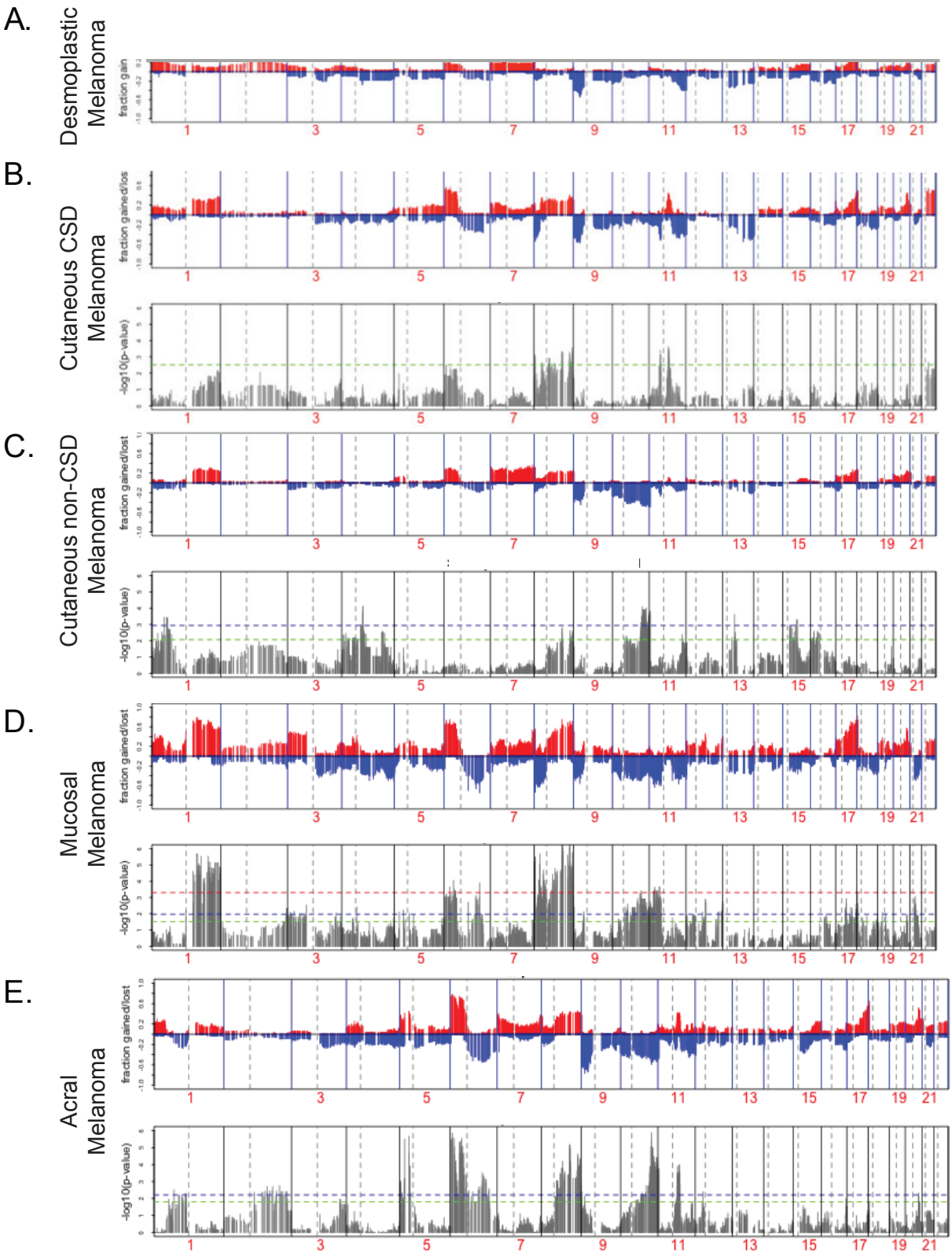
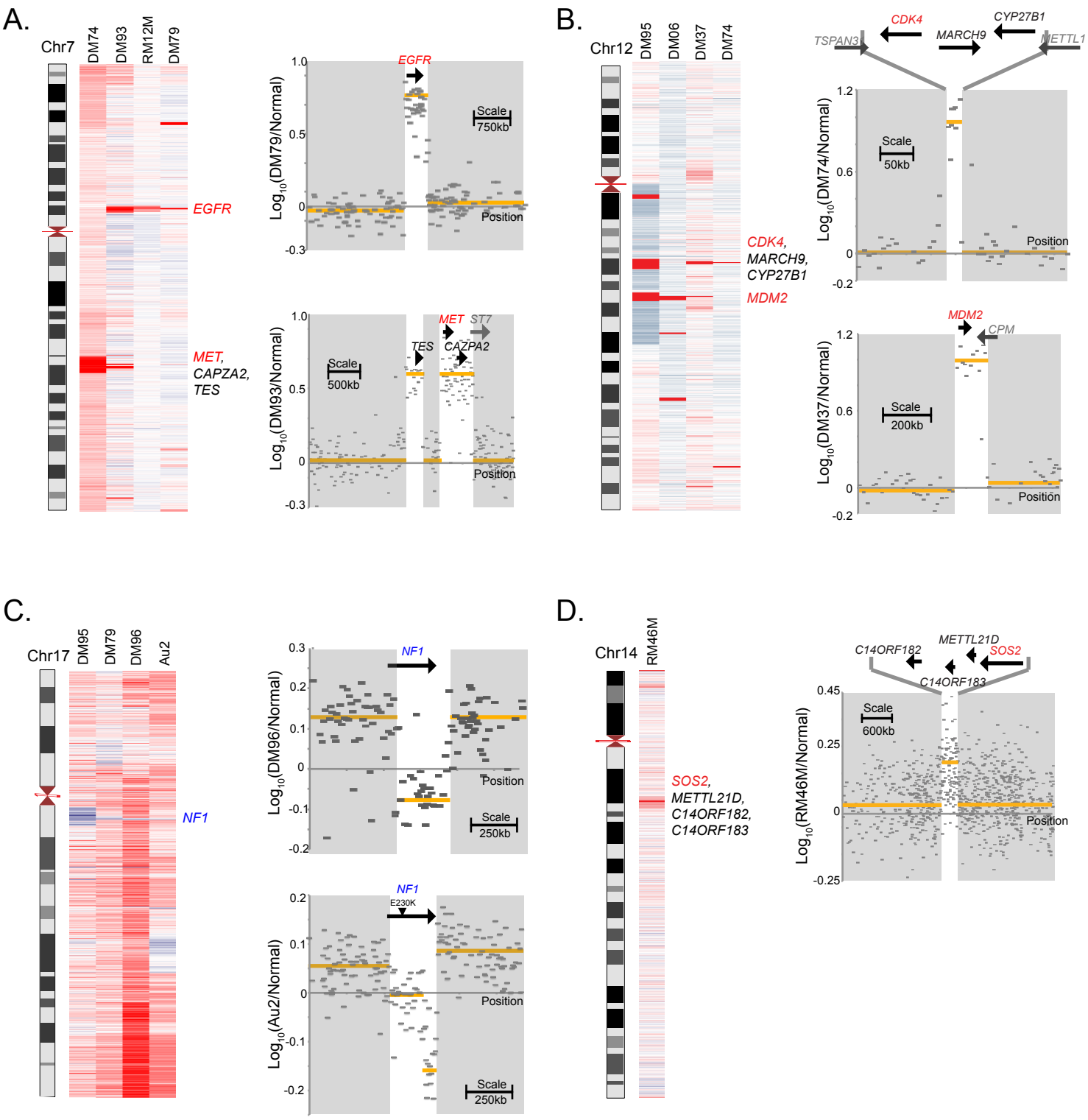
Supplementary Figure 1.



