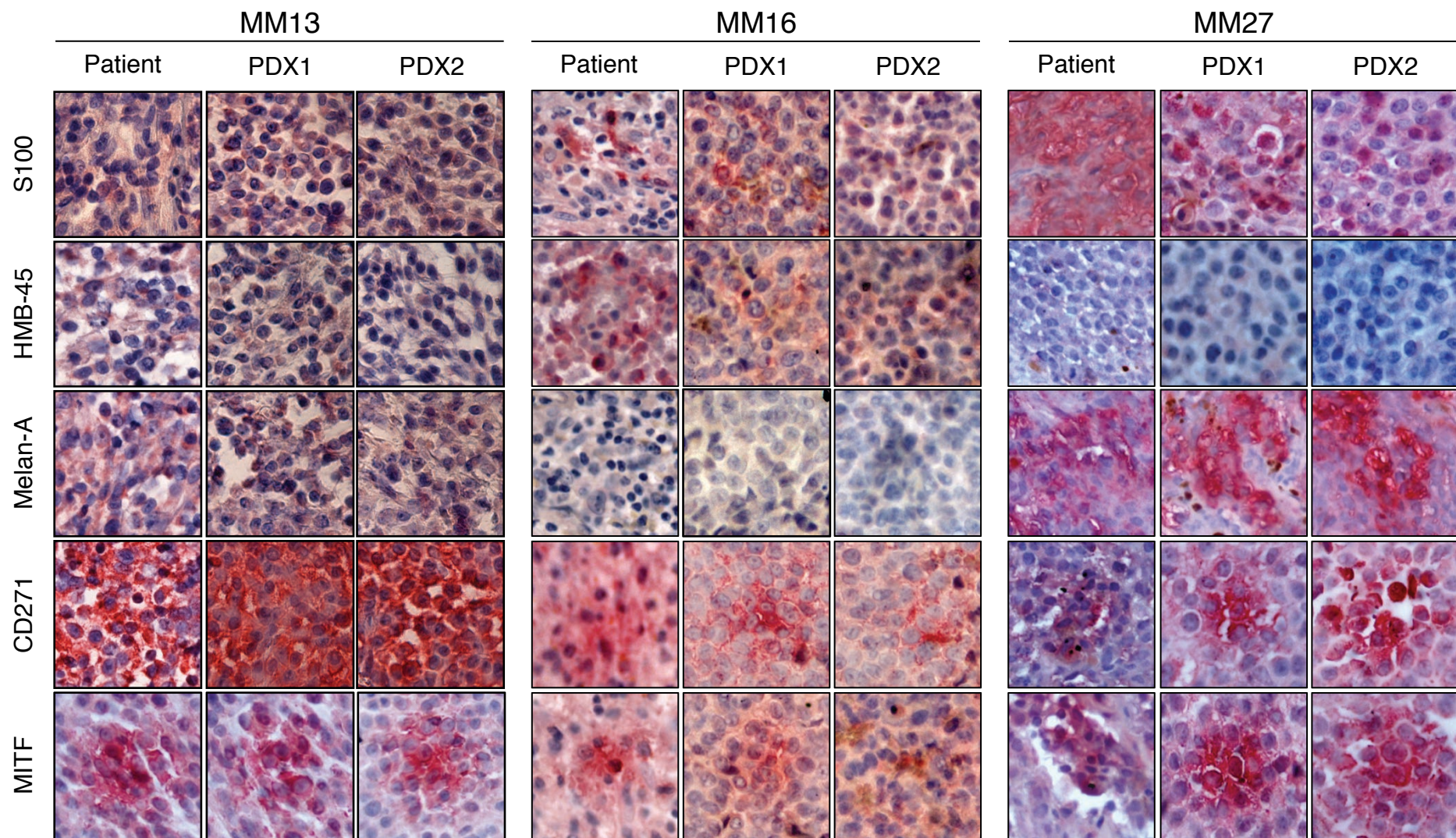
