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Poster P7

CGG repeat expansions in Charcot-Marie-Tooth disease: insights from the 100 000 Genomes Project

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Background: CGG expansions in NOTCH2NLC and LRP12 were recently identified as a cause of Charcot-Marie-Tooth disease (CMT) in 1.2%-10.6% of genetically undiagnosed patients in China, Taiwan and Japan. However, their relevance in CMT patients of different ethnic origin is still unknown.

Methods: Here, we leveraged short-read whole genome sequencing data from the 100 000 Genomes Project to investigate the presence and frequency of CGG expansions in NOTCH2NLC, LRP12 and additional genes associated with oculopharyngodistal myopathy (OPDM), in 560 genetically unsolved patients diagnosed with CMT and 32 509 non-neurological controls.

Results: Repeat expansions in NOTCH2NLC, LRP12, RILPL1, NUTM2B-AS1 and ABCD3 were absent from 560 genetically unsolved patients with CMT, mostly of Northern European ancestry. One patient of African ancestry carried an expanded allele in GIPC1, below the reported pathogenic threshold. However, rare expansions in this gene, as well as in NOTCH2NLC, NUTM2B-AS1 and ABCD3, were also detected in controls (≤0.05%). The distribution of repeat size at these loci varied significantly across different ethnicities, with larger non-pathogenic intermediate alleles of NOTCH2NLC and LRP12 typically observed in East Asians.

Conclusions: CGG expansions in NOTCH2NLC, LRP12 and other OPDM-associated genes do not appear to be a relevant cause of CMT in the UK. The larger size of non-pathogenic intermediate alleles of NOTCH2NLC and LRP12 in East Asians could explain their ancestry-specific propensity to further expand into the full pathogenic range.