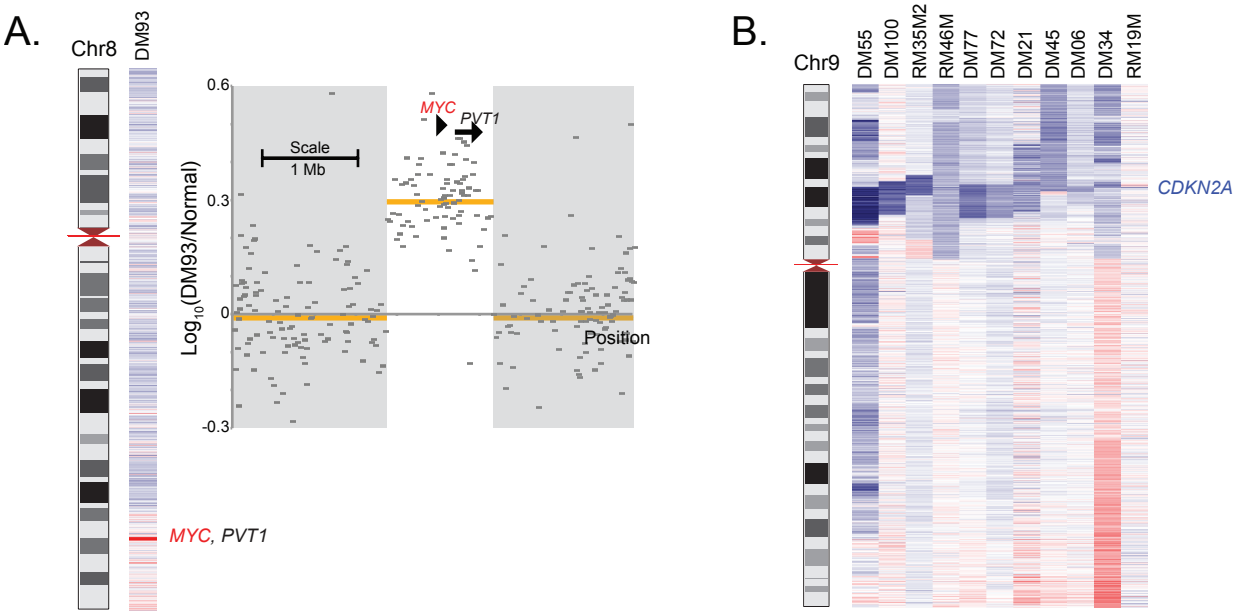
Supplementary Figure 1. DMs have comparatively few copy number alterations and an overall copy number spectrum most similar to chronically sun damaged cutaneous melanomas. A-E. Gains (red) and losses (blue) across melanoma subtypes determined as described (see methods). To avoid obscuring copy number changes, only melanomas with limited stromal cell contamination were included. Note that DMs typically have fewer copy number alterations than other subtypes of melanomas. Copy number data from non-desmoplastic melanomas was previously published(39). In panels B-E, the lower plot notes regions of significant difference between DMs and each subtype – note that DMs were most similar to cutaneous CSD melanomas. In these panels, the green, blue, and red horizontal dotted lines correspond to q values of 0.1, 0.05, and 0.01 respectively.

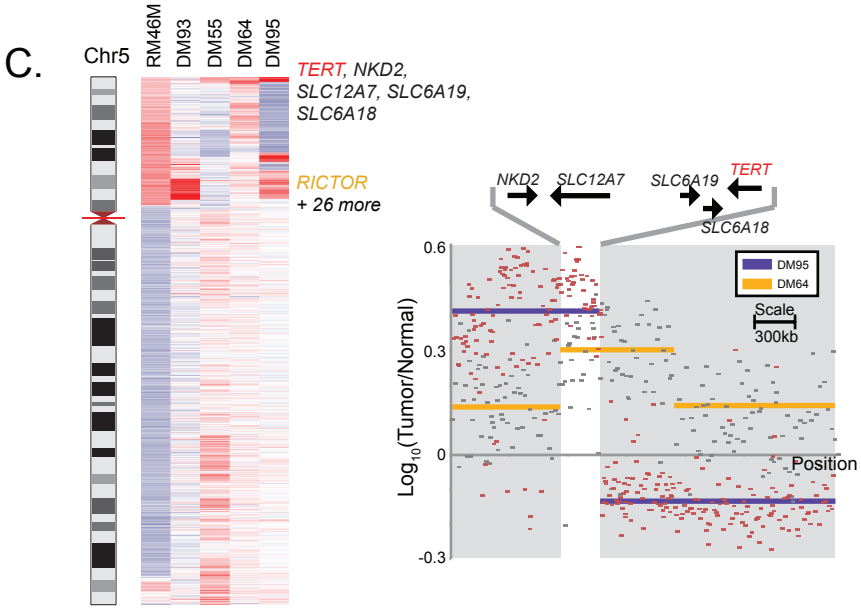
Supplementary Figure 2.

