Abstracts

Articles appearing in the June 2018 issue

Absence of NEFL in patient-specific neurons in early-onset Charcot-Marie-Tooth neuropathy

Objective We used patient-specific neuronal cultures to characterize the molecular genetic mechanism of recessive nonsense mutations in neurofilament light (*NEFL*) underlying early-onset Charcot-Marie-Tooth (CMT) disease.

Methods Motor neurons were differentiated from induced pluripotent stem cells of a patient with early-onset CMT carrying a novel homozygous nonsense mutation in *NEFL*. Quantitative PCR, protein analytics, immunocytochemistry, electron microscopy, and single-cell transcriptomics were used to investigate patient and control neurons.

Results We show that the recessive nonsense mutation causes a nearly total loss of *NEFL* messenger RNA (mRNA), leading to the absence of NEFL protein in patient's cultured neurons. Yet the cultured neurons were able to differentiate and form neuronal networks and neurofilaments. Single-neuron gene expression fingerprinting pinpointed *NEFL* as the most downregulated gene in the patient neurons and provided data of intermediate filament transcript abundance and dynamics in cultured neurons. Blocking of nonsense-mediated decay partially rescued the loss of *NEFL* mRNA.

Conclusions The strict neuronal specificity of neurofilament has hindered the mechanistic studies of recessive *NEFL* nonsense mutations. Here, we show that such mutation leads to the absence of NEFL, causing childhood-onset neuropathy through a loss-of-function mechanism. We propose that the neurofilament accumulation, a common feature of many neurodegenerative diseases, mimics the absence of NEFL seen in recessive CMT if aggregation prevents the proper localization of wild-type NEFL in neurons. Our results suggest that the removal of NEFL as a proposed treatment option is harmful in humans.

[NPub.org/NG/9109a](https://pubmed.ncbi.nlm.nih.gov/30109910/)

Determining the incidence of familiarity in ALS: A study of temporal trends in Ireland from 1994 to 2016

Objective To assess temporal trends in familial amyotrophic lateral sclerosis (FALS) incidence rates in an Irish population and to determine factors influencing FALS ascertainment.

Methods Population-based data collected over 23 years, using the Irish amyotrophic lateral sclerosis (ALS) register and DNA biobank, were analyzed and age-standardized rates of FALS and associated familial neuropsychiatric endophenotypes were identified.

Results Between 1994 and 2016, 269 patients with a family history of ALS from 197 unique families were included on the register. Using stringent diagnostic criteria for FALS, the mean age-standardized FALS incidence rate for the study period was 11.1% (95% confidence interval [CI] 8.8–13.4). The FALS incidence rate increased steadily from 5.2% in 1994 to 19.1% in 2016, an annual increase of 0.7% (95% CI 0.5–0.9, $p < 0.0001$). Inclusion of the presence of neuropsychiatric endophenotypes within kindreds increased the FALS incidence rate to 30%. The incidence of FALS in newly diagnosed individuals from known families increased significantly with time, accounting for 50% of all FALS diagnoses by 2016. The mean annual rate of recategorization from sporadic ALS to FALS was 3% (95% CI 2.6–3.8).

Conclusions The true population-based rate of FALS is at least 20%. Inclusion of extended endophenotypes within kindreds increases the rate of FALS to 30%. Cross-sectional analysis of clinic-based cohorts and stringent definitions of FALS underestimate the true rate of familial disease. This has implications for genetic counseling and in the recognition of presymptomatic stages of ALS.

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