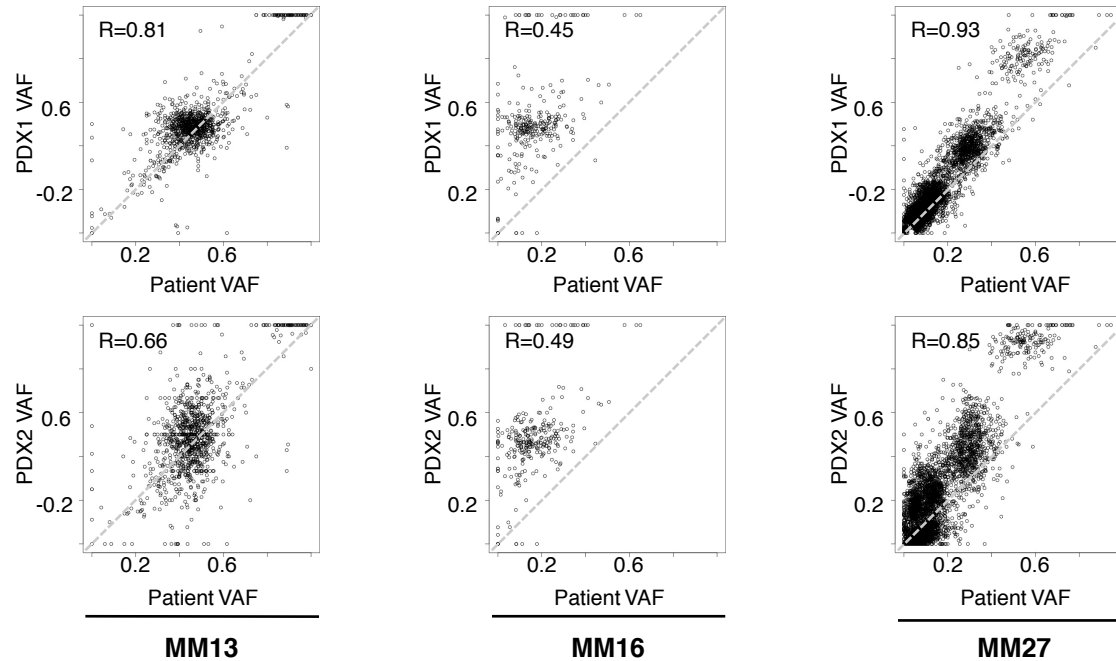




