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Variant: NM_002055.5(GFAP):c.262C>T (p.Arg88Cys)

Version: 1.0

CA217183

16172 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: d71ae79a-ecbd-4026-8c82-ffc399191684
Approved on: 2026/8/18
Published on: 2026/8/18

HGVS expressions

NM_002055.5(GFAP):c.262C>T (p.Arg88Cys)
NM_002055.5:c.262C>T
NC_000017.11:g.44915225G>A
CM000679.2:g.44915225G>A
NC_000017.10:g.42992593G>A
CM000679.1:g.42992593G>A
NC_000017.9:g.40348119G>A
NG_008401.1:g.5322C>T
ENST00000253408.11:c.262C>T
ENST00000435360.8:c.262C>T
ENST00000253408.10:c.262C>T
ENST00000435360.7:c.262C>T
ENST00000586793.6:c.262C>T
ENST00000588735.3:c.262C>T
ENST00000591327.2:n.275C>T
ENST00000592320.6:c.262C>T
ENST00000638281.1:c.262C>T
ENST00000639277.1:c.262C>T
ENST00000640552.1:n.276C>T
ENST00000253408.9:c.262C>T
ENST00000376990.8:c.262C>T
ENST00000435360.6:c.262C>T
ENST00000585728.5:c.181+81C>T
ENST00000586793.5:c.262C>T
ENST00000588037.1:c.262C>T
ENST00000588316.1:c.262C>T
ENST00000588735.1:c.82+180C>T
ENST00000588957.5:c.-272+592C>T
ENST00000591327.1:n.276C>T
ENST00000592320.5:c.262C>T
NM_001131019.2:c.262C>T
NM_001242376.1:c.262C>T
NM_002055.4:c.262C>T
NM_001363846.1:c.262C>T
NM_001131019.3:c.262C>T
NM_001242376.2:c.262C>T
NM_001242376.3:c.262C>T

NM_001363846.2:c.262C>T

Pathogenic

Met criteria codes 5

PP4_Strong | PS2 | PS3 | PS4 | PM1

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.262C>T, variant in GFAP is a missense variant predicited to cause a substitution of arginine by cysteine at amino acid 88 (p.Arg88Cys). At least one proband with this variant displayed elevated GFAP protein levels in plasma, serum, or CSF, which is highly specific for Alexander Disease (PP4_[Strong], PMID: 26478912). This variant has been reported in three 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; PMID:23364391, PMID:15732097) This variant has been identified as a de novo occurrence with confirmed parental relationships in two individual 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; PMID:23364391). Immunoassay with Western blot in iPSC cells transfected with the variant showed protein aggregation compared to wild type controls indicating that this variant impacts protein function (PS3; PMID: 30355500). This variant resides within a region, amino acids 59 - 88, of GFAP that is defined as a region with significant missense constraint by the ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0 (PM1). In summary, this variant meets the criteria to be classified as Pathogenic for Alexander Disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy VCEP: PS2, PS3, PS4, PM1, PP4_strong (ClinGen Leukodystrophy and Leukoencephalopathy VCEP Specifications Version 1.0.0).

Met criteria codes

PP4_Strong	✔	At least one patient with this variant displayed elevated GFAP protein levels in plasma, serum, or CSF, which is highly specific for Alexander Disease (PP4_[strong], PMID: 26478912).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed paternal relationships in two individual 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; PMID:23364391).
PS3	✔	Immunoassay with Western blot in iPSC cells transvected with the variant showed protein aggregation compared to wild type controls indicating that this variant impacts protein function (PMID: 30355500)(PS3).
PS4	✔	This variant has been reported in three 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_[Strong]; PMID:23364391, 15732097)

PM1 ✔ This variant resides within a region, amino acids 59 - 88, of GFAP that is defined as a region with significant missense constraint by the ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0 (PM1).

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.262C>T (p.Arg8...	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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