COMMENTARY

General Parameters on Biomarker Drug Discovery

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DESCRIPTION

It is essential to use genomics-driven drug discovery to accelerate the creation of new therapeutic targets. However, the paradigm for drug development based on data from Genome-Wide Association Studies (GWASs), particularly for cross-population GWAS meta-analysis, has not yet been developed. The three approaches included in the drug discovery framework were used to treat the 13 main illnesses that GBMI (Global Biobank Meta-analysis Initiative) was aiming to target. Drugs and drug targets were thoroughly verified by reference to previously established drug-disease associations, which were complementary ranked by individual approaches. Integration of the three methodologies provided a comprehensive catalogue of candidate drugs for repositioning, nominating promising drug candidates targeting the genes involved in the coagulation process for venous thromboembolism as well as the gout signalling pathways, interleukin-4 and interleukin-13. Using cross-population meta-analyses, we identified key factors for successful genomics-driven drug discovery. Efficient screening of novel therapeutic targets is critical for accelerating drug discovery. Despite enormous effort to develop novel drugs, the overall success rate of clinical application has been decreasing due to significant increases in both cost and duration. One of the promising solutions is genomic-driven drug discovery, because drug targets with human genetic support are more likely to succeed in clinical development. Rare-variant studies for Mendelian diseases, in particular, have resulted in drug development, such as PSCK9 inhibitors for low-density lipoprotein cholesterol. Genome-Wide Association Studies (GWAS) have provided valuable opportunities for drug discovery in common diseases. Nonetheless, drug discovery based on GWAS remains difficult. There are few bioinformatics tools that directly prioritise candidate drugs, and there are no practical guidelines for conducting genomics-driven drug discovery.

A growing number of large-scale GWAS meta-analyses of multiple populations have been conducted recently. These have revealed important insights into the biological processes underlying complex diseases, allowing for more in-depth use of genomics-driven drug discovery. However, the vast majority of previous genomics-driven drug discovery projects focused on GWAS of a single European ancestry, with few successful applications to cross-population GWAS meta-analyses. The global heterogeneity of genetic background (eg: different allele frequencies and Linkage Disequilibrium [LD]) among populations makes downstream analyses like gene expression prediction difficult. Furthermore, causal effect sizes vary by population, particularly in functionally important regions. As a result, cross-population GWAS meta-analyses necessitate the use of a specialised drug discovery framework. The framework for cross-population drug discovery that includes three major methodologies. The first step is to identify drug repurposing opportunities by overlapping enrichment of disease risk genes with targets of existing drugs. Second, endo phenotype MR and subsequent quality controls, such as co-localization analyses, establish causal links between proteins and disease processes. Finally, negative correlations between genetically regulated disease case-control gene expression and compound-regulated gene expression profiles can be used to identify compounds that may correct disease-related gene expression changes.

The mentioned framework was applied to the 13 common and relatively rare disease GWAS included in GBMI: asthma, Primary Open-Angle Glaucoma (POAG), gout, Chronic Obstructive Pulmonary Disease (COPD), Venous ThromboEmbolism (VTE), Thyroid Cancer (ThC), Abdominal Aortic Aneurysm (AAA), Heart Failure (HF), Idiopathic Pulmonary Fibrosis (IPF), stroke, uterine cancer. Individual methodologies were validated by examining the overlap enrichment of prioritised results in disease-relevant medication categories. The integration of candidate drugs and compounds across methodologies resulted in a comprehensive catalogue of 266 drug/compound-disease pairs for repositioning. Using a cross-population GWAS meta-analysis, the utility of genomics-driven drug discovery identified key factors for successful drug discovery. Meta-analyses of multi-ethnic GWAS included populations with diverse genetic backgrounds and architectures. Matching genetic ancestry is critical for functional interpretation of GWAS results using omics data, including drug discovery. The differences in ancestry-matching strategies among components were determined by the availability of the corresponding omics resource requested for each analysis at the time. More public resources with diverse ancestry should be expected to accumulate.

For genomics-driven drug discovery, a large number of GWAS loci were required, particularly for the overlap enrichment analysis and negative correlation tests. Global biobank collaborations, such as GBMI, have the potential to increase the power of genetic association studies in detecting novel GWAS signals by incorporating diverse populations with large sample sizes, as well as to facilitate genomics-driven drug discovery. Notably, our framework successfully nominated drug candidates and target genes, particularly for VTE, which had the fifth-most GWAS loci among the 13 diseases. Other than the number of GWAS loci, there may be other factors that are important for the success of VTE drug discovery. Among traits with a large number of loci, VTE had the lowest polygenicity, which could help in identifying disease-relevant genes. The VTE GWAS genes were mostly concentrated in the coagulation cascade. Drugs targeting coagulation factors have been actively developed, and these drugs may be promising candidates for repositioning to coagulation disorders other than the disease for which they were originally developed.

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