ARTICLE

doi:10.1038/nature22071

Whole-genome landscapes of major melanoma subtypes

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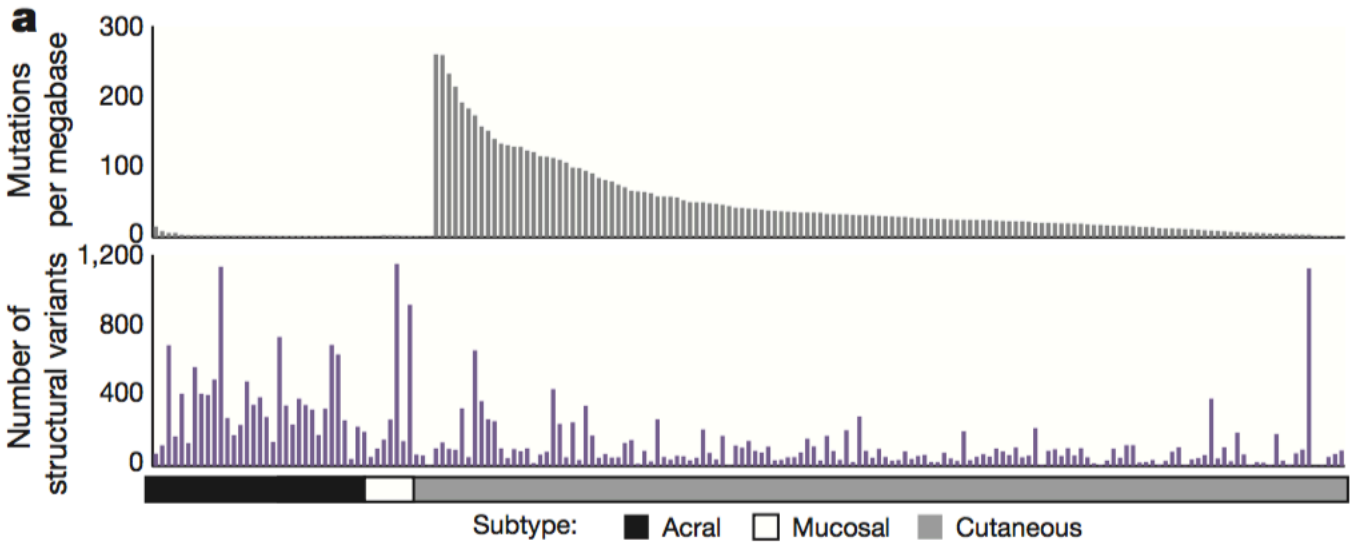
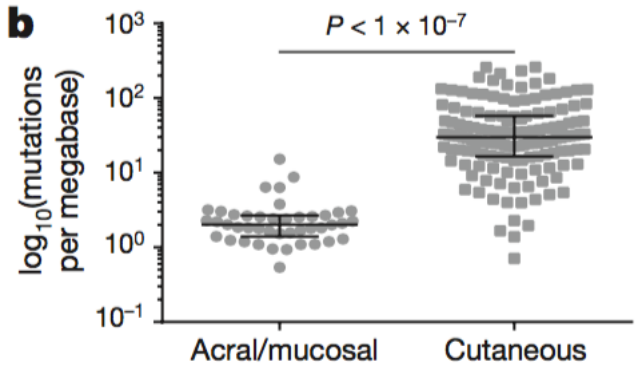
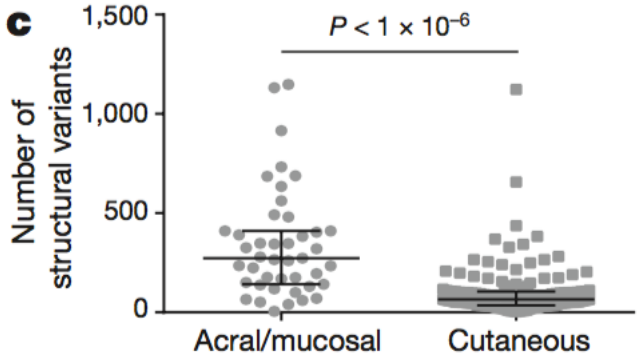
Materials & Methods

