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Variant: NM_001083962.2(TCF4):c.1706G>A (p.Arg569Gln)

Version: 1.0

CA402528992

3235863 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: a66a7ce4-4bb6-40df-a39c-29b67d272f82
Approved on: Mon, 24 Aug 2026 00:00:00 +0000
Published on: Fri, 16 Oct 2026 00:00:00 +0000

HGVS expressions

NM_001083962.2(TCF4):c.1706G>A (p.Arg569Gln)
NM_001083962.2:c.1706G>A
NC_000018.10:g.55229020C>T
CM000680.2:g.55229020C>T
NC_000018.9:g.52896251C>T
CM000680.1:g.52896251C>T
NC_000018.8:g.51047249C>T
NG_011716.1:g.364610G>A
NG_011716.2:g.411974G>A
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ENST00000635990.2:n.1386G>A
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ENST00000636822.2:c.1316G>A
ENST00000637115.2:c.*1584G>A
ENST00000637169.2:c.1058G>A
ENST00000637239.2:n.1761G>A
ENST00000637250.2:n.1400G>A
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ENST00000674764.1:c.*1317G>A
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NM_003199.3:c.1694G>A
NM_001243230.2:c.1685G>A

Pathogenic

Met criteria codes 6

PS2_Very Strong | PM2_Supporting | PS4_Moderate | PM1 | PM5 | PP3

Not Met criteria codes 1

PP4

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.Arg569Gln variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in at least 2 individuals with clinical features of Pitt-Hopkins syndrome (internal database - GeneDx; internal database - Greenwood Genetic Center) (PS2_Very Strong). The p.Arg569Gln variant has been observed in at least 1 additional individual with clinical features of Pitt-Hopkins syndrome (internal database - GeneDx) (PS4_Moderate). The p.Arg569Gln variant in TCF4 has been reported in an individual with autism spectrum disorder (PMID 40869941) (no criteria met). The p.Arg569Gln variant occurs in the well-characterized Basic Helix-Loop-Helix functional domain of the TCF4 gene (PM1). A pathogenic missense variant (p.Arg569Trp) has been previously identified within this codon which indicates that

this residue is critical to the function of the protein (PMID 29695756) (PM5). The p.Arg569Gln 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.Arg569Gln variant in TCF4 is classified as Pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PS2_Very Strong, PM1, PM5, PS4_Moderate, PM2_Supporting, PP3). (TCF4 Specifications v6.0; curation approved on 8/24/2026)

Met criteria codes

PS2_Very Strong	✔	The p.Arg569Gln variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in at least 2 individuals with clinical features of Pitt-Hopkins syndrome (internal database - GeneDx; internal database - Greenwood Genetic Center) (PS2_Very Strong).
PM2_Supporting	✔	The p.Arg569Gln variant in TCF4 is absent from gnomAD v4.1 (PM2_Supporting).
PS4_Moderate	✔	The p.Arg569Gln variant has been observed in 3 individuals with clinical features of Pitt-Hopkins syndrome (internal database - GeneDx; internal database - Greenwood Genetic Center) (PS4_Moderate).
PM1	✔	The p.Arg569Gln variant occurs in the well-characterized Basic Helix-Loop-Helix functional domain of the TCF4 gene (PM1).
PM5	✔	A pathogenic missense variant (p.Arg569Trp) has been previously identified within this codon which indicates that this residue is critical to the function of the protein (PMID 29695756) (PM5).
PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3).

Not Met criteria codes

PP4	✖	The p.Arg569Gln variant in TCF4 has been reported in an individual with autism spectrum disorder (PMID 40869941) (no criteria met).

Curation History

Showing 1 to 1 of 1 rows

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