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A unified mixed effects likelihood framework for direct mapping of rare quantitative trait loci variants using sib and unrelated individuals with extreme quantitative phenotypes: application to sequence data.

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Abstract:
Next generation sequencing makes it possible to carry-out direct association mapping of rare variants in quantitative trait loci (rvQTL). In designing association studies, sampling related and unrelated individuals with extreme quantitative trait values (QTVs) can be used to enrich causal rare variants and improve power. Collecting a specific family type (e.g. discordant-sib-pairs) can be difficult therefore it is desirable to be able to combine data from families and unrelated individuals. Existing methods are limited in combining data and not appropriate for direct association mapping. We propose a flexible mixed-effects framework of modeling extreme trait genetic associations with rvQTL (MEGA-rvQTL) for analyzing related and unrelated individuals with extreme QTVs. MEGA-rvQTL detects associations through likelihood based tests. Parameters of genetic interests (e.g heritability) can be efficiently estimated. We investigated the power of the MEGA-rvQTL method for ten selective sampling strategies when a given number of individuals are sequenced. Data was generated via forward-time simulation using parameters estimated from re-sequencing data and phenotypic models based upon clinically-relevant traits. When selective sampling is carried-out with pre-specified thresholds, we demonstrate that analysis of sequence data from one sib per extreme-concordant-sib-pair (ECSP) is consistently the most powerful design. Analyzing sequence data for both sibs from ECSP or extreme-discordant-and-concordant-sib-pairs are also more powerful than studying unrelated individuals with extreme QTVs. When selective sampling is implemented within an existing cohort, sequencing one sib with extreme QTVs per sib-pair selected by one proband is the most powerful design. Overall, MEGA-rvQTL is a powerful approach to analyze next generation sequence data from related and unrelated individuals with extreme phenotypes.