**Supplementary Tables and Figures**

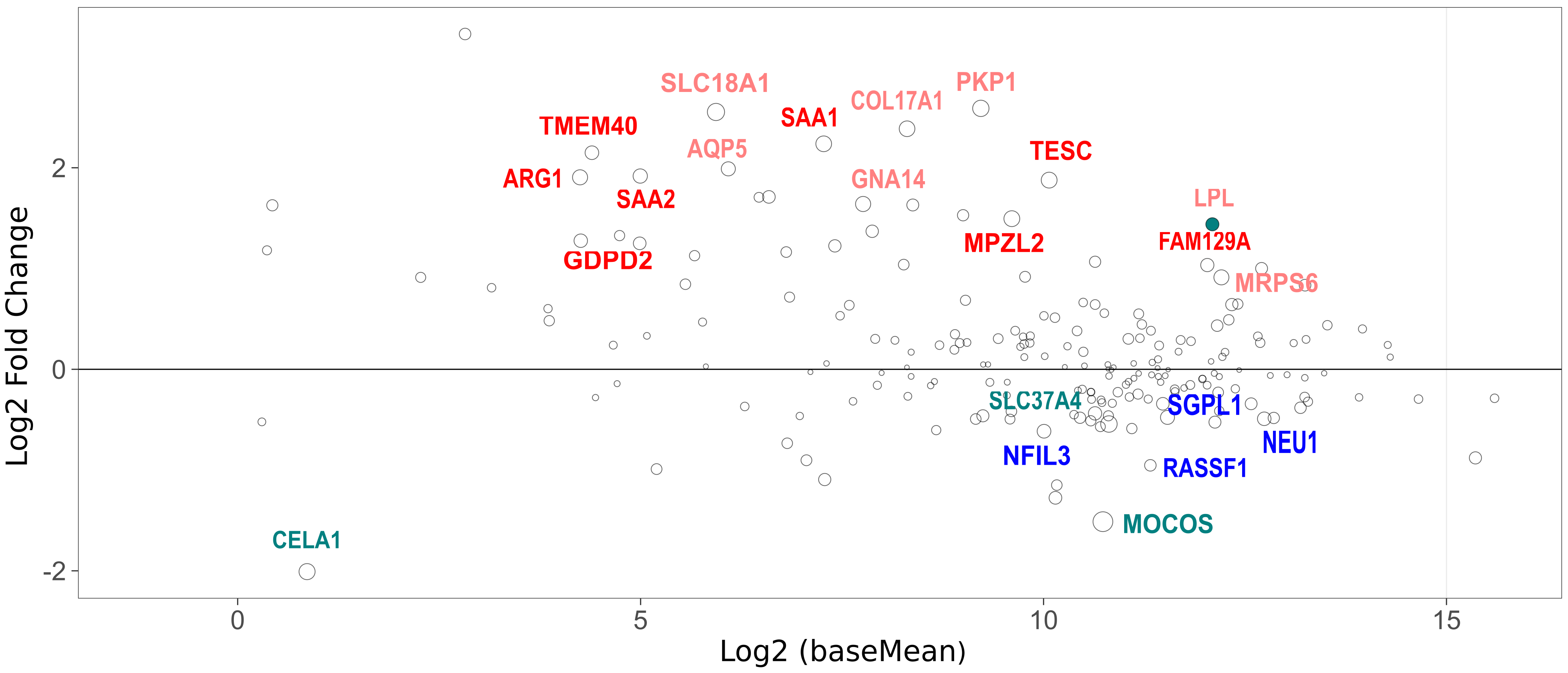
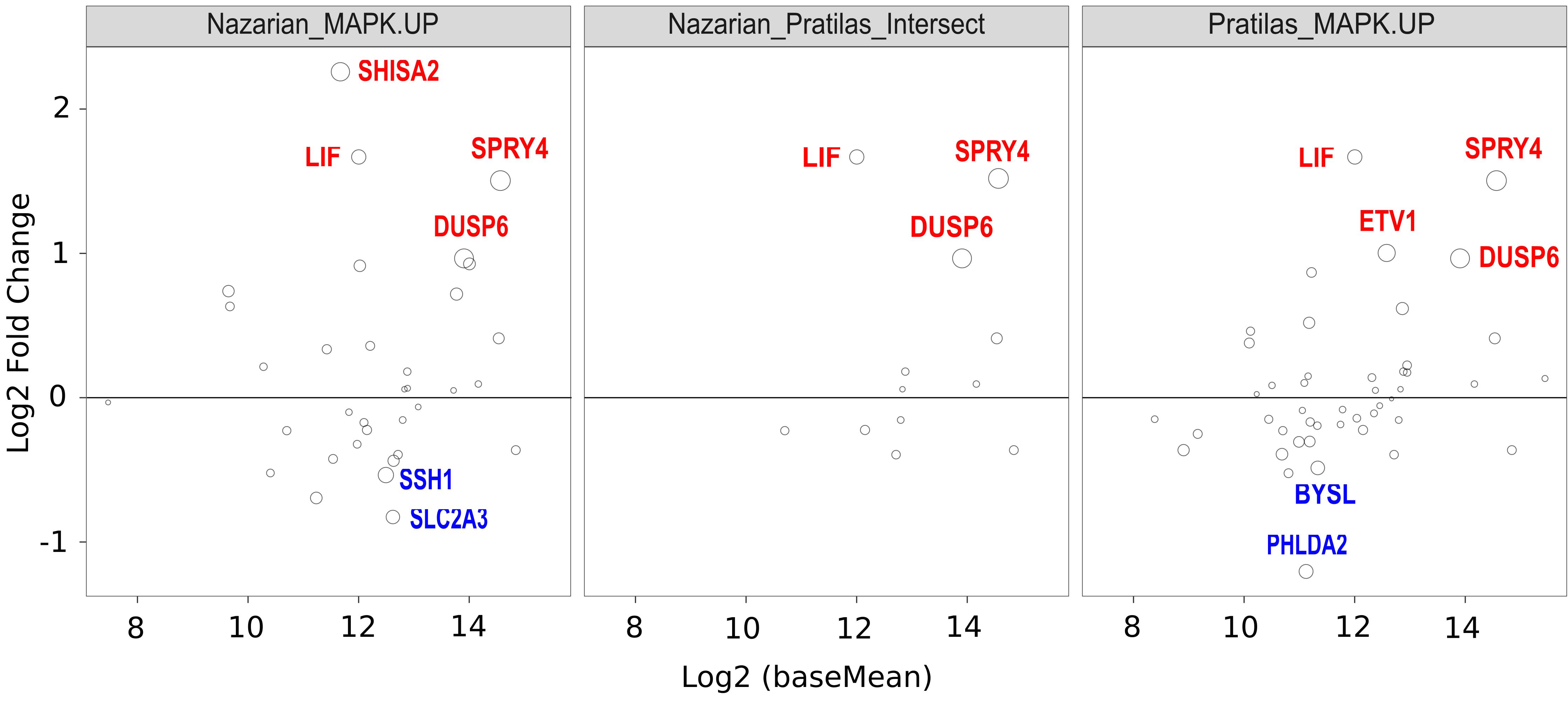
**Supplementary Table 1.** Top 30 differentially expressed genes between V600E and V600K mutant melanomas (nanostring).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| geneSymbol | logFC | AveExpr | t | P.Value | adj.P.Val | B |
| DUSP6 | 1.093248 | 11.087046 | 4.392472 | 2.949E-05 | 0.02400718 | 1.937835 |
| ETS1 | -0.75632 | 9.2882729 | -3.79274 | 0.0002639 | 0.10740773 | 0.175064 |
| ETV4 | 1.455176 | 8.4998006 | 3.446136 | 0.0008543 | 0.23179737 | -0.76304 |
| ALDH1B1 | 1.029451 | 7.1760882 | 3.1431 | 0.0022415 | 0.40328281 | -1.52727 |
| Wnt3 | 1.402862 | 4.2011239 | 3.110585 | 0.0024772 | 0.40328281 | -1.60605 |
| GCNT1 | 0.972424 | 5.9155856 | 3.031305 | 0.0031517 | 0.4275831 | -1.79543 |
| PIK3CB | -0.67063 | 8.0043331 | -2.73648 | 0.007431 | 0.68847247 | -2.4647 |
