100,000 Genomes Project

The 100,000 Genomes Project is a UK Government project that is sequencing whole genomes from National Health Service patients. The project is focusing on rare diseases, some common types of cancer, and infectious diseases.

NOTCH2NLC is 1 of 3 nearly identical, functional human NOTCH2 (600275)-like genes on chromosome 1q21.1 The NOTCH2L proteins appear to regulate Notch signaling pathway and promote cortical neurogenesis.

The objective of Yau et al. in a study was to determine the prevalence of the GGC-repeat expansion in NOTCH2NLC in whites presenting with movement disorders.

They searched for the GGC-repeat expansion in NOTCH2NLC using repeat-primed polymerase chain reaction in 203 patients with essential tremor, 825 patients with PD, 194 patients with spinocerebellar ataxia, 207 patients with “possible” or “probable” MSA, and 336 patients with pathologically confirmed MSA. They also screened 30,008 patients enrolled in the 100,000 Genomes Project for the same mutation using ExpansionHunter, followed by a repeat-primed polymerase chain reaction. All possible expansions were confirmed by Southern blotting and/or long-read sequencing.

They identified 1 patient who carried the NOTCH2NLC mutation in the essential tremor cohort, and 1 patient presenting with recurrent encephalopathy and postural tremor/parkinsonism in the 100,000 Genomes Project.

GGC-repeat expansion in NOTCH2NLC is rare in whites presenting with movement disorders. In addition, existing whole-genome sequencing data are useful in case ascertainment [1].

Neuronal intranuclear inclusion disease (NIID) is a clinically heterogeneous neurodegenerative condition characterized by pathological intranuclear eosinophilic inclusions. A CGG repeat expansion in NOTCH2NLC was recently identified to be associated with NIID in patients of Japanese descent. We screened pathologically confirmed European NIID, cases of neurodegenerative disease with intranuclear inclusions and applied in silico-based screening using whole-genome sequencing data from 20 536 participants in the 100 000 Genomes Project. We identified a single European case harbouring the pathogenic repeat expansion with a distinct haplotype structure. Thus, we propose new diagnostic criteria as European NIID represents a distinct disease entity from East Asian cases [2].

1)
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2)
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