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RESEARCH ARTICLE

Screening GGC repeat expansion in the *NOTCH2NLC* in early-onset dementia: The Longitudinal Study of Early Onset Dementia and Family Members (LEAF) Study

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Abstract

BACKGROUND: Neuronal intranuclear inclusion disease (NIID) is neurodegenerative disorder caused by GGC repeat expansion in *NOTCH2NLC*. Given its frequency in young East Asian adults and overlap with cognitive impairment in young adults, a key feature of early-onset dementia (EOD), we screened *NOTCH2NLC* GGC repeat expansions in Korean patients with EOD.

METHODS: We screened *NOTCH2NLC* GGC repeat expansions in 410 Korean patients with EOD using repeat-primed and amplicon length polymerase chain reaction. Plasma biomarkers in adult-onset leukodystrophy were additionally measured using Simoa-based ultrasensitive immunoassays.

RESULTS: GGC repeat expansions were not identified in early-onset Alzheimer's disease (AD) or frontotemporal dementia (FTD), while four of eleven patients with adult-onset leukodystrophy (36.3%) had abnormal expansions. Plasma neurofilament light chain (NfL) level was lower in NIID than in colony-stimulating factor 1 receptor–related disorder.

DISCUSSION: These findings support recent arguments that the concept of *NOTCH2NLC*-related GGC repeat expansion disorder (NRED) should be reconsidered. Plasma NfL may be useful in differential diagnosis of adult-onset leukodystrophy.

KEYWORDS
early-onset dementia, leukodystrophy, neuronal intranuclear inclusion disease, *NOTCH2NLC* GGC repeat expansion, *NOTCH2NLC*-related GGC repeat expansion disorder

Seung-yeon Lee, Takeshi Mizuguchi and Hee Jin Kim contributed equally as first authors.

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Highlights

- We screened 410 Korean patients with early-onset dementia for *NOTCH2NLC* GGC expansions.
- Among 11 patients with leukodystrophy, 4 were clinically suspected of having neuronal intranuclear inclusion disease (NIID) and were confirmed to carry GGC repeat expansions, whereas no expansions were identified in patients with early-onset Alzheimer's disease or frontotemporal dementia.
- Findings align with a recent study raising the need to reconsider the *NOTCH2NLC*-related GGC repeat expansion disorder concept.
- Plasma neurofilament light chain and glial fibrillary acidic protein levels were lower in NIID than in colony-stimulating factor 1 receptor–related disorder.

1 | BACKGROUND

Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disorder characterized by the presence of eosinophilic intranuclear inclusions in various cell types.[1] The genetic cause of NIID is an abnormal expansion of GGC repeats in the *NOTCH2NLC* gene, translated into a toxic polyglycine protein that forms intranuclear inclusions, with expansions of > 60 repeats being a key pathogenetic hallmark.[2–4] NIID is an early-onset disease that typically manifests before the age of 60 years, with onset varying based on the dominant phenotype or ethnicity.[5,6] NIID is associated with a wide range of symptoms, including cognitive impairment, episodic neurogenic events, movement symptoms, and neuromuscular symptoms[7] accompanied by distinct brain magnetic resonance imaging (MRI) findings, such as corticomedullary junction (CMJ) hyperintensity on diffusion-weighted imaging (DWI) or paravermal high signals on fluid-attenuated inversion recovery (FLAIR).[8]

Owing to the overlapping symptoms of NIID with those of other neurological disorders, numerous studies have been conducted to screen for GGC repeat expansions in the *NOTCH2NLC* gene across various disease cohorts (Table 1), in addition to inherited peripheral neuropathy,[9] and adult-onset leukoencephalopathy.[10–13] Using repeat primed polymerase chain reaction (RP-PCR) and fluorescence amplicon length analysis PCR (AL-PCR), GGC expansions were identified in patients with Parkinson's disease,[14–16] essential tremor,[17–19] Alzheimer's disease (AD),[15,20] frontotemporal dementia (FTD),[20] amyotrophic lateral sclerosis (ALS),[21,22] cerebral small vessel disease,[23] and Charcot–Marie–Tooth disease.[24] Based on these findings, a new concept called *NOTCH2NLC*-related GGC repeat expansion disorder (NRED) was proposed to encompass diverse diseases associated with the GGC repeat expansion of *NOTCH2NLC*.[5,25] However, there has been controversy regarding NRED. In other words, there is disagreement regarding whether *NOTCH2NLC* GGC repeat expansion can be seen a genetic cause of various neurodegenerative diseases.[5,6]

Early-onset dementia (EOD) occurring before the age of 65 can manifest in various clinical phenotypes, including AD dementia (ADD), FTD, and other neurodegenerative dementias.[26] Although NIID is relatively prevalent among young East Asian adults and cognitive impairment or dementia is a major clinical symptom,[6,8,27,28] there have been no reports investigating NRED in EOD cohorts. Therefore, this study aimed to determine the frequency of NRED by screening *NOTCH2NLC* GGC repeat expansions in the Longitudinal Study of Early Onset Dementia and Family Members (LEAF), a Korean EOD cohort. To further identify potential biomarkers that might differentiate NIID from adult-onset leukodystrophies, we investigated whether neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), amyloid beta (Aβ)42/Aβ40, and phosphorylated tau (p-tau)181 levels differed between patients with adult-onset leukodystrophy with and without *NOTCH2NLC* GGC repeat expansion.

