Using structural bioinformatics to investigate the impact of non synonymous SNPs and disease mutations: scope and limitations
Supplementary Material

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Tables

Supplementary Table S1 - Types of data sets used to train and test SNP classifiers.
The column "Size of data set" refers to the range of the data sets used, i.e. the smallest and largest data sets.

Origin data set	Size of data set	Number of studies	References
Neutral variations			
Mutagenesis studies	111-3706	9	[1–9]
Orthologs	888-16682	3	[3, 9, 10]
SwissProt SNP	502-12944	6	[3, 8, 11–14]
OMIM	558	1	[15]
dbSNP	5177-21471	2	[16, 17]
Disease mutations			
Mutagenesis studies	159-1750	8	[1–9]
COSMIC database	879	1	[18]
HGMD	3768-10263	1	[9]
OMIM	879-2249	5	[3, 8, 13, 15, 18]
SwissProt Disease	175-9610	9	[3, 8, 10–14, 19, 20]
Data from Haluschka *et al.* [21]	209	1	[20]
Data from Cargill *et al.* [22]	185	2	[19, 20]

Supplementary Table S2 - Performance of state-of-the-art predictors on representative data sets. The performance of a few selected tools on SwissProt disease associated mutations and SNP data are shown. The false positive rate (FPR = 1 - specificity), the true positive rate (TPR = sensitivity) and the Matthews correlation coefficient (MCC) are shown where available. Although all analyses use the variation data from the SwissProt knowledge base, the effective size of the data set varies between analyses.

Study	**Method**	**FPR**	**TPR**	**MCC**	**Size data set**
Bao *et al* [11]	Random Forest	0.3	0.76	0.46	205
Capriotti *et al* [13]	HybridMeth	-	-	0.46	21185
Karchin *et al* [14]	SVM	0.2	0.81	0.61	3691
Ng & Henikoff [19]	SIFT	0.19	0.69	0.50	5333
Wang & Moult [20]	Stability	0.3	0.9	0.61	262
Worth *et al* [16]	Combined	0.09	0.32	0.28	9143
Yue & Moult [9]	SVM	0.15	0.74	0.59	6077

Supplementary Table S3 - Variation of the performance of SIFT on different data sets. The false positive rate (FPR = 1 - specificity), the true positive rate (TPR = sensitivity) and the Matthews correlation coefficient (MCC) are shown where available.

Study	**Dataset**	**FPR**	**TPR**	**MCC**
Bao *et al* [11]	Test set	0.33	0.62	0.29
Saunders *et al* [8]	Human	0.4	0.65	0.25
Ng & Henikoff [7]	lac I repressor	0.22	0.57	0.36
Ng & Henikoff [7]	HIV 1-protease	0.3	0.88	0.59
Ng & Henikoff [7]	T4 lysozyme	0.41	0.72	0.31
Ng & Henikoff [19]	SwissProt disease	0.19	0.69	0.50
Worth *et al* [16]	SwissProt + dbSNP	0.41	0.71	0.30
Our evaluation	SwissProt	0.79	0.69	-0.12

