Finding molecular secrets hidden in premature aging diseases and cancer using AI

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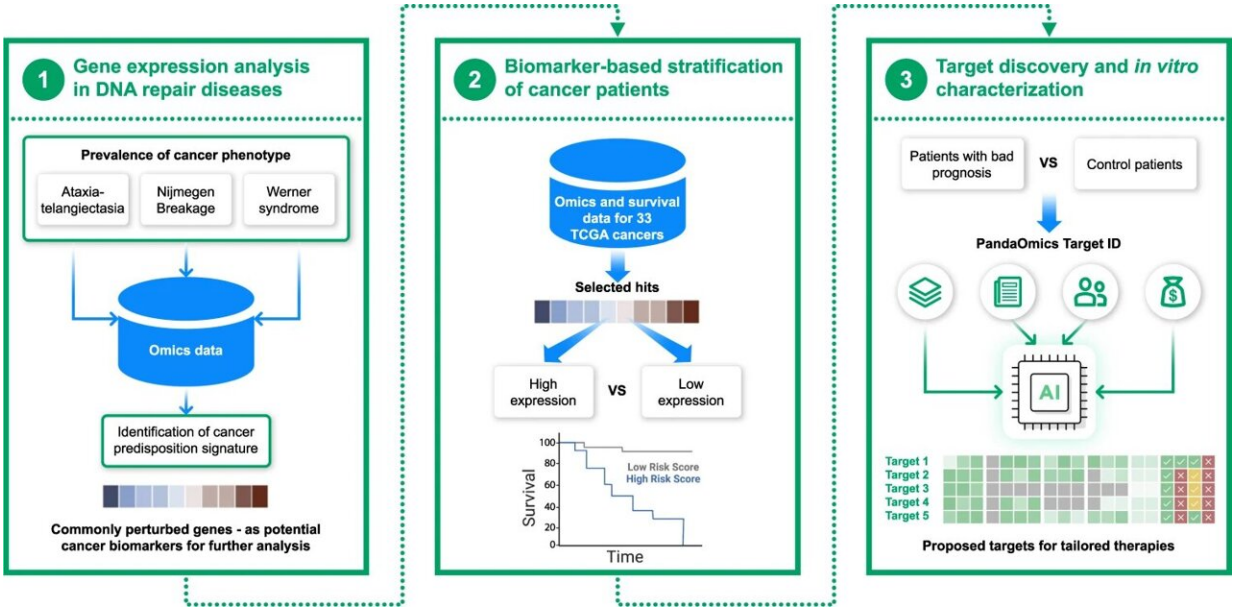

Schematic representation of the PandaOmics application for a rapid biomarker discovery and target characterization in cancer. Gene expression signatures have been examined in DNA repair diseases with high cancer predisposition (1), followed by the analysis of the most significantly perturbed genes as potential biomarkers stratifying cancer patients based on their survival rates (2). The group of patients with low survival outcomes have been further used for identification of potential therapeutic candidates for cancer treatment via PandaOmics Target ID approach (3). Data types used to generate target hypotheses included: omics-, text-, key opinion leaders (KOLs) and funding-based scores. Credit: *Cell Death & Disease* (2022). DOI: 10.1038/s41419-022-05437-w

New research published in *Cell Death & Disease* covers the first batch of results from collaborative work directed to perform multi-omics-based analyses in the context of age-related diseases using an AI-driven target and drug discovery pipeline.

The findings were developed by Insilico Medicine, a clinical-stage end-to-end artificial intelligence (AI)-driven drug discovery company, with support from the University of Copenhagen and the University of Chicago.

Existing therapeutic strategies for treating major cancer types may not be effective for all patients. The heterogeneous clinical outcomes seen among patients with the same cancer type as well as incomplete understanding of cancer-related molecular signatures contributes to failed clinical trials and limits the development of advanced tailored therapies.

Discovery of the biomarkers associated with treatment response is urgently needed, researchers note, to optimize a patient's selection criteria for clinical trials, reach efficacy endpoints, and improve already existing therapies.

In order to find these biomarkers, the team of scientists investigated gene expression datasets derived from DNA repair diseases with increased cancer risk to find commonly dysregulated genes potentially involved in cancer progression. With the most significantly perturbed genes serving as biomarkers, researchers performed survival analysis across 33 cancer types and selected those that showed high confidence stratification among cancer patients.

The latter is particularly important for subsequent target discovery, since

patients with unfavored clinical outcomes would benefit the most from more tailored therapies. Insilico Medicine's AI-driven PandaOmics platform was used to perform a comprehensive differential gene expression analysis, survival stratification, and target discovery.

Researchers discovered 10 significantly perturbed genes with a similar expression pattern among the selected DNA repair deficient disorders. Importantly, the majority of the disclosed genes were further shown to stratify at least three cancer types based on the survival analysis. The researchers focused on the most downregulated gene, CEP135, which possesses a crucial function in centrosome biogenesis and cell division and correlates with the severity of survival in sarcoma patients.

Applying PandaOmics, they discovered potential target candidates for the group of sarcoma patients with poor clinical outcome. The authors identified PLK1 as one of the top scoring hits that functions in the same molecular pathway as CEP135, and further validated the identified targets in vitro.

"It is amazing that we were able to generate and analyze data and, in general, to validate hypotheses in such a short period of time by using AI algorithms developed by Insilico Medicine," said Garik Mkrtchyan, Assistant Professor at the Center for Healthy Aging, University of Copenhagen, one of the lead researchers of the study.

"We were very happy to make contributions to the cancer field and highlight the importance of biomarker discoveries for patient stratification and further therapy improvements. I am also thankful for support from Dr. Evgeny Izumchenko, an expert cancer biologist at the University of Chicago, for his guidance and advice throughout the study."

"This is the latest in a series of collaborations with the University of

Copenhagen, and specifically Morten's lab, one of the leading groups working in the field of healthy productive longevity," said Alex Zhavoronkov, Ph.D., founder and CEO of Insilico Medicine.

"This ongoing collaboration enabled the publication of the study we present today, highlighting the strong connection between DNA repair deficiencies and cancer. We are extremely proud that PandaOmics is capable of searching for and justifying relevant targets and biomarkers across multiple disease areas."

"I am very excited that we have been able to demonstrate the utility of the PandaOmics platform in a practical setting," said Morten Scheibye-Knudsen, MD, Ph.D., Associate Professor at the Center for Healthy Aging at the University of Copenhagen, a corresponding author of the project.

"The use of massive datasets will allow us to greatly increase the potential of personalized medicine in the future, an area where Insilico Medicine is taking a leading position."

Researchers noted that the findings are not limited to the particular gene or cancer type in the study, but also feature the advantages of high confidence AI application for omics analysis broadly applicable to the cancer research community, as it provides a panel of genes and survival data for biomarker and target discovery across multiple cancer types.

More information: Garik V. Mkrtchyan et al, High-confidence cancer patient stratification through multiomics investigation of DNA repair disorders, *Cell Death & Disease* (2022). DOI: 10.1038/s41419-022-05437-w

Provided by Insilico Medicine