Article

Novel DNMT3A Germline Variant in a Patient with Multiple Paragangliomas and Papillary Thyroid Carcinoma

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Supplementary Materials:

Figure S1. Hierarchical clustering performed with one AML sample carrying the p.Gly332Arg DNMT3A mutation (black circle) and 12 AML samples from TCGA [48] carrying mutations known to cause global methylation alterations: loss-of-function p.Arg882Cys/His DNMT3A mutations (blue boxes), and TET2 frameshift mutations (purple boxes). Profiling was based on methylation data from the 213 probes, out of the 307 significantly differentially methylated between DNMT3A-mutated and non-mutated tissues in patients with PPGL, contained in the Infinium HumanMethylation450 BeadChip.
**Figure S2.** Schematic representation of the methylation analysis pipeline.
Table S1. Filtered exome variants found in ClinVar.

| ClinVar ID   | Chr | Coordinate | Gene Name | Transcript Consequence | Protein Consequence | dbSNP          | PredictSNP1 (Confidence) | gnomAD Allele Frequency | Clinical Significance | Condition                          |
|--------------|-----|------------|-----------|------------------------|---------------------|-----------------|--------------------------|-------------------------|-----------------------|-----------------------------------|
| VCV000519902 | X   | 70339307   | MED12     | c.184G>A               | p.Val62Ile          | rs1039763693    | Neutral (83%)            | -                       | Uncertain             | Cardiovascular phenotype          |
| VCV000407388 | 4   | 55127414   | PDGFRA    | c.202G>A               | p.Asp68Asn          | rs1060501504    | Neutral (83%)            | 0.0000239               | Uncertain             | Gastrointestinal stromal tumor    |
| VCV000981258 | 2   | 25470480   | DNMT3A    | c.994G>A               | p.Gly322Arg         | Deleterious (87%) | 0.0000119               | Uncertain               | Intellectual disability          |
| VCV000284047 | 20  | 61467852   | COL9A3    | c.1571G>A              | p.Arg524His         | rs373382239     | Neutral (74%)            | 0.0000252               | Uncertain             | Not provided                     |
| VCV000666692 | 12  | 15818756   | EPS8      | c.670G>A               | p.Val224Ile         | rs758506896     | Neutral (83%)            | 0.0000887               | Likely benign         | Not specified                    |
| VCV000812325 | 3   | 50231196   | GNAT1     | c.460G>T               | p.Asp154Tyr         | rs1293620319    | Neutral (72%)            | 0.00000413              | Pathogenic            | Retinitis pigmentosa             |
Table S2. Variants affecting the PWWP domain found in gnomAD.

| rsID           | Transcript Consequence | Protein Consequence | Found in COSMIC | Found in AML in COSMIC | Leukemogenic Variant | Varsome Prediction | Allele Frequency |
|----------------|------------------------|---------------------|----------------|------------------------|----------------------|-------------------|------------------|
| 1  rs777306476  | c.875T>C               | p.Ile292Thr         | yes            | yes                    | no                   | Likely Pathogenic | 6,38162E-05      |
| 2  rs1402705749 | c.887T>G               | p.Val296Gly         | yes            | yes                    | no                   | Likely Pathogenic | 3,98909E-06      |
| 3  rs1402705749 | c.887T>A               | p.Val296Glu         | no             | no                     | no                   | Likely Pathogenic | 3,98909E-06      |
| 4  rs1410828051 | c.893G>A               | p.Gly298Glu         | yes            | yes                    | no                   | Likely Pathogenic | 3,98746E-06      |
| 5  rs776841024  | c.918G>T               | p.Trp306Cys         | yes            | yes                    | no                   | Likely Pathogenic | 3,98178E-06      |
| 6  rs759380437  | c.920C>G               | p.Pro307Arg         | yes            | yes                    | yes                  | Likely Pathogenic | 3,98137E-06      |
| 7  rs759380437  | c.920C>A               | p.Pro307Gln         | no             | no                     | no                   | Likely Pathogenic | 3,98137E-06      |
| 8  rs757575202  | c.926G>C               | p.Arg309Pro         | yes            | no                     | no                   | Likely Pathogenic | 3,98105E-06      |
| 9  rs774128516  | c.928A>T               | p.Ile310Phe         | no             | no                     | no                   | Likely Pathogenic | 3,97975E-06      |
| 10 rs747448117  | c.976C>T               | p.Arg326Cys         | yes            | yes                    | yes                  | Uncertain significance | 3,97845E-05 |
| 11 rs758881009  | c.977G>T               | p.Arg326Leu         | yes            | no                     | yes                  | Likely Pathogenic | 7,95691E-06      |
| 12 rs758881009  | c.977G>A               | p.Arg326His         | yes            | yes                    | yes                  | Likely Pathogenic | 2,38705E-05      |
| 13 rs76593136   | c.985A>G               | p.Met329Val         | yes            | no                     | no                   | Uncertain significance | 3,9789E-06 |
| 14 rs753896945  | c.991T>G               | p.Phe331Val         | no             | no                     | no                   | Likely Pathogenic | 3,98004E-06      |
| 15 rs151221034  | c.993C>G               | p.Phe331Leu         | no             | no                     | no                   | Likely Pathogenic | 3,9807E-06       |
| 16 rs760854242  | c.994G>A               | p.Gly332Arg         | yes            | yes                    | yes                  | Likely Pathogenic | 1,19427E-05      |
| 17 rs1024296111 | c.1000G>A              | p.Gly334Ser         | yes            | no                     | no                   | Uncertain significance | 3,98356E-06 |
| 18 rs773208295  | c.1010C>T              | p.Ser337Leu         | no             | no                     | no                   | Likely Pathogenic | 1,19556E-05      |
| 19 rs749817324  | c.1031T>C              | p.Leu344Pro         | yes            | yes                    | yes                  | Likely Pathogenic | 3,98819E-06      |
| 20 rs749817324  | c.1031T>A              | p.Leu344Gln         | yes            | yes                    | yes                  | Likely Pathogenic | 3,18776E-05      |
| 21 rs1308281604 | c.1037C>T              | p.Pro346Leu         | no             | no                     | no                   | Likely Pathogenic | 3,98559E-06      |
| 22 rs139053291  | c.1055G>A              | p.Ser352Asn         | yes            | yes                    | no                   | Likely benign     | 0,00004247       |
| 23 rs1326972729 | c.1058C>T              | p.Ala353Val         | no             | no                     | no                   | Uncertain significance | 0,00003982 |
| 24 rs1220753680 | c.1082A>G              | p.Lys361Arg         | yes            | no                     | no                   | Likely Pathogenic | 0,00003981       |
| 25 rs774855118  | c.1091T>C              | p.Met364Thr         | no             | no                     | no                   | Uncertain significance | 0,00003982 |
| 26 rs144062658  | c.1094A>G              | p.Tyr365Cys         | no             | no                     | no                   | Likely Pathogenic | 0,00003983       |
| No. | rsID        | SNP          | Gene | Variant Type | Mutation | p Value | Result          | p Value |
|-----|------------|--------------|------|--------------|----------|---------|----------------|---------|
| 28  | rs767236033| c.1097G>A    | Arg566His | no          | no       | yes     | Likely Pathogenic | 0.00001063 |
| 29  | rs773941479| c.1106T>A    | Ile369Asn | yes         | no       | no      | Likely Pathogenic | 0.000003985 |
| 30  | rs371677904| c.1114G>A    | Val372Ile | no          | no       | no      | Likely benign     | 0.00002483 |
| 31  | rs773722655| c.1115T>C    | Val372Ala | no          | no       | no      | Uncertain significance | 0.000003991 |

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Table S3. List of differentially methylated CpGs between DNMT3A-mutated and non-mutated samples.

