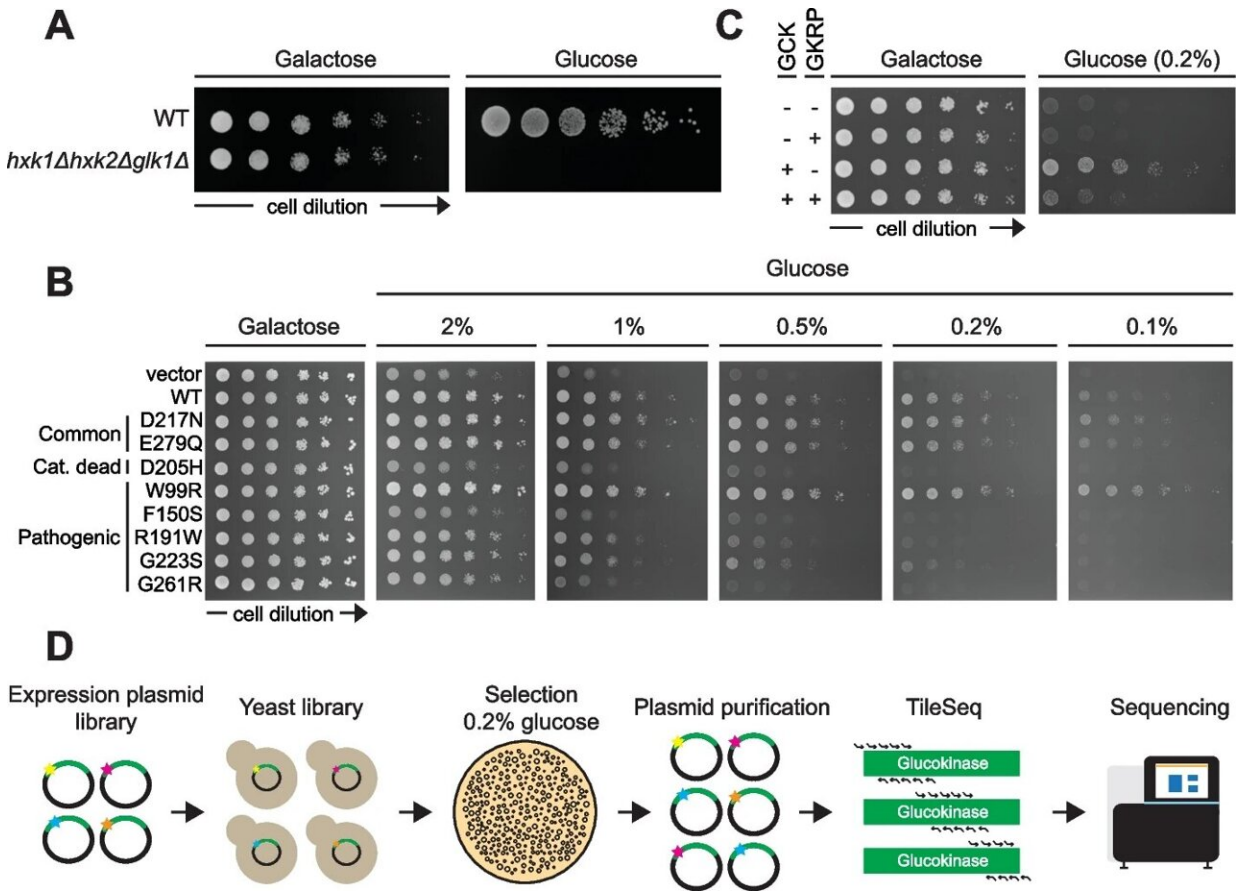
High-throughput experiments might ensure a better diagnosis of hereditary diseases

