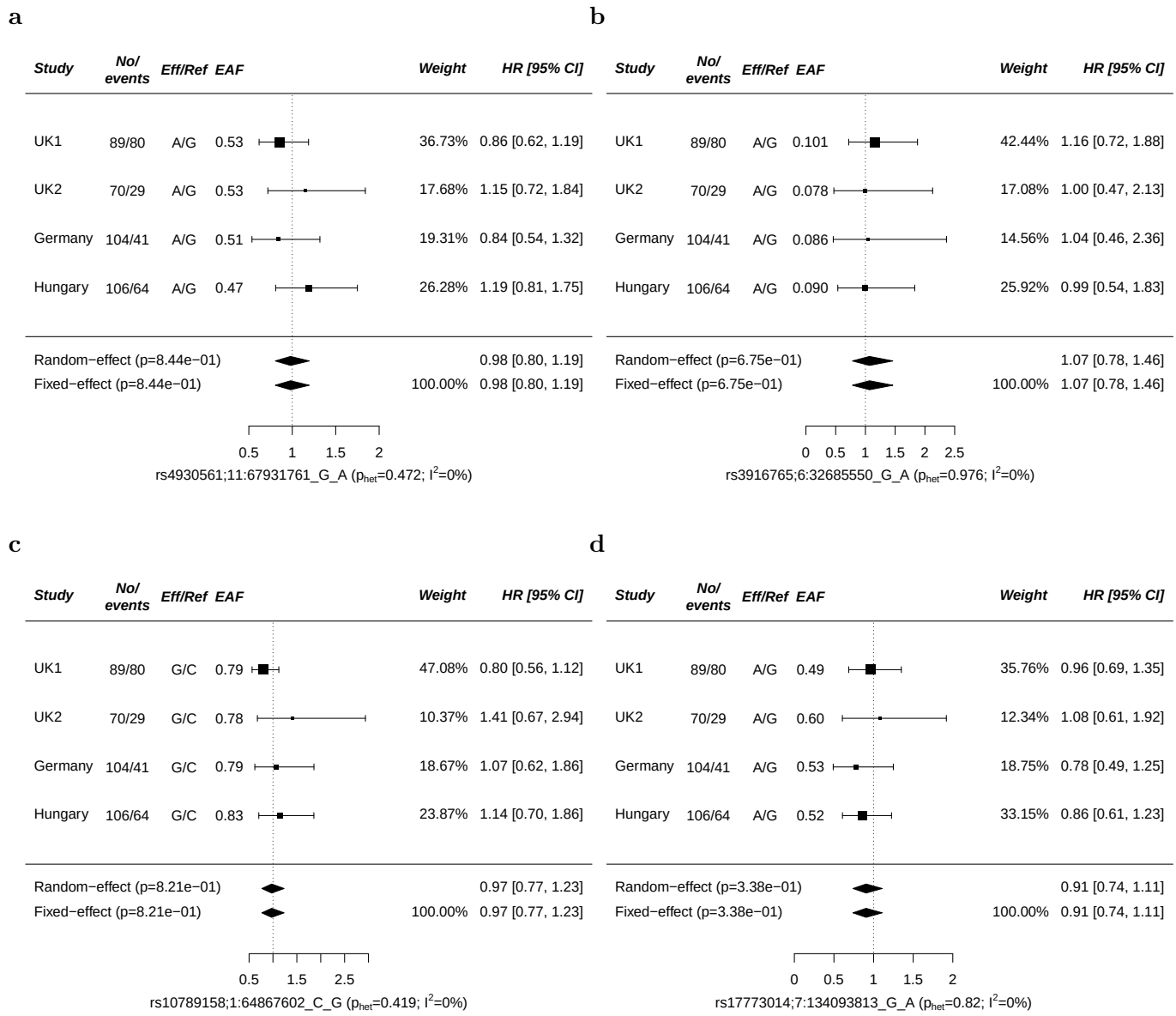

Supplementary Figure 17: **Regional association and linkage disequilibrium plots for association analysis conditioning on the top variant at the chromosome 7q33 susceptibility locus for cytogenetically normal AML.** Regional association plot showing the chromosome 7q33 AML susceptibility locus conditioning on rs17773014. For each GWAS, association tests were performed for all AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to all four GWAS, in fixed effects models using PLINK. SNP coordinates based on genomic build b37/h19 are shown on the x-axis and $-log_{10}$ (P values) on the y-axis. SNPs are coloured according to their linkage disequilibrium (pairwise $r^2$) with the lead SNP (annotated) based on the 1000 Genomes European panel. Reference genes in the region are shown in the lower panel, with arrows indicating transcript direction, dense blocks representing exons and horizontal lines representing introns. All statistical tests were two-sided and no adjustments were made for multiple comparisons.



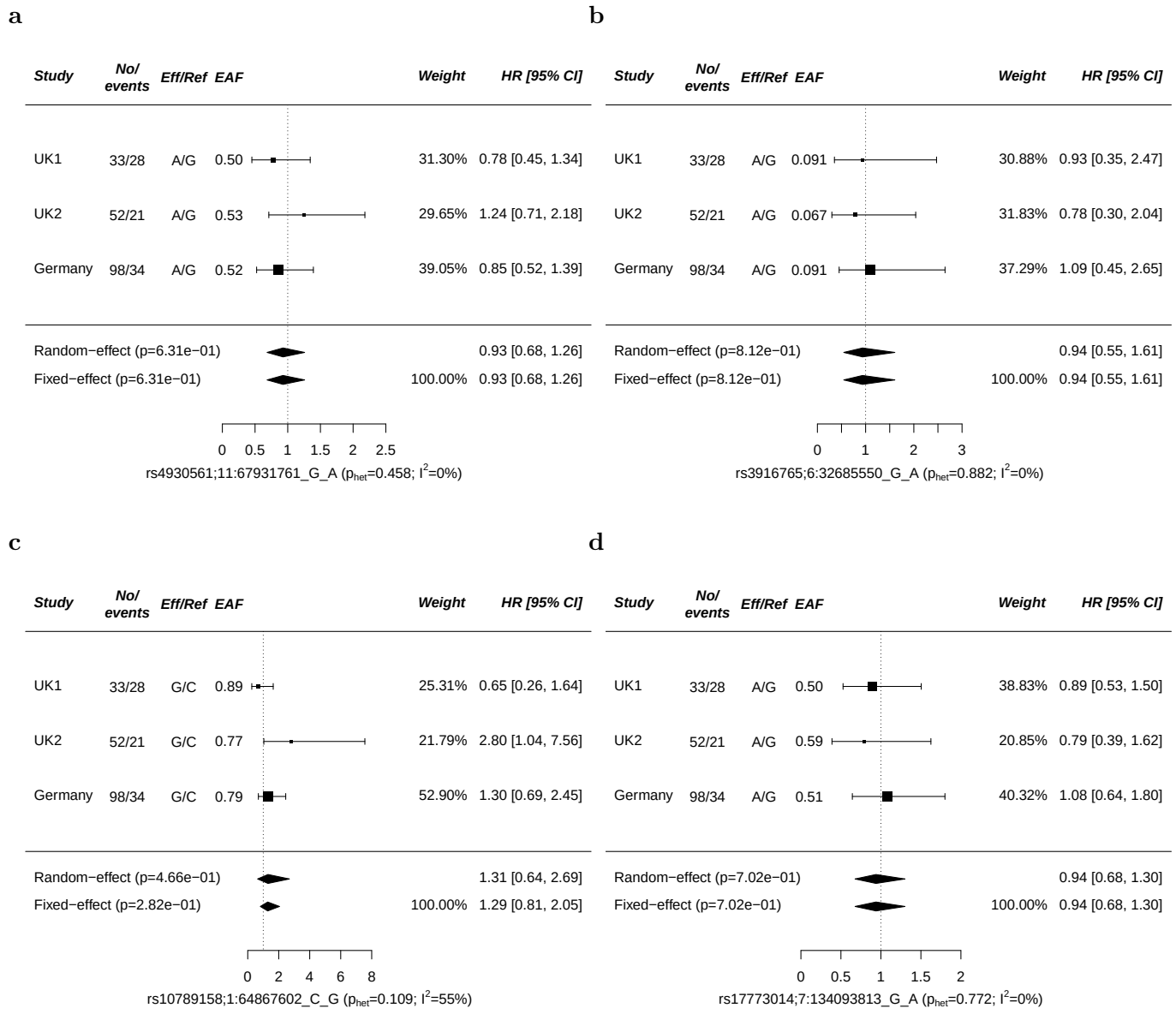

Supplementary Figure 18: **SNP effects on AML overall survival (OS) by study.** a rs4930561 b rs3916765 c rs10789158 d rs17773014. Study cohorts (UK1, UK2, Germany and Hungary), number of AML cases (cases), events, effect (Eff) and reference (Ref) allele, effect allele frequencies (EAF) and estimated hazard ratios (HR). The vertical line corresponds to the null hypothesis (HR=1). The horizontal lines and square brackets indicate 95% confidence intervals (95% CI). Areas of the boxes are proportional to the weight of the study. Diamonds represent combined estimates for fixed-effect and random-effect analysis. Cochran's $Q$ statistic was used to test for heterogeneity such that $P_{HET} > 0.05$ indicates the presence of non-significant heterogeneity. The heterogeneity index, $I^2$ (0-100) was also measured which quantifies the proportion of the total variation due to heterogeneity. Overall survival was defined as the time from diagnosis to the date of last follow-up or death (event) from any cause. Cox regression analysis was used to estimate allele specific hazard ratios and 95% CIs.




