Poster 24295

Amyotrophic lateral sclerosis caused by the *C9orf72* expansion in Norway – prevalence, ancestry, clinical and demographic variables

Cathrine Goberg Olsen (1,2), Vetle Nilsen Malmberg (3), Maria Fahlström (1), Karl Bjørnar Alstadhaug (4), Ingrid Kristine Bjørnå (5), Geir Julius Braathen (1), Geir Bråthen (6), Natasha Demic (7), Erika Hallerstig (8), Ineke HogenEsch (9), Morten Horn (10), Margitta T. Kampman (11), Grethe Kleveland (12) Unn Ljøstad (13,14), Angelina Maniaol (10), Åse Hagen Morsund (15), Ola Nakken (16), Katrin Schlüter (17), Stephan Schuler (18), Elin Seim (19), Heidi Øyen Flemmen (3) Ole-Bjørn Tysnes (20), Trygve Holmøy (2,16), Helle Høyer (1,2*)

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

Introduction

- ✓ Expansion of *C9orf72* is the most common genetic cause of amyotrophic lateral sclerosis (ALS).
- ✓ The *C9orf72* expansion cause ALS, frontotemporal dementia (FTD) or a combination of ALS and FTD.
- ✓ The *C9orf72* expansion has high incidence in Norway's neighboring countries Sweden and Finland.

AIM OF THE STUDY:

1) Determine the prevalence, geographic distribution and ancestry of *C9orf72*-positive ALS patients in Norway.
2) Identify differences between *C9orf72*-positive and *C9orf72*-negative ALS patients with regard to clinical presentation, family history and sociodemographic variables.

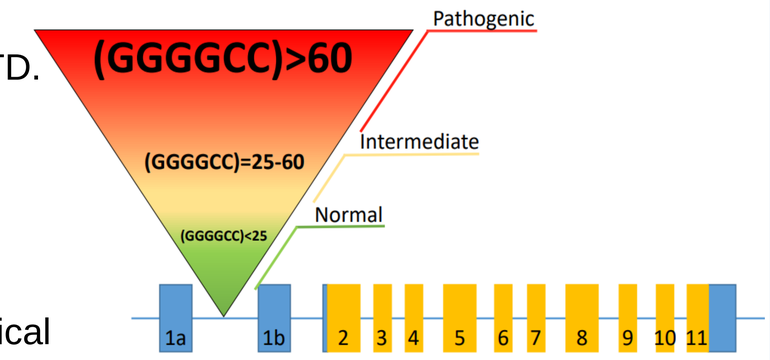
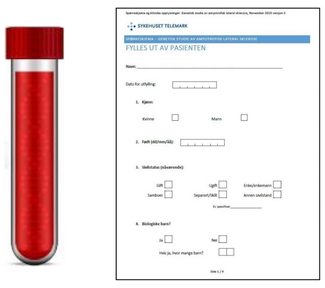
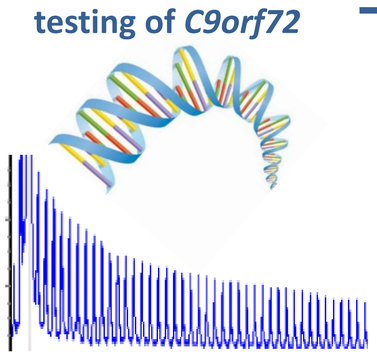


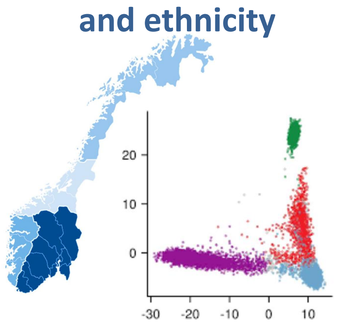
Fig 1: Illustration of *C9orf72* repeats size.
Inspired by S. Breevoort et al. 2022

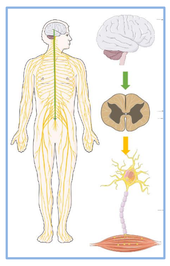
Methods

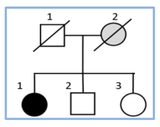
500 patients with ALS from all parts of Norway → **Sample collection, clinical evaluation and questionnaires** → **Genetic expansion testing of *C9orf72*** → **Identification of regional differences and ethnicity** → **Comparison of *C9orf72* positive and negative ALS patients**







