

Variant: NM_001083962.2(TCF4):c.990G>A (p.Ser330=)

Version: 3.0

CA272714 [↗](#)

160092 (ClinVar) [↗](#)

Gene: TCF4 ([HGNC:6925](#))

Condition: Pitt-Hopkins syndrome ([MONDO:0012589](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 919996d2-6306-4345-9cff-1b4b6bd7694d

Approved on: 2024/2/23

Published on: 2024/3/31

HGVS expressions

NM_001083962.2(TCF4):c.990G>A (p.Ser330=)

NM_001083962.2:c.990G>A

NC_000018.10:g.55261466C>T

CM000680.2:g.55261466C>T

NC_000018.9:g.52928697C>T

CM000680.1:g.52928697C>T

NC_000018.8:g.51079695C>T

NG_011716.1:g.332164G>A

NG_011716.2:g.379528G>A

ENST00000354452.8:c.990G>A

ENST00000630720.3:c.510G>A

ENST00000635822.2:c.990G>A

ENST00000635990.2:n.670G>A

ENST00000636400.2:c.918G>A

ENST00000636751.2:c.*698G>A

ENST00000636822.2:c.600G>A

ENST00000637115.2:c.*880G>A

ENST00000637169.2:c.342G>A

ENST00000637239.2:n.1057G>A

ENST00000637250.2:n.684G>A

ENST00000637923.2:c.588G>A

ENST00000638154.3:c.1020G>A

ENST00000643689.1:c.600G>A

ENST00000674764.1:c.*601G>A

ENST00000675707.1:c.600G>A

ENST00000354452.7:c.990G>A

ENST00000356073.8:c.990G>A

ENST00000398339.5:c.1296G>A

ENST00000457482.7:c.510G>A

ENST00000537578.5:c.918G>A

ENST00000537856.7:c.600G>A

ENST00000540999.5:c.918G>A

ENST00000543082.5:c.864G>A

ENST00000544241.6:c.777G>A

ENST00000561831.7:c.510G>A

ENST00000561992.5:c.600G>A

ENST00000562680.5:n.1081G>A

ENST00000563760.5:n.582G>A
ENST00000564228.5:c.777G>A
ENST00000564403.6:c.1008G>A
ENST00000564999.5:c.990G>A
ENST00000565018.6:c.738G>A
ENST00000566279.5:c.810G>A
ENST00000566286.5:c.984G>A
ENST00000567880.5:c.810G>A
ENST00000568673.5:c.918G>A
ENST00000568740.5:c.915G>A
ENST00000570146.3:c.254G>A
ENST00000570177.6:c.600G>A
ENST00000570287.6:c.510G>A
ENST00000616053.4:c.738G>A
ENST00000626584.2:c.342G>A
ENST00000627136.2:n.591G>A
ENST00000628078.2:c.600G>A
ENST00000628360.1:n.87G>A
ENST00000628636.2:c.600G>A
ENST00000628689.2:c.*133G>A
ENST00000629343.2:c.600G>A
ENST00000629387.2:c.990G>A
ENST00000630720.2:c.510G>A
NM_001083962.1:c.990G>A
NM_001243226.2:c.1296G>A
NM_001243227.1:c.918G>A
NM_001243228.1:c.1008G>A
NM_001243230.1:c.984G>A
NM_001243231.1:c.864G>A
NM_001243232.1:c.777G>A
NM_001243233.1:c.600G>A
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NM_001243235.1:c.510G>A
NM_001243236.1:c.510G>A
NM_001306207.1:c.918G>A
NM_001306208.1:c.777G>A
NM_003199.2:c.990G>A
NM_001330604.2:c.990G>A
NM_001330605.2:c.600G>A
NM_001348211.1:c.864G>A
NM_001348212.1:c.600G>A
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NM_001348214.1:c.510G>A
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NM_001330604.3:c.990G>A
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NM_001369567.1:c.990G>A
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NM_001369570.1:c.987G>A
NM_001369571.1:c.990G>A
NM_001369572.1:c.990G>A
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NM_001369574.1:c.990G>A
NM_001369575.1:c.918G>A
NM_001369576.1:c.915G>A
NM_001369577.1:c.918G>A
NM_001369578.1:c.915G>A
NM_001369579.1:c.918G>A
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NM_001369582.1:c.918G>A
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NM_001369585.1:c.915G>A
NM_001369586.1:c.918G>A
NM_003199.3:c.990G>A
NM_001243230.2:c.984G>A

Pathogenic

Met criteria codes 5

- PM2_Supporting
- PS4_Supporting
- PP3
- PM6
- PS2_Very Strong

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 3.0.0
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Rett and Angelman-like Disorders VCEP

The p.Ser330= variant in TCF4 is absent from gnomAD v4 (PM2_supporting). Splice prediction analysis using multiple computational tools suggests an impact to splicing (PP3). The p.Ser330= variant has been observed in at least 2 individuals with intellectual disability/autism (PMIDs: 29695756, 25693842) (PS4_supporting). The p.Ser330= variant in TCF4 has been reported as a de novo occurrence (biological parentage unconfirmed) in an individual with intellectual disability (PMID: 25693842, internal database -Invitae) (PM6). The p.Ser330= variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in at least 3 individuals with intellectual disability/autism (PMIDs: 29695756, 29158550, 31785789, 1981491, 33767182, internal database - Invitae) (PS2_very strong). In summary, the p.Ser330= variant in TCF4 is classified as pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PM2_supporting, PP3, PS4_supporting, PM6, PS2_very strong).

Met criteria codes

PM2_Supporting			The p.Ser330= variant in TCF4 is absent from gnomAD v4 (PM2_supporting).
PS4_Supporting			The p.Ser330= variant has been observed in at least 2 individuals with intellectual disability/autism (PMIDs: 29695756, 25693842) (PS4_supporting).
PP3			Splice prediction analysis using multiple computational tools suggests an impact to splicing (PP3).
PM6			The p.Ser330= variant in TCF4 has been reported as a de novo occurrence (biological parentage unconfirmed) in an individual with intellectual disability (PMID: 25693842, internal database -Invitae) (PM6).
PS2_Very Strong			The p.Ser330= variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in at least 3 individuals with intellectual disability/autism (PMIDs: 29695756, 29158550, 31785789, 31981491, 33767182, internal database -Invitae) (PS2_very strong).

Curation History



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