GEN-02

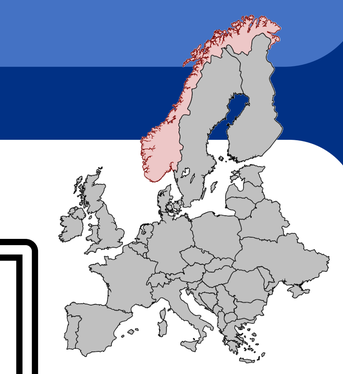
Clinical and genetic characteristics of sporadic ALS in Norway

Camilla Novy[1,2], Maria Fahlström[1], Cathrine Goberg Olsen[1], Ole-Bjørn Tysnes[3,4], Karl Bjørnar Alstadhaug[5], Ingrid Kristine Bjørnå[6], Geir Bråthen[7], Hanne Elisabeth Eide-Leigh[7], Agnethe Eltoft[8], Natasha Demic[9], Heidi Øyen Flemmen[10], Kristine Forselv[11], Anna Kristine Grav[12], Erika Hallerstig[13], Ineke HogenEsch[14], Grethe Kleveland[15], Angelina Maniaol[16], Åse Hagen Morsund[17], Katrin Schlüter[18], Elin Seim[19], Gudveig Lunde Toverud[8], Øystein Holla[1], Trygve Holmøy[2,20], Helle Høyer[1,2].

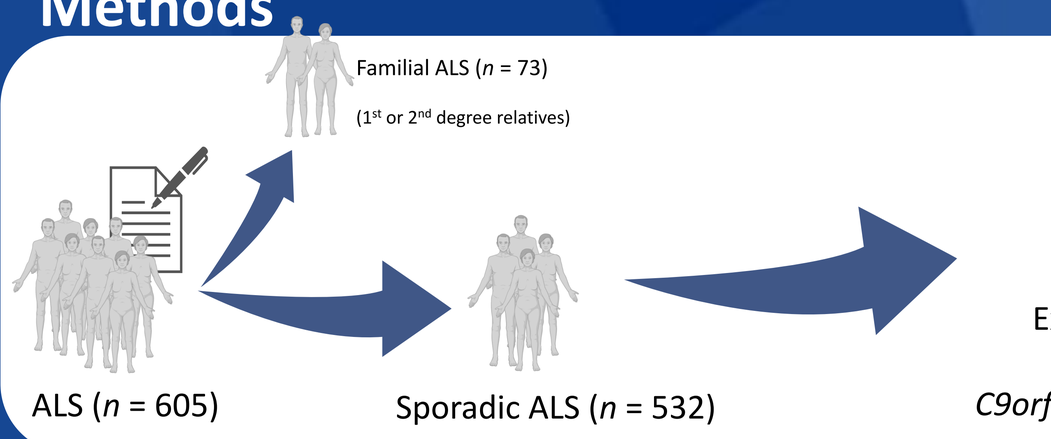
[1]Department of Medical Genetics, Telemark Hospital Trust, Skien, Norway, [2]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Neurology, Haukeland University Hospital, Bergen, Norway, [4]Clinical Department, University of Bergen, Bergen, Norway, [5]Department of Neurology, Nordland Hospital Trust, Bodø, Norway, [6]Department of Neurology, Vestre Viken Hospital Trust, Drammen, Norway, [7]Department of Neurology and Clinical Neurophysiology, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [8]Department of Neurology, University Hospital of North Norway, Tromsø, Norway, [9]Department of Neurology, Vestfold Hospital Trust, Tønsberg, Norway, [10]Department of Neurology, Telemark Hospital Trust, Skien, Norway, [11]Department of Neurology, Sørlandet Hospital Trust, Kristiansand, Norway, [12]Department of Neurology, Nord-Trøndelag Hospital Trust, Namsos, Norway, [13]Department of Neurology, Østfold Hospital Trust, Grålum, Norway, [14]Department of Neurology, Fonna Hospital Trust, Haugesund, Norway, [15]Department of Neurology, Innlandet Hospital Trust, Lillehammer, Norway, [16]Department of Neurology, Oslo University Hospital, Oslo, Norway, [17]Department of Neurology, Møre og Romsdal Hospital Trust, Molde, Norway, [18]Department of Neurology, Stavanger University Hospital, Stavanger, Norway, [19]Department of Neurology, Førde Hospital Trust, Førde, Norway, [20]Department of Neurology, Akershus University Hospital, Lørenskog, Norway.

Introduction

- Genetic discoveries have increasingly blurred the line between familial and sporadic amyotrophic lateral sclerosis (ALS).
- About 10% of ALS cases are traditionally classified as familial ALS (fALS), and recent studies have demonstrated that a notable proportion of patients with no known family history, so-called sporadic ALS (sALS), carry pathogenic variants in genes commonly associated with fALS. These findings raise important questions about how we define "sporadic" disease, and how genetic information should guide clinical practice.
- In this study, we investigated the clinical and genetic characteristics of Norwegian patients with sALS retrieved from the genetic study of ALS in Norway (the GAIN-study).



