UNC13A and the risk of ALS in a Norwegian cohort

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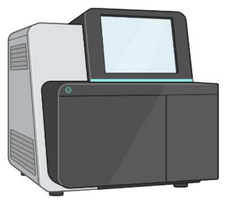
Introduction

- ✓ Amyotrophic lateral sclerosis (ALS) is a fatal and progressive neurodegenerative disease.
- ✓ The rs12608932 variant (c.2473-324T>G) in *UNC13A* is a risk factor and modifier of the ALS phenotype due to cryptic exon inclusion.
- ✓ The CC genotype of the rs12608932 variant is linked to shorter survival, higher age at onset, and more frequently bulbar onset
- ✓ The rs12608932 variant occur at a high frequency (10%) in healthy individuals of European ancestry

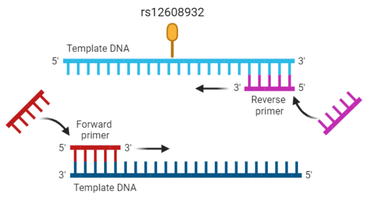
Methods

ALS patients (*n* = 500)

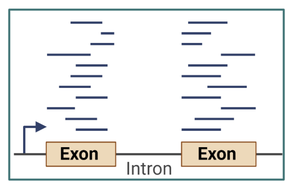
→ **Sanger sequencing & Exome sequencing**



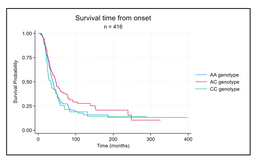
→ ***UNC13A* Rs12608932**



\+ **70 ALS genes**



→ **Statistical analyses of survival, risk and clinical characteristics**



Results : risk and survival

UNC13A rs12608932

Frequency in our ALS cohort: 0.438
- Frequency in gnomAD: 0.365
- Frequency in a Norwegian Database : 0.365

ALS risk (C-allele):
- Risk ratio: 1.4 (CI 1.2-1.5)

CI; confidence interval

Table 1: Risk of C-allele and CC-genotype of the UNC13A rs12608932 variant in both total ALS cases and the two sub-groups (no genetic variants and with genetic variants) compared to the frequency in gnomAD and a Norwegian database, respectively.

		GnomAD (n = 75771)		Norwegian database (n = 5871)	
Risk of ALS with CC-genotype	***n* (%)**	**Risk ratio**	**p-value**	**Risk ratio**	**p-value**
Total ALS cases (*n* = 500)					
$UNC13A^{AA+AC}$	399 (79.8)	1.6 (1.3-1.9)	**0.0001**	1.5 (1.2-1.8)	**0.0003**
$UNC13A^{CC}$	101 (20.2)				
ALS cases (no genetic variants) (*n* = 416)					
$UNC13A^{AA+AC}$	333 (80.0)	1.5 (1.2-2.0)	**0.0004**	1.5 (1.2-1.8)	**0.0014**
$UNC13A^{CC}$	83 (20.0)				
ALS cases (with genetic variants) (*n* = 84)					
$UNC13A^{AA+AC}$	66 (78.6)	1.7 (1.0-2.8)	**0.0469**	1.6 (1.0-2.7)	0.0612
$UNC13A^{CC}$	18 (21.4)				
		GnomAD (AC = 151542)		**Norwegian database (AC = 11742)**	
Risk of ALS with C-allele	***n* (%)**	**Risk ratio**	**p-value**	**Risk ratio**	**p-value**
Total ALS cases (AC = 1000)					
A-allele	562 (56.2)	1.4 (1.2-1.5)	**< 0.0001**	1.3 (1.2-1.5)	**< 0.0001**
C-allele	438 (43.8)				
ALS cases (no genetic variants) (AC = 832)					
A-allele	469 (56.4)	1.4 (1.2-1.5)	**< 0.0001**	1.3 (1.2-1.5)	**< 0.0001**
C-allele	363 (43.6)				
ALS cases (with genetic variants) (AC = 168)					
A-allele	93 (55.4)	1.4 (1.0-1.9)	**0.0281**	1.4 (1.0-1.9)	**0.0304**
C-allele	75 (44.6)				

