Nonsense or Frameshift

- Predicted to undergo NMD [b] (Upstream of c.1285)
  - Exon is present in biologically-relevant transcript(s) (NM_000277.3) → PVS1
  - Exon is absent from biologically-relevant transcript(s) → N/A
- Not predicted to undergo NMD [b]
  - Truncated/altered region is critical to protein function [c] (oligomerization domain, amino acid residues 411–452) → PVS1_Strong
  - Role of region in protein function is unknown
    - LoF variants in this exon are frequent in the general population and/or exon is absent from biologically-relevant transcript(s) → N/A
    - LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
      - Variant removes >10% of protein → PVS1_Strong
      - Variant removes <10% of protein → PVS1_Moderate

GT--AG 1,2 splice sites [a]

- Exon skipping or use of a cryptic splice site disrupts reading frame and is predicted to undergo NMD [b]
  - Exon is present in biologically-relevant transcript(s) → PVS1
  - Exon is absent from biologically-relevant transcript(s) → N/A
- Exon skipping or use of a cryptic splice site disrupts reading frame and is **NOT** predicted to undergo NMD [b] (exon 13)
  - Truncated/altered region is critical to protein function [c] (oligomerization domain, amino acid residues 411–452) → PVS1_Strong
  - Role of region in protein function is unknown
    - LoF variants in this exon are frequent in the general population and/or exon is absent from biologically-relevant transcript(s) → N/A
    - LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
      - Variant removes >10% of protein → PVS1_Strong
      - Variant removes <10% of protein → PVS1_Moderate
- Exon skipping or use of a cryptic splice site preserves reading frame (exons 1, 9, 10)
  - Role of region in protein function is unknown
    - LoF variants in this exon are frequent in the general population and/or exon is absent from biologically-relevant transcript(s) → N/A
    - LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
      - Variant removes >10% of protein → PVS1_Strong
      - Variant removes <10% of protein → PVS1_Moderate
  - Truncated/altered region is critical to protein function [c] (autoregulatory sequence, amino acid residues 1-33; PAH catalytic domain, amino acid residues 143-410) → PVS1_Strong

Deletion (Single exon to full gene)

- Full gene deletion → PVS1 [d]
- Single to multi exon deletion – Disrupts reading frame and is predicted to undergo NMD [b]
  - Exon is present in biologically-relevant transcript(s) → PVS1
  - Exon is absent from biologically-relevant transcript(s) → N/A
- Single to multi exon deletion – Disrupts reading frame and is **NOT** predicted to undergo NMD [b]
  - Truncated/altered region is critical to protein function [c] (autoregulatory sequence, amino acid residues 1-33; PAH catalytic domain, amino acid residues 143-410; oligomerization domain, amino acid residues 411–452) → PVS1_Strong
  - Role of region in protein function is unknown
    - LoF variants in this exon are frequent in the general population and/or exon is absent from biologically-relevant transcript(s) → N/A
    - LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
      - Variant removes >10% of protein → PVS1_Strong
      - Variant removes <10% of protein → PVS1_Moderate
- Single to multi exon deletion – Preserves reading frame
  - Truncated/altered region is critical to protein function [c] (autoregulatory sequence, amino acid residues 1-33; PAH catalytic domain, amino acid residues 143-410; oligomerization domain, amino acid residues 411–452) → PVS1_Strong
  - Role of region in protein function is unknown
    - LoF variants in this exon are frequent in the general population and/or exon is absent from biologically-relevant transcript(s) → N/A
    - LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
      - Variant removes >10% of protein → PVS1_Strong
      - Variant removes <10% of protein → PVS1_Moderate

Duplication (≥1 exon in size and must be completely contained within gene)

- Proven in tandem
  - Reading frame disrupted and NMD predicted to occur → PVS1
  - No or unknown impact on reading frame and NMD → N/A
- Presumed in tandem
  - Reading frame presumed disrupted and NMD predicted to occur → PVS1_Strong
- Proven not in tandem → N/A

Initiation Codon

- No known alternative start codon in other transcripts
  - ≥1 pathogenic variant(s) upstream of closest potential in-frame start codon (p.Met180) → PVS1_Strong