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Variant: NM_001083962.2(TCF4):c.1826T>C (p.Leu609Pro)

Version: 2.0

CA16608769

393171 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5d0fcac9-7b04-4d3f-92d8-91250132dcb7
Approved on: 2026/1/28
Published on: 2026/3/31

HGVS expressions

NM_001083962.2:c.1826T>C
NM_001083962.2(TCF4):c.1826T>C (p.Leu609Pro)
NC_000018.10:g.55228900A>G
CM000680.2:g.55228900A>G
NC_000018.9:g.52896131A>G
CM000680.1:g.52896131A>G
NC_000018.8:g.51047129A>G
NG_011716.1:g.364730T>C
NG_011716.2:g.412094T>C
ENST00000354452.8:c.1826T>C
ENST00000635822.2:c.1706T>C
ENST00000635990.2:n.1506T>C
ENST00000636400.2:c.1754T>C
ENST00000636751.2:c.*1534T>C
ENST00000636822.2:c.1436T>C
ENST00000637115.2:c.*1704T>C
ENST00000637169.2:c.1178T>C
ENST00000637239.2:n.1881T>C
ENST00000637250.2:n.1520T>C
ENST00000637923.2:c.1424T>C
ENST00000638154.3:c.1853T>C
ENST00000643689.1:c.1436T>C
ENST00000674764.1:c.*1437T>C
ENST00000675707.1:c.1436T>C
ENST00000354452.7:c.1826T>C
ENST00000356073.8:c.1814T>C
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ENST00000457482.7:c.1346T>C
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ENST00000537856.7:c.1424T>C
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ENST00000544241.6:c.1613T>C
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ENST00000561992.5:c.1424T>C
ENST00000562680.5:n.5349T>C
ENST00000564228.5:c.1601T>C

ENST00000564403.6:c.1844T>C
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ENST00000565018.6:c.1562T>C
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ENST00000566286.5:c.1805T>C
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NM_001369576.1:c.1751T>C
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NM_001369579.1:c.1751T>C
NM_001369580.1:c.1751T>C
NM_001369581.1:c.1751T>C
NM_001369582.1:c.1742T>C
NM_001369583.1:c.1742T>C
NM_001369584.1:c.1739T>C
NM_001369585.1:c.1739T>C
NM_001369586.1:c.1757T>C
NM_003199.3:c.1814T>C
NM_001243230.2:c.1805T>C

Likely Pathogenic

Met criteria codes 4

PM1 PS2 PM2_Supporting PP3

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 5.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Leu609Pro variant in TCF4 occurs in the de novo state (biological parentage confirmed) in an affected individual (GeneDx- internal database) (PS2). The p.Leu609Pro variant occurs in the well-characterized basic Helix-Loop-Helix domain (bHLH) functional domain of TCF4 (PM1). The p.Leu609Pro 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.Leu609Pro 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 v.5.0; curation approved on 01/28/2026)

Met criteria codes

PM1	✔	This variant is located in the basic Helix-Loop-Helix domain (bHLH).
PS2	✔	The p.Leu609Pro variant in TCF4 occurs in the de novo state (biological parentage confirmed) in an affected individual (GeneDx- internal database) (PS2).
PM2_Supporting	✔	The p.Leu609Pro variant in TCF4 is absent from gnomAD v4.1.
PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own.

Curation History

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