Nonsense or Frameshift

- Predicted to undergo NMD [b] 5' or at c.2816 (exons 1-12)
  - Exon is present in biologically-relevant transcript(s) NM_001204.7 → PVS1
  - Exon is absent from biologically-relevant transcript(s) → N/A
- Not predicted to undergo NMD [b] 3' to c.2816 (exon 13) and p.Trp13X (W13X)
  - Truncated/altered region is critical to protein function [c] (If relevant please specify regions) → N/A
  - 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] (includes skipping of exon 13)
  - Truncated/altered region is critical to protein function [c] (If relevant please specify regions) → N/A
  - 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 (in-frame exons: ex1, 2, 3, 4, 6 not expected to undergo NMD)
  - 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] (ligand binding aa33-131, kinase domain aa203-504, heterodimerization domain aa485-492, transmembrane domain aa151-171) → PVS1_Strong

Non-canonical splice site + RNA data

- Loss of wt acceptor/donor, disrupts reading frame, and/or affects critical region → PVS1

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.] (i.e. involving exons 1-12)
  - 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] (i.e. exon 13)
  - Truncated/altered region is critical to protein function [c] → N/A
  - 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_Moderate
- Single to multi exon deletion – Preserves reading frame
  - Truncated/altered region is critical to protein function [c] (ligand binding aa33-131, kinase domain aa203-504, heterodimerization domain aa485-492, transmembrane domain aa151-171) → 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 (i.e. involving exons 1-12) → PVS1
  - No or unknown impact on reading frame and NMD (i.e. exon 13) → N/A
  - Reading frame presumed disrupted and NMD predicted to occur (i.e. involving exons 1-12) → PVS1_Strong
- Presumed in tandem
- Proven not in tandem → N/A

Initiation Codon (exon 1)

- No known alternative start codon in other transcripts → ≥1 pathogenic variant(s) upstream of closest potential in-frame start codon → PVS1_Moderate