2 | METHODS

2.1 | Participants

We conducted a genetic analysis of patients recruited through LEAF, a nationwide Korean EOD cohort.[29] A total of 410 patients were enrolled from 31 centers across Korea from 2021 to 2023. Patients were categorized into three groups: LEAF-AD (n = 258), LEAF-FTD (n = 86), and EOD due to various other causes (LEAF-Other, n = 66).

LEAF-AD included patients within the early-onset AD (EOAD) continuum who were Aβ-positive (Aβ+) AD dementia,[30] mild cognitive impairment (MCI),[31] and subjective cognitive decline (SCD),[32] following established diagnostic criteria.[30–32] Patients were clinically diagnosed when they showed progressive cognitive decline with onset before 65 years of age. The diagnosis and cognitive level were determined based on clinical history, neurological examination, and comprehensive neuropsychological assessment such as Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) and Seoul Neuropsychological Screening Battery (SNSB).[33,34] The Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) were

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RESEARCH IN CONTEXT

1. **Systematic Review**: GGC repeat expansion in *NOTCH2NLC* has been identified in various neurodegenerative diseases, leading to the proposal of the concept of *NOTCH2NLC*-related GGC repeat expansion disorder (NRED). Because no investigation of NRED has been conducted in patients with early-onset dementia (EOD), this study is the first to investigate NRED in a Korean EOD cohort, in which participants were classified based on strictly applied clinical diagnostic criteria. Additionally, plasma biomarker profiles were examined among patients with adult-onset leukodystrophy.
2. **Interpretation**: GGC repeat expansion in the *NOTCH2NLC* gene were not detected in major EOD subtypes such as early-onset Alzheimer's disease and frontotemporal dementia but were observed exclusively in four adult-onset leukodystrophy patients who were clinically suspected of having neuronal intranuclear inclusion disease. These findings may support a recent study that have raised questions about the validity of the NRED concept. Plasma neurofilament light chain and glial fibrillary acidic protein are expected to be useful for the differential diagnosis of adult-onset leukodystrophy including NIID.
3. **Future Directions**: Larger studies are needed to clarify the association between *NOTCH2NLC* expansion and EOD, which may help refine the NRED concept. Concurrently, larger plasma biomarker studies are required to identify potential disease-specific biomarkers for adult-onset leukodystrophies.

used as global cognitive measures. Brain MRI was reviewed for atrophy pattern consistent with AD and to exclude alternative diagnoses, such as vascular brain injuries or conditions associated with severe white matter hyperintensities. Amyloid positivity was then confirmed by cerebrospinal fluid (CSF) analysis or amyloid positron emission tomography (PET).

The LEAF-FTD group included patients with behavioral variant FTD (bvFTD),[35] semantic variant primary progressive aphasia (svPPA),[36] non-fluent/agrammatic variant primary progressive aphasia (nfvPPA),[36] FTD-motor neuron disease (FTD-MND),[37] corticobasal syndrome (CBS),[38] and progressive supranuclear palsy syndrome (PSPS).[39] The diagnosis was determined based on clinical history, neurological examination, and comprehensive neuropsychological assessment using the SNSB.[34] Brain MRI was reviewed for atrophy pattern consistent with FTD and excluding alternative diagnosis. Participants were enrolled regardless of age at onset if they met the respective clinical diagnostic criteria.[35–39]

The LEAF-Other group was divided into three categories. LEAF-Other I (n = 11) included adult-onset leukodystrophy, of which the diagnosis was based on severe confluent white matter hyperintensity unexplained by vascular risk factor with no lacunes on brain MRI. LEAF-Other II (n = 45) included neurodegenerative dementias other than EOAD or FTD such as vascular dementia, dementia with Lewy bodies, and amyloid-negative neurodegenerative EOD initially suspected to be EOAD. The remaining EOD with unclear or atypical etiologies was in LEAF-Other III (n = 10). This group included patients with alternative neurodegenerative dementias, amyloid-negative early-onset dementia initially suspected to be EOD, and other EODs with unclear or atypical etiologies, with symptom onset before 65 years of age.

The diagnosis for each participant was initially determined by an experienced neurologist specializing in dementia at each referral center and subsequently reviewed by six dementia expert neurologists during a consensus meeting of the LEAF committee (Supplementary Appendix in supporting information). The overall information and detailed demographics of the participants are presented in Table 2. This study was approved by the institutional review board at each center, and all participants provided written informed consent.