Supplementary Figure 19: **SNP effects on AML relapse-free survival (RFS) by study.** a rs4930561 b rs3916765 c rs10789158 d rs17773014. Study cohorts (UK1, UK2, Germany), number of AML cases (cases), events, effect (Eff) and reference (Ref) allele, effect allele frequencies (EAF) and estimated hazard ratios (HR). The vertical line corresponds to the null hypothesis (HR=1). The horizontal lines and square brackets indicate 95% confidence intervals (95% CI). Areas of the boxes are proportional to the weight of the study. Diamonds represent combined estimates for fixed-effect and random-effect analysis. Cochran's $Q$ statistic was used to test for heterogeneity such that $P_{HET} > 0.05$ indicates the presence of non-significant heterogeneity. The heterogeneity index, $I^2$ (0-100) was also measured which quantifies the proportion of the total variation due to heterogeneity. Relapse-free survival was defined as the time from first remission to the date of last follow-up or relapse (event). Cox regression analysis was used to estimate allele specific hazard ratios and 95% CIs.

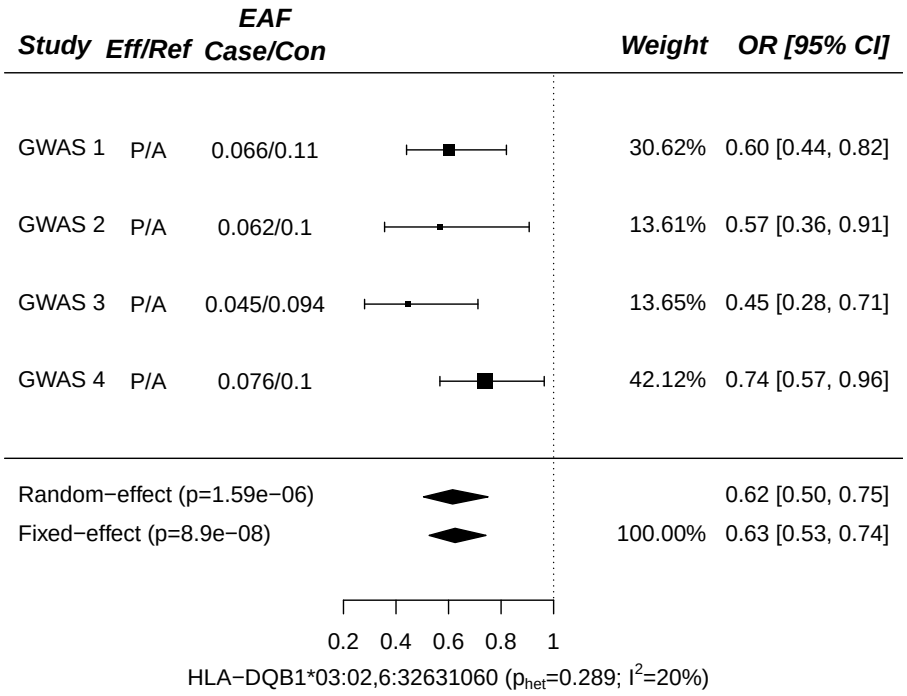



Supplementary Figure 20: **SNP effects on AML overall survival (OS) by study in cytogenetically normal AML.** a rs4930561 b rs3916765 c rs10789158 d rs17773014. Study cohorts (UK1, UK2, Germany and Hungary), number of AML cases (cases), events, effect (Eff) and reference (Ref) allele, effect allele frequencies (EAF) and estimated hazard ratios (HR). The vertical line corresponds to the null hypothesis (HR=1). The horizontal lines and square brackets indicate 95% confidence intervals (95% CI). Areas of the boxes are proportional to the weight of the study. Diamonds represent combined estimates for fixed-effect and random-effect analysis. Cochran's $Q$ statistic was used to test for heterogeneity such that $P_{HET} > 0.05$ indicates the presence of non-significant heterogeneity. The heterogeneity index, $I^2$ (0-100) was also measured which quantifies the proportion of the total variation due to heterogeneity. Overall survival was defined as the time from diagnosis to the date of last follow-up or death (event) from any cause. Cox regression analysis was used to estimate allele specific hazard ratios and 95% CIs.

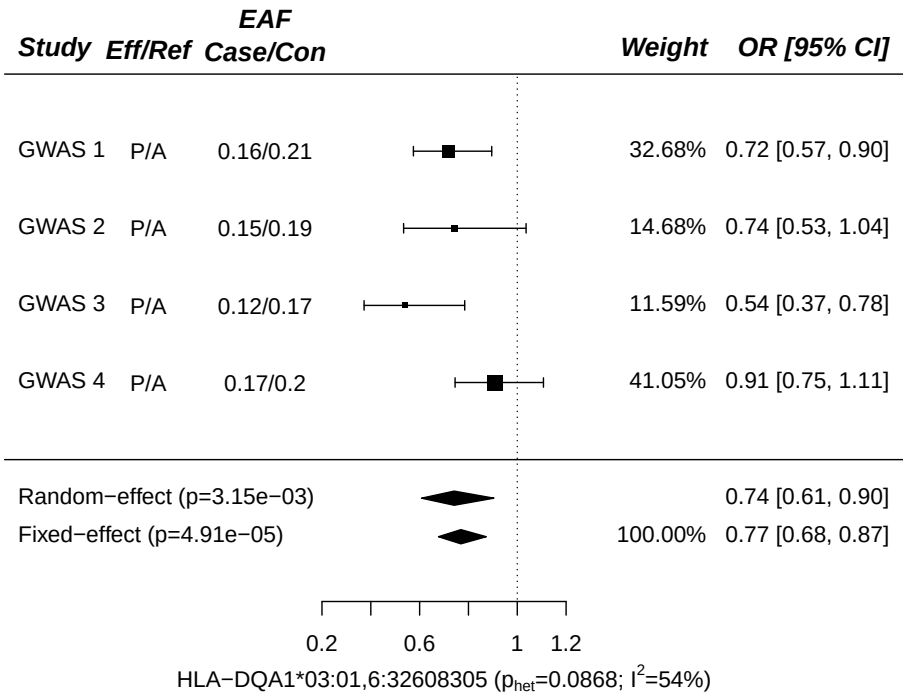



Supplementary Figure 21: **SNP effects on AML relapse-free survival (RFS) by study in cytogenetically normal AML.** a rs4930561 b rs3916765 c rs10789158 d rs17773014. Study cohorts (UK1, UK2, Germany), number of AML cases (cases), events, effect (Eff) and reference (Ref) allele, effect allele frequencies (EAF) and estimated hazard ratios (HR). The vertical line corresponds to the null hypothesis (HR=1). The horizontal lines and square brackets indicate 95% confidence intervals (95% CI). Areas of the boxes are proportional to the weight of the study. Diamonds represent combined estimates for fixed-effect and random-effect analysis. Cochran's $Q$ statistic was used to test for heterogeneity such that $P_{HET} > 0.05$ indicates the presence of non-significant heterogeneity. The heterogeneity index, $I^2$ (0-100) was also measured which quantifies the proportion of the total variation due to heterogeneity. Relapse-free survival was defined as the time from first remission to the date of last follow-up or relapse (event). Cox regression analysis was used to estimate allele specific hazard ratios and 95% CIs.

