"There are methods existing in order to evaluate potential effects of low-allele-frequency variants in unbiased ways (SIFT, PolyPhen2, MutationTaster, and many others). I would like to see how exactly your method adds up to this ... One could for example create a small set of variants and analyse these with one or two of the "common" tools to predict the deleteriousness of SNVs (e.g. PolyPhen2 and MutationTaster2, since these are generally considered the most accurate ones) and then check if there are disease variants predicted as "harmless" by these tools (i.e. false negative) which are then correctly seen as locally maximal frustrated by your method..."

→ Find HGMD SNVs not captured by PolyPhen (yet are captured through frustration)

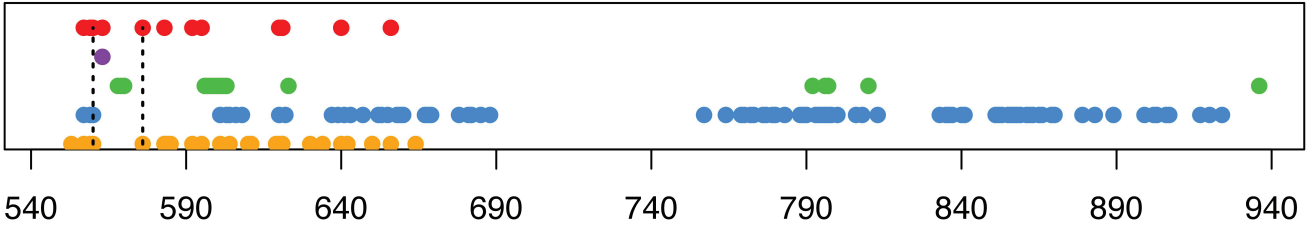
single chain PDBs

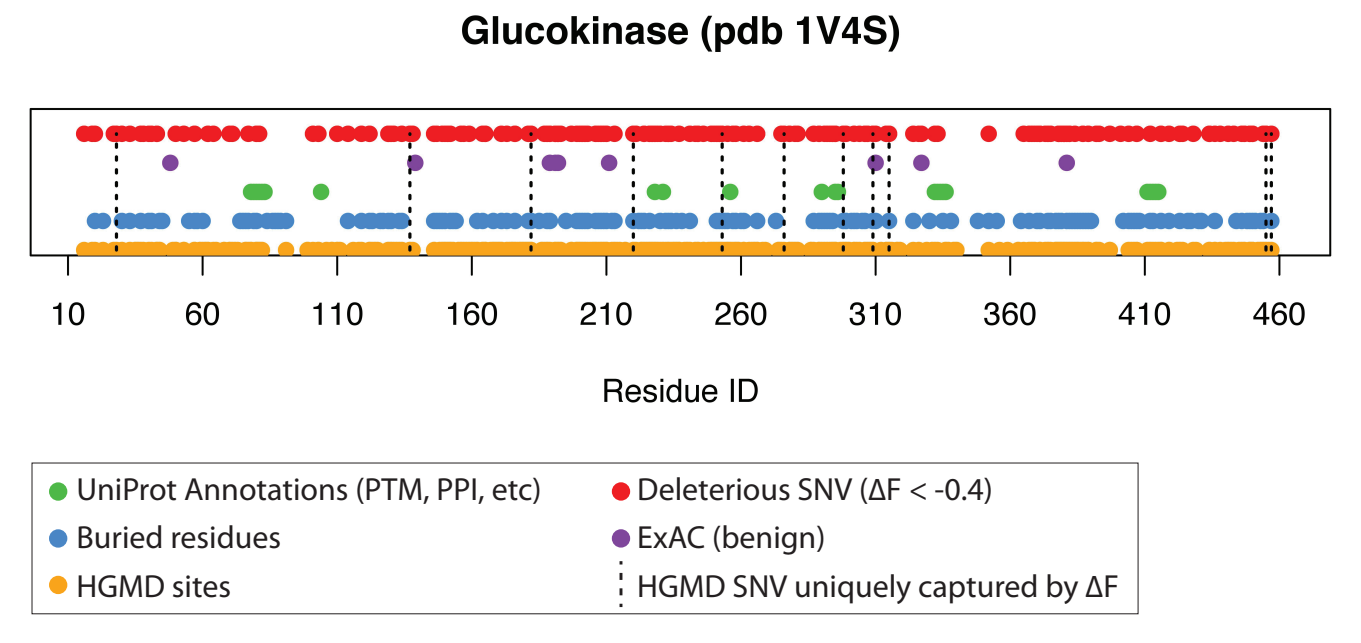
PDB	*# HGMD SNVs*
1T45	2
1V4S	15
1KQ6	1
3PXA	1
1AD6	1
2AMY	1
1OG5	1
2X6U	1

