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Variant: NM_001083962.1(TCF4):c.1727G>A (p.Arg576Gln)

Version: 1.0

CA16607615

381549 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: b79ddda3-bf1e-4cee-8b49-6cc1423ac1a7
Approved on: 2021/3/26
Published on: 2021/5/17

HGVS expressions

NM_001083962.1(TCF4):c.1727G>A (p.Arg576Gln)
NM_001083962.1:c.1727G>A
NC_000018.10:g.55228999C>T
CM000680.2:g.55228999C>T
NC_000018.9:g.52896230C>T
CM000680.1:g.52896230C>T
NC_000018.8:g.51047228C>T
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NG_011716.2:g.411995G>A
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NM_001243230.2:c.1706G>A

Pathogenic

Met criteria codes 7

PM1 PS2_Very Strong PS4_Supporting PS3_Supporting PM2_Supporting PP3 PP4

Evidence Links 2

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.Arg576Gln variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in at least 2 individuals with Pitt-Hopkins syndrome (PMID 23033978, 28726809) (PS2_VS, PS4_supporting, PP4). The p.Arg576Gln variant in TCF4 is absent from gnomAD (PM2_supporting). In vitro binding assays have shown that this variant impacts protein function (PMID 22460224) (PS3_supporting). The p.Arg576Gln variant occurs in the well-characterized basic Helix-Loop-Helix domain of TCF4 (PM1). Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3). In summary, the p.Arg576Gln variant in TCF4 is classified as Pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PS2_VS, PM1, PS4_supporting, PM2_supporting, PP3, PP4).

Met criteria codes

PM1	✔	The p.Arg576Gln variant occurs in the well-characterized basic Helix-Loop-Helix domain of TCF4.
PS2_Very Strong	✔	The p.Arg576Gln in TCF4 has been reported as a confirmed de novo occurrence in at least 2 individuals with Pitt-Hopkins syndrome (PMID 23033978 and 28726809). The p.Arg576Gln in TCF4 has been reported as a de novo occurrence as part of an exome trio in an individual with Pitt-Hopkins syndrome. PubMed:28726809 The p.Arg576Gln in TCF4 has been reported as a de novo occurrence as part of an exome trio in an individual with severe intellectual disability. PubMed:23033978
PS4_Supporting	✔	Found in two patients with Pitt-Hopkins syndrome Found in affected individual PubMed:28726809 Found in affected individual PubMed:23033978
PS3_Supporting	✔	In vitro binding assays have shown that this variant impacts homodimer and heterodimer formation (PMID 22460224).
PM2_Supporting	✔	The p.Arg576Gln in TCF4 is absent from gnomAD.
PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own.
PP4	✔	The p.Arg576Gln in TCF4 has been reported as a confirmed de novo occurrence in at least 2 individuals with Pitt-Hopkins syndrome (PMID 23033978 and 28726809). Found in patient with Pitt-Hopkins syndrome PubMed:28726809 Found in patient with Pitt-Hopkins syndrome PubMed:23033978

Curation History

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