Integrated pharmacogenetic signature for the prediction of prostatic neoplasms in men with metabolic disorders

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Oncogenic processes are delineated by metabolic dysregulation. Drug likeness is pharmacokinetically tested through the cytochrome P450 (CYP450) enzymatic system, whose genetic aberrations under epigenetic stress could shift male organisms into prostate cancer (PCa) pathways. To predict susceptibility to prostatic neoplasia, focusing on benign prostatic hyperplasia (BPH) and prostate cancer (PCa), based on the pharmacoepigenetic and metabolic profile of Caucasian individuals. Two independent cohorts of 47,389 individuals in total were assessed to find risk associations between CYP450 gene variants and prostatic neoplasia risk. The metabolic profile of the first cohort was evaluated statistically, and frequencies of absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics were calculated. Additionally, pharmacoepigenetic targeting by microRNAs (miRNAs) was predicted. Patients with benign prostatic hyperplasia (BPH) and prostate cancer (PCa) in the first cohort exhibited common cardiometabolic patterns. Drug classes C08CA, C09AA, C09CA, C10AA, and C10AX (cardiovascular system), as well as G04CA and G04CB (genitourinary system), were associated with an increased risk of prostate cancer (PCa), while C03CA and N06AB of the cardiovascular and nervous systems were associated with a low prostate cancer (PCa) risk. The CYP3A4*1B polymorphism emerged as the most significant pharmacogenetic variant linked to PCa susceptibility. miR-200c-3p and miR-27b-3p appear to target CYP3A4, indicating possible epigenetic regulation of prostate cancer (PCa) risk. Metabolomic profiling revealed that 11β-OHT, 2β-OHT, 15β-OHT, 2α-OHT, and 6β-OHT were associated with high risk, while 16α-OHT and 16β-OHT indicated intermediate risk of the disease. Our results suggest a novel integrative molecular signature for prostate cancer susceptibility that combines pharmacogenetic, epigenetic, and metabolomic features. Further studies are warranted to validate its predictive utility.

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