

Supplemental Table 1. Metabolite-CpG pairs with FDR &lt; 0.05 in models 1 and their effect size in models 2, and 3 in fixed-effect meta-analysis

| Metabolite    | CpG        | CHR | BP        | Gene            | CpG Island | Feature                          | Model 1 |        |          | Model 2 |        |          | Model 3 |        |          | L_square |
|---------------|------------|-----|-----------|-----------------|------------|----------------------------------|---------|--------|----------|---------|--------|----------|---------|--------|----------|----------|
|               |            |     |           |                 |            |                                  | Beta    | SE     | P        | Beta    | SE     | P        | Beta    | SE     | P        |          |
| Betaine       | cg09805709 | 1   | 6552273   | PLEKHG5         | S_Shore    |                                  | -0.0066 | 0.0013 | 4.44e-07 | -0.0069 | 0.0013 | 2.77e-07 | -0.0069 | 0.0013 | 3.42e-07 | 0.77     |
| Betaine       | cg01327202 | 1   | 17215511  |                 | Island     | Enhancer, HMM island, regulatory | -0.0088 | 0.0018 | 8.46e-07 | -0.008  | 0.0017 | 5.17e-06 | -0.0079 | 0.0018 | 7.82e-06 | 0        |
| Betaine       | cg05712748 | 1   | 43472312  |                 | N_Shore    | Enhancer, HMM island             | -0.0051 | 0.001  | 1.08e-07 | -0.0049 | 0.001  | 8e-07    | -0.005  | 0.001  | 3.99e-07 | 0        |
| Betaine       | cg27032760 | 5   | 143974763 |                 | N_Shelf    | HMM island                       | -0.01   | 0.0019 | 1.09e-07 | -0.0096 | 0.0019 | 2.58e-07 | -0.0097 | 0.0019 | 3.08e-07 | 0        |
| Betaine       | cg15083522 | 10  | 134188873 | LRRC27          |            | Enhancer, HMM island             | -0.0119 | 0.0017 | 9.45e-12 | -0.0112 | 0.0018 | 2.67e-10 | -0.0113 | 0.0018 | 3.27e-10 | 0.6      |
| Betaine       | cg04592747 | 11  | 66035942  | RAB1B           | Island     | HMM island, regulatory           | 0.0031  | 0.0006 | 6.75e-08 | 0.0028  | 0.0006 | 8.58e-07 | 0.0028  | 0.0006 | 1.17e-06 | 0.37     |
| Betaine       | cg17058475 | 11  | 68607737  | CPT1A           | N_Shore    | HMM island                       | 0.0049  | 0.001  | 1.19e-06 | 0.005   | 0.001  | 1.69e-06 | 0.0048  | 0.001  | 5.28e-06 | 0.75     |
| Betaine       | cg18705301 | 15  | 41695430  | NDUFAF1         | S_Shore    |                                  | -0.0263 | 0.0045 | 7.16e-09 | -0.0255 | 0.0045 | 1.3e-08  | -0.0254 | 0.0045 | 1.63e-08 | 0        |
| Betaine       | cg08914678 | 16  | 334889    | PDIA2           | N_Shore    | HMM island, regulatory           | 0.0197  | 0.0026 | 1.34e-14 | 0.0202  | 0.0026 | 5.49e-15 | 0.0203  | 0.0026 | 5.1e-15  | 0        |
| Betaine       | cg01454815 | 16  | 23193933  | SCNN1G          | Island     | Enhancer, HMM island, regulatory | -0.0057 | 0.0012 | 1.03e-06 | -0.0058 | 0.0011 | 1.18e-07 | -0.0058 | 0.0011 | 1.19e-07 | 0.7      |
| Betaine       | cg18593708 | 18  | 21853454  | OSBPL1A         | S_Shore    |                                  | -0.0089 | 0.0018 | 5.55e-07 | -0.0089 | 0.0018 | 5.88e-07 | -0.0088 | 0.0018 | 8.65e-07 | 0        |
| Betaine       | cg02288165 | 20  | 3687992   | SIGLEC1         |            |                                  | 0.0103  | 0.0018 | 1.38e-08 | 0.0105  | 0.0019 | 3.56e-08 | 0.0105  | 0.0019 | 5.47e-08 | 0.85     |
| Butyrobetaine | cg07795402 | 1   | 2938954   | ACTRT2          | Island     | HMM island                       | 0.0031  | 0.0006 | 1.17e-07 | 0.0034  | 0.0006 | 8.17e-08 | 0.0034  | 0.0006 | 8.61e-08 | 0.38     |
| Butyrobetaine | cg00703019 | 1   | 7831811   | VAMP3           | Island     | HMM island                       | 0.0024  | 0.0005 | 1.05e-06 | 0.0025  | 0.0005 | 5.81e-07 | 0.0029  | 0.0005 | 1.25e-07 | 0.81     |
| Butyrobetaine | cg24087235 | 1   | 54665621  | CYB5RL;MRPL37   | N_Shore    | HMM island, regulatory           | 0.0009  | 0.0002 | 3.96e-06 | 0.0009  | 0.0002 | 3.56e-05 | 0.001   | 0.0002 | 1.27e-05 | 0        |
| Butyrobetaine | cg17466510 | 1   | 116877566 |                 |            | Enhancer                         | 0.0055  | 0.0012 | 3.24e-06 | 0.006   | 0.0012 | 8.4e-07  | 0.0059  | 0.0014 | 2.65e-05 | 0        |
| Butyrobetaine | cg23803022 | 1   | 154908781 | PMVK            | N_Shore    | Regulatory                       | 0.0082  | 0.0017 | 7.61e-07 | 0.0087  | 0.0017 | 6.04e-07 | 0.0094  | 0.0019 | 3.62e-07 | 0.76     |
| Butyrobetaine | cg22076160 | 1   | 235805690 | GNG4            | Island     | Enhancer, HMM island, regulatory | 0.0083  | 0.0017 | 6.76e-07 | 0.0087  | 0.0017 | 3.49e-07 | 0.0082  | 0.0017 | 2.05e-06 | 0.54     |
| Butyrobetaine | cg20345923 | 2   | 1983190   | MYT1L           |            | HMM island                       | 0.0052  | 0.001  | 1.51e-07 | 0.0055  | 0.0012 | 1.89e-06 | 0.006   | 0.0013 | 1.98e-06 | 0        |
| Butyrobetaine | cg04059696 | 2   | 27211953  | MAPRE3          |            | Enhancer                         | 0.0051  | 0.001  | 9.89e-07 | 0.0056  | 0.0011 | 2.46e-07 | 0.0059  | 0.0012 | 1.35e-06 | 0        |
| Butyrobetaine | cg25072436 | 2   | 30454560  | LBH             | Island     | DMR, HMM island, regulatory      | 0.002   | 0.0004 | 2.43e-06 | 0.0021  | 0.0004 | 2.34e-06 | 0.0022  | 0.0005 | 2.03e-06 | 0.19     |
| Butyrobetaine | cg05655116 | 2   | 37899435  | CDC42EP3        | Island     | Enhancer, HMM island, regulatory | 0.0018  | 0.0004 | 2.79e-06 | 0.0018  | 0.0004 | 5.98e-06 | 0.0018  | 0.0004 | 2.66e-05 | 0        |
| Butyrobetaine | cg03389926 | 2   | 42651266  |                 |            | Enhancer                         | 0.0081  | 0.0017 | 1.55e-06 | 0.0092  | 0.0019 | 2.21e-06 | 0.0107  | 0.0021 | 3.73e-07 | 0        |
| Butyrobetaine | cg23513644 | 2   | 71357140  | MPHOSPH10;MCEE  | N_Shore    | Enhancer, HMM island, regulatory | 0.0013  | 0.0003 | 3.46e-06 | 0.0014  | 0.0003 | 3.06e-06 | 0.0015  | 0.0003 | 9.68e-07 | 0.61     |
| Butyrobetaine | cg03034070 | 2   | 190044841 | COL5A2          |            |                                  | -0.0119 | 0.0026 | 3.3e-06  | -0.0121 | 0.0026 | 4.25e-06 | -0.0111 | 0.0026 | 1.73e-05 | 0        |
| Butyrobetaine | cg23339656 | 2   | 234159882 | ATG16L1         | N_Shore    | Regulatory                       | 0.0099  | 0.0018 | 4.35e-08 | 0.0101  | 0.002  | 3.25e-07 | 0.0101  | 0.002  | 5.66e-07 | 0        |
| Butyrobetaine | cg27367871 | 2   | 237478030 | CXCR7           | S_Shore    | DMR, regulatory                  | 0.0079  | 0.0015 | 1.02e-07 | 0.0081  | 0.0015 | 1.26e-07 | 0.0078  | 0.0016 | 1.52e-06 | 0.1      |
| Butyrobetaine | cg06651286 | 3   | 197477426 | FYTDD1;KIAA0226 | Island     | Enhancer, HMM island             | -0.0004 | 0.0001 | 3.76e-06 | -0.0004 | 0.0001 | 2.87e-06 | -0.0004 | 0.0001 | 2.83e-07 | 0.87     |
| Butyrobetaine | cg19596468 | 4   | 4864110   | MSX1            | N_Shore    | DMR, HMM island                  | 0.0118  | 0.0025 | 2.97e-06 | 0.0108  | 0.0025 | 1.15e-05 | 0.01    | 0.0026 | 0.000108 | 0.8      |
| Butyrobetaine | cg16044573 | 4   | 48833093  | OCIAD1          | Island     | Enhancer, HMM island, regulatory | 0.0015  | 0.0003 | 5.14e-06 | 0.0017  | 0.0004 | 1.11e-05 | 0.0017  | 0.0004 | 5.31e-06 | 0.52     |
| Butyrobetaine | cg16368147 | 4   | 62111221  |                 |            | Enhancer                         | 0.0064  | 0.0014 | 3.36e-06 | 0.0069  | 0.0016 | 1.22e-05 | 0.0073  | 0.0015 | 2.16e-06 | 0        |
| Butyrobetaine | cg05606878 | 5   | 126432189 |                 |            | Enhancer                         | 0.0068  | 0.0015 | 4.86e-06 | 0.0065  | 0.0015 | 2.38e-05 | 0.0065  | 0.0017 | 8.54e-05 | 0        |
| Butyrobetaine | cg02006915 | 5   | 175991129 | PCDH24          |            |                                  | 0.0068  | 0.0015 | 4.49e-06 | 0.0076  | 0.0017 | 9e-06    | 0.0088  | 0.0018 | 6.18e-07 | 0        |
| Butyrobetaine | cg26747317 | 6   | 31829793  | NEU1            | N_Shore    |                                  | 0.0093  | 0.0017 | 6.91e-08 | 0.0094  | 0.0018 | 1.73e-07 | 0.01    | 0.0019 | 1.35e-07 | 0        |
| Butyrobetaine | cg04346459 | 6   | 41068666  | NFYA;LOC221442  | Island     | Enhancer, HMM island             | 0.0177  | 0.0033 | 7.36e-08 | 0.0167  | 0.0036 | 2.87e-06 | 0.0183  | 0.0037 | 7.87e-07 | 0        |
| Butyrobetaine | cg09580153 | 6   | 41068724  | NFYA;LOC221442  | Island     | Enhancer, HMM island             | 0.0101  | 0.0018 | 2.32e-08 | 0.0095  | 0.002  | 1.31e-06 | 0.0101  | 0.002  | 5.93e-07 | 0        |
| Butyrobetaine | cg03644281 | 6   | 41068752  | NFYA;LOC221442  | Island     | Enhancer, HMM island             | 0.0121  | 0.0023 | 1.11e-07 | 0.0114  | 0.0025 | 3.47e-06 | 0.0123  | 0.0025 | 1.18e-06 | 0        |
| Butyrobetaine | cg07014126 | 6   | 169717713 |                 |            | HMM island                       | 0.0042  | 0.0009 | 5.16e-06 | 0.0046  | 0.001  | 5.62e-06 | 0.0049  | 0.0011 | 6.36e-06 | 0        |
| Butyrobetaine | cg01824931 | 7   | 1642224   |                 | N_Shore    | HMM island                       | 0.0057  | 0.0012 | 4.35e-06 | 0.0072  | 0.0015 | 1.28e-06 | 0.0069  | 0.0015 | 4.07e-06 | 0.64     |
| Butyrobetaine | cg20109393 | 7   | 19748466  | TWISTNB         | Island     | HMM island, regulatory           | -0.0004 | 0.0001 | 3.19e-06 | -0.0004 | 0.0001 | 1.68e-06 | -0.0005 | 0.0001 | 2.44e-06 | 0        |
| Butyrobetaine | cg08500172 | 8   | 127908827 |                 |            | Enhancer                         | 0.0043  | 0.0009 | 3.3e-06  | 0.0048  | 0.0009 | 3.95e-07 | 0.0054  | 0.0013 | 2.09e-05 | 0        |
| Butyrobetaine | cg21161526 | 9   | 123691672 |                 | Island     | HMM island                       | 0.0059  | 0.0012 | 4.95e-07 | 0.0062  | 0.0011 | 4.77e-08 | 0.007   | 0.0012 | 4.92e-09 | 0.34     |
| Butyrobetaine | cg11009695 | 10  | 29358074  |                 |            | Enhancer                         | 0.006   | 0.0013 | 6.11e-06 | 0.0067  | 0.0015 | 1.14e-05 | 0.0075  | 0.0015 | 1.05e-06 | 0        |
| Butyrobetaine | cg06073535 | 11  | 733406    |                 | N_Shore    | HMM island                       | 0.0045  | 0.0008 | 3.63e-08 | 0.0051  | 0.0009 | 1.12e-08 | 0.0053  | 0.0009 | 4.74e-09 | 0.83     |
| Butyrobetaine | cg00243281 | 11  | 2597838   | KCNQ1           | S_Shore    | HMM island                       | 0.004   | 0.0009 | 5.1e-06  | 0.0037  | 0.0009 | 3.23e-05 | 0.0037  | 0.0009 | 9.89e-05 | 0        |
| Butyrobetaine | cg11527344 | 11  | 57972167  | OR1S2           |            |                                  | 0.0037  | 0.0008 | 5.65e-06 | 0.0039  | 0.0008 | 3.62e-06 | 0.0041  | 0.0009 | 4.5e-06  | 0        |
| Butyrobetaine | cg06079620 | 11  | 58978082  | MPEG1           |            |                                  | 0.0058  | 0.0011 | 2.2e-07  | 0.0066  | 0.0013 | 2.28e-07 | 0.0067  | 0.0012 | 3.61e-08 | 0        |
| Butyrobetaine | cg26561797 | 11  | 68437843  |                 | Island     | HMM island                       | 0.0048  | 0.0009 | 1.19e-07 | 0.0051  | 0.0009 | 5.78e-08 | 0.005   | 0.001  | 4.84e-07 | 0        |
| Butyrobetaine | cg17306339 | 12  | 124198578 | ATP6V0A2        | S_Shore    | DMR, regulatory                  | 0.0072  | 0.0014 | 3.9e-07  | 0.0079  | 0.0018 | 1.33e-05 | 0.0089  | 0.002  | 8.38e-06 | 0        |
| Butyrobetaine | cg05446322 | 13  | 36053408  | MIR548F5;NBEA   | S_Shore    | DMR                              | 0.0105  | 0.0023 | 3.09e-06 | 0.0115  | 0.0024 | 1.14e-06 | 0.0118  | 0.0025 | 3.77e-06 | 0.64     |

|                |               |    |           |               |         |                                       |         |        |          |         |        |          |         |        |          |      |
|----------------|---------------|----|-----------|---------------|---------|---------------------------------------|---------|--------|----------|---------|--------|----------|---------|--------|----------|------|
| Butyrobetaine  | cg19946956    | 13 | 114768348 | RASA3         | S_Shore | HMM island                            | 0.0025  | 0.0004 | 3.72e-09 | 0.0026  | 0.0005 | 1.62e-08 | 0.0024  | 0.0005 | 6.65e-07 | 0.68 |
| Butyrobetaine  | cg27481208    | 13 | 115079979 | ZNF828        | Island  | Enhancer, HMM island, regulatory      | -0.0003 | 0.0001 | 3.32e-06 | -0.0003 | 0.0001 | 1.98e-06 | -0.0003 | 0.0001 | 2.1e-05  | 0    |
| Butyrobetaine  | cg19503462    | 14 | 47872288  | MDGA2         |         | Enhancer                              | 0.0255  | 0.0038 | 2.06e-11 | 0.0249  | 0.0041 | 9.36e-10 | 0.0269  | 0.0041 | 5.56e-11 | 0.79 |
| Butyrobetaine  | cg23323891    | 14 | 57200519  |               |         | Enhancer                              | 0.0119  | 0.0026 | 3.54e-06 | 0.0121  | 0.0026 | 2.16e-06 | 0.013   | 0.0027 | 1.26e-06 | 0    |
| Butyrobetaine  | cg18548879    | 15 | 41914454  |               | S_Shore | HMM island, regulatory                | 0.0042  | 0.0009 | 1.24e-06 | 0.0044  | 0.001  | 3.21e-06 | 0.0045  | 0.0012 | 0.000106 | 0    |
| Butyrobetaine  | cg10517312    | 15 | 45027253  | TRIM69        |         |                                       | 0.0066  | 0.0012 | 1.34e-07 | 0.007   | 0.0013 | 8.06e-08 | 0.0085  | 0.0016 | 4.14e-08 | 0    |
| Butyrobetaine  | cg01764904    | 15 | 60289326  |               | Island  | DMR, HMM island, regulatory           | 0.0062  | 0.0014 | 5.44e-06 | 0.007   | 0.0014 | 8.55e-07 | 0.0074  | 0.0015 | 1.36e-06 | 0.81 |
| Butyrobetaine  | cg24737374    | 15 | 77933785  |               |         |                                       | 0.0038  | 0.0008 | 2.52e-06 | 0.0039  | 0.0008 | 2.28e-06 | 0.0039  | 0.0009 | 6.51e-06 | 0.25 |
| Butyrobetaine  | cg01090433    | 16 | 82673506  | CDH13         |         | Enhancer, regulatory                  | 0.0093  | 0.0019 | 1.06e-06 | 0.0095  | 0.002  | 1.81e-06 | 0.0102  | 0.0021 | 1.59e-06 | 0    |
| Butyrobetaine  | cg10760240    | 17 | 35414006  | AATF          |         | HMM island                            | 0.0077  | 0.0015 | 2.91e-07 | 0.0075  | 0.0016 | 3.44e-06 | 0.0078  | 0.0017 | 2.5e-06  | 0    |
| Butyrobetaine  | cg09309112    | 17 | 53571325  |               |         | Enhancer                              | 0.005   | 0.001  | 5.27e-07 | 0.0054  | 0.001  | 2.06e-07 | 0.0052  | 0.0011 | 2.34e-06 | 0    |
| Butyrobetaine  | cg26853549    | 17 | 60781627  | MARCH10       | Island  | HMM island, regulatory                | -0.0003 | 0.0001 | 5.96e-06 | -0.0003 | 0.0001 | 6.35e-06 | -0.0003 | 0.0001 | 4.06e-05 | 0.39 |
| Butyrobetaine  | cg14608770    | 19 | 17571873  | NXNL1         |         |                                       | 0.0155  | 0.0027 | 4.92e-09 | 0.0155  | 0.0028 | 5.3e-08  | 0.0148  | 0.0029 | 3.42e-07 | 0.36 |
| Butyrobetaine  | cg01885692    | 22 | 21804711  | HIC2          | S_Shelf |                                       | 0.004   | 0.0009 | 5e-06    | 0.0038  | 0.0009 | 1.29e-05 | 0.0042  | 0.0009 | 5.83e-06 | 0    |
| Butyrobetaine  | cg15550654    | 22 | 30277968  | MTMR3         | N_Shore |                                       | 0.0066  | 0.0014 | 2.59e-06 | 0.0062  | 0.0016 | 0.000138 | 0.0065  | 0.0016 | 4.39e-05 | 0.38 |
| Carnitine      | cg16491274    | 1  | 16678832  | FBXO42        | Island  | HMM island, regulatory                | -0.0032 | 0.0006 | 1.18e-07 | -0.0032 | 0.0006 | 3.83e-07 | -0.0033 | 0.0006 | 2.03e-07 | 0.81 |
| Carnitine      | cg13349742    | 2  | 235080074 |               |         | HMM island                            | 0.0045  | 0.0009 | 5.42e-07 | 0.005   | 0.001  | 3.15e-07 | 0.005   | 0.001  | 3.28e-07 | 0.39 |
| Carnitine      | cg19408207    | 3  | 178755197 | ZMAT3         |         | Enhancer, regulatory                  | 0.0078  | 0.0015 | 2.33e-07 | 0.0084  | 0.0016 | 7.66e-08 | 0.0084  | 0.0017 | 5.47e-07 | 0    |
| Carnitine      | cg06487937    | 16 | 5116160   | C16orf89      |         |                                       | -0.015  | 0.003  | 4.35e-07 | -0.0141 | 0.0031 | 4.37e-06 | -0.0139 | 0.0033 | 2.23e-05 | 0    |
| Carnitine      | cg21367586    | 18 | 34327498  | FHOD3         | S_Shore |                                       | 0.0157  | 0.0022 | 2.19e-12 | 0.0163  | 0.0023 | 1.41e-12 | 0.0162  | 0.0023 | 3.33e-12 | 0    |
| Choline        | cg05398737    | 1  | 12078755  | MIIP          | N_Shore |                                       | -0.0029 | 0.0003 | 2.02e-17 | -0.0028 | 0.0004 | 3.1e-14  | -0.0028 | 0.0004 | 1.93e-13 | 0.64 |
| Choline        | cg18757828    | 2  | 132233784 | TUBA3D        | Island  | HMM island                            | -0.011  | 0.0017 | 2.3e-10  | -0.0117 | 0.0018 | 3.33e-11 | -0.0121 | 0.0018 | 3.31e-11 | 0.55 |
| Choline        | cg15877769    | 4  | 1062280   |               | N_Shore |                                       | 0.0192  | 0.0037 | 2.81e-07 | 0.019   | 0.0038 | 5.52e-07 | 0.0197  | 0.0039 | 5e-07    | 0    |
| Choline        | cg21501305    | 7  | 157280713 |               |         | HMM island                            | -0.0064 | 0.0009 | 4.86e-13 | -0.0053 | 0.0009 | 4.89e-10 | -0.0055 | 0.0009 | 4.96e-10 | 0.68 |
| Choline        | cg18875674    | 11 | 73026651  | ARHGEF17      |         | Enhancer                              | 0.0101  | 0.0018 | 2.94e-08 | 0.0098  | 0.002  | 1.05e-06 | 0.01    | 0.0021 | 1.53e-06 | 0    |
| Choline        | cg03606258    | 20 | 57426935  | GNAS          | Island  | DMR, enhancer, HMM island, regulatory | 0.0189  | 0.0031 | 7.26e-10 | 0.017   | 0.0032 | 1.7e-07  | 0.0172  | 0.0034 | 3.68e-07 | 0.09 |
| Crotonobetaine | cg11798909    | 1  | 1567820   | MMP23A;MMP23B | Island  | HMM island                            | 0.0062  | 0.0012 | 5.07e-07 | 0.0065  | 0.0012 | 2.32e-07 | 0.0067  | 0.0014 | 9.21e-07 | 0.74 |
| Crotonobetaine | cg03396604    | 1  | 3193944   | PRDM16        | N_Shore |                                       | -0.0083 | 0.0018 | 7.1e-06  | -0.0085 | 0.002  | 1.93e-05 | -0.0086 | 0.002  | 2.09e-05 | 0    |
| Crotonobetaine | cg08877374    | 1  | 31845904  | FABP3         |         | HMM island                            | 0.0044  | 0.001  | 5.82e-06 | 0.0038  | 0.001  | 0.000139 | 0.0041  | 0.001  | 7.26e-05 | 0.51 |
| Crotonobetaine | cg15522171    | 1  | 33547626  | ADC           | S_Shore | Enhancer, HMM island, regulatory      | 0.0072  | 0.0014 | 1.66e-07 | 0.0075  | 0.0014 | 1.17e-07 | 0.0076  | 0.0015 | 1.55e-07 | 0.2  |
| Crotonobetaine | cg03537032    | 1  | 75139139  | C1orf173      |         | HMM island                            | 0.0048  | 0.001  | 1.53e-06 | 0.0049  | 0.001  | 2.37e-06 | 0.0051  | 0.0011 | 2.49e-06 | 0.58 |
| Crotonobetaine | cg24737783    | 1  | 109204304 | C1orf59       | Island  | DMR, regulatory                       | 0.0067  | 0.0013 | 3.62e-07 | 0.0071  | 0.0013 | 1.7e-07  | 0.007   | 0.0014 | 8.21e-07 | 0.74 |
| Crotonobetaine | cg02063759    | 1  | 119543295 |               | Island  | HMM island                            | 0.0044  | 0.001  | 4.25e-06 | 0.0044  | 0.001  | 1.04e-05 | 0.0045  | 0.001  | 1.75e-05 | 0.64 |
| Crotonobetaine | cg13681752    | 1  | 120143242 |               |         |                                       | 0.005   | 0.0011 | 3.59e-06 | 0.0044  | 0.0011 | 8.85e-05 | 0.0048  | 0.0012 | 5.76e-05 | 0    |
| Crotonobetaine | cg12730323    | 1  | 200004757 | NR5A2         | Island  | DMR, enhancer, HMM island             | 0.0042  | 0.0009 | 3.02e-06 | 0.0041  | 0.0009 | 8.62e-06 | 0.0041  | 0.001  | 2.37e-05 | 0    |
| Crotonobetaine | cg13877974    | 1  | 201708888 | NAV1          | Island  | HMM island, regulatory                | 0.0024  | 0.0005 | 1.88e-06 | 0.0024  | 0.0005 | 1.61e-06 | 0.0023  | 0.0005 | 4.78e-06 | 0.71 |
| Crotonobetaine | cg04945350    | 1  | 228605010 | TRIM17        | S_Shore |                                       | 0.0059  | 0.0012 | 1.47e-06 | 0.0052  | 0.0013 | 4.05e-05 | 0.0051  | 0.0013 | 9.62e-05 | 0.47 |
| Crotonobetaine | cg18305853    | 2  | 2713323   |               |         | HMM island                            | -0.0024 | 0.0005 | 9.96e-08 | -0.0025 | 0.0005 | 3.86e-07 | -0.0026 | 0.0005 | 1.82e-07 | 0.53 |
| Crotonobetaine | cg18794891    | 2  | 25261606  |               | N_Shelf |                                       | 0.0037  | 0.0008 | 7.21e-06 | 0.0035  | 0.0008 | 1.12e-05 | 0.0038  | 0.0008 | 4.97e-06 | 0    |
| Crotonobetaine | cg17517296    | 2  | 43107458  |               |         | Enhancer                              | 0.0032  | 0.0007 | 5.63e-06 | 0.0031  | 0.0007 | 2.97e-05 | 0.0033  | 0.0008 | 2.47e-05 | 0.77 |
| Crotonobetaine | cg08944893    | 2  | 105461870 |               | S_Shore | Enhancer, DMR, HMM island             | 0.0028  | 0.0006 | 4.77e-06 | 0.0026  | 0.0006 | 5.7e-05  | 0.0027  | 0.0007 | 3.76e-05 | 0    |
| Crotonobetaine | cg01886514    | 2  | 105478395 |               | N_Shore | Regulatory                            | 0.0038  | 0.0008 | 1.22e-06 | 0.0032  | 0.0008 | 2.55e-05 | 0.0036  | 0.0008 | 1.29e-05 | 0.62 |
| Crotonobetaine | cg22541830    | 2  | 114048868 | LOC440839     | Island  | HMM island                            | 0.0058  | 0.0013 | 4.83e-06 | 0.0046  | 0.0015 | 0.00187  | 0.0056  | 0.0014 | 5.75e-05 | 0.53 |
| Crotonobetaine | cg12974733    | 2  | 162273524 | TBR1          | Island  | DMR, HMM island                       | 0.0048  | 0.001  | 3.79e-06 | 0.0048  | 0.0011 | 7.44e-06 | 0.0049  | 0.0011 | 7.98e-06 | 0.53 |
| Crotonobetaine | cg22140756    | 2  | 177895827 |               |         | Enhancer                              | 0.0057  | 0.0012 | 1.98e-06 | 0.0054  | 0.0013 | 2.13e-05 | 0.0056  | 0.0013 | 2.61e-05 | 0.74 |
| Crotonobetaine | cg25975856    | 3  | 19930780  | EFHB          |         | Enhancer                              | 0.0179  | 0.0039 | 5.6e-06  | 0.0192  | 0.0041 | 2.9e-06  | 0.0211  | 0.0043 | 7.68e-07 | 0    |
| Crotonobetaine | cg21124497    | 3  | 32859377  | TRIM71        | Island  | HMM island, regulatory                | 0.0025  | 0.0005 | 3.5e-06  | 0.0023  | 0.0006 | 2.61e-05 | 0.0023  | 0.0006 | 7.79e-05 | 0.84 |
| Crotonobetaine | ch.3.1012680R | 3  | 48211137  | CDC25A        |         |                                       | -0.0042 | 0.0009 | 1.89e-06 | -0.004  | 0.0009 | 1.51e-05 | -0.0042 | 0.001  | 2.28e-05 | 0.17 |
| Crotonobetaine | cg24163658    | 3  | 58182370  | DNASE1L3      |         | Regulatory                            | 0.0052  | 0.001  | 8.1e-07  | 0.0054  | 0.0011 | 7.25e-07 | 0.0054  | 0.0012 | 4.02e-06 | 0    |
| Crotonobetaine | cg18073906    | 3  | 122641029 | SEMA5B        | Island  | Enhancer, HMM island                  | 0.0053  | 0.0011 | 1.86e-06 | 0.005   | 0.0012 | 5.91e-05 | 0.0047  | 0.0013 | 0.000201 | 0    |
| Crotonobetaine | cg17483361    | 4  | 54243829  | FIP1L1        | Island  | Enhancer, HMM island, regulatory      | 0.0011  | 0.0002 | 3.92e-08 | 0.0011  | 0.0002 | 7.66e-08 | 0.0011  | 0.0002 | 1.36e-07 | 0    |
| Crotonobetaine | cg26298470    | 4  | 86396765  | ARHGAP24      |         | HMM island                            | 0.0018  | 0.0004 | 7.08e-06 | 0.002   | 0.0004 | 4.44e-07 | 0.0019  | 0.0004 | 2.26e-06 | 0    |
| Crotonobetaine | cg21575861    | 4  | 148538494 | TMEM184C      | Island  | HMM island, regulatory                | -0.0006 | 0.0001 | 3.88e-06 | -0.0005 | 0.0001 | 2.77e-05 | -0.0006 | 0.0001 | 2.45e-05 | 0.63 |