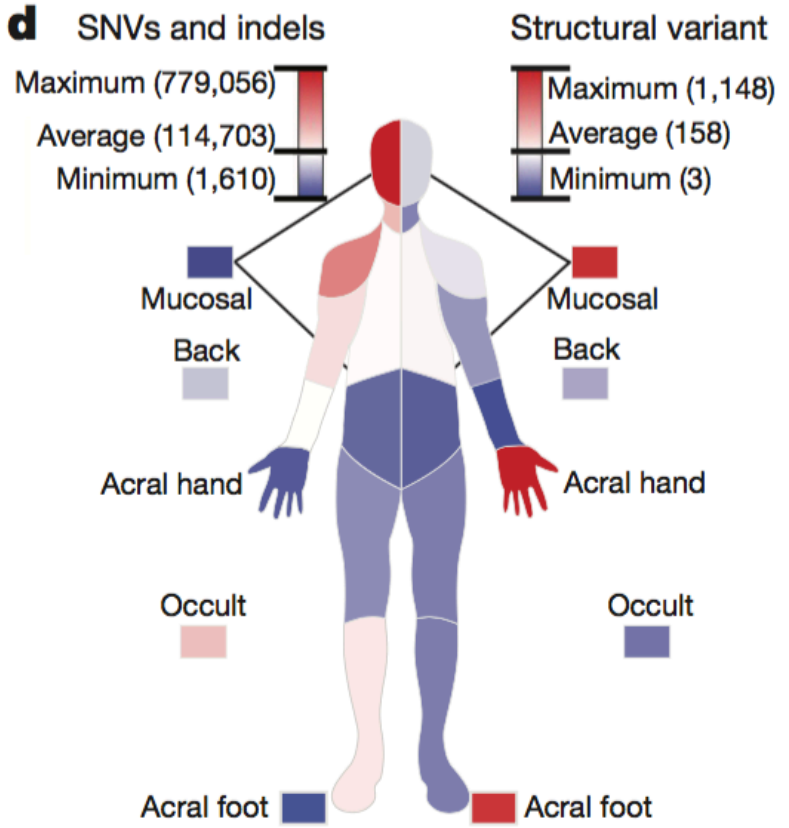
- 183 melanoma samples = 140 cutaneous + 35 acral + 8 mucosal
- fresh-frozen tissue and blood samples
- average depth 85× (range 43–219×) in the tumour sample
- average depth 64× (range 30–214×) in the matched normal
- Mutations calling pipelines
  - somatic mutations and germline variants: qSNP and GATK
  - somatic Indels of 1–50 bp in length: Pindel
  - somatic copy number and ploidy: TITAN tool
  - structural variants: qSV tool

