Bizarre models for human diseases

Plants shed light on disfigured faces, and yeast and blood vessels find common ground.

Janelle Weaver

Yeast could help model diseases affecting the growth of blood vessels in humans. The search for models of human diseases might just have become easier, thanks to a data-mining technique that screens genetic databases to find subtle links to organisms as distant from humans as plants.

The new tool integrates information from existing databases that associate gene mutations with observable traits in a range of species, including humans, mice, yeast, worms and plants. And the method identifies genes in the non-human species that are more likely than by chance to contribute to human disease.

Mutations in the same gene can cause dramatically different effects in humans from those seen in other species. For instance, mutations in the *RB1* gene are associated with eye cancer in humans but cause worm genitalia to develop in the wrong place. Although such genes remain conserved across species, they evolve different functions, says Edward Marcotte, a systems biologist at the University of Texas, Austin.

On the basis of this principle, Marcotte and his colleagues set out to identify obscure gene candidates for human diseases. After screening a human database and identifying genes implicated in breast cancer,

he searched for their function in the worm database and found that they were involved in producing male progeny. Moreover, he uncovered 13 genes in this worm network that might contribute to breast cancer in humans; nine of them had not previously been implicated in the disease. His findings are published today in *Proceedings of the National Academy of Sciences*.

Strange models

Marcotte found other unusual patterns. Genes responsible for sensing gravity in plants were linked to those associated with a developmental disorder in humans called Waardenburg syndrome, which causes abnormal pigmentation in the skin and hair, cleft palate and lip, and hearing loss. His analysis indicated that three genes in the plant 'gravity' network might be linked to the human syndrome. To investigate this further, he examined gene-expression patterns in frog embryos. One gene, *sec23ip*, was expressed in neural-crest cells, which are precursors of pigment cells and cranial tissue. Reducing the expression of the gene caused severe defects in the migration patterns of neural-crest cells. These results suggest that *SEC23IP* might be involved in Waardenburg syndrome.

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Marcotte also found that genes underlying blood-vessel growth in mice influence how well yeast grow in the presence of the cholesterol-lowering drug lovastatin. His analysis pulled out 62 genes associated with lovastatin sensitivity in yeast that may relate to angiogenesis — the formation of new blood vessels. Five out of 59 genes that had not previously been implicated in blood-vessel growth were expressed in the developing blood vessels of frogs. Reducing the expression of one gene, *sox13*, led to severe defects in vascular development in frogs and human cells. The findings suggest that yeast can be used to model the development of blood vessels in humans.

"Yeast don't have blood or blood vessels, but they inform us about how the vasculature forms. And plants don't have heads, but they help

us predict genes that are involved in the correct formation of the head," Marcotte says.

"It's a nice illustration of how evolution completely co-opted entire genetic and molecular pathways," says Nipam Patel, an evolutionary developmental biologist at the University of California, Berkeley. "I was surprised how well it worked over that kind of evolutionary distance."

Disease databases

The impact of the study comes from the scope of the data mining — the integration and analysis of existing data sets, which altogether encompass more than 200,000 associations between genes and observable traits.

"I hope this study will encourage people to painstakingly annotate gene functions, which is not done universally," says Paul Sternberg, a molecular geneticist who studies worm development at the California Institute of Technology in Pasadena. He estimates that less than 5% of known gene functions are entered into databases.

The approach will be most useful for identifying subtle associations related to complex diseases, Sternberg says. It might also speed up the identification of disease pathways and drug discovery, because carrying out experiments on organisms such as plants and yeast is cheaper and faster than studying mice and humans.

But as the method relies entirely on statistics, there's no guarantee of accurate results. "It remains to be seen how well the technique will work for a range of diseases," Patel says. "It may not work for everything, but even if it works for a reasonable number of human diseases, it will still be exciting."

References

McGary, K. L. *et al. Proc. Natl Acad. Sci. USA* doi: 10.1073/pnas.0910200107 (2010).