Figures

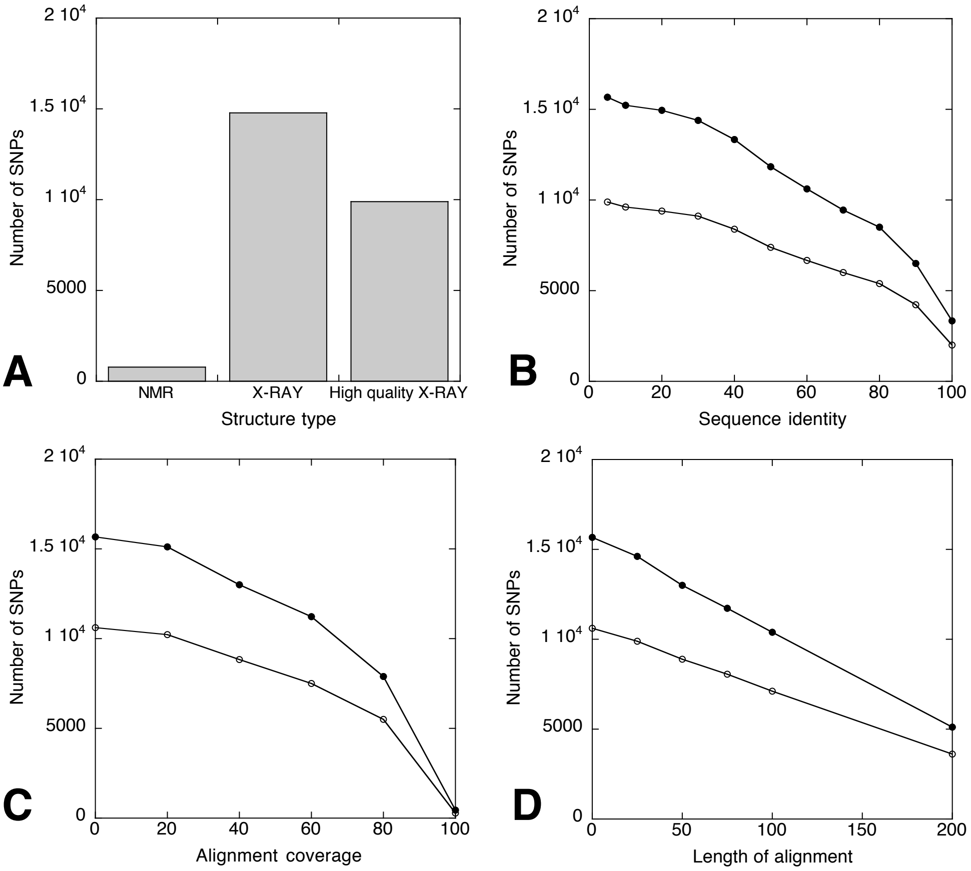


Figure S1. Structural coverage of Ensembl non synonymous SNP data. A. Number of SNPs in structures determined by NMR and X-ray crystallography studies or models of these structures. 11% of all non synonymous SNPs can be mapped on crystallography structures, and 7% of all SNPs can be modeled on a high-quality X-ray structure (resolution $\leq$ 2.5Å). **B. Number of SNPs covered by structural data versus the sequence identity between the query sequence and the structural model.** The number of SNPs that can be modeled on X-ray structures (●) decreases from 15% of all nsSNPs (15685 nsSNPs, 5% sequence identity) to 2.5% (3341) of all SNPs for which the structure of the wild type sequence has been determined experimentally (100% sequence identity). When only high quality structures are considered (○), this amount is reduced by half to 7.4% for a sequence identity of 5% and 1.5% for exact models. **C. Number of SNPs covered by structural data versus the sequence coverage of the wild type sequence.** There are almost no SNPs for which the full length of the protein sequence is covered (100% coverage), but for 80% coverage almost 8000 SNPs can be selected, of which circa 5500 in high quality structures. **D. Number of SNPs covered by structural data versus the length of the alignment between protein sequence and structural model.** About a third of the SNPs that can be modeled are located in a structural alignment that is less than 100 amino acids long, both for models based on all X-ray structures (●) and based on high resolution structures only (○).

