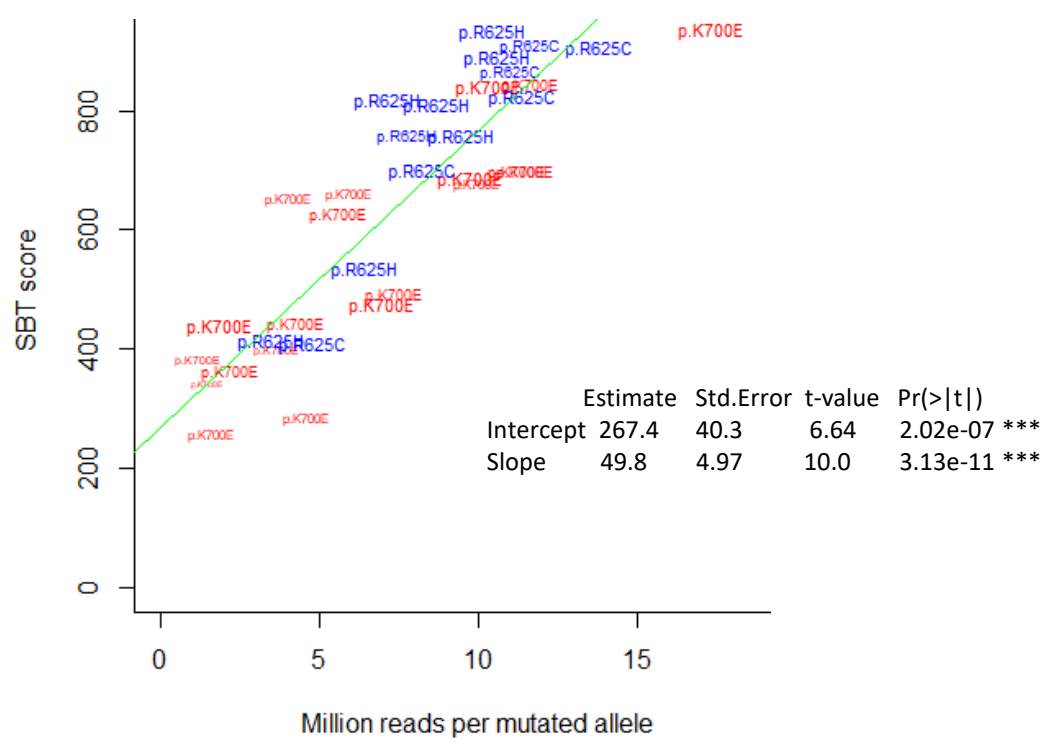
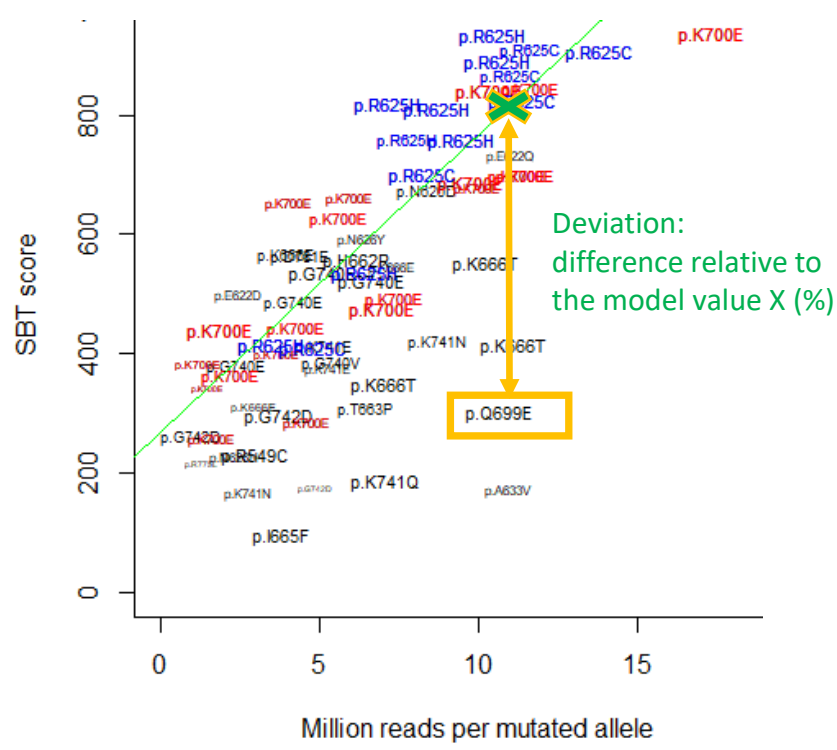


