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Variant: NM_002055.5(GFAP):c.1138C>T (p.Pro380Ser)

Version: 1.0

CA399842378

3344171 (ClinVar)

Gene: GFAP (HGNC:2670)
Condition: Alexander disease (MONDO:0008752)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3171e28f-9b5e-4f98-ba5c-ff48a663a2a2
Approved on: Tue, 27 Oct 2026 00:00:00 +0000
Published on: Tue, 27 Oct 2026 00:00:00 +0000

HGVS expressions

NM_002055.5(GFAP):c.1138C>T (p.Pro380Ser)
NM_002055.5:c.1138C>T
NC_000017.11:g.44910648G>A
CM000679.2:g.44910648G>A
NC_000017.10:g.42988016G>A
CM000679.1:g.42988016G>A
NC_000017.9:g.40343542G>A
NG_008401.1:g.9899C>T
ENST00000253408.11:c.1138C>T
ENST00000435360.8:c.1138C>T
ENST00000253408.10:c.1138C>T
ENST00000435360.7:c.1138C>T
ENST00000585543.6:n.291C>T
ENST00000586125.2:c.73C>T
ENST00000586127.6:n.1667C>T
ENST00000586793.6:c.1003C>T
ENST00000588735.3:c.1138C>T
ENST00000591327.2:n.2292C>T
ENST00000591880.2:c.68C>T
ENST00000592320.6:c.715C>T
ENST00000638281.1:c.1138C>T
ENST00000638304.1:c.57C>T
ENST00000638488.1:n.79C>T
ENST00000638618.1:c.793C>T
ENST00000639042.1:c.75C>T
ENST00000639277.1:c.1138C>T
ENST00000639921.1:c.311C>T
ENST00000640552.1:n.1152C>T
ENST00000253408.9:c.1138C>T
ENST00000435360.6:c.1138C>T
ENST00000585543.5:n.291C>T
ENST00000586793.5:c.1138C>T
ENST00000588640.5:n.518C>T
ENST00000588735.1:c.83-2532C>T
ENST00000591880.1:c.4C>T
ENST00000592320.5:c.715C>T
NM_001131019.2:c.1138C>T

NM_001242376.1:c.1138C>T
NM_002055.4:c.1138C>T
NM_001363846.1:c.1138C>T
NM_001131019.3:c.1138C>T
NM_001242376.2:c.1138C>T
NM_001242376.3:c.1138C>T
NM_001363846.2:c.1138C>T

Pathogenic

Met criteria codes 3

PP4_Strong PM2_Supporting PS2

Not Met criteria codes 10

PM6 PM1 PM5 BA1 BS1
BS3 PS1 PS3 PS4 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.1138C>T variant in GFAP is a missense variant predicted to cause substitution of Proline by Serine at amino acid 380 (p.Pro380Ser). This variant has been identified as a de novo occurrence with confirmed 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 (PS2) who displayed CSF GFAP levels (research-based) that were significantly elevated when compared to age-matched controls, which is highly specific for Alexander Disease (PP4_Strong, PMID: 41513585). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for Autosomal Dominant Alexander disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Leukodystrophy and Leukoencephalopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GFAP Version 1.0.0: PS2, PP4_Strong, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	At least one patient with this variant displayed CSF GFAP levels that were significantly elevated when compared to age-matched controls., which is highly specific for Alexander Disease (PP4_Strong], PMID: 41513585).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual with "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 (PS2).

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	Variant NOT affecting an amino acid at or in between positions 59-88.
PM5	✖	The current variant is the only variant found in this codon in ClinVar as of 4/19/2026.
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No functional studies for this variant.
PS1	✖	No other reported pathogenic variants with different nucleotide change that lead to the same amino acid change.
PS3	✖	No functional studies for this variant.

PS4		✖	PS4 not met because PP4 was applied. However, proband met "definite" diagnostic criteria (3pts) which would have met PS2_supporting if PP4 had not be applied.
PP1		✖	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.1138C>T (p.Pro...	Pathogenic	Alexander Disease	2026-10-27	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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