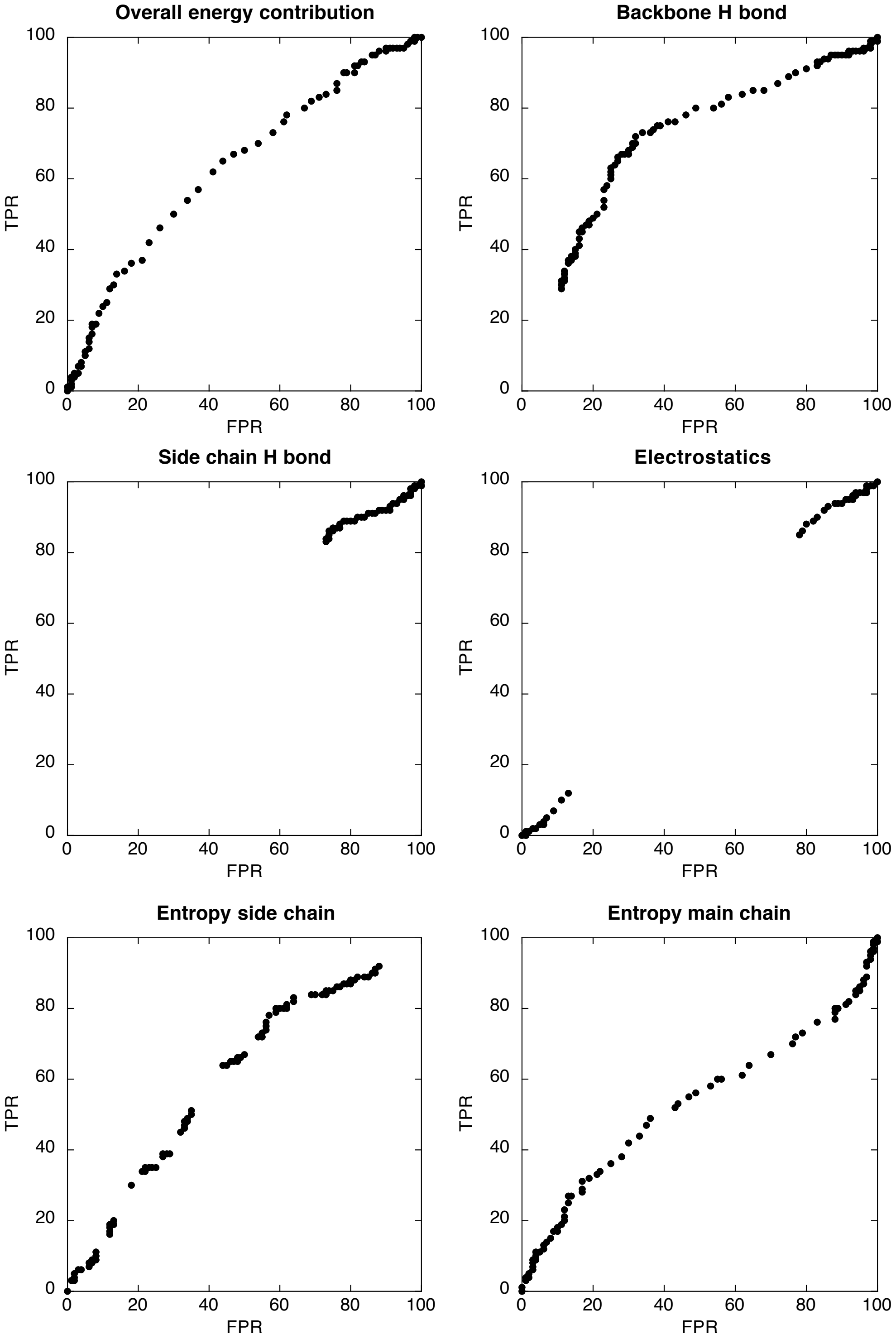
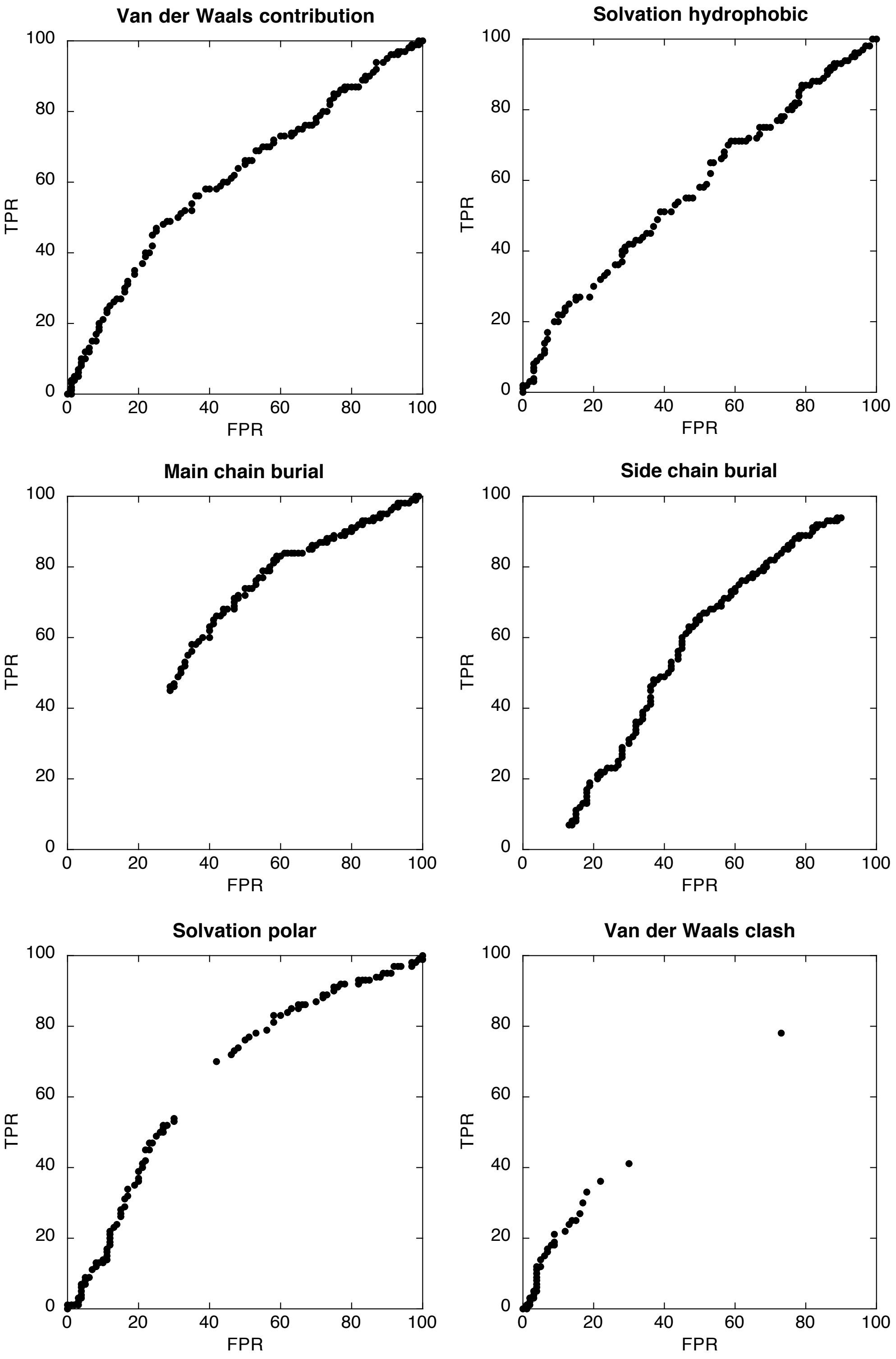


