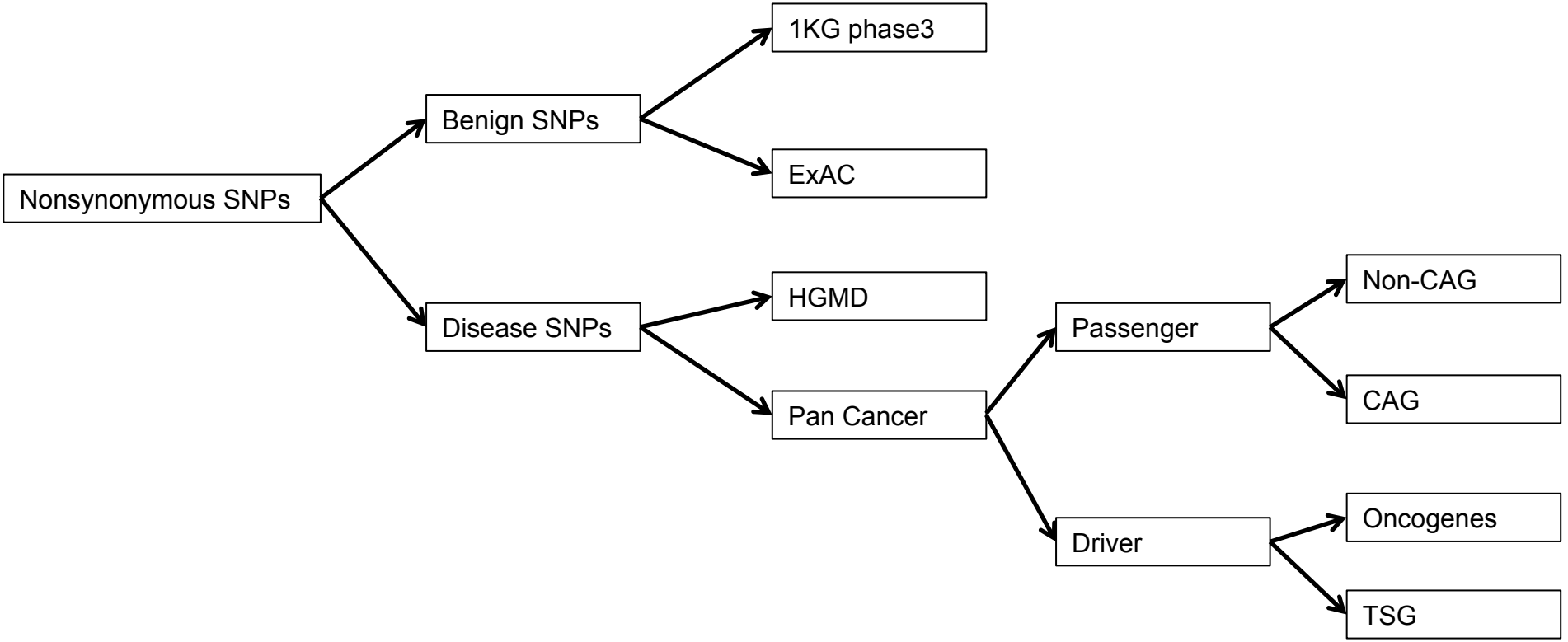
Packing Analysis

Objectives of the work

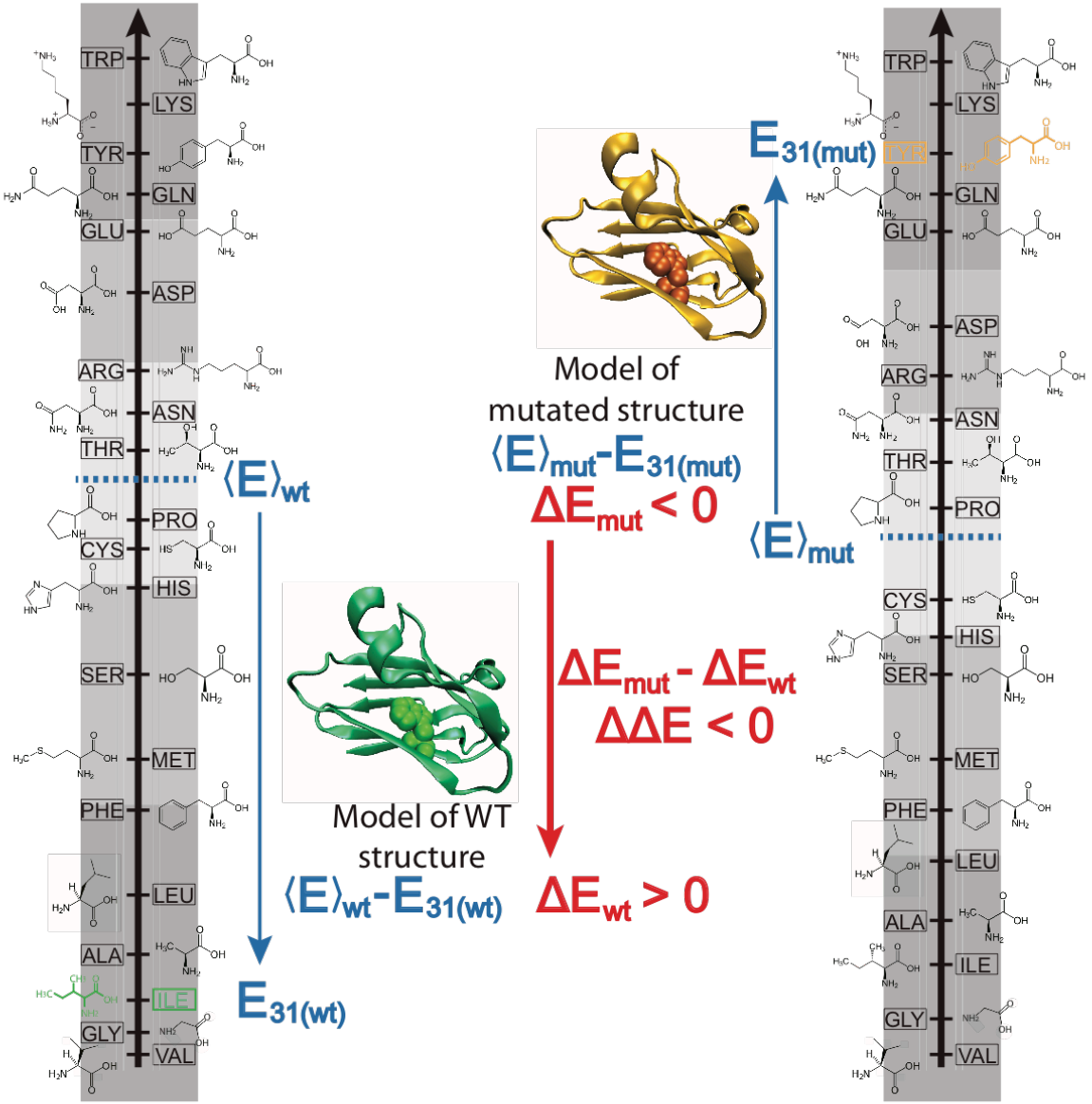
Investigate the impact of non-synonymous SNVs on packing within protein structures and their interactions.

