Mapping of relatedness in a Norwegian ALS cohort

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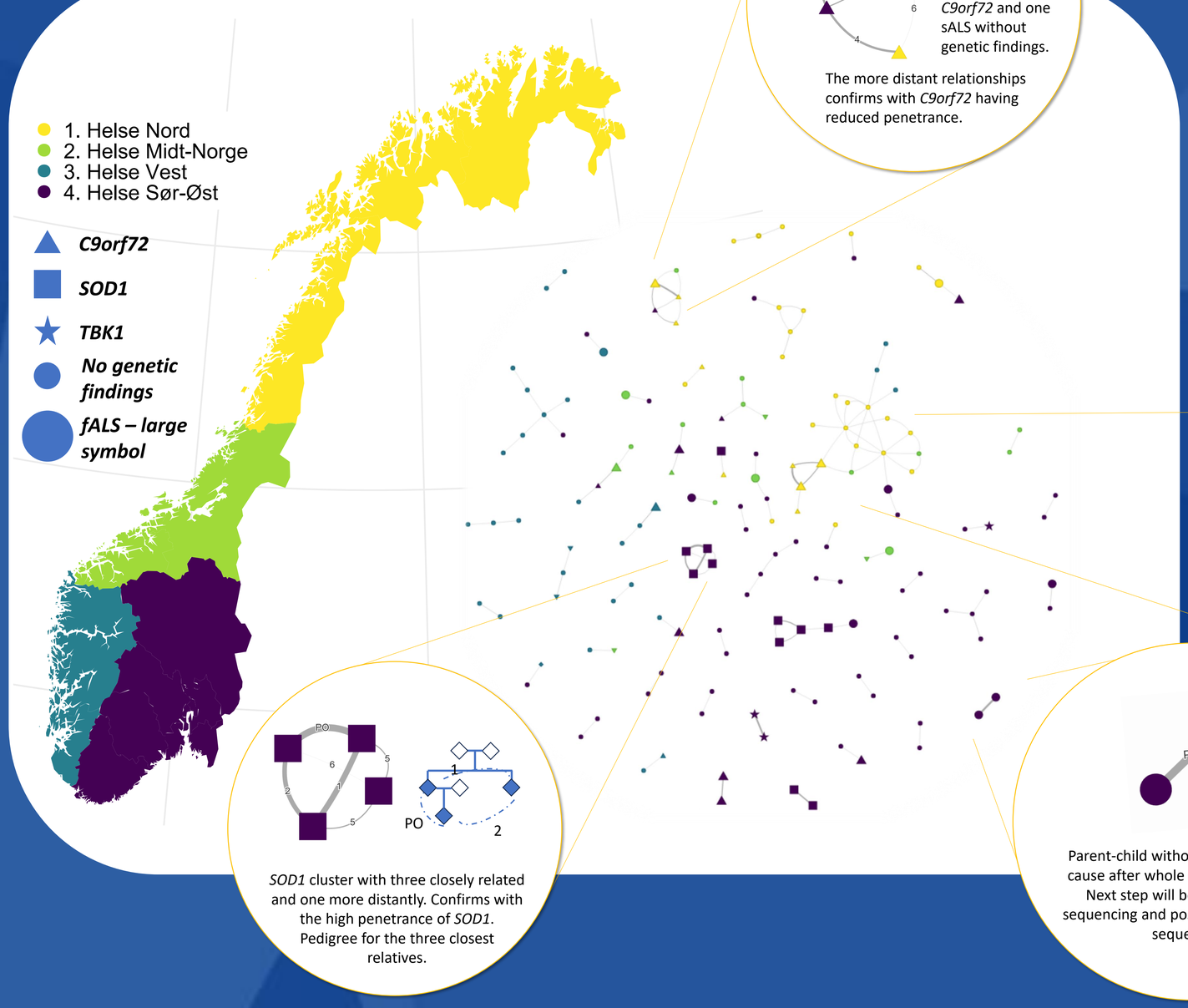
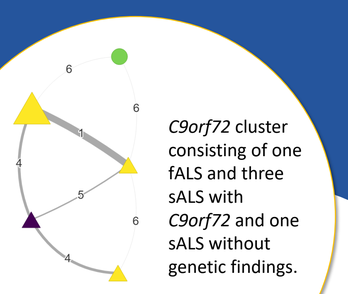
Background:

The GAIN study, 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.

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).





C9orf72 cluster consisting of one fALS and three sALS with *C9orf72* and one sALS without genetic findings.

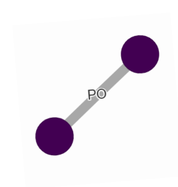
The more distant relationships confirms with *C9orf72* having reduced penetrance.

SOD1 cluster with three closely related and one more distantly. Confirms with the high penetrance of *SOD1*. Pedigree for the three closest relatives.

	fALS	sALS	Total
GAIN	84 (14%)	521 (76%)	605
TRIBES degrees			
PO - 2nd	11	2	13
3rd - 4th	9	4	13
5th - 6th	16	112	128
Total PO - 6th	36	118	154
>6th or unrelated	48	402	450

Large cluster with many individuals without a known genetic cause.

This is a promising subgroup for future analysis of shared genetic causes.



Parent-child without a known genetic cause after whole exome sequencing. Next step will be whole genome sequencing and possibly also long-read sequencing.

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.

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