CHEK2: CanVIG-UK Gene-Specific Guidance

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CanVIG-UK review of *CHEK2* April 2022: Consensus to use relevant recommendations from the ClinGen ATM VCEP guidance (attached and also available at: https://clinicalgenome.org/affiliation/50039/) for *CHEK2* variants reported under indication R208 of the UK Genomic Test Directory. This scope of this test indication currently includes truncating variants (defined as: nonsense, frameshift and canonical splice site (+/- 1/2) variants). Additional points of specification are given below. Evidence items in grey are not relevant to truncating variants.

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

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to CHEK2
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_STR	As per *ATM* VCEP guidance.
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_SUP	As per *ATM* VCEP guidance.
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	Truncating variants prior to c.1493: use PVS1_vstr *(variants up to the last 50bp of the penultimate exon, therefore predicted to undergo nonsense mediated decay)* Truncating variants occurring from c.1494 to c.1566: use PVS1_str *(not predicted to undergo NMD, truncated/altered region includes nuclear localisation signal and therefore critical to protein function)* Truncating variants from c.1567: use PVS1_mod (*not predicted to undergo NMD, role of region unknown, variant removes <10% of protein*) Truncating variants within the first 100bp: use PVS1_mod

PS1: Same amino acid change as an established variant	_MOD _SUP	As per *ATM* VCEP guidance.
PM4: Protein-length-changing variant	_MOD	As per *ATM* VCEP guidance.
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_SUP	PM5_sup can be used for truncating variants after the first 100bp and prior to c.1493.
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	PP3 not to be used in combination with PVS1 so N/A for truncating variants.
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		PM1/PP2 N/A for truncating variants.
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	_MOD _SUP	No functional assays in *CHEK2* assessed by CanVIG-UK.
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease		N/A as per *ATM* VCEP guidance
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history		N/A as per *ATM* VCEP guidance
PM3: in trans with a pathogenic variant (**recessive disorders)**		N/A no recessive phenotype
PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation		N/A as per *ATM* VCEP guidance
PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)		N/A as per *ATM* VCEP guidance

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	As per *ATM* VCEP guidance
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		N/A as per *ATM* VCEP guidance

BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	_SUP	N/A for truncating variants
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease		N/A for truncating variants
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_STR _MOD _SUP	As per *ATM* VCEP guidance (BP7_O)
BP3: In-frame deletions/insertions in a repetitive region		N/A as per *ATM* VCEP guidance
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing	_MOD _SUP	No functional studies assessed by CanVIG-UK
BS4: Non segregation with disease		N/A as per *ATM* VCEP guidance
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR _MOD _SUP	As per *ATM* VCEP guidance
BP6: Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation		N/A as per *ATM* VCEP guidance
BP5: Alternate molecular basis for disease		N/A as per *ATM* VCEP guidance

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
1.1	25/05/23	--	Changed opening statement to clarify that these CanVIG guidelines should be used in conjunction with ClinGen VCEP guidelines.	Allen	