**Figure S1**

**A**

| SNV/InDel Number (%) |                            |               |                |               |                |
|----------------------|----------------------------|---------------|----------------|---------------|----------------|
|                      | Patient<br>(VAF $\geq$ 5%) | PDX1          |                | PDX2          |                |
|                      |                            | Conserved     | <i>de novo</i> | Conserved     | <i>de novo</i> |
| MM13                 | 907                        | 905 (99.8%)   | 2 (0.2%)       | 903 (99.6%)   | 6 (0.7%)       |
| MM16                 | 245                        | 242 (98.8%)   | 15 (6.1%)      | 242 (98.8%)   | 12 (4.9%)      |
| MM27                 | 3,119                      | 3,116 (99.9%) | 13 (0.4%)      | 3,034 (97.3%) | 20 (0.6%)      |

**B****C**

|      |                         | PDX1<br>(R) | PDX2 <sup>shLuc</sup><br>(R) |
|------|-------------------------|-------------|------------------------------|
| MM13 | PDX2 <sup>shKMT2D</sup> | 0,84        | 0,92                         |
| MM27 | PDX2 <sup>shKMT2D</sup> | 0,74        | 0,96                         |

**D**

|      |                       | PDX1<br>(R) | PDX2 <sup>shKMT2D</sup><br>(R) |
|------|-----------------------|-------------|--------------------------------|
| MM13 | PDX2 <sup>shLuc</sup> | 0,8         | 0,92                           |
| MM27 | PDX2 <sup>shLuc</sup> | 0,72        | 0,96                           |