| JUN | -0.61588 | 7.6461292 | -2.71903 | 0.0078037 | 0.68847247 | -2.50258 |
| SFRP1 | 2.389482 | 8.2153922 | 2.690373 | 0.0084571 | 0.68847247 | -2.56466 |
| RET | -0.97839 | 1.0404869 | -2.64456 | 0.0095974 | 0.68847247 | -2.66225 |
| KDM4D | -0.79621 | 4.1646853 | -2.59609 | 0.0109528 | 0.68847247 | -2.7639 |
| FGF1 | 1.521741 | 4.7644421 | 2.59033 | 0.0111261 | 0.68847247 | -2.77594 |
| EPHA2 | 1.013922 | 7.3254063 | 2.579234 | 0.0114647 | 0.68847247 | -2.79896 |
| GPNMB | -0.89339 | 12.786077 | -2.55255 | 0.0123176 | 0.68847247 | -2.85397 |
| DUSP4 | 0.786288 | 10.838461 | 2.541478 | 0.0126868 | 0.68847247 | -2.87661 |
| MRE11A | -0.58244 | 6.532016 | -2.49815 | 0.0142292 | 0.72390825 | -2.96439 |
| Wnt2B | -0.94011 | 2.5805589 | -2.428 | 0.0171005 | 0.81881154 | -3.10425 |
| CD226 | -0.85039 | 4.9180096 | -2.38006 | 0.0193445 | 0.83946273 | -3.19772 |
| ITGAX | -0.59273 | 8.1687041 | -2.37489 | 0.0195943 | 0.83946273 | -3.20752 |
