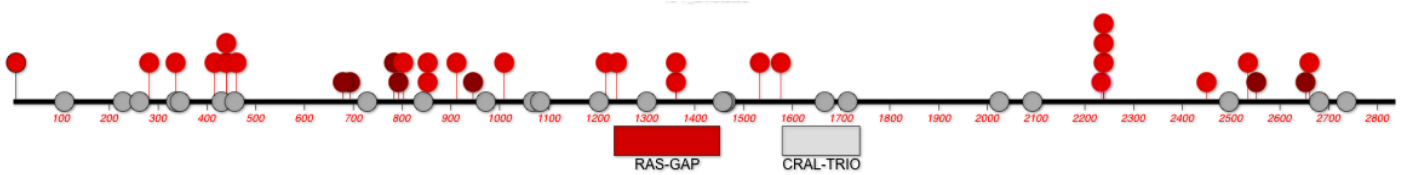
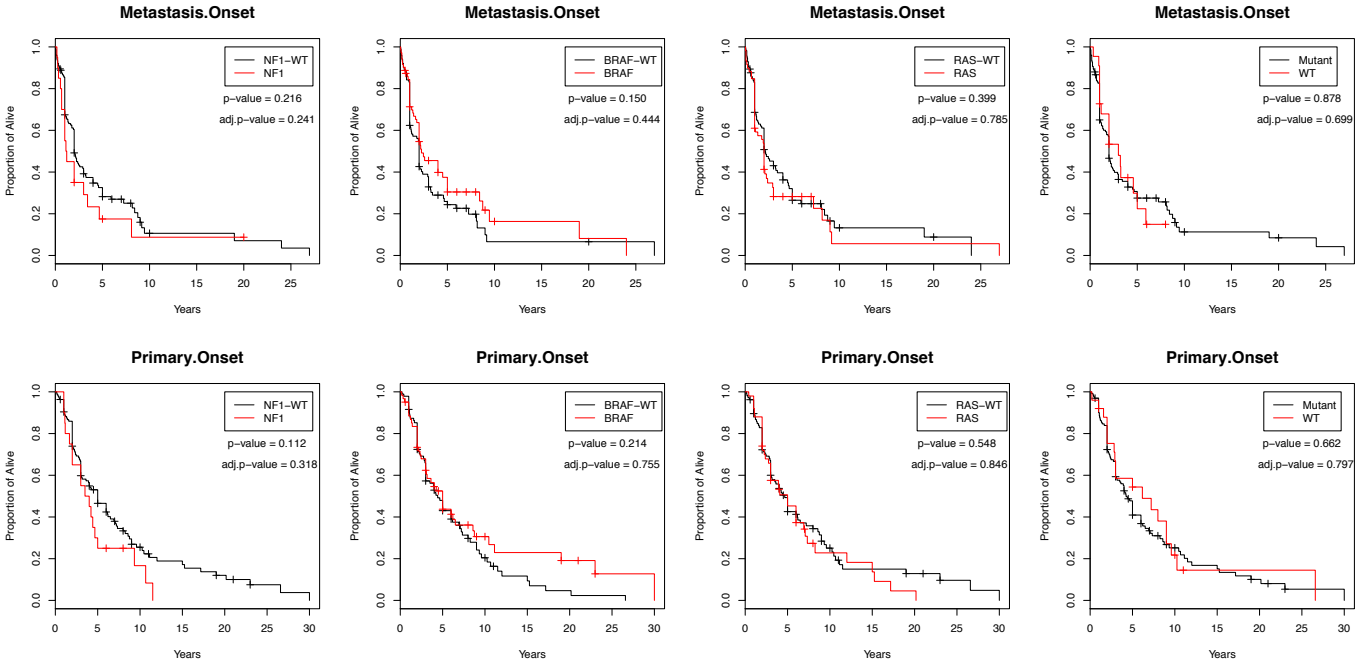


Supplementary Figure 1.