| TargetID   | Chr | Coordinate | GENE      | logFC Tumors | FDR (DNMT3A-Tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|------------|-----|------------|-----------|--------------|----------------------------------|-------------|----------------------------------|
| cg10818676 | 1   | 167098094  | DUSP27    | 6,358        | 0,031                            | 4,377       | 0,056                            |
| cg17018201 | 6   | 33269769   | TAPBP     | 5,908        | 0,077                            | 4,274       | 0,056                            |
| cg16893499 | 18  | 35069156   | CELF4     | 6,103        | 0,077                            | 3,415       | 0,097                            |
| cg26444086 | 7   | 1162748    | C7orf50   | 6,825        | 0,077                            | 4,355       | 0,103                            |
| cg12088417 | 17  | 78574716   | RPTOR     | 4,872        | 0,077                            | 5,934       | 0,137                            |
| cg20999878 | 2   | 223176167  |           | -5,756       | 0,077                            | -2,924      | 0,137                            |
| cg19080354 | 11  | 288021     | ATHL1     | -6,133       | 0,077                            | -2,782      | 0,137                            |
| cg05746069 | 5   | 153857907  | HAND1     | -4,361       | 0,077                            | -1,408      | 0,147                            |
| cg07397108 | 15  | 22562214   |           | 4,595        | 0,078                            | 3,761       | 0,111                            |
| cg23121156 | 4   | 154710421  | SFRP2     | -4,353       | 0,078                            | -1,664      | 0,137                            |
| cg08886727 | 17  | 46801084   | PRAC2     | -4,767       | 0,078                            | -2,251      | 0,139                            |
| cg10824810 | 16  | 54967714   | IRX5      | -4,471       | 0,078                            | -1,594      | 0,142                            |
| cg05712748 | 1   | 43472312   |           | 6,026        | 0,078                            | 4,417       | 0,056                            |
| cg02694427 | 2   | 176964512  | HOXD12    | -4,746       | 0,078                            | -1,755      | 0,137                            |
| cg19748684 | 2   | 175197431  | SP9       | -4,573       | 0,078                            | -1,823      | 0,141                            |
| cg01915516 | 1   | 3568243    | TP73      | -5,129       | 0,082                            | -1,491      | 0,137                            |
| cg06354054 | 12  | 125440391  | DHX37     | 5,789        | 0,082                            | 3,820       | 0,056                            |
| cg09684233 | 2   | 175206966  |           | -4,483       | 0,082                            | -1,404      | 0,139                            |
| cg08216425 | 1   | 43476956   |           | 5,513        | 0,085                            | 4,360       | 0,119                            |
| cg13125157 | 17  | 50237403   | CA10      | -4,878       | 0,087                            | -1,891      | 0,137                            |
| cg02668233 | 12  | 125813494  | TMEM132B  | 4,885        | 0,091                            | 3,265       | 0,069                            |
| cg10776061 | 19  | 12768390   | MAN2B1    | -4,965       | 0,091                            | -2,886      | 0,086                            |
| cg19151808 | 4   | 89619051   | NAP1L5    | -4,570       | 0,091                            | -4,169      | 0,097                            |
| cg08893358 | 2   | 38528761   | ATL2      | 3,975        | 0,091                            | 3,547       | 0,131                            |
| cg08307231 | 17  | 78642620   | RPTOR     | 4,052        | 0,091                            | 4,654       | 0,132                            |
| cg13085030 | 7   | 1090504    | C7orf50   | 4,765        | 0,091                            | 3,892       | 0,136                            |
| cg21907107 | 5   | 76932062   | OTP       | -4,075       | 0,091                            | -1,807      | 0,137                            |
| cg00072839 | X   | 91035267   | PCDH11X   | -3,838       | 0,091                            | -2,212      | 0,137                            |
| cg05835105 | 4   | 111543401  | PITX2     | -4,543       | 0,091                            | -1,914      | 0,137                            |
| cg10375890 | 1   | 50892511   |           | -3,839       | 0,091                            | -1,439      | 0,139                            |
| cg24914355 | 2   | 176959229  | HOXD13    | -4,795       | 0,091                            | -1,573      | 0,139                            |
| cg24118384 | 7   | 155302908  | CNPY1     | -3,815       | 0,091                            | -2,138      | 0,142                            |
| cg01326836 | 7   | 27224836   | HOXA11-AS | -3,698       | 0,091                            | -1,408      | 0,142                            |
| cg02071600 | 5   | 78808852   | HOMER1    | -4,543       | 0,091                            | -1,606      | 0,144                            |
| cg02597299 | 5   | 151304559  | GLRA1     | -4,187       | 0,091                            | -1,810      | 0,147                            |
| cg17964510 | 2   | 17519694   | SP9       | -5,291       | 0,092                            | -2,732      | 0,126                            |
| cg20049415 | 20  | 21377671   | NKX2-4    | -3,855       | 0,092                            | -2,028      | 0,145                            |
| cg11904056 | 5   | 92918910   | NR2F1     | -3,534       | 0,092                            | -1,695      | 0,146                            |
| cg09289202 | 2   | 242443982  | STK25     | 3,469        | 0,095                            | 3,947       | 0,059                            |
| cg07570618 | 1   | 1992389    | PRKCB     | 4,259        | 0,095                            | 4,252       | 0,086                            |
| TargetID   | Chr. | Coordinate | GENE       | logFC Tumor s | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|------------|------|------------|------------|---------------|---------------------------------|-------------|---------------------------------|
| cg05394800 | 13   | 50707050   | DLEU1      | -4,241        | 0,095                           | -2,055      | 0,137                           |
| cg03086663 | 5    | 92918912   | NR2F1      | -3,991        | 0,095                           | -1,676      | 0,137                           |
| cg27210166 | 17   | 78574692   | RPTOR      | 5,556         | 0,099                           | 5,609       | 0,061                           |
