|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Amino acid Impact (Neutral/Deleterious) | Molecular mechanisms | Biological impact | Protein stability |
| **Motif** | **Mutation** | **PS** | **MP** | **Ph-S** | **PP-1** | **PP-2** | **SF** | **SP** | **MutPred2** | **Pr** | **P-value** | **Affected functional sites** | **AG** | **AM** | **IM** | **MP** |
| Walker A | P37A [2] | N | N | N | N | N | D | D | Altered ordered interfaceLoss of relative solvent accessibilityGain of allosteric site at N38Altered DNA binding Altered metal binding Gain of catalytic site at G39Gain of methylation at K42  | 0.340.320.280.250.240.190.17 | 7.3e-035.8e-033.3e-038.1e-030.020.018.9e-03 | -N-myristoylation site-ATP/GTP-binding site motif A (P-loop) | No | No | ↓ | ↓ |
| Zinc hook | C680G [8] | N | N | N | D | N | D | D | Gain of N-linked glycosylation at N677  | 0.02 | 0.03 | - N-glycosylation site- Glycosaminoglycan attachment site-N-myristoylation site | No | No | ↓ | ↓ |
| P682R [11] | D | D | N | N | D | D | D | Gain of helix Altered coiled coil Loss of N-linked glycosylation at N677  | 0.320.090.02 | 2.8e-030.040.04 | None | No | No | ↓ | ↓ |
| C684G [8] | D | D | D | D | D | D | D | No effect | - | - | None | No | No | ↓ | ↓ |
| R686A [8] | D | D | N | D | D | D | D | No effect | - | - | None | No | No | ↓ | ↓ |
| Signature motif | A1203G [16] | D | D | D | D | D | D | D | Gain of allosteric site at R1200 Gain of catalytic site at R1200 Gain of methylation at K1206  | 0.220.200.10 | 0.020.010.04 | - PKA Phosphorylation site- Glycosaminoglycan attachment site | No | No | ↓ | ↓ |
| K1206G [13] | D | D | D | D | D | D | D | Loss of catalytic site at K1206  | 0.09 | 0.05 | N-myristoylation site | ↑ | No | ↓ | ↓ |
| R1214L | D | D | D | D | D | D | D | Loss of allosteric site at R1214  | 0.22 | 0.03 | - Nuclear receptor box- SUMO interaction site- ATP-binding cassette, ABC transporter-type, signature and profile | ↑ | ↓ | ↓ | ↓ |
| R1214W [13] | D | D | D | D | D | D | D | Loss of allosteric site at R1214 | 0.21 | 0.04 | - ATP-binding cassette, ABC transporter-type, signature and profile | ↑ | ↓ | ↓ | ↓ |
| L1215F [13] | D | D | D | D | D | D | N | Gain of allosteric site at R1214  | 0.19 | 0.05 | None | ↑ | No | ↓ | ↓ |
| Walker B | D1231N [5] | D | D | D | D | D | D | D | Altered metal binding Altered ordered interface Loss of catalytic site at D1231 Loss of allosteric site at P1233 Altered transmembrane protein  | 0.420.290.290.250.12 | 5.8e-030.032.3e-030.010.03 | - SUMO interaction site | No | No | ↓ | ↓ |
| D-loopATPase domain/ coiled-coil | E1240Q [2] | N | N | N | D | D | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| N1241A[2] | D | D | D | D | D | D | D | Altered ordered interface Altered metal binding Loss of allosteric site at N1236 Altered coiled coil Loss of catalytic site at D1238  | 0.360.270.200.130.13 | 3.8e-037.8e-030.040.030.03 | -USP7 binding motif | No | No | ↓ | ↓ |
| S14P [3] | D | D | D | D | D | D | D | Altered DNA binding Loss of allosteric site at R13 Loss of strand Loss of proteolytic cleavage at R13 | 0.320.310.260.15 | 1.7e-033.1e-030.040.01 | RRM domain ligands | No | No | ↓ | ↓ |
| Q23K [3] | N | N | N | N | D | N | D | Loss of strand Gain of B-factor  | 0.270.25 | 0.020.03 | - PP1-docking motif RVXF- MAPK docking motifs | ↓ | No | ↓ | ↓ |
| T65E [3] | D | D | N | D | D | D | D | Altered metal bindingAltered ordered interface Loss of methylation at K62  | 0.300.280.09 | 5.5e-030.040.05 | - GSK3 phosphorylation site- SH3 ligand- N-myristoylation site | No | No | ↓ | ↓ |
| Q81K [3] | N | D | D | N | D | N | N | Altered DNA binding Altered stability  | 0.190.12 | 0.020.03 | - PP1-docking motif RVXF- MAPK docking motifs | No | No | ↓ | ↓ |
