

Association of Clonal Hematopoiesis with Chronic Obstructive Pulmonary Disease

Supplemental Appendix

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Figure S1. Distribution of age across cohorts and COPD status (except UK Biobank)

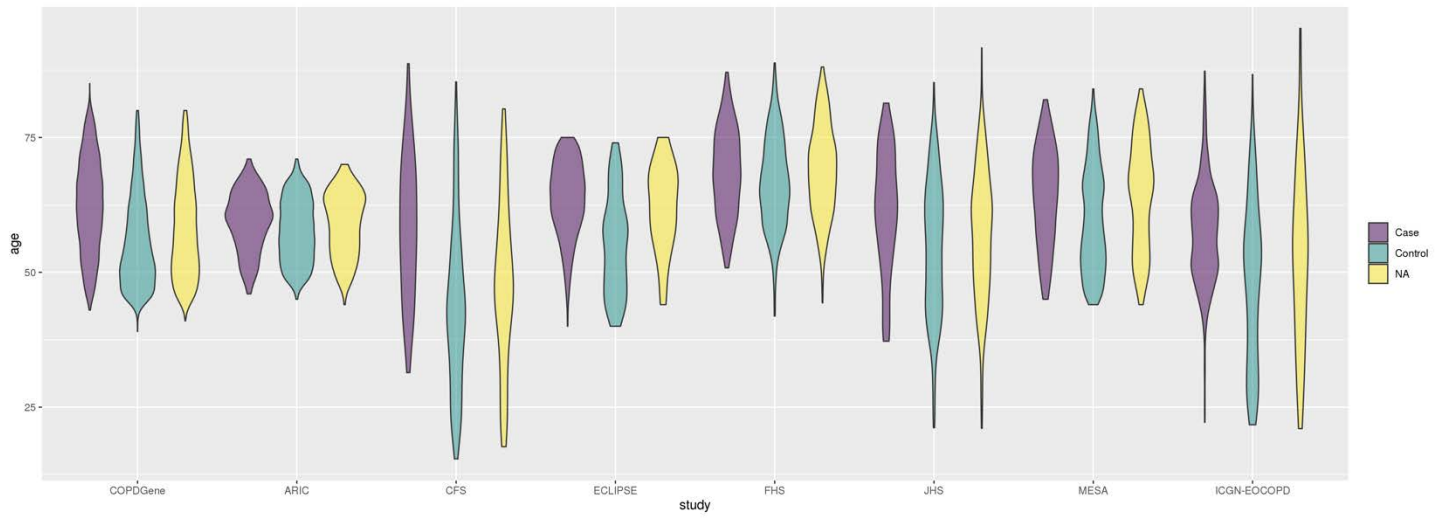
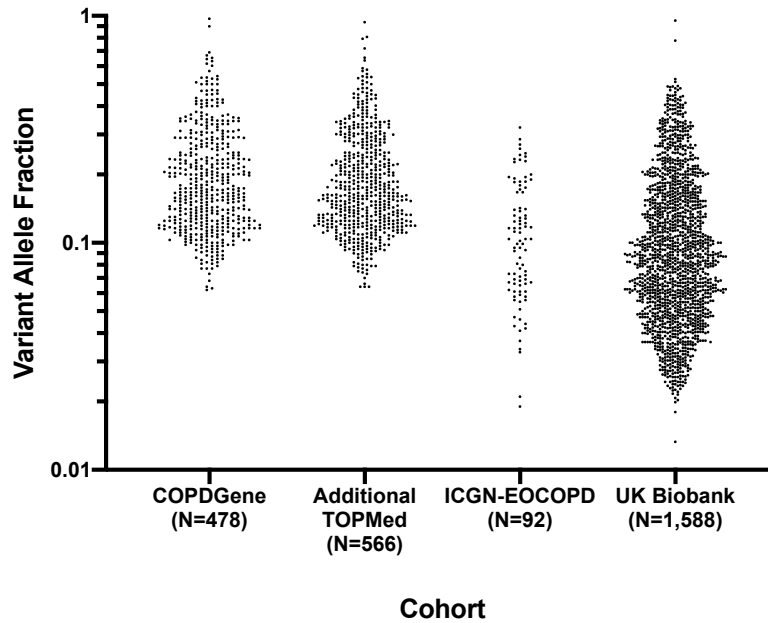


Figure S2. Clonal hematopoietic mutations variant allele frequencies (VAF) across cohorts and distribution between cases and controls. (A) Distribution of variant allele frequencies (VAFs) across the cohorts. For patients with multiple mutations, the VAF for the largest clone is shown. The difference in the lowest detected VAFs is a result of COPDGene and TOPMed using whole genome sequencing whereas ICGN-EOCOPD and the UK Biobank utilized whole exome sequencing. The depth of coverage in whole exome sequencing allows for more sensitive detection of smaller clones (See Bick et al, Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes." bioRxiv: 782748.) (B) Distribution of mutations in controls (red) and moderate to very severe COPD cases (cyan) with CHIP. P-values for comparisons of mutations, controlled for covariates, are shown in Supplemental table S13.

A



B

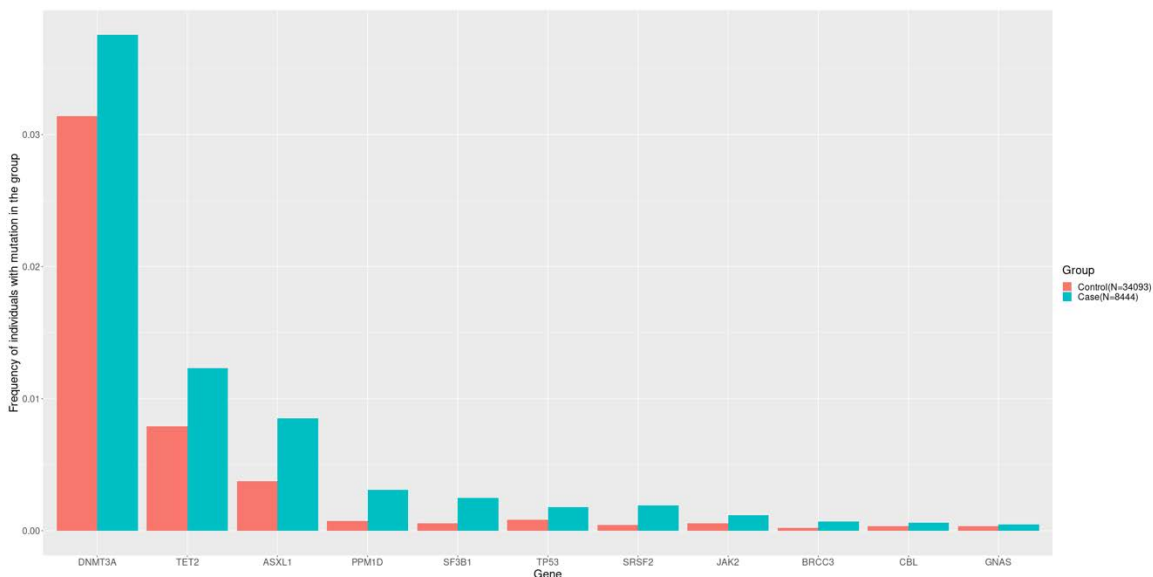


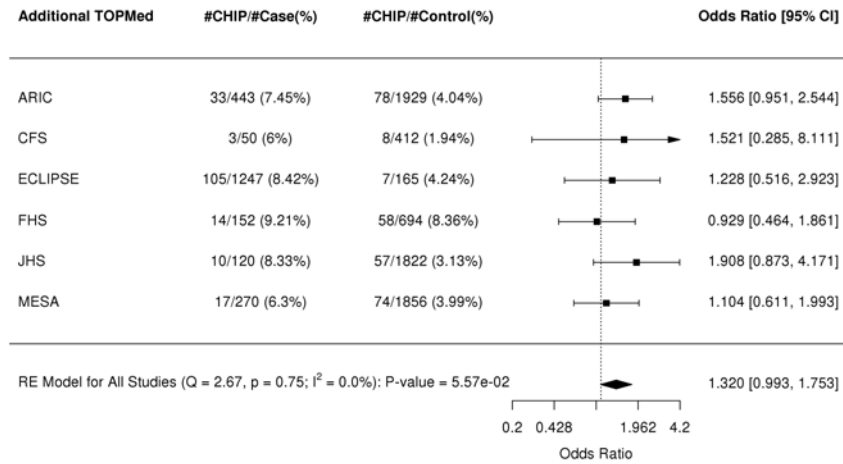
Figure S3. Association between CHIP and COPD in Additional TOPMed Cohorts

(A) Association results between CHIP status and moderate-to-severe COPD (GOLD level 2-4) across additional TOPMed cohorts.

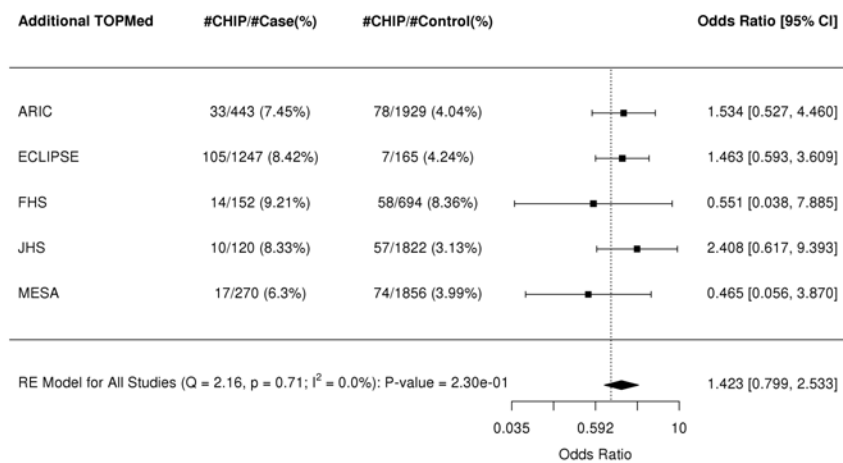
(B) Association results between CHIP status and severe COPD (GOLD level 3-4) across additional TOPMed cohorts.

(C) Association results between CHIP status and COPD severity (GOLD level 3-4 versus GOLD level 2) across additional TOPMed cohorts.

A



B



C

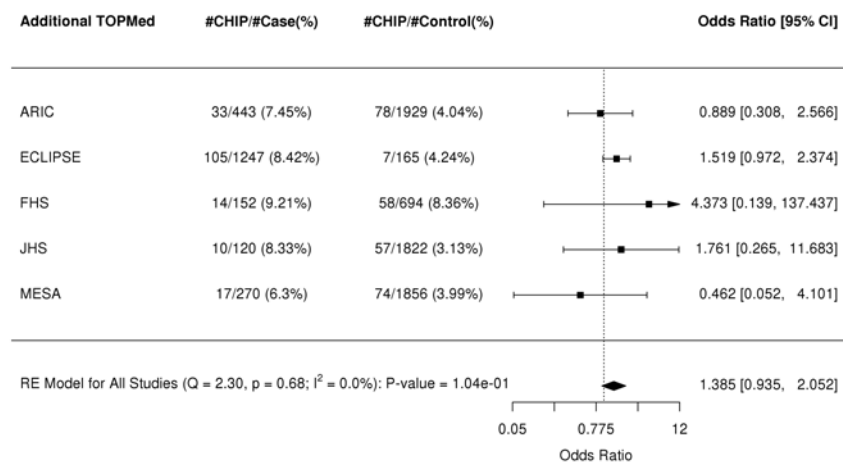
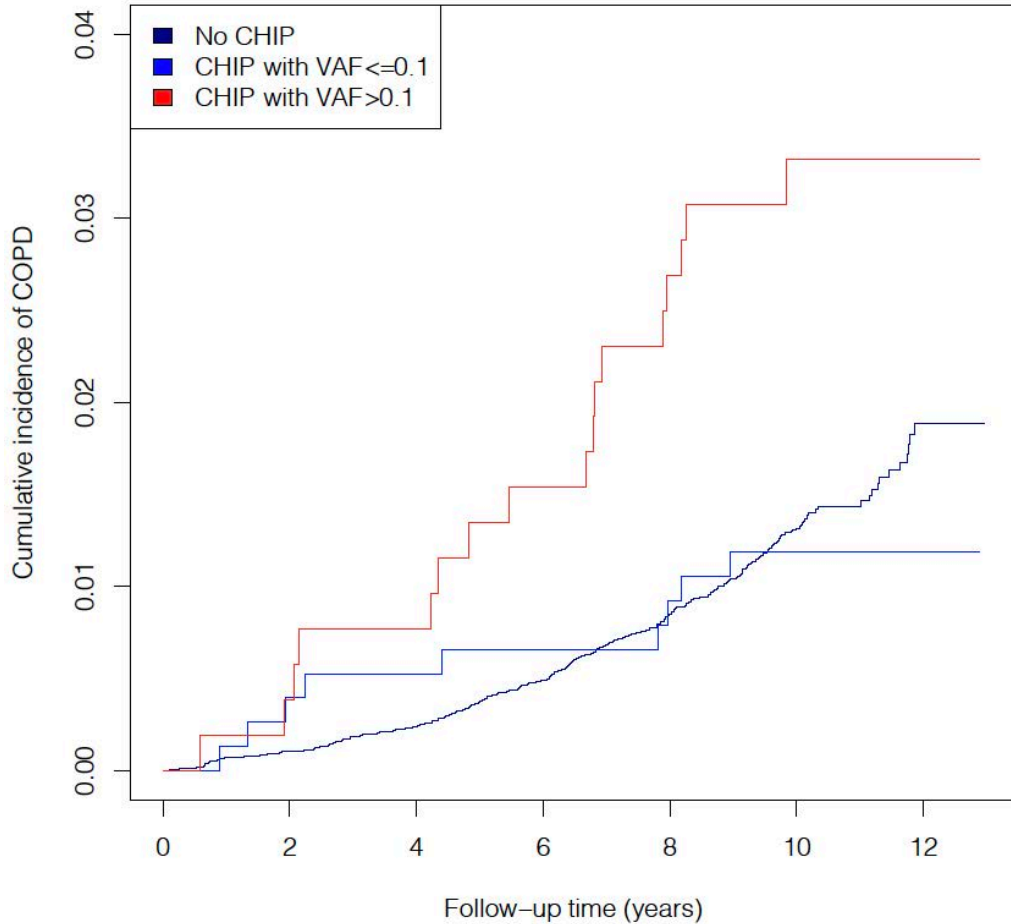


Figure S4. Incidence Analysis in UK Biobank.

After excluding individuals with COPD at baseline using our study definition (n=3,676) or with prevalent COPD at study enrollment by self-report or ICD code (additional n=336), there were 23,605 individuals at risk for incident COPD. Using ICD code-based incident COPD ascertainment (ICD-10 J41, J41.0, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9; ICD-9 491, 491.2, 491.9, 492, 492.9, 496, 496.9), 337 individuals (1.4%) developed incident COPD over a median 10.0 [IQR 0.9-10.2] years of follow-up.



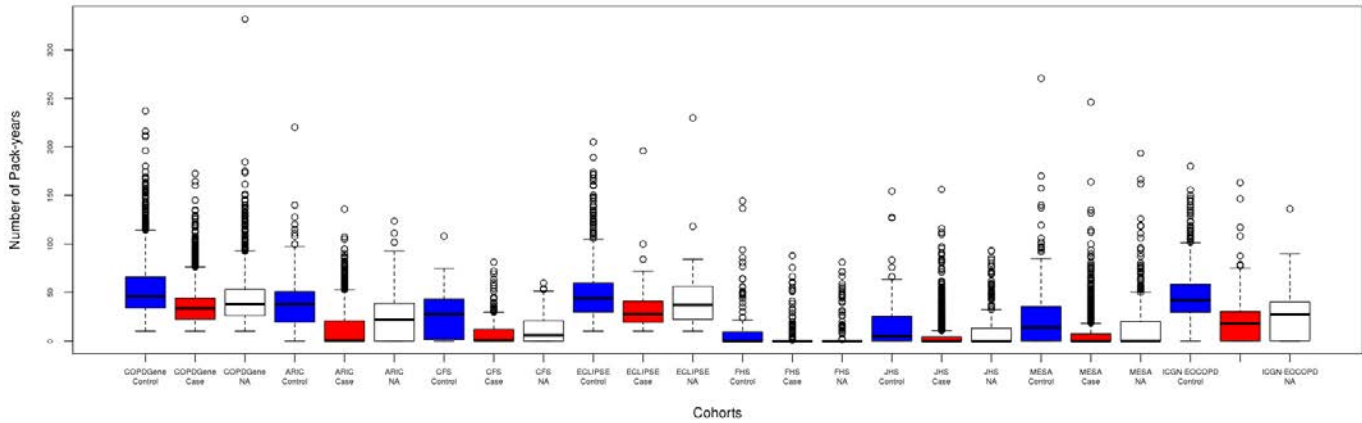
	0	2.5	5	7.5	10	12.5
No CHIP	22326	22291	22220	22134	12562	486
CHIP with VAF <= 0.1	759	755	753	752	418	16
CHIP with VAF > 0.1	520	516	513	508	271	7

Figure S5. Smoking and CHIP.

(A) Distribution of pack-years across cohorts.

(B) Logistic regression was applied on CHIP status as the binary response, while adjusting for gender, age, sequencing center, race, and top 10 principal components in each cohort. Random-effects meta-analyses across the TOPMed cohorts, and across all cohorts were conducted using the R package metafor.

A



B

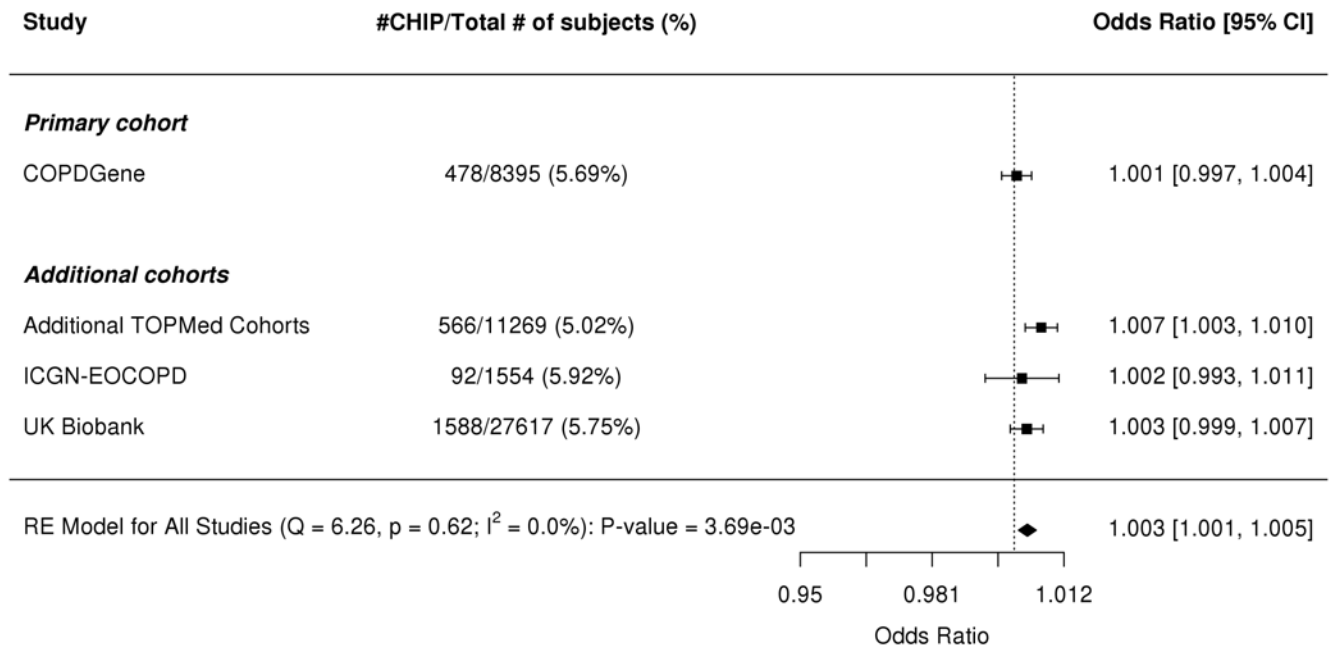


Figure S6. Distribution of the difference in the number of years between blood draw and assessment of COPD status using spirometry measures in the COPDGene and additional TOPMed cohorts

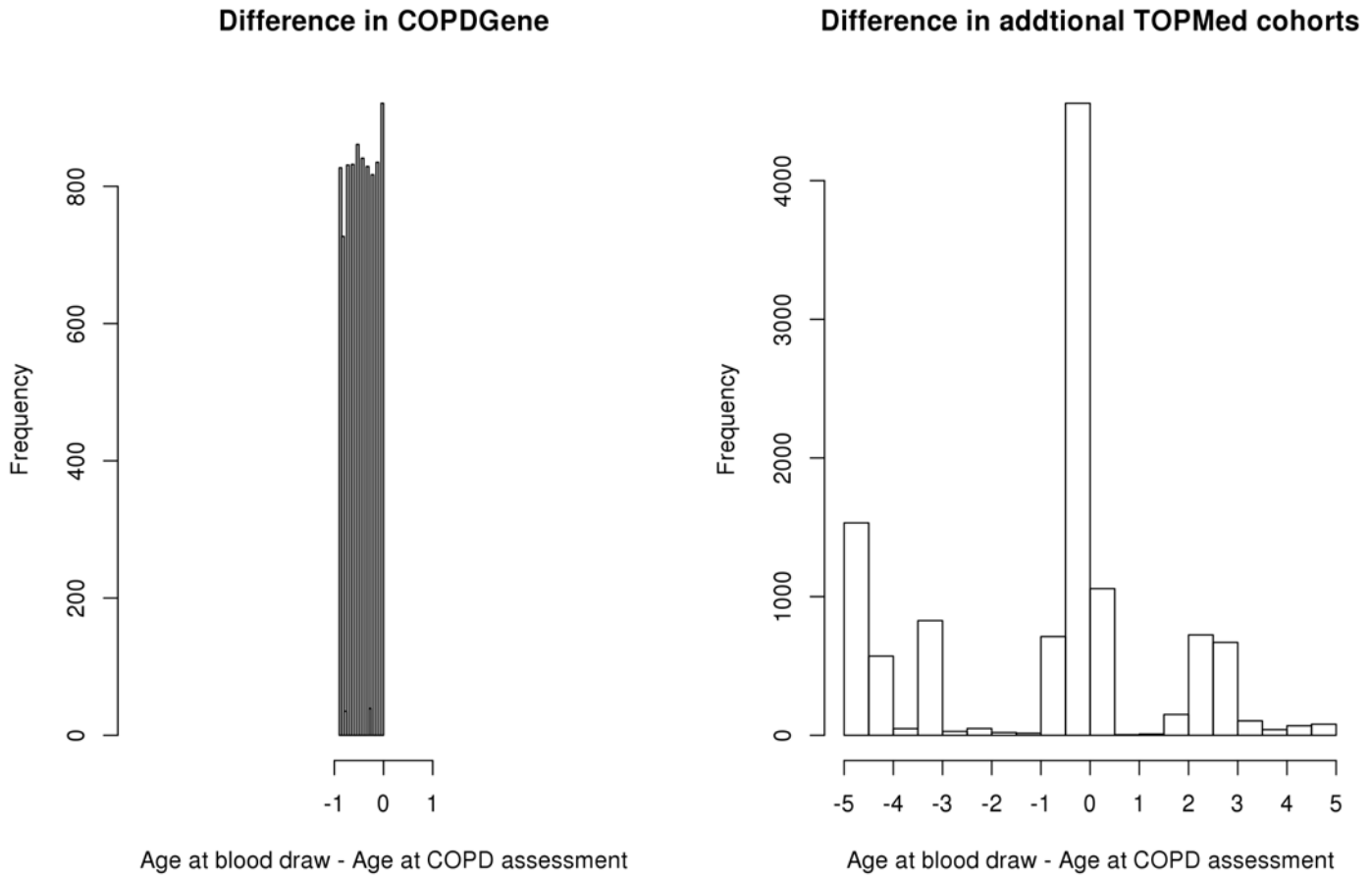


Figure S7. Meta-analysis results of CHIP and GOLD 2 COPD within different strata of smoking exposure: A) non-smokers only; B) ever-smokers; C) current smokers; D) former smokers; E) heavy smokers (number of pack-years > 30); F) light smokers (number of pack-years < 15).

Note: There are no non-smokers in COPDGene (panel A) and there are only 3 light smokers with CHIP in the ICGN-EOCOPD cohort (panel F), thus the confidence interval is too wide to contribute to the meta-analysis.

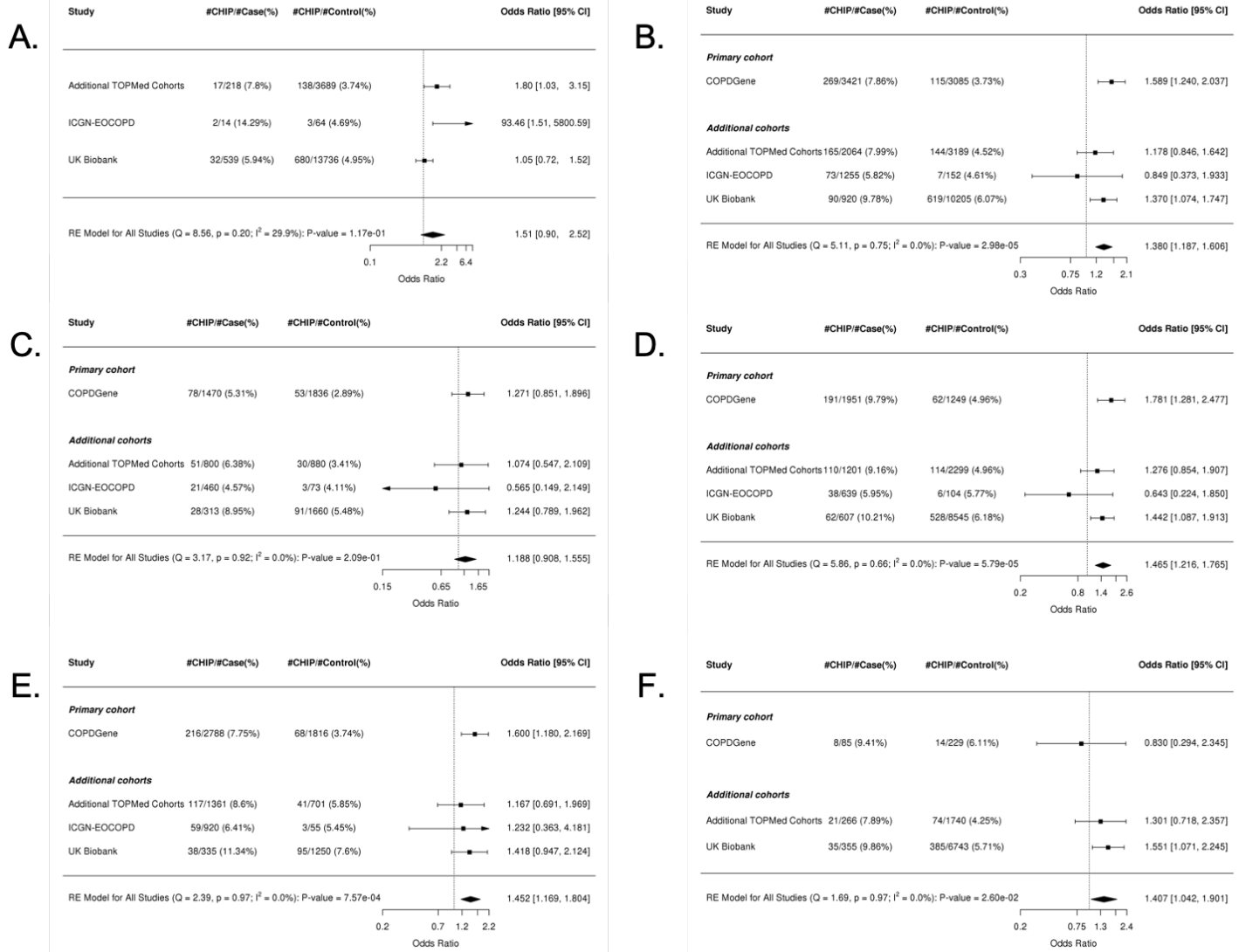


Figure S8. Effect of Hematopoietic *Tet2* Deletion on Emphysema Development in Smoke Exposure Models.

- A) Schematic of experimental approach for mice with 15% *Tet2*-wild-type or *Tet2*-knockout bone marrow treated with cigarette smoke for 6 months.
- B) Representative images of airspace destruction from experiment outlined in (A) in *Tet2* wild-type and *Tet2* knockout mice (left) and quantification of emphysema in *Tet2* wild-type (n=5) and *Tet2* knockout (n=4) mice. Shown are SEM.
- C) Peripheral blood chimerism in the six-month exposure experiment of *Tet2*-wild-type (top) or *Tet2*-knockout (bottom) mice measured in the air (black) and smoke-exposure (gray) mice (n=5, shown are SEM.).
- D) Quantification of emphysema in *Tet2* wild-type (n=5) and *Tet2* knockout (n=5) mice air controls for the six month cigarette smoke exposure. Shown are SEM.
- E) Quantification of emphysema in *Tet2* wild-type (n=5) and *Tet2* knockout (n=5) mice exposed to air as a control for the cigarette smoke and poly(I:C) exposure (see Figures 4A-B). Shown are SEM.
- F) Quantification of emphysema in *Tet2* wild-type (n=5) and *Tet2* knockout (n=5) mice exposed to cigarette smoke only as a control for the cigarette smoke and poly(I:C) exposure (see Figures 4A-B). Shown are SEM.
- G) Quantification of emphysema in *Tet2* wild-type (n=5) and *Tet2* knockout (n=5) mice exposed to poly(I:C) only as a control for the cigarette smoke and poly(I:C) exposure (see Figures 4A-B). Shown are SEM.

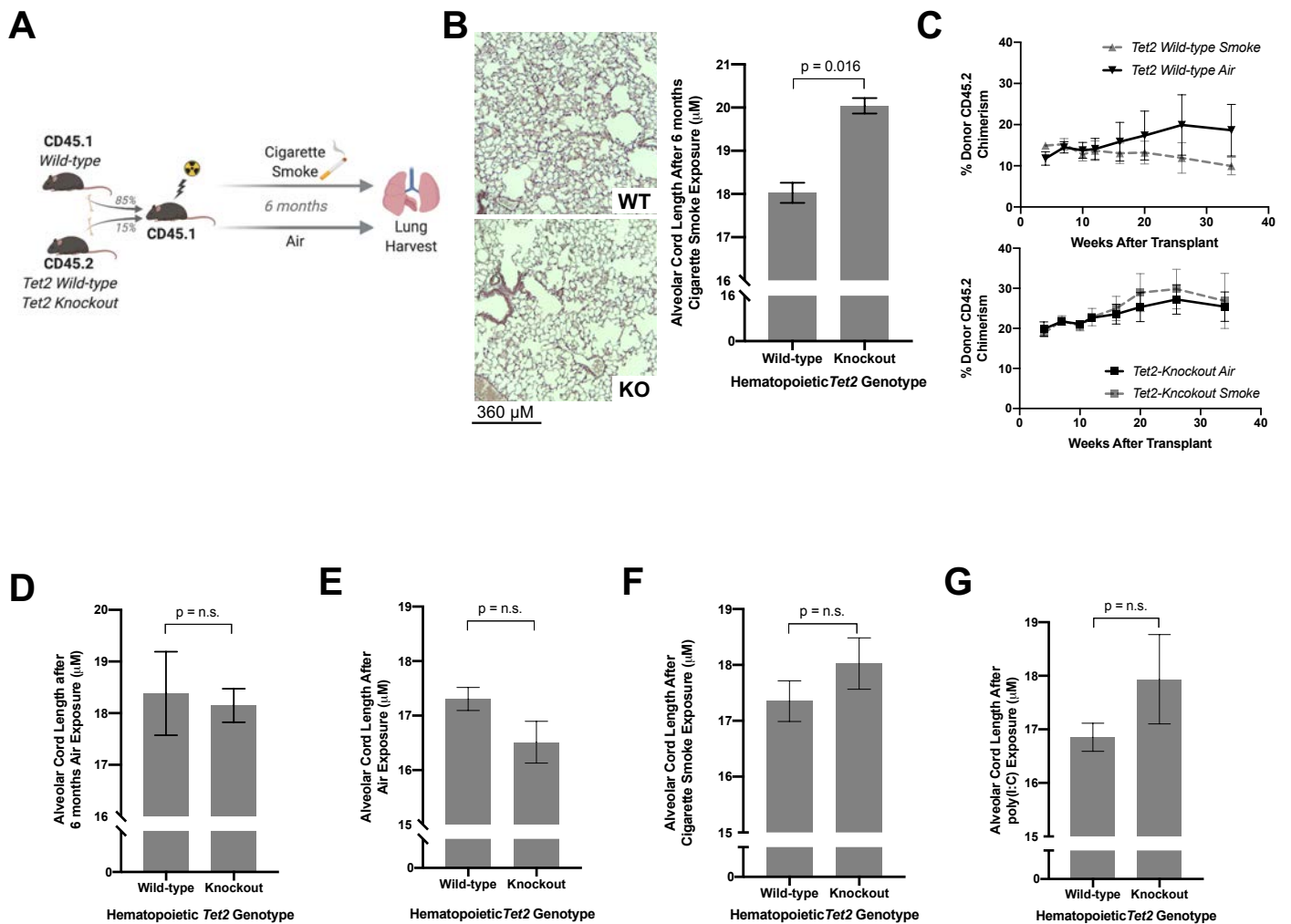


Figure S9. Single Cell RNA-Sequencing Data in Mouse Model of COPD and CHIP.

A) Balloon plot showing the expression of selected marker genes across different populations identified using single-cell RNA-sequencing.

B) Frequency of non-hematopoietic, natural killer, myeloid, B-lymphoid, and T/NK-T Lymphoid cells recovered per mouse (n=4 for *Tet2*-wild-type Air, *Tet2*-mutant Air, *Tet2*-mutant CS/ poly(I:C), and n=3 for *Tet2*-wild-type CS/ poly(I:C)). Error bars represent the SEM.

C) Assessment of 50 Hallmark signature scores of mice exposed to cigarette smoke and poly(I:C) across all cells. A positive value (blue) represents higher scores in *Tet2*-wild-type and negative value (orange) reflects higher scores in *Tet2*-knockout. Shown are the five signatures most enriched in each genotype. The P-values were calculated using a Wilcoxin test and adjusted using a Bonferroni correction.

D) Gene set enrichment analysis using Hallmark interferon- α (top) and interferon- γ (bottom) signatures comparing *Tet2*-knockout to *Tet2*-wild-type cells across the different clusters of cells in mice exposed to cigarette smoke and poly(I:C).

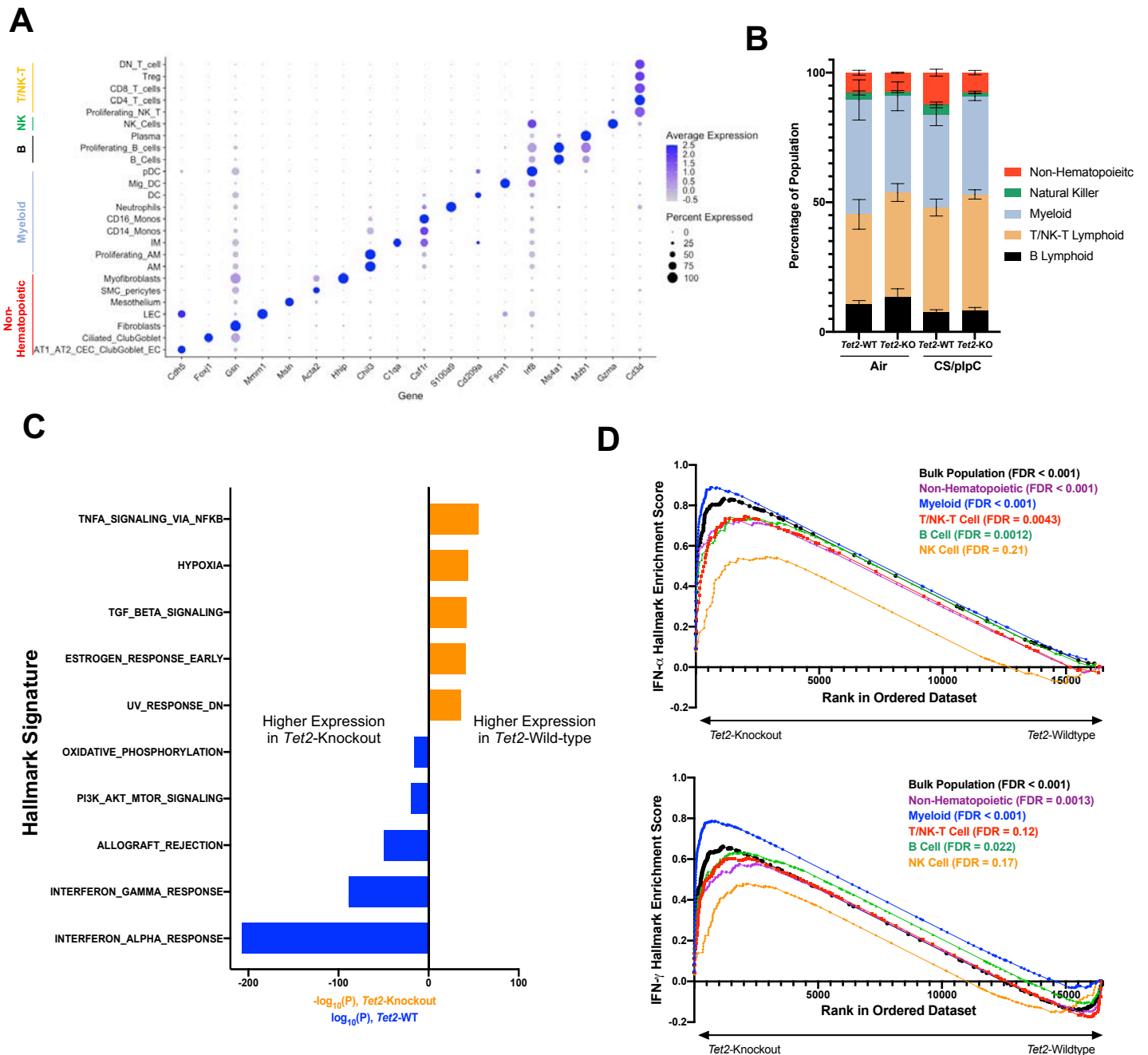


Figure S10. Single Cell RNA-Sequencing and In Vitro Macrophage Analysis.

A) Balloon plot showing expression of interferon- γ across all cell types as detected in the scRNA-seq from the lungs of mice exposed to cigarette smoke and poly(I:C). Interferon Type I cytokines were below the detection limit of scRNA-seq.

B) Balloon plot showing expression of tumor growth factor beta (Tgfb) isoforms across all cell types in the lungs of mice exposed to cigarette smoke and poly(I:C).

C) Ratio of cytokine levels between *Tet2*-knockout and *Tet2*-wild-type pulmonary macrophages grown in vitro then exposed to poly(I:C) for 24 hours. Shown in red are cytokines that are significantly higher in cultures of *Tet2*-knockout compared to *Tet2*-wild-type pulmonary macrophages.

D) A signature comprised of the seven cytokines detected at significantly higher levels from *Tet2*-knockout pulmonary macrophages (shown in F) was assessed in the single cell transcriptional data in the monocyte/macrophage cells (CD14⁺ monocytes, CD16⁺ monocytes, interstitial macrophages, alveolar macrophages, and proliferating alveolar macrophages) from *Tet2*-wild-type and *Tet2*-knockout lungs in mice exposed to cigarette smoke and poly(I:C). A negative value (orange) reflects higher scores in *Tet2*-knockout. The adjusted P-values were adjusted using a Bonferroni correction.

