



Supplementary Fig. 2: Analyses of mutational hotspots grouped by their statistical ranking (dark pink: upper 50%; light pink: lower 50%). **A**, Distribution of upper- and lower-ranked hotspots on proteins with regard to protein interaction interfaces. Enrichment was calculated as the ratio of the observed fraction of hotspots/variants that occur on interaction interfaces over the fraction of interface residues on corresponding proteins (expected fraction). **B**, Average number of protein interactions affected by upper-/lower-ranked hotspots and non-recurrent variants. **C**, Average edge betweenness of interactions affected by upper-/lower-ranked hotspots and non-recurrent variants. **D,G**, Association of genes harboring interface and non-interface hotspots with previously known cancer genes (**D/G**: upper-/lower-ranked hotspots). **E,H**, Association of hotspot-affected interaction partners and interaction pairs with known cancer genes (**E/H**: upper-/lower-ranked hotspots). An interaction pair was counted when both the gene carrying hotspot and its interaction partner are known cancer genes. **F,I**, Association of proteins in the hotspot-affected and hotspot-unaffected networks with previously known cancer proteins (**F/I**: upper-/lower-ranked hotspots).