NF1 mutations in melanomas (n=213). The horizontal bar shows the 2,839 AAs of NF1 (NM_001042492.2).

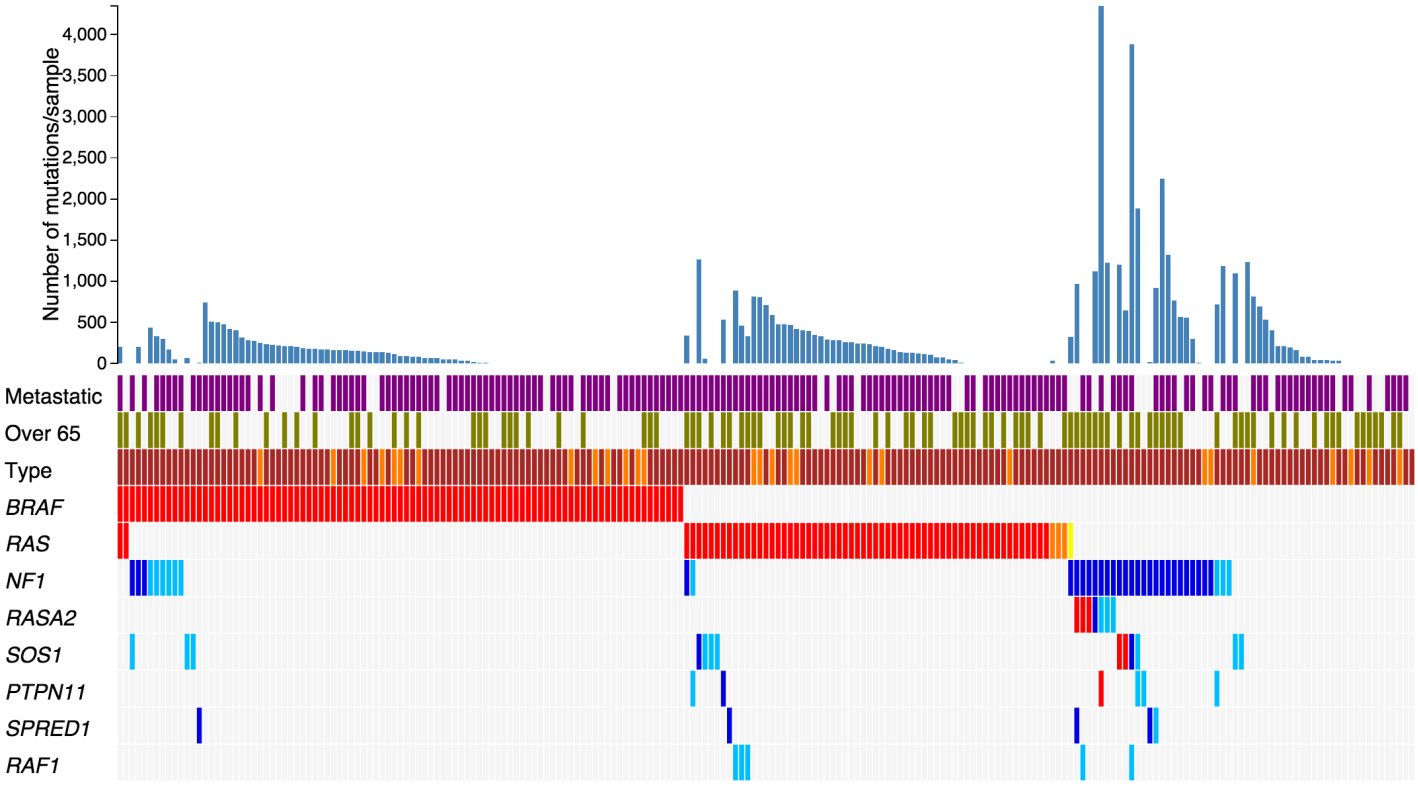
The red bar indicates the RAS-GAP domain, and the grey bar the CRAL-TRIO domain that binds small lipophilic molecules. The circles indicate mutations as follows: Red: nonsense; Brown: InDels; Gray: damaging missense mutations.



