

Mapping of relatedness in Norwegian ALS cohort

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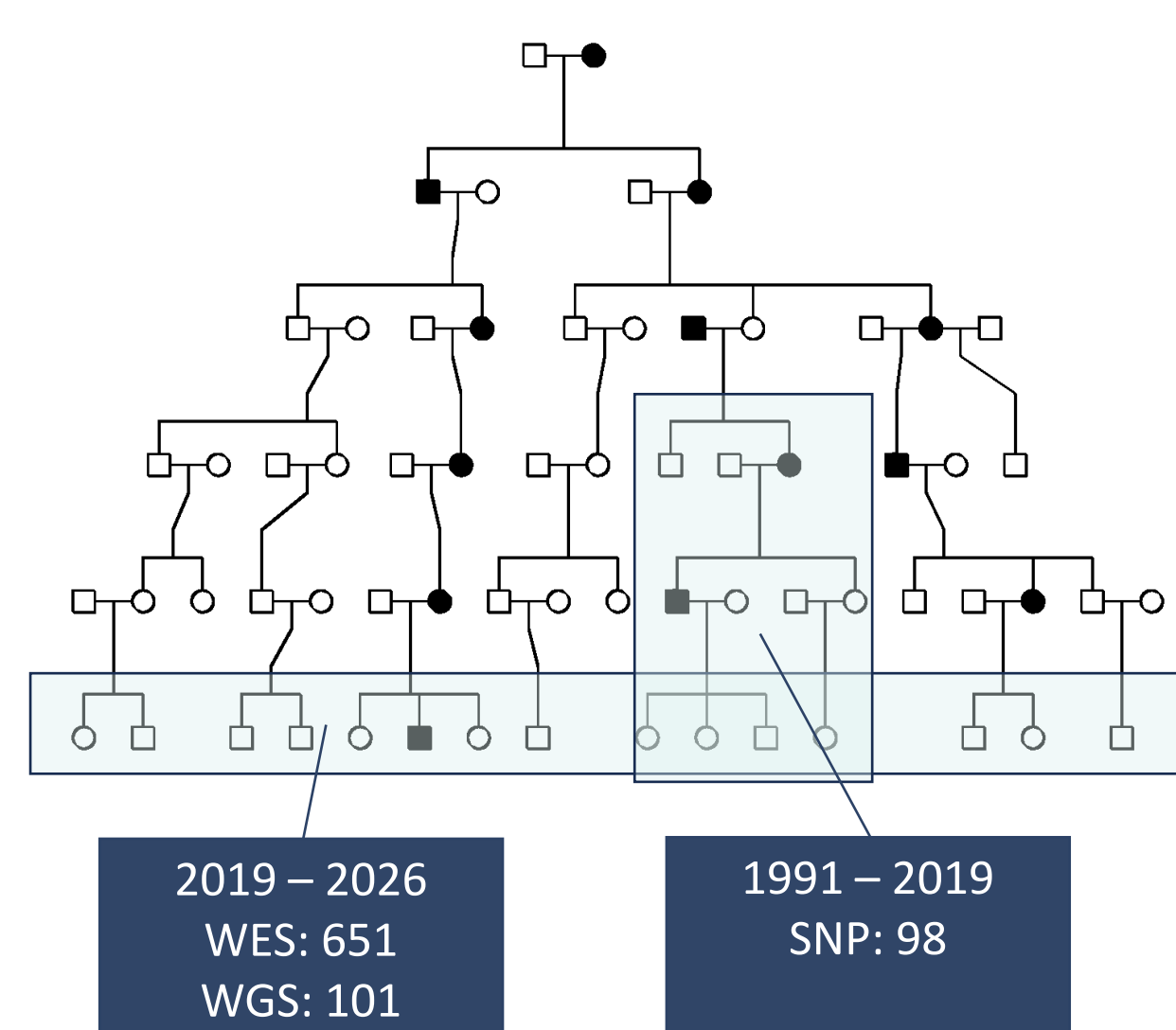
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