Abstract:

Prostate cancer (PrCa) is the third-leading cause of cancer mortality among men, with heritability estimated at ~58%. Although genome-wide association studies (GWAS) have identified ~269 common SNPs associated with PrCa risk, much of the genetic contribution to disease susceptibility remains unexplained. Given that GWAS predominantly interrogate bi-allelic single nucleotide variants, a plausible hypothesis is that multi-allelic short tandem repeats (STRs)—which often exist in partial linkage disequilibrium with SNPs—account for a proportion of the missing heritability.

In this study, we used genome-wide STR imputation to evaluate the contribution of STR variation to PrCa risk. SNP array genotype data from the OncoArray consortium (64,087 individuals: 37,992 cases and 26,086 controls) were imputed using the SNP-STR reference panel generated by the Gymrek group, derived from whole-genome sequencing of 479 SSC family quads. After standard SNP quality control, STR genotypes were imputed with Beagle 5, yielding 445,735 autosomal STRs for downstream analysis. Case–control association testing was performed using logistic regression, adjusting for age and principal components.

We obtained association statistics for 407,879 STRs, of which 336 surpassed a 5% FDR threshold. Several significant STRs localised to known PrCa risk regions, suggesting that repeat-length variation may refine signals attributed to nearby SNPs and point to underlying functional mechanisms. Although the reference panel has demonstrated high concordance (~96.7%) with STR calls from whole-genome sequencing, further experimental validation will be required to confirm these associations and assess their regulatory effects.

Our findings provide the first genome-wide evidence that STR variation contributes to PrCa genetic risk. Incorporating multi-allelic repeat polymorphisms into association studies offers complementary insight beyond SNP-based GWAS and may help elucidate previously unresolved biological drivers of prostate cancer susceptibility.