| TYRP1 | -3.38685 | 7.6809201 | -2.33872 | 0.021485 | 0.85427188 | -3.277 |
| PLCB4 | 1.937507 | 5.0876119 | 2.321872 | 0.0224161 | 0.85427188 | -3.30898 |
| DOT1L | 0.352341 | 8.8823709 | 2.281672 | 0.0247752 | 0.85427188 | -3.38429 |
| SPRY2 | 0.739135 | 9.2970567 | 2.280686 | 0.0248435 | 0.85427188 | -3.38627 |
| KIT | -1.61158 | 5.1888555 | -2.25813 | 0.0262686 | 0.85427188 | -3.42809 |
| CSNK1G2 | 0.309151 | 8.2594189 | 2.254061 | 0.0265253 | 0.85427188 | -3.43546 |
| STRA6 | 1.812438 | 4.1268084 | 2.230601 | 0.0281047 | 0.85427188 | -3.47863 |
| CCL28 | -0.86092 | 7.2055077 | -2.20966 | 0.0295754 | 0.85427188 | -3.5167 |
| CDX4 | -0.91493 | 1.366066 | -2.20812 | 0.0296863 | 0.85427188 | -3.51949 |
| HLA-E | -0.50953 | 12.051143 | -2.19108 | 0.0309284 | 0.85427188 | -3.5501 |
| BCL2 | -0.60528 | 7.5775725 | -2.1728 | 0.0323237 | 0.85427188 | -3.58289 |

