

Variant: NM_001164508.2(NEB):c.19097G>T (p.Ser636Ile)

Version: 1.0

CA1907773 [↗](#)

496132 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0e36a3d1-723a-4b5b-ac30-0fabfeff6e8d

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HGVS expressions

NM_001164508.2:c.19097G>T

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NC_000002.12:g.151561212C>A

CM000664.2:g.151561212C>A

NC_000002.11:g.152417726C>A

CM000664.1:g.152417726C>A

NC_000002.10:g.152125972C>A

NG_009382.2:g.178276G>T

ENST00000690043.1:c.1948G>T

ENST00000397345.8:c.19097G>T

ENST00000427231.7:c.19097G>T

ENST00000172853.14:c.13994G>T

ENST00000397345.7:c.19097G>T

ENST00000409198.5:c.13994G>T

ENST00000413693.5:c.3287G>T

ENST00000427231.6:c.19097G>T

ENST00000603639.5:c.19097G>T

ENST00000604864.5:c.19097G>T

ENST00000618972.4:c.19097G>T

NM_001164507.1:c.19097G>T

NM_001164508.1:c.19097G>T

NM_001271208.1:c.19097G>T

NM_004543.4:c.13994G>T

NM_001271208.2:c.19097G>T

NM_004543.5:c.13994G>T

NM_001164507.2:c.19097G>T

Pathogenic

Met criteria codes **4**

PM3_Very Strong PS3 PP3 PP4

Not Met criteria codes **4**

BP4 PM2 BA1 BS1

Evidence Links **0**

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

Evidence submitted by expert panel

Congenital Myopathies VCEP

The c.19097G>T (p.Ser6366Ile) variant in NEB is a missense variant predicted to cause substitution of serine by isoleucine at amino acid 6366. The highest population minor allele frequency in gnomAD v4.1.0 is 0.0004723 (30/63518 alleles) in the European (Finnish) population, which is higher than the ClinGen Congenital Myopathies VCEP threshold (MAF≥0.000237) for BS1. However, this variant is excluded from the application of BA1/BS1 by the ClinGen Congenital Myopathies VCEP as it is a well established pathogenic variant. The computational predictor REVEL gives a score of 0.829, which is above the threshold of 0.7, evidence that correlates with impact to NEB function (PP3). This variant has been detected in 10 individuals with nemaline myopathy. Eight of those individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 2 of those were confirmed in trans by family testing. Two individuals were homozygous for the variant (PMIDs: 25205138, 15336686, 17525139) (PM3_VeryStrong). At least one patient with this variant displayed nemaline rods, which is highly specific for nemaline myopathy (PP4, PMID: 17525139). A typical NM mouse model with compound heterozygous variants (p.Ser6366Ile and NebΔExon55) mimics features found in NM patients such as growth-retardation, muscle weakness, and atrophic muscles that contain nemaline rods and structural features consistent with NM. The S6366I-Homozygous model has a phenotype that develops with age and appears to share similarities with Finnish distal myopathy patients (PMID: 32483185) (PS3). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive nemaline myopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PM3_VeryStrong, PS3, PP3, PP4. (ClinGen Congenital Myopathies VCEP specifications version 1; 8/7/2024)

Met criteria codes

PM3_Very Strong			detected in 10 individuals with nemaline myopathy. Eight of those individuals were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 2 of those were confirmed in trans by family testing. Two individuals were homozygous for the variant (PMIDs: 25205138, 15336686, 17525139)
PS3			A typical NM mouse model with compound heterozygous variants (p.Ser6366Ile and NebΔExon55) mimics features found in NM patients such as growth-retardation, muscle weakness, and atrophic muscles that contain nemaline rods and structural features consistent with NM. The S6366I-Homozygous model has a phenotype that develops with age and appears to share similarities with Finnish distal myopathy patients (PMID: 32483185)
PP3			REVEL gives a score of 0.829, which is above the threshold of 0.7, evidence that correlates with impact to NEB function
PP4			At least one patient with this variant displayed nemaline rods, which is highly specific for nemaline myopathy (PMID: 17525139)

Not Met criteria codes

BP4			REVEL gives a score of 0.829, which is above the threshold of 0.7, evidence that correlates with impact to NEB function
PM2			

The gnomAD v4.1.0 highest population MAF is 0.0004723 (30/63518 alleles) in Finnish European which does not meet the threshold for PM2_P application

BA1





The gnomAD v4.1.0 highest population MAF is 0.0004723 (30/63518 alleles) in Finnish European but is excluded from the BA1/BS1 as it is a well-established pathogenic variant

BS1





The gnomAD v4.1.0 highest population MAF is 0.0004723 (30/63518 alleles) in Finnish European but is excluded from the BA1/BS1 as it is a well-established pathogenic variant

Curation History

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