Figure S2. ROC curves for classification of disease mutations and neutral variation by using structural properties of the amino acid substitution site.



Van der Waals contribution

Solvation hydrophobic

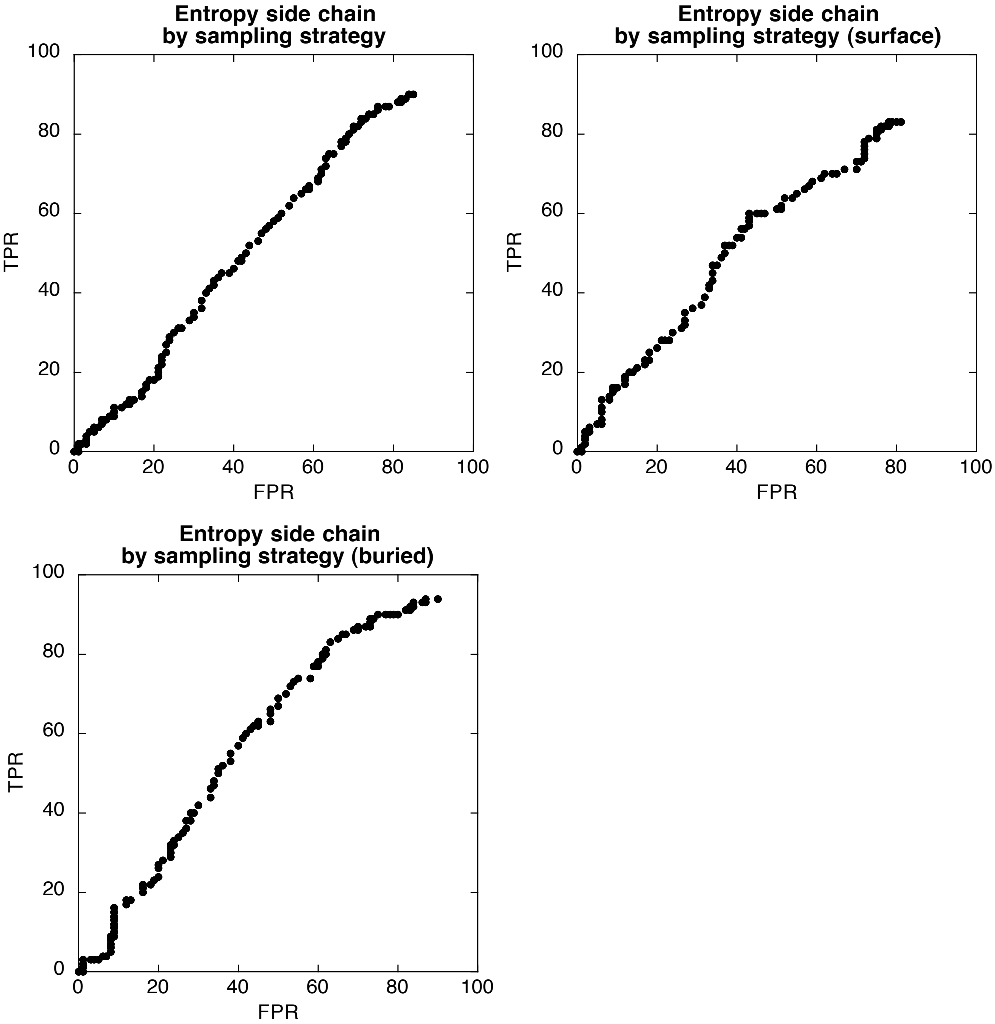
Main chain burial

Side chain burial

Solvation polar

Van der Waals clash

Figure S2 ***(continued).*** ROC curves for classification of disease mutations and neutral variation by using structural properties of the amino acid substitution site.



Entropy side chain by sampling strategy

Entropy side chain by sampling strategy (surface)

Entropy side chain by sampling strategy (buried)

Figure S2 ***(continued).*** ROC curves for classification of disease mutations and neutral variation by using structural properties of the amino acid substitution site.

