PTEN: CanVIG-UK Gene-Specific Guidance

Date: 01/11/2022 Version: 1.0

CanVIG-UK review of PTEN ClinGen Expert Group guidance. Consensus for use of the PTEN ClinGen Expert Group guidance with the additional points of specification as below.

Relevant documents:

(i) The ClinGen PTEN Expert Panel Specifications Version 2

(ii) A Clinical Scoring System for Selection of Patients for PTEN Mutation Testing Is Proposed on the Basis of a Prospective Study of 3042 Probands (Tan *et al.*, 2011) - *use of the Cleveland Clinic Scoring System*

(iii) Clinical likelihood ratios and balanced accuracy for 44 in silico tools against multiple large-scale functional assays of cancer susceptibility genes (Cubuk *et al.*, 2021)

For use in conjunction with the ClinGen PTEN Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2. Evidence lines for which there are no gene-specific recommendations should be reviewed in context of the ClinGen PTEN Expert Panel Specifications.

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to PTEN
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_VSTR _STR _MOD _SUP	**AMENDED FROM VCEP GUIDANCE** Using the Cleveland Clinic (CC) scoring system for phenotype specificity: • Adults: ○ 1 point per proband with a Cleveland Clinic (CC) score of ≥25. ○ 0.5 points per proband with a CC score of 20-24. Where family members of a proband attain a CC score as described above, their point score may be used in addition to achieve higher evidence strength for PS4. When combining phenotype scores from additional family members for PS4, at least one family member must have one of the following three critical phenotypes: • Macrocephaly • Lhermitte-Duclos Disease • GI Hamartoma **If multiple members from the same family are used for PS4, do not apply PP1 where the same family is used as evidence for PP1 and PS4.** Otherwise sum points towards the phenotypic specificity score, and use phenotypic specificity score ranges as per VCEP guidance. For paediatric cases, use scoring as specified in VCEP guidance.
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_MOD _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	
PM4: Protein-length-changing variant	_MOD _SUP	
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_STR _MOD _SUP	**AMENDED FROM VCEP GUIDANCE** PP3: May be applied at SUP where REVEL ≥ 0.7 (see Cubuk *et al*., 2021, GIM)
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	
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	_STR _MOD _SUP	Otherwise, **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	_VSTR _STR _MOD _SUP	**AS PER VCEP**
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	_VSTR _STR _MOD _SUP	**AS PER VCEP** **Note:** See PS4: Case-control regarding co-usage where there are multiple affected family members.
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history	_STR _MOD _SUP	**AS PER VCEP**
PM3: in trans with a pathogenic variant (**recessive disorders)**	_STR _MOD _SUP	**DO NOT USE: 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	_SUP	**DO NOT USE: AS PER VCEP**
PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)	_STR _MOD _SUP	**DO NOT USE: AS PER VCEP (specificity part of PS4)**

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 _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.)	_SUP	May be applied at SUP where REVEL ≤ 0.4.

BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease	_SUP	**DO NOT USE: AS PER VCEP**
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_SUP	**AS PER VCEP**
BP3: In-frame deletions/insertions in a repetitive region	_SUP	**DO NOT USE: AS PER VCEP**
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing	_STR _MOD _SUP	**AS PER VCEP**
BS4: Non segregation with disease	_STR _SUP	**AS PER VCEP**
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR _SUP	**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	_STR _SUP	**DO NOT USE: AS PER VCEP**
BP5: Alternate molecular basis for disease	_SUP	**AS PER VCEP**

Revised version	Date	Section	Update	Amended by	Approved by
1.0	*01/11/2022*	*All*	*Original Version: draft*	*Allen*	*Turnbull*