Supplementary Figure 2**.**

Survival analysis (n=213). Cox-proportional hazard analysis of patient survival from onset of metastatic melanoma (top), and primary melanoma (bottom).

The group labels indicate melanomas with BRAF (p.V600), RAS (p.Q61/G12/G13), or NF1 mutations (all inactivating and predicated damaging variants). WT indicates triple-WT melanomas.

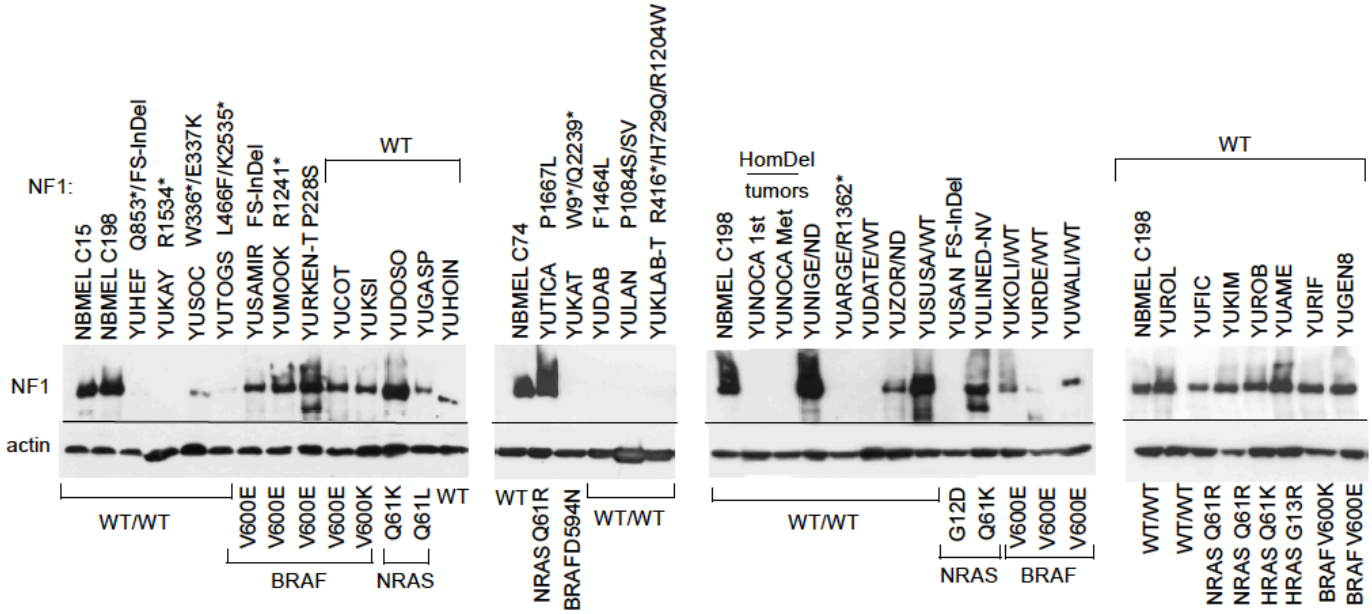


Supplementary Figure 3.

Mutations in *RASA2*, *PTPN11*, *SOS1*, *RAF1* and *SPRED1* across the Yale melanoma cohort (n=213).

Mutations counts correspond to novel mutations that are not found in repositories of common human variants. Purple, metastatic melanoma; Green, over 65 years old; Brown and orange are melanomas from sun-exposed and unknown origin, respectively; red, mutations at recurrent positions; dark blue, inactivating mutations (stop, splice, indel); light blue, predicted harmful mutations. Mutations in *HRAS* and *KRAS* are marked in light orange and yellow, respectively.