**a**

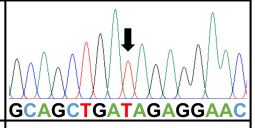
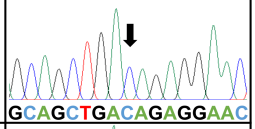
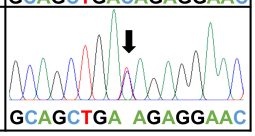



**b**



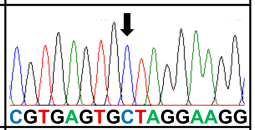
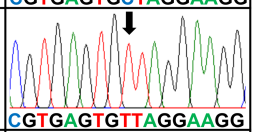
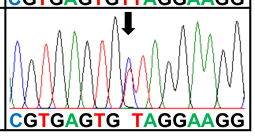

Supplementary Figure 22: **Forest plots for HLA-DQB1*03:02 and HLA-DQA1*03:01 associations with cytogenetically normal AML.** Effect allele frequencies (EAF) and estimated odds ratios (OR) for HLA-DQB1*03:02 a and HLA-DQA1*03:01 b. The vertical line corresponds to the null hypothesis (OR= 1). The horizontal lines and square brackets indicate 95% confidence intervals (95% CI). Areas of the boxes are proportional to the weight of the study. Diamonds represent combined estimates for fixedeffects and randomeffects analysis. Cochran's $Q$ statistic was used to test for heterogeneity such that $P_{HET} > 0.05$ indicates the presence of non-significant heterogeneity. The heterogeneity index $I^2$ (0-100) was also measured which quantifies the proportion of the total variation due to heterogeneity. All statistical tests were two-sided and no adjustments were made for multiple comparisons. P, present; A, absent; Eff, effect; Ref, reference.

rs4930561 (chr. 11)

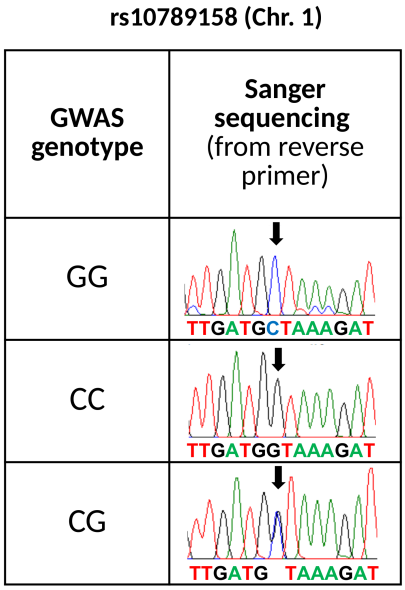
| GWAS genotype | Sanger sequencing (from reverse primer) |
|---|---|
| AA |   |
| GG |   |
| AG |   |

Supplementary Figure 23: **Representative genotype results for rs4930561.** Sanger sequencing was successful for 124 AML cases with 100% (124/124) concordance between GWAS genotyping and Sanger sequencing. Primer sequences for rs4930561 were 5'CCGATTCTTCTGGGGCTTGT3' (forward) and 5'TCTGCAGCATGATTGGAGCA3' (reverse).

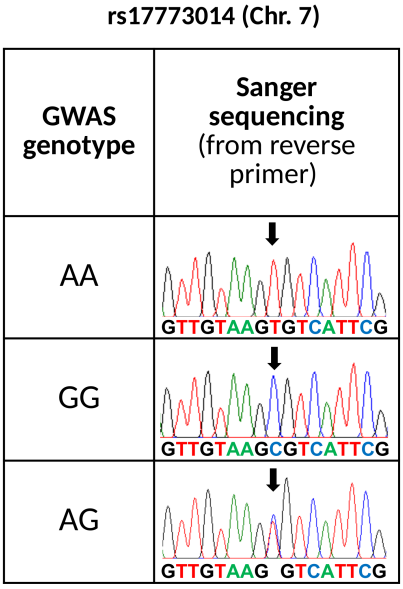
rs3916765 (Chr. 6)

| GWAS genotype | Sanger sequencing (from reverse primer) |
|---|---|
| GG |   |
| AA |   |
| AG |   |

Supplementary Figure 24: **Representative genotype results for rs3916765.** Sanger sequencing was successful for 139 AML cases with 100% (139/139) concordance between GWAS genotyping and Sanger sequencing. Primer sequences for rs3916765 were 5'TTGGTACCTGGGGTATGCTGAA3' (forward) and 5'TGGAGGCTGCCTTGAGATACTA3'(reverse).




Supplementary Figure 25: **Representative genotype results for rs10789158.** Sanger sequencing was successful for 130 AML cases with 98.5% (128/130) concordance between GWAS genotyping and Sanger sequencing. Primer sequences for rs10789158 were 5'AGCACGTTACAGACTATGCCT3' (forward) and 5'AGCTCAAAGACATGGGGCAA3' (reverse).




Supplementary Figure 26: **Representative genotype results for rs17773014.** Sanger sequencing was successful for 120 AML cases with 99.2% (119/120) concordance between GWAS genotyping and Sanger sequencing. Primer sequences for rs17773014 were 5'TGTATAACCAAGGGACCGCAC3' (forward) and 5'CACCCCGTCCCATATCCAATG3' (reverse).

**SUPPLEMENTARY TABLES**

Genome-wide association study identifies susceptibility loci for acute myeloid leukemia

Lin *et al*

**Supplementary Table 1 –Acute myeloid leukemia (AML) case and control characteristics**

N, number; GWAS, genome wide association study; APL, acute promyelocytic leukemia; CBF, core binding factor (CBF AML is defined as t(8;21) or inv(16)); Complex karyotype is defined as 3 or more independent alterations; Monosomal karyotype is defined as the presence of 2 or more autosomal monosomies or a single autosomal monosomy with at least one structural abnormality. For some cases age and/or gender was not declared or not known. Some cytogenetic sub-groups are not mutually exclusive.

| | GWAS 1 | | GWAS 2 | | GWAS 3 | | GWAS 4 | |
|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Controls** | **Cases** | **Controls** | **Cases** | **Controls** | **Cases** | **Controls** |
| **Total, N** | 1119 | 2671 | 931 | 2477 | 991 | 1612 | 977 | 3728 |
| **Age, years** | | | | | | | | |
| Median (range) | 54 (13-91) | 45 (45-45) | 49 (<1-95) | 45 (15-65) | 60 (12-93) | 62 (32-81) | 63 (<1-93) | 57 (40-70) |
| **Sex, N (%)** | | | | | | | | |
| Males | 605 (54) | 1377 (50) | 486 (52) | 1225 (49) | 500 (50) | 785 (49) | 511 (52) | 1746 (47) |
| Females | 514 (46) | 1294 (50) | 444 (48) | 1252 (51) | 478 (48) | 827 (51) | 466 (48) | 1982 (53) |
| Not known | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 13 (2) | 0 (0) | 0 (0) | 0 (0) |
| **Cytogenetics, N (%)** | | | | | | | | |
| Successful cytogenetics | 879 (100) | - | 654 (100) | - | 666 (100) | - | 718 (100) | - |
| Normal cytogenetics | 359 (41) | - | 177 (27) | - | 286 (43) | - | 465 (65) | - |
| Abnormal cytogenetics | 520 (59) | - | 477 (73) | - | 380 (57) | - | 253 (35) | - |
| APL t(15.17) | 131 (15) | - | 380 (58) | - | 108 (16) | - | 38 (5) | - |
| CBF AML | 72 (8) | - | 50 (8) | - | 219 (33) | - | 27 (4) | - |
| del5.del7 | 65 (7) | - | 58 (9) | - | 68 (10) | - | 57 (8) | - |
| Complex (3 or more) | 69 (8) | - | 61 (9) | - | 89 (13) | - | 82 (11) | - |
| Any translocation | 241 (27) | - | 459 (70) | - | 253 (38) | - | 105 (15) | - |
| Any trisomy | 106 (12) | - | 70 (11) | - | 55 (8) | - | 104 (14) | - |
| Any monosomy | 54 (6) | - | 56 (9) | - | 67 (10) | - | 62 (9) | - |
| Monosomal karyotype | 20 (2) | - | 34 (5) | - | 54 (8) | - | 46 (6) | - |

**Supplementary Table 2 – SNPs showing evidence of an association with risk of acute myeloid leukemia (AML) at $P \leq 10^{-6}$.**

Association tests were performed for all AML cases and cytogenetically normal AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to GWAS 1, GWAS 2 and GWAS 3, in fixed effects models using PLINK. All statistical tests were two-sided and no adjustments were made for multiple comparisons. Results are based on meta-analysis of GWAS 1, GWAS 2 and GWAS 3. SNP, single nucleotide polymorphism; Chr, chromosome; OR, odds ratio; Q, Cochran's Q statistic; $I^2$, heterogeneity index $I^2$. [a]hg19 coordinates. All statistical tests were two sided.