2.2 | *NOTCH2NLC* GGC repeats expansion screening

To identify GGC repeat expansions in *NOTCH2NLC*, RP-PCR and AL-PCR were performed using genomic DNA (gDNA) extracted from peripheral blood samples. gDNA was collected from each participant and subsequently analyzed at Yokohama City University, Japan. The PCR reaction mix for both methods included 1× PrimeSTAR GXL Buffer (Takara); 0.25 U PrimeSTAR GXL DNA Polymerase (Takara); 200 μM each of dATP, dTTP, and dCTP (Takara); 7-deaza-2′-deoxy-guanosine-5′-triphosphate (Sigma-Aldrich); 5% dimethyl sulfoxide (Sigma-Aldrich); 1 M betaine (Sigma-Aldrich); and the respective primers, with a total reaction volume of 10 μL. Electrophoresis was conducted using a 3500xl Genetic Analyzer (Thermo Fisher Scientific). Data were analyzed using GeneMapper software.[2]

For RP-PCR, 100 ng of gDNA was used as the template, and the primer mix comprised NOTCH2NLC-RP-F (5′-FAM-GGCATTTGCGCCTGTGCTTCGGACCGT-3′), M13-(GGC)4(GGA)2-R (5′-CAGGAAACAGCTATGACCTCCTCCGCCGCCGCCGCC-3′), M13-linker-R (5′-CAGGAAACAGCTATGACC-3′). For AL-PCR, 50 ng of gDNA was used, and the primer pair consisted of: NOTCH2NLC-AL-F (5′-VIC-CATTTGCGCCTGTGCTTCGGAC-3′), NOTCH2NLC-AL-R (5′-AGAGCGGCGCAGGGCGGGCATCTT-3′).

The thermal cycling conditions were identical for both methods except for the elongation time. For RP-PCR, elongation was performed at 68°C for 8 minutes, whereas for AL-PCR, elongation was reduced to 4 minutes. The ramp rate was set to 0.5°C per second for RP-PCR and to the default setting of the T100 thermal cycler (Bio-Rad) for AL-PCR.

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TABLE 1 Screening GGC repeats expansion in *NOTCH2NLC*.

Cohort disease	Prevalence of GGC repeats expansion	Nation	Genetic analysis	References
Inherited peripheral neuropathy	26/1783 (1.5%)	Japan	RP-PCR, AL-PCR	9
Adult-onset non-vascular leukoencephalopathy	0/52 (0.0%)	Europe	RP-PCR, whole-exome sequencing	10
	34/161 (21.12%)	Taiwan	RP-PCR, AL-PCR	11
	16/90 (17.8%)	Korea	Cas9-mediated nanopore sequencing, RP-PCR	12
	12/93 (12.9%)	Japan	RP-PCR, AL-PCR	13
Parkinson's disease	13/1000 (1.3%)	Singapore	Long-read sequencing, RP-PCR	14
	3/ 205 (1.5%)	China	Long-read sequencing, RP-PCR	15
	11/1011 (1.1%)	China	RP-PCR, AL-PCR	16
Essential tremor	10/602 (1.66%)	China	RP-PCR	17
	27/197 (13.7%)	China	Long-read sequencing, RP-PCR	18
	0/204 (0.0%)	Europe	Whole genome sequencing	19
AD	2/140 (1.4%)	China	Long-read sequencing, RP-PCR	15
	3/861 (0.4%)	China	RP-PCR	20
FTD	1/57 (1.8%)	China	RP-PCR	20
ALS	0/304 (0.0%)	Taiwan	RP-PCR, AL-PCR	21
	4/545 (0.7%)	China	RP-PCR	22
Cerebral small vessel disease	9/814 (1.11%)	China	RP-PCR, AL-PCR, whole-exome sequencing	23
Charcot–Marie–Tooth disease	7/66 (10.6%)	Taiwan	RP-PCR	24

Abbreviations: AD, Alzheimer's disease; AL-PCR, fluorescent amplicon length polymerase chain reaction; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; RP-PCR, repeat-primed polymerase chain reaction.

TABLE 2 Demographic table of study participants.

	Total ($n = 410$)	LEAF-AD ($n = 258$)	LEAF-FTD ($n = 86$)	LEAF-other ($n = 66$)
Age of onset, mean (± SD), years	56.8 (7.0)	56.5 (5.2)	60.5 (7.2)	52.4 (9.8)
Sex, *n*				
Male	158 (38.5%)	85 (32.9%)	33 (38.0%)	40 (60.6%)
Female	252 (61.5%)	173 (67.1%)	53 (61.6%)	26 (39.4%)
MMSE, mean (± SD)	19.0 (7.4)	18.5 (6.7)	17.6 (8.6)	23.3 (6.4)
CDR-SB, mean (± SD)	$n = 408$	$n = 257$	$n = 85$	$n = 66$
	6.1 (5.0)	6.1 (4.7)	6.7 (5.5)	4.7 (5.1)

Abbreviations: CDR-SB, Clinical Dementia Rating Sum of Boxes; EOAD, early-onset Alzheimer's disease; EOD, early-onset dementia; FTD, frontotemporal dementia; LEAF, Longitudinal Study of Early Onset Dementia and Family Members; MMSE, Mini-Mental State Examination; SD, standard deviation.