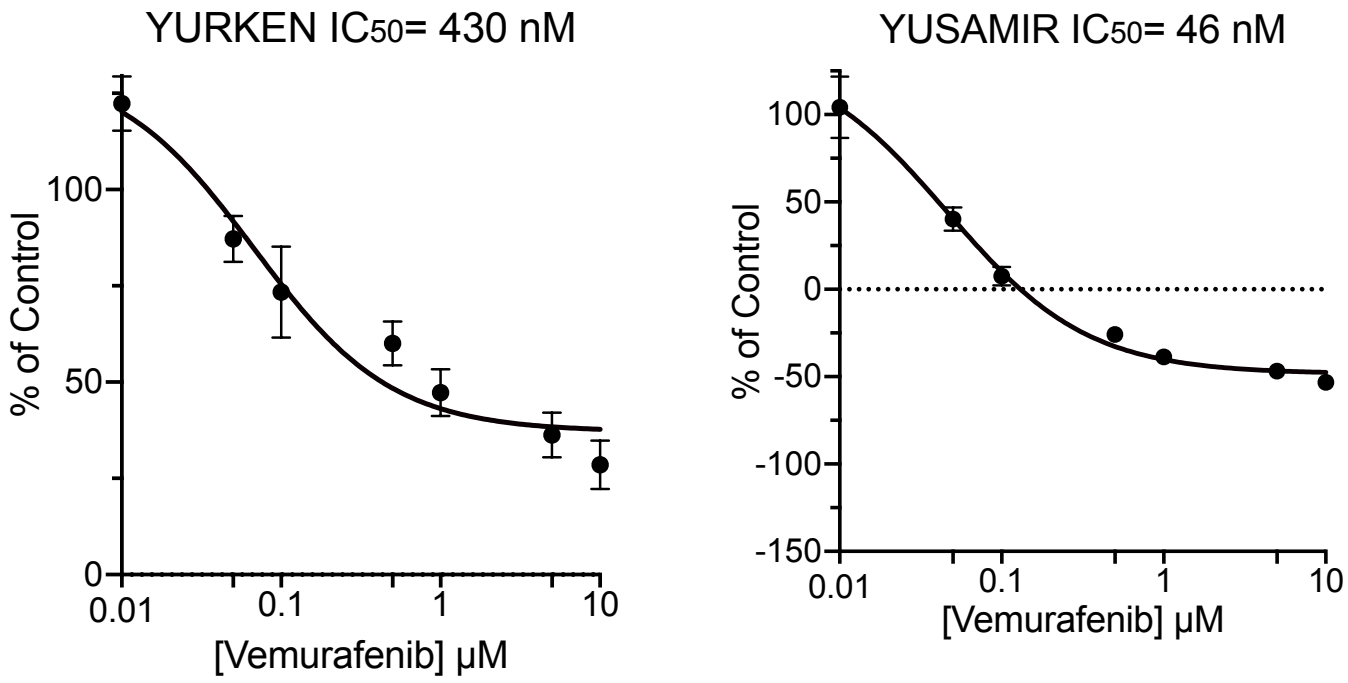
Nature Genetics: doi:10.1038/ng.3361



Supplementary Figure 4.

NF1 expression in normal melanocytes and melanoma cells.

