**Supplementary Table 1.** **Correlation analysis between FREM1 and related genes and markers of immune cells in TIMER.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Description** | **Gene markers** | **BRCA** | | | | **Her2** | | | | **BRCA-Basal** | | | | **BRCA-luminal** | | | |
| **None** | | **Purity** | | **None** | | **Purity** | | **None** | | **Purity** | | **None** | | **Purity** | |
| **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** |
| CD8+ T cell | CD8A | 0.498 | \*\*\* | 0.495 | \*\*\* | 0.729 | \*\*\* | 0.697 | \*\*\* | 0.346 | \*\*\* | 0.378 | \*\*\* | 0.542 | \*\*\* | 0.545 | \*\*\* |
| CD8B | 0.431 | \*\*\* | 0.430 | \*\*\* | 0.703 | \*\*\* | 0.684 | \*\*\* | 0.253 | \* | 0.292 | \*\* | 0.526 | \*\*\* | 0.527 | \*\*\* |
| T cell (general) | CD3D | 0.454 | \*\*\* | 0.451 | \*\*\* | 0.712 | \*\*\* | 0.687 | \*\*\* | 0.347 | \*\*\* | 0.383 | \*\*\* | 0.524 | \*\*\* | 0.523 | \*\*\* |
| CD3E | 0.497 | \*\*\* | 0.493 | \*\*\* | 0.722 | \*\*\* | 0.686 | \*\*\* | 0.385 | \*\*\* | 0.415 | \*\*\* | 0.555 | \*\*\* | 0.555 | \*\*\* |
| CD2 | 0.446 | \*\*\* | 0.440 | \*\*\* | 0.717 | \*\*\* | 0.679 | \*\*\* | 0.357 | \*\*\* | 0.383 | \*\*\* | 0.509 | \*\*\* | 0.507 | \*\*\* |
| B cell | CD19 | 0.420 | \*\*\* | 0.411 | \*\*\* | 0.685 | \*\*\* | 0.682 | \*\*\* | 0.434 | \*\*\* | 0.456 | \*\*\* | 0.473 | \*\*\* | 0.460 | \*\*\* |
| CD79A | 0.479 | \*\*\* | 0.469 | \*\*\* | 0.707 | \*\*\* | 0.700 | \*\*\* | 0.408 | \*\*\* | 0.428 | \*\*\* | 0.559 | \*\*\* | 0.547 | \*\*\* |
| Monocyte | CD86 | 0.202 | \*\*\* | 0.187 | \*\*\* | 0.552 | \*\*\* | 0.494 | \*\*\* | 0.283 | \*\* | 0.291 | \*\* | 0.207 | \*\*\* | 0.198 | \*\*\* |
| CD115 (CSF1R) | 0.352 | \*\*\* | 0.342 | \*\*\* | 0.593 | \*\*\* | 0.574 | \*\*\* | 0.323 | \*\* | 0.332 | \*\* | 0.346 | \*\*\* | 0.342 | \*\*\* |
| TAM | CCL2 | 0.258 | \*\*\* | 0.258 | \*\*\* | 0.379 | \*\* | 0.331 | 0.011 | 0.097 | 0.256 | 0.110 | 0.215 | 0.326 | \*\*\* | 0.337 | \*\*\* |
| CD68 | 0.165 | \*\*\* | 0.156 | \*\*\* | 0.512 | \*\*\* | 0.483 | \*\* | 0.251 | \* | 0.265 | \* | 0.165 | \*\*\* | 0.160 | \*\* |
| IL10 | 0.235 | \*\*\* | 0.218 | \*\*\* | 0.563 | \*\*\* | 0.509 | \*\*\* | 0.274 | \* | 0.261 | \* | 0.222 | \*\*\* | 0.204 | \*\*\* |
| M1 Macrophage | INOS (NOS2) | 0.024 | 0.429 | 0.020 | 0.521 | -0.095 | 0.442 | -0.084 | 0.528 | -0.055 | 0.517 | -0.075 | 0.396 | 0.028 | 0.484 | 0.023 | 0.596 |
