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Variant: NM_001083962.2(TCF4):c.1774G>A (p.Gly592Ser)

Version: 1.0

CA8970151

598113 (ClinVar)

Gene: TCF4 (HGNC:6925)
Condition: Pitt-Hopkins syndrome (MONDO:0012589)
Inheritance Mode: Autosomal dominant inheritance
UUID: f61eb051-8b88-40ab-83be-8229d724edd6
Approved on: 2024/8/30
Published on: 2024/12/13

HGVS expressions

NM_001083962.2:c.1774G>A
NM_001083962.2(TCF4):c.1774G>A (p.Gly592Ser)
NC_000018.10:g.55228952C>T
CM000680.2:g.55228952C>T
NC_000018.9:g.52896183C>T
CM000680.1:g.52896183C>T
NC_000018.8:g.51047181C>T
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NG_011716.2:g.412042G>A
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ENST00000637250.2:n.1468G>A
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NM_003199.3:c.1762G>A
NM_001243230.2:c.1753G>A

Likely Pathogenic

Met criteria codes 3

PP1 PM1 PS2

Not Met criteria codes 3

BA1 PM2 BS1

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 p.Gly592Ser variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with a neurodevelopmental disorder (internal database - GeneDx) (PS2). The p.Gly592Ser variant occurs in the well-characterized Basic Helix-Loop-Helix domain (bHLH) (aa 564-617) functional domain of the TCF4 (PM1). The variant has been reported to segregate in three informative meioses (internal database - GeneDx) with limited clinical information provided (PP1). The highest population minor allele frequency of the p.Gly592Ser variant in TCF4 in gnomAD v4.1 is 8.474e-7 (1/1180018 alleles) in European (non-Finnish) population (not

sufficient to meet BS1 criteria). Of note, this variant was observed once in gnomAD v4.1. In summary, the p.Gly592Ser variant in TCF4 is classified as likely pathogenic for Pitt-Hopkins syndrome based on the ACMG/AMP criteria (PS2, PM1, PP1). (TCF4 specification v.3; approved on 8/30/2024)

Met criteria codes

PP1	✔	The variant has been reported to segregate in three informative meioses (internal database - GeneDx) with limited clinical information provided (PP1).
PM1	✔	The p.Gly592Ser variant occurs in the well-characterized Basic Helix-Loop-Helix domain (bHLH) (aa 564-617) functional domain of TCF4 (PM1).
PS2	✔	The p.Gly592Ser variant in TCF4 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with a neurodevelopmental disorder (internal database - GeneDx).

Not Met criteria codes

BA1	✖	The highest population minor allele frequency of the p.Gly592Ser variant in TCF4 in gnomAD v4.1 is 8.474e-7 (1/1180018 alleles) in European (non-Finnish) population (not sufficient to meet BA1 criteria).
PM2	✖	The highest population minor allele frequency of the p.Gly592Ser variant in TCF4 in gnomAD v4.1 is 8.474e-7 (1/1180018 alleles) in European (non-Finnish) population (not sufficient to meet PM2 criteria).
BS1	✖	The highest population minor allele frequency of the p.Gly592Ser variant in TCF4 in gnomAD v4.1 is 8.474e-7 (1/1180018 alleles) in European (non-Finnish) population (not sufficient to meet BS1 criteria).

Curation History

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