Rainbow Project 3:

Inching in on the mechanisms behind complex disease phenotypes

In recent years, Genome Wide Association Studies have revealed thousands of genetic variants associated with hundreds of disease phenotypes. But the knowledge that there is an association, however robust, does not explain the mechanism that eventually leads to the manifestation of the disease in question. And why does the same genetic predisposition in two individuals not automatically lead to the same outcome? The aim of Rainbow Project 3 'A nation-wide functional genomics infrastructure enabling mechanistic insights into complex disease phenotypes' is to provide data and methods that may help lift the fog.

The more information you have, the more you can find out, is the deceptively simple assumption behind the functional genomics Rainbow Project set up by Dr Bas Heijmans (LUMC), Dr Lude Franke (UMCG), Dr Aaron Isaacs (EMCR), and Dr Rick Jansen (VUmc). Franke: "Simply put, we want to measure everything at once and use as many samples as possible. That will provide a solid basis for functional studies on humans." Heijmans: "We want to combine GWAS data with epigenetic and transcriptomic data, in order to uncover the mechanisms that start with an identified SNP and end in a complex disease—or not. We are confident that a functional genomics approach is feasible, in fact, some studies have already been conducted combining genetic and transcriptomic data and it turns out that some SNPs affect the gene expression on an adjacent gene, while others influence a gene on another chromosome. Especially this last category holds a lot of promise for researchers trying to figure out the underlying mechanism. Add data about the epigenome, which is the interface between the genome and the transcriptome, and you have a sound basis for research, given large enough numbers of samples."

GWAS biobanks

In the course of the next two years, the project will go through a number of stages. The first is the assembly of samples and data that are already there. All biobanks containing GWAS data will be asked to participate. Franke: "We are already collaborating with the Genome of the Netherlands project and we will put out the call to other biobanks soon. We feel we are offering the participating institutions many exciting opportunities. After all, we are developing methods and pipelines that will facilitate Dutch biobank research on many levels and prepare biobanks for similar initiatives within the BBMRI Europe network. Plus, what we accrue here is a unique dataset worldwide, at least for the time being."
Data generation and harmonization are next on the agenda, providing the necessary unified structure for creating that unique dataset. Then, omics-specific data-analysis and fully integrated analysis will follow. In this stage of the project, new methodology will be developed to follow the effect of a genetic variant to disease phenotypes. In order to detect novel, integrated genetic risk factors a prediction-focused pipeline will be developed. Ultimately, a proof-of-principle for metabolic risk factors is set to prove the applicability of the functional genomics infrastructure as a means to accelerate research.

Experience

The project is quite an ambitious one, but then, so are the four project leaders. Isaacs: "We are none of us senior research fellows or professors, but I think that is a good thing. It means we can devote much of our time and attention to this project. We will be hands-on involved on a day-to-day basis. And given the fact that we were awarded maximum funding by BBMRI-NL, it behooves us to create an excellent project." Jansen: "I think that our organisation structure is just as it should be: the seniority lies with the members of the Steering Committee, who have given us their vote of confidence to execute the work. Besides, we are no novices: what we are creating is a major database, and we have vast experience in that field."
The functional genomics infrastructure the four hope to create will be one of a kind, they think. Franke: "We just had a good idea that makes a lot of sense. Executing that idea will be quite a challenge, but definitely one worth undertaking." Heijmans: "It is now up to us to prove we can do it. And if we can, it will certainly put the Netherlands even more solidly on the international research map than it already is."
While ambitious, the four are also realistic about what they can achieve. Isaacs: "Ten years ago, the research community was buzzing with excitement when the Human Genome Project yielded the first complete human genome. We'd all be out of work in a couple of years, and personalized medicine was just around the corner. Ten years on we are still talking about personalized medicine as a development of the future. The first human genome turned out to be a great starting point, but nevertheless just a starting point. I feel it is the same with our project. If we can reliably predict mechanisms underlying complex disease phenotypes, we will be a step closer to understanding how disease evolves; and that may give us a starting point towards finding out how we can prevent, slow down or even cure diseases. But we are taking it one step at a time."

The four project leaders, fltr: Rick Jansen, Lude Franke (sitting), Aaron Isaacs, and Bas Heijmans (standing). (photo Thijs Rooimans)