**Supplementary Table 2.** Top 30 genes differentially mutated between V600E and V600K mutant melanomas (NGS).

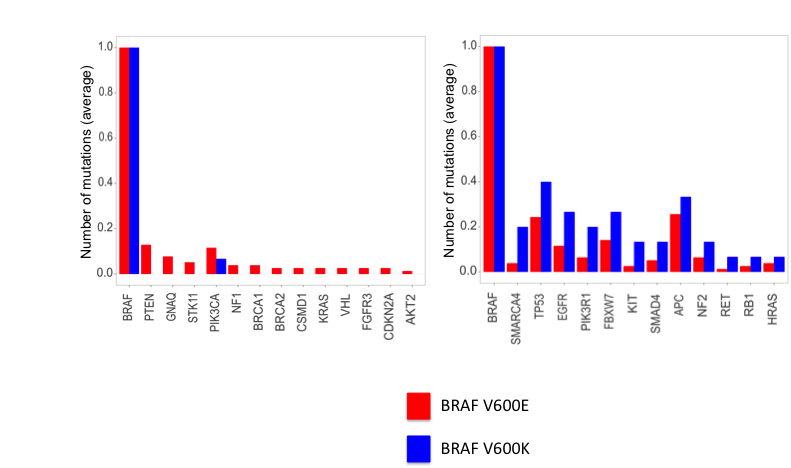
|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gene  Symbol | Total  Counts | Mean  Counts | brafV600E  totalCounts | brafV600K  totalCounts | brafV600E  meanCounts | brafV600K  meanCounts | brafK-brafE  meanCounts | fisher  Pvalue |
| BRAF | 93 | 1 | 78 | 15 | 1 | 1 | 0 | NA |
| TP53 | 25 | 0.268817204 | 19 | 6 | 0.243589744 | 0.4 | 0.156410256 | 0.219104191 |
| APC | 25 | 0.268817204 | 20 | 5 | 0.256410256 | 0.333333333 | 0.076923077 | 0.537328667 |
| FBXW7 | 15 | 0.161290323 | 11 | 4 | 0.141025641 | 0.266666667 | 0.125641026 | 0.254065852 |
| EGFR | 13 | 0.139784946 | 9 | 4 | 0.115384615 | 0.266666667 | 0.151282051 | 0.213765762 |
| PIK3CA | 10 | 0.107526882 | 9 | 1 | 0.115384615 | 0.066666667 | -0.048717949 | 1 |
| PTEN | 10 | 0.107526882 | 10 | 0 | 0.128205128 | 0 | -0.128205128 | 0.356712316 |