|                |            |    |           |               |         |                                  |         |        |          |         |        |          |         |        |          |      |
|----------------|------------|----|-----------|---------------|---------|----------------------------------|---------|--------|----------|---------|--------|----------|---------|--------|----------|------|
| Crotonobetaine | cg12331505 | 5  | 3093646   |               |         | HMM island                       | 0.0048  | 0.001  | 3.5e-06  | 0.0041  | 0.0011 | 0.000171 | 0.0041  | 0.0011 | 0.000253 | 0.77 |
| Crotonobetaine | cg13900348 | 5  | 76114646  | F2RL1         | Island  | HMM island, regulatory           | 0.0018  | 0.0004 | 3.84e-06 | 0.0017  | 0.0004 | 9.45e-06 | 0.0018  | 0.0004 | 2.83e-05 | 0    |
| Crotonobetaine | cg10812634 | 5  | 126409211 | FLJ44606      | Island  | HMM island, regulatory           | 0.0124  | 0.0026 | 1.75e-06 | 0.0127  | 0.0032 | 5.27e-05 | 0.0135  | 0.0034 | 9.17e-05 | 0    |
| Crotonobetaine | cg27183454 | 6  | 28547741  | SCAND3        |         |                                  | 0.0038  | 0.0008 | 5.4e-06  | 0.0035  | 0.0009 | 4.63e-05 | 0.0034  | 0.0009 | 0.000172 | 0    |
| Crotonobetaine | cg02718200 | 6  | 31324269  | HLA-B         | Island  | HMM island, regulatory           | 0.0057  | 0.0012 | 1.4e-06  | 0.0056  | 0.0012 | 6.5e-06  | 0.0056  | 0.0013 | 1.52e-05 | 0    |
| Crotonobetaine | cg08877853 | 6  | 97247547  | GPR63         |         |                                  | 0.0078  | 0.0015 | 1.01e-07 | 0.0074  | 0.0016 | 2.05e-06 | 0.0075  | 0.0016 | 3.07e-06 | 0.52 |
| Crotonobetaine | cg18419694 | 6  | 143832440 | FUCA2         | Island  | Enhancer, HMM island, regulatory | -0.0009 | 0.0002 | 5.13e-06 | -0.0009 | 0.0002 | 1.41e-05 | -0.0009 | 0.0002 | 6.57e-05 | 0    |
| Crotonobetaine | cg06649410 | 6  | 154360483 | OPRM1         | N_Shore |                                  | 0.0065  | 0.0013 | 1.08e-06 | 0.0062  | 0.0014 | 5.64e-06 | 0.0061  | 0.0014 | 2e-05    | 0.21 |
| Crotonobetaine | cg10146442 | 7  | 884056    | UNC84A;UNC84A | N_Shelf | HMM island                       | -0.0059 | 0.0006 | 1.93e-25 | -0.0059 | 0.0006 | 3.21e-22 | -0.0058 | 0.0006 | 4.76e-21 | 0    |
| Crotonobetaine | cg12658982 | 7  | 29603541  | PRR15;PRR15   | Island  | Enhancer, HMM island             | 0.0014  | 0.0003 | 4.85e-06 | 0.0014  | 0.0003 | 1.02e-05 | 0.0013  | 0.0003 | 4.49e-05 | 0.65 |
| Crotonobetaine | cg18669823 | 7  | 30725669  |               | S_Shelf |                                  | -0.009  | 0.0017 | 6.1e-08  | -0.0102 | 0.0018 | 6.43e-09 | -0.0102 | 0.002  | 2.12e-07 | 0    |
| Crotonobetaine | cg14113240 | 9  | 110572138 |               |         | Enhancer                         | 0.0072  | 0.0013 | 4.61e-08 | 0.0064  | 0.0013 | 1.9e-06  | 0.006   | 0.0014 | 7.98e-06 | 0.84 |
| Crotonobetaine | cg14299044 | 10 | 19972179  |               |         | Enhancer                         | 0.0025  | 0.0006 | 4.21e-06 | 0.0024  | 0.0006 | 1.43e-05 | 0.0025  | 0.0006 | 1.41e-05 | 0    |
| Crotonobetaine | cg18513313 | 10 | 46970868  | SYT15         | Island  | Enhancer, HMM island, regulatory | 0.0017  | 0.0004 | 2.2e-06  | 0.0017  | 0.0004 | 5.31e-06 | 0.0018  | 0.0004 | 3.03e-06 | 0.81 |
| Crotonobetaine | cg02979795 | 10 | 102626509 |               |         | Enhancer, HMM island, regulatory | 0.0093  | 0.0019 | 1.68e-06 | 0.0089  | 0.002  | 4.62e-06 | 0.009   | 0.0018 | 1.07e-06 | 0    |
| Crotonobetaine | cg13641898 | 11 | 75258876  |               |         | Enhancer, regulatory             | 0.005   | 0.0011 | 4.01e-06 | 0.0049  | 0.0012 | 1.79e-05 | 0.005   | 0.0012 | 2.83e-05 | 0.1  |
| Crotonobetaine | cg14415816 | 12 | 106978920 | RFX4          | N_Shore | DMR, enhancer, HMM island        | 0.0039  | 0.0008 | 2.62e-06 | 0.0042  | 0.0009 | 1.11e-06 | 0.0048  | 0.001  | 3.99e-07 | 0.36 |
| Crotonobetaine | cg03900474 | 12 | 115106786 |               | S_Shore | Enhancer, HMM island             | 0.0025  | 0.0006 | 7.25e-06 | 0.0025  | 0.0006 | 1.19e-05 | 0.0026  | 0.0006 | 1.64e-05 | 0    |
| Crotonobetaine | cg16713625 | 12 | 124968359 | NCOR2         |         | HMM island                       | 0.0035  | 0.0008 | 5.91e-06 | 0.0033  | 0.0008 | 4.24e-05 | 0.0025  | 0.0011 | 0.0198   | 0.61 |
| Crotonobetaine | cg15982991 | 14 | 23564610  | ACIN1         | Island  | HMM island, regulatory           | -0.0007 | 0.0001 | 1.6e-06  | -0.0007 | 0.0001 | 7.94e-06 | -0.0007 | 0.0001 | 1.27e-05 | 0.4  |
| Crotonobetaine | cg20005934 | 14 | 100706390 | YY1           | Island  | Enhancer, HMM island, regulatory | -0.0006 | 0.0001 | 2.68e-06 | -0.0006 | 0.0001 | 4.72e-06 | -0.0006 | 0.0001 | 1.86e-05 | 0    |
| Crotonobetaine | cg03469805 | 14 | 105330648 | KIAA0284      | Island  | Enhancer, HMM island             | 0.0049  | 0.001  | 1.53e-06 | 0.0047  | 0.0011 | 9.93e-06 | 0.0052  | 0.0012 | 1.09e-05 | 0    |
| Crotonobetaine | cg03643241 | 15 | 44487910  | FRMD5         | S_Shore | Regulatory                       | 0.0042  | 0.0009 | 1.39e-06 | 0.0046  | 0.0008 | 2.6e-08  | 0.0047  | 0.0009 | 5.19e-08 | 0    |
| Crotonobetaine | cg26589251 | 15 | 100786492 | ADAMTS17      |         |                                  | 0.0161  | 0.0032 | 4.67e-07 | 0.0147  | 0.0033 | 9.13e-06 | 0.0155  | 0.0034 | 5.74e-06 | 0.89 |
| Crotonobetaine | cg01283685 | 16 | 2986893   | FLYWCH1       |         |                                  | -0.01   | 0.0021 | 2.58e-06 | -0.0103 | 0.0022 | 4.76e-06 | -0.0104 | 0.0023 | 5.81e-06 | 0    |
| Crotonobetaine | cg09404429 | 17 | 21367130  |               | Island  | Regulatory                       | 0.0064  | 0.0014 | 3.51e-06 | 0.0061  | 0.0013 | 1.38e-06 | 0.0065  | 0.0013 | 8.25e-07 | 0.59 |
| Crotonobetaine | cg20215112 | 17 | 43065055  |               |         | Enhancer, regulatory             | 0.0039  | 0.0008 | 1.43e-06 | 0.0039  | 0.0008 | 3.92e-06 | 0.0045  | 0.0009 | 4.11e-07 | 0    |
| Crotonobetaine | cg24801230 | 17 | 43978533  | MAPT          | S_Shelf | DMR                              | 0.0184  | 0.003  | 1.55e-09 | 0.0201  | 0.0032 | 3.39e-10 | 0.0245  | 0.0034 | 2.57e-13 | 0.9  |
| Crotonobetaine | cg01737415 | 17 | 72919525  | OTOP2;USH1G   | Island  | Enhancer, HMM island, regulatory | 0.0035  | 0.0007 | 1.21e-06 | 0.0037  | 0.0008 | 9.29e-07 | 0.0037  | 0.0008 | 1.09e-05 | 0    |
| Crotonobetaine | cg03729508 | 19 | 10563615  | PDE4A         |         | Enhancer                         | 0.0073  | 0.0016 | 3.3e-06  | 0.0075  | 0.0017 | 1.14e-05 | 0.0072  | 0.0017 | 2.22e-05 | 0.65 |
| Crotonobetaine | cg14884776 | 19 | 15122181  | CCDC105       | S_Shore |                                  | 0.0033  | 0.0007 | 2.08e-06 | 0.0034  | 0.0007 | 2.31e-06 | 0.0035  | 0.0007 | 4.06e-06 | 0    |
| Crotonobetaine | cg26496291 | 19 | 17799325  | UNC13A        | Island  | DMR, regulatory                  | 0.0027  | 0.0006 | 3.17e-06 | 0.0029  | 0.0006 | 1.67e-06 | 0.0034  | 0.0007 | 3.76e-07 | 0.73 |
| Crotonobetaine | cg11086760 | 19 | 18901446  | COMP          | Island  | HMM island                       | 0.0042  | 0.0008 | 2.13e-07 | 0.0038  | 0.0008 | 4.25e-06 | 0.0042  | 0.0009 | 1.26e-06 | 0.82 |
| Crotonobetaine | cg25799433 | 20 | 1600623   | SIRPB1        |         |                                  | 0.0041  | 0.0008 | 1.01e-06 | 0.0041  | 0.0009 | 3.34e-06 | 0.0041  | 0.0009 | 5.66e-06 | 0.78 |
| Crotonobetaine | cg14043737 | 20 | 61637672  | BHLHE23       | Island  | HMM island                       | 0.0052  | 0.001  | 4.6e-07  | 0.005   | 0.001  | 1.41e-06 | 0.0051  | 0.0011 | 2.45e-06 | 0.16 |
| Crotonobetaine | cg21234269 | 21 | 18884869  | CXADR         | Island  | HMM island, regulatory           | 0.0028  | 0.0006 | 3.15e-06 | 0.0033  | 0.0007 | 4.36e-07 | 0.0032  | 0.0007 | 1.66e-06 | 0.41 |
| TMAO           | cg20768669 | 1  | 149137508 |               | N_Shore | Regulatory                       | 0.0075  | 0.0015 | 3.59e-07 | 0.0047  | 0.001  | 3.61e-06 | 0.0042  | 0.0011 | 7.58e-05 | 0    |
| TMAO           | cg18798289 | 5  | 72530245  |               | S_Shore | DMR, HMM island                  | 0.0055  | 0.0011 | 4.03e-07 | 0.0056  | 0.0011 | 3.6e-07  | 0.0058  | 0.0012 | 4.67e-07 | 0.81 |
| TMAO           | cg13728834 | 9  | 35846324  | TMEM8B        | Island  |                                  | 0.0085  | 0.0016 | 1.8e-07  | 0.0086  | 0.0017 | 1.98e-07 | 0.0093  | 0.0017 | 4.78e-08 | 0.78 |
| TMAO           | cg07152869 | 16 | 27741555  | KIAA0556      |         | Enhancer                         | -0.0125 | 0.0023 | 1.06e-07 | -0.0121 | 0.0024 | 2.79e-07 | -0.0123 | 0.0024 | 4.21e-07 | 0    |

I-square was derived based on model 1 analysis

Covaraites in model 1: sex, age, study sites, blood cells composition, technical variables (cohort-specific), education level, household income, and recent antibiotic use

Covaraites in model 2: model 1 covariates plus smoking status (none, former, current), alcohol intake, physical activity, diet quality scores

Covaraites in model 3: model 2 covariates plus BMI and eGFR

Supplemental Table 2. CpG pairs with Pearson correlation coefficients  $\geq 0.5$ 

| CpG1       | Metabolite1    | CpG2       | Metabolite2    | <i>r</i> | <i>P</i> |
|------------|----------------|------------|----------------|----------|----------|
| cg04059696 | butyrobetaine  | cg17517296 | crotonobetaine | -0.66    | 0        |
| cg10517312 | butyrobetaine  | cg17517296 | crotonobetaine | -0.62    | 0        |
| cg00703019 | butyrobetaine  | cg13877974 | crotonobetaine | 0.61     | 0        |
| cg00703019 | butyrobetaine  | cg03900474 | crotonobetaine | 0.60     | 0        |
| cg17466510 | butyrobetaine  | cg17517296 | crotonobetaine | 0.60     | 0        |
| cg00703019 | butyrobetaine  | cg01737415 | crotonobetaine | 0.58     | 0        |
| cg00703019 | butyrobetaine  | cg03643241 | crotonobetaine | 0.58     | 0        |
| cg00703019 | butyrobetaine  | cg18513313 | crotonobetaine | 0.56     | 0        |
| cg23513644 | butyrobetaine  | cg13877974 | crotonobetaine | 0.55     | 0        |
| cg00703019 | butyrobetaine  | cg11086760 | crotonobetaine | 0.54     | 0        |
| cg00703019 | butyrobetaine  | cg14884776 | crotonobetaine | 0.53     | 0        |
| cg10517312 | butyrobetaine  | cg19408207 | carnitine      | 0.53     | 0        |
| cg24737374 | butyrobetaine  | cg25799433 | crotonobetaine | -0.53    | 0        |
| cg09309112 | butyrobetaine  | cg25799433 | crotonobetaine | -0.53    | 0        |
| cg23513644 | butyrobetaine  | cg18513313 | crotonobetaine | 0.53     | 0        |
| cg04059696 | butyrobetaine  | cg25799433 | crotonobetaine | -0.52    | 0        |
| cg09309112 | butyrobetaine  | cg17517296 | crotonobetaine | -0.52    | 0        |
| cg01886514 | crotonobetaine | cg20768669 | TMAO           | 0.52     | 0        |
| cg17058475 | betaine        | cg17517296 | crotonobetaine | 0.52     | 0        |
| cg26561797 | butyrobetaine  | cg17517296 | crotonobetaine | -0.52    | 0        |
| cg01737415 | crotonobetaine | cg20768669 | TMAO           | 0.52     | 0        |
| cg14884776 | crotonobetaine | cg20768669 | TMAO           | 0.52     | 0        |
| cg11009695 | butyrobetaine  | cg17517296 | crotonobetaine | -0.52    | 0        |
| cg23513644 | butyrobetaine  | cg03900474 | crotonobetaine | 0.52     | 0        |
| cg08877374 | crotonobetaine | cg13728834 | TMAO           | 0.51     | 0        |
| cg16044573 | butyrobetaine  | cg13877974 | crotonobetaine | 0.51     | 0        |
| cg17306339 | butyrobetaine  | cg17517296 | crotonobetaine | -0.51    | 0        |
| cg26561797 | butyrobetaine  | cg08877374 | crotonobetaine | -0.50    | 0        |
| cg23513644 | butyrobetaine  | cg01737415 | crotonobetaine | 0.50     | 0        |
| cg26561797 | butyrobetaine  | cg25799433 | crotonobetaine | -0.50    | 0        |

Supplemental Table 3. Gene set enrichment analysis based on the updated MSigDB gene sets using Illumina annotated genes

| Category                 | Label   | GeneSet                                                   | N_genes | N_overlap | P       | adjusted P | Genes                                                                                                   |
|--------------------------|---------|-----------------------------------------------------------|---------|-----------|---------|------------|---------------------------------------------------------------------------------------------------------|
| Cell_type_signature      | CTS1    | MANNO_MIDBRAIN_NEUROTYPES_HNBML5                          | 465     | 10        | 2.74E-7 | 2.3E-4     | NBEA:MYT1L:MAPRE3:NAV1:CXADR:UNC13A:MDGA2:CDH13:FRMD5:FABP3                                             |
| Cell_type_signature      | CTS2    | MANNO_MIDBRAIN_NEUROTYPES_HGABA                           | 1106    | 14        | 6.75E-7 | 2.83E-4    | NBEA:MYT1L:MAPRE3:NAV1:CXADR:UNC13A:MDGA2:CDH13:FRMD5:CD42EP3:FHOD3:OPRM1:ARHGAP24:LBH                  |
| Cell_type_signature      | CTS3    | ZHONG_PFC_C3_MICROGLIA                                    | 488     | 9         | 3.9E-6  | 1.09E-3    | NBEA:MYT1L:MAPRE3:NAV1:FABP3:CD42EP3:MAPT:GNG4:PDIA2                                                    |
| Cell_type_signature      | CTS4    | MURARO_PANCREAS_BETA_CELL                                 | 946     | 10        | 1.3E-4  | 2.74E-2    | NBEA:CD42EP3:MAPT:GNG4:GNAS:OC1AD1:ZMAT3:NCOR2:FYT1D1:NEU1                                              |
| Curated_gene_sets        | CGS1    | PEREZ_TP53_TARGETS                                        | 1201    | 15        | 3.08E-7 | 1.78E-3    | MSX1:GNAS:CXADR:ARHGEF17:KCNQ1:FRMD5:ACKR3:COL5A2:HIC2:ZMAT3:LBH:CEP170B:SUN1:TRIM71:TMEM184C           |
| Curated_gene_sets        | CGS2    | MEISSNER_BRAIN_HCP_WITH_H3K4ME3_AND_H3K27ME3              | 1074    | 14        | 4.77E-7 | 1.78E-3    | MSX1:GNAS:CXADR:ARHGEF17:SCNN1G:TBR1:ADAMTS17:MMP23B:PDE4A:F2RL1:CDH13:SEMA5B:CPT1A:PRDM16              |
| Curated_gene_sets        | CGS3    | BENPORATH_ES_WITH_H3K27ME3                                | 1115    | 14        | 7.43E-7 | 1.85E-3    | MSX1:KCNQ1:SCNN1G:TBR1:ADAMTS17:MAPT:COMP:HLA-B:USH1G:BHLHE23:OTOP2:AATF:AZIN2:RFX4                     |
| Curated_gene_sets        | CGS4    | YOSHIMURA_MAPK8_TARGETS_UP                                | 1281    | 14        | 3.73E-6 | 6.68E-3    | GNAS:FRMD5:SCNN1G:MMP23B:PDE4A:F2RL1:MAPT:COMP:OPRM1:NR5A2:DNASE1L3:RAB1B:MYT1L:UNC13A                  |
| Curated_gene_sets        | CGS5    | KAAB_HEART_ATRIUM_VS_VENTRICLE_DN                         | 262     | 7         | 4.47E-6 | 6.68E-3    | GNAS:CXADR:KCNQ1:MMP23B:CDH13:FABP3:NDUFAF1                                                             |
| Curated_gene_sets        | CGS6    | TARTE_PLASMA_CELL_VS_PLASMABLAST_UP                       | 398     | 8         | 7.38E-6 | 9.18E-3    | MSX1:CXADR:KCNQ1:PDE4A:HLA-B:OPRM1:FABP3:GNG4                                                           |
| Curated_gene_sets        | CGS7    | BENPORATH_EED_TARGETS                                     | 1059    | 12        | 1.36E-5 | 1.45E-2    | MSX1:KCNQ1:SCNN1G:TBR1:MAPT:COMP:HLA-B:USH1G:BHLHE23:OTOP2:AATF:FUCA2                                   |
| Curated_gene_sets        | CGS8    | PETRETTO_HEART_MASS_QTL_CIS_DN                            | 28      | 3         | 4.7E-5  | 4.18E-2    | ARHGEF17:NDUFAF1:ARHGAP24                                                                               |
| Curated_gene_sets        | CGS9    | JINESH_BLEBBISHIELD_TO_IMMUNE_CELL_FUSION_PBSHMS_UP       | 382     | 7         | 5.04E-5 | 4.18E-2    | ACKR3:COL5A2:HIC2:ZMAT3:MAPT:CD42EP3:OSBPL1A                                                            |
| Curated_gene_sets        | CGS10   | BENPORATH_SUZ12_TARGETS                                   | 1035    | 11        | 5.64E-5 | 4.21E-2    | MSX1:GNAS:LBH:SCNN1G:TBR1:CDH13:MAPT:COMP:USH1G:BHLHE23:OTOP2                                           |
| Curated_gene_sets        | CGS11   | REACTOME_SIGNALING_BY_GPCR                                | 702     | 9         | 6.78E-5 | 4.6E-2     | GNAS:ARHGEF17:ACKR3:PDE4A:F2RL1:OPRM1:GNG4:NBEA:PLEKHG5                                                 |
| Curated_gene_sets        | CGS12   | REACTOME_OPIOID_SIGNALING                                 | 90      | 4         | 7.86E-5 | 4.89E-2    | PDE4A:OPRM1:GNG4:NBEA                                                                                   |
| GO_BP                    | GO_BP1  | GOBP_HOMOTYPIC_CELL_CELL_ADHESION                         | 100     | 5         | 5.43E-6 | 7.2E-3     | GNAS:COMP:CXADR:PDIA2:CDHR2                                                                             |
| GO_BP                    | GO_BP2  | GOBP_IMPORT_INTO_CELL                                     | 926     | 11        | 2.06E-5 | 1.44E-2    | KCNQ1:SCNN1G:RUBCN:USH1G:ACKR3:F2RL1:OC1AD1:SIGLEC1:CDH13:SIRPB1:FABP3                                  |
| GO_BP                    | GO_BP3  | GOBP_CALCICUM_MEDIATED_SIGNALING                          | 228     | 6         | 2.41E-5 | 1.55E-2    | MAPT:ACKR3:CDH13:NR5A2:EFHB:RASA3                                                                       |
| GO_BP                    | GO_BP4  | GOBP_MULTICELLULAR_ORGANISMAL_LEVEL_HOMEOSTASIS           | 814     | 10        | 3.77E-5 | 2.17E-2    | PRDM16:GNAS:KCNQ1:SCNN1G:COMP:CXADR:USH1G:OC1AD1:NXNL1:ACIN1                                            |
| GO_BP                    | GO_BP5  | GOBP_REGULATION_OF_BODY_FLUID_LEVELS                      | 375     | 7         | 4.49E-5 | 2.35E-2    | GNAS:SCNN1G:COMP:PDIA2:F2RL1:VAMP3:NCOR2                                                                |
| GO_BP                    | GO_BP6  | GOBP_CELL_PROJECTION_ORGANIZATION                         | 1644    | 14        | 5.92E-5 | 2.57E-2    | MAPT:KCNQ1:UNC13A:TBR1:ARHGAP24:CDHR2:USH1G:F2RL1:CDH13:CD42EP3:SEMA5B:RFX4:BHLHE23:ERICH3              |
| GO_BP                    | GO_BP7  | GOBP_CARDIAC_CELL_DEVELOPMENT                             | 94      | 4         | 9.31E-5 | 3.26E-2    | YY1:FHOD3:CXADR:LRR27                                                                                   |
| GO_BP                    | GO_BP8  | GOBP_INTRACELLULAR_SIGNALING_CASSETTE                     | 1952    | 15        | 1E-4    | 3.43E-2    | MAPT:ARHGAP24:PLEKHG5:RUBCN:ACKR3:F2RL1:OPRM1:CDH13:NR5A2:EFHB:RASA3:CD42EP3:LBH:ARHGEF17:PDE4A         |
| GO_BP                    | GO_BP9  | GOBP_RESPONSE_TO_ENDOGENOUS_STIMULUS                      | 1735    | 14        | 1.05E-4 | 3.44E-2    | PRDM16:GNAS:MAPT:YY1:KCNQ1:SCNN1G:MSX1:COMP:OPRM1:CDH13:NR5A2:NCOR2:TRIM71:LBH                          |
| GO_BP                    | GO_BP10 | GOBP_CELL_ADHESION                                        | 1542    | 13        | 1.22E-4 | 3.55E-2    | GNAS:COMP:FRMD5:CXADR:PDIA2:CDHR2:ACKR3:SIGLEC1:VAMP3:CDH13:SIRPB1:AATF:TMEM8B                          |
| GO_BP                    | GO_BP11 | GOBP_VESICLE_MEDIATED_TRANSPORT                           | 1561    | 13        | 1.38E-4 | 3.59E-2    | UNC13A:RUBCN:USH1G:ACKR3:F2RL1:OC1AD1:SIGLEC1:VAMP3:OSBPL1A:CDH13:SIRPB1:SYT15:RAB1B                    |
| GO_BP                    | GO_BP12 | GOBP_MUSCLE_CELL_DEVELOPMENT                              | 204     | 5         | 1.65E-4 | 3.79E-2    | YY1:FHOD3:COMP:CXADR:LRR27                                                                              |
| GO_BP                    | GO_BP13 | GOBP_TAXIS                                                | 469     | 7         | 1.8E-4  | 4.02E-2    | TBR1:PLEKHG5:CXADR:ACKR3:F2RL1:CDH13:SEMA5B                                                             |
| GO_BP                    | GO_BP14 | GOBP_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION      | 1853    | 14        | 2.07E-4 | 4.5E-2     | MAPT:MSX1:ARHGAP24:PLEKHG5:RUBCN:ACKR3:F2RL1:OPRM1:CDH13:EFHB:RASA3:LBH:ARHGEF17:PDE4A                  |
| GO_BP                    | GO_BP15 | GOBP_CELL_GROWTH                                          | 484     | 7         | 2.17E-4 | 4.55E-2    | MAPT:YY1:UNC13A:MSX1:CDHR2:GNG4:SEMA5B                                                                  |
| GO_CC                    | GO_CC1  | GOCC_ENDOSOME                                             | 1077    | 12        | 1.6E-5  | 1.29E-2    | HLA-B:KCNQ1:ATP6V0A2:RUBCN:ACKR3:F2RL1:OC1AD1:SIGLEC1:OPRM1:VAMP3:OSBPL1A:ATG16L1                       |
| GO_CC                    | GO_CC2  | GOCC_TRANSCRIPTION_REGULATOR_COMPLEX                      | 521     | 8         | 5.03E-5 | 2.46E-2    | PRDM16:YY1:MSX1:NR5A2:NCOR2:AATF:NFYA:FLYWCHI                                                           |
| GO_CC                    | GO_CC3  | GOCC_PHAGOCYTIC_VESICLE_MEMBRANE                          | 81      | 4         | 5.21E-5 | 2.47E-2    | HLA-B:ATP6V0A2:MPEG1:VAMP3                                                                              |
| GO_CC                    | GO_CC4  | GOCC_SUPRAMOLECULAR_COMPLEX                               | 1435    | 13        | 5.96E-5 | 2.57E-2    | MAPT:FHOD3:COL5A2:CHAMP1:EFHB:LRR27:TRIM71:TUBA3D:NAV1:MAPRE3:TEKTL1:CEP170B:HENMT1                     |
| GO_CC                    | GO_CC5  | GOCC_SIDE_OF_MEMBRANE                                     | 742     | 9         | 1.03E-4 | 3.44E-2    | GNAS:HLA-B:KCNQ1:SCNN1G:ACKR3:CDH13:RASA3:GNG4:MDGA2                                                    |
| GO_CC                    | GO_CC6  | GOCC_TRANSPORT_VESICLE                                    | 439     | 7         | 1.2E-4  | 3.55E-2    | HLA-B:KCNQ1:UNC13A:VAMP3:AZIN2:SYT15:RAB1B                                                              |
| GO_CC                    | GO_CC7  | GOCC_NEURON_PROJECTION                                    | 1336    | 12        | 1.26E-4 | 3.55E-2    | MAPT:KCNQ1:UNC13A:PLEKHG5:CXADR:USH1G:OPRM1:VAMP3:CDH13:NXNL1:NAV1:AZIN2                                |
| GO_CC                    | GO_CC8  | GOCC_EARLY_ENDOSOME                                       | 445     | 7         | 1.3E-4  | 3.55E-2    | HLA-B:KCNQ1:RUBCN:ACKR3:F2RL1:SIGLEC1:VAMP3                                                             |
| GO_CC                    | GO_CC9  | GOCC_MICROTUBULE                                          | 483     | 7         | 2.15E-4 | 4.55E-2    | MAPT:EFHB:TUBA3D:NAV1:MAPRE3:TEKTL1:CEP170B                                                             |
| GO_MF                    | GO_CC10 | GOMF_G_PROTEIN_BETA_SUBUNIT_BINDING                       | 23      | 3         | 2.56E-5 | 1.59E-2    | F2RL1:OPRM1:GNG4                                                                                        |
| GO_MF                    | GO_CC11 | GOMF_PHOSPHOLIPID_BINDING                                 | 490     | 7         | 2.34E-4 | 4.75E-2    | MAPT:KCNQ1:UNC13A:RUBCN:OSBPL1A:NR5A2:SYT15::                                                           |
| Human Phenotype Ontology | HPO1    | HP_POLYPHAGIA                                             | 76      | 6         | 3.92E-8 | 6.31E-4    | PRDM16:GNAS:MAPT:YY1:MMP23B:MYT1L                                                                       |
| Human Phenotype Ontology | HPO2    | HP_ABNORMAL_CONSUMPTION_BEHAVIOR                          | 280     | 8         | 5.47E-7 | 2.41E-3    | PRDM16:GNAS:MAPT:YY1:MMP23B:MYT1L:HLA-B:FIP1L1                                                          |
| Human Phenotype Ontology | HPO3    | HP_ABNORMAL_PATTERN_OF_RESPIRATION                        | 774     | 12        | 5.54E-7 | 2.41E-3    | PRDM16:GNAS:MAPT:HLA-B:FIP1L1:KCNQ1:SCNN1G:UNC13A:DNASE1L3:MSX1:TBR1:KATNP                              |
| Human Phenotype Ontology | HPO4    | HP_CONSTITUTIONAL_SYMPTOM                                 | 1266    | 15        | 5.98E-7 | 2.41E-3    | PRDM16:GNAS:YY1:HLA-B:FIP1L1:KCNQ1:SCNN1G:UNC13A:DNASE1L3:CPT1A:FHOD3:COMP:COL5A2:FRMD5:ARHGAP24        |
| Human Phenotype Ontology | HPO5    | HP_ABNORMAL_EATING_BEHAVIOR                               | 125     | 6         | 7.61E-7 | 2.45E-3    | PRDM16:GNAS:MAPT:YY1:MMP23B:MYT1L                                                                       |
| Human Phenotype Ontology | HPO6    | HP_ABNORMALITY_OF_CARDIOVASCULAR_SYSTEM_ELECTROPHYSIOLOGY | 574     | 10        | 1.83E-6 | 4.93E-3    | PRDM16:GNAS:YY1:HLA-B:KCNQ1:SCNN1G:CPT1A:FHOD3:NEU1:NDUFAF1                                             |
| Human Phenotype Ontology | HPO7    | HP_KYPHOSIS                                               | 462     | 9         | 2.5E-6  | 5.2E-3     | PRDM16:GNAS:MAPT:MMP23B:HLA-B:COMP:NEU1:NDUFAF1:ATP6V0A2                                                |
| Human Phenotype Ontology | HPO8    | HP_ABNORMAL_ESOPHAGUS_PHYSIOLOGY                          | 898     | 12        | 2.58E-6 | 5.2E-3     | PRDM16:GNAS:MAPT:YY1:MMP23B:HLA-B:UNC13A:MSX1:COL5A2:NEU1:CHAMP1:MCEE                                   |
| Human Phenotype Ontology | HPO9    | HP_ABNORMAL_MUSCULOSKELETAL_PHYSIOLOGY                    | 1659    | 16        | 3.54E-6 | 6.28E-3    | PRDM16:GNAS:YY1:MMP23B:HLA-B:FIP1L1:KCNQ1:SCNN1G:TBR1:COMP:COL5A2:NEU1:ATP6V0A2:CHAMP1:PLEKHG5:ADAMTS17 |
| Human Phenotype Ontology | HPO10   | HP_FATIGUE                                                | 488     | 9         | 3.9E-6  | 6.28E-3    | PRDM16:YY1:HLA-B:FIP1L1:KCNQ1:SCNN1G:UNC13A:CPT1A:COL5A2                                                |
| Human Phenotype Ontology | HPO11   | HP_DYSPNEA                                                | 497     | 9         | 4.52E-6 | 6.61E-3    | PRDM16:GNAS:MAPT:HLA-B:FIP1L1:KCNQ1:SCNN1G:UNC13A:DNASE1L3                                              |
| Human Phenotype Ontology | HPO12   | HP_LANGUAGE_IMPAIRMENT                                    | 1156    | 13        | 6.28E-6 | 7.2E-3     | PRDM16:GNAS:MAPT:YY1:MMP23B:MYT1L:UNC13A:MSX1:TBR1:ATP6V0A2:CHAMP1:NBEA:RUBCN                           |
| Human Phenotype Ontology | HPO13   | HP_ABNORMALITY_OF_CONNECTIVE_TISSUE                       | 1542    | 15        | 6.65E-6 | 7.2E-3     | PRDM16:GNAS:YY1:MMP23B:HLA-B:KCNQ1:MSX1:TBR1:COL5A2:NEU1:ATP6V0A2:CHAMP1:PLEKHG5:MPEG1:USH1G            |
| Human Phenotype Ontology | HPO14   | HP_ABNORMAL_HEART_MORPHOLOGY                              | 1549    | 15        | 7.02E-6 | 7.2E-3     | PRDM16:YY1:MMP23B:HLA-B:KCNQ1:DNASE1L3:MSX1:KATNP:CPT1A:FHOD3:COL5A2:FRMD5:NEU1:NDUFAF1:ATP6V0A2        |
| Human Phenotype Ontology | HPO15   | HP_MOTOR_DELAY                                            | 993     | 12        | 7.16E-6 | 7.2E-3     | YY1:MYT1L:TBR1:CPT1A:COL5A2:FRMD5:NEU1:ATP6V0A2:CHAMP1:MCEE:NBEA:RUBCN                                  |
| Human Phenotype Ontology | HPO16   | HP_GAIT_DISTURBANCE                                       | 1225    | 13        | 1.16E-5 | 1.1E-2     | PRDM16:MAPT:YY1:MMP23B:HLA-B:TBR1:KATNP:COMP:NEU1:CHAMP1:PLEKHG5:NBEA:RUBCN                             |
| Human Phenotype Ontology | HPO17   | HP_MUSCLE_WEAKNESS                                        | 1060    | 12        | 1.37E-5 | 1.21E-2    | GNAS:MAPT:YY1:HLA-B:FIP1L1:SCNN1G:UNC13A:CPT1A:COL5A2:NEU1:NDUFAF1:PLEKHG5                              |
| Human Phenotype Ontology | HPO18   | HP_UNUSUAL_INFECTION                                      | 1064    | 12        | 1.42E-5 | 1.21E-2    | YY1:HLA-B:FIP1L1:SCNN1G:DNASE1L3:MSX1:KATNP:COL5A2:ATP6V0A2:CHAMP1:NBEA:MPEG1                           |
| Human Phenotype Ontology | HPO19   | HP_VASCULAR_SKIN_ABNORMALITY                              | 590     | 9         | 1.77E-5 | 1.36E-2    | PRDM16:GNAS:MMP23B:HLA-B:FIP1L1:DNASE1L3:COL5A2:NEU1:ATP6V0A2                                           |
| Human Phenotype Ontology | HPO20   | HP_OSTEOARTHRITIS                                         | 64      | 4         | 2.06E-5 | 1.44E-2    | GNAS:HLA-B:COMP:COL5A2                                                                                  |
| Human Phenotype Ontology | HPO21   | HP_RECURRENT_MALADAPTIVE_BEHAVIOR                         | 1110    | 12        | 2.16E-5 | 1.45E-2    | PRDM16:GNAS:MAPT:YY1:MMP23B:MYT1L:HLA-B:FIP1L1:UNC13A:TBR1:CHAMP1:NBEA                                  |
| Human Phenotype Ontology | HPO22   | HP_ABNORMAL_CEREBRAL_CORTEX_MORPHOLOGY                    | 798     | 10        | 3.19E-5 | 1.9E-2     | PRDM16:GNAS:MAPT:YY1:MMP23B:TBR1:KATNP:FRMD5:ATP6V0A2:USH1G                                             |
| Human Phenotype Ontology | HPO23   | HP_ABNORMAL_CONJUGATE_EYE_MOVEMENT                        | 1182    | 12        | 3.97E-5 | 2.2E-2     | PRDM16:GNAS:MAPT:YY1:MMP23B:KATNP:FRMD5:NEU1:NDUFAF1:ATP6V0A2:CHAMP1:ACKR3                              |
| Human Phenotype Ontology | HPO24   | HP_ABNORMAL_CURVATURE_OF_THE_VERTEBRAL_COLUMN             | 1198    | 12        | 4.51E-5 | 2.35E-2    | PRDM16:GNAS:MAPT:MMP23B:HLA-B:KATNP:COMP:COL5A2:NEU1:NDUFAF1:ATP6V0A2:PLEKHG5                           |
| Human Phenotype Ontology | HPO25   | HP_PAIN                                                   | 835     | 10        | 4.67E-5 | 2.35E-2    | GNAS:HLA-B:FIP1L1:KCNQ1:SCNN1G:UNC13A:DNASE1L3:COMP:COL5A2:ARHGAP24                                     |

