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29498452[uid]

Format: Abstract

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Eur J Neurol. 2018 Jun;25(6):841-847. doi: 10.1111/ene.13607. Epub 2018 Mar 26.



Ryanodine receptor type 3 (RYR3) as a novel gene associated with a myopathy with nemaline bodies.

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Abstract

BACKGROUND AND PURPOSE: Nemaline myopathy (NEM) has been associated with mutations in 12 genes to date. However, for some patients diagnosed with NEM, definitive mutations are not identified in the known genes, suggesting that there are other genes involved. This study describes compound heterozygosity for rare variants in ryanodine receptor type 3 (RYR3) gene in one such patient.

METHODS AND RESULTS: Clinical examination of the patient at 22 years of age revealed a long narrow face, high arched palate and bilateral facial weakness. She had proximal weakness in all four limbs, mild scapular winging but no scoliosis. Muscle biopsy revealed wide variation in fibre size with type 1 fibre predominance and atrophy. Abundant nemaline bodies were located in perinuclear and subsarcolemmal areas, and within the cytoplasm. No likely pathogenic mutations in known NEM genes were identified. Copy number variation in known NEM genes was excluded by NEM-targeted comparative genomic hybridization array. Next-generation sequencing revealed compound heterozygous missense variants in the RYR3 gene. RYR3 transcripts are expressed in human fetal and adult skeletal muscle as well as in human brain and cauda equina samples. Immunofluorescence of human skeletal muscle revealed a 'single-row' appearance of RYR3, interspersed between the 'double rows' of ryanodine receptor type 1 (RYR1) at each A-I junction.

CONCLUSION: The results suggest that variants in RYR3 may cause a recessive muscle disease with pathological features including nemaline bodies. We characterize the expression pattern of RYR3 in human skeletal muscle and brain, and the subcellular localization of RYR1 and RYR3 in human skeletal muscle.

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KEYWORDS: RYR3; intracellular Ca²⁺ channels; nemaline myopathy; ryanodine receptors

PMID: **29498452** DOI: [10.1111/ene.13607](https://doi.org/10.1111/ene.13607)

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Publication types, MeSH terms, Substance

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