Poster #188

TBK1-associated ALS in a Norwegian population-based cohort

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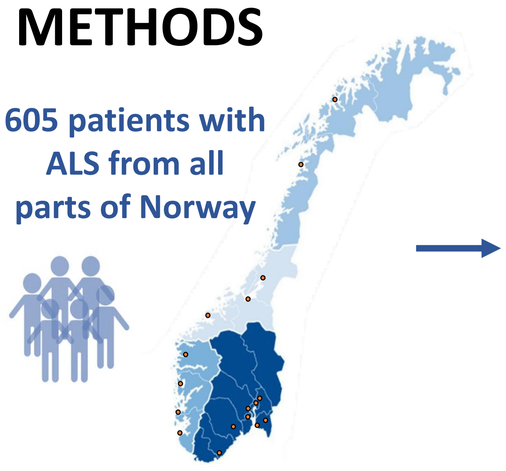
OBJECTIVES

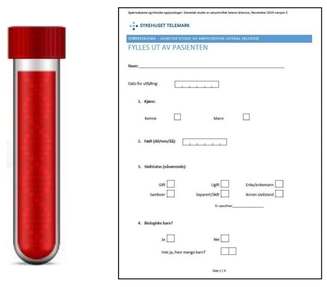
- ***TBK1*** **variants are known to cause of autosomal dominant amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), with considerable clinical heterogeneity.**
- ***TBK1*** **plays a central role in inflammation and rare biallelic variants have been linked to autoinflammation with arthritis and vasculitis.**
- **Vascular or inflammatory CNS manifestations have not previously been reported in *TBK1* associated ALS/FTD.**
- **This study aimed to characterize the clinical, genetic, and neuroimaging features of ALS patients carrying *TBK1* variants in a Norwegian population-based cohort.**

METHODS

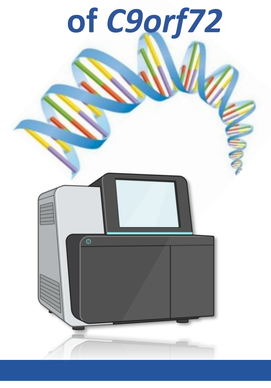
605 patients with ALS from all parts of Norway



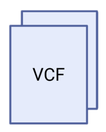
Sample collection, clinical evaluation and questionnaires



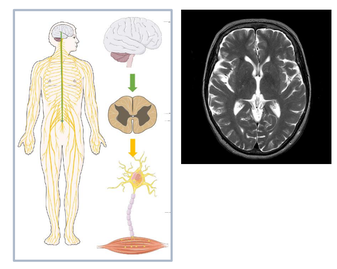
Whole-exome sequencing and expansion testing of *C9orf72*



Extraction of data on *TBK1* variants



Collection of supplemental clinical characteristics and MRI scans



RESULTS

- ✓ **9/605 patients (1.5%) carried *TBK1* variants.**
- ✓ **7 pathogenic or likely pathogenic and 2 uncertain variants were identified.**
- ✓ **Clinical presentation was variable, with both bulbar and spinal onset and cognitive defects in several patients, two had clear FTD features.**
- ✓ **Most patients reported a family history of ALS and/or cognitive disorders.**
- ✓ **MRI was normal or showed mild age-related changes in 8/9 cases. Taken 0 to16 months (mean 8 ± 5,0 months) after symptom onset.**
- ✓ **One patient, had progressive white matter changes and microbleeds, suggestive of vasculopathy.**

