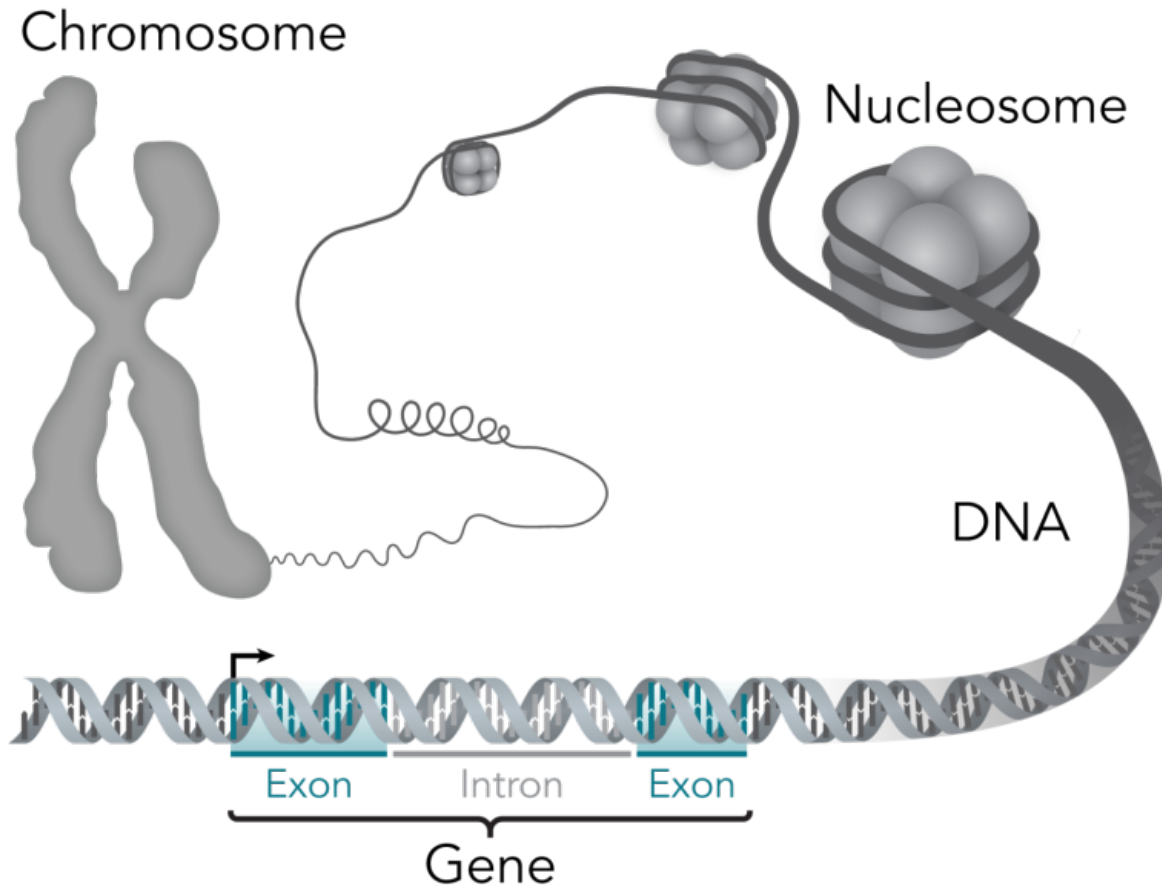


Effects of genes often influenced by network

February 27 2017



This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas Splettstoesser/Wikipedia/CC BY-SA 4.0

When many genes regulate a single trait, they commonly work together in large clusters or 'networks'. Taking this into account allows better predictions of how an individual's genetic make-up affects the trait concerned. The risk of perceiving the importance of an individual gene incorrectly is also reduced. This has been shown by researchers at Uppsala University, through a detailed analysis of thousands of related yeast cells.

Today, an individual's entire genome can be mapped in a matter of days. The big bottleneck in [genetic studies](#) is therefore no longer the problem of finding DNA differences among individuals. Instead, the great challenge is to identify which of the millions of differences affect how single cells or whole organisms function, and to understand how this happens. Researchers usually study one [gene variant](#) at a time, on the assumption that the effects of different genes are mutually independent. In so doing, they hope to identify the single most important gene variants and obtain a sound grasp of how useful they are for such purposes as predicting which individuals run the highest risk of falling ill or suffering side-effects from a drug.

"Today, companies are already offering DNA-based services for genealogy, to find relatives, for example. But the hope is that in the future we'll also be able to predict individuals' traits based on their genes. For example, one could then customise treatments and give individualised advice on health and lifestyle issues," says PhD student Simon Forsberg who, jointly with senior lecturer Örjan Carlborg, headed the study.

The researchers conducted a detailed analysis of DNA and traits from thousands of genetically different [yeast cells](#). The results showed that it was common for genes to work together. Once it was known how the

genes do so, the information could be used both to gain a better understanding of the importance of various genes in regulating the trait and to predict individual yeast cell's traits from their genetic composition.

"No doubt, in fact, few geneticists have believed that a gene variant has exactly the same effect on all individuals. But only now has it become possible to collect data from large enough experiments that enable us to investigate how important it is," Carlborg says.

The researchers found that many of the genes proved to be working together in large networks. It was particularly striking that some of them served as 'master regulator switches' for many other genes. When they were 'switched off', the other gene variants in the network had no effect on the traits studied.

"It was remarkable that the effects of these genes were entirely dependent on the other genes in the networks. Along with certain variants, they seemed to have a tremendous effect, while they hardly had any effect at all in combination with others," says Simon Forsberg.

The study shows that, in many cases, it is difficult to predict the outcome for an individual by summarising the effects of individual genes.

"We hope that what we've arrived at here will help others to analyse and interpret results from genetic studies in humans, plants and animals too, in a better way. It's important for us to become aware of what risks there may be if we don't consider the way [genes](#) work together. This applies, for example, when the aim is to use DNA information to predict how high a risk there is of an individual falling ill or suffering severe side-effects from a drug treatment," Carlborg concludes.

The study is published in *Nature Genetics*.

More information: Accounting for genetic interactions improves modeling of individual quantitative trait phenotypes in yeast, *Nature Genetics*, [nature.com/articles/doi:10.1038/ng.3800](https://doi.org/10.1038/ng.3800)

Provided by Uppsala University

Citation: Effects of genes often influenced by network (2017, February 27) retrieved 4 May 2024 from <https://medicalxpress.com/news/2017-02-effects-genes-network.html>

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