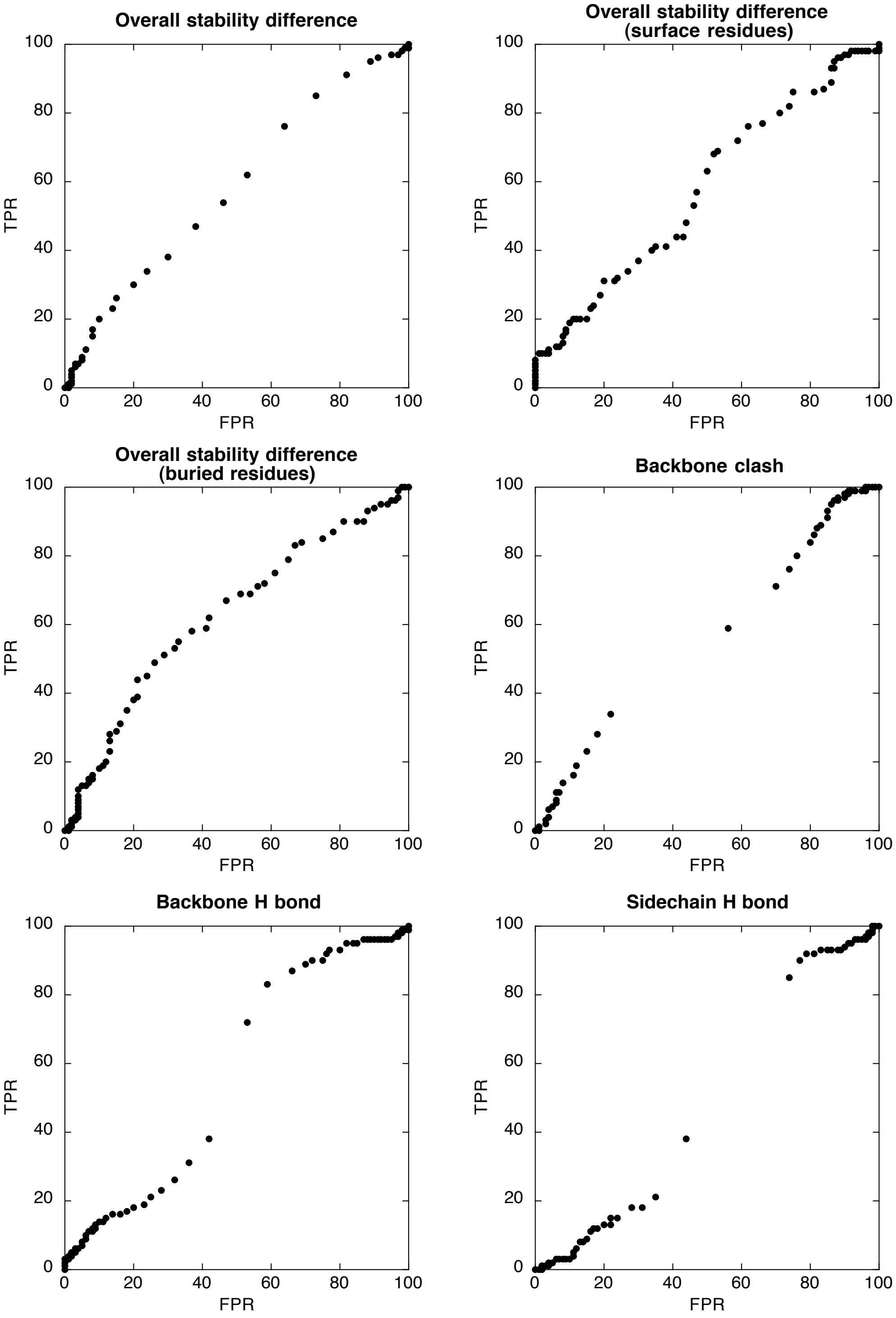


Figure S3. ROC curves for classification of disease mutations and neutral variation by using structural differences between the wild type and variant protein.