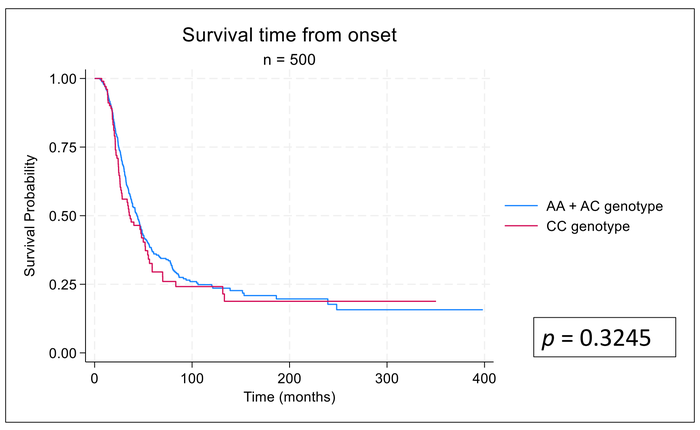


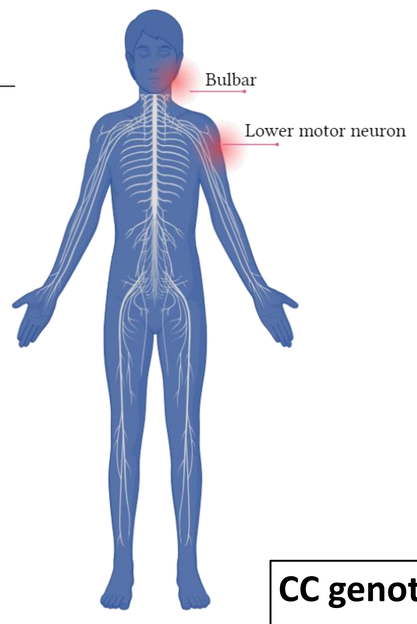
Figure 1: Survival months from onset comparing CC genotype and AA + AC genotype for the rs12608932 variant.

Results: clinical characteristics

Table 2: The association of clinical characteristics and the CC genotype compared to the AA + AC genotype in the two different sub-groups; with no genetic variant and with genetic variants.

	No genetic variants (n= 416)			With genetic variants (n =84)		
	$UNC13A^{AA+AC}$ (n = 333) 80%	$UNC13A^{CC}$ (n = 83) 20%	p-value	$UNC13A^{AA+AC}$ (n= 66) 79%	$UNC13A^{CC}$ (n= 18) 21%	p-value
Age at onset, years						
Median (IQR)	66.0 (58-72)	66.8 (56-74)	0.6432	60.7 (51-69)	65.8 (51-70)	0.3598
Gender, n (%)						
Female	133 (39.9)	36 (43.4)	0.569	31 (47.0)	10 (55.6)	0.518
Male	200 (60.1)	47 (56.6)		35 (53.0)	8 (44.4)	
ALS family history, n (%)						
sALS	312 (93.7)	79 (95.2)	0.808	40 (60.6)	7 (38.9)	0.100
fALS	20 (6.0)	4 (4.8)		26 (39.4)	11 (61.1)	
Unknown	1 (0.3)	0 (0)		0 (0)	0 (0)	
Site of onset (n, %)						
Bulbar	81 (24.3)	33 (39.8)	**0.006**	13 (19.7)	4 (22.2)	0.783[a]
Spinal	215 (64.6)	41 (49.4)		45 (68.2)	11 (61.1)	
Both	37 (11.1)	8 (9.6)		8 (12.1)	3 (16.7)	
Unknown	0 (0)	1 (1.2)		0 (0)	0 (0)	
Motor neuron (n, %)						
Dominant upper motor neuron	10 (3.0)	1 (1.2)	**0.011**	0 (0.0)	1 (5.6)	0.186[a]
Dominant lower motor neuron	47 (14.1)	24 (28.9)		12 (18.2)	4 (22.2)	
Both	274 (82.3)	57 (68.7)		54 (81.8)	13 (72.2)	
Unknown	2 (0.6)	1 (1.2)		0 (0)	0 (0)	
Cognitive impairment (n, %)						
Yes	25 (7.5)	7 (8.4)	0.334	6 (9.1)	1 (5.6)	1.000[a]
No	293 (88.0)	69 (83.1)		58 (87.9)	17 (94.4)	
Unknown	15 (4.5)	7 (8.4)		2 (3.0)	0 (0)	

[a]Fisher exact test



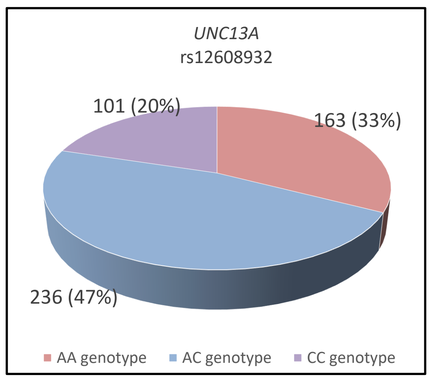


Figure 2: Distribution of the three genotypes for the *UNC13A* rs12608932 variant

CC genotype:
- Bulbar onset (p = 0.006)
- Dominant LMN manifestations (p = 0.011)

LMN; lower motor neuron

Conclusions

- ✓ The rs12608932 variant in UNC13A is associated with increased risk of ALS
- ✓ The CC genotype is associated with more frequently bulbar onset and dominant LMN manifestations
- ✓ The rs12608932 variant modify the phenotype solely in ALS cases lacking a known genetic basis

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The authors declare no conflicts of interest