|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***AIP* mutation** | **Prevalence within *AIP*mut PitNETs (n=167)** | **Mutation type** | **Location in the AIP protein** | **References to previously published mutations / brief description of patients with novel mutations** |
| g.4856\_4857CG>AA (p.?) | 2 (1.2%) | *Promoter* | 5-UTR (not in protein) | ([1-3](#_ENREF_1)) |
| c.1-?\_993+?del- (p.0?) (whole gene deletion) | 8 (4.8%) | *Large genomic deletion* | Absence of whole protein | ([1](#_ENREF_1)) |
| **c.(?-50)\_(99+1\_100-1)del (p.0?) (exon 1 deletion)** | 1 (0.6%) | *Large genomic deletion* | Absence of whole protein | **Female, age at onset 17yr, age at diagnosis 19yr, acromegaly, macroadenoma** |
| c.3G>A (p.?) | 2 (1.2%) | *Start codon* | N-terminus | ([4](#_ENREF_4)) |
| c.40C>T (p.Q14\*) | 2 (1.2%) | *Nonsense* | N-terminus | ([5-8](#_ENREF_5)) |
| c.70G>T (p.E24\*) | 7 (4.2%) | *Nonsense* | N-terminus | ([2](#_ENREF_2),[9](#_ENREF_9)) |
| c.74\_81delins7 (p.L25Pfs\*130) | 4 (2.4%) | *Frameshift* | PPIase domain | ([1](#_ENREF_1),[10](#_ENREF_10)) |
| c.100-1025\_279+357del (p.A34\_K93del) (exon 2 deletion) | 6 (3.6%) | *Large genomic deletion* | PPIase domain | ([11](#_ENREF_11)) |
| c.140\_163del (p.G47\_R54del) | 1 (0.6%) | In-frame deletion | PPIase domain | ([12](#_ENREF_12)) |
| c.240\_241delinsTG (p.M80\_R81delinsIG) | 1 (0.6%) | In-frame deletion insertion | PPIase domain | ([13](#_ENREF_13)) |
| c.241C>T (p.R81\*) | 7 (4.2%) | *Nonsense* | PPIase domain | ([2](#_ENREF_2),[3](#_ENREF_3),[14-16](#_ENREF_14)) |
| c.249G>T (p.G83Afs\*15) | 3 (1.8%) | *Splice site* | PPIase domain | ([1](#_ENREF_1)) |
| c.333delC (p.K112Rfs\*44) | 1 (0.6%) | *Frameshift* | PPIase domain | ([13](#_ENREF_13)) |
| c.338\_341dup (p.L115Pfs\*16) | 2 (1.2%) | *Frameshift* | PPIase domain | ([6](#_ENREF_6),[17](#_ENREF_17)) |
| **c.344delT (p.L115Rfs\*41)** | **1 (0.6%)** | ***Frameshift*** | **PPIase domain** | **Male, age at onset 15yr, age at diagnosis 16yr, prolactinoma, microadenoma** |
| c.376\_377delCA (p.Q126Dfs\*3) | 1 (0.6%) | *Frameshift* | PPIase domain | ([13](#_ENREF_13)) |
| c.427C>T (p.Q143\*) | 2 (1.2%) | *Nonsense* | Between PPlase and TPR1 domains | ([6](#_ENREF_6)) |
| c.469-2A>G (p.E158\_Q184del) | 1 (0.6%) | *Splice site (resulting in in-frame deletion)* | TPR1 domain | ([18-20](#_ENREF_18)) |
| c.490C>T (p.Q164\*) | 2 (1.2%) | *Nonsense* | Between PPlase and TPR1 domains | ([1](#_ENREF_1)) |
| c.504G>A (p.W168\*) | 1 (0.6%) | *Nonsense* | TPR1 domain | ([21](#_ENREF_21)) |
| c.562C>T(p.R188W) | 1 (0.6%) | Missense | TPR1 domain | ([22](#_ENREF_22)) |
| c.570C>G (p.Y190\*) | 4 (2.4%) | *Nonsense* | TPR1 domain | ([6](#_ENREF_6)) |
| c.605A>G (p.Y202C) | 1 (0.6%) | Missense | TPR1 domain | ([13](#_ENREF_13)) |
| c.645+1G>C (p.?) | 1 (0.6%) | *Splice site* | TPR1 domain | ([13](#_ENREF_13)) |
| c.662dupC (p.E222\*) | 2 (1.2%) | *Frameshift* | Between TPR1 and TPR2 domains | ([1](#_ENREF_1)) |
