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Variant: NM_001083962.1(TCF4):c.1738C>T (p.Arg580Trp)

Version: 1.0

CA254160

7370 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: b4b4e028-4434-4362-a57e-8a50ad94182f
Approved on: 2021/3/26
Published on: 2021/5/17

HGVS expressions

NM_001083962.1(TCF4):c.1738C>T (p.Arg580Trp)
NM_001083962.1:c.1738C>T
NC_000018.10:g.55228988G>A
CM000680.2:g.55228988G>A
NC_000018.9:g.52896219G>A
CM000680.1:g.52896219G>A
NC_000018.8:g.51047217G>A
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NG_011716.2:g.412006C>T
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ENST00000637169.2:c.1090C>T
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ENST00000637250.2:n.1432C>T
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ENST00000537856.7:c.1336C>T
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ENST00000543082.5:c.1600C>T
ENST00000544241.6:c.1525C>T
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NM_001369586.1:c.1669C>T
NM_003199.3:c.1726C>T
NM_001243230.2:c.1717C>T

Pathogenic

Met criteria codes 7

PM1 PM6_Strong PP3 PP4 PM2_Supporting PS4_Supporting PS3_Supporting

Evidence Links 1

Expert Panel

Rett and Angelman-like Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Arg580Trp variant in TCF4 has been reported in at least 2 de novo occurrences (biological parentage unconfirmed) in individuals with Pitt-Hopkins syndrome (PMID 17436254, 22045651) (PM6_strong, PS4_supporting, PP4). The p.Arg580Trp in TCF4 is absent from gnomAD (PM2_supporting). The p.Arg580Trp variant occurs in the well-characterized basic Helix-Loop-Helix domain of TCF4 (PM1). In vitro binding assays have shown that this variant impacts protein function (PMID 22460224) (PS3_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.Arg580Trp variant in TCF4 is classified as Pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PM6_strong, PM1, PM2_supporting, PS4_supporting, PP3, PP4).

Met criteria codes

PM1	✔	The p.Arg580Trp variant occurs in the well-characterized basic Helix-Loop-Helix domain of TCF4.
PM6_Strong	✔	The p.Arg580Trp variant in TCF4 has been reported in at least 2 unconfirmed de novo occurrences in individuals with Pitt-Hopkins syndrome (as p.R576W in PMID 17436254). The p.Arg580Trp variant (reported as as p.R576W) in TCF4 has been reported in 2 unconfirmed de novo occurrences in individuals with Pitt-Hopkins syndrome. PubMed:17436254
PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own.
PP4	✔	The p.Arg580Trp variant in TCF4 has been reported in at least 2 unconfirmed de novo occurrences in individuals with Pitt-Hopkins syndrome (as p.R576W in PMID 17436254). The p.Arg580Trp variant in TCF4 has been reported in at least 2 unconfirmed de novo occurrences in individuals with Pitt-Hopkins syndrome PubMed:17436254
PM2_Supporting	✔	The p.Arg580Trp in TCF4 is absent from gnomAD.
PS4_Supporting	✔	The p.Arg580Trp variant in TCF4 has been reported in at least 2 unconfirmed de novo occurrences in individuals with Pitt-Hopkins syndrome (as p.R576W in PMID 17436254). The p.Arg580Trp variant in TCF4 has been reported in at least 2 unconfirmed de novo occurrences in individuals with Pitt-Hopkins syndrome PubMed:17436254
PS3_Supporting	✔	In vitro binding assays have shown that this variant impacts homodimer and heterodimer formation (PMID 22460224).

Curation History

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