Mutation Burden

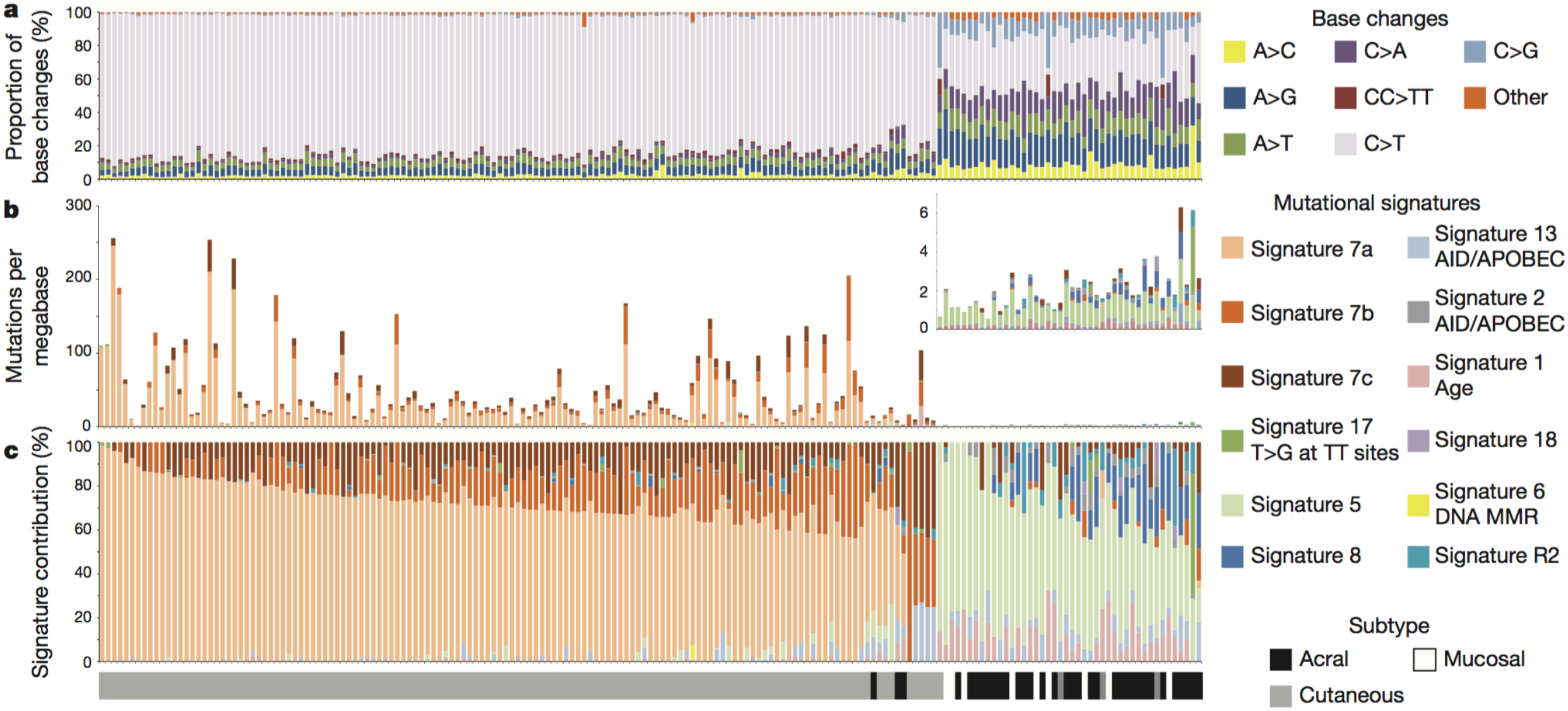




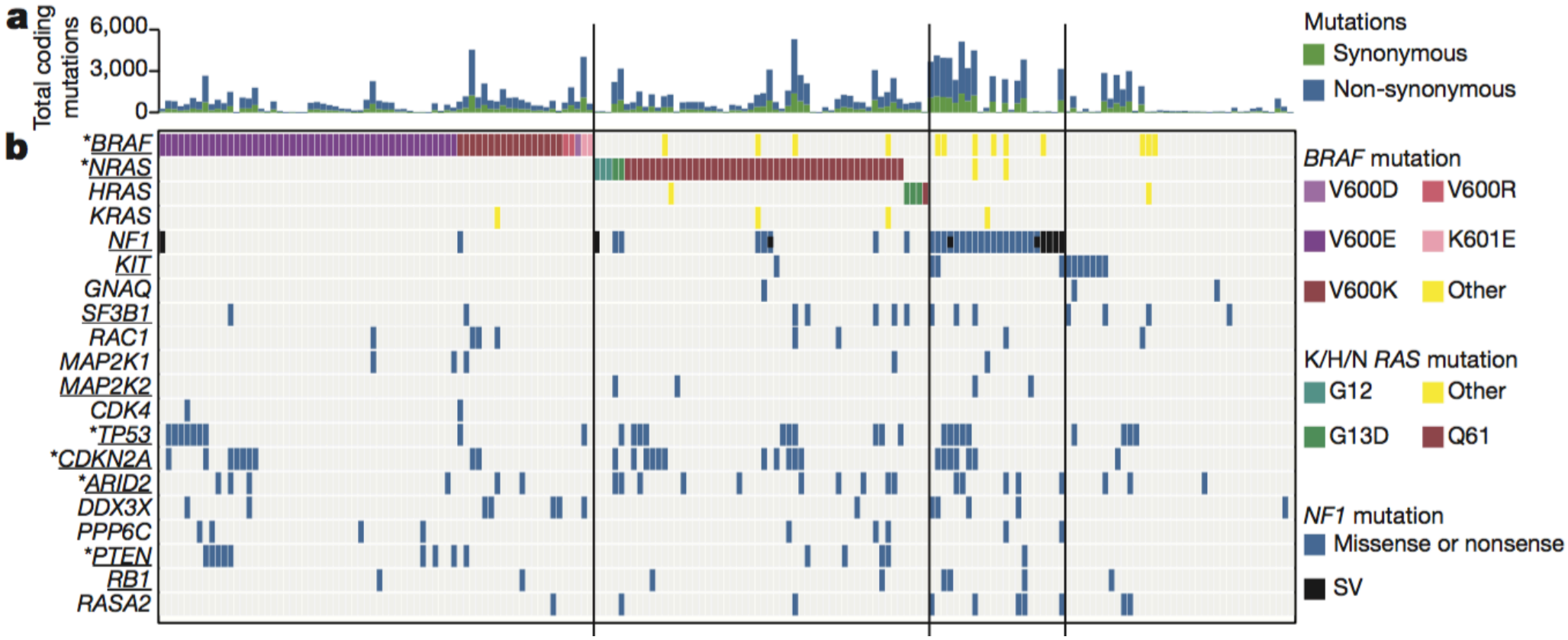




Mutational Processes



Mutations and copy number changes in selected