Comparison of packing changes upon mutation (1000 Genome, EXAC, HGMD and Pancancer data)

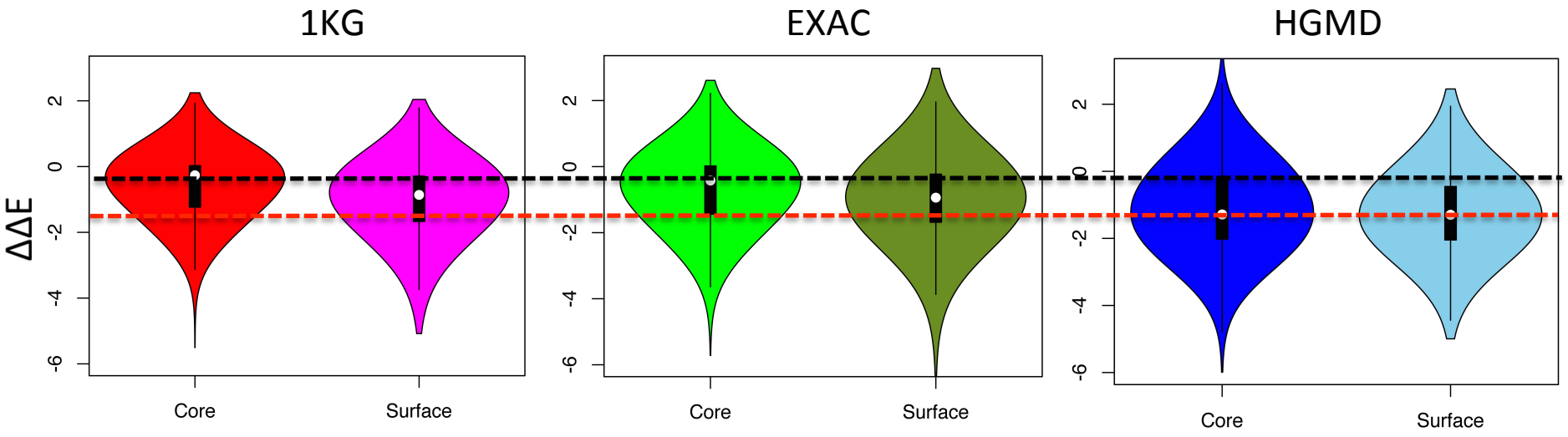
SNV datasets for packing analysis



Schematic Diagram



Effects of SNVs on well-packed residues

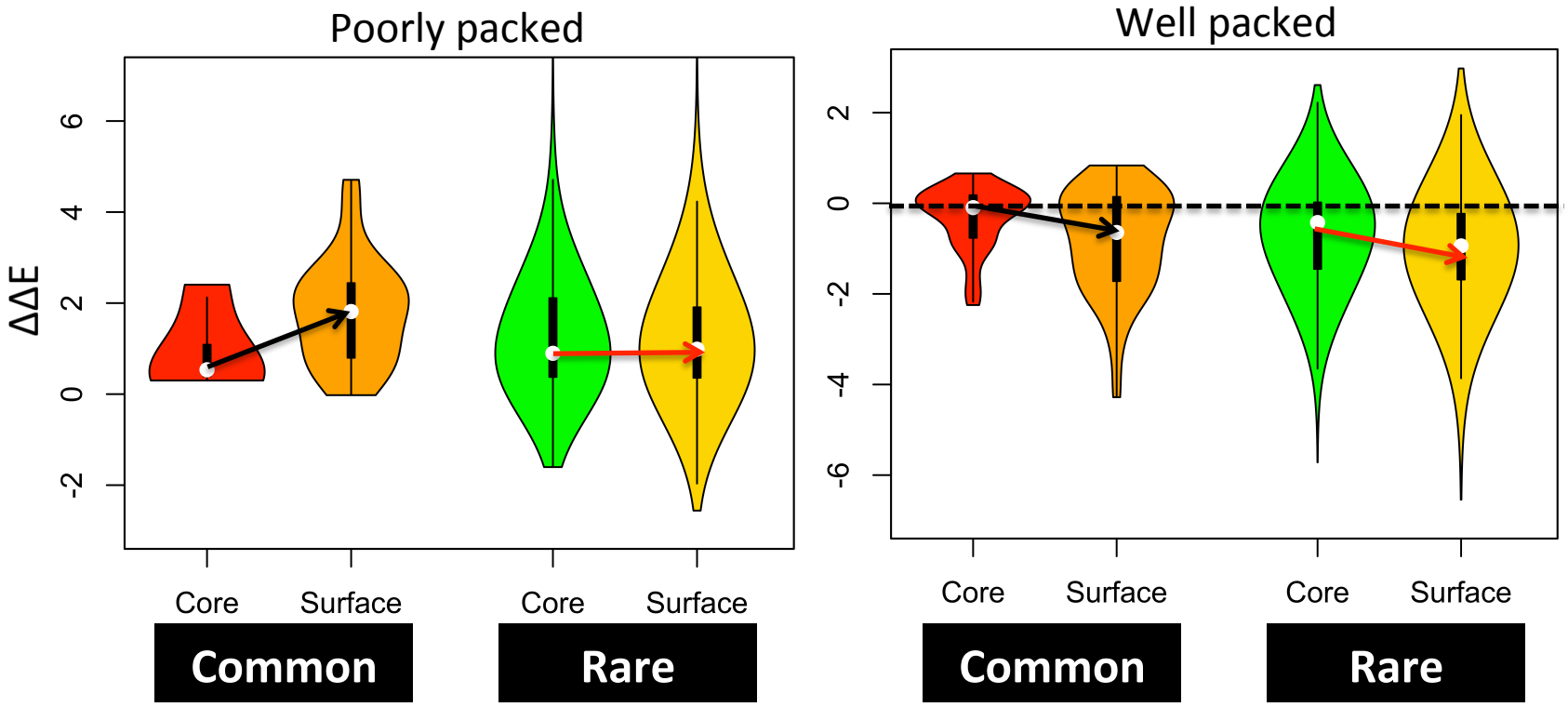


For benign SNVs: greater disruptions in packing occur at the surface than within the core

For disease SNVs: large disruptions in packing occur both within the core and on the surface
+ no core-surface disparity is observed for these SNVs
+ disease SNVs impart greater disruptions than benign SNVs

Rationale:
Large packing disruptions within the core are not observed for benign SNVs (large disruptions in the core would be deleterious). This also explains why no core-surface disparity exists for disease SNVs.

Benign SNVs (ExAC): Common vs. Rare



Left:

Common SNVs on poorly packed residues at the surface improve packing more than common SNVs in the core.

