Assessment of pharmacogenomic agreement

Inconsistencies between two large-scale pharmacogenomics screens previously published elsewhere, are highlighted in a new paper published on the Open Science platform F1000Research. The research, which has just passed peer review, highlights the importance of assessing reproducibility of drug sensitivity predictors before translating them into clinical settings.

Zhaleh Safikhani and colleagues re-analysed the methods and results from the recent comparative studies jointly performed by the Genomics of Drug Sensitivity in Cancer (GDSC) and the Cancer Cell Line Encyclopedia (CCLE) teams in which they reported reasonable drug response and gene-drug associations (Stransky et al., Nature 2015). If confirmed, these results would have important implications for identifying potential anticancer drugs for use in precision medicine.

Patients with cancer often present heterogeneous responses to anticancer treatments and these responses are determined in part by patient-specific alterations in the cancer genome and changes in gene expression. Pharmacogenomics studies, cancer cell lines studies in particular, have been widely used to test the efficacy of therapeutic agents and explore genomic factors associated with drug response. These correlate genomic profiles and sensitivity to drug exposure in an attempt to identify molecular predictors of drug response. Assessing consistency between independent results is key to develop robust drug sensitivity predictors to test in clinical phases.

While analysing the data and methods of the GDSC/CCLE comparative study, Safikhani et al. noticed that the GDSC and CCLE investigators made a number of choices in their analysis that contributed to their assertion of consistency between drug sensitivity predictors obtained. Safikhani et al. noted that the GDSC/CCLE analysis did not directly compare the same drug response measurements generated independently both previous studies, but used different drug sensitivity measures from each study. The data also selected a single source of genomic data (using only data from CCLE in one analysis, and only data from GDSC in another), neglecting to account for the noise. These analytical choices contributed substantially to the discrepancy between the GDSC/CCLE reanalysis and the analysis by Haibe-Kains et al. (Nature, 2013), which took into account variations in both genomic and pharmacological data.
This new analysis by Safikhani et al. points to a fundamental problem in the assessment of pharmacological drug response and the evaluation of the robustness of such studies. Their findings support the need for standardisation of drug response measurements or development of new and robust sensitivity assays that make it possible to reliably identify genomic predictors of drug response.

As long as there is a lack of standardisation in experimental assays and analysis methods, users of pharmacogenomics data sets should be cautious in their interpretation of results derived from their analyses and particularly wary about making predictions of clinical response based on in vitro measurements.

The study is published in the Preclinical Reproducibility and Robustness channel, a new F1000Research publishing channel that encourages and facilitates transparent publication and discussion of confirmatory and non-confirmatory studies in biomedical research.

Rebecca Lawrence, Managing Director of F1000 said: “The issues around reproducibility are proving a significant challenge in the life sciences and at F1000Research we are keen to support efforts to address these issues by changing how studies that either confirm or question previous studies are reported. We believe that transparent publication and discussion are crucial in these efforts, and are pleased to see research like this being published in our Preclinical Reproducibility and Robustness channel.”

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