| SNP | AML karotype | Chr | Position[a] | Chr band | Allele 1 | Allele 2 | Meta *P* value (fixed effect) | Meta P (random effect) | Meta OR (fixed effect) | Meta OR (random effect) | Q | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs4674579 | All AML | 2 | 222167434 | 2q36.1 | C | T | 7.00E-07 | 7.00E-07 | 0.8063 | 0.8063 | 0.63 | 0 |
| rs2621279 | All AML | 3 | 158940084 | 3q25.32 | A | G | 4.63E-07 | 4.63E-07 | 0.815 | 0.815 | 0.7933 | 0 |
| rs13164987 | All AML | 5 | 168247045 | 5q35.1 | C | T | 4.79E-07 | 4.79E-07 | 0.7885 | 0.7885 | 0.6976 | 0 |
| rs13183143 | All AML | 5 | 168247046 | 5q35.1 | A | G | 4.37E-07 | 4.37E-07 | 0.7876 | 0.7876 | 0.6849 | 0 |
| rs11481 | All AML | 11 | 67820335 | 11q13.2 | A | T | 8.04E-07 | 8.04E-07 | 1.2044 | 1.2044 | 0.4994 | 0 |
| rs10896298 | All AML | 11 | 67931459 | 11q13.2 | T | C | 9.83E-07 | 9.83E-07 | 1.1777 | 1.1777 | 0.4718 | 0 |
| rs4930561 | All AML | 11 | 67931761 | 11q13.2 | A | G | 9.26E-07 | 9.26E-07 | 1.1781 | 1.1781 | 0.468 | 0 |
| rs6056038 | All AML | 20 | 8701468 | 20p12.3 | C | T | 8.90E-07 | 8.90E-07 | 0.762 | 0.762 | 0.9602 | 0 |
| rs6056041 | All AML | 20 | 8702867 | 20p12.3 | C | T | 5.41E-07 | 5.41E-07 | 0.7569 | 0.7569 | 0.9746 | 0 |
| rs6077414 | All AML | 20 | 8704552 | 20p12.3 | C | T | 3.77E-07 | 3.77E-07 | 0.7533 | 0.7533 | 0.9702 | 0 |
| rs6056043 | All AML | 20 | 8705496 | 20p12.3 | C | A | 3.94E-07 | 3.94E-07 | 0.7534 | 0.7534 | 0.9756 | 0 |
| rs75391980 | Normal | 4 | 96948521 | 4q22.3 | C | T | 3.40E-08 | 3.40E-08 | 1.7457 | 1.7457 | 0.4139 | 0 |
| rs9275092 | Normal | 6 | 32648987 | 6p21.32 | T | C | 6.47E-07 | 6.47E-07 | 0.5511 | 0.5511 | 0.566 | 0 |
| rs9275095 | Normal | 6 | 32649088 | 6p21.32 | G | C | 5.48E-07 | 5.48E-07 | 0.5456 | 0.5456 | 0.5911 | 0 |
| rs9275097 | Normal | 6 | 32649126 | 6p21.32 | G | A | 4.48E-07 | 4.48E-07 | 0.5486 | 0.5486 | 0.5575 | 0 |
| rs9275098 | Normal | 6 | 32649161 | 6p21.32 | T | C | 4.88E-07 | 4.88E-07 | 0.553 | 0.553 | 0.5503 | 0 |
| rs9275167 | Normal | 6 | 32653263 | 6p21.32 | G | A | 4.94E-07 | 4.94E-07 | 0.5616 | 0.5616 | 0.6229 | 0 |
| rs9275184 | Normal | 6 | 32654714 | 6p21.32 | C | T | 5.22E-07 | 5.22E-07 | 0.5631 | 0.5631 | 0.6254 | 0 |
| rs9275203 | Normal | 6 | 32656947 | 6p21.32 | A | G | 4.92E-07 | 4.92E-07 | 0.5623 | 0.5623 | 0.6321 | 0 |
| rs9275207 | Normal | 6 | 32657710 | 6p21.32 | G | A | 4.36E-07 | 4.36E-07 | 0.5603 | 0.5603 | 0.6523 | 0 |
| rs9275213 | Normal | 6 | 32658335 | 6p21.32 | C | T | 4.39E-07 | 4.39E-07 | 0.5605 | 0.5605 | 0.6568 | 0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs9275214 | Normal | 6 | 32658665 | 6p21.32 | A | G | 4.47E-07 | 4.47E-07 | 0.5606 | 0.5606 | 0.6594 | 0 |
| rs9275221 | Normal | 6 | 32659099 | 6p21.32 | C | T | 4.62E-07 | 4.62E-07 | 0.5609 | 0.5609 | 0.6583 | 0 |
| rs9275223 | Normal | 6 | 32659839 | 6p21.32 | A | G | 4.68E-07 | 4.68E-07 | 0.5611 | 0.5611 | 0.6645 | 0 |
| rs9275275 | Normal | 6 | 32662607 | 6p21.32 | A | G | 4.94E-07 | 4.94E-07 | 0.5616 | 0.5616 | 0.6731 | 0 |
| rs9275293 | Normal | 6 | 32663308 | 6p21.32 | C | T | 5.06E-07 | 5.06E-07 | 0.5619 | 0.5619 | 0.6777 | 0 |
| rs9275296 | Normal | 6 | 32663431 | 6p21.32 | C | T | 5.08E-07 | 5.08E-07 | 0.562 | 0.562 | 0.6791 | 0 |
| rs9275300 | Normal | 6 | 32664126 | 6p21.32 | G | A | 4.47E-07 | 4.47E-07 | 0.5598 | 0.5598 | 0.6864 | 0 |
| rs9275307 | Normal | 6 | 32664990 | 6p21.32 | T | A | 5.11E-07 | 5.11E-07 | 0.562 | 0.562 | 0.678 | 0 |
| rs9275308 | Normal | 6 | 32665255 | 6p21.32 | A | T | 5.10E-07 | 5.10E-07 | 0.5616 | 0.5616 | 0.6714 | 0 |
| rs9275310 | Normal | 6 | 32665319 | 6p21.32 | G | T | 4.96E-07 | 4.96E-07 | 0.5614 | 0.5614 | 0.6725 | 0 |
| rs9275311 | Normal | 6 | 32665640 | 6p21.32 | T | G | 4.97E-07 | 4.97E-07 | 0.5615 | 0.5615 | 0.6729 | 0 |
| rs9275313 | Normal | 6 | 32665759 | 6p21.32 | T | G | 4.25E-07 | 4.25E-07 | 0.5594 | 0.5594 | 0.662 | 0 |
| rs9275314 | Normal | 6 | 32665909 | 6p21.32 | A | C | 5.17E-07 | 5.17E-07 | 0.5618 | 0.5618 | 0.6682 | 0 |
| rs9275315 | Normal | 6 | 32665912 | 6p21.32 | A | C | 5.17E-07 | 5.17E-07 | 0.5618 | 0.5618 | 0.6687 | 0 |
| rs9275324 | Normal | 6 | 32666635 | 6p21.32 | T | C | 4.51E-07 | 4.51E-07 | 0.5577 | 0.5577 | 0.6839 | 0 |
| rs9275325 | Normal | 6 | 32666651 | 6p21.32 | T | G | 4.97E-07 | 4.97E-07 | 0.5585 | 0.5585 | 0.6767 | 0 |
| rs9275326 | Normal | 6 | 32666660 | 6p21.32 | T | C | 5.05E-07 | 5.05E-07 | 0.5588 | 0.5588 | 0.6767 | 0 |
| rs9275334 | Normal | 6 | 32667107 | 6p21.32 | C | T | 5.06E-07 | 5.06E-07 | 0.5616 | 0.5616 | 0.6756 | 0 |
| rs9275373 | Normal | 6 | 32668411 | 6p21.32 | A | G | 2.40E-07 | 2.40E-07 | 0.5639 | 0.5639 | 0.4842 | 0 |
| rs9275382 | Normal | 6 | 32668831 | 6p21.32 | C | T | 2.54E-07 | 2.54E-07 | 0.5419 | 0.5419 | 0.8059 | 0 |
| rs9275383 | Normal | 6 | 32668846 | 6p21.32 | T | G | 2.49E-07 | 2.49E-07 | 0.5483 | 0.5483 | 0.7753 | 0 |
