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**Format:** Abstract**Full text links**Neuromuscul Disord. 2018 May;28(5):422-426. doi: 10.1016/j.nmd.2018.02.011. Epub 2018 Feb 26.

Parental mosaicism in RYR1-related Central Core Disease.

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Abstract

Myopathies due to mutations in the skeletal muscle ryanodine receptor (RYR1) gene are amongst the most common non-dystrophic neuromuscular disorders and have been associated with both dominant and recessive inheritance. Several cases with apparently de novo dominant inheritance have been reported. Here we report two siblings with features of Central Core Disease (CCD) born to unaffected parents. Genetic testing revealed a heterozygous dominant RYR1 c.14582G>A (p. Arg4861His) mutation previously identified in other CCD pedigrees. The variant was absent in blood from the asymptomatic mother but detected at low but variable levels in blood- and saliva-derived DNA from the unaffected father, suggesting that this mutation has arisen as a paternal post-zygotic de novo event. These findings suggest that parental mosaicism should be considered in RYR1-related myopathies, and may provide one possible explanation for the marked intergenerational variability seen in some RYR1 pedigrees.

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KEYWORDS: Central Core Disease (CCD); Mosaicism; Skeletal muscle ryanodine receptor (RYR1) gene

PMID: 29576327 DOI: [10.1016/j.nmd.2018.02.011](https://doi.org/10.1016/j.nmd.2018.02.011)

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