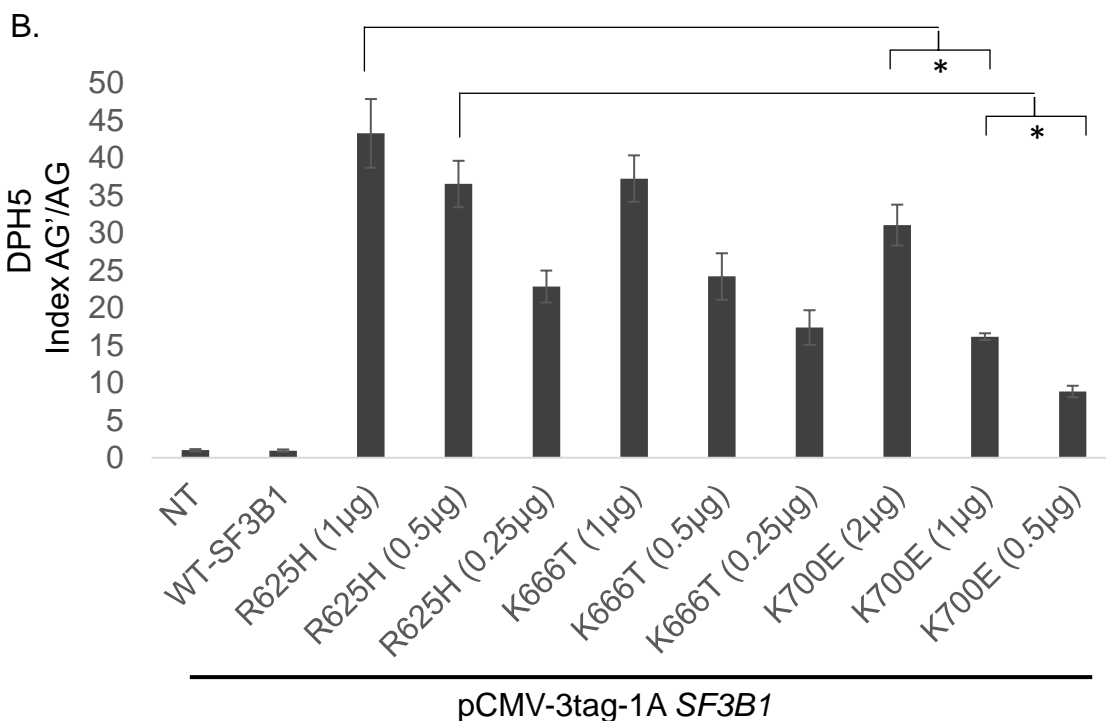
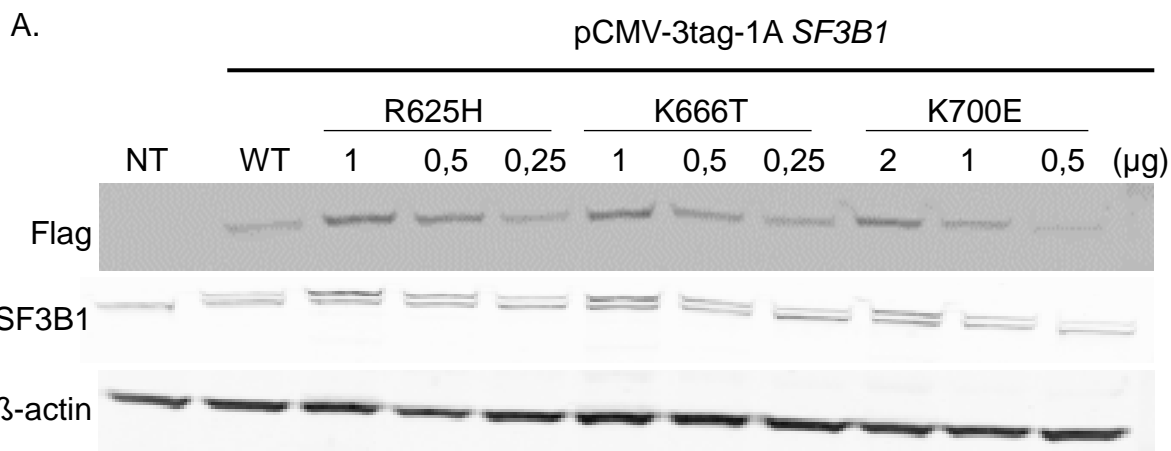
A.