| rs9275387 | Normal | 6 | 32669013 | 6p21.32 | C | T | 5.18E-07 | 5.18E-07 | 0.5619 | 0.5619 | 0.6764 | 0 |
| rs9275394 | Normal | 6 | 32669454 | 6p21.32 | C | A | 5.12E-07 | 5.12E-07 | 0.5616 | 0.5616 | 0.6776 | 0 |
| rs9275395 | Normal | 6 | 32669483 | 6p21.32 | G | A | 5.10E-07 | 5.10E-07 | 0.5615 | 0.5615 | 0.6777 | 0 |
| rs9275400 | Normal | 6 | 32669761 | 6p21.32 | G | C | 5.16E-07 | 5.16E-07 | 0.5619 | 0.5619 | 0.6768 | 0 |
| rs9275422 | Normal | 6 | 32670548 | 6p21.32 | A | G | 5.03E-07 | 5.03E-07 | 0.5616 | 0.5616 | 0.6713 | 0 |
| rs9275426 | Normal | 6 | 32670912 | 6p21.32 | C | T | 5.10E-07 | 5.10E-07 | 0.5615 | 0.5615 | 0.6725 | 0 |
| rs9275429 | Normal | 6 | 32671057 | 6p21.32 | A | G | 5.11E-07 | 5.11E-07 | 0.5616 | 0.5616 | 0.6756 | 0 |
| rs9275430 | Normal | 6 | 32671086 | 6p21.32 | T | C | 5.13E-07 | 5.13E-07 | 0.5617 | 0.5617 | 0.674 | 0 |
| rs9275434 | Normal | 6 | 32671247 | 6p21.32 | T | C | 5.13E-07 | 5.13E-07 | 0.5617 | 0.5617 | 0.6709 | 0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs9275435 | Normal | 6 | 32671332 | 6p21.32 | C | G | 5.12E-07 | 5.12E-07 | 0.5616 | 0.5616 | 0.6704 | 0 |
| rs9275437 | Normal | 6 | 32671412 | 6p21.32 | T | C | 5.13E-07 | 5.13E-07 | 0.5616 | 0.5616 | 0.6703 | 0 |
| rs9275442 | Normal | 6 | 32671755 | 6p21.32 | A | G | 5.09E-07 | 5.09E-07 | 0.5616 | 0.5616 | 0.6708 | 0 |
| rs9275476 | Normal | 6 | 32672624 | 6p21.32 | C | T | 5.40E-07 | 5.40E-07 | 0.5615 | 0.5615 | 0.6702 | 0 |
| rs9275477 | Normal | 6 | 32672641 | 6p21.32 | C | A | 5.74E-07 | 5.74E-07 | 0.5516 | 0.5516 | 0.721 | 0 |
| rs9275486 | Normal | 6 | 32673099 | 6p21.32 | A | T | 5.34E-07 | 5.34E-07 | 0.5621 | 0.5621 | 0.6669 | 0 |
| rs9275490 | Normal | 6 | 32673385 | 6p21.32 | G | C | 5.37E-07 | 5.37E-07 | 0.5622 | 0.5622 | 0.6672 | 0 |
| rs9275495 | Normal | 6 | 32673574 | 6p21.32 | T | A | 5.59E-07 | 5.59E-07 | 0.5626 | 0.5626 | 0.6731 | 0 |
| rs9275503 | Normal | 6 | 32673931 | 6p21.32 | G | A | 6.37E-07 | 6.37E-07 | 0.5566 | 0.5566 | 0.7228 | 0 |
| rs9275530 | Normal | 6 | 32675523 | 6p21.32 | C | G | 5.52E-07 | 5.52E-07 | 0.5627 | 0.5627 | 0.6811 | 0 |
| rs9275532 | Normal | 6 | 32675634 | 6p21.32 | G | C | 5.47E-07 | 5.47E-07 | 0.5625 | 0.5625 | 0.6785 | 0 |
| rs9275541 | Normal | 6 | 32676159 | 6p21.32 | G | C | 5.40E-07 | 5.40E-07 | 0.5623 | 0.5623 | 0.6747 | 0 |
| rs4273728 | Normal | 6 | 32678491 | 6p21.32 | C | T | 4.82E-07 | 4.82E-07 | 0.5606 | 0.5606 | 0.6383 | 0 |
| rs9275583 | Normal | 6 | 32680299 | 6p21.32 | A | G | 4.18E-07 | 4.18E-07 | 0.5587 | 0.5587 | 0.6045 | 0 |
| rs9275592 | Normal | 6 | 32680620 | 6p21.32 | T | G | 4.16E-07 | 4.16E-07 | 0.5586 | 0.5586 | 0.5971 | 0 |
| rs7454108 | Normal | 6 | 32681483 | 6p21.32 | C | T | 3.77E-07 | 3.77E-07 | 0.5575 | 0.5575 | 0.5786 | 0 |
| rs3957146 | Normal | 6 | 32681530 | 6p21.32 | C | T | 3.76E-07 | 3.76E-07 | 0.5575 | 0.5575 | 0.5777 | 0 |
| rs3998159 | Normal | 6 | 32682019 | 6p21.32 | C | A | 5.21E-07 | 5.21E-07 | 0.5625 | 0.5625 | 0.5693 | 0 |
| rs3957148 | Normal | 6 | 32682137 | 6p21.32 | G | A | 3.15E-07 | 3.15E-07 | 0.5546 | 0.5546 | 0.6094 | 0 |
| rs9275599 | Normal | 6 | 32682429 | 6p21.32 | T | C | 4.58E-08 | 4.58E-08 | 0.5071 | 0.5071 | 0.6565 | 0 |
| rs3997854 | Normal | 6 | 32682915 | 6p21.32 | G | T | 4.18E-09 | 2.78E-08 | 0.5204 | 0.5172 | 0.3289 | 10.06 |
| rs3873448 | Normal | 6 | 32683055 | 6p21.32 | T | C | 8.51E-09 | 9.63E-06 | 0.5296 | 0.5117 | 0.1801 | 41.67 |
| rs3873453 | Normal | 6 | 32683382 | 6p21.32 | T | C | 3.95E-07 | 1.15E-05 | 0.5858 | 0.5758 | 0.2628 | 25.17 |
| rs9275607 | Normal | 6 | 32683645 | 6p21.32 | G | A | 1.10E-07 | 1.10E-07 | 0.5883 | 0.5883 | 0.6732 | 0 |
| rs9275610 | Normal | 6 | 32683750 | 6p21.32 | C | T | 7.52E-08 | 7.52E-08 | 0.5838 | 0.5838 | 0.6345 | 0 |
| rs9275611 | Normal | 6 | 32683763 | 6p21.32 | A | G | 2.01E-08 | 1.82E-06 | 0.5405 | 0.5289 | 0.252 | 27.45 |
| rs9275613 | Normal | 6 | 32684105 | 6p21.32 | T | C | 2.07E-08 | 1.47E-06 | 0.5444 | 0.5335 | 0.259 | 25.98 |
| rs9275614 | Normal | 6 | 32684257 | 6p21.32 | G | A | 2.11E-08 | 1.89E-06 | 0.5451 | 0.5334 | 0.2516 | 27.54 |
| rs9275615 | Normal | 6 | 32684272 | 6p21.32 | A | T | 2.13E-08 | 1.81E-06 | 0.5452 | 0.5337 | 0.253 | 27.25 |
| rs6916779 | Normal | 6 | 32684317 | 6p21.32 | C | T | 8.43E-08 | 8.43E-08 | 0.5888 | 0.5888 | 0.6183 | 0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs9275618 | Normal | 6 | 32684387 | 6p21.32 | G | A | 2.17E-08 | 1.64E-06 | 0.5455 | 0.5343 | 0.2566 | 26.49 |
| rs9275638 | Normal | 6 | 32684760 | 6p21.32 | T | C | 1.30E-07 | 1.30E-07 | 0.5861 | 0.5861 | 0.5088 | 0 |
| rs3916765 | Normal | 6 | 32685550 | 6p21.32 | A | G | 8.53E-09 | 2.14E-07 | 0.5327 | 0.525 | 0.2939 | 18.33 |
| rs10969985 | Normal | 9 | 30943593 | 9p21.1 | T | C | 6.52E-07 | 0.00471 | 2.1281 | 1.9632 | 0.1071 | 55.25 |
| rs143280565 | Normal | 13 | 63147291 | 13q21.31 | T | G | 1.01E-07 | 1.38E-05 | 2.793 | 2.8335 | 0.2212 | 33.72 |