| PIK3R1 | 8 | 0.086021505 | 5 | 3 | 0.064102564 | 0.2 | 0.135897436 | 0.115833108 |
| NF2 | 7 | 0.075268817 | 5 | 2 | 0.064102564 | 0.133333333 | 0.069230769 | 0.314446392 |
| SMARCA4 | 6 | 0.064516129 | 3 | 3 | 0.038461538 | 0.2 | 0.161538462 | 0.051102847 |
| SMAD4 | 6 | 0.064516129 | 4 | 2 | 0.051282051 | 0.133333333 | 0.082051282 | 0.247594171 |
| GNAQ | 6 | 0.064516129 | 6 | 0 | 0.076923077 | 0 | -0.076923077 | 0.584561199 |
| KIT | 4 | 0.043010753 | 2 | 2 | 0.025641026 | 0.133333333 | 0.107692308 | 0.120617111 |
| HRAS | 4 | 0.043010753 | 3 | 1 | 0.038461538 | 0.066666667 | 0.028205128 | 0.51145395 |
| STK11 | 4 | 0.043010753 | 4 | 0 | 0.051282051 | 0 | -0.051282051 | 1 |
| RB1 | 3 | 0.032258065 | 2 | 1 | 0.025641026 | 0.066666667 | 0.041025641 | 0.413744741 |
| BRCA1 | 3 | 0.032258065 | 3 | 0 | 0.038461538 | 0 | -0.038461538 | 1 |
| NF1 | 3 | 0.032258065 | 3 | 0 | 0.038461538 | 0 | -0.038461538 | 1 |
