PALB2: CanVIG-UK Gene-Specific Guidance

Date: 02/06/2023 Version: 1.0

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CanVIG-UK review of *PALB2* May 2023: Consensus to use relevant recommendations from the ClinGen *PALB2* VCEP guidance (available at: https://clinicalgenome.org/affiliation/50039/) for *PALB2* variants reported under indication R208 of the UK Genomic Test Directory. Evidence items in grey are not relevant as per the ClinGen VCEP guidance (last reviewed: Version 1.0.0, released 03/17/2023).

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to PALB2
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_STR	As per VCEP
PP4: Phenotypic specificity/case counting (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)		Not applicable as per VCEP
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_SUP	As per VCEP
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	As per VCEP
PS1: Same amino acid change as an established variant	_STR MOD SUP	As per VCEP
PM4: Protein-length-changing variant		Not applicable as per VCEP

PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_SUP	As per VCEP
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	As per VCEP
PM1, PP2: Enrichment/constraint: **PP2**: Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease **PM1:** Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation		Not applicable as per VCEP
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product		Not applicable as per VCEP
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	_STR _MOD _SUP	As per VCEP
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history		Not applicable as per VCEP
PM3: in trans with a pathogenic variant (**recessive disorders)**	_STR _MOD _SUP	As per VCEP
PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to		Not applicable as per VCEP

perform an independent evaluation		

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	As per VCEP
BS2: Observation in controls inconsistent with disease penetrance. Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age	_STR _MOD _SUP	As per VCEP
BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)		Not applicable as per VCEP
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease	_SUP	As per VCEP
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_STR _MOD _SUP	As per VCEP
BP3: In-frame deletions/insertions in a repetitive region		Not applicable as per VCEP
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing		Not applicable as per VCEP
BS4: Non segregation with disease	_STR _MOD _SUP	As per VCEP
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis		Not applicable as per VCEP
BP6: Reputable source recently reports variant as benign, but the evidence is not available to the		Not applicable as per VCEP

laboratory to perform an independent evaluation		
BP5: Alternate molecular basis for disease		Not applicable as per VCEP

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
1.0	02/06/2023	--	Initial Version	--	