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Variant: NM_002055.5(GFAP):c.278A>C (p.Gln93Pro)

Version: 1.0

CA347193

190340 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0fc507b3-7e05-4952-bd4c-fc0e70cc5764
Approved on: Mon, 14 Sep 2026 00:00:00 +0000
Published on: Mon, 14 Sep 2026 00:00:00 +0000

HGVS expressions

NM_002055.5(GFAP):c.278A>C (p.Gln93Pro)
NM_002055.5:c.278A>C
NC_000017.11:g.44915209T>G
CM000679.2:g.44915209T>G
NC_000017.10:g.42992577T>G
CM000679.1:g.42992577T>G
NC_000017.9:g.40348103T>G
NG_008401.1:g.5338A>C
ENST00000253408.11:c.278A>C
ENST00000435360.8:c.278A>C
ENST00000253408.10:c.278A>C
ENST00000435360.7:c.278A>C
ENST00000586793.6:c.278A>C
ENST00000588735.3:c.278A>C
ENST00000591327.2:n.291A>C
ENST00000592320.6:c.278A>C
ENST00000638281.1:c.278A>C
ENST00000639277.1:c.278A>C
ENST00000640552.1:n.292A>C
ENST00000253408.9:c.278A>C
ENST00000376990.8:c.278A>C
ENST00000435360.6:c.278A>C
ENST00000585728.5:c.182-74A>C
ENST00000586793.5:c.278A>C
ENST00000588037.1:c.278A>C
ENST00000588316.1:c.278A>C
ENST00000588735.1:c.82+196A>C
ENST00000588957.5:c.-272+608A>C
ENST00000591327.1:n.292A>C
ENST00000592320.5:c.278A>C
NM_001131019.2:c.278A>C
NM_001242376.1:c.278A>C
NM_002055.4:c.278A>C
NM_001363846.1:c.278A>C
NM_001131019.3:c.278A>C
NM_001242376.2:c.278A>C
NM_001242376.3:c.278A>C

NM_001363846.2:c.278A>C

Likely Pathogenic

Met criteria codes 3

PM6 PP4_Strong PM2_Supporting

Not Met criteria codes 3

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 c.278A>C variant in GFAP is a missense variant predicted to cause substitution of glutamine by proline at amino acid 93 (p.Gln93Pro). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one individual with a definite diagnosis of Alexander Disease per ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0 who had elevated GFAP levels in CSF when compared to age-matched controls which is highly specific for Alexander disease (PM6, PP4_strong; PMID: 16217707). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for Alexander disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel: PM6, PM2_supporting, PP4_strong (ClinGen Leukodystrophy and Leukoencephalopathy VCEP Specifications Version 1.0.0).

Met criteria codes

PM6	✔	PMID 16217707 : 1 pb w/Definite (A4, A5, B1, B5, B6) diagnosis of Alexander disease per VCEP criteria; de novo with unconfirmed parental relationships (4 points) "Late infantile Alexander disease was suspected and confirmed by a heterozygous missense mutation in the GFAP gene by DNA sequence analysis. Glutamine was replaced by proline (p.Q93P) as a result of a base substitution in exon 1 (c.278A > C). The mutation was not detected in any of the parents."
PP4_Strong	✔	PMID 16217707: Patient 2 - CSF diagnostics showed slightly elevated albumin 225 mg/L(< 150). CSF marker proteins for neuronal damage were unremarkable but GFAP showed a sharp increase to 30 000 ng/L(< 175).
PM2_Supporting	✔	absent gnomADv4; This variant is absent from gnomAD v4.1.1 (PM2_Supporting).

Not Met criteria codes

PS3	✖	no functional study
PS4	✖	

PMID 16217707 (Kyllerman 2005): 1 9yo female (Patient 2) w/Definite (A4, A5, B1, B5, B6) diagnosis of Alexander disease per VCEP criteria; de novo with unconfirmed parental relationships (4 points) -A4 Motor symptoms: muscle weakness, spastic paresis, cerebellar ataxia, muscle rigidity: slow and clumsy motor function -A5 Bulbar/ pseudobulbar palsy: dysphagia, dysarthria, dysphonia: increasing dysarthia noted since 3yo, dysphagia since 4yo causing severe weight loss and G-tube feeds, noted to have pseudobulbar paresis on exam, incomprehensible speech -B1 Cerebral white matter abnormalities with frontal lobe predominance: Fig 2 hyperintense frontal and subcortical white matter. In addition there are hyperintense lesions in the dorsal pons with exten- sion up into the mesencephalon and down into the medulla oblongata. -B5 Signal abnormalities in midbrain: (above) -B6 Signal abnormalities or atrophy of the medulla oblongata and/or cervical cord or hyperintensities in the brainstem: (above) PMID 21917775 (Prust 2011): cites Kyllerman 2005, Table e-3 PMID 34146839 (Heshmatzad 2021): cites Kyllerman 2005, Table 1, 2 PMID 36088400 (Heshmatzad 2022): cites Kyllerman 2005, Table 1

PM1		✖	not within amino acids 59 – 88

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.278A>C (p.Gln9...	Likely Pathogenic	Alexander Disease	2026-09-14	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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