| S99P [3] | D | D | D | D | D | D | N | Altered DNA binding Altered ordered interface Altered coiled coil Altered stability  | 0.370.300.110.11 | 6.0e-040.020.040.03 | - GSK3 phosphorylation site- SH3 ligand | No | No | ↓ | ↓ |
| V101K [3] | N | N | N | N | N | N | N | No effect | - | - | None | No | No | ↓ | ↓ |
| Q174A [13] | N | D | N | N | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| T191D [6] | N | D | N | N | N | D | N | Altered coiled coil Loss of acetylation at K187 Gain of ubiquitylation at K187  | 0.290.280.15 | 0.025.8e-030.04 | - PP1-docking motif RVXF- Protein kinase C phosphorylation site | No | No | ↓ | ↓ |
| Q194S [11] | N | N | N | N | N | N | N | No effect | - | - | None | No | No | ↓ | ↓ |
| M208C [10] | N | N | N | D | N | N | N | No effect | - | - | None | No | No | ↓ | ↓ |
| K256P [10] | D | D | N | D | D | N | D | No effect | - | - | None | No | No | ↓ | ↓ |
| M293A [11] | N | D | N | N | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| S603Y [11] | N | N | N | D | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| K921V [3] | N | N | N | D | D | D | N | No effect | - | - | None | No | No | ↑ | ↑ |
| L673V [11] | N | N | N | N | D | D | N | No effect | - | - | None | No | No | ↓ | ↑ |
| L694Q [11] | N | N | N | D | N | D | N | Gain of intrinsic disorder  | 0.40 | 7.9e-03 | - FHA phosphopeptide ligands- Actin-binding motifs | No | No | ↓ | ↓ |
| V697F [11] | N | N | N | N | N | D | D | No effect | - | - | None | No | ↑ | ↓ | ↓ |
| Q886I [11] | D | D | N | D | D | D | N | No effect | - | - | None | No  | No  | ↑ | ↓ |
| S936P [3] | N | D | N | D | N | N | D | No effect | - | - | None | No | No | ↓ | ↓ |
| C990S [10] | N | N | N | N | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| N1028P [10] | N | D | N | N | N | N | N | No effect | - | - | None | No | No | ↑ | ↓ |
| E110K [6] | N | N | N | N | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| K126E [6] | N | D | N | N | N | D | D | No effect | - | - | None | No | No | ↓ | ↑ |
| V127E [6] | D | N | D | N | D | D | D | Gain of intrinsic disorder Loss of strand Gain of B-factor Altered transmembrane protein Altered stability  | 0.430.300.280.260.10 | 5.3e-032.4e-035.9e-031.3e-030.04 | -MAPK docking motifs |  |  | ↓ | ↓ |
| K122E [6] | N | N | N | N | N | N | D | No effect | - | - | None | No | No | ↓ | ↓ |
| SNPs | I94L  | N | N | N | N | N | N | N | No effect | - | - | None | No | No | ↓ | ↓ |
| V127I  | N | N | N | N | D | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| T191I  | N | N | N | N | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| R193W | D | D | N | D | D | D | D | Altered coiled coil  | 0.93 | 6.7e-04 | - NEK2 phosphorylation site- Protein kinase C phosphorylation site | No | No | ↑ | ↓ |
| R224H | N | N | N | N | D | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| V315L | N | N | N | N | N | D | N | No effect | - | - | None | No | No | ↓ | ↓ |
| G469A | N | N | N | N | N | N | N | No effect | - | - | None | No | No | ↓ | ↓ |
| K616E | N | N | N | N | N | N | N | No effect | - | - | None | No | No | ↓ | ↓ |
| V697A | N | D | N | N | N | D | N | No effect | - | - | None | No | ↑ | ↓ | ↓ |
| V842A | N | D | N | N | N | N | N | No effect | - | - | None | No | No | ↑ | ↓ |
| Y964H | D | N | D | D | D | D | N | No effect | - | - | None | No | ↓ | ↓ | ↓ |
| K973M | N | N | N | D | D | N | N | No effect | - | - | None | No | No | ↑ | ↓ |
| R1038G | N | D | N | N | N | N | D | No effect | - | - | None | No | No | ↓ | ↓ |
| Abbreviation:  |
| IM- ImutantMP- MuProPS-PredictSNP MP-MAPP PhS-PhD-SNP PP1-Poly-Phen1 PP2-Poly-Phen2 | SF- SIFT SN- SNAPPr-ProbabilityAG- protein aggregationAM- Amyloid aggregationIM- ImutantMP-MuPro |