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Variant: NM_001083962.2(TCF4):c.1990G>A (p.Ala664Thr)

Version: 1.0

CA319091

207527 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: e9bb91ba-79af-46e0-8fd4-35d9ec3eefa8
Approved on: 2024/8/30
Published on: 2024/12/13

HGVS expressions

NM_001083962.2(TCF4):c.1990G>A (p.Ala664Thr)
NM_001083962.2:c.1990G>A
NC_000018.10:g.55228251C>T
CM000680.2:g.55228251C>T
NC_000018.9:g.52895482C>T
CM000680.1:g.52895482C>T
NC_000018.8:g.51046480C>T
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ENST00000637250.2:n.1684G>A
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ENST00000354452.7:c.1990G>A
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NM_001243230.2:c.1969G>A

Benign

Met criteria codes 4

BA1 BS2 BP5 BP4

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

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The highest population minor allele frequency of the p.Ala664Thr variant in TCF4 in gnomAD v4.1 is 0.007675 in the Amish population, which is higher than the ClinGen Rett and Angelman-like Disorders VCEP threshold (≥0.0003) for BA1, and therefore meets this criterion (BA1). The p.Ala664Thr variant is observed in at least 2 unaffected individuals (internal database - GeneDx) (BS2). Computational analysis prediction tools suggest that the p.Ala664Thr variant does not have a deleterious impact; however this information does not predict clinical significance on its own (BP4). The p.Ala664Thr variant is found in a patient with an alternate molecular basis of disease (internal

database - GeneDx) (BP5). In summary, the p.Ala664Thr variant in TCF4 is classified as benign based on the ACMG/AMP criteria (BA1, BS2, BP4, BP5). (TCF4 specification v.3; approved on 8/30/2024)

Met criteria codes

BA1	✔	The highest population minor allele frequency of the p.Ala664Thr variant in TCF4 in gnomAD v4.1 is 0.007675 in the Amish population, which is higher than the ClinGen Rett and Angelman-like Disorders VCEP threshold (≥0.0003) for BA1, and therefore meets this criterion (BA1).
BS2	✔	The p.Ala664Thr variant is observed in at least 2 unaffected individuals (internal database - GeneDx) (BS2).
BP5	✔	The p.Ala664Thr variant is found in a patient with an alternate molecular basis of disease (internal database - GeneDx) (BP5).
BP4	✔	Computational analysis prediction tools suggest that the p.Ala664Thr variant does not have a deleterious impact; however this information does not predict clinical significance on its own (BP4).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001083962.2(TCF4):c.1990G>A (p....	Benign	Pitt-Hopkins Syndrome	2024-12-13	1.0	ClinGen Rett and Angelman-like Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TCF4 Version 3.0.0	TCF4

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