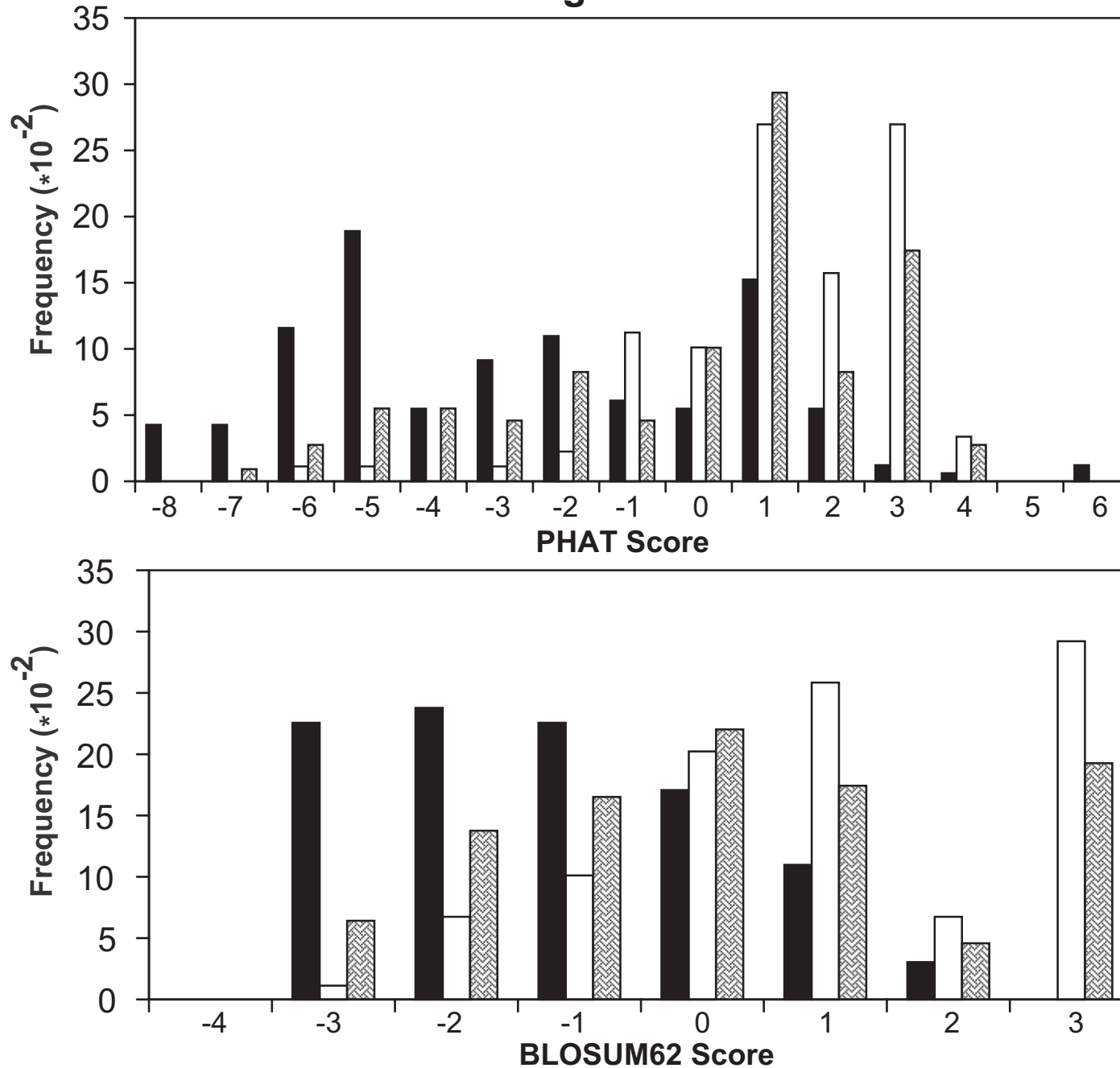
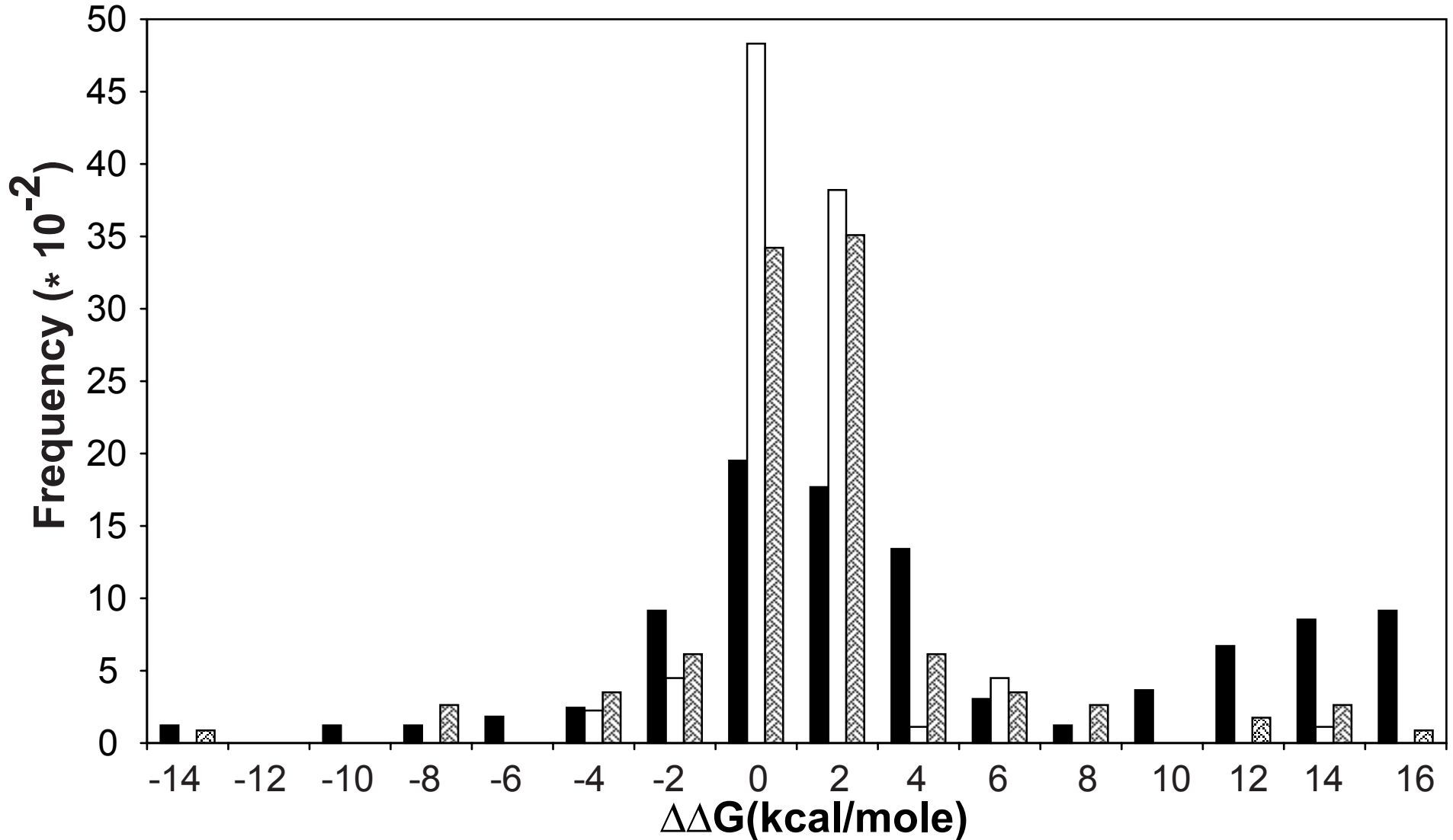


**Figure 1S**



Frequency distribution of PHAT and BLOSUM62 substitutions scores for the disease-causing (black bars), neutral (white bars) and dbSNP variation (shaded bars) datasets in transmembrane regions.

**Figure 2S**



Frequency distribution of  $\Delta\Delta G$  values (change in free energy of hydrophathy) for the disease-causing (black bars), neutral (white bars) and dbSNP (shaded bars) variation datasets.