| cg07592775 | 1    | 19210017   | ALDH4A1    | 3,991         | 0,099                           | 4,461       | 0,097                           |
| cg10613919 | 13   | 79168573   | RNF219-AS1 | -4,518        | 0,099                           | -2,985      | 0,097                           |
| cg18116968 | 7    | 25900668   |            | -3,541        | 0,099                           | -2,356      | 0,126                           |
| cg03685272 | 6    | 100062830  | PRDM13     | -4,016        | 0,099                           | -2,225      | 0,131                           |
| cg22616881 | 7    | 96642096   | DLX6-AS1   | -3,520        | 0,099                           | -2,216      | 0,137                           |
| cg17358883 | 4    | 11159134   | PITX2      | -3,362        | 0,099                           | -1,816      | 0,137                           |
| cg22508145 | 19   | 17015427   | CPAMD8     | 5,827         | 0,099                           | 4,391       | 0,057                           |
| cg16471877 | 6    | 99817927   | COQ3       | 4,271         | 0,099                           | 4,642       | 0,071                           |
| cg08871399 | 12   | 62672755   | USP15      | 3,953         | 0,099                           | 4,387       | 0,111                           |
| cg07744432 | 19   | 20608532   | ZNF826P    | 3,350         | 0,099                           | 3,360       | 0,112                           |
| cg02879244 | 11   | 20181911   | DBX1       | -3,433        | 0,099                           | -1,884      | 0,137                           |
| cg10068417 | 13   | 50706583   | DLEU1      | -3,383        | 0,099                           | -1,757      | 0,137                           |
| cg25027832 | 2    | 176948544  | EVX2       | -4,416        | 0,099                           | -1,893      | 0,137                           |
| cg07201017 | 10   | 102996571  | FLJ41350   | -3,622        | 0,099                           | -1,752      | 0,137                           |
| cg01008088 | 12   | 131517623  | ADGRD1     | 3,993         | 0,099                           | 4,589       | 0,137                           |
| cg18442187 | 6    | 50794722   | TFAP2B     | -3,855        | 0,099                           | -1,663      | 0,137                           |
| cg11664139 | 2    | 175204249  |            | -3,200        | 0,099                           | -1,842      | 0,137                           |
| cg08434574 | 6    | 99292438   |            | -3,307        | 0,099                           | -1,886      | 0,137                           |
| cg00548708 | 17   | 48041547   |            | -3,340        | 0,099                           | -2,343      | 0,137                           |
| cg02730303 | 11   | 103480630  |            | -3,989        | 0,099                           | -1,780      | 0,137                           |
| cg02897537 | 10   | 124893832  | HMX3       | -3,274        | 0,099                           | -1,536      | 0,137                           |
| cg17495715 | 2    | 176950273  |            | -4,057        | 0,099                           | -1,699      | 0,137                           |
| cg10776919 | 1    | 50889442   | DMRTA2     | -5,247        | 0,099                           | -1,601      | 0,137                           |
| cg18168844 | 5    | 50262917   |            | -3,356        | 0,099                           | -1,363      | 0,139                           |
| cg05196231 | X     | 40944772   | USP9X      | -4,052        | 0,099                           | -3,293      | 0,140                           |
| cg23767994 | 7    | 96612323   | DLX6-AS1   | -3,282        | 0,099                           | -1,289      | 0,144                           |
| cg08238319 | 5    | 404713     | AHRR       | 3,817         | 0,099                           | 4,600       | 0,056                           |
| cg23348270 | 2    | 17696912   | HOXD11     | -3,801        | 0,099                           | -1,938      | 0,137                           |
| cg07875786 | 5    | 92918927   | NR2F1      | -3,519        | 0,099                           | -1,965      | 0,137                           |
| cg27583307 | 2    | 200320750  | SATB2      | -3,634        | 0,101                           | -1,307      | 0,142                           |
| cg17326555 | 1    | 119535693  |            | -3,416        | 0,101                           | -1,630      | 0,143                           |
| cg01299579 | 2    | 10830716   | NOL10      | -3,468        | 0,101                           | -2,169      | 0,131                           |
| cg16044109 | 3    | 124762597  | HEG1       | 3,358         | 0,101                           | 1,713       | 0,137                           |
| cg00917569 | 16   | 51187388   | SALL1      | -3,320        | 0,101                           | -1,821      | 0,137                           |
| cg21726372 | 4    | 111540884  | PITX2      | -3,606        | 0,101                           | -2,165      | 0,137                           |
| cg11801727 | 1    | 228659093  |            | -4,700        | 0,101                           | -2,484      | 0,111                           |
| cg04961582 | 14   | 95239464   |            | -3,805        | 0,101                           | -2,183      | 0,119                           |
| cg08660326 | 17   | 50237401   | CA10       | -3,623        | 0,101                           | -1,720      | 0,137                           |
| cg11746813 | 12   | 54448090   | HOXC4      | -3,638        | 0,101                           | -2,013      | 0,137                           |
| TargetID  | Chr. | Coordinate | GENE          | logFC Tumor s | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|-----------|------|------------|---------------|---------------|----------------------------------|-------------|---------------------------------|
| cg18109320 | 5    | 87985809   | LINCC00461    | -3.340        | 0.101                            | -1.868      | 0.137                           |
| cg19883384 | 8    | 25905478   | EBF2         | -4.923        | 0.101                            | -1.858      | 0.137                           |
| cg27642784 | 3    | 157813670  | SHOX2        | -5.430        | 0.101                            | -2.621      | 0.137                           |
| cg04105760 | 2    | 175199722  | SP9          | -3.974        | 0.101                            | -1.700      | 0.139                           |
| cg23254393 | 4    | 85423132   |              | -2.954        | 0.101                            | -1.383      | 0.143                           |
