

TP53: CanVIG-UK Gene-Specific Guidance

Date: 04/03/2022 Version: 1.5

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 CanVIG-UK Consensus Specification for Cancer susceptibility Genes of ACGS Best Practice Guidelines for Variant Classification. Evidence lines for which there are no gene-specific recommendations should be reviewed in context of CanVIG-UK Consensus Specification for Cancer Susceptibility Genes.

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	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_VSTR</div> <div style="background-color: #f08080; padding: 2px;">_STR</div> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	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	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	
PVS1: Predicted null variant (in a gene where LOF is a known mechanism of disease)	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_VSTR</div> <div style="background-color: #f08080; padding: 2px;">_STR</div> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	
PS1: Same amino acid change as an established variant	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_STR</div> </div>	For PM1_mod: the ≥10 occurrences on cancerhotspots.org, must be of the exact same amino acid substitution .
PM4: Protein-length-changing variant	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_STR</div> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	For PM1_sup: ≥5 occurrences on cancerhotspots.org, where the exact same amino acid substitution counts as 1 occurrence and substitution of a different amino acid at the same residue counts as 0.5 of an occurrence.
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	
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	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_STR</div> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	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
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_VSTR</div> <div style="background-color: #f08080; padding: 2px;">_STR</div> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: #f08080; padding: 2px;">_VSTR</div> <div style="background-color: #f08080; padding: 2px;">_STR</div> <div style="background-color: #f0e68c; padding: 2px;">_MOD</div> <div style="background-color: #90ee90; padding: 2px;">_SUP</div> </div>	

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 <i>in vitro</i> or <i>in vivo</i> 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