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Variant: NM_001083962.2(TCF4):c.1741G>T (p.Val581Phe)

Version: 2.0

CA272702

160079 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: 79c2b5b6-3037-44fa-ae71-0b48cd373e7a
Approved on: Wed, 01 Jul 2026 00:00:00 +0000
Published on: Fri, 16 Oct 2026 00:00:00 +0000

HGVS expressions

NM_001083962.2(TCF4):c.1741G>T (p.Val581Phe)
NM_001083962.2:c.1741G>T
NC_000018.10:g.55228985C>A
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NC_000018.9:g.52896216C>A
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Likely Pathogenic

Met criteria codes 5

PP3 PM6 PM1 PM2_Supporting PS4_Supporting

Evidence Links 0

Expert Panel

Rett and Angelman-like Disorders VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Rett and Angelman-like Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TCF4 Version 6.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Val581Phe variant in TCF4 is located in the basic Helix-Loop-Helix domain (bHLH) (PMID 17436254, 22045651) (PM1). This variant is absent from gnomAD (PM2_supporting). The p.Val581Phe variant in TCF4 occurs in the de novo state (biological parentage unconfirmed) in an individual with delays, hypotonia, not walking, dysmorphic features (University of Chicago internal database) (PM6). Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3). The p.Val581Phe variant in TCF4 has been observed in at least 2 individuals with neurodevelopmental phenotype (University of Chicago internal database, Labcorp Genetics (formerly Invitae) internal database) (PS4_supporting). In summary, the p.Val581Phe variant in TCF4

is classified as likely pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PM1, PM2_supporting, PM6, PP3, PS4_supporting). (TCF4 Specifications v6.0.0; curation approved on 7/1/2026.)

Met criteria codes

PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own.
PM6	✔	The p.Val581Phe variant in TCF4 occurs in the de novo state (biological parentage unconfirmed) in an individual with delays, hypotonia, not walking, dysmorphic features (University of Chicago internal database).
PM1	✔	This variant is located in the basic Helix-Loop-Helix domain (bHLH) (PMID 17436254, 22045651).
PM2_Supporting	✔	The p.Val581Phe variant in TCF4 is absent from gnomAD.
PS4_Supporting	✔	The p.Val581Phe variant in TCF4 has been observed in at least 2 individuals with neurodevelopmental phenotype (University of Chicago internal database, Labcorp Genetics (formerly Invitae) internal database).

Curation History

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