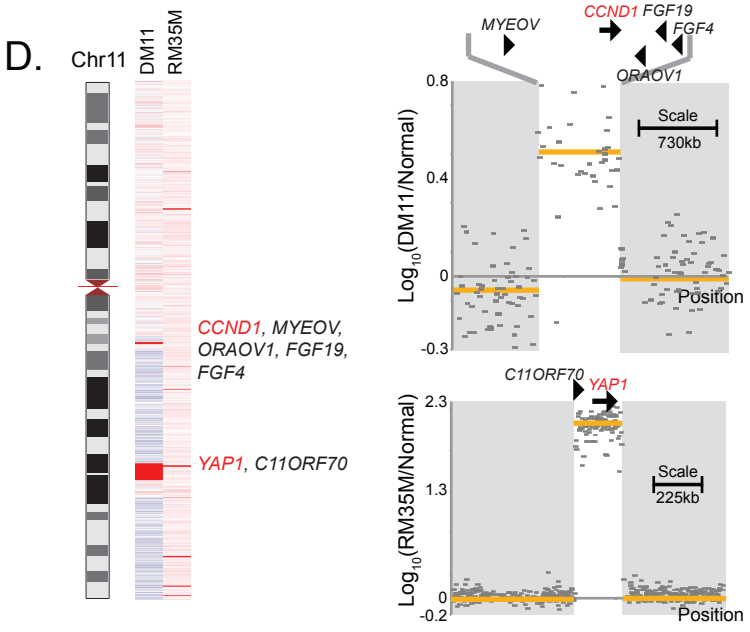


Supplementary Figure 2. Focal copy number alterations striking *EGFR*, *MET*, *CDK4*, *MDM2*, *NF1*, and *SOS2*. In all panels, a heatmap and scatterplots are shown. Heatmaps depict chromosomal gains (red) and losses (blue) striking select genes (labeled). All genes in the minimal copy number alteration (CNA) are listed with the presumed driver colored red (oncogene) or blue (tumor suppressor). To the right of each heatmap is a scatterplot of the most minimal CNA with the location of all UCSC genes annotated. The y-axis notes the log10 ratios from copy number data with chromosomal position along the x-axis. **A.** Focal amplification of *EGFR* and *MET* on chromosome 7. **B.** Focal amplification of *CDK4* and *MDM2* on chromosome 12. **C.** Focal deletion of *NF1* on chromosome 17. **D.** Focal amplification of *SOS2* on chromosome 14.

Supplementary Figure 3.