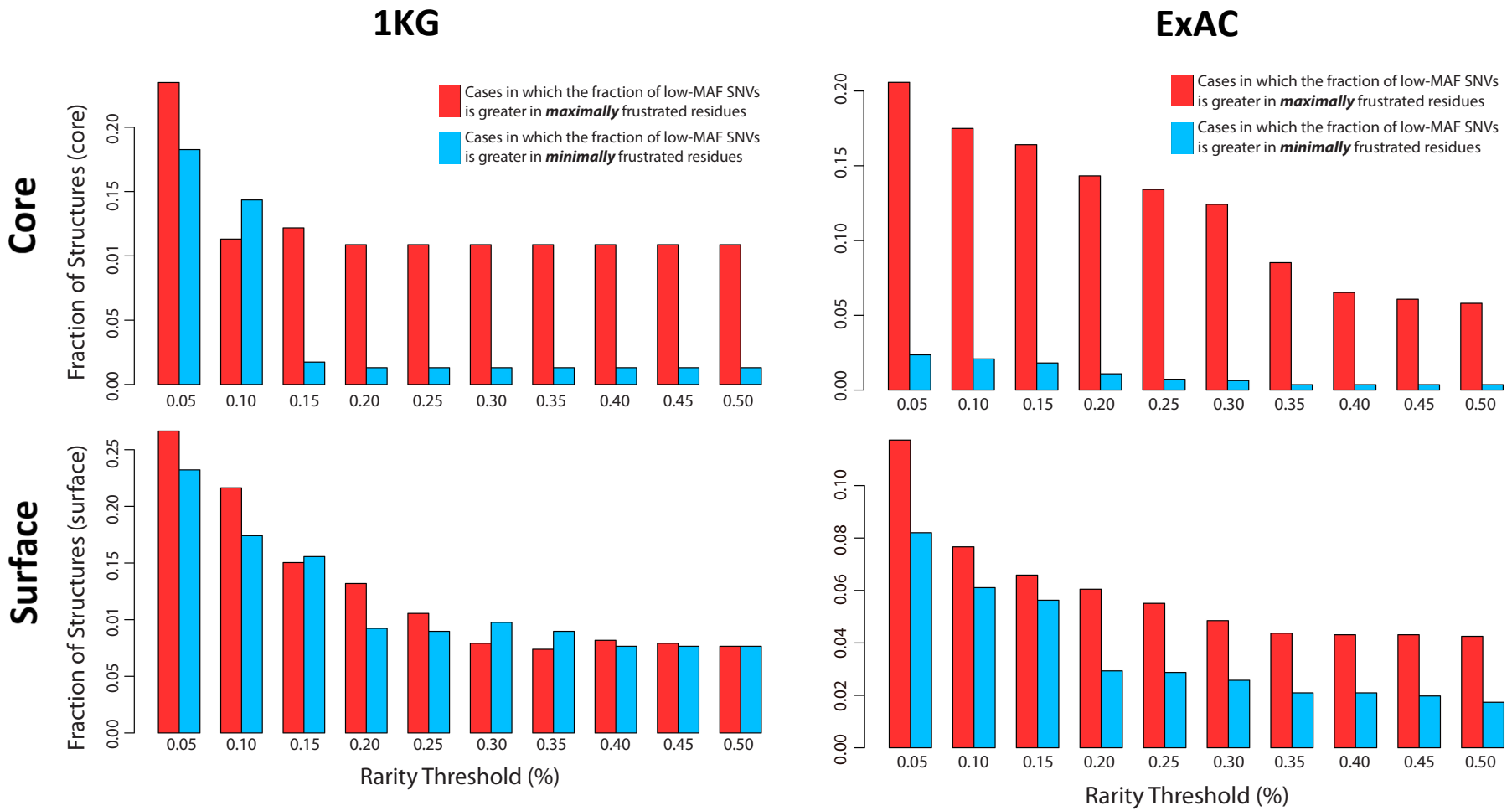
+ For ***rare*** SNVs, no such surface-core disparity is observed

Right:

Rare SNVs on well packed residues more strongly disrupt packing than do ***common*** SNVs on well-packed residues.