Supplemental Table 3. Gene set enrichment analysis based on the updated MSigDB gene sets using Illumina annotated genes

| Category                     | Label | GeneSet                                                                   | N_genes | N_overlap | P        | adjusted P | Genes                                                                                           |
|------------------------------|-------|---------------------------------------------------------------------------|---------|-----------|----------|------------|-------------------------------------------------------------------------------------------------|
| Human Phenotype Ontology     | HPO26 | HP_FUNCTIONAL_ABNORMALITY_OF_THE_GASTROINTESTINAL_TRACT                   | 1236    | 12        | 6.08E-5  | 2.57E-2    | PRDM16:GNAS:MAPT:YY1:MMP23B:HLA-B:UNC13A:MSX1:COL5A2:NEU1:CHAMP1:MCEE                           |
| Human Phenotype Ontology     | HPO27 | HP_DYSPHAGIA                                                              | 537     | 8         | 6.22E-5  | 2.57E-2    | PRDM16:MAPT:YY1:MMP23B:HLA-B:UNC13A:MSX1:NEU1                                                   |
| Human Phenotype Ontology     | HPO28 | HP_ABNORMAL_CARDIOVASCULAR_SYSTEM_PHYSIOLOGY                              | 1451    | 13        | 6.67E-05 | 2.69E-2    | PRDM16:GNAS:YY1:HLA-B:FIPL1L1:KCNQ1:SCNN1G:CPT1A:FHOD3:COL5A2:NEU1:NDUFAF1:ATP6V0A2             |
| Human Phenotype Ontology     | HPO29 | HP_HEMOPHTYSIS                                                            | 88      | 4         | 7.2E-5   | 2.83E-2    | HLA-B:SCNN1G:DNASE1L3:COL5A2                                                                    |
| Human Phenotype Ontology     | HPO30 | HP_FUNCTIONAL_ABNORMALITY_OF_THE_INNER_EAR                                | 1070    | 11        | 7.58E-5  | 2.91E-2    | PRDM16:GNAS:MMP23B:HLA-B:FIPL1L1:KCNQ1:DNASE1L3:NEU1:NDUFAF1:MPEGI:USH1G                        |
| Human Phenotype Ontology     | HPO31 | HP_ABNORMALITY_OF_THE_UPPER_URINARY_TRACT                                 | 1474    | 13        | 7.81E-5  | 2.93E-2    | PRDM16:GNAS:YY1:MMP23B:HLA-B:FIPL1L1:KCNQ1:SCNN1G:DNASE1L3:CPT1A:ARHGAP24:NEU1:NDUFAF1          |
| Human Phenotype Ontology     | HPO32 | HP_ABNORMALITY_OF_MUSCLE_SIZE                                             | 730     | 9         | 9.12E-5  | 3.26E-2    | GNAS:YY1:KCNQ1:UNC13A:CPT1A:COMP:NEU1:ATP6V0A2:PLEKHG5                                          |
| Human Phenotype Ontology     | HPO33 | HP_DELAYED_ABILITY_TO_WALK                                                | 291     | 6         | 9.32E-5  | 3.26E-2    | YY1:MYT1L:TBRI:CHAMP1:NBEA:RUBCN                                                                |
| Human Phenotype Ontology     | HPO34 | HP_ABNORMAL_ANTERIOR_EYE_SEGMENT_MORPHOLOGY                               | 1321    | 12        | 1.14E-4  | 3.55E-2    | PRDM16:GNAS:YY1:MMP23B:HLA-B:TBRI:KATNIP:COL5A2:NEU1:ADAMTS17:USH1G:TUBA3D                      |
| Human Phenotype Ontology     | HPO35 | HP_SOMATIC_SENSORY_DYSFUNCTION                                            | 436     | 7         | 1.15E-4  | 3.55E-2    | GNAS:MAPT:YY1:HLA-B:COMP:CHAMP1:PLEKHG5                                                         |
| Human Phenotype Ontology     | HPO36 | HP_ABNORMAL_UVEA_MORPHOLOGY                                               | 592     | 8         | 1.22E-4  | 3.55E-2    | PRDM16:MMP23B:HLA-B:DNASE1L3:TBRI:KATNIP:ADAMTS17:USH1G                                         |
| Human Phenotype Ontology     | HPO37 | HP_ABNORMALITY_OF_JOINT_MOBILITY                                          | 1333    | 12        | 1.24E-4  | 3.55E-2    | PRDM16:GNAS:YY1:MMP23B:HLA-B:TBRI:COMP:COL5A2:ATP6V0A2:CHAMP1:PLEKHG5:ADAMTS17                  |
| Human Phenotype Ontology     | HPO38 | HP_ABNORMALITY_OF_THE_VERTEBRAL_COLUMN                                    | 1547    | 13        | 1.26E-4  | 3.55E-2    | PRDM16:GNAS:MAPT:MMP23B:HLA-B:TBRI:KATNIP:COMP:COL5A2:NEU1:NDUFAF1:ATP6V0A2:PLEKHG5             |
| Human Phenotype Ontology     | HPO39 | HP_ABNORMAL_MYOCARDIUM_MORPHOLOGY                                         | 600     | 8         | 1.34E-04 | 3.58E-2    | PRDM16:MMP23B:HLA-B:KCNQ1:CPT1A:FHOD3:NEU1:NDUFAF1                                              |
| Human Phenotype Ontology     | HPO40 | HP_NEOPLASM_OF_THE_NERVOUS_SYSTEM                                         | 196     | 5         | 1.37E-4  | 3.59E-2    | PRDM16:GNAS:MAPT:YY1:MMP23B                                                                     |
| Human Phenotype Ontology     | HPO41 | HP_ABNORMALITY_OF_IMMUNE_SYSTEM_PHYSIOLOGY                                | 1787    | 14        | 1.42E-4  | 3.62E-2    | GNAS:YY1:HLA-B:FIPL1L1:SCNN1G:DNASE1L3:MSX1:KATNIP:COL5A2:ARHGAP24:ATP6V0A2:CHAMP1:NBEA:MPEGI   |
| Human Phenotype Ontology     | HPO42 | HP_ABNORMAL_CEREBRAL_VENTRICLE_MORPHOLOGY                                 | 958     | 10        | 1.44E-4  | 3.62E-2    | PRDM16:GNAS:YY1:MMP23B:MYT1L:KCNQ1:KATNIP:NEU1:ATP6V0A2:TRIM71                                  |
| Human Phenotype Ontology     | HPO43 | HP_FEEDING_DIFFICULTIES                                                   | 1153    | 11        | 1.46E-4  | 3.62E-2    | PRDM16:YY1:MMP23B:SCNN1G:MSX1:KATNIP:CPT1A:FRMD5:NDUFAF1:ATP6V0A2:CHAMP1                        |
| Human Phenotype Ontology     | HPO44 | HP_ABNORMAL_LIVER_METABOLITE_CONCENTRATION                                | 200     | 5         | 1.5E-4   | 3.66E-2    | PRDM16:GNAS:MMP23B:CPT1A:NDUFAF1                                                                |
| Human Phenotype Ontology     | HPO45 | HP_ABNORMALITY_OF_THE ABDOMINAL_ORGANS                                    | 1367    | 12        | 1.56E-4  | 3.76E-2    | PRDM16:GNAS:YY1:MMP23B:HLA-B:KCNQ1:SCNN1G:DNASE1L3:CPT1A:ARHGAP24:NEU1:NDUFAF1                  |
| Human Phenotype Ontology     | HPO46 | HP_JOINT_STIFFNESS                                                        | 203     | 5         | 1.61E-4  | 3.79E-2    | PRDM16:MMP23B:HLA-B:COMP:ADAMTS17                                                               |
| Human Phenotype Ontology     | HPO47 | HP_ABNORMALITY_OF_THE_PERIPHERAL_NERVOUS_SYSTEM                           | 462     | 7         | 1.64E-4  | 3.79E-2    | MAPT:KCNQ1:KATNIP:COMP:COL5A2:NEU1:PLEKHG5                                                      |
| Human Phenotype Ontology     | HPO48 | HP_ABNORMALITY_OF_THE PANCREAS                                            | 327     | 6         | 1.76E-4  | 3.98E-2    | PRDM16:GNAS:YY1:MMP23B:HLA-B:KCNQ1                                                              |
| Human Phenotype Ontology     | HPO49 | HP_RED_EYE                                                                | 114     | 4         | 1.96E-4  | 4.33E-2    | GNAS:MAPT:HLA-B:DNASE1L3                                                                        |
| Human Phenotype Ontology     | HPO50 | HP_ABNORMALITY_OF_COORDINATION                                            | 1204    | 11        | 2.12E-4  | 4.55E-2    | MAPT:HLA-B:DNASE1L3:KATNIP:FRMD5:NEU1:NDUFAF1:ATP6V0A2:CHAMP1:RUBCN:USH1G                       |
| Human Phenotype Ontology     | HPO51 | HP_UPPER_MOTOR_NEURON_DYSFUNCTION                                         | 1219    | 11        | 2.36E-4  | 4.75E-2    | PRDM16:MAPT:MMP23B:HLA-B:UNC13A:DNASE1L3:CPT1A:FRMD5:NEU1:ATP6V0A2:MCEE                         |
| Human Phenotype Ontology     | HPO52 | HP_ABNORMAL_ORAL_PHYSIOLOGY                                               | 346     | 6         | 2.38E-4  | 4.75E-2    | HLA-B:FIPL1L1:SCNN1G:UNC13A:MSX1:CHAMP1                                                         |
| Human Phenotype Ontology     | HPO53 | HP_GENERALIZED_JOINT_HYPERMOBILITY                                        | 48      | 3         | 2.39E-4  | 4.75E-2    | COMP:COL5A2:ATP6V0A2                                                                            |
| Human Phenotype Ontology     | HPO54 | HP_DIMINISHED_MOTIVATION                                                  | 65      | 8         | 2.42E-4  | 4.75E-2    | GNAS:MAPT:YY1:HLA-B:UNC13A:CPT1A:NDUFAF1:USH1G                                                  |
| Human Phenotype Ontology     | HPO55 | HP_THORACIC_AORTIC_ANEURYSM                                               | 122     | 4         | 2.54E-04 | 4.94E-2    | PRDM16:MMP23B:HLA-B:COL5A2                                                                      |
| Human Phenotype Ontology     | HPO56 | HP_ABNORMAL_JOINT_MORPHOLOGY                                              | 1233    | 11        | 2.6E-4   | 4.98E-2    | PRDM16:GNAS:YY1:MMP23B:HLA-B:DNASE1L3:TBRI:COMP:COL5A2:ATP6V0A2:PLEKHG5                         |
| Immunologic_signatures       | IMS1  | GSE2770_UNTREATED_VS_IL12_TREATED_ACT_CD4_TCELL_2H_UP                     | 200     | 6         | 1.15E-5  | 4.61E-2    | NEU1:NDUFAF1:KCNQ1:ATP6V0A2:KATNIP:GNAS                                                         |
| Immunologic_signatures       | IMS2  | GSE15624_CTRL_VS_6H_HALOFUGINONE_TREATED_CD4_TCELL_UP                     | 133     | 5         | 2.17E-5  | 4.61E-2    | TMEM184C:NAV1:RASAS3:MYT1L:SCNN1G                                                               |
| Immunologic_signatures       | IMS3  | GSE7509_UNSTIM_VS_FCGR1B_STIM_DC_UP                                       | 174     | 5         | 7.81E-5  | 4.61E-2    | NEU1:PLEKHG5:PMVK:NCOR2:LRR27                                                                   |
| Immunologic_signatures       | IMS4  | GSE22886_IL2_VS_IL15_STIM_NKCELL_DN                                       | 195     | 5         | 1.33E-4  | 4.61E-2    | NDUFAF1:HIC2:TRIM17:AATF:CDHR2                                                                  |
| Immunologic_signatures       | IMS5  | GSE42088_UNINF_VS_LEISHMANIA_INF_DC_8H_DN                                 | 197     | 5         | 1.4E-4   | 4.61E-2    | NBEA:ACKR3:FHOD3:GPR63:MAPT                                                                     |
| Immunologic_signatures       | IMS6  | GSE17974_0.5H_VS_72H_UNTREATED_IN_VITRO_CD4_TCELL_DN                      | 199     | 5         | 1.47E-4  | 4.61E-2    | NDUFAF1:MCEE:MRPL37:TUBA3D:CD25A                                                                |
| Immunologic_signatures       | IMS7  | GSE21670_UNTREATED_VS_TGFB_TREATED_CD4_TCELL_DN                           | 199     | 5         | 1.47E-4  | 4.61E-2    | NBEA:CD42EP3:HLA-B:OSBPL1A:PRDM16                                                               |
| Immunologic_signatures       | IMS8  | GSE3039_NKT_CELL_VS_B1_BCELL_UP                                           | 199     | 5         | 1.47E-4  | 4.61E-2    | CD42EP3:ACIN1:ERICH3:PDE4A:LBH                                                                  |
| Immunologic_signatures       | IMS9  | GSE32034_UNTREATED_VS_ROSIGLIZATONE_TREATED_LY6C_HIGH_MONOCYTE_DN         | 199     | 5         | 1.47E-4  | 4.61E-2    | ACKR3:MCEE:VAMP3:FABP3:ZMAT3                                                                    |
| Immunologic_signatures       | IMS10 | GSE37416_CTRL_VS_48H_F_TULARENSIS_LVS_NEUTROPHIL_DN                       | 199     | 5         | 1.47E-4  | 4.61E-2    | NEU1:SIRPB1:TRIM69:RAB1B:FBXO42                                                                 |
| Immunologic_signatures       | IMS11 | GSE11961_MARGINAL_ZONE_BCELL_VS_MEMORY_BCELL_DAY7_DN                      | 200     | 5         | 1.5E-4   | 4.61E-2    | KCNQ1:HIC2:RFX4:ARHGAP24:SEMA5B                                                                 |
| Immunologic_signatures       | IMS12 | GSE13306_TREG_VS_TCONV_SPLEEN_UP                                          | 200     | 5         | 1.5E-4   | 4.61E-2    | TRIM17:NBEA:VAMP3:MTMR3:MSX1                                                                    |
| Immunologic_signatures       | IMS13 | GSE15930_STIM_VS_STIM_AND_IFNAB_24H_CD8_T_CELL_UP                         | 200     | 5         | 1.5E-4   | 4.61E-2    | CDH13:SIGLEC1:PRR15:MPHOSPH10:FIPL1L1                                                           |
| Immunologic_signatures       | IMS14 | GSE20715_0H_VS_48H_OZONE_TLR4_KO_LUNG_UP                                  | 200     | 5         | 1.5E-4   | 4.61E-2    | PLEKHG5:FABP3:CDH13:CPT1A:SUN1                                                                  |
| Immunologic_signatures       | IMS15 | GSE29618_MONOCYTE_VS_MDC_DAY7_FLU_VACCINE_UP                              | 200     | 5         | 1.5E-4   | 4.61E-2    | CD42EP3:HLA-B:VAMP3:SIRPB1:MTMR3                                                                |
| Immunologic_signatures       | IMS16 | GSE4142_PLASMA_CELL_VS_GC_BCELL_UP                                        | 200     | 5         | 1.5E-4   | 4.61E-2    | PLEKHG5:MTMR3:MIIP:ATG16L1:TMEM8B                                                               |
| Immunologic_signatures       | IMS17 | GSE46606_UNSTIM_VS_CD40L_IL2_IL5_3DAY_STIMULATED_IRF4HIGH_SORTED_BCELL_UI | 200     | 5         | 1.5E-4   | 4.61E-2    | AATF:RFX4:MSX1:MIIP:POLR1F                                                                      |
| Transcription_Factor_Targets | TFT1  | LFA1_Q6                                                                   | 251     | 7         | 3.38E-6  | 3.76E-3    | NR5A2:TBRI:USH1G:OTOP2:MSX1:RFX4:RAB1B                                                          |
| Transcription_Factor_Targets | TFT2  | MYOCD_TARGET_GENES                                                        | 1560    | 15        | 7.63E-6  | 4.26E-3    | NR5A2:TBRI:FYTTD1:LRR27:EFHB:CD25A:RUBCN:PRDM16:GNAS:ARHGEF17:PLEKHG5:NCOR2:NEU1:FBXO42:KATNIP  |
| Transcription_Factor_Targets | TFT3  | GATA_Q6                                                                   | 201     | 6         | 1.18E-5  | 4.4E-3     | NR5A2:USH1G:OTOP2:CD42EP3:MMP23B:MMP23A                                                         |
| Transcription_Factor_Targets | TFT4  | CTGACGY_UNKNOWN                                                           | 779     | 10        | 2.61E-5  | 5.79E-3    | USH1G:OTOP2:FYTTD1:MAPT:ATG16L1:CDH13:ZMAT3:SEMA5B:NBEA:ACIN1                                   |
| Transcription_Factor_Targets | TFT5  | DNMT1_TARGET_GENES                                                        | 233     | 6         | 2.72E-05 | 5.79E-3    | LRR27:EFHB:ARHGAP24:PDE4A:MAPRE3:SUN1                                                           |
| Transcription_Factor_Targets | TFT6  | CEBP2_TARGET_GENES                                                        | 1549    | 14        | 3.11E-5  | 5.79E-3    | LRR27:CD25A:MAPT:ATG16L1:MRPL37:NDUFAF1:CYB5RL:FRMD5:ATP6V0A2:GNG4:MCEE:MPHOSPH10:TMEM184C:MIP  |
| Transcription_Factor_Targets | TFT7  | ZBED5_TARGET_GENES                                                        | 1646    | 14        | 5.99E-5  | 9.55E-3    | USH1G:OTOP2:FYTTD1:RUBCN:MRPL37:NDUFAF1:CYB5RL:FIPL1L1:OPRM1:CDHR2:UNC13A:CHAMP1:POLR1F:C5orf63 |
| Transcription_Factor_Targets | TFT8  | TGACCTY_ERR1_Q2                                                           | 1065    | 11        | 7.28E-5  | 1.01E-2    | NR5A2:MSX1:PRDM16:CD42EP3:CDH13:ZMAT3:ARHGAP24:MRPL37:NFYA:FABP3:ACKR3                          |
| Transcription_Factor_Targets | TFT9  | YTAATTA_LHX3_01                                                           | 192     | 5         | 1.24E-4  | 1.54E-2    | TBRI:SEMA5B:FIPL1L1:OPRM1:NFYA                                                                  |
| Transcription_Factor_Targets | TFT10 | YGCYRCGC_UNKNOWN                                                          | 326     | 6         | 1.73E-4  | 1.93E-2    | FYTTD1:GNAS:MAPT:AATF:MTMR3:HIC2                                                                |
| Transcription_Factor_Targets | TFT11 | CTTTAA_UNKNOWN                                                            | 995     | 10        | 1.96E-4  | 1.95E-2    | NR5A2:TBRI:RFX4:PRDM16:NBEA:FIPL1L1:OPRM1:F2RL1:GPR63:HLA-B                                     |
| Transcription_Factor_Targets | TFT12 | TAATTA_CHX10_01                                                           | 824     | 9         | 2.25E-4  | 1.95E-2    | TBRI:MSX1:GNAS:CD42EP3:SEMA5B:FIPL1L1:OPRM1:NFYA:ADAMTS17                                       |
| Transcription_Factor_Targets | TFT13 | BRCA2_TARGET_GENES                                                        | 1671    | 13        | 2.68E-4  | 1.95E-2    | MSX1:FYTTD1:RUBCN:GNAS:ARHGEF17:PLEKHG5:ACIN1:NDUFAF1:FRMD5:FABP3:PMVK:MARCHF10:TRIM69          |
| Transcription_Factor_Targets | TFT14 | ZSCAN4_TARGET_GENES                                                       | 1460    | 12        | 2.85E-4  | 1.95E-2    | RFX4:LRR27:ARHGEF17:NCOR2:ATG16L1:ARHGAP24:PDE4A:NDUFAF1:ATP6V0A2:MDGA2:C16orf89:COMP           |
| Transcription_Factor_Targets | TFT15 | ZNFX2_TARGET_GENES                                                        | 1462    | 12        | 2.89E-4  | 1.95E-2    | PLEKHG5:NCOR2:ATG16L1:PDE4A:F2RL1:PMVK:MARCHF10:PRR15:SIGLEC1:SCAND3:HENMT1:AZIN2               |
| Transcription_Factor_Targets | TFT16 | LHX3_01                                                                   | 232     | 5         | 2.98E-4  | 1.95E-2    | TBRI:FIPL1L1:OPRM1:NFYA:ADAMTS17                                                                |
| Transcription_Factor_Targets | TFT17 | AACITTT_UNKNOWN                                                           | 1927    | 14        | 3.08E-4  | 1.95E-2    | NR5A2:RFX4:PRDM16:GNAS:ARHGEF17:CDH13:FRMD5:GNG4:FIPL1L1:ACKR3:F2RL1:GPR63:PRR15:CPT1A          |
| Transcription_Factor_Targets | TFT18 | IRF2_01                                                                   | 129     | 4         | 3.15E-4  | 1.95E-2    | MSX1:RFX4:PRDM16:DNASE1L3                                                                       |
| Transcription_Factor_Targets | TFT19 | IRX2_TARGET_GENES                                                         | 239     | 5         | 3.42E-4  | 2E-2       | FYTTD1:RUBCN:PDE4A:TRIM69:OCIAD1                                                                |