| c.713G>A (p.C238Y) | 3 (1.8%) | Missense | TPR2 domain | ([2](#_ENREF_2),[9](#_ENREF_9)) |
| c.760T>C (p.C254R) | 1 (0.6%) | Missense | TPR2 domain | ([22](#_ENREF_22)) |
| c.762C>G (p.C254W) | 2 (1.2%) | Missense | TPR2 domain | ([22](#_ENREF_22)) |
| **c.773T>G (p.L258R)** | **1 (0.6%)** | **Missense#** | **TPR2 domain** | **Male, age at onset 21yr, age at diagnosis 29yr, prolactinoma, macroadenoma** |
| **c.779delA (p.K260Sfs\*44)** | **1 (0.6%)** | ***Frameshift*** | **PPIase domain** | **Male, age at onset 8yr, age at diagnosis 12yr, gigantism, macroadenoma** |
| c.783C>G (p.Y261\*) | 2 (1.2%) | *Nonsense* | TPR2 domain | ([6](#_ENREF_6),[18](#_ENREF_18),[23](#_ENREF_23)) |
| c.804C>A (p.Y268\*) | 3 (1.8%) | *Nonsense* | TPR3 domain | ([6](#_ENREF_6),[16](#_ENREF_16),[24](#_ENREF_24)) |
| c.805\_825dup (p.F269\_H275dup) | 16 (9.6%) | In-frame insertion | TPR3 domain | ([2](#_ENREF_2),[3](#_ENREF_3),[18](#_ENREF_18)) |
| c.811C>T (p.R271W) | 8 (4.8%) | Missense | TPR3 domain | ([1](#_ENREF_1),[25-27](#_ENREF_25)) |
| c.815G>A (p.G272D) | 1 (0.6%) | Missense | TPR3 domain | ([4](#_ENREF_4),[28](#_ENREF_28)) |
| c.816delC (p.K273Rfs\*30) | 1 (0.6%) | *Frameshift* | TPR3 domain | ([6](#_ENREF_6)) |
| **c.863\_864del (p.F288Cfs\*?)** | **1 (0.6%)** | ***Frameshift*** | **TPR3 domain** | **Female, age at onset 16yr, age at diagnosis 31yr, acromegaly, macroadenoma** |
| c.868A>T (p.K290\*) | 1 (0.6%) | *Nonsense* | TPR3 domain | ([6](#_ENREF_6)) |
| c.872\_877delTGCTGG (p.V291\_L292del) | 1 (0.6%) | In-frame deletion | TPR3 domain | ([29](#_ENREF_29)) |
| c.910C>T (p.R304\*) | 57 (34.1%) | *Nonsense* | C-terminal α-helix | ([2](#_ENREF_2),[8](#_ENREF_8),[18](#_ENREF_18),[19](#_ENREF_19),[23](#_ENREF_23),[25](#_ENREF_25),[26](#_ENREF_26),[30](#_ENREF_30)) |
| c.967delC (p.R323Gfs\*39) | 1 (0.6%) | *Frameshift* | C-terminal α-helix | ([6](#_ENREF_6)) |
| c.976\_977insC (p.G326Afs\*?) | 1 (0.6%) | *Frameshift* | C-terminal α-helix | ([6](#_ENREF_6)) |
| c.978dupG (p.I327Dfs\*?) | 1 (0.6%) | *Frameshift* | C-terminal α-helix | ([6](#_ENREF_6)) |
| c.991T>C (p.\*331R) | 1 (0.6%) | Stop-loss | C-terminal α-helix | ([13](#_ENREF_13)) |

**Supplemental Table 2: List of pathogenic/likely pathogenic *AIP* mutations identified in our cohort.** Mutations in italic are truncating or predicted truncating mutations. Mutations in bold are novel mutations not previously described. None of these were found in the GnomAD database (<https://gnomad.broadinstitute.org/gene/ENSG00000110711>). All 5 patients with novel mutations were simplex cases. #Revel score ([31](#_ENREF_31)) of this variant is 0.989 out of the maximum 1, strongly suggesting pathogenic status and Gavin score ([32](#_ENREF_32)) is ‘pathogenic’. *AIP*mut, *AIP* mutation-positive; GH, growth hormone; PitNET, pituitary neuroendocrine tumor; PPIase, peptidylprolyl isomerase; TPR, tetratricopeptide repeat; UTR, untranslated region.

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