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Trans-ethnic colocalization: A novel approach to assess the transferability of trait loci across populations

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Most previous genome-wide association studies for complex traits were based on samples with European ancestry. Consequently, it is important to determine the transferability of findings to other ancestry groups. Here we ask the fundamental question whether causal variants for

lipids are shared between populations.

Differences in linkage disequilibrium structure, allele frequencies and sample size make it difficult to assess replication for individual loci. Therefore, we propose a new strategy to assess evidence for shared causal variants between two populations: trans-ethnic colocalization (TEColoc). We re-purposed a method originally developed for colocalization of GWAS and eQTL results: Joint Likelihood Mapping (JLIM). In order to assess its performance for GWAS results from samples with different ancestry, we carried out a simulation study. UK Biobank (UKB) was used as a European ancestry reference and compared to data from Chinese and Ugandan samples. Phenotypes were simulated.

In the simulations of distinct causal variants, the relative frequencies of false negatives were all close to 0.05, as expected. The power to detect shared associations was 73.1% for the Ugandan samples and 93.1% for the Chinese samples. This suggests that the power of TEColoc decreases somewhat with greater genetic distance between the populations that are compared. We applied TEColoc to assess whether loci that have been linked to depression are shared across different ancestry groups.

We applied TEColoc to assess whether lipid-associated loci from large European discovery cohorts are shared across different ancestry groups using data from Uganda (N=6,407), China (N=21,295), Japan (N=162,255), the UK (N=9,961) and Greece (N=3,586). In each study, >60% of major lipid loci displayed evidence of replication with one exception. There was evidence for an effect on serum levels in the Ugandan samples for only 10% of major triglyceride loci. Specific replicating loci were identified using TEColoc. We then compared replicating with non-replicating loci. Ten of the fourteen loci that did not replicate in the Ugandan samples had pleiotropic associations with BMI in European data while none of the replicating loci did. The non-replicating loci might affect lipids by modifying food intake only in environments offering diets rich in certain nutrients, which suggests an important role for gene-environment interactions. Incorporating this into genetic risk prediction could help ensure that the health benefits of precision medicine are widely shared within and across populations.

In combination with increased efforts to recruit more diverse samples, methodological tool development is important in order to ensure analytical challenges related to ancestral diversity in genetic studies are met and questions, such as the transferability of findings, can be addressed.