2.3 | Plasma biomarker analysis

Plasma p-tau181 and NfL levels were measured using the Simoa Human p-Tau181 Advantage V2 assay (Quanterix, PN/104111) and NF-Light Advantage assay (Quanterix, PN/103186) in Hanyang University College of Medicine and Bredis Healthcare Inc. (Seoul, South Korea). For a typical run setup, each sample and control were transferred into 96-well Quanterix plates for duplicate tests with an onboard 4× dilution by the instrument. The assay was performed using a Simoa HD-X Analyzer (Quanterix) in a two-step immunoassay. Plasma samples were subjected to a single thawing and refreezing cycle before analyzing p-tau181 and NfL.

Plasma GFAP levels and Aβ42/Aβ40 ratios were measured at the Department of Psychiatry and Neurochemistry, University of Gothenburg, using Simoa-based methods and the Neurology 4-Plex E kit (Quanterix). These measurements followed

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previously established protocols used in prior studies from the same institution.[40,41]

2.4 | Statistical analysis

Statistical analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing). Analysis of covariance (ANCOVA) was performed to adjust for age and sex, and post hoc pairwise comparisons were conducted using the Tukey honestly significant difference test via the emmeans package. Graphs were generated using GraphPad Prism version 10.2.0 (GraphPad Software; https://www.graphpad.com/). Statistical significance was assigned as $P < 0.05$.

3 | RESULT

3.1 | Detection of the GGC repeat expansion in *NOTCH2NLC*

We identified *NOTCH2NLC* GGC repeat expansions in four patients with adult-onset leukodystrophy, representing 36.3% of the LEAF-Other I of adult-onset leukodystrophy subcohort (4/11) and 1.0% of the overall LEAF cohort (4/410; Figure 1). Four patients with *NOTCH2NLC* GGC repeat expansion were clinically suspected of having NIID before gene confirmation, three of whom have been previously reported.[42–44] The remaining seven patients with adult-onset leukodystrophy consisted of four with colony-stimulating factor 1 receptor (*CSF1R*)-related disorder (*CSF1R*-RD), also known as adult-onset leukoencephalopathy with spheroids and pigmented glia (ALSP), one with variant of uncertain significance (VUS; c.1069A > T) in *CSF1R* gene, one with cerebrotendinous xanthomatosis (CTX),[45] and two family members with familial Korean dementia, both carrying a c.800G > C VUS in the integral membrane protein 2B (*ITM2B*) gene[46] (Table 3).

There were no patients with *NOTCH2NLC* GGC repeat expansion in LEAF-AD, LEAF-FTD, or LEAF-Other II or III.

3.2 | Description of the cases with the *NOTCH2NLC* GGC repeat expansion

The main characteristics of the four patients with *NOTCH2NLC* GGC repeat expansion are shown in Table 3.

The first case, in his early 40s, had episodic visual disturbances and vomiting since his mid-30s; later this was accompanied by confusion. Brain MRI revealed CMJ lesions on DWI and FLAIR (Figure 1). The patient's brother developed similar symptoms in his late 20s and died in his late 30s. Skin biopsy followed by ubiquitin immunohistochemi-