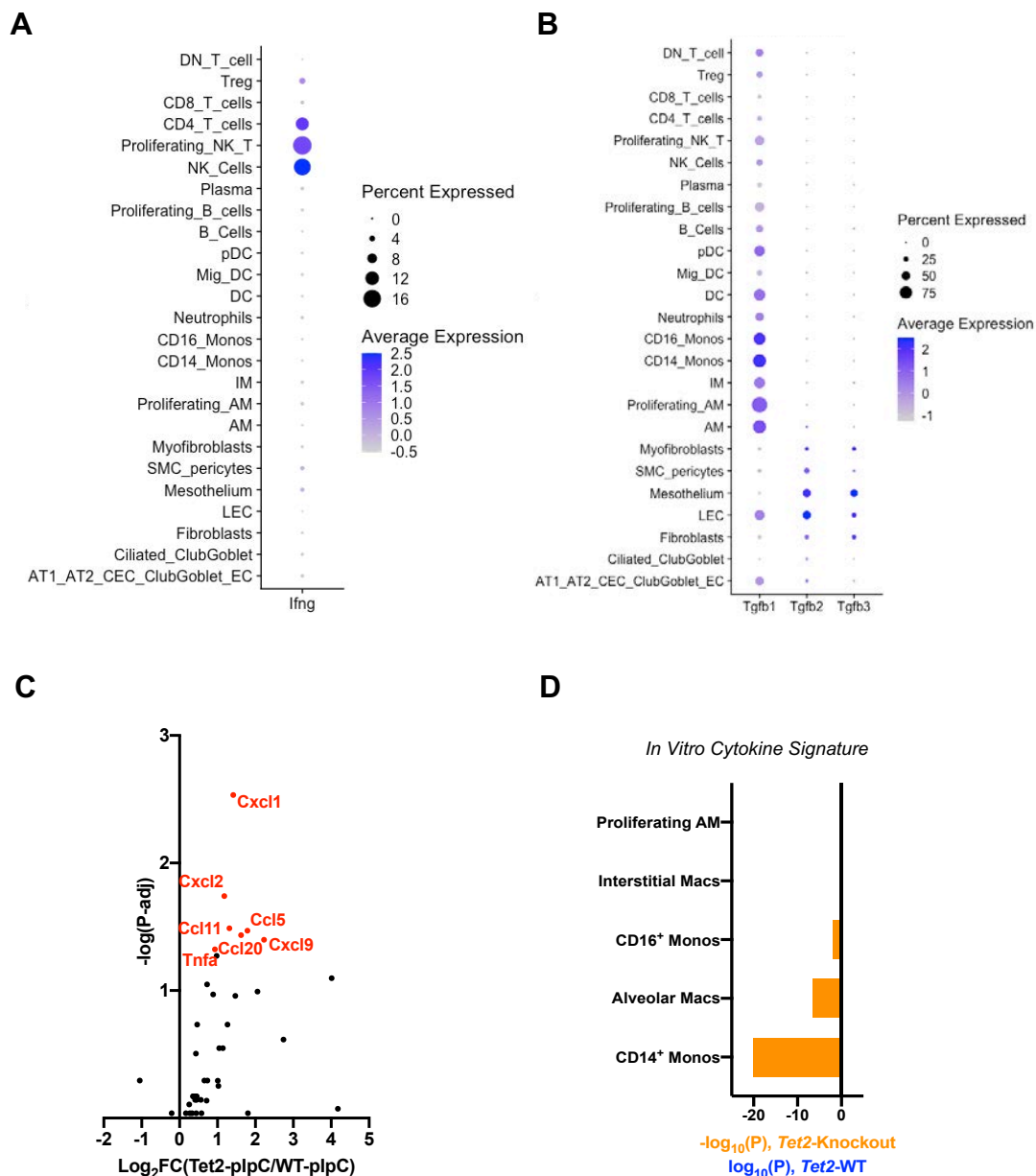


Table S1. Detailed Cohort Characteristics

Cohorts	N	# CHIP	# GOLD 1	# COPD (GOLD 2-4)	# COPD (GOLD 3-4)	# Controls (GOLD 0)	Age (SD)	#Smokers	# Pack-years (SD)	FEV1% predicted (SD)
COPDGene	8,395	478	710	3,421	1,698	3,085	59.5 (9.1)	8,395	44.3 (25.0)	73 (25.6)
TOPMed	11,269	566	1,076	2,282	945	6,878	59.9 (11.0)	6,515	16.1 (24.7)	87.7 (23.0)
ARIC	3,010	134	405	443	67	1,929	57.1 (5.8)	1,890	18.9 (23.5)	91.2 (17.1)
CFS	573	14	17	50	15	412	47.2 (15.5)	339	10.9 (16.5)	91.0 (20.2)
ECLIPSE	1,440	116	14	1,247	789	165	62.6 (7.7)	1,440	47.0 (28.3)	52.6 (23.2)
FHS	1,134	98	235	152	13	694	67.0 (8.6)	644	3.8 (14.1)	96.1 (19.1)
JHS	2,365	84	48	120	27	1,822	55.0 (12.5)	761	7.1 (16.0)	92.4 (17.5)
MESA	2,747	120	357	270	34	1,856	65.3 (9.7)	1,441	10.5 (21.3)	94.2 (17.8)
ICGN-EOCOPD	1,554	92	24	1,282	853	216	55.8 (11.0)	1,462	42.0 (26.7)	47.7 (26.8)
UK Biobank	27,617	1,588	2,217	1,459	149	23,941	56.8 (7.8)	12,321	6.2 (13.12)	100.8 (16.6)
Total	48,835	2,724	4,027	8,444	3,645	34,093	57.9 (9.1)	28,693	16.1 (24.1)	91.3 (24.2)

Table S2. Covariate information between COPD cases (GOLD 2-4) and controls for each study. UK Biobank coded pack-years as NA if quit before age 16 (recoded a 0 for these analyses) or as 0 if total smoking duration <1 year. Median (IQR) are shown for age and pack-years.

study	#female in case (%)	#female in control (%)	#smokers in case (%)	#smokers in control (5)
COPDGene	1526(28.7)	1462(29.4)	3421(64.4)	3085(62)
ARIC	194(17.9)	1058(41.2)	390(36.1)	1024(39.9)
CFS	21(13)	217(41.5)	40(24.8)	228(43.6)
FHS	82(18.6)	408(41.5)	124(28.2)	342(34.8)
JHS	56(10.3)	1185(52.8)	62(11.4)	542(24.1)
MESA	112(12.6)	996(40.2)	201(22.6)	888(35.8)
ECLIPSE	437(34.3)	71(36.8)	1247(97.8)	165(85.5)
ICGN-EOCOPD	672(52.4)	97(44.9)	1268(98.9)	152(70.4)
UK Biobank	656(50.0)	13650(57.0)	920(63.1%)	10205(42.6%)

study	age in case	age in control	packyears in case	packyears in control
COPDGene	63(56-69)	54(49-61)	46(34-66)	33.8(22.6-44.1)
ARIC	60(56-64)	57(53-63)	37.8(19.3-50.7)	0.5(0-21)
CFS	57.8(47.9-67.5)	42.4(32.3-52.6)	27.9(1.7-42.7)	0.6(0-11.9)
FHS	68.3(62.2-74.8)	66(60.3-72.8)	0(0-9.3)	0(0-0)
JHS	62.1(54.1-70.7)	54.8(44.5-64)	5.1(0-25.2)	0(0-4.3)
MESA	65(57.2-71)	59(52-67)	13.9(0-35.4)	0(0-7.3)
ECLIPSE	64(59-69)	56(47-61)	44(30-60)	28(19-41)
ICGN-EOCOPD	57.2(50.8-63.4)	50.5(34.7-58.3)	57.2(29.9-58.5)	17.7(0-30.2)
UK Biobank	61(55-65)	57(50-63)	21.3(5-38)*	7.5(0-19.5)*

Table S3. Prevalence of CHIP across COPD status and cohorts.

Cohorts	# GOLD 2-4 cases with CHIP / # GOLD 2-4 cases (%)	# GOLD 3-4 cases with CHIP / # GOLD 3-4 cases (%)	# controls with CHIP / # controls (%)
COPDGene	269/3421 (7.86%)	164/1698 (9.66%)	115/3085 (3.73%)
TOPMed	269/3421 (7.86%)	164/1698 (9.66%)	115/3085 (3.73%)
ARIC	33/443 (7.45%)	5/67 (7.46%)	78/1929 (4.04%)
CFS	3/50 (6%)	0/15 (0%)	8/412 (1.94%)
ECLIPSE	105/1247 (8.42%)	74/789 (9.38%)	7/165 (4.24%)
FHS	14/152 (9.21%)	1/13 (7.69%)	58/694 (8.36%)
JHS	10/120 (8.33%)	3/27 (11.11%)	57/1822 (3.13%)
MESA	17/270 (6.3%)	1/34 (2.94%)	74/1856 (3.99%)
ICGN-EOCPD	77/1282 (6.01%)	59/853 (6.92%)	10/216 (4.63%)
UK Biobank	122/1459 (8.36%)	16/149 (10.74%)	1299/23941 (5.43%)

Table S4. Association between CHIP and COPD-related phenotypes in the COPDGene study.

*The 95% CI has been adjusted for the six phenotypes examined using the primary cohort.

†P-values presented are two-sided and are raw. They should be compared with the significance level $0.05/6 = 0.00833$.

Phenotype	Effect size estimate (adjusted 95% CI*)	P-value†
# Pack-years	1.001 (0.996 - 1.005)	0.75
COPD GOLD 2-4 in all subjects	1.589 (1.138 - 2.22)	0.0003
GOLD 3-4 in GOLD 2-4 subjects	1.631 (1.105 - 2.406)	0.0009
GOLD 3-4 in all subjects	2.163 (1.471 - 3.181)	<0.0001
FEV1% predicted in all subjects	-5.762 (-8.729 - -2.795)	<0.0001
FEV1% predicted in GOLD 2-4 subjects	-2.576 (-5.128 - 0.024)	0.0078

Table S5. Association between CHIP and COPD after adjusting for possible confounders in COPDGene

Independent variables	Original Model		Model 1		Model 2		Model 3		Model 4	
	OR	P	OR	P	OR	P	OR	P	OR	P
CHIP	1.59	0.0003	1.61	0.0002	1.54	0.0007	1.56	0.0005	1.53	0.001
Cancer Comorbidities										
Lung cancer			2.97	3.34E-06					2.87	8.70E-06
Breast cancer			0.79	0.24					0.82	0.34
Prostate cancer			0.99	0.98					1.08	0.72
Colon cancer			0.89	0.77					0.97	0.93
Bladder cancer			1.13	0.8					1.18	0.72
Cardiovascular comorbidities										
Heart attack					1.53	0.0055			1.51	0.0082
Congestive Heart Failure					3.08	5.98E-09			3.01	1.76E-08
Angina					1.06	0.74			1.06	0.7
Coronary artery disease					0.84	0.25			8.28	0.21
Stroke					1.4	0.08			1.41	0.08
Socioeconomic status										
Highest levels of school							0.78	6.87E-22	0.78	< 2e-16
Original model: COPD ~ CHIP + age + age2 + sex + sequencing center + 10 PCs + pack-years										
Model 1: COPD ~ CHIP + lung cancer + age + age2 + sex + sequencing center + 10 PCs + pack-years										
Model 2: COPD ~ CHIP + CVD composite score + age + age2 + sex + sequencing center + 10 PCs + pack-years										
Model 3: COPD ~ CHIP + Townsend deprivation index + highest levels of school + age + age2 + sex + sequencing center + 10 PCs + pack-years										
Model 4: COPD ~ CHIP + lung cancer + CVD composite score + Townsend deprivation index + highest levels of school + age + age2 + sex + sequencing center + 10 PCs + pack-years										

Table S6. Association between CHIP driver genes and COPD in the COPDGene dataset.

** The 95% CI has been adjusted for the multiple testing of nine genes*

GOLD 2-4					
GENE	# GOLD 2-4 cases with mutation / # GOLD 2-4 cases (%)	# controls with mutation/ # controls (%)	OR (GOLD2-4)	Adjusted 95% CI (GOLD 2-4)*	P-value
DNMT3A	125/3277(3.8%)	73/3043(2.4%)	1.40	0.88 - 2.21	0.043
ASXL1	33/3185(1%)	15/2985(0.5%)	1.23	0.48 - 3.14	0.541
SRSF2	10/3162(0.3%)	2/2972(0.1%)	2.39	0.27 - 21.27	0.269
TET2	46/3198(1.4%)	8/2978(0.3%)	3.49	1.1 - 11.03	0.003
GNAS	1/3153(0%)	2/2972(0.1%)	0.56	0.02 - 19.56	0.649
JAK2	5/3157(0.2%)	1/2971(0%)	2.43	0.11 - 54.8	0.429
TP53	5/3157(0.2%)	1/2971(0%)	2.51	0.1 - 60.26	0.422
SF3B1	11/3163(0.3%)	0/2970(0%)	163990.23	NA	0.938
PPM1D	6/3158(0.2%)	6/2976(0.2%)	0.64	0.12 - 3.41	0.459

GOLD 3-4					
GENE	# GOLD 3-4 cases with mutation / # GOLD 3-4 cases (%)	# controls with mutation/ # controls (%)	OR (GOLD 3-4)	Adjusted 95% CI (GOLD 3-4)*	P-value
DNMT3A	70/1604(4.4%)	73/3043(2.4%)	1.77	1.03 - 3.06	0.004
ASXL1	20/1554(1.3%)	15/2985(0.5%)	1.86	0.64 - 5.42	0.108
SRSF2	8/1542(0.5%)	2/2972(0.1%)	4.59	0.46 - 45.65	0.066
TET2	27/1561(1.7%)	8/2978(0.3%)	3.68	1.01 - 13.42	0.005
GNAS	1/1535(0.1%)	2/2972(0.1%)	1.95	0.05 - 70.41	0.606
JAK2	4/1538(0.3%)	1/2971(0%)	6.72	0.25 - 178.94	0.107
TP53	3/1537(0.2%)	1/2971(0%)	4.26	0.11 - 171.69	0.277
SF3B1	9/1543(0.6%)	0/2970(0%)	1254894.90	NA	0.959
PPM1D	6/1540(0.4%)	6/2976(0.2%)	1.01	0.18 - 5.58	0.983

Table S7. Association between CHIP and COPD-related phenotypes in the meta-analyses of TOPMed cohorts.

*P-values presented are two-sided.

Phenotype	Effect size estimate (95% CI)	P-value
# Pack-years	1.007 (1.003 - 1.01)	0.001
COPD GOLD 2-4 in all subjects	1.320 (0.993 - 1.753)	0.06
GOLD 3-4 in GOLD 2-4 subjects	1.385 (0.935 - 2.052)	0.10
GOLD 3-4 in all subjects	1.423 (0.799 - 2.533)	0.23
FEV1% predicted in all subjects	-0.701 (-2.207 - 0.805)	0.36
FEV1% predicted in GOLD 2-4 subjects	-1.215 (-3.688 - 1.259)	0.33

Table S8. Association between CHIP and COPD-related phenotypes in the UK Biobank data.

*P-values presented are two-sided.

Phenotype	Effect size estimate (95% CI)	P-value
# Pack-years	1.003 (0.999 - 1.007)	0.14
COPD GOLD 2-4 in all subjects	1.26 (1.03 - 1.54)	0.025
GOLD 3-4 in GOLD 2-4 subjects	1.30 (0.74 - 2.28)	0.37
GOLD 3-4 in all subjects	1.58 (0.93 - 2.69)	0.09
FEV1% predicted in all subjects	-0.79 (-1.623 - 0.043)	0.06
FEV1% predicted in GOLD 2-4 subjects	-1.449 (-3.557 - 0.658)	0.18

Table S9. Association between CHIP and COPD-related phenotypes in the ICGN-EOCOPD dataset.

*P-values presented are two-sided.

Phenotype	Effect size estimate (95% CI)	P-value
# Pack-years	1.002 (0.993 - 1.011)	0.677
COPD GOLD 2-4 in all subjects	1.041 (0.455 - 2.385)	0.924
GOLD 3-4 in GOLD 2-4 subjects	1.403 (0.829 - 2.376)	0.207
GOLD 3-4 in all subjects	1.162 (0.494 - 2.733)	0.731
FEV1% predicted in all subjects	-6.372 (-11.587 - -1.157)	0.017
FEV1% predicted in GOLD 2-4 subjects	-4.953 (-9.076 - -0.83)	0.019

Table S10. Association between CHIP and COPD after adjusting for possible confounders in UK Biobank.

Independent variables	Original Model		Model 1		Model 2		Model 3		Model 4	
	OR	P	OR	P	OR	P	OR	P	OR	P
CHIP	1.26	0.025	1.25	0.029	1.26	0.025	1.26	0.026	1.25	0.03
Cancer Comorbidities										
Prevalent lung cancer			3.9	5.00E-03					3.66	8.00E-03
Cardiovascular comorbidities										
Prevalence CVD Composite score*					1.37	0.0007			1.3	0.005
Socioeconomic status										
Townsend deprivation index							1.05	5.19E-08	1.05	0.029
Education level: A-levels							0.75	0.031	0.75	0.03
Education level: College/University							0.94	0.515	0.95	0.571
Education level: Professional degree							0.87	0.092	0.87	0.095
Education level: Other education							1.18	4.20E-02	1.17	0.052
*A composite score of CAD, MI, angina, HF, ischemic stroke										
Original model: COPD ~ CHIP + age + age2 + sex + 10 PCs + ever-smoking + pack-years										
Model 1: COPD ~ CHIP + lung cancer + age + age2 + sex + 10 PCs + ever-smoking + pack-years										
Model 2: COPD ~ CHIP + CVD composite score + age + age2 + sex + 10 PCs + ever-smoking + pack-years										
Model 3: COPD ~ CHIP + Townsend deprivation index + highest levels of school + age + age2 + sex + 10 PCs + ever-smoking + pack-years										
Model 4: COPD ~ CHIP + lung cancer + CVD composite score + Townsend deprivation index + highest levels of school + age + age2 + sex + 10 PCs + ever-smoking + pack-years										

Table S11. Association between CHIP and COPD-related phenotypes in the meta-analyses of all cohorts.

*P-values presented are two-sided.

Phenotype	Effect size estimate (95% CI)	P-value
# Pack-years	1.003 (1.001 - 1.005)	0.0037
COPD GOLD 2-4 in all subjects	1.357 (1.185 - 1.554)	< 0.0001
GOLD 3-4 in GOLD 2-4 subjects	1.488 (1.219 - 1.816)	< 0.0001
GOLD 3-4 in all subjects	1.843 (1.474 - 2.303)	< 0.0001
FEV1% predicted in all subjects	-1.851 (-3.523 - -0.18)	0.03
FEV1% predicted in GOLD 2-4 subjects	-2.073 (-3.204 - -0.941)	0.0003

Table S12. Meta-analyses results of the association between GOLD 2-4 COPD and CHIP within different strata of smoking exposure.

Strata	OR	95% CI	P-value	#CHIP/#Case (%)	#CHIP/#Cont (%)
Non-smokers	1.51	0.9-2.52	1.17E-01	51/771(6.61%)	821/17489(4.69%)
Smokers	1.38	1.19-1.61	2.98E-05	597/7660(7.79%)	885/16631(5.32%)
Current smokers	1.19	0.91-1.56	2.09E-01	178/3043(5.85%)	177/4449(3.98%)
Former smokers	1.47	1.22-1.77	5.79E-05	401/4398(9.12%)	710/12197(5.82%)
Heavy smokers	1.45	1.17-1.8	7.57E-04	430/5404(7.96%)	207/3822(5.42%)
Light smokers	1.41	1.04-1.9	2.60E-02	67/775(8.65%)	473/8752(5.4%)

Table S13. Association between CHIP driver genes and COPD in the meta-analyses of all cohorts.

* The 95% CI has been adjusted for the multiple testing of nine genes

GOLD 2-4			
GENE	OR (GOLD 2-4)	Adjusted 95% CI (GOLD 2-4)*	P-value
<i>DNMT3A</i>	1.30	1.02 - 1.67	0.003
<i>ASXL1</i>	1.30	0.73 - 2.34	0.209
<i>SRSF2</i>	2.11	0.44 - 10.1	0.187
<i>TET2</i>	1.48	0.87 - 2.51	0.043
<i>GNAS</i>	0.56	0.02 - 19.56	0.649
<i>JAK2</i>	1.85	0.35 - 9.76	0.303
<i>TP53</i>	1.79	0.39 - 8.27	0.291
<i>SF3B1</i>	1.06	0.17 - 6.59	0.926
<i>PPM1D</i>	1.44	0.46 - 4.46	0.374

GOLD 3-4			
GENE	OR (GOLD 3-4)	Adjusted 95% CI (GOLD 3-4)*	P-value
<i>DNMT3A</i>	1.68	1.08 - 2.63	0.001
<i>ASXL1</i>	1.95	0.76 - 4.98	0.048
<i>SRSF2</i>	4.42	0.51 - 38.1	0.056
<i>TET2</i>	2.41	1.03 - 5.63	0.004
<i>GNAS</i>	1.95	0.05 - 70.41	0.606
<i>JAK2</i>	6.72	0.25 - 178.94	0.107
<i>TP53</i>	9.19	1.46 - 57.72	0.001
<i>SF3B1</i>	1.43	0.04 - 47.85	0.777
<i>PPM1D</i>	1.41	0.36 - 5.48	0.483

Table S14. Association between CHIP driver genes and number of pack-years in the meta-analyses of all cohorts.

GENE	OR	Adjusted 95% CI	P-value
<i>DNMT3A</i>	0.086	0.91 - 1.31	0.20
<i>ASXL1</i>	-0.002	0.98 - 1.02	0.72
<i>SRSF2</i>	0.027	0.99 - 1.07	0.08
<i>TET2</i>	0.258	0.67 - 2.51	0.28
<i>GNAS</i>	-0.075	0.72 - 1.2	0.43
<i>JAK2</i>	-0.094	0.76 - 1.1	0.17
<i>TP53</i>	0.002	0.96 - 1.04	0.91
<i>SF3B1</i>	-0.007	0.95 - 1.04	0.68
<i>PPM1D</i>	0.020	0.98 - 1.06	0.16

Table S15. Individual Values of Mouse Alveolar Cord Length Quantification from Cigarette Smoke (CS) and poly(I:C) Exposure Experiment

The median cord length (μM) for each mouse is listed.

<i>Tet2</i> Wild-Type CS+ Poly(I:C)	<i>Tet2</i>-Knockout CS+ Poly(I:C)
16.03	17.18
16.15	17.38
16.03	16.31
17.31	18.53
16.02	17.96
17.42	19.04
16.54	19.33
17.65	16.85
17.41	19.42
16.91	17.49

<i>Tet2</i> Wild-Type Air	<i>Tet2</i>-Knockout Air	<i>Tet2</i> Wild-Type CS Only	<i>Tet2</i>-Knockout CS Only	<i>Tet2</i> Wild-Type Poly(I:C) Only	<i>Tet2</i>-Knockout Poly(I:C) Only
17.68	16.73	16.96	17.89	17.89	17.82
17.30	15.98	17.90	17.26	16.66	21.14
16.54	17.08	16.53	16.84	16.56	17.04
17.71	17.45	18.49	18.91	16.70	17.32
17.30	15.32	16.88	19.22	16.45	16.36

Table S16. Individual Values of Mouse Alveolar Cord Length Quantification from Six Month Cigarette Smoke Exposure Experiment

The median cord length (μM) for each mouse is listed.

<i>Tet2</i> Wild-Type Air	<i>Tet2</i>-Knockout Air	<i>Tet2</i> Wild-Type CS	<i>Tet2</i>-Knockout CS
15.85	18.22	18.31	19.54
18.71	17.89	18.04	20.06
17.37	17.87	18.55	20.39
19.51	17.42	17.17	20.17
20.46	19.35	18.06	

Table S17. Transcript and Gene Information from Single Cell RNA-Sequencing.

mouse	genotype	exposure	UMIs_mean	UMIs_min	UMIs_max	Genes_mean	Genes_min	Genes_max
1	WT	CS.plpC	4223	2001	61323	1531	999	7127
3	WT	CS.plpC	4613	2001	67611	1620	999	7232
4	WT	CS.plpC	4734	2002	40843	1621	1001	6975
5	Tet2	CS.plpC	4089	1996	37208	1548	998	4881
6	Tet2	CS.plpC	4236	2000	32546	1574	999	6442
7	Tet2	CS.plpC	4194	1999	35689	1547	997	6681
8	Tet2	CS.plpC	4243	2004	40974	1499	999	6104
9	WT	Air	4763	1999	48126	1640	999	7366
10	WT	Air	4671	1999	37740	1572	998	4705
11	WT	Air	5137	2001	47491	1770	999	6512
12	WT	Air	5307	1999	42612	1871	999	6465
13	Tet2	Air	4515	2000	39267	1596	999	5650
14	Tet2	Air	4232	1999	42919	1484	999	5908
15	Tet2	Air	4367	2004	25921	1595	998	5233
16	Tet2	Air	4212	1998	28595	1527	999	6251

Table S18. Marker Genes Identified for Each Cluster in Single Cell RNA Sequencing Data (see online)

Table S19. Signature scores for Hallmark Pathways tested on all cells from mice treated with cigarette smoke and poly(I:C)

Signature Name	average_WT	average_Tet2	Difference	P.wilcox	P.wilcox.bonferroni	LOG(P.wilcox.bonferroni)
HALLMARK_TNFA_SIGNALING_VIA_NFKB	0.15263704	0.119324487	-0.033312553	4.0464E-58	2.02318E-56	55.69396561
HALLMARK_HYPOXIA	0.074836068	0.057142306	-0.017693762	2.5858E-46	1.2929E-44	43.88843636
HALLMARK_TGF_BETA_SIGNALING	0.055354603	0.032697245	-0.022657359	9.1837E-45	4.59187E-43	42.33801061
HALLMARK_ESTROGEN_RESPONSE_EARLY	-0.014719994	-0.022088687	-0.007368693	1.22E-43	6.09994E-42	41.21467448
HALLMARK_UV_RESPONSE_DN	-0.02076375	-0.033156117	-0.012392367	2.6648E-38	1.3324E-36	35.87536485
HALLMARK_P53_PATHWAY	0.099420085	0.090447092	-0.008972993	7.3674E-28	3.68371E-26	25.43371498
HALLMARK_UV_RESPONSE_UP	0.05991021	0.048232144	-0.011678066	3.8456E-26	1.92278E-24	23.71607142
HALLMARK_APOPTOSIS	0.078811455	0.063755602	-0.015055853	9.6363E-25	4.81814E-23	22.31712091
HALLMARK_MYOGENESIS	-0.012176846	-0.021648704	-0.009471858	4.9261E-24	2.46304E-22	21.60852767
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	0.016840474	-0.001844493	-0.018684967	8.3382E-23	4.1691E-21	20.37995812
HALLMARK_IL6_JAK_STAT3_SIGNALING	0.011458067	-0.002243789	-0.013701856	1.2396E-19	6.19819E-18	17.20773487
HALLMARK_WNT_BETA_CATENIN_SIGNALING	-0.011406563	-0.020304313	-0.008897749	2.4447E-19	1.22237E-17	16.91279692
HALLMARK_COAGULATION	0.002608326	-0.011945501	-0.014553827	1.1114E-18	5.5569E-17	16.25516734
HALLMARK_XENOBIOTIC_METABOLISM	-0.009213917	-0.01647749	-0.007263573	1.4245E-18	7.12228E-17	16.14738078
HALLMARK_ESTROGEN_RESPONSE_LATE	-0.008019295	-0.013370591	-0.005351296	5.3947E-17	2.69735E-15	14.56906337
HALLMARK_BILE_ACID_METABOLISM	-0.006568216	-0.011202424	-0.004634207	7.2391E-17	3.61956E-15	14.44134465
HALLMARK_HEME_METABOLISM	0.003627469	-0.001199039	-0.004826508	1.6029E-14	8.01437E-13	12.09613039
HALLMARK_UNFOLDED_PROTEIN_RESPONSE	0.08730158	0.080969196	-0.006332384	3.8022E-13	1.9011E-11	10.72099463
HALLMARK_ANDROGEN_RESPONSE	0.013772106	0.00626789	-0.007504216	9.931E-13	4.96549E-11	10.3040383
HALLMARK_ANGIOGENESIS	-0.010276816	-0.019602803	-0.009325987	1.0567E-10	5.2833E-09	8.277094855
HALLMARK_APICAL_SURFACE	-0.049454877	-0.054794665	-0.005339788	8.4411E-10	4.22054E-08	7.374631475
HALLMARK_KRAS_SIGNALING_UP	0.018001215	0.01347925	-0.004521966	5.2553E-09	2.62767E-07	6.580429188
HALLMARK_IL2_STAT5_SIGNALING	0.015806442	0.012124636	-0.003681806	9.6837E-08	4.84184E-06	5.314989225
HALLMARK_PEROXISOME	-0.004850805	-0.009327331	-0.004476525	3.988E-07	1.99398E-05	4.700278407
HALLMARK_KRAS_SIGNALING_DN	-0.01280705	-0.01407623	-0.001269181	1.1354E-06	5.67707E-05	4.245875415
HALLMARK_NOTCH_SIGNALING	-0.011847159	-0.016141967	-0.004294808	4.8069E-06	0.000240346	3.619163925
HALLMARK_CHOLESTEROL_HOMEOSTASIS	0.024474476	0.018388532	-0.006085944	4.9518E-06	0.000247591	3.606264861
HALLMARK_PROTEIN_SECRETION	0.000779095	-0.004671248	-0.005450342	1.027E-05	0.000513503	3.289457187
HALLMARK_REACTIVE_OXYGEN_SPECIES_PATHWAY	0.040822394	0.033418794	-0.007403601	8.3048E-05	0.004152375	2.381703421
HALLMARK_INFLAMMATORY_RESPONSE	0.012901398	0.011769548	-0.001131849	0.00509903	0.254951259	0.593542839
HALLMARK_ADIPOGENESIS	0.034031753	0.029958229	-0.004073524	0.00873099	0.436549605	0.359966401
HALLMARK_GLYCOLYSIS	0.007796718	0.006003385	-0.001793333	0.01901132	0.950565795	0.022017817
HALLMARK_MITOTIC_SPINDLE	-0.012793528	-0.011530431	0.001263097	0.93769681	1	0
HALLMARK_HEDGEHOG_SIGNALING	-0.020850349	-0.021686413	-0.000836063	0.39398264	1	0
HALLMARK_COMPLEMENT	0.086536007	0.084139733	-0.002396274	0.73292219	1	0
HALLMARK_MYC_TARGETS_V2	-0.020509116	-0.018623519	0.001885597	0.68301341	1	0
HALLMARK_FATTY_ACID_METABOLISM	-0.003717563	-0.005631575	-0.001914012	0.06301535	1	0
HALLMARK_SPERMATOGENESIS	-0.010851717	-0.010282242	0.000569475	0.85636899	1	0
HALLMARK_PANCREAS_BETA_CELLS	-0.026601793	-0.027622639	-0.001020846	0.12187744	1	0
HALLMARK_MTORC1_SIGNALING	0.050943634	0.053440119	0.002496485	0.0063984	0.319919922	-0.494958714
HALLMARK_G2M_CHECKPOINT	-0.014752355	-0.004675107	0.010077248	0.0006916	0.034579796	-1.461177574
HALLMARK_APICAL_JUNCTION	0.059494834	0.061501523	0.002006689	9.7255E-06	0.000486274	-3.313119191
HALLMARK_E2F_TARGETS	-0.0350354	-0.020963713	0.014071687	9.9189E-07	4.95946E-05	-4.304565624
HALLMARK_MYC_TARGETS_V1	0.215534792	0.227712206	0.012177414	1.9119E-07	9.55952E-06	-5.019563934
HALLMARK_DNA_REPAIR	0.002302796	0.008159569	0.005856774	1.2818E-07	6.40903E-06	-5.193207943
HALLMARK_OXIDATIVE_PHOSPHORYLATION	0.149396688	0.157939747	0.008543059	1.2518E-18	6.25925E-17	-16.20347788
HALLMARK_PI3K_AKT_MTOR_SIGNALING	0.071802188	0.080881931	0.009079743	1.1358E-21	5.67912E-20	-19.24571902
HALLMARK_ALLOGRAFT_REJECTION	0.156665907	0.173746869	0.017080962	5.699E-52	2.84951E-50	-49.54523049
HALLMARK_INTERFERON_GAMMA_RESPONSE	0.050613795	0.073757024	0.023143229	4.3791E-91	2.18957E-89	-88.65964158
HALLMARK_INTERFERON_ALPHA_RESPONSE	0.019333637	0.060436802	0.041103165	5.876E-210	2.938E-208	-207.5319419

Table S20. Signature scores for Interferon and TGF Beta pathways tested on all cells from mice treated with cigarette smoke and poly(I:C)

Signature Name	Nick Name	average_WT	average_Tet2	Difference	P.wilcox	P.wilcox.bonferroni	LOG(P.wilcox.bonferroni)
HALLMARK_INTERFERON_ALPHA_RESPONSE	(H) IFNA RESPONSE	0.009539031	0.051534216	0.041995185	3.46E-201	5.50E-199	-198.2600283
HALLMARK_INTERFERON_GAMMA_RESPONSE	(H) IFNG RESPONSE	0.046249155	0.069647796	0.023398641	8.15E-88	1.30E-85	-84.88771144
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	(R) IFNA/B SIGNALING	-0.043004346	-0.00483522	0.038169125	3.90E-76	6.20E-74	-73.20778778
WP_TYPE_III_INTERFERON_SIGNALING	(W) TYPEIII IFN SIGNALING	-0.097786898	-0.052024354	0.045762545	3.36E-37	5.35E-35	-34.27178508
BIOCARTA_IFNA_PATHWAY	(B) IFNA PATHWAY	-0.068852889	-0.032336253	0.036516636	4.91E-28	7.80E-26	-25.10763465
REACTOME_INTERFERON_SIGNALING	(R) IFN SIGNALING	0.090186061	0.099607919	0.009421857	3.91E-23	6.21E-21	-20.20689688
REACTOME_INTERFERON_GAMMA_SIGNALING	(R) IFNG SIGNALING	0.018507323	0.028341095	0.009833772	3.18E-14	5.05E-12	-11.29658745
REACTOME_REGULATION_OF_IFNA_SIGNALING	(R) REGULATION IFNA SIGNALING	-0.09544761	-0.076726056	0.018721554	2.77E-11	4.41E-09	-8.355995941
WP_TYPE_II_INTERFERON_SIGNALING_IFNG	(W) TYPEII IFN SIGNALING	-0.068098181	-0.049877448	0.018220733	9.11E-09	1.45E-06	-5.838989413
WP_INTERFERON_TYPE_I_SIGNALING_PATHWAYS	(W) IFN TYPEI SIGNALING	0.097370352	0.105241829	0.007871476	1.26E-07	2.00E-05	-4.698466724
BIOCARTA_IFNG_PATHWAY	(B) IFNG PATHWAY	0.022326573	0.029380759	0.007054186	0.143309263	1	0
REACTOME_REGULATION_OF_IFNG_SIGNALING	(R) REGULATION IFNG SIGNALING	-0.077870433	-0.080470056	-0.002599623	0.561017289	1	0
PID_IFNG_PATHWAY	(P) IFNG PATHWAY	0.024161919	0.016622801	-0.007539117	7.40E-04	0.117667785	0.929342423
PID_TGFBR_PATHWAY	(P) TGFBR PATHWAY	-0.021995654	-0.032366588	-0.010370934	1.86E-15	2.96E-13	12.52822503
WP_TGFBETA_SIGNALING_PATHWAY	(W) TGFB SIGNALING PATHWAY	0.065712055	0.053647369	-0.012064687	4.37E-26	6.95E-24	23.15818414
BIOCARTA_TGFB_PATHWAY	(B) TGFB PATHWAY	-0.08217898	-0.102424268	-0.020245289	2.68E-27	4.25E-25	24.37117483
WP_CANONICAL_AND_NONCANONICAL_TGFB_SIGNALING	(W) NON-CANONICAL TGFB SIGNALING	-0.052243522	-0.06967806	-0.017434539	1.03E-29	1.64E-27	26.78564317
KEGG_TGF_BETA_SIGNALING_PATHWAY	(K) TGFB SIGNALING	7.45E-04	-0.011999715	-0.012745088	1.03E-31	1.64E-29	28.78476008
REACTOME_TGF_BETA_RECEPTOR_SIGNALING_ACTIVATES_SMADS	(R) TGFB SIGNALING SMADS	0.151720747	0.131327138	-0.020393609	3.97E-33	6.32E-31	30.19950871
REACTOME_SIGNALING_BY_TGF_BETA_RECEPTOR_COMPLEX	(R) SIGNALING BY TGFBR	0.128386448	0.115148544	-0.013237904	2.03E-33	3.22E-31	30.49192525
WP_TGFBETA_RECEPTOR_SIGNALING	(W) TGFBR SIGNALING	-0.017335748	-0.038149897	-0.020814149	1.69E-37	2.69E-35	34.56972972
REACTOME_SIGNALING_BY_TGFB_FAMILY_MEMBERS	(R) SIGNALING TGFB FAMILY	0.10235474	0.090331696	-0.012023045	6.59E-42	1.05E-39	38.97946385
HALLMARK_TGF_BETA_SIGNALING	(H) TGFB SIGNALING	0.054100435	0.03108239	-0.023018045	5.69E-44	9.04E-42	41.04376195

