

Variant: *NM_001164508.2(NEB):c.19944G>A (p.Ser6648=)*

Version: 1.0

CA1907493 [↗](#)

235402 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 78612d0a-b94c-43f5-94f6-40cb61b477a3

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HGVS expressions

NM_001164508.2(NEB):c.19944G>A (p.Ser6648=)

NM_001164508.2:c.19944G>A

NC_000002.12:g.151551738C>T

CM000664.2:g.151551738C>T

NC_000002.11:g.152408252C>T

CM000664.1:g.152408252C>T

NC_000002.10:g.152116498C>T

NG_009382.2:g.187750G>A

ENST00000434685.6:c.26+3193G>A

ENST00000690043.1:c.2795G>A

ENST00000397345.8:c.19944G>A

ENST00000427231.7:c.19944G>A

ENST00000172853.14:c.14841G>A

ENST00000397345.7:c.19944G>A

ENST00000409198.5:c.14841G>A

ENST00000413693.5:c.4134G>A

ENST00000427231.6:c.19944G>A

ENST00000603639.5:c.19944G>A

ENST00000604864.5:c.19944G>A

ENST00000618972.4:c.19944G>A

NM_001164507.1:c.19944G>A

NM_001164508.1:c.19944G>A

NM_001271208.1:c.19944G>A

NM_004543.4:c.14841G>A

NM_001271208.2:c.19944G>A

NM_004543.5:c.14841G>A

NM_001164507.2:c.19944G>A

Pathogenic

Met criteria codes 5

PS3 PM3_Strong PP1 PP3 PP4

Not Met criteria codes 21

PS1 PS2 PS4 BP5 BP7 BP4
BP3 BP1 BP2 PP2 PM6

Expert Panel

[Congenital Myopathies VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Congenital Myopathies
Expert Panel Specifications to the ACMG/AMP Variant

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001164508.2(NEB):c.19944G>A (p.Ser6648=) variant in NEB is a synonymous variant located at the intron exon boundary of exon 129. mRNA characterization of homozygous probands displayed that the variant abolishes the normal donor splice site, shifting towards the use of an alternative (cryptic) splice site in intron 129 which causes a partial intronic retention of 120bp that creates a premature stop codon and shorter polypeptide (PS3) (PMID: 26841830, PMID: 25205138). The computational splicing predictor SpliceAI gives a score of 0.77 for donor loss, predicting splice site disruption (PP3). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001659 (1/6026) alleles) in an unspecified ethnic group (no population codes met). This variant has been identified in at least 9 probands in either a homozygous state or with a second likely pathogenic, pathogenic, or rare uncertain variant (PM3_Strong) (PMID 26841830, 36233295, 25205138, 36233295, 37460656, 32222963, 36714460). At least one proband homozygous for the variant had an affected sibling also homozygous for the variant (PP1) (PMID: 37460656). Nemaline rods have been observed in at least one proband identified with the variant (PP4) (PMID: 26841830). In summary, this variant meets the criteria to be classified as pathogenic for Nemaline Myopathy for autosomal recessive inheritance based on the ACMG/AMP criteria applied as specified by the ClinGen Congenital Myopathy VCEP: (PS3, PM3_Strong, PP4, PP3, PP1); ClinGen Congenital Myopathies VCEP Specifications version 1.0.0; 5/12/2025)

Met criteria codes

PS3			Variant is located at the intron exon boundary of exon 129 in NEB, in which loss of function is a known mechanism of disease. PMID: 26841830 discusses in P3 who is homozygous for the variant had characterization of the mRNA level where the mutation abolishes the normal donor splice site, shifting towards the use of an alternative (cryptic) splice site in intron 129 which originates a premature stop codon and shorter polypeptide. The variant was also described in two families in PMID: 25205138. The outcome of the splice site change is a partial intronic retention 120bp creating a premature termination codon and a shortened nebulin protein.
PM3_Strong			Variant currently scores 2.5 points on the PM3 chart. This variant has been identified in at least 9 probands in either a homozygous state or with a second likely pathogenic, pathogenic, or rare uncertain variant (PM3_Strong) (PMID 26841830, 36233295, 25205138, 36233295, 37460656, 32222963, 36714460).
PP1			PMID: 37460656 reported the variant in an assumed homozygous state in 2 siblings. Their father was heterozygous and their mother was not tested
PP3			SpliceAI is >0.5 (0.77 for donor loss) which is above the threshold for calling PP3
PP4			PMID: 26841830 describes P3, the patient homozygous for the variant, as having rods seen in their muscle biopsy

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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PS2			Recessive condition, variants appear to be inherited
PS4			No case control studies identified.
BP5			No alternate molecular basis for disease
BP7			Splicing appears affected
BP4			Computational evidence suggests a deleterious effect on gene or gene product.
BP3			Synonymoys variant
BP1			Synonymous variant
BP2			Autosomal recessive condition without other pathogenic variants in trans
PP2			Synonymous variant
PM6			Recessive condition, variants appear to be inherited
PM2			The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001659 (1/6026) alleles) in an unspecified ethnic group, which is above the ClinGen Congenital Myopathies VCEP threshold (≤ 0.0000559) for PM2_Supporting, but lower than the ClinGen Congenital Myopathies VCEP threshold (≥ 0.000237) for BS1 therefore population criteria cannot be invoked.
PM1			No defined hot spots for NEB
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			Synonymous variant
BA1			PM2 met; Allele frequency is 0.00002820 in gnomAD, which is below the NEB threshold of 0.0000559 to invoke PM2
BS2			No homozygotes in gnomAD
BS1			PM2 met; Allele frequency is 0.00002820 in gnomAD, which is below the NEB threshold of 0.0000559 to invoke PM2
BS4			Variant appears to segregate in affected individuals
BS3			Functional studies support a damaging effect

PVS1



Functional data supporting criteria used instead of PVS1

Curation History

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