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Near Optimal Trans-ethnic Meta-Analysis of Smoking Phenotypes in 1.3 Million Individuals

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Smoking is main causes to many preventable diseases and reduces the health of smokers. Previous studies have examined genetics architecture on European population, while non-European population is still not well studied and established. Additionally, though majority of genetic effects are homogenous, heterogeneity by race/ethnicity has been identified. To fill this gap in knowledge, we proposed a new trans-ethnic meta-analysis method MEMO (**M**ixed **E**ffect **M**eta-regression for **O**ptimal trans-ethnic meta-analysis) that synthesized the strength of fixed effect model, random effects meta-analysis and meta-regression. MEMO outperformed existing methods consistently in simulations, even for scenarios that favor alternative approaches.

We applied MEMO to a trans-ancestry GWAS meta-analysis of nicotine use in up to 1.3 million individuals, that consists GWAS of 1.2 million individuals and 150,000 sequenced individuals from TOPMed. We identified 297 significant loci across all 4 smoking related traits, i.e. AgeSmk, CigDay, SmkCes and SmkInit, with p-value threshold of $5x10^{-9}$, among which 70 were novel and attained genome-wide significant for the first time. Conditional analysis revealed 635 conditional independent variants. 40% of loci exhibit signs of allelic heterogeneity and contain >1 independent variants. For loci heterogeneity analysis, 83% show homogenous effect and the rest 49 loci show heterogeneity between European and non-European ancestries. We also extended MEMO to fine-mapping analysis. Among 297 loci, 44% were fine mapped to 90% credible sets of single gene, while 60% were fine mapped of less than 4 genes. Together our results represent a major step forward understanding the genetic architecture of smoking traits in non-European samples.