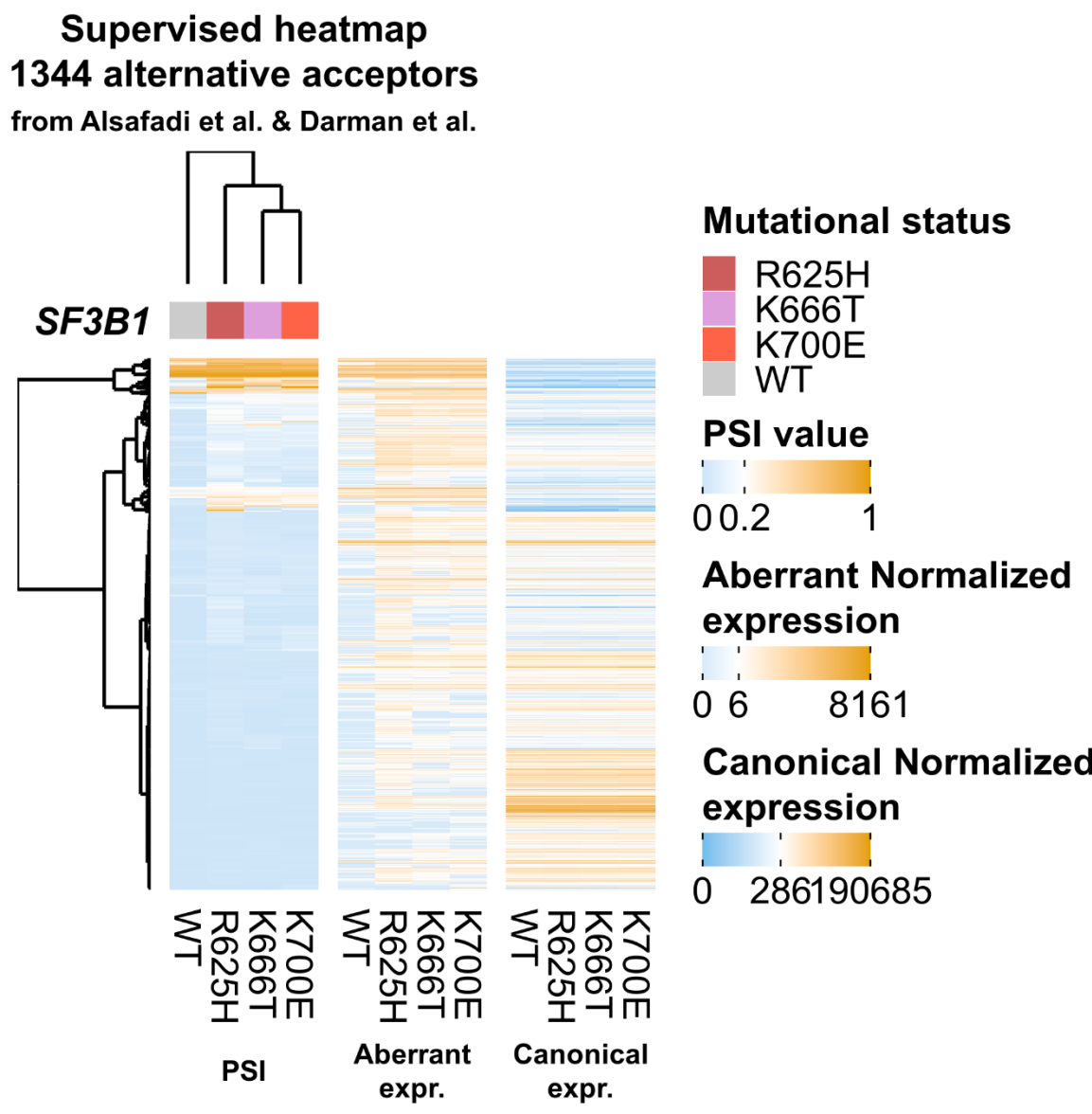
B.