**Supplementary Table 3 – Risk loci for acute myeloid leukemia (AML) stratified by age.** Table shows fixed effects meta odds ratios for risk loci at 11q13.2 (rs4930561), 1p31.3 (rs10789158), 6p21.32 (rs3916765) and 7q33 (rs17773014) stratified by age. Cases and controls were stratified into those < 55 years and ≥ 55 years. GWAS 1 was not included in the meta-analysis for the ≥ 55 age group because the controls were recruited to the 1958 Birth Cohort and were all genotyped at the age of 45 years. For some cases age was not declared or not known. For each GWAS, association tests were performed for all AML cases and cytogenetically normal AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to all four GWAS for < 55 year olds and common to GWAS 2, GWAS 3 and GWAS 4 for ≥ 55 year olds, in fixed effects models using PLINK. All statistical tests were two-sided and no adjustments were made for multiple comparisons. N, number; OR, odds ratio; 95% CI, 95% confidence interval; Q, Cochran's Q statistic; $I^2$, heterogeneity index $I^2$; *P*, *P* value.

| **AML risk variant** | **Cytogenetics** | **Age (years)** | **Case, N / Control, N** | **GWAS, N** | **OR (95% CI)** | ***P* value** | **$I^2$** | ***P*Q** |
|---|---|---|---|---|---|---|---|---|
| rs4930561 | All AML | All ages | 4018/10488 | 4 | 1.17 (1.11-1.24) | 2.15e-08 | 0.00 | 0.665 |
| | | < 55 | 1401/7019 | 4 | 1.21 (1.11-1.32) | 3.0e-05 | 10.07 | 0.34 |
| | | ≥ 55 | 1222/3469 | 3 | 1.10 (0.99-1.22) | 0.08 | 0.00 | 0.76 |
| | | | | | Test for heterogeneity | | 46.87 | 0.17 |
| rs10789158 | All AML | All ages | 4018/10488 | 4 | 1.22 (1.13-1.31) | 2.25e-07 | 0.00 | 0.422 |
| | | < 55 | 1401/7019 | 4 | 1.22 (1.09-1.38) | 8.8e-04 | 0.00 | 0.82 |
| | | ≥ 55 | 1222/3469 | 3 | 1.10 (0.95-1.27) | 0.19 | 0.00 | 0.74 |
| | | | | | Test for heterogeneity | | 16.99 | 0.27 |
| rs3916765 | Normal | All ages | 1287/10488 | 4 | 1.72 (1.46-2.03) | 1.51e-10 | 26 | 0.256 |
| | | < 55 | 480/7019 | 4 | 1.64 (1.25-2.16) | 3.5e-04 | 0.00 | 1.00 |
| | | ≥ 55 | 518/3470 | 3 | 1.66 (1.27-2.17) | 2.1e-04 | 43.90 | 0.17 |
| | | | | | Test for heterogeneity | | 0.00 | 0.95 |
| rs17773014 | Normal | All ages | 1287/10488 | 4 | 1.26 (1.15-1.37) | 4.09e-07 | 15 | 0.315 |
| | | < 55 | 480/7019 | 4 | 1.36 (1.18-1.58) | 4.3e-05 | 50.84 | 0.11 |
| | | ≥ 55 | 518/3470 | 3 | 1.18 (1.03-1.37) | 0.02 | 59.09 | 0.09 |
| | | | | | Test for heterogeneity | | 50.10 | 0.16 |

**Supplementary Table 4 – Risk loci for acute myeloid leukemia (AML) stratified by sex.** Table shows fixed effects meta odds ratios for risk loci at 11q13.2 (rs4930561), 1p31.3 (rs10789158), 6p21.32 (rs3916765) and 7q33 (rs17773014) stratified by sex. For some cases sex was not declared or not known. For each GWAS, association tests were performed for all AML cases and cytogenetically normal AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to all four GWAS, in fixed effects models using PLINK. All statistical tests were two-sided and no adjustments were made for multiple comparisons. N, number; OR, odds ratio; 95% CI, 95% confidence interval; Q, Cochran's Q statistic; $I^2$, heterogeneity index $I^2$; *P*, *P* value.

| **AML risk variant** | **Cytogenetics** | **Sex** | **Case, N / Control, N** | **GWAS, N** | **OR (95% CI)** | ***P* value** | **$I^2$** | ***P*Q** |
|---|---|---|---|---|---|---|---|---|
| rs4930561 | All AML | All | 4018/10488 | 4 | 1.17 (1.11-1.24) | 2.15e-08 | 0.00 | 0.665 |
| | | Males | 2102/5133 | 4 | 1.18 (1.09-1.27) | 4.5e-05 | 28.77 | 0.24 |
| | | Females | 1902/5255 | 4 | 1.17 (1.08-1.27) | 1.1e-04 | 0.00 | 0.67 |
| | | | | | Test for heterogeneity | | 0.00 | 0.88 |
| rs10789158 | All AML | All | 4018/10488 | 4 | 1.22 (1.13-1.31) | 2.25e-07 | 0.00 | 0.422 |
| | | Males | 2102/5133 | 4 | 1.27 (1.14-1.41) | 9.8e-06 | 0.00 | 0.83 |
| | | Females | 1902/5255 | 4 | 1.18 (1.06-1.31) | 2.4e-03 | 36.69 | 0.19 |
| | | | | | Test for heterogeneity | | 0.00 | 0.34 |
| rs3916765 | Normal | All | 1287/10488 | 4 | 1.72 (1.46-2.03) | 1.51e-10 | 26 | 0.256 |
| | | Males | 642/5133 | 4 | 1.45 (1.16-1.80) | 1.1e-03 | 55.10 | 0.08 |
| | | Females | 645/5355 | 4 | 2.11 (1.63-2.73) | 1.2e-08 | 0.00 | 0.86 |
| | | | | | Test for heterogeneity | | 78.47 | 0.03 |
| rs17773014 | Normal | All | 1287/10488 | 4 | 1.26 (1.15-1.37) | 4.09e-07 | 15 | 0.315 |
| | | Males | 642/5133 | 4 | 1.27 (1.12-1.44) | 2.3e-04 | 0.00 | 0.65 |
| | | Females | 645/5355 | 4 | 1.24 (1.09-1.40) | 7.0e-03 | 4.30 | 0.37 |
| | | | | | Test for heterogeneity | | 0.00 | 0.79 |

**Supplementary Table 5 - *cis*-eQTL analysis of rs4930561 in whole blood.** *cis*-eQTL data for loci annotated to within 500kb of rs4930561 derived from whole blood expression data collated by the eQTLGen Consortium (http://www.eqtlgen.org/cis-eqtls.html). SNP, single nucleotide polymorphism; QTL, expression quantitative trait loci; Chr, chromosome. [a]hg19 coordinates; [b]Unadjusted *P* value; [c]Benjamini-Hochberg corrected *P* value.

| SNP | SNP Position[a] | Assessed allele eQTL | Chr | Gene | Gene Symbol | Gene Position[a] | P value eQTL[b] | $P_{BH}$ eQTL[c] | Z score |
|---|---|---|---|---|---|---|---|---|---|
| rs4930561 | 67931761 | G | 11 | ENSG00000160172 | FAM86C2P | 67565963 | 0.552111 | 0.763212 | 0.5947 |
| | | | | ENSG00000255306 | RP5-901A4.1 | 67795102 | 1.75E-25 | 4.1E-24 | -10.4334 |
| | | | | ENSG00000110717 | NDUFS8 | 67801097 | 3.23E-05 | 0.000169 | -4.1564 |
| | | | | ENSG00000110719 | TCIRG1 | 67812422 | 1.33E-05 | 7.83E-05 | 4.3546 |
| | | | | ENSG00000255031 | RP11-802E16.3 | 67819718 | 7.19E-16 | 6.76E-15 | -8.0671 |
| | | | | ENSG00000110721 | CHKA | 67854618 | 2.21E-15 | 1.73E-14 | 7.9291 |
| | | | | ENSG00000239559 | RPL37P2 | 67450386 | 0.954545 | 0.99533 | 0.0571 |
| | | | | ENSG00000132746 | ALDH3B2 | 67439152 | 0.432923 | 0.678246 | -0.7841 |
| | | | | ENSG00000132744 | ACY3 | 67414078 | 0.19532 | 0.437145 | -1.2949 |
| | | | | ENSG00000167799 | NUDT8 | 67396405 | 0.46968 | 0.700717 | -0.723 |
| | | | | ENSG00000231793 | DOC2GP | 67381926 | 1.96E-13 | 1.32E-12 | -7.3514 |
| | | | | ENSG00000110066 | KMT5B | 67951812 | 0.966818 | 0.99533 | 0.0418 |
| | | | | ENSG00000167792 | NDUFV1 | 67377164 | 0.966339 | 0.99533 | 0.0422 |
| | | | | ENSG00000084207 | GSTP1 | 67352598 | 0.50605 | 0.720739 | -0.665 |
| | | | | ENSG00000171067 | C11orf24 | 68034136 | 0.974153 | 0.99533 | 0.0324 |
| | | | | ENSG00000162337 | LRP5 | 68148410 | 0.853072 | 0.99533 | -0.1852 |
| | | | | ENSG00000167797 | CDK2AP2 | 67275044 | 0.297134 | 0.537126 | -1.0426 |
| | | | | ENSG00000110697 | PITPNM1 | 67266486 | 0.028351 | 0.095177 | -2.1923 |
| | | | | ENSG00000110711 | AIP | 67254543 | 0.25487 | 0.520821 | 1.1386 |
| | | | | ENSG00000172663 | TMEM134 | 67234283 | 0.227278 | 0.485549 | -1.2073 |
| | | | | ENSG00000269913 | CTC-1337H24.1 | 67227561 | 0.9469 | 0.99533 | -0.0666 |
| | | | | ENSG00000175544 | CABP4 | 67223288 | 0.419551 | 0.678246 | -0.8071 |
| | | | | ENSG00000175514 | GPR152 | 67219486 | 0.841637 | 0.99533 | -0.1997 |
| | | | | ENSG00000213402 | PTPRCAP | 67204259 | 0.382663 | 0.642327 | 0.873 |