+ As with poorly packed residues, disruptions are stronger at the surface.

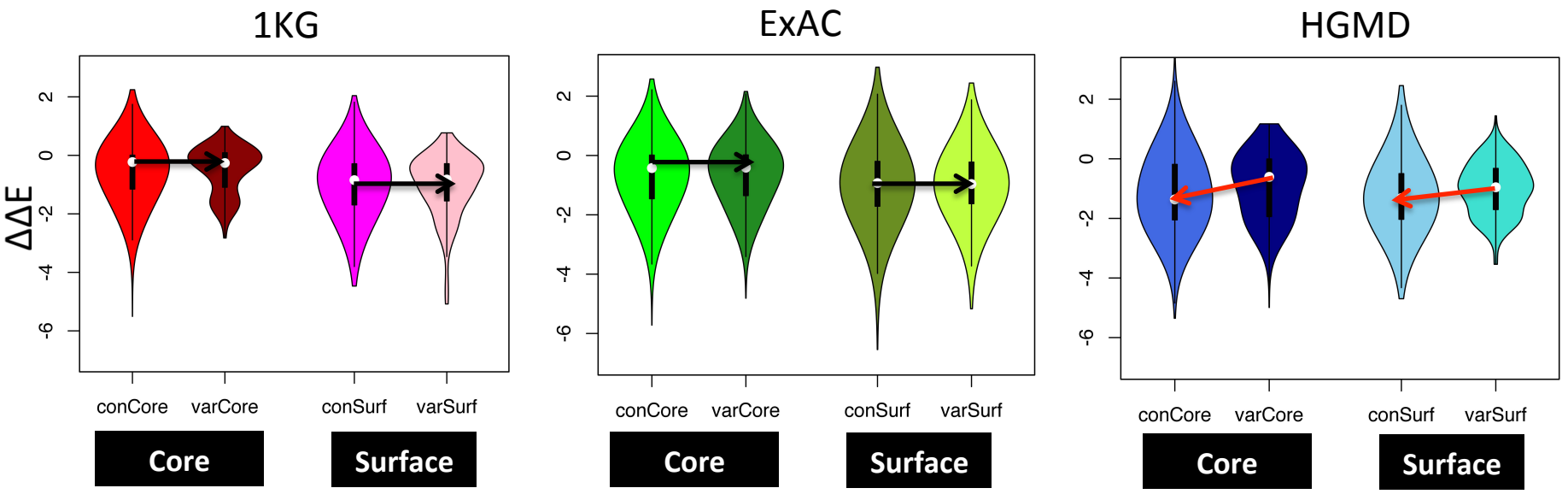
Changes at the surface are more extreme than changes in cores for benign SNPs. Extreme changes in core will have systematic impact on the stability of the protein.



