Results: Among 3,001 individuals, 39 (1.3%) carried pathogenic or likely pathogenic *NOTCH3* variants. The mean age of carriers was 53.9 ± 15.3 years, and 33.3% were male, with no significant differences compared with non-carriers. Genotype distribution was dominated by the p.Arg544Cys variant (87.2%), followed by p.Arg578Cys (5.1%), p.Arg75Pro (5.1%), and p.Arg640Cys (2.6%), consistent with a strong regional founder effect. Only one carrier reported a prior history of stroke, with no significant difference compared with non-carriers (2.6% vs. 0.8%, p=0.289).

Conclusions: In this population-based cohort, pathogenic *NOTCH3* variants were identified in more than 1% of individuals, whereas the observed burden of clinical stroke was remarkably low. These findings suggest substantial age-dependent penetrance and highlight the need for long-term follow-up to clarify lifetime stroke risk and modifying vascular factors among *NOTCH3* variant carriers detected through population-based genomic screening.

Conflict of interest: Jay Chol Choi: nothing to disclose. Hyeon Ju Kim: nothing to disclose. JeHoon Jun: nothing to disclose. Sungwoong Jho: nothing to disclose.

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HIGH PREVALENCE BUT LOW STROKE BURDEN AMONG PATHOGENIC NOTCH3 VARIANT CARRIERS IN A POPULATION-BASED GENOMIC SCREENING COHORT

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Background and aims: The Jeju Genome Project (JGP) is a population-based genomic initiative integrating whole-genome sequencing with clinical data from community-dwelling adults in Jeju, South Korea. We aimed to investigate the prevalence, genotype distribution, and stroke burden associated with pathogenic *NOTCH3* variants in a community-based genomic cohort.

Methods: Of 5,309 JGP participants, 3,001 apparently healthy community-dwelling adults were included. Whole-genome sequencing was performed using standard high-throughput platforms with a mean depth of 36.5×. Pathogenic and likely pathogenic *NOTCH3* variants were identified based on ClinVar annotations. Demographic characteristics, vascular risk factors, family history of stroke, and self-reported stroke history were compared between variant carriers and non-carriers.