**Figure S2**

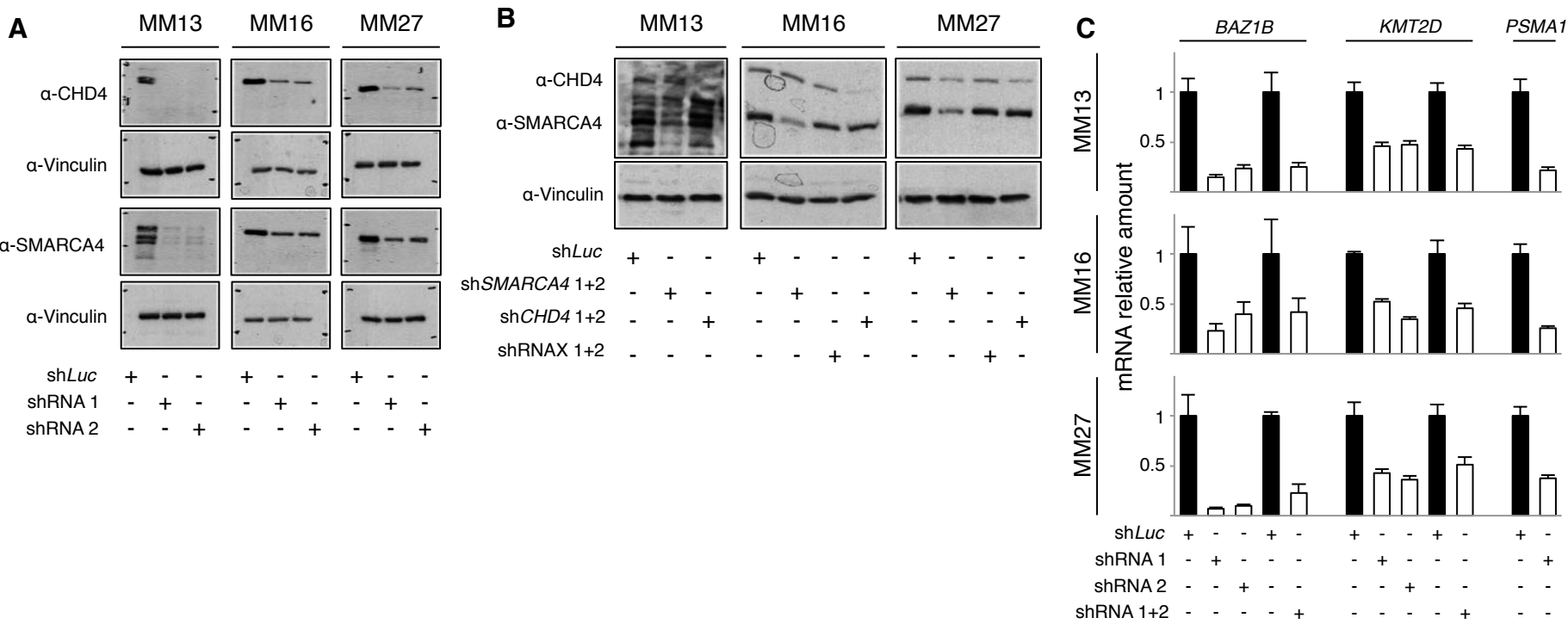