| RET | 2 | 0.021505376 | 1 | 1 | 0.012820513 | 0.066666667 | 0.053846154 | 0.298036466 |
| CDKN2A | 2 | 0.021505376 | 2 | 0 | 0.025641026 | 0 | -0.025641026 | 1 |
| FGFR3 | 2 | 0.021505376 | 2 | 0 | 0.025641026 | 0 | -0.025641026 | 1 |
| VHL | 2 | 0.021505376 | 2 | 0 | 0.025641026 | 0 | -0.025641026 | 1 |
| KRAS | 2 | 0.021505376 | 2 | 0 | 0.025641026 | 0 | -0.025641026 | 1 |
| CSMD1 | 2 | 0.021505376 | 2 | 0 | 0.025641026 | 0 | -0.025641026 | 1 |
| BRCA2 | 2 | 0.021505376 | 2 | 0 | 0.025641026 | 0 | -0.025641026 | 1 |
| PDGFRA | 1 | 0.010752688 | 1 | 0 | 0.012820513 | 0 | -0.012820513 | 1 |
| CTNNB1 | 1 | 0.010752688 | 1 | 0 | 0.012820513 | 0 | -0.012820513 | 1 |
| AKT2 | 1 | 0.010752688 | 1 | 0 | 0.012820513 | 0 | -0.012820513 | 1 |
| MET | 1 | 0.010752688 | 1 | 0 | 0.012820513 | 0 | -0.012820513 | 1 |

**Supplementary Figure 1**



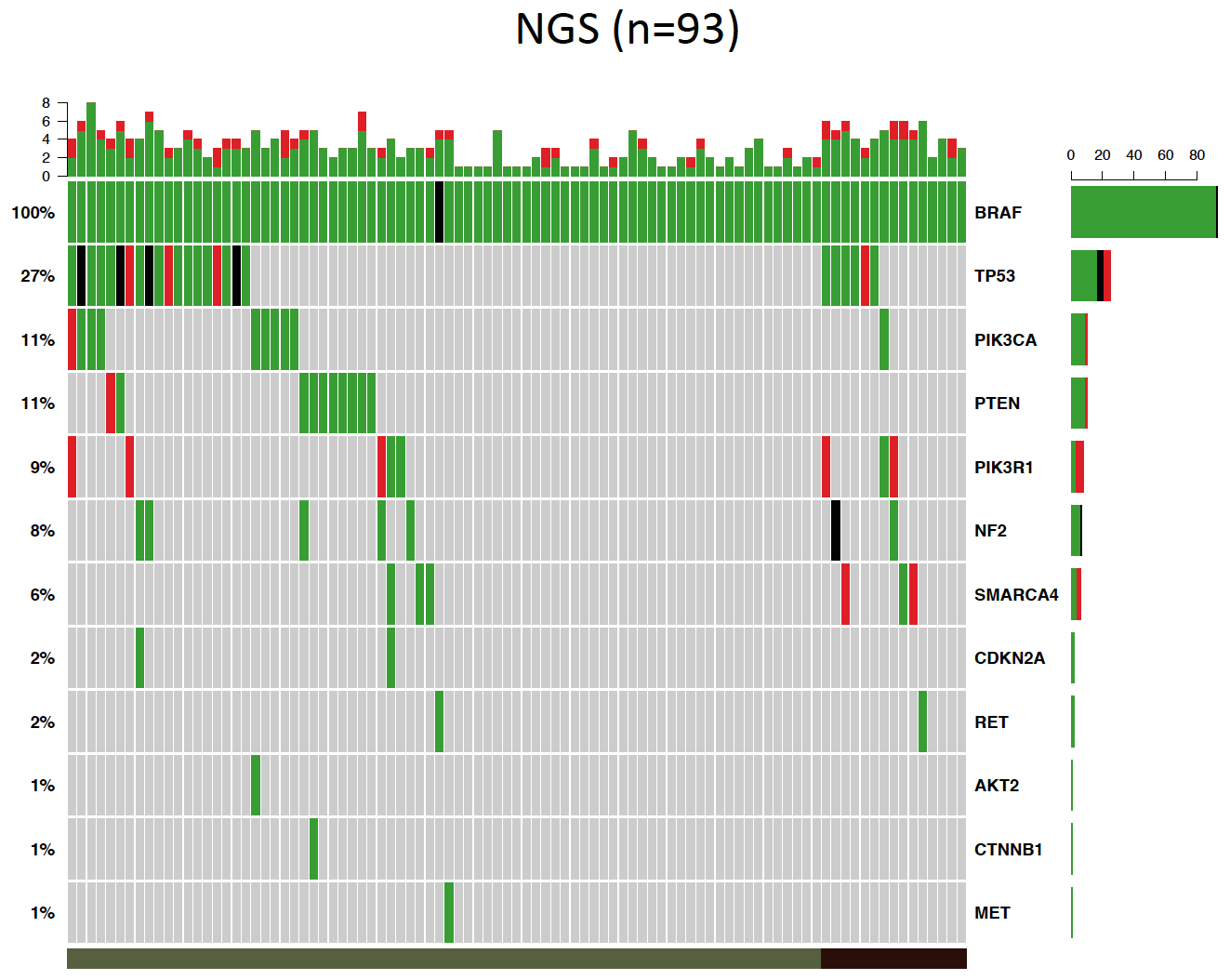