Supplemental Table 3. Gene set enrichment analysis based on the updated MSigDB gene sets using Illumina annotated genes

| Category                     | Label | GeneSet             | N_genes | N_overlap | P        | adjusted P | Genes                                                                     |
|------------------------------|-------|---------------------|---------|-----------|----------|------------|---------------------------------------------------------------------------|
| Transcription_Factor_Targets | TFT20 | CIZ_01              | 254     | 5         | 4.51E-4  | 2.48E-2    | NR5A2:RFX4:FRMD5:ACKR3:ADAMTS17                                           |
| Transcription_Factor_Targets | TFT21 | ARNT_02             | 256     | 5         | 4.67E-4  | 2.48E-2    | RFX4:GNAS:FABP3:AATF:CPT1A                                                |
| Transcription_Factor_Targets | TFT22 | MEIS1BHOXA9_01      | 146     | 4         | 5.03E-4  | 2.55E-2    | TBR1:USH1G:OTOP2:CDH13                                                    |
| Transcription_Factor_Targets | TFT23 | AP4_01              | 267     | 5         | 5.65E-4  | 2.65E-2    | CDH13:ZMAT3:MAPRE3:MTMR3:FLYWCHI                                          |
| Transcription_Factor_Targets | TFT24 | HOXD11_TARGET_GENES | 151     | 4         | 5.7E-4   | 2.65E-2    | EFHB:MCEE:MPHOSPH10:AATF                                                  |
| Transcription_Factor_Targets | TFT25 | NKX2_5_TARGET_GENES | 1594    | 12        | 6.23E-4  | 2.76E-2    | EFHB:GNAS:NEU1:ATG16L1:ACIN1:ARHGAP24:SUN1:NDUFAF1:MCEE:FIP1L1:PMVK:KCNQ1 |
| Transcription_Factor_Targets | TFT26 | PAX5_01             | 156     | 4         | 6.44E-4  | 2.76E-2    | RFX4:MMP23B:MMP23A:HIC2                                                   |
| Transcription_Factor_Targets | TFT27 | TTANTCA_UNKNOWN     | 967     | 9         | 7.14E-4  | 2.95E-2    | NR5A2:TBR1:RFX4:ZMAT3:SEMA5B:ARHGAP24:ACKR3:SIGLEC1:CXADR                 |
| Transcription_Factor_Targets | TFT28 | KMT2D_TARGET_GENES  | 810     | 8         | 9.72E-04 | 3.87E-2    | ARHGAP24:SUN1:CDHR2:PMVK:PRR15:CXADR:NAV1:FHOD3                           |
| Transcription_Factor_Targets | TFT29 | NCX_01              | 176     | 4         | 1.01E-3  | 3.88E-2    | TBR1:GNAS:SEMA5B:GNG4                                                     |
| Transcription_Factor_Targets | TFT30 | CACGTG_MYC_Q2       | 1057    | 9         | 1.33E-3  | 4.93E-2    | RFX4:GNAS:MMP23B:MMP23A:FABP3:AATF:ADAMTS17:CPT1A:PDIA2                   |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category           | GeneSet                                                                                   | N_genes | N_overlap | P        | adjusted P | Genes                                                                                           |
|--------------------|-------------------------------------------------------------------------------------------|---------|-----------|----------|------------|-------------------------------------------------------------------------------------------------|
| Curated_gene_sets  | KLEIN_PRIMARY_EFFUSION_LYMPHOMA_DN                                                        | 55      | 8         | 1.74E-10 | 1.13E-06   | BCL11A:CD72:MS4A1:CD19:CD79B:CD22:CD79A:PKIG                                                    |
| Curated_gene_sets  | PASQUALUCCI_LYMPHOMA_BY_GC_STAGE_DN                                                       | 164     | 10        | 5.05E-09 | 1.64E-05   | FCRLA:BCL11A:AFF3:BANK1:PAX5:BCL7A:CD19:FAM129C:CD22:CD79A                                      |
| Curated_gene_sets  | SMID_BREAST_CANCER_NORMAL_LIKE_UP                                                         | 441     | 14        | 1.72E-08 | 3.73E-05   | FCRL2:BCL11A:STAP1:BANK1:BTN3A2:HLA-DOB:CD72:PAX5:MS4A1:TCL1A:CD19:CD79B:CD22:CD79A             |
| Curated_gene_sets  | HADDAD_B_LYMPHOCYTE_PROGENITOR                                                            | 250     | 11        | 2.49E-08 | 4.04E-05   | BANK1:PTPRK:CD72:PAX5:MS4A1:TCL1A:CORO2B:CD19:CD79B:CD22:CD79A                                  |
| Curated_gene_sets  | DODD_NASOPHARYNGEAL_CARCCINOMA_UP                                                         | 1593    | 24        | 1.95E-07 | 2.54E-04   | CD72:PAX5:STK32C:EPS8L2:MS4A1:GDPD5:TCL1A:CEP170B:SNX22:CD19:CD79B:FCER2:FAM129C:CD22:TNFRSF13C |
| Curated_gene_sets  | WP_EXTRAFOLLICULAR_AND_FOLLICULAR_B_CELL_ACTIVATION_BY_SARSCOV2                           | 70      | 6         | 9.32E-07 | 9.24E-04   | PDCD1:PAX5:MS4A1:CD19:CD22:CD79A                                                                |
| Curated_gene_sets  | REACTOME_CD22_MEDIATED_BCR_REGULATION                                                     | 5       | 3         | 9.95E-07 | 9.24E-04   | CD79B:CD22:CD79A                                                                                |
| Curated_gene_sets  | SHIN_B_CELL_LYMPHOMA_CLUSTER_9                                                            | 19      | 4         | 1.67E-06 | 1.23E-03   | BCL11A:PAX5:CD19:CD79A                                                                          |
| Curated_gene_sets  | ZHAN_MULTIPLE_MYELOMA_CD2_UP                                                              | 43      | 5         | 1.71E-06 | 1.23E-03   | BEND5:PAX5:MS4A1:CD79A:TNFRSF13C                                                                |
| Curated_gene_sets  | BORCZUK_MALIGNANT_MESOTHELIOMA_DN                                                         | 89      | 6         | 3.85E-06 | 2.50E-03   | MS4A1:CD19:CD79B:FCER2:CD22:CD79A                                                               |
| Curated_gene_sets  | REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_BCR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS | 29      | 4         | 9.88E-06 | 5.79E-03   | CD19:CD79B:CD22:CD79A                                                                           |
| Curated_gene_sets  | PID_BCR_5PATHWAY                                                                          | 62      | 5         | 1.07E-05 | 5.79E-03   | CD72:CD19:CD79B:CD22:CD79A                                                                      |
| Curated_gene_sets  | KUMAR_TARGETS_OF_MLL_AF9_FUSION                                                           | 382     | 10        | 1.21E-05 | 6.07E-03   | FCRLA:COL19A1:TSPAN13:CD72:PAX5:MS4A1:CORO2B:CD19:FCER2:CD79A                                   |
| Curated_gene_sets  | MORI_PLASMA_CELL_DN                                                                       | 34      | 4         | 1.89E-05 | 8.79E-03   | BCL11A:MS4A1:CD22:TNFRSF13C                                                                     |
| Curated_gene_sets  | KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY                                                    | 74      | 5         | 2.55E-05 | 1.10E-02   | CD72:CD19:CD79B:CD22:CD79A                                                                      |
| Curated_gene_sets  | MORI_PRE_BI_LYMPHOCYTE_DN                                                                 | 78      | 5         | 3.29E-05 | 1.29E-02   | FCRLA:CD72:MS4A1:CD79B:CD22                                                                     |
| Curated_gene_sets  | BOYLAN_MULTIPLE_MYELOMA_C_D_UP                                                            | 130     | 6         | 3.39E-05 | 1.29E-02   | BCL11A:AFF3:PAX5:BCL7A:FAM129C:PKIG                                                             |
| Canonical_Pathways | WP_EXTRAFOLLICULAR_AND_FOLLICULAR_B_CELL_ACTIVATION_BY_SARSCOV2                           | 70      | 6         | 9.32E-07 | 1.54E-03   | PDCD1:PAX5:MS4A1:CD19:CD22:CD79A                                                                |
| Canonical_Pathways | REACTOME_CD22_MEDIATED_BCR_REGULATION                                                     | 5       | 3         | 9.95E-07 | 1.54E-03   | CD79B:CD22:CD79A                                                                                |
| Canonical_Pathways | REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_BCR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS | 29      | 4         | 9.88E-06 | 8.26E-03   | CD19:CD79B:CD22:CD79A                                                                           |
| Canonical_Pathways | PID_BCR_5PATHWAY                                                                          | 62      | 5         | 1.07E-05 | 8.26E-03   | CD72:CD19:CD79B:CD22:CD79A                                                                      |
| Canonical_Pathways | KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY                                                    | 74      | 5         | 2.55E-05 | 1.57E-02   | CD72:CD19:CD79B:CD22:CD79A                                                                      |
| Reactome           | REACTOME_CD22_MEDIATED_BCR_REGULATION                                                     | 5       | 3         | 9.95E-07 | 1.65E-03   | CD79B:CD22:CD79A                                                                                |
| Reactome           | REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_BCR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS | 29      | 4         | 9.88E-06 | 8.17E-03   | CD19:CD79B:CD22:CD79A                                                                           |
| TF_targets         | MAML1_TARGET_GENES                                                                        | 228     | 10        | 1.16E-07 | 1.29E-04   | AFF3:DNASE1L3:CD72:LCN10:MS4A1:RAB30:CD19:CD79B:FCER2:FAM129C                                   |
| KEGG               | KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY                                                    | 74      | 5         | 2.55E-05 | 4.74E-03   | CD72:CD19:CD79B:CD22:CD79A                                                                      |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category                | GeneSet                                                         | N_genes | N_overlap | P        | adjusted P | Genes                                                             |
|-------------------------|-----------------------------------------------------------------|---------|-----------|----------|------------|-------------------------------------------------------------------|
| KEGG                    | KEGG_CELL_ADHESION_MOLECULES_CAMS                               | 125     | 5         | 3.07E-04 | 1.60E-02   | PDCD1:HLA-C:HLA-DOB:HLA-DOA:CD22                                  |
| KEGG                    | KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION                        | 71      | 4         | 3.48E-04 | 1.60E-02   | HLA-C:HLA-DOB:HLA-DOA:NFYA                                        |
| KEGG                    | KEGG_ALLOGRAFT_REJECTION                                        | 32      | 3         | 4.50E-04 | 1.60E-02   | HLA-C:HLA-DOB:HLA-DOA                                             |
| KEGG                    | KEGG_GRAFT_VERSUS_HOST_DISEASE                                  | 32      | 3         | 4.50E-04 | 1.60E-02   | HLA-C:HLA-DOB:HLA-DOA                                             |
| KEGG                    | KEGG_PRIMARY_IMMUNODEFICIENCY                                   | 34      | 3         | 5.40E-04 | 1.60E-02   | CD19:CD79A:TNFRSF13C                                              |
| KEGG                    | KEGG_HEMATOPOIETIC_CELL_LINEAGE                                 | 82      | 4         | 6.02E-04 | 1.60E-02   | MS4A1:CD19:FCER2:CD22                                             |
| KEGG                    | KEGG_TYPE_I_DIABETES_MELLITUS                                   | 38      | 3         | 7.51E-04 | 1.75E-02   | HLA-C:HLA-DOB:HLA-DOA                                             |
| KEGG                    | KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION               | 42      | 3         | 1.01E-03 | 2.08E-02   | HLA-DOB:HLA-DOA:TNFRSF13C                                         |
| KEGG                    | KEGG_AUTOIMMUNE_THYROID_DISEASE                                 | 47      | 3         | 1.40E-03 | 2.60E-02   | HLA-C:HLA-DOB:HLA-DOA                                             |
| GO_bp                   | GOBP_B_CELL_RECEPTOR_SIGNALING_PATHWAY                          | 60      | 7         | 1.25E-08 | 9.70E-05   | STAP1:BANK1:MS4A1:CD19:CD79B:CD22:CD79A                           |
| GO_bp                   | GOBP_ANTIGEN_RECEPTOR_MEDIATED_SIGNALING_PATHWAY                | 170     | 8         | 1.35E-06 | 5.25E-03   | STAP1:BANK1:BTN3A2:MS4A1:CD19:CD79B:CD22:CD79A                    |
| GO_bp                   | GOBP_B_CELL_ACTIVATION                                          | 267     | 9         | 4.55E-06 | 1.17E-02   | FCRL1:BANK1:PAX5:MS4A1:CD19:CD79B:CD22:CD79A:TNFRSF13C            |
| Wikipathways            | WP_EXTRAFOLLICULAR_AND_FOLLICULAR_B_CELL_ACTIVATION_BY_SARSCOV2 | 70      | 6         | 9.32E-07 | 6.83E-04   | PDCD1:PAX5:MS4A1:CD19:CD22:CD79A                                  |
| Computational_gene_sets | MODULE_292                                                      | 123     | 11        | 1.30E-11 | 6.65E-09   | FCRL2:FCRLA:CD200:BANK1:CD72:MS4A1:TCL1A:CD19:CD79B:CD22:CD79A    |
| Computational_gene_sets | MODULE_436                                                      | 125     | 11        | 1.55E-11 | 6.65E-09   | FCRL2:FCRL1:FCRLA:CD200:BANK1:HLA-C:MS4A1:TCL1A:CD79B:FCER2:CD79A |
| Computational_gene_sets | MODULE_345                                                      | 114     | 9         | 3.18E-09 | 9.10E-07   | FCRL2:FCRLA:BANK1:HLA-C:MS4A1:TCL1A:CD19:CD79B:CD79A              |
| Computational_gene_sets | MODULE_145                                                      | 102     | 8         | 2.63E-08 | 5.64E-06   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                 |
| Computational_gene_sets | MODULE_188                                                      | 128     | 8         | 1.55E-07 | 2.66E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                 |
| Computational_gene_sets | MODULE_361                                                      | 137     | 8         | 2.62E-07 | 3.75E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                 |
| Computational_gene_sets | MODULE_301                                                      | 145     | 8         | 4.05E-07 | 4.97E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                 |
| Computational_gene_sets | MODULE_238                                                      | 151     | 8         | 5.52E-07 | 5.92E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                 |
| Computational_gene_sets | MODULE_46                                                       | 379     | 10        | 1.13E-05 | 1.04E-03   | PDCD1:HLA-C:HLA-DOA:CD72:PAX5:MS4A1:CD19:CD79B:CD22:CD79A         |
| Computational_gene_sets | MODULE_75                                                       | 382     | 10        | 1.21E-05 | 1.04E-03   | PDCD1:HLA-C:HLA-DOA:CD72:PAX5:MS4A1:CD19:CD79B:CD22:CD79A         |
| Computational_gene_sets | MODULE_143                                                      | 13      | 3         | 2.77E-05 | 2.16E-03   | HLA-C:HLA-DOB:HLA-DOA                                             |
| Computational_gene_sets | MODULE_41                                                       | 537     | 10        | 2.10E-04 | 1.50E-02   | PDCD1:TRIM15:CCHCR1:HLA-DOB:COL19A1:CD72:TCL1A:SCN4A:PDE4A:CD22   |
| Computational_gene_sets | MODULE_96                                                       | 34      | 3         | 5.40E-04 | 3.31E-02   | CD72:FCER2:CD22                                                   |
| Computational_gene_sets | MODULE_410                                                      | 34      | 3         | 5.40E-04 | 3.31E-02   | CD72:FCER2:CD22                                                   |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category               | GeneSet                                                                                                                                 | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                                    |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-----------|----------|------------|--------------------------------------------------------------------------------------------------------------------------|
| GO_cc                  | GOCC_CELL_SURFACE                                                                                                                       | 832     | 17        | 2.74E-07 | 2.76E-04   | FCRL2:FCRL1:PCD1:CLDND1:CD200:TIGIT:BTN3A2:HLA-C:PTPRK:MS4A1:CD19:CD79B:FCER2:CLEC17A:CD22:CD79A:TNFRSF13C               |
| GO_cc                  | GOCC_EXTERNAL_SIDE_OF_PLASMA_MEMBRANE                                                                                                   | 340     | 11        | 5.52E-07 | 2.79E-04   | PDCD1:BTN3A2:HLA-C:MS4A1:CD19:CD79B:FCER2:CLEC17A:CD22:CD79A:TNFRSF13C                                                   |
| GO_cc                  | GOCC_SIDE_OF_MEMBRANE                                                                                                                   | 537     | 12        | 7.72E-06 | 2.60E-03   | PDCD1:RAB5A:BTN3A2:HLA-C:MS4A1:CD19:CD79B:FCER2:CLEC17A:CD22:CD79A:TNFRSF13C                                             |
| GO_cc                  | GOCC_MHC_PROTEIN_COMPLEX                                                                                                                | 20      | 3         | 1.08E-04 | 2.72E-02   | HLA-C:HLA-DOB:HLA-DOA                                                                                                    |
| GO_cc                  | GOCC_B_CELL_RECEPTOR_COMPLEX                                                                                                            | 5       | 2         | 2.16E-04 | 4.36E-02   | CD79B:CD79A                                                                                                              |
| Immunologic_signatures | GSE4984_UNTREATED_VS_GALECTIN1_TREATED_DC_DN                                                                                            | 157     | 25        | 6.43E-32 | 3.36E-28   | DOA:PTPRK:TSPAN13:ABCB4:PPAPDC1B:CD72:MS4A1:BCL7A:TCL1A:CORO2B:CD19:CD79B:FCER2:FAM129C:CD22:CD79A:PKIG:PMEPA1           |
| Immunologic_signatures | GSE10325_CD4_TCELL_VS_BCELL_DN                                                                                                          | 168     | 23        | 9.18E-28 | 2.40E-24   | DOA:PTPRK:TSPAN13:ABCB4:CD72:PAX5:MS4A1:RAB30:BCL7A:TCL1A:CD19:CD79B:FCER2:CD22:CD79A:PKIG:LARGE                         |
| Immunologic_signatures | SOBOLEV_PBMIC_PANDEMRIX_AGE_18_64YO_MEDIUM_HIGH_ADVERSE_EVENT_SUBJECTS_1DY_UP                                                           | 35      | 15        | 1.03E-26 | 1.79E-23   | FCRL2:FCRL1:FCRLA:BANK1:TSPAN13:CD72:MS4A1:CD19:CD79B:FCER2:FAM129C:CD22:CD79A:LARGE:TNFRSF13C                           |
| Immunologic_signatures | SOBOLEV_PBMIC_PANDEMRIX_AGE_18_64YO_HIGH_VS_LOW_RESPONDERS_MEDIUM_HIGH_ADVERSE_EVENTS_SCORE_1DY_CORRELATED_WITH_TRANSITIONAL_B_CELLS_UP | 21      | 13        | 4.25E-26 | 5.54E-23   | FCRL2:FCRL1:FCRLA:BANK1:TSPAN13:CD72:MS4A1:CD19:CD79B:FCER2:FAM129C:CD22:LARGE                                           |
| Immunologic_signatures | GSE4748_CYANOBACTERIUM_LPISLIKE_VS_LPS_AND_CYANOBACTERIUM_LPISLIKE_STIM_DC_3H_UP                                                        | 171     | 22        | 6.09E-26 | 6.05E-23   | DOA:PTPRK:TSPAN13:ABCB4:PPAPDC1B:CD72:PAX5:CORO2B:CD79B:FCER2:FAM129C:CD22:CD79A:PMEPA1                                  |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_MONOCYTE_UP                                                                                                     | 172     | 22        | 6.96E-26 | 6.05E-23   | DOA:PTPRK:TSPAN13:ABCB4:CD72:PAX5:MS4A1:BCL7A:TCL1A:CORO2B:CD19:CD79B:CD22:CD79A:LARGE:SLC9A7                            |
| Immunologic_signatures | GSE10325_BCELL_VS_MYELOID_UP                                                                                                            | 177     | 22        | 1.34E-25 | 9.99E-23   | DOA:PTPRK:TSPAN13:ABCB4:CD72:PAX5:MS4A1:BCL7A:TCL1A:CD19:CD79B:FCER2:CD22:CD79A:PKIG:LARGE                               |
| Immunologic_signatures | GSE22886_TCELL_VS_BCELL_NAIVE_DN                                                                                                        | 186     | 21        | 1.53E-23 | 9.96E-21   | DOA:TSPAN13:CD72:MS4A1:RAB30:BCL7A:TCL1A:CORO2B:CD19:CD79B:CD22:CD79A:PKIG:LARGE:SLC9A7                                  |
| Immunologic_signatures | FOURATI_BLOOD_TWINRIX_AGE_25_83YO_RESPONDERS_VS_POOR_RESPONDERS_0DY_UP                                                                  | 529     | 29        | 1.80E-23 | 1.04E-20   | DOA:PTPRK:TSPAN13:ABCB4:PPAPDC1B:CD72:MS4A1:RAB30:BCL7A:SNX22:CD79B:FCER2:FAM129C:CD22:CD79A:PKIG:PMEPA1:LARGE:TNFRSF13C |
| Immunologic_signatures | GSE29618_BCELL_VS_MONOCYTE_UP                                                                                                           | 166     | 20        | 5.07E-23 | 2.65E-20   | DOA:TSPAN13:ABCB4:CD72:PAX5:MS4A1:RAB30:BCL7A:CD19:CD79B:FCER2:CD22:CD79A:PKIG                                           |
| Immunologic_signatures | GSE29618_BCELL_VS_MONOCYTE_DAY7_FLU_VACCINE_UP                                                                                          | 170     | 19        | 2.95E-21 | 1.40E-18   | DOA:TSPAN13:ABCB4:CD72:PAX5:MS4A1:BCL7A:TCL1A:CD19:CD79B:FCER2:CD22:CD79A:PKIG                                           |
| Immunologic_signatures | GSE22886_CD8_TCELL_VS_BCELL_NAIVE_DN                                                                                                    | 185     | 19        | 1.52E-20 | 6.62E-18   | DOA:PTPRK:TSPAN13:CD72:MS4A1:RAB30:BCL7A:TCL1A:CORO2B:CD19:CD22:PKIG:LARGE:SLC9A7                                        |
| Immunologic_signatures | GSE10325_LUPUS_CD4_TCELL_VS_LUPUS_BCELL_DN                                                                                              | 171     | 18        | 1.09E-19 | 4.36E-17   | DOA:TSPAN13:ABCB4:CD72:PAX5:MS4A1:TCL1A:CD19:CD79B:FCER2:CD22:CD79A:PKIG                                                 |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_NEUTROPHIL_UP                                                                                                   | 168     | 16        | 7.04E-17 | 2.62E-14   | DOA:TSPAN13:CD72:BCL7A:UPF3A:TCL1A:CD19:CD79B:CD22:CD79A:PKIG                                                            |
| Immunologic_signatures | GSE29618_BCELL_VS_MDC_UP                                                                                                                | 171     | 15        | 2.44E-15 | 8.49E-13   | FCRL2:STAP1:BANK1:TSPAN13:CD72:PAX5:MS4A1:RAB30:TCL1A:CD19:CD79B:FCER2:CD22:CD79A:PKIG                                   |
| Immunologic_signatures | GSE29618_BCELL_VS_PDC_UP                                                                                                                | 177     | 15        | 4.09E-15 | 1.33E-12   | DOA:ABCB4:CD72:PAX5:MS4A1:RAB30:CD19:CD79B:FCER2:CD22:CD79A:PKIG                                                         |
| Immunologic_signatures | GSE22886_CD4_TCELL_VS_BCELL_NAIVE_DN                                                                                                    | 181     | 15        | 5.72E-15 | 1.76E-12   | BCL11A:DNASE1L3:CD200:BANK1:PTPRK:TSPAN13:CD72:MS4A1:TCL1A:CORO2B:CD19:CD79B:CD22:LARGE:SLC9A7                           |
| Immunologic_signatures | GSE45881_CXCR6HI_VS_CXCR1LO_COLONIC_LAMINA_PROPRIA_DN                                                                                   | 190     | 15        | 1.18E-14 | 3.42E-12   | FCRL2:MAPRE3:BCL11A:CD200:STAP1:ABCB4:CD72:PAX5:EPS8L2:TCL1A:CD19:CD79B:FCER2:CD79A:PKIG                                 |
| Immunologic_signatures | GSE29618_BCELL_VS_MDC_DAY7_FLU_VACCINE_UP                                                                                               | 168     | 14        | 4.57E-14 | 1.25E-11   | FCRL2:CD200:STAP1:BANK1:PTPRK:PAX5:MS4A1:TCL1A:CD19:CD79B:FCER2:CD22:CD79A:PKIG                                          |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_DC_UP                                                                                                           | 167     | 13        | 9.45E-13 | 2.47E-10   | BCL11A:CD200:STAP1:HLA-DOB:HLA-DOA:CD72:MS4A1:BCL7A:TCL1A:CORO2B:CD19:CD22:LARGE                                         |
| Immunologic_signatures | GSE10325_LUPUS_BCELL_VS_LUPUS_MYELOID_UP                                                                                                | 173     | 13        | 1.49E-12 | 3.70E-10   | FCRL2:BCL11A:STAP1:BANK1:HEATR2:TSPAN13:CD72:PAX5:MS4A1:TCL1A:CD19:CD79B:CD79A                                           |
| Immunologic_signatures | VOIGT_PBMIC_FLUARIX_AGE_50_74YO_FEMALES_VS_MALES_0DY_TO_28D_UP                                                                          | 19      | 7         | 1.91E-12 | 4.52E-10   | FCRL2:STAP1:PTPRK:TSPAN13:CD19:FAM129C:CD22                                                                              |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category               | GeneSet                                                                                               | N_genes | N_overlap | P        | adjusted P | Genes                                                                            |
|------------------------|-------------------------------------------------------------------------------------------------------|---------|-----------|----------|------------|----------------------------------------------------------------------------------|
| Immunologic_signatures | GSE3982_BCELL_VS_NKCELL_UP                                                                            | 185     | 13        | 3.51E-12 | 7.96E-10   | FCRL2:BCL11A:CD200:BANK1:HLA-DOB:PTPRK:CD72:EPS8L2:TCL1A:NDUFAF1:CD19:FCER2:PKIG |
| Immunologic_signatures | GSE6269_STAPH_AUREUS_VS_STREP_PNEUMO_INF_PBMC_DN                                                      | 171     | 12        | 2.56E-11 | 5.57E-09   | FCRL2:BCL11A:DNASE1L3:BANK1:HLA-DOB:CD72:MS4A1:CD19:FCER2:CD22:CD79A:PKIG        |
| Immunologic_signatures | GSE29618_BCELL_VS_PDC_DAY7_FLU_VACCINE_UP                                                             | 175     | 12        | 3.36E-11 | 7.01E-09   | FCRL2:CD200:STAP1:BANK1:CD72:PAX5:MS4A1:CD19:CD79B:FCER2:CD22:CD79A              |
| Immunologic_signatures | GSE3982_MEMORY_CD4_TCELL_VS_BCELL_DN                                                                  | 181     | 12        | 4.99E-11 | 1.00E-08   | BCL11A:CD200:STAP1:BANK1:HLA-DOB:TSPAN13:CD72:PAX5:MS4A1:CD79B:FCER2:PKIG        |