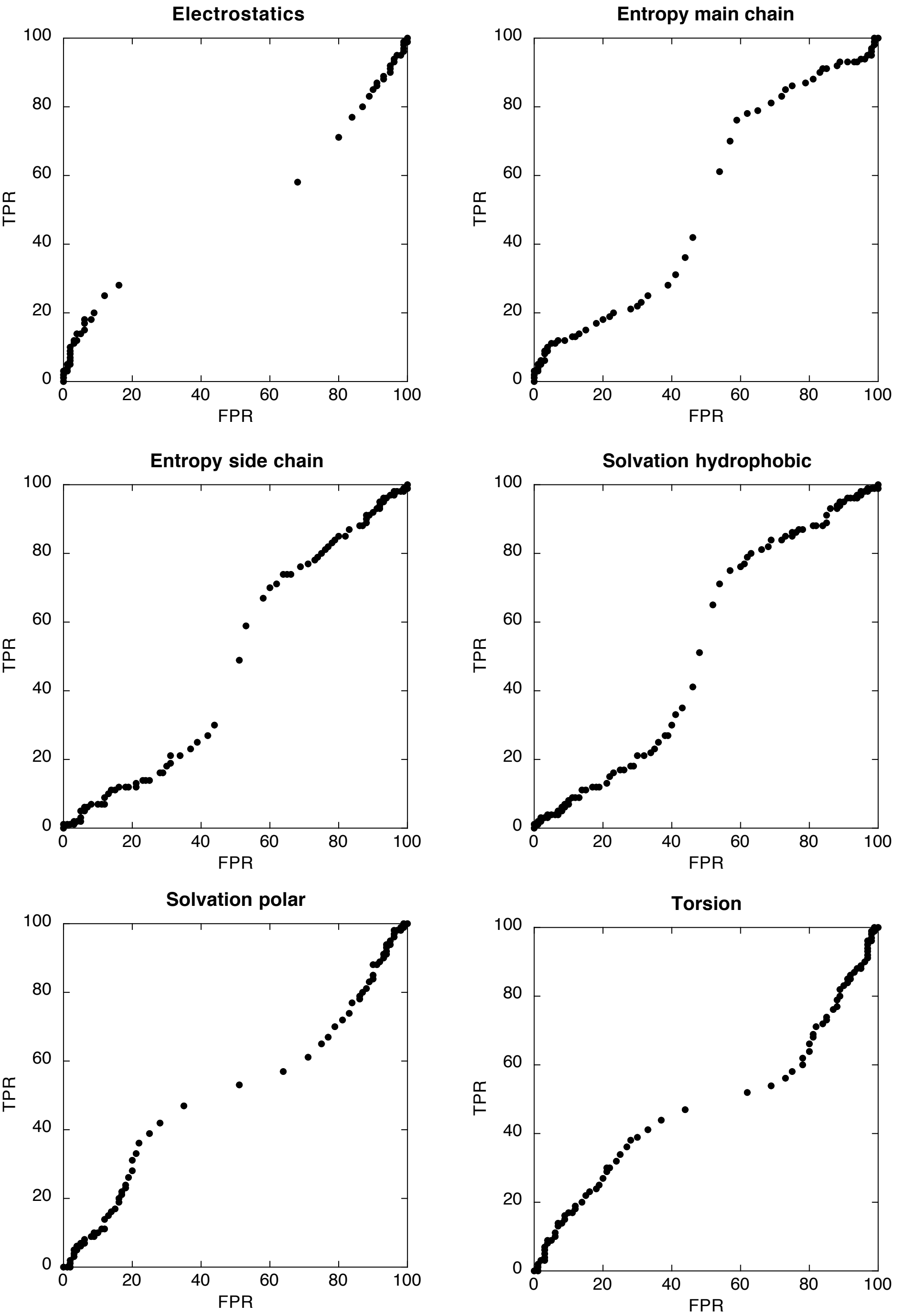


Figure S3 ***(continued).*** ROC curves for classification of disease mutations and neutral variation by using structural differences between the wild type and variant protein.

