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I B M INSIGHTS IN BIOLOGY AND MEDICINE
ISSN 2639-6769

Short Review

Transcriptome-wide association study: Opportunity and challenges for cancer studies

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Abstract

Genome-wide association studies (GWAS) have uncovered thousands of single nucleotide polymorphism (SNP) loci that are associated with complex traits. However, the majority of GWAS discoveries are located in non-coding regions and the biological mechanisms behind these associations are not well understood. Transcriptome-wide association studies (TWAS) have gained popularity in recent years by generating biological interpretable discoveries and facilitating the identification of novel associations that have been missed by GWAS. TWAS has identified more than hundreds of susceptibility genes for many complex diseases and traits, including cancers. Here, in this review, we first summarize TWAS methods, then discuss the opportunities for cancer studies and finally review current challenges and future directions for this method.

More Information

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Submitted: July 23, 2022
Approved: August 10, 2022
Published: August 11, 2022

How to cite this article: Shang K, He J. Transcriptome-wide association study: Opportunity and challenges for cancer studies. Insights Biol Med. 2022; 6: 017-021.

DOI: 10.29328/journal.ibm.1001023

Keywords: TWAS; GWAS; Breast cancer; Prostate cancer; Lung cancer

Introduction

Transcriptome-wide association studies (TWAS) have uncovered more than hundreds of susceptibility genes for many complex diseases and traits, including cancers [1-6]. In contrast to genome-wide association studies (GWAS), TWAS associates disease susceptibility with imputed gene expression using aggregated information trained from reference genotype and gene expression panels [7,8]. Being a gene-level-based methods, TWAS has gained popularity in recent years by generating biological interpretable discoveries and facilitating the identification of novel associations that have been missed by GWAS

Overview of methods

The first known method was developed by Amazon, et al. called PrediXcan1. Pioneered by PrediXcan method [1], TWAS was typically conducted in two steps: First, a model is trained to impute genetically regulated gene expression levels by combining transcriptional regulatory effects of the eQTLs for a gene using different statistical or machine-learning models. A typical model includes but isnot limited to a linear model, such as Elastic Net (PrediXcan) [1], Bayesian regression (BSLMM) [2,9] and deep learning auto-encoder models (MLP-SAE) [10,11]. A reference dataset, such as Genotype-Tissue Expression (GTEx) [12], BLUEPRINT [13], MESA [14] and single-cell eQTLGEN [15], contains paired expression and genotype data is used for training such genotype-to-expression prediction models. Then, the next step was to aggregate the imputed gene expression levels from the first step with the phenotype of interest to conduct genotype-to-phenotype association mapping. The target GWAS cohort only contains genotype and phenotype information and the phenotype can either be dichotomous, such as case/control of the disease's status, or continuous variables, such as blood pressure levels.

Numerous GWAS summary statistics-based TWAS approaches, such as FUSION [2], S-PrediXcan [16] and UTMOST [17], have swiftly emerged after the introduction of PrediXcan [18]. When compared to TWAS based on individual-level data, GWAS summary statistics-based TWAS was more computationally efficient and could integrate the correlations between SNPs while accounting for linkage disequilibrium (LD) regions. Subsequently, researchers have extended the initial Elastic Net- and Bayesian-based models by incorporating multiple tissues [17], including trans-eQTLs [19], integrating kernel-based models [20,21] and utilizing other middle-omices data (i.e. imaging-wide association study [22] and proteome-wide association study [23-25]). Compared

with initial TWAS models, these emerging TWAS methods have been proven to boost the statistical power of gene-trait associations and enhance biological interpretation for GWAS discoveries. Although existing TWAS methods prioritized disease susceptibility genes, there are no guarantees of causality [26]. To address this, a probabilistic framework, FOCUS [27], that performs statistical fine-mapping over the TWAS signals has been proposed, which provides more evidence when interpreting TWAS results and identifying disease causal genes.

Opportunities for cancer studies

TWAS can detect more genes than other aggregation-based GWAS methods and facilitates the identification of novel associations that have been missed by GWAS [18], thus, have created opportunities for cancer studies. Traditional TWAS approaches, like PrediXcan, FUSION and UTMOST, have been broadly applied to large population cohorts for a variety of cancer types. In the context below, we listed examples for TWAS studies on three common cancers, including breast, prostate and lung cancers.

