

# New study sheds light on effectiveness of cholesterol medication in individuals

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Professor Paul Atkinson and Dr Andrew Munkacsi. Credit: Victoria University of Wellington

A study by a team of Victoria University of Wellington scientists spotlights the role of gene networks in how people respond to one of the world's most prescribed medications.

The research team investigated the genetic network response to

cholesterol-lowering drugs called statins, a medication prescribed to about 30 million people worldwide. The researchers say it is a significant step towards more targeted, personalised medication.

The work was begun by Dr. Bede Busby as a Ph.D. student at the University, working with chemical geneticists Professor Paul Atkinson and Dr. Andrew Munkacsı from the University's School of Biological Sciences and Centre for Biodiscovery. It appears in the prestigious scientific journal *npj Systems Biology and Applications*, published by *Nature*.

"Statins work and deservedly have a good reputation. But 15 percent of patients suffer painful side effects and 50 percent have inadequate response," says Professor Atkinson. "So what we've found out about how statins work can lead to modifying statins to make them more precise, based on personal differences in genetic interaction networks. The aim is to make them effective for people they don't currently work for (these people are resistant to statins) and this requires understanding complex traits, that is traits that involve many genes, as is the case with all drug responses."

"To explain a complex trait, it was previously thought that all you had to do was add up the contributing genes—tallness, for example, would be the sum of more than 200 genes," he says. "But what we've shown is that the synergistic interactions between each of the genes turn out to be just as important. The synergies form gene networks and these differ in individuals, so you have to look at the gene network variation of individuals to get a complete picture of how traits are specified by genes and inherited."

The study of complex traits needs simplifying short cuts so the researchers used [baker's yeast](#), which is a widely used and a very productive model to study [human genetics](#) and how therapeutic drugs

work.

"We can do things with yeast that you can't yet easily do with human cells," explains Dr. Munkacsi. "If you want to know how 6000 genes work synergistically together, you study all pairwise combinations of genes—this is classic methodology in yeast genetics that we adapted to study different genetic backgrounds and it is not yet adapted to study the 21,000 human [genes](#)."

Dr. Munkacsi says the research specifically used yeast strains that were resistant to statins. "We did experiments in the resistant yeast strains and worked out the biology of those interactions—that means we have a sense of what processes are involved in that resistance."

"We integrated advanced biology experimentation, mathematics, statistics, network medicine and adapted [social network analysis](#) for complex genetic data in a new approach to looking at drug response. We're continuing to use this methodology to study other drugs and diseases," Professor Atkinson says.

"We've opened a box that hasn't really been considered before—it's experimentally difficult to systematically consider both genetic backgrounds and genetic synergistic interactions so [pharmaceutical companies](#) haven't done it in their drug discovery process," explains Dr. Munkacsi. "But we've shown that yes, you should consider both of these as part of [drug](#) discovery—used early in the process it could save companies millions of dollars if it identifies undesirable responses."

All nine co-authors of the paper are currently or formerly based at the University, with Dr. Busby now at the European Molecular Biology Laboratory in Heidelberg. "Typically publishing papers requires an international effort, but this one is all New Zealand—and impressively the majority are postgraduate students in our Chemical Genetics

Laboratory at Victoria University of Wellington," says Dr. Munkacsi.

"It's very satisfying to get this research out there, and like all significant research it's not the end of the road—it opens doors," says Professor Atkinson. "Our work demonstrates principles that were not necessarily understood before, that also can be applied more widely—to other drugs and diseases, for example. We haven't discovered a magic bullet but we have discovered some good science."

**More information:** Bede P. Busby et al. Genetic interaction networks mediate individual statin drug response in *Saccharomyces cerevisiae*, *npj Systems Biology and Applications* (2019). [DOI: 10.1038/s41540-019-0112-5](https://doi.org/10.1038/s41540-019-0112-5)

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