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Variant: NM_002055.5(GFAP):c.259G>A (p.Val87Ile)

Version: 1.0

CA347191

190339 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7d76bb1e-ffab-4a9f-9c80-dabe9dbabdc0
Approved on: 2026/8/18
Published on: 2026/8/18

HGVS expressions

NM_002055.5(GFAP):c.259G>A (p.Val87Ile)
NM_002055.5:c.259G>A
NC_000017.11:g.44915228C>T
CM000679.2:g.44915228C>T
NC_000017.10:g.42992596C>T
CM000679.1:g.42992596C>T
NC_000017.9:g.40348122C>T
NG_008401.1:g.5319G>A
ENST00000253408.11:c.259G>A
ENST00000435360.8:c.259G>A
ENST00000253408.10:c.259G>A
ENST00000435360.7:c.259G>A
ENST00000586793.6:c.259G>A
ENST00000588735.3:c.259G>A
ENST00000591327.2:n.272G>A
ENST00000592320.6:c.259G>A
ENST00000638281.1:c.259G>A
ENST00000639277.1:c.259G>A
ENST00000640552.1:n.273G>A
ENST00000253408.9:c.259G>A
ENST00000376990.8:c.259G>A
ENST00000435360.6:c.259G>A
ENST00000585728.5:c.181+78G>A
ENST00000586793.5:c.259G>A
ENST00000588037.1:c.259G>A
ENST00000588316.1:c.259G>A
ENST00000588735.1:c.82+177G>A
ENST00000588957.5:c.-272+589G>A
ENST00000591327.1:n.273G>A
ENST00000592320.5:c.259G>A
NM_001131019.2:c.259G>A
NM_001242376.1:c.259G>A
NM_002055.4:c.259G>A
NM_001363846.1:c.259G>A
NM_001131019.3:c.259G>A
NM_001242376.2:c.259G>A
NM_001242376.3:c.259G>A

NM_001363846.2:c.259G>A

Pathogenic

Met criteria codes 6

PS4_Moderate PP4_Strong PM2_Supporting PM6 PM1 PM5

Not Met criteria codes 1

PS2

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.259G>A, variant in GFAP is a missense variant predicited to cause a substitution of valine by isoleucine at amino acid 87 (p.Val87Ile). This variant has been reported in three 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_Moderate; PMID: 21902566, PMID: 24306001). The variant was identified as a de novo occurrence with unconfirmed parental relationships in one of these probands (PM6; PMID: 21902566). Another of these probands displayed elevated GFAP protein levels in plasma and CSF, which is highly specific for Alexander Disease (PP4_[Strong], PMID: 26478912). This variant is absent from gnomAD v[4.1.1] (PM2_Supporting). 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). One missense variant, c.259G>C, p.Val87Leu [ClinVar Variation ID: 66477], in the same codon has been classified as pathogenic for Alexander Disease (PM5). In summary, this variant meets the criteria to be classified Pathogenic for Alexander Disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy VCEP: PP4_Strong, PM1, PS4_Moderate, PM6, PM5, PM2_Supporting, (ClinGen Leukodystrophy and Leukoencephalopathy VCEP Specifications Version 1.0.0).

Met criteria codes

PS4_Moderate	✔	This variant has been reported in two 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_Supporting; PMID: 21902566).
PP4_Strong	✔	At least one proband with this variant displayed elevated GFAP protein levels in plasma and CSF, which is highly specific for Alexander Disease (PP4_[Strong], PMID: 26478912).
PM2_Supporting	✔	This variant is absent from gnomAD v[4.1.1] (PM2_Supporting).
PM6	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one 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 (PM6; PMID: 21902566).

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).
PM5		✔	One missense variant, c.259G>C, p.Val87Leu [ClinVar Variation ID: 66477], in the same codon has been classified as pathogenic for Alexander Disease [PM5].

Not Met criteria codes

PS2		✖	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.259G>A (p.Val8...	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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