TCF4 (NM_001083962.1)

Nonsense or Frameshift

Predicted to undergo NMD
- Exon is present in biologically-relevant transcript(s) → PVS1
- Exon is absent from biologically-relevant transcript(s) → N/A

Not predicted to undergo NMD
- Upstream of most de novo distal LOF variant (p.643); Frameshift that results in a read-through of the stop codon → PVS1
- Downstream of the most distal de novo LOF variant (p.643) but does not result in a read-through of the stop codon → PVS1_Moderate

GT--AG 1,2 splice sites

Exon skipping or use of a cryptic splice site disrupts reading frame and is predicted to undergo NMD
- 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
Exon 19
- Truncated/altered region is critical to protein function
  Exon 19 → PVS1

Exon skipping or use of a cryptic splice site preserves reading frame
Exon 15
- Truncated/altered region is critical to protein function
  Exon 15 → PVS1

Deletion (Single exon to full gene)

Full gene deletion → PVS1

Single to multi exon deletion – Disrupts reading frame and is predicted to undergo NMD
- 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
Exon 19
- Truncated/altered region is critical to protein function
  Exon 19 → PVS1

Single to multi exon deletion – Preserves reading frame
Single exon 15 deletion; Other in-frame combinations.
- Role of region in protein function is unknown → 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
  - Variant removes <10% of protein → PVS1_Strong
- Truncated/altered region is critical to protein function
  Exon 15 + any in-frame combination that includes the PM1 functional domain p.564_617 (bHLH) → PVS1

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

Proven in tandem
- Reading frame disrupted and NMD predicted to occur → PVS1

Presumed in tandem
- No or unknown impact on reading frame and NMD → N/A
- 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 medically relevant transcripts
- No pathogenic variant(s) upstream of closest potential in-frame start codon → PVS1_Supp