Table 21. List of CHIP-Associated Somatic Variants Identified in the Cohort

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
ASXL1	20	32436944	G	A	W1411X	0.22	Additional TOPMED - FHS
ASXL1	20	32436833	T	TG	V1374fs	0.16	COPDGene
ASXL1	20	32436652	C	CT	Q1315fs	0.15	UK Biobank
ASXL1	20	32436445	G	T	E1245X	0.12	Additional TOPMED - ECLIPSE
ASXL1	20	32436439	C	T	Q1243X	0.12	Additional TOPMED - ARIC
ASXL1	20	32436421	TC	T	F1238fs	0.38	UK Biobank
ASXL1	20	32436149	C	A	S1146*	0.06	UK Biobank
ASXL1	20	32435860	A	AT	M1050fs	0.16	COPDGene
ASXL1	20	32435827	C	T	Q1039*	0.12	UK Biobank
ASXL1	20	32435814	AC	A	N1036fs	0.04	UK Biobank
ASXL1	20	32435731	GGT	G	G1007fs	0.21	UK Biobank
ASXL1	20	32435641	C	T	Q977*	0.06	UK Biobank
ASXL1	20	32435638	C	T	Q976X	0.36	COPDGene
ASXL1	20	32435605	C	T	R965*	0.10	UK Biobank
ASXL1	20	32435605	C	T	R965X	0.34	COPDGene
ASXL1	20	32435600	CA	C	P963fs	0.15	COPDGene
ASXL1	20	32435554	G	T	E948X	0.14	Additional TOPMED - ARIC
ASXL1	20	32435551	G	T	E947X	0.14	Additional TOPMED - MESA
ASXL1	20	32435543	T	A	L944*	0.03	UK Biobank
ASXL1	20	32435518	AC	A	T936fs	0.23	COPDGene
ASXL1	20	32435440	C	T	Q910*	0.03	UK Biobank
ASXL1	20	32435437	A	T	K909X	0.11	Additional TOPMED - CFS
ASXL1	20	32435436	G	GA	Q910fs	0.06	UK Biobank
ASXL1	20	32435390	AC	A	N893fs	0.33	UK Biobank
ASXL1	20	32435356	C	T	Q882*	0.30	UK Biobank
ASXL1	20	32435356	C	T	Q882*	0.11	UK Biobank
ASXL1	20	32435356	C	T	Q882X	0.17	COPDGene
ASXL1	20	32435356	C	T	Q882X	0.11	Additional TOPMED - MESA
ASXL1	20	32435349	T	TA	D879fs	0.12	Additional TOPMED - FHS
ASXL1	20	32435347	GA	G	D879fs	0.22	COPDGene
ASXL1	20	32435289	CAG	C	R860fs	0.29	Additional TOPMED - FHS
ASXL1	20	32435284	C	T	Q858X	0.12	Additional TOPMED - FHS
ASXL1	20	32435273	CTGAT	C	T854fs	0.11	Additional TOPMED - ECLIPSE
ASXL1	20	32435242	AC	A	S846fs	0.17	UK Biobank
ASXL1	20	32435242	AC	A	S846fs	0.13	UK Biobank
ASXL1	20	32435234	TA	T	V841fs	0.26	COPDGene
ASXL1	20	32435206	GAC	G	D832fs	0.20	COPDGene
ASXL1	20	32435180	T	A	L823*	0.09	UK Biobank
ASXL1	20	32435180	T	G	L823X	0.12	COPDGene
ASXL1	20	32435178	AT	A	L823X	0.22	Additional TOPMED - ARIC
ASXL1	20	32435175	T	TA	T822fs	0.21	UK Biobank
ASXL1	20	32435175	T	TA	T822fs	0.07	UK Biobank
ASXL1	20	32435174	ATACATTAGAGAAAGGAAGTGGC	A	T822fs	0.10	UK Biobank
ASXL1	20	32435133	TC	T	P808fs	0.33	Additional TOPMED - ECLIPSE
ASXL1	20	32435133	TC	T	P808fs	0.10	COPDGene
ASXL1	20	32435133	TC	T	P808fs	0.09	COPDGene
ASXL1	20	32435099	G	A	W796*	0.10	UK Biobank
ASXL1	20	32435095	TC	T	S795fs	0.22	Additional TOPMED - JHS
ASXL1	20	32435095	TC	T	S795fs	0.10	COPDGene
ASXL1	20	32435081	AG	A	E790fs	0.15	UK Biobank
ASXL1	20	32435079	T	A	C789X	0.32	Additional TOPMED - ECLIPSE
ASXL1	20	32435074	GAATGT	G	E788fs	0.29	COPDGene
ASXL1	20	32435050	C	T	Q780*	0.14	UK Biobank
ASXL1	20	32435050	C	T	Q780X	0.36	Additional TOPMED - ARIC
ASXL1	20	32435036	T	A	L775X	0.32	COPDGene
ASXL1	20	32435036	T	A	L775X	0.21	Additional TOPMED - ARIC
ASXL1	20	32435034	AT	A	L775X	0.19	Additional TOPMED - FHS
ASXL1	20	32435014	C	T	Q768*	0.36	UK Biobank
ASXL1	20	32434993	GC	G	A761fs	0.17	COPDGene
ASXL1	20	32434990	C	T	Q760X	0.14	Additional TOPMED - ARIC
ASXL1	20	32434979	AC	A	D756fs	0.29	COPDGene
ASXL1	20	32434972	AC	A	T754fs	0.06	UK Biobank
ASXL1	20	32434971	CA	C	T754fs	0.19	UK Biobank
ASXL1	20	32434968	T	TC	A752fs	0.13	Additional TOPMED - ARIC
ASXL1	20	32434965	T	TG	V751fs	0.51	COPDGene
ASXL1	20	32434958	TC	T	L749fs	0.31	COPDGene
ASXL1	20	32434948	GC	G	S747fs	0.05	UK Biobank
ASXL1	20	32434934	A	ATG	G742fs	0.20	UK Biobank
ASXL1	20	32434912	AG	A	R734fs	0.41	COPDGene
ASXL1	20	32434906	C	CTA	Q733fs	0.09	UK Biobank
ASXL1	20	32434902	C	A	C730X	0.21	Additional TOPMED - ARIC
ASXL1	20	32434891	G	T	E727X	0.13	COPDGene
ASXL1	20	32434888	A	T	K726X	0.29	COPDGene
ASXL1	20	32434886	GA	G	R725fs	0.14	COPDGene
ASXL1	20	32434868	AG	A	E719fs	0.22	Additional TOPMED - ECLIPSE
ASXL1	20	32434853	CCA	C	S714fs	0.48	Additional TOPMED - ARIC
ASXL1	20	32434840	GGAAC	G	G710fs	0.09	Additional TOPMED - ARIC
ASXL1	20	32434839	CG	C	G710fs	0.48	Additional TOPMED - FHS
ASXL1	20	32434839	CG	C	G710fs	0.16	Additional TOPMED - FHS
ASXL1	20	32434834	C	T	Q708*	0.06	UK Biobank
ASXL1	20	32434834	C	T	Q708X	0.20	Additional TOPMED - FHS
ASXL1	20	32434831	ACC	A	Q708fs	0.28	UK Biobank
ASXL1	20	32434825	G	G	E705*	0.39	UK Biobank
ASXL1	20	32434825	G	T	E705X	0.16	COPDGene
ASXL1	20	32434825	G	T	E705X	0.09	Additional TOPMED - JHS
ASXL1	20	32434821	TG	T	E705fs	0.04	UK Biobank
ASXL1	20	32434795	C	CA	Q695fs	0.20	COPDGene
ASXL1	20	32434795	CA	C	Q695fs	0.15	Additional TOPMED - FHS
ASXL1	20	32434789	C	T	R693*	0.13	UK Biobank
ASXL1	20	32434789	C	T	R693*	0.11	UK Biobank
ASXL1	20	32434789	C	T	R693X	0.11	COPDGene
ASXL1	20	32434786	C	T	Q692X	0.32	Additional TOPMED - ARIC
ASXL1	20	32434778	C	G	S689X	0.36	COPDGene
ASXL1	20	32434773	T	A	C687X	0.31	COPDGene
ASXL1	20	32434769	AGT	A	K686fs	0.19	Additional TOPMED - ECLIPSE
ASXL1	20	32434740	G	GC	E676fs	0.44	Additional TOPMED - FHS
ASXL1	20	32434733	A	ACCCTGAG	H674fs	0.16	COPDGene
ASXL1	20	32434721	AGG	A	E670fs	0.13	COPDGene
ASXL1	20	32434681	G	T	E657*	0.08	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
ASXL1	20	32434638	A	AG	G642fs	0.57	Additional TOPMED - JHS
ASXL1	20	32434638	A	AG	G642fs	0.56	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.54	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.54	Additional TOPMED - ARIC
ASXL1	20	32434638	A	AG	G642fs	0.45	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.45	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.43	Additional TOPMED - FHS
ASXL1	20	32434638	A	AG	G642fs	0.42	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.40	Additional TOPMED - ARIC
ASXL1	20	32434638	A	AG	G642fs	0.40	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.35	Additional TOPMED - ARIC
ASXL1	20	32434638	A	AG	G642fs	0.35	COPDGene
ASXL1	20	32434638	A	AG	G642fs	0.32	Additional TOPMED - FHS
ASXL1	20	32434638	A	AG	G642fs	0.31	COPDGene
ASXL1	20	32434638	A	AG	G646fs	0.44	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.43	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.38	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.37	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.32	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.32	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.31	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.31	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.27	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.25	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.24	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.21	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.20	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.20	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.17	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.17	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.15	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.13	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.13	UK Biobank
ASXL1	20	32434638	A	AG	G646fs	0.10	UK Biobank
ASXL1	20	32434637	G	GA	G643fs	0.09	UK Biobank
ASXL1	20	32434637	G	GA	G643fs	0.08	UK Biobank
ASXL1	20	32434635	CGGAGG	C	G644fs	0.20	UK Biobank
ASXL1	20	32434629	TGCCATCGGAGG	T	A640fs	0.12	UK Biobank
ASXL1	20	32434628	CTGCCATCGGAGGGGGGGT	C	T639fs	0.40	COPDGene
ASXL1	20	32434624	ACC	A	T638fs	0.20	COPDGene
ASXL1	20	32434612	AGAGAGGCGGCCACCACTGCCATC	A	R634fs	0.10	COPDGene
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.37	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.22	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.21	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.20	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.19	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.11	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.09	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.09	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.06	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	E635fs	0.04	UK Biobank
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	H630fs	0.17	Additional TOPMED - FHS
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	H630fs	0.16	Additional TOPMED - ECLIPSE
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	H630fs	0.15	COPDGene
ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	H630fs	0.10	Additional TOPMED - ARIC
ASXL1	20	32434596	AGGTCACCACCTGCCATAGAGAGGCGC	A	G629fs	0.08	Additional TOPMED - ECLIPSE
ASXL1	20	32434579	C	T	Q623*	0.09	UK Biobank
ASXL1	20	32434579	C	T	Q623*	0.07	UK Biobank
ASXL1	20	32434562	T	TTAAA	I617fs	0.44	COPDGene
ASXL1	20	32434562	T	TA	I617fs	0.11	Additional TOPMED - ARIC
ASXL1	20	32434515	G	GGAGT	T601fs	0.22	Additional TOPMED - FHS
ASXL1	20	32434494	C	A	C594X	0.20	Additional TOPMED - JHS
ASXL1	20	32434490	T	TA	I593fs	0.53	COPDGene
ASXL1	20	32434486	C	T	Q592X	0.30	Additional TOPMED - ARIC
ASXL1	20	32434486	C	T	Q592X	0.18	COPDGene
ASXL1	20	32434485	C	A	Y591*	0.27	UK Biobank
ASXL1	20	32434485	C	A	Y591X	0.30	Additional TOPMED - ARIC
ASXL1	20	32434485	C	A	Y591X	0.27	COPDGene
ASXL1	20	32434485	C	G	Y591X	0.19	COPDGene
ASXL1	20	32434485	C	A	Y591X	0.17	COPDGene
ASXL1	20	32434485	C	G	Y591X	0.13	Additional TOPMED - ARIC
ASXL1	20	32434483	T	TA	Y591 Q592delinsX	0.16	Additional TOPMED - ARIC
ASXL1	20	32434483	T	TA	Y591 Q592delinsX	0.16	Additional TOPMED - ECLIPSE
ASXL1	20	32434483	T	TA	Y591fs	0.09	UK Biobank
ASXL1	20	32434483	T	TA	Y591fs	0.07	UK Biobank
ASXL1	20	32434474	C	T	Q588*	0.15	UK Biobank
ASXL1	20	32434472	G	GT	G587fs	0.23	Additional TOPMED - ARIC
ASXL1	20	32434462	G	GT	V584fs	0.06	Additional TOPMED - ARIC
ASXL1	20	32434461	G	A	W583X	0.18	Additional TOPMED - FHS
ASXL1	20	32434461	G	A	W583X	0.16	Additional TOPMED - ARIC
ASXL1	20	32434460	G	A	W583*	0.15	UK Biobank
ASXL1	20	32434460	G	A	W583X	0.15	Additional TOPMED - ECLIPSE
ASXL1	20	32434430	A	A	c.1720-2A>G	0.33	Additional TOPMED - MESA
ASXL1	20	32434430	A	T	c.e13-2A>T	0.10	UK Biobank
ASXL1	20	32433916	G	A	R573Q	0.48	UK Biobank
ASXL1	20	32433846	AAC	A	T551fs	0.14	UK Biobank
ASXL1	20	32433839	C	CT	R549fs	0.16	UK Biobank
ASXL1	20	32433839	C	CT	S547fs	0.36	COPDGene
ASXL1	20	32433829	A	AT	R545fs	0.11	UK Biobank
ASXL1	20	32433819	C	CGGCTTGA	D544fs	0.41	UK Biobank
ASXL1	20	32433807	G	T	E537*	0.33	UK Biobank
ASXL1	20	32433783	C	T	Q529*	0.04	UK Biobank
ASXL1	20	32433783	C	T	Q529X	0.27	Additional TOPMED - ECLIPSE
ASXL1	20	32433783	C	T	Q529X	0.17	COPDGene
ASXL1	20	32433774	TCCCTTTGAGCAGGC GGCCTCTGCATCCCTTTCC CGAAAAGAGGCC	T	S526fs	0.17	COPDGene
ASXL1	20	32433747	C	T	Q517*	0.04	UK Biobank
ASXL1	20	32433739	CTG	C	T514fs	0.23	COPDGene

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort	
ASXL1	20	32433732	C	T	Q512*	0.15	UK Biobank	
ASXL1	20	32433732	C	T	Q512*	0.09	UK Biobank	
ASXL1	20	32433732	C	T	Q512*	0.07	UK Biobank	
ASXL1	20	32433732	C	T	Q512X	0.20	Additional TOPMED - ARIC	
ASXL1	20	32433732	C	T	Q512X	0.14	COVDGene	
ASXL1	20	32433616	C	CA	P474fs	0.07	UK Biobank	
ASXL1	20	32433594	CTG	C	L466fs	0.29	COVDGene	
ASXL1	20	32433568	AC	A	D457fs	0.17	Additional TOPMED - ECLIPSE	
ASXL1	20	32433555	G	T	E453*	0.15	UK Biobank	
ASXL1	20	32433544	AC	A	Y449fs	0.10	UK Biobank	
ASXL1	20	32433529	C	A	S444X	0.22	COVDGene	
ASXL1	20	32433487	C	G	S430*	0.16	UK Biobank	
ASXL1	20	32433480	C	T	Q428X	0.29	COVDGene	
ASXL1	20	32433473	C	CA	Q428fs	0.40	UK Biobank	
ASXL1	20	32433473	C	CA	Q428fs	0.17	UK Biobank	
ASXL1	20	32433473	C	A	Y425*	0.06	UK Biobank	
ASXL1	20	32433447	C	T	R417*	0.08	UK Biobank	
ASXL1	20	32433408	C	T	R404*	0.41	UK Biobank	
ASXL1	20	32433408	C	T	R404*	0.21	UK Biobank	
ASXL1	20	32433408	C	T	R404*	0.11	UK Biobank	
ASXL1	20	32433408	C	T	R404*	0.08	UK Biobank	
ASXL1	20	32433408	C	T	R404*	0.07	UK Biobank	
ASXL1	20	32433408	C	T	R404*	0.04	UK Biobank	
ASXL1	20	32433408	C	T	R404X	0.33	Additional TOPMED - ECLIPSE	
ASXL1	20	32433373	C	G	S392*	0.17	UK Biobank	
ASXL1	20	32433373	C	G	S392X	0.43	Additional TOPMED - ECLIPSE	
ASXL1	20	32433366	G	G	G390X	0.13	COVDGene	
ASXL1	20	32433315	C	T	Q373X	0.34	COVDGene	
ASXL1	20	32433312	C	T	Q372*	0.07	UK Biobank	
ASXL1	20	32433312	C	T	Q372X	0.11	COVDGene	
ASXL1	20	32433297	A	T	K367*	0.07	UK Biobank	
ASXL1	20	32432985	A	G	K362R	0.42	UK Biobank	
ASXL1	20	32432985	A	G	K362R	0.39	UK Biobank	
ASXL1	20	31024758	C	T	R1415*	0.07	ICGN-EOCOVD	
ASXL1	20	31024662	G	T	E1383*	0.10	ICGN-EOCOVD	
ASXL1	20	31024116	CA	C	K1202fs	0.19	ICGN-EOCOVD	
ASXL1	20	31023408	C	T	R965*	0.32	ICGN-EOCOVD	
ASXL1	20	31022277	C	T	Q588*	0.23	ICGN-EOCOVD	
ASXL1	20	31022233	A	C		0.06	ICGN-EOCOVD	
ASXL1	20	31021332	C	G	S444*	0.09	ICGN-EOCOVD	
ASXL1	20	31021250	C	T	R417*	0.23	ICGN-EOCOVD	
ASXL1	20	31015977	AGGAGCCAGAGGACACGGCTGATGTGGAGAGC TGTGGGCTTAAGAGCCAGCACTGTGAGTGGT GAAAACGATGGTAAGGACCCCTTTAATGGATGGG	TGAG	A		0.02	ICGN-EOCOVD
ASXL2	2	25972857	G	GT	T523fs	0.07	ICGN-EOCOVD	
ASXL2	2	25965949	G	T	S1086*	0.09	ICGN-EOCOVD	
ASXL2	2	25750016	T	A	K514X	0.30	Additional TOPMED - FHS	
ASXL2	2	25742786	TCC	T	E1183fs	0.33	Additional TOPMED - ARIC	
BCOR	X	40074111	TTCCGGGCATG	C	H409fs	0.03	UK Biobank	
BCOR	X	40073540	CG	T	P602fs	0.04	UK Biobank	
BCOR	X	40072349	C	T	Q999G	0.08	UK Biobank	
BCOR	X	40071638	T	C	E1017G	0.13	UK Biobank	
BCOR	X	40063917	A	AG	S1180fs	0.97	COVDGene	
BCOR	X	40063726	AG	A	P1243fs	0.35	COVDGene	
BCOR	X	40062170	A	AG	L1466fs	0.62	COVDGene	
BCOR	X	40055512	G	T	P1533T	0.09	UK Biobank	
BCOR	X	40053912	A	AT	Y1650_N1651delins X	0.11	Additional TOPMED - ECLIPSE	
BCORL1	X	130056125	T	GT	C1709fs	0.55	Additional TOPMED - ARIC	
BCORL1	X	130051967	GA	G	D1602fs	0.23	COVDGene	
BCORL1	X	130051965	C	G	S1601X	0.60	COVDGene	
BCORL1	X	130028794	C	A	S1413*	0.07	UK Biobank	
BCORL1	X	130025210	G	A	W1303X	0.56	COVDGene	
BCORL1	X	130015122	C	T	R784*	0.04	UK Biobank	
BCORL1	X	130014985	TCA	T	N739fs	0.04	UK Biobank	
BCORL1	X	130014695	AC	A	M644fs	0.03	UK Biobank	
BCORL1	X	130014671	TC	T	P634fs	0.04	UK Biobank	
BCORL1	X	130014555	TC	T	S595fs	0.20	COVDGene	
BCORL1	X	130013743	C	G	S324X	0.21	COVDGene	
BRCC3	X	155099364	AT	A	I200fs	0.44	UK Biobank	
BRCC3	X	155089313	CT	C	L152fs	0.11	Additional TOPMED - JHS	
BRCC3	X	155077291	T	A	c.315+2T>A	0.12	COVDGene	
BRCC3	X	155077245	GA	G	I92fs	0.05	UK Biobank	
BRCC3	X	155071642	ATAGGGGAGGTGAGTAGTCTGT	A	I39fs	0.24	Additional TOPMED - JHS	
BRCC3	X	155071555	C	T	Q10X	0.18	COVDGene	
BRCC3	X	155071548	GGCGGTGGAGCCGGT	G	A8fs	0.14	COVDGene	
BRCC3	X	155071546	C	T	Q7*	0.07	UK Biobank	
BRCC3	X	155071546	C	T	Q7*	0.07	UK Biobank	
BRCC3	X	155071546	C	T	Q7X	0.63	COVDGene	
BRCC3	X	155071546	C	T	Q7X	0.18	Additional TOPMED - ARIC	
BRCC3	X	155071546	C	T	Q7X	0.14	Additional TOPMED - JHS	
BRCC3	X	155071537	C	T	Q4X	0.29	Additional TOPMED - JHS	
BRCC3	X	155071537	C	T	Q4X	0.27	COVDGene	
BRCC3	X	154348353	A	AGGGGAGAGTGGAAACATGCT	N294fs	0.07	ICGN-EOCOVD	
BRCC3	X	154317537	G	A		0.13	ICGN-EOCOVD	
CALR	19	12943813	A	ATTGTC	K385fs	0.42	UK Biobank	
CALR	19	12943813	A	ATTGTC	K385fs	0.23	UK Biobank	
CALR	19	12943813	A	ATTGTC	K385fs	0.05	UK Biobank	
CALR	19	12943787	CAA	C	K377fs	0.37	UK Biobank	
CBL	11	119278541	G	A	R420Q	0.07	UK Biobank	
CBL	11	119278540	C	G	R420G	0.13	COVDGene	
CBL	11	119278529	G	C	C416S	0.12	UK Biobank	
CBL	11	119278525	G	A	G415S	0.34	UK Biobank	
CBL	11	119278297	G	T	Q409H	0.57	COVDGene	
CBL	11	119278294	G	T	W408C	0.15	Additional TOPMED - ARIC	
CBL	11	119278294	G	T	W408C	0.12	COVDGene	
CBL	11	119278290	C	T	S407F	0.35	UK Biobank	
CBL	11	119278272	G	A	C401Y	0.14	Additional TOPMED - ECLIPSE	
CBL	11	119278269	T	G	M400R	0.14	UK Biobank	
CBL	11	119278266	T	C	L399P	0.19	COVDGene	
CBL	11	119278263	A	G	H398R	0.21	UK Biobank	
CBL	11	119278248	T	C	I393T	0.06	UK Biobank	

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
CBL	11	119278236	A	G	K389R	0.22	UK Biobank
CBL	11	119278235	A	G	K389E	0.14	UK Biobank
CBL	11	119278221	G	A	C384Y	0.53	Additional TOPMED - FHS
CBL	11	119278221	G	A	C384Y	0.29	COPDGene
CBL	11	119148991	G	A	C404Y	0.07	ICGN-EOCOPD
CBL	11	119148929	A	G	I383M	0.07	ICGN-EOCOPD
CEBPA	19	33302168	G	A	Q83*	0.04	UK Biobank
CEBPA	19	33301789	TG	T	Q209fs	0.22	COPDGene
CREBBP	16	3782810	G	A	R483*	0.08	UK Biobank
CREBBP	16	3778053	G	A	Q691*	0.09	UK Biobank
CREBBP	16	3749627	G	A	P1279L	0.32	UK Biobank
CSF3R	1	36466597	GC	G	G757fs	0.10	UK Biobank
CSF3R	1	36466576	TG	T	P764fs	0.44	UK Biobank
CTCF	16	67628551	G	A	R567Q	0.08	UK Biobank
CTCF	16	67621447	A	T	K405*	0.09	UK Biobank
CUX1	7	102248888	C	A	S1455*	0.06	UK Biobank
CUX1	7	102239483	G	GT	Y1263fs	0.43	UK Biobank
CUX1	7	102204469	C	T	R996*	0.26	UK Biobank
CUX1	7	102204447	G	A	W988*	0.10	UK Biobank
CUX1	7	102202102	C	G	Y935*	0.03	UK Biobank
CUX1	7	102201933	G	A	W879*	0.06	UK Biobank
CUX1	7	102196844	T	TTGCA	F478fs	0.20	COPDGene
CUX1	7	102196788	CTT	C	F460fs	0.15	COPDGene
CUX1	7	101845002	C	T	Q809*	0.12	ICGN-EOCOPD
DNMT3A	2	25470584	C	G	W297S	0.23	ICGN-EOCOPD
DNMT3A	2	25470583	C	T	W297*	0.12	ICGN-EOCOPD
DNMT3A	2	25470583	C	A	W297C	0.10	ICGN-EOCOPD
DNMT3A	2	254705116	G	A	R320*	0.04	ICGN-EOCOPD
DNMT3A	2	25470498	G	A	R326C	0.04	ICGN-EOCOPD
DNMT3A	2	25470460	C	T	V338V	0.04	ICGN-EOCOPD
DNMT3A	2	25469959	CT	C	K361fs	0.14	ICGN-EOCOPD
DNMT3A	2	25469083	TC	T	K459fs	0.24	ICGN-EOCOPD
DNMT3A	2	25468122	CT	C	K518fs	0.07	ICGN-EOCOPD
DNMT3A	2	25467428	C	T	G550R	0.07	ICGN-EOCOPD
DNMT3A	2	25467125	AG	A	Y584fs	0.14	ICGN-EOCOPD
DNMT3A	2	25467118	C	T	C586Y	0.26	ICGN-EOCOPD
DNMT3A	2	25466852	C	T		0.13	ICGN-EOCOPD
DNMT3A	2	25466799	C	T	R635Q	0.08	ICGN-EOCOPD
DNMT3A	2	25463568	A	G	I705T	0.20	ICGN-EOCOPD
DNMT3A	2	25463289	T	C	Y735C	0.19	ICGN-EOCOPD
DNMT3A	2	25463287	G	A	R736C	0.18	ICGN-EOCOPD
DNMT3A	2	25463287	G	A	R736C	0.10	ICGN-EOCOPD
DNMT3A	2	25463271	G	A	A741V	0.17	ICGN-EOCOPD
DNMT3A	2	25463247	C	T	R749H	0.06	ICGN-EOCOPD
DNMT3A	2	25463184	G	A	S770L	0.11	ICGN-EOCOPD
DNMT3A	2	25463182	G	A	R771*	0.10	ICGN-EOCOPD
DNMT3A	2	25462074	A	C	V778G	0.06	ICGN-EOCOPD
DNMT3A	2	25462054	C	T	V785M	0.08	ICGN-EOCOPD
DNMT3A	2	25462023	C	T	W795*	0.13	ICGN-EOCOPD
DNMT3A	2	25462023	C	T	W795*	0.04	ICGN-EOCOPD
DNMT3A	2	25462009	CG	C	G800fs	0.10	ICGN-EOCOPD
DNMT3A	2	25458696	T	C		0.20	ICGN-EOCOPD
DNMT3A	2	25458627	G	A	P849L	0.09	ICGN-EOCOPD
DNMT3A	2	25458593	C	T	W860*	0.20	ICGN-EOCOPD
DNMT3A	2	25458580	C	T	R865K	0.08	ICGN-EOCOPD
DNMT3A	2	25457243	G	A	R882C	0.17	ICGN-EOCOPD
DNMT3A	2	25457243	G	A	R882C	0.12	ICGN-EOCOPD
DNMT3A	2	25457192	G	A	R899C	0.11	ICGN-EOCOPD
DNMT3A	2	25457192	G	A	R899C	0.09	ICGN-EOCOPD
DNMT3A	2	25300139	CG	C	P59fs	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25300139	CG	C	P59fs	0.05	UK Biobank
DNMT3A	2	25300139	CG	C	P59fs	0.04	UK Biobank
DNMT3A	2	25282651	G	A	Q80*	0.09	UK Biobank
DNMT3A	2	25282462	G	A	R143*	0.06	UK Biobank
DNMT3A	2	25275080	C	CG	R167fs	0.17	COPDGene
DNMT3A	2	25248213	CA	C	V227fs	0.07	UK Biobank
DNMT3A	2	25248213	C	CAGCA	V227fs	0.04	UK Biobank
DNMT3A	2	25248210	C	A	E228*	0.05	UK Biobank
DNMT3A	2	25248206	TC	T	E229fs	0.09	UK Biobank
DNMT3A	2	25248201	G	A	Q231*	0.33	UK Biobank
DNMT3A	2	25248200	T	TGGTTTCTTCCCCC	Q231fs	0.09	UK Biobank
DNMT3A	2	25248192	C	CG	G234fs	0.13	UK Biobank
DNMT3A	2	25248191	C	CT	G234fs	0.05	UK Biobank
DNMT3A	2	25248189	C	A	E235X	0.67	COPDGene
DNMT3A	2	25248183	G	A	Q237*	0.04	UK Biobank
DNMT3A	2	25248183	G	A	Q237X	0.11	Additional TOPMED - ARIC
DNMT3A	2	25248182	T	TGA	Q237fs	0.03	UK Biobank
DNMT3A	2	25248180	T	TC	K238fs	0.31	COPDGene
DNMT3A	2	25248171	CCT	C	E240fs	0.06	UK Biobank
DNMT3A	2	25248170	TC	T	E241fs	0.10	Additional TOPMED - ARIC
DNMT3A	2	25248157	AGGAGG	A	P244fs	0.07	UK Biobank
DNMT3A	2	25248157	AG	A	P245fs	0.27	UK Biobank
DNMT3A	2	25248154	AG	A	A246fs	0.05	UK Biobank
DNMT3A	2	25248150	G	A	Q248*	0.11	UK Biobank
DNMT3A	2	25248148	CTG	C	Q248fs	0.29	Additional TOPMED - ECLIPSE
DNMT3A	2	25248147	G	A	Q249*	0.11	UK Biobank
DNMT3A	2	25248147	G	A	Q249*	0.06	UK Biobank
DNMT3A	2	25248147	G	A	Q249X	0.16	Additional TOPMED - MESA
DNMT3A	2	25248147	G	A	Q249X	0.12	Additional TOPMED - MESA
DNMT3A	2	25248141	TGGGCTGCTGCACAGCAGGA	T	P244fs	0.22	COPDGene
DNMT3A	2	25248128	GA	G	S255fs	0.09	UK Biobank
DNMT3A	2	25248116	GC	G	A259fs	0.27	COPDGene
DNMT3A	2	25248099	CG	C	V265fs	0.04	UK Biobank
DNMT3A	2	25248086	GC	GC	A269fs	0.16	Additional TOPMED - JHS
DNMT3A	2	25248045	C	A	E283*	0.08	UK Biobank
DNMT3A	2	25248045	C	A	E283*	0.07	UK Biobank
DNMT3A	2	25248045	C	A	E283*	0.05	UK Biobank
DNMT3A	2	25248045	C	CCA	E283fs	0.05	UK Biobank
DNMT3A	2	25248039	C	A	E285X	0.34	Additional TOPMED - FHS

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25248036	C	T	c.855+1G>A	0.15	COPDGene
DNMT3A	2	25248036	C	T	c.e7-1G>A	0.05	UK Biobank
DNMT3A	2	25248036	C	A	c.e7-1G>T	0.07	UK Biobank
DNMT3A	2	25247751	T	C	c.289-2A>G	0.28	Additional TOPMED - MESA
DNMT3A	2	25247751	T	G	c.e8+2A>C	0.07	UK Biobank
DNMT3A	2	25247751	T	C	c.e8+2A>G	0.07	UK Biobank
DNMT3A	2	25247736	A	G	F290S	0.10	COPDGene
DNMT3A	2	25247730	A	G	I292T	0.49	UK Biobank
DNMT3A	2	25247728	C	T	G293R	0.23	UK Biobank
DNMT3A	2	25247728	C	T	G293R	0.09	UK Biobank
DNMT3A	2	25247727	CCAATGCCAA	C	290_293FGIG>W	0.04	UK Biobank
DNMT3A	2	25247725	C	A	E294X	0.16	Additional TOPMED - JHS
DNMT3A	2	25247725	CCCCAA	C	I292fs	0.03	UK Biobank
DNMT3A	2	25247724	TC	T	E294fs	0.09	UK Biobank
DNMT3A	2	25247721	A	G	L295P	0.15	UK Biobank
DNMT3A	2	25247721	A	T	L295Q	0.23	Additional TOPMED - ARIC
DNMT3A	2	25247719	C	G	V296L	0.14	UK Biobank
DNMT3A	2	25247719	C	G	V296L	0.10	UK Biobank
DNMT3A	2	25247719	C	T	V296M	0.36	Additional TOPMED - FHS
DNMT3A	2	25247719	C	T	V296M	0.16	COPDGene
DNMT3A	2	25247719	C	T	V296M	0.06	UK Biobank
DNMT3A	2	25247719	C	T	V296M	0.06	UK Biobank
DNMT3A	2	25247719	C	T	V296M	0.05	UK Biobank
DNMT3A	2	25247719	C	T	V296M	0.04	UK Biobank
DNMT3A	2	25247718	A	C	V296G	0.24	COPDGene
DNMT3A	2	25247715	C	T	W297*	0.09	UK Biobank
DNMT3A	2	25247715	C	T	W297*	0.04	UK Biobank
DNMT3A	2	25247715	C	T	W297*	0.04	UK Biobank
DNMT3A	2	25247715	CA	C	W297fs	0.14	COPDGene
DNMT3A	2	25247715	C	G	W297S	0.08	UK Biobank
DNMT3A	2	25247714	C	T	W297*	0.29	UK Biobank
DNMT3A	2	25247714	C	A	W297C	0.09	UK Biobank
DNMT3A	2	25247713	C	G	G298R	0.17	Additional TOPMED - ECLIPSE
DNMT3A	2	25247713	C	G	G298R	0.15	UK Biobank
DNMT3A	2	25247713	C	G	G298R	0.03	UK Biobank
DNMT3A	2	25247713	C	A	G298W	0.18	Additional TOPMED - MESA
DNMT3A	2	25247712	C	T	G298E	0.08	Additional TOPMED - JHS
DNMT3A	2	25247712	C	T	G298E	0.07	UK Biobank
DNMT3A	2	25247712	C	T	G298E	0.03	UK Biobank
DNMT3A	2	25247710	T	TC	K299fs	0.23	Additional TOPMED - FHS
DNMT3A	2	25247706	A	T	L300Q	0.07	UK Biobank
DNMT3A	2	25247704	GC	G	R301fs	0.09	UK Biobank
DNMT3A	2	25247704	G	A	R301W	0.07	UK Biobank
DNMT3A	2	25247704	G	A	R301W	0.06	UK Biobank
DNMT3A	2	25247704	G	A	R301W	0.03	UK Biobank
DNMT3A	2	25247699	GC	G	G302fs	0.11	UK Biobank
DNMT3A	2	25247697	A	T	F303Y	0.02	UK Biobank
DNMT3A	2	25247693	GGA	G	S304fs	0.20	UK Biobank
DNMT3A	2	25247691	C	T	W305*	0.03	UK Biobank
DNMT3A	2	25247691	C	T	W305*	0.03	UK Biobank
DNMT3A	2	25247691	CAG	C	W305fs	0.02	UK Biobank
DNMT3A	2	25247691	C	T	W305X	0.33	COPDGene
DNMT3A	2	25247691	C	T	W305X	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25247690	C	T	W305*	0.10	UK Biobank
DNMT3A	2	25247690	C	T	W305*	0.09	UK Biobank
DNMT3A	2	25247690	C	T	W305*	0.07	UK Biobank
DNMT3A	2	25247690	C	T	W305*	0.05	UK Biobank
DNMT3A	2	25247690	C	T	W305*	0.04	UK Biobank
DNMT3A	2	25247690	C	T	W305*	0.03	UK Biobank
DNMT3A	2	25247690	C	T	W305*	0.02	UK Biobank
DNMT3A	2	25247689	AC	A	W305fs	0.03	UK Biobank
DNMT3A	2	25247689	A	C	W306G	0.03	UK Biobank
DNMT3A	2	25247688	C	T	W306*	0.08	UK Biobank
DNMT3A	2	25247688	C	T	W306X	0.36	COPDGene
DNMT3A	2	25247687	C	T	W306*	0.09	UK Biobank
DNMT3A	2	25247687	C	C	W306C	0.11	COPDGene
DNMT3A	2	25247686	G	A	P307S	0.05	UK Biobank
DNMT3A	2	25247686	G	T	P307T	0.11	UK Biobank
DNMT3A	2	25247685	G	A	P307L	0.05	UK Biobank
DNMT3A	2	25247685	G	C	P307R	0.09	UK Biobank
DNMT3A	2	25247685	G	C	P307R	0.06	UK Biobank
DNMT3A	2	25247685	G	C	P307R	0.05	UK Biobank
DNMT3A	2	25247682	C	T	G308D	0.35	UK Biobank
DNMT3A	2	25247680	G	T	R309S	0.03	UK Biobank
DNMT3A	2	25247679	C	T	R309H	0.03	UK Biobank
DNMT3A	2	25247679	C	T	R309H	0.03	UK Biobank
DNMT3A	2	25247676	A	T	I310N	0.03	UK Biobank
DNMT3A	2	25247676	A	C	I310S	0.15	COPDGene
DNMT3A	2	25247676	A	C	I310S	0.06	UK Biobank
DNMT3A	2	25247676	A	G	I310T	0.06	UK Biobank
DNMT3A	2	25247676	A	G	I310T	0.06	UK Biobank
DNMT3A	2	25247676	A	G	I310T	0.05	UK Biobank
DNMT3A	2	25247676	A	G	I310T	0.04	UK Biobank
DNMT3A	2	25247667	C	T	W313*	0.38	UK Biobank
DNMT3A	2	25247667	C	T	W313*	0.02	UK Biobank
DNMT3A	2	25247667	CA	C	W313fs	0.02	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.19	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.06	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.05	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.04	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.04	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.04	UK Biobank
DNMT3A	2	25247666	C	T	W313*	0.02	UK Biobank
DNMT3A	2	25247666	C	T	W313X	0.22	Additional TOPMED - ECLIPSE
DNMT3A	2	25247666	C	T	W313X	0.13	COPDGene
DNMT3A	2	25247664	C	T	W314*	0.15	UK Biobank
DNMT3A	2	25247664	C	T	W314*	0.08	UK Biobank
DNMT3A	2	25247664	C	T	W314*	0.05	UK Biobank
DNMT3A	2	25247663	C	T	W314X	0.31	Additional TOPMED - FHS