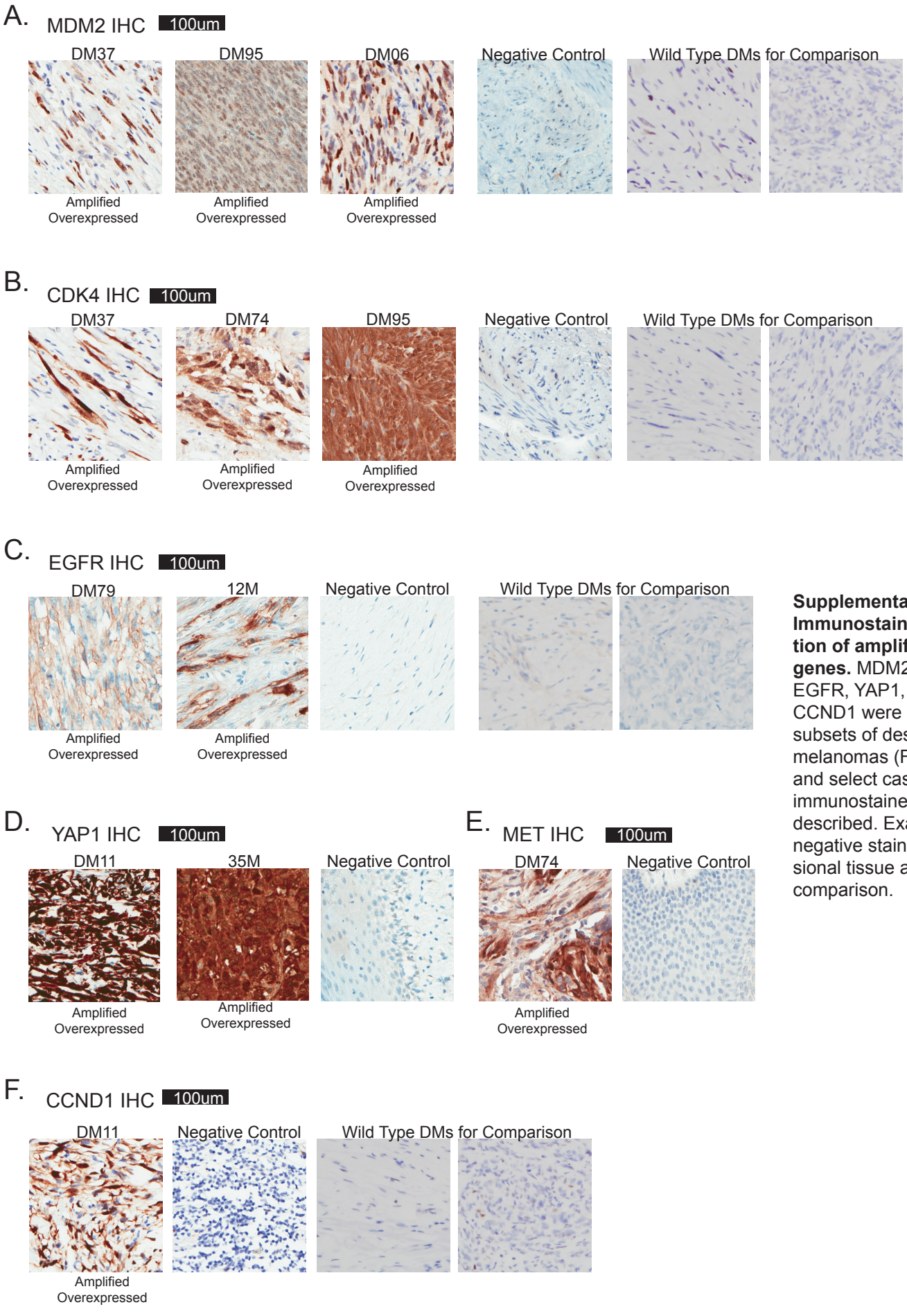






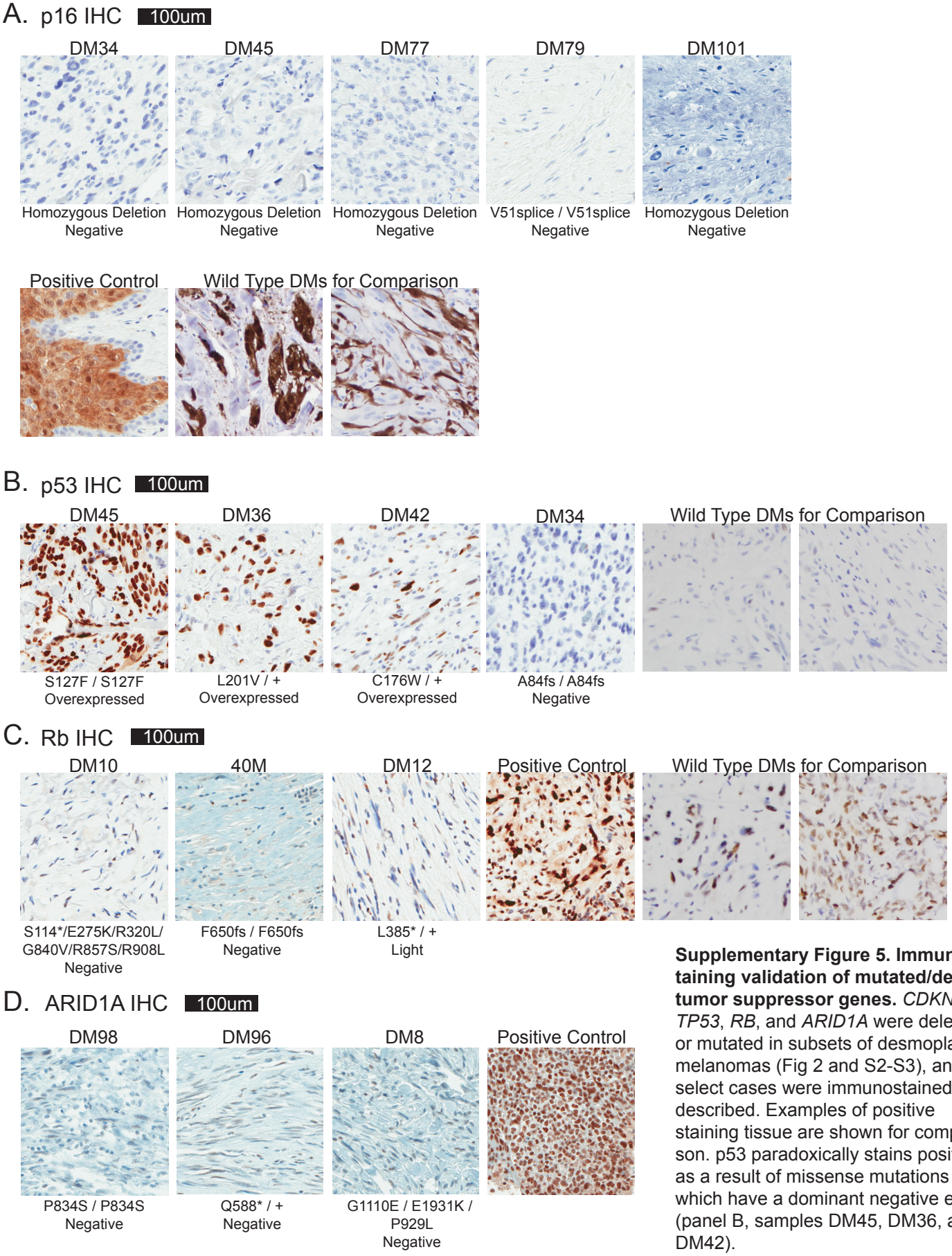
Supplementary Figure 3. Focal copy number alterations striking *MYC*, *CDKN2A*, *TERT*, *CCND1*, and *YAP1*. Data from all panels are plotted as in Figure S2 (see figure legend for further description). **A.** Focal amplification of *MYC* on chromosome 8. **B.** Focal deletions of *CDKN2A* on chromosome 9. **C.** Focal amplification of *TERT* on chromosome 5. Below *TERT* was a recurrent amplification, commonly seen in many melanoma subtypes that harbored 27 genes, including *RICTOR*, one of the leading candidate drivers. **D.** Focal amplification of *CCND1* and *YAP1* on chromosome 11.

Supplementary Figure 4.



Supplementary Figure 4. Immunostaining validation of amplified oncogenes. MDM2, CDK4, EGFR, YAP1, MET, and CCND1 were amplified in subsets of desmoplastic melanomas (Fig S2-3), and select cases were immunostained as described. Examples of negative staining non-lesional tissue are shown for comparison.

Supplementary Figure 5.



Supplementary Figure 5. Immunostaining validation of mutated/deleted tumor suppressor genes. *CDKN2A*, *TP53*, *RB*, and *ARID1A* were deleted or mutated in subsets of desmoplastic melanomas (Fig 2 and S2-S3), and select cases were immunostained as described. Examples of positive staining tissue are shown for comparison. p53 paradoxically stains positive as a result of missense mutations which have a dominant negative effect (panel B, samples DM45, DM36, and DM42).

Supplementary Figure 6.

