Letter: This format begins with an introductory paragraph (not abstract) of approximately 150 words, summarizing the background, rationale, main results and implications.

Currently at 251 words.

Loss-of-function variants (LOF) are ~~clinically~~ relevant because they are known to be disease-causing. However, recent sequencing efforts indicate the presence of null variants in seemingly healthy humans. Moreover, a few beneficial LOF variants have been recently identified. ~~Here, we present a method to predict the functional impact of premature Stop-causing variants, a class of LOF variants.~~ We have developed ALOFT (Annotation of Loss-of-Function Transcripts), a pipeline to annotate putative LOF variants with a variety of functional and evolutionary features. Using these features, we built a classifier to distinguish between benign, recessive and dominant disease-causing LOF variants. We applied our classifier to several datasets ranging from healthy cohorts to disease datasets. Our method correctly predicts the mode of inheritance and pathogenicity of all of the truncating variants in recently published Mendelian disease studies, predicts that autism patients have a higher proportion of deleterious *de-novo* LOF variants than controls and that somatic LOF variants in cancer driver genes are pathogenic. Application of this method to LOF variants in the 1000 Genomes dataset shows that on an average, each individual is a carrier of xx number of recessive and yy number of benign premature Stop-causing variants. Thus, this method can be used to differentiate high impact LOF variants from low impact LOF variants and allows prioritization of LOF variants for disease diagnosis and development of therapeutics that restores function of the protein. It also provides new opportunities for development of drug inhibitors against proteins that harbor benign LOF variants and are associated with beneficial phenotypes.