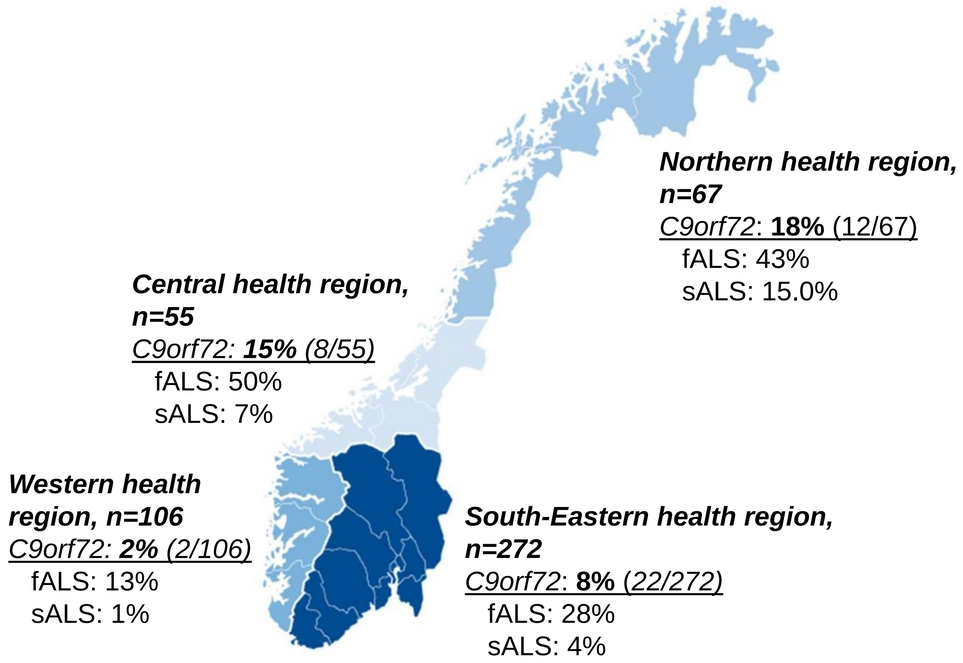




Clinical, familial and socio-demographic variables

Results: Prevalence, regional differences and ethnicity

Norwegian ALS patients, n=500
C9orf72 positive = 44/500 (8,8%)

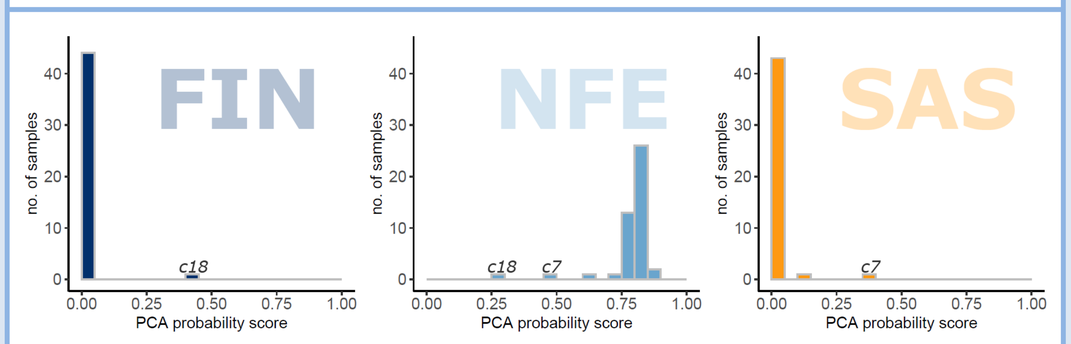


Northern health region, n=67
C9orf72: **18%** (12/67)
fALS: 43%
sALS: 15.0%

Central health region, n=55
*C9orf72: **15%** (8/55)*
fALS: 50%
sALS: 7%

Western health region, n=106
*C9orf72: **2%** (2/106)*
fALS: 13%
sALS: 1%

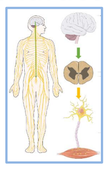
South-Eastern health region, n=272
C9orf72: **8%** (22/272)
fALS: 28%
sALS: 4%



Genetic ethnicity of the included *C9orf72* positive ALS patients detected by PCA on NGS data. 43 out of 44 C9pos patients were of non-Finnish European descent. One patient had ~50% Finnish ancestry, and another had a partly South Asian ancestry. No African, American, East Asian, or Ashkenazi Jewish ancestry was detected.
Abbreviations: FIN: Finnish; NFE: Non-Finnish European; SAS: South Asian.

