Mapping of relatedness in a Norwegian ALS cohort

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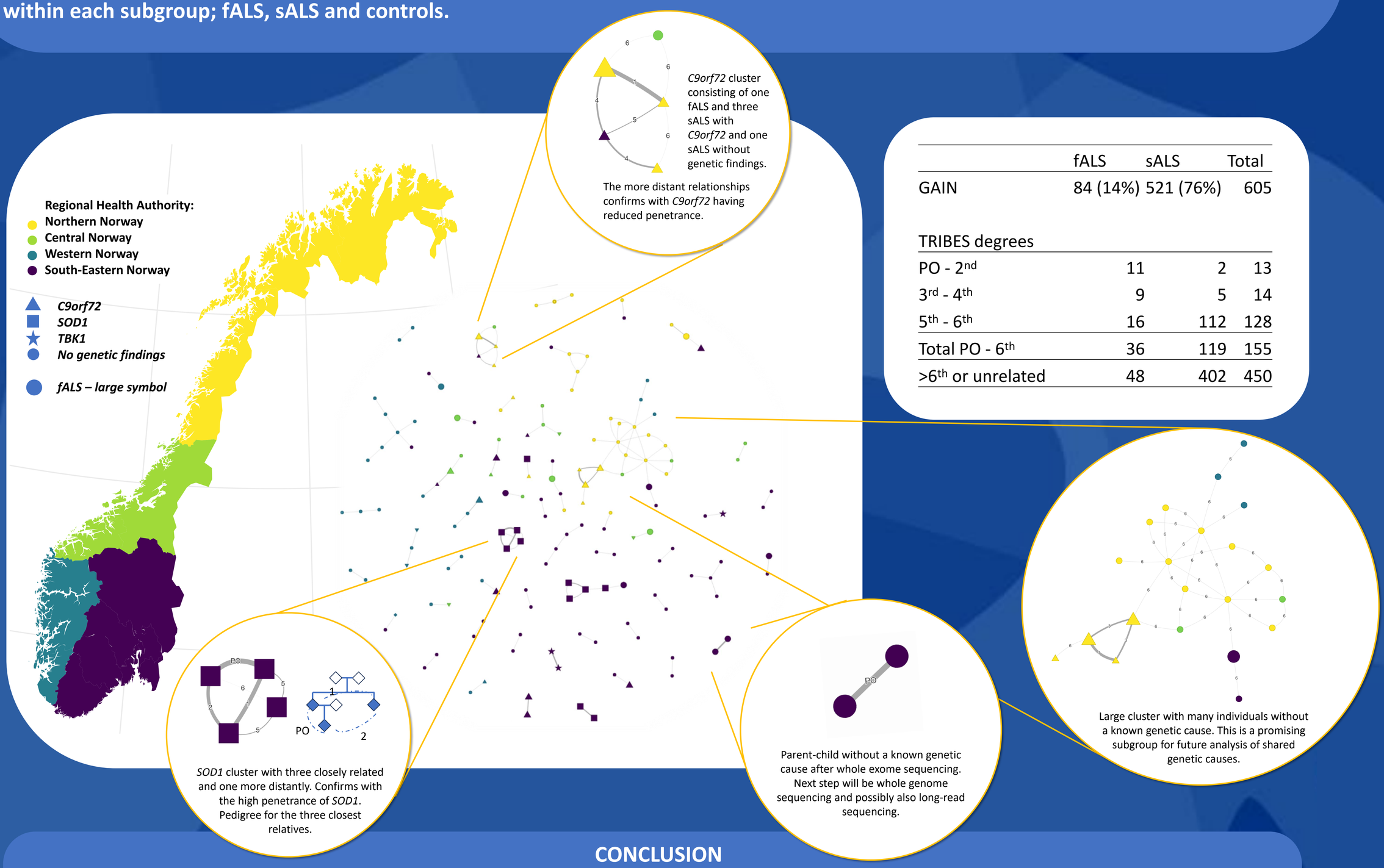
INTRODUCTION

The GAIN study (Genetics of ALS in Norway) , initiated in 2019, has enrolled over 700 ALS patients, collecting data on both close and distant relatives with ALS. Given that most people are not aware of disease history and cause of death of their distant relatives, identifying alternative measures of familial aggregation would enhance our understanding of the underlying genetics of ALS in Norway. In this study, we used an Identity-by-Descent (IBD) analysis tool to investigate close and distant relationships (parent-offspring (PO) – 6th degree) within the cohort. In particular, we were interested in clusters of participants with identical genetic variants. Further, we aimed to determine the proportion of relatedness among ALS patients compared to geographically matched controls.

METHODS

Whole-exome sequencing data from 605 ALS patients were processed using an in-house Nextflow pipeline. All participants provided written informed consent. IBD analysis was performed with the TRIBES[1] pipeline (minimum IBD segment length set to 7 cM), focusing on pairwise relationships up to the 6th degree. Results were visualized as a network, with samples annotated by place of residence, pathogenic genetic variants, and self-reported familial (fALS) or sporadic ALS (sALS). To compare the proportion of relatedness between the ALS cohort and geographically matched controls, a permutation test was performed to assess the average degree of relatedness within each subgroup; fALS, sALS and controls.



	fALS	sALS	Total
GAIN	84 (14%)	521 (76%)	605
TRIBES degrees			
PO - 2nd	11	2	13
3rd - 4th	9	5	14
5th - 6th	16	112	128
Total PO - 6th	36	119	155
>6th or unrelated	48	402	450

CONCLUSION

The study reveals previously unrecognized distant relationships among ALS patients in the GAIN cohort, across both familial and sporadic cases. Clustering of *SOD1*- and *C9orf72*-patients confirm high penetrance of *SOD1* and intermediate penetrance of *C9orf72*. Clusters including patients without variants in known ALS genes are promising subgroups for future analysis of shared genetic causes. Unfortunately, the permutation test did not give a conclusive result due to too small cohort.

[1]Twine, N. A., Piotr, S., Henden, L., McCann, E.P., Blair, I.P., Williams, K.L, Bauer, D.C. TRIBES: A user-friendly pipeline for relatedness detection and disease gene discovery. *BioRxiv* (2019). https://doi.org/https://doi.org/10.1101/686253