



α -Klotho Levels in Frontotemporal Lobar Degeneration Are Unaffected by *KLOTHO*-VS Genotype

Katonova Alzbeta¹, Veverova Katerina¹, Jurasova Vanesa¹, Vyhnaek Martin¹, Hort Jakub¹

(1) Memory Clinic, Department of Neurology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic



I. Background

α -Klotho is a longevity-associated protein implicated in neurological disorders, including Alzheimer's disease (AD), multiple sclerosis, and Parkinson's disease. Its role in frontotemporal lobar degeneration (FTLD), however, remains poorly understood. Prior research has shown reduced *KLOTHO* (KL) gene expression in peripheral mononuclear blood cells of FTLD patients¹, but no studies have assessed α -Klotho protein levels in biofluids of individuals with FTLD. Moreover, the influence of the *KL*-VS genotype on α -Klotho levels, established in AD^{2,3}, has not been examined in FTLD.

Our aims were to evaluate:

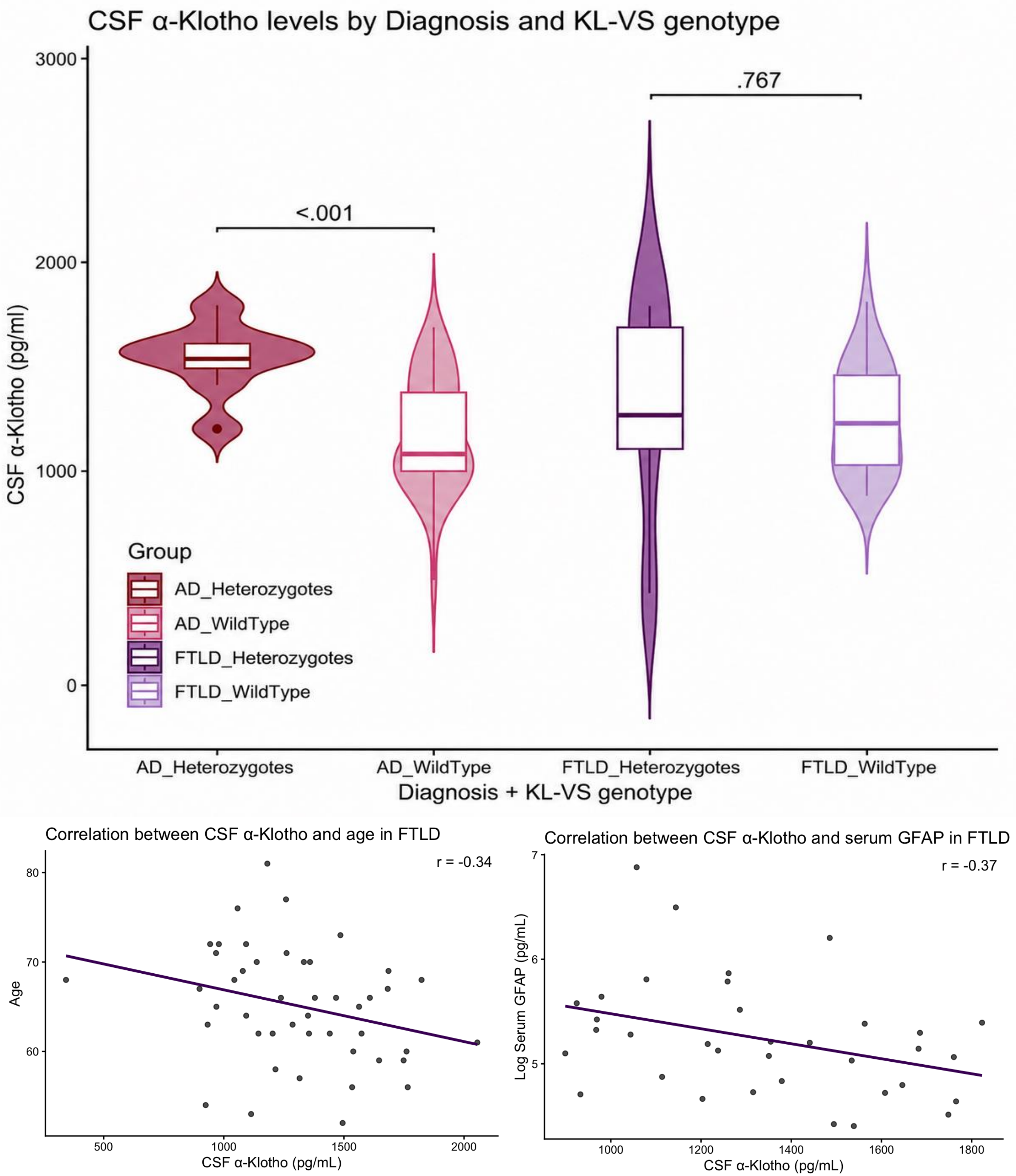
- (1) cerebrospinal fluid (CSF) and serum α -Klotho protein levels and their associations with neurodegeneration-related biomarkers in FTLD, and
- (2) The influence of the *KL*-VS genotype on α -Klotho levels in FTLD.