Methods

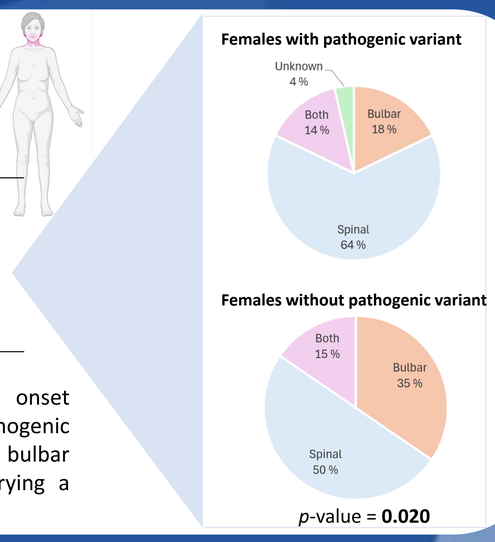


Results

Table 1: Overview of the site of onset in sporadic ALS patients

p-value = **0.001**	**Male** ***n*** **= 316**	**Female** ***n*** **= 216**
Bulbar	64 (20.3 %)	70 (32.4 %)
Spinal	218 (69.0 %)	112 (51.9 %)
Both	34 (10.8 %)	33 (15.3 %)
Unknown	0 (0.0 %)	1 (0.5 %)

Male sALS patients had more frequently spinal onset compared to females, independently of a pathogenic variant. Female sALS patients had more frequently bulbar onset, and even higher frequence when not carrying a pathogenic variant.



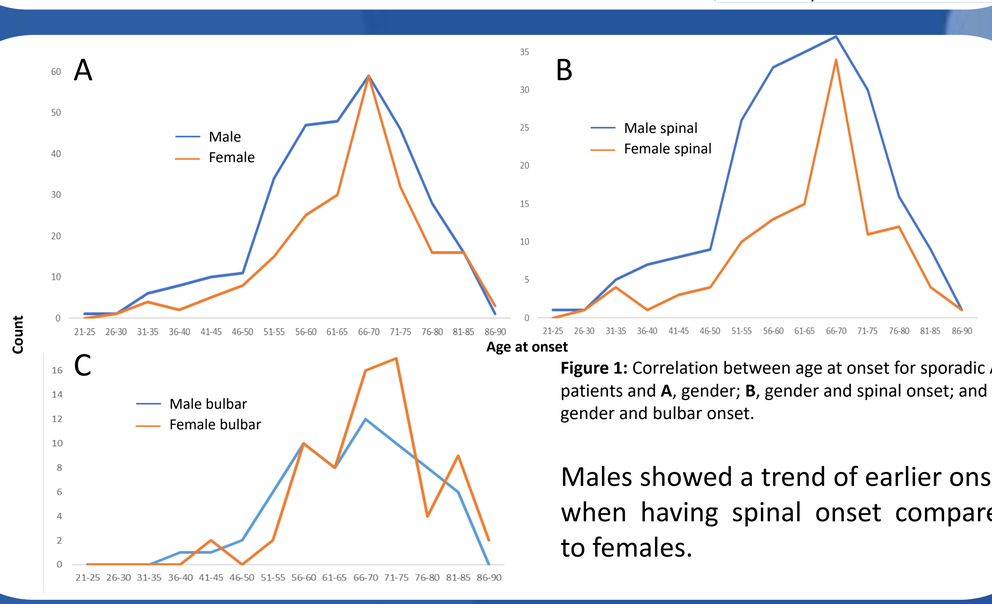


Figure 1: Correlation between age at onset for sporadic ALS patients and **A**, gender; **B**, gender and spinal onset; and **C**, gender and bulbar onset.

Males showed a trend of earlier onset when having spinal onset compared to females.

Table 2: Pathogenic and likely pathogenic variants in 65 sporadic ALS patients. ; three individuals carried two variants.

Gene	**Consequence**	**Number of variants** ***n*** **= 68**
C9orf72	≥ 145 repeats	34 (52.3 %)
SOD1	p.Asp91Ala	4 (6.2 %)
SOD1	p.Cys147Gly	1 (1.5 %)
SOD1	p.Ile150Met	1 (1.5 %)
SOD1	p.Ile150Leu	1 (1.5 %)
ATXN2	≥ 29 repeats	12 (18.5 %)
NEK1	p.Ser1036*	5 (7.7 %)
NEK1	p.Arg127*	3 (4.6 %)
NEK1	p.Asn1114Thrfs*48	1 (1.5 %)
OPTN	p.Asp124fs	1 (1.5 %)
TARDBP	p.Ile383Val	1 (1.5 %)
TBK1	c.701+1G>A	1 (1.5 %)
TBK1	P.Glu696Lys	1 (1.5 %)
TBK1	p.Glu643del	2 (3.1 %)

Pathogenic and likely pathogenic variants were identified in 65 of 532 patients (12.2%), including 27 females (12.5%) and 38 males (12.0%).

Importantly, 2.1% (*n* = 11) of the sALS patients reported more distant relatives (not 1st or 2nd degree) with ALS, and 4 of these patients carried pathogenic variants.

Conclusion

- Male sporadic ALS patients had more frequently spinal onset, while female sporadic ALS patients had more frequently bulbar onset, and even more frequent when carrying a pathogenic variant.
- A notable share of sporadic ALS patients (12.2 %) carry pathogenic variants, often in genes with reduced penetrance. Expanding genetic testing for all ALS cases—regardless of family history—requires cautious interpretation and further research into the impact of these findings and risk for family members.

Presenting author:
Camilla Novy | PhD-candidate
Section of Medical Genetics
Telemark Hospital Trust
Skien, Norway
camnov@sthf.no
Phone: +47 35 00 31 46

The authors declare no conflicts of interest