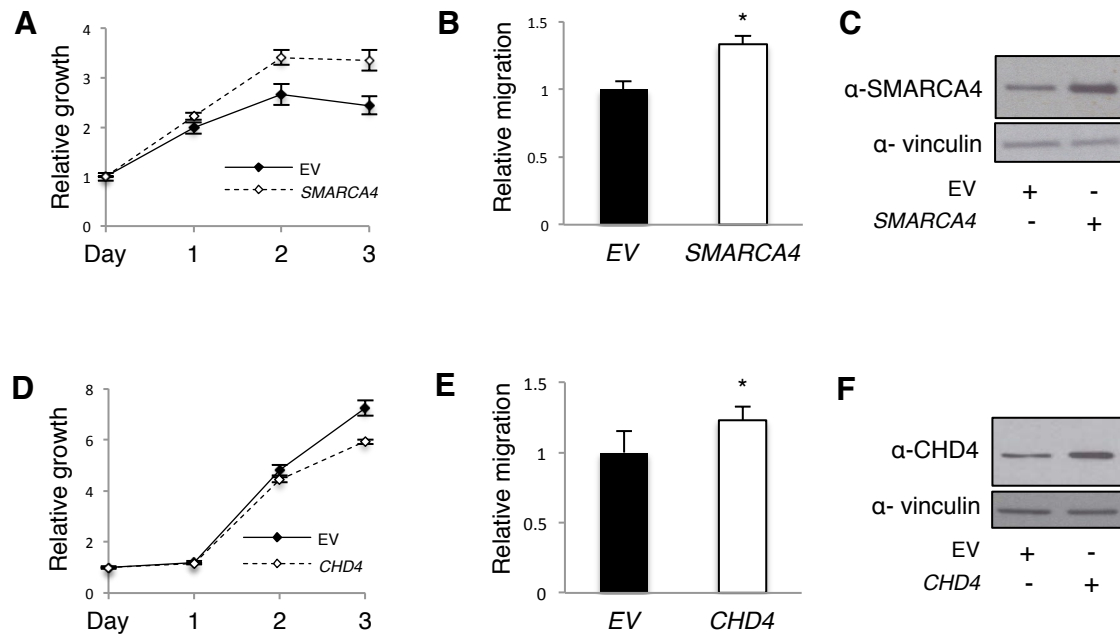
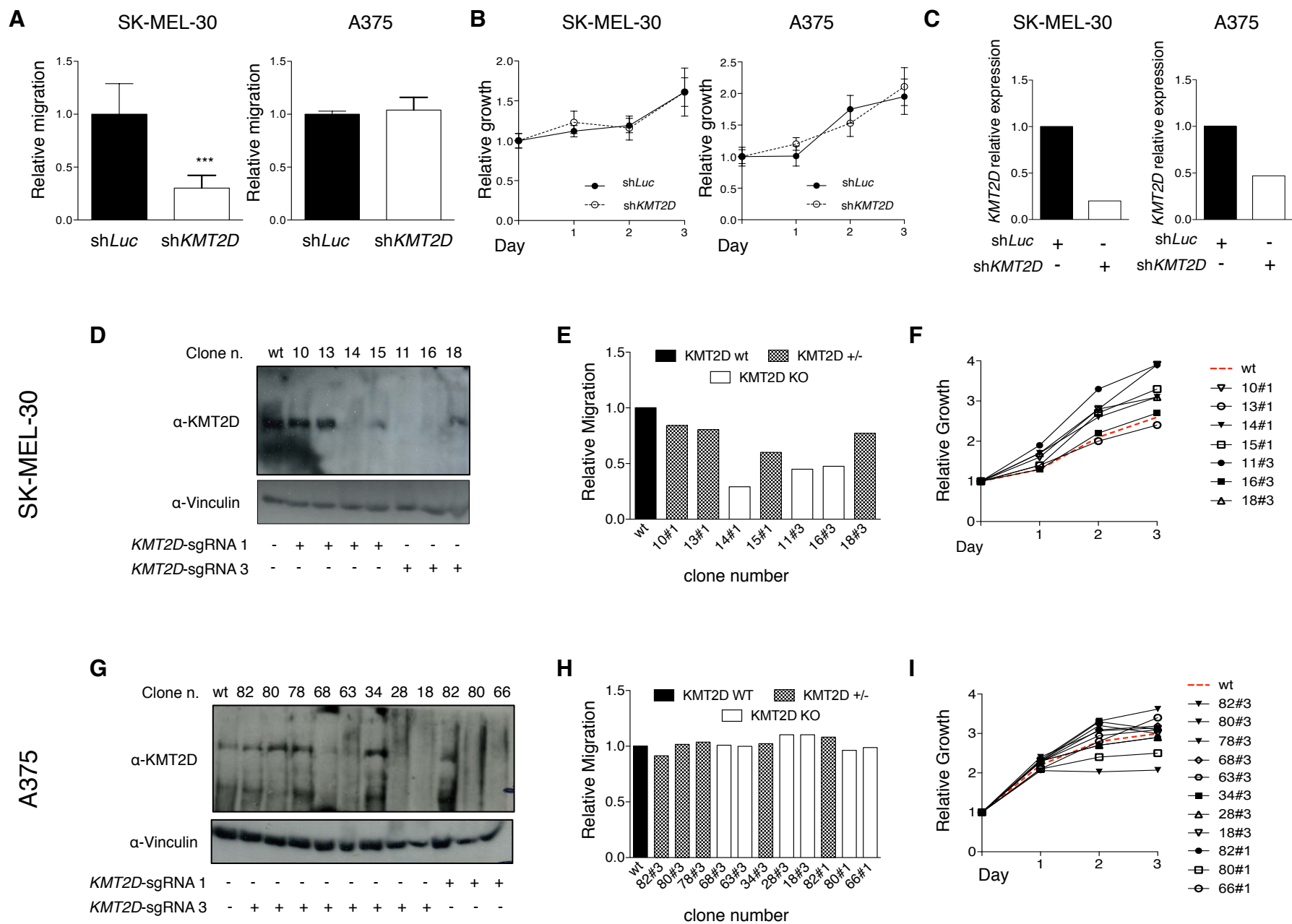