Sample	1,295,228 Status	1,295,250 Status	Copy Number
DM1	Mut	Mut	
DM11	WT	Mut	
DM2	Mut	WT	
DM14	Mut	WT	
49M	Mut	WT	
46M	Mut	WT	
Au2	WT	Mut	
40M	Mut	WT	
35M	Mut	WT	
Au1	Mut	WT	
19M	Mut	WT	
Au10	WT	WT	
37M	WT	WT	
DM95	WT	WT	Amp
Au8	WT	Mut	
Au4	Mut	WT	
Au9	Mut	WT	
Au3	WT	Mut	
71M	WT	Mut	
12M	Mut	WT	
DM16		WT	
11M	Mut		
53M	Mut		
DM55		WT	Amp
DM64			Amp
DM102			
Au7			
Au5			
DM77			
DM51			
DM58			
DM6			
Au6			
DM94			
DM8			
DM101			
DM34			
DM28			
DM98			
DM59			
DM79			
DM4			
DM43			
DM45			
DM17			
DM96			
DM37			
DM65			
DM36			
DM93			
DM25			
DM74			
DM42			
DM31			
DM18			
DM48			
DM26			
DM29			
DM99			
DM10			
DM12			
DM49			

Legend

WT Mut -- 95% Confidence

WT Mut -- 90% Confidence

"WT" -- Wild Type

"Mut" -- Mutant

"Amp" -- Amplified

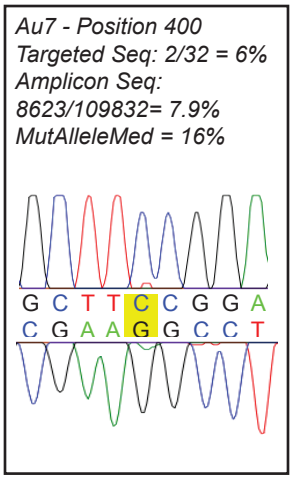
85% (11/13) mutant at 95% confidence

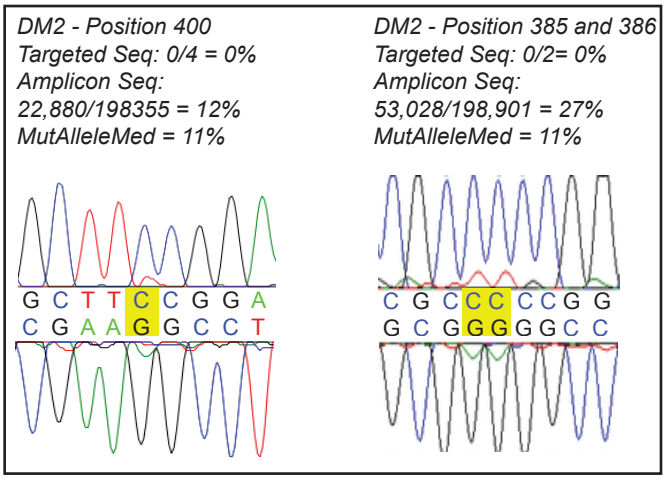
85% (17/20) mutant at 90% confidence

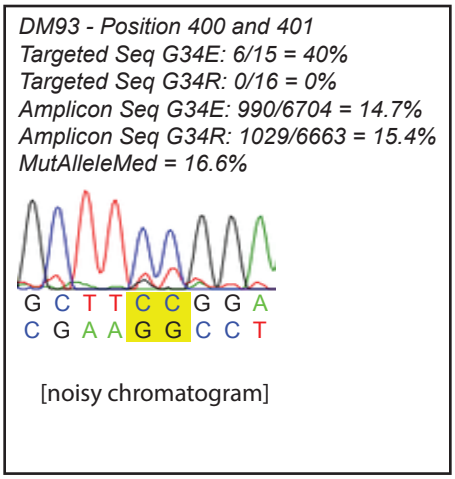
5% (3/62) focal, high amplitude amplification

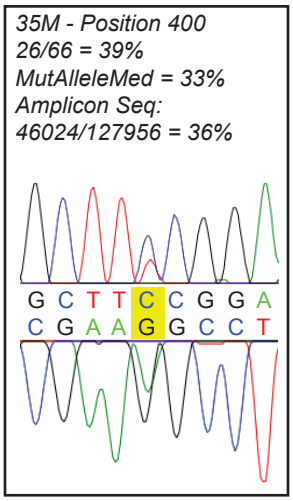
Supplementary Figure 6. *TERT* promoter mutation status. Coverage over the *TERT* promoter was generally low. Samples are rank ordered by our ability to call mutations at the 228 and 250 *TERT* promoter mutational hotspots as described. 85% of "callable" samples had a *TERT* promoter mutation.

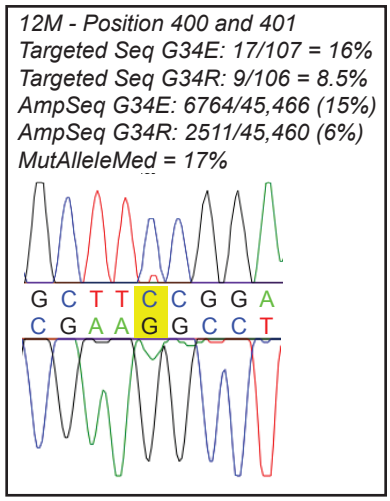
Supplementary Figure 7.