| IRF5 | 0.044 | 0.140 | 0.040 | 0.205 | 0.476 | \*\*\* | 0.483 | \*\* | 0.121 | 0.154 | 0.150 | 0.089 | 0.038 | 0.343 | 0.031 | 0.472 |
| COX2 (PTGS2) | 0.465 | \*\*\* | 0.465 | \*\*\* | 0.266 | 0.030 | 0.232 | 0.077 | 0.083 | 0.329 | 0.041 | 0.643 | 0.597 | \*\*\* | 0.604 | \*\*\* |
| M2 Macrophage | CD163 | 0.191 | \*\*\* | 0.180 | \*\*\* | 0.483 | \*\*\* | 0.452 | \*\* | 0.245 | \*\*\* | 0.247 | \*\*\* | 0.185 | \*\*\* | 0.182 | \*\*\* |
| VSIG4 | 0.167 | \*\*\* | 0.165 | \*\*\* | 0.256 | 0.036 | 0.235 | 0.073 | 0.122 | 0.042 | 0.146 | 0.019 | 0.162 | \*\*\* | 0.166 | \*\* |
| MS4A4A | 0.330 | \*\*\* | 0.320 | \*\*\* | 0.483 | \*\*\* | 0.424 | \*\* | 0.230 | \*\*\* | 0.317 | \*\*\* | 0.353 | \*\*\* | 0.350 | \*\*\* |
| Neutrophils | CD66b (CEACAM8) | 0.027 | 0.370 | 0.036 | 0.252 | -0.030 | 0.809 | -0.090 | 0.499 | 0.100 | 0.239 | 0.134 | 0.131 | 0.055 | 0.173 | 0.055 | 0.203 |
| CD11b (ITGAM) | 0.213 | \*\*\* | 0.216 | \*\*\* | 0.502 | \*\*\* | 0.456 | \*\* | 0.187 | 0.027 | 0.205 | 0.020 | 0.182 | \*\*\* | 0.186 | \*\*\* |
| CCR7 | 0.494 | \*\*\* | 0.487 | \*\*\* | 0.728 | \*\*\* | 0.682 | \*\*\* | 0.425 | \*\*\* | 0.436 | \*\*\* | 0.541 | \*\*\* | 0.529 | \*\*\* |
| Natural killer cell | KIR2DL1 | 0.188 | \*\*\* | 0.183 | \*\*\* | 0.378 | \* | 0.365 | \* | 0.194 | 0.022 | 0.220 | 0.012 | 0.184 | \*\*\* | 0.185 | \*\*\* |
| KIR2DL3 | 0.188 | \*\*\* | 0.190 | \*\*\* | 0.453 | \*\* | 0.432 | \*\* | 0.174 | 0.039 | 0.173 | 0.050 | 0.195 | \*\*\* | 0.202 | \*\*\* |
| KIR2DL4 | 0.152 | \*\*\* | 0.142 | \*\*\* | 0.409 | \*\* | 0.375 | \* | 0.138 | 0.105 | 0.175 | 0.047 | 0.220 | \*\*\* | 0.208 | \*\*\* |
| KIR3DL1 | 0.267 | \*\*\* | 0.263 | \*\*\* | 0.517 | \*\*\* | 0.457 | \*\* | 0.280 | \*\* | 0.276 | \* | 0.309 | \*\*\* | 0.318 | \*\*\* |
| KIR3DL2 | 0.280 | \*\*\* | 0.279 | \*\*\* | 0.478 | \*\*\* | 0.453 | \*\* | 0.246 | \* | 0.261 | \* | 0.346 | \*\*\* | 0.363 | \*\*\* |
| KIR3DL3 | 0.091 | \* | 0.081 | 0.010 | 0.137 | 0.270 | 0.093 | 0.485 | 0.049 | 0.566 | 0.035 | 0.694 | 0.128 | \* | 0.137 | \* |
| KIR2DS4 | 0.200 | \*\*\* | 0.202 | \*\*\* | 0.241 | 0.049 | 0.186 | 0.159 | 0.139 | 0.101 | 0.156 | 0.078 | 0.248 | \*\*\* | 0.265 | \*\*\* |
| *(Continued)* | | | | | | | | | | | | | | | | | |
| **Description** | **Gene markers** | **BRCA** | | | | **Her2** | | | | **BRCA-Basal** | | | | **BRCA-luminal** | | | |