| Immunologic_signatures | GSE16266_LPS_VS_HEATSHOCK_AND_LPS_STIM_MEF_UP                                                         | 190     | 12        | 8.78E-11 | 1.70E-08   | FCRL1:BCL11A:HLA-DOB:HLA-DOA:CD72:MS4A1:CD19:CD79B:FCER2:CD22:CD79A:TNFRSF13C    |
| Immunologic_signatures | GSE40666_UNTREATED_VS_IFNA_STIM_STAT1_KO_CD8_TCELL_90MIN_DN                                           | 193     | 12        | 1.05E-10 | 1.96E-08   | BEND5:FCRL1:BCL11A:STAP1:TSPAN13:ABCB4:PPAPDC1B:CD72:RAB30:TCL1A:FCER2:CD22      |
| Immunologic_signatures | GSE32901_NAIVE_VS_THI7_NEG_CD4_TCELL_UP                                                               | 168     | 11        | 3.83E-10 | 6.90E-08   | FCRL1:FCRLA:CCR4:BANK1:ZNRD1:MS4A1:CD19:CD79B:CD22:CD79A:TNFRSF13C               |
| Immunologic_signatures | GSE12366_NAIVE_VS_MEMORY_BCELL_UP                                                                     | 174     | 11        | 5.58E-10 | 9.71E-08   | FCRL1:DNASE1L3:CD200:PTPRK:TSPAN13:ABCB4:CD72:TCL1A:CD79B:FCER2:FAM129C          |
| Immunologic_signatures | GSE23568_ID3_KO_VS_WT_CD8_TCELL_DN                                                                    | 193     | 11        | 1.68E-09 | 2.82E-07   | FCRLA:ZNRD1:HLA-DOB:HLA-DOA:CD72:MS4A1:CD19:CD79B:FCER2:CD22:PKIG                |
| Immunologic_signatures | ZAK_PBMC_MRKAD5_HIV_1_GAG_POL_NEF_AGE_20_50YO_1DY_DN                                                  | 781     | 19        | 2.89E-09 | 4.71E-07   | DOA:PAX5:MS4A1:RAB30:BCL7A:TCL1A:CD79B:FAM129C:CD22:CD79A:SLC9A7                 |
| Immunologic_signatures | GSE22886_NAIVE_VS_IGG_IGA_MEMORY_BCELL_UP                                                             | 186     | 10        | 1.69E-08 | 2.67E-06   | DNASE1L3:TSPAN13:ABCB4:CD72:BCL7A:TCL1A:CORO2B:FCER2:CD22:LCARGE                 |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_BLOOD_PLASMA_CELL_UP                                                          | 188     | 10        | 1.87E-08 | 2.87E-06   | CD200:BANK1:HLA-DOB:PTPRK:CD72:MS4A1:TCL1A:CORO2B:CD22:PKIG                      |
| Immunologic_signatures | GSE33424_CD161_HIGH_VS_NEG_CD8_TCELL_UP                                                               | 190     | 10        | 2.07E-08 | 3.09E-06   | FCRLA:HLA-DOB:CD72:MS4A1:CORO2B:CD19:CD79B:FCER2:CD22:PKIG                       |
| Immunologic_signatures | GSE33425_CD8_ALPHAALPHA_VS_ALPHABETA_CD161_HIGH_TCELL_UP                                              | 193     | 10        | 2.40E-08 | 3.48E-06   | FCRLA:HLA-DOB:HLA-DOA:CD72:MS4A1:CD19:CD79B:CD22:CD79A:PKIG                      |
| Immunologic_signatures | GSE29618_MONOCYTE_VS_MDC_DN                                                                           | 176     | 9         | 1.41E-07 | 1.98E-05   | BEND5:AFF3:BANK1:HLA-DOB:HLA-DOA:CD72:BCL7A:CD22:SLC9A7                          |
| Immunologic_signatures | GSE3982_BCELL_VS_CENT_MEMORY_CD4_TCELL_UP                                                             | 183     | 9         | 1.96E-07 | 2.69E-05   | BCL11A:CD200:BANK1:HLA-DOB:PAX5:MS4A1:TCL1A:FCER2:PKIG                           |
| Immunologic_signatures | GSE45739_UNSTIM_VS_ACD3_ACD28_STIM_NRAS_KO_CD4_TCELL_DN                                               | 186     | 9         | 2.25E-07 | 3.01E-05   | HLA-C:PTPRK:CD72:PAX5:BCL7A:CD19:PDE4A:CD79A:PKIG                                |
| Immunologic_signatures | GSE16266_CTRL_VS_LPS_STIM_MEF_DN                                                                      | 192     | 9         | 2.95E-07 | 3.84E-05   | BCL11A:HLA-DOA:CD72:EPS8L2:MS4A1:CD19:CD79B:CD79A:TNFRSF13C                      |
| Immunologic_signatures | GSE3039_ALPHAALPHA_VS_ALPHABETA_CD8_TCELL_DN                                                          | 195     | 9         | 3.36E-07 | 4.28E-05   | FCRL1:BCL11A:HLA-DOB:HLA-DOA:ABCB4:RAB30:CD79B:CD79A:TNFRSF13C                   |
| Immunologic_signatures | GSE6269_FLU_VS_STAPH_AUREUS_INF_PBMC_UP                                                               | 178     | 8         | 1.91E-06 | 2.38E-04   | FCRL2:BCL11A:HLA-DOB:PTPRK:ABCB4:CD72:CD19:CD22                                  |
| Immunologic_signatures | FOURATI_BLOOD_TWINRIX_AGE_65_81YO_RESPONDERS_VS_POOR_RESPONDERS_TRAINING_SET_0DY_NETWORK_INFERENCE_UP | 6       | 3         | 1.98E-06 | 2.41E-04   | BANK1:TSPAN13:MS4A1                                                              |
| Immunologic_signatures | GSE13411_PLASMA_CELL_VS_MEMORY_BCELL_DN                                                               | 188     | 8         | 2.88E-06 | 3.41E-04   | BEND5:BANK1:PTPRK:ABCB4:CD72:CD19:CD79B:PKIG                                     |
| Immunologic_signatures | GSE39556_UNTREATED_VS_3H_POLYIC_INJ_MOUSE_CD8A_DC_UP                                                  | 192     | 8         | 3.36E-06 | 3.90E-04   | HLA-DOB:PTPRK:ABCB4:CD72:MS4A1:BCL7A:TCL1A:CD19                                  |
| Immunologic_signatures | GSE29618_MONOCYTE_VS_MDC_DAY7_FLU_VACCINE_DN                                                          | 179     | 7         | 2.14E-05 | 2.43E-03   | BCL11A:AFF3:BANK1:HLA-DOB:HLA-DOA:CD72:BCL7A                                     |
| Immunologic_signatures | GSE22886_IGA_VS_IGM_MEMORY_BCELL_DN                                                                   | 189     | 7         | 3.04E-05 | 3.37E-03   | FCRL2:DNASE1L3:ABCB4:CD72:BCL7A:TCL1A:CD79B                                      |
| Immunologic_signatures | GSE40274_FOXP3_VS_FOXP3_AND_PBX1_TRANSDUCE_ACTIVATED_CD4_TCELL_UP                                     | 192     | 7         | 3.36E-05 | 3.62E-03   | CCR4:CORO2B:TMEM8A:CD79B:FCER2:CD22:TNFRSF13C                                    |
| Immunologic_signatures | GSE39556_CD8A_DC_VS_NK_CELL_DN                                                                        | 193     | 7         | 3.47E-05 | 3.62E-03   | DNASE1L3:ZKSCAN4:ABCB4:CD72:BCL7A:CD19:CD22                                      |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category               | GeneSet                                                                                                                 | N_genes | N_overlap | P        | adjusted P | Genes                                           |
|------------------------|-------------------------------------------------------------------------------------------------------------------------|---------|-----------|----------|------------|-------------------------------------------------|
| Immunologic_signatures | GSE23502_BM_VS_COLON_TUMOR_MYELOID_DERIVED_SUPPRESSOR_CELL_DN                                                           | 193     | 7         | 3.47E-05 | 3.62E-03   | FCRL1:BCL11A:CD200:HLA-DOB:CD72:FCER2:TNFRSF13C |
| Immunologic_signatures | GSE33425_CD161_INT_VS_NEG_CD8_TCELL_DN                                                                                  | 194     | 7         | 3.59E-05 | 3.67E-03   | FCRLA:HLA-DOB:MS4A1:CD19:CD79B:CD22:PKIG        |
| Immunologic_signatures | GSE6259_FLT3L_INDUCED_33D1_POS_DC_VS_CD8_TCELL_DN                                                                       | 143     | 6         | 5.78E-05 | 5.80E-03   | DNASE1L3:TSPAN13:PPAPDC1B:CD72:CD22:PMEPA1      |
| Immunologic_signatures | GSE21927_SPLEEN_MONOCYTE_VS_GMCSF_GCSF_BONE_MARROW_UP                                                                   | 163     | 6         | 1.19E-04 | 1.17E-02   | TSPAN13:ABCB4:RAB30:BCL7A:TCL1A:FAM129C         |
| Immunologic_signatures | GSE32901_NAIVE_VS_TH1_CD4_TCELL_DN                                                                                      | 164     | 6         | 1.23E-04 | 1.19E-02   | PAX5:MS4A1:CD19:CD79B:CD79A:TNFRSF13C           |
| Immunologic_signatures | FRANCO_BLOOD_SANOFI_PASTEUR_SA_INACTIVATED_INFLUENZA_VACCINE_CORRELATED_WITH_ANTIBODY_RESPONSE_AGE_18_40YO_0DY_POSITIVE | 21      | 3         | 1.25E-04 | 1.19E-02   | FCRLA:TCL1A:CD79B                               |
| Immunologic_signatures | GSE9509_10MIN_VS_30MIN_LPS_STIM_IL10_KO_MACROPHAGE_DN                                                                   | 172     | 6         | 1.60E-04 | 1.49E-02   | BANK1:GET4:PAX5:CD19:CD79B:CD22                 |
| Immunologic_signatures | GSE34205_HEALTHY_VS_FLU_INF_INFANT_PBMG_UP                                                                              | 175     | 6         | 1.76E-04 | 1.61E-02   | FCRLA:BCL11A:HLA-DOB:HLA-DOA:TSPAN13:LARGE      |
| Immunologic_signatures | GSE9509_LPS_VS_LPS_AND_IL10_STIM_IL10_KO_MACROPHAGE_30MIN_DN                                                            | 177     | 6         | 1.87E-04 | 1.68E-02   | CD72:PAX5:CD19:CD79B:FAM129C:CD22               |
| Immunologic_signatures | GSE29618_MONOCYTE_VS_PDC_DN                                                                                             | 180     | 6         | 2.05E-04 | 1.81E-02   | BCL11A:AFF3:DNASE1L3:TSPAN13:BCL7A:SLC9A7       |
| Immunologic_signatures | GSE11057_PBMG_VS_MEM_CD4_TCELL_UP                                                                                       | 182     | 6         | 2.17E-04 | 1.89E-02   | FCRL1:HLA-DOA:PAX5:TCL1A:CD19:CD79A             |
| Immunologic_signatures | GSE13411_NAIVE_VS_IGM_MEMORY_BCELL_UP                                                                                   | 185     | 6         | 2.37E-04 | 2.00E-02   | CD200:NFYA:TCL1A:CEP170B:CORO2B:LARGE           |
| Immunologic_signatures | GSE3982_BCELL_VS_EFF_MEMORY_CD4_TCELL_UP                                                                                | 185     | 6         | 2.37E-04 | 2.00E-02   | CD200:HLA-DOB:PAX5:NDUFAF1:FCER2:PKIG           |
| Immunologic_signatures | ZAK_PBMG_MRKAD5_HIV_1_GAG_POL_NEF_AGE_20_50YO_AD5_NAB_TITERS_GTE_200_VS_LTE_200_1DY_UP                                  | 119     | 5         | 2.45E-04 | 2.03E-02   | FCRL1:BANK1:MS4A1:TCL1A:CD22                    |
| Immunologic_signatures | GSE22886_NAIVE_VS_IGM_MEMORY_BCELL_UP                                                                                   | 187     | 6         | 2.51E-04 | 2.05E-02   | CD200:TSPAN13:BCL7A:RPAP1:CORO2B:LARGE          |
| Immunologic_signatures | GSE43863_DAY6_EFF_VS_DAY150_MEM_TH1_CD4_TCELL_DN                                                                        | 189     | 6         | 2.66E-04 | 2.10E-02   | BEND5:FCRL1:CD200:CD19:FCER2:FAM129C            |
| Immunologic_signatures | GSE17721_12H_VS_24H_LPS_BMDC_DN                                                                                         | 190     | 6         | 2.74E-04 | 2.10E-02   | HLA-C:HLA-DOA:CD72:MS4A1:CD16:TRIM69            |
| Immunologic_signatures | GSE7460_WT_VS_FOXP3_HET_ACT_WITH_TGFB_TCONV_UP                                                                          | 191     | 6         | 2.82E-04 | 2.10E-02   | C5orf63:HLA-DOB:SUN1:RTF1:TMEM8A:LARGE          |
| Immunologic_signatures | GSE43863_TFH_VS_LY6C_LOW_CXCR5NEG_EFFECTOR_CD4_TCELL_UP                                                                 | 191     | 6         | 2.82E-04 | 2.10E-02   | BEND5:FCRL1:VAR5:CD19:FCER2:PMEPA1              |
| Immunologic_signatures | GSE21379_WT_VS_SAP_KO_CD4_TCELL_DN                                                                                      | 192     | 6         | 2.90E-04 | 2.10E-02   | FCRLA:BCL7A:FAM129C:CD22:CD79A:PKIG             |
| Immunologic_signatures | GSE23505_UNTREATED_VS_4DAY_IL6_IL1_IL23_TREATED_CD4_TCELL_DN                                                            | 192     | 6         | 2.90E-04 | 2.10E-02   | BEND5:BANK1:HLA-DOB:HLA-DOA:FCER2:CD22          |
| Immunologic_signatures | GSE40666_UNTREATED_VS_IFNA_STIM_STAT4_KO_EFFECTOR_CD8_TCELL_90MIN_DN                                                    | 192     | 6         | 2.90E-04 | 2.10E-02   | BEND5:CD200:NFYA:PTPRK:ABCB4:PPAPDC1B           |
| Immunologic_signatures | GSE17580_UNINFECTED_VS_S_MANSONI_INF_TEFF_UP                                                                            | 193     | 6         | 2.98E-04 | 2.10E-02   | FCRL1:FCRLA:HLA-DOB:MS4A1:CD79B:CD79A           |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_BM_PLASMA_CELL_UP                                                                               | 193     | 6         | 2.98E-04 | 2.10E-02   | CD200:CD72:MS4A1:TCL1A:CD22:PKIG                |
| Immunologic_signatures | GSE33425_CD161_HIGH_VS_INT_CD8_TCELL_UP                                                                                 | 194     | 6         | 3.06E-04 | 2.10E-02   | FCRLA:HLA-DOB:MS4A1:CD19:CD79B:PKIG             |
| Immunologic_signatures | GSE23502_WT_VS_HDC_KO_MYELOID_DERIVED_SUPPRESSOR_CELL_BM_UP                                                             | 194     | 6         | 3.06E-04 | 2.10E-02   | FCRL1:CD200:STAP1:HLA-DOB:HLA-DOA:TNFRSF13C     |
| Immunologic_signatures | GSE34179_THPOK_KO_VS_WT_VA14I_NKTCCELL_DN                                                                               | 194     | 6         | 3.06E-04 | 2.10E-02   | BCL11A:ZKSCAN4:STK32C:FCER2:PMEPA1:TNFRSF13C    |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category               | GeneSet                                                                  | N_genes | N_overlap | P        | adjusted P | Genes                                                                                               |
|------------------------|--------------------------------------------------------------------------|---------|-----------|----------|------------|-----------------------------------------------------------------------------------------------------|
| Immunologic_signatures | GSE23568_CTRL_TRANSDUCED_VS_WT_CD8_TCELL_UP                              | 195     | 6         | 3.15E-04 | 2.13E-02   | FCRLA:MS4A1:CD19:CD79B:CD22:PKIG                                                                    |
| Immunologic_signatures | GSE7831_1H_VS_4H_INFLUENZA_STIM_PDC_DN                                   | 196     | 6         | 3.23E-04 | 2.16E-02   | AFF3:BANK1:HLA-DOB:COL19A1:CD79A:PKIG                                                               |
| Immunologic_signatures | OVSYANNIKOVA_PBMC_FLUARIX_AGE_55_64YO_RESPONDERS_VS_NONRESPONDERS_0DY_UP | 29      | 3         | 3.35E-04 | 2.21E-02   | SNX22:CD22:PKIG                                                                                     |
| Immunologic_signatures | GSE32255_UNSTIM_VS_4H_LPS_STIM_DC_DN                                     | 145     | 5         | 6.07E-04 | 3.96E-02   | RAB5A:DNASE1L3:TIGIT:CORO2B:CD22                                                                    |
| Cell_type_signature    | TRAVAGLINI_LUNG_B_CELL                                                   | 148     | 23        | 4.25E-29 | 3.53E-26   | PAX5:MS4A1:BCL7A:TCL1A:SNX22:CD19:CD79B:FCER2:FAM129C:CD22:CD79A:PKIG:TNFRSF13C                     |
| Cell_type_signature    | HAY_BONE_MARROW_FOLLICULAR_B_CELL                                        | 128     | 18        | 4.97E-22 | 2.06E-19   | DOA:COL19A1:ABCB4:PPAPDC1B:MS4A1:RAB30:CD19:FCER2:CD22:CD79A:LARGE:TNFRSF13C                        |
| Cell_type_signature    | FAN_EMBRYONIC_CTX_BRAIN_B_CELL                                           | 90      | 16        | 2.18E-21 | 6.03E-19   | FCRL2:FCRL1:FCRLA:AFF3:BANK1:HLA-C:CD72:PAX5:MS4A1:BCL7A:TCL1A:CD19:CD79B:FAM129C:CD22:CD79A        |
| Cell_type_signature    | AIZARANI_LIVER_C34_MHC_II_POS_B_CELLS                                    | 118     | 16        | 2.14E-19 | 4.43E-17   | FCRL2:FCRL1:FCRLA:BCL11A:AFF3:BANK1:PAX5:MS4A1:TCL1A:CD19:CD79B:FAM129C:CD22:CD79A:TNFRSF13C:SLC9A7 |
| Cell_type_signature    | DESCARTES_FETAL_PANCREAS_LYMPHOID_CELLS                                  | 124     | 14        | 6.24E-16 | 1.04E-13   | FCRL2:FCRL1:FCRLA:PDCD1:CCR4:TIGIT:CD72:PAX5:MS4A1:TCL1A:CD19:CD79B:CD22:CD79A                      |
| Cell_type_signature    | DESCARTES_MAIN_FETAL_LYMPHOID_CELLS                                      | 123     | 13        | 1.75E-14 | 2.42E-12   | FCRL2:FCRL1:FCRLA:TIGIT:STAP1:BTN3A2:PAX5:TCL1A:CD19:CD79B:FAM129C:CD22:CD79A                       |
| Cell_type_signature    | DESCARTES_FETAL_LUNG_LYMPHOID_CELLS                                      | 128     | 13        | 2.96E-14 | 3.51E-12   | FCRL2:FCRL1:FCRLA:PDCD1:TIGIT:STAP1:PAX5:MS4A1:TCL1A:CD19:CD79B:FAM129C:CD79A                       |
| Cell_type_signature    | DESCARTES_FETAL_LIVER_LYMPHOID_CELLS                                     | 99      | 12        | 3.53E-14 | 3.66E-12   | FCRL2:FCRL1:FCRLA:TIGIT:CD72:PAX5:MS4A1:TCL1A:CD19:CD79B:FAM129C:CD79A                              |
| Cell_type_signature    | DESCARTES_FETAL_SPLEEN_LYMPHOID_CELLS                                    | 100     | 12        | 4.00E-14 | 3.69E-12   | FCRL2:FCRL1:TIGIT:STAP1:COL19A1:PAX5:MS4A1:FCER2:FAM129C:CD22:CD79A:TNFRSF13C                       |
| Cell_type_signature    | DESCARTES_FETAL_ADRENAL_LYMPHOID_CELLS                                   | 142     | 12        | 2.83E-12 | 2.35E-10   | FCRL2:FCRL1:FCRLA:TIGIT:HLA-DOB:PAX5:MS4A1:TCL1A:CD19:CD79B:FAM129C:CD79A                           |
| Cell_type_signature    | DESCARTES_FETAL_HEART_LYMPHOID_CELLS                                     | 94      | 10        | 2.03E-11 | 1.53E-09   | FCRL2:FCRL1:FCRLA:PDCD1:TIGIT:PAX5:MS4A1:TCL1A:CD19:CD79B                                           |
| Cell_type_signature    | DESCARTES_FETAL_KIDNEY_LYMPHOID_CELLS                                    | 167     | 11        | 3.60E-10 | 2.49E-08   | FCRL2:FCRL1:TIGIT:HLA-DOB:PAX5:MS4A1:TCL1A:CD19:CD79B:FAM129C:CD79A                                 |
| Cell_type_signature    | RUBENSTEIN_SKELETAL_MUSCLE_B_CELLS                                       | 144     | 10        | 1.43E-09 | 9.10E-08   | FCRL1:FCRLA:BANK1:HLA-DOB:PPAPDC1B:MS4A1:TCL1A:CD79B:FCER2:CD79A                                    |
| Cell_type_signature    | DURANTE_ADULT_OLFACTORY_NEUROEPITHELIUM_B_CELLS                          | 29      | 5         | 2.22E-07 | 1.31E-05   | BANK1:MS4A1:CD79B:CD79A:TNFRSF13C                                                                   |
| Cell_type_signature    | HE_LIM_SUN_FETAL_LUNG_C5_CD5_POS_CCL22_NEG_MATURE_B_CELL                 | 151     | 8         | 5.52E-07 | 3.05E-05   | FCRL2:HLA-DOB:COL19A1:PPAPDC1B:FCER2:CLEC17A:PKIG:TNFRSF13C                                         |
| Cell_type_signature    | HAY_BONE_MARROW_CD34_POS_PRE_B                                           | 87      | 6         | 3.37E-06 | 1.73E-04   | AFF3:PAX5:BCL7A:TCL1A:CD79B:FAM129C                                                                 |
| Cell_type_signature    | HE_LIM_SUN_FETAL_LUNG_C2_PDC_CELL                                        | 136     | 7         | 3.55E-06 | 1.73E-04   | BCL11A:DNASE1L3:TSPAN13:BCL7A:TCL1A:FAM129C:PMEPA1                                                  |
| Cell_type_signature    | DESCARTES_FETAL_INTESTINE_LYMPHOID_CELLS                                 | 138     | 7         | 3.91E-06 | 1.80E-04   | CCR4:STAP1:PAX5:MS4A1:TCL1A:CD79B:CD79A                                                             |
| Cell_type_signature    | AIZARANI_LIVER_C22_RESIDENT_B_CELLS_2                                    | 30      | 4         | 1.14E-05 | 4.90E-04   | HLA-DOB:PPAPDC1B:RAB30:CD79A                                                                        |
| Cell_type_signature    | TRAVAGLINI_LUNG_PLASMACYTOID_DENDRITIC_CELL                              | 108     | 6         | 1.18E-05 | 4.90E-04   | BCL11A:AFF3:DNASE1L3:TSPAN13:FAM129C:PMEPA1                                                         |
| Cell_type_signature    | GAO_LARGE_INTESTINE_ADULT_CI_MESENCHYMAL_CELLS                           | 329     | 9         | 2.41E-05 | 9.53E-04   | FCRL2:STAP1:HLA-DOB:RELT:RAB30:TRIM69:CD19:CD79B:CD79A                                              |
| Cell_type_signature    | DESCARTES_FETAL_STOMACH_LYMPHOID_CELLS                                   | 74      | 5         | 2.55E-05 | 9.61E-04   | PAX5:MS4A1:CD79B:FAM129C:CD79A                                                                      |
| Cell_type_signature    | HE_LIM_SUN_FETAL_LUNG_C5_CD5_NEG_MATURE_B_CELL                           | 49      | 4         | 8.20E-05 | 2.96E-03   | HLA-DOB:COL19A1:PPAPDC1B:FCER2                                                                      |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category                          | GeneSet                                         | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                    |
|-----------------------------------|-------------------------------------------------|---------|-----------|----------|------------|----------------------------------------------------------------------------------------------------------|
| Cell_type_signature               | DESCARTES_FETAL_THYMUS_ANTIGEN_PRESENTING_CELLS | 161     | 6         | 1.11E-04 | 3.85E-03   | DNASE1L3:HLA-DOB:TSPAN13:PAX5:MS4A1:SLC9A7                                                               |
| Cell_type_signature               | HE_LIM_SUN_FETAL_LUNG_C2_HSC_ELP_CELL           | 383     | 8         | 4.39E-04 | 1.46E-02   | BEND5:BCL11A:CD200:STAP1:VARS2:CD79B:FAM129C:CD79A                                                       |
| Cell_type_signature               | HE_LIM_SUN_FETAL_LUNG_C2_DC1_CELL               | 309     | 7         | 6.30E-04 | 2.01E-02   | BEND5:DNASE1L3:HLA-DOB:TSPAN13:RAB30:SNX22:SLC9A7                                                        |
| Cell_type_signature               | HE_LIM_SUN_FETAL_LUNG_C2_ADC_1_CELL             | 163     | 5         | 1.03E-03 | 3.16E-02   | CD200:HLA-DOB:TSPAN13:RAB30:ARL17B:ARL17A                                                                |
| Cell_type_signature               | HE_LIM_SUN_FETAL_LUNG_C2_PRE_PDC_DC5_CELL       | 551     | 9         | 1.12E-03 | 3.33E-02   | BCL11A:CD200:BANK1:TSPAN13:PHF19:BCL7A:FAM129C:CD22:PKIG                                                 |
| Cell_type_signature               | HE_LIM_SUN_FETAL_LUNG_C2_HSC_CELL               | 1512    | 16        | 1.67E-03 | 4.77E-02   | BEND5:HENMT1:CD200:STAP1:ZKSCAN4:NFYA:TSPAN13:PPAPDC1B:PHF19:CPT1A:BCL7A:NDUFAF1:RPAP1:CD79B:PKIG:SLC9A7 |
| Cancer_modules                    | MODULE_292                                      | 123     | 11        | 1.30E-11 | 3.34E-09   | FCRL2:FCRLA:CD200:BANK1:CD72:MS4A1:TCL1A:CD19:CD79B:CD22:CD79A                                           |
| Cancer_modules                    | MODULE_436                                      | 125     | 11        | 1.55E-11 | 3.34E-09   | FCRL2:FCRL1:FCRLA:CD200:BANK1:HLA-C:MS4A1:TCL1A:CD79B:FCER2:CD79A                                        |
| Cancer_modules                    | MODULE_345                                      | 114     | 9         | 3.18E-09 | 4.57E-07   | FCRL2:FCRLA:BANK1:HLA-C:MS4A1:TCL1A:CD19:CD79B:CD79A                                                     |
| Cancer_modules                    | MODULE_145                                      | 102     | 8         | 2.63E-08 | 2.83E-06   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                                                        |
| Cancer_modules                    | MODULE_188                                      | 128     | 8         | 1.55E-07 | 1.34E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                                                        |
| Cancer_modules                    | MODULE_361                                      | 137     | 8         | 2.62E-07 | 1.88E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                                                        |
| Cancer_modules                    | MODULE_301                                      | 145     | 8         | 4.05E-07 | 2.49E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                                                        |
| Cancer_modules                    | MODULE_238                                      | 151     | 8         | 5.52E-07 | 2.97E-05   | FCRL2:FCRL1:FCRLA:CD200:BANK1:COL19A1:TCL1A:FCER2                                                        |
| Cancer_modules                    | MODULE_46                                       | 379     | 10        | 1.13E-05 | 5.24E-04   | PDCD1:HLA-C:HLA-DOA:CD72:PAX5:MS4A1:CD19:CD79B:CD22:CD79A                                                |
| Cancer_modules                    | MODULE_75                                       | 382     | 10        | 1.21E-05 | 5.24E-04   | PDCD1:HLA-C:HLA-DOA:CD72:PAX5:MS4A1:CD19:CD79B:CD22:CD79A                                                |
| Cancer_modules                    | MODULE_143                                      | 13      | 3         | 2.77E-05 | 1.09E-03   | HLA-C:HLA-DOB:HLA-DOA                                                                                    |
| Cancer_modules                    | MODULE_41                                       | 537     | 10        | 2.10E-04 | 7.53E-03   | PDCD1:TRIM15:CCHCR1:HLA-DOB:COL19A1:CD72:TCL1A:SCN4A:PDE4A:CD22                                          |
| Cancer_modules                    | MODULE_96                                       | 34      | 3         | 5.40E-04 | 1.66E-02   | CD72:FCER2:CD22                                                                                          |
| Cancer_modules                    | MODULE_410                                      | 34      | 3         | 5.40E-04 | 1.66E-02   | CD72:FCER2:CD22                                                                                          |
| Cancer_modules                    | MODULE_293                                      | 11      | 2         | 1.17E-03 | 3.36E-02   | HLA-C:HLA-DOA                                                                                            |
| Cancer_modules                    | MODULE_208                                      | 110     | 4         | 1.80E-03 | 4.84E-02   | CD200:BANK1:MS4A1:CD79A                                                                                  |
| Cancer_modules                    | MODULE_543                                      | 14      | 2         | 1.91E-03 | 4.85E-02   | HLA-DOB:HLA-DOA                                                                                          |
| Chemical_and_Genetic_perturbation | KLEIN_PRIMARY EFFUSION_LYMPHOMA_DN              | 55      | 8         | 1.74E-10 | 5.94E-07   | BCL11A:CD72:MS4A1:CD19:CD79B:CD22:CD79A:PKIG                                                             |
| Chemical_and_Genetic_perturbation | PASQUALUCCI_LYMPHOMA_BY_GC_STAGE_DN             | 164     | 10        | 5.05E-09 | 8.59E-06   | FCRLA:BCL11A:AFF3:BANK1:PAX5:BCL7A:CD19:FAM129C:CD22:CD79A                                               |
| Chemical_and_Genetic_perturbation | SMID_BREAST_CANCER_NORMAL_LIKE_UP               | 441     | 14        | 1.72E-08 | 1.96E-05   | FCRL2:BCL11A:STAP1:BANK1:BTN3A2:HLA-DOB:CD72:PAX5:MS4A1:TCL1A:CD19:CD79B:CD22:CD79A                      |
| Chemical_and_Genetic_perturbation | HADDAD_B_LYMPHOCYTE_PROGENITOR                  | 250     | 11        | 2.49E-08 | 2.12E-05   | BANK1:PTPRK:CD72:PAX5:MS4A1:TCL1A:CORO2B:CD19:CD79B:CD22:CD79A                                           |

