The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_002055.5(GFAP):c.219G>A (p.Met73Ile)

Version: 1.0

CA399848755

2132009 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: 290c266d-c176-4aa8-b4da-2314df121a14
Approved on: 2026/8/17
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HGVS expressions

NM_002055.5(GFAP):c.219G>A (p.Met73Ile)
NM_002055.5:c.219G>A
NC_000017.11:g.44915268C>T
CM000679.2:g.44915268C>T
NC_000017.10:g.42992636C>T
CM000679.1:g.42992636C>T
NC_000017.9:g.40348162C>T
NG_008401.1:g.5279G>A
ENST00000253408.11:c.219G>A
ENST00000435360.8:c.219G>A
ENST00000253408.10:c.219G>A
ENST00000435360.7:c.219G>A
ENST00000586793.6:c.219G>A
ENST00000588735.3:c.219G>A
ENST00000591327.2:n.232G>A
ENST00000592320.6:c.219G>A
ENST00000638281.1:c.219G>A
ENST00000639277.1:c.219G>A
ENST00000640552.1:n.233G>A
ENST00000253408.9:c.219G>A
ENST00000376990.8:c.219G>A
ENST00000435360.6:c.219G>A
ENST00000585728.5:c.181+38G>A
ENST00000586793.5:c.219G>A
ENST00000588037.1:c.219G>A
ENST00000588316.1:c.219G>A
ENST00000588735.1:c.82+137G>A
ENST00000588957.5:c.-272+549G>A
ENST00000591327.1:n.233G>A
ENST00000592320.5:c.219G>A
NM_001131019.2:c.219G>A
NM_001242376.1:c.219G>A
NM_002055.4:c.219G>A
NM_001363846.1:c.219G>A
NM_001131019.3:c.219G>A
NM_001242376.2:c.219G>A
NM_001242376.3:c.219G>A

NM_001363846.2:c.219G>A

Likely Pathogenic

Met criteria codes 4

PM1 PM2_Supporting PS3_Moderate PS4

Not Met criteria codes 2

BS1 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.219G>A, variant in GFAP is a missense variant predicited to cause a substitution of methionine by isoleucine at amino acid 73 (p.Met73Ile). This variant has been reported in 4 least four 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:37658208, PMID:31781017). In an immunocytochemistry assay HeLa cells showed abnormal GFAP aggregation indicating that is variant impacts protein function (PMID: 31781017) (PS3_Moderate). 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). This variant is absent from gnomAD v[4.1.1] (PM2_Supporting). In summary, this variant meets the criteria to be classified Likely Pathogenic for Alexander Disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy VCEP: PS4, PM1, PS3_Moderate, PM2_Supporting (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).
PM2_Supporting	✔	This variant is absent from gnomAD v[4.1.1] (PM2_Supporting).
PS3_Moderate	✔	In an immunocytochemistry assay HeLa cells showed abnormal GFAP aggregation indicating that is variant impacts protein function (PMID: 31781017) (PS3_Moderate).
PS4	✔	This variant has been reported in at least four 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:37658208, PMID:31781017)

Not Met criteria codes

BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	Not met due to current evidence being applied to PP4 instead.

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.219G>A (p.Met7...	Likely Pathogenic	Alexander Disease	2026-08-17	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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