| cg06993307 | 16   | 54969051   | CTD-3032H12.2| -4.310        | 0.101                            | -1.807      | 0.145                           |
| cg25397922 | 4    | 113431869  |              | -4.513        | 0.102                            | -2.036      | 0.139                           |
| cg27002522 | 12   | 54426772   | HOXC5        | -3.301        | 0.103                            | -1.424      | 0.145                           |
| cg23506042 | 5    | 50262673   | CTD-2089N3.1 | -3.624        | 0.104                            | -1.559      | 0.147                           |
| cg15250633 | 17   | 80627638   | RAB40B       | 3.624         | 0.104                            | 3.844       | 0.083                           |
| cg22902288 | 7    | 9250302    | GET4         | 5.288         | 0.104                            | 5.524       | 0.097                           |
| cg05056349 | 2    | 207629824  | FASTKD2      | -2.971        | 0.104                            | -2.231      | 0.131                           |
| cg18279094 | 1    | 63790044   | FOXD3        | -4.449        | 0.104                            | -2.128      | 0.131                           |
| cg08806496 | 5    | 92918943   | NR2F1        | -3.201        | 0.104                            | -2.133      | 0.131                           |
| cg05391318 | 1    | 200011684  | NR5A2        | -3.904        | 0.104                            | -1.549      | 0.137                           |
| cg06497668 | 2    | 45155703   | RP11-89K21.1 | -3.383        | 0.104                            | -1.558      | 0.137                           |
| cg18205770 | 5    | 87439353   |              | -3.128        | 0.104                            | -1.531      | 0.137                           |
| cg01069159 | 5    | 161275865  | GABRA1       | -2.909        | 0.104                            | -1.491      | 0.138                           |
| cg01337207 | 6    | 32063835   | TXNBP2       | -3.085        | 0.104                            | -1.757      | 0.145                           |
| cg10441934 | 10   | 100995640  | HPSE2        | -3.638        | 0.104                            | -1.649      | 0.137                           |
| cg11719362 | 7    | 25900355   |              | -3.359        | 0.104                            | -1.794      | 0.137                           |
| cg15074403 | 7    | 55141475   | EGFR         | 3.749         | 0.106                            | 3.656       | 0.056                           |
| cg13733314 | 7    | 20830816   |              | -3.837        | 0.107                            | -1.656      | 0.137                           |
| cg00037457 | 17   | 59531744   | TBX4         | -3.074        | 0.108                            | -2.095      | 0.126                           |
| cg06199336 | 2    | 200329942  | SATB2        | -3.104        | 0.108                            | -1.677      | 0.137                           |
| cg04109990 | 9    | 12795679   | LURAP1L      | 5.201         | 0.109                            | 5.278       | 0.056                           |
| cg08187687 | 2    | 176943914  | EVX2         | -3.494        | 0.109                            | -1.427      | 0.137                           |
| cg09175972 | 10   | 50534598   | C10orf71     | 4.496         | 0.110                            | 4.489       | 0.101                           |
| cg10738003 | 11   | 120233535  | ARHGEF12     | -4.606        | 0.110                            | -2.402      | 0.126                           |
| cg13479204 | 17   | 46641708   | HOXB3        | 3.701         | 0.110                            | 2.770       | 0.137                           |
| cg06776712 | 5    | 54528369   | CCNO         | -2.894        | 0.110                            | -1.782      | 0.137                           |
| cg27625479 | 7    | 121943287  | FEZF1        | -3.216        | 0.110                            | -1.519      | 0.137                           |
| cg18443359 | 5    | 134374693  | C5orf66      | -2.827        | 0.110                            | -1.816      | 0.140                           |
| cg05299558 | 13   | 100624288  | ZIC5         | -2.881        | 0.110                            | -1.418      | 0.141                           |
| cg22072375 | 21   | 38081480   | SIM2         | -3.411        | 0.110                            | -1.993      | 0.144                           |
| cg27455578 | 7    | 86850357   | TMEM243      | -3.018        | 0.110                            | -1.461      | 0.139                           |
| cg24875029 | 2    | 105471438  | POU3F3       | -3.061        | 0.110                            | -2.030      | 0.129                           |
| cg00316839 | 4    | 85414135   | NKX6-1       | -5.019        | 0.110                            | -1.997      | 0.137                           |
| cg23634124 | 17   | 48049952   | DLX4         | -2.726        | 0.110                            | -1.251      | 0.146                           |
| cg27307729 | 5    | 50264628   | CTD-2089N3.3 | -2.833        | 0.111                            | -1.883      | 0.133                           |
| TargetID | Chr. | Coordinate | GENE  | logFC Tumor | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|----------|------|------------|-------|-------------|----------------------------------|-------------|---------------------------------|
| cg01438365 | 17   | 59480470   | TBX2  | -2.738      | 0.111                            | -2.068      | 0.139                           |
| cg25593948 | 6    | 50786670   | TFAP2B | -3.882      | 0.111                            | -1.639      | 0.139                           |
| cg04738965 | 3    | 147127662  | ZIC1  | -3.079      | 0.111                            | -1.415      | 0.147                           |
| cg03388193 | 10   | 100996070  | HPSE2 | -3.405      | 0.112                            | -1.545      | 0.138                           |
| cg21226224 | 8    | 55370171   | SOX17 | -3.781      | 0.112                            | -2.716      | 0.085                           |
| cg16247826 | 2    | 54614692   |       | 3.309       | 0.112                            | 4.074       | 0.086                           |
| cg06523784 | 3    | 171870145  | FNDC3B| 3.611       | 0.112                            | 2.730       | 0.137                           |
| cg21128569 | 2    | 176956396  | HOXD13| -2.705      | 0.112                            | -1.737      | 0.137                           |
| cg18063495 | 5    | 50262976   |       | -3.076      | 0.112                            | -1.894      | 0.137                           |
