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GENETIC AND PHENOTYPIC MODULATORS OF COGNITIVE AND BEHAVIORAL IMPAIRMENT IN ALS

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INTRODUCTION

In ALS, the extent and nature of cognitive (ALSci) and behavioral (ALSbi) impairments, including frontotemporal dementia (FTD), can vary based on genetic mutations, clinical, and demographic data. Particularly, the distinction between spinal and bulbar onset, as well as gender, may influence cognitive and behavioral profiles, while genetic factors can further modulate these outcomes.

OBJECTIVES

- To assess whether specific **genetic mutations** are associated with distinct cognitive and behavioral patterns
- To explore the influence of **gender**, **age**, **and onset type** on cognitive and behavioural profiles.

METHODS

Patients with ALS were enrolled (**Fig 1**). All underwent neuropsychological assessments to evaluate cognitive function, behavioral changes, and mood according to Strong's criteria. Genetic analysis was conducted to identify mutations linked to ALS. Patients were stratified by sex and onset type (bulbar Vs. spinal). Multivariate regression models were used to investigate the relationships between neuropsychological outcomes, genetic, demographic, and clinical data.

TABLE 1	ALSFRSR		Disease duration		Age (yrs)		Education (yrs)		HADS-MND		FBI-ALS		ECAS-SPE		ECAS-nonSPE		ECAS tot	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
SOD1	40.1	3.38	31.8	22.3	54.6	4.65	12.9	3.84	7.10	5.88	3.70	3.92	81.8	6.65	28.3	3.89	110	9.68
TARDBP	36.1	8.43	20.3	16.0	61.0	10.4	12.7	3.90	9.80	4.92	5.33	6.50	72.5	17.5	26.1	3.42	98.6	19.7
C9orf72	37.8	7.63	16.6	12.9	60.8	9.54	12.4	3.99	6.28	5.74	6.72	7.61	69.6	18.5	23.6	6.24	93.2	23.3
Other GM-ALS	38.0	5.48	26.8	24.0	62.0	12.6	12.1	3.73	9.16	5.32	5.05	6.36	70.9	11.5	25.5	5.18	96.4	14.6
WT-ALS	38.7	6.41	22.9	22.5	62.8	11.1	11.8	4.44	8.23	6.18	4.60	6.26	71.5	17.4	25.7	5.48	97.2	21.3

RESULTS

The study included 467 ALS patients without pathogenic variants (**wild-type ALS**, **WT-ALS**) and 105 patients carrying ALS-associated gene mutations (**GM-ALS).** See **Fig. 1** for details.
The GM-ALS group was divided according to genotype: **C9orf72** (N = 48), **TARDBP** (N = 15), **SOD1** (N = 10), and a group with less common mutations, including FUS, OPTN, and SQSTM1 (**other GM-ALS**, N = 24).The bulbar-to-spinal onset ratio was higher in TARDBP-ALS (0.87) and C9orf72-ALS (0.77) compared to WT-ALS (0.29) (**Fig. 2**).
Both WT-ALS and GM-ALS groups had a similar male-to-female ratio (1.2 and 1.0, respectively; Fig. 3).
The Strong et al. classification criteria were applied to all groups (**Fig. 4**). Older age (**Fig. 5**) and lower educational levels (**Fig. 6**) were significant predictors (p<0.001) for ALSci, ALSbi, ALScbi, and ALS-FTD (collectively referred to as **ALSimp**), with patients carrying C9orf72 mutations at higher risk (OR = 2.1; p = 0.040) of developing ALSimp compared to WT-ALS. Older age (p = 0.005) and male gender (p<0.001) were also significant predictors of behavioral changes (**Fig. 7**). C9orf72-ALS patients had a higher risk of exhibiting disinhibited behaviors and loss of insight compared to WT-ALS patients (**Fig. 8**). Specific cognitive deficits were associated with gender and bulbar onset, in addition to age and educational level, with the C9orf72 genotype linked to language, memory, and visuospatial impairments (**Table 2**). Mood disturbances were consistent across subgroups but were negatively influenced by older age and spinal onset (**Table 2**).