| **None** | | **Purity** | | **None** | | **Purity** | | **None** | | **Purity** | | **None** | | **Purity** | |
| **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** | **Cor** | ***P*** |
| Dendritic cell | HLA-DPB1 | 0.413 | \*\*\* | 0.405 | \*\*\* | 0.531 | \*\*\* | 0.495 | \*\*\* | 0.337 | \*\*\* | 0.352 | \*\*\* | 0.445 | \*\*\* | 0.436 | \*\*\* |
| HLA-DQB1 | 0.271 | \*\*\* | 0.272 | \*\*\* | 0.463 | \*\*\* | 0.429 | \*\* | 0.227 | \*\* | 0.220 | 0.012 | 0.298 | \*\*\* | 0.302 | \*\*\* |
| HLA-DRA | 0.364 | \*\*\* | 0.359 | \*\*\* | 0.553 | \*\*\* | 0.515 | \*\*\* | 0.310 | \*\* | 0.326 | \*\* | 0.381 | \*\*\* | 0.377 | \*\*\* |
| HLA-DPA1 | 0.388 | \*\*\* | 0.382 | \*\*\* | 0.545 | \*\*\* | 0.510 | \*\*\* | 0.333 | \*\*\* | 0.348 | \*\*\* | 0.392 | \*\*\* | 0.384 | \*\*\* |
| BDCA-1 (CD1C) | 0.643 | \*\*\* | 0.647 | \*\*\* | 0.747 | \*\*\* | 0.727 | \*\*\* | 0.470 | \*\*\* | 0.481 | \*\*\* | 0.684 | \*\*\* | 0.688 | \*\*\* |
| BDCA-4 (NRP1) | 0.448 | \*\*\* | 0.444 | \*\*\* | 0.230 | 0.061 | 0.207 | 0.116 | 0.283 | \*\* | 0.249 | \* | 0.489 | \*\*\* | 0.503 | \*\*\* |
| CD11c (ITGAX) | 0.245 | \*\*\* | 0.248 | \*\*\* | 0.585 | \*\*\* | 0.544 | \*\*\* | 0.320 | \*\* | 0.346 | \*\*\* | 0.209 | \*\*\* | 0.212 | \*\*\* |
| Th1 | T-bet (TBX21) | 0.468 | \*\*\* | 0.465 | \*\*\* | 0.675 | \*\*\* | 0.630 | \*\*\* | 0.375 | \*\*\* | 0.408 | \*\*\* | 0.521 | \*\*\* | 0.524 | \*\*\* |
| STAT4 | 0.508 | \*\*\* | 0.497 | \*\*\* | 0.714 | \*\*\* | 0.682 | \*\*\* | 0.404 | \*\*\* | 0.422 | \*\*\* | 0.542 | \*\*\* | 0.533 | \*\*\* |
| STAT1 | 0.078 | \* | 0.070 | 0.027 | 0.406 | \*\* | 0.379 | \* | 0.189 | 0.026 | 0.197 | 0.025 | 0.090 | 0.025 | 0.088 | 0.041 |
| IFN-γ (IFNG) | 0.242 | \*\*\* | 0.239 | \*\*\* | 0.536 | \*\*\* | 0.510 | \*\*\* | 0.244 | \* | 0.274 | \* | 0.308 | \*\*\* | 0.317 | \*\*\* |
| TNF-α (TNF) | 0.015 | 0.617 | 0.021 | 0.509 | 0.445 | \*\* | 0.483 | \*\* | -0.027 | 0.749 | -0.006 | 0.947 | 0.015 | 0.708 | 0.012 | 0.782 |
| Th2 | GATA3 | -0.122 | \*\*\* | -0.116 | \*\* | -0.058 | 0.641 | -0.052 | 0.692 | -0.033 | 0.698 | -0.000 | 0.996 | -0.299 | \*\*\* | -0.300 | \*\*\* |
| STAT6 | 0.232 | \*\*\* | 0.246 | \*\*\* | -0.119 | 0.338 | -0.208 | 0.115 | 0.056 | 0.509 | 0.053 | 0.550 | 0.224 | \*\*\* | 0.238 | \*\*\* |
| STAT5A | 0.358 | \*\*\* | 0.356 | \*\*\* | 0.562 | \*\*\* | 0.563 | \*\*\* | 0.032 | 0.707 | 0.037 | 0.678 | 0.384 | \*\*\* | 0.388 | \*\*\* |