| cg06925855 | 1    | 63792239   | FOXD3 | -3.536      | 0.113                            | -1.985      | 0.137                           |
| cg26153054 | 2    | 132152814  |       | 3.230       | 0.114                            | 1.650       | 0.139                           |
| cg04636269 | 17   | 35300868   | LHX1  | -2.780      | 0.114                            | -2.026      | 0.131                           |
| cg14367020 | 6    | 99292286   |       | -3.191      | 0.115                            | -2.570      | 0.103                           |
| cg01783394 | 5    | 50262941   |       | -2.878      | 0.115                            | -1.690      | 0.137                           |
| cg25226247 | 6    | 50785152   | TFAP2B| -2.911      | 0.115                            | -1.630      | 0.137                           |
| cg17790928 | 7    | 1277790    | UNCX  | -3.075      | 0.115                            | -1.519      | 0.137                           |
| cg05090195 | 12   | 54379493   | HOXC10| -3.833      | 0.115                            | -1.774      | 0.143                           |
| cg05836145 | 7    | 20827117   | SP8   | -2.776      | 0.115                            | -1.290      | 0.144                           |
| cg00705280 | 2    | 219866493  | MIR375| -4.165      | 0.115                            | -2.256      | 0.144                           |
| cg07673740 | 4    | 85414194   |       | -3.089      | 0.115                            | -1.968      | 0.131                           |
| cg18451114 | 1    | 38511677   | POU3F1| -3.683      | 0.115                            | -1.879      | 0.137                           |
| cg01825295 | 3    | 147131617  | ZIC1  | -2.956      | 0.115                            | -1.758      | 0.139                           |
| cg00586817 | 2    | 200329872  | SATB2 | -3.592      | 0.115                            | -1.811      | 0.137                           |
| cg19987665 | 2    | 223159250  | PAX3  | -2.577      | 0.116                            | -1.670      | 0.137                           |
| cg04613734 | 8    | 116663921  | TRPS1 | 4.554       | 0.116                            | 4.027       | 0.074                           |
| cg05578840 | 5    | 76934327   | OTP   | -4.606      | 0.116                            | -2.228      | 0.137                           |
| cg00316222 | 6    | 137817512  |       | -2.793      | 0.116                            | -1.800      | 0.137                           |
| cg04388989 | 19   | 30715606   |       | -2.701      | 0.117                            | -1.645      | 0.137                           |
| cg15353709 | 7    | 27238007   |       | -3.891      | 0.117                            | -1.447      | 0.139                           |
| cg19264651 | 9    | 126780399  | LHX2  | -3.459      | 0.117                            | -1.742      | 0.139                           |
| cg01688609 | 19   | 1987279    | BTBD2 | 3.460       | 0.118                            | 5.176       | 0.111                           |
| cg00083018 | 6    | 101840329  | GRIK2 | -3.051      | 0.118                            | -1.356      | 0.137                           |
| cg11145899 | 3    | 128778725  | GP9   | 3.629       | 0.118                            | 2.431       | 0.144                           |
| cg03442378 | 11   | 44332385   | ALX4  | -3.336      | 0.118                            | -2.297      | 0.137                           |
| cg08138075 | 16   | 54968787   |       | -2.676      | 0.118                            | -1.757      | 0.137                           |
| cg21585766 | 13   | 100636870  | ZIC2  | -3.947      | 0.118                            | -1.544      | 0.137                           |
| cg18322569 | 1    | 91182777   | BARHL2| -3.105      | 0.118                            | -2.011      | 0.137                           |
| cg04779860 | 10   | 131763929  | EBF3  | -2.664      | 0.118                            | -1.660      | 0.139                           |
| cg25609528 | 1    | 38510182   | POU3F1| -3.166      | 0.118                            | -1.286      | 0.142                           |
| cg01524278 | 12   | 54355460   |       | -2.728      | 0.118                            | -1.347      | 0.147                           |
| TargetID    | Chr. | Coordinate | GENE | logFC Tumor s | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|------------|------|------------|------|---------------|---------------------------------|-------------|---------------------------------|
| cg18063312 | 5    | 72740737   | RP11-79P5.6 | -4,077        | 0,118                           | -2,586      | 0,112                           |
| cg01983682 | 2    | 1622839799 | SLC4A10    | -2,791        | 0,118                           | -1,441      | 0,137                           |
| cg08693140 | 7    | 6653510    | ZNF853     | 3,073         | 0,119                           | 3,558       | 0,121                           |
| cg03555697 | 5    | 87983545   | LINCO00461 | -2,624        | 0,119                           | -1,419      | 0,140                           |
| cg19944876 | 17   | 8905866    |           | -2,654        | 0,119                           | -1,287      | 0,142                           |
| cg03119308 | 7    | 127950724  | RMB28      | 2,765         | 0,119                           | 3,280       | 0,068                           |
| cg17840250 | 6    | 32822857   | PSMB9      | 4,173         | 0,119                           | 4,491       | 0,121                           |
| cg06580725 | 13   | 100637930  | ZIC2       | -3,229        | 0,119                           | -2,089      | 0,126                           |
| cg05825073 | 7    | 27282237   | EVX1       | -3,284        | 0,119                           | -2,470      | 0,137                           |
| cg05380019 | 7    | 19146555   | TWIST1     | -3,250        | 0,119                           | -1,609      | 0,137                           |
| cg27565650 | 1    | 88151065   |           | 3,127         | 0,119                           | 2,836       | 0,137                           |
| cg05875410 | 16   | 51187572   | SALL1      | -2,854        | 0,119                           | -1,567      | 0,140                           |
| cg09863450 | 7    | 19159534   | AC003986.7 | -2,928        | 0,119                           | -1,283      | 0,142                           |
| cg02600430 | 13   | 100623942  | ZIC5       | -2,736        | 0,119                           | -1,842      | 0,137                           |
| cg01376826 | 3    | 147129826  | ZIC1       | -3,852        | 0,120                           | -2,017      | 0,137                           |
