TP53: CanVIG-UK Gene-Specific Guidance

Date: 25/05/2023 Version: 1.6

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CanVIG-UK review of TP53 Jan 2020. Consensus to use TP53 ClinGen Expert Group guidance with additional points of specification as below.
Relevant documents:

(i) ClinGen *TP53* Expert Panel Specifications v1_2.1
(ii) Corresponding HMG publication from ClinGen Expert group (Fortuno et al 2020)
(iii) New surveillance guidelines for Li-Fraumeni and hereditary *TP53* related cancer syndrome: implications for germline *TP53* testing in breast cancer (Evans and Woodward 2020).

For use in conjunction with the ClinGen TP53 VCEP Guidance. Evidence lines for which there are no gene-specific recommendations should be reviewed in context of the ClinGen TP53 VCEP Guidance.

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to TP53
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_VSTR _STR _MOD _SUP	**Exclusion of CHIP should be considered where P/LP variant is detected** in cases for which (i) there is no familial transmission evident AND (ii) VAF<40% AND (iii) phenotype is equivocal. Testing of normal tumour tissue is recommended if possible; otherwise testing of fibroblasts from skin biopsy should be considered). See flowchart in Evans and Woodward 2020
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_MOD _SUP	
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	
PS1: Same amino acid change as an established variant	_STR	For PM1_mod: the ≥10 occurrences on cancerhotspots.org, must be ***of the exact same amino acid substitution.***
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	For PM1_sup: ≥5 occurrences on cancerhotspots.org, where the exact same amino acid substitution counts as 1 occurrence and

PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	substitution of a different amino acid at the same residue counts as 0.5 of an occurrence. For PS1/PM5, reference variants should be classified as P/LP by ClinGen Expert Group. Until such a list exists, we suggest using 'or equivalent' to define a reference P/LP variant
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	
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	
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	_VSTR _STR _MOD _SUP	
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history	_STR _MOD _SUP	
PM3: in trans with a pathogenic variant (**recessive disorders)**	_STR _MOD _SUP	
PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation	_SUP	
PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)	_STR _MOD _SUP	

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	
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	
BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	_SUP	
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease	_SUP	
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_SUP	
BP3: In-frame deletions/insertions in a repetitive region	_SUP	
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing	_STR _MOD _SUP	

BS4: Non segregation with disease	_STR _SUP	
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR _SUP	
BP6: Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation	_STR _SUP	
BP5: Alternate molecular basis for disease	_SUP	

Revised version	Date	Section	Update	Amended by	Approved by
1.5	***04/03/22***	PM1	Recommendations for application at supporting level of evidence. Clarification that PM1_mod to be applied where ≥10 occurrences of exactly the same amino acid substitution	Garrett	CStAG
1.6	***25/05/23***	--	Clarified to use guidance in conjunction with ClinGen guidance	Allen	