Supplemental Table 4. Gene set enrichment analysis based on FUMA platform using both cis- and trans-CpG-associated genes

| Category                          | GeneSet                              | N_genes | N_overlap | P        | adjusted P | Genes                                                                                         |
|-----------------------------------|--------------------------------------|---------|-----------|----------|------------|-----------------------------------------------------------------------------------------------|
| Chemical_and_Genetic_perturbation | DODD_NASOPHARYNGEAL_CARCINOMA_UP     | 1593    | 24        | 1.95E-07 | 1.33E-04   | 72:PAX5:STK32C:EPS8L2:MS4A1:GDPD5:TCL1A:CEP170B:SNX22:CD19:CD79B:FCER2:FAM129C:CD22:TNFRSF13C |
| Chemical_and_Genetic_perturbation | SHIN_B_CELL_LYMPHOMA_CLUSTER_9       | 19      | 4         | 1.67E-06 | 8.30E-04   | BCL11A:PAX5:CD19:CD79A                                                                        |
| Chemical_and_Genetic_perturbation | ZHAN_MULTIPLE_MYELOMA_CD2_UP         | 43      | 5         | 1.71E-06 | 8.30E-04   | BEND5:PAX5:MS4A1:CD79A:TNFRSF13C                                                              |
| Chemical_and_Genetic_perturbation | BORCZUK_MALIGNANT_MESOTHELIOMA_DN    | 89      | 6         | 3.85E-06 | 1.64E-03   | MS4A1:CD19:CD79B:FCER2:CD22:CD79A                                                             |
| Chemical_and_Genetic_perturbation | KUMAR_TARGETS_OF_MLL_AF9_FUSION      | 382     | 10        | 1.21E-05 | 4.60E-03   | FCRLA:COL19A1:TSPAN13:CD72:PAX5:MS4A1:CORO2B:CD19:FCER2:CD79A                                 |
| Chemical_and_Genetic_perturbation | MORI_PLASMA_CELL_DN                  | 34      | 4         | 1.89E-05 | 6.45E-03   | BCL11A:MS4A1:CD22:TNFRSF13C                                                                   |
| Chemical_and_Genetic_perturbation | MORI_PRE_BI_LYMPHOCYTE_DN            | 78      | 5         | 3.29E-05 | 9.61E-03   | FCRLA:CD72:MS4A1:CD79B:CD22                                                                   |
| Chemical_and_Genetic_perturbation | BOYLAN_MULTIPLE_MYELOMA_C_D_UP       | 130     | 6         | 3.39E-05 | 9.61E-03   | BCL11A:AFF3:PAX5:BCL7A:FAM129C:PKIG                                                           |
| Chemical_and_Genetic_perturbation | SENGUPTA_NASOPHARYNGEAL_CARCINOMA_DN | 340     | 8         | 1.98E-04 | 4.88E-02   | FCRLA:CCDC74A:BANK1:PAX5:MS4A1:TCL1A:CD19:TNFRSF13C                                           |
| Chemical_and_Genetic_perturbation | SMID_BREAST_CANCER_LUMINAL_B_DN      | 534     | 10        | 2.01E-04 | 4.88E-02   | BCL11A:STAP1:BANK1:BTN3A2:HLA-DOB:MS4A1:TCL1A:CD19:CD79B:CD79A                                |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category               | GeneSet                                                                                   | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                                                                                                                                      |
|------------------------|-------------------------------------------------------------------------------------------|---------|-----------|----------|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Curated_gene_sets      | PASQUALUCCI_LYMPHOMA_BY_GC_STAGE_DN                                                       | 172     | 11        | 2.23E-12 | 1.16E-8    | CD19:CD22:PAX5:IGHD:FCRLA:AFF3:NIBAN3:CD79A:BCL11A:BANK1:BCL7A                                                                                                                                                             |
| Curated_gene_sets      | DODD_NASOPHARYNGEAL_CARCCINOMA_DN                                                         | 1816    | 26        | 4.22E-12 | 1.16E-8    | CD19:CD22:PAX5:IGHD:FCRLA:AFF3:NIBAN3:MS4A1:CD79B:CD72:FCRL2:TNFRSF13C:BEND5:FCER2:SNX22                                                                                                                                   |
| Curated_gene_sets      | KLEIN_PRIMARY_EFFUSION_LYMPHOMA_DN                                                        | 58      | 8         | 4.67E-12 | 1.16E-8    | CD19:CD22:CD79A:BCL11A:MS4A1:CD79B:CD72:PKIG                                                                                                                                                                               |
| Curated_gene_sets      | SMID_BREAST_CANCER_NORMAL_LIKE_UP                                                         | 485     | 14        | 9.12E-11 | 1.7E-7     | CD19:CD22:PAX5:IGHD:CD79A:BCL11A:BANK1:MS4A1:CD79B:CD72:FCRL2:BTN3A2:HLA-DOB:STAP1                                                                                                                                         |
| Curated_gene_sets      | HADDAD_B_LYMPHOCYTE_PROGENITOR                                                            | 290     | 11        | 6.08E-10 | 9.07E-7    | CD19:CD22:PAX5:CD79A:BANK1:MS4A1:CD79B:CD72:CORO2B:PTPRK:TCL6                                                                                                                                                              |
| Curated_gene_sets      | ZHAN_MULTIPLE_MYELOMA_CD2_UP                                                              | 48      | 6         | 4.45E-9  | 5.53E-6    | PAX5:CD79A:MS4A1:TNFRSF13C:BEND5:LINC02397                                                                                                                                                                                 |
| Curated_gene_sets      | BORCZUK_MALIGNANT_MESOTHELIOMA_DN                                                         | 106     | 7         | 2.04E-8  | 1.95E-5    | CD19:CD22:IGHD:CD79A:MS4A1:CD79B:FCER2                                                                                                                                                                                     |
| Curated_gene_sets      | KUMAR_TARGETS_OF_MLL_AF9_FUSION                                                           | 408     | 11        | 2.09E-8  | 1.95E-5    | CD19:PAX5:IGHD:FCRLA:CD79A:MS4A1:CD72:FCER2:CORO2B:TSPAN13:COL19A1                                                                                                                                                         |
| Curated_gene_sets      | WP_EXTRAFOLLICULAR_AND_FOLLICULAR_B_CELL_ACTIVATION_BY_SARSCOV2                           | 74      | 6         | 6.33E-8  | 5.25E-5    | CD19:CD22:PAX5:CD79A:MS4A1:PDCCI                                                                                                                                                                                           |
| Curated_gene_sets      | SHIN_B_CELL_LYMPHOMA_CLUSTER_9                                                            | 19      | 4         | 2.1E-7   | 1.57E-4    | CD19:PAX5:CD79A:BCL11A                                                                                                                                                                                                     |
| Curated_gene_sets      | REACTOME_ADAPTIVE_IMMUNE_SYSTEM                                                           | 828     | 13        | 5.53E-7  | 3.75E-4    | CD19:CD22:IGHD:CD79A:CD79B:BTN3A2:HLA-DOB:PDCCI:HLA-C:HLA-DOA:CD16:CD200:TRIM69                                                                                                                                            |
| Curated_gene_sets      | PID_BCR_SPATHWAY                                                                          | 63      | 5         | 9.28E-7  | 5.77E-4    | CD19:CD22:CD79A:CD79B:CD72                                                                                                                                                                                                 |
| Curated_gene_sets      | KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY                                                    | 75      | 5         | 2.22E-6  | 1.27E-3    | CD19:CD22:CD79A:CD79B:CD72                                                                                                                                                                                                 |
| Curated_gene_sets      | MORI_PRE_BI_LYMPHOCYTE_DN                                                                 | 80      | 5         | 3.06E-6  | 1.46E-3    | CD22:FCRLA:MS4A1:CD79B:CD72                                                                                                                                                                                                |
| Curated_gene_sets      | MORI_PLASMA_CELL_DN                                                                       | 36      | 4         | 3.08E-6  | 1.46E-3    | CD22:BCL11A:MS4A1:TNFRSF13C                                                                                                                                                                                                |
| Curated_gene_sets      | BOYLAN_MULTIPLE_MYELOMA_C_D_UP                                                            | 143     | 6         | 3.12E-6  | 1.46E-3    | PAX5:AFF3:NIBAN3:BCL11A:BCL7A:PKIG                                                                                                                                                                                         |
| Curated_gene_sets      | REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_BCR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS | 86      | 5         | 4.37E-6  | 1.92E-3    | CD19:CD22:IGHD:CD79A:CD79B                                                                                                                                                                                                 |
| Curated_gene_sets      | JIANG_MELANOMA_TRM10_LAMINA_PROPRIA                                                       | 91      | 5         | 5.77E-6  | 2.32E-3    | BTN3A2:PDCCI:HLA-C:CLDN1:TIGIT                                                                                                                                                                                             |
| Curated_gene_sets      | SMID_BREAST_CANCER_LUMINAL_B_DN                                                           | 587     | 10        | 5.91E-6  | 2.32E-3    | CD19:IGHD:CD79A:BCL11A:BANK1:MS4A1:CD79B:BTN3A2:HLA-DOB:STAP1                                                                                                                                                              |
| Curated_gene_sets      | MORI_MATURE_B_LYMPHOCYTE_UP                                                               | 95      | 5         | 7.13E-6  | 2.66E-3    | IGHD:MS4A1:FCER2:HLA-DOB:HLA-DOA                                                                                                                                                                                           |
| Curated_gene_sets      | REACTOME_CD22_MEDIATED_BCR_REGULATION                                                     | 61      | 4         | 2.59E-5  | 9.2E-3     | CD22:IGHD:CD79A:CD79B                                                                                                                                                                                                      |
| Curated_gene_sets      | BILBAN_B_CELL_LPL_UP                                                                      | 64      | 4         | 3.13E-5  | 1.06E-2    | IGHD:BCL7A:FCER2:CPT1A                                                                                                                                                                                                     |
| Curated_gene_sets      | PUJANA_ATM_PCC_NETWORK                                                                    | 1394    | 14        | 3.34E-5  | 1.08E-2    | CD19:CD22:CD79A:BCL7A:MS4A1:CD79B:CD72:FCER2:HLA-DOA:CPT1A:RAB30:ZKSCAN4:SIRPB1:CCHCR1                                                                                                                                     |
| Curated_gene_sets      | KEGG_CELL_ADHESION_MOLECULES_CAMS                                                         | 133     | 5         | 3.64E-5  | 1.13E-2    | CD22:HLA-DOB:PDCCI:HLA-C:HLA-DOA                                                                                                                                                                                           |
| Curated_gene_sets      | GAZDA_DIAMOND_BLACKFAN_ANEMIA_ERYTHROID_DN                                                | 471     | 8         | 5.35E-5  | 1.6E-2     | SUN1:CPT1A:FAM30A:NFYA:RPL23A1:PAQR4:MFN2:RPAP1                                                                                                                                                                            |
| Curated_gene_sets      | RYAN_MANTLE_CELL_LYMPHOMA_NOTCH_DIRECT_UP                                                 | 148     | 5         | 6.05E-5  | 1.74E-2    | PAX5:CD72:FCRL2:DNASE1L3:CLEC17A                                                                                                                                                                                           |
| Curated_gene_sets      | SENGUPTA_NASOPHARYNGEAL_CARCCINOMA_DN                                                     | 358     | 7         | 6.64E-5  | 1.84E-2    | CD19:PAX5:FCRLA:BANK1:MS4A1:TNFRSF13C:CCDC74A                                                                                                                                                                              |
| Curated_gene_sets      | GOZGIT_ESR1_TARGETS_DN                                                                    | 786     | 10        | 7.06E-5  | 1.88E-2    | AFF3:PTPRK:TSPAN13:CPT1A:RAB30:PGAP6:PMPEA1:MAPRE3:SLC9A7:LARGE1                                                                                                                                                           |
| Curated_gene_sets      | VECCHI_GASTRIC_CANCER_EARLY_DN                                                            | 382     | 7         | 9.95E-5  | 2.47E-2    | AFF3:CD79A:BEND5:HLA-DOB:STAP1:CLDN1:FAM30A                                                                                                                                                                                |
| Curated_gene_sets      | REACTOME_SIGNALING_BY_THE_B_CELL_RECEPTOR_BCR                                             | 166     | 5         | 1.04E-4  | 2.47E-2    | CD19:CD22:IGHD:CD79A:CD79B                                                                                                                                                                                                 |
| Curated_gene_sets      | KEGG_HEMATOPOIETIC_CELL_LINEAGE                                                           | 87      | 4         | 1.04E-4  | 2.47E-2    | CD19:CD22:MS4A1:FCER2                                                                                                                                                                                                      |
| Curated_gene_sets      | VALK_AML_CLUSTER_10                                                                       | 33      | 3         | 1.07E-4  | 2.47E-2    | CD22:BCL7A:FAM30A                                                                                                                                                                                                          |
| Curated_gene_sets      | KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION                                                  | 88      | 4         | 1.09E-4  | 2.47E-2    | HLA-DOB:HLA-C:HLA-DOA:NFYA                                                                                                                                                                                                 |
| Curated_gene_sets      | KEGG_PRIMARY_IMMUNODEFICIENCY                                                             | 35      | 3         | 1.27E-4  | 2.79E-2    | CD19:CD79A:TNFRSF13C                                                                                                                                                                                                       |
| Curated_gene_sets      | SENGUPTA_NASOPHARYNGEAL_CARCCINOMA_WITH_LMP1_DN                                           | 175     | 5         | 1.33E-4  | 2.84E-2    | MS4A1:CD72:DNASE1L3:LINC00926:LINC02397                                                                                                                                                                                    |
| Curated_gene_sets      | MARTENS_TRETINOIN_RESPONSE_UP                                                             | 855     | 10        | 1.4E-4   | 2.91E-2    | CD22:PAX5:CD79A:CD79B:FCER2:CEP170B:EPS8L2:TCL6:PDCCI:PGAP6                                                                                                                                                                |
| Curated_gene_sets      | KEGG_ALLOGRAFT_REJECTION                                                                  | 37      | 3         | 1.51E-4  | 3.04E-2    | HLA-DOB:HLA-C:HLA-DOA                                                                                                                                                                                                      |
| Curated_gene_sets      | WP_B_CELL_RECEPTOR_SIGNALING                                                              | 97      | 4         | 1.59E-4  | 3.13E-2    | CD19:CD22:CD79A:CD79B                                                                                                                                                                                                      |
| Curated_gene_sets      | POOLA_INVASIVE_BREAST_CANCER_UP                                                           | 292     | 6         | 1.71E-4  | 3.28E-2    | CD19:CD79A:BANK1:MS4A1:CD79B:COL5A2                                                                                                                                                                                        |
| Curated_gene_sets      | SABATES_COLORECTAL_ADENOMA_DN                                                             | 299     | 6         | 1.95E-4  | 3.63E-2    | FCRLA:AFF3:MS4A1:TNFRSF13C:BEND5:STAP1                                                                                                                                                                                     |
| Curated_gene_sets      | KEGG_GRAFT_VERSUS_HOST_DISEASE                                                            | 41      | 3         | 2.05E-4  | 3.71E-2    | HLA-DOB:HLA-C:HLA-DOA                                                                                                                                                                                                      |
| Curated_gene_sets      | WALLACE_PROSTATE_CANCER_RACE_UP                                                           | 303     | 6         | 2.09E-4  | 3.71E-2    | MS4A1:DNASE1L3:BTN3A2:STAP1:HLA-J:CROCCP2                                                                                                                                                                                  |
| Curated_gene_sets      | KEGG_TYPE_1_DIABETES_MELLITUS                                                             | 43      | 3         | 2.36E-4  | 4.1E-2     | HLA-DOB:HLA-C:HLA-DOA                                                                                                                                                                                                      |
| Curated_gene_sets      | SHEDDEN_LUNG_CANCER_GOOD_SURVIVAL_A12                                                     | 318     | 6         | 2.71E-4  | 4.59E-2    | CD19:PAX5:IGHD:CD79A:FCRL2:FAM30A                                                                                                                                                                                          |
| Curated_gene_sets      | KLEIN_TARGETS_OF_BCR_ABL1_FUSION                                                          | 46      | 3         | 2.89E-4  | 4.7E-2     | CD19:PAX5:CD79A                                                                                                                                                                                                            |
| Curated_gene_sets      | MIKKELSEN_MEF_ICP_WITH_H3K27ME3                                                           | 207     | 5         | 2.9E-4   | 4.7E-2     | PAX5:CD72:TNFRSF13C:CUTALP:TRIM15                                                                                                                                                                                          |
| Immunologic_signatures | GSE4984_UNTREATED_VS_GALECTIN1_TREATED_DC_DN                                              | 190     | 28        | 1.42E-40 | 7.43E-37   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:ABC4:PTPRK:BCL7A:PKIG:NIBAN3:FCRL1:FCRLA:LINC00926:AFF3:PLPP5:PMPEA1:CD19:MIR600HG:CORO2B                                            |
| Immunologic_signatures | FOURATI_BLOOD_TWINRIX_AGE_25_83YO_RESPONDERS_VS_POOR_RESPONDERS_0DY_UP                    | 587     | 34        | 3.47E-35 | 9.06E-32   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:ABC4:PTPRK:BCL7A:PKIG:NIBAN3:FCRL1:FCRLA:LINC00926:AFF3:PLPP5:PMPEA1:LARGE1:BCL11A:RAB30:TNFRSF13C:KCNH8:SLC9A7:TCL6:LINC02397:SNX22 |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category               | GeneSet                                                                                                                                 | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                                                                     |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-----------|----------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immunologic_signatures | GSE10325_CD4_TCELL_VS_BCELL_DN                                                                                                          | 195     | 25        | 1.22E-34 | 2.13E-31   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:ABCB4:PTPRK:BCL7A:PKIG:CD19:MIR600HG:LARGE1:BCL11A:RAB30:PAX5:BEND5 |
| Immunologic_signatures | SOBOLEV_PBM_C_PANDEMRIX_AGE_18_64YO_MEDIUM_HIGH_ADVERSE_EVENT_SUBJECTS_IDY_UP                                                           | 39      | 17        | 4.88E-34 | 6.36E-31   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:NIBAN3:FCRL1:FCRLA:LINCO0926:CD19:LARGE1:TNFRSF13C                                           |
| Immunologic_signatures | GSE4748_CYANOBACTERIUM_LPSLIKE_VS_LPS_AND_CYANOBACTERIUM_LPSLIKE_STIM_D_C_3H_UP                                                         | 194     | 24        | 7.08E-33 | 7.39E-30   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:STAP1:HLA-DOB:CD200:IGHD:ABCB4:PTPRK:NIBAN3:FCRL1:FCRLA:AFF3:PLPP5:PMEPA1:MIR600HG:CORO2B:BCL11A:KCNH8:PAX5     |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_MONOCYTE_UP                                                                                                     | 197     | 24        | 1.04E-32 | 9.05E-30   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:ABCB4:PTPRK:BCL7A:CD19:MIR600HG:CORO2B:LARGE1:BCL11A:SLC9A7:PAX5:HLA-DOA  |
| Immunologic_signatures | GSE10325_BCELL_VS_MYELOID_UP                                                                                                            | 197     | 23        | 6.4E-31  | 4.71E-28   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:ABCB4:PTPRK:BCL7A:PKIG:CD19:LARGE1:BCL11A:PAX5:BEND5                |
| Immunologic_signatures | GSE22886_TCELL_VS_BCELL_NAIVE_DN                                                                                                        | 198     | 23        | 7.22E-31 | 4.71E-28   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:BCL7A:PKIG:CD19:MIR600HG:CORO2B:LARGE1:BCL11A:RAB30:SLC9A7:TCL6:HLA-DOA        |
| Immunologic_signatures | GSE29618_BCELL_VS_MONOCYTE_UP                                                                                                           | 195     | 22        | 2.94E-29 | 1.7E-26    | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:IGHD:ABCB4:BCL7A:PKIG:AFF3:CD19:BCL11A:RAB30:PAX5:HLA-DOA                      |
| Immunologic_signatures | GSE22886_CD8_TCELL_VS_BCELL_NAIVE_DN                                                                                                    | 198     | 22        | 4.16E-29 | 2.17E-26   | CD22:BANK1:CD72:TSPAN13:MS4A1:FAM30A:STAP1:HLA-DOB:CD200:IGHD:PTPRK:BCL7A:PKIG:CD19:MIR600HG:CORO2B:LARGE1:BCL11A:RAB30:SLC9A7:TCL6:DNASEIL3              |
| Immunologic_signatures | SOBOLEV_PBM_C_PANDEMRIX_AGE_18_64YO_HIGH_VS_LOW_RESPONDERS_MEDIUM_HIGH_ADVERSE_EVENTS_SCORE_IDY_CORRELATED_WITH_TRANSITIONAL_B_CELLS_UP | 21      | 13        | 5.74E-29 | 2.72E-26   | CD22:BANK1:CD72:TSPAN13:CD79B:FCER2:MS4A1:FCRL2:NIBAN3:FCRL1:FCRLA:CD19:LARGE1                                                                            |
| Immunologic_signatures | GSE29618_BCELL_VS_MONOCYTE_DAY7_FLU_VACCINE_UP                                                                                          | 196     | 20        | 9.33E-26 | 4.06E-23   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:ABCB4:BCL7A:PKIG:CD19:BCL11A:PAX5                                   |
| Immunologic_signatures | GSE10325_LUPUS_CD4_TCELL_VS_LUPUS_BCELL_DN                                                                                              | 196     | 19        | 4.51E-24 | 1.81E-21   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:IGHD:ABCB4:PKIG:CD19:BCL11A:PAX5:BEND5                                         |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_NEUTROPHIL_UP                                                                                                   | 199     | 18        | 2.69E-22 | 1E-19      | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:HLA-DOB:CD200:IGHD:BCL7A:PKIG:CD19:BCL11A:UPF3A:CROCCP2                                |
| Immunologic_signatures | GSE29618_BCELL_VS_MDC_UP                                                                                                                | 194     | 16        | 2.85E-19 | 9.93E-17   | CD22:BANK1:CD72:TSPAN13:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:IGHD:PKIG:CD19:RAB30:PAX5                                                              |
| Immunologic_signatures | GSE22886_CD4_TCELL_VS_BCELL_NAIVE_DN                                                                                                    | 196     | 16        | 3.37E-19 | 1.03E-16   | CD22:BANK1:CD72:TSPAN13:CD79B:MS4A1:FAM30A:CD200:PTPRK:CD19:MIR600HG:CORO2B:LARGE1:BCL11A:SLC9A7:DNASEIL3                                                 |
| Immunologic_signatures | GSE29618_BCELL_VS_PDC_UP                                                                                                                | 196     | 16        | 3.37E-19 | 1.03E-16   | CD22:BANK1:CD72:CD79B:CD79A:FCER2:MS4A1:FCRL2:STAP1:HLA-DOB:IGHD:ABCB4:PKIG:CD19:RAB30:PAX5                                                               |
| Immunologic_signatures | GSE29618_BCELL_VS_MDC_DAY7_FLU_VACCINE_UP                                                                                               | 193     | 14        | 3.31E-16 | 9.2E-14    | CD22:BANK1:CD79B:CD79A:FCER2:MS4A1:FAM30A:FCRL2:STAP1:CD200:PTPRK:PKIG:CD19:PAX5                                                                          |
| Immunologic_signatures | VOIGT_PBM_C_FLUARIX_AGE_50_74YO_FEMALES_VS_MALES_0DY_TO_28D_UP                                                                          | 20      | 8         | 3.35E-16 | 9.2E-14    | CD22:TSPAN13:FCRL2:STAP1:PTPRK:NIBAN3:CD19:TCL6                                                                                                           |
| Immunologic_signatures | GSE10325_LUPUS_BCELL_VS_LUPUS_MYELOID_UP                                                                                                | 195     | 14        | 3.83E-16 | 1E-13      | BANK1:CD72:TSPAN13:CD79B:CD79A:MS4A1:FAM30A:FCRL2:STAP1:IGHD:CD19:BCL11A:PAX5:DNAAF5                                                                      |
| Immunologic_signatures | GSE3982_MEMORY_CD4_TCELL_VS_BCELL_DN                                                                                                    | 197     | 14        | 4.42E-16 | 1.1E-13    | BANK1:CD72:TSPAN13:CD79B:FCER2:MS4A1:FAM30A:STAP1:HLA-DOB:CD200:IGHD:PKIG:BCL11A:PAX5                                                                     |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_DC_UP                                                                                                           | 198     | 14        | 4.75E-16 | 1.13E-13   | CD22:CD72:MS4A1:FAM30A:STAP1:HLA-DOB:CD200:BCL7A:CD19:MIR600HG:CORO2B:LARGE1:BCL11A:HLA-DOA                                                               |
| Immunologic_signatures | GSE45881_CXCR6HI_VS_CXCR1LO_COLONIC_LAMINA_PROPRIA_DN                                                                                   | 199     | 14        | 5.09E-16 | 1.16E-13   | CD72:CD79B:CD79A:FCER2:FCRL2:STAP1:CD200:ABCB4:PKIG:CD19:BCL11A:PAX5:EPS8L2:MAPRE3                                                                        |
| Immunologic_signatures | GSE6269_STAPH_AUREUS_VS_STREP_PNEUMO_INF_PBM_C_DN                                                                                       | 179     | 13        | 3.91E-15 | 8.49E-13   | CD22:BANK1:CD72:CD79A:FCER2:MS4A1:FCRL2:HLA-DOB:IGHD:PKIG:CD19:BCL11A:DNASEIL3                                                                            |
| Immunologic_signatures | GSE29618_BCELL_VS_PDC_DAY7_FLU_VACCINE_UP                                                                                               | 194     | 13        | 1.11E-14 | 2.32E-12   | CD22:BANK1:CD72:CD79B:CD79A:FCER2:MS4A1:FCRL2:STAP1:CD200:IGHD:CD19:PAX5                                                                                  |
| Immunologic_signatures | GSE3982_BCELL_VS_NKCELL_UP                                                                                                              | 197     | 13        | 1.36E-14 | 2.73E-12   | BANK1:CD72:FCER2:FAM30A:FCRL2:HLA-DOB:CD200:PTPRK:PKIG:CD19:BCL11A:EPS8L2:NDUFAF1                                                                         |
| Immunologic_signatures | ZAK_PBM_C_MR_KAD5_HIV_1_GAG_POL_NEF_AGE_20_50YO_IDY_DN                                                                                  | 1012    | 22        | 7.26E-14 | 1.4E-11    | CD22:BANK1:CD79B:CD79A:MS4A1:HLA-DOB:CD200:IGHD:BCL7A:NIBAN3:FCRL1:FCRLA:AFF3:RAB30:SLC9A7:LINC02397:PAX5:HLA-DOA:CCR4:MZT2A:TIGIT:LINC02210              |
