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Variant: NM_001083962.2(TCF4):c.1817C>T (p.Thr606Ile)

Version: 1.0

CA402528512

1164050 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: f6d6c268-b8c3-422c-bafc-9dde1cd92932
Approved on: 2025/5/7
Published on: 2025/6/30

HGVS expressions

NM_001083962.2(TCF4):c.1817C>T (p.Thr606Ile)
NM_001083962.2:c.1817C>T
NC_000018.10:g.55228909G>A
CM000680.2:g.55228909G>A
NC_000018.9:g.52896140G>A
CM000680.1:g.52896140G>A
NC_000018.8:g.51047138G>A
NG_011716.1:g.364721C>T
NG_011716.2:g.412085C>T
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ENST00000636822.2:c.1427C>T
ENST00000637115.2:c.*1695C>T
ENST00000637169.2:c.1169C>T
ENST00000637239.2:n.1872C>T
ENST00000637250.2:n.1511C>T
ENST00000637923.2:c.1415C>T
ENST00000638154.3:c.1844C>T
ENST00000643689.1:c.1427C>T
ENST00000674764.1:c.*1428C>T
ENST00000675707.1:c.1427C>T
ENST00000354452.7:c.1817C>T
ENST00000356073.8:c.1805C>T
ENST00000398339.5:c.2123C>T
ENST00000457482.7:c.1337C>T
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ENST00000564999.5:c.1805C>T
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NM_001369582.1:c.1733C>T
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NM_001369585.1:c.1730C>T
NM_001369586.1:c.1748C>T
NM_003199.3:c.1805C>T
NM_001243230.2:c.1796C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PM1 PS2

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 4.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Thr606Ile variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with global developmental delay, epilepsy, ventriculomegaly, and dysmorphic facial features (PMID 34580403) (PS2). The p.Thr606Ile variant occurs in the well-characterized Basic Helix-Loop-Helix functional domain of the TCF4 gene (PM1). The p.Thr606Ile variant in TCF4 is absent from gnomAD v4.1 (PM2_Supporting). Computational prediction analysis tools suggests a deleterious impact; however, this information does not

predict clinical significance on its own (PP3). In summary, the p.Thr606Ile variant in TCF4 is classified as likely pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PS2, PM1, PM2_supporting, PP3). (TCF4 Specifications v4.0; curation approved on [5/7/2025])

Met criteria codes

PM2_Supporting	✔	The p.Thr606Ile variant in TCF4 is absent from gnomAD v4.1 (PM2_Supporting).
PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3).
PM1	✔	The p.Thr606Ile variant occurs in the well-characterized Basic Helix-Loop-Helix functional domain of the TCF4 gene (PM1).
PS2	✔	The p.Thr606Ile variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with global developmental delay, epilepsy, ventriculomegaly, and dysmorphic facial features (PMID 34580403).

Curation History

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