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25247658	G	A	T316M	0.06	UK Biobank
DNMT3A	2	25247658	G	A	T316M	0.03	UK Biobank
DNMT3A	2	25247652	CG	C	R318fs	0.20	COPDGene
DNMT3A	2	25247652	CG	T	R318Q	0.02	UK Biobank
DNMT3A	2	25247648	G	T	S319R	0.03	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.34	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.26	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.15	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.12	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.07	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.07	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.06	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.05	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.05	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.03	UK Biobank
DNMT3A	2	25247647	G	A	R320*	0.03	UK Biobank
DNMT3A	2	25247638	CA	C	E323fs	0.11	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.20	COPDGene
DNMT3A	2	25247629	G	A	R326C	0.17	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.10	Additional TOPMED - JHS
DNMT3A	2	25247629	G	A	R326C	0.10	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.09	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.06	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.05	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.05	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.03	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.03	UK Biobank
DNMT3A	2	25247629	G	A	R326C	0.02	UK Biobank
DNMT3A	2	25247629	G	T	R326S	0.13	Additional TOPMED - MESA
DNMT3A	2	25247629	G	T	R326S	0.06	UK Biobank
DNMT3A	2	25247629	G	T	R326S	0.04	UK Biobank
DNMT3A	2	25247629	G	T	R326S	0.03	UK Biobank
DNMT3A	2	25247629	G	T	R326S	0.02	UK Biobank
DNMT3A	2	25247628	C	T	R326H	0.47	Additional TOPMED - MESA
DNMT3A	2	25247628	C	T	R326H	0.38	COPDGene
DNMT3A	2	25247628	C	T	R326H	0.30	UK Biobank
DNMT3A	2	25247628	C	T	R326H	0.24	COPDGene
DNMT3A	2	25247628	C	T	R326H	0.19	Additional TOPMED - FHS
DNMT3A	2	25247628	C	T	R326H	0.16	UK Biobank
DNMT3A	2	25247628	C	T	R326H	0.10	Additional TOPMED - ARIC
DNMT3A	2	25247628	C	T	R326H	0.08	UK Biobank
DNMT3A	2	25247628	C	T	R326H	0.03	UK Biobank
DNMT3A	2	25247628	C	T	R326H	0.03	UK Biobank
DNMT3A	2	25247628	C	T	R326H	0.02	UK Biobank
DNMT3A	2	25247627	G	G	A322fs	0.09	COPDGene
DNMT3A	2	25247625	C	T	W327*	0.29	UK Biobank
DNMT3A	2	25247624	C	T	W327*	0.04	UK Biobank
DNMT3A	2	25247623	C	A	V328F	0.10	UK Biobank
DNMT3A	2	25247623	C	A	V328F	0.07	UK Biobank
DNMT3A	2	25247622	A	C	V328G	0.18	Additional TOPMED - MESA
DNMT3A	2	25247616	C	T	W330*	0.05	UK Biobank
DNMT3A	2	25247616	C	T	W330*	0.05	UK Biobank
DNMT3A	2	25247615	C	T	W330*	0.14	UK Biobank
DNMT3A	2	25247615	C	T	W330*	0.03	UK Biobank
DNMT3A	2	25247615	C	T	W330*	0.02	UK Biobank
DNMT3A	2	25247615	C	T	W330X	0.11	COPDGene
DNMT3A	2	25247614	A	T	F331I	0.04	UK Biobank
DNMT3A	2	25247614	A	C	F331V	0.21	UK Biobank
DNMT3A	2	25247614	A	C	F331V	0.13	Additional TOPMED - ARIC
DNMT3A	2	25247614	A	C	F331V	0.06	UK Biobank
DNMT3A	2	25247611	C	T	G332R	0.09	UK Biobank
DNMT3A	2	25247611	C	T	G332R	0.04	UK Biobank
DNMT3A	2	25247611	C	T	G332R	0.03	UK Biobank
DNMT3A	2	25247611	C	T	G332R	0.01	UK Biobank
DNMT3A	2	25247610	C	T	G332E	0.16	Additional TOPMED - ARIC
DNMT3A	2	25247596	A	C	S337A	0.13	Additional TOPMED - MESA
DNMT3A	2	25247596	A	G	S337P	0.24	UK Biobank
DNMT3A	2	25247595	G	A	S337L	0.35	Additional TOPMED - JHS
DNMT3A	2	25247595	G	A	S337L	0.21	COPDGene
DNMT3A	2	25247595	G	A	S337L	0.09	UK Biobank
DNMT3A	2	25247595	G	A	S337L	0.07	UK Biobank
DNMT3A	2	25247595	G	A	S337L	0.05	UK Biobank
DNMT3A	2	25247595	G	A	S337L	0.02	UK Biobank
DNMT3A	2	25247595	G	C	S337X	0.20	Additional TOPMED - ECLIPSE
DNMT3A	2	25247160	T	C	c.1015-2A>G	0.37	Additional TOPMED - FHS
DNMT3A	2	25247160	T	C	c.1015-2A>G	0.14	Additional TOPMED - FHS
DNMT3A	2	25247160	T	C	c.e9+2A>G	0.48	UK Biobank
DNMT3A	2	25247160	T	C	c.e9+2A>G	0.17	UK Biobank
DNMT3A	2	25247160	T	C	c.e9+2A>G	0.10	UK Biobank
DNMT3A	2	25247160	T	C	c.e9+2A>G	0.10	UK Biobank
DNMT3A	2	25247160	T	C	c.e9+2A>G	0.10	UK Biobank
DNMT3A	2	25247160	T	C	c.e9+2A>G	0.05	UK Biobank
DNMT3A	2	25247160	T	A	c.e9+2A>T	0.14	UK Biobank
DNMT3A	2	25247159	CT	C	c.1015-2A>-	0.08	Additional TOPMED - FHS
DNMT3A	2	25247159	C	T	c.e9+1G>A	0.06	UK Biobank
DNMT3A	2	25247159	C	G	c.e9+1G>C	0.18	UK Biobank
DNMT3A	2	25247150	AAC	A	V341fs	0.35	COPDGene
DNMT3A	2	25247144	C	CGG	K343fs	0.17	COPDGene
DNMT3A	2	25247142	A	G	L344P	0.09	UK Biobank
DNMT3A	2	25247142	A	T	L344Q	0.09	UK Biobank
DNMT3A	2	25247142	A	T	L344Q	0.07	UK Biobank
DNMT3A	2	25247142	A	C	L344R	0.36	COPDGene
DNMT3A	2	25247139	AT	A	M345fs	0.05	UK Biobank
DNMT3A	2	25247137	G	GC	P346fs	0.26	UK Biobank
DNMT3A	2	25247137	G	A	P346S	0.04	UK Biobank
DNMT3A	2	25247133	A	G	L347P	0.16	UK Biobank
DNMT3A	2	25247133	A	G	L347P	0.08	COPDGene
DNMT3A	2	25247133	A	T	L347Q	0.14	UK Biobank
DNMT3A	2	25247133	AGCG	A	P346del	0.12	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25247121	CA	C	C351fs	0.17	UK Biobank
DNMT3A	2	25247121	CA	C	C351fs	0.13	UK Biobank
DNMT3A	2	25247121	CAA	C	F350fs	0.09	Additional TOPMED - ARIC
DNMT3A	2	25247118	CT	C	S352fs	0.07	UK Biobank
DNMT3A	2	25247112	A	G	F354S	0.15	UK Biobank
DNMT3A	2	25247109	TG	T	H355fs	0.05	UK Biobank
DNMT3A	2	25247109	TG	T	H355fs	0.03	UK Biobank
DNMT3A	2	25247107	G	A	Q356X	0.14	Additional TOPMED - ARIC
DNMT3A	2	25247107	G	A	Q356X	0.13	Additional TOPMED - JHS
DNMT3A	2	25247106	TGGTGGAAACGCACACTGCAAAACGAGCTCAGCGG	T	P346fs	0.08	Additional TOPMED - ARIC
DNMT3A	2	25247105	CT	C	Q356fs	0.16	UK Biobank
DNMT3A	2	25247103	GC	G	A357fs	0.38	UK Biobank
DNMT3A	2	25247089	G	A	Q362*	0.18	UK Biobank
DNMT3A	2	25247089	G	A	Q362*	0.07	UK Biobank
DNMT3A	2	25247089	G	A	Q362*	0.05	UK Biobank
DNMT3A	2	25247085	G	GGC	P363fs	0.06	UK Biobank
DNMT3A	2	25247083	TG	T	P363fs	0.13	Additional TOPMED - FHS
DNMT3A	2	25247079	T	C	Y365C	0.04	UK Biobank
DNMT3A	2	25247078	G	C	Y365X	0.15	Additional TOPMED - ECLIPSE
DNMT3A	2	25247077	G	A	R366C	0.32	UK Biobank
DNMT3A	2	25247077	G	A	R366C	0.20	UK Biobank
DNMT3A	2	25247077	G	A	R366C	0.15	UK Biobank
DNMT3A	2	25247077	G	A	R366C	0.12	COPDGene
DNMT3A	2	25247076	C	T	R366H	0.08	UK Biobank
DNMT3A	2	25247076	C	T	R366H	0.04	UK Biobank
DNMT3A	2	25247076	C	T	R366H	0.03	UK Biobank
DNMT3A	2	25247076	C	T	R366H	0.03	UK Biobank
DNMT3A	2	25247076	C	G	R366P	0.08	UK Biobank
DNMT3A	2	25247073	TTGCGGTACATG	T	P363fs	0.11	Additional TOPMED - ECLIPSE
DNMT3A	2	25247071	C	T	A368T	0.19	UK Biobank
DNMT3A	2	25247071	C	T	A368T	0.09	UK Biobank
DNMT3A	2	25247070	G	A	A368D	0.07	UK Biobank
DNMT3A	2	25247070	G	A	A368V	0.08	UK Biobank
DNMT3A	2	25247062	C	A	E371*	0.06	UK Biobank
DNMT3A	2	25247060	CT	C	E371fs	0.11	UK Biobank
DNMT3A	2	25247059	C	T	V372I	0.08	UK Biobank
DNMT3A	2	25247058	A	T	V372D	0.06	UK Biobank
DNMT3A	2	25247050	C	T	c.e9-1G>A	0.29	UK Biobank
DNMT3A	2	25247050	C	T	c.e9-1G>A	0.13	UK Biobank
DNMT3A	2	25247049	AC	A	c.e9-2GT>T	0.28	UK Biobank
DNMT3A	2	25246778	T	C	c.556-2A>G	0.14	Additional TOPMED - ECLIPSE
DNMT3A	2	25246778	T	C	c.e10+2A>G	0.04	UK Biobank
DNMT3A	2	25246778	T	C	c.e10+2A>G	0.04	UK Biobank
DNMT3A	2	25246777	C	G	c.1123-1G>C	0.16	COPDGene
DNMT3A	2	25246770	TG	T	A376fs	0.08	COPDGene
DNMT3A	2	25246768	GCTGGCCAC	G	V375fs	0.07	UK Biobank
DNMT3A	2	25246764	G	A	R379C	0.24	Additional TOPMED - ECLIPSE
DNMT3A	2	25246764	G	A	R379C	0.16	UK Biobank
DNMT3A	2	25246764	G	A	R379C	0.12	COPDGene
DNMT3A	2	25246764	G	C	R379G	0.04	UK Biobank
DNMT3A	2	25246755	TC	T	G381fs	0.12	COPDGene
DNMT3A	2	25246745	G	A	P385L	0.47	UK Biobank
DNMT3A	2	25246744	CG	C	P385fs	0.21	UK Biobank
DNMT3A	2	25246744	CG	C	P385fs	0.15	UK Biobank
DNMT3A	2	25246744	CG	C	P385fs	0.15	UK Biobank
DNMT3A	2	25246744	CG	C	P385fs	0.08	UK Biobank
DNMT3A	2	25246744	CG	C	P385fs	0.03	UK Biobank
DNMT3A	2	25246738	G	T	C387*	0.04	UK Biobank
DNMT3A	2	25246732	GTC	G	D389fs	0.03	UK Biobank
DNMT3A	2	25246725	C	A	E392*	0.04	UK Biobank
DNMT3A	2	25246723	C	CT	E392fs	0.09	Additional TOPMED - FHS
DNMT3A	2	25246710	T	A	K397X	0.14	Additional TOPMED - FHS
DNMT3A	2	25246695	G	A	Q402*	0.06	UK Biobank
DNMT3A	2	25246695	G	A	Q402*	0.03	UK Biobank
DNMT3A	2	25246679	A	C	H407S	0.15	COPDGene
DNMT3A	2	25246674	A	T	W409R	0.16	Additional TOPMED - MESA
DNMT3A	2	25246673	C	T	W409*	0.03	UK Biobank
DNMT3A	2	25246666	CA	C	L411fs	0.05	UK Biobank
DNMT3A	2	25246665	C	CA	G412fs	0.18	COPDGene
DNMT3A	2	25246665	C	CA	G412fs	0.05	UK Biobank
DNMT3A	2	25246661	C	A	G413V	0.07	Additional TOPMED - MESA
DNMT3A	2	25246660	G	GC	F414fs	0.06	UK Biobank
DNMT3A	2	25246659	A	C	F414V	0.11	Additional TOPMED - MESA
DNMT3A	2	25246659	AG	A	G413fs	0.09	COPDGene
DNMT3A	2	25246658	A	G	F414S	0.30	COPDGene
DNMT3A	2	25246657	GA	G	F414fs	0.49	UK Biobank
DNMT3A	2	25246648	AG	A	S417fs	0.05	UK Biobank
DNMT3A	2	25246645	GC	G	G418fs	0.19	Additional TOPMED - ECLIPSE
DNMT3A	2	25246645	GC	G	G418fs	0.06	COPDGene
DNMT3A	2	25246619	C	G	c.1279+1G>C	0.14	COPDGene
DNMT3A	2	25246619	C	T	c.e10-1G>A	0.11	UK Biobank
DNMT3A	2	25246619	C	T	c.e10-1G>A	0.06	UK Biobank
DNMT3A	2	25246295	AG	A	Y432fs	0.17	UK Biobank
DNMT3A	2	25246276	T	TC	D438fs	0.18	COPDGene
DNMT3A	2	25246272	CA	C	M439fs	0.16	Additional TOPMED - MESA
DNMT3A	2	25246270	C	T	W440*	0.11	UK Biobank
DNMT3A	2	25246270	C	T	W440*	0.06	UK Biobank
DNMT3A	2	25246269	C	T	W440*	0.06	UK Biobank
DNMT3A	2	25246269	C	CCA	W440fs	0.16	UK Biobank
DNMT3A	2	25246245	G	C	Y448X	0.15	COPDGene
DNMT3A	2	25246230	TG	T	P453fs	0.22	Additional TOPMED - ECLIPSE
DNMT3A	2	25246221	C	CT	P457fs	0.14	UK Biobank
DNMT3A	2	25246220	GC	G	K456fs	0.07	UK Biobank
DNMT3A	2	25246216	CG	C	R458fs	0.19	Additional TOPMED - JHS
DNMT3A	2	25246216	CG	C	R458fs	0.15	COPDGene
DNMT3A	2	25246216	CG	C	R458fs	0.06	UK Biobank
DNMT3A	2	25246214	TC	T	K459fs	0.06	UK Biobank
DNMT3A	2	25246214	TC	T	R458fs	0.19	Additional TOPMED - ARIC
DNMT3A	2	25246214	TC	T	R458fs	0.14	COPDGene

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25246202	C	A	E463*	0.23	UK Biobank
DNMT3A	2	25246202	C	A	E463*	0.04	UK Biobank
DNMT3A	2	25246198	TTC	T	E463fs	0.53	COPDGene
DNMT3A	2	25246186	T	C	K468R	0.19	Additional TOPMED - JHS
DNMT3A	2	25246185	C	CT	E469fs	0.06	UK Biobank
DNMT3A	2	25246184	C	A	E469*	0.18	UK Biobank
DNMT3A	2	25246163	T	A	R476*	0.06	UK Biobank
DNMT3A	2	25246162	C	CT	R476fs	0.07	UK Biobank
DNMT3A	2	25246159	C	T	c.1429+1G>A	0.09	COPDGene
DNMT3A	2	25246159	C	A	c.1429+1G>T	0.19	COPDGene
DNMT3A	2	25246159	C	T	c.e11-1G>A	0.16	UK Biobank
DNMT3A	2	25246159	C	T	c.e11-1G>A	0.14	UK Biobank
DNMT3A	2	25246159	C	T	c.e11-1G>A	0.14	UK Biobank
DNMT3A	2	25246159	C	T	c.e11-1G>A	0.11	UK Biobank
DNMT3A	2	25246159	C	T	c.e11-1G>A	0.05	UK Biobank
DNMT3A	2	25246159	C	T	c.e11-1G>A	0.05	UK Biobank
DNMT3A	2	25246159	C	A	c.e11-1G>T	0.16	UK Biobank
DNMT3A	2	25246159	C	T	c.e11-1G>T	0.08	UK Biobank
DNMT3A	2	25246159	C	A	c.e11-1G>T	0.07	UK Biobank
DNMT3A	2	25246066	T	C	c.1430-2A>G	0.23	COPDGene
DNMT3A	2	25246066	T	G	c.e12+2A>C	0.08	UK Biobank
DNMT3A	2	25246066	T	A	c.e12+2A>T	0.13	UK Biobank
DNMT3A	2	25246065	C	A	c.1430-1G>T	0.43	Additional TOPMED - ARIC
DNMT3A	2	25246065	C	T	c.e12+1G>A	0.06	UK Biobank
DNMT3A	2	25246059	GC	G	L479fs	0.05	UK Biobank
DNMT3A	2	25246045	CACCTCGT	C	Y481fs	0.13	UK Biobank
DNMT3A	2	25246042	CCGCACCT	C	E482fs	0.12	Additional TOPMED - FHS
DNMT3A	2	25246041	G	A	Q485*	0.03	UK Biobank
DNMT3A	2	25246041	G	A	Q485X	0.13	Additional TOPMED - ECLIPSE
DNMT3A	2	25246041	G	A	Q485X	0.13	COPDGene
DNMT3A	2	25246037	TTCTGCCGC	T	V483fs	0.18	COPDGene
DNMT3A	2	25246036	CT	C	K486fs	0.13	Additional TOPMED - ARIC
DNMT3A	2	25246036	CT	C	K486fs	0.06	UK Biobank
DNMT3A	2	25246031	CG	C	R488fs	0.17	COPDGene
DNMT3A	2	25246029	TC	T	N489fs	0.10	UK Biobank
DNMT3A	2	25246023	C	CA	E491_D492delinsX	0.16	COPDGene
DNMT3A	2	25246023	C	CA	E491_D492delinsX	0.11	COPDGene
DNMT3A	2	25246023	CA	C	I490fs	0.10	Additional TOPMED - ARIC
DNMT3A	2	25246019	C	T	c.907+1G>A	0.21	Additional TOPMED - FHS
DNMT3A	2	25246019	C	T	c.e12-1G>A	0.31	UK Biobank
DNMT3A	2	25246019	C	T	c.e12-1G>A	0.12	UK Biobank
DNMT3A	2	25246019	C	T	c.e12-1G>A	0.06	UK Biobank
DNMT3A	2	25246019	C	G	c.e12-1G>C	0.34	UK Biobank
DNMT3A	2	25245333	C	A	c.908-1G>T	0.12	Additional TOPMED - ARIC
DNMT3A	2	25245333	C	G	c.e13+1G>C	0.08	UK Biobank
DNMT3A	2	25245326	C	T	C494Y	0.17	COPDGene
DNMT3A	2	25245324	TG	T	C494X	0.14	COPDGene
DNMT3A	2	25245324	TGCAGATGCTGGAAA	T	D492fs	0.17	COPDGene
DNMT3A	2	25245317	C	C	C497Y	0.10	COPDGene
DNMT3A	2	25245317	C	T	C497Y	0.08	COPDGene
DNMT3A	2	25245300	T	TA	T503fs	0.15	UK Biobank
DNMT3A	2	25245299	GT	G	T503fs	0.12	UK Biobank
DNMT3A	2	25245298	GGT	G	T503fs	0.11	UK Biobank
DNMT3A	2	25245294	C	A	E505*	0.09	UK Biobank
DNMT3A	2	25245292	TTCCAGGG	T	T503fs	0.17	COPDGene
DNMT3A	2	25245288	G	GGT	P507fs	0.28	COPDGene
DNMT3A	2	25245276	CA	C	V510fs	0.12	COPDGene
DNMT3A	2	25245275	C	T	G511E	0.23	COPDGene
DNMT3A	2	25245266	CA	C	C514fs	0.20	Additional TOPMED - MESA
DNMT3A	2	25245264	G	A	Q515X	0.12	Additional TOPMED - ARIC
DNMT3A	2	25245252	C	T	c.e13-1G>A	0.10	UK Biobank
DNMT3A	2	25245252	C	T	c.e13-1G>A	0.09	UK Biobank
DNMT3A	2	25244654	T	C	c.e14+2A>G	0.18	UK Biobank
DNMT3A	2	25244654	T	C	c.e14+2A>G	0.09	UK Biobank
DNMT3A	2	25244653	C	G	c.1555-1G>C	0.11	COPDGene
DNMT3A	2	25244651	TTCTAGACAGCAGCGGAAGGG	T	c.e14-1CCCTTCCCGCTGCTGTAGAA>A	0.04	UK Biobank
DNMT3A	2	25244648	C	CA	C520fs	0.16	UK Biobank
DNMT3A	2	25244648	CAG	C	N519fs	0.12	COPDGene
DNMT3A	2	25244640	C	A	E523X	0.20	COPDGene
DNMT3A	2	25244639	TC	T	E523fs	0.05	UK Biobank
DNMT3A	2	25244633	GCA	G	A525fs	0.06	UK Biobank
DNMT3A	2	25244633	GCA	G	C524fs	0.21	Additional TOPMED - JHS
DNMT3A	2	25244633	GCA	G	C524fs	0.14	COPDGene
DNMT3A	2	25244628	G	A	Q527X	0.37	COPDGene
DNMT3A	2	25244627	T	G	Q527P	0.14	UK Biobank
DNMT3A	2	25244623	G	T	Y528*	0.13	UK Biobank
DNMT3A	2	25244622	C	T	D529N	0.16	Additional TOPMED - FHS
DNMT3A	2	25244622	C	T	D529N	0.15	Additional TOPMED - MESA
DNMT3A	2	25244622	C	T	D529N	0.10	UK Biobank
DNMT3A	2	25244621	T	A	D529V	0.10	COPDGene
DNMT3A	2	25244616	C	T	D531N	0.20	UK Biobank
DNMT3A	2	25244613	C	T	G532S	0.23	UK Biobank
DNMT3A	2	25244609	T	C	Y533C	0.31	COPDGene
DNMT3A	2	25244607	G	A	Q534X	0.21	Additional TOPMED - JHS
DNMT3A	2	25244606	TG	T	Q534fs	0.09	UK Biobank
DNMT3A	2	25244601	AG	A	S535fs	0.43	COPDGene
DNMT3A	2	25244601	AG	A	S535fs	0.13	Additional TOPMED - ECLIPSE
DNMT3A	2	25244599	GT	G	Y536fs	0.27	COPDGene
DNMT3A	2	25244599	G	C	Y536X	0.38	Additional TOPMED - FHS
DNMT3A	2	25244597	C	T	C537Y	0.08	UK Biobank
DNMT3A	2	25244596	G	T	C537X	0.15	Additional TOPMED - JHS
DNMT3A	2	25244594	GTGCAGTA	G	Y536fs	0.22	COPDGene
DNMT3A	2	25244589	AGATG	A	I539fs	0.18	UK Biobank
DNMT3A	2	25244582	C	A	G542V	0.15	Additional TOPMED - ARIC
DNMT3A	2	25244580	C	A	G543C	0.31	COPDGene
DNMT3A	2	25244580	C	A	G543C	0.21	Additional TOPMED - JHS
DNMT3A	2	25244580	C	A	G543C	0.19	UK Biobank
DNMT3A	2	25244580	C	A	G543C	0.16	UK Biobank
DNMT3A	2	25244580	C	A	G543C	0.15	Additional TOPMED - FHS

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25244580	C	A	G543C	0.09	UK Biobank
DNMT3A	2	25244580	C	A	G543C	0.08	UK Biobank
DNMT3A	2	25244580	C	A	G543C	0.04	UK Biobank
DNMT3A	2	25244579	C	G	G543A	0.27	UK Biobank
DNMT3A	2	25244579	C	G	G543A	0.23	Additional TOPMED - ECLIPSE
DNMT3A	2	25244579	C	G	G543A	0.09	Additional TOPMED - ARIC
DNMT3A	2	25244579	C	T	G543D	0.13	UK Biobank
DNMT3A	2	25244579	C	A	G543V	0.10	COPDGene
DNMT3A	2	25244579	C	A	G543V	0.05	UK Biobank
DNMT3A	2	25244579	C	A	G543V	0.02	UK Biobank
DNMT3A	2	25244577	GGCCCC	G	G542fs	0.06	UK Biobank
DNMT3A	2	25244568	G	A	L547F	0.44	Additional TOPMED - MESA
DNMT3A	2	25244567	AG	A	L547fs	0.23	COPDGene
DNMT3A	2	25244567	A	C	L547R	0.13	Additional TOPMED - ARIC
DNMT3A	2	25244567	A	C	L547R	0.07	UK Biobank
DNMT3A	2	25244564	A	C	M548R	0.08	UK Biobank
DNMT3A	2	25244563	CAT	C	M548fs	0.17	Additional TOPMED - FHS
DNMT3A	2	25244563	C	T	M548I	0.23	COPDGene
DNMT3A	2	25244559	C	T	G550R	0.47	COPDGene
DNMT3A	2	25244559	C	T	G550R	0.26	UK Biobank
DNMT3A	2	25244559	C	T	G550R	0.20	COPDGene
DNMT3A	2	25244559	C	T	G550R	0.13	COPDGene
DNMT3A	2	25244559	C	T	G550R	0.12	Additional TOPMED - JHS
DNMT3A	2	25244559	C	T	G550R	0.06	Additional TOPMED - JHS
DNMT3A	2	25244559	C	A	G550X	0.17	COPDGene
DNMT3A	2	25244557	TC	T	G550fs	0.07	UK Biobank
DNMT3A	2	25244550	TG	T	N552fs	0.21	Additional TOPMED - ECLIPSE
DNMT3A	2	25244550	TG	T	N552fs	0.12	UK Biobank
DNMT3A	2	25244550	TG	T	N552fs	0.10	UK Biobank
DNMT3A	2	25244547	A	C	C554G	0.08	UK Biobank
DNMT3A	2	25244546	C	T	C554Y	0.09	Additional TOPMED - ECLIPSE
DNMT3A	2	25244541	T	C	R556G	0.27	UK Biobank
DNMT3A	2	25244541	T	C	R556G	0.10	Additional TOPMED - ARIC
DNMT3A	2	25244541	T	C	R556G	0.10	Additional TOPMED - MESA
DNMT3A	2	25244539	C	T	c.1667+1G>A	0.25	COPDGene
DNMT3A	2	25244539	C	T	c.1667+1G>A	0.13	COPDGene
DNMT3A	2	25244539	C	G	c.1667+1G>C	0.17	Additional TOPMED - FHS
DNMT3A	2	25244539	C	T	c.e14-1G>A	0.19	UK Biobank
DNMT3A	2	25244539	C	T	c.e14-1G>A	0.15	UK Biobank
DNMT3A	2	25244539	C	T	c.e14-1G>A	0.13	UK Biobank
DNMT3A	2	25244539	C	T	c.e14-1G>A	0.10	UK Biobank
DNMT3A	2	25244539	C	T	c.e14-1G>A	0.08	UK Biobank
DNMT3A	2	25244539	C	A	c.e14-1G>T	0.20	UK Biobank
DNMT3A	2	25244538	A	T	c.e14-2T>A	0.31	UK Biobank
DNMT3A	2	25244339	C	G	c.1101-1G>C	0.40	Additional TOPMED - ECLIPSE
DNMT3A	2	25244339	C	T	c.e15+1G>A	0.27	UK Biobank
DNMT3A	2	25244339	C	T	c.e15+1G>A	0.20	UK Biobank
DNMT3A	2	25244338	C	A	R556S	0.12	UK Biobank
DNMT3A	2	25244338	C	A	R556S	0.09	Additional TOPMED - FHS
DNMT3A	2	25244336	C	T	C557Y	0.14	UK Biobank
DNMT3A	2	25244336	C	T	C557Y	0.08	UK Biobank
DNMT3A	2	25244331	A	G	C559R	0.21	UK Biobank
DNMT3A	2	25244330	CA	C	C559fs	0.12	UK Biobank
DNMT3A	2	25244329	GCAAAGCAC	G	556 559RCFC>S	0.05	UK Biobank
DNMT3A	2	25244325	C	A	E561*	0.10	UK Biobank
DNMT3A	2	25244322	AC	A	E561fs	0.03	UK Biobank
DNMT3A	2	25244321	C	A	C562F	0.09	UK Biobank
DNMT3A	2	25244321	C	A	C562F	0.08	UK Biobank
DNMT3A	2	25244321	C	G	C562S	0.07	UK Biobank
DNMT3A	2	25244321	C	T	C562Y	0.23	Additional TOPMED - JHS
DNMT3A	2	25244321	C	T	C562Y	0.18	UK Biobank
DNMT3A	2	25244319	C	T	V563M	0.27	UK Biobank
DNMT3A	2	25244319	C	T	V563M	0.17	COPDGene
DNMT3A	2	25244315	TC	T	D564fs	0.04	UK Biobank
DNMT3A	2	25244303	CCCA	C	V567del	0.03	UK Biobank
DNMT3A	2	25244301	GC	G	G568fs	0.21	Additional TOPMED - FHS
DNMT3A	2	25244294	GC	G	A571fs	0.17	UK Biobank
DNMT3A	2	25244294	GCC	G	A571fs	0.11	UK Biobank
DNMT3A	2	25244290	GGCA	G	A572del	0.08	UK Biobank
DNMT3A	2	25244289	G	A	Q573*	0.07	UK Biobank
DNMT3A	2	25244289	G	A	Q573*	0.05	UK Biobank
DNMT3A	2	25244289	G	A	Q573*	0.05	UK Biobank
DNMT3A	2	25244289	G	A	Q573*	0.03	UK Biobank
DNMT3A	2	25244287	CTGGGCAG	C	A571fs	0.16	UK Biobank
DNMT3A	2	25244285	GC	G	A574fs	0.11	UK Biobank
DNMT3A	2	25244284	TG	T	A574fs	0.06	UK Biobank
DNMT3A	2	25244284	TGCCTGGGCA	T	AQA572del	0.15	UK Biobank
DNMT3A	2	25244284	TGCCTGGGCA	T	AQA572del	0.08	UK Biobank
DNMT3A	2	25244283	C	G	A575P	0.23	UK Biobank
DNMT3A	2	25244283	C	G	A575P	0.21	UK Biobank
DNMT3A	2	25244283	C	G	A575P	0.07	UK Biobank
DNMT3A	2	25244279	ATGGCTGCCTGGGCAGC	A	A571fs	0.04	UK Biobank
DNMT3A	2	25244270	TCTCCCTAATGGCTGC	T	A574fs	0.15	UK Biobank
DNMT3A	2	25244265	AG	A	W581fs	0.34	UK Biobank
DNMT3A	2	25244265	AG	A	W581fs	0.10	UK Biobank
DNMT3A	2	25244265	AG	A	W581fs	0.09	UK Biobank
DNMT3A	2	25244265	A	G	W581R	0.20	Additional TOPMED - MESA
DNMT3A	2	25244264	C	T	W581*	0.06	UK Biobank
DNMT3A	2	25244263	C	T	W581*	0.09	UK Biobank
DNMT3A	2	25244263	C	T	W581*	0.03	UK Biobank
DNMT3A	2	25244263	C	G	W581C	0.30	Additional TOPMED - FHS
DNMT3A	2	25244263	C	A	W581C	0.22	COPDGene
DNMT3A	2	25244263	C	G	W581C	0.18	UK Biobank
DNMT3A	2	25244263	C	A	W581C	0.16	UK Biobank
DNMT3A	2	25244263	C	G	W581C	0.14	COPDGene
DNMT3A	2	25244263	C	G	W581C	0.13	UK Biobank
DNMT3A	2	25244263	C	A	W581C	0.03	UK Biobank
DNMT3A	2	25244259	A	T	C583S	0.07	UK Biobank
DNMT3A	2	25244257	G	T	C583*	0.26	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25244257	G	T	C583*	0.07	UK Biobank
DNMT3A	2	25244253	TG	T	Y584X	0.15	Additional TOPMED - FHS
DNMT3A	2	25244251	CA	C	M585fs	0.13	Additional TOPMED - FHS
DNMT3A	2	25244250	A	AC	C586fs	0.22	COPDGene
DNMT3A	2	25244250	A	G	C586R	0.13	Additional TOPMED - ARIC
DNMT3A	2	25244249	C	CA	C586fs	0.25	Additional TOPMED - ARIC
DNMT3A	2	25244248	G	T	C586*	0.07	UK Biobank
DNMT3A	2	25244248	G	T	C586*	0.04	UK Biobank
DNMT3A	2	25244243	TG	T	H588fs	0.04	UK Biobank
DNMT3A	2	25244239	CT	C	K589fs	0.22	UK Biobank
DNMT3A	2	25244229	C	T	G593R	0.46	UK Biobank
DNMT3A	2	25244222	A	G	L595P	0.17	Additional TOPMED - ECLIPSE
DNMT3A	2	25244222	A	G	L595P	0.05	UK Biobank
DNMT3A	2	25244222	A	C	L595R	0.43	UK Biobank
DNMT3A	2	25244221	CA	C	L595fs	0.26	Additional TOPMED - ECLIPSE
DNMT3A	2	25244220	G	A	R596W	0.03	UK Biobank
DNMT3A	2	25244214	G	A	R598*	0.22	UK Biobank
DNMT3A	2	25244214	G	A	R598*	0.17	UK Biobank
DNMT3A	2	25244214	G	A	R598*	0.13	UK Biobank
DNMT3A	2	25244214	G	A	R598*	0.06	UK Biobank
DNMT3A	2	25244214	G	A	R598*	0.04	UK Biobank
DNMT3A	2	25244214	G	A	R598*	0.04	UK Biobank
DNMT3A	2	25244214	G	A	R598X	0.33	Additional TOPMED - JHS
DNMT3A	2	25244214	G	A	R598X	0.17	COPDGene
DNMT3A	2	25244214	G	A	R598X	0.14	COPDGene
DNMT3A	2	25244214	G	A	R598X	0.09	Additional TOPMED - ARIC
DNMT3A	2	25244211	C	A	E599*	0.09	UK Biobank
DNMT3A	2	25244209	CT	C	E599fs	0.02	UK Biobank
DNMT3A	2	25244204	C	T	W601*	0.05	UK Biobank
DNMT3A	2	25244195	CG	C	R604fs	0.22	UK Biobank
DNMT3A	2	25244195	C	T	R604Q	0.10	UK Biobank
DNMT3A	2	25244190	G	A	Q606*	0.07	UK Biobank
DNMT3A	2	25244190	G	A	Q606*	0.03	UK Biobank
DNMT3A	2	25244190	G	A	Q606*	0.03	UK Biobank
DNMT3A	2	25244190	G	A	Q606*	0.03	UK Biobank
DNMT3A	2	25244179	GAA	G	F609fs	0.02	UK Biobank
DNMT3A	2	25244163	G	A	Q615X	0.14	Additional TOPMED - ECLIPSE
DNMT3A	2	25244162	TG	T	Q615fs	0.13	UK Biobank
DNMT3A	2	25244160	C	A	E616X	0.19	Additional TOPMED - MESA
DNMT3A	2	25244159	TCC	T	Q615fs	0.21	Additional TOPMED - ECLIPSE
DNMT3A	2	25244154	C	T	c.1851+1G>A	0.09	COPDGene
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.10	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.08	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.07	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.05	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.04	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.04	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.03	UK Biobank
DNMT3A	2	25244154	C	T	c.e15-1G>A	0.03	UK Biobank
DNMT3A	2	25244154	CA	C	c.e15-1TG>G	0.19	UK Biobank
DNMT3A	2	25244154	CA	C	c.e15-1TG>G	0.04	UK Biobank
DNMT3A	2	25244153	A	T	c.e15-2T>A	0.06	UK Biobank
DNMT3A	2	25244153	A	C	c.e15-2T>G	0.40	UK Biobank
DNMT3A	2	25243983	C	T	c.e16+1G>A	0.08	UK Biobank
DNMT3A	2	25243965	G	C	Y623*	0.05	UK Biobank
DNMT3A	2	25243953	TG	T	P627fs	0.10	UK Biobank
DNMT3A	2	25243946	T	A	K630X	0.17	COPDGene
DNMT3A	2	25243942	C	G	R631T	0.07	UK Biobank
DNMT3A	2	25243936	G	T	P633H	0.05	UK Biobank
DNMT3A	2	25243936	G	A	P633L	0.13	Additional TOPMED - MESA
DNMT3A	2	25243936	G	A	P633L	0.05	UK Biobank
DNMT3A	2	25243936	G	A	P633L	0.05	UK Biobank
DNMT3A	2	25243934	T	A	I634F	0.26	UK Biobank
DNMT3A	2	25243934	T	A	I634F	0.16	COPDGene
DNMT3A	2	25243933	A	G	I634T	0.25	COPDGene
DNMT3A	2	25243933	A	G	I634T	0.16	UK Biobank
DNMT3A	2	25243933	A	G	I634T	0.04	UK Biobank
DNMT3A	2	25243931	G	C	R635G	0.18	UK Biobank
DNMT3A	2	25243931	G	C	R635G	0.10	UK Biobank
DNMT3A	2	25243931	G	C	R635G	0.06	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.35	COPDGene
DNMT3A	2	25243931	G	A	R635W	0.33	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.29	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.25	COPDGene
DNMT3A	2	25243931	G	A	R635W	0.20	Additional TOPMED - JHS
DNMT3A	2	25243931	G	A	R635W	0.19	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.16	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.16	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.13	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.12	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.06	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.06	UK Biobank
DNMT3A	2	25243931	G	A	R635W	0.05	UK Biobank
DNMT3A	2	25243930	C	A	R635L	0.21	Additional TOPMED - FHS
DNMT3A	2	25243930	C	G	R635P	0.35	Additional TOPMED - FHS
DNMT3A	2	25243930	C	G	R635P	0.12	UK Biobank
DNMT3A	2	25243930	C	G	R635P	0.09	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.50	Additional TOPMED - ARIC
DNMT3A	2	25243930	C	T	R635Q	0.26	COPDGene
DNMT3A	2	25243930	C	T	R635Q	0.25	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.20	COPDGene
DNMT3A	2	25243930	C	T	R635Q	0.17	Additional TOPMED - ECLIPSE
DNMT3A	2	25243930	C	T	R635Q	0.10	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.04	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.04	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.03	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.03	UK Biobank
DNMT3A	2	25243930	C	T	R635Q	0.03	UK Biobank
DNMT3A	2	25243928	C	A	V636L	0.13	COPDGene