Fig. 1: Patient selection

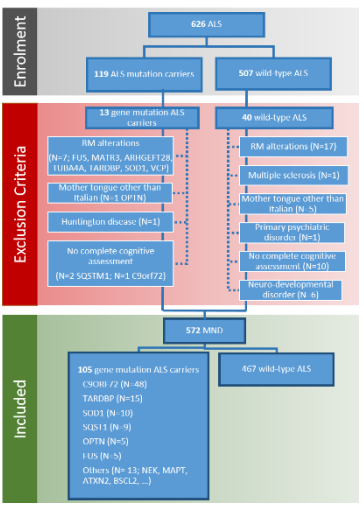

Fig. 2

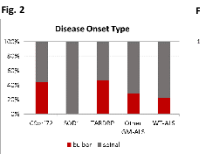

Fig. 3

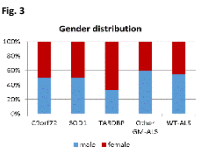

Fig. 4

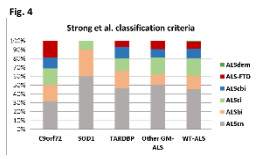

Fig. 5

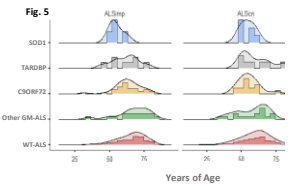

Fig. 6

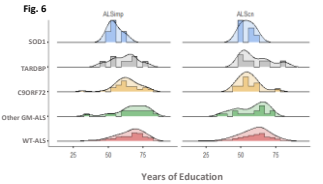

Fig. 7

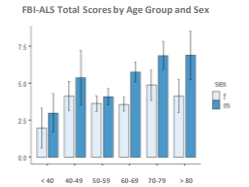

Fig. 8

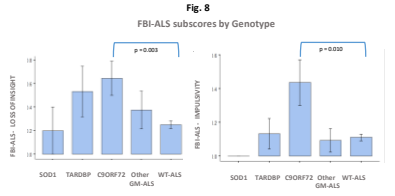

TABLE 2: BINOMIAL LOGISTIC REGRESSION	LANGUAGE DEFICIT			EXECUTIVE FUNCTION DEFICIT			SOCIAL COGNITION DEFICIT			MEMORY DEFICIT			VISUO-SPATIAL DEFICIT			BEHAVIOURAL CHANGES			MOOD ALTERATION		
	R^2McF=0.070			R^2McF=0.071			R^2McF=0.070			R^2McF=0.057			R^2McF=0.110			R^2McF=0.045			R^2McF=0.028		
PREDICTORS	X^2	p	OR	X^2	p	OR	X^2	p	OR	X^2	p	OR	X^2	p	OR	X^2	p	OR	X^2	p	OR
Age	4.17	**0.041**	1.023	4.980	**0.026**	1.023	2.270	0.132	10.262	73.678	**0.007**	104.944	0.0119	0.913	100.272	11.83	**<.001**	1.031	4.80	**0.028**	0.981
Educational Level	12.69	**<.001**	0.911	14.267	**<.001**	0.912	3.192	0.074	0.9328	0.1839	0.668	0.983	0.1983	0.656	102.707	1.88	0.171	0.971	1.01	0.314	0.979
Bulbar Vs. Spinal (ref)	11.52	**<.001**	2.266	6.814	**0.009**	1.821	9.746	**0.002**	29.077	0.0335	0.855	0.930	20748	0.150	210.518	1.08	0.299	1.251	6.27	**0.012**	1.726
female Vs. Male (ref)	1.44	0.230	0.768	0.992	0.319	1.225	0.257	0.612	11.777	0.2707	0.603	0.836	63502	**0.012**	387.615	11.09	**<.001**	0.540	3.41	0.065	0.717
C9orf71, TARDBP, SOD1, GM-ALS Vs. WT-ALS (ref)	2.08	0.720	-	5.684	0.224	-	1.039	0.904	-	77.565	0.101	-	56149	0.230	-	6.21	0.184	-	8.55	0.073	-
Sig. Contrasts (* = p < 0.05)										C9orf72 vs WT-ALS*		301.016	C9orf72 vs WT-ALS*		131.647	C9orf72 vs WT-ALS*		2.103	C9orf72 vs WT-ALS*		2.100

CONCLUSION

The strength of this study lies in the large sample size and the neuropsychological evaluation designed to assess both cognitive and behavioral impairments, as well as mood alterations. We found that older age and lower educational level are risk factors for decline in cognitive functions and behavior. While behavioral alterations appear to be more strongly associated with male gender and the C9orf72 mutation, cognitive impairments seem to be primarily influenced by the type of disease onset. Patients with bulbar-onset ALS are at higher risk for executive dysfunction, as well as language and social cognition deficits, compared to those with spinal-onset ALS. Patients harboring the C9orf72 mutation showed greater impairment in visuospatial and memory domains than those with WT-ALS. Mood alterations were associated with older age and spinal-onset ALS. These findings underscore the importance of considering genetic and phenotypic factors in shaping the cognitive-behavioral spectrum of ALS.