

Validation of identity-by-descent tools applied to whole-exome sequencing data

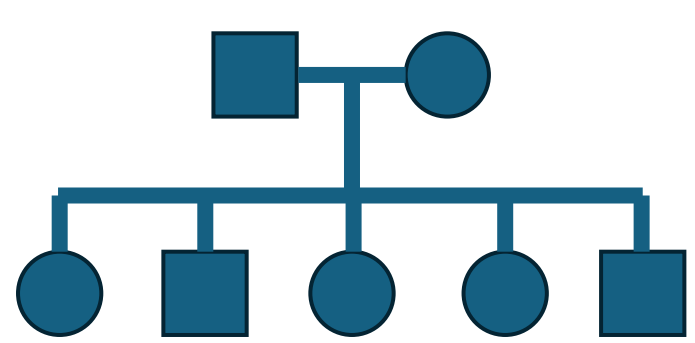
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Background: In many studies, it is important to know the degree of relatedness between participants. Most current tools for relatedness detection are primarily designed for SNP array or whole-genome sequencing data. This poses a challenge for labs relying on whole-exome sequencing (WES), as it remains unclear how these tools perform with WES data. We investigated the use of WES data to uncover close and distant relationships by validating four identity-by-descent (IBD) tools: TRIBES, GRAPE, XIBD and DRUID.

- 30 individuals from a Norwegian family with a known tenth-generation pedigree
- 30 presumed unrelated individuals from a Norwegian ALS cohort
- In total 1,770 pairwise relationships