Using the fraction of rare variants to quantify negative selection, poorly packed residues tend to be somewhat more conserved than well packed residues, and this trend is more pronounced in the core.

Rationale: Biologically, this could be a result of the functional roles played by poorly packed residues (allostery, binding, etc).

GERP score based analysis for well packed residues



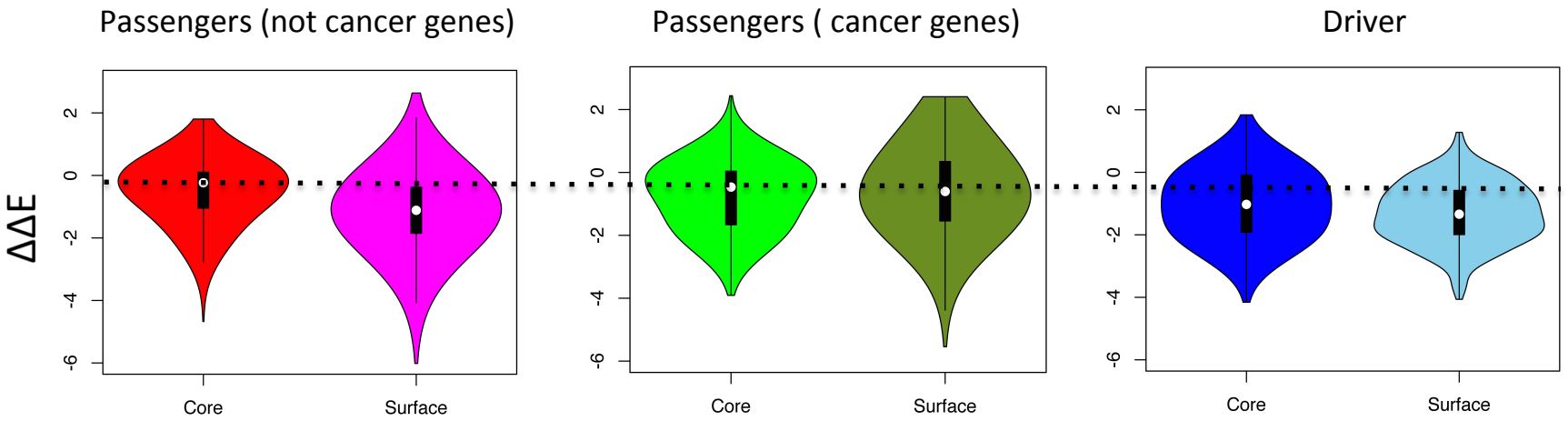
Well-packed residues in both conserved and variable regions exhibit the same disruptions in packing upon mutation with benign SNVs

Rationale: benign SNVs should not impart large disruptions in packing.

