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Variant: NM_002055.5(GFAP):c.715C>T (p.Arg239Cys)

Version: 1.0

CA217208

16167 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9bfe9d06-67ba-4afb-9bd4-95ef3f81338c
Approved on: 2026/8/18
Published on: 2026/8/18

HGVS expressions

NM_002055.5(GFAP):c.715C>T (p.Arg239Cys)
NM_002055.5:c.715C>T
NC_000017.11:g.44913334G>A
CM000679.2:g.44913334G>A
NC_000017.10:g.42990702G>A
CM000679.1:g.42990702G>A
NC_000017.9:g.40346228G>A
NG_008401.1:g.7213C>T
ENST00000253408.11:c.715C>T
ENST00000435360.8:c.715C>T
ENST00000253408.10:c.715C>T
ENST00000435360.7:c.715C>T
ENST00000586127.6:n.1244C>T
ENST00000586793.6:c.715C>T
ENST00000587997.6:n.191C>T
ENST00000588735.3:c.715C>T
ENST00000591327.2:n.1869C>T
ENST00000592320.6:c.618+394C>T
ENST00000638281.1:c.715C>T
ENST00000638618.1:c.370C>T
ENST00000639277.1:c.715C>T
ENST00000640552.1:n.729C>T
ENST00000253408.9:c.715C>T
ENST00000376990.8:c.*114C>T
ENST00000435360.6:c.715C>T
ENST00000585728.5:c.*359C>T
ENST00000586793.5:c.715C>T
ENST00000587997.5:c.191C>T
ENST00000588316.1:c.619C>T
ENST00000588735.1:c.82+2071C>T
ENST00000588957.5:c.-18C>T
ENST00000590922.1:n.365C>T
ENST00000592320.5:c.618+394C>T
NM_001131019.2:c.715C>T
NM_001242376.1:c.715C>T
NM_002055.4:c.715C>T
NM_001363846.1:c.715C>T

NM_001131019.3:c.715C>T
NM_001242376.2:c.715C>T
NM_001242376.3:c.715C>T
NM_001363846.2:c.715C>T

Pathogenic

Met criteria codes 4

PS2_Very Strong | PM2_Supporting | PS3_Very Strong | PS4_Very Strong

Not Met criteria codes 1

PP1

Evidence Links 0

Expert Panel

Leukodystrophy and Leukoencephalopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Leukodystrophy and Leukoencephalopathy VCEP

The NM_002055.5(GFAP):c.715C>T, variant in GFAP is a missense variant predicted to cause a substitution of arginine by cysteine at amino acid 239 (p.Arg239Cys). This variant has been reported in five probands who met definite diagnostic criteria for Alexander Disease per ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0 (PS4_Very Strong; PMID:15732097) and identified as a de novo occurrence with confirmed parental relationships in two individuals who met definite diagnostic criteria for Alexander Disease per ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0 (PS2_Very Strong; PMID: 23364391). This variant is absent from gnomAD v[4.1.1] (PM2_Supporting). An aggregation assay in a zebrafish model showed a significantly higher number of GFAP aggregates than wild-type GFAP indicating that this variant impacts protein function (PMID: 28882119) (PS3_Very Strong). In summary, this variant meets the criteria to be classified as a pathogenic for Alexander Disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy VCEP: PS2_Very Strong, PS3_Very Strong, PS4_Very Strong, PM2_Supporting (ClinGen Leukodystrophy and Leukoencephalopathy VCEP Specifications Version 1.0.0).

Met criteria codes

PS2_Very Strong	✔	This variant has been identified as a de novo occurrence with confirmed paternal relationships in 2 individuals who met diagnostic criteria for Alexander Disease per ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0 (PS2_[Very Strong]; PMID: 23364391)
PM2_Supporting	✔	This variant is absent from gnomAD v[4.1.1] (PM2_Supporting).
PS3_Very Strong	✔	An aggregation assay in zebrafish model showed a significantly higher number of GFAP aggregates than wild-type GFAP indicating that this variant impacts protein function (PMID: 28882119) (PS3_[Very Strong]).
PS4_Very Strong	✔	This variant has been reported in 5 probands who met diagnostic criteria for Alexander Disease per ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation

Guidelines for GFAP Version 1.0.0 (PS4_[Very Strong]; PMID:15732097)

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002055.5(GFAP):c.715C>T (p.Arg2...	Pathogenic	Alexander Disease	2026-08-18	1.0	ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0	GFAP

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