published melanoma driver genes



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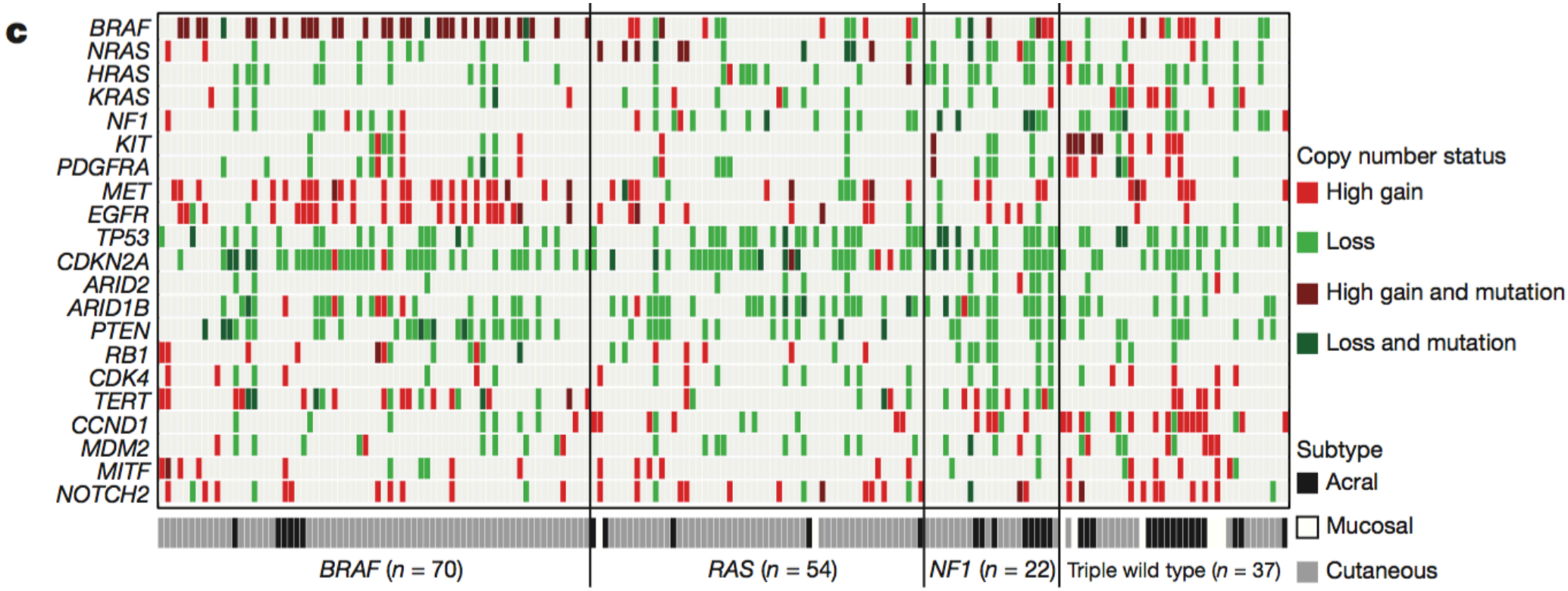
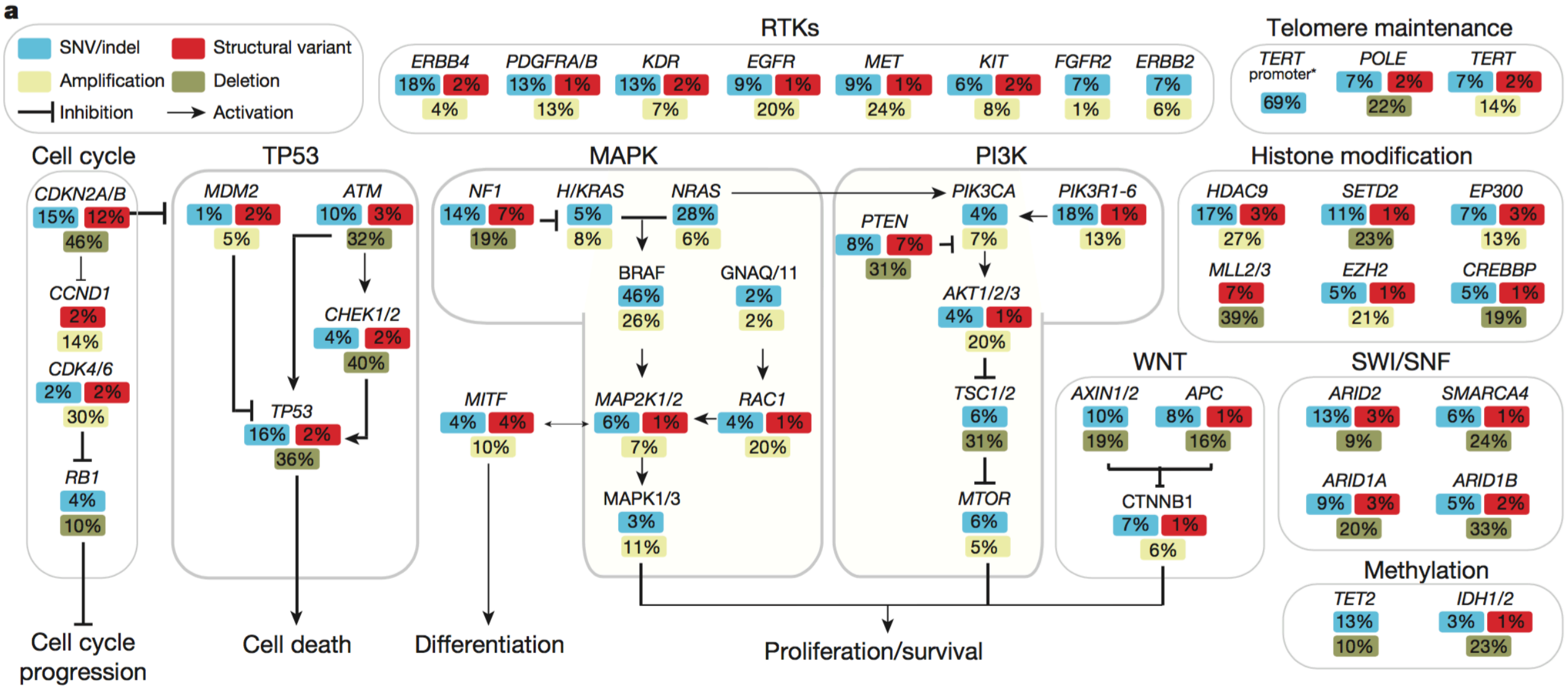