II. Methods

- 241 biomarker-defined participants from Czech Brain Aging Study were included: 149 AD, 51 FTLD and 41 cognitively unimpaired (CU) individuals.
- They underwent clinical examination, neuropsychological assessment, blood draw, lumbar puncture; a subset also underwent *KL*-VS genotyping.
- Commercial ELISA kits measured α -Klotho and neurofilament light chain (NfL) levels in CSF and serum.
- Commercial SIMOA kit measured serum GFAP levels.

	AD	FTLD	CU Controls	p
Demographics	N = 149	N = 51	N = 41	
Age, years $\pm$ SD	71.1 $\pm$ 7.9***	65.2 $\pm$ 7.1***	64.0 $\pm$ 9.3	<.001
Female, n (%)	97 (65.1)	21 (41.2%)	31 (75.6%)	.001
MMSE score $\pm$ SD	21.7 $\pm$ 5.0***	23.4 $\pm$ 5.1***	29.0 $\pm$ 1.2	<.001
<i>KL</i> -VS HET, n (%)	15 (10)	5 (9.8)	4 (9.8)	.188
Biomarkers				
CSF α -Klotho, pg/ml $\pm$ SD	1287.8 $\pm$ 289.2	1311.4 $\pm$ 318.1	1326.0 $\pm$ 281.7	.763
Serum α -Klotho, pg/ml $\pm$ SD	1003.6 $\pm$ 364.9	1048.3 $\pm$ 728.1	1156.9 $\pm$ 503.2	.271
CSF NfL, pg/ml $\pm$ SD	1429.7 $\pm$ 909.1**	2893.1 $\pm$ 2029.5***	666.5 $\pm$ 483.1	<.001
Serum NfL, pg/ml $\pm$ SD	38.3 $\pm$ 30.5*	56.2 $\pm$ 49.3***	16.3 $\pm$ 6.3	<.001
CSF Neurogranin, pg/ml $\pm$ SD	261.1 $\pm$ 103.3*	188.8 $\pm$ 70.0**	182.5 $\pm$ 70.3	.002
Serum GFAP, pg/ml $\pm$ SD	628.9 $\pm$ 1026.3	228.4 $\pm$ 171.0*	198.1 $\pm$ 81.7	.011

p refers to the main effect across all groups. P values are comparisons using Tukey post hoc tests (one-way analysis of variance was used to test the main between group differences). For p values indicating the level of significance compared with control group: *p <.05; **p <.01; ***p <.001***; compared with AD group: *p <.05; **p <.01; ***p <.001.



III. Results

- FTLD showed no *KL*-VS heterozygosity-related increase in CSF α -Klotho (p = .767), unlike AD, where *KL*-VS heterozygosity was associated with higher CSF α -Klotho levels (p < .001).
- CSF α -Klotho declined with age (r = -0.34, p = .02), while serum α -Klotho showed no age association in FTLD (r = -0.13, p = .37).
- Higher CSF α -Klotho was associated with lower serum GFAP in FTLD (r = -0.37, p = .03).
- CSF and serum α -Klotho did not differ significantly across AD, FTLD, and CU after adjusting for age and sex (CSF p = .673; serum p = .367).

IV. Conclusions

(1) The *KL*-VS heterozygosity effect on CSF α -Klotho was disease-specific to AD and not seen in FTLD, suggesting *KL*-VS does not universally regulate α -Klotho across neurodegenerative diseases and may instead reflect AD-specific biology. Given the established neuroprotective properties of α -Klotho, the absence of a *KL*-VS-associated increase in FTLD may indicate that patients with FTLD do not benefit from this genotype-driven neuroprotective mechanism.

(2) CSF α -Klotho declines with age in FTLD, indicating that aging-related effects on α -Klotho remain preserved in FTLD.

(3) Higher CSF α -Klotho was associated with lower serum GFAP, suggesting its potential protective role in modulating astrogliosis and inflammation in FTLD.

References

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Acknowledgment

This study was supported by the project National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107), the Institutional Support of Excellence 2. LF UK (Grant No. 6980382), and by the Alzheimer Foundation Czech Republic.

