

## Prevalence and Characterization of *NOTCH2NLC* GGC Repeat Expansions in Koreans: From a Hospital Cohort Analysis to a Population-Wide Study

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GGC repeat expansions in the *NOTCH2NLC* gene are associated with a broad spectrum of progressive neurological disorders, notably neuronal intranuclear inclusion disease (NIID). However, the population-wide prevalence and clinical manifestations have yet to be fully characterized. We conducted a study using two different cohorts from the Korean population. Patients with available brain MRI scans from Seoul National University Hospital (SNUH) were thoroughly reviewed, and NIID-suspected patients presenting the zigzag edging signs underwent genetic evaluation for *NOTCH2NLC* repeats by Cas9-mediated nanopore sequencing. Additionally, we analyzed whole genome sequencing data from 3,887 individuals in the Korea Biobank cohort to estimate the distribution of the repeat counts in Koreans and to identify putative patients with expanded alleles and neurological phenotypes. In the SNUH cohort, among 90 adult-onset leukoencephalopathy patients with unknown etiologies, we found 20 patients with zigzag edging signs. Except for two

diagnosed with fragile X-associated tremor/ataxia syndrome and two for whom samples were unavailable, all 16 patients (17.8%) were diagnosed with NIID (repeat range: 87–217). By analyzing the Korea Biobank cohort, we estimated the distribution of repeat counts and threshold (>64) for Korean, identifying six potential NIID patients. Furthermore, long-read sequencing enabled the elucidation of transmission and epigenetic patterns of NOTCH2NLC repeats within a family affected by pediatric-onset NIID. This study presents the population-wide distribution of *NOTCH2NLC* repeats and the estimated prevalence of NIID in Koreans, providing valuable insights into the association between repeat counts and disease manifestations in diverse neurological disorders.