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Variant: NM_001164508.2(NEB):c.22144A>C (p.Thr7382Pro)

Version: 1.0

CA1906766

506284 (ClinVar)

Gene: NEB (HGNC:4703)
Condition: nemaline myopathy (MONDO:0018958)
Inheritance Mode: Autosomal recessive inheritance
UUID: fdc5cc5f-5822-45d1-a94c-b5e124392663
Approved on: 2024/8/7
Published on: 2024/10/1

HGVS expressions

NM_001164508.2(NEB):c.22144A>C (p.Thr7382Pro)
NM_001164508.2:c.22144A>C
NC_000002.12:g.151525975T>G
CM000664.2:g.151525975T>G
NC_000002.11:g.152382489T>G
CM000664.1:g.152382489T>G
NC_000002.10:g.152090735T>G
NG_009382.2:g.213513A>C
ENST00000434685.6:c.1605-702A>C
ENST00000690043.1:c.4995A>C
ENST00000693000.1:n.1169A>C
ENST00000693286.1:c.843A>C
ENST00000397345.8:c.22144A>C
ENST00000427231.7:c.22144A>C
ENST00000172853.14:c.17041A>C
ENST00000397345.7:c.22144A>C
ENST00000409198.5:c.17041A>C
ENST00000413693.5:c.6334A>C
ENST00000427231.6:c.22144A>C
ENST00000434685.5:c.12A>C
ENST00000603639.5:c.22144A>C
ENST00000604864.5:c.22144A>C
ENST00000618972.4:c.22249A>C
NM_001164507.1:c.22144A>C
NM_001164508.1:c.22144A>C
NM_001271208.1:c.22249A>C
NM_004543.4:c.17041A>C
NM_001271208.2:c.22249A>C
NM_004543.5:c.17041A>C
NM_001164507.2:c.22144A>C

Pathogenic

Met criteria codes 3

PP4 PM3_Strong PP1_Strong

Not Met criteria codes 6

PS3 PP3 PM2 BA1 BS1 BP4

Evidence Links 1

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**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The c.22144A>C p.(Thr7382Pro) variant in NEB is a missense variant predicted to cause substitution of Threonine by Proline at amino acid 7382. The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001406 (9/64028 alleles) in the Finnish population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a SCORE of 0.286 which is neither above nor below the thresholds predicting a damaging or benign impact on NEB function. This variant has been detected in 4 individuals with typical nemaline myopathy. Two of those individuals were compound heterozygous with an LP/P variant, phase confirmed and two were homozygous (PMID:16917880, 17525139) (PM3_Strong). At least two individuals with this variant displayed nemaline bodies (confirmed by electron microscopy), which is highly specific for nemaline myopathy (PP4, PMID:17525139). The variant has been reported to segregate with nemaline myopathy in 3 individuals with biallelic occurrence and 5 unaffected family members did not have biallelic occurrence in 2 families (PP1_Strong; PMID:17525139). Binding experiments for the nebulin super repeats, using co-sedimentation and GST (glutathione-S-transferase) pull-down assays (PMID: 25110572) showed weaker binding than WT proteins to tropomyosin. However, this assay does not meet the requirements for use by the ClinGen Congenital Myopathies VCEP. 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_Strong, PP1_Strong, PP4. (Congenital Myopathies VCEP specifications version 1; 8/7/2024)

Met criteria codes

PP4	✔	At least two individuals with this variant displayed nemaline bodies (confirmed by electron microscopy), which is highly specific for nemaline myopathy (PMID:17525139)
PM3_Strong	✔	This variant has been detected in 4 individuals with typical nemaline myopathy. Two of those individuals were compound heterozygous with an LP/P variant, phase confirmed and two were homozygous (PMID: 16917880, 17525139)
PP1_Strong	✔	The variant has been reported to segregate with nemaline myopathy in 3 individuals with biallelic occurrence and 5 unaffected family members did not have biallelic occurrence in 2 families.

Not Met criteria codes

PS3	✖	Binding experiments for the nebulin super repeats, using co-sedimentation and GST (glutathione-S-transferase) pull-down assays (PMID: 25110572) showed weaker binding than WT proteins to tropomyosin. However, this assay does not meet the requirements for use by the ClinGen Congenital Myopathies VCEP.

Binding experiments for the nebulin super repeats, using co-sedimentation and GST (glutathione-S-transferase) pull-down assays (PMID: 25110572) showed weaker binding than WT proteins to tropomyosin. However, this assay does not meet the requirements for use by the ClinGen Congenital Myopathies VCEP. PubMed:25110572

PP3	ℹ	✖	The computational predictor REVEL gives a SCORE of 0.286 which is neither above nor below the thresholds predicting a damaging or benign impact on NEB function).
PM2		✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001406 (9/64028 alleles) in the Finnish population. PM2_Supporting, BS1, and BA1 are not met.
BA1	ℹ	✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001406 (9/64028 alleles) in the Finnish population. PM2_Supporting, BS1, and BA1 are not met.
BS1	ℹ	✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001406 (9/64028 alleles) in the Finnish population. PM2_Supporting, BS1, and BA1 are not met.
BP4	ℹ	✖	The computational predictor REVEL gives a SCORE of 0.286 which is neither above nor below the thresholds predicting a damaging or benign impact on NEB function).

Curation History

Showing 1 to 1 of 1 rows

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