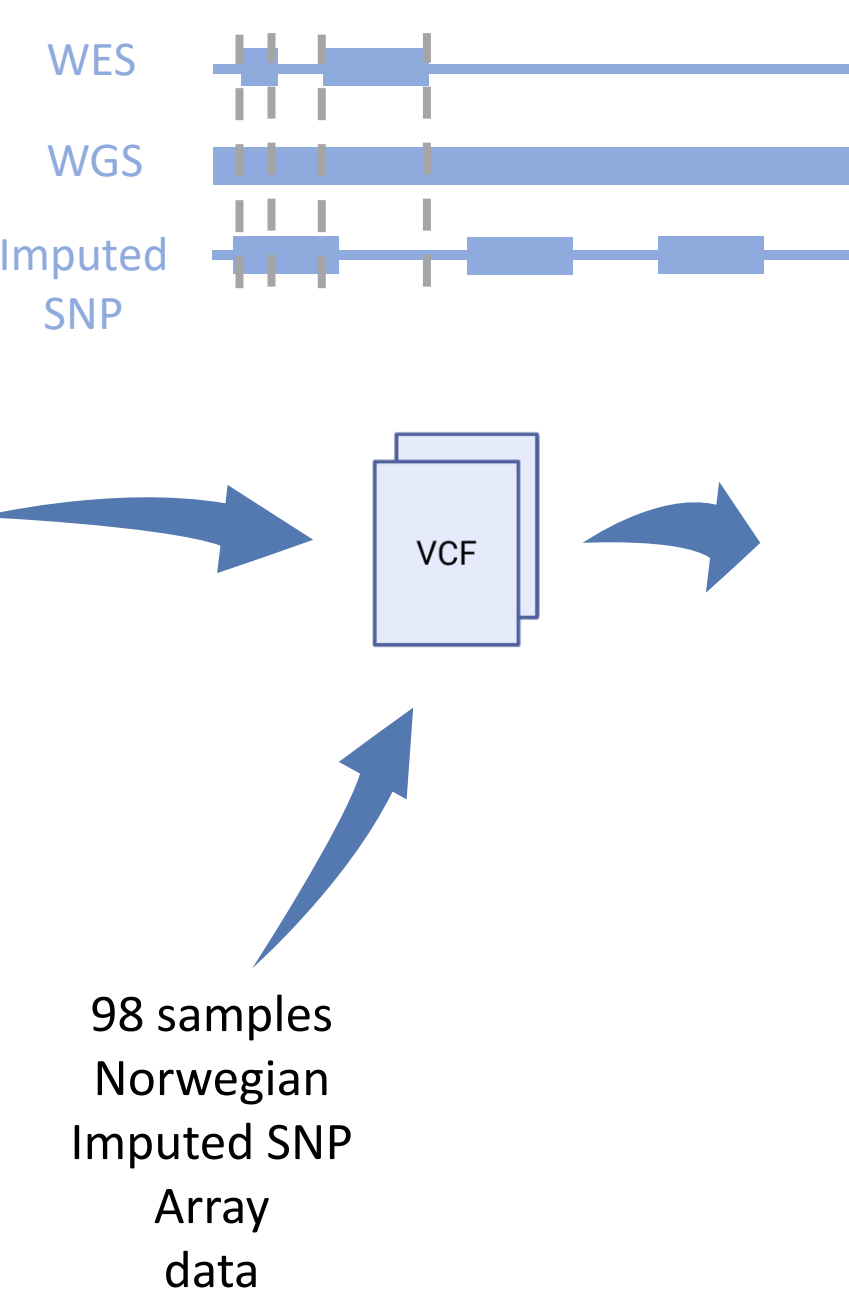
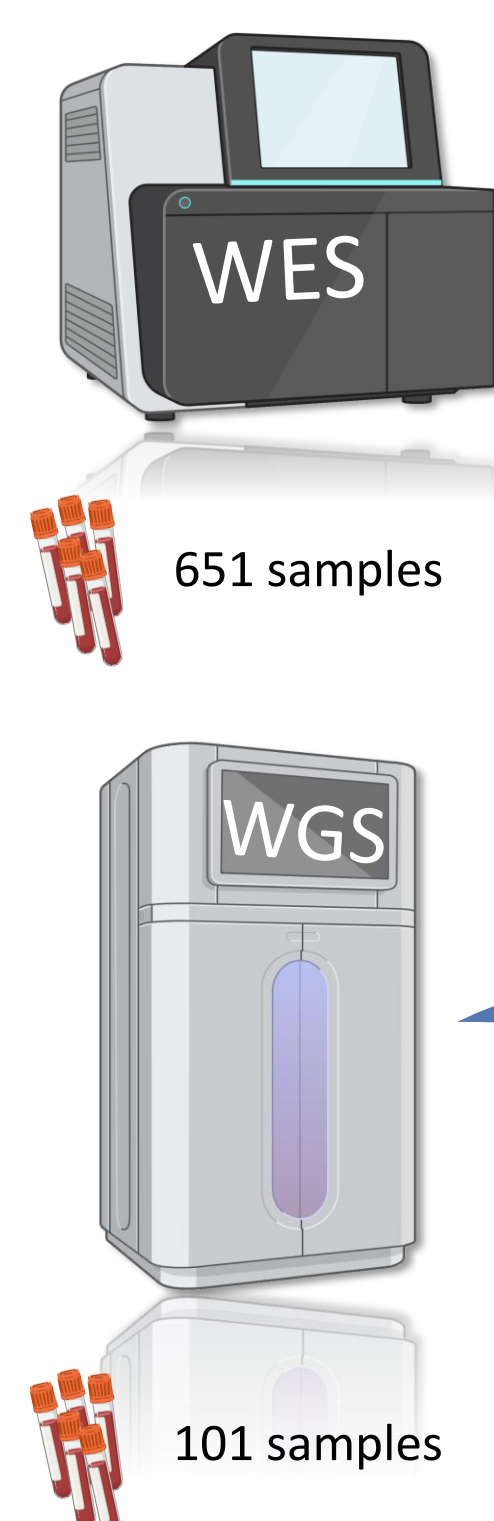
OBJECTIVES