| | | | | | |
|---|---|---|---|---|---|
| ENSG00000175634 | RPS6KB2 | 67199401 | 0.082 | 0.226705 | -1.7391 |
| ENSG00000172531 | PPP1CA | 67177154 | 0.002583 | 0.011038 | 3.0134 |
| ENSG00000172508 | CARNS1 | 67187758 | 0.477084 | 0.700717 | -0.711 |
| ENSG00000175463 | TBC1D10C | 67174473 | 0.057775 | 0.169715 | -1.8973 |
| ENSG00000172613 | RAD9A | 67162528 | 0.613278 | 0.820949 | -0.5052 |
| ENSG00000175505 | CLCF1 | 67136643 | 0.757778 | 0.937252 | 0.3084 |
| ENSG00000110075 | PPP6R3 | 68305494 | 0.179207 | 0.421137 | 1.3433 |
| ENSG00000175482 | POLD4 | 67121345 | 0.282643 | 0.53137 | 1.0745 |
| ENSG00000172830 | SSH3 | 67075498 | 0.121911 | 0.301571 | -1.5467 |
| ENSG00000172932 | ANKRD13D | 67062987 | 0.027426 | 0.095177 | -2.2053 |
| ENSG00000173020 | ADRBK1 | 67043954 | 0.68254 | 0.86701 | 0.4091 |
| ENSG00000260808 | CTD-2007L18.5 | 68382273 | 0.893244 | 0.99533 | 0.1342 |
| ENSG00000179038 | AP001885.1 | 66964014 | 0.111925 | 0.292249 | 1.5897 |
| ENSG00000173120 | KDM2A | 66955940 | 0.365359 | 0.635996 | 0.9053 |
| ENSG00000132749 | MTL5 | 68496970 | 0.997128 | 0.997128 | -0.0035 |
| ENSG00000110057 | UNC93B1 | 67765513 | 0.000232 | 0.001092 | -3.6809 |
| ENSG00000110090 | CPT1A | 68566983 | 0.04056 | 0.127088 | -2.0479 |
| ENSG00000006534 | ALDH3B1 | 67786396 | 2.86E-19 | 4.48E-18 | -8.974 |
| ENSG00000197345 | MRPL21 | 68665023 | 1.60E-30 | 7.5E-29 | 11.4837 |
| ENSG00000132740 | IGHMBP2 | 68689690 | 2.43E-17 | 2.85E-16 | -8.4711 |
| ENSG00000162341 | TPCN2 | 68837218 | 0.628812 | 0.820949 | 0.4835 |
| ENSG00000259799 | RP11-554A11.9 | 68925299 | 0.002932 | 0.011483 | -2.9747 |

**Supplementary Table 6 – Chromosome 6p21.32 risk locus for acute myeloid leukemia (AML) stratified by *NPM1* and *FLT3* mutation status.** Table shows fixed-effects meta odds ratios for the risk locus at 6p21.32 (rs3916765) stratified by *NPM1* and *FLT3* mutation status. *NPM1* and *FLT3* mutation status was available for cases recruited to GWAS 2 and GWAS 4 only. For each GWAS, association tests were performed for cytogenetically normal AML cases assuming an additive genetic model, with nominally significant principal components included in the analysis as covariates. Association summary statistics were combined for variants common to GWAS 2 and GWAS 4, in fixed effects models using PLINK. All statistical tests were two-sided and no adjustments were made for multiple comparisons. N, number; OR, odds ratio; 95% CI, 95% confidence interval; Q, Cochran's Q statistic; $I^2$, heterogeneity index $I^2$.

| **AML risk variant** | **AML cytogenetics** | **Mutation status** | **Case, N / Control, N** | **GWAS, N** | **OR (95% CI)** | ***P* value** | **$I^2$** | ***P*Q** |
|---|---|---|---|---|---|---|---|---|
| rs3916765 | All AML | All cases | 4018/10488 | 4 | 1.20 (1.09-1.32) | 1.15e-04 | 37 | 0.187 |
| | | NPM1-negative | 422/6205 | 2 | 1.28 (0.97-1.68) | 0.08 | 0.00 | 0.62 |
| | | NPM1-positive | 231/6205 | 2 | 1.96 (1.29-2.98) | 1.7e-03 | 1.12 | 0.94 |
| | | | | | Test for heterogeneity | | 63.88 | 0.10 |
| | | FLT3-negative | 594/6205 | 2 | 1.26 (1.01-1.58) | 0.04 | 0.00 | 0.85 |
| | | FLT3-positive | 271/6205 | 2 | 1.52 (1.07-2.16) | 0.02 | 81.37 | 0.02 |
| | | | | | Test for heterogeneity | | 0.00 | 0.38 |
| | Normal | All cases | 1287/10488 | 4 | 1.72 (1.46-2.03) | 1.51e-10 | 26 | 0.256 |
| | | NPM1-negative | 205/6205 | 2 | 1.32 (0.91-1.92) | 0.14 | 0.00 | 0.63 |
| | | NPM1-positive | 206/6205 | 2 | 1.95 (1.26-3.01) | 2.8e-03 | 0.00 | 0.96 |
| | | | | | Test for heterogeneity | | 43.74 | 0.18 |
| | | FLT3-negative | 328/6205 | 2 | 1.49 (1.10-2.02) | 0.01 | 0.00 | 0.38 |
| | | FLT3-positive | 200/6205 | 2 | 1.84 (1.20-2.81) | 5.1e-03 | 0.00 | 0.52 |
| | | | | | Test for heterogeneity | | 0.00 | 0.43 |

**Supplementary Table 7- *cis*-eQTL analysis of rs10789158 in whole blood.** *cis*-eQTL data for loci annotated to within 500Kb of rs10789158 derived from whole blood expression data collated by the eQTLGen Consortium (http://www.eqtlgen.org/cis-eqtls.html). SNP, single nucleotide polymorphism; QTL, expression quantitative trait loci; Chr, chromosome. [a]hg19 coordinates; [b]Unadjusted *P* value; [c]Benjamini-Hochberg corrected *P* value.

| SNP | SNP Position[a] | Assessed allele eQTL | Chr | Gene | Gene Symbol | Gene Position[a] | P value eQTL[b] | PBH eQTL[c] | Z score |
|---|---|---|---|---|---|---|---|---|---|
| rs10789158 | 64867602 | C | 1 | ENSG00000162433 | AK4 | 65655530 | 0.0019144 | 0.012561175 | 3.1032 |
| | | | | ENSG00000226891 | RP11-182I10.3 | 65453033 | 0.04860961 | 0.121411686 | 1.9721 |
| | | | | ENSG00000088035 | ALG6 | 63868747 | 0.05518713 | 0.121411686 | 1.9175 |
| | | | | ENSG00000079739 | PGM1 | 64092431 | 0.11328477 | 0.207688745 | 1.5838 |
| | | | | ENSG00000142856 | ITGB3BP | 63982916 | 0.45349565 | 0.623556519 | 0.7498 |
| | | | | ENSG00000162434 | JAK1 | 65365549 | 0.67463156 | 0.742094716 | 0.4199 |
| | | | | ENSG00000185031 | RP11-182I10.4 | 65451030 | 0.76265206 | 0.76265206 | -0.3019 |
| | | | | ENSG00000158966 | CACHD1 | 65047584 | 0.61468307 | 0.742094716 | -0.5033 |
| | | | | ENSG00000203965 | EFCAB7 | 64013703 | 0.31163369 | 0.489710084 | -1.0117 |
| | | | | ENSG00000116675 | DNAJC6 | 65797727 | 0.02633742 | 0.09657054 | -2.221 |
| | | | | ENSG00000162437 | RAVER2 | 65254846 | 0.00228385 | 0.012561175 | -3.0505 |