| IL13 | 0.180 | \*\*\* | 0.184 | \*\*\* | 0.326 | \*\* | 0.286 | 0.028 | 0.203 | 0.016 | 0.224 | 0.011 | 0.176 | \*\*\* | 0.170 | \*\*\* |
| Tfh | BCL6 | 0.192 | \*\*\* | 0.206 | \*\*\* | 0.001 | 0.992 | -0.002 | 0.989 | 0.201 | 0.017 | 0.203 | 0.021 | 0.125 | \* | 0.135 | \* |
| IL21 | 0.204 | \*\*\* | 0.198 | \*\*\* | 0.461 | \*\*\* | 0.456 | \*\* | 0.344 | \*\*\* | 0.344 | \*\*\* | 0.257 | \*\*\* | 0.257 | \*\*\* |
| Th17 | STAT3 | 0.161 | \*\*\* | 0.174 | \*\*\* | 0.165 | 0.182 | 0.160 | 0.225 | 0.032 | 0.709 | 0.048 | 0.592 | 0.137 | \*\* | 0.153 | \*\* |
| IL17A | 0.108 | \*\* | 0.099 | \* | 0.205 | 0.096 | 0.104 | 0.433 | 0.095 | 0.266 | 0.122 | 0.170 | 0.152 | \*\* | 0.158 | \*\* |
| Treg | FOXP3 | 0.238 | \*\*\* | 0.278 | \*\*\* | 0.559 | \*\*\* | 0.520 | \*\*\* | 0.318 | \*\* | 0.327 | \*\* | 0.261 | \*\*\* | 0.264 | \*\*\* |
| CCR8 | 0.189 | \*\*\* | 0.180 | \*\*\* | 0.479 | \*\*\* | 0.423 | \*\* | 0.358 | \*\*\* | 0.353 | \*\*\* | 0.194 | \*\*\* | 0.194 | \*\*\* |
| STAT5B | 0.358 | \*\*\* | 0.370 | \*\*\* | 0.506 | \*\*\* | 0.521 | \*\*\* | 0.213 | 0.011 | 0.213 | 0.015 | 0.263 | \*\*\* | 0.280 | \*\*\* |
| TGFβ (TGFB1) | 0.344 | \*\*\* | 0.346 | \*\*\* | 0.304 | 0.013 | 0.345 | \* | 0.359 | \*\*\* | 0.377 | \*\*\* | 0.319 | \*\*\* | 0.311 | \*\*\* |
| T cell exhaustion | PDCD1 | 0.377 | \*\*\* | 0.371 | \*\*\* | 0.633 | \*\*\* | 0.591 | \*\*\* | 0.264 | \* | 0.294 | \*\* | 0.450 | \*\*\* | 0.443 | \*\*\* |
| CTLA4 | 0.285 | \*\*\* | 0.281 | \*\*\* | 0.616 | \*\*\* | 0.560 | \*\*\* | 0.345 | \*\*\* | 0.364 | \*\*\* | 0.305 | \*\*\* | 0.304 | \*\*\* |
| LAG3 | 0.087 | \* | 0.076 | 0.017 | 0.425 | \*\* | 0.359 | \* | 0.183 | 0.030 | 0.219 | 0.013 | 0.131 | \* | 0.117 | \* |
| HAVCR2 | 0.176 | \*\*\* | 0.169 | \*\*\* | 0.501 | \*\*\* | 0.461 | \*\* | 0.289 | \*\* | 0.302 | \*\* | 0.163 | \*\*\* | 0.163 | \*\* |
| GZMB | 0.285 | \*\*\* | 0.277 | \*\*\* | 0.555 | \*\*\* | 0.523 | \*\*\* | 0.183 | 0.031 | 0.212 | 0.159 | 0.395 | \*\*\* | 0.396 | \*\*\* |

*BRCA, breast invasive carcinoma; TAM, tumour-associated macrophage; Th, T helper cell; Tfh, Follicular helper T cell; Treg, regulatory T cell; Cor, R value of Spearman’s correlation; None, correlation without adjustment. Purity, correlation adjusted by purity.*

*\*P < 0.01; \*\*P < 0.001; \*\*\*P < 0.0001.*