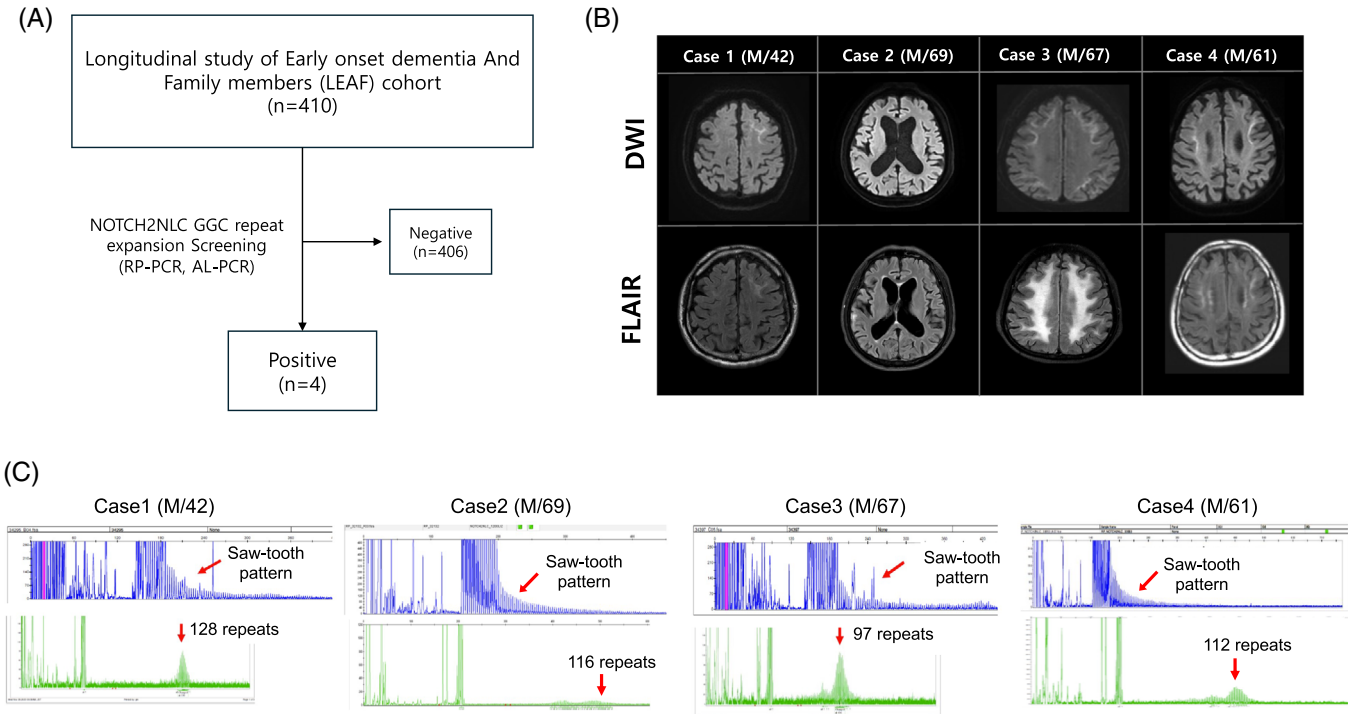


FIGURE 1 *NOTCH2NLC GGC* repeat expansions in the LEAF cohort using RP-PCR and AL-PCR. A, Study cohorts and overall workflow. Four patients (1.0% of the total EOD cohort and 36.3% of the adult-onset leukodystrophy subgroup) showed GGC repeat expansion. B, Representative brain MRI images showing CMJ abnormalities in four genetically confirmed NIID cases. C, Results of RP-PCR analysis showing a characteristic saw-tooth pattern in the electropherogram, and AL-PCR analysis showing the *NOTCH2NLC* GGC repeat sizes ranging from 97 to 128. AL-PCR, fluorescent amplicon length polymerase chain reaction; CMJ, corticomedullary junction; DWI, diffusion-weighted imaging; EOD, early-onset dementia; FLAIR, fluid-attenuated inversion recovery; LEAF, Longitudinal Study of Early Onset Dementia and Family Members; MRI, magnetic resonance imaging; NIID, neuronal intranuclear inclusion disease; RP-PCR, repeat-primed polymerase chain reaction.

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TABLE 3 Clinical and genetic features of the 11 cases with adult-onset leukodystrophy.

Case no.	Sex	Age at diagnosis	Onset age	Diagnosis	Gene mutation		Family history of leukodystrophy	Main clinical symptoms	MMSE	Ref.
					Gene	GGC repeat number or variant				
1	M	Early 40s	Early 30s	NIID	*NOTCH2NLC*	128 GGC repeats	+	Recurrent episodic event Nausea/vomiting, confusion Visual disturbance	28	35
2	M	Late 60s	Late 50s	NIID	*NOTCH2NLC*	116 GGC repeats	+	Recurrent episodic event Headache, Visual field defect Confusion, seizure	21	36
3	M	Late 60s	Late 50s	NIID	*NOTCH2NLC*	97 GGC repeats	–	Progressive memory decline Tremor, Peripheral neuropathy	24	–
4	M	Early 60s	Mid 50s	NIID	*NOTCH2NLC*	112 GGC repeats	+	Recurrent headache Disorientation Visual disturbance	21	37
5	M	Late 40s	Late 30s	CSF1R-RD	*CSF1R*	p.M766V (LPV)	+	Gait disturbance	28	–
6	F	Mid 50s	Early 50s	CSF1R-RD	*CSF1R*	G798R (LPV)	–	Personality change	23	–
7	F	Early 40s	Late 30s	CSF1R-RD	*CSF1R*	R782H (PV)	+	Progressive memory decline Visuospatial dysfunctions Speech disorder	24	–
8	M	Early 40s	Early 40s	Leukodystrophy	*CSF1R*	c.1069A > T (VUS)	+	Cognitive decline, gait disturbances	0	–
9	F	Late 50s	Mid 50s	CTX	*CYP27A1*	R474W (PV) M334K (LPV)	–	Abnormal behavior Cognitive decline	26	38
10	M	Late 40s	Early 40s	Familial Korean dementia	*ITM2B*	*p.*Ter267SerextTer11 (VUS)	+	Cognitive decline	22	39
11	F	Early 40s	Early 40s	Familial Korean dementia	*ITM2B*	*p.*Ter267SerextTer11 (VUS)	+	Cognitive decline	22	39

Abbreviations: CSF1R, colony-stimulating factor 1 receptor; CSF1R-RD, colony-stimulating factor 1 receptor–related disorder; CTX, cerebrotendinous xanthomatotic; ITM2B, integral membrane protein 2; LPV, likely pathogenic; MMSE, Mini-Mental State Examination; NIID, neuronal intranuclear inclusion disease; PV, pathogenic; VUS, variant of uncertain significance.

