

PS1 Same amino acid change as a previously established pathogenic variant regardless of nucleotide change

- **Missense:** Do not use. Missense changes are not yet confirmed as a mechanism of disease for *PALB2*.
- **Splicing:** Use *PALB2* PS1 Splicing table for splicing variants with similar predictions or observations of splice defect. (PMID: 36865205)

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
Located outside donor/acceptor $\pm 1,2$ dinucleotide positions	PP3	Same nucleotide	PS1	PS1_Moderate
	PP3	Within same donor/acceptor motif (including at $\pm 1,2$ positions)	PS1_Moderate	PS1_Supporting
Located at donor/acceptor $\pm 1,2$ dinucleotide positions	PVS1	Within the same donor/acceptor dinucleotide	PS1_Supporting	N/A
	PVS1	Within same donor/acceptor motif, but outside dinucleotide#	PS1_Supporting	PS1_Supporting
	PVS1_Strong, PVS1_Moderate, or PVS1_Supporting	Within the same donor/acceptor dinucleotide	PS1	N/A
	PVS1_Strong, PVS1_Moderate, or PVS1_Supporting	Within same donor/acceptor motif, but outside 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. Donor/acceptor dinucleotide refers to donor and acceptor $\pm 1,2$ dinucleotides in reference transcript/s used for curation. Designated donor and acceptor motif ranges should be based on position weight matrices for intron category. For GT-AG introns these are defined as follows: the donor motif, last 3 bases of the exon and 6 nucleotides of intronic sequence adjacent to the exon; acceptor 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 the donor/acceptor $\pm 1,2$ dinucleotide positions may be used to update a PVS1 decision tree, and hence the applicable PVS1 code for a donor/acceptor dinucleotide variant.