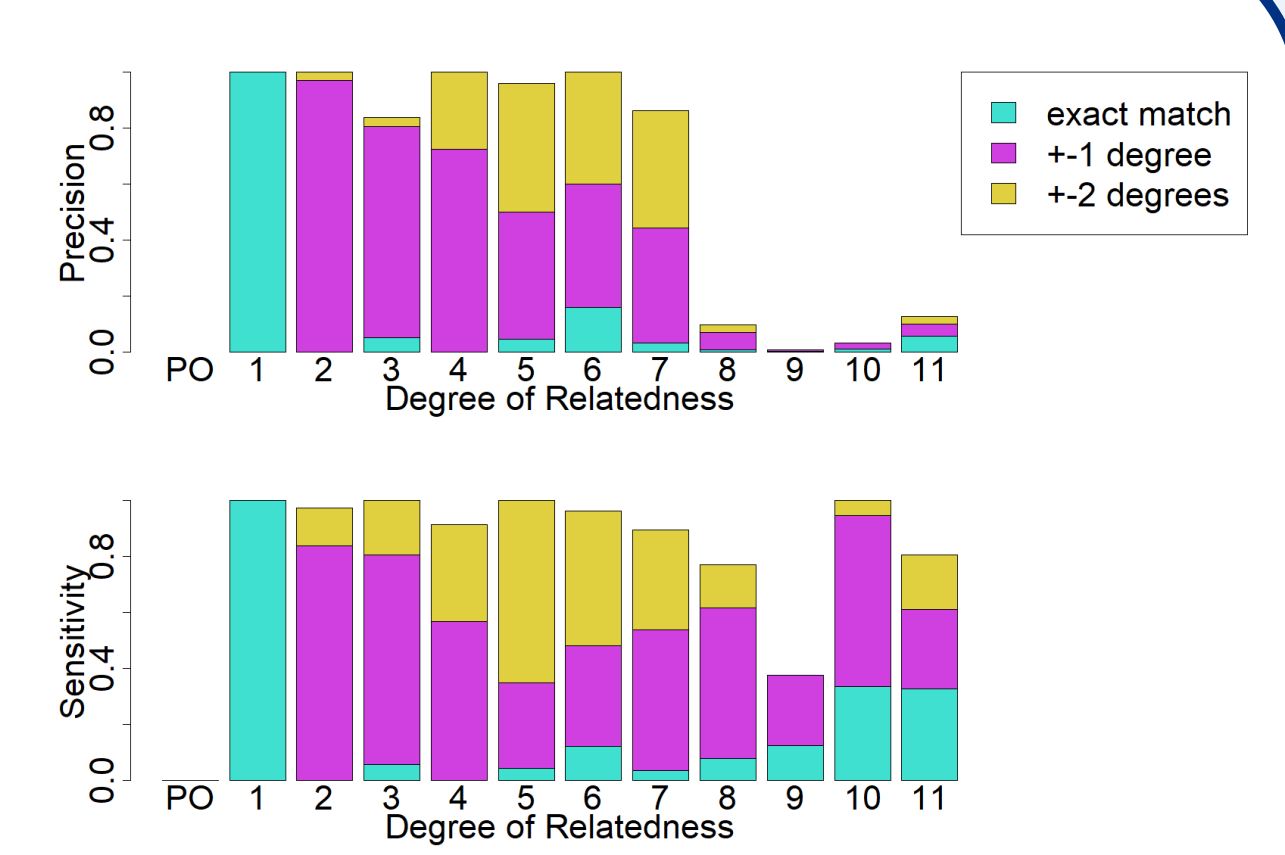
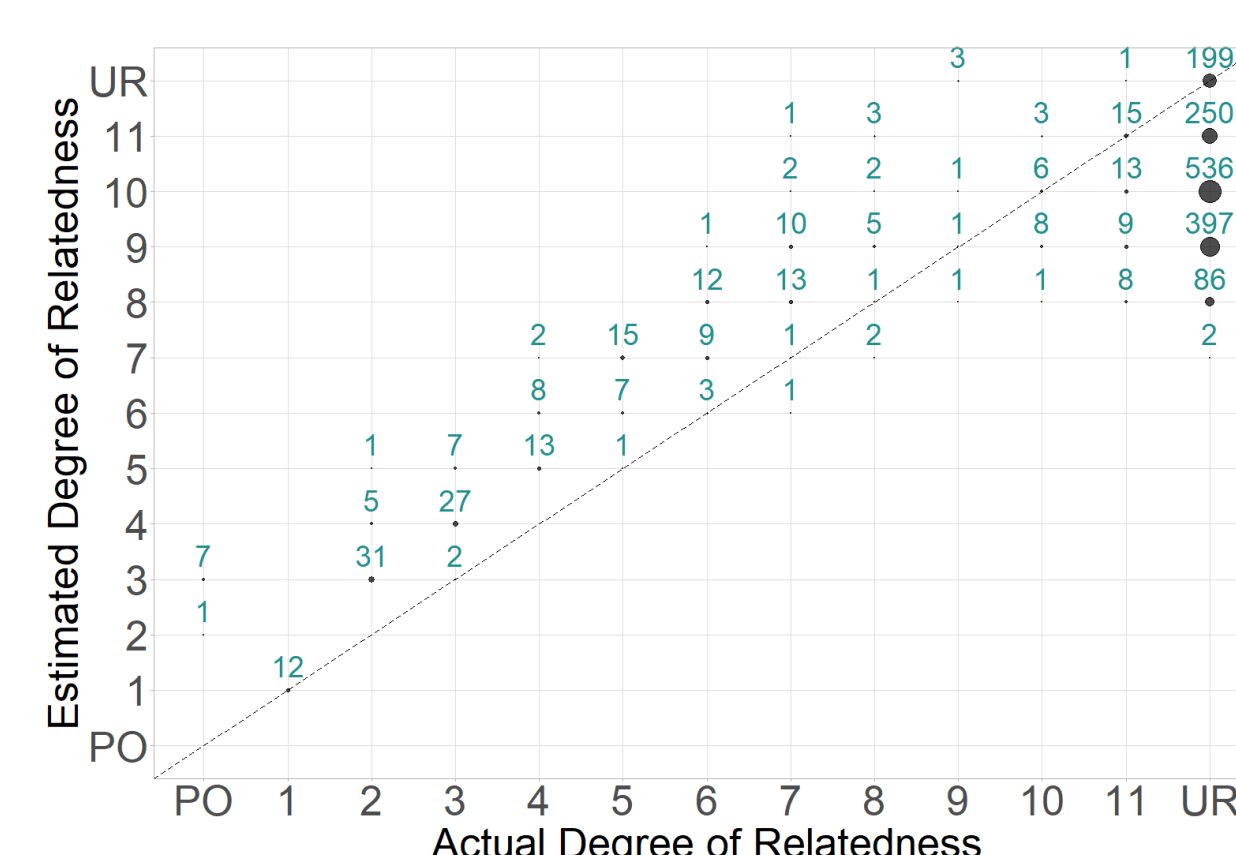