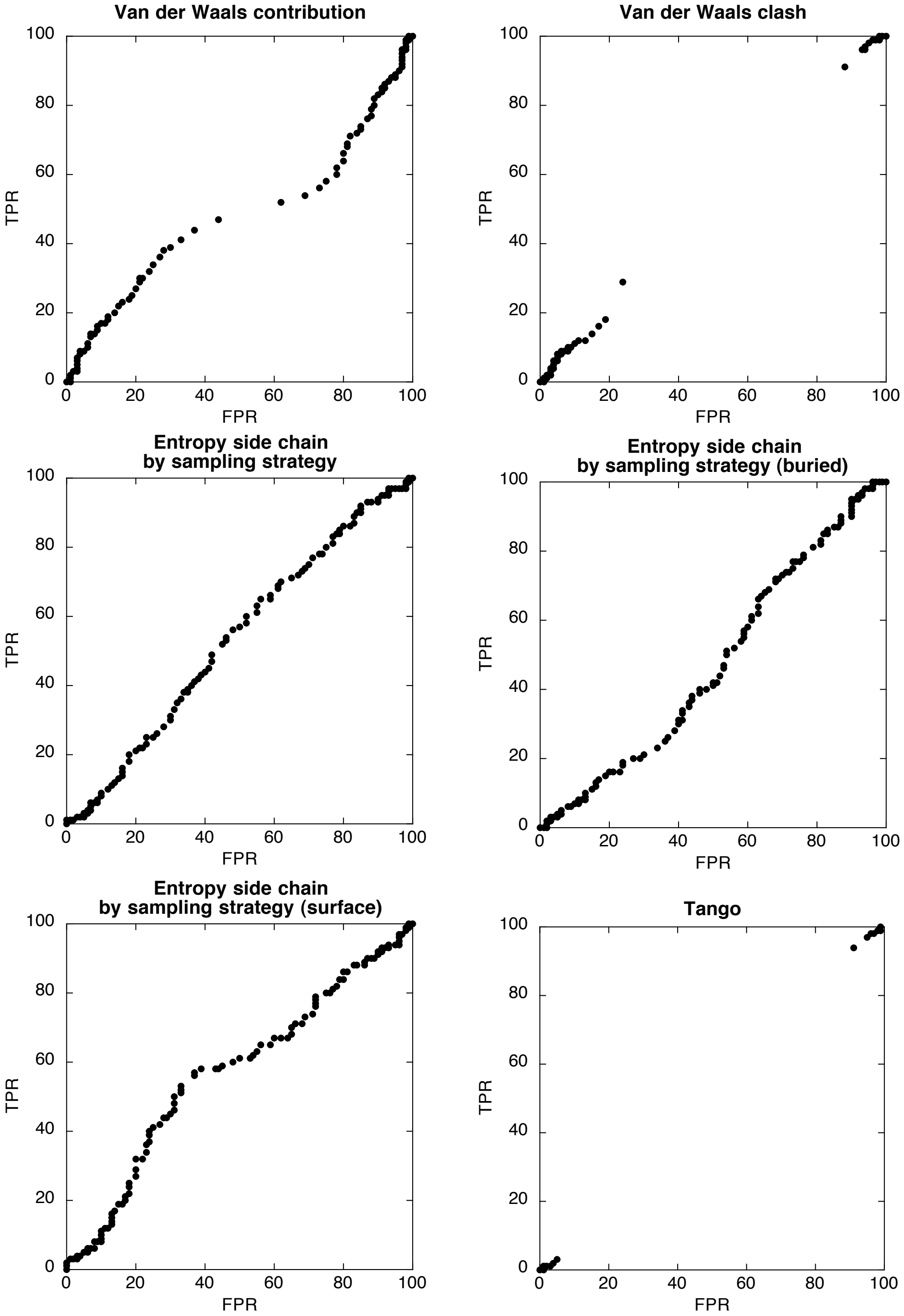


Figure S3 ***(continued).*** ROC curves for classification of disease mutations and neutral variation by using structural differences between the wild type and variant protein.

