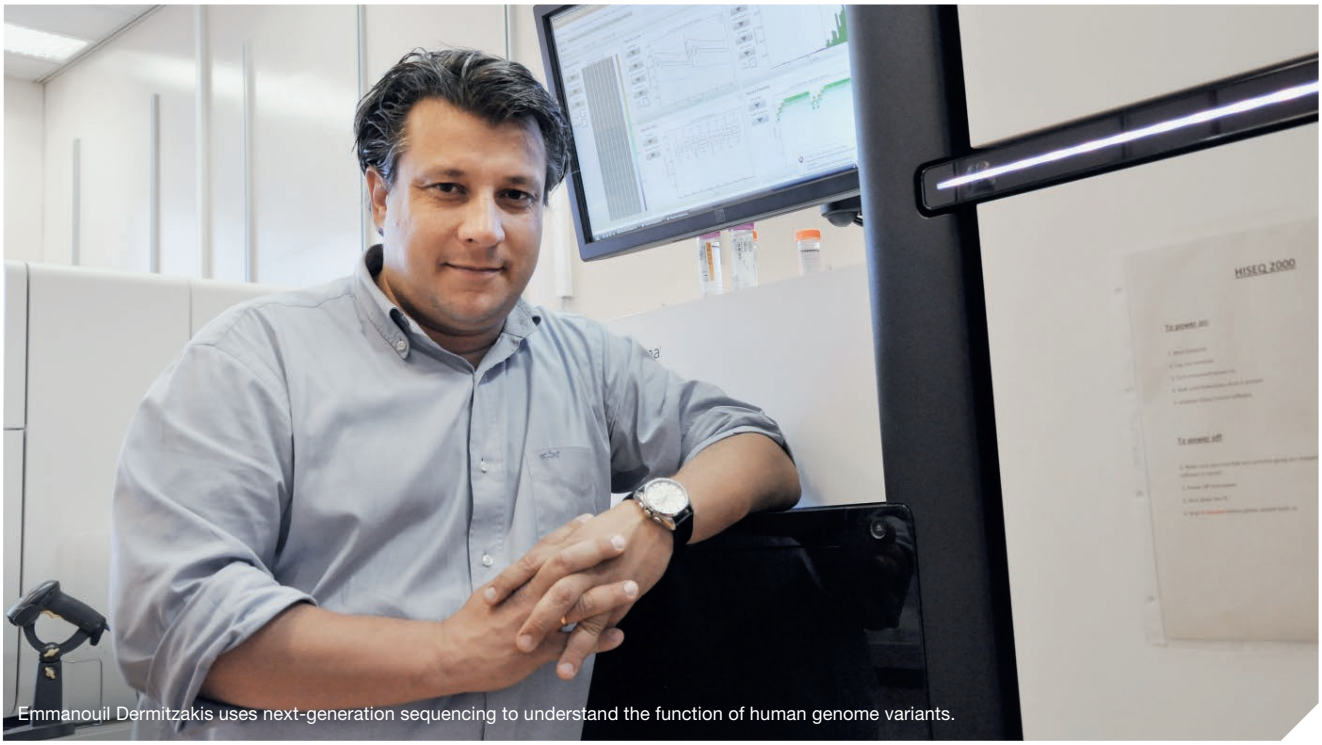

Emmanouil Dermitzakis uses next-generation sequencing to understand the function of human genome variants.

Cellular systems genetics in humans (SysGenetiX)

Turning to natural mutations to understand gene regulation

Our genes determine many aspects of who we are. But it's not just the genes themselves that play a role in establishing our biological traits. If and how they are expressed, which is crucially controlled by regulatory elements, is also a major factor. The goal of the SysGenetiX project is to closely investigate these regulatory elements, as well as their manifold interactions with genes. The findings may in future contribute to advancing our understanding of why some people are more predisposed to contracting particular diseases than others.

It makes sense that not all of our genes are expressed at all times throughout our bodies. For example, during embryo development, genes have to be turned on and off at different times according to a fixed pattern to result in the formation of distinct body parts and tissues. Even within the fully developed body, the cells of different tissues express different sets of genes so that these tissues can carry out their specialized functions. Regulatory elements make sure that the right genes are expressed at the right time in response to specific stimuli.