Unlike benign SNVs, disease SNVs within conserved regions strongly disrupt packing in well packed regions. This trend is more pronounced within the core.

Rationale: disease SNVs impacting conserved region of the genome should impart large disruptions in packing.

Impact of cancer SNVs on well packed residues

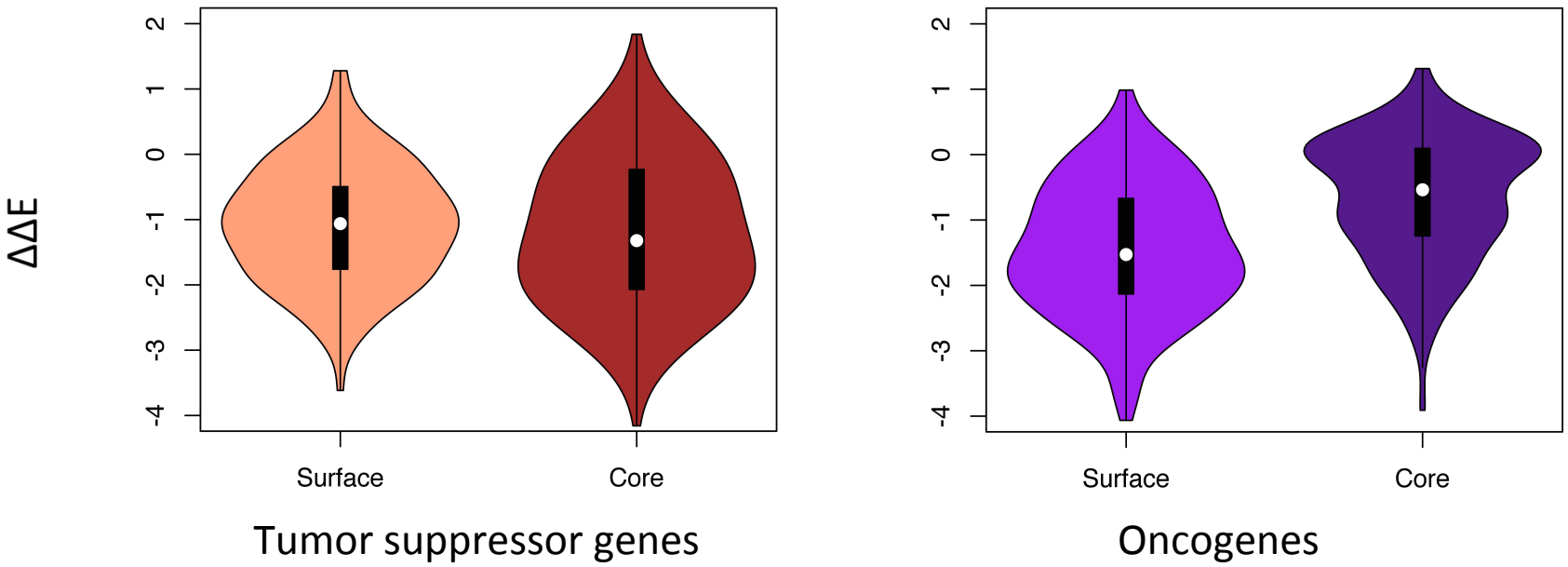


Driver SNVs strongly disrupt the packing efficiency of well packed residues. (like disease SNVs from slide5)

For well-packed residues hit by passenger SNVs, there is a greater loss in packing efficiency at the surface than within the core.

Rationale:
Large packing disruptions within the core are not observed for passenger SNVs (large disruptions in the core would be deleterious). This also explains why no core-surface disparity exists for driver SNVs.

Impact of cancer SNVs on well packed residues



There are two distinct mechanism by which driver mutations can disrupt packing efficiency.

A) Driver mutation impacting TSG are often LOF events. LOF easily imparted by disrupting core packing.

B) Driver mutation impacting oncogenes are often GOF events. Disruption of surface packing will drive non-specific protein interactions.