| cg01708273 | 2    | 176974060  | HOXD11     | -2,614        | 0,121                           | -1,234      | 0,144                           |
| cg06440305 | 20   | 21378427   | NKX2-4     | -2,835        | 0,122                           | -2,050      | 0,126                           |
| cg08545493 | 6    | 6004762    | NRN1       | -2,770        | 0,122                           | -1,699      | 0,149                           |
| cg01557547 | 3    | 157823089  | SHOX2      | -3,057        | 0,122                           | -1,557      | 0,142                           |
| cg26400885 | 3    | 147126119  | ZIC4       | -3,019        | 0,122                           | -1,251      | 0,143                           |
| cg24104938 | 6    | 108487078  | NR2E1      | -2,815        | 0,122                           | -1,464      | 0,137                           |
| cg26296371 | 6    | 5442953    | FARS2      | 3,461         | 0,123                           | 4,328       | 0,131                           |
| cg21849844 | 13   | 100611865  |           | -3,121        | 0,123                           | -1,677      | 0,137                           |
| cg10393811 | 2    | 176983927  | HOXD10     | -3,427        | 0,123                           | -2,116      | 0,137                           |
| cg00040007 | 15   | 41222276   | DLL4       | -2,963        | 0,123                           | -1,374      | 0,147                           |
| cg23946695 | 6    | 1609223    | FOXC1      | -2,773        | 0,123                           | -2,239      | 0,137                           |
| cg19515484 | 6    | 1606877    | FOXC1      | -3,410        | 0,123                           | -1,369      | 0,139                           |
| cg06134910 | 10   | 26730561   | APBB1P     | 3,380         | 0,125                           | 4,130       | 0,056                           |
| cg01414116 | 12   | 130720805  |           | 4,550         | 0,125                           | 3,773       | 0,062                           |
| cg01961105 | 16   | 54968783   | CTD-303212.2 | -3,594       | 0,125                           | -1,611      | 0,137                           |
| cg18322025 | 6    | 170055332  | WDR27      | -2,807        | 0,125                           | -2,436      | 0,137                           |
| cg10032131 | 11   | 57283055   | SLC43A1    | -3,545        | 0,125                           | -5,466      | 0,085                           |
| cg13691003 | 1    | 75603099   | LHX8       | -3,268        | 0,125                           | -1,372      | 0,138                           |
| cg26678970 | 13   | 79171469   | RNF219-AS1 | -2,675        | 0,125                           | -2,551      | 0,111                           |
| cg26489108 | 9    | 975856     | DMR13      | -3,021        | 0,125                           | -1,761      | 0,137                           |
| cg03958979 | 6    | 108486387  | NR2E1      | -2,685        | 0,126                           | -1,644      | 0,137                           |
| cg19025113 | 2    | 45155201   | RP11-89K21.1 | -2,625      | 0,126                           | -1,644      | 0,137                           |
| cg15425541 | 14   | 61118751   | SIX1       | -3,667        | 0,126                           | -2,580      | 0,137                           |
| cg09492451 | 16   | 54967389   | IRX5       | -3,153        | 0,126                           | -1,234      | 0,145                           |
| cg09739413 | 6    | 32729498   | HLA-DQB1   | -2,696        | 0,126                           | -1,351      | 0,148                           |
| TargetID   | Chr | Coordinate | GENE     | logFC Tumor s | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|------------|-----|------------|----------|---------------|----------------------------------|-------------|----------------------------------|
| cg12399700 | 12  | 113902262  | LHX5     | -3,095        | 0,126                             | -1,898      | 0,137                            |
| cg08767182 | 5   | 92940163   |          | -3,050        | 0,126                             | -1,712      | 0,143                            |
| cg02245004 | 15  | 76634887   | RP11-685G9.2 | -2,736     | 0,126                             | -1,316      | 0,147                            |
| cg099919570| 16  | 49311782   | CBLN1    | -2,545        | 0,126                             | -1,614      | 0,138                            |
| cg20785796 | 2   | 200326721  | SATB2    | -2,505        | 0,127                             | -1,682      | 0,137                            |
| cg08600862 | 11  | 76939558   |          | -2,961        | 0,127                             | -1,512      | 0,137                            |
| cg21592065 | 1   | 50889124   | DMRTA2   | -2,689        | 0,127                             | -1,490      | 0,137                            |
| cg02067712 | 13  | 28364724   |          | -3,128        | 0,127                             | -1,520      | 0,138                            |
| cg024893799| 10  | 124893766  | HMX3     | -3,256        | 0,128                             | -2,076      | 0,126                            |
| cg18277979 | 9   | 79630127   |          | -2,482        | 0,128                             | -1,596      | 0,137                            |
| cg18606375 | 5   | 134365728  | PITX1    | -2,939        | 0,128                             | -1,356      | 0,139                            |
| cg14106680 | 19  | 50733985   | MYH14    | -3,082        | 0,128                             | -2,743      | 0,137                            |
| cg18468917 | 12  | 47353065   |          | 2,668         | 0,130                             | 4,015       | 0,056                            |
| cg05640538 | 9   | 126772210  | LHX2     | -2,920        | 0,130                             | -1,586      | 0,137                            |
| cg23120061 | 2   | 176951595  |          | -2,579        | 0,130                             | -2,679      | 0,145                            |
| cg17939889 | 2   | 240174650  | HDAC4    | 2,541         | 0,130                             | 1,347       | 0,143                            |
| cg08364561 | 11  | 31846844   | RCN1     | -2,844        | 0,130                             | -2,827      | 0,137                            |
| cg23934731 | 15  | 89904873   |          | -3,899        | 0,130                             | -1,560      | 0,137                            |
| cg11604182 | 5   | 177433673  | FAM153C  | -2,521        | 0,130                             | -1,376      | 0,138                            |
| cg13692446 | 13  | 112759719  |          | -3,725        | 0,130                             | -1,733      | 0,137                            |
