Title: Genetic and epidemiological architecture of 5-alpha reductase inhibitor users

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Abstract

Prior studies indicate that host genetic variation modulates susceptibility to medication-induced syndromic phenotypes and vaccine-related adverse events, with clinical profiles that in some cases parallel the post–COVID-19 condition (long COVID). Five-alpha-reductase inhibitors (5-ARIs) such as finasteride and dutasteride are widely prescribed in men for Benign Prostate Hyperplasia(BPH) and alopecia but the extent of the associated potential ramifications of use of this class of drugs are poorly understood. Using FinnGen, we conducted a Genome-wide Association Study(GWAS) in 31,634 male 5-ARIs users and 190,847 male controls who never used 5-ARIs. We identified 23 independent loci associated with use of 5-ARI. Statistical fine-mapping (SuSiE) to establish causative SNPs showed 17 variants with Posterior Inclusion Probability ≥ 0.9, spanning 3 genomic regions and 2 credible sets. Interrogation of multi-tissue eQTL resources (FinnGen Annotool; 51 tissues) for the 1,377 GWAS-significant variants identified 806 variant–gene–tissue associations involving 173 unique variants and 17 target eGenes, all significant after Bonferroni correction (Padj = 0.05/806). Eqtl Associations were most abundant in testis and immune cell types with expression across multiple brain regions, and effect directions were highly concordant within loci, nominating tissue programs plausibly mediating 5-ARI–related biology. Complementary epidemiology analysis showed enrichment of traits related to prostate disorder, along with the use of hypnotics, which is surprising noteworthy for this cohort. LD Score regression identified False Discovery Rate(FDR)-significant positive genetic correlations between 5-ARI use and hypnotic/sedative and antidepressant medication use (rg ≈ 0.23 and 0.19), alongside very strong correlation with BPH.Interestingly, a patient survey in young 5-ARI users mainly for alopecia, corroborated real-world evidence of adverse-effect patterns in these patients.