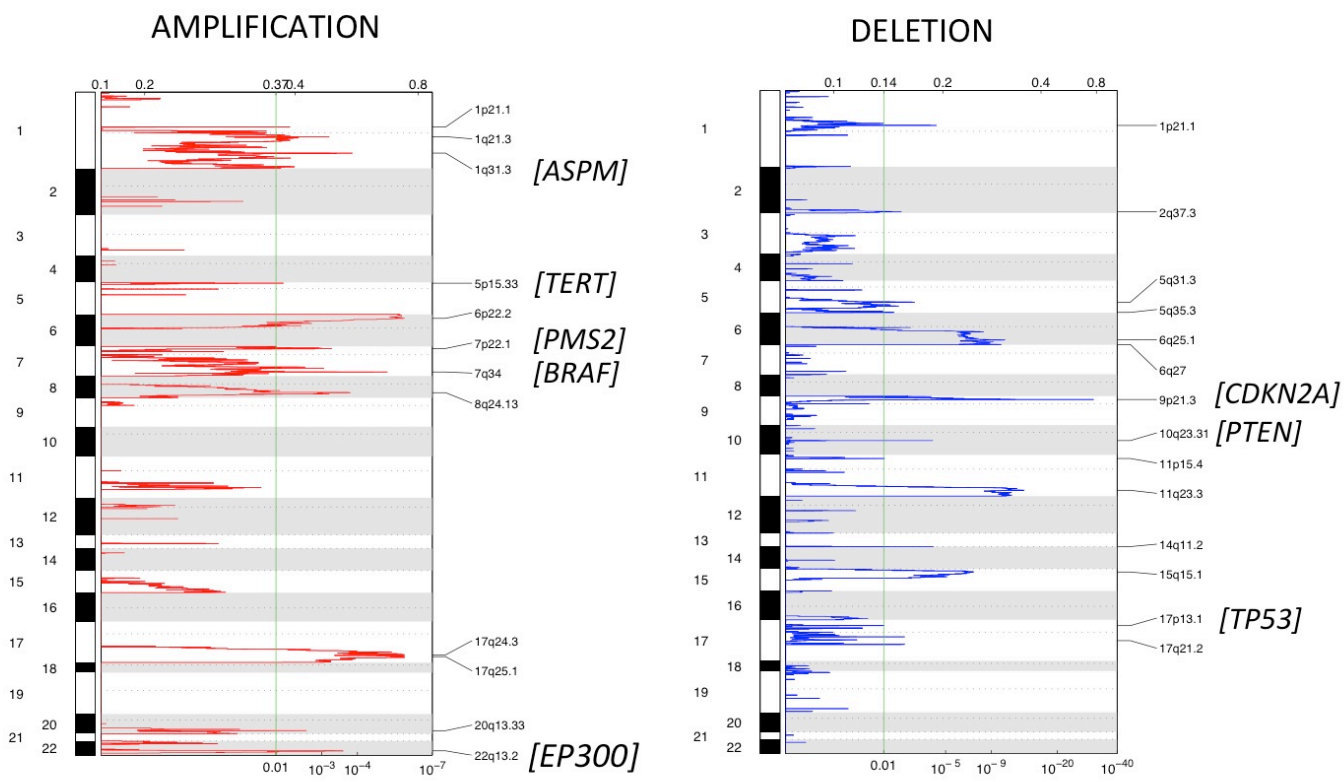
Western blot showing NF1 expression in melanoma cells (YU designation) relative to newborn normal human melanocytes (NBMEL) derived from independent Caucasian foreskins and melanocytes from a congenital nevus (NV); β-actin was used as a loading control. Samples marked with –T or Tumors are from snap-frozen tumors. These blots contain two mucosal melanoma (YUHOIN, YUNOCA) described before[3].



Supplementary Figure 5.

***BRAF*^{V600E} mutant melanomas that carry also NF1 mutations YUSAMIR (*NF1*^{P228S}) and YURKEN (*NF1*$^{FS-InDe}$) growth response to increasing concentrations of vemurafenib**.

