# *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 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 CHEK2 |
|---|---|---|
| **PS4: Case-control:** The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls | _STR | |
| **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<br>_STR<br>_MOD<br>_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)*<br><br>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)*<br><br>Truncating variants from c.1567: use PVS1_mod (*not predicted to undergo NMD, role of region unknown, variant removes <10% of protein*)<br><br>Truncating variants within the first 100bp: use PVS1_mod |

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|---|---|---|
| **PS1: Same amino acid change** as an established variant | | PM5_supp can be used for truncating variants after the first 100bp and prior to c.1493.<br><br>PS1/PM1/PM4/PP2 N/A for truncating variants PP3 not to be used in combination with PVS1 so N/A for truncating variants. |
| **PM4: Protein-length-changing variant** | | |
| **PM5: Novel missense change** at an amino acid residue where a different missense change determined to be pathogenic seen before | _SUP | |
| **PP3: In silico:** Multiple lines of computational evidence support a deleterious effect on the gene or gene product | | |
| **PM1, PP2: Enrichment/constraint:**<br>**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<br>**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 | | |
| **PS3: Functional:** Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product | _VSTR<br>_STR<br>_MOD<br>_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 | _SUP | 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***

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|---|---|---|
| **BA1/BS1: Allele frequency** is "too high" in ExAC or gnomAD for disorder | _SA<br>_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 |

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|---|---|---|
| **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 | | N/A for truncating variants |
| **BP3: In-frame deletions/insertions in a repetitive region** | | N/A for truncating variants |
| **BS3: Well-established *in vitro* or *in vivo* functional studies** show no damaging effect on protein function or splicing | _STR<br>_MOD<br>_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 | | N/A 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 |
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