| Immunologic_signatures | GSE12366_NAIVE_VS_MEMORY_BCELL_UP                                                                                                       | 195     | 12        | 3.38E-13 | 6.3E-11    | CD72:TSPAN13:CD79B:FCER2:CD200:ABCB4:PTPRK:NIBAN3:FCRL1:LINC00926:MIR600HG:DNASEIL3                                                                       |
| Immunologic_signatures | GSE40666_UNTREATED_VS_IFNA_STIM_STAT1_KO_CD8_TCELL_90MIN_DN                                                                             | 198     | 12        | 4.05E-13 | 7.3E-11    | CD22:CD72:TSPAN13:FCER2:STAP1:ABCB4:FCRL1:PLPP5:BCL11A:RAB30:TCL6:BEND5                                                                                   |
| Immunologic_signatures | GSE16266_LPS_VS_HEATSHOCK_AND_LPS_STIM_MEF_UP                                                                                           | 199     | 12        | 4.3E-13  | 7.49E-11   | CD22:CD72:CD79B:CD79A:FCER2:MS4A1:HLA-DOB:FCRL1:CD19:BCL11A:TNFRSF13C:HLA-DOA                                                                             |
| Immunologic_signatures | GSE32901_NAIVE_VS_TH17_NEG_CD4_TCELL_UP                                                                                                 | 172     | 11        | 2.23E-12 | 3.75E-10   | CD22:BANK1:CD79B:CD79A:MS4A1:FCRL1:FCRLA:CD19:TNFRSF13C:CCR4:POLR1H                                                                                       |
| Immunologic_signatures | GSE23568_ID3_KO_VS_WT_CD8_TCELL_DN                                                                                                      | 200     | 11        | 1.15E-11 | 1.88E-9    | CD22:CD72:CD79B:FCER2:MS4A1:HLA-DOB:PKIG:FCRLA:CD19:HLA-DOA:POLR1H                                                                                        |
| Immunologic_signatures | GSE22886_NAIVE_VS_IGG_IGA_MEMORY_BCELL_UP                                                                                               | 198     | 10        | 2.37E-10 | 3.64E-8    | CD22:CD72:TSPAN13:FCER2:IGHD:ABCB4:BCL7A:CORO2B:LARGE1:DNASEIL3                                                                                           |
| Immunologic_signatures | GSE3982_BCELL_VS_CENT_MEMORY_CD4_TCELL_UP                                                                                               | 198     | 10        | 2.37E-10 | 3.64E-8    | BANK1:FCER2:MS4A1:FAM30A:HLA-DOB:CD200:IGHD:PKIG:BCL11A:PAX5                                                                                              |
| Immunologic_signatures | GSE29618_MONOCYTE_VS_MDC_DN                                                                                                             | 200     | 10        | 2.62E-10 | 3.69E-8    | CD22:BANK1:CD72:HLA-DOB:BCL7A:AFF3:SLC9A7:BEND5:HLA-DOA:MZT2A                                                                                             |
| Immunologic_signatures | GSE33424_CD161_HIGH_VS_NEG_CD8_TCELL_UP                                                                                                 | 200     | 10        | 2.62E-10 | 3.69E-8    | CD22:CD72:CD79B:FCER2:MS4A1:HLA-DOB:PKIG:FCRLA:CD19:CORO2B                                                                                                |
| Immunologic_signatures | GSE33425_CD8_ALPHAALPHA_VS_ALPHABETA_CD161_HIGH_TCELL_UP                                                                                | 200     | 10        | 2.62E-10 | 3.69E-8    | CD22:CD72:CD79B:CD79A:MS4A1:HLA-DOB:PKIG:FCRLA:CD19:HLA-DOA                                                                                               |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category               | GeneSet                                                                                                                  | N_genes | N_overlap | P       | adjusted P | Genes                                                                   |
|------------------------|--------------------------------------------------------------------------------------------------------------------------|---------|-----------|---------|------------|-------------------------------------------------------------------------|
| Immunologic_signatures | GSE45739_UNSTIM_VS_ACD3_ACD28_STIM_NRAS_KO_CD4_TCELL_DN                                                                  | 199     | 9         | 5.11E-9 | 6.8E-7     | CD72:CD79A:FAM30A:PTPRK:BCL7A:PKIG:CD19:PAX5:HLA-C                      |
| Immunologic_signatures | GSE16266_CTRL_VS_LPS_STIM_MEF_DN                                                                                         | 200     | 9         | 5.34E-9 | 6.8E-7     | CD72:CD79B:CD79A:MS4A1:CD19:BCL11A:TNFRSF13C                            |
| Immunologic_signatures | GSE22886_NAIVE_BCELL_VS_BLOOD_PLASMA_CELL_UP                                                                             | 200     | 9         | 5.34E-9 | 6.8E-7     | CD22:BANK1:CD72:MS4A1:HLA-DOB:CD200:PTPRK:PKIG:CORO2B                   |
| Immunologic_signatures | GSE3039_ALPHAALPHA_VS_ALPHABETA_CD8_TCELL_DN                                                                             | 200     | 9         | 5.34E-9 | 6.8E-7     | CD79B:CD79A:HLA-DOB:ABCB4:FCRL1:BCL11A:RAB30:TNFRSF13C:HLA-DOA          |
| Immunologic_signatures | GSE6269_FLU_VS_STAPH_AUREUS_INF_PBMC_UP                                                                                  | 185     | 8         | 5.31E-8 | 6.6E-6     | CD22:CD72:FCRL2:HLA-DOB:ABCB4:PTPRK:CD19:BCL11A                         |
| Immunologic_signatures | GSE13411_PLASMA_CELL_VS_MEMORY_BCELL_DN                                                                                  | 197     | 8         | 8.62E-8 | 1.05E-5    | BANK1:CD72:CD79B:ABCB4:PTPRK:PKIG:CD19:BEND5                            |
| Immunologic_signatures | GSE39556_UNTREATED_VS_3H_POLYIC_INJ_MOUSE_CD8A_DC_UP                                                                     | 199     | 8         | 9.32E-8 | 1.11E-5    | CD72:MS4A1:HLA-DOB:IGHD:ABCB4:PTPRK:BCL7A:CD19                          |
| Immunologic_signatures | GSE29618_MONOCYTE_VS_MDC_DAY7_FLU_VACCINE_DN                                                                             | 200     | 8         | 9.69E-8 | 1.12E-5    | BANK1:CD72:HLA-DOB:BCL7A:AFF3:BCL11A:HLA-DOA:MZT2A                      |
| Immunologic_signatures | FOURATI_BLOOD_TWINRIX_AGE_65_81Y0_RESPONDERS_VS_POOR_RESPONDERS_TRAININ                                                  |         |           |         |            |                                                                         |
| Immunologic_signatures | G_SET_0DY_NETWORK_INFERENCE_UP                                                                                           | 7       | 3         | 7.2E-7  | 8.17E-5    | BANK1:TSPAN13:MS4A1                                                     |
| Immunologic_signatures | GSE12366_GC_VS_NAIVE_BCELL_DN                                                                                            | 195     | 7         | 1.3E-6  | 1.44E-4    | CD72:FCER2:ABCB4:PMEPA1:MIR600HG:BTN3A2:GARS1-DT                        |
| Immunologic_signatures | GSE13411_NAIVE_VS_IGM_MEMORY_BCELL_UP                                                                                    | 196     | 7         | 1.35E-6 | 1.44E-4    | CD200:IGHD:MIR600HG:CORO2B:LARGE1:NFYA:CEP170B                          |
| Immunologic_signatures | GSE11057_PBMC_VS_MEM_CD4_TCELL_UP                                                                                        | 197     | 7         | 1.39E-6 | 1.44E-4    | CD79A:IGHD:FCRL1:CD19:PAX5:HLA-DOA:SIRPB1                               |
| Immunologic_signatures | GSE22886_NAIVE_VS_IGM_MEMORY_BCELL_UP                                                                                    | 197     | 7         | 1.39E-6 | 1.44E-4    | TSPAN13:CD200:IGHD:BCL7A:CORO2B:LARGE1:RPAP1                            |
| Immunologic_signatures | GSE39556_CD8A_DC_VS_NK_CELL_DN                                                                                           | 198     | 7         | 1.44E-6 | 1.44E-4    | CD22:CD72:ABCB4:BCL7A:CD19:DNASE1L3:ZKSCAN4                             |
| Immunologic_signatures | GSE3982_BCELL_VS_EFF_MEMORY_CD4_TCELL_UP                                                                                 | 198     | 7         | 1.44E-6 | 1.44E-4    | FCER2:FAM30A:HLA-DOB:CD200:PKIG:PAX5:NDUFAF1                            |
| Immunologic_signatures | GSE22886_IGA_VS_IGM_MEMORY_BCELL_DN                                                                                      | 200     | 7         | 1.54E-6 | 1.44E-4    | CD72:CD79B:FCRL2:IGHD:ABCB4:BCL7A:DNASE1L3                              |
| Immunologic_signatures | GSE23502_BM_VS_COLON_TUMOR_MYELOID_DERIVED_SUPPRESSOR_CELL_DN                                                            | 200     | 7         | 1.54E-6 | 1.44E-4    | CD72:FCER2:HLA-DOB:CD200:FCRL1:BCL11A:TNFRSF13C                         |
| Immunologic_signatures | GSE33425_CD161_INT_VS_NEG_CD8_TCELL_DN                                                                                   | 200     | 7         | 1.54E-6 | 1.44E-4    | CD22:CD79B:MS4A1:HLA-DOB:PKIG:FCRLA:CD19                                |
| Immunologic_signatures | GSE40274_FOXP3_VS_FOXP3_AND_PBX1_TRANSDUCED_ACTIVATED_CD4_TCELL_UP                                                       | 200     | 7         | 1.54E-6 | 1.44E-4    | CD22:CD79B:FCER2:CORO2B:TNFRSF13C:CCR4:PGAP6                            |
| Immunologic_signatures | OVSYANNIKOVA_PBMC_FLUARIX_AGE_55_64Y0_RESPONDERS_VS_NONRESPONDERS_0DY_UP                                                 | 31      | 4         | 1.66E-6 | 1.52E-4    | CD22:FAM30A:PKIG:SNX22                                                  |
| Immunologic_signatures | GSE6259_FLT3L_INDUCED_33D1_POS_DC_VS_CD8_TCELL_DN                                                                        | 150     | 6         | 4.12E-6 | 3.71E-4    | CD22:CD72:TSPAN13:PLPP5:PMEPA1:DNASE1L3                                 |
| Immunologic_signatures | NAKAYA_B_CELL_FLUMIST_AGE_18_50YO_7DY_UP                                                                                 | 475     | 9         | 7.58E-6 | 6.71E-4    | CD22:FCRL2:CD200:IGHD:ABCB4:LARGE1:TCL6:HLA-DOA:ARL17B                  |
| Immunologic_signatures | GSE32901_NAIVE_VS_TH1_CD4_TCELL_DN                                                                                       | 170     | 6         | 8.44E-6 | 7.34E-4    | CD79B:CD79A:MS4A1:CD19:TNFRSF13C:PAX5                                   |
| Immunologic_signatures | GSE21927_SPLEEN_MONOCYTE_VS_GMCSF_GCSF_BONE_MARROW_UP                                                                    | 189     | 6         | 1.54E-5 | 1.32E-3    | TSPAN13:ABCB4:BCL7A:NIBAN3:LINC00926:RAB30                              |
| Immunologic_signatures | GSE9509_LPS_VS_LPS_AND_IL10_STIM_IL10_KO_MACROPHAGE_30MIN_DN                                                             | 193     | 6         | 1.74E-5 | 1.32E-3    | CD22:CD72:CD79B:NIBAN3:CD19:PAX5                                        |
| Immunologic_signatures | GSE9509_10MIN_VS_30MIN_LPS_STIM_IL10_KO_MACROPHAGE_DN                                                                    | 194     | 6         | 1.79E-5 | 1.32E-3    | CD22:BANK1:CD79B:CD19:PAX5:GET4                                         |
| Immunologic_signatures | GSE11057_NAIVE_VS_MEMORY_CD4_TCELL_UP                                                                                    | 195     | 6         | 1.84E-5 | 1.32E-3    | STAP1:PTPRK:PKIG:MIR600HG:BEND5:COL5A2                                  |
| Immunologic_signatures | GSE12845_PRE_GC_VS_DARKZONE_GC_TONSIL_BCELL_UP                                                                           | 196     | 6         | 1.89E-5 | 1.32E-3    | BANK1:CD72:CD200:IGHD:PTPRK:HLA-C                                       |
| Immunologic_signatures | GSE29618_MONOCYTE_VS_PDC_DN                                                                                              | 197     | 6         | 1.95E-5 | 1.32E-3    | TSPAN13:BCL7A:AFF3:BCL11A:SLC9A7:DNASE1L3                               |
| Immunologic_signatures | GSE3982_MAST_CELL_VS_BCELL_DN                                                                                            | 197     | 6         | 1.95E-5 | 1.32E-3    | CD72:FCER2:FAM30A:HLA-DOB:BCL7A:PAX5                                    |
| Immunologic_signatures | GSE34205_HEALTHY_VS_FLU_INF_INFANT_PBMC_UP                                                                               | 198     | 6         | 2E-5    | 1.32E-3    | TSPAN13:HLA-DOB:FCRLA:LARGE1:BCL11A:HLA-DOA                             |
| Immunologic_signatures | GSE12845_IGD_POS_VS_NEG_BLOOD_BCELL_UP                                                                                   | 199     | 6         | 2.06E-5 | 1.32E-3    | CD22:CD79A:FCER2:BCL7A:CD19:TCL6                                        |
| Immunologic_signatures | GSE21379_WT_VS_SAP_KO_CD4_TCELL_DN                                                                                       | 199     | 6         | 2.06E-5 | 1.32E-3    | CD22:CD79A:BCL7A:PKIG:NIBAN3:FCRLA                                      |
| Immunologic_signatures | GSE23505_UNTREATED_VS_4DAY_IL6_IL1_IL23_TREATED_CD4_TCELL_DN                                                             | 199     | 6         | 2.06E-5 | 1.32E-3    | CD22:BANK1:FCER2:HLA-DOB:BEND5:HLA-DOA                                  |
| Immunologic_signatures | GSE33292_DN3_THYMOCYTE_VS_TCF1_KO_TCELL_LYMPHOMA_UP                                                                      | 199     | 6         | 2.06E-5 | 1.32E-3    | MS4A1:HLA-DOB:IGHD:PTPRK:PKIG:NDUFAF1                                   |
| Immunologic_signatures | GSE34179_THPOK_KO_VS_WT_VA141_NKTCCELL_DN                                                                                | 199     | 6         | 2.06E-5 | 1.32E-3    | FCER2:PMEPA1:BCL11A:TNFRSF13C:ZKSCAN4:STK32C                            |
| Immunologic_signatures | GSE40666_UNTREATED_VS_IFNA_STIM_STAT4_KO_EFFECTOR_CD8_TCELL_90MIN_DN                                                     | 199     | 6         | 2.06E-5 | 1.32E-3    | CD200:ABCB4:PTPRK:PLPP5:BEND5:NFYA                                      |
| Immunologic_signatures | GSE43863_DAY6_EFF_VS_DAY150_MEM_TH1_CD4_TCELL_DN                                                                         | 199     | 6         | 2.06E-5 | 1.32E-3    | FCER2:CD200:NIBAN3:FCRL1:CD19:BEND5                                     |
| Immunologic_signatures | GSE43863_TFH_VS_LY6C_LOW_CXCR5NEG_EFFECTOR_CD4_TCELL_UP                                                                  | 199     | 6         | 2.06E-5 | 1.32E-3    | FCER2:FCRL1:PMEPA1:CD19:BEND5:VAR52                                     |
| Immunologic_signatures | GSE7831_1H_VS_4H_INFLUENZA_STIM_PDC_DN                                                                                   | 199     | 6         | 2.06E-5 | 1.32E-3    | BANK1:CD79A:HLA-DOB:PKIG:AFF3:COL19A1                                   |
| Immunologic_signatures | GSE17580_UNINFECTED_VS_S_MANSONI_INF_TEFF_UP                                                                             | 200     | 6         | 2.12E-5 | 1.32E-3    | CD79B:CD79A:MS4A1:HLA-DOB:FCRL1:FCRLA                                   |
| Immunologic_signatures | GSE17721_12H_VS_24H_LPS_BMDC_DN                                                                                          | 200     | 6         | 2.12E-5 | 1.32E-3    | CD72:MS4A1:HLA-DOA:HLA-C:TRIM69:CD16                                    |
| Immunologic_signatures | GSE23502_WT_VS_HDC_KO_MYELOID_DERIVED_SUPPRESSOR_CELL_BM_UP                                                              | 200     | 6         | 2.12E-5 | 1.32E-3    | STAP1:HLA-DOB:CD200:FCRL1:TNFRSF13C:HLA-DOA                             |
| Immunologic_signatures | GSE23568_CTRL_TRANSDUCED_VS_WT_CD8_TCELL_UP                                                                              | 200     | 6         | 2.12E-5 | 1.32E-3    | CD22:CD79B:MS4A1:PKIG:FCRLA:CD19                                        |
| Immunologic_signatures | GSE33425_CD161_HIGH_VS_INT_CD8_TCELL_UP                                                                                  | 200     | 6         | 2.12E-5 | 1.32E-3    | CD79B:MS4A1:HLA-DOB:PKIG:FCRLA:CD19                                     |
| Immunologic_signatures | GSE7460_WT_VS_FOXP3_HET_ACT_WITH_TGFB_TCONV_UP                                                                           | 200     | 6         | 2.12E-5 | 1.32E-3    | HLA-DOB:LARGE1:PGAP6:SUN1:RTF1:C5orf63                                  |
| Immunologic_signatures | GSE7764_NKCELL_VS_SPLENOCYTE_DN                                                                                          | 200     | 6         | 2.12E-5 | 1.32E-3    | CD79A:STAP1:CD19:RAB30:HLA-DOA:SIRPB1                                   |
| Immunologic_signatures | FRANCO_BLOOD_SANOFI_PASTEUR_SA_INACTIVATED_INFLUENZA_VACCINE_CORRELATE_D_WITH_ANTIBODY_RESPONSE_AGE_18_40YO_0DY_POSITIVE | 22      | 3         | 3.07E-5 | 1.89E-3    | CD79B:FCRLA:MIR600HG                                                    |
| Immunologic_signatures | NAKAYA_PBMC_FLUARIX_FLUVIRIN_AGE_18_50YO_CORRELATED_WITH_HAI_28DY_RESPO                                                  |         |           |         |            |                                                                         |
| Immunologic_signatures | NSE_AT_7DY_NEGATIVE                                                                                                      | 474     | 8         | 5.59E-5 | 3.39E-3    | BANK1:MS4A1:FCRL2:STAP1:NIBAN3:FCRL1:AFF3:RAB5A                         |
| Immunologic_signatures | GSE32255_UNSTIM_VS_4H_LPS_STIM_DC_DN                                                                                     | 154     | 5         | 7.3E-5  | 4.38E-3    | CD22:CORO2B:DNASE1L3:TIGIT:RAB5A                                        |
| Immunologic_signatures | HARALAMBIEVA_PBMC_M_M_R_II_AGE_11_22YO_VACCINATED_VS_UNVACCINATED_7YR_UP                                                 | 973     | 11        | 8.7E-5  | 5.16E-3    | CD72:TSPAN13:STAP1:HLA-DOB:CD200:CORO2B:PAX5:DNASE1L3:TRIM69:PCDC1:HCG4 |
| Immunologic_signatures | GSE37301_PRO_BCELL_VS_RAG2_KO_NK_CELL_DN                                                                                 | 179     | 5         | 1.48E-4 | 8.68E-3    | BANK1:CD79B:CD200:CCR4:CLDN1                                            |
| Immunologic_signatures | GSE21927_UNTREATED_VS_GMCSF_IL6_TREATED_BONE_MARROW_DN                                                                   | 185     | 5         | 1.73E-4 | 9.57E-3    | CD79B:FAM30A:ABCB4:FCRL1:RAB30                                          |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category                 | GeneSet                                                                 | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                                                    |
|--------------------------|-------------------------------------------------------------------------|---------|-----------|----------|------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Immunologic_signatures   | NAKAYA_PBMF_FLUARIX_FLUVIRIN_AGE_18_50YO_7DY_UP                         | 573     | 8         | 2.05E-4  | 9.57E-3    | CD79B:CD79A:MS4A1:FAM30A:IGHD:PLPP5:UPF3A:CDC16                                                                                          |
| Immunologic_signatures   | GSE11057_CD4_CENT_MEM_VS_PBMF_DN                                        | 195     | 5         | 2.2E-4   | 9.57E-3    | IGHD:CD19:PAX5:HLA-DOA:SIRPB1                                                                                                            |
| Immunologic_signatures   | GSE1740_MCSF_VS_MCSF_AND_IFNG_DAY2_DERIVED_MACROPHAGE_UP                | 196     | 5         | 2.26E-4  | 9.57E-3    | HLA-DOB:RAB30:BTN3A2:GARS1-DT:TRIM69                                                                                                     |
| Immunologic_signatures   | GSE21670_STAT3_KO_VS_WT_CD4_TCELL_UP                                    | 197     | 5         | 2.31E-4  | 9.57E-3    | CD72:IGHD:PMPEA1:TNFRSF13C:HLA-J                                                                                                         |
| Immunologic_signatures   | GSE3982_BCELL_VS_TH2_UP                                                 | 197     | 5         | 2.31E-4  | 9.57E-3    | FAM30A:HLA-DOB:IGHD:PKIG:ZKSCAN4                                                                                                         |
| Immunologic_signatures   | GSE3982_DC_VS_BCELL_DN                                                  | 197     | 5         | 2.31E-4  | 9.57E-3    | CD72:FAM30A:HLA-DOB:PKIG:BCL11A                                                                                                          |
| Immunologic_signatures   | GSE22886_IGM_MEMORY_BCELL_VS_BLOOD_PLASMA_CELL_UP                       | 198     | 5         | 2.36E-4  | 9.57E-3    | BANK1:STAP1:HLA-DOB:PKIG:PAX5                                                                                                            |
| Immunologic_signatures   | GSE26030_UNSTIM_VS_RESTIM_TH17_DAY5_POST_POLARIZATION_DN                | 198     | 5         | 2.36E-4  | 9.57E-3    | FCER2:BCL7A:RAB30:DNASE1L3:MFN2                                                                                                          |
| Immunologic_signatures   | GSE2770_UNTREATED_VS_ACT_CD4_TCELL_2H_UP                                | 198     | 5         | 2.36E-4  | 9.57E-3    | CD22:CD72:CD79A:AFF3:HLA-DOA                                                                                                             |
| Immunologic_signatures   | GSE17580_UNINFECTED_VS_S_MANSONI_INF_TREG_UP                            | 199     | 5         | 2.42E-4  | 9.57E-3    | CD22:FCER2:MS4A1:CD19:HLA-C                                                                                                              |
| GO_BP                    | GOBP_ACTIVATION_OF_IMMUNE_RESPONSE                                      | 583     | 10        | 5.57E-6  | 3.9E-3     | CD19:MS4A1:CD79A:CD79B:CD22:BTN3A2:BANK1:STAP1:IGHD:TRIM15                                                                               |
| GO_BP                    | GOBP_ADAPTIVE_IMMUNE_RESPONSE                                           | 756     | 11        | 8.81E-6  | 4.89E-3    | CD19:CD79A:CD79B:FCER2:PDCD1:BTN3A2:HLA-C:TNFRSF13C:IGHD:HLA-DOA:HLA-DOB                                                                 |
| GO_BP                    | GOBP_ANTIGEN_RECEPTOR_MEDIATED_SIGNALING_PATHWAY                        | 210     | 9         | 8.17E-9  | 1.46E-5    | CD19:MS4A1:CD79A:CD79B:CD22:BTN3A2:BANK1:STAP1:IGHD                                                                                      |
| GO_BP                    | GOBP_B_CELL_ACTIVATION                                                  | 278     | 9         | 9.11E-8  | 9.78E-5    | CD19:MS4A1:CD79A:CD79B:CD22:TNFRSF13C:FCRL1:BANK1:PAX5                                                                                   |
| GO_BP                    | GOBP_B_CELL_DIFFERENTIATION                                             | 155     | 5         | 7.53E-5  | 2.1E-2     | CD19:MS4A1:CD79A:CD79B:PAX5                                                                                                              |
| GO_BP                    | GOBP_B_CELL_PROLIFERATION                                               | 104     | 5         | 1.11E-5  | 5.67E-3    | CD19:MS4A1:CD79A:CD22:TNFRSF13C                                                                                                          |
| GO_BP                    | GOBP_B_CELL_RECEPTOR_SIGNALING_PATHWAY                                  | 78      | 8         | 5.46E-11 | 2.93E-7    | CD19:MS4A1:CD79A:CD79B:CD22:BANK1:STAP1:IGHD                                                                                             |
| GO_BP                    | GOBP_CELL_ACTIVATION                                                    | 1126    | 18        | 2.28E-9  | 6.68E-6    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:PDCD1:TNFRSF13C:CD200:SIRPB1:TIGIT:FCRL1:BANK1:STAP1:HLA-DOA:HLA-DOB:DNASE1L3:PAX5                     |
| GO_BP                    | GOBP_IMMUNE_EFFECTOR_PROCESS                                            | 718     | 9         | 1.83E-4  | 3.78E-2    | CD19:CD22:FCER2:PDCD1:BTN3A2:HLA-C:STAP1:IGHD:DNASE1L3                                                                                   |
| GO_BP                    | GOBP_IMMUNE_RESPONSE_REGULATING_CELL_SURFACE_RECEPTOR_SIGNALING_PATHWAY | 368     | 10        | 8.78E-8  | 9.78E-5    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:BTN3A2:BANK1:STAP1:IGHD                                                                                |
| GO_BP                    | GOBP_IMMUNE_RESPONSE_REGULATING_SIGNALING_PATHWAY                       | 577     | 11        | 6.67E-7  | 6.32E-4    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:BTN3A2:BANK1:STAP1:IGHD:TRIM15                                                                         |
| GO_BP                    | GOBP_LEUKOCYTE_MEDIATED_IMMUNITY                                        | 469     | 8         | 5.19E-5  | 1.6E-2     | CD19:FCER2:PDCD1:BTN3A2:HLA-C:STAP1:IGHD:DNASE1L3                                                                                        |
| GO_BP                    | GOBP_LYMPHOCYTE_ACTIVATION                                              | 807     | 14        | 5.85E-8  | 8.57E-5    | CD19:MS4A1:CD79A:CD79B:CD22:PDCD1:TNFRSF13C:SIRPB1:TIGIT:FCRL1:BANK1:HLA-DOA:HLA-DOB:PAX5                                                |
| GO_BP                    | GOBP_NEGATIVE_REGULATION_OF_IMMUNE_SYSTEM_PROCESS                       | 535     | 8         | 1.29E-4  | 3.01E-2    | CD22:PDCD1:CD200:TIGIT:BANK1:STAP1:HLA-DOA:HLA-DOB                                                                                       |
| GO_BP                    | GOBP_POSITIVE_REGULATION_OF_IMMUNE_RESPONSE                             | 783     | 15        | 5.11E-9  | 1.03E-5    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:BTN3A2:HLA-C:TNFRSF13C:SIRPB1:STAP1:IGHD:HLA-DOA:HLA-DOB:TRIM15:CPT1A                                  |
| GO_BP                    | GOBP_POSITIVE_REGULATION_OF_IMMUNE_SYSTEM_PROCESS                       | 1120    | 17        | 1.42E-8  | 2.28E-5    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:BTN3A2:HLA-C:TNFRSF13C:SIRPB1:BANK1:STAP1:IGHD:HLA-DOA:HLA-DOB:TRIM15:CPT1A                            |
| GO_BP                    | GOBP_REGULATION_OF_B_CELL_RECEPTOR_SIGNALING_PATHWAY                    | 24      | 3         | 4.03E-5  | 1.38E-2    | CD19:CD22:STAP1                                                                                                                          |
| GO_BP                    | GOBP_REGULATION_OF_CELL_ACTIVATION                                      | 638     | 11        | 1.77E-6  | 1.58E-3    | CD19:CD22:PDCD1:TNFRSF13C:CD200:SIRPB1:TIGIT:BANK1:STAP1:HLA-DOA:HLA-DOB                                                                 |
| GO_BP                    | GOBP_REGULATION_OF_IMMUNE_RESPONSE                                      | 981     | 17        | 2.01E-9  | 6.68E-6    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:PDCD1:BTN3A2:HLA-C:TNFRSF13C:CD200:SIRPB1:TIGIT:BANK1:STAP1:IGHD:HLA-DOA:HLA-DOB:TRIM15:CPT1A          |
| GO_BP                    | GOBP_REGULATION_OF_IMMUNE_SYSTEM_PROCESS                                | 1626    | 21        | 4.04E-9  | 9.29E-6    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:PDCD1:BTN3A2:HLA-C:TNFRSF13C:CD200:SIRPB1:TIGIT:BANK1:STAP1:IGHD:HLA-DOA:HLA-DOB:TRIM15:CPT1A:DNASE1L3 |
| GO_BP                    | GOBP_REGULATION_OF_LYMPHOCYTE_ACTIVATION                                | 511     | 9         | 1.35E-5  | 6.41E-3    | CD19:CD22:PDCD1:TNFRSF13C:SIRPB1:TIGIT:BANK1:HLA-DOA:HLA-DOB                                                                             |
| GO_CC                    | GOCC_CELL_SURFACE                                                       | 907     | 20        | 8.65E-13 | 1.39E-8    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:PDCD1:BTN3A2:HLA-C:TNFRSF13C:CCR4:FCRL2:FCRLA:CLEC17A:CD200:SIRPB1:TIGIT:FCRL1:PTPRK:CLDN1             |
| GO_CC                    | GOCC_EXTERNAL_SIDE_OF_PLASMA_MEMBRANE                                   | 405     | 14        | 8.45E-12 | 6.81E-8    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:PDCD1:BTN3A2:HLA-C:TNFRSF13C:CCR4:FCRL2:FCRLA:CLEC17A                                                  |
| GO_CC                    | GOCC_MHC_PROTEIN_COMPLEX                                                | 26      | 3         | 5.15E-5  | 1.6E-2     | HLA-C:HLA-DOA:HLA-DOB                                                                                                                    |
| GO_CC                    | GOCC_SIDE_OF_MEMBRANE                                                   | 742     | 15        | 2.49E-9  | 6.68E-6    | CD19:MS4A1:CD79A:CD79B:CD22:FCER2:PDCD1:BTN3A2:HLA-C:TNFRSF13C:CCR4:FCRL2:FCRLA:CLEC17A:RAB5A                                            |
| GO_MF                    | GOMF_IMMUNOGLOBULIN_BINDING                                             | 26      | 3         | 5.15E-5  | 1.6E-2     | MS4A1:CD22:FCER2                                                                                                                         |
| GO_MF                    | GOMF_MHC_CLASS_II_PROTEIN_COMPLEX_BINDING                               | 27      | 3         | 5.78E-5  | 1.69E-2    | MS4A1:HLA-DOA:HLA-DOB                                                                                                                    |
| GO_MF                    | GOMF_MHC_PROTEIN_COMPLEX_BINDING                                        | 37      | 3         | 1.51E-4  | 3.41E-2    | MS4A1:HLA-DOA:HLA-DOB                                                                                                                    |
| GO_MF                    | GOMF_MOLECULAR_TRANSDUCER_ACTIVITY                                      | 1534    | 14        | 9.27E-5  | 2.49E-2    | CD79A:CD79B:FCER2:PDCD1:TNFRSF13C:CCR4:FCRL2:FCRLA:FCRL1:PTPRK:HLA-DOA:HLA-DOB:CD72:PAQR4                                                |
| Human Phenotype Ontology | HP_ABNORMAL ABDOMEN MORPHOLOGY                                          | 823     | 10        | 1.03E-4  | 2.63E-2    | CD19:MS4A1:TNFRSF13C:CPT1A:DNASE1L3:SCN4A:ABC4:BCL11A:MFN2:NDUFAF1                                                                       |
