**S3 supplementary table: *In silico* analysis of reported variants in *CDK13***

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| c.DNA sequence change | c.2140G>C | c.2149G>A | c.2156T>G | c.2201A>G | c.2252G>A | c.2524A>G | c.2525A>G | c.2579G>A | c.2620G>T | c.2686G>A | c.2898-1G>A |
| *De novo* in reported cases? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | NC |
| Predicted protein change1 | Gly714Arg | p.Gly717Arg | p.Val719Gly | p.Lys734Arg | p.Arg751Gln | p.Asn842Asp | p.Asn842Ser | p.Arg860Gln | p.Val874Leu | p.Asp896Asn | p.Ile967\_Asp1010del |
| Consurf Grade2 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | NA |
| Variety at this position (and % representation in MSA)2 | Gly (99.33%); other (0.67%) | Gly (98.00%); Ala (1.33%); other (0.67%) | Val (99.33%); 0ther (0.67%) | Lys (100.00%) | Arg (100.00%) | Asn (100.00%) | Asn (100.00%) | Arg (98.00%); Lys (2.00%) | Val (100.00%) | Asp (100.00%) | NA |
| Conserved amino acid? (species compared: chimpanzee, mouse, chicken, xenopus, zebrafish, drosophila, *C. elegans*)3 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NA |
| Variants at this position on gnomAD? 4 | No | No | No | No | No | No | No | No | No | No | No |
| Variant at this position on Exome Variant Server?5 | No | No | No | No | No | No | No | No | No | No | No |
| CADD6 | 32 | 34 | 28.7 | 27.8 | 34 | 25.6 | 24.4 | 35 | 33 | 34 | 26.9 |
| Polyphen27 | Probably damaging (1) | Probably damaging (1) | Probably damaging (1) | Probably damaging (1) | Probably damaging (1) | Probably damaging (1) | Probably damaging (0.992) | Probably damaging (1) | Probably damaging (0.999) | Probably damaging (0.997) | NA |
| SIFT8 | Deleterious (0) | Deleterious (0) | Deleterious (0) | Deleterious (0.001) | Deleterious (0) | Deleterious (0) | Deleterious (0) | Deleterious (0) | Deleterious (0.01) | Deleterious (0) | NA |
| FoldX ∆∆*G* (kcal/mol) | +3.48 | +14.59 | +2.90 | +0.53 | +1.03 | +6.36 | +4.05 | +0.95 | +2.25 | +3.97 | NA |
| CDK13-cyclin K interaction energy (kcal/mol)9 | -21.95 | -21.91 | -21.95 | -21.95 | -21.01 | -21.96 | -21.96 | -21.76 | -21.93 | -21.93 | not determined |
| role in CDK1310 | Nucleotide binding domain | ADP/ATP binding | CycK binding | ADP/ATP binding | Activation loop | Structural | Nucleotide binding |

NC = inheritance not confirmed

1 Numbered according to the canonical 1,512 residue form of CDK13 encoded by Ensembl transcript ENST00000181839

2 The Consurf server. <http://consurf.tau.ac.il/>

3 Decipher Genome Browser: <https://decipher.sanger.ac.uk>

4 The Genome Aggregation Database (gnomAD): <http://gnomad.broadinstitute.org/>

5 <http://evs.gs.washington.edu/EVS/>

6 Combined Annotation Dependent Depletion (CADD). <http://cadd.gs.washington.edu/>

7 PolyPhen-2. <http://genetics.bwh.harvard.edu/pph2/>

8 Sorting Intolerant from Tolerant (SIFT). <http://sift.jcvi.org/>

9 average value for two CDK13-cyclin K dimers in crystal structure 5efq; the average value for wild type CDK13-cyclin K dimers was -21.94 kcal/mol

10 UniProt Knowledgebase (UniProtKB): <http://www.uniprot.org/> and PDBsum database: http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl?pdbcode=index.html