Team finds cancer drug resistance genes and possibly how to limit their effects

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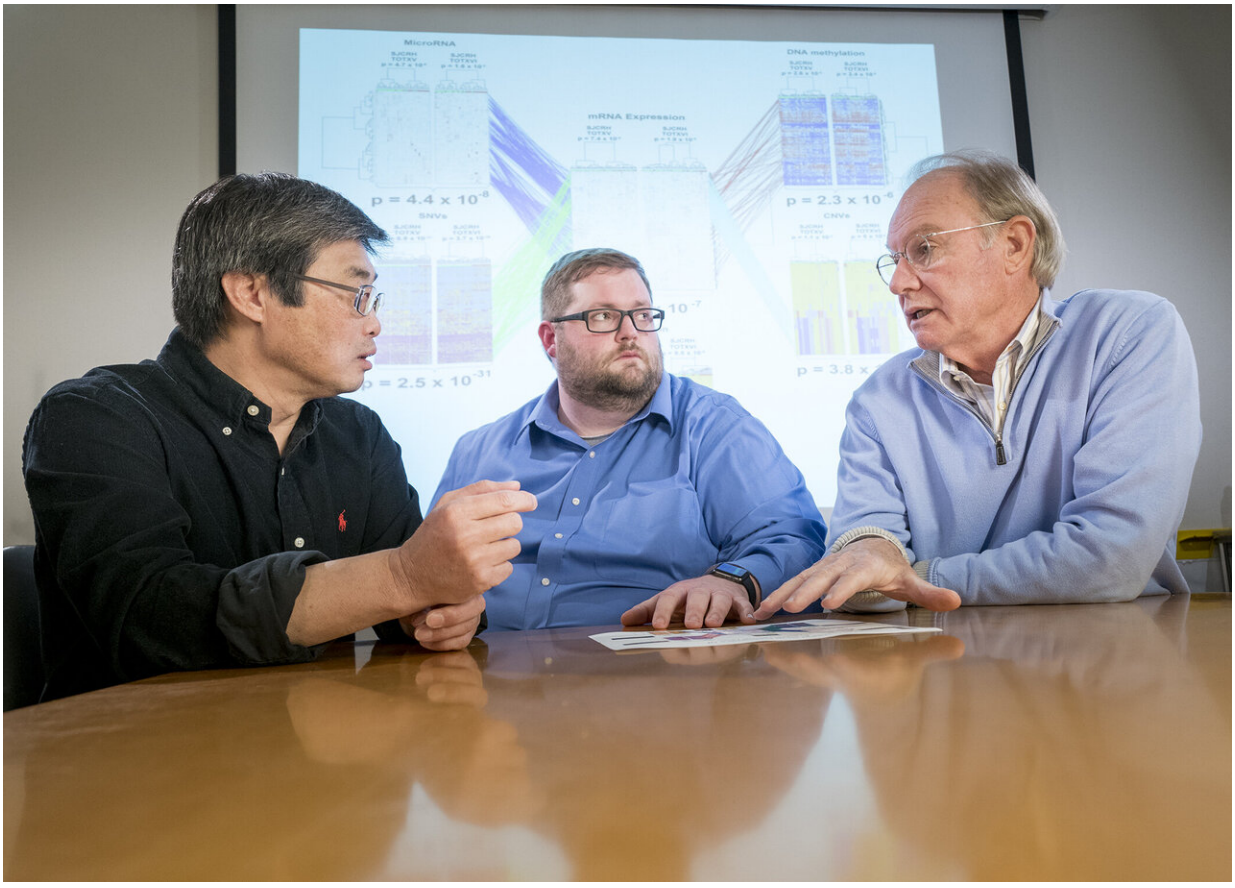

Left to right: Cheng Cheng, Ph.D., of the St. Jude Department of Biostatistics; Robert Autry, of St. Jude and a graduate student at the University of Tennessee Health Science Center; and William Evans, Pharm.D., of the St. Jude Department of Pharmaceutical Sciences Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital scientists have discovered a gene associated with about half of glucocorticoid resistance in children with the most common pediatric cancer. Researchers have also identified a drug that may counter resistance. The research appears today in the journal *Nature Cancer*.

St. Jude researchers developed a novel strategy to identify genes that cause leukemia cells to be resistant to chemotherapy. The approach extends the momentum generated by whole genome sequencing and shows the power of incorporating other dimensions of the genome.

Investigators used the method to identify a new gene, CELSR2, associated with acute lymphoblastic leukemia (ALL) resistance to glucocorticoids. It is one of 14 newly identified genes implicated in resistance to steroids, drug that are essential for curing ALL. The findings led investigators to the drug venetoclax and evidence that it may reverse resistance.

"Drug resistance is a major cause of treatment failure for children and adults with disseminated cancers like leukemia," said corresponding author William Evans, Pharm.D., of the St. Jude Department of Pharmaceutical Sciences. Although about 90% of children and adolescents with acute lymphoblastic leukemia (ALL) now become long-term survivors, ALL remains a leading cause of pediatric cancer deaths and is less curable in adults.

"Steroids play an essential role in the treatment of acute lymphoblastic leukemia," Evans said. "About 20% of children with acute lymphoblastic leukemia and twice as many adults are highly resistant. Yet, the underlying cause of resistance often remains unknown."

Mining data for answers

For answers, researchers measured six types of genomic and epigenetic features in leukemia cells, then created a computational pipeline to aggregate each genetic feature to individual genes. The goal was to determine which genes were most strongly associated with steroid resistance.

Then researchers used cutting-edge methods like CRISPR gene editing and a sophisticated statistical tool to prioritize genes for further investigation.

This study focused on leukemia resistance to steroids such as prednisone and dexamethasone. The pipeline is also being used to study leukemia resistance to 14 other cancer drugs.

The methods included analyzing and validating data from about 500 St. Jude patients newly diagnosed with ALL. Investigators looked for connections between steroid resistance and gene variations, gene expression, gene regulation and other factors.

Co-author Cheng Cheng, Ph.D., of the St. Jude Department of Biostatistics and his colleagues developed a statistical tool to rank the contribution of more than 19,700 genes to steroid resistance. The tool is called truncated aggregation of P-values or TAP.

Working in a human ALL cell line, investigators used CRISPR gene editing to knock out genes across the genome as another way to recognize drug resistance.

Along with identifying novel genes, the strategy identified 78% of the 38 genes known to cause steroid resistance and 100% of the molecular pathways involved.

Foiling steroid resistance

CELSR2 was the gene most strongly associated with steroid resistance. Decreased CELSR2 expression in leukemia cells from patients and ALL cells in the lab was associated with increased steroid resistance. About half of steroid-resistant ALL in children and adults in this study had reduced CELSR2 expression.

Researchers showed that reduced levels of CELSR2 protein likely contributes to steroid resistance by promoting increased expression of the protein BCL2. The protein inhibits a cell death pathway. Venetoclax, a drug commonly used to treat leukemia subtypes common in older adults, inhibits BCL2.

In a model system in the laboratory and in mice with human ALL expressing low CELSR2, venetoclax mitigated steroid resistance by inhibiting BCL2. Mice with steroid-resistant human ALL lived longer when steroid treatment was combined with venetoclax.

"The findings point to the potential benefit of combining venetoclax with current remission-induction therapy as a strategy to overcome steroid resistance and improve the effectiveness of ALL chemotherapy," Evans said.

More information: Integrative genomic analyses reveal mechanisms of glucocorticoid resistance in acute lymphoblastic leukemia, *Nature Cancer* (2020). DOI: 10.1038/s43018-020-0037-3 , nature.com/articles/s43018-020-0037-3

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