The GAIN study (Genetics of ALS in Norway) was initiated in 2019 and has so far enrolled over 1,000 ALS patients from all 17 neurological clinics in Norway. For the first five years all samples underwent whole exome sequencing (WES), whereas from 2025 onwards, whole genome sequencing (WGS) has been applied. At inclusion, participants report of any known relatives with ALS. However, many ALS patients report no family history and might be unaware of more distant relatives. GAIN has been collecting data for the past six years and while it captures 60–80% of ALS cases in Norway, it likely misses links to earlier generations, limiting its ability to detect relatedness among Norwegian ALS patients. To improve the relatedness estimation, Norwegian imputed SNP array data from a previous project led by Peter Andersen was included.

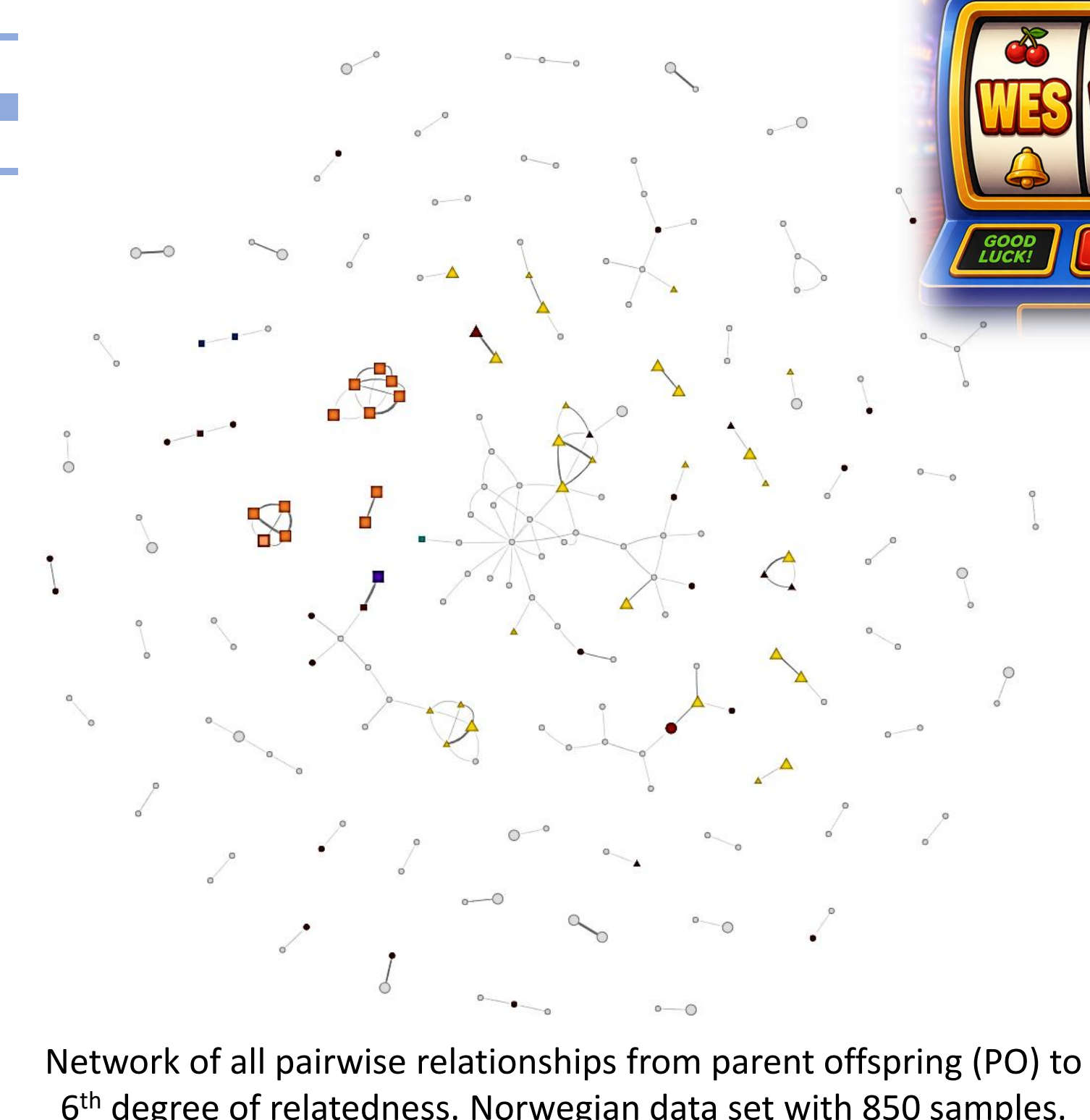
Our objective was to investigate close and distant relationships (parent-child to 6th degree) using an Identity-by-descent (IBD) analysis tool in a Norwegian cohort using a combination of WES, WGS and imputed SNP array data.