All samples underwent WES and were processed with an inhouse nextflow pipeline to produce a quality-filtered jointvcf



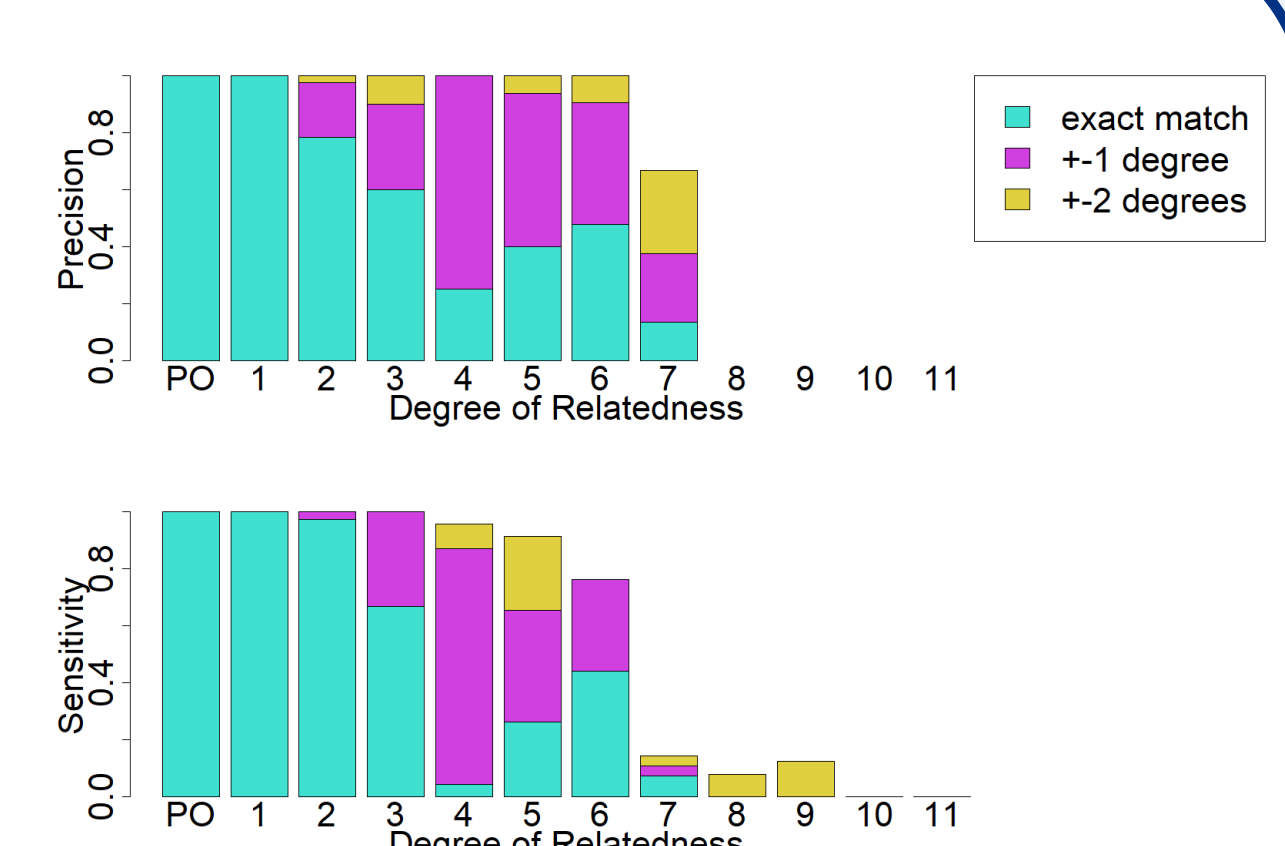
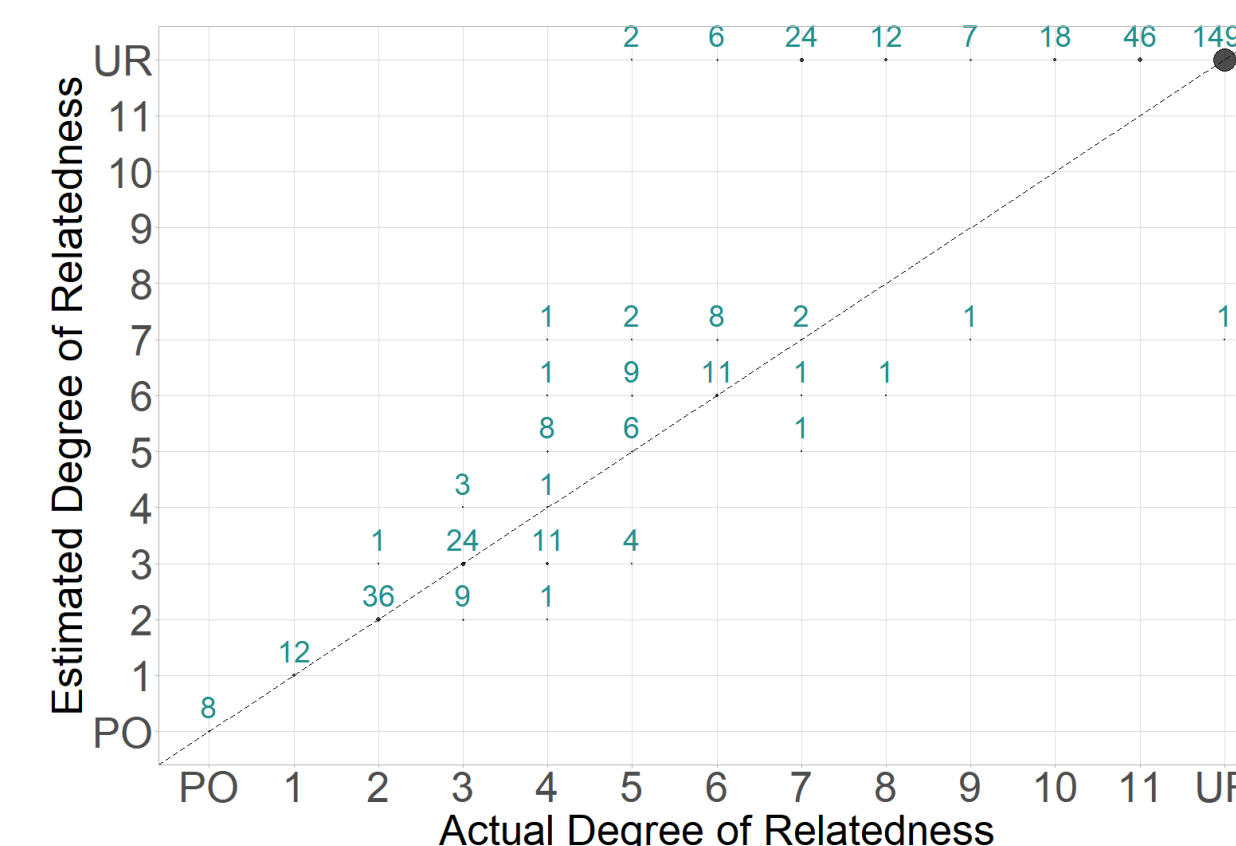
DRUID¹

Tool taking ibd-segments produced by RefinedIBD and performing relatedness inference in two steps. Set up with nextflow pipeline to use jointvcf as input. Default settings.



