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Variant: NM_001083962.2(TCF4):c.759C>G (p.Ser253Arg)

Version: 2.0

CA402701458

432062 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1c53d5a5-faa3-4994-be9b-d5aef8d0405c
Approved on: 2026/1/28
Published on: 2026/3/31

HGVS expressions

NM_001083962.2:c.759C>G
NM_001083962.2(TCF4):c.759C>G (p.Ser253Arg)
NC_000018.10:g.55275649G>C
CM000680.2:g.55275649G>C
NC_000018.9:g.52942880G>C
CM000680.1:g.52942880G>C
NC_000018.8:g.51093878G>C
NG_011716.1:g.317981C>G
NG_011716.2:g.365345C>G
ENST00000354452.8:c.759C>G
ENST00000630720.3:c.279C>G
ENST00000635822.2:c.759C>G
ENST00000635990.2:n.439C>G
ENST00000636400.2:c.687C>G
ENST00000636751.2:c.*467C>G
ENST00000636822.2:c.369C>G
ENST00000637115.2:c.*649C>G
ENST00000637169.2:c.111C>G
ENST00000637239.2:n.826C>G
ENST00000637250.2:n.453C>G
ENST00000637923.2:c.357C>G
ENST00000638154.3:c.789C>G
ENST00000643689.1:c.369C>G
ENST00000674764.1:c.*370C>G
ENST00000675707.1:c.369C>G
ENST00000354452.7:c.759C>G
ENST00000356073.8:c.759C>G
ENST00000398339.5:c.1065C>G
ENST00000457482.7:c.279C>G
ENST00000537578.5:c.687C>G
ENST00000537856.7:c.369C>G
ENST00000540999.5:c.687C>G
ENST00000543082.5:c.633C>G
ENST00000544241.6:c.546C>G
ENST00000561831.7:c.279C>G
ENST00000561992.5:c.369C>G
ENST00000562030.3:c.369C>G

ENST00000562607.5:c.369C>G
ENST00000562680.5:n.850C>G
ENST00000563686.5:n.614C>G
ENST00000563760.5:n.351C>G
ENST00000564228.5:c.546C>G
ENST00000564403.6:c.777C>G
ENST00000564999.5:c.759C>G
ENST00000565018.6:c.507C>G
ENST00000565580.3:n.508C>G
ENST00000566279.5:c.579C>G
ENST00000566286.5:c.753C>G
ENST00000566514.5:c.720C>G
ENST00000566777.5:c.369C>G
ENST00000567880.5:c.579C>G
ENST00000568169.5:c.771C>G
ENST00000568673.5:c.687C>G
ENST00000568740.5:c.684C>G
ENST00000569012.5:c.369C>G
ENST00000570146.3:c.23C>G
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ENST00000570287.6:c.279C>G
ENST00000616053.4:c.507C>G
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ENST00000625925.2:c.369C>G
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ENST00000627136.2:n.524-14116C>G
ENST00000628078.2:c.369C>G
ENST00000628636.2:c.369C>G
ENST00000628689.2:c.175+3902C>G
ENST00000629343.2:c.369C>G
ENST00000629387.2:c.759C>G
ENST00000630268.2:c.369C>G
ENST00000630319.2:c.528C>G
ENST00000630712.2:c.369C>G
ENST00000630720.2:c.279C>G
ENST00000630828.2:c.549C>G
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NM_001243227.1:c.687C>G
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NM_001243231.1:c.633C>G
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NM_001243236.1:c.279C>G
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NM_001369584.1:c.684C>G
NM_001369585.1:c.684C>G
NM_001369586.1:c.687C>G
NM_003199.3:c.759C>G
NM_001243230.2:c.753C>G

Pathogenic

Met criteria codes 4

PS4_Moderate | PP4 | PS2_Very Strong | PM2_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 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.Ser253Arg variant in TCF4 has been observed as a de novo occurrence (biological parentage both confirmed and unconfirmed) in 3 individuals with features of Pitt-Hopkins syndrome (PMID 29322350; PMID 26993267, described as p.Ser355Arg; University of Chicago-internal database) (PS2_Very strong). The p.Ser253Arg variant has been observed in 3 individuals with Pitt-Hopkins syndrome (PMID 29322350; 26993267, described as p.Ser355Arg) (PS4_Moderate, PP4). The p.Ser253Arg variant in TCF4 is absent from gnomAD v4.1 (PM2_Supporting). In summary, the p.Ser253Arg variant in TCF4 is classified as Pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PS2_Very strong, PS4_moderate, PM2_supporting, PP4). (TCF4 Specifications v.5.0; curation approved on 01/28/2026).

Met criteria codes

PS4_Moderate	✔	The p.Ser253Arg variant has been observed in 3 other individuals with Pitt-Hopkins syndrome (PMIDs 29322350; 26993267, described as p.Ser355Arg)
PP4	✔	The p.Ser253Arg variant in TCF4 has been reported in an individual with a clinical phenotype suggestive of Pitt–Hopkins syndrome (PMID: 26993267, described as p.Ser355Arg).
PS2_Very Strong	✔	The p.Ser253Arg variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with Pitt-Hopkins syndrome (PMID 29322350) (PS2_Very strong).
PM2_Supporting	✔	The p.Ser253Arg variant in TCF4 is absent from gnomAD v4.1.

Curation History

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