These regulatory elements are segments of DNA, mostly promoters or enhancers, that are coupled to particular genes. When specific proteins dock onto these elements, they trigger a whole network of reactions. These ensure that the corresponding genes are transcribed at the right moment, along with the correct amount of mRNA, which in turn prompts the production of proteins. Ideally, this all happens smoothly and according to plan.

Mistakes in gene regulation can lead to disease

However, just like the genes themselves, regulatory elements are susceptible to mutations. If they present no immediate disadvantage, mutations will be passed on, resulting in different variants of these DNA segments. These variants can either be completely neutral, have a positive effect, or entail drawbacks. That being the case, some of the mutations are being linked to predisposition to certain diseases.

"Until now, this relationship has only been shown in terms of a statistical correlation," explains Emmanouil Dermitzakis, Professor of Genetics in the Department of Genetic Medicine and Development at the University of Geneva Medical School, and SysGenetiX project leader. "What's not yet been investigated is what these variants do exactly, and how they lead to increased susceptibility to certain diseases," adds the researcher. The SysGenetiX consortium now aims to close this gap in knowledge, and is working on bringing the detailed interactions between regulatory elements and their associated genes to light.

Examining natural genetic mutations

To this end, the SysGenetiX team is following a slightly different approach than is normally used in systems biology. "Instead of interfering with a system and inspecting what happens, we're look-

Maja Schaffner

ing for and analyzing the naturally occurring mutations in the regulatory elements," states Dermitzakis.

The scientists are working with a considerable sample size, encompassing blood and skin cells from almost 300 individuals. They are quantifying how much the chromatin – that is, the DNA with all its associated proteins – is methylated and acetylated, which determines what genes are accessible to transcription. They are also looking at how much mRNA is transcribed, as well as its composition. In addition, they analyze which proteins are synthesized in what quantities. Using all this data, they are able to reconstruct the activation mechanisms and regulatory networks of the individual genes.

Dermitzakis sees every gene as a mini system comprising a network of interactions and a variable output. "Our goal is to gain an understanding of the universal rules of gene regulation, and also to find out how each individual gene is regulated," he explains. The mutations, and the way in which they perturb the system, help the scientists understand how the system normally works, and what happens when something goes wrong.

High variability

The project still has a long way to go. The first results have already been obtained, but not yet published. The ways in which the mutations affect different tissue types are still to be analyzed. However, what is already clear is that there is great variability in the ways in which different genes are regulated. "For example, we've seen the case where 20 regulatory elements regulate three genes, another case where ten of these elements regulate just one gene, and yet another where a single one regulates three genes," illustrates Dermitzakis. The team has also shown that some mutations influence the methylation and acetylation of the chromatin and hence the accessibility of the DNA, and that other mutations have an effect on the quantity of proteins that are synthesized.

The researchers now want to divide all of these very differently regulated genes into categories with similar mechanisms. They also plan to make the knowledge gained within SysGenetiX available to other scientists through an Internet database. Anyone who is interested in a particular gene and its regulation will simply be able to look it up.

A better understanding of the causes of disease

"The work we carry out on this project is basic research," emphasizes Dermitzakis. However, knowing what goes on at the level of gene regulation, and what effects mutations in the regulatory elements have, could decisively contribute to a better understanding of how diseases such as diabetes, cardiovascular disease or cancer arise. Such knowledge may indeed one day lead to early diagnosis and better treatment options. "And even," adds the researcher, "long before the first symptoms become apparent."

SysGenetiX at a glance

Principal investigator: Prof. Emmanouil Dermitzakis

Research groups:

- Prof. Emmanouil Dermitzakis, Department of Genetic Medicine and Development, University of Geneva Medical School – Population genomics and systems medicine
- Prof. Stylianos Antonarakis, Department of Genetic Medicine and Development, University of Geneva Medical School – Genomic medicine
- Prof. Philipp Bucher, Swiss Institute for Experimental Cancer Research, EPF Lausanne – Bioinformatics
- Prof. Alexandre Reymond, Center for Integrative Genomics, University of Lausanne – Disease genomics
- Prof. Sven Bergmann, Department of Computational Biology, University of Lausanne – Statistical genetics
- Manolis Kellis, MIT Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology (USA) – Computational biology

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Project type: Research, Technology and Development (RTD) Project

SysGenetiX
Cellular Systems Genetics in Humans