Peter Andersen's project Norwegian data



TRIBES¹ – relatedness estimation tool



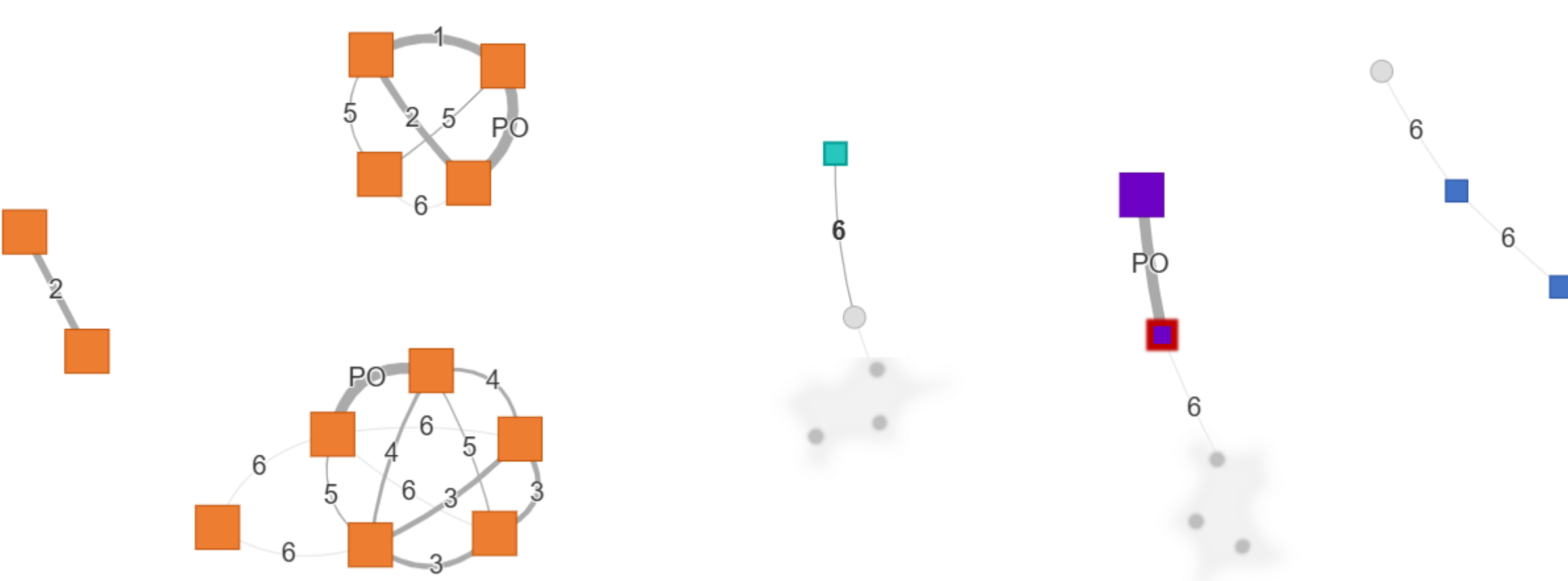
SOD1

Class	Variant	No. with variant n=850	Estimated relatedness PO – 6 th	Reported fALS	Reported sALS
5	het p.(Ile114Thr)	2	2	1	1
5	het p.(Asp91Ala)	5	1	1	4
5	het p.(Ala5Val)	1	-	1	0
5	het p.(His47Arg)	14	12	14	0
5	het p.(Gly94Ser)	1	-	1	0
4	het p.(Cys147Gly)	1	-	1	0
4	het p.(Glu101Lys)	1	-	1	0
4	het p.(Ile150Met)	1	-	-	1
4	het p.(Ile150Leu)	2	2	-	2
Total		27	13	19	8