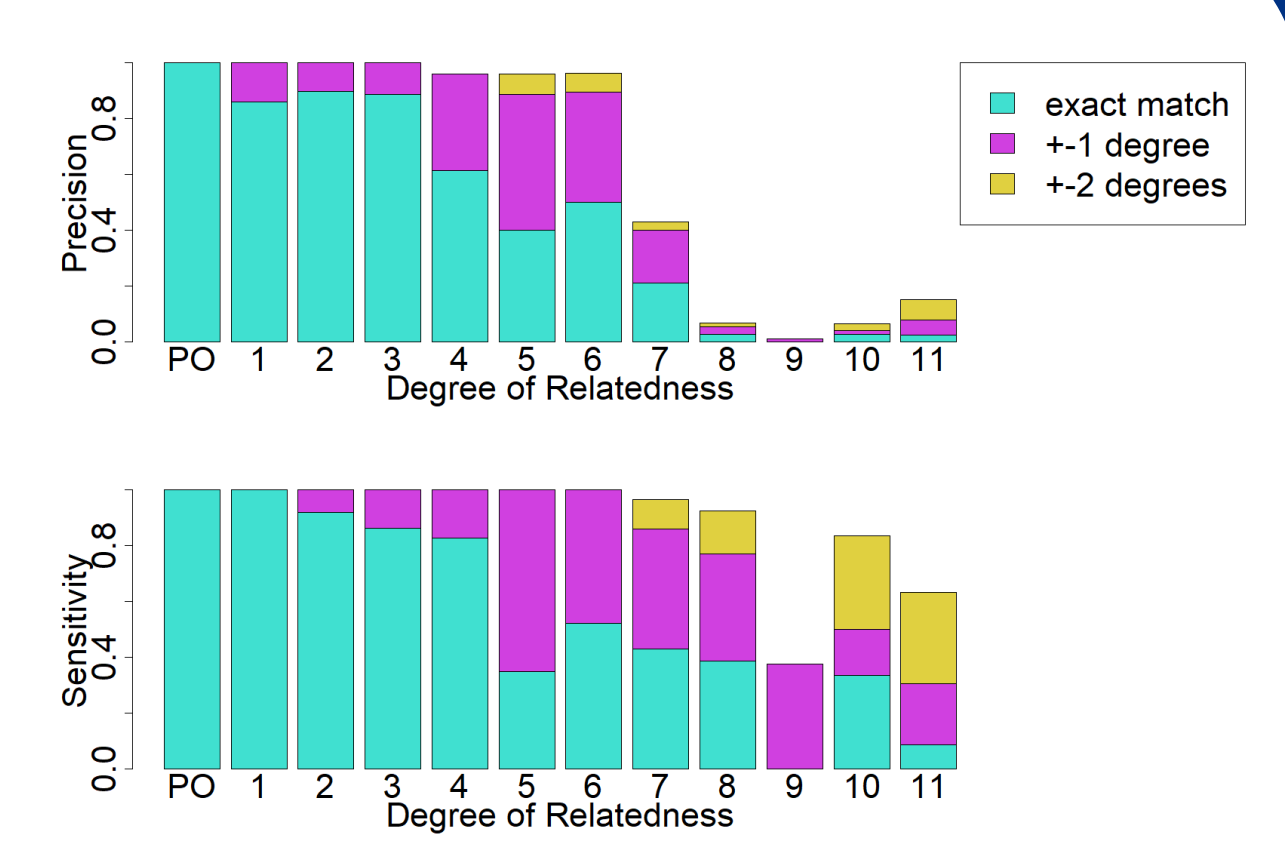