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cal staining revealed weak positivity for intranuclear inclusions in the sweat gland cells. Finally, 128 GGC repeats in the *NOTCH2NLC* gene were confirmed.[42]

The second case, in his late 60s, experienced recurrent thunderclap headache, hemianopsia, and confusion over 11 years. Though initially suspected to have reversible cerebral vasoconstriction syndrome, he showed progressive cognitive decline and cortical atrophy. Brain MRI showed high signal intensities at CMJ on FLAIR without DWI lesions (Figure 1). Finally, 116 GGC repeats in the *NOTCH2NLC* gene were confirmed.[43]

The third case was a male in his late 60s. He presented with progressive memory decline starting in his mid-60s, including difficulty recalling recent events, reduced speech, wandering, slowed gait, and hand tremors. The patient had no family history of dementia. Brain MRI revealed bilateral diffusion-restricted lesions at CMJ on DWI and extensive white matter hyperintensities on FLAIR (Figure 1). A nerve conduction study revealed sensory-motor polyneuropathy. Genetic testing for fragile X syndrome revealed normal CGG expansion of *FMR1* in Xq27.3. Based on clinical and radiological findings, NIID was suspected, and 97 GGC repeats were detected in the *NOTCH2NLC* gene.

The fourth case, in his early 60s, had unilateral headaches, nausea, vomiting, and visual field defects one to two times per year over a decade. He also experienced recurrent episodes of confusion which lasted for a week. A strong family history of leukodystrophy was noted in four of his five siblings. MRI showed high signal intensities at CMJ on DWI and FLAIR (Figure 1). Skin biopsy revealed anti-P62 positive intranuclear inclusions in dermal cells. Finally, 112 GGC repeats in the *NOTCH2NLC* gene were confirmed.[44]

3.3 | Plasma biomarker characteristics in patients with adult-onset leukodystrophy

Comparisons were made only between patients with NIID and *CSF1R*-RD. One patient each with CTX and a VUS in *CSF1R* gene, and two with a VUS in *ITM2B* gene, were excluded from the statistical analyses.

The plasma NfL level was significantly lower in NIID (31.24 ± 3.25 pg/mL) compared to *CSF1R*-RD (70.79 ± 2.67 pg/mL), adjusted for age and sex ($P = 0.0117$; Figure 2). GFAP levels also tended to be lower in NIID (52.08 ± 22.18 pg/ml) than in *CSF1R*-RD (167.3 ± 68.7 pg/mL), but there was no statistical difference. No differences were observed in the plasma p-tau181 or Aβ42/Aβ40 ratios between the NIID and *CSF1R*-RD groups.

4 | DISCUSSION

We screened for GGC expansions in *NOTCH2NLC* to identify patients with NIID or NRED within a LEAF cohort of 410 patients with EOD, including those with EOAD, FTD, and other EOD (adult-onset leukodystrophy, other neurodegenerative EOD, and EOD of unclear or atypical etiologies). We confirmed pathogenic *NOTCH2NLC* GGC expansion in 4 out of 11 adult-onset leukodystrophy patients who were clinically suspected of having NIID. However, we found no GGC expansions in the *NOTCH2NLC* gene among the EOAD, FTD, and other neurodegenerative EOD, or EOD of unclear or atypical etiologies. In other words, none of the patients were diagnosed with NRED through genetic screening in cases in which NIID was not initially suspected.

We did not identify GGC expansion in *NOTCH2NLC* in patients with EOAD or FTD. Previous studies have reported varying prevalences of GGC repeat expansions in cohorts with AD, FTD, and adult-onset leukoencephalopathy. Specifically, GGC repeat expansions have been detected in 0.4% to 1.4% of patients with AD,[15,20] 1.8% of patients with FTD,[20] and 17.8% to 21.12% of patients with adult-onset non-vascular leukoencephalopathy.[11,12] Because NIID cases may have been misclassified as AD, FTD, or ALS due to limited clinical observations or the absence of genetic testing, previous studies may have overestimated the prevalence of NRED.[6] By contrast, our study minimized the likelihood of NIID misclassification by applying a strict diagnosis process. The EOAD group included only patients who met clinical diagnostic criteria[30–32,47] and had positive amyloid biomarkers on PET or CSF, and the FTD group consisted of those who strictly met the established diagnostic criteria.[35,36] Furthermore, the diagnosis of each participant was confirmed by six dementia expert neurologists at a LEAF committee consensus meeting. In addition, FLAIR and DWI images were reviewed before patient recruitment, allowing the identification of suspected NIID cases based on characteristic CMJ and paravermal signal changes. Our findings further support the suggestion that *NOTCH2NLC*-related expansions may be more specifically associated with clinical NIID itself, or adult-onset leukodystrophy rather than broadly contributing to EOD, reinforcing the need to refine the concept of NRED.[6] A recent study screening for *NOTCH2NLC* GGC repeat expansion in another Korean population cohort ($n = 2737$) reported that most patients (5 out of 6) with abnormal expansion had clinical symptoms suspected of being NIID, which is in line with our findings.[12]