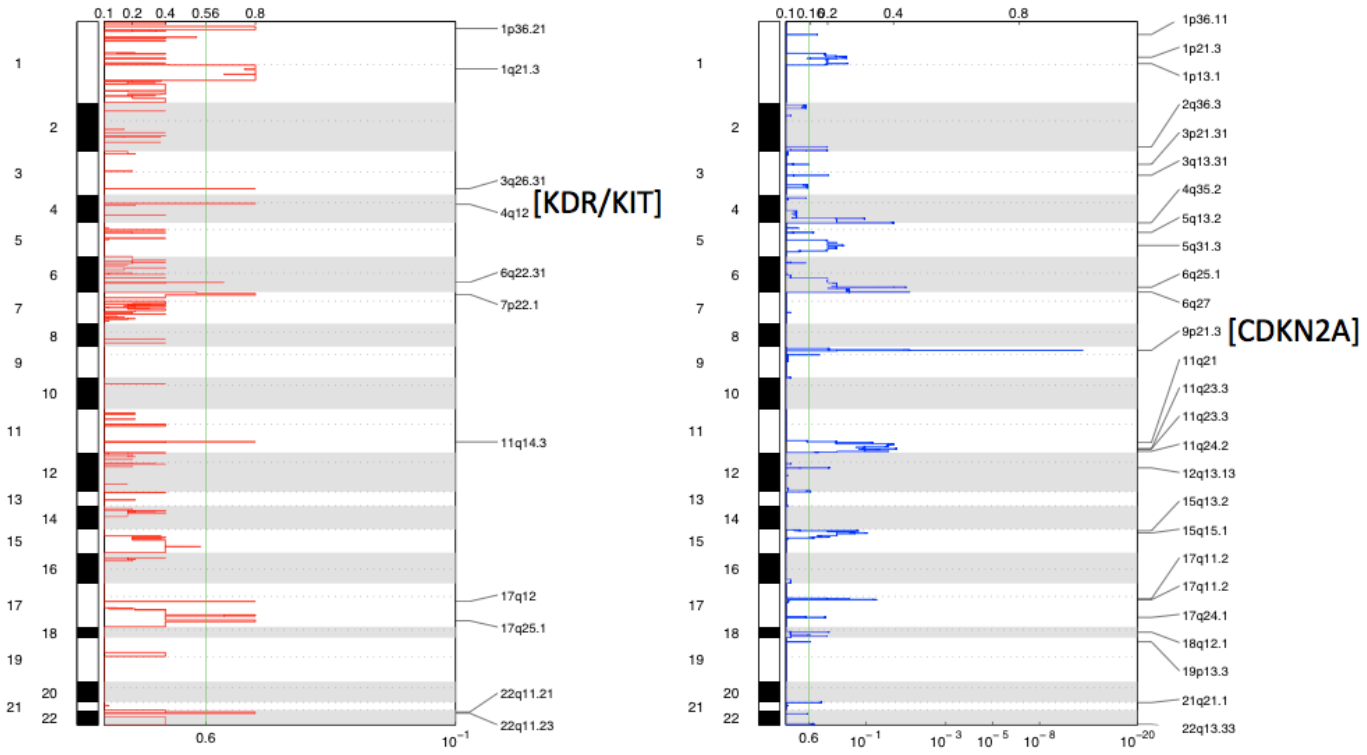
Growth responses were measured in CellTiter-Glo Luminescent Cell Viability Assay at the end of 72 hrs treatment. Vertical bars show the SEM.



Supplementary Figure 6:

GISTIC CNV Analysis in sun-exposed melanomas.

Nature Genetics: doi:10.1038/ng.3361

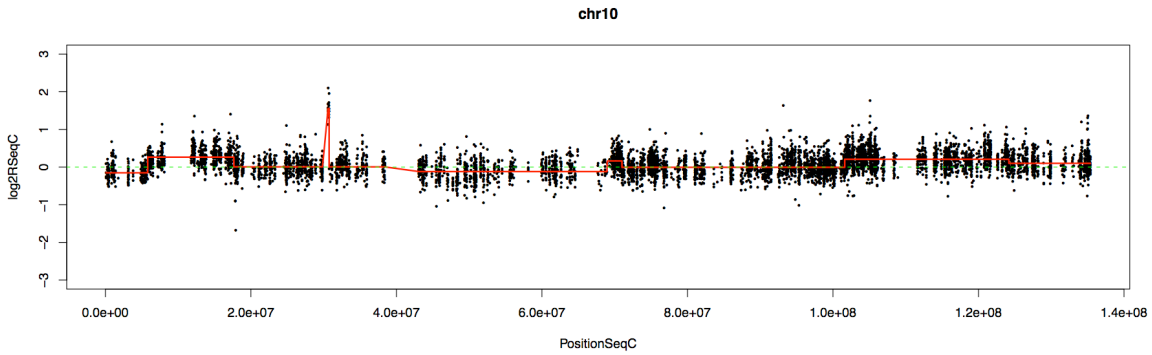


Supplementary Figure 7.