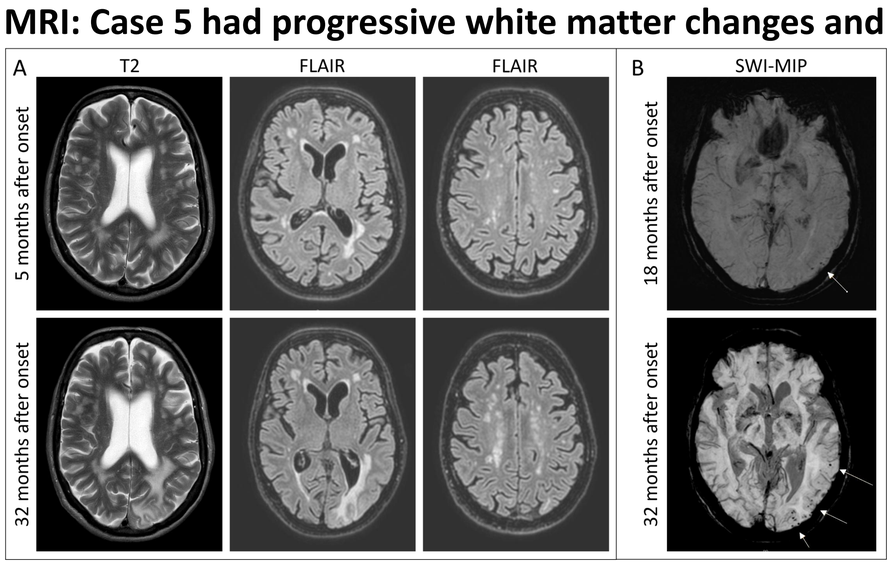
Genetic variants identified in *TBK1*.

The two class 3 variants have previously been published in two separate ALS patients, PMID: 25803835: and PMID: 35896380.

Case ID	Variant*	Variant type	GnomAD AF v.4 (%)	Revel score	ACMG	Other genetic variant
1	c.254T>C p.(Ile85Thr)	Missense	0,0001	0.328	3	
2,3	c.701+1G>A p.(?)	Splice	-	-	5	
4	c.914T>C p.(Ile305Thr)	Missense	0,0006	0.461	3	C9orf72 exp
5,6	c.992+1G>A p.(?)	Splice	0,0006	-	5	
7,8	c.1928_1930del p.(Glu643del)	Deletion	0,0009	-	5	
9	c.2086G>A p.(Glu696Lys)	Missense	0,0002	0.278	4	

Abbreviations: ACMG = American College of Medical Genetics, exp = expansion, GnomAD = Genome Aggregation Database. Reference sequence according to NM_013254.4. *All variants were identified in a heterozygous state.

MRI: Case 5 had progressive white matter changes and microbleeds



(A) T2-weighted imaging (T2) and fluid-attenuated inversion recovery (FLAIR) in case five, obtained five months after symptom onset and at 32-month follow-up, demonstrated progression of neurovascular T2-hyperintense white matter abnormalities with confluent involvement of the left parietotemporal region. **B)** Susceptibility-weighted imaging (SWI) with maximum intensity projection (MIP) reconstruction in case five, obtained 18 and 32 months after symptom onset, demonstrated progressive microhemorrhagic foci in the left temporo-occipital hemisphere.

Clinical characteristics and family history

Case no.	Gender	Onset (years)	Type at onset	UMN signs	LMN signs	Cognitive symptoms	Neuro-physiology	El Escorial *	Survival time (months)	Family w. ALS	Family w. dementia (AD/FTD)
1	M	55	Bulbar	Yes	Yes	No	Mild denervation	Yes	21	No	No
2	F	64	Spinal	Yes	Yes	No	Denervation	Yes	77	Yes	No
3	F	66	Bulbar	Yes	Yes	Yes	Normal	Yes	36**	Yes	No
4	M	66	Bulbar	Yes	Yes	No	Axonal neuropathy	Yes	15	Yes	Yes
5	F	75	Spinal	Yes	Yes	Yes	Mild denervation, mild axonal neuropathy	Yes	58	Yes	Yes
6	F	68	Spinal	Yes	Yes	Yes	Denervation	Yes	26	Yes	Yes
7	M	73	Spinal	Yes	Yes	No	Denervation	yes	51	No	No
8	M	64	Bulbar	Yes	Yes	No	Denervation and reinnervation	Yes	33	No	Yes
9	M	54	Spinal	Yes	Yes	Yes	Denervation and reinnervation	Yes	20	No	Yes

Abbreviations: AD = Alzheimers Disease, F= female, FTD = frontotemporal dementia, LMN = lower motor neuron, M = male, UMN = upper motor neuron, w = with. * El Escorial refers to whether or not the patient fulfilled the criteria for probable or definite ALS according to the revised El Escorial criteria[34]. ** Censored, patient alive at last follow-up.

CONCLUSION

Our findings expand the clinical spectrum of TBK1-associated ALS and raises the question of possible vascular involvement.

The authors declare no conflicts of interest

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