Genes and signaling pathways recurrently altered in melanoma



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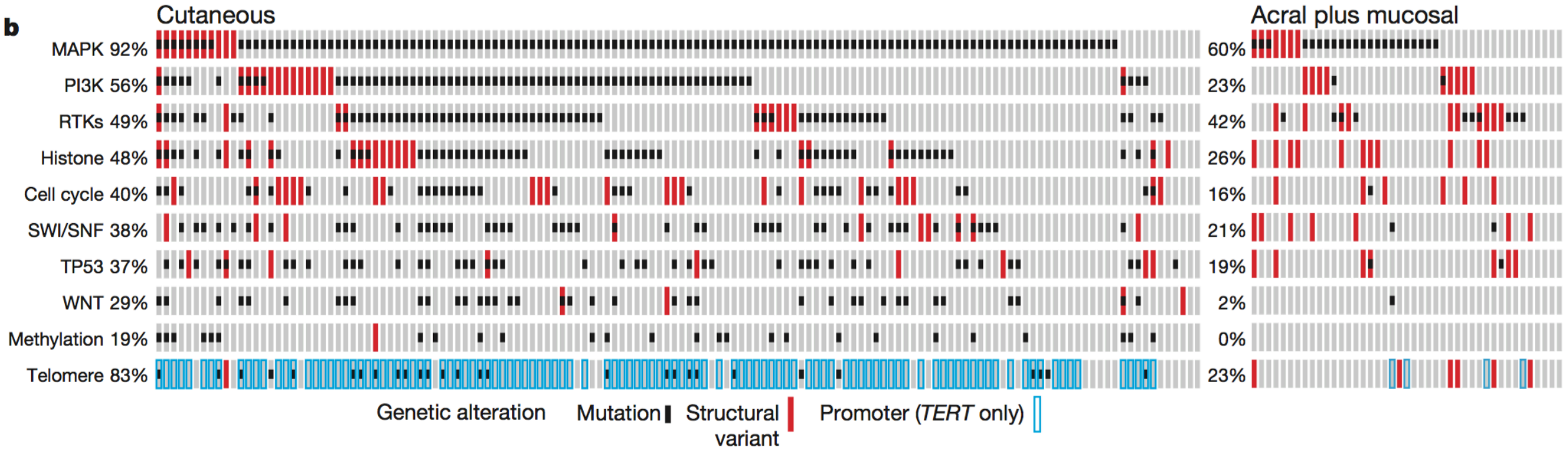
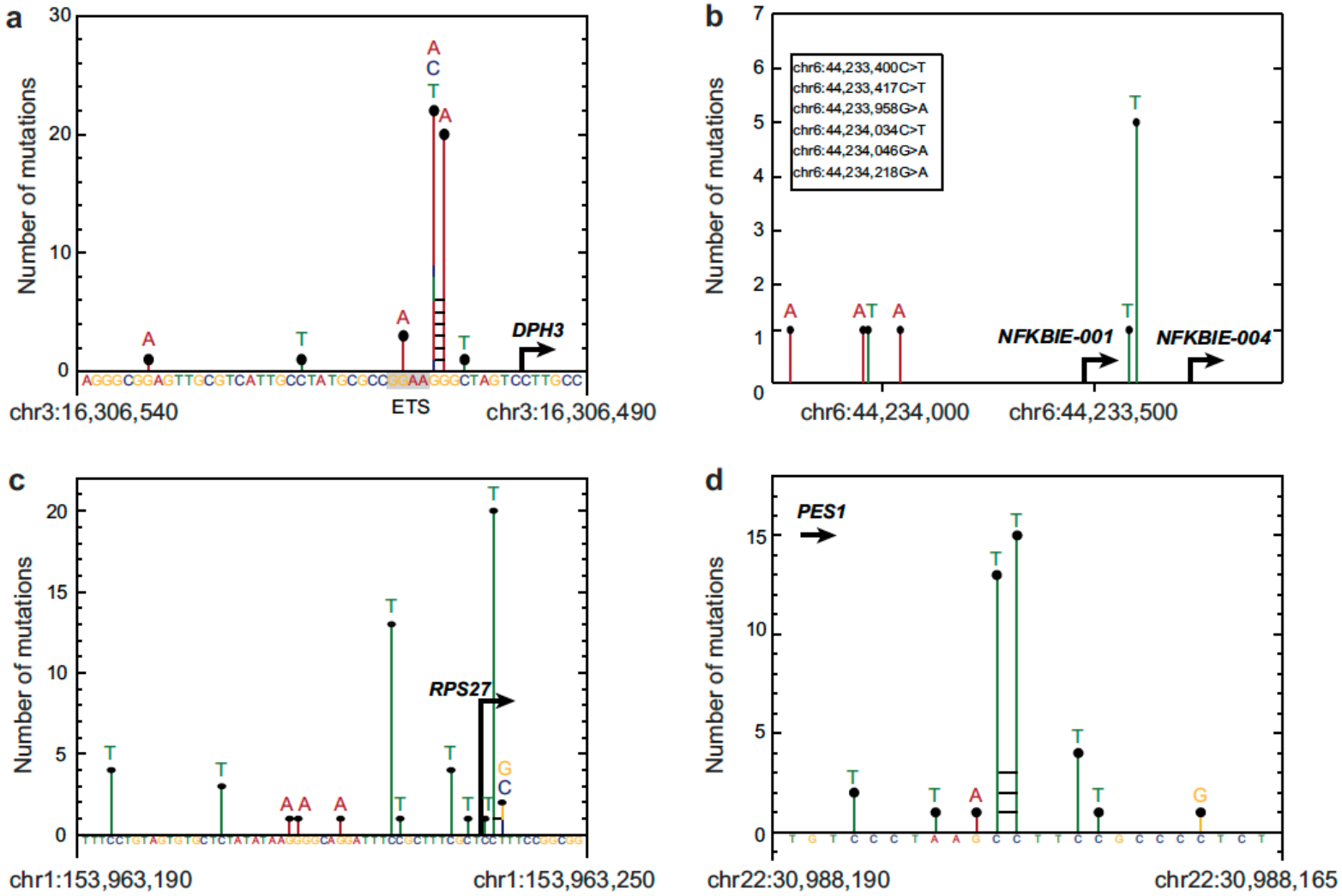
