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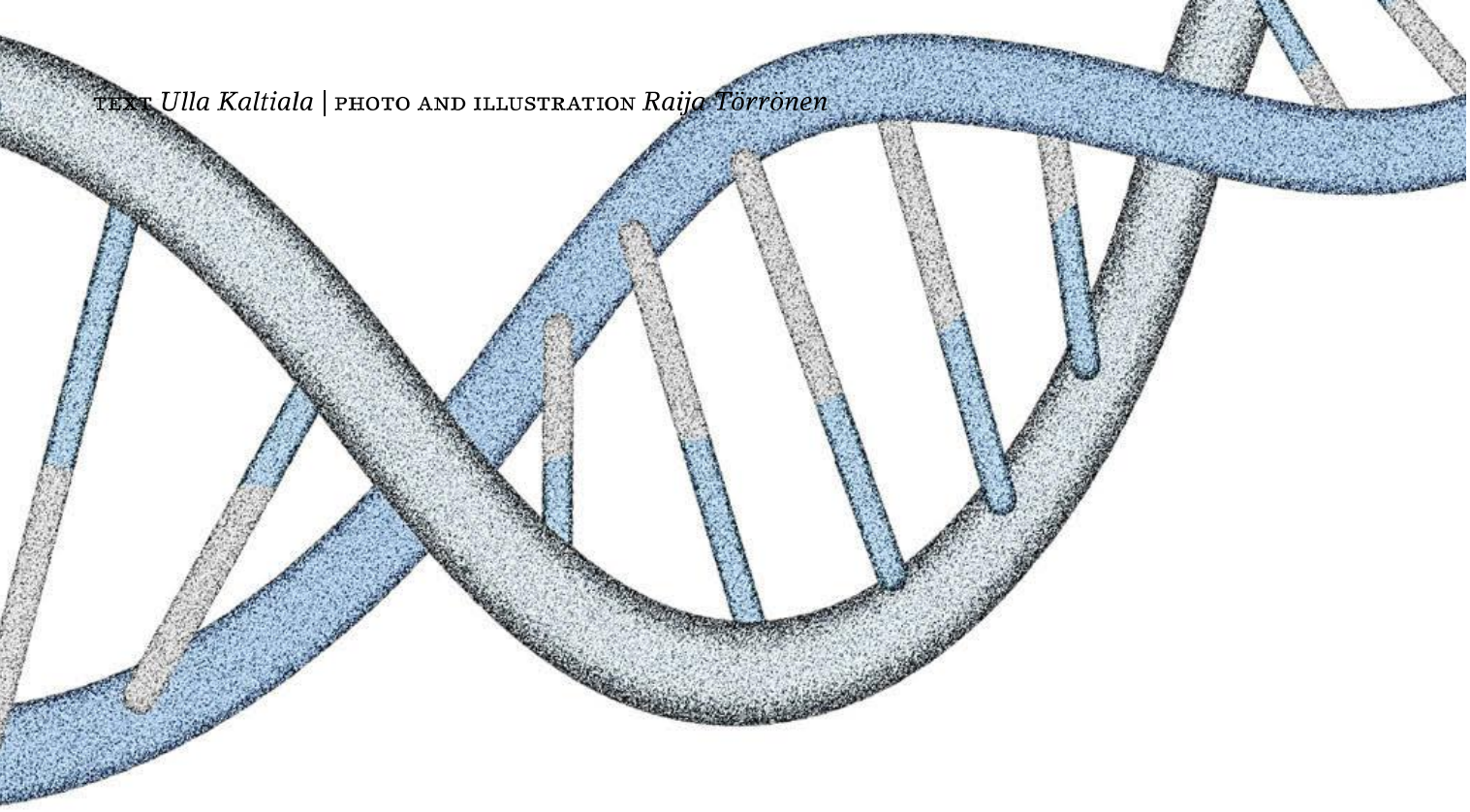

Genes tell a tale: many faces of type 2 diabetes

Researchers are uncovering the genes behind type 2 diabetes at an increasing speed. Genetics research has already shaped our understanding of the pathogenesis of the disease.

According to Academy Professor **Markku Laakso**, the analysis of the entire genome has shaped our understanding of the main disease mechanisms of type 2 diabetes.

"Today, we know that the majority of risk genes for type 2 diabetes are associated with insulin secretion. Previously, it was thought that impairment of tissue insulin sensitivity was essential for the pathogenesis of the disease. However, its significance as a risk factor for diabetes is smaller than previously thought."

According to Professor Laakso, there is a demand for drugs that help maintain the patient's own insulin secretion. Indeed, the drug market has already witnessed the entry of drugs which mimic the function of a hormone that increases insulin secretion, i.e. the incretin hormone GLP-1.

UNIq UE DATA

Professor Laakso is one of the world's leading researchers of the genetics of type 2 diabetes and, at the University of Eastern Finland, his studies are among those most frequently cited internationally. His research group also comprises part of the Centre of Excellence in Cardiovascular Diseases and Type 2 Diabetes Research of the Academy of Finland. Furthermore, Professor Laakso's population-based METSIM (METabolic Syndrome in Men) study has gathered a unique set of data involving 10,000 men from eastern Finland, and this data has also attracted worldwide attention among researchers.

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diseases. Indeed, eastern Finland is a Mecca for genetics research."

However, it took a while before genetics research got wind in its sails. "When we started 15 years ago, the candidate gene approach, i.e. the analysis of pre-specified genes assumed to have an association with type 2 diabetes, was widely used. Not too many risk genes were discovered, though."

