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Variant: NM_004992.3(MECP2):c.916C>T (p.Arg306Cys)

Version: 1.0

CA212529

11824 (ClinVar)

Gene: MECP2 (HGNC:4204)
Condition: Rett syndrome (MONDO:0010726)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: 306280ba-f29e-479c-a220-4d3eb2bc93d9
Approved on: 2021/3/26
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HGVS expressions

NM_004992.3:c.916C>T
NM_004992.3(MECP2):c.916C>T (p.Arg306Cys)
NC_000023.11:g.154030912G>A
CM000685.2:g.154030912G>A
NC_000023.10:g.153296363G>A
CM000685.1:g.153296363G>A
NC_000023.9:g.152949557G>A
NG_007107.2:g.111216C>T
NG_007107.3:g.111192C>T
ENST00000303391.11:c.916C>T
ENST00000453960.7:c.952C>T
ENST00000637917.1:c.90C>T
ENST00000303391.10:c.916C>T
ENST00000407218.5:c.*288C>T
ENST00000453960.6:c.952C>T
ENST00000619732.4:c.916C>T
ENST00000622433.4:c.902C>T
ENST00000628176.2:c.*288C>T
NM_001110792.1:c.952C>T
NM_001316337.1:c.637C>T
NM_001110792.2:c.952C>T
NM_001316337.2:c.637C>T
NM_001369391.2:c.637C>T
NM_001369392.2:c.637C>T
NM_001369393.2:c.637C>T
NM_001369394.1:c.637C>T
NM_001369394.2:c.637C>T
NM_001386137.1:c.247C>T
NM_001386138.1:c.247C>T
NM_001386139.1:c.247C>T
NM_004992.4:c.916C>T

Pathogenic

Met criteria codes 6

PM1 PS2_Very Strong PS3_Supporting PS4

Expert Panel

Rett and Angelman-like Disorders VCEP

PM2_Supporting PP1

Evidence Links 0

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Arg306Cys variant in MECP2 has been reported as a de novo occurrence (biological parentage both confirmed and unconfirmed) in at least 3 individuals with Rett Syndrome (PMID 10577905, 11309679, 19189931; internal database, GeneDx) (PS2_very strong). This variant has been observed in at least 4 other individuals with Rett syndrome (PMID 24511209, 23238081, RettBase) (PS4). The p.Arg306Cys variant occurs in the well-characterized transcriptional repression domain (TRD) functional domain of MECP2 (PMID 21326358, 23770565) (PM1). This variant is absent in gnomAD (PM2_supporting). Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3). In summary, p.Arg306Cys variant in MECP2 is classified as Pathogenic for Rett syndrome based on the ACMG/AMP criteria (PS2_very strong, PS4, PM1, PM2_supporting, PP3).

Met criteria codes

PM1	✔	Met NM_004992.3(MECP2):c.916C>T (p.Arg306Cys) is located in a mutational hot spot, NCoR/SMRT interaction (NID)): aa 285-310
PS2_Very Strong	✔	The p.Arg306Cys variant in MECP2 has been reported as a de novo occurrence (biological parentage both confirmed and unconfirmed) in at least 3 individuals with Rett syndrome (PMID 10577905; internal database, GeneDx).
PS3_Supporting	✔	Experimental studies have shown that this variant impacts protein function (PMID 23770565)
PS4	✔	The p.XX variant has been observed in at least 4 other individuals with Rett syndrome (PMID: 10577905, 11309679, 19189931)
PM2_Supporting	✔	The variant is absent in gnomAD (PM2)
PP1	✔	Met Variant observed to segregate with disease in 2 individuals in a single family. RettBASE Patient ID 28,29

Curation History

Showing 1 to 1 of 1 rows

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