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25243928	C	A	V636L	0.08	UK Biobank
DNMT3A	2	25243928	C	A	V636L	0.04	UK Biobank
DNMT3A	2	25243928	C	T	V636M	0.37	Additional TOPMED - MESA
DNMT3A	2	25243928	C	T	V636M	0.30	Additional TOPMED - MESA
DNMT3A	2	25243928	C	T	V636M	0.13	Additional TOPMED - MESA
DNMT3A	2	25243928	C	T	V636M	0.11	COPDGene
DNMT3A	2	25243928	C	T	V636M	0.10	UK Biobank
DNMT3A	2	25243928	C	T	V636M	0.09	UK Biobank
DNMT3A	2	25243928	C	T	V636M	0.06	Additional TOPMED - ARIC
DNMT3A	2	25243928	C	T	V636M	0.05	UK Biobank
DNMT3A	2	25243927	A	T	V636E	0.04	UK Biobank
DNMT3A	2	25243924	A	G	L637P	0.29	Additional TOPMED - MESA
DNMT3A	2	25243924	A	T	L637Q	0.27	UK Biobank
DNMT3A	2	25243924	A	T	L637Q	0.21	COPDGene
DNMT3A	2	25243924	A	T	L637Q	0.09	UK Biobank
DNMT3A	2	25243924	A	C	L637R	0.49	UK Biobank
DNMT3A	2	25243924	A	C	L637R	0.27	Additional TOPMED - ARIC
DNMT3A	2	25243924	A	C	L637R	0.14	Additional TOPMED - ARIC
DNMT3A	2	25243922	AC	A	S638fs	0.07	UK Biobank
DNMT3A	2	25243921	G	A	S638F	0.30	UK Biobank
DNMT3A	2	25243921	G	T	S638Y	0.27	UK Biobank
DNMT3A	2	25243920	AG	A	S638fs	0.08	Additional TOPMED - JHS
DNMT3A	2	25243919	G	A	L639F	0.04	UK Biobank
DNMT3A	2	25243917	GA	G	L639fs	0.13	UK Biobank
DNMT3A	2	25243916	A	G	F640L	0.05	UK Biobank
DNMT3A	2	25243913	C	A	D641Y	0.13	UK Biobank
DNMT3A	2	25243913	C	A	D641Y	0.06	UK Biobank
DNMT3A	2	25243910	C	T	G642R	0.09	UK Biobank
DNMT3A	2	25243907	T	TTCCA	I643fs	0.28	UK Biobank
DNMT3A	2	25243906	A	G	I643T	0.18	UK Biobank
DNMT3A	2	25243905	G	GA	A644fs	0.15	UK Biobank
DNMT3A	2	25243905	GA	G	I643fs	0.04	UK Biobank
DNMT3A	2	25243897	C	G	c.1369+1G>C	0.18	Additional TOPMED - MESA
DNMT3A	2	25243897	C	T	c.e16-1G>A	0.15	UK Biobank
DNMT3A	2	25241709	T	C	c.e17+2A>G	0.07	UK Biobank
DNMT3A	2	25241708	C	T	c.1937-1G>A	0.20	COPDGene
DNMT3A	2	25241708	C	G	c.1937-1G>C	0.13	Additional TOPMED - JHS
DNMT3A	2	25241708	C	G	c.1937-1G>C	0.12	Additional TOPMED - JHS
DNMT3A	2	25241708	C	T	c.e17+1G>A	0.47	UK Biobank
DNMT3A	2	25241708	C	T	c.e17+1G>A	0.11	UK Biobank
DNMT3A	2	25241708	C	T	c.e17+1G>A	0.04	UK Biobank
DNMT3A	2	25241707	CC	AA	c.e17+0GG>TT	0.40	UK Biobank
DNMT3A	2	25241707	C	T	G646E	0.11	COPDGene
DNMT3A	2	25241705	G	T	L647I	0.04	UK Biobank
DNMT3A	2	25241704	A	T	L647H	0.11	COPDGene
DNMT3A	2	25241704	A	G	L647P	0.13	UK Biobank
DNMT3A	2	25241704	A	G	L647P	0.06	UK Biobank
DNMT3A	2	25241704	A	G	L647P	0.04	UK Biobank
DNMT3A	2	25241704	A	C	L647R	0.42	COPDGene
DNMT3A	2	25241704	A	C	L647R	0.16	Additional TOPMED - ECLIPSE
DNMT3A	2	25241704	A	C	L647R	0.06	UK Biobank
DNMT3A	2	25241699	C	G	V649L	0.03	UK Biobank
DNMT3A	2	25241699	C	T	V649M	0.10	UK Biobank
DNMT3A	2	25241699	C	T	V649M	0.08	UK Biobank
DNMT3A	2	25241697	CA	C	V649fs	0.09	UK Biobank
DNMT3A	2	25241695	A	G	L650P	0.10	UK Biobank
DNMT3A	2	25241695	A	T	L650Q	0.05	UK Biobank
DNMT3A	2	25241695	A	C	L650R	0.06	UK Biobank
DNMT3A	2	25241694	C	CA	K651fs	0.34	UK Biobank
DNMT3A	2	25241691	CT	C	K651fs	0.32	UK Biobank
DNMT3A	2	25241688	GT	G	D652fs	0.04	UK Biobank
DNMT3A	2	25241687	AG	A	L653fs	0.07	UK Biobank
DNMT3A	2	25241687	A	C	L653V	0.08	UK Biobank
DNMT3A	2	25241686	A	G	L653S	0.05	UK Biobank
DNMT3A	2	25241686	A	G	L653S	0.04	UK Biobank
DNMT3A	2	25241686	A	C	L653W	0.20	COPDGene
DNMT3A	2	25241686	A	C	L653W	0.12	Additional TOPMED - MESA
DNMT3A	2	25241686	A	T	L653X	0.36	COPDGene
DNMT3A	2	25241685	C	G	L653F	0.06	UK Biobank
DNMT3A	2	25241684	C	T	G654S	0.04	UK Biobank
DNMT3A	2	25241678	G	A	Q656*	0.06	UK Biobank
DNMT3A	2	25241675	C	T	V657M	0.21	COPDGene
DNMT3A	2	25241675	C	T	V657M	0.16	UK Biobank
DNMT3A	2	25241675	C	T	V657M	0.09	Additional TOPMED - MESA
DNMT3A	2	25241675	C	T	V657M	0.05	UK Biobank
DNMT3A	2	25241675	C	T	V657M	0.04	UK Biobank
DNMT3A	2	25241675	C	T	V657M	0.03	UK Biobank
DNMT3A	2	25241675	C	T	V657M	0.03	UK Biobank
DNMT3A	2	25241672	CC	AA	D658Y	0.04	UK Biobank
DNMT3A	2	25241670	G	T	D658E	0.04	UK Biobank
DNMT3A	2	25241669	G	C	R659G	0.24	Additional TOPMED - JHS
DNMT3A	2	25241668	C	T	R659H	0.19	UK Biobank
DNMT3A	2	25241668	C	T	R659H	0.11	UK Biobank
DNMT3A	2	25241668	C	T	R659H	0.09	Additional TOPMED - FHS
DNMT3A	2	25241666	A	C	Y660D	0.12	Additional TOPMED - FHS
DNMT3A	2	25241666	A	G	Y660H	0.11	UK Biobank
DNMT3A	2	25241666	A	G	Y660H	0.11	Additional TOPMED - ECLIPSE
DNMT3A	2	25241666	A	G	Y660H	0.03	UK Biobank
DNMT3A	2	25241665	T	C	Y660C	0.06	UK Biobank
DNMT3A	2	25241665	T	C	Y660C	0.05	UK Biobank
DNMT3A	2	25241665	T	G	Y660S	0.07	UK Biobank
DNMT3A	2	25241662	A	T	I661N	0.15	UK Biobank
DNMT3A	2	25241662	A	C	I661S	0.23	UK Biobank
DNMT3A	2	25241656	G	C	S663W	0.13	Additional TOPMED - MESA
DNMT3A	2	25241655	CGAGGCAAT	C	I661fs	0.28	COPDGene
DNMT3A	2	25241651	C	T	V665M	0.10	UK Biobank
DNMT3A	2	25241650	A	C	V665G	0.32	UK Biobank
DNMT3A	2	25241644	TCA	T	C666fs	0.06	UK Biobank
DNMT3A	2	25241641	TC	T	D668fs	0.06	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25241638	G	A	S669F	0.08	UK Biobank
DNMT3A	2	25241638	G	A	S669F	0.02	UK Biobank
DNMT3A	2	25241638	G	T	S669Y	0.21	UK Biobank
DNMT3A	2	25241636	T	TG	I670fs	0.24	UK Biobank
DNMT3A	2	25241621	C	T	V675M	0.28	Additional TOPMED - CFS
DNMT3A	2	25241621	C	T	V675M	0.05	UK Biobank
DNMT3A	2	25241618	G	C	R676G	0.11	UK Biobank
DNMT3A	2	25241618	G	A	R676W	0.05	UK Biobank
DNMT3A	2	25241618	G	A	R676W	0.04	UK Biobank
DNMT3A	2	25241618	G	A	R676W	0.03	UK Biobank
DNMT3A	2	25241618	G	A	R676W	0.03	UK Biobank
DNMT3A	2	25241616	C	CCG	R676fs	0.13	Additional TOPMED - ECLIPSE
DNMT3A	2	25241612	G	A	Q678X	0.14	COPDGene
DNMT3A	2	25241606	TC	T	K680fs	0.18	UK Biobank
DNMT3A	2	25241604	C	G	K680N	0.04	UK Biobank
DNMT3A	2	25241601	G	C	I681M	0.08	UK Biobank
DNMT3A	2	25241600	TG	T	I681fs	0.45	Additional TOPMED - ECLIPSE
DNMT3A	2	25241600	TG	T	M682fs	0.06	UK Biobank
DNMT3A	2	25241597	A	C	Y683D	0.15	COPDGene
DNMT3A	2	25241595	G	T	Y683*	0.06	UK Biobank
DNMT3A	2	25241595	G	T	Y683*	0.02	UK Biobank
DNMT3A	2	25241594	C	A	V684F	0.07	Additional TOPMED - ARIC
DNMT3A	2	25241593	A	T	V684D	0.06	UK Biobank
DNMT3A	2	25241591	C	G	G685R	0.16	COPDGene
DNMT3A	2	25241591	C	G	G685R	0.06	UK Biobank
DNMT3A	2	25241591	C	T	G685R	0.04	UK Biobank
DNMT3A	2	25241591	C	T	G685R	0.04	UK Biobank
DNMT3A	2	25241591	C	T	G685R	0.04	UK Biobank
DNMT3A	2	25241591	C	T	G685R	0.03	UK Biobank
DNMT3A	2	25241591	C	A	G685W	0.05	UK Biobank
DNMT3A	2	25241590	C	T	G685E	0.12	UK Biobank
DNMT3A	2	25241590	C	T	G685E	0.10	UK Biobank
DNMT3A	2	25241590	C	T	G685E	0.06	UK Biobank
DNMT3A	2	25241588	C	G	D686H	0.06	UK Biobank
DNMT3A	2	25241587	T	C	D686G	0.11	UK Biobank
DNMT3A	2	25241587	T	A	D686V	0.23	Additional TOPMED - FHS
DNMT3A	2	25241586	G	C	D686E	0.10	UK Biobank
DNMT3A	2	25241586	G	T	D686E	0.03	UK Biobank
DNMT3A	2	25241585	C	A	V687F	0.17	Additional TOPMED - MESA
DNMT3A	2	25241585	C	A	V687F	0.12	COPDGene
DNMT3A	2	25241585	C	A	V687F	0.03	UK Biobank
DNMT3A	2	25241582	G	A	R688C	0.15	UK Biobank
DNMT3A	2	25241582	G	A	R688C	0.14	COPDGene
DNMT3A	2	25241582	G	A	R688C	0.04	UK Biobank
DNMT3A	2	25241582	G	A	R688C	0.03	UK Biobank
DNMT3A	2	25241582	G	T	R688S	0.04	UK Biobank
DNMT3A	2	25241581	C	T	R688H	0.20	COPDGene
DNMT3A	2	25241581	C	T	R688H	0.14	COPDGene
DNMT3A	2	25241581	C	T	R688H	0.11	Additional TOPMED - MESA
DNMT3A	2	25241581	C	T	R688H	0.10	Additional TOPMED - ARIC
DNMT3A	2	25241581	C	T	R688H	0.08	COPDGene
DNMT3A	2	25241581	C	T	R688H	0.04	UK Biobank
DNMT3A	2	25241581	C	A	R688L	0.25	UK Biobank
DNMT3A	2	25241576	C	A	V690F	0.11	UK Biobank
DNMT3A	2	25241575	A	C	V690G	0.11	Additional TOPMED - MESA
DNMT3A	2	25241575	A	C	V690G	0.05	UK Biobank
DNMT3A	2	25241572	G	A	T691I	0.23	COPDGene
DNMT3A	2	25241568	CTG	C	Q692fs	0.15	Additional TOPMED - MESA
DNMT3A	2	25241567	T	A	K693*	0.04	UK Biobank
DNMT3A	2	25241565	C	CTTA	692_693insN	0.10	UK Biobank
DNMT3A	2	25241564	G	A	H694Y	0.10	COPDGene
DNMT3A	2	25241561	C	T	c.e17-1G>A	0.07	UK Biobank
DNMT3A	2	25241560	A	G	c.1515+2T>C	0.25	Additional TOPMED - MESA
DNMT3A	2	25240732	T	C	c.1516-2A>G	0.09	COPDGene
DNMT3A	2	25240731	C	G	c.1516-1G>C	0.16	Additional TOPMED - MESA
DNMT3A	2	25240731	C	G	c.e18+1G>C	0.39	UK Biobank
DNMT3A	2	25240726	TG	T	Q696fs	0.25	Additional TOPMED - ECLIPSE
DNMT3A	2	25240726	TG	T	Q696fs	0.22	Additional TOPMED - JHS
DNMT3A	2	25240726	TG	T	Q696fs	0.09	Additional TOPMED - ECLIPSE
DNMT3A	2	25240720	C	G	W698S	0.16	UK Biobank
DNMT3A	2	25240720	C	G	W698S	0.14	UK Biobank
DNMT3A	2	25240720	C	G	W698S	0.06	UK Biobank
DNMT3A	2	25240719	C	T	W698*	0.06	UK Biobank
DNMT3A	2	25240719	C	G	W698C	0.12	COPDGene
DNMT3A	2	25240719	C	T	W698X	0.18	Additional TOPMED - MESA
DNMT3A	2	25240718	C	G	G699R	0.23	COPDGene
DNMT3A	2	25240718	C	T	G699S	0.28	Additional TOPMED - ECLIPSE
DNMT3A	2	25240718	C	T	G699S	0.17	COPDGene
DNMT3A	2	25240717	C	C	G699D	0.41	COPDGene
DNMT3A	2	25240717	C	T	G699D	0.21	UK Biobank
DNMT3A	2	25240717	C	T	G699D	0.15	Additional TOPMED - JHS
DNMT3A	2	25240717	C	T	G699D	0.15	UK Biobank
DNMT3A	2	25240717	C	T	G699D	0.08	COPDGene
DNMT3A	2	25240717	C	A	G699V	0.05	UK Biobank
DNMT3A	2	25240716	GC	G	G699fs	0.24	COPDGene
DNMT3A	2	25240716	GC	G	G699fs	0.06	UK Biobank
DNMT3A	2	25240715	G	C	P700A	0.17	COPDGene
DNMT3A	2	25240715	G	T	P700T	0.21	Additional TOPMED - JHS
DNMT3A	2	25240714	G	A	P700L	0.35	COPDGene
DNMT3A	2	25240714	G	A	P700L	0.07	UK Biobank
DNMT3A	2	25240714	G	C	P700R	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25240710	G	GA	F701fs	0.51	COPDGene
DNMT3A	2	25240708	T	C	D702G	0.13	UK Biobank
DNMT3A	2	25240708	T	A	D702V	0.08	COPDGene
DNMT3A	2	25240706	G	C	L703V	0.11	COPDGene
DNMT3A	2	25240705	A	G	L703P	0.08	UK Biobank
DNMT3A	2	25240702	A	G	V704A	0.17	COPDGene
DNMT3A	2	25240699	A	T	I705N	0.07	UK Biobank
DNMT3A	2	25240699	A	T	I705N	0.06	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25240699	A	C	I705S	0.06	COPDGene
DNMT3A	2	25240699	A	G	I705T	0.16	UK Biobank
DNMT3A	2	25240699	A	G	I705T	0.08	Additional TOPMED - FHS
DNMT3A	2	25240699	A	G	I705T	0.06	UK Biobank
DNMT3A	2	25240699	A	G	I705T	0.05	UK Biobank
DNMT3A	2	25240699	A	G	I705T	0.05	UK Biobank
DNMT3A	2	25240697	C	A	G706W	0.11	Additional TOPMED - FHS
DNMT3A	2	25240697	CA	C	I705fs	0.21	UK Biobank
DNMT3A	2	25240697	CA	C	I705fs	0.13	COPDGene
DNMT3A	2	25240697	CA	C	I705fs	0.10	COPDGene
DNMT3A	2	25240696	C	T	G706E	0.19	Additional TOPMED - ARIC
DNMT3A	2	25240696	C	T	G706E	0.12	COPDGene
DNMT3A	2	25240693	C	T	G707D	0.19	COPDGene
DNMT3A	2	25240693	C	T	G707D	0.13	Additional TOPMED - ARIC
DNMT3A	2	25240693	C	T	G707D	0.11	UK Biobank
DNMT3A	2	25240693	C	T	G707D	0.04	UK Biobank
DNMT3A	2	25240692	GC	G	G707fs	0.21	COPDGene
DNMT3A	2	25240692	GC	G	G707fs	0.10	UK Biobank
DNMT3A	2	25240692	GC	G	G707fs	0.05	UK Biobank
DNMT3A	2	25240692	GCC	G	G707fs	0.05	UK Biobank
DNMT3A	2	25240685	A	T	C710S	0.40	UK Biobank
DNMT3A	2	25240683	G	T	C710*	0.22	UK Biobank
DNMT3A	2	25240678	TCATTGCAGGGACTGCC	T	G707fs	0.04	UK Biobank
DNMT3A	2	25240677	G	GT	D712fs	0.06	UK Biobank
DNMT3A	2	25240675	A	AC	L713fs	0.15	COPDGene
DNMT3A	2	25240674	GA	LM	L713fs	0.12	Additional TOPMED - MESA
DNMT3A	2	25240672	G	C	S714C	0.22	UK Biobank
DNMT3A	2	25240672	G	C	S714C	0.16	Additional TOPMED - CFS
DNMT3A	2	25240672	G	C	S714C	0.13	Additional TOPMED - ECLIPSE
DNMT3A	2	25240672	G	C	S714C	0.12	Additional TOPMED - JHS
DNMT3A	2	25240672	G	C	S714C	0.11	UK Biobank
DNMT3A	2	25240672	G	C	S714C	0.07	UK Biobank
DNMT3A	2	25240672	G	C	S714C	0.04	UK Biobank
DNMT3A	2	25240670	T	TG	I715fs	0.07	UK Biobank
DNMT3A	2	25240669	ATGGAGAGG	A	L713fs	0.18	UK Biobank
DNMT3A	2	25240668	GAT	G	I715fs	0.13	UK Biobank
DNMT3A	2	25240667	C	T	V716I	0.30	UK Biobank
DNMT3A	2	25240667	C	T	V716I	0.17	UK Biobank
DNMT3A	2	25240667	C	T	V716I	0.15	COPDGene
DNMT3A	2	25240667	C	T	V716I	0.10	COPDGene
DNMT3A	2	25240667	C	T	V716I	0.05	UK Biobank
DNMT3A	2	25240666	A	T	V716D	0.27	Additional TOPMED - JHS
DNMT3A	2	25240666	A	T	V716D	0.21	COPDGene
DNMT3A	2	25240663	T	A	N717I	0.12	COPDGene
DNMT3A	2	25240663	T	A	N717S	0.05	UK Biobank
DNMT3A	2	25240649	C	CCTTGCGA	G722fs	0.15	COPDGene
DNMT3A	2	25240641	G	T	Y724*	0.18	UK Biobank
DNMT3A	2	25240640	C	T	E725K	0.13	Additional TOPMED - JHS
DNMT3A	2	25240639	C	T	c.1606+1G>A	0.15	Additional TOPMED - ARIC
DNMT3A	2	25240639	C	T	c.1606+1G>A	0.11	Additional TOPMED - ECLIPSE
DNMT3A	2	25240639	C	T	c.2173+1G>A	0.15	COPDGene
DNMT3A	2	25240639	C	T	c.e18-1G>A	0.09	UK Biobank
DNMT3A	2	25240639	C	T	c.e18-1G>A	0.09	UK Biobank
DNMT3A	2	25240638	AC	A	c.1606+1G>-	0.11	Additional TOPMED - CFS
DNMT3A	2	25240638	AC	A	c.e18-2GT>T	0.31	UK Biobank
DNMT3A	2	25240452	T	C	c.e19+2A>G	0.06	UK Biobank
DNMT3A	2	25240452	T	C	c.e19+2A>G	0.06	UK Biobank
DNMT3A	2	25240451	T	T	c.e19+1G>A	0.08	UK Biobank
DNMT3A	2	25240448	CCT	C	E725fs	0.10	Additional TOPMED - MESA
DNMT3A	2	25240447	C	A	G726V	0.13	COPDGene
DNMT3A	2	25240440	GC	G	G728fs	0.16	COPDGene
DNMT3A	2	25240439	G	C	R729G	0.18	UK Biobank
DNMT3A	2	25240439	G	C	R729G	0.17	UK Biobank
DNMT3A	2	25240439	G	C	R729G	0.16	COPDGene
DNMT3A	2	25240439	G	C	R729G	0.12	Additional TOPMED - JHS
DNMT3A	2	25240439	G	A	R729W	0.25	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.24	COPDGene
DNMT3A	2	25240439	G	A	R729W	0.23	COPDGene
DNMT3A	2	25240439	G	A	R729W	0.20	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.14	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.13	COPDGene
DNMT3A	2	25240439	G	A	R729W	0.12	COPDGene
DNMT3A	2	25240439	G	A	R729W	0.10	Additional TOPMED - FHS
DNMT3A	2	25240439	G	A	R729W	0.09	Additional TOPMED - JHS
DNMT3A	2	25240439	G	A	R729W	0.07	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.07	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.05	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.05	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.05	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.04	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.03	UK Biobank
DNMT3A	2	25240439	G	A	R729W	0.03	UK Biobank
DNMT3A	2	25240438	C	G	R729P	0.11	UK Biobank
DNMT3A	2	25240438	C	T	R729Q	0.45	Additional TOPMED - MESA
DNMT3A	2	25240438	C	T	R729Q	0.32	UK Biobank
DNMT3A	2	25240438	C	T	R729Q	0.11	Additional TOPMED - ARIC
DNMT3A	2	25240438	C	T	R729Q	0.10	UK Biobank
DNMT3A	2	25240438	C	T	R729Q	0.10	COPDGene
DNMT3A	2	25240438	C	T	R729Q	0.09	Additional TOPMED - FHS
DNMT3A	2	25240438	C	T	R729Q	0.06	UK Biobank
DNMT3A	2	25240438	C	T	R729Q	0.05	UK Biobank
DNMT3A	2	25240438	C	T	R729Q	0.04	UK Biobank
DNMT3A	2	25240438	C	T	R729Q	0.03	UK Biobank
DNMT3A	2	25240435	A	G	L730P	0.06	UK Biobank
DNMT3A	2	25240434	GAGCCGGCC	G	G728fs	0.16	UK Biobank
DNMT3A	2	25240433	A	G	F731L	0.24	COPDGene
DNMT3A	2	25240433	A	G	F731L	0.13	Additional TOPMED - MESA
DNMT3A	2	25240433	A	G	F731L	0.03	UK Biobank
DNMT3A	2	25240432	A	C	F731C	0.03	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25240432	A	C	F731C	0.03	UK Biobank
DNMT3A	2	25240432	A	T	F731Y	0.11	UK Biobank
DNMT3A	2	25240431	G	C	F731L	0.17	UK Biobank
DNMT3A	2	25240431	G	T	F731L	0.10	Additional TOPMED - MESA
DNMT3A	2	25240430	A	G	F732L	0.14	COPDGene
DNMT3A	2	25240429	A	C	F732C	0.22	COPDGene
DNMT3A	2	25240429	A	C	F732C	0.03	UK Biobank
DNMT3A	2	25240429	A	C	F732C	0.03	UK Biobank
DNMT3A	2	25240429	A	G	F732S	0.16	UK Biobank
DNMT3A	2	25240429	A	G	F732S	0.12	UK Biobank
DNMT3A	2	25240429	A	G	F732S	0.09	Additional TOPMED - FHS
DNMT3A	2	25240428	AAAG	A	731_732del	0.22	Additional TOPMED - FHS
DNMT3A	2	25240428	AAAG	A	731_732del	0.20	COPDGene
DNMT3A	2	25240428	AAAG	A	732_732del	0.12	Additional TOPMED - ARIC
DNMT3A	2	25240428	AAAG	A	F732del	0.14	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.10	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.07	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.06	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.06	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.05	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.04	UK Biobank
DNMT3A	2	25240428	AAAG	A	F732del	0.03	UK Biobank
DNMT3A	2	25240427	C	CA	E733_F734delinsX	0.17	COPDGene
DNMT3A	2	25240427	C	CA	E733fs	0.24	UK Biobank
DNMT3A	2	25240427	C	CA	E733fs	0.09	UK Biobank
DNMT3A	2	25240427	C	CA	E733fs	0.06	UK Biobank
DNMT3A	2	25240427	C	CA	E733fs	0.04	UK Biobank
DNMT3A	2	25240427	C	T	E733K	0.04	UK Biobank
DNMT3A	2	25240427	C	G	E733Q	0.06	UK Biobank
DNMT3A	2	25240427	CAAAG	C	F731fs	0.03	UK Biobank
DNMT3A	2	25240427	CAAAG	C	F732del	0.03	UK Biobank
DNMT3A	2	25240426	T	A	E733V	0.15	UK Biobank
DNMT3A	2	25240424	A	C	F734V	0.27	COPDGene
DNMT3A	2	25240422	G	C	F734L	0.18	Additional TOPMED - MESA
DNMT3A	2	25240422	G	C	F734L	0.10	Additional TOPMED - JHS
DNMT3A	2	25240422	G	C	F734L	0.05	UK Biobank
DNMT3A	2	25240421	A	C	Y735D	0.02	UK Biobank
DNMT3A	2	25240421	A	G	Y735H	0.16	COPDGene
DNMT3A	2	25240420	T	C	Y735C	0.43	COPDGene
DNMT3A	2	25240420	T	C	Y735C	0.28	Additional TOPMED - ARIC
DNMT3A	2	25240420	T	C	Y735C	0.22	COPDGene
DNMT3A	2	25240420	T	C	Y735C	0.20	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.16	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.15	COPDGene
DNMT3A	2	25240420	T	C	Y735C	0.15	Additional TOPMED - ECLIPSE
DNMT3A	2	25240420	T	C	Y735C	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25240420	T	C	Y735C	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25240420	T	C	Y735C	0.12	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.11	Additional TOPMED - MESA
DNMT3A	2	25240420	T	C	Y735C	0.11	Additional TOPMED - ARIC
DNMT3A	2	25240420	T	C	Y735C	0.09	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.08	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.08	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.08	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.08	COPDGene
DNMT3A	2	25240420	T	C	Y735C	0.08	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.07	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.06	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.06	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.05	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.05	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.05	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.05	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.05	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.05	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.04	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.04	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.04	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.04	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.04	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.03	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.02	UK Biobank
DNMT3A	2	25240420	T	C	Y735C	0.02	UK Biobank
DNMT3A	2	25240419	G	T	Y735*	0.13	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.32	Additional TOPMED - MESA
DNMT3A	2	25240418	G	A	R736C	0.26	COPDGene
DNMT3A	2	25240418	G	A	R736C	0.23	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.14	Additional TOPMED - FHS
DNMT3A	2	25240418	G	A	R736C	0.13	COPDGene
DNMT3A	2	25240418	G	A	R736C	0.11	COPDGene
DNMT3A	2	25240418	G	A	R736C	0.10	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.10	Additional TOPMED - ARIC
DNMT3A	2	25240418	G	A	R736C	0.09	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.08	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.06	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.06	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.05	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.05	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.05	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.04	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.04	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.04	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.04	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.03	UK Biobank
DNMT3A	2	25240418	G	A	R736C	0.03	UK Biobank
DNMT3A	2	25240418	G	C	R736G	0.19	COPDGene
DNMT3A	2	25240418	G	C	R736G	0.04	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.33	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.28	Additional TOPMED - JHS
DNMT3A	2	25240417	C	T	R736H	0.23	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.14	COPDGene
DNMT3A	2	25240417	C	T	R736H	0.13	Additional TOPMED - ARIC
DNMT3A	2	25240417	C	T	R736H	0.11	Additional TOPMED - ARIC
DNMT3A	2	25240417	C	T	R736H	0.10	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25240417	C	T	R736H	0.10	Additional TOPMED - MESA
DNMT3A	2	25240417	C	T	R736H	0.08	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.08	Additional TOPMED - MESA
DNMT3A	2	25240417	C	T	R736H	0.08	COPDGene
DNMT3A	2	25240417	C	T	R736H	0.06	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.06	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.05	UK Biobank
DNMT3A	2	25240417	C	T	R736H	0.04	UK Biobank
DNMT3A	2	25240414	A	C	L737R	0.12	Additional TOPMED - ARIC
DNMT3A	2	25240414	A	C	L737R	0.06	UK Biobank
DNMT3A	2	25240411	AG	A	L738fs	0.18	Additional TOPMED - ARIC
DNMT3A	2	25240411	AG	A	L738fs	0.07	UK Biobank
DNMT3A	2	25240411	A	G	L738P	0.13	Additional TOPMED - FHS
DNMT3A	2	25240411	A	G	L738P	0.04	UK Biobank
DNMT3A	2	25240411	A	T	L738Q	0.13	Additional TOPMED - MESA
DNMT3A	2	25240411	A	T	L738Q	0.03	UK Biobank
DNMT3A	2	25240402	G	T	A741E	0.05	UK Biobank
DNMT3A	2	25240402	G	T	A741E	0.04	UK Biobank
DNMT3A	2	25240402	G	C	A741G	0.16	COPDGene
DNMT3A	2	25240402	G	C	A741G	0.10	UK Biobank
DNMT3A	2	25240402	G	A	A741V	0.07	UK Biobank
DNMT3A	2	25240402	G	A	A741V	0.04	UK Biobank
DNMT3A	2	25240402	G	A	A741V	0.03	UK Biobank
DNMT3A	2	25240399	C	CG	R742fs	0.10	UK Biobank
DNMT3A	2	25240399	C	G	R742P	0.12	UK Biobank
DNMT3A	2	25240397	G	C	P743A	0.09	UK Biobank
DNMT3A	2	25240396	G	A	P743L	0.14	Additional TOPMED - MESA
DNMT3A	2	25240396	G	A	P743L	0.14	COPDGene
DNMT3A	2	25240391	C	A	E745*	0.07	UK Biobank
DNMT3A	2	25240379	G	A	R749C	0.35	COPDGene
DNMT3A	2	25240379	G	A	R749C	0.20	COPDGene
DNMT3A	2	25240379	G	A	R749C	0.17	UK Biobank
DNMT3A	2	25240379	G	A	R749C	0.16	UK Biobank
DNMT3A	2	25240379	G	A	R749C	0.15	COPDGene
DNMT3A	2	25240379	G	A	R749C	0.14	UK Biobank
DNMT3A	2	25240379	G	A	R749C	0.12	Additional TOPMED - JHS
DNMT3A	2	25240379	G	A	R749C	0.11	Additional TOPMED - MESA
DNMT3A	2	25240379	G	A	R749C	0.07	Additional TOPMED - ARIC
DNMT3A	2	25240379	G	A	R749C	0.06	UK Biobank
DNMT3A	2	25240379	G	A	R749C	0.04	UK Biobank
DNMT3A	2	25240379	G	A	R749C	0.03	UK Biobank
DNMT3A	2	25240379	G	C	R749G	0.17	Additional TOPMED - ARIC
DNMT3A	2	25240379	G	C	R749G	0.04	UK Biobank
DNMT3A	2	25240378	C	T	R749H	0.33	Additional TOPMED - ARIC
DNMT3A	2	25240378	C	T	R749H	0.14	Additional TOPMED - CFS
DNMT3A	2	25240378	C	T	R749H	0.10	UK Biobank
DNMT3A	2	25240378	C	T	R749H	0.08	UK Biobank
DNMT3A	2	25240378	C	T	R749H	0.06	UK Biobank
DNMT3A	2	25240378	C	T	R749H	0.04	UK Biobank
DNMT3A	2	25240378	C	T	R749H	0.04	UK Biobank
DNMT3A	2	25240378	C	A	R749L	0.17	Additional TOPMED - MESA
DNMT3A	2	25240378	C	G	R749P	0.11	UK Biobank
DNMT3A	2	25240376	G	A	P750S	0.07	UK Biobank
DNMT3A	2	25240373	AG	A	F751fs	0.12	UK Biobank
DNMT3A	2	25240373	A	AG	F751fs	0.04	UK Biobank
DNMT3A	2	25240373	A	C	F751V	0.26	UK Biobank
DNMT3A	2	25240373	A	C	F751V	0.10	COPDGene
DNMT3A	2	25240371	G	C	F751L	0.11	UK Biobank
DNMT3A	2	25240370	AG	A	F752fs	0.12	UK Biobank
DNMT3A	2	25240370	A	T	F752L	0.10	COPDGene
DNMT3A	2	25240370	A	G	F752L	0.27	COPDGene
DNMT3A	2	25240369	AAG	A	F752fs	0.34	UK Biobank
DNMT3A	2	25240369	A	G	F752S	0.06	UK Biobank
DNMT3A	2	25240368	GA	G	F752fs	0.02	UK Biobank
DNMT3A	2	25240368	G	C	F752L	0.34	Additional TOPMED - JHS
DNMT3A	2	25240368	G	C	F752L	0.08	UK Biobank
DNMT3A	2	25240367	A	G	W753R	0.22	UK Biobank
DNMT3A	2	25240367	A	T	W753R	0.04	UK Biobank
DNMT3A	2	25240366	CAGA	C	F752del	0.21	UK Biobank
DNMT3A	2	25240366	CAGA	C	F752del	0.11	UK Biobank
DNMT3A	2	25240366	C	A	W753L	0.29	Additional TOPMED - MESA
DNMT3A	2	25240366	C	A	W753L	0.12	COPDGene
DNMT3A	2	25240363	A	T	L754H	0.13	UK Biobank
DNMT3A	2	25240363	A	C	L754R	0.11	Additional TOPMED - ARIC
DNMT3A	2	25240361	A	C	F755V	0.05	UK Biobank
DNMT3A	2	25240361	AGAGCCAGAAGAAGGGCC	A	R749fs	0.08	COPDGene
DNMT3A	2	25240360	A	G	F755S	0.29	Additional TOPMED - ECLIPSE
DNMT3A	2	25240360	A	G	F755S	0.16	Additional TOPMED - MESA
DNMT3A	2	25240360	A	G	F755S	0.15	Additional TOPMED - MESA
DNMT3A	2	25240360	A	G	F755S	0.11	Additional TOPMED - MESA
DNMT3A	2	25240360	A	G	F755S	0.10	Additional TOPMED - MESA
DNMT3A	2	25240360	A	G	F755S	0.08	UK Biobank
DNMT3A	2	25240360	A	G	F755S	0.08	UK Biobank
DNMT3A	2	25240360	A	G	F755S	0.05	UK Biobank
DNMT3A	2	25240360	A	G	F755S	0.04	UK Biobank
DNMT3A	2	25240360	A	G	F755S	0.04	UK Biobank
DNMT3A	2	25240360	A	G	F755S	0.04	UK Biobank
DNMT3A	2	25240360	A	G	F755S	0.02	UK Biobank
DNMT3A	2	25240358	CAA	C	F755fs	0.25	Additional TOPMED - CFS
DNMT3A	2	25240358	CA	C	F755fs	0.04	UK Biobank
DNMT3A	2	25240349	CCA	C	V758fs	0.04	UK Biobank
DNMT3A	2	25240343	T	C	M761V	0.12	Additional TOPMED - MESA
DNMT3A	2	25240343	T	C	M761V	0.12	COPDGene
DNMT3A	2	25240341	CAT	C	M761fs	0.30	Additional TOPMED - JHS
DNMT3A	2	25240326	CTT	C	K766fs	0.12	COPDGene
DNMT3A	2	25240325	T	C	R767G	0.34	UK Biobank
DNMT3A	2	25240324	CT	C	R767fs	0.06	UK Biobank
DNMT3A	2	25240324	CT	C	R767fs	0.06	UK Biobank
DNMT3A	2	25240322	C	T	D768N	0.09	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25240320	G	T	D768E	0.17	Additional TOPMED - ARIC
DNMT3A	2	25240319	T	C	I769V	0.06	UK Biobank
DNMT3A	2	25240319	T	C	I769V	0.03	UK Biobank
DNMT3A	2	25240315	G	A	S770L	0.32	UK Biobank
DNMT3A	2	25240315	G	A	S770L	0.23	COPDGene
DNMT3A	2	25240315	G	A	S770L	0.23	COPDGene
DNMT3A	2	25240315	G	A	S770L	0.22	Additional TOPMED - JHS
DNMT3A	2	25240315	G	A	S770L	0.19	UK Biobank
DNMT3A	2	25240315	G	A	S770L	0.18	UK Biobank
DNMT3A	2	25240315	G	A	S770L	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25240315	G	A	S770L	0.06	COPDGene
DNMT3A	2	25240315	G	A	S770L	0.06	UK Biobank
DNMT3A	2	25240315	G	A	S770L	0.04	UK Biobank
DNMT3A	2	25240315	G	C	S770W	0.04	UK Biobank
DNMT3A	2	25240313	G	GCGA	770_771insS	0.06	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.24	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.22	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.18	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.18	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.14	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.13	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.12	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.12	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.12	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.07	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.05	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.05	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.04	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.03	UK Biobank
DNMT3A	2	25240313	G	A	R771*	0.03	UK Biobank
DNMT3A	2	25240313	G	C	R771G	0.14	COPDGene
DNMT3A	2	25240313	G	C	R771G	0.04	UK Biobank
DNMT3A	2	25240313	G	A	R771X	0.38	Additional TOPMED - ECLIPSE
DNMT3A	2	25240313	G	A	R771X	0.27	COPDGene
DNMT3A	2	25240313	G	A	R771X	0.21	COPDGene
DNMT3A	2	25240313	G	A	R771X	0.17	Additional TOPMED - JHS
DNMT3A	2	25240313	G	A	R771X	0.13	COPDGene
DNMT3A	2	25240313	G	A	R771X	0.13	COPDGene
DNMT3A	2	25240313	G	A	R771X	0.12	COPDGene
DNMT3A	2	25240313	G	A	R771X	0.11	COPDGene
DNMT3A	2	25240313	G	A	R771X	0.10	Additional TOPMED - ECLIPSE
DNMT3A	2	25240312	C	A	R771L	0.22	COPDGene
DNMT3A	2	25240312	C	A	R771L	0.15	Additional TOPMED - MESA
DNMT3A	2	25240312	C	A	R771L	0.11	UK Biobank
DNMT3A	2	25240312	C	A	R771L	0.04	UK Biobank
DNMT3A	2	25240312	C	A	R771L	0.03	UK Biobank
DNMT3A	2	25240312	C	G	R771P	0.08	UK Biobank
DNMT3A	2	25240312	C	T	R771Q	0.24	UK Biobank
DNMT3A	2	25240312	C	T	R771Q	0.23	Additional TOPMED - ECLIPSE
DNMT3A	2	25240312	C	T	R771Q	0.10	Additional TOPMED - ARIC
DNMT3A	2	25240312	C	T	R771Q	0.06	UK Biobank
DNMT3A	2	25240312	C	T	R771Q	0.05	UK Biobank
DNMT3A	2	25240312	C	T	R771Q	0.05	UK Biobank
DNMT3A	2	25240312	C	T	R771Q	0.04	UK Biobank
DNMT3A	2	25240312	C	T	R771Q	0.04	UK Biobank
DNMT3A	2	25240312	CGCGAGATGTCCCTCTTGCTACTA	T	S764fs	0.02	UK Biobank
DNMT3A	2	25240307	G	C	L773V	0.03	UK Biobank
DNMT3A	2	25240304	C	A	E774*	0.34	UK Biobank
DNMT3A	2	25240304	C	A	E774*	0.20	UK Biobank
DNMT3A	2	25240304	C	A	E774*	0.16	UK Biobank
DNMT3A	2	25240304	C	A	E774*	0.06	UK Biobank
DNMT3A	2	25240303	T	A	E774V	0.11	COPDGene
DNMT3A	2	25240302	G	G	E774D	0.05	UK Biobank
DNMT3A	2	25240301	C	A	c.1755+1G>T	0.22	Additional TOPMED - CFS
DNMT3A	2	25240301	C	T	c.e19-1G>A	0.09	UK Biobank
DNMT3A	2	25240300	ACCTCGAGAAATCGCGAGAT	A	c.e19-2ATCTCGCGATTTCGAGGT>T	0.05	UK Biobank
DNMT3A	2	25240300	AC	A	c.e19-2GT>T	0.06	UK Biobank
DNMT3A	2	25240300	A	G	c.e19-2T>C	0.05	UK Biobank
DNMT3A	2	25240300	A	G	c.e19-2T>C	0.04	UK Biobank
DNMT3A	2	25239217	T	G	c.1756-2A>C	0.17	Additional TOPMED - ARIC
DNMT3A	2	25239217	T	C	c.e20+2A>G	0.21	UK Biobank
DNMT3A	2	25239217	T	C	c.e20+2A>G	0.10	UK Biobank
DNMT3A	2	25239217	T	C	c.e20+2A>G	0.09	UK Biobank
DNMT3A	2	25239216	C	T	c.2323-1G>A	0.50	COPDGene
DNMT3A	2	25239216	C	T	c.2323-1G>A	0.15	Additional TOPMED - ARIC
DNMT3A	2	25239216	C	T	c.e20+1G>A	0.10	UK Biobank
DNMT3A	2	25239209	G	A	P777S	0.25	Additional TOPMED - MESA
DNMT3A	2	25239209	G	A	P777S	0.22	Additional TOPMED - CFS
DNMT3A	2	25239209	G	A	P777S	0.18	Additional TOPMED - ECLIPSE
DNMT3A	2	25239209	G	A	P777S	0.18	Additional TOPMED - FHS
DNMT3A	2	25239208	G	C	P777R	0.13	COPDGene
DNMT3A	2	25239199	A	C	I780S	0.30	Additional TOPMED - JHS
DNMT3A	2	25239199	A	C	I780S	0.11	UK Biobank
DNMT3A	2	25239199	A	G	I780T	0.34	Additional TOPMED - ECLIPSE
DNMT3A	2	25239199	A	G	I780T	0.19	Additional TOPMED - MESA
DNMT3A	2	25239199	A	G	I780T	0.14	UK Biobank
DNMT3A	2	25239199	A	G	I780T	0.13	Additional TOPMED - JHS
DNMT3A	2	25239199	A	G	I780T	0.12	COPDGene
DNMT3A	2	25239199	A	G	I780T	0.12	Additional TOPMED - JHS
DNMT3A	2	25239199	A	G	I780T	0.10	Additional TOPMED - ECLIPSE
DNMT3A	2	25239193	G	A	A782V	0.05	UK Biobank
DNMT3A	2	25239181	GAC	G	V785fs	0.10	Additional TOPMED - FHS
DNMT3A	2	25239179	CT	C	S786fs	0.10	COPDGene
DNMT3A	2	25239173	GTGCAGC	G	AA787del	0.35	UK Biobank
DNMT3A	2	25239171	G	C	H789Q	0.15	COPDGene
DNMT3A	2	25239163	CG	C	R792fs	0.04	UK Biobank
DNMT3A	2	25239163	C	T	R792H	0.42	COPDGene
DNMT3A	2	25239159	G	T	Y793*	0.06	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25239159	G	C	Y793X	0.31	COPDGene
DNMT3A	2	25239158	A	G	F794L	0.50	COPDGene
DNMT3A	2	25239158	A	G	F794L	0.14	Additional TOPMED - ECLIPSE
DNMT3A	2	25239157	A	ATACAC	F794fs	0.17	Additional TOPMED - MESA
DNMT3A	2	25239155	AG	A	F794fs	0.11	Additional TOPMED - MESA
DNMT3A	2	25239155	A	T	W795R	0.17	COPDGene
DNMT3A	2	25239154	C	T	W795*	0.09	UK Biobank
DNMT3A	2	25239154	C	A	W795L	0.27	Additional TOPMED - MESA
DNMT3A	2	25239154	C	A	W795L	0.03	UK Biobank
DNMT3A	2	25239154	C	T	W795X	0.14	COPDGene
DNMT3A	2	25239154	C	T	W795X	0.14	COPDGene
DNMT3A	2	25239154	C	T	W795X	0.13	Additional TOPMED - FHS
DNMT3A	2	25239153	C	G	W795C	0.05	UK Biobank
DNMT3A	2	25239152	C	A	G796C	0.20	UK Biobank
DNMT3A	2	25239151	C	T	G796D	0.14	UK Biobank
DNMT3A	2	25239151	C	T	G796D	0.08	UK Biobank
DNMT3A	2	25239148	T	C	N797S	0.17	UK Biobank
DNMT3A	2	25239146	G	GGTAA	L798fs	0.11	COPDGene
DNMT3A	2	25239145	A	C	L798R	0.14	COPDGene
DNMT3A	2	25239145	A	C	L798R	0.06	UK Biobank
DNMT3A	2	25239143	G	C	P799A	0.15	COPDGene
DNMT3A	2	25239143	G	A	P799S	0.15	COPDGene
DNMT3A	2	25239143	G	A	P799S	0.11	COPDGene
DNMT3A	2	25239143	G	A	P799S	0.09	Additional TOPMED - ARIC
DNMT3A	2	25239143	G	T	P799T	0.11	Additional TOPMED - MESA
DNMT3A	2	25239140	CG	C	P799fs	0.59	Additional TOPMED - FHS
DNMT3A	2	25239140	CG	C	P799fs	0.13	Additional TOPMED - JHS
DNMT3A	2	25239137	T	C	M801V	0.22	Additional TOPMED - JHS
DNMT3A	2	25239137	T	C	M801V	0.13	UK Biobank
DNMT3A	2	25239136	A	C	M801R	0.24	Additional TOPMED - FHS
DNMT3A	2	25239135	C	T	M801I	0.17	COPDGene
DNMT3A	2	25239132	GT	G	N802fs	0.21	Additional TOPMED - JHS
DNMT3A	2	25239131	T	C	R803G	0.09	UK Biobank
DNMT3A	2	25239131	T	C	R803G	0.07	UK Biobank
DNMT3A	2	25239130	C	T	R803K	0.28	Additional TOPMED - ARIC
DNMT3A	2	25239130	C	T	R803K	0.13	UK Biobank
DNMT3A	2	25239130	C	T	R803K	0.13	UK Biobank
DNMT3A	2	25239130	C	T	R803K	0.10	UK Biobank
DNMT3A	2	25239129	C	T	c.2408+1G>A	0.23	Additional TOPMED - JHS
DNMT3A	2	25239129	C	T	c.2408+1G>A	0.08	COPDGene
DNMT3A	2	25239128	A	G	c.2408+2T>C	0.11	COPDGene
DNMT3A	2	25239128	A	T	c.e20-2T>A	0.07	UK Biobank
DNMT3A	2	25237007	T	G	c.2409-2A>C	0.22	COPDGene
DNMT3A	2	25237007	T	C	c.e21+2A>G	0.08	UK Biobank
DNMT3A	2	25237006	C	G	c.e21+1G>C	0.09	UK Biobank
DNMT3A	2	25237005	C	A	R803S	0.26	Additional TOPMED - MESA
DNMT3A	2	25237003	G	A	P804L	0.14	UK Biobank
DNMT3A	2	25236999	CA	C	L805fs	0.16	Additional TOPMED - ARIC
DNMT3A	2	25236997	GC	G	A806fs	0.06	UK Biobank
DNMT3A	2	25236994	GATGCC	G	L805fs	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25236994	G	GATGCC	S807fs	0.10	COPDGene
DNMT3A	2	25236983	CA	C	N810fs	0.10	UK Biobank
DNMT3A	2	25236969	CAGCTCCAGCTTATCATTACAGTGA	C	S807fs	0.10	Additional TOPMED - MESA
DNMT3A	2	25236968	G	A	Q816X	0.33	COPDGene
DNMT3A	2	25236955	T	C	E820G	0.08	UK Biobank
DNMT3A	2	25236951	AT	A	H821fs	0.12	COPDGene
DNMT3A	2	25236944	T	TC	I824fs	0.14	Additional TOPMED - ARIC
DNMT3A	2	25236937	T	C	K826R	0.26	Additional TOPMED - ARIC
DNMT3A	2	25236937	T	C	K826R	0.12	Additional TOPMED - MESA
DNMT3A	2	25236937	T	C	K826R	0.06	UK Biobank
DNMT3A	2	25236936	C	T	K826K	0.21	UK Biobank
DNMT3A	2	25236936	C	G	K826N	0.09	Additional TOPMED - FHS
DNMT3A	2	25236935	CCT	T	c.2478+1G>A	0.30	Additional TOPMED - FHS
DNMT3A	2	25236935	CCT	C	c.e21-1AGG>G	0.06	UK Biobank
DNMT3A	2	25236935	C	T	c.e21-1G>A	0.18	UK Biobank
DNMT3A	2	25236935	C	T	c.e21-1G>A	0.09	UK Biobank
DNMT3A	2	25236934	A	G	c.e21-2T>C	0.06	UK Biobank
DNMT3A	2	25236934	A	C	c.e21-2T>G	0.13	UK Biobank
DNMT3A	2	25235827	T	C	c.e22+2A>G	0.20	UK Biobank
DNMT3A	2	25235803	G	GT	T834fs	0.39	UK Biobank
DNMT3A	2	25235801	TA	T	T834fs	0.36	Additional TOPMED - ARIC
DNMT3A	2	25235800	G	A	T835M	0.20	Additional TOPMED - MESA
DNMT3A	2	25235792	T	C	N838D	0.16	Additional TOPMED - ARIC
DNMT3A	2	25235792	T	C	N838D	0.16	COPDGene
DNMT3A	2	25235792	T	C	N838D	0.14	Additional TOPMED - MESA
DNMT3A	2	25235792	T	C	N838D	0.09	COPDGene
DNMT3A	2	25235792	T	C	N838D	0.08	UK Biobank
DNMT3A	2	25235768	G	A	Q846*	0.28	UK Biobank
DNMT3A	2	25235768	G	A	Q846X	0.11	COPDGene
DNMT3A	2	25235758	G	C	P849R	0.07	UK Biobank
DNMT3A	2	25235750	T	G	M852L	0.12	UK Biobank
DNMT3A	2	25235750	T	C	M852V	0.26	UK Biobank
DNMT3A	2	25235735	CCT	C	E856fs	0.16	Additional TOPMED - FHS
DNMT3A	2	25235727	TAA	T	L859fs	0.19	Additional TOPMED - JHS
DNMT3A	2	25235726	A	AT	W860fs	0.19	Additional TOPMED - ARIC
DNMT3A	2	25235726	A	G	W860R	0.35	UK Biobank
DNMT3A	2	25235726	A	G	W860R	0.10	UK Biobank
DNMT3A	2	25235726	A	G	W860R	0.10	COPDGene
DNMT3A	2	25235726	A	G	W860R	0.08	UK Biobank
DNMT3A	2	25235725	C	T	W860*	0.19	UK Biobank
DNMT3A	2	25235725	C	T	W860*	0.11	UK Biobank
DNMT3A	2	25235725	C	T	W860X	0.09	COPDGene
DNMT3A	2	25235724	C	T	W860X	0.32	Additional TOPMED - MESA
DNMT3A	2	25235724	C	T	W860X	0.29	Additional TOPMED - FHS
DNMT3A	2	25235724	C	T	W860X	0.16	Additional TOPMED - MESA
DNMT3A	2	25235723	A	G	C861R	0.35	UK Biobank
DNMT3A	2	25235716	T	A	E863V	0.12	UK Biobank
DNMT3A	2	25235706	C	T	c.2030+1G>A	0.12	Additional TOPMED - MESA
DNMT3A	2	25235706	C	A	c.2597+1G>T	0.21	COPDGene

