PALB2: CanVIG-UK Gene-Specific Guidance

Date: 30/10/2023 Version: 1.1

A Garrett[1], S.Allen[1], L Loong[1], M Durkie[2], J. Drummond[3] , G.J. Burghel[4], R. Robinson[5], A Callaway[6,7], J. Field[7], T. McDevitt[8], T. McVeigh[9], H. Hanson[1,10], C.Turnbull[1,9]

1) Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK.
2) Sheffield Diagnostic Genetics Service, NEY Genomic Laboratory Hub, Sheffield Children's NHS Foundation Trust, Sheffield, UK
3) East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
4) Manchester Centre for Genomic Medicine and NW Laboratory Genetics Hub, Manchester University Hospitals NHS Foundation Trust, Manchester, UK
5) Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK
6) Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust, Salisbury, UK
7) Genomics and Molecular Medicine Service, Nottingham University Hospitals NHS Trust, Nottingham, UK
8) Department of Clinical Genetics, CHI at Crumlin, Dublin, Ireland
9) The Royal Marsden NHS Foundation Trust, Fulham Road, London
10) St George's University Hospitals NHS Foundation Trust, Tooting, London, UK

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 (**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	There should be a minimum of 2 case observations before PS4 can be applied. Female-only population controls are recommended for use. See main CanVIG-UK consensus specification for database recommendations. Otherwise follow VCEP recommendations.
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	Female-only population controls are recommended for use. See main CanVIG-UK consensus specification for database recommendations.
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 perform an independent evaluation		Not applicable as per VCEP

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	_STR _MOD _SUP	As per VCEP

penetrance expected at an early age		
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 laboratory to perform an independent evaluation		Not applicable as per VCEP
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	--	
1.1	04/08/2023	PM2	Specified to use female-only sex matched controls.	Allen	CStAG
1.1	30/10/2023	PS4	Requirement for a minimum of 2 case observations and female-only sex matched controls.	Garrett	CStAG