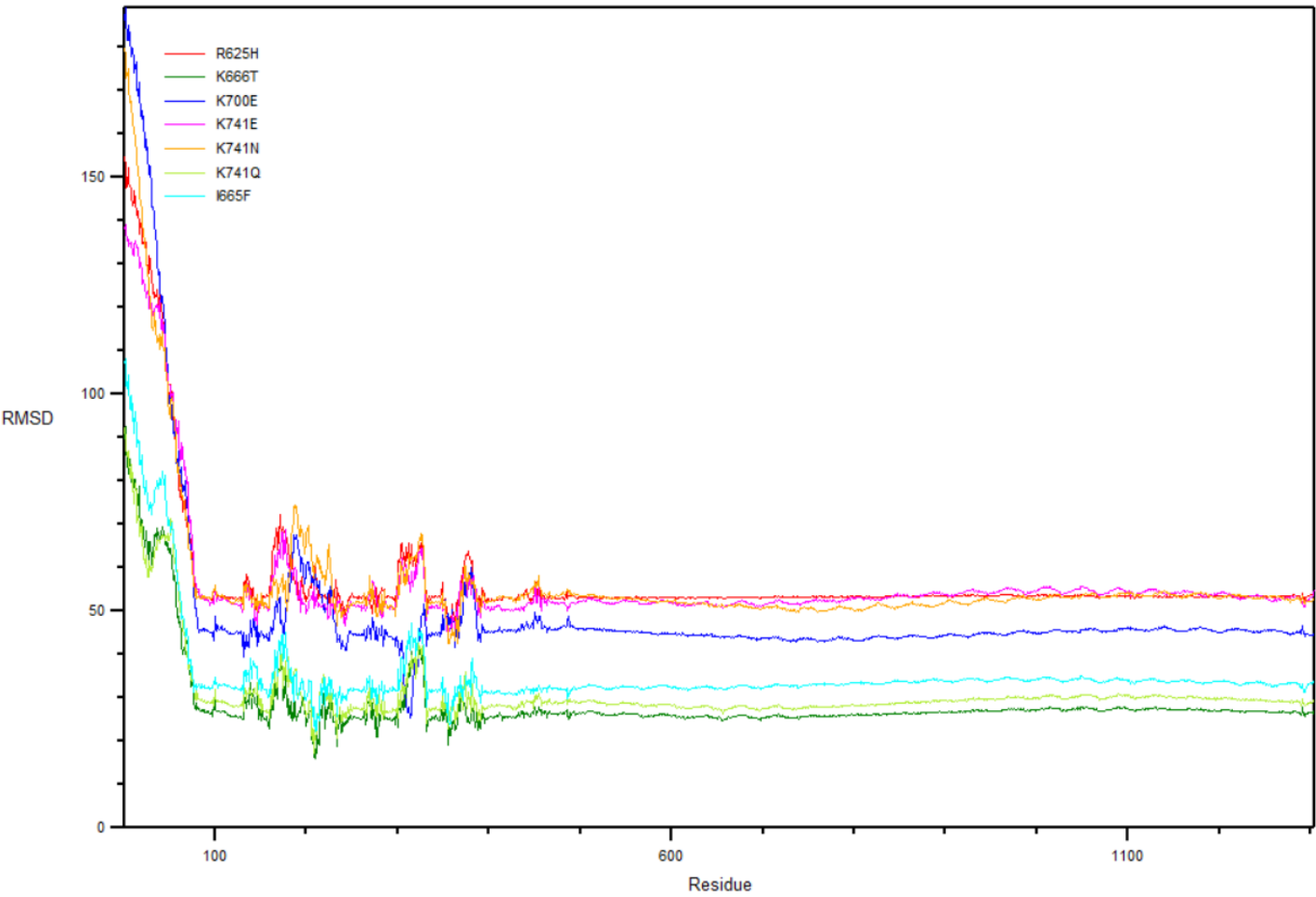
Supplementary Fig 1 : Linear model of SBT score (measured mutation impact) depending on RNA-sequencing coverage and *SF3B1* mutation variant allele frequency (VAF). Million reads per mutated allele equals the total number of junction reads aligned in RNA-sequencing multiplied by *SF3B1* mutation VAF. **A.** The linear model (lm) is built on 625 and 700 mutations using R lm function (parameters of linear model are shown). **B.** Deviation from the linear model was calculated for each mutation as the difference between actual SBT score and a model value divided by the model value. Deviation as a percent of “expected” value depending on RNA-sequencing coverage and mutation VAF.



Supplementary Fig 2 : Comparison of the intensities of the aberrant splice pattern induced by *SF3B1* hotspot mutants at increasing ranges of expression levels. **A.** Protein expression analysis of exogenous flag-*SF3B1* and endogenous *SF3B1* in transfected HEK293T cells by immunoblotting with anti-Flag and anti-*SF3B1*, respectively. β -actin antibody was used as a loading control. **B.** Effect of the different mutations of *SF3B1* on the AG'/AG transcript expression ratio of *DPH5* in HEK293T cells. Ratios of expression levels of alternative AG' form to the expression level of canonical AG form (AG'/AG) of *DPH5* were determined by quantitative RT-PCR. The results are average of three replicates and are represented as mean \pm sd. Paired t-test was used to generate the p-values by comparing each condition to the *SF3B1*-R625H condition; * $p < 0.05$.



Supplementary Fig 3 : Heatmap of differential splice 3'ss junctions in HEK293T overexpressing SF3B1 wild-type or mutants. The corresponding expression levels of aberrant transcripts and canonical transcripts is shown on the right panel for comparison (differential expression of junctions is not the consequence of differential gene expression).



Supplementary Fig 4 : RMSD plots of each residue along the mutant backbone compared to Wild-Type SF3B1 backbone.