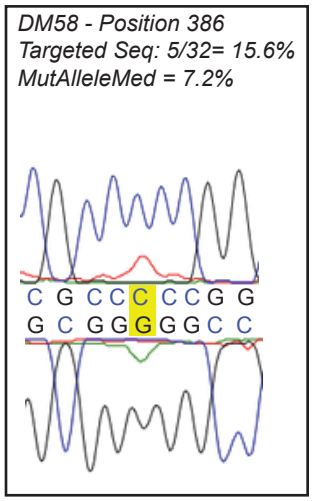


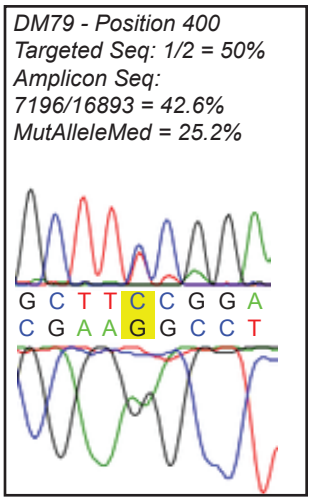


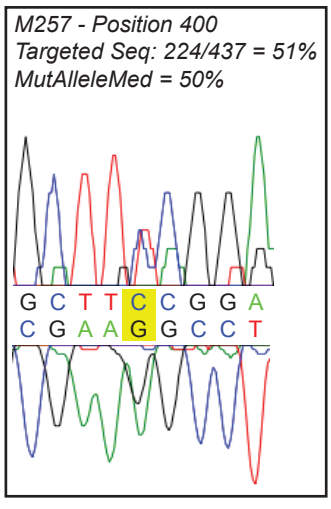






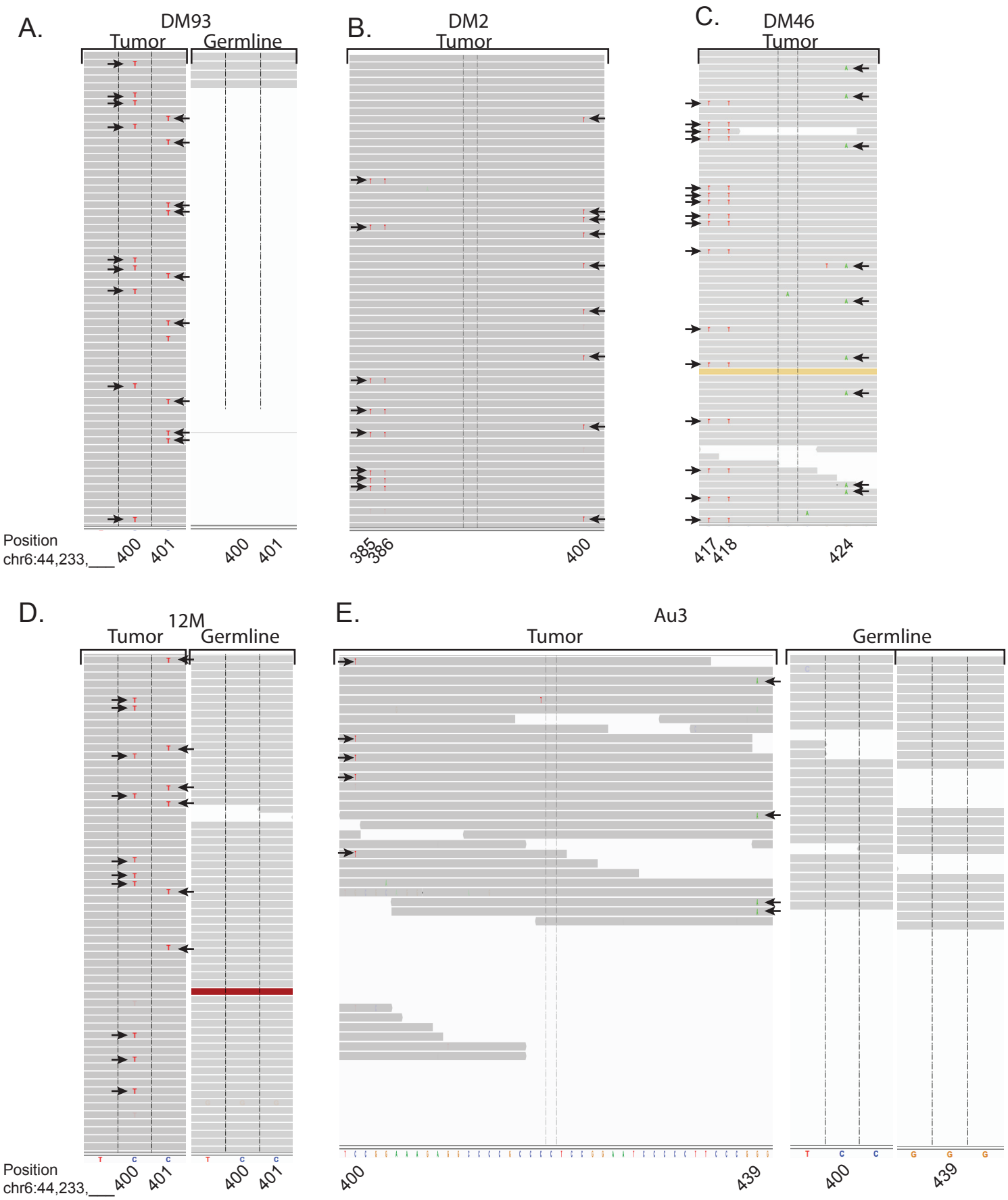






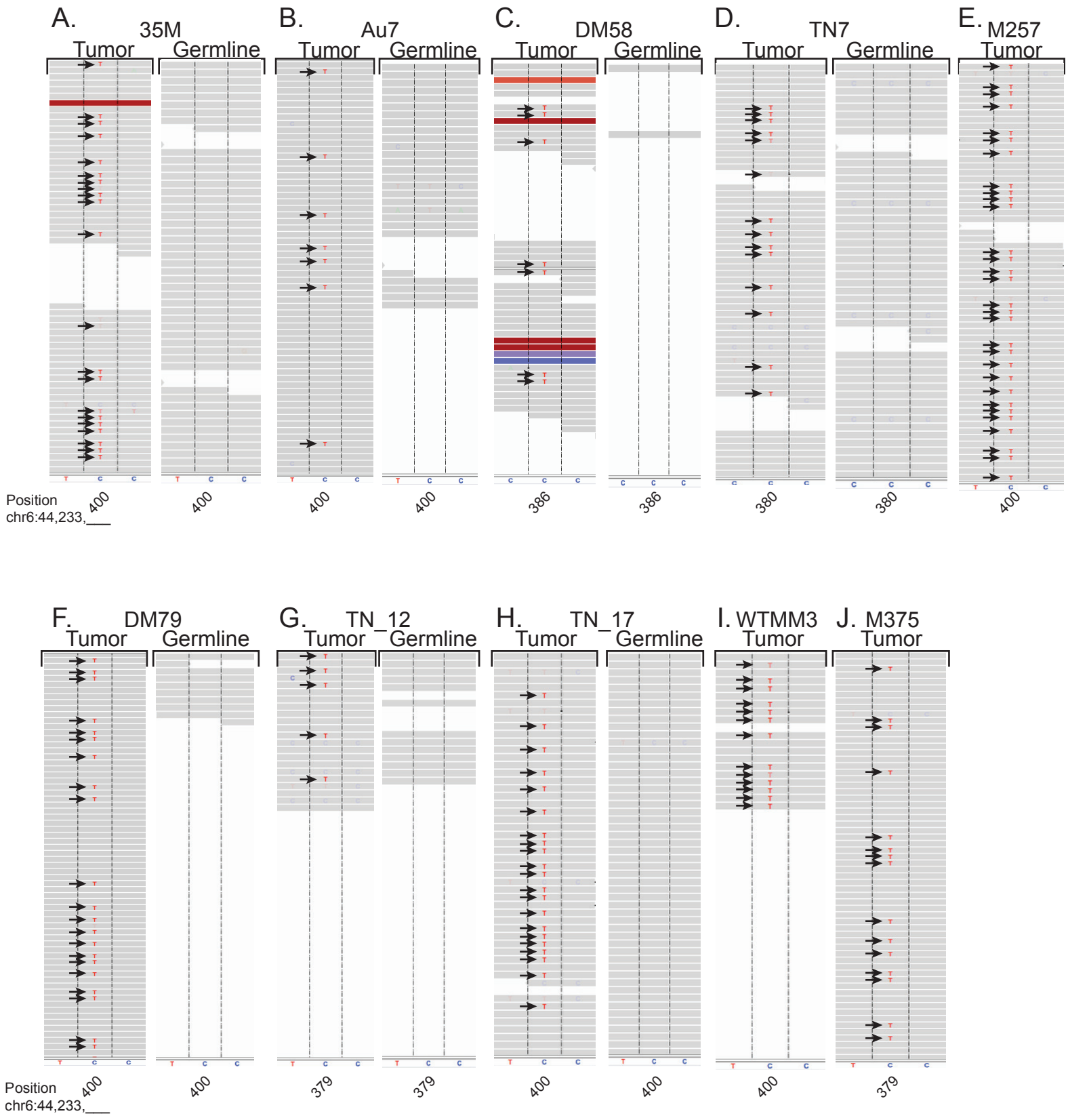
Supplementary Figure 7. Validation of *NFKBIE* hotspot mutations. All *NFKBIE* hotspot mutations from the discovery and validation cohorts were detected using at least two of the following assays: targeted sequencing, whole genome sequencing, Sanger sequencing, and amplicon sequencing (summarized in table S6). Supporting read summaries and Sanger sequencing chromatograms associated with each mutation.

Supplementary Figure 8.



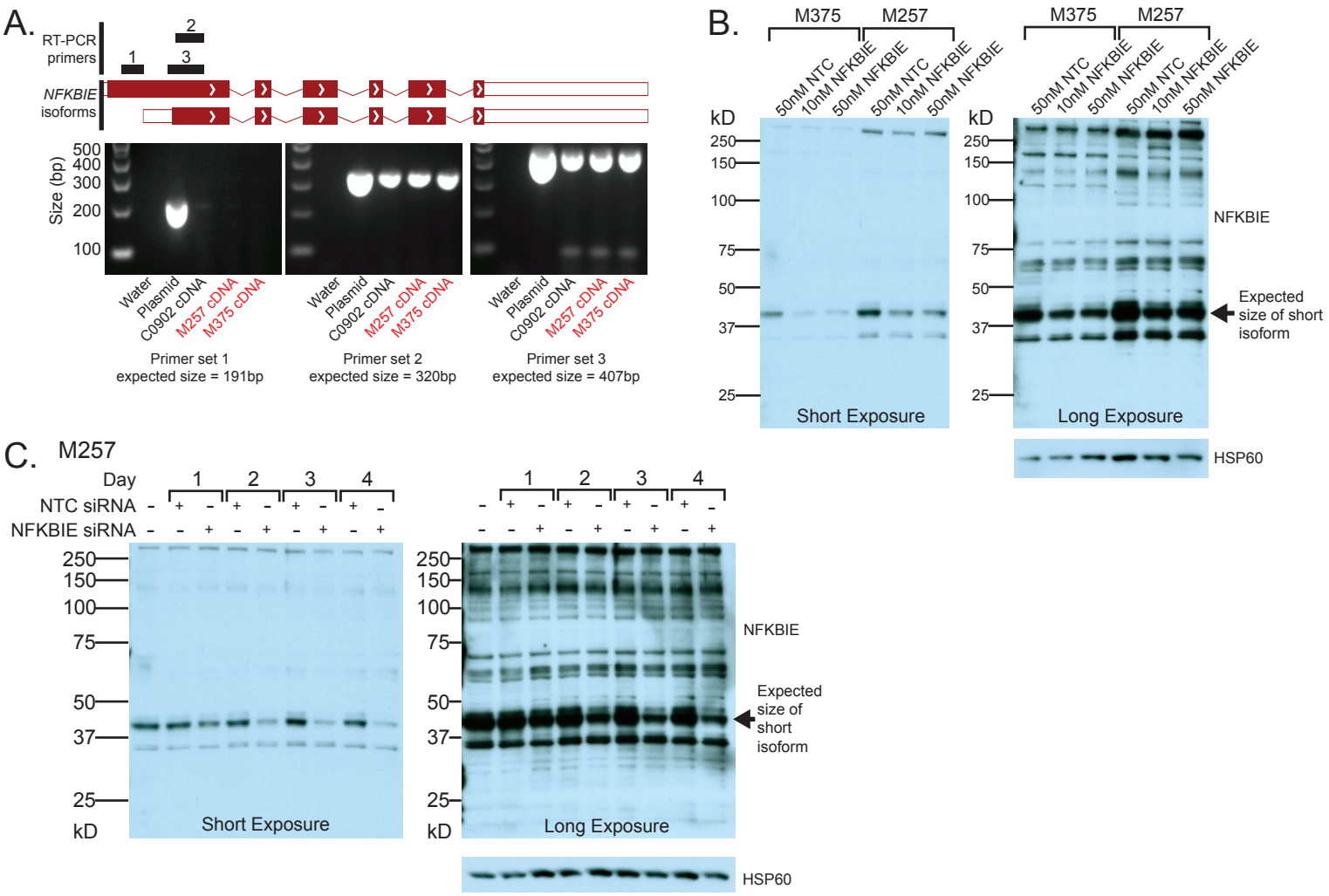
Supplementary Figure 8. *NFKBIE* hotspot mutations striking both alleles. A-E. Five samples had two *NFKBIE* mutations at nearby genomic coordinates. IGV views of mutant and wildtype germline reads. The mutually exclusive mutant read pattern in each of these cases indicates that the mutations affect both alleles.

