

Variant: *NM_001164508.2(NEB):c.1493A>G (p.Asp498Gly)*

Version: 1.0

CA348825220 [↗](#)

533979 (ClinVar) [↗](#)

Gene: NEB ([HGNC:4703](#))

Condition: nemaline myopathy ([MONDO:0018958](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 79266f92-7df8-40de-be2e-c648de9e1355

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HGVS expressions

NM_001164508.2(NEB):c.1493A>G (p.Asp498Gly)

NM_001164508.2:c.1493A>G

NC_000002.12:g.151696713T>C

CM000664.2:g.151696713T>C

NC_000002.11:g.152553227T>C

CM000664.1:g.152553227T>C

NC_000002.10:g.152261473T>C

NG_009382.2:g.42775A>G

ENST00000397345.8:c.1493A>G

ENST00000427231.7:c.1493A>G

ENST00000172853.14:c.1493A>G

ENST00000397345.7:c.1493A>G

ENST00000409198.5:c.1493A>G

ENST00000427231.6:c.1493A>G

ENST00000489048.1:n.392A>G

ENST00000603639.5:c.1493A>G

ENST00000604864.5:c.1493A>G

ENST00000618972.4:c.1493A>G

NM_001164507.1:c.1493A>G

NM_001164508.1:c.1493A>G

NM_001271208.1:c.1493A>G

NM_004543.4:c.1493A>G

NM_001271208.2:c.1493A>G

NM_004543.5:c.1493A>G

NM_001164507.2:c.1493A>G

Likely Pathogenic

Met criteria codes 3

PM3_Strong

PP4

PM2_Supporting

Not Met criteria codes 23

BP5

BP7

BP4

BP3

BP1

BP2

BS1

BS4

BS3

BS2

PP1

PP2

PP3

PM6

PS1

PS2

PS3

PS4

BA1

PM1

PM5

PM4

PVS1

Expert Panel

Congenital Myopathies VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for NEB Version 1.0.0

[↗](#) **Criteria Specification Approval History**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001164508.2 c.1493A>G (p.Asp498Gly) variant in NEB is a missense variant predicted to cause a substitution of aspartic acid by glycine at amino acid 498. The highest population minor allele frequency in gnomAD v4.1.0 is 0.00005120 (1/19532) alleles) in East Asian population, which is lower than the ClinGen Congenital Myopathies VCEP threshold (≤ 0.0000559) for PM2_Supporting, meeting this criterion (PM2_Supporting). This variant has previously been observed in probands who have had nemaline bodies on muscle biopsy (PMID:32403337; Invitae internal data SCV000659742.9) (PP4). The variant has previously been reported in trans with pathogenic variants or rare variants of uncertain significance in 4 probands with clinical features of congenital myopathy (PMID: 33333461; Synnovis internal data SCV001468505.1; Invitae internal data SCV000659742.9) (PM3_Strong). In summary, this variant meets the criteria to be classified as likely pathogenic for Nemaline Myopathy for autosomal recessive inheritance based on the ACMG/AMP criteria applied as specified by the ClinGen Congenital Myopathy VCEP: (PM3_Strong, PP4, PM2_Supporting; ClinGen Congenital Myopathies VCEP Specifications version 1.0.0; 3/10/2025).

Met criteria codes

PM3_Strong			PMID: 33333461 observed a case where a patient was found to have this variant with the NM_001271208.1(NEB):c.21076C>T p.Arg7026* variant (ClinVar: Pathogenic/Likely Pathogenic). The same proband may also be observed in PMID: 32403337 where both variants were found along with a similar phenotype and the papers have similar authors. Internal data also found the variant in a homozygous state for a proband. Invitae reported 3 internal patients with nemaline myopathy and muscle weakness who had the variant with a second pathogenic NEB variant.
PP4			In PMID:32403337, the patient observed with the variant was noted to have nemaline bodies on muscle biopsy.
PM2_Supporting			The variant has a minor allele frequency of 0.00001, which is less than the 0.0000559 threshold set for NEB

Not Met criteria codes

BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			This variant is a missense variant
BP4			The REVEL score is 0.182, which is above the 0.15 threshold
BP3			This variant is a missense variant
BP1			Both missense and truncating variants can be pathogenic in NEB and therefore BP1 cannot be applied
BP2			

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
BS4			No segregation data available
BS3			Experimental studies were not performed
BS2			This variant was not observed in a homozygous healthy adult
PP1			No segregation data available
PP2			PP2 does not apply to NEB because missense variants are not constrained.
PP3			The REVEL score is 0.182, which is below the 0.7 threshold
PM6			No segregation data is available
PS1			No other variants are identified in the same codon
PS2			No segregation data is available
PS3			Experimental studies were not performed
PS4			No case-control studies were found and NEB is a recessive gene so PS4 cannot be applied
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			There are no hot spots or critical domains in NEB at this time
PM5			No other variants are identified in the same codon
PM4			This variant is a missense variant
PVS1			This is a missense variant

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