**Supplementary Figure 1.** RNAseq pathway analysis (TCGA data): *Upper panel,* Expression of ERK pathway genes in V600E versus V600K melanoma, using Nazarian and Pratilas genesets; and *Lower panel*, Expression of PI3K-AKT pathway genes in V600E versus V600K melanoma (downSet – *light red/blue*; upSet – *dark red/blue*).Hotelling T2 test was used for the comparison of the mean expression for ERK (*Upper panel*) and PI3K-AKT (*Lower panel*) genes between V600E and V600K groups. Genes above the line are significantly more expressed in V600E (*red*) compared to V600K(*blue*)-mutant melanoma, and that expression increases from the left to the right in the plot.

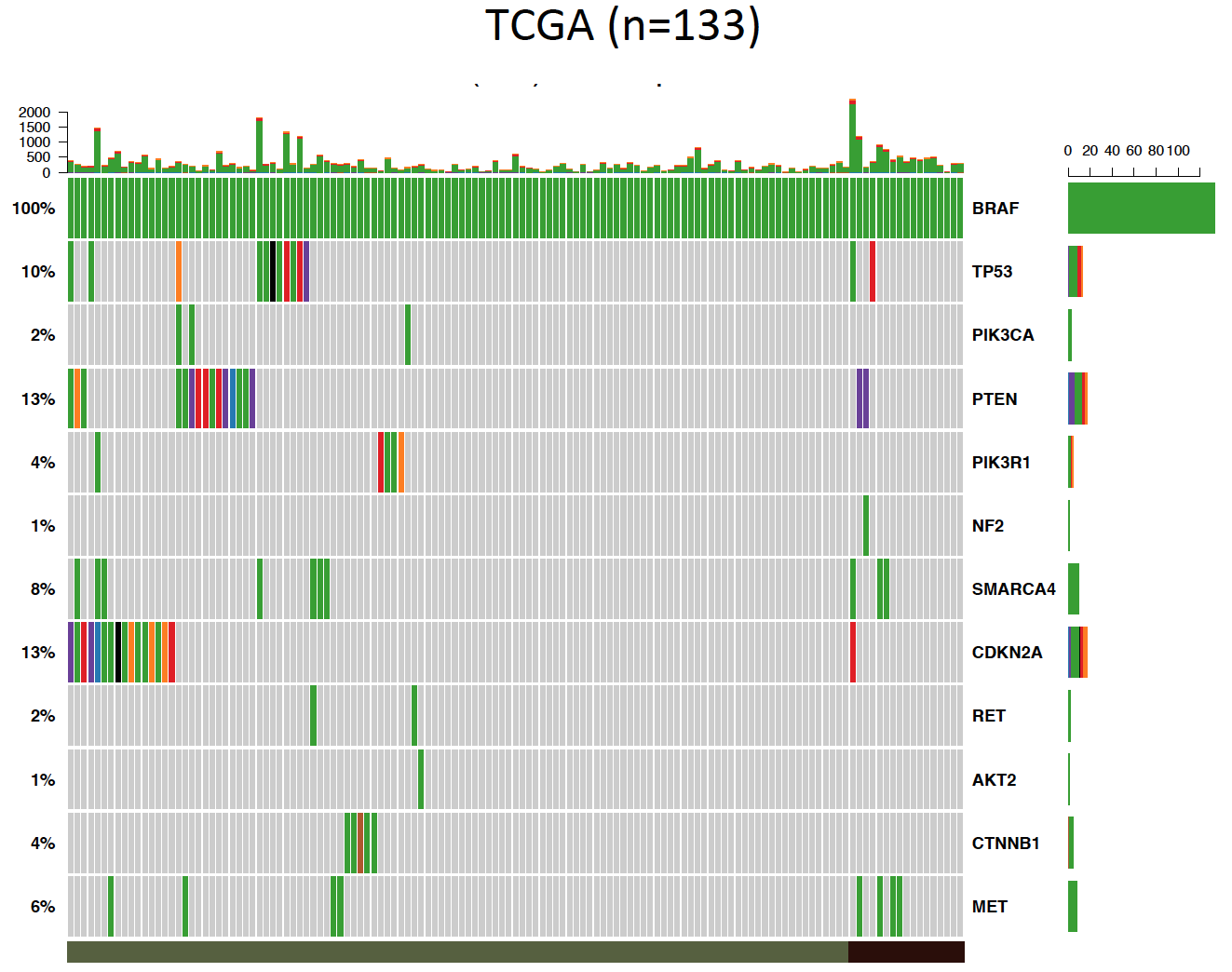
**Supplementary Figure 2**

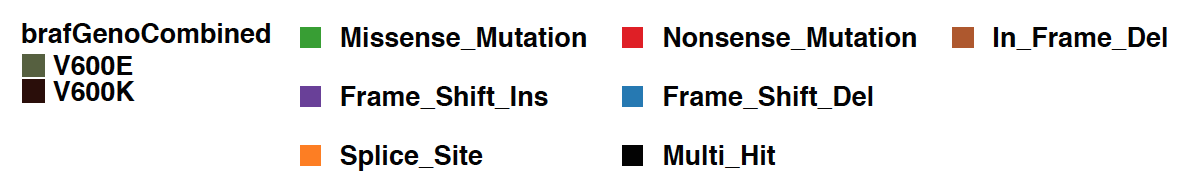


**Supplementary Figure 2.** Frequency of mutations per gene between V600E (*red*) and V600K (*blue*) melanoma (NGS data). *Left panel*, genes more mutated in V600E; *Right panel*, genes more mutated in V600K.

**Supplementary Figure 3**

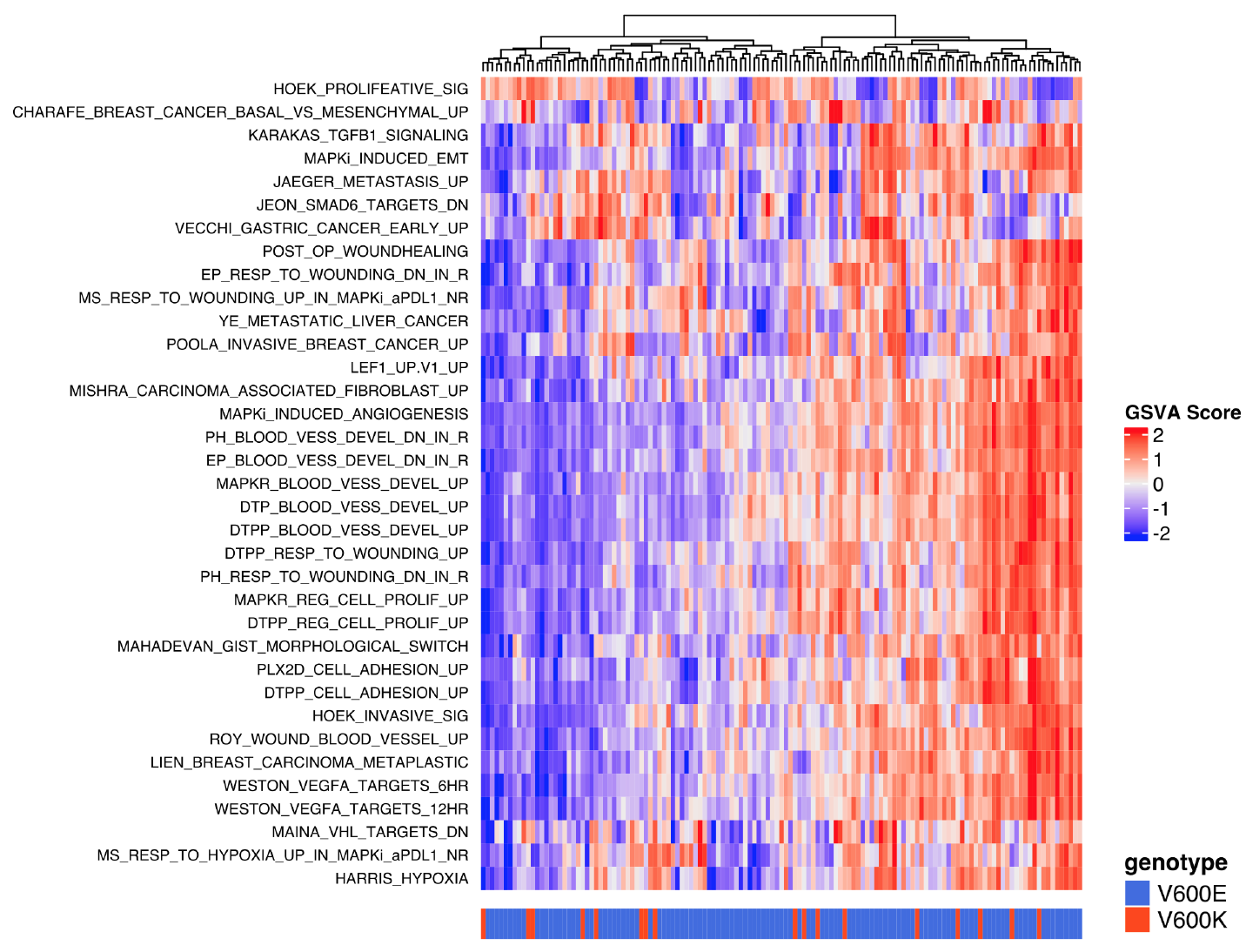