Results: Comparison of *C9orf72* positive and negative patients

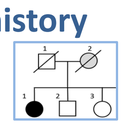
Clinical characteristics



- $C9_{pos}$ patients had shorter mean survival time compared to $C9_{neg}$ patients.
- Gender distribution, age, site of onset and cognitive impairment did not differ significantly.

	$C9_{pos}$ 8.8% (n=44)	$C9_{neg}$ 91.2% (n=456)	p Value
Sex male, % (n)	52.3% (23)	58.8% (268)	0.404
Age at onset, median years (IQR)	63 (54.3-69.0)	66 (57.0-72.0)	0.258
Site of onset, % (n)			0.079
Bulbar	28.6% (12)	26.0% (118)	
Spinal	50.0% (21)	63.3% (286)	
Both	21.4% (9)	10.6% (48)	
Cognitive impairment (YES), % (n)	11.9% (5)	7.6% (34)	0.585
Uncertain	2.4% (1)	3.3% (15)	
Motor neuron sign, % (n)			0.322
Upper domination	6.8% (3)	2.7% (12)	
Lower domination	15.9% (7)	16.5% (73)	
Both	77.3% (34)	80.8% (358)	
Months from diagnosis until death	n=29	n=253	**0.042**
Median (IQR)	16 (9.25-23)	19 (10-35)	

Family history



- $C9_{pos}$ patients had more often a family history of ALS.
- $C9_{pos}$ patients had more often family members with FTD, Alzheimer and dementia.

	$C9_{pos}$ 8.8% (n=44)	$C9_{neg}$ 91.2% (n=456)	p Value
Relatives with ALS, % (n)	**50.0% (22)**	**11.0% (50)**	**<0.001**
1st degree	34.1% (15)	6.8% (31)	
2nd degree	9.1% (4)	2.4% (11)	
3rd – 5th degree	6.8% (3)	1.8% (8)	
Relatives with neurodegen. dis. % (n)	**50.0% (22)**	**31.6% (144)**	**0.011**
FTD	4.6% (2)	0.7% (3)	
Alzheimer	6.8% (3)	2.0% (9)	
Dementia unspecified	18.2% (8)	11.0% (50)	
Parkinson	9.1% (4)	6.6% (30)	
Unspecified/other	13.6% (6)	12.9% (59)	

Sociodemographic variables

- $C9_{pos}$ patients were more likely to be unmarried and have fewer children.
- Education level and place of residence did not differ between $C9_{pos}$ and $C9_{pos}$ patients.

	$C9_{pos}$ 8.8% (n=44)	$C9_{neg}$ 91.2% (n=456)	p Value
Relationship status, % (n)			**<0.001**
Married/cohabitating	72.1% (31)	78.6% (352)	
Unmarried/single	20.5% (9)	4.3% (19)	
Widow/widower	4.5% (2)	8.1% (36)	
Divorced	2.3% (1)	9.2% (41)	
Number of children, % (n)			**0.024**
None	23.3% (10)	9.1% (41)	
One child	7.0% (3)	11.8% (53)	
Two or more children	69.8% (30)	79.2% (357)	
Education level, % (n)			0.641
Primary school (≤ 10 years)	16.7% (7)	17.8% (80)	
Secondary school (10-13 years)	42.9% (18)	35.6% (160)	
Graduate school (≥ 14 years)	40.5% (17)	46.5% (209)	
Centrality index, % (n)			0.996
Urban (1 or 2)	40.9% (18)	40.8% (184)	
Suburban (3 or 4)	43.2% (19)	42.8% (193)	
Rural (5 or 6)	15.9% (7)	16.4% (74)	

Conclusion

- ➢ *C9orf72* is detected in 9% of Norwegian ALS patients with large regional differences.
- ➢ *C9orf72* patients are more likely to have a shorter disease duration, be unmarried, and have fewer children.
- ➢ Half of the *C9orf72* patients report no family history of ALS, highlighting the importance of considering genetic testing for all ALS patients.

Presenting author:
Helle Høyer, PhD
Clinical laboratory geneticist / Researcher
Department of Medical Genetics, Telemark Hospital
Division of Medicine and Laboratory Sciences, University of Oslo
Norway
helle.hoyer@sthf.no | +47 35 00 31 46

The authors declare no conflicts of interest