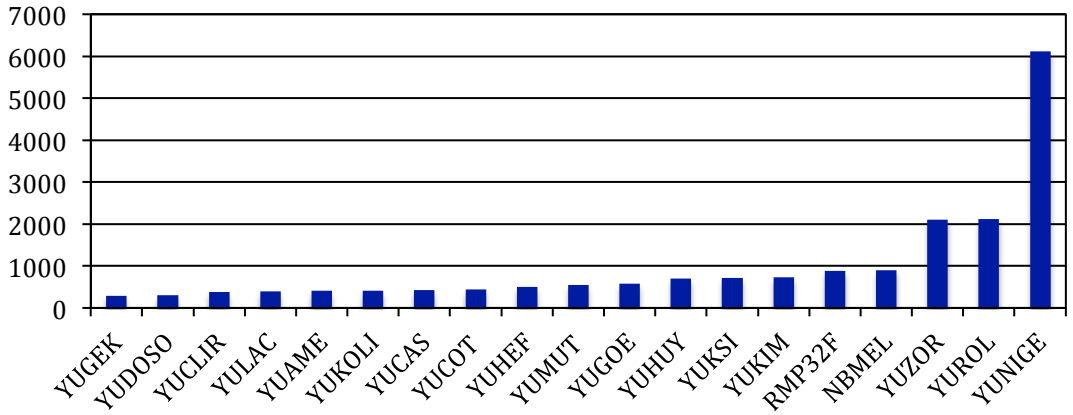
GISTIC CNV Analysis in Triple WT melanomas.

Left, Amplification; Right, Deletions

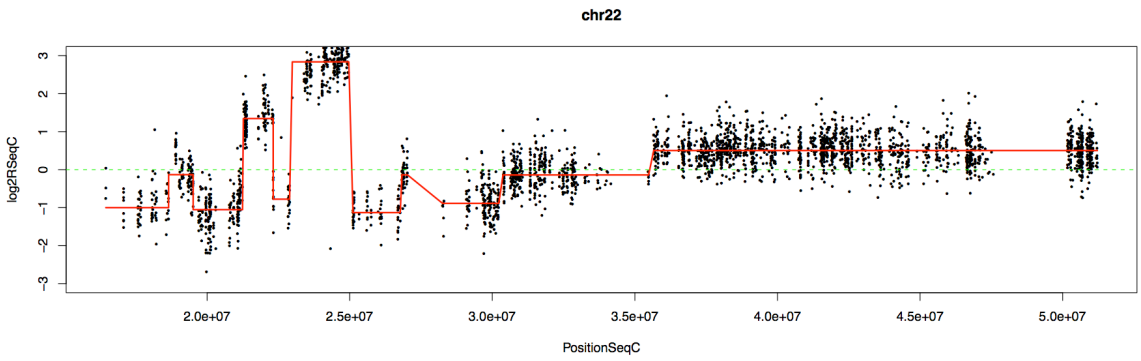
a



b



c



Supplementary Figure 8.

Focal amplifications in triple WT melanomas.

(a) Distinct amplification peak at position 30,700,00 on chromosome 10, covering the MAP3K8 locus in YUROL melanoma.
(b) MAP3K8 gene expression values across melanomas derived from NimbleGen whole genome arrays. YUZOR and YUNIGE melanoma cell lines that also have high expression were not included in the WES study.
(c) Amplification across the ERK2 locus (chr22:22,170,000) in YUDATE melanoma.