In studies on hormone-regulated cancers, such as breast cancer, Wu, et al. have successfully identified 48 TWAS-significant genes, including 14 genes at 11 loci that are 500 kb away from any risk variant identified in prior GWAS (refer to Table 1 from reference [4]). They conducted their analysis utilizing the S-PrediXcan method [16] and performing associations with breast cancer risk using the summary statistics data from the BCAC Consortium (122,977 cases and 105,974 controls). According to a more recent study, by comparing associations with breast cancer estrogen receptor-specific subtypes (ER+ and ER-) using a case-only TWAS approach, they identified two genes, *STXBP4* and *HIST2H2BA* that were specifically associated with ER+ but not with ER- breast cancer [28]. In this study, they also detected 30 genes with overall breast cancer risk at a Bonferroni-corrected $p < 0.05$ [28], including four genes, *MAEA*, *GDI2*, *ULK3*, and *HSD17B1P1*, that were not identified in previous TWAS [4,29,30] or eQTL studies [31].

Prostate Cancer (PrCA) is one of the most common cancers in men. By performing multi-tissue TWAS using the FUSION method [2], Nicholas, et al. incorporated the largest PrCa GWAS (81,318 cases and 61,074 controls) with gene expression across 45 tissues and identified 217 genes with 9 genes at 9 novel independent loci that were located 1 Mb away from any previously reported GWAS risk variants (refer to Table 1 from reference [32]). Quickly followed by this study, Wu, et al. used different TWAS strategies for modeling gene expression prediction models and conducted association analyses using summary statistics data from the PRACTICAL consortium (79,194 cases and 61,112 controls) and identified 137 significant genes with 9 novel genes in 9 independent association signals that remained statistically significant after conditioning on the previously reported GWAS risk variants (refer to Table 1 from reference [3]). Most recently, researchers extended the traditional TWAS method to microRNA TWAS (miTWAS) for studying the associations between microRNA dysregulation and PrCa risks [33]. Their miTWAS framework was built based on the FUSION method [2]. Two significant TWAS microRNA connections with PrCa risks were found in normal tissue (*miR-941* family overexpression and reduced *miR-3617-5p* expression), while one significant link with *miR-941* overexpression was seen in tumor tissue [33].

Another common type of cancer, lung cancer, has been the leading cause of cancer deaths around the world [34]. Two TWAS methods, S-PrediXcan [16] and FUSION [2], were utilized by Bossé, et al. to train gene expression prediction models for lung cancer overall and certain histological or smoking subgroups, respectively [35]. Both approaches showed some evidence of associations between previously established lung cancer risk loci with TWAS-identified genes. Additionally, they reported a new susceptibility gene, *AQP3* (9p13.3), which showed strong evidence as an underlying causal gene for lung adenocarcinoma [35].

Challenges and future directions

Even though TWAS is a promising method for disease and cancer gene discovery, there have been several challenges and limitations [26,36]. First, the accuracy of prediction models is limited by the gene expression heritability (h^2) that determines the upper bound of prediction accuracy [1,37]. Secondly, due to the computational burden, most existing TWAS methods do not assess distant trans-eQTL that are known to explain a large portion of the genetic heritability of gene expression levels for most genes [38,39]. Thirdly, prediction accuracy may be jeopardized by the inclusion of non-regulatory variants or variants in nonspecific regulatory elements, which may not be relevant to disease-driving states [26,36,40,41]. Lastly, there is still a lack of eQTL data from different ancestry groups, medical conditions, age, sex, etc [42].

Understanding the genetic architecture of cancers is still an ongoing task in the field of translational medicine. With the establishment of more epigenomic, chromatin interactions (i.e. Hi-C, 3D), single-cell multi-omics data, etc., new approaches that integrate prior knowledge of disease-specific regulatory elements are essential to improve the detection of disease susceptibility genes. Also, much is needed to explore the eQTLs in different geographical ancestry in the areas of functional genetic studies.

Acknowledgement

We sincerely thank the journal editors for their kind invitations.

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