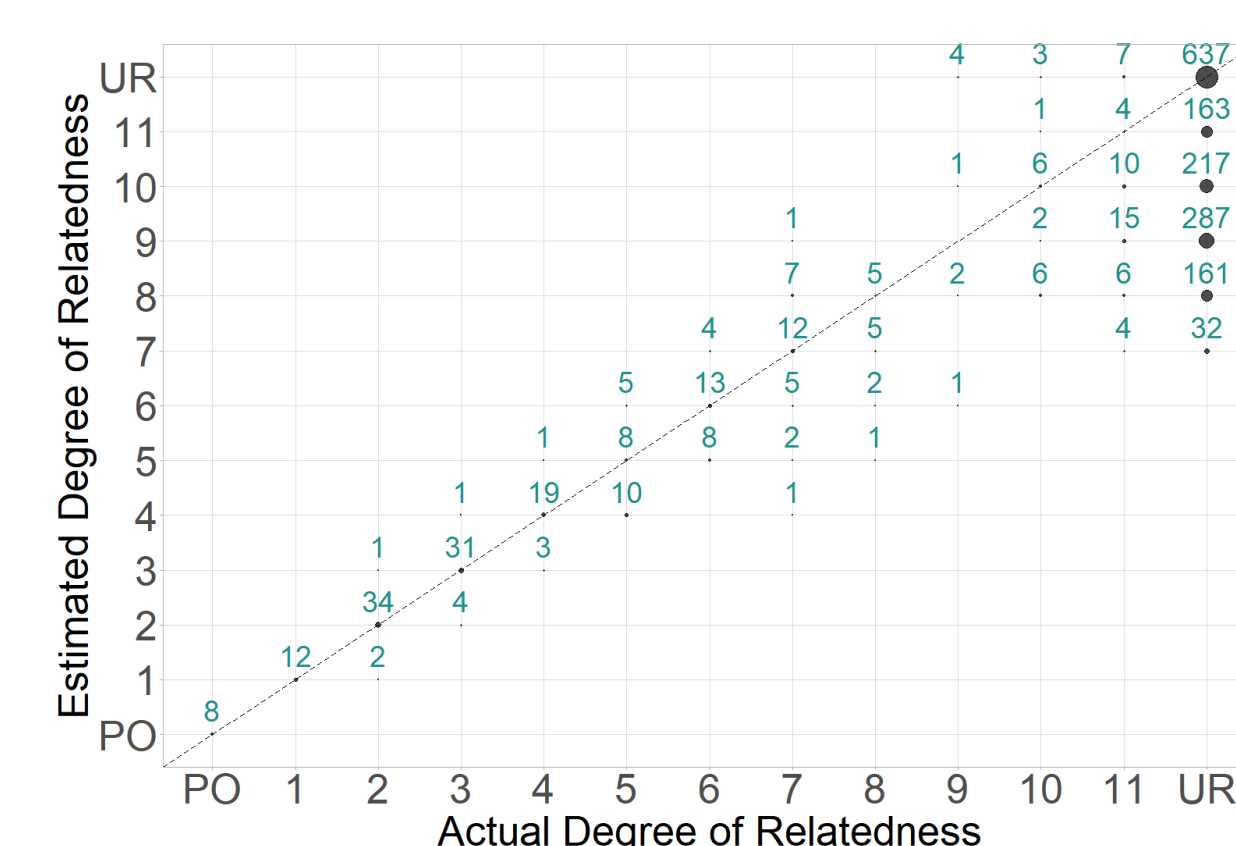
GRAPE²