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25235705	A	C	c.e22-2T>G	0.13	UK Biobank
DNMT3A	2	25234421	C	T	c.2598-1G>A	0.24	Additional TOPMED - ARIC
DNMT3A	2	25234418	AC	A	V867fs	0.43	COPDGene
DNMT3A	2	25234414	A	C	F868L	0.33	COPDGene
DNMT3A	2	25234413	C	CAAAT	G869fs	0.13	Additional TOPMED - FHS
DNMT3A	2	25234412	C	A	G869V	0.14	COPDGene
DNMT3A	2	25234411	AC	A	G869fs	0.23	UK Biobank
DNMT3A	2	25234401	G	C	H873D	0.06	UK Biobank
DNMT3A	2	25234392	C	T	D876N	0.29	UK Biobank
DNMT3A	2	25234392	C	T	D876N	0.11	UK Biobank
DNMT3A	2	25234391	T	G	D876A	0.03	UK Biobank
DNMT3A	2	25234390	G	GT	D876fs	0.33	UK Biobank
DNMT3A	2	25234383	T	C	N879D	0.11	UK Biobank
DNMT3A	2	25234383	T	C	N879D	0.10	UK Biobank
DNMT3A	2	25234380	T	C	M880V	0.12	Additional TOPMED - FHS
DNMT3A	2	25234380	T	C	M880V	0.12	Additional TOPMED - FHS
DNMT3A	2	25234380	T	C	M880V	0.09	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.42	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.31	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.30	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.30	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.29	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.24	Additional TOPMED - MESA
DNMT3A	2	25234374	G	A	R882C	0.23	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.23	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.21	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.21	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.20	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.20	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.20	Additional TOPMED - ECLIPSE
DNMT3A	2	25234374	G	A	R882C	0.20	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.19	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.19	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.19	Additional TOPMED - MESA
DNMT3A	2	25234374	G	A	R882C	0.18	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.18	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.18	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.17	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.16	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.16	Additional TOPMED - JHS
DNMT3A	2	25234374	G	A	R882C	0.15	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.15	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.15	Additional TOPMED - JHS
DNMT3A	2	25234374	G	A	R882C	0.14	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.14	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.14	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.14	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.13	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.13	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.12	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.11	Additional TOPMED - ECLIPSE
DNMT3A	2	25234374	G	A	R882C	0.11	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.10	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.10	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.10	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.10	COPDGene
DNMT3A	2	25234374	G	A	R882C	0.10	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.10	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.09	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.09	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.09	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.09	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.08	Additional TOPMED - ARIC
DNMT3A	2	25234374	G	A	R882C	0.08	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.07	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.05	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.05	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.05	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.05	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.05	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.05	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.04	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.03	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.03	UK Biobank
DNMT3A	2	25234374	G	A	R882C	0.03	UK Biobank
DNMT3A	2	25234374	G	T	R882S	0.31	COPDGene
DNMT3A	2	25234374	G	T	R882S	0.06	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.47	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.42	Additional TOPMED - CFS
DNMT3A	2	25234373	C	T	R882H	0.41	Additional TOPMED - ECLIPSE
DNMT3A	2	25234373	C	T	R882H	0.34	Additional TOPMED - FHS
DNMT3A	2	25234373	C	T	R882H	0.34	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.33	Additional TOPMED - JHS
DNMT3A	2	25234373	C	T	R882H	0.32	Additional TOPMED - ECLIPSE
DNMT3A	2	25234373	C	T	R882H	0.32	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.31	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.30	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.30	Additional TOPMED - JHS
DNMT3A	2	25234373	C	T	R882H	0.30	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.29	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.29	Additional TOPMED - ARIC
DNMT3A	2	25234373	C	T	R882H	0.29	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.29	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.29	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.28	Additional TOPMED - ECLIPSE
DNMT3A	2	25234373	C	T	R882H	0.28	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.27	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.26	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.26	Additional TOPMED - MESA
DNMT3A	2	25234373	C	T	R882H	0.25	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25234373	C	T	R882H	0.24	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.24	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.24	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.24	Additional TOPMED - MESA
DNMT3A	2	25234373	C	T	R882H	0.24	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.23	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.22	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.22	Additional TOPMED - CFS
DNMT3A	2	25234373	C	T	R882H	0.22	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.22	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.21	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.21	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.19	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.19	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.18	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.18	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.17	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.17	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.17	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.16	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.16	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.16	Additional TOPMED - ARIC
DNMT3A	2	25234373	C	T	R882H	0.16	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.15	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.15	Additional TOPMED - ECLIPSE
DNMT3A	2	25234373	C	T	R882H	0.15	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.15	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.15	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.14	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.13	Additional TOPMED - ARIC
DNMT3A	2	25234373	C	T	R882H	0.13	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.12	Additional TOPMED - MESA
DNMT3A	2	25234373	C	T	R882H	0.12	Additional TOPMED - ARIC
DNMT3A	2	25234373	C	T	R882H	0.12	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.12	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.12	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.11	Additional TOPMED - JHS
DNMT3A	2	25234373	C	T	R882H	0.11	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.11	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.11	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.11	Additional TOPMED - ECLIPSE
DNMT3A	2	25234373	C	T	R882H	0.11	Additional TOPMED - CFS
DNMT3A	2	25234373	C	T	R882H	0.11	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.11	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.11	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.11	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.10	Additional TOPMED - ARIC
DNMT3A	2	25234373	C	T	R882H	0.10	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.10	COPDGene
DNMT3A	2	25234373	C	T	R882H	0.10	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.10	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.09	Additional TOPMED - MESA
DNMT3A	2	25234373	C	T	R882H	0.09	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.08	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.08	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.08	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.07	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.07	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.07	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.07	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.06	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.06	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.06	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.06	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.05	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.04	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.04	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.04	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.03	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.03	UK Biobank
DNMT3A	2	25234373	C	T	R882H	0.03	UK Biobank
DNMT3A	2	25234373	C	A	R882L	0.16	UK Biobank
DNMT3A	2	25234373	C	A	R882L	0.10	UK Biobank
DNMT3A	2	25234373	C	G	R882P	0.28	COPDGene
DNMT3A	2	25234372	GC	AG	R882P	0.13	UK Biobank
DNMT3A	2	25234370	A	T	L883*	0.09	UK Biobank
DNMT3A	2	25234369	CA	C	L883fs	0.15	Additional TOPMED - FHS
DNMT3A	2	25234367	G	A	A884V	0.05	UK Biobank
DNMT3A	2	25234365	TC	T	R885fs	0.15	UK Biobank
DNMT3A	2	25234362	G	A	Q886X	0.24	Additional TOPMED - MESA
DNMT3A	2	25234362	G	A	Q886X	0.15	COPDGene
DNMT3A	2	25234362	G	A	Q886X	0.14	Additional TOPMED - JHS
DNMT3A	2	25234362	G	A	Q886X	0.12	Additional TOPMED - ECLIPSE
DNMT3A	2	25234356	GTC	G	R887fs	0.12	UK Biobank
DNMT3A	2	25234349	C	T	G890D	0.12	UK Biobank
DNMT3A	2	25234349	C	T	G890D	0.08	UK Biobank
DNMT3A	2	25234348	G	GC	R891fs	0.06	UK Biobank
DNMT3A	2	25234346	CG	C	R891fs	0.08	UK Biobank
DNMT3A	2	25234346	CG	C	R891fs	0.04	UK Biobank
DNMT3A	2	25234341	A	G	W893R	0.10	UK Biobank
DNMT3A	2	25234340	C	G	W893S	0.13	UK Biobank
DNMT3A	2	25234339	CC	AG	W893S	0.17	UK Biobank
DNMT3A	2	25234339	C	T	W893X	0.11	Additional TOPMED - FHS
DNMT3A	2	25234338	T	TC	S894fs	0.22	UK Biobank
DNMT3A	2	25234336	G	C	S894R	0.07	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
DNMT3A	2	25234336	G	T	S894R	0.03	UK Biobank
DNMT3A	2	25234335	C	T	V895M	0.11	Additional TOPMED - ARIC
DNMT3A	2	25234331	G	A	P896L	0.32	UK Biobank
DNMT3A	2	25234331	G	T	P896Q	0.04	UK Biobank
DNMT3A	2	25234328	G	C	V897G	0.20	COPDGene
DNMT3A	2	25234327	GA	G	V897fs	0.03	UK Biobank
DNMT3A	2	25234324	GA	G	I898fs	0.05	UK Biobank
DNMT3A	2	25234323	GGAT	G	I898del	0.05	UK Biobank
DNMT3A	2	25234323	G	A	R899C	0.20	UK Biobank
DNMT3A	2	25234323	G	A	R899C	0.16	Additional TOPMED - MESA
DNMT3A	2	25234323	G	A	R899C	0.13	Additional TOPMED - MESA
DNMT3A	2	25234323	G	A	R899C	0.12	Additional TOPMED - JHS
DNMT3A	2	25234323	G	A	R899C	0.11	UK Biobank
DNMT3A	2	25234323	G	A	R899C	0.09	UK Biobank
DNMT3A	2	25234323	G	A	R899C	0.09	COPDGene
DNMT3A	2	25234323	G	A	R899C	0.06	UK Biobank
DNMT3A	2	25234323	G	A	R899C	0.04	UK Biobank
DNMT3A	2	25234323	G	A	R899C	0.03	UK Biobank
DNMT3A	2	25234322	CG	C	R899fs	0.25	Additional TOPMED - ECLIPSE
DNMT3A	2	25234322	C	T	R899H	0.03	UK Biobank
DNMT3A	2	25234316	AG	A	L901fs	0.04	UK Biobank
DNMT3A	2	25234316	A	G	L901P	0.15	Additional TOPMED - ARIC
DNMT3A	2	25234316	A	G	L901P	0.10	COPDGene
DNMT3A	2	25234316	A	G	L901P	0.04	UK Biobank
DNMT3A	2	25234316	A	C	L901R	0.18	Additional TOPMED - JHS
DNMT3A	2	25234316	A	C	L901R	0.16	Additional TOPMED - FHS
DNMT3A	2	25234311	C	T	A903T	0.31	Additional TOPMED - JHS
DNMT3A	2	25234311	C	T	A903T	0.03	UK Biobank
DNMT3A	2	25234309	AGC	A	A903fs	0.05	UK Biobank
DNMT3A	2	25234308	G	C	P904A	0.10	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.40	COPDGene
DNMT3A	2	25234307	G	A	P904L	0.30	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.20	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.14	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.14	Additional TOPMED - ARIC
DNMT3A	2	25234307	G	A	P904L	0.13	COPDGene
DNMT3A	2	25234307	G	A	P904L	0.12	COPDGene
DNMT3A	2	25234307	G	A	P904L	0.12	COPDGene
DNMT3A	2	25234307	G	A	P904L	0.12	COPDGene
DNMT3A	2	25234307	G	A	P904L	0.11	Additional TOPMED - MESA
DNMT3A	2	25234307	G	A	P904L	0.10	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.09	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.08	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.06	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.06	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.06	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.06	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.06	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.05	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.05	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.04	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.04	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.03	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.03	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.03	UK Biobank
DNMT3A	2	25234307	G	A	P904L	0.02	UK Biobank
DNMT3A	2	25234307	G	T	P904Q	0.17	COPDGene
DNMT3A	2	25234306	CG	C	P904fs	0.05	UK Biobank
DNMT3A	2	25234304	A	T	L905Q	0.14	UK Biobank
DNMT3A	2	25234303	C	CA	L905fs	0.17	Additional TOPMED - ARIC
DNMT3A	2	25234300	C	CT	E907fs	0.06	UK Biobank
DNMT3A	2	25234300	CT	C	K906fs	0.06	UK Biobank
DNMT3A	2	25234299	C	A	E907*	0.11	UK Biobank
DNMT3A	2	25234298	T	TC	E907fs	0.08	UK Biobank
DNMT3A	2	25234296	A	ACTC	907_908insE	0.07	UK Biobank
DNMT3A	2	25234296	A	C	Y908D	0.10	Additional TOPMED - ARIC
DNMT3A	2	25234296	A	T	Y908N	0.14	UK Biobank
DNMT3A	2	25234295	T	C	Y908C	0.15	COPDGene
DNMT3A	2	25234295	T	C	Y908C	0.14	UK Biobank
DNMT3A	2	25234295	T	C	Y908C	0.05	UK Biobank
DNMT3A	2	25234295	T	C	Y908C	0.03	UK Biobank
DNMT3A	2	25234295	T	C	Y908C	0.03	UK Biobank
DNMT3A	2	25234294	A	C	Y908*	0.06	UK Biobank
DNMT3A	2	25234294	A	C	Y908X	0.19	Additional TOPMED - MESA
DNMT3A	2	25234292	A	C	F909C	0.23	COPDGene
DNMT3A	2	25234292	A	G	F909S	0.20	UK Biobank
DNMT3A	2	25234292	A	G	F909S	0.12	UK Biobank
DNMT3A	2	25234290	C	G	A910P	0.04	UK Biobank
DNMT3A	2	25234290	CAA	C	F909fs	0.05	UK Biobank
DNMT3A	2	25234289	G	T	A910E	0.03	UK Biobank
DNMT3A	2	25234289	G	A	A910V	0.16	UK Biobank
DNMT3A	2	25234289	G	A	A910V	0.12	COPDGene
DNMT3A	2	25234289	G	A	A910V	0.08	UK Biobank
DNMT3A	2	25234286	C	T	C911Y	0.12	Additional TOPMED - MESA
DNMT3A	2	25234286	C	T	C911Y	0.03	UK Biobank
DNMT3A	2	25234286	C	T	C911Y	0.02	UK Biobank
EED	11	85988028	G	T	E325*	0.07	ICGN-EOCOCPD
EP300	22	41137655	C	CTTTTTT	P542fs	0.09	COPDGene
ETNK1	12	22659061	A	G	N244S	0.30	UK Biobank
ETNK1	12	22659061	A	G	N244S	0.29	Additional TOPMED - FHS
ETNK1	12	22659061	A	G	N244S	0.25	COPDGene
ETNK1	12	22659061	A	G	N244S	0.12	Additional TOPMED - FHS
ETV6	12	11884573	TG	T	W380fs	0.18	COPDGene
ETV6	12	11884446	C	A	D337E	0.05	UK Biobank
ETV6	12	11889601	CG	C	P214fs	0.25	COPDGene
ETV6	12	11853514	CTA	C	S139fs	0.17	Additional TOPMED - ECLIPSE
ETV6	12	11839289	CG	C	R105fs	0.12	COPDGene
ETV6	12	11752531	C	T	R39*	0.33	UK Biobank
EZH2	7	148826615	GC	T	E249fs	0.15	COPDGene
EZH2	7	148815507	CT	C	K510fs	0.07	UK Biobank
EZH2	7	148814014	C	T	W594X	0.69	COPDGene

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
EZH2	7	148809381	AC	A	V675fs	0.05	UK Biobank
EZH2	7	148512130	G	C	D511E	0.12	ICGN-EEOCPD
GATA2	3	128485998	AC	A	G200fs	0.09	UK Biobank
GNAS	20	58910765	G	A	R374H	0.15	Additional TOPMED - ECLIPSE
GNAS	20	58910761	C	T	R373C	0.50	Additional TOPMED - CFS
GNAS	20	58909542	G	C	Q227H	0.19	Additional TOPMED - FHS
GNAS	20	58909542	G	T	Q227H	0.11	COPDGene
GNAS	20	58909542	G	T	Q227H	0.08	UK Biobank
GNAS	20	58909366	G	A	R201H	0.25	Additional TOPMED - ARIC
GNAS	20	58909366	G	A	R201H	0.15	Additional TOPMED - MESA
GNAS	20	58909366	G	A	R201H	0.14	UK Biobank
GNAS	20	58909366	G	A	R201H	0.14	UK Biobank
GNAS	20	58909366	G	A	R201H	0.13	Additional TOPMED - ECLIPSE
GNAS	20	58909366	G	A	R201H	0.10	COPDGene
GNAS	20	58909366	G	A	R201H	0.09	UK Biobank
GNAS	20	58909366	G	A	R201H	0.08	Additional TOPMED - MESA
GNAS	20	58909366	G	A	R201H	0.07	UK Biobank
GNAS	20	58909366	G	A	R201H	0.06	UK Biobank
GNAS	20	58909366	G	A	R201H	0.05	UK Biobank
GNAS	20	58909365	C	T	R201C	0.09	COPDGene
GNAS	20	58909365	C	T	R201C	0.08	Additional TOPMED - ARIC
GNAS	20	58909365	C	T	R201C	0.07	Additional TOPMED - FHS
GNAS	20	58909365	C	T	R201C	0.06	UK Biobank
GNB1	1	1815790	T	C	K57E	0.36	UK Biobank
GNB1	1	1815790	T	C	K57E	0.26	Additional TOPMED - MESA
GNB1	1	1815790	T	C	K57E	0.22	UK Biobank
GNB1	1	1815790	T	C	K57E	0.18	UK Biobank
GNB1	1	1815790	T	C	K57E	0.15	UK Biobank
GNB1	1	1815790	T	C	K57E	0.13	Additional TOPMED - JHS
GNB1	1	1815790	T	C	K57E	0.12	COPDGene
GNB1	1	1815790	T	C	K57E	0.11	UK Biobank
GNB1	1	1815790	T	C	K57E	0.10	UK Biobank
GNB1	1	1815790	T	C	K57E	0.09	UK Biobank
GNB1	1	1815790	T	C	K57E	0.09	UK Biobank
GNB1	1	1815790	T	C	K57E	0.08	UK Biobank
GNB1	1	1815790	T	C	K57E	0.06	UK Biobank
IDH1	2	208248388	C	T	R132H	0.20	Additional TOPMED - ECLIPSE
IDH1	2	208248388	C	T	R132H	0.13	COPDGene
IDH2	15	90088703	G	A	R140W	0.40	Additional TOPMED - FHS
IDH2	15	90088702	C	T	R140Q	0.17	UK Biobank
IDH2	15	90088702	C	T	R140Q	0.14	Additional TOPMED - ECLIPSE
IDH2	15	90088702	C	T	R140Q	0.13	Additional TOPMED - JHS
IDH2	15	90088702	C	T	R140Q	0.13	UK Biobank
IDH2	15	90088702	C	T	R140Q	0.13	COPDGene
IDH2	15	90088702	C	T	R140Q	0.07	UK Biobank
IKZF1	7	50400310	AC	A	N416fs	0.03	UK Biobank
IKZF2	2	213007512	G	A	R477X	0.10	Additional TOPMED - ECLIPSE
JAK2	9	5073770	G	T	V617F	0.95	UK Biobank
JAK2	9	5073770	G	T	V617F	0.94	Additional TOPMED - JHS
JAK2	9	5073770	G	T	V617F	0.78	UK Biobank
JAK2	9	5073770	G	T	V617F	0.72	Additional TOPMED - ARIC
JAK2	9	5073770	G	T	V617F	0.65	COPDGene
JAK2	9	5073770	G	T	V617F	0.65	COPDGene
JAK2	9	5073770	G	T	V617F	0.48	Additional TOPMED - JHS
JAK2	9	5073770	G	T	V617F	0.44	Additional TOPMED - FHS
JAK2	9	5073770	G	T	V617F	0.43	COPDGene
JAK2	9	5073770	G	T	V617F	0.35	UK Biobank
JAK2	9	5073770	G	T	V617F	0.34	COPDGene
JAK2	9	5073770	G	T	V617F	0.31	UK Biobank
JAK2	9	5073770	G	T	V617F	0.30	Additional TOPMED - ARIC
JAK2	9	5073770	G	T	V617F	0.29	UK Biobank
JAK2	9	5073770	G	T	V617F	0.27	Additional TOPMED - ARIC
JAK2	9	5073770	G	T	V617F	0.25	Additional TOPMED - JHS
JAK2	9	5073770	G	T	V617F	0.25	UK Biobank
JAK2	9	5073770	G	T	V617F	0.24	UK Biobank
JAK2	9	5073770	G	T	V617F	0.24	Additional TOPMED - MESA
JAK2	9	5073770	G	T	V617F	0.23	UK Biobank
JAK2	9	5073770	G	T	V617F	0.22	Additional TOPMED - ECLIPSE
JAK2	9	5073770	G	T	V617F	0.20	UK Biobank
JAK2	9	5073770	G	T	V617F	0.19	UK Biobank
JAK2	9	5073770	G	T	V617F	0.18	UK Biobank
JAK2	9	5073770	G	T	V617F	0.18	Additional TOPMED - FHS
JAK2	9	5073770	G	T	V617F	0.17	UK Biobank
JAK2	9	5073770	G	T	V617F	0.14	Additional TOPMED - MESA
JAK2	9	5073770	G	T	V617F	0.14	UK Biobank
JAK2	9	5073770	G	T	V617F	0.14	Additional TOPMED - FHS
JAK2	9	5073770	G	T	V617F	0.14	Additional TOPMED - ARIC
JAK2	9	5073770	G	T	V617F	0.13	UK Biobank
JAK2	9	5073770	G	T	V617F	0.13	COPDGene
JAK2	9	5073770	G	T	V617F	0.12	COPDGene
JAK2	9	5073770	G	T	V617F	0.12	UK Biobank
JAK2	9	5073770	G	T	V617F	0.12	COPDGene
JAK2	9	5073770	G	T	V617F	0.12	UK Biobank
JAK2	9	5073770	G	T	V617F	0.11	COPDGene
JAK2	9	5073770	G	T	V617F	0.11	COPDGene
JAK2	9	5073770	G	T	V617F	0.09	COPDGene
JAK2	9	5073770	G	T	V617F	0.09	Additional TOPMED - ARIC
JAK2	9	5070022	TCACAAA	T	HK538del	0.10	UK Biobank
KDM6A	X	45107495	CG	C	T1323fs	0.10	UK Biobank
KDM6A	X	45083582	TG	T	M1136fs	0.11	COPDGene
KDM6A	X	45082640	AGTAAGTCATTTTTAATGCCACTTAGTATTTCTTTTAAAGGCATGTTTCTAATACTGTGTCTCTTTT TTAAG	A	c.e21+0AGTAAGTCATTTTTAATGTCCA CTTAGTATTTCTTTT TAAAGGCATGTTT CTAATACTGTGTCT CTTTTTAAG>A	0.20	UK Biobank
KDM6A	X	45082640	A	G	N1070S	0.10	UK Biobank
KDM6A	X	45069839	TGAACAAGCAG	T	E729fs	0.13	Additional TOPMED - ARIC
KDM6A	X	45069836	GC	G	F728fs	0.09	UK Biobank
KDM6A	X	45069783	C	T	Q710X	0.90	COPDGene
KDM6A	X	45063556	TCAGCC	T	Q555fs	0.10	Additional TOPMED - ECLIPSE
KDM6A	X	45020659	C	T	R165*	0.08	UK Biobank
KDM6A	X	45020659	C	T	R165X	0.79	Additional TOPMED - FHS
KDM6A	X	44922952	G	T	G605*	0.06	ICGN-EEOCPD

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
KRAS	12	25380277	G	T	G61K	0.06	ICGN-EOCPD
KRAS	12	25245350	C	A	G12V	0.05	UK Biobank
KRAS	12	25245347	C	T	G13D	0.29	Additional TOPMED - FHS
KRAS	12	25245345	C	T	V14I	0.05	UK Biobank
KRAS	12	25225714	T	C	K117R	0.11	UK Biobank
KRAS	12	25225713	T	A	K117N	0.28	Additional TOPMED - ECLIPSE
KRAS	12	25225627	G	A	A146V	0.19	COPDGene
KRAS	12	25225627	G	A	A146V	0.17	UK Biobank
MPL	1	43349352	C	A	H520N	0.08	UK Biobank
MPL	1	43349338	G	T	W515L	0.20	Additional TOPMED - FHS
MPL	1	43349311	C	T	A506V	0.06	UK Biobank
NF1	17	31358481	C	T	H2658Y	0.11	UK Biobank
NF1	17	31350209	C	T	R2450*	0.07	UK Biobank
NF1	17	31338733	CACCT	C	T2263fs	0.18	Additional TOPMED - JHS
NF1	17	31337858	C	T	Q2207X	0.12	Additional TOPMED - ECLIPSE
NF1	17	31260462	TC	T	R1509fs	0.24	UK Biobank
NF1	17	31258409	TATCA	T	N1415fs	0.18	UK Biobank
NF1	17	31235728	C	T	R1276X	0.22	Additional TOPMED - MESA
NF1	17	31229118	C	T	Q835*	0.20	UK Biobank
NF1	17	31226459	A	AC	I679fs	0.11	UK Biobank
NF1	17	31214479	GC	G	S474fs	0.32	Additional TOPMED - ECLIPSE
NF1	17	31201083	CT	C	P370fs	0.22	COPDGene
NF1	17	31182537	GA	G	D254fs	0.06	UK Biobank
NF1	17	29685993	GT	G	F2708fs	0.14	ICGN-EOCPD
NRAS	1	114713912	C	T	G60R	0.13	UK Biobank
PSSSB	13	32758086	G	T	c.3057-1G>T	0.13	Additional TOPMED - JHS
PSSSB	13	32710081	GA	G	E700fs	0.12	Additional TOPMED - MESA
PSSSB	13	32687286	A	A	c.e12+1G>A	0.13	UK Biobank
PSSSB	13	32687279	G	ATG	D450fs	0.13	COPDGene
PSSSB	13	32673357	G	GT	c.846+1->T	0.35	COPDGene
PHF6	X	134417220	G	C	A296P	0.22	UK Biobank
PHF6	X	134413562	A	T	K164X	0.58	Additional TOPMED - FHS
PHF6	X	134378042	A	G	N59S	0.23	UK Biobank
PHF6	X	133512112	G	T	K72N	0.07	ICGN-EOCPD
PHIP	6	79724872	GAA	G	S484fs	0.12	ICGN-EOCPD
PHIP	6	79668210	AG	A	L1255fs	0.02	ICGN-EOCPD
PHIP	6	79664644	G	A	Q1314*	0.06	ICGN-EOCPD
PHIP	6	79060791	C	CAG	D73fs	0.32	COPDGene
PHIP	6	79025518	CTTTAT	C	I307fs	0.28	Additional TOPMED - ECLIPSE
PHIP	6	78963165	C	T	W1156X	0.13	COPDGene
PHIP	6	78958595	ACCCGCCCT	A	R1219fs	0.10	COPDGene
PHIP	6	78947703	C	A	E1376X	0.37	COPDGene
PHIP	6	78946770	TATGGTATTTCTTTTATG	T	H1432fs	0.50	COPDGene
PPM1D	17	60663536	CTGTT	C	C603fs	0.51	UK Biobank
PPM1D	17	60663506	GA	G	N592fs	0.41	UK Biobank
PPM1D	17	60663475	C	T	R581*	0.45	UK Biobank
PPM1D	17	60663475	C	T	R581*	0.23	UK Biobank
PPM1D	17	60663475	C	T	R581*	0.17	UK Biobank
PPM1D	17	60663475	C	T	R581X	0.42	Additional TOPMED - ECLIPSE
PPM1D	17	60663455	ACT	A	N574fs	0.12	Additional TOPMED - ECLIPSE
PPM1D	17	60663448	C	T	R572X	0.52	Additional TOPMED - ECLIPSE
PPM1D	17	60663448	C	T	R572X	0.16	COPDGene
PPM1D	17	60663388	C	T	R552*	0.11	UK Biobank
PPM1D	17	60663388	C	T	R552*	0.10	UK Biobank
PPM1D	17	60663388	C	T	R552*	0.05	UK Biobank
PPM1D	17	60663388	C	T	R552X	0.16	Additional TOPMED - ECLIPSE
PPM1D	17	60663388	C	T	R552X	0.14	Additional TOPMED - JHS
PPM1D	17	60663388	C	T	R552X	0.13	Additional TOPMED - ECLIPSE
PPM1D	17	60663388	C	T	R552X	0.11	Additional TOPMED - JHS
PPM1D	17	60663380	AG	A	K549fs	0.14	Additional TOPMED - MESA
PPM1D	17	60663376	A	T	K548X	0.13	COPDGene
PPM1D	17	60663365	G	GC	G544fs	0.12	Additional TOPMED - ARIC
PPM1D	17	60663352	GA	G	E540fs	0.24	Additional TOPMED - ECLIPSE
PPM1D	17	60663346	TTA	T	L538fs	0.08	UK Biobank
PPM1D	17	60663343	AC	A	T537fs	0.08	UK Biobank
PPM1D	17	60663340	AG	A	R536fs	0.37	COPDGene
PPM1D	17	60663333	CT	C	F534fs	0.17	COPDGene
PPM1D	17	60663333	C	CT	K535fs	0.31	UK Biobank
PPM1D	17	60663333	C	CTT	N533fs	0.45	Additional TOPMED - MESA
PPM1D	17	60663333	C	CT	N533fs	0.11	COPDGene
PPM1D	17	60663329	CA	C	T532fs	0.21	COPDGene
PPM1D	17	60663326	CA	C	P531fs	0.17	Additional TOPMED - ECLIPSE
PPM1D	17	60663324	TC	T	P531fs	0.19	Additional TOPMED - MESA
PPM1D	17	60663292	CA	C	Q520fs	0.13	Additional TOPMED - ECLIPSE
PPM1D	17	60663281	C	A	S516*	0.16	UK Biobank
PPM1D	17	60663269	AT	A	N512fs	0.12	COPDGene
PPM1D	17	60663262	CA	C	N512fs	0.08	UK Biobank
PPM1D	17	60663262	CA	C	N512fs	0.06	UK Biobank
PPM1D	17	60663262	CA	C	N512fs	0.05	UK Biobank
PPM1D	17	60663262	C	CA	Q510fs	0.30	Additional TOPMED - ARIC
PPM1D	17	60663253	G	GTC	V507fs	0.08	Additional TOPMED - MESA
PPM1D	17	60663185	T	G	L484*	0.30	UK Biobank
PPM1D	17	60663185	T	A	L484X	0.19	Additional TOPMED - MESA
PPM1D	17	60663185	T	G	L484X	0.13	COPDGene
PPM1D	17	60663181	AC	A	T483fs	0.38	COPDGene
PPM1D	17	60663168	C	A	C478X	0.81	Additional TOPMED - CFS
PPM1D	17	60663151	CCACTTGA	A	P473fs	0.20	COPDGene
PPM1D	17	60663122	G	CT	G463fs	0.31	COPDGene
PPM1D	17	60663121	GGT	G	G463fs	0.21	COPDGene
PPM1D	17	60663088	GT	G	V452fs	0.18	Additional TOPMED - ARIC
PPM1D	17	60663083	T	G	L450X	0.23	Additional TOPMED - MESA
PPM1D	17	60663019	AG	A	R429fs	0.26	COPDGene
PPM1D	17	60663014	G	A	W427X	0.17	COPDGene
PPM1D	17	60656804	TGA	A	V408fs	0.14	COPDGene
PPM1D	17	60656793	AGAAACCT	T	E405fs	0.20	COPDGene
PPM1D	17	58740884	C	T	Q597*	0.19	ICGN-EOCPD
PPM1D	17	58740836	C	T	R581*	0.05	ICGN-EOCPD
PPM1D	17	58740809	C	T	R572*	0.08	ICGN-EOCPD

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
PPM1D	17	58740806	C	T	Q571*	0.07	ICGN-EOCOPD
PPM1D	17	58740749	C	T	R552*	0.27	ICGN-EOCOPD
PPM1D	17	58740749	C	T	R552*	0.13	ICGN-EOCOPD
PPM1D	17	58740623	CA	C	N512fs	0.06	ICGN-EOCOPD
PPM1D	17	58740517	TG	T	E475fs	0.10	ICGN-EOCOPD
PPM1D	17	58740505	TC	T	P471fs	0.03	ICGN-EOCOPD
PPM1D	17	58740375	G	A	W427*	0.23	ICGN-EOCOPD
PRPF8	17	1660445	A	T	M1591K	0.06	UK Biobank
PRPF8	17	1660436	C	T	C1594Y	0.13	UK Biobank
PRPF8	17	1660435	A	C	C1594W	0.22	Additional TOPMED - ECLIPSE
PRPF8	17	1660435	A	C	C1594W	0.13	COPDGene
PRPF8	17	1659995	C	T	D1598N	0.40	Additional TOPMED - ECLIPSE
PRPF8	17	1659994	T	A	D1598V	0.33	Additional TOPMED - ECLIPSE
PTEN	10	87957918	C	T	R234W	0.33	COPDGene
PTEN	10	87933099	G	T	E114X	0.12	Additional TOPMED - ECLIPSE
PTPN11	12	112891153	A	A	G163S	0.04	ICGN-EOCOPD
PTPN11	12	112489084	A	A	G503E	0.12	COPDGene
RAD21	8	116857372	ACT	A	E194fs	0.10	Additional TOPMED - MESA
RAD21	8	116856290	T	A	c.815-2A>T	0.20	Additional TOPMED - FHS
RAD21	8	116852549	C	G	D441H	0.10	UK Biobank
RAD21	8	116852092	CTCATCTGCAATTGG	C	ce11-4CCAATTGCAGATGAG>G	0.08	UK Biobank
RUNX1	21	36231809	GCT	G	R164fs	0.25	ICGN-EOCOPD
RUNX1	21	34880569	G	A	R139X	0.33	COPDGene
RUNX1	21	34834586	A	T	L183Q	0.07	UK Biobank
RUNX1	21	34792610	G	A	T296M	0.10	UK Biobank
RUNX1	21	34792321	C	CCCCCAGGAGAACAGGGAGGGCCGGCCGAG	G393fs	0.07	UK Biobank
RUNX1	21	34792310	C	GCGCCGGAGT	R396H	0.06	UK Biobank
SETBP1	18	44951954	G	A	G872R	0.09	UK Biobank
SETBP1	18	44951931	C	T	T864M	0.05	UK Biobank
SETBP1	18	44951912	G	A	E858K	0.22	UK Biobank
SETD2	3	47168146	C	A	E27*	0.08	ICGN-EOCOPD
SETD2	3	47123438	G	A	R400*	0.08	UK Biobank
SETD2	3	47121248	T	A	K1130*	0.05	UK Biobank
SETD2	3	47098424	G	A	Q2284*	0.07	ICGN-EOCOPD
SETDB1	1	150951078	G	GGT	G734fs	0.46	Additional TOPMED - ECLIPSE
SETDB1	1	150951078	G	GGT	G734fs	0.26	Additional TOPMED - ARIC
SF3B1	2	198267359	C	G	K666N	0.19	ICGN-EOCOPD
SF3B1	2	198266834	T	C	K700E	0.13	ICGN-EOCOPD
SF3B1	2	198266611	C	T	G742D	0.19	ICGN-EOCOPD
SF3B1	2	197403602	G	A	R568C	0.09	UK Biobank
SF3B1	2	197403016	G	T	P580Q	0.09	UK Biobank
SF3B1	2	197402774	A	T	M620K	0.26	UK Biobank
SF3B1	2	197402767	C	G	E622D	0.45	UK Biobank
SF3B1	2	197402765	T	C	Y623C	0.22	UK Biobank
SF3B1	2	197402765	T	C	Y623C	0.07	UK Biobank
SF3B1	2	197402760	G	C	R625G	0.34	COPDGene
SF3B1	2	197402647	G	T	H662Q	0.14	COPDGene
SF3B1	2	197402647	G	C	H662Q	0.12	COPDGene
SF3B1	2	197402645	G	A	T663I	0.33	COPDGene
SF3B1	2	197402645	G	A	T663I	0.12	UK Biobank
SF3B1	2	197402645	G	A	T663I	0.10	Additional TOPMED - FHS
SF3B1	2	197402636	T	C	K666R	0.31	Additional TOPMED - ECLIPSE
SF3B1	2	197402636	T	C	K666R	0.18	Additional TOPMED - ECLIPSE
SF3B1	2	197402636	T	C	K666R	0.11	Additional TOPMED - ECLIPSE
SF3B1	2	197402636	T	G	K666T	0.17	UK Biobank
SF3B1	2	197402636	T	G	K666T	0.14	COPDGene
SF3B1	2	197402635	C	A	K666N	0.47	COPDGene
SF3B1	2	197402635	C	G	K666N	0.36	Additional TOPMED - ARIC
SF3B1	2	197402635	C	G	K666N	0.34	Additional TOPMED - ARIC
SF3B1	2	197402635	C	G	K666N	0.34	Additional TOPMED - JHS
SF3B1	2	197402635	C	A	K666N	0.31	COPDGene
SF3B1	2	197402635	C	A	K666N	0.29	COPDGene
SF3B1	2	197402635	C	A	K666N	0.20	COPDGene
SF3B1	2	197402635	C	A	K666N	0.18	COPDGene
SF3B1	2	197402635	C	A	K666N	0.16	COPDGene
SF3B1	2	197402635	C	A	K666N	0.07	UK Biobank
SF3B1	2	197402110	T	C	K700E	0.34	Additional TOPMED - ARIC
SF3B1	2	197402110	T	C	K700E	0.31	Additional TOPMED - ECLIPSE
SF3B1	2	197402110	T	C	K700E	0.19	Additional TOPMED - ECLIPSE
SF3B1	2	197402110	T	C	K700E	0.18	Additional TOPMED - ECLIPSE
SF3B1	2	197402110	T	C	K700E	0.17	UK Biobank
SF3B1	2	197402110	T	C	K700E	0.16	Additional TOPMED - ECLIPSE
SF3B1	2	197402110	T	C	K700E	0.14	UK Biobank
SF3B1	2	197402110	T	C	K700E	0.14	UK Biobank
SF3B1	2	197402110	T	C	K700E	0.13	COPDGene
SF3B1	2	197402110	T	C	K700E	0.13	UK Biobank
SF3B1	2	197402110	T	C	K700E	0.13	Additional TOPMED - JHS
SF3B1	2	197402110	T	C	K700E	0.12	COPDGene
SF3B1	2	197402110	T	C	K700E	0.11	Additional TOPMED - ECLIPSE
SF3B1	2	197402097	A	G	I704T	0.12	UK Biobank
SF3B1	2	197402068	C	T	E714K	0.09	UK Biobank
SF3B1	2	197402001	C	T	R736H	0.09	UK Biobank
SF3B1	2	197401989	C	T	G740E	0.13	COPDGene
SF3B1	2	197401887	C	T	G742D	0.20	UK Biobank
SF3B1	2	197401497	C	T	G800D	0.13	UK Biobank
SMC1A	X	53412899	A	T	ce5-TG>A	0.09	UK Biobank
SMC1A	X	53411824	AT	A	N397fs	0.06	UK Biobank
SMC1A	X	53410078	T	TG	N1024fs	0.10	ICGN-EOCOPD
SMC1A	X	53405146	G	A	Q688*	0.04	UK Biobank
SMC1A	X	53382640	G	A	R1051*	0.04	UK Biobank
SMC3	10	110602642	C	T	Q1092*	0.11	UK Biobank
SMC3	10	110599701	TA	T	T773fs	0.05	UK Biobank
SRSF2	17	76736878	G	C	P95A	0.27	UK Biobank
SRSF2	17	76736878	G	C	P95A	0.24	COPDGene
SRSF2	17	76736878	G	A	P95S	0.37	Additional TOPMED - ARIC
SRSF2	17	76736878	G	T	P95T	0.44	Additional TOPMED - FHS
SRSF2	17	76736878	G	T	P95T	0.21	UK Biobank
SRSF2	17	76736878	G	T	P95T	0.21	UK Biobank
SRSF2	17	76736877	G	GGC	94 95insR	0.04	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
SRSF2	17	76736877	G	T	P95H	0.48	Additional TOPMED - FHS
SRSF2	17	76736877	G	T	P95H	0.45	COPDGene
SRSF2	17	76736877	G	T	P95H	0.40	COPDGene
SRSF2	17	76736877	G	T	P95H	0.36	Additional TOPMED - MESA
SRSF2	17	76736877	G	T	P95H	0.34	COPDGene
SRSF2	17	76736877	G	T	P95H	0.29	COPDGene
SRSF2	17	76736877	G	T	P95H	0.29	COPDGene
SRSF2	17	76736877	G	T	P95H	0.28	COPDGene
SRSF2	17	76736877	G	T	P95H	0.28	COPDGene
SRSF2	17	76736877	G	T	P95H	0.26	Additional TOPMED - FHS
SRSF2	17	76736877	G	T	P95H	0.21	UK Biobank
SRSF2	17	76736877	G	T	P95H	0.20	COPDGene
SRSF2	17	76736877	G	T	P95H	0.19	COPDGene
SRSF2	17	76736877	G	T	P95H	0.17	UK Biobank
SRSF2	17	76736877	G	T	P95H	0.17	COPDGene
SRSF2	17	76736877	G	T	P95H	0.14	Additional TOPMED - ECLIPSE
SRSF2	17	76736877	G	T	P95H	0.14	Additional TOPMED - ECLIPSE
SRSF2	17	76736877	G	T	P95H	0.11	COPDGene
SRSF2	17	76736877	G	T	P95H	0.10	UK Biobank
SRSF2	17	76736877	G	T	P95H	0.05	UK Biobank
SRSF2	17	76736877	G	A	P95L	0.48	UK Biobank
SRSF2	17	76736877	G	A	P95L	0.46	COPDGene
SRSF2	17	76736877	G	A	P95L	0.21	COPDGene
SRSF2	17	76736877	G	A	P95L	0.14	Additional TOPMED - MESA
SRSF2	17	76736877	G	A	P95L	0.11	COPDGene
SRSF2	17	76736877	G	A	P95L	0.11	Additional TOPMED - ARIC
SRSF2	17	76736877	G	A	P95L	0.10	UK Biobank
SRSF2	17	76736877	G	A	P95L	0.07	UK Biobank
SRSF2	17	76736877	G	C	P95R	0.41	Additional TOPMED - FHS
SRSF2	17	76736877	G	C	P95R	0.34	Additional TOPMED - ECLIPSE
SRSF2	17	76736877	G	C	P95R	0.32	Additional TOPMED - FHS
SRSF2	17	76736877	G	C	P95R	0.29	COPDGene
SRSF2	17	76736877	G	C	P95R	0.29	COPDGene
SRSF2	17	76736877	G	C	P95R	0.27	UK Biobank
SRSF2	17	76736877	G	C	P95R	0.25	Additional TOPMED - FHS
SRSF2	17	76736877	G	C	P95R	0.18	Additional TOPMED - ARIC
SRSF2	17	76736877	G	C	P95R	0.16	COPDGene
SRSF2	17	76736877	G	C	P95R	0.13	COPDGene
SRSF2	17	76736877	G	C	P95R	0.12	COPDGene
SRSF2	17	76736877	G	C	P95R	0.06	UK Biobank
STAG2	X	124063868	AC	A	Q615fs	0.16	COPDGene
STAG2	X	124061769	A	T	c.1535-2A>T	0.18	Additional TOPMED - MESA
STAG2	X	124051395	G	A	c.1196+1G>A	0.23	Additional TOPMED - FHS
STAG2	X	124050293	G	A	W334*	0.11	UK Biobank
STAG2	X	124047461	C	T	R259X	0.32	COPDGene
STAG2	X	124042567	A	G	c.e7-2A>G	0.09	UK Biobank
STAG2	X	124031126	G	A	c.288+1G>A	0.15	Additional TOPMED - JHS
STAG2	X	124031042	C	T	R69*	0.07	UK Biobank
STAG2	X	123220396	G	T		0.06	ICGN-EEOCPD
SUZ12	17	31993250	G	T	E404X	0.28	Additional TOPMED - JHS
TET2	4	106197338	A	G	R1891G	0.12	ICGN-EEOCPD
TET2	4	106196306	C	T	Q1547*	0.07	ICGN-EEOCPD
TET2	4	106193977	C	A	S1480Y	0.06	ICGN-EEOCPD
TET2	4	106193723	A	ATG	T1397fs	0.18	ICGN-EEOCPD
TET2	4	106190850	C	CT	C1378fs	0.29	ICGN-EEOCPD
TET2	4	106182962	C	A	A1334E	0.05	ICGN-EEOCPD
TET2	4	106182930	GTC	G	H1325fs	0.12	ICGN-EEOCPD
TET2	4	106180810	AC	A	C1281fs	0.05	ICGN-EEOCPD
TET2	4	106180775	G	A		0.07	ICGN-EEOCPD
TET2	4	106164920	G	A	C1263Y	0.14	ICGN-EEOCPD
TET2	4	106164861	ACT	A	Y1245fs	0.16	ICGN-EEOCPD
TET2	4	106164734	G	A	R1201H	0.07	ICGN-EEOCPD
TET2	4	106164082	TG	T	V1199fs	0.06	ICGN-EEOCPD
TET2	4	106164003	G	T	K1171N	0.04	ICGN-EEOCPD
TET2	4	106158275	C	G	S1059*	0.07	ICGN-EEOCPD
TET2	4	106157624	C	A	S842*	0.07	ICGN-EEOCPD
TET2	4	106157059	CA	C	K655fs	0.04	ICGN-EEOCPD
TET2	4	106157059	CA	C	K655fs	0.03	ICGN-EEOCPD
TET2	4	106156869	TC	T	Q591fs	0.12	ICGN-EEOCPD
TET2	4	106156570	C	T	Q491*	0.24	ICGN-EEOCPD
TET2	4	105276482	T	C	F1991S	0.08	UK Biobank
TET2	4	105276348	C	CA	V1949fs	0.41	UK Biobank
TET2	4	105276347	G	C	G1946A	0.37	UK Biobank
TET2	4	105276336	GA	G	K1943fs	0.53	UK Biobank
TET2	4	105276302	A	G	E1931G	0.03	UK Biobank
TET2	4	105276284	C	A	A1925D	0.04	UK Biobank
TET2	4	105276281	A	C	K1924T	0.06	UK Biobank
TET2	4	105276274	G	C	A1922P	0.14	UK Biobank
TET2	4	105276244	C	C	H1912D	0.13	Additional TOPMED - ECLIPSE
TET2	4	105276244	C	T	H1912Y	0.30	Additional TOPMED - ECLIPSE
TET2	4	105276223	A	G	K1905E	0.11	UK Biobank
TET2	4	105276221	A	G	H1904R	0.23	UK Biobank
TET2	4	105276221	A	G	H1904R	0.14	Additional TOPMED - FHS
TET2	4	105276218	A	C	Q1903P	0.08	UK Biobank
TET2	4	105276217	C	T	Q1903*	0.11	UK Biobank
TET2	4	105276205	C	A	L1899I	0.03	UK Biobank
TET2	4	105276203	C	G	S1898C	0.08	UK Biobank
TET2	4	105276203	C	T	S1898F	0.37	Additional TOPMED - ARIC
TET2	4	105276191	C	A	P1894H	0.39	COPDGene
TET2	4	105276191	C	G	P1894R	0.50	COPDGene
TET2	4	105276162	C	CGTTG	P1885fs	0.08	UK Biobank
TET2	4	105276160	A	G	T1884A	0.24	UK Biobank
TET2	4	105276160	A	G	T1884A	0.03	UK Biobank
TET2	4	105276155	C	T	A1882V	0.18	UK Biobank
TET2	4	105276152	A	C	H1881P	0.02	UK Biobank
TET2	4	105276151	C	T	H1881Y	0.20	UK Biobank
TET2	4	105276145	G	A	E1879K	0.12	UK Biobank
TET2	4	105276136	G	A	A1876T	0.23	UK Biobank
TET2	4	105276135	T	A	C1875*	0.04	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
TET2	4	105276128	T	G	I1873S	0.35	COPDGene
TET2	4	105276128	T	C	I1873T	0.20	Additional TOPMED - ECLIPSE
TET2	4	105276128	T	C	I1873T	0.16	UK Biobank
TET2	4	105276128	T	C	I1873T	0.13	UK Biobank
TET2	4	105276128	T	C	I1873T	0.09	UK Biobank
TET2	4	105276128	T	C	I1873T	0.08	UK Biobank
TET2	4	105276128	T	C	I1873T	0.06	UK Biobank
TET2	4	105276128	T	C	I1873T	0.03	UK Biobank
TET2	4	105276126	CATTG	C	I1873fs	0.04	UK Biobank
TET2	4	105276126	C	CA	L1872fs	0.14	Additional TOPMED - JHS
TET2	4	105276112	C	T	H1868Y	0.15	UK Biobank
TET2	4	105276112	C	T	H1868Y	0.13	UK Biobank
TET2	4	105276098	C	T	A1863V	0.36	Additional TOPMED - ARIC
TET2	4	105276092	G	A	G1861E	0.07	UK Biobank
TET2	4	105276092	G	T	G1861V	0.20	Additional TOPMED - MESA
TET2	4	105276091	G	A	G1861R	0.18	UK Biobank
TET2	4	105276085	AT	A	I1859fs	0.22	COPDGene
TET2	4	105276084	CA	C	I1859fs	0.37	COPDGene
TET2	4	105276053	C	G	S1848*	0.04	UK Biobank
TET2	4	105276053	C	G	S1848*	0.04	UK Biobank
TET2	4	105276053	C	CA	S1848fs	0.09	Additional TOPMED - JHS
TET2	4	105276051	G	A	W1847*	0.08	UK Biobank
TET2	4	105276050	G	A	W1847*	0.07	UK Biobank
TET2	4	105276050	G	A	W1847*	0.05	UK Biobank
TET2	4	105276050	G	A	W1847X	0.14	Additional TOPMED - MESA
TET2	4	105276037	ACCGATGAG	A	N1843fs	0.11	Additional TOPMED - FHS
TET2	4	105276031	G	T	E1841X	0.25	COPDGene
TET2	4	105276011	AG	A	Q1834fs	0.22	COPDGene
TET2	4	105276010	C	T	Q1834X	0.21	COPDGene
TET2	4	105276010	C	T	Q1834X	0.15	Additional TOPMED - JHS
TET2	4	105275992	C	T	Q1828*	0.29	UK Biobank
TET2	4	105275983	C	T	Q1825*	0.08	UK Biobank
TET2	4	105275983	C	T	Q1825*	0.08	UK Biobank
TET2	4	105275957	TACACAATTAAGTGATGCTA	T	L1816fs	0.10	COPDGene
TET2	4	105275872	GA	G	D1788fs	0.12	COPDGene
TET2	4	105275857	CA	C	Q1783fs	0.23	COPDGene
TET2	4	105275808	CA	C	S1767fs	0.25	COPDGene
TET2	4	105275808	C	G	Y1766X	0.13	Additional TOPMED - FHS
TET2	4	105275786	CT	C	S1760fs	0.08	UK Biobank
TET2	4	105275763	TA	T	N1753fs	0.05	UK Biobank
TET2	4	105275637	T	A	C1709*	0.11	UK Biobank
TET2	4	105275598	TG	T	G1697fs	0.16	UK Biobank
TET2	4	105275569	C	T	Q1687*	0.08	UK Biobank
TET2	4	105275569	C	T	Q1687X	0.27	COPDGene
TET2	4	105275569	C	T	Q1687X	0.21	COPDGene
TET2	4	105275564	ATAGCCAGAGTT	A	N1685fs	0.14	Additional TOPMED - ARIC
TET2	4	105275522	G	GTC	S1671fs	0.21	Additional TOPMED - MESA
TET2	4	105275459	CT	C	S1650fs	0.13	Additional TOPMED - MESA
TET2	4	105275457	T	G	Y1649*	0.07	UK Biobank
TET2	4	105275423	C	G	S1638*	0.07	UK Biobank
TET2	4	105275399	CA	C	Y1631fs	0.20	UK Biobank
TET2	4	105275387	CCCAATAT	C	T1626fs	0.11	Additional TOPMED - FHS
TET2	4	105275380	C	T	Q1624*	0.13	UK Biobank
TET2	4	105275305	TC	T	S1599fs	0.28	COPDGene
TET2	4	105275270	AT	A	D1587fs	0.07	UK Biobank
TET2	4	105275270	A	AT	I1588fs	0.12	UK Biobank
TET2	4	105275173	G	GA	E1555fs	0.15	Additional TOPMED - MESA
TET2	4	105275171	C	CA	T1554fs	0.42	COPDGene
TET2	4	105275167	C	CA	T1554fs	0.06	UK Biobank
TET2	4	105275095	C	T	Q1529*	0.09	UK Biobank
TET2	4	105275086	C	T	Q1526*	0.10	UK Biobank
TET2	4	105275086	C	T	Q1526X	0.12	COPDGene
TET2	4	105275075	T	TG	Q1523fs	0.09	UK Biobank
TET2	4	105275064	AG	A	G1519fs	0.13	COPDGene
TET2	4	105275056	C	T	R1516*	0.15	UK Biobank
TET2	4	105275056	C	T	R1516X	0.21	Additional TOPMED - MESA
TET2	4	105275056	C	T	R1516X	0.18	Additional TOPMED - ARIC
TET2	4	105272919	G	A	c.4537+1G>A	0.11	COPDGene
TET2	4	105272909	C	T	Q1510X	0.39	Additional TOPMED - MESA
TET2	4	105272871	G	A	S1497*	0.07	UK Biobank
TET2	4	105272855	GA	G	K1493fs	0.15	UK Biobank
TET2	4	105272825	CT	C	L1482fs	0.17	UK Biobank
TET2	4	105272798	A	AT	K1473fs	0.12	UK Biobank
TET2	4	105272774	C	T	R1465*	0.37	UK Biobank
TET2	4	105272774	C	T	R1465*	0.23	UK Biobank
TET2	4	105272774	C	T	R1465*	0.14	UK Biobank
TET2	4	105272774	C	T	R1465*	0.04	UK Biobank
TET2	4	105272741	G	GTA	V1454fs	0.26	COPDGene
TET2	4	105272738	A	T	K1453X	0.12	Additional TOPMED - JHS
TET2	4	105272735	C	T	R1452*	0.07	UK Biobank
TET2	4	105272735	C	T	R1452*	0.04	UK Biobank
TET2	4	105272735	C	T	R1452X	0.48	Additional TOPMED - ECLIPSE
TET2	4	105272714	C	T	Q1445X	0.11	Additional TOPMED - ECLIPSE
TET2	4	105272692	G	GA	E1437fs	0.33	COPDGene
TET2	4	105272692	G	GA	R1440fs	0.43	UK Biobank
TET2	4	105272692	G	GA	R1440fs	0.21	UK Biobank
TET2	4	105272674	TGTGGAAGCTCAGGAGGAGAAAAACCGA	T	V1432fs	0.54	Additional TOPMED - FHS
TET2	4	105272652	CT	C	S1424fs	0.10	COPDGene
TET2	4	105272644	CAA	C	K1422fs	0.43	UK Biobank
TET2	4	105272637	CT	C	P1419fs	0.30	COPDGene
TET2	4	105272621	C	T	Q1414*	0.04	UK Biobank
TET2	4	105272603	G	T	G1408*	0.18	UK Biobank
TET2	4	105272591	C	T	R1404*	0.15	UK Biobank
TET2	4	105272574	T	C	L1398P	0.34	Additional TOPMED - JHS
TET2	4	105272571	C	A	T1397N	0.10	UK Biobank
TET2	4	105272563	G	A	c.4183-1G>A	0.17	Additional TOPMED - FHS
TET2	4	105272562	AG	A	c.e10-2AG>A	0.25	UK Biobank
TET2	4	105272562	AG	A	c.e10-2AG>A	0.09	UK Biobank
TET2	4	105269748	G	GT	c.e9+1G>GT	0.08	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
TET2	4	105269741	C	A	S1392R	0.08	UK Biobank
TET2	4	105269715	G	A	D1384N	0.06	UK Biobank
TET2	4	105269710	A	C	H1382P	0.12	Additional TOPMED - ARIC
TET2	4	105269710	A	G	H1382R	0.27	UK Biobank
TET2	4	105269710	A	G	H1382R	0.04	UK Biobank
TET2	4	105269708	CCA	C	H1382fs	0.23	COPDGene
TET2	4	105269703	C	G	H1380D	0.20	COPDGene
TET2	4	105269703	C	C	H1380Y	0.09	COPDGene
TET2	4	105269699	T	TGC	C1378fs	0.08	COPDGene
TET2	4	105269698	G	A	C1378Y	0.09	UK Biobank
TET2	4	105269686	G	A	C1374Y	0.28	UK Biobank
TET2	4	105269673	G	T	G1370W	0.32	UK Biobank
TET2	4	105269671	C	T	S1369L	0.06	UK Biobank
TET2	4	105269671	C	A	S1369X	0.14	COPDGene
TET2	4	105269669	C	G	F1368L	0.23	Additional TOPMED - ECLIPSE
TET2	4	105269666	AT	A	F1368fs	0.45	Additional TOPMED - FHS
TET2	4	105269662	G	A	R1366H	0.25	UK Biobank
TET2	4	105269662	G	A	R1366H	0.21	UK Biobank
TET2	4	105269662	G	A	R1366H	0.10	UK Biobank
TET2	4	105269662	G	C	R1366P	0.12	UK Biobank
TET2	4	105269661	C	A	R1366S	0.06	UK Biobank
TET2	4	105269646	G	A	G1361S	0.20	UK Biobank
TET2	4	105269644	T	G	L1360R	0.19	Additional TOPMED - MESA
TET2	4	105269640	C	T	R1359C	0.41	COPDGene
TET2	4	105269640	C	T	R1359C	0.13	UK Biobank
TET2	4	105269640	C	A	R1359S	0.09	UK Biobank
TET2	4	105269638	G	A	C1358Y	0.09	UK Biobank
TET2	4	105269624	CAG	C	R1354fs	0.31	Additional TOPMED - ECLIPSE
TET2	4	105269624	CAG	C	R1354fs	0.27	Additional TOPMED - JHS
TET2	4	105269624	CAG	C	R1354fs	0.06	Additional TOPMED - FHS
TET2	4	105269615	AT	A	Y1351fs	0.05	UK Biobank
TET2	4	105269609	G	A	c.4045-1G>A	0.32	Additional TOPMED - MESA
TET2	4	105269609	G	T	c.4045-1G>T	0.12	Additional TOPMED - JHS
TET2	4	105261849	G	A	c.e8+1G>A	0.20	UK Biobank
TET2	4	105261847	A	G	Q1348R	0.22	Additional TOPMED - FHS
TET2	4	105261824	T	TG	L1340fs	0.16	COPDGene
TET2	4	105261808	CA	C	P1335fs	0.51	Additional TOPMED - JHS
TET2	4	105261790	T	C	L1329P	0.13	COPDGene
TET2	4	105261790	T	A	L1329Q	0.29	COPDGene
TET2	4	105261764	GA	G	K1321fs	0.22	COPDGene
TET2	4	105259739	G	GT	K1310fs	0.12	UK Biobank
TET2	4	105259734	AG	A	R1307fs	0.14	COPDGene
TET2	4	105259734	A	G	R1307G	0.09	UK Biobank
TET2	4	105259715	T	G	F1300L	0.10	UK Biobank
TET2	4	105259714	T	G	F1300C	0.11	UK Biobank
TET2	4	105259708	G	GT	C1298fs	0.11	Additional TOPMED - JHS
TET2	4	105259708	G	A	C1298Y	0.13	Additional TOPMED - JHS
TET2	4	105259708	G	A	C1298Y	0.12	COPDGene
TET2	4	105259705	G	A	G1297E	0.20	COPDGene
TET2	4	105259696	A	G	Y1294C	0.18	Additional TOPMED - ECLIPSE
TET2	4	105259694	G	GT	Y1294fs	0.10	UK Biobank
TET2	4	105259687	G	A	W1291*	0.06	UK Biobank
TET2	4	105259684	C	T	S1290L	0.16	Additional TOPMED - MESA
TET2	4	105259681	G	T	C1289F	0.06	UK Biobank
TET2	4	105259675	T	C	F1287S	0.24	UK Biobank
TET2	4	105259675	T	C	F1287S	0.08	UK Biobank
TET2	4	105259675	T	C	F1287S	0.05	UK Biobank
TET2	4	105259672	C	CTT	G1288fs	0.11	UK Biobank
TET2	4	105259639	G	A	G1275E	0.12	UK Biobank
TET2	4	105259628	C	G	C1271W	0.34	COPDGene
TET2	4	105259626	T	TG	C1271fs	0.11	COPDGene
TET2	4	105259625	T	TTG	T1270fs	0.10	Additional TOPMED - FHS
TET2	4	105243757	G	A	R1261H	0.10	UK Biobank
TET2	4	105243756	C	T	R1261C	0.35	COPDGene
TET2	4	105243756	C	T	R1261C	0.34	COPDGene
TET2	4	105243756	C	T	R1261C	0.20	COPDGene
TET2	4	105243756	C	T	R1261C	0.17	UK Biobank
TET2	4	105243756	C	T	R1261C	0.11	UK Biobank
TET2	4	105243756	C	T	R1261C	0.08	UK Biobank
TET2	4	105243756	C	A	R1261S	0.15	Additional TOPMED - JHS
TET2	4	105243740	C	A	Y1255*	0.06	UK Biobank
TET2	4	105243718	T	G	L1248R	0.29	COPDGene
TET2	4	105243709	ACTCGGAG	A	S1246fs	0.40	UK Biobank
TET2	4	105243706	T	C	L1244P	0.13	Additional TOPMED - FHS
TET2	4	105243704	ACT	A	Y1245fs	0.15	UK Biobank
TET2	4	105243704	ACT	A	Y1245fs	0.05	UK Biobank
TET2	4	105243690	TC	T	S1239fs	0.24	Additional TOPMED - ARIC
TET2	4	105243664	T	TC	I1230fs	0.29	COPDGene
TET2	4	105243646	C	G	A1224G	0.03	UK Biobank
TET2	4	105243631	A	C	H1219P	0.05	UK Biobank
TET2	4	105243622	G	A	R1216Q	0.22	COPDGene
TET2	4	105243621	C	T	R1216*	0.07	UK Biobank
TET2	4	105243621	C	T	R1216*	0.06	UK Biobank
TET2	4	105243621	C	T	R1216*	0.05	UK Biobank
TET2	4	105243621	C	T	R1216*	0.04	UK Biobank
TET2	4	105243621	C	T	R1216X	0.43	COPDGene
TET2	4	105243621	C	T	R1216X	0.39	Additional TOPMED - FHS
TET2	4	105243616	G	A	R1214Q	0.12	UK Biobank
TET2	4	105243616	G	A	R1214Q	0.04	UK Biobank
TET2	4	105243615	C	T	R1214W	0.08	UK Biobank
TET2	4	105243615	C	T	R1214W	0.05	UK Biobank
TET2	4	105243615	C	T	R1214W	0.05	UK Biobank
TET2	4	105243612	G	A	V1213M	0.30	Additional TOPMED - ECLIPSE
TET2	4	105243612	G	A	V1213M	0.09	UK Biobank
TET2	4	105243610	T	C	L1212S	0.07	UK Biobank
TET2	4	105243607	G	A	C1211Y	0.36	COPDGene
TET2	4	105243601	T	C	L1209P	0.24	COPDGene
TET2	4	105243597	A	T	K1208*	0.11	UK Biobank
TET2	4	105243587	C	A	S1204R	0.05	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
TET2	4	105243569	G	T	c.e6-1G>T	0.12	UK Biobank
TET2	4	105242929	T	C	c.3594+2T>C	0.16	COPDGene
TET2	4	105242920	C	CT	K1197fs	0.29	UK Biobank
TET2	4	105242914	C	G	P1194R	0.24	UK Biobank
TET2	4	105242912	TC	T	P1194fs	0.16	Additional TOPMED - FHS
TET2	4	105242904	C	T	Q1191X	0.13	COPDGene
TET2	4	105241429	G	A	R1167K	0.33	UK Biobank
TET2	4	105241421	G	A	M1164I	0.13	COPDGene
TET2	4	105241402	C	T	A1158V	0.07	UK Biobank
TET2	4	105241389	G	A	G1154S	0.16	Additional TOPMED - FHS
TET2	4	105241372	A	G	Y1148C	0.21	Additional TOPMED - FHS
TET2	4	105241338	G	A	c.3410-1G>A	0.12	Additional TOPMED - JHS
TET2	4	105241320	TCTTCTATTATCTCAACAGAG	T	E1137fs	0.11	COPDGene
TET2	4	105237352	G	C	c.e3+1G>C	0.06	UK Biobank
TET2	4	105237352	G	GT	c.e3+1G>GT	0.41	UK Biobank
TET2	4	105237351	G	A	E1137K	0.21	COPDGene
TET2	4	105237349	TAG	T	V1136fs	0.20	Additional TOPMED - ARIC
TET2	4	105237347	T	G	C1135W	0.15	Additional TOPMED - MESA
TET2	4	105237346	GT	G	C1135fs	0.20	UK Biobank
TET2	4	105237346	G	A	C1135Y	0.20	UK Biobank
TET2	4	105237325	A	ATT	Y1128fs	0.09	Additional TOPMED - MESA
TET2	4	105237305	T	TA	D1121fs	0.32	Additional TOPMED - ECLIPSE
TET2	4	105237297	T	A	L1119I	0.08	UK Biobank
TET2	4	105237289	TA	T	N1118fs	0.13	UK Biobank
TET2	4	105237281	T	TA	D1113fs	0.11	COPDGene
TET2	4	105237274	T	A	L1111*	0.14	UK Biobank
TET2	4	105237253	TTATA	T	F1104fs	0.08	UK Biobank
TET2	4	105237249	AATTT	A	N1103fs	0.21	UK Biobank
TET2	4	105237226	GAA	G	R1095fs	0.15	COPDGene
TET2	4	105237204	T	TC	E1089fs	0.04	UK Biobank
TET2	4	105237157	C	CA	A1072fs	0.29	Additional TOPMED - MESA
TET2	4	105237144	C	T	Q1068*	0.17	UK Biobank
TET2	4	105237127	TCA	T	V1062fs	0.31	COPDGene
TET2	4	105237099	C	T	Q1053X	0.44	Additional TOPMED - FHS
TET2	4	105237093	C	T	Q1051*	0.26	UK Biobank
TET2	4	105237093	C	T	Q1051X	0.14	COPDGene
TET2	4	105237080	T	TA	T1047fs	0.33	UK Biobank
TET2	4	105237044	GT	G	H1036fs	0.09	UK Biobank
TET2	4	105237044	G	GT	Q1034fs	0.53	COPDGene
TET2	4	105237030	C	T	Q1030X	0.35	Additional TOPMED - JHS
TET2	4	105237027	G	T	E1029*	0.09	UK Biobank
TET2	4	105237000	C	T	Q1020X	0.11	COPDGene
TET2	4	105236989	GT	G	C1016fs	0.07	COPDGene
TET2	4	105236983	C	CA	A1014fs	0.31	Additional TOPMED - JHS
TET2	4	105236961	A	AT	T1007fs	0.14	UK Biobank
TET2	4	105236958	GTAAC	G	V1006fs	0.19	Additional TOPMED - MESA
TET2	4	105236951	GA	G	K1004fs	0.34	Additional TOPMED - MESA
TET2	4	105236951	GA	G	K1005fs	0.06	UK Biobank
TET2	4	105236951	GA	G	K1005fs	0.05	UK Biobank
TET2	4	105236921	GC	G	H994fs	0.05	UK Biobank
TET2	4	105236879	GC	G	P980fs	0.11	Additional TOPMED - ECLIPSE
TET2	4	105236877	AG	A	R979fs	0.20	COPDGene
TET2	4	105236861	C	A	C973*	0.05	UK Biobank
TET2	4	105236847	C	T	Q969X	0.32	Additional TOPMED - MESA
TET2	4	105236841	C	T	Q967*	0.04	UK Biobank
TET2	4	105236826	C	T	Q962X	0.24	Additional TOPMED - FHS
TET2	4	105236820	C	T	Q960*	0.03	UK Biobank
TET2	4	105236803	G	A	W954*	0.23	UK Biobank
TET2	4	105236769	C	T	Q943*	0.07	UK Biobank
TET2	4	105236758	AG	A	T940fs	0.07	UK Biobank
TET2	4	105236752	ACACT	A	H937fs	0.10	Additional TOPMED - ARIC
TET2	4	105236742	G	T	G934X	0.12	COPDGene
TET2	4	105236728	CTG	C	V930fs	0.09	UK Biobank
TET2	4	105236699	C	G	Y919*	0.07	UK Biobank
TET2	4	105236696	G	GT	Y919fs	0.31	UK Biobank
TET2	4	105236694	AG	A	R918fs	0.09	Additional TOPMED - ARIC
TET2	4	105236688	C	T	Q916*	0.13	UK Biobank
TET2	4	105236688	C	T	Q916*	0.11	UK Biobank
TET2	4	105236674	CT	C	A911fs	0.08	Additional TOPMED - MESA
TET2	4	105236673	G	GC	A912fs	0.14	UK Biobank
TET2	4	105236637	TATAA	T	Y899fs	0.27	UK Biobank
TET2	4	105236634	G	T	G898*	0.15	UK Biobank
TET2	4	105236631	C	T	Q897*	0.19	UK Biobank
TET2	4	105236613	C	T	Q891X	0.27	Additional TOPMED - ECLIPSE
TET2	4	105236583	AG	A	R881fs	0.22	COPDGene
TET2	4	105236568	C	T	Q876*	0.07	UK Biobank
TET2	4	105236568	C	T	Q876*	0.03	UK Biobank
TET2	4	105236567	GC	G	Q876fs	0.38	COPDGene
TET2	4	105236563	CA	C	K875fs	0.16	UK Biobank
TET2	4	105236543	T	G	Y867*	0.20	UK Biobank
TET2	4	105236486	TA	T	T849fs	0.15	UK Biobank
TET2	4	105236481	C	T	Q847*	0.10	UK Biobank
TET2	4	105236463	GT	G	S842fs	0.39	UK Biobank
TET2	4	105236459	C	CCTAG	H839fs	0.09	COPDGene
TET2	4	105236458	AC	A	H839fs	0.22	COPDGene
TET2	4	105236453	TACAC	T	T838fs	0.19	Additional TOPMED - ARIC
TET2	4	105236446	C	G	S835X	0.28	Additional TOPMED - ECLIPSE
TET2	4	105236426	CA	C	K829fs	0.20	Additional TOPMED - CFS
TET2	4	105236416	C	G	S825*	0.28	UK Biobank
TET2	4	105236349	C	T	Q803X	0.24	Additional TOPMED - FHS
TET2	4	105236349	C	T	Q803X	0.14	Additional TOPMED - JHS
TET2	4	105236347	TC	T	V802fs	0.46	Additional TOPMED - MESA
TET2	4	105236325	AGC	A	S795fs	0.64	Additional TOPMED - FHS
TET2	4	105236323	C	G	S794X	0.36	Additional TOPMED - ARIC
TET2	4	105236308	AT	A	Q790fs	0.18	UK Biobank
TET2	4	105236304	GAA	G	N789fs	0.19	UK Biobank
TET2	4	105236303	TG	T	E788fs	0.20	UK Biobank
TET2	4	105236272	GC	G	G777fs	0.19	Additional TOPMED - MESA
TET2	4	105236250	C	T	Q770*	0.07	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
TET2	4	105236227	A	AC	H762fs	0.13	COPDGene
TET2	4	105236198	TA	T	K753fs	0.10	COPDGene
TET2	4	105236193	A	T	K751X	0.16	Additional TOPMED - ECLIPSE
TET2	4	105236187	C	T	Q749X	0.11	COPDGene
TET2	4	105236172	C	T	Q744*	0.06	UK Biobank
TET2	4	105236149	C	A	S736*	0.05	UK Biobank
TET2	4	105236133	C	T	Q731X	0.13	Additional TOPMED - ECLIPSE
TET2	4	105236108	GC	G	P723fs	0.17	UK Biobank
TET2	4	105236089	C	G	S716*	0.05	UK Biobank
TET2	4	105236089	C	G	S716X	0.17	Additional TOPMED - MESA
TET2	4	105236088	TCA	T	S716fs	0.26	COPDGene
TET2	4	105236074	AG	A	E711fs	0.06	UK Biobank
TET2	4	105236058	C	T	Q706*	0.15	UK Biobank
TET2	4	105236055	CA	C	Q705fs	0.10	UK Biobank
TET2	4	105236054	T	TC	Q705fs	0.14	UK Biobank
TET2	4	105236027	GT	G	S696fs	0.12	UK Biobank
TET2	4	105236025	AT	A	M695fs	0.20	COPDGene
TET2	4	105235995	C	T	Q685X	0.15	COPDGene
TET2	4	105235992	C	T	Q684*	0.26	UK Biobank
TET2	4	105235992	C	T	Q684X	0.11	Additional TOPMED - ARIC
TET2	4	105235988	C	CTG	G678fs	0.30	UK Biobank
TET2	4	105235962	C	T	Q674*	0.08	UK Biobank
TET2	4	105235962	C	T	Q674*	0.07	UK Biobank
TET2	4	105235953	GC	G	A671fs	0.12	Additional TOPMED - MESA
TET2	4	105235946	AC	A	P669fs	0.27	UK Biobank
TET2	4	105235907	AC	A	P656fs	0.13	Additional TOPMED - FHS
TET2	4	105235902	CA	C	K655fs	0.04	UK Biobank
TET2	4	105235900	TC	T	F653fs	0.08	COPDGene
TET2	4	105235896	C	T	Q652*	0.33	UK Biobank
TET2	4	105235892	TC	T	L651fs	0.17	UK Biobank
TET2	4	105235887	C	T	Q649*	0.09	UK Biobank
TET2	4	105235874	AG	A	G645fs	0.12	UK Biobank
TET2	4	105235873	AAGGT	A	G645fs	0.11	UK Biobank
TET2	4	105235836	CA	C	Q632fs	0.22	Additional TOPMED - MESA
TET2	4	105235836	C	T	Q632X	0.37	Additional TOPMED - ECLIPSE
TET2	4	105235803	AC	A	Q622fs	0.04	UK Biobank
TET2	4	105235794	C	T	Q618*	0.05	UK Biobank
TET2	4	105235778	TG	T	L615fs	0.05	UK Biobank
TET2	4	105235778	T	TG	P612fs	0.45	Additional TOPMED - JHS
TET2	4	105235719	C	T	Q593*	0.27	UK Biobank
TET2	4	105235719	C	T	Q593*	0.06	UK Biobank
TET2	4	105235715	G	GT	Y592fs	0.22	UK Biobank
TET2	4	105235713	C	T	Q591X	0.29	COPDGene
TET2	4	105235705	C	A	S588*	0.14	UK Biobank
TET2	4	105235705	C	G	S588X	0.43	Additional TOPMED - ARIC
TET2	4	105235662	C	T	Q574*	0.38	UK Biobank
TET2	4	105235658	T	TCA	F572fs	0.13	COPDGene
TET2	4	105235657	TTCACCAAGCGGAA	T	H573fs	0.05	UK Biobank
TET2	4	105235647	GC	G	P570fs	0.09	UK Biobank
TET2	4	105235634	G	A	W564*	0.15	UK Biobank
TET2	4	105235619	T	A	Y559*	0.07	UK Biobank
TET2	4	105235619	T	A	Y559X	0.19	COPDGene
TET2	4	105235611	C	T	Q557*	0.10	UK Biobank
TET2	4	105235592	AG	A	D551fs	0.25	Additional TOPMED - ARIC
TET2	4	105235590	C	T	R550*	0.15	UK Biobank
TET2	4	105235590	C	T	R550*	0.11	UK Biobank
TET2	4	105235590	C	T	R550*	0.08	UK Biobank
TET2	4	105235590	C	T	R550X	0.22	Additional TOPMED - MESA
TET2	4	105235543	GAAC	G	N535fs	0.06	UK Biobank
TET2	4	105235543	GAAC	G	R534fs	0.07	COPDGene
TET2	4	105235537	T	A	L532X	0.52	COPDGene
TET2	4	105235479	A	T	K513*	0.20	UK Biobank
TET2	4	105235468	C	G	S509X	0.17	Additional TOPMED - ARIC
TET2	4	105235436	TC	T	P499fs	0.15	Additional TOPMED - ARIC
TET2	4	105235421	AG	A	T495fs	0.44	UK Biobank
TET2	4	105235420	CA	C	A493fs	0.13	Additional TOPMED - MESA
TET2	4	105235411	T	TA	Q491fs	0.05	UK Biobank
TET2	4	105235289	G	GAA	I451fs	0.08	UK Biobank
TET2	4	105235260	C	T	Q440*	0.14	UK Biobank
TET2	4	105235253	C	A	Y437*	0.10	UK Biobank
TET2	4	105235234	TA	T	E432fs	0.34	UK Biobank
TET2	4	105235218	CTGAA	C	L426fs	0.10	COPDGene
TET2	4	105235172	TC	T	P411fs	0.14	Additional TOPMED - JHS
TET2	4	105235158	CT	C	L406fs	0.17	Additional TOPMED - ECLIPSE
TET2	4	105235149	C	T	Q403X	0.24	Additional TOPMED - ARIC
TET2	4	105235096	C	A	S385*	0.15	UK Biobank
TET2	4	105235052	T	G	Y370X	0.15	Additional TOPMED - MESA
TET2	4	105235003	C	G	S354*	0.27	UK Biobank
TET2	4	105235003	C	G	S354X	0.12	COPDGene
TET2	4	105234975	A	T	K345X	0.27	Additional TOPMED - MESA
TET2	4	105234966	G	T	G342X	0.21	COPDGene
TET2	4	105234963	C	T	Q341*	0.08	UK Biobank
TET2	4	105234934	T	TA	C332fs	0.09	UK Biobank
TET2	4	105234933	AT	A	I331fs	0.31	Additional TOPMED - FHS
TET2	4	105234922	C	A	S327*	0.08	UK Biobank
TET2	4	105234915	C	T	Q325*	0.17	UK Biobank
TET2	4	105234915	C	T	Q325X	0.24	Additional TOPMED - ARIC
TET2	4	105234912	C	T	Q324*	0.12	UK Biobank
TET2	4	105234900	GA	G	E320fs	0.13	COPDGene
TET2	4	105234893	GA	G	K318fs	0.10	COPDGene
TET2	4	105234891	C	T	Q317*	0.04	UK Biobank
TET2	4	105234784	ACT	A	S282fs	0.09	UK Biobank
TET2	4	105234780	TC	T	S280fs	0.18	UK Biobank
TET2	4	105234763	TC	T	I274fs	0.17	Additional TOPMED - MESA
TET2	4	105234763	TC	T	I274fs	0.10	Additional TOPMED - ARIC
TET2	4	105234763	TC	T	I274fs	0.10	COPDGene
TET2	4	105234763	TC	T	N275fs	0.15	UK Biobank
TET2	4	105234763	TC	T	N275fs	0.13	UK Biobank
TET2	4	105234763	TC	T	N275fs	0.10	UK Biobank

Gene	Chromosome	Position	Reference	Alternate	Consequence	Variant Allele Fraction	Cohort
TET2	4	105234763	TC	T	N275fs	0.07	UK Biobank
TET2	4	105234763	TC	T	N275fs	0.06	UK Biobank
TET2	4	105234700	ACAGT	A	S254fs	0.14	UK Biobank
TET2	4	105234681	TCTCA	T	H248fs	0.17	UK Biobank
TET2	4	105234636	C	T	Q232*	0.16	UK Biobank
TET2	4	105234633	TC	T	S231fs	0.23	UK Biobank
TET2	4	105234621	GA	G	T229fs	0.18	UK Biobank
TET2	4	105234621	G	GA	T229fs	0.17	UK Biobank
TET2	4	105234591	TC	T	V218fs	0.41	UK Biobank
TET2	4	105234565	C	CT	N209fs	0.05	UK Biobank
TET2	4	105234527	GA	G	N196fs	0.11	COPDGene
TET2	4	105234499	A	AG	K188fs	0.21	UK Biobank
TET2	4	105234368	CG	C	D143fs	0.13	Additional TOPMED - ARIC
TET2	4	105234368	CG	C	D143fs	0.05	UK Biobank
TET2	4	105234361	A	ATG	D143fs	0.06	UK Biobank
TET2	4	105234245	TTCTC	T	S104fs	0.05	UK Biobank
TET2	4	105234210	C	T	Q90X	0.22	Additional TOPMED - ARIC
TET2	4	105234191	AG	A	G84fs	0.16	COPDGene
TET2	4	105234164	GA	G	S75fs	0.15	Additional TOPMED - ARIC
TET2	4	105234155	T	TA	N71fs	0.25	Additional TOPMED - ECLIPSE
TP53	17	7676193	C	A	G59V	0.07	UK Biobank
TP53	17	7676121	G	A	A83V	0.04	UK Biobank
TP53	17	7675995	G	A	T125M	0.09	UK Biobank
TP53	17	7675992	A	A	c.e4-2T>G	0.32	UK Biobank
TP53	17	7675233	A	T	S127T	0.08	UK Biobank
TP53	17	7675230	G	T	P128T	0.28	UK Biobank
TP53	17	7675217	T	A	K132M	0.18	Additional TOPMED - ECLIPSE
TP53	17	7675183	CACAGGGCAGGCTTGGCCAGTTGGCA	C	C135fs	0.06	UK Biobank
TP53	17	7675139	C	A	R158L	0.22	UK Biobank
TP53	17	7675119	G	A	Q165X	0.18	COPDGene
TP53	17	7675088	C	T	R175H	0.05	UK Biobank
TP53	17	7675070	C	T	R181H	0.13	UK Biobank
TP53	17	7674962	G	A	P190L	0.19	UK Biobank
TP53	17	7674947	A	G	I195T	0.10	UK Biobank
TP53	17	7674918	A	C	Y205D	0.03	UK Biobank
TP53	17	7674872	T	C	Y220C	0.15	COPDGene
TP53	17	7674872	T	C	Y220C	0.13	COPDGene
TP53	17	7674864	GC	G	P222fs	0.08	Additional TOPMED - FHS
TP53	17	7674263	A	T	Y234N	0.08	UK Biobank
TP53	17	7674257	A	G	Y236H	0.11	UK Biobank
TP53	17	7674252	C	T	M237I	0.47	COPDGene
TP53	17	7674250	C	T	C238Y	0.35	Additional TOPMED - FHS
TP53	17	7674241	G	A	S241F	0.16	UK Biobank
TP53	17	7674238	C	T	C242Y	0.14	Additional TOPMED - FHS
TP53	17	7674229	C	T	G245D	0.20	COPDGene
TP53	17	7674220	C	T	R248Q	0.66	Additional TOPMED - ARIC
TP53	17	7674220	C	T	R248Q	0.26	COPDGene
TP53	17	7674214	G	A	P250L	0.11	UK Biobank
TP53	17	7673835	C	T	G262D	0.13	COPDGene
TP53	17	7673806	C	T	V272M	0.13	UK Biobank
TP53	17	7673802	C	T	R273H	0.42	UK Biobank
TP53	17	7673802	C	T	R273H	0.14	Additional TOPMED - ECLIPSE
TP53	17	7673802	C	T	R273H	0.13	Additional TOPMED - ECLIPSE
TP53	17	7673802	C	T	R273H	0.12	Additional TOPMED - ECLIPSE
TP53	17	7673802	C	T	R273H	0.07	UK Biobank
TP53	17	7673802	C	T	R273H	0.05	UK Biobank
TP53	17	7673782	T	C	R280G	0.04	UK Biobank
TP53	17	7673779	C	T	D281N	0.41	Additional TOPMED - JHS
TP53	17	7673776	G	A	R282W	0.10	UK Biobank
TP53	17	7673776	G	A	R282W	0.08	UK Biobank
TP53	17	7673772	C	T	R283H	0.07	UK Biobank
TP53	17	7673767	C	T	E285K	0.08	UK Biobank
TP53	17	7673764	C	T	E286K	0.07	UK Biobank
TP53	17	7673744	TTCTTGCGGAGATTCTC	C	E287fs	0.10	Additional TOPMED - MESA
TP53	17	7673739	T	T	E294G	0.04	UK Biobank
TP53	17	7673610	T	A	c.e9+2A>T	0.09	UK Biobank
TP53	17	7669672	CT	C	K373fs	0.09	UK Biobank
TP53	17	7579374	C	T	G105S	0.10	ICGN-EOCOPD
TP53	17	7577091	G	C	R283G	0.03	ICGN-EOCOPD
TP53	17	7577018	C	T	T	0.05	ICGN-EOCOPD
U2AF1	21	43094667	T	C	Q157R	0.62	COPDGene
U2AF1	21	43094667	T	G	Q157R	0.54	Additional TOPMED - FHS
U2AF1	21	43094667	T	G	Q157R	0.54	COPDGene
U2AF1	21	43094667	T	G	Q157R	0.40	COPDGene
WT1	11	32428495	A	C	c.769+2T>G	0.16	Additional TOPMED - ECLIPSE
ZRSR2	X	15823052	C	T	S420*	0.04	UK Biobank
ZRSR2	X	15822249	C	G	Q110*	0.17	ICGN-EOCOPD
ZRSR2	X	15818644	T	A	c.e9+2T>A	0.37	UK Biobank
ZRSR2	X	15790976	G	GTC	K29fs	0.08	UK Biobank

Extended Methods

Cohort Descriptions

Trans-Omics for Precision Medicine (TOPMed)

The Trans-Omics for Precision Medicine (TOPMed) program is sponsored by the National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI) to improve scientific understanding of the biological processes that underlie heart, lung, and sleep disorders.¹ TOPMed consists of over 155,000 participants from > 80 studies with different study design. For this analysis, we selected six studies (including COPDGene).

The COPDGene study

The COPDGene study is a multi-center epidemiologic and genetic study of current and ex-smokers, with the goal of discovering genetic factors contributing to the development of COPD. COPDGene has enrolled 10,198 smokers with and without COPD across GOLD stages, including both Non-Hispanic White (NHW) and African-American (AA) subjects. The details have been described elsewhere². Blood samples of 8808 COPDGene subjects went through whole genome sequencing in the TOPMed Freeze 5b release. After filtering based on phenotype quality and number of years between spirometry measure and blood draw, 8395 subjects were included as the discovery dataset (Table 1).

Additional TOPMed Cohorts

The six studies include the Atherosclerosis Risk in Communities (ARIC) Study, the Cleveland Family (CFS) study, the Framingham Heart (FHS) study, the Jackson Heart (JHS) study, and the Multi-Ethnic Study of Atherosclerosis (MESA).³ The ARIC study is a prospective population-based study conducted in four U.S. communities to study risk factors for atherosclerosis. The CFS study is a family-based study ascertained through probands with obstructive sleep apnea (OSA) identified in Cleveland. The FHS study recruited multi-generations of individuals from the town of Framingham, Massachusetts to study the risk factors contributing to cardiovascular disease (CVS). The JHS is a mixed family and population-based study of adult African Americans in Jackson, Mississippi. Lastly, MESA is a multi-ethnic population-based study from six communities in the U.S. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study was a longitudinal study of subjects with COPD, enrolled at multiple study centers in Europe, the USA, Canada, and New Zealand, with a small number of controls with normal lung function⁴. 12756 samples in these six studies were in the TOPMed Freeze 5b release with valid phenotype information after quality control, and CHIP status. We removed samples whose absolute difference between age at blood draw and assessment of COPD status using spirometry measures were greater than 5 years. This removed 1 subject from COPDGene, 83 subjects from ARIC, 122 subjects from CFS, 693 subjects from FHS, 21 subjects from JHS, 466 subjects from MESA, and no subject from ECLIPSE. After excluding these samples, 19664 subjects were included in the analyses. A histogram of the distribution of this time difference among the filtered samples in the COPDGene and additional TOPMed cohorts can be found in Figure S6.

The EOCOPD study and the ICGN study (ICGN-EOCOPD)

The Boston Early-Onset COPD study (EOCOPD) and the International COPD Genetics Network (ICGN) study are family-based studies focusing on families with severe COPD. Probands from EOCOPD were selected to be subjects with physician-diagnosis of COPD with $FEV1 \leq 40\%$ predicted, aged ≤ 53 years old, without severe alpha-1 antitrypsin deficiency. All first-degree relatives, older second-degree relatives, and additional affected family members were enrolled. In the ICGN study, probands were selected to be COPD cases with $FEV1 < 60\%$ predicted, $FEV1/FVC < 90\%$ predicted at ages 45-65 years, pack-years ≥ 5 , and have at least one eligible sibling. 196 families from EOCOPD and 462 families from the ICGN study were selected for whole exome sequencing (Table 2). The times at blood draw and assessment of COPD status using pulmonary function data are the same for all samples.

UK Biobank

The UK Biobank is a population-based cohort of >500,000 UK adult residents aged 40-69 years at recruitment between 2006-2010.⁵ Baseline assessment included medical history, smoking history, vital signs, phlebotomy, and spirometry to obtain the forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) (Pneumotrac 6800, Vitalograph). For the present analysis, the UK Biobank study cohort included 27,617 unrelated white European ancestry individuals with available whole exome sequences and spirometry data. Related individuals within 3 degree of relatedness were identified using the Kinship-Based Inference for Genome-Wide Association Studies tool and excluded.⁶ Individuals with extreme pulmonary function test outliers (defined as Z>5 or Z<-5 for FEV₁, FVC, and/or the FEV₁/FVC ratio) were additionally excluded. These analyses were conducted under UK Biobank application numbers 40375, 50834, and 7089.

Predicted FEV₁ was calculated using predictive models derived from the full UK Biobank (excluding extreme pulmonary function test outliers) using age, age², sex, race, and height as covariates. COPD was defined based on spirometry data as FEV₁/FVC <0.7, and GOLD stages were designated based on percent predicted FEV₁ (GOLD stage 1: FEV₁ ≥80% predicted; GOLD stage 2: FEV₁ ≥50% and <80% predicted; GOLD stage 3: FEV₁ ≥30% and <50% predicted; GOLD stage 4: FEV₁ <30% predicted). The times at blood draw and assessment of COPD status using spirometry measures are the same for all samples in the UK Biobank.

DNA Sequencing Information

Whole genome sequencing in TOPMed

TOPMed WGS genotype call sets (called Freezes) of peripheral blood samples are being released on dbGaP periodically, with the analyses described here performed on Freeze 5b with the exception of the ECLIPSE cohort from Freeze 8. The DNA sample handling and sequencing were done at six sequencing centers (New York Genome Center, the Broad Institute of MIT and Harvard, the University of Washington Northwest Genomics Center, Illumina Genomic Services, Macrogen Corp., and Baylor Human Genome Sequencing Center), with different processing pipelines. Details about the sequencing methods can be found here: <https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-project-freeze-5b-phases-1-and-2>. The resulting sequencing data were realigned and harmonized by the TOPMed Informatics Research Center (IRC) to create joint genotype calling set. Quality control was performed at each stage of the process by the Sequencing Centers, the IRC, and the TOPMed Data Coordinating Center (DCC). Details are found on the TOPMed website (<https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-project-freeze-5b-phases-1-and-2>). The WGS data in TOPMed had an average of 30x coverage and have been quality controlled using multiple criteria, including but not limited to excess heterozygosity filter and mendelian discordance filter.

Whole exome sequencing in ICGN-EOCOPD and the UKBiobank

The whole exome sequencing process for the ICGN-EOCOPD blood samples were performed at the University of Washington using Nimblegen V2 exome capture and Illumina platforms. Alignment, variant calling and quality control were performed using bwa, GATK, and in-house pipelines respectively, as previously described.⁷ The median exome sequencing coverage for observed polymorphic CHIP variants in ICGN-EOCOPD is 26.

Genomic DNA from blood samples for the UK Biobank was sequenced at the Regeneron Genetics Center from the UK Biobank.⁸ Briefly, multiplexed DNA libraries were created and IDT's xGen probe library was used for exome target capture. The multiplexed samples were pooled and sequenced using 75 base pair paired-end reads on the Illumina Novaseq 6000 platform using the S2 flow cells. Sample-specific FASTQ files, representing all the reads generated for that sample, were then aligned to the GRCh38 genome reference with BWA-mem2. The resultant binary alignment file (BAM) for each sample contained the mapped reads' genomic coordinates, quality information, and the degree to which a particular read differed from the reference at its mapped location. Aligned reads in the BAM file were then evaluated to identify and flag duplicate reads with the Picard3 MarkDuplicates tool, producing an alignment file with all potential duplicate reads marked for exclusion in downstream analyses. Upon completion of variant calling, individual sample BAM files were converted to fully lossless CRAM files using samtools.

Following completion of sample sequencing, samples showing disagreement between genetically determined and reported sex, high rates of heterozygosity/contamination (D-stat > 0.4), low sequence coverage (less than 85% of targeted bases achieving 20X coverage) or genetically identified sample duplicates, and WES variants discordant with genotyping chip were excluded. The CRAM files were then submitted by the Regeneron Genetics Center to the UK Biobank data repository for distribution. For a random 1000 samples, the median coverage with a mapping quality >30 was 56 in the UK Biobank,

Variant Identification and Determination of CHIP

Putative somatic SNPs and short indels were called from the CRAM files with GATK (version 4.1.1.0) Mutect2 (<https://software.broadinstitute.org/gatk>). Briefly, Mutect2 searches for sites where there is evidence for variation, and then performs local reassembly. It uses an external reference of recurrent sequencing artifacts termed a “panel of normal” derived from 100 sequenced samples to filter out these sites, and calls variants at sites where there is evidence for somatic variation. An external reference of germline variants from the gnomad resource (<https://gnomad.broadinstitute.org/>) was provided to filter out likely germline calls. We deployed this variant calling process on Google Cloud using the Terra platform (www.terra.bio). The cloud workflow scripts are available from download from the github repository (<https://github.com/gatk-workflows/gatk4-somatic-snvs-indels>) and docker images with configured cloud software are available at the dockstore repository (https://dockstore.org/workflows/github.com/gatk-workflows/gatk4-somatic-snvs-indels/mutect2_nio:2.5.0?tab=info). The caller was run individually for each sample with the same settings.

To identify samples CHIP, we utilized a previously published pre-specified list of variants in genes known to be recurrent drivers of myeloid malignancies.⁹ The variants were selected on the basis of being reported in the literature and/or the Catalog of Somatic Mutations in Cancer (COSMIC, <http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>). We used minimum variant read counts of 3 reads and required evidence of a variant on both forward and reverse reads. Frameshift, nonsense, and splice-site mutations were further excluded if they occurred in the first or last 10% of the gene open reading frame, unless mutations in those regions had been previously reported, (e.g. *DNMT3A*). Frameshift mutations were also excluded if the insertions/deletions occurred in homo-polymer repeats (5 consecutive reads of the same nucleotide). For *TET2*, all missense variants in particular regions were considered somatic if the variant allele fraction (VAF) significantly deviated from the expected distribution for a germline allele (defined as a p-value from a binomial test of less than 0.001 assuming a probability of success in a single Bernoulli experiment of 0.5 and using the alternate allele read count as the number of successes and the alternate allele read count + reference allele read count as the number of trials). Specific quality control metrics from these cohorts were previously performed by determining the concordance of mutation calls made from whole genome sequencing and deep, targeted sequencing. In 100% of cases the mutations called from the whole genome data were validated.⁹

Statistical Methods

All statistical methods were performed using R 3.6.3 (www.r-project.org) or Prism 8.4.3.

CHIP and COPD

We examined the effect of CHIP status on moderate-to-severe COPD, severe or very severe COPD, and FEV₁% predicted as a continuous measure. Moderate-to-severe COPD was defined as Global Initiative for Chronic Obstructive Lung Diseases (GOLD) stages GOLD 2-4 subjects with pre-bronchodilator FEV₁% predicted < 80% and FEV₁/FVC < 0.70. Severe COPD was defined as GOLD stages 3-4 subjects with FEV₁% predicted < 50% and FEV₁/FVC < 0.70. To look at CHIP and COPD severity, we examined the association between CHIP and FEV₁% predicted within all subjects and within GOLD 2-4 COPD..

For the COPDGene and UK Biobank data, logistic regression was applied to examine the associations between moderate-to-severe COPD status and CHIP, severe COPD status and CHIP, and COPD severity and

CHIP, while adjusting for age (at blood draw), age-squared, gender, sequencing center, number of pack-years, ever versus never smoking status, and top 10 principal components of genetic ancestry. Moderate-to-severe COPD status was defined to be 1 for patients with GOLD airflow limitation severity level 2-4, and 0 for patients with normal spirometry (GOLD 0). Severe or very severe COPD status was defined to be 1 for patients with GOLD level 3-4, and 0 for patients with GOLD level 0. To compare COPD GOLD 3-4 to GOLD 2, case status was represented as a binary variable that equals 1 for patients with GOLD level 3-4 and 0 for patients with GOLD level 2. CHIP was represented using a binary variable that equals 1 for carriers of pre-specified list of CHIP variants (described above) and 0 for non-carriers.

For the additional TOPMed cohorts and ICGN-EOCOPD datasets, generalized linear mixed effect models and linear mixed effect models were applied to take into account the family relatedness between subjects using the GENESIS package.¹⁰ The same set of covariates were adjusted as in COPDGene. Random-effects meta-analyses were conducted for the additional TOPMed cohorts for all the phenotypes using the metafor package. The 95% CI reported for the primary cohort (COPDGene) was adjusted for the six phenotypes we examined, and the significance level was defined as $0.05/6=0.00833$ for the primary cohort. Replication was defined as reaching a nominal significance level of 0.05 using a one-sided test with consistent direction of effect in at least one of the three replication cohorts. The reported 95% CIs for the additional cohorts (TOPMed, ICGN-EOCOPD, and UK Biobank) were not adjusted for multiple testing.

As secondary analyses, we also examined whether there is any specific gene (as a binary variable with reference to no CHIP at all) associated with COPD status. We looked within subjects with CHIP to test whether the maximum VAF of the CHIP genes are associated with COPD status in the discovery cohort. We also examined within COPD cases that whether there were any genes with CHIP mutations that were more frequent in the severe or very severe COPD cases (GOLD level 3-4) than moderate COPD cases (GOLD level 2) using logistic regression. Finally, we determined if the associations between CHIP and COPD remained after incorporation of the polygenic risk score (PRS), a measure of germline genetic variation, which was calculated for all participants in COPDGene as previously described.¹¹ We also adjusted for incident lung cancer, lung cancer mortality, other self-reported cancers, cardiovascular disease, and the highest degree of school completed as a measure of socioeconomic status in COPDGene and UK Biobank.

For the incidence analysis in UK Biobank we first excluded individuals with COPD at baseline using our study definition ($n=3,676$) or with prevalent COPD at study enrollment by self-report or ICD code (additional $n=336$), yielding 23,605 individuals at risk for incident COPD. Using ICD code-based incident COPD ascertainment (ICD-10 J41, J41.0, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9; ICD-9 491, 491.2, 491.9, 492, 492.9, 496, 496.9), 337 individuals (1.4%) developed incident COPD over a median 10.0 [IQR 0.9-10.2] years of follow-up. To identify the hazard ratios for the development of COPD with presence of CHIP with a VAF > 0.1 and VAF < 0.1, we used the following Cox model: Incident COPD ~ age + sex + PC 1-10 + ever-smoking + pack-years + educational attainment + Townsend deprivation index + CHIP.

CHIP and lung function

For the analysis between CHIP and lung function, linear regression on pre-bronchodilator FEV₁% predicted was applied while adjusting for the same set of covariates as for COPD. We also examined the association between CHIP and FEV₁% predicted within subjects with moderate-to-severe COPD (GOLD level 2-4) subjects.

CHIP and Smoking

We examined the effect of number of pack years of smoking on CHIP status. We applied logistic regression with CHIP status as the binary response, while adjusting for age (at blood drawn), gender, ever versus never smoking status, sequencing center, race, and top 10 principal components of ancestry in each cohort. We conducted random-effects meta-analyses of the TOPMed cohorts using the metafor package in R since the ascertainment criteria vary across the cohorts. The Dersimonian and Laird method was used to estimate the between-study variance for the binary outcomes, and the restricted maximum likelihood estimator (REML) was

used for the continuous outcomes. The distribution of age and number of pack-years of smoking across all TOPMed cohorts can be found in Supplementary Figures S1 and S5A, respectively.

Mouse Models

Mice carrying *Tet2*-deleted or *Tet2*-wild-type hematopoietic cells were generated by bone marrow transplantation of 8 week old donors as previously described.¹² For the full chimerism smoke and poly(I:C) experiments, RBC-lysed whole bone marrow from CD45.2⁺; *Tet2*^{+/+}; *Vav1-Cre* or CD45.2⁺; *Tet2*^{fl/-}; *Vav1-Cre* were transplanted into lethally irradiated (475 cGy x 2) CD45.1⁺ recipient animals. Sixteen weeks later, the mice were exposed to air or mixed mainstream and side-stream cigarette smoke from 1R3F Kentucky Research cigarettes 6 days per week for a total of 2 hours per day in Teague chambers (Teague Enterprises, Woodland, CA). The cigarette smoke exposures produced daily total suspended particles counts ~150 mg/m³. Mice were weighed at baseline and every two weeks thereafter. During weeks five and six of smoke exposure, the mice were treated by intraperitoneal injection with 50 ug poly(I:C) suspended in PBS (total volume 30 uL) twice per week (every other day) for two weeks, after which time the mice were euthanized.

For the partial chimerism, cigarette smoke experiment, c-kit selection (Miltenyi Biotec) was performed on whole bone marrow after RBC lysis from CD45.2⁺; *Tet2*^{+/+}; *Vav1-Cre*, CD45.2⁺; *Tet2*^{fl/-}; *Vav1-Cre* or CD45.1⁺ (SJL) animals. The cells were counted and mixed such that 15% were CD45.2⁺ (either *Tet2*^{+/+}; *Vav1-Cre* or *Tet2*^{fl/-}; *Vav1-Cre*) and 85% CD45.1⁺. The mixture ratios were confirmed by flow cytometry then transplanted into lethally irradiated (475 cGy x 2) CD45.1⁺ recipient animals. Four weeks after transplant CD45.1/CD45.2 chimerism was confirmed. The mice were then exposed to air or mixed mainstream and side-stream cigarette smoke from 1R3F Kentucky Research cigarettes 6 days per week for a total of 2 hours per day in Teague chambers (Teague Enterprises, Woodland, CA). The cigarette smoke exposures produced daily total suspended particles counts ~150 mg/m³. Peripheral blood chimerism was checked approximately every month for six months, at which time the mice were euthanized.

At the time of euthanasia, the lungs were flushed with saline then fixed at constant pressure of 25 cm H₂O with formalin. The lungs were then sectioned and stained for analysis. For quantification of emphysema, sections of lungs subject to Gill's staining were imaged at 10x. The images were then analyzed using Scion image (available at Wikiversity.org) as previously described.¹³

Single-cell RNA-sequencing

Single-cell RNA-sequencing was performed on fresh mouse lung tissue. Sixteen mice were processed: four *Tet2*-wild-type exposed to air, four *Tet2*-wild-type exposed to cigarettes smoke and poly(I:C), four *Tet2*-knockout exposed to air, and four *Tet2*-knockout exposed to cigarettes smoke and poly(I:C) (Figure 4A). The mice were euthanized and after flushing the pulmonary vasculature via instillation of 30 mL phosphate buffer saline into the right ventricle the lungs were extracted, manually minced, then incubated in Collagenase (2mg/mL Sigma) in Hanks buffered salt solution for 30 minutes at 37 degrees with agitation. The samples were then passed through a 40uM filter to generate single cell suspensions then subject to RBC lysis. Dead cells were then depleted using the dead cell removal kit from Miltenyi (Cat 130-090-101) and LS columns. The cells were counted manually using trypan blue and resuspended at a concentration of 1000 cells per uL of PBS with 2% fetal bovine serum. Next, 10,000 - 15,000 cells were loaded onto a 10x Genomics chip. Further processing was done using the recommended procedures for the 10x Genomics 3' v3 chemistry. Libraries were sequenced on the NovaSeq S1 (28+8+91 cycles).

Single-cell RNA-seq analysis

Fastq files were demultiplexed using the mkfastq command from cellranger v3.1.0, followed by cellranger count (with mm10 as a reference) and aggr to generate batch-corrected gene expression matrices. Mouse 2 (*Tet2*-wild-type CS/ poly(I:C)) was excluded because it had much fewer reads per cell. Only cells with >2000 UMIs and >1000 genes and <15% mitochondrial reads and <15% rRNA alignments were kept for further analysis.

Dimensionality reduction and cluster annotation

Data were imported into Seurat version 3.2.2 using R version 3.6.1. Normalization, variable feature identification and data scaling were performed using Seurat defaults. Using 50 dimensions from the principal component analysis, we generated UMAP coordinates using the RunUMAP function and clusters using FindNeighbors and FindClusters functions (resolution = 0.4). Clusters were annotated by expression of both canonical marker genes (such as CD3 for T cells and CD19 for B cells) and previously published gene sets that define cell clusters in the mouse lung.¹³ Some clusters consisted of cells that co-expressed multiple lineage-defining marker genes (such as CD3 and CD19). These doublet clusters were removed from further analyses (6.0% of cells). After doublet removal, 25 clusters remained (Figure 4C, Table S17), some of which included multiple cell types, particularly among the non-hematopoietic cells. Further sub-clustering was deferred given the small number of cells within these mixed cell type clusters. The top 25 marker genes of the 25 clusters by fold change was determined using the Seurat function FindAllMarkers with logfc.threshold = 0.25, min.pct = 0.1, test.use = "roc" and return.thresh = 0.4 (Table S18).

Signature scoring

Signatures were assembled from Hallmark, Reactome, Biocarta, KEGG and Wikipathways. We used all 50 signatures from the Hallmark collection then manually curated interferon and tumor growth factor beta pathways related to inflammatory signaling (Supplemental Tables S19 and S20). Symbols were converted from human to mouse with the R libraries biomaRt version 2.42.1 and org.Mm.eg.db version 3.10.0, using the function getLDS. We scored each individual cell in the dataset for each signature using Seurat's AddModuleScore function. A Wilcoxin Rank Sum test was used to compare the scores for each cell from the *Tet2*-wildtype mice to those from the *Tet2*-knockout mice (all exposed to CS/ poly(I:C)) for each signature, adjusting for multiple hypothesis using a Bonferroni correction (Figures 4D and S9C). For scatter plots in Figures 4E-F, we filtered for CS/ poly(I:C) mice and used the mean of cell signature scores in each cluster as x- (*Tet2*-knockout) and y-coordinates (*Tet2*-wild-type). The P-value between genotypes was calculated using the Wilcoxon Rank Sum test followed by fdr adjustment for multiple testing. Gene Set Enrichment Analyses in Figure S9D were performed with the GSEA4.1.0 software, using the Hallmark Interferon alpha and Interferon gamma gene lists that were pre-ranked by the mean difference between *Tet2*-wild-type and *Tet2*-knockout cells of the indicated. Multiple GSEA curves were combined on the same plot using GraphPad Prism software.

Data and software availability

The scRNA-seq data, gene expression matrices and cell type annotations will be deposited in the Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>). R Scripts written for the analysis of scRNA-seq data will be made available on Github (<https://github.com/vangalenlab>).

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NHLBI Trans-Omics for Precision Medicine Consortium Investigators

Namiko Abe
Christine Albert
Laura Almasy
Alvaro Alonso
Seth Ament
Peter Anderson
Pramod Anugu
Deborah Applebaum-Bowden
Dan Arking
Allison Ashley-Koch
Stella Aslibekyan
Tim Assimes
Dimitrios Avramopoulos
John Barnard
R. Graham Barr
Emily Barron-Casella
Lucas Barwick
Terri Beaty
Gerald Beck
Diane Becker
Rebecca Beer
Amber Beitelshes
Emelia Benjamin
Panagiotis Benos
Marcos Bezerra
Larry Bielak
Russell Bowler
Jennifer Brody
Ulrich Broeckel
Karen Bunting
Carlos Bustamante
Jonathan Cardwell
Vincent Carey
Cara Carty
Richard Casaburi
James Casella
Peter Castaldi
Mark Chaffin
Christy Chang
Yi-Cheng Chang
Daniel Chasman

Sameer Chavan
Bo-Juen Chen
Wei-Min Chen
Seung Hoan Choi
Lee-Ming Chuang
Mina Chung
Ren-Hua Chung
Clary Clish
Suzy Comhair
Elaine Cornell
Carolyn Crandall
James Crapo
Jeffrey Curtis
Coleen Damcott
Sayantan Das
Sean David
Colleen Davis
Michael DeBaun
Ranjan Deka
Dawn DeMeo
Scott Devine
Qing Duan
Ravi Duggirala
Susan Dutcher
Charles Eaton
Lynette Ekunwe
Adel El Boueiz
Leslie Emery
Serpil Erzurum
Charles Farber
Matthew Flickinger
Nora Franceschini
Chris Frazar
Mao Fu
Stephanie M. Fullerton
Lucinda Fulton
Stacey Gabriel
Weiniu Gan
Shanshan Gao
Yan Gao
Margery Gass
Bruce Gelb
Xiaoqi (Priscilla) Geng

Mark Geraci
Soren Germer
Robert Gerszten
Auyon Ghosh
Richard Gibbs
Chris Gignoux
Mark Gladwin
David Glahn
Da-Wei Gong
Harald Goring
Sharon Graw
Daniel Grine
C. Charles Gu
Yue Guan
Namrata Gupta
Jeff Haessler
Michael Hall
Daniel Harris
Nicola L. Hawley
Ben Heavner
Ryan Hernandez
David Herrington
Craig Hersh
Bertha Hidalgo
Brian Hobbs
John Hokanson
Elliott Hong
Karin Hoth
Chao (Agnes) Hsiung
Yi-Jen Hung
Haley Huston
Chii Min Hwu
Rebecca Jackson
Deepti Jain
Cashell Jaquish
Min A. Jhun
Craig Johnson
Rich Johnston
Kimberly Jones
Hyun Min Kang
Shannon Kelly
Michael Kessler
Alyna Khan

Wonji Kim
Greg Kinney
Holly Kramer
Christoph Lange
Meryl LeBoff
Seunggeun Shawn Lee
Wen-Jane Lee
Jonathon LeFaive
David Levine
Joshua Lewis
Xiaohui Li
Yun Li
Henry Lin
Honghuang Lin
Keng Han Lin
Xihong Lin
Simin Liu
Yu Liu
Kathryn Lunetta
James Luo
Michael Mahaney
Barry Make
Ani Manichaikul
Lauren Margolin
Lisa Martin
Susan Mathai
Susanne May
Patrick McArdle
Merry-Lynn McDonald
Sean McFarland
Daniel McGoldrick
Caitlin McHugh
Hao Mei
Luisa Mestroni
Julie Mikulla
Nancy Min
Mollie Minear
Ryan L. Minster
Matt Moll
Courtney Montgomery
Solomon Musani
Stanford Mwasongwe
Josyf C. Mychaleckyj

Girish Nadkarni
Rakhi Naik
Take Naseri
Sergei Nekhai
Sarah C. Nelson
Bonnie Neltner
Deborah Nickerson
Jeff O'Connell
Tim O'Connor
Heather Ochs-Balcom
David Paik
James Pankow
George Papanicolaou
Afshin Parsa
Marco Perez
James Perry
Ulrike Peters
Patricia Peyser
Lawrence S. Phillips
Toni Pollin
Wendy Post
Julia Powers Becker
Meher Preethi Boorgula
Michael Preuss
Pankaj Qasba
Dandi Qiao
Zhaohui Qin
Laura Rasmussen-Torvik
Aakrosh Ratan
Robert Reed
Elizabeth Regan
Muagututi'a Sefuiva Reupena
Ken Rice
Carolina Roselli
Ingo Ruczinski
Pamela Russell
Sarah Ruuska
Kathleen Ryan
Danish Saleheen
Shabnam Salimi
Steven Salzberg
Kevin Sandow
Christopher Scheller

Ellen Schmidt
Karen Schwander
Frank Sciurba
Christine Seidman
Jonathan Seidman
Vivien Sheehan
Stephanie L. Sherman
Amol Shetty
Aniket Shetty
Brian Silver
Josh Smith
Tanja Smith
Sylvia Smoller
Beverly Snively
Michael Snyder
Tamar Sofer
Nona Sotoodehnia
Adrienne M. Stilp
Garrett Storm
Elizabeth Streeten
Jessica Lasky Su
Yun Ju Sung
Jody Sylvia
Adam Szpiro
Carole Sztalryd
Daniel Taliun
Hua Tang
Matthew Taylor
Simeon Taylor
Marilyn Telen
Timothy A. Thornton
Machiko Threlkeld
Lesley Tinker
David Tirschwell
Sarah Tishkoff
Hemant Tiwari
Catherine Tong
Michael Tsai
Dhananjay Vaidya
David Van Den Berg
Peter VandeHaar
Scott Vrieze
Tarik Walker

Robert Wallace
Avram Walts
Heming Wang
Karol Watson
Bruce Weir
Lu-Chen Weng
Jennifer Wessel
Cristen Willer
Kayleen Williams
Carla Wilson
Joseph Wu
Huichun Xu
Lisa Yanek
Rongze Yang
Norann Zaghoul
Yingze Zhang
Snow Xueyan Zhao
Wei Zhao
Degui Zhi
Xiang Zhou
Xiaofeng Zhu
Michael Zody
Sebastian Zoellner

COPDGene Investigators

Administrative Center

Regan, MD, PhD

Genetic Analysis Center

MD, MPH; Adel El Boueiz, MD, MMSc; Marilyn G. Foreman, MD, MS; Auyon Ghosh, MD; Lystra P. Hayden, MD, MMSc; Craig P. Hersh, MD, MPH; Jacqueline Hetmanski, MS; Brian D. Hobbs, MD, MMSc; John E. Hokanson, MPH, PhD; Wonji Kim, PhD; Nan Laird, PhD; Christoph Lange, PhD; Sharon M. Lutz, PhD; Merry-Lynn McDonald, PhD; Dmitry Prokopenko,

Imaging Center

PhD; MeiLan K. Han, MD, MS; Eric A. Hoffman, Stephen Humphries, PhD; Francine L. Jacobson, MD, MPH; Philip F. Judy, PhD; Ella A. Kazerooni, MD; Alex Kluiber; David A. Lynch, MB; Pietro Nardelli, PhD; John D. Newell, Jr., MD; Aleena Notary; Andrea Oh, MD; Elizabeth A. Regan, MD, PhD; James C. Ross, PhD; Raul San Jose Estepar, PhD; Joyce Schroeder, MD;

PFT QA Center

Robert Jensen, PhD

Data Coordinating Center and Biostatistics

Wilson, MS

Epidemiology Core

PhD; Kendra A. Young, PhD

Mortality Adjudication Core

Barry Make, MD; Susan Murray, ScD; Elizabeth Regan, MD; Xavier Soler, MD; Carla G.

Biomarker Core

Russell P. Bowler, MD, PhD; Katerina Kechris, PhD; Farnoush Banaei-Kashani, PhD

COPDGene® Investigators – Clinical Centers

Ann Arbor VA: Jeffrey L. Curtis, MD; Perry G. Pernicano, MD

Boriek, PhD; Kalpatha Guntupalli, MD; Elizabeth Guy, MD; Amit Parulekar, MD;

MPH; Francine L. Jacobson, MD, MPH; George Washko, MD

D'Souza, MD; Byron Thomashow, MD

Lacey Washington, MD

Tashjian, MD

Hansel, MD, MPH; Karen Horton, MD; Allison Lambert, MD, MHS; Nirupama Putcha, MD, MHS

Richard Casaburi, PhD, MD; Alessandra Adami, PhD; Matthew Budoff, MD; Hans Fischer, MD;

Janos Porszasz, MD, PhD; Harry Rossiter, PhD; William Stringer, MD Michael E. DeBakey

Minneapolis VA: Christine Wendt, MD; Brian Bell, MD; Ken M. Kunisaki, MD, MS

Mario Ponce, MD; Silanath Terpenning, MD; Gloria Westney, MD, MS
National Jewish Health, Denver, CO: Russell Bowler, MD, PhD; David A. Lynch, MB
Reliant Medical Group, Worcester, MA: Richard Rosiello, MD; David Pace, MD
Temple University, Philadelphia, PA: Gerard Chiriac, MD; David Giacobello, MD; Francis
Cordova, MD; Chandra Dass, MD; Gilbert D'Alonzo, DO; Parag Desai, MD; Michael Jacobs,
PharmD; Steven Kelsen, MD, PhD; Victor Kim, MD; A. James Mamary, MD; Nathaniel
Marchetti, DO; Aditi Satti, MD; Kartik Shenoy, MD; Robert M. Steiner, MD; Alex Swift, MD;
Bhatt, MD; Anand Iyer, MD; Hrudaya Nath, MD; J. Michael Wells, MD
Yen, MD
Jr., MD; Brad Thompson, MD
Wassim Labaki, MD MS; Craig Galban, PhD; Dharshan Vummidi, MD
Allen, MD
MD, MSc; Joel Weissfeld, MD, MPH
Adams, MD; Diego Maselli-Caceres, MD; Mario E. Ruiz, MD; Harjinder Singh