Adult-onset leukodystrophies often present with overlapping clinical features, which complicates diagnosis. To date, there have been very few studies examining plasma biomarkers in adult-onset leukodystrophy including NIID or *CSF1R*-RD. Plasma NfL, an indicator of axonal integrity, and plasma GFAP, another marker of neurodegeneration, may increase in adult-onset leukodystrophy.[40,48] Previous studies have reported elevated plasma NfL and GFAP levels in patients with NIID compared to healthy controls[48,49] and elevated NfL in patients with *CSF1R*-RD compared to those in healthy controls and patients with multiple sclerosis.[50] However, there are no studies directly comparing plasma biomarkers between patients with *CSF1R*-RD and NIID. Our data showed that the plasma NfL levels were significantly lower in patients with NIID than in those with *CSF1R*-RD, and plasma GFAP levels also showed a lower trend in NIID, although this difference did not reach statistical significance (Figure 2). These findings suggest distinct biomarker profiles between the two disorders. It is important to note that the diagnosis of leukodystrophy requires comprehensive clinical and radiological evaluation. Characteristic brain MRI findings, particularly diffusion restriction along the CMJ on DWI, are highly suggestive of NIID whereas splenium involvement is more suggestive of

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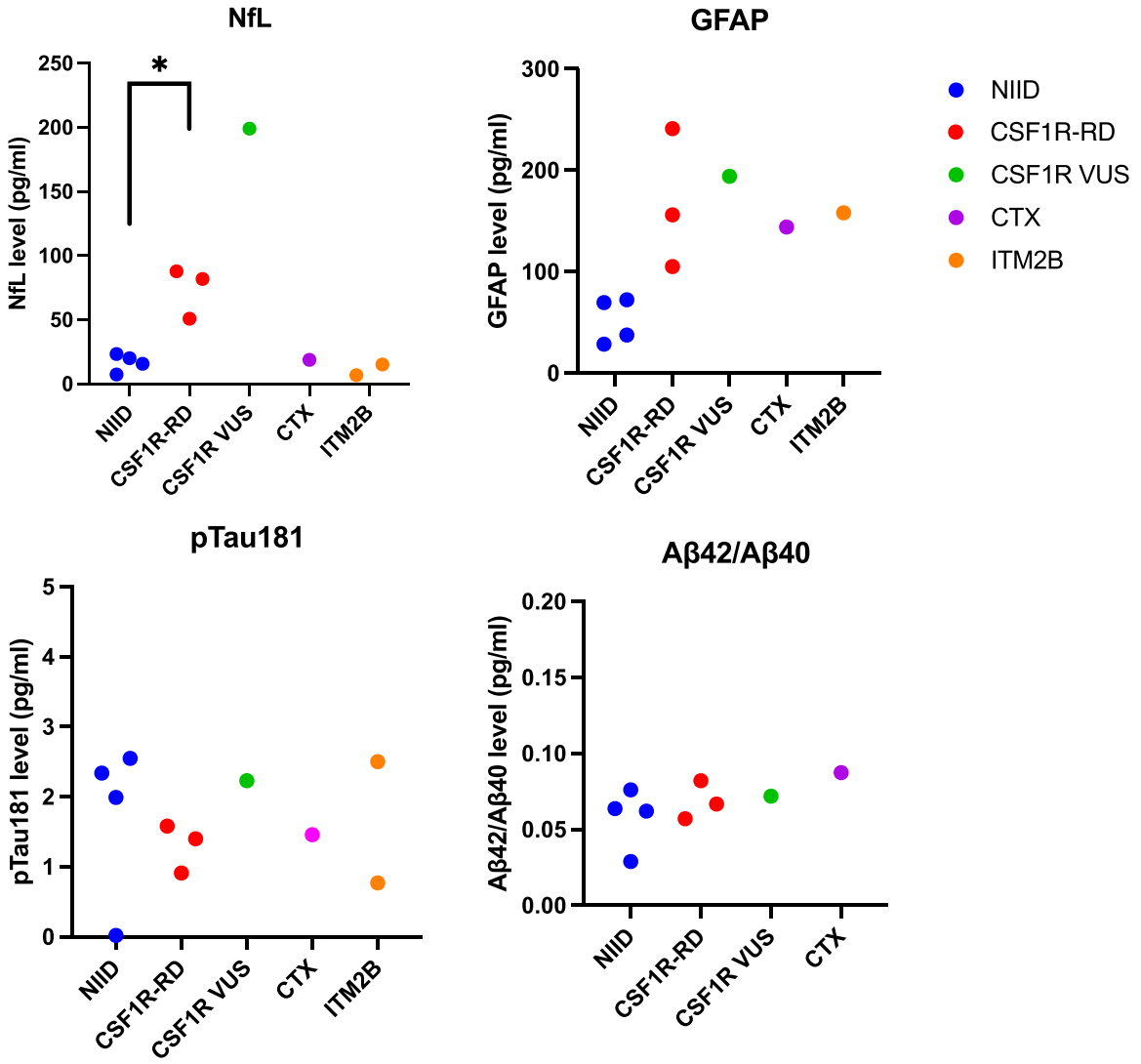