Pipeline for relatedness detection in SNP data. Using jointvcf as input and combining IBIS and ERSa to compute degree of relatedness. Default settings.



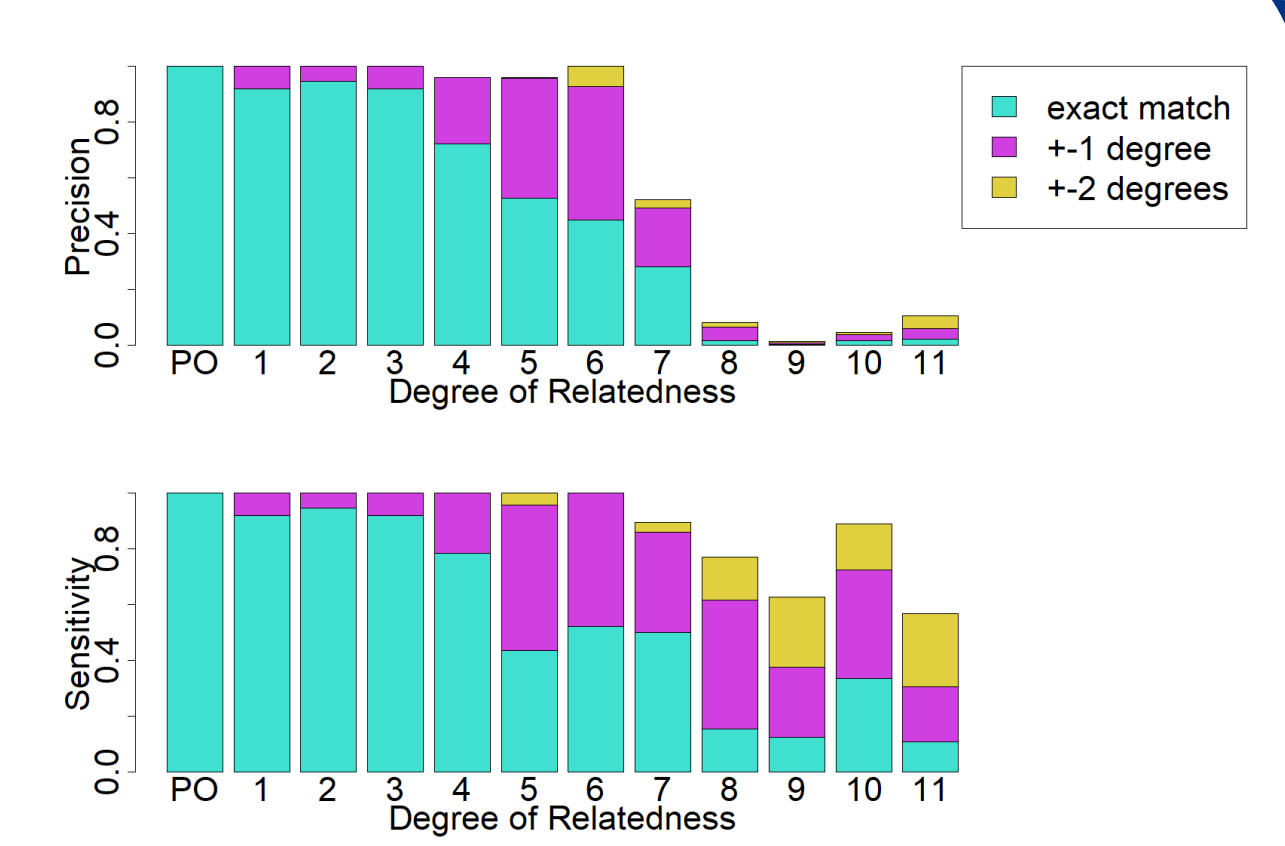
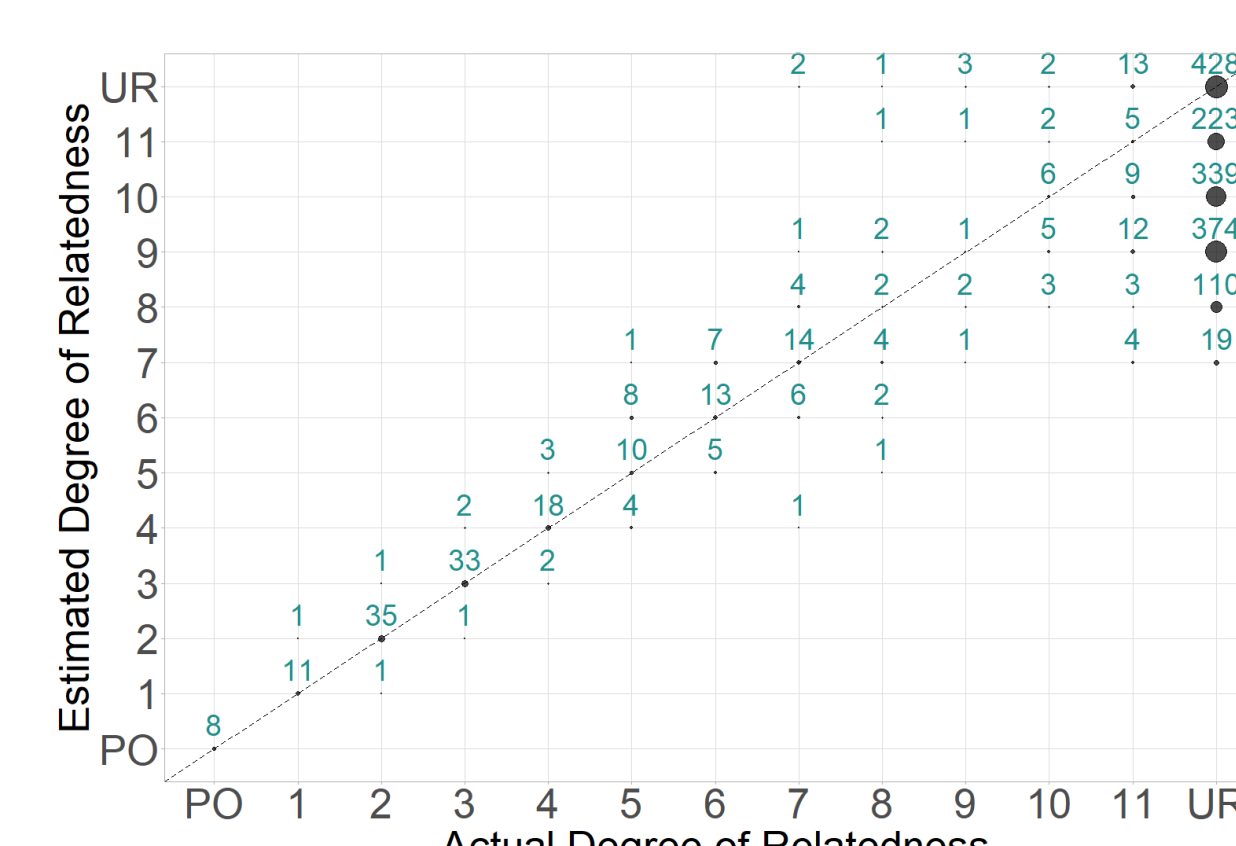
TRIBES³

Pipeline for relatedness detection in WGS data. Using jointvcf as input and combining BEAGLE and GERMLINE to compute degree of relatedness. Default settings.



XIBD⁴

Assumes plink formatted SNP-data. Run with model 2 which is based on the HMM implemented in RELATE. Set up with nextflow to use jointvcf as input. MinIBDlength set to 1.95.



Results: GRAPE is conservative and is less likely to map unrelated (UR) pairs to 7th to 11th degree. However, TRIBES and XIBD demonstrate greater sensitivity and therefore identify more instances of relatedness. DRUID, on the other hand, did not yield satisfactory results with WES data.

Conclusion: Whole-exome sequencing data can be effectively used to detect relatedness up to the sixth degree using IBD tools.

¹Inferring Identical-by-Descent Sharing of Sample Ancestors Promotes High-Resolution Relative Detection Ramstetter et al. (2018)

²GRAPE: genomic relatedness detection pipeline Medvedev et al. (2023)

³TRIBES: A user-friendly pipeline for relatedness detection and disease gene discovery Twine et al. (2019)

⁴XIBD: software for inferring pairwise identity by descent on the X chromosome Henden et al. (2016)