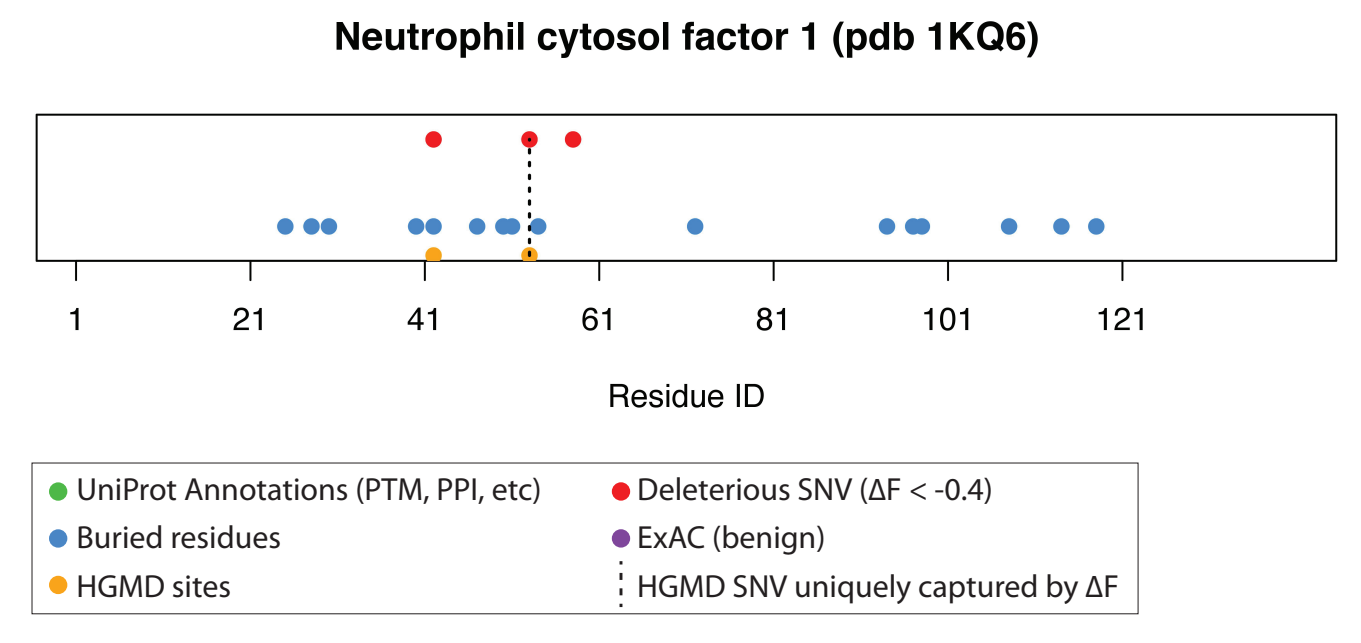
Multi- chain PDBs

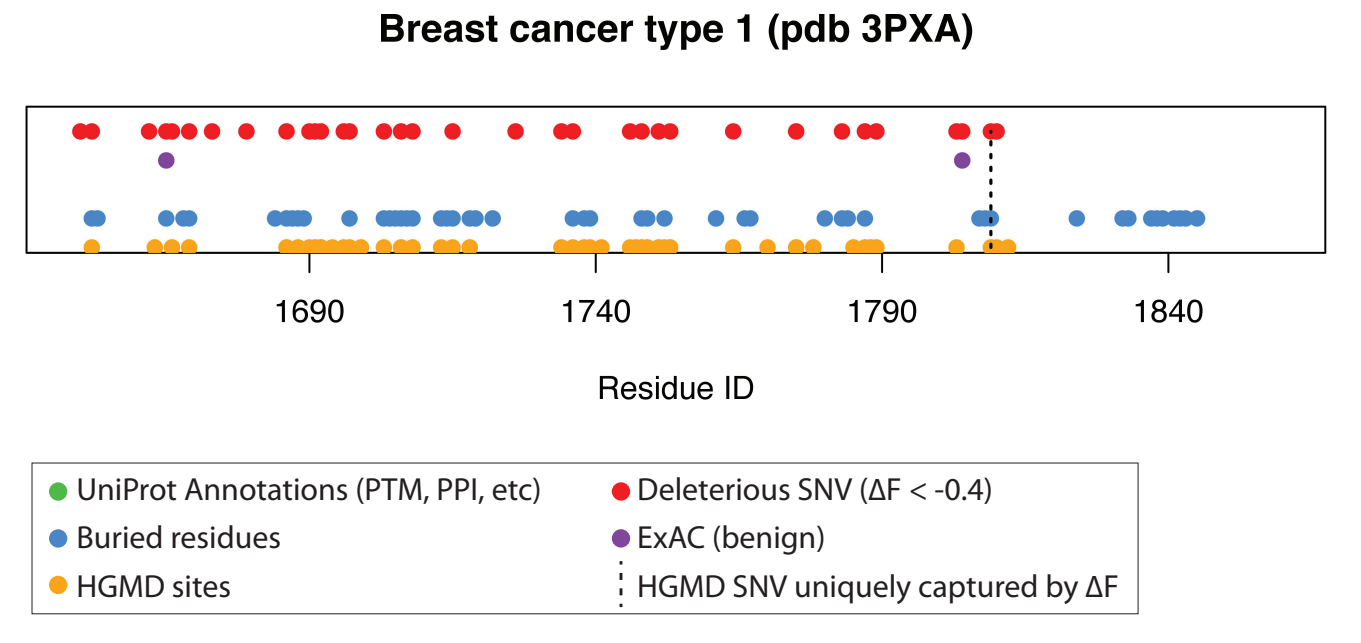
PDB	*# HGMD SNVs*
2VGB	2
3GXP	7
1A4I	1
1IIL	1
2O4H	1
3HN3	1

C-KIT TYROSINE KINASE (pdb 1T45)




Glucokinase (pdb 1V4S)
10
60
110
160
210
260
310
360
410
460
Residue ID
UniProt Annotations (PTM, PPI, etc)
Deleterious SNV (ΔF < -0.4)
Buried residues
ExAC (benign)
HGMD sites
HGMD SNV uniquely captured by ΔF


Neutrophil cytosol factor 1 (pdb 1KQ6)
1
21
41
61
81
101
121
Residue ID
UniProt Annotations (PTM, PPI, etc)
Buried residues
HGMD sites
Deleterious SNV (ΔF < -0.4)
ExAC (benign)
HGMD SNV uniquely captured by ΔF


Breast cancer type 1 (pdb 3PXA)
1690
1740
1790
1840
Residue ID
UniProt Annotations (PTM, PPI, etc)
Buried residues
HGMD sites
Deleterious SNV (ΔF < -0.4)
ExAC (benign)
HGMD SNV uniquely captured by ΔF