FIGURE 2 Plasma biomarkers among patients with adult-onset leukodystrophy. Plasma levels of NfL, GFAP, Aβ42/Aβ40, and p-tau181 were measured in patients with adult-onset leukodystrophy, including those with NIID, *CSF1R*-RD, *CSF1R* VUS, CTX, familial dementia carrying VUS in *ITM2B*. NfL level was significantly lower in NIID compared to *CSF1R*-RD. Aβ42 level in the familial dementia carrying VUS in *ITM2B* was undetectably low, preventing reliable quantification. GFAP was measured in only one of the two patients with *ITM2B* VUS. Statistical analysis used analysis of covariance (age and sex adjusted) with a Tukey post hoc test. $P < 0.05$ (*). Aβ, amyloid beta; *CSF1R*, colony-stimulating factor 1 receptor; *CSF1R*-RD, colony-stimulating factor 1 receptor–related disorder; CTX, cerebrotendinous xanthomatosis; GFAP, glial fibrillary acidic protein; *ITM2B*, integral membrane protein 2 B; NfL, neurofilament light chain; NIID, neuronal intranuclear inclusion disease; p-tau, phosphorylated tau; VUS, variant of uncertain significance.

CSF1R-RD.[51] In addition, systemic manifestations such as peripheral neuropathy and autonomic dysfunction are more commonly observed in NIID but less frequently reported in *CSF1R*-RD.[52,53] In our recent nationwide Korean cohort study, peripheral neuropathy was observed in 60% of patients with NIID, and autonomic dysfunction—most commonly bladder dysfunction—was present in 48%.[54] Therefore, combining plasma biomarkers with characteristic MRI findings and associated clinical features, including peripheral neuropathy and autonomic dysfunction, may facilitate more accurate differentiation between NIID and *CSF1R*-RD.

Given the rarity of NIID and *CSF1R*-RD, our current analysis is inevitably limited by a small sample size. Nonetheless, the observed differences in plasma biomarkers between these two disease groups highlight the need for larger, well-controlled studies in the future. Incorporating age- and sex-matched non-neurodegenerative controls will be critical to establish the diagnostic value of these markers more definitively.

5 | CONCLUSION

We searched for *NOTCH2NLC* GGC expansions in an LEAF-EOD cohort and found no patients with NRED among EOAD, FTD, or other EOD. Four patients clinically suspected to have NIID were confirmed to

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have *NOTCH2NLC* GGC abnormal expansion. As this is the first screening study of *NOTCH2NLC* GGC expansion in an EOD cohort, further research is needed in more EOD cohorts, leading to a constructive discussion of the concept of NRED. Additionally, more studies with larger sample sizes are needed to develop promising plasma biomarkers for the differential diagnosis and disease progression of adult-onset leukodystrophy, including NIID.

AUTHOR CONTRIBUTIONS

Seung-yeon Lee and Hee Jin Kim analyzed the data, figure preparation and wrote the initial draft of the manuscript. Takeshi Mixuguchi, Seong-Ho Koh, Henrik Zetterberg, Liana G. Apostolova, and Naomichi Matsumoto provided experimental data and validated the results. Young-Eun Kim, Cho Hanna, Won-Joo Kim, Gha-Hyun Lee, Ahro Kim, Ji-Yun Park, Eun Joo Chung, Hyemin Jang, Na-Yeon Jung, Sun Min Lee, and Sang Won Seo contributed to participant recruitment and provided clinical data. So Young Moon and Eun-Joo Kim conceptualized and supervised the study and acquired funding. All authors reviewed and critically revised the manuscript and approved the fianl version for publication. The contributions of the LEAF Investigators are provided separately in the Appendix.

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CONFLICT OF INTEREST STATEMENT

Dr. Apostolova participates on boards at IQVIA, NIA, UAB Nathan Schock Center, New Mexico Exploratory ADRC, and FDA. Dr. Apostolova holds leadership positions at Medical Science Council Alzheimer's Association Greater IN Chapter, Alzheimer's Association Science Program Committee, FDA PCNS Advisory Committee, and Beeson Program Committee. She also reports research support from the NIH, Life Molecular Imaging, the Alzheimer's Association, Roche Diagnostics, AVID Pharmaceuticals, and Eli Lilly; consulting fees from Biogen, GE Healthcare, Prothena, Eisai, IQVIA, Roche Diagnostics,

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Genentech, Alnylam, Siemens, Otsuka, Corium, and Eli Lilly; and honoraria from the American Academy of Neurology (AAN), Weill Cornell, MillerMed, MedLearning Group, NACC CME, Prothena, CME Institute, MJH Physician Education Resource, WebMD, and PeerView. H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD; is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program; and is a shareholder of MicThera (outside submitted work). The remaining authors report no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants and their family members enrolled in the LEAF (Longitudinal Study of Early-Onset Dementia And Family Members) cohort provided informed consent prior to participation in this study.

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