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# Predicting How Individuals Differ from Their Genome Sequences

ScienceDaily (Nov. 15, 2011) — It now only costs a few thousand Euros to sequence the genome of an individual human. However, for most of us, knowing our genome sequence would not be useful. Each human has more than 20 000 genes, and in each of us several thousand of these genes carry mutations. We do not know what happens when most human genes are altered, which means that we cannot yet make many useful predictions about our health from the sequence of our genome. Put another way, for most common human diseases we do not know most of the genes that are important, and so we cannot predict whether a person will develop a disease from their DNA sequence.

To assess whether it is possible to make useful predictions about the biology of individuals, the CRG researchers turned to a simpler and better understood species -- budding yeast. Budding yeast is used to make bread, beer and wine, and is studied as a "model organism" by thousands of researchers. This means that the 6000 genes of budding yeast are probably better understood than those of any other species on the planet.

"The key point is that in a model organism we can test how good our predictions are. We have a much better idea of the genes that are important for each process, and so we can really test whether we can make useful predictions about the biology of individuals, such as whether they are affected by a drug," says Ben Lehner, coordinator of the study and ICREA Research Professor at the CRG. "In yeast we can make predictions, and then we can use a large number of fast and cheap experiments to test whether these predictions are correct. This is very important -- to be able to experimentally test how well prediction methods actually work."

The researchers evaluated predictions about the phenotypes of 19 varieties of yeast (Saccharomyces cerevisiae). The first challenge faced was to determine which of the approximately 3000 mutated genes in each individual are actually altered in function. Then, based on this variation, they had to predict whether each individual is likely to be abnormal for a particular phenotype such as growth in a different environmental condition. In the last part of the project, more than 1,600 experimental tests were carried out under different conditions. The results showed that it is possible to make accurate predictions about the phenotype of a strain of S. cerevisiae.

According to the researchers, there are at least, two necessary conditions for such a project: very good knowledge about the genes that are important for a phenotype, and experiments performed on individuals under controlled conditions to evaluate how accurate the predictions are. In the case of human, this is very difficult to achieve, as thousands of variables are involved (from molecular to environmental) and most genes that affect particular phenotypes and diseases remain to be identified. This is the current major drawback with personalised medicine: not having the

knowledge or tools necessary to test all of the variables involved.

In contrast, making and testing phenotypic predictions in a simple model organism such as yeast allows researchers to test which alternative models and methodologies provide the best predictions. Indeed the researchers suggest in the article that future improvements might be best achieved by organising 'phenotype prediction competitions' involving many different laboratories.

"The most important thing is to have comprehensive knowledge about the genes that are important for a particular phenotype. It is not possible to predict accurately if we only know a subset of the genes that are important," says Dutch first author of the study Rob Jelier, a Juan de la Cierva post-doctoral researcher at the CRG. "However, we found that, when our understanding of gene function is good, quite accurate predictions can be made using a surprisingly simple genetic model. This provides some hope for the future of personalised and predictive medicine in humans."

The study will be published in the journal *Nature Genetics* and was funded by the Ministry of Science and Innovation (MMCINN) and the European Research Council (ERC).



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**Journal Reference**:

1. Rob Jelier, Jennifer I Semple, Rosa Garcia-Verdugo, Ben Lehner. **Predicting phenotypic variation in yeast from individual genome sequences**. *Nature Genetics*, 2011; DOI: 10.1038/ng.1007

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