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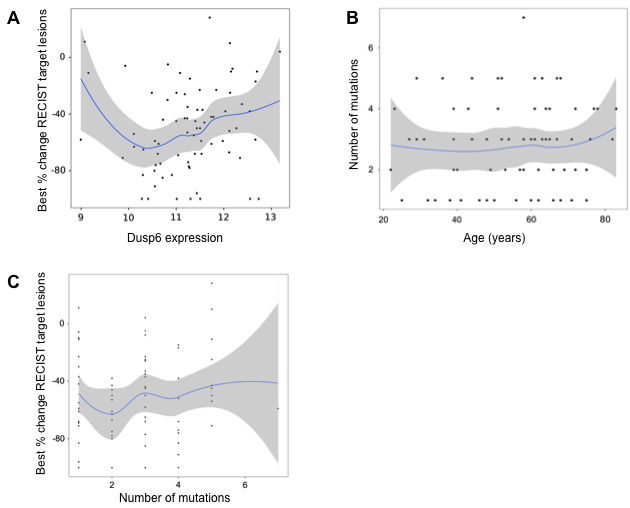
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**Supplementary Figure 3.** Oncoplot of mutations in V600E and V600K melanoma. Frequency of mutations per gene in the NGS (*upper panel*) and TCGA (*lower panel*) cohorts.

**Supplementary Figure 4**

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**Supplementary Figure 4.** Heatmap showing the Gene Set Variance Analysis (GSVA) scores of gene signatures in the V600E versus V600K mutant melanomas (TCGA dataset).



**Supplementary Figure 5.** Spectrum of BRAF V600E-mutant melanomas. **A**. Association between DUSP6 expression and response (best % tumor change from baseline); **B**. Association between mutational burden and age; and **C**. Association between mutational burden and response (best % tumor change from baseline), in V600E-mutant melanomas