C9orf72

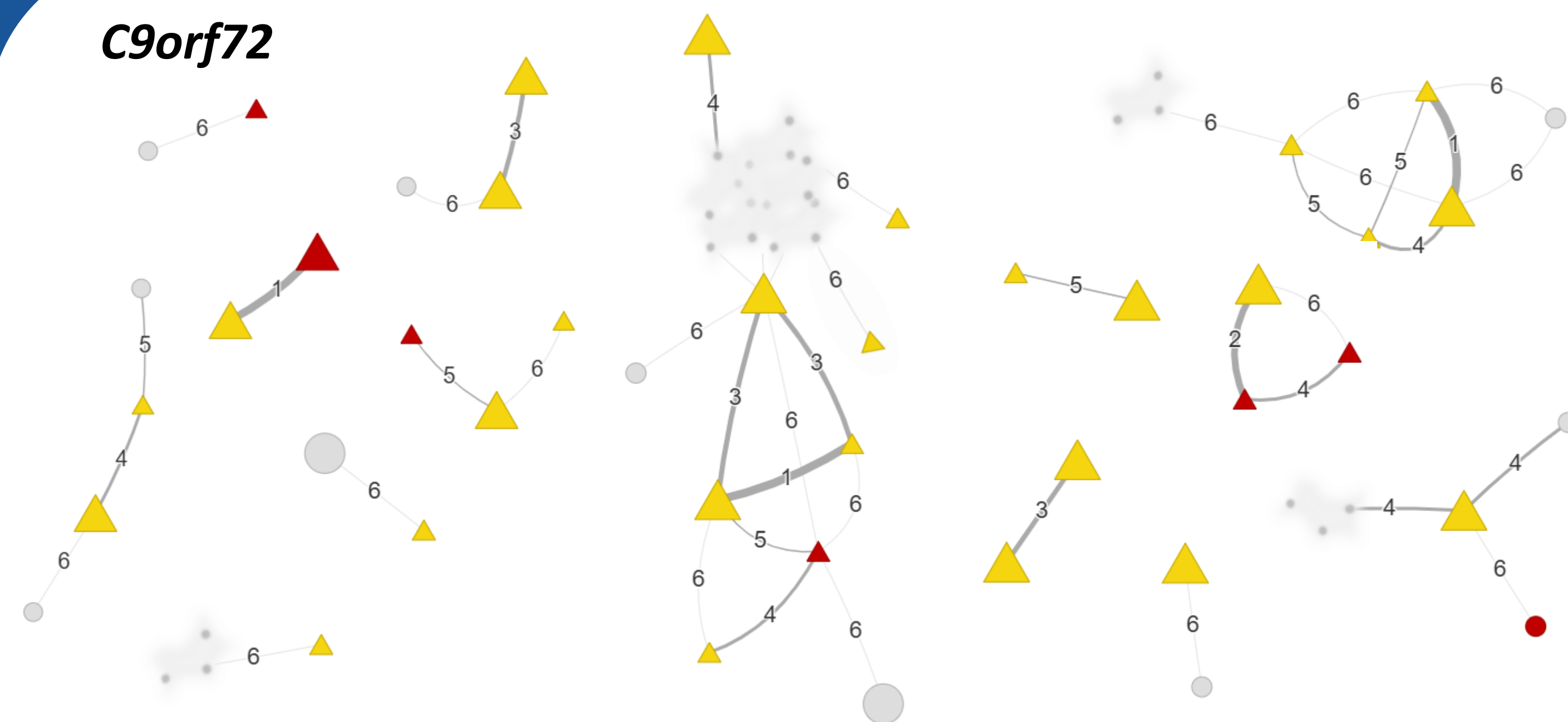
	No. with variant n=850	Estimated relatedness PO – 6 th	Reported fALS	Reported sALS
Expansion > 60, WES and WGS	75	27	34	41
Expansion > 60, Imputed SNP	12	6	3	9
Total	87	33	37	50

SOD1



12 of 14 patients with a *SOD1* p.(His47Arg) variant (orange) are estimated within six degrees as being related with another individual within the GAIN project. One Norwegian family of p.(His47Arg) has very well documented genealogical records and 11 of the 14 individuals belong to this pedigree.

C9orf72



For patients with a *C9orf72* expansion (triangles), usually with a more rapidly progressing ALS and lower penetrance, the individuals from the previous project with Peter Andersen (red triangles) creates important links between the generations. Large clusters with no known genetic cause (grey) are promising subgroups for future analysis of shared genetic causes.

CONCLUSION

The analysis identifies several previously unknown relationships and also displays distinct clusters in the Norwegian ALS cohort when including up to 6th degree relations. Clusters including patients without variants in known ALS genes are promising subgroups for future analysis of shared genetic causes.

For slowly progressing ALS, caused by *SOD1* p.(His47Arg), several generations affected by the disease will be alive at the same time and six years of data is sufficient to display the tight relatedness. While for faster progressing ALS caused by expansions in *C9orf72*, data going back 30 years in time are invaluable to show clustering and also closer relationships like siblings and avunculars.