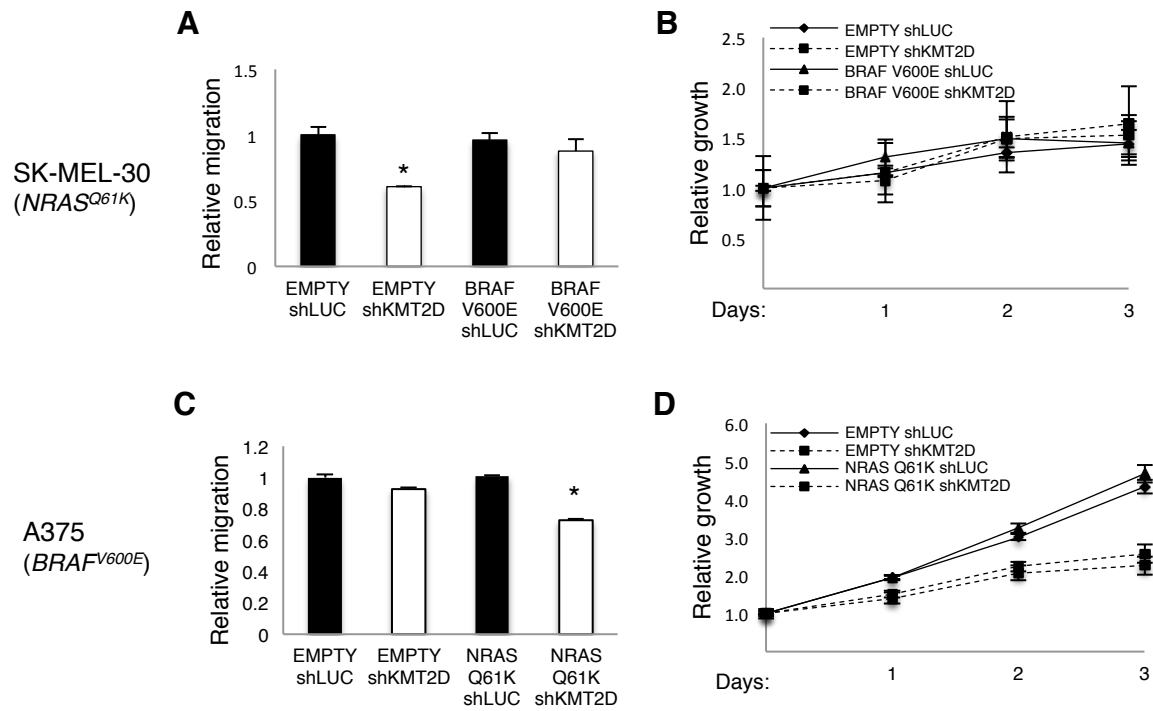
Figure S3



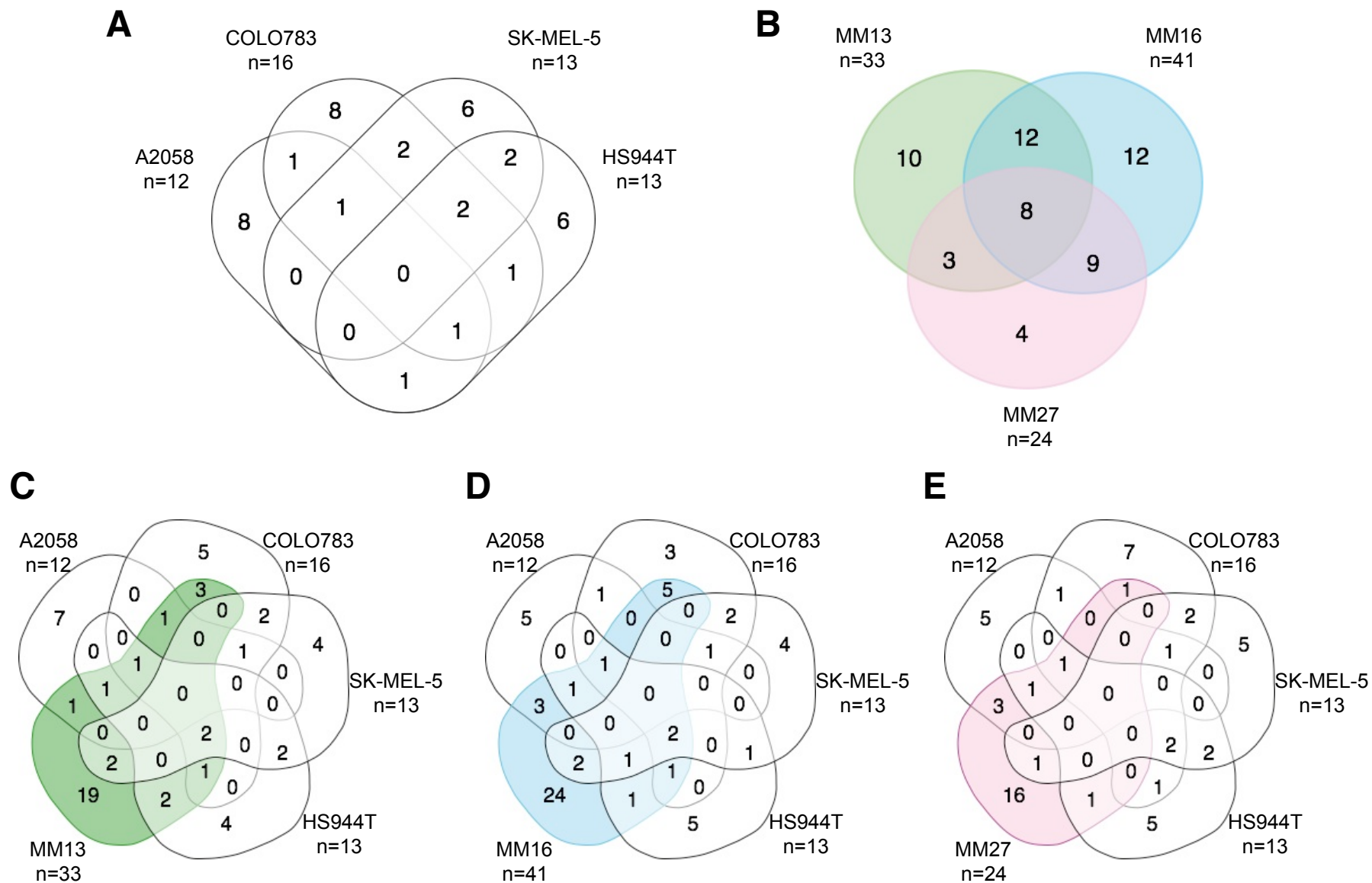
**Figure S4**



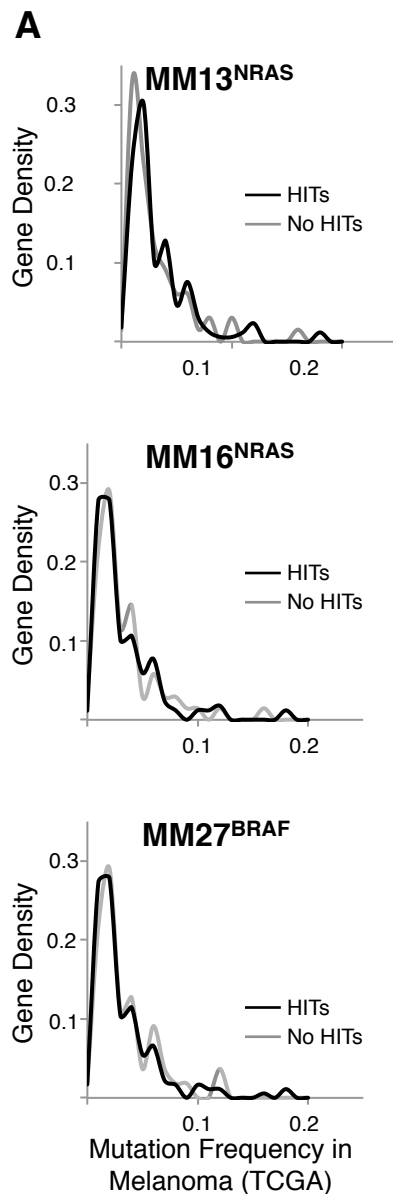
**Figure S5**



**Figure S6**



**Figure S7**



B

|                      |         | Number of Genes | Mutated Genes |            |         |
|----------------------|---------|-----------------|---------------|------------|---------|
|                      |         |                 | Number        | Percentage | p-value |
| MM13 <sup>NRAS</sup> | HITs    | 66              | 3             | 4.6%       | 0.84    |
|                      | no HITs | 170             | 12            | 7.0%       |         |
|                      | Total   | 236             | 15            | 6.3%       |         |
| MM16 <sup>NRAS</sup> | HITs    | 69              | 0             | 0.0%       | 1.00    |
|                      | no HITs | 167             | 2             | 1.2%       |         |
|                      | Total   | 236             | 2             | 0.8%       |         |
| MM27 <sup>BRAF</sup> | HITs    | 55              | 15            | 25.5%      | 0.52    |
|                      | no HITs | 181             | 48            | 26.4%      |         |
|                      | Total   | 236             | 63            | 26.2%      |         |

**C**

| Gene           | PDXs with gene depletion | Actionable | Clinically Actionable |
|----------------|--------------------------|------------|-----------------------|
| <i>IDH2</i>    | MM13                     |            | yes                   |
| <i>TAF1</i>    | MM13                     | yes        |                       |
| <i>BRD4</i>    | MM13 MM16                | yes        |                       |
| <i>SMARCA4</i> | MM13 MM16 MM27           | yes        |                       |
| <i>BRD2</i>    | MM16                     | yes        |                       |
| <i>DNMT1</i>   | MM16                     |            | yes                   |
| <i>SMARCB1</i> | MM16                     |            | yes                   |
| <i>TET2</i>    | MM16                     |            | yes                   |
| <i>ARID1A</i>  | MM16 MM27                | yes        |                       |
| <i>KMT2A</i>   | MM16 MM27                |            | yes                   |

**Figure S8**