| cg17222645 | 3   | 197808017  | ANKRD18D | -2,662        | 0,131                             | -2,479      | 0,137                            |
| cg23698978 | 7   | 20838631   | P         | -3,278        | 0,131                             | -1,619      | 0,137                            |
| cg27069921 | 5   | 54523727   | RP11-528L24.3 | -3,121     | 0,132                             | -1,580      | 0,137                            |
| cg02973171 | 11  | 82443614   | FAM181B  | -3,606        | 0,132                             | -1,924      | 0,138                            |
| cg08880082 | 14  | 90165664   | RP11-33N16.3 | 2,665      | 0,133                             | 4,192       | 0,056                            |
| cg27299712 | 1   | 6550532    | PLEKHG5  | 2,920         | 0,133                             | 2,830       | 0,142                            |
| cg07747970 | 17  | 35293719   | LHX1     | -2,555        | 0,133                             | -1,264      | 0,147                            |
| cg14527649 | 14  | 69412803   | ACTN1    | 3,269         | 0,134                             | 3,570       | 0,137                            |
| cg03465861 | 15  | 76630660   | ISL2     | -3,301        | 0,134                             | -1,502      | 0,147                            |
| cg14775296 | 2   | 66672841   | MEIS1    | 3,126         | 0,134                             | 1,832       | 0,150                            |
| cg07335343 | 5   | 78829309   | Y_RNA    | 3,464         | 0,135                             | 4,541       | 0,120                            |
| cg13496838 | 2   | 223164747  | PAX3     | -3,019        | 0,135                             | -1,637      | 0,137                            |
| cg04591032 | 17  | 46827458   |          | -2,472        | 0,135                             | -1,552      | 0,140                            |
| cg20268039 | 7   | 25900167   |          | -2,843        | 0,135                             | -1,376      | 0,147                            |
| cg04655510 | 20  | 21378703   | NKX2-4   | -3,126        | 0,135                             | -1,644      | 0,137                            |
| cg24616539 | 11  | 31848828   | RCN1     | -2,734        | 0,135                             | -1,140      | 0,149                            |
| cg26066870 | 8   | 11559039   | GATA4    | -2,453        | 0,135                             | -1,271      | 0,142                            |
| cg11342452 | 10  | 134600463  | NKX6-2   | -3,100        | 0,135                             | -1,940      | 0,137                            |
| cg07476673 | 6   | 170602968  | FAM120B  | -2,403        | 0,135                             | -1,245      | 0,141                            |
| TargetID   | Chr. | Coordinate | GENE      | logFC TumorS | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|------------|------|------------|-----------|--------------|----------------------------------|--------------|---------------------------------|
| cg00565688 | 1    | 3568212    | TP73      | -4,892       | 0,136                            | -1,452       | 0,137                           |
| cg08787268 | 17   | 47072857   | RP11-50IC14.5 | -2,888   | 0,136                            | -1,522       | 0,142                           |
| cg27234067 | 11   | 32460799   | WTI1-AS   | -2,356       | 0,136                            | -1,871       | 0,142                           |
| cg11382529 | 8    | 65409013   | LOC401463 | -3,357       | 0,136                            | -2,314       | 0,137                           |
| cg21781761 | 19   | 20608600   | ZNF826P   | 2,324        | 0,137                            | 3,174        | 0,106                           |
| cg02280088 | 2    | 119615605  |           | -3,212       | 0,137                            | -2,178       | 0,131                           |
| cg08463788 | 1    | 197888068  | LHX9      | -2,645       | 0,137                            | -1,660       | 0,137                           |
| cg20012315 | 7    | 6740598    | ZNF12     | 3,583        | 0,137                            | 3,590        | 0,071                           |
| cg03449967 | 15   | 28200653   | OCA2      | -4,501       | 0,137                            | -2,052       | 0,137                           |
| cg10425754 | 16   | 49311483   | CBLN1     | -2,516       | 0,137                            | -1,543       | 0,138                           |
| cg08460041 | 1    | 165325136  | LMX1A     | -2,554       | 0,137                            | -1,469       | 0,142                           |
| cg09890891 | 15   | 96904723   | RP11-522B15.3 | -2,454   | 0,137                            | -1,378       | 0,145                           |
| cg07699771 | 8    | 1153329    |           | -2,487       | 0,137                            | -1,495       | 0,137                           |
| cg00014830 | 17   | 77765733   |           | -3,437       | 0,137                            | -1,508       | 0,137                           |
| cg26327666 | 5    | 76937963   |           | -2,431       | 0,137                            | -2,134       | 0,139                           |
| cg04087742 | 5    | 50264462   | CTD-2089N3.3 | -2,508   | 0,138                            | -2,514       | 0,140                           |
| cg22239201 | 4    | 95678703   | BMPR1B    | -3,147       | 0,138                            | -1,223       | 0,142                           |
| cg17450425 | 8    | 70982255   | PRDM14    | -2,454       | 0,138                            | -2,437       | 0,137                           |
| cg11855516 | 2    | 175207244  | CTD-2281E23.2 | -3,753   | 0,138                            | -1,662       | 0,137                           |
| cg04130163 | 4    | 42401214   | SHISA3    | -2,430       | 0,138                            | -1,239       | 0,142                           |
| cg25221239 | 10   | 131764419  | EBF3      | -3,148       | 0,138                            | -1,167       | 0,148                           |
| cg11988733 | 2    | 176968814  | HOXD11    | -2,392       | 0,138                            | -1,814       | 0,137                           |
| cg05022105 | 11   | 32460980   | WTI1      | -2,830       | 0,138                            | -2,212       | 0,117                           |
| cg01582980 | 7    | 20825545   | SP8       | -2,386       | 0,138                            | -1,290       | 0,144                           |
| cg15254559 | 7    | 27292145   | PAX6      | -2,369       | 0,139                            | -1,183       | 0,148                           |