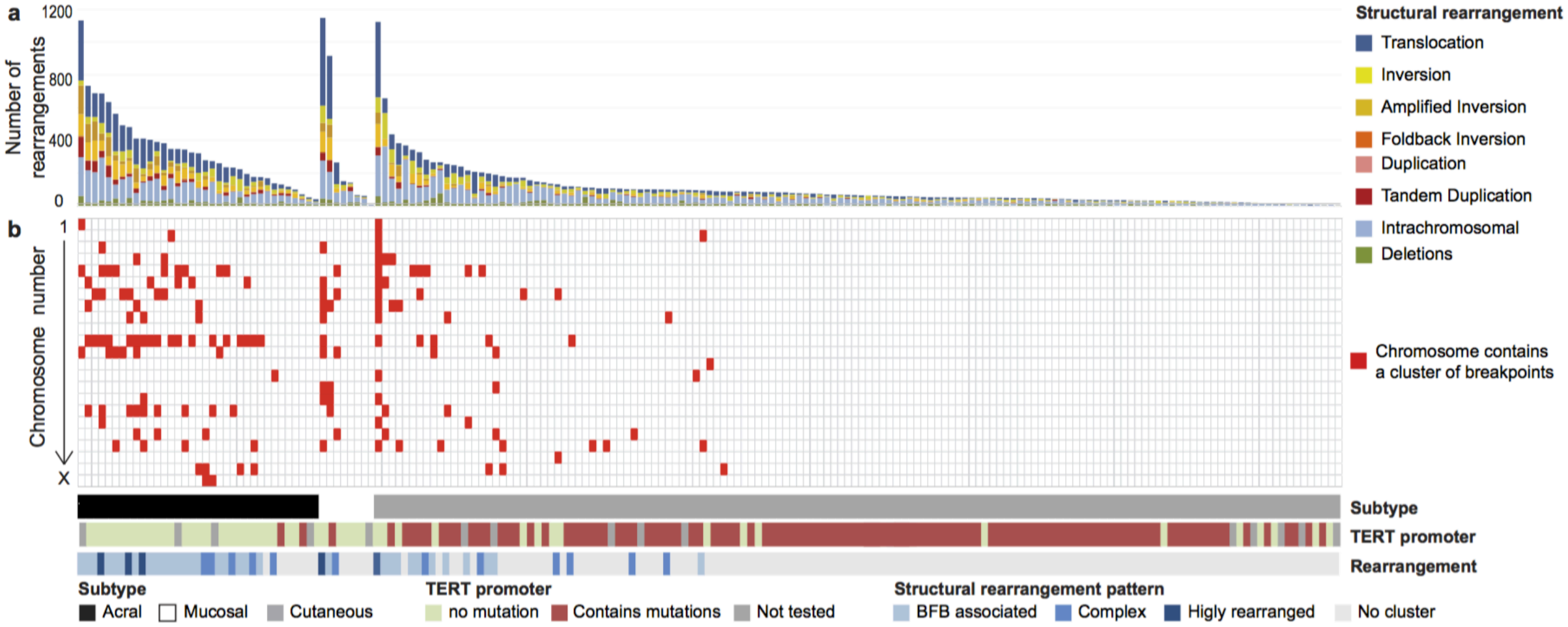


- A pathway was considered altered in a given sample if at least one gene in the pathway contained an SNV/indel or structural variant.