May 3 2023



Yeast complementation as a readout for human glucokinase variant activity. **A** Yeast growth assay of wild-type (WT) and *hxk1Δ hxk2Δ glk1Δ* yeast strains on galactose and glucose media. **B** The growth of the *hxk1Δ hxk2Δ glk1Δ* yeast strain expressing either a vector control, wild-type GCK (WT) or a GCK variant was compared on media containing galactose or varying concentrations of glucose. **C** Growth assay of different combinations of vectors (-), GCK and GKRP expressed in the *hxk1Δ hxk2Δ glk1Δ* yeast strain on galactose and glucose

media. **D** Illustration of the multiplexed assay for GCK variant activity. Credit: *Genome Biology* (2023). DOI: 10.1186/s13059-023-02935-8

All human beings are genetically very similar, sharing approximately 99.9% of the DNA code. The remaining 0.1% explains the natural differences between people, including our predisposition to hereditary diseases.

Although sequencing of our genetic material is becoming a routine diagnostic analysis, it is unfortunately far from simple to determine whether specific small differences in our DNA affect our risk of developing disease. The usefulness of DNA sequencing is therefore often limited to the few cases where it is already known if a gene variant increases the risk of disease.

Researchers at the Department of Biology, University of Copenhagen, have now contributed to solving this problem for a specific gene called GCK. The study has just been published in *Genome Biology*.

Rasmus Hartmann-Petersen, Professor at the Department of Biology, explains, "The GCK gene, which codes for the enzyme glucokinase, regulates the secretion of insulin in the pancreas. GCK gene variants can therefore cause a form of hereditary diabetes. Although the connection between GCKand diabetes has been known for several years, we have, until now, only known the effect of a few percent of the possible variants of this gene."

Together with colleagues at the PRISM center, UCPH, who are currently studying the effects of genetic variations, the researchers measured the effect of all of the possible variants of GCK.

Ph.D. student Sarah Gersing, who is the first author of the article, explains, "We used yeast cells to measure the activity of over 9,000 different GCK variants. In this way, we were able to generate a list of the effects—both of already known variants, but also of variants that patients might carry, but that have not yet been discovered. This provides us with a reference for future GCK diagnostics."

Prof. Kresten Lindorff-Larsen, who heads the PRISM center, continues, "Our results are quite unique; not only have we measured the effect of several thousand variants, but for many of the variants, we can now explain what they do to the glucokinase protein. In our center, we have gathered researchers working across a range of research fields, bridging from data analysis and biophysics to cell biology and medicine, and it is now clear how this broad approach pays off in explaining how diseases arise."

Gene variants of GCK can, among other things, cause a form of hereditary diabetes called "GCK maturity onset diabetes of the young" (GCK-MODY).

Professor of genetics Torben Hansen, who is also a member of the PRISM center, says, "Although GCK-MODY patients exhibit elevated blood glucose levels, this is often not associated with complications. Hence, unlike other forms of diabetes, most GCK-MODY patients might therefore not need to be treated with medication. However, due to missing or inaccurate genetic data, more than half of the GCK-MODY patients are classified with having either type 1 or type 2 diabetes—and are therefore unnecessarily medicated."

"We estimate that approx. 1% of those who have recently been diagnosed with type 2 diabetes in Denmark have a variant in the GCK gene, meaning that they don't need treatment, or need to be treated differently. Our new map of GCK variants can hopefully help give these

patients a more correct diagnosis."

The next step for PRISM is to transfer these methods to other genes and diseases. "We are already well underway with genes involved in e.g., neurodegenerative diseases, and we are trying to develop precise methods that can provide us with insights on disease mechanisms," says Rasmus Hartmann-Petersen.

Kresten Lindorff-Larsen continues, "Our data gives us the opportunity to test and develop computational models for variant effects, which will then be transferable to other genes and diseases."

"Now, we have measured the effects of almost all variants of GCK, giving us knowledge on which variants that function, and which that do not. The next step is to understand why, and how the same underlying molecular mechanisms can give rise to a wide range of different diseases," concludes Sarah Gersing.

More information: Sarah Gersing et al, A comprehensive map of human glucokinase variant activity, *Genome Biology* (2023). DOI: 10.1186/s13059-023-02935-8

Provided by University of Copenhagen