Clinical and Genetic Characterization of SPT Complex Variants in Amyotrophic Lateral Sclerosis

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Introduction

Recent literature has identified rare variants of SPTLC1 and SPTLC2 in Amyotrophic Lateral Sclerosis (ALS) patients[1]. These genes encode subunits of the serine palmitoyltransferase (SPT) complex, which catalyzes the first step in sphingolipid biosynthesis, that is negatively regulated by ORMDL3[2].

Methods

Rare-coding variants in *SPTLC1, SPTLC2, SPTSSA, SPTSSB* and *ORMDL3* were screened in 1324 ALS patients from the Piemonte and Aosta Register for ALS (PARALS) and filtered in Project MinE consortium dataset (6596 ALS patients and 2454 controls). Identified variants were classified according to ACMG criteria.
Set-level and gene-level over-representation of rare variants in patients were examined with burden testing.

Results

Overall, the frequency of variants in the examined genes was **higher** in **ALS** patients rather healthy controls, yet statistical significance was not reached neither in PARALS nor in MinE consortium.

SPTLC1

In literature, **mutations in SPTLC1** described **in ALS** patients fell in its **first transmembrane domain (S1,Ala20-Phe40),** which is supposed to interact with and be negatively regulated by ORMDL3[1,3].

However, in the PARALS cohort, the 6 affected ALS patients with mutated SPTLC1 only had mutations outside of this domain.

SPTLC2 and ORMDL3

In **SPTLC2**, scattered **mutations** were observed along the whole protein. However, potential mutational clusters were found in those **cytosolic regions interacting with ORMDL3**[4].

A single mutated patient in ORMDL3 was found in the PARALS cohort.

Discussion

In the PARALS cohort, we found 3 ALS patients mutated in SPTLC1, 3 in SPTLC2 and 1 in ORMDL3 (see table below).

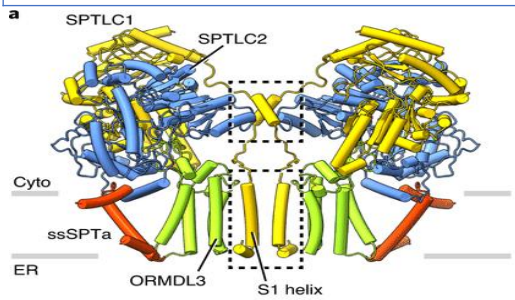
PARALS COHORT	SPTLC1 (3 c)	SPTLC2 (3 c)	ORMDL3 (1 c)
Median survival (y)	7.17	2.66	7.49
Median age of onset (y)	62.19	60.39	64
Spinal phenotypes (n)	2	2	1

Previous data reported that **SPTLC1 mutations** are associated with an **early onset of the disease**, i.e. adolescence or even childhood, with a **severe clinical course**[1,4]. Conversely, the mutated patients in this study developed ALS **in late adulthood** with a tendency toward **spinal phenotypes**, with a **better survival**.

Notable**, SPTLC1 mutations** found **among adult ALS cases fall out of** its **first transmembrane domain (S1),** which is the region of SPTLC1 that binds to ORMDL3, which negatively regulates the complex. While the pathogenicity of the non-S1 *SPTCL1* variants need to be established, based on our data it could be speculated that **different sites of mutation within the same gene might cause a different, more benign, ALS phenotype.**

Mutations in SPTLC2 were on the cytosolic side and those patients had a **worse survival.**

Up to our knowledge, no mutations in ORMDL3 were described in literature, thus data are too scarce to further discuss hypothesis.



Conclusions

The authors of this study **recommend** in favor of **screening ALS patients for mutations in SPTCL1 and SPTCL2**, irrespectively of the age at which disease manifested.
Further research with broader cohorts is needed to clarify and unravel the complex interplay between ALS and SPT.

References: 1, Serine Palmitoyltransferase (SPT)-related Neurodegenerative and Neurodevelopmental Disorders, Mohassel et al. , 2 Structural insights into the assembly and substrate selectivity of human SPT–ORMDL3 complex, Li et al., 3 Highly accurate protein structure prediction with AlphaFold, Jumper, J. et al., 4 Childhood amyotrophic lateral sclerosis caused by excess sphingolipid synthesis, Mohassel et al.