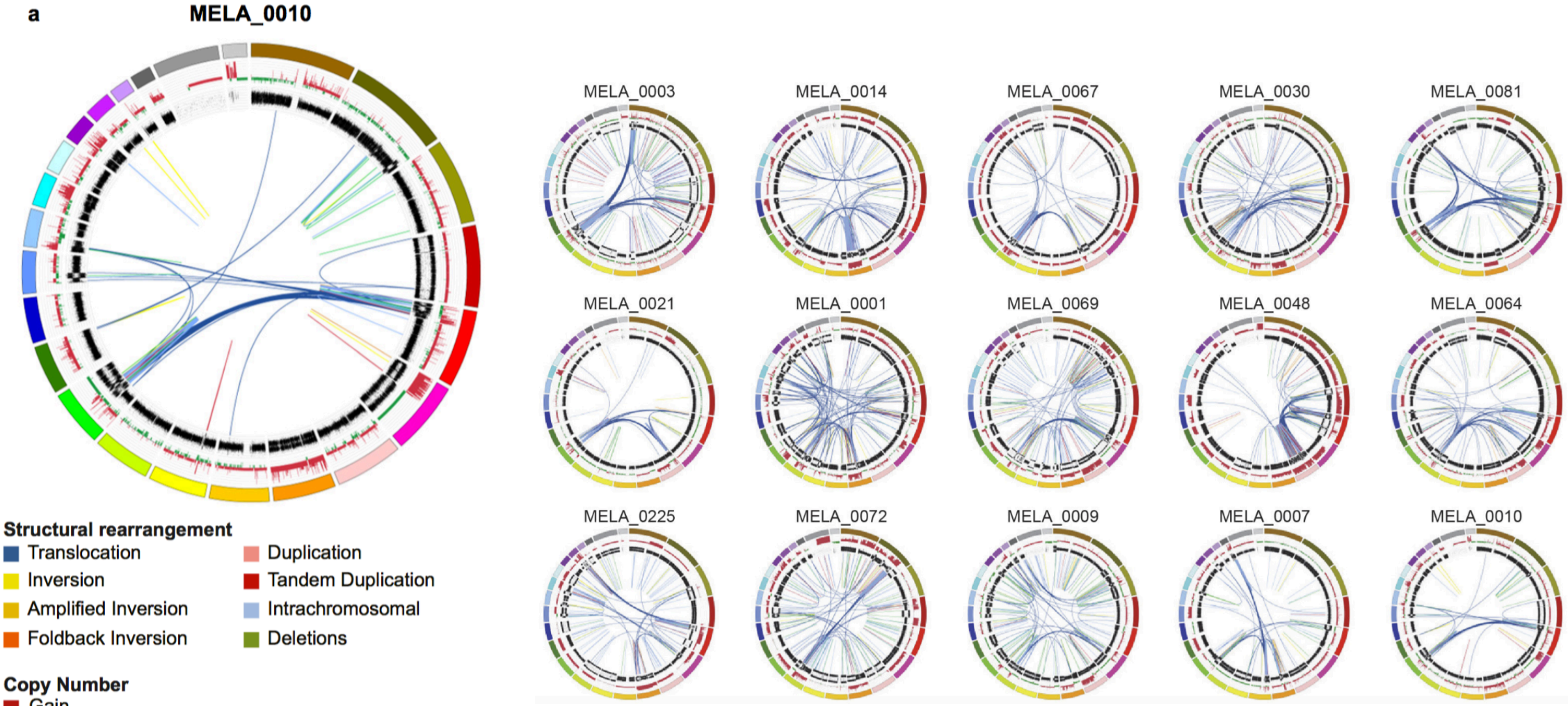
Recurrent promoter mutations: *DPH3, NFKBIE, RPS27 and PES1*

