PS1 code weights for variants with the same predicted splicing event as a known (likely) pathogenic variant*

Variant Under Assessment (VUA)	Baseline computational/predictive code applicable to VUA	Position of reference variant compared to VUA	PS1(Splicing) code applicable to VUA	
			with P reference variant	with LP reference variant
Outside canonical dinucleotide	PP3	Same nucleotide	PS1	PS1_Moderate
Outside canonical dinucleotide	PP3	Within same splice motif (including within canonical dinucleotide)	PS1_Moderate	PS1_Supporting
Canonical dinucleotide	PVS1	Within same canonical dinucleotide	PS1_Supporting	N/A
Canonical dinucleotide	PVS1	Within same splice motif, but outside canonical dinucleotide#	PS1_Supporting	PS1_Supporting
Canonical dinucleotide	PVS1_Strong, PVS1_Moderate, or PVS1_Supporting	Within same canonical dinucleotide	PS1	N/A
Canonical dinucleotide	PVS1_Strong, PVS1_Moderate, or PVS1_Supporting	Within same splice motif, but outside canonical dinucleotide#	PS1_Moderate	PS1_Supporting

* Prerequisite for all: The predicted event of the VUA must precisely match the predicted event of the known (likely) pathogenic variant (e.g. both predicted to lead to exon A skipping, or both to enhanced use of cryptic site B), AND the strength of the prediction for the VUA must be of similar or higher strength than the strength of the prediction for the known (likely) pathogenic variant. (Likely) pathogenic variant should be assigned classification using VCEP specifications. For an exonic variant, predicted or proven functional effect of missense substitution/s encoded by the VUA and (likely) pathogenic variant should also be considered before application of this code. Canonical dinucleotide refers to donor and acceptor dinucleotides in reference transcript/s used for curation. Designated donor and acceptor site motifs ranges should be based on position weight matrices for intron category (see methods). For GT-AG introns these are defined as follows: the donor site motif, last 3 bases of the exon and 6 nucleotides of intronic sequence adjacent to the exon; acceptor site motif, first base of the exon and 20 nucleotides upstream from the exon boundary. Consider other motif ranges for non GT-AG introns.

If relevant, splicing data for a pathogenic variant outside a canonical dinucleotide may be used to update a PVS1 decision tree, and hence the applicable PVS1 code for a canonical dinucleotide variant.