|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Family ID** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Patient ID** | **IV:3** | **IV:3, IV:4** | **IV:1, IV:3** | **IV:2, IV:3, IV:4** | **IV:1** | **IV:1, IV:2** |
| **Variant annotation** | NC\_000011.10GRCh38/hg38 position(DNA change) | 11:g.799456G>A | 11:g.801587C>T | 11:g.800373 GTCACdel | 11:g.801283TGdel | 11:g.800874CCdel |
| cDNA change ( NM\_145886.4) | c.2584C>T | c.1340G>A | c.2116\_2120del | c.1564\_1565del | c.1804\_1805del |
| Protein change ( NP\_665893.2) | p.(Arg862Trp) | p.(Trp447\*) | p.(Val706Hisfs\*30) | p.(Gln522Glufs\*44) | p.(Gly602fs\*26) |
| Zygosity | Hom | Hom | Hom | Hom | Hom |
| dbSNP ID | rs747620551 | - | - | - |  |
| gnomAD v3(highest subpopulation) | 0.00001247,3/273,7200.00002780, 3/107906(Euepean-non-finish) |  absnet | absent | absent | absent |
| **Allele frequencies (PM2)** | gnomAD v2.1.1(highest subpopulation) | 0.00001971 3/1521740.00004826 2/414468(African/African-American) | absnet | absent | absent | absent |
| Frequency in ensembl browser | absent | absent | absent | absent | absent |
| Iranome | absent | absent | absent | absent | absent |
| GME Variome | absent | absent | absent | absent | absent |
| 100.000 Genome project | absent | absent | absent | absent | absent |
| Centogene | absent | absent | absent | 1(hmz) | 1(hmz, 2htz) |
| UK Biobank | absent | absent | absent | absent | absent |
| in-house database | absent | absent | absent | absent | absent |
| GERP | 4.74 | 2.9 | - | - |  |
| ***In silico* predictions (PP3)** | CADD | 31 | 50 | - | - | - |
|  | Polyphen-2 | Probably damaging |  |  | - |  |
|  | SIFT | Damaging |  |  | - |  |
|  | Provean | Damaging |  |  | - |  |
|  | MutationTaster | Disease causing | Disease causing | Disease causing | Disease causing | Disease causing |
| **ACMG classification** |  | Likely pathogenic (PM2,PP3,PP1,PP4) | Pathogenic (PVS1,PM2,PP1PP3) | Pathogenic(PVS1,PM2,PP1) | Likely pathogenic(PVS1,PM2) | Likely pathogenic(PVS1,PM2) |

Reference sequence: NM\_004269

**Supplemental table 1:*PIDD1* variant characteristics**

Legend ACMG criteria:

PVS1 Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease;

PM2 Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium; PP1 Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease; PP3 Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.); PP4 patient’s phenotype or family history is highly specific for a disease with a single genetic etiology.