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Title: Candidate eQTL detection for risk refinement using paired DNA-RNA panel data

Introduction:

Inference of regulatory haplotypes which modify expressivity and penetrance of coding hereditary cancer-risk mutations is a key goal of precision medicine, potentially enabling deeper insight into individual risk profiles and therapeutic responses. Previous seminal work has already established that powerful functional readouts of latent regulatory variants acting on genes using phased haplotypes of coding variants and regulatory variants, including expression quantitative trait loci (eQTL) mapping in cis, can elucidate the enrichment of penetrance increasing configurations for pathogenic variants. In this work we demonstrate the feasibility of eQTL detection using Ambry CancerNext and RNAInsight data from 56176 matched patients and also present a preliminary eQTL analytic association analysis for risk refinement.

Methods:

Ambry CancerNext and RNAInsight data from N = 56176 samples were analyzed using genetic test results and matched gene expression measurements (TPM) respectively. GTEx v8 (whole blood) was used as a gold standard set to test for eQTL candidates in the Ambry data. Association and covariate renormalization analyses were carried out using penalized linear models and ordinary statistical hypothesis testing.

Results:

Applying first-principles batch renormalization to mitigate technical covariate effects and noise in panel-based CancerNext and RNAInsight data, we identified 59 eQTLs previously profiled in GTExv8 whole blood, including both up and down regulating eQTLs. Furthermore, we observed a strongly additive dosage pattern ($R2 = 1$, $p <\sim 1e\text{-}16$). Using select eQTLs we showed that age of onset in patients positive with loss of function mutations and variants of uncertain significance is correlated with eQTL genotype even after accounting for possible clinical and technical confounders.