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Transcription factor binding profiling using chemically induced genes by ChIPEA

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Modification of disease-elicited gene expression is one of the core aspects in numerous drugs' modes of action. To predict drug–disease associations, transcriptomics-based approaches with pathway analysis, graph theory and supervised machine learning-based calculation were developed. However, the pharmacological mechanism employed by drugs remain largely unknown.

In this study, we focused on transcription factors (TFs) that integratively regulate differentially expressed genes (DEGs) in response to drug treatment. In particular, TF enrichment analysis by analyzing large-scale ChIP-seq data obtained from ChIP-Atlas database (ChIPEA) was performed for each chemical to identify TFs with enriched binding for chemically perturbed DEGs. Performance evaluation with area under the ROC curve (AUC) suggests the reliability of ChIPEA in drug target discovery (global AUC = 0.66). Furthermore, we successfully identified the pivotal factors that link drugs to diseases or side effects by utilizing protein–disease database (global AUC = 0.68). This approach is with high confidence because it is fully based on actual experiments of given transcriptome data and public ChIP-seq data. In the pharmaceutical field, ChIPEA is useful to shed light on compounds failed to be approved by identifying TFs primarily involved in the modes of action, together with the factors associated with potential side effects. Approved drugs including agents composed of unidentified ingredients such as traditional herbal medicines can also be re-examined for novel targets and actions, thus beneficial to drug repositioning research.