An Innovative Pipeline Integrating Mendelian Randomization for Personalized Disease Risk Assessment and Therapeutic Drug Identification

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Disease pathogenesis is closely associated with genetically influenced metabolites. The identification of individualized metabolite-disease associations is crucial in advancing personalized treatments. Mendelian Randomization (MR) is a modern biostatistical approach utilizing genetic variants (SNPs) linked to a modifiable exposure to estimate its causal relationship with an outcome, providing unbiased, time-efficient, and cost-effective results. In this study, Two-Sample MR was employed to identify causal relationships between human serum metabolites and 10 prevalent diseases, yielding 262 metabolite-disease associations. Utilizing MR results, the SNPs with the greatest impacts on the metabolite-disease associations were defined as TOP SNPs. Input whole genome sequence data was analyzed, and a TOP SNP based regression analysis was performed to determine disease risk. Furthermore, drug repositioning and discovery were used to offer personalized therapeutic intervention strategies based on the individual's genomic profile. Drug repositioning was automated using Pharos; FDA-approved drugs targeting eight metabolites were identified to be used in the risk reduction of seven diseases. Additionally, blind docking and sequence-based deep learning were used in tandem for custom drug discovery. Three potential drug compounds (PubChem IDs 849659, 847243, 846402) were identified to adjust levels of metabolites arachidonate, bilirubin and mannose aiming to mitigate risk in six diseases. This end-to-end process was implemented on a user-friendly web-UI for efficient use. This novel pipeline will be used to identify targetable causal metabolite-disease associations, make personalized risk assessments, and provide custom drug repositioning and discovery options for risk reduction.

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