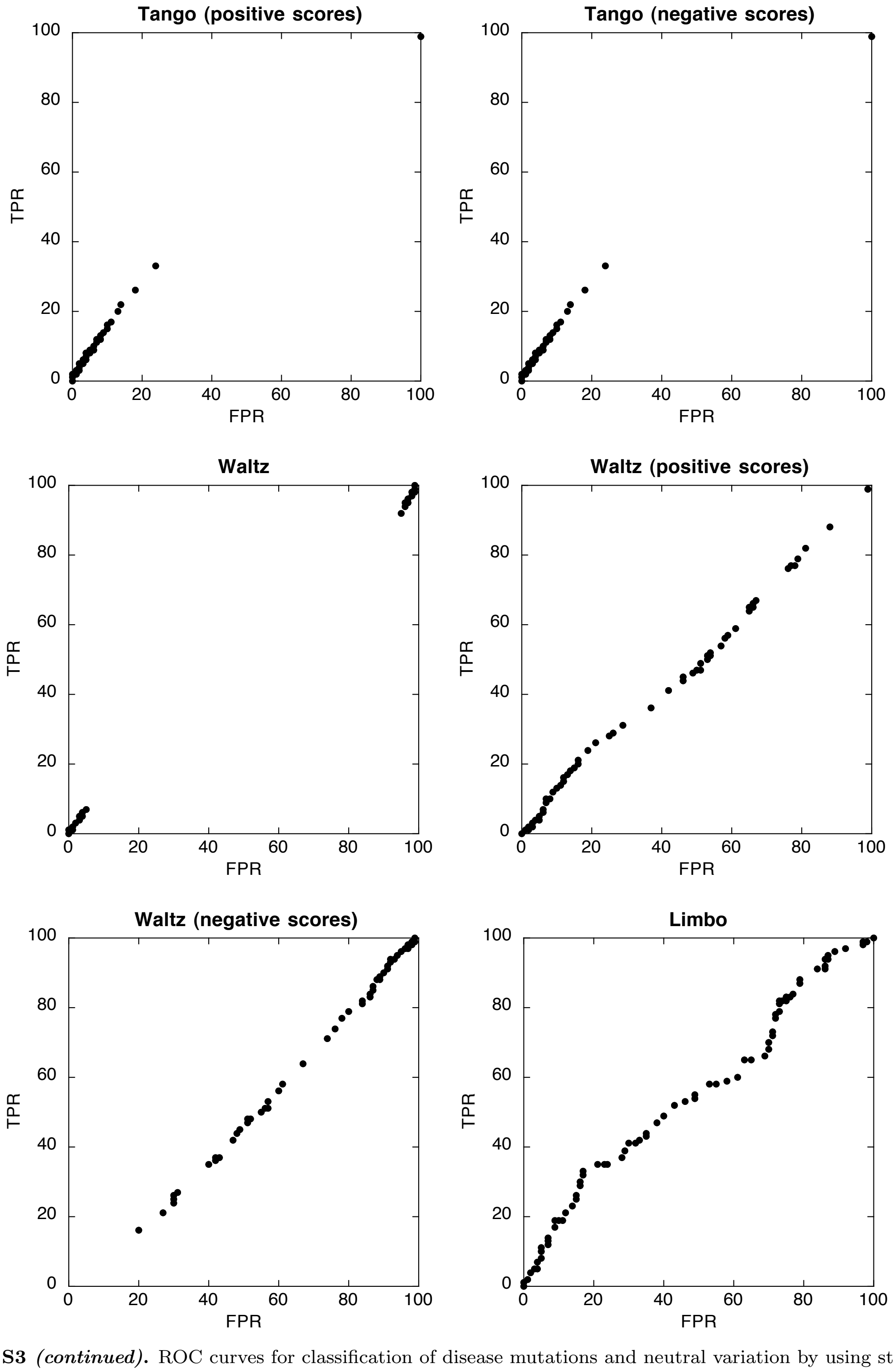


Figure S3 ***(continued).*** ROC curves for classification of disease mutations and neutral variation by using structural differences between the wild type and variant protein.

References

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