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Variant: NM_002055.5(GFAP):c.218T>A (p.Met73Lys)

Version: 1.0

CA217156

66464 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: 219456ce-06da-4759-94c0-2d92a53354e1
Approved on: 2026/8/18
Published on: 2026/8/18

HGVS expressions

NM_002055.5(GFAP):c.218T>A (p.Met73Lys)
NM_002055.5:c.218T>A
NC_000017.11:g.44915269A>T
CM000679.2:g.44915269A>T
NC_000017.10:g.42992637A>T
CM000679.1:g.42992637A>T
NC_000017.9:g.40348163A>T
NG_008401.1:g.5278T>A
ENST00000253408.11:c.218T>A
ENST00000435360.8:c.218T>A
ENST00000253408.10:c.218T>A
ENST00000435360.7:c.218T>A
ENST00000586793.6:c.218T>A
ENST00000588735.3:c.218T>A
ENST00000591327.2:n.231T>A
ENST00000592320.6:c.218T>A
ENST00000638281.1:c.218T>A
ENST00000639277.1:c.218T>A
ENST00000640552.1:n.232T>A
ENST00000253408.9:c.218T>A
ENST00000376990.8:c.218T>A
ENST00000435360.6:c.218T>A
ENST00000585728.5:c.181+37T>A
ENST00000586793.5:c.218T>A
ENST00000588037.1:c.218T>A
ENST00000588316.1:c.218T>A
ENST00000588735.1:c.82+136T>A
ENST00000588957.5:c.-272+548T>A
ENST00000591327.1:n.232T>A
ENST00000592320.5:c.218T>A
NM_001131019.2:c.218T>A
NM_001242376.1:c.218T>A
NM_002055.4:c.218T>A
NM_001363846.1:c.218T>A
NM_001131019.3:c.218T>A
NM_001242376.2:c.218T>A
NM_001242376.3:c.218T>A

NM_001363846.2:c.218T>A

Likely Pathogenic

Met criteria codes 4

PM1 PM5 PM2_Supporting PS4_Supporting

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.218T>A, variant in GFAP is a missense variant predicited to cause a substitution of methionine by lysine at amino acid 73 (p.Met73Lys). This variant has been reported in 1 proband meeting the 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: 17894839). 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, [GFAP c.219A>G, p.Met73Val] [Variation ID: 1173085], in the same codon have been classified as Pathogenic for Alexander Disease [PM5]. In summary, this variant meets the criteria to be classified as likely pathogenic based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy VCEP: PS4_Supporting, PM1, PM2_Supporting, PM5 (ClinGen Leukodystrophy and Leukoencephalopathy VCEP Specifications Version 1.0.0).

Met criteria codes

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	✔	A different missense variant, [GFAP c.219A>G, p.Met73Val] [Variation ID: 1173085], in the same codon has been classified as Pathogenic for Alexander Disease [PM5].
PM2_Supporting	✔	This variant is absent from gnomAD v[4.1.1] (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in 1 proband meeting the 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: 17894839).

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.218T>A (p.Met7…	Likely 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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