| Human Phenotype Ontology | HP_ABNORMAL B CELL MORPHOLOGY                                           | 99      | 4         | 1.72E-4  | 3.71E-2    | CD19:MS4A1:CD79A:CD79B                                                                                                                   |
| Human Phenotype Ontology | HP_ABNORMAL BRONCHUS MORPHOLOGY                                         | 216     | 6         | 3.27E-5  | 1.22E-2    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5                                                                                                  |
| Human Phenotype Ontology | HP_ABNORMAL CONJUNCTIVA MORPHOLOGY                                      | 170     | 5         | 1.16E-4  | 2.8E-2     | CD19:CD79A:CD79B:TNFRSF13C:DNASE1L3                                                                                                      |
| Human Phenotype Ontology | HP_ABNORMAL JOINT MORPHOLOGY                                            | 1233    | 13        | 3.96E-5  | 1.38E-2    | CD79A:CD79B:PDCD1:HLA-C:BANK1:DNASE1L3:SCN4A:COL5A2:MFN2:KANSL1:LARGE1:GET4:AFF3                                                         |
| Human Phenotype Ontology | HP_ABNORMAL LIVER MORPHOLOGY                                            | 896     | 10        | 2.04E-4  | 4.13E-2    | CD19:CD79A:CD79B:TNFRSF13C:CPT1A:DNASE1L3:SCN4A:ABC4:MFN2:NDUFAF1                                                                        |
| Human Phenotype Ontology | HP_ABNORMAL LYMPH NODE MORPHOLOGY                                       | 260     | 6         | 9.11E-5  | 2.49E-2    | CD19:MS4A1:PDCD1:TNFRSF13C:BANK1:DNASE1L3                                                                                                |
| Human Phenotype Ontology | HP_ABNORMAL MIDDLE EAR MORPHOLOGY                                       | 386     | 7         | 1.06E-4  | 2.67E-2    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5:KANSL1                                                                                           |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category                     | GeneSet                                              | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                       |
|------------------------------|------------------------------------------------------|---------|-----------|----------|------------|-------------------------------------------------------------------------------------------------------------|
| Human Phenotype Ontology     | HP_ABNORMAL_PARANASAL_SINUS_MORPHOLOGY               | 191     | 6         | 1.64E-5  | 7.32E-3    | CD19:CD79A:CD79B:TNFRSF13C:DNAAF5:COL5A2                                                                    |
| Human Phenotype Ontology     | HP_ABNORMAL_T_CELL_MORPHOLOGY                        | 118     | 5         | 2.05E-5  | 8.24E-3    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C                                                                            |
| Human Phenotype Ontology     | HP_ABNORMAL_TRACHEOBRONCHIAL_MORPHOLOGY              | 380     | 7         | 9.63E-5  | 2.52E-2    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5:KANSL1                                                              |
| Human Phenotype Ontology     | HP_ABNORMALITY_OF_HUMORAL_IMMUNITY                   | 331     | 8         | 4.27E-6  | 3.28E-3    | CD19:MS4A1:CD79A:CD79B:PDCD1:TNFRSF13C:BANK1:DNASE1L3                                                       |
| Human Phenotype Ontology     | HP_ABNORMALITY_OF_IMMUNE_SYSTEM_PHYSIOLOGY           | 1787    | 16        | 3.54E-5  | 1.27E-2    | CD19:MS4A1:CD79A:CD79B:PDCD1:HLA-C:TNFRSF13C:BANK1:DNASE1L3:DNAAF5:SCN4A:ZFP57:ABCB4:COL5A2:BCL11A:KANSL1   |
| Human Phenotype Ontology     | HP_ABNORMALITY_OF_SKIN_PHYSIOLOGY                    | 573     | 8         | 2.05E-4  | 4.13E-2    | CD79A:CD79B:PDCD1:HLA-C:BANK1:DNASE1L3:ABCB4:KANSL1                                                         |
| Human Phenotype Ontology     | HP_ABNORMALITY_OF_THE ABDOMINAL_ORGANS               | 1367    | 13        | 1.12E-4  | 2.77E-2    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:CPT1A:DNASE1L3:DNAAF5:SCN4A:ABCB4:BCL11A:MFN2:NDUFAF1                      |
| Human Phenotype Ontology     | HP_ABNORMALITY_OF_THE_UPPER_RESPIRATORY_TRACT        | 513     | 9         | 1.4E-5   | 6.43E-3    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5:SCN4A:COL5A2:KANSL1                                                 |
| Human Phenotype Ontology     | HP_ABNORMALITY_ON_PULMONARY_FUNCTION_TESTING         | 187     | 5         | 1.81E-4  | 3.78E-2    | CD19:MS4A1:TNFRSF13C:DNASE1L3:SCN4A                                                                         |
| Human Phenotype Ontology     | HP_ANEMIA_DUE_TO_REDUCED_LIFE_SPAN_OF_RED_CELLS      | 168     | 6         | 7.89E-6  | 4.71E-3    | CD19:MS4A1:PDCD1:TNFRSF13C:BANK1:BCL11A                                                                     |
| Human Phenotype Ontology     | HP_ANTI_NUCLEAR_ANTIBODY_POSITIVITY                  | 71      | 4         | 4.72E-5  | 1.58E-2    | MS4A1:PDCD1:BANK1:DNASE1L3                                                                                  |
| Human Phenotype Ontology     | HP_ARTHRALGIA                                        | 205     | 6         | 2.44E-5  | 9.57E-3    | CD19:MS4A1:TNFRSF13C:COL5A2:BCL11A:MFN2                                                                     |
| Human Phenotype Ontology     | HP_ARTHRITIS                                         | 244     | 7         | 5.72E-6  | 3.9E-3     | CD79A:CD79B:PDCD1:HLA-C:BANK1:DNASE1L3:COL5A2                                                               |
| Human Phenotype Ontology     | HP_AUTOIMMUNE_ANTIBODY_POSITIVITY                    | 168     | 6         | 7.89E-6  | 4.71E-3    | MS4A1:PDCD1:BANK1:DNASE1L3:SCN4A:ZFP57                                                                      |
| Human Phenotype Ontology     | HP_AUTOIMMUNITY                                      | 303     | 9         | 1.89E-7  | 1.9E-4     | CD19:MS4A1:PDCD1:TNFRSF13C:BANK1:DNASE1L3:SCN4A:ZFP57:ABCB4                                                 |
| Human Phenotype Ontology     | HP_BRONCHIECTASIS                                    | 178     | 6         | 1.1E-5   | 5.67E-3    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5                                                                     |
| Human Phenotype Ontology     | HP_BRONCHITIS                                        | 75      | 6         | 6.87E-8  | 8.68E-5    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5                                                                     |
| Human Phenotype Ontology     | HP_CHRONIC_OTITIS_MEDIA                              | 163     | 6         | 6.64E-6  | 4.28E-3    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNAAF5                                                                     |
| Human Phenotype Ontology     | HP_COMBINED_IMMUNODEFICIENCY                         | 37      | 3         | 1.51E-4  | 3.41E-2    | CD19:MS4A1:TNFRSF13C                                                                                        |
| Human Phenotype Ontology     | HP_CONSTITUTIONAL_SYMPTOM                            | 1266    | 14        | 1.16E-5  | 5.67E-3    | CD19:MS4A1:CD79A:CD79B:PDCD1:TNFRSF13C:BANK1:CPT1A:DNASE1L3:SCN4A:ABCB4:COL5A2:BCL11A:MFN2                  |
| Human Phenotype Ontology     | HP_DECREASED_CIRCULATING_COMPLEMENT_C3_CONCENTRATION | 43      | 3         | 2.36E-4  | 4.7E-2     | PDCD1:BANK1:DNASE1L3                                                                                        |
| Human Phenotype Ontology     | HP_DECREASED_CIRCULATING_COMPLEMENT_C4_CONCENTRATION | 35      | 3         | 1.27E-4  | 3.01E-2    | PDCD1:BANK1:DNASE1L3                                                                                        |
| Human Phenotype Ontology     | HP_DIARRHEA                                          | 420     | 7         | 1.78E-4  | 3.78E-2    | CD19:CD79A:CD79B:TNFRSF13C:CPT1A:DNASE1L3:ABCB4                                                             |
| Human Phenotype Ontology     | HP_EMPHYSEMA                                         | 65      | 4         | 3.33E-5  | 1.22E-2    | CD19:MS4A1:TNFRSF13C:DNASE1L3                                                                               |
| Human Phenotype Ontology     | HP_GASTROINTESTINAL_STROMA_TUMOR                     | 19      | 3         | 1.95E-5  | 8.04E-3    | CD19:MS4A1:TNFRSF13C                                                                                        |
| Human Phenotype Ontology     | HP_INCREASED_INFLAMMATORY_RESPONSE                   | 1271    | 13        | 5.39E-5  | 1.61E-2    | CD19:MS4A1:CD79A:CD79B:PDCD1:HLA-C:TNFRSF13C:BANK1:DNASE1L3:DNAAF5:ABCB4:COL5A2:KANSL1                      |
| Human Phenotype Ontology     | HP_LUPUS_NEPHRITIS                                   | 32      | 3         | 9.71E-5  | 2.52E-2    | PDCD1:BANK1:DNASE1L3                                                                                        |
| Human Phenotype Ontology     | HP_LYMPHOPENIA                                       | 185     | 5         | 1.73E-4  | 3.71E-2    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C                                                                            |
| Human Phenotype Ontology     | HP_MENINGITIS                                        | 80      | 5         | 3.06E-6  | 2.46E-3    | CD19:CD79A:CD79B:TNFRSF13C:DNASE1L3                                                                         |
| Human Phenotype Ontology     | HP_POSTERIOR_PHARYNGEAL_CLEFT                        | 13      | 3         | 5.82E-6  | 3.9E-3     | CD19:MS4A1:TNFRSF13C                                                                                        |
| Human Phenotype Ontology     | HP_RECURRENT_BACTERIAL_INFECTIONS                    | 215     | 7         | 2.49E-6  | 2.11E-3    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C:DNASE1L3:DNAAF5                                                            |
| Human Phenotype Ontology     | HP_RECURRENT_BRONCHITIS                              | 38      | 5         | 7E-8     | 8.68E-5    | CD19:MS4A1:CD79A:CD79B:TNFRSF13C                                                                            |
| Human Phenotype Ontology     | HP_RECURRENT_OTITIS_MEDIA                            | 216     | 6         | 3.27E-5  | 1.22E-2    | CD19:CD79A:CD79B:TNFRSF13C:DNAAF5:KANSL1                                                                    |
| Human Phenotype Ontology     | HP_RECURRENT_SINUSITIS                               | 73      | 4         | 5.26E-5  | 1.6E-2     | CD19:TNFRSF13C:DNAAF5:COL5A2                                                                                |
| Human Phenotype Ontology     | HP_RED_EYE                                           | 114     | 5         | 1.73E-5  | 7.54E-3    | CD19:CD79A:CD79B:TNFRSF13C:DNASE1L3                                                                         |
| Human Phenotype Ontology     | HP_RESTRICTIVE_VENTILATORY_DEFECT                    | 105     | 5         | 1.16E-5  | 5.67E-3    | CD19:MS4A1:TNFRSF13C:DNASE1L3:SCN4A                                                                         |
| Human Phenotype Ontology     | HP_SKIN_RASH                                         | 170     | 6         | 8.44E-6  | 4.86E-3    | CD79A:CD79B:PDCD1:BANK1:DNASE1L3:ABCB4                                                                      |
| Human Phenotype Ontology     | HP_UNUSUAL_INFECTION_BY_ANATOMICAL_SITE              | 116     | 5         | 1.88E-5  | 7.99E-3    | CD19:CD79A:CD79B:TNFRSF13C:DNASE1L3                                                                         |
| Human Phenotype Ontology     | HP_VASCULITIS                                        | 72      | 4         | 4.99E-5  | 1.6E-2     | CD19:MS4A1:TNFRSF13C:DNASE1L3                                                                               |
| Transcription_Factor_Targets | MAML1_TARGET_GENES                                   | 323     | 10        | 2.6E-8   | 2.9E-5     | MS4A1:AFF3:RAB30:FCER2:NIBAN3:CD72:LCN10:CD19:CD79B:DNASE1L3                                                |
| Transcription_Factor_Targets | ZNF320_TARGET_GENES                                  | 1605    | 16        | 9.59E-6  | 5.35E-3    | RELT:NDUFAF1:KANSL1:PMEP1:EPS8L2:HLA-C:KANSL1-AS1:DNAAF5:PKIG:CORO2B:PTPRK:ZKSCAN4:SLC9A7:PGAP6:TIGIT:CD200 |
| Transcription_Factor_Targets | ZNF597_TARGET_GENES                                  | 893     | 11        | 4.05E-5  | 1.51E-2    | MS4A1:AFF3:RAB30:FCER2:NIBAN3:CD72:LCN10:TRIM69:LINC00926:SUN1:BANK1                                        |
| Transcription_Factor_Targets | OLF1_01                                              | 275     | 6         | 1.24E-4  | 3.45E-2    | MS4A1:AFF3:CD19:CD79B:RELT:CD79A                                                                            |
| computational_gene_sets      | MODULE_436                                           | 138     | 11        | 1.97E-13 | 1.98E-10   | BANK1:FCRL2:FCRLA:CD79B:MS4A1:CD79A:CD200:HLA-C:MST1L:FCER2:FCRL1                                           |
| computational_gene_sets      | MODULE_292                                           | 136     | 10        | 5.75E-12 | 2.89E-9    | BANK1:FCRL2:FCRLA:CD79B:MS4A1:CD79A:CD200:CD19:CD22:CD72                                                    |
| computational_gene_sets      | MODULE_345                                           | 126     | 9         | 8.88E-11 | 2.98E-8    | BANK1:FCRL2:FCRLA:CD79B:MS4A1:CD79A:HLA-C:MST1L:CD19                                                        |
| computational_gene_sets      | GAVISH_3CA_METAPROGRAM_B_CELLS_STRESS                | 50      | 6         | 5.73E-9  | 1.44E-6    | FCER2:CD22:CD72:TSPAN13:LINC00926:IGHD                                                                      |
| computational_gene_sets      | MODULE_145                                           | 111     | 7         | 2.81E-8  | 5.65E-6    | BANK1:FCRL2:FCRLA:CD200:FCER2:FCRL1:COL19A1                                                                 |
| computational_gene_sets      | MODULE_188                                           | 139     | 7         | 1.32E-7  | 2.22E-5    | BANK1:FCRL2:FCRLA:CD200:FCER2:FCRL1:COL19A1                                                                 |
| computational_gene_sets      | MODULE_46                                            | 394     | 10        | 1.65E-7  | 2.28E-5    | CD79B:MS4A1:CD79A:HLA-C:CD19:CD22:CD72:HLA-DOA:PDCD1:PAX5                                                   |
| computational_gene_sets      | MODULE_75                                            | 398     | 10        | 1.81E-7  | 2.28E-5    | CD79B:MS4A1:CD79A:HLA-C:CD19:CD22:CD72:HLA-DOA:PDCD1:PAX5                                                   |
| computational_gene_sets      | MODULE_361                                           | 149     | 7         | 2.13E-7  | 2.38E-5    | BANK1:FCRL2:FCRLA:CD200:FCER2:FCRL1:COL19A1                                                                 |
| computational_gene_sets      | MODULE_301                                           | 158     | 7         | 3.17E-7  | 3.18E-5    | BANK1:FCRL2:FCRLA:CD200:FCER2:FCRL1:COL19A1                                                                 |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category                | GeneSet                                                      | N_genes | N_overlap | P        | adjusted P | Genes                                                                                                                                           |
|-------------------------|--------------------------------------------------------------|---------|-----------|----------|------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| computational_gene_sets | MODULE_238                                                   | 164     | 7         | 4.07E-7  | 3.73E-5    | BANK1:FCRL2:FCRLA:CD200:FCER2:FCRL1:COL19A1                                                                                                     |
| computational_gene_sets | MODULE_143                                                   | 14      | 3         | 7.39E-6  | 6.19E-4    | HLA-C:HLA-DOA:HLA-DOB                                                                                                                           |
| computational_gene_sets | MODULE_64                                                    | 517     | 8         | 1.02E-4  | 7.89E-3    | CD79B:MS4A1:CD79A:HLA-C:FCER2:CD19:CD22:HLA-DOA                                                                                                 |
| computational_gene_sets | MODULE_410                                                   | 36      | 3         | 1.39E-4  | 9.96E-3    | FCER2:CD22:CD72                                                                                                                                 |
| computational_gene_sets | MODULE_96                                                    | 37      | 3         | 1.51E-4  | 1.01E-2    | FCER2:CD22:CD72                                                                                                                                 |
| computational_gene_sets | MODULE_41                                                    | 566     | 8         | 1.89E-4  | 1.19E-2    | CD22:CD72:COL19A1:PDCD1:HLA-DOB:CCHCR1:TRIM15:SCN4A                                                                                             |
| computational_gene_sets | GAVISH_3CA_METAPROGRAM_CD4_T_CELLS_DYSFUNCTION               | 49      | 3         | 3.48E-4  | 1.77E-2    | CD200:PDCD1:TIGIT                                                                                                                               |
| computational_gene_sets | MODULE_48                                                    | 335     | 6         | 3.57E-4  | 1.77E-2    | CD72:CCHCR1:HC64:TCL6:LRR37A:BEND5                                                                                                              |
| computational_gene_sets | GAVISH_3CA_METAPROGRAM_B_CELLS_GERMINAL_CENTER               | 50      | 3         | 3.7E-4   | 1.77E-2    | CD79B:CD22:BCL7A                                                                                                                                |
| computational_gene_sets | GAVISH_3CA_METAPROGRAM_B_CELLS_MHC_II                        | 50      | 3         | 3.7E-4   | 1.77E-2    | BANK1:CD79B:MS4A1                                                                                                                               |
| computational_gene_sets | GAVISH_3CA_METAPROGRAM_B_CELLS_PROGENITOR                    | 50      | 3         | 3.7E-4   | 1.77E-2    | CD72:BCL7A:NIBAN3                                                                                                                               |
| computational_gene_sets | MODULE_208                                                   | 124     | 4         | 4.07E-4  | 1.86E-2    | BANK1:MS4A1:CD79A:CD200                                                                                                                         |
| computational_gene_sets | MODULE_27                                                    | 355     | 6         | 4.85E-4  | 2.07E-2    | CD79B:CD79A:HLA-C:FCER2:CD72:HLA-DOA                                                                                                            |
| computational_gene_sets | MODULE_171                                                   | 138     | 4         | 6.09E-4  | 2.45E-2    | BANK1:MS4A1:CD79A:CD200                                                                                                                         |
| computational_gene_sets | MODULE_13                                                    | 519     | 7         | 6.32E-4  | 2.45E-2    | CD19:CD22:COL19A1:HLA-DOB:CCHCR1:TRIM15:LARGE1                                                                                                  |
| computational_gene_sets | MODULE_119                                                   | 143     | 4         | 6.96E-4  | 2.59E-2    | BANK1:CD79B:CD200:CD19                                                                                                                          |
| computational_gene_sets | MODULE_84                                                    | 546     | 7         | 8.5E-4   | 3.06E-2    | CD79A:HLA-C:MST1L:CD22:CD72:CCHCR1:DNASE1L3                                                                                                     |
| computational_gene_sets | MODULE_117                                                   | 723     | 8         | 9.46E-4  | 3.28E-2    | CD79B:MS4A1:FCER2:HLA-DOA:PAX5:HC64:ABC84:RAB30                                                                                                 |
| Cell_type_signature     | TRAVAGLINI_LUNG_B_CELL                                       | 155     | 23        | 1.92E-33 | 1.62E-30   | FCRL1:FCRL2:CD79A:MS4A1:CD22:LINC00926:CD19:FCRLA:BANK1:TNFRSF13C:STAP1:FCER2:PAX5:NIBAN3:CD79B:AFF3:CD72:BCL7A:BCL11A:PKIG:CD200:TSPAN13:SNX22 |
| Cell_type_signature     | HAY_BONE_MARROW_FOLLICULAR_B_CELL                            | 142     | 20        | 1.12E-28 | 4.69E-26   | FCRL1:FCRL2:CD79A:MS4A1:CD22:LINC00926:CD19:FCRLA:BANK1:TNFRSF13C:STAP1:FCER2:LINC02397:COL19A1:HLA-DOB:PLPP5:RAB30:HLA-DOA:ABC84:LARGE1        |
| Cell_type_signature     | FAN_EMBRYONIC_CTX_BRAIN_B_CELL                               | 101     | 16        | 5.53E-24 | 1.55E-21   | FCRL1:FCRL2:CD79A:MS4A1:CD22:LINC00926:CD19:FCRLA:BANK1:PAX5:NIBAN3:CD79B:AFF3:CD72:BCL7A:HLA-C                                                 |
| Cell_type_signature     | AIZARANI_LIVER_C34_MHC_II_POS_B_CELLS                        | 134     | 16        | 6.52E-22 | 1.37E-19   | FCRL1:FCRL2:CD79A:MS4A1:CD22:LINC00926:TNFRSF13C:STAP1:FCER2:PAX5:NIBAN3:LINC02397:COL19A1:TIGIT:IGHD                                           |
| Cell_type_signature     | DESCARTES_FETAL_SPLEEN_LYMPHOID_CELLS                        | 127     | 15        | 1.57E-20 | 2.63E-18   | FCRL1:FCRL2:CD79A:MS4A1:CD22:CD19:FCRLA:PAX5:CD79B:CD72:LINC02397:TIGIT:IGHD:TCL6:PDCD1:CCR4                                                    |
| Cell_type_signature     | DESCARTES_FETAL_PANCREAS_LYMPHOID_CELLS                      | 168     | 16        | 2.74E-20 | 3.83E-18   | FCRL1:FCRL2:CD79A:MS4A1:CD19:FCRLA:PAX5:NIBAN3:CD79B:CD72:TIGIT:IGHD:TCL6                                                                       |
| Cell_type_signature     | DESCARTES_FETAL_LIVER_LYMPHOID_CELLS                         | 127     | 13        | 4.21E-17 | 5.05E-15   | FCRL1:FCRL2:CD79A:CD22:CD19:FCRLA:STAP1:PAX5:NIBAN3:CD79B:TIGIT:IGHD:BTN3A2                                                                     |
| Cell_type_signature     | DESCARTES_MAIN_FETAL_LYMPHOID_CELLS                          | 158     | 13        | 7.61E-16 | 8E-14      | FCRL1:FCRL2:CD79A:MS4A1:CD19:FCRLA:STAP1:PAX5:NIBAN3:CD79B:TIGIT:IGHD:PDCD1                                                                     |
| Cell_type_signature     | DESCARTES_FETAL_LUNG_LYMPHOID_CELLS                          | 160     | 13        | 8.98E-16 | 8.39E-14   | FCRL1:FCRL2:CD79A:MS4A1:CD19:FCRLA:STAP1:PAX5:NIBAN3:CD79B:TIGIT:IGHD:PDCD1                                                                     |
| Cell_type_signature     | DESCARTES_FETAL_ADRENAL_LYMPHOID_CELLS                       | 164     | 12        | 4.25E-14 | 3.57E-12   | FCRL1:FCRL2:CD79A:MS4A1:CD19:FCRLA:PAX5:NIBAN3:CD79B:HLA-DOB:TIGIT:IGHD                                                                         |
| Cell_type_signature     | DESCARTES_FETAL_HEART_LYMPHOID_CELLS                         | 113     | 10        | 8.85E-13 | 6.76E-11   | FCRL1:FCRL2:MS4A1:CD19:FCRLA:PAX5:CD79B:LINC02397:TIGIT:PDCD1                                                                                   |
| Cell_type_signature     | DESCARTES_FETAL_KIDNEY_LYMPHOID_CELLS                        | 212     | 11        | 2.16E-11 | 1.51E-9    | FCRL1:FCRL2:CD79A:MS4A1:CD19:PAX5:NIBAN3:CD79B:HLA-DOB:TIGIT:IGHD                                                                               |
| Cell_type_signature     | RUBENSTEIN_SKELETAL_MUSCLE_B_CELLS                           | 177     | 10        | 7.89E-11 | 5.1E-9     | FCRL1:CD79A:MS4A1:LINC00926:FCRLA:BANK1:FCER2:CD79B:HLA-DOB:PLPP5                                                                               |
| Cell_type_signature     | DURANTE_ADULT_OLFACTORY_NEUROEPITHELIUM_B_CELLS              | 35      | 6         | 6.06E-10 | 3.63E-8    | CD79A:MS4A1:LINC00926:BANK1:TNFRSF13C:CD79B                                                                                                     |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C5_CD5_POS_CCL22_NEG_MATURE_B_CELL     | 160     | 9         | 7.51E-10 | 4.2E-8     | FCRL2:LINC00926:TNFRSF13C:FCER2:PKIG:COL19A1:HLA-DOB:PLPP5:CLEC17A                                                                              |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_HSC_ELP_CELL                        | 412     | 10        | 2.49E-7  | 1.3E-5     | CD79A:STAP1:NIBAN3:CD79B:BCL11A:CD200:IGHD:BEND5:FAM30A:VAR52                                                                                   |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C5_CD5_NEG_MATURE_B_CELL               | 52      | 5         | 3.52E-7  | 1.74E-5    | LINC00926:FCER2:COL19A1:HLA-DOB:PLPP5                                                                                                           |
| Cell_type_signature     | DESCARTES_FETAL_INTESTINE_LYMPHOID_CELLS                     | 165     | 7         | 4.24E-7  | 1.98E-5    | CD79A:MS4A1:STAP1:PAX5:CD79B:IGHD:CCR4                                                                                                          |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_HSC_CELL                            | 1635    | 18        | 6.15E-7  | 2.72E-5    | STAP1:CD79B:BCL7A:PKIG:CD200:TSPAN13:PLPP5:SLC9A7:BEND5:FAM30A:PHF19:CPT1A:HENMT1:LRRC27:ZKSCAN4:RPAP1:NFYA:NDUFAF1                             |
| Cell_type_signature     | TRAVAGLINI_LUNG_PLASMACYTOID_DENDRITIC_CELL                  | 111     | 6         | 7.12E-7  | 2.99E-5    | NIBAN3:AFF3:BCL11A:TSPAN13:DNASE1L3:PMEPA1                                                                                                      |
| Cell_type_signature     | GAO_LARGE_INTESTINE_ADULT_CI_MESENCHYMAL_CELLS               | 361     | 9         | 8.14E-7  | 3.26E-5    | FCRL2:CD79A:CD19:STAP1:CD79B:HLA-DOB:RAB30:TRIM69:RELT                                                                                          |
| Cell_type_signature     | AIZARANI_LIVER_C22_RESIDENT_B_CELLS_2                        | 33      | 4         | 2.16E-6  | 8.23E-5    | CD79A:HLA-DOB:PLPP5:RAB30                                                                                                                       |
| Cell_type_signature     | DESCARTES_FETAL_STOMACH_LYMPHOID_CELLS                       | 82      | 5         | 3.45E-6  | 1.26E-4    | CD79A:MS4A1:PAX5:NIBAN3:CD79B                                                                                                                   |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_PDC_CELL                            | 147     | 6         | 3.66E-6  | 1.28E-4    | NIBAN3:BCL7A:BCL11A:TSPAN13:DNASE1L3:PMEPA1                                                                                                     |
| Cell_type_signature     | HAY_BONE_MARROW_CD34_POS_PRE_B                               | 100     | 5         | 9.16E-6  | 3.01E-4    | PAX5:NIBAN3:CD79B:AFF3:BCL7A                                                                                                                    |
| Cell_type_signature     | DESCARTES_FETAL_THYMUS_ANTIGEN_PRESENTING_CELLS              | 173     | 6         | 9.33E-6  | 3.01E-4    | MS4A1:PAX5:TSPAN13:HLA-DOB:SLC9A7:DNASE1L3                                                                                                      |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_PRE_PDC_DC5_CELL                    | 578     | 9         | 3.55E-5  | 1.1E-3     | CD22:BANK1:NIBAN3:BCL7A:BCL11A:PKIG:CD200:TSPAN13:PHF19                                                                                         |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_DC1_CELL                            | 328     | 7         | 3.83E-5  | 1.15E-3    | TSPAN13:SNX22:HLA-DOB:RAB30:SLC9A7:BEND5:DNASE1L3                                                                                               |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C5_CD5_POS_CCL22_POS_MATURE_B_CELL     | 666     | 9         | 1.05E-4  | 3.03E-3    | FCRL2:LINC00926:TNFRSF13C:STAP1:PKIG:RAB30:CLEC17A:VAR52:PHF19                                                                                  |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_ADC1_CELL                           | 172     | 5         | 1.23E-4  | 3.44E-3    | CD200:TSPAN13:HLA-DOB:RAB30:ARL17B                                                                                                              |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C2_MEGAKARYOCYTE                       | 694     | 8         | 7.28E-4  | 1.92E-2    | BANK1:PKIG:TSPAN13:PLPP5:RAB30:CCR4:BTN3A2:FAM30A                                                                                               |
| Cell_type_signature     | DESCARTES_FETAL_PLACENTA_LYMPHOID_CELLS                      | 145     | 4         | 7.33E-4  | 1.92E-2    | CD79A:STAP1:CD79B:TIGIT                                                                                                                         |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C3_SCG3_POS_LYMPHATIC_ENDOTHELIAL_CELL | 604     | 7         | 1.52E-3  | 3.86E-2    | BCL7A:PLPP5:BEND5:CPT1A:MAPRE3:COL5A2:PTPRK                                                                                                     |
| Cell_type_signature     | HE_LIM_SUN_FETAL_LUNG_C4_ILCP_CELL                           | 182     | 4         | 1.7E-3   | 4.19E-2    | AFF3:TSPAN13:PHF19:EPS8L2                                                                                                                       |

Supplemental Table 5. Gene set enrichment analysis based on the updated MSigDB gene sets using both cis- and trans-associated genes

| Category            | GeneSet                                            | N_genes | N_overlap | P       | adjusted P | Genes                            |
|---------------------|----------------------------------------------------|---------|-----------|---------|------------|----------------------------------|
| Cell_type_signature | GAO_LARGE_INTESTINE_ADULT_CA_ENTEROENDOCRINE_CELLS | 312     | 5         | 1.82E-3 | 4.38E-2    | AFF3:MAPRE3:COL5A2:CCDC74A:KCNH8 |