**Supplementary Table 8 - *cis*-eQTL analysis of rs17773014 in whole blood.** *cis*-eQTL data for loci annotated to within 500Kb of rs17773014 derived from whole blood expression data collated by the eQTLGen Consortium (http://www.eqtlgen.org/cis-eqtls.html). SNP, single nucleotide polymorphism; QTL, expression quantitative trait loci; Chr, chromosome. [a]hg19 coordinates; [b]Unadjusted *P* value; [c]Benjamini-Hochberg corrected *P* value.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **rs17773014** | **134093813** | **G** | **7** | **ENSG00000205060** | **SLC35B4** | **133987943** | **0.02245394** | ***0.06736182*** | **2.2827** |
| | | | | ENSG00000085662 | AKR1B1 | 134135569 | 5.92E-24 | 5.32863E-23 | -10.0931 |
| | | | | ENSG00000155530 | LRGUK | 133880697 | 0.84461017 | 0.950186441 | -0.196 |
| | | | | ENSG00000172331 | BPGM | 134348062 | 0.30442046 | 0.524218755 | -1.0269 |
| | | | | ENSG00000122786 | CALD1 | 134542241 | 0.99888296 | 0.99888296 | -0.0012 |
| | | | | ENSG00000131558 | EXOC4 | 133344585 | 0.08572368 | 0.19287828 | -1.7184 |
| | | | | ENSG00000146859 | TMEM140 | 134841737 | 0.34947917 | 0.524218755 | 0.9357 |
| | | | | ENSG00000122783 | C7orf49 | 134816331 | 0.40937159 | 0.526334901 | -0.825 |
| | | | | ENSG00000105875 | WDR91 | 134882453 | 0.01182917 | 0.053231265 | -2.517 |

**Supplementary Table 9 – Ethical approvals for studies contributing AML cases and/or controls to GWAS 1, GWAS 2, GWAS 3 and GWAS 4.**

| Cohort | Ethics Committee providing approval | Decision |
|---|---|---|
| GWAS 1 Cases | | |
| UK MRC/NCRI AML clinical trials (N=529) | NHS York Research Ethics committee (REF 06/Q1108/92) and Newcastle University FMS Ethics Committee (REF BH36664 (7078) | Approved |
| Eurobank transplant study (N=70) | NHS North East Newcastle and North Tyneside 1 Research Ethics Committee | Approved |
| Leukaemia and Lymphoma Research adult acute Leukaemia study (N=222) | NHS York Research Ethics committee (REF 06/Q1108/92) and Newcastle University FMS Ethics Committee (REF BH36664 (7078) | Approved |
| Newcastle University Haematology Biobank (N=48) | NHS North East - Newcastle and North Tyneside 1 Research Ethics Committee (REF 17/NE/0361) | Approved |
| Institutional biobank of University of Chicago (N=250) | University of Chicago Medical Center Institutional Review Board | Approved |
| GWAS 1 Controls | | |
| British 1958 Birth Cohort (N=2671) | NHS North West – Haydock Research Ethics Committee (REF 14/NW/1179) | Approved |
| GWAS 2 Cases | | |
| Central England Haemato-Oncology and Oncology Research Bank (N=120) | NHS East Midlands - Derby Research Ethics Committee (REF 09/H0405/12+5) | Approved |
| King's College London Medical School (N=144) | NHS Wales Multicentre Research Ethics Committee (REF 08/MRE09/29) | Approved |
| Study Alliance Leukemia biobank at Dresden University (N=208) | Institutional Review Board of the Medical Faculty of Dresden (Medizinische Fakultat Dresden; IRB #EK98032010) | Approved |
| CALGB 9710 APL clinical trial (N=101) | University of Chicago Medical Center Institutional Review Board (REF CALGB 9710; NCT00003934) | Approved |
| Newcastle University Haematology Biobank (N=248) | NHS North East - Newcastle & North Tyneside Research Ethics Committee (REF 17/NE/0361) | Approved |
| Munich Leukemia Laboratory (N=53) | Bavarian Medical Association (Bayerische Landesärztekammer)(REF 5117) | Approved |
| Medical University of Graz (N=32) | Ethics Committee of the Medical University of Graz (REF 26-369 ex 13/14) | Approved |
| University Hospital Rigshospitalet Copenhagen (N=13) | The Capital Region of Denmark Ethic Committee (Historic samples - ethical approval not required) | Waived |

| | | |
|---|---|---|
| Universita Cattolica Sacro Cuore Rome (N=12) | Institutional Review Board of the Policlinico Tor Vergata of Rome | Approved |
| GWAS 2 Controls | | |
| UK Blood Service Control Group (N=2477) | NHS South East multicentre research ethics committee (REF 05/Q0106/74)(UK Blood Services Controls) | Approved |
| GWAS 3 Cases | | |
| University of Heidelberg, Germany (N=82) | Medical Ethics Committee II of the Medical Faculty Mannheim of the Heidelberg University (REF 2013-509N-MA ) | Approved |
| Centre Hospitalier Universitaire Nice, France (N=42) | Comité de Protection des Personnes Centre Hospitalier Universitaire de Nice (REF NCT01210274) | Approved |
| University of London UK (GSE20672)(N=40) | Data is in the public domain | Not applicable |
| Austrian Academy of Sciences (N=223) | Ethics Committee of the Medical University of Vienna | Approved |
| ALFA Clinical Trials at the University of Lille, France (N=278) | Institutional Review Borard of CHRU of Lille (CSTMT089) | Approved |
| Biobank La Fe at the Hospital Universitari i Politècnic La Fe, Spain (N=15) | Research Ethics Board of the Hospital Universitari i Politècnic La Fe, Spain (CEIB; Comité Ético de Investigación Biomédica). | Approved |
| German-Austria AML Study Group (GSE32462, N=189[70)] | Data is in the public domain | Not applicable |
| German-Austria AML Study Group ( GSE34542, N=33[71]) | Data is in the public domain | Not applicable |
| German-Austria AML Study Group (GSE46745, N=33) | Data is in the public domain | Not applicable |
| German-Austria AML Study Group (GSE46951, N=51) | Data is in the public domain | Not applicable |
| KORA study (N=5) | Ethics Committee of the Bavarian Medical Association and the Bavarian commissioner for data protection and privacy. | Approved |
| GWAS 3 Controls | | |
| KORA study (N=1612) | Ethics Committee of the Bavarian Medical Association and the Bavarian commissioner for data protection and privacy. | Approved |
| GWAS 4 Cases | | |
| Central England Haemato-Oncology and Oncology Research Bank (N=515) | NHS East Midlands - Derby Research Ethics Committee (REF 09/H0405/12+5) | Approved |
| Hematology Division at Semmelweis University, Budapest (N=202) | Ethical Committee of the Hungarian Medical Research Council (REF 45371-2/2016/EKU) | Approved |

| | | |
|---|---|---|
| UK Biobank (N=260) | NHS North West Multi-centre Research Ethics Committee (MREC)(REF 16/NW/0274) | Approved |
| GWAS 4 Controls | | |
| UK Biobank (N=3728) | NHS North West Multi-centre Research Ethics Committee (MREC)(REF 16/NW/0274) | Approved |

**Supplementary Table 10 – Primers used for *NPM1* and *FLT3* sequence analysis**

| | |
|---|---|
| *NPM1* Fragment analysis primer sequences | |
| *NPM1* Frag Forward | 5’ TGT CTA TGA AGT GTT GTG GTT CC 3’ |
| *NPM1* Frag Reverse | 5’ VIC-AAA AAG GAC AGC CAG ATA TCA A 3’ |
| | |
| *NPM1* Sequencing primers | |
| *NPM1* Exon 12 Forward | 5’ TGT CTA TGA AGT GTT GTG GTT CC 3’ |
| *NPM1* Exon 12 Reverse | 5’ TTT GGA CAA CAC ATT CTT 3’ |
| | |
| *FLT3* Sequencing primers | |
| *FLT3* Forward | 5’ 6-FAM-GCA ATT TAG GTA TGA AAG CCA GC 3’ |
| *FLT3* Reverse | 5’ CTT TCA GCA TTT TGA CGG CAA CC 3’ |