Nevertheless, in 1998, Professor Laakso's research groups successfully used the candidate gene approach to identify the first verified risk gene for type 2 diabetes, namely the PPARG2 gene. "We got incredibly lucky," he says.

After the launch of genome-wide association analyses in 2007, the genetic background of type 2 diabetes began to unravel rapidly. "We were also able to identify genes with no previous association with this disease. Today, we know over 50 risk genes for type 2 diabetes."

The majority of risk genes have been found in extensive international studies involving several groups, including Professor Laakso's group. "Genetics research is a collaborative effort on a global scale, and everyone is working towards a common goal," he explains.

WE ALL CARRY A RISK GENE

"Everyone carries risk genes for type 2 diabetes," Professor Laakso says. "However, the risk of actually catching the disease does not grow significantly until there are several risk gene variants at play. Moreover, healthy lifestyle choices can prevent the development of the disease, despite the presence of risk genes."

The presence of the TCF7L2 gene, a major risk gene among those commonly known, increases a person's risk of contracting type 2 diabetes by as much as 30–40%. However, a diabetes prevention study carried out in Kuopio showed that the risk percentage can be brought down close to zero by means of weight loss, physical exercise and a healthy diet.

FOCUSING ON EXON MUTATIONS

Recently, genetics research has taken a new course. "We are now searching for rare mutations which increase the risk of type 2 diabetes more significantly than the commonly known risk genes." Being a carrier of this type of a mutation may increase the risk of contracting type 2 diabetes by as much as 100%.

"Research is now focusing on exons, the protein-coding sequences of genes. We will publish our findings on rare mutations in exons in one year's time. At this point, I can already say that we

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have found several rare mutations and, in addition to being associated with the risk for diabetes, they are also linked to blood lipids and blood pressure, among other things," Professor Laakso says.

A new discovery is a gene mutation, which causes a diabetes-like disease that is not type 1 or type 2 diabetes, although it resembles the latter. "These kind of discoveries also play a role in deepening our understanding of the pathogenesis of diabetes."

Funding from the US National Institutes of Health, NIH, among others, has made the expensive analyses possible. Dr Francis Collins, the current Director of NIH and the previous leader of the Human Genome Project, is a long-term research partner of Professor Laakso.

Professor Laakso's research project comprises several sub-projects. For instance, the DIRECT and DEXLIFE projects funded by the EU study the association between the presence of risk genes and the progression of the disease in men from eastern Finland. The UEF's own spearhead project GENENUTRI, on the other hand, brings together the search for new diabetes genes and nutrigenomics, that is, it studies the effects of genes and diet on health. The latter project is led by Professor **Matti Uusitupa**.

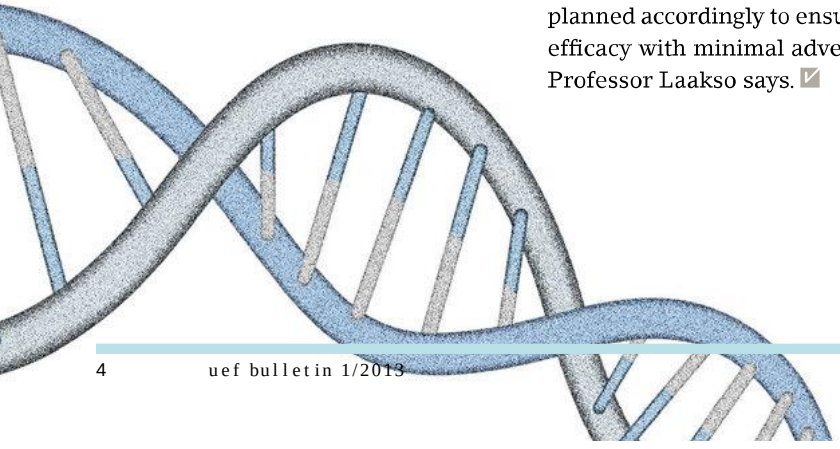
GENES DETERMINE THE BEST COURSE OF TREATMENT

The genes discovered by Professor Laakso's research group have served as an inspiration for developing diagnostics services for rare monogenic diseases and, currently, the Genome Centre of Eastern Finland offers diagnostic tests for as many as 20 monogenic diseases. In addition to rare diabetes types, tests are also available for cardiac and metabolic diseases.

Furthermore, the range of services includes pharmacogenomics, i.e. the use of genetic analysis to optimise drug therapy. For example, a gene test can identify patients in whom statins will cause myopathy and patients in whom warfarin treatment will prove inefficient.

According to Professor Laakso, the significance of pharmacogenomics will also increase in the treatment of diabetes. In light of genetics, type 2 diabetes is not a single disease; instead, it is a range of different conditions caused by several risk gene combinations. In consequence, the optimal treatment should be determined on the basis of the patient's genes.

"It's not a dream to think that in ten or twenty years' time, all patients will be tested for their individual diabetes risk genes and their treatment will be planned accordingly to ensure maximal efficacy with minimal adverse effects," Professor Laakso says.



Novel information on insulin secretion

DISTURBANCES IN insulin secretion constitute the main susceptibility factor for type 2 diabetes. A Finnish-American team of researchers used an exome chip to discover new genes associated with the regulation of insulin synthesis and secretion.

An article published recently in Nature Genetics reports the discovery of new and rare gene mutations which affect insulin synthesis and insulin secretion. In consequence, the study sheds important new light on the factors behind the pathogenesis of type 2 diabetes.

"Studying genetic mutations helps us understand the pathogenetic mechanisms of