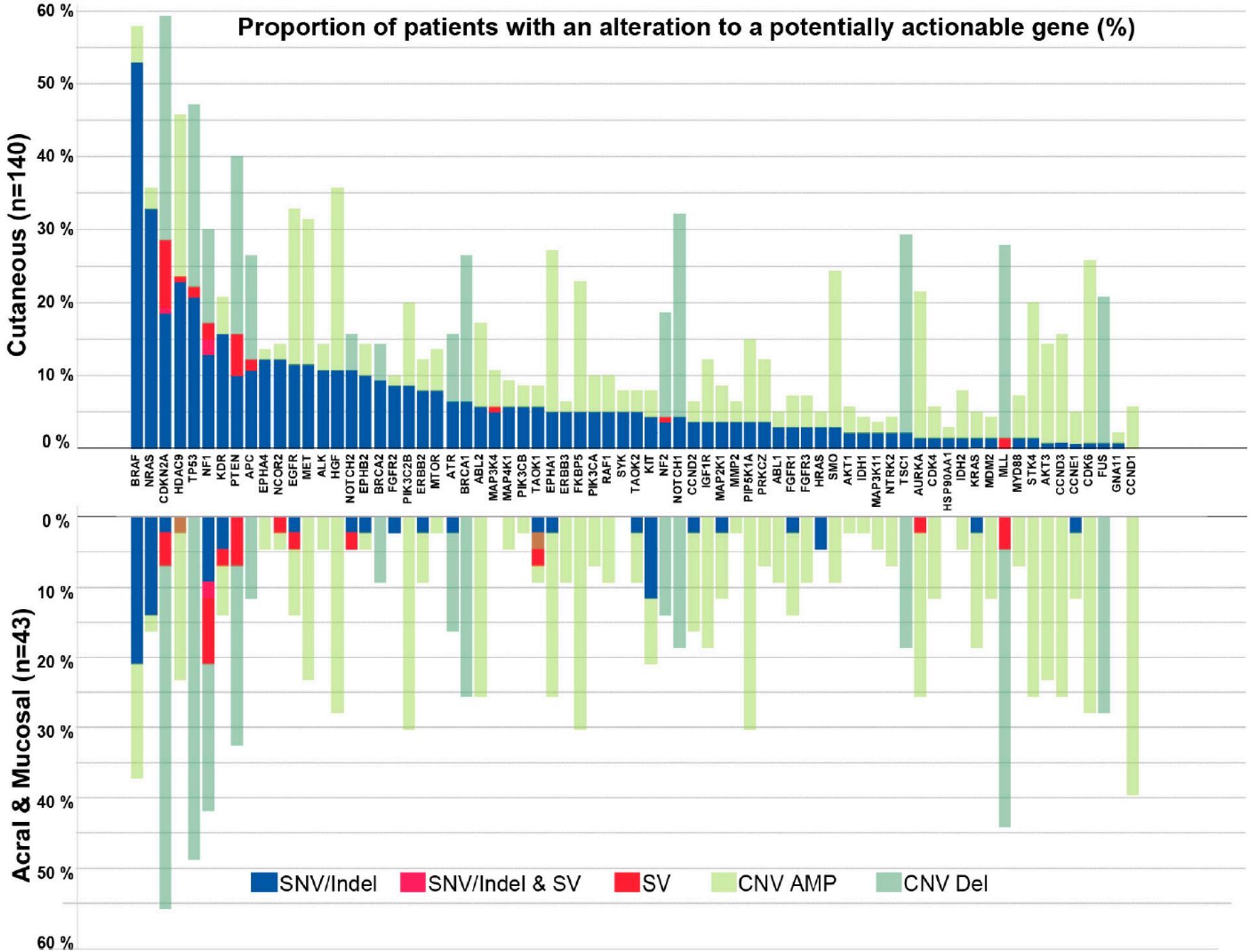


Overview of structural variants



Complex structural rearrangements




Proportion of patients with an alteration to a potentially actionable gene (%)
Cutaneous (n=140)
Acral & Mucosal (n=43)
60 %
50 %
40 %
30 %
20 %
10 %
0 %
BRAF NRAS CDKN2A HDAC9 TP53 NF1 KDR PTEN APC EPHA4 NCOR2 EGFR MET ALK HGF NOTCH2 EPHB2 BRCA2 FGFR2 PIK3C2B ERBB2 MTOR ATR BRCA1 ABL2 MAP3K4 MAP4K1 PIK3CB TAOK1 EPHA1 ERBB3 FKBP5 PIK3CA RAF1 SYK TAOK2 KIT NF2 NOTCH1 CCND2 IGF1R MAP2K1 MMP2 PIP5K1A PRKCZ ABL1 FGFR1 FGFR3 HRAS SMO AKT1 IDH1 MAP3K11 NTRK2 TSC1 AURKA CDK4 HSP90AA1 IDH2 KRAS MDM2 MLL MYD88 STK4 AKT3 CCND3 CCNE1 CDK6 FUS GNA11 CCND1
SNV/Indel
SNV/Indel & SV
SV
CNV AMP
CNV Del

Summary

- Melanoma of the skin is a common cancer only in Europeans, whereas it arises in internal body surfaces (mucosal sites) and on the hands and feet (acral sites) in people throughout the world.
- In cutaneous melanomas, heavily mutated landscape of coding and noncoding mutations resolved novel signatures attributable to ultraviolet radiation.
- However, acral and mucosal melanomas were dominated by structural changes and mutation signatures of unknown aetiology.
- Significantly mutated genes included BRAF, CDKN2A, NRAS and TP53 in cutaneous melanoma, BRAF, NRAS and NF1 in acral melanoma and SF3B1 in mucosal melanoma.
- Mutations affecting the TERT promoter were the most frequent of all.
- Most melanomas had potentially actionable mutations, most in components of the mitogen-activated protein kinase and phosphoinositol kinase pathways.