Supplementary Figure 9.



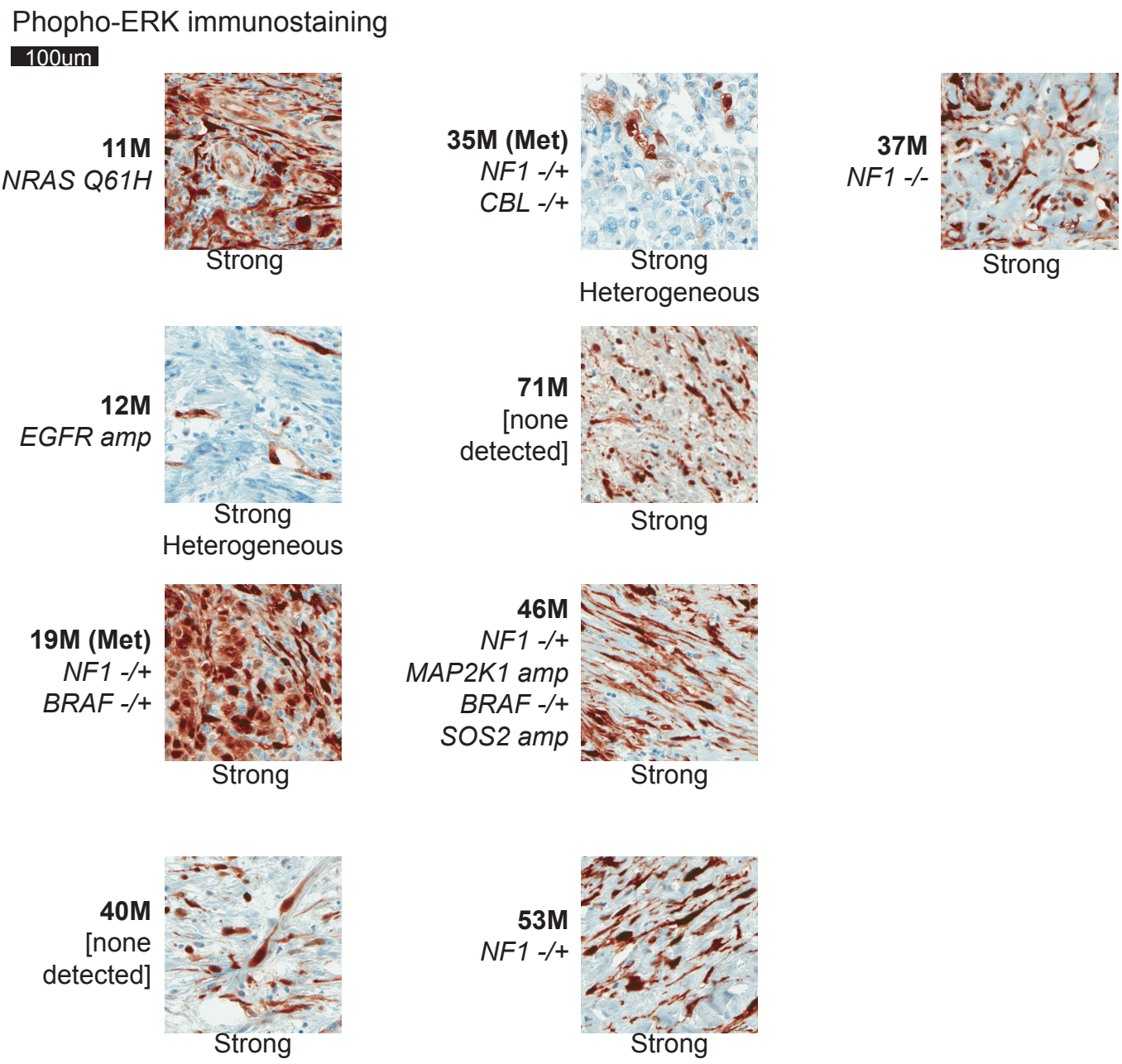
Supplementary Figure 9. *NFKBIE* hotspot mutations affecting one allele. IGV views of mutant and wildtype germline reads in samples with one *NFKBIE* mutation.

Supplementary Figure 10.



Supplementary Figure 10. The short isoform of *NFKBIE* is expressed in *NFKBIE*-mutant cell lines. The *NFKBIE* locus encodes two potential isoforms as described (Fig 4). **A.** RT-PCR primers were designed to detect the long isoform (primer set 1) or both isoforms (primer sets 2 and 3). *NFKBIE*-mutant (M257 and M375) and nonmutant (C0902) cell lines exclusively expressed the short isoform. **B-C.** The short and long isoforms should respectively yield proteins of 45kD or 62kD. Only one specific band at approximately 45kD was observed in NFKBIE mutant cell lines M257 and M375. **D.** Cell fractionation indicates that NFkB transcription factors and *NFKBIE* are cytoplasmic in *NFKBIE*-mutant cell lines as compared to A375. All cell lines were grown in full serum.

Supplementary Figure 11.



Supplementary Figure 11. Phospho-ERK staining is ubiquitous in desmoplastic melanoma. Phospho-ERK staining was strong in all (9/9) desmoplastic melanomas stained. Staining was heterogeneous for samples 12M and 35M.