| cg15301794 | 11   | 31822243   | CA10      | -3,431       | 0,139                            | -1,482       | 0,137                           |
| cg07723251 | 17   | 50237742   | ROBO3     | -3,405       | 0,139                            | -1,572       | 0,140                           |
| cg09251429 | 11   | 124735128  | SP6       | -2,624       | 0,139                            | -1,608       | 0,137                           |
| cg17733447 | 17   | 45929399   | ZIC2      | -2,659       | 0,140                            | -2,181       | 0,126                           |
| cg18383890 | 13   | 100636252  | RP4-665J23.1 | -2,900   | 0,140                            | -1,834       | 0,137                           |
| cg09793883 | 1    | 91300559   | DLX6-AS1  | -3,112       | 0,140                            | -1,683       | 0,137                           |
| cg02153806 | 7    | 96641232   | DLX6-AS1  | -3,112       | 0,140                            | -1,683       | 0,137                           |
| cg00645884 | 10   | 6110377    |           | 2,574        | 0,140                            | 1,924        | 0,139                           |
| cg07339662 | 7    | 1271925    | UNCX      | -2,305       | 0,141                            | -1,292       | 0,148                           |
| cg10666140 | 7    | 855006     | SUN1      | -3,207       | 0,141                            | -1,295       | 0,148                           |
| cg24051749 | 1    | 39340282   | MYCBP     | 3,408        | 0,141                            | 4,361        | 0,056                           |
| cg14964115 | 10   | 116634877  | FAM160B1  | -3,499       | 0,141                            | -3,311       | 0,111                           |
| cg17875555 | 8    | 23564490   | NKX2-6    | -3,171       | 0,142                            | -2,070       | 0,131                           |
| cg26824678 | 1    | 19777949   | CAPZB     | 3,739        | 0,142                            | 4,016        | 0,071                           |
| TargetID   | Chr. | Coordinate | GENE          | logFC Tumors (DNMT3A-tumors vs. Controls) | FDR (DNMT3A-tumors vs. Controls) | logFC Blood | FDR (DNMT3A-Blood vs. Controls) |
|------------|------|------------|---------------|------------------------------------------|----------------------------------|-------------|---------------------------------|
| cg13023870 | 14   | 37124018   | RP11-964E11.2 | -3.666                                   | 0.143                            | -1.582      | 0.137                           |
| cg05425699 | 7    | 47580148   | TNS3         | 3.325                                    | 0.143                            | 1.382       | 0.148                           |
| cg23468312 | 8    | 130426887  | CCDC26       | 2.232                                    | 0.144                            | 1.760       | 0.137                           |
| cg05301866 | 2    | 162279964  | TBR1         | -2.278                                   | 0.145                            | -1.479      | 0.137                           |
| cg17833476 | 5    | 170736201  | TLX3         | -3.525                                   | 0.145                            | -1.885      | 0.140                           |
| cg00931201 | X    | 15756372   | CASB         | -2.326                                   | 0.146                            | -2.284      | 0.131                           |
| cg09162333 | 2    | 19556876   | OSR1         | -3.164                                   | 0.146                            | -2.004      | 0.137                           |
| cg24697433 | 6    | 28876508   | TRIM27       | 3.289                                    | 0.146                            | 4.648       | 0.056                           |
| cg01998213 | 7    | 19149989   | TWIST1       | -3.169                                   | 0.146                            | -1.592      | 0.137                           |
| cg15920743 | 10   | 102984393  | RNA219-AS1   | -2.784                                   | 0.146                            | -1.438      | 0.137                           |
| cg27268520 | 6    | 27198236   | OTP          | -2.291                                   | 0.146                            | -2.505      | 0.137                           |
| cg13343639 | 10   | 100995599  | HPSE2        | -2.311                                   | 0.146                            | -1.632      | 0.137                           |
| cg03261929 | 13   | 79168211   | RNF219-AS1   | -2.763                                   | 0.147                            | -1.727      | 0.137                           |
| cg26365545 | 5    | 76932016   | OTP          | -2.406                                   | 0.147                            | -1.829      | 0.137                           |
| cg02573472 | 5    | 76940356   | OTP          | -2.629                                   | 0.147                            | -1.612      | 0.137                           |
| cg04184019 | 4    | 85424288   | HOMER1       | -2.555                                   | 0.148                            | -1.731      | 0.137                           |
| cg16810310 | 11   | 66104993   | BRMS1        | 2.703                                    | 0.148                            | 3.552       | 0.056                           |
| cg24851478 | 3    | 62355150   | RP11-204J18.3| -2.810                                   | 0.148                            | -1.182      | 0.144                           |
| cg12421755 | 15   | 53080933   | ONECUT1      | -2.582                                   | 0.148                            | -1.813      | 0.137                           |
| cg03665912 | X    | 136511413  | ZIC5         | -2.240                                   | 0.149                            | -1.696      | 0.137                           |
| cg18161327 | 13   | 100627703  | GATA5        | -2.249                                   | 0.149                            | -1.709      | 0.145                           |
| cg14388488 | 20   | 61051777   | GATA5        | -2.249                                   | 0.149                            | -1.622      | 0.137                           |
| cg11841038 | 6    | 1380898    | IRX3         | -2.168                                   | 0.150                            | -1.852      | 0.142                           |
| cg17486263 | 1    | 200011726  | NR5A2        | -2.168                                   | 0.150                            | -1.960      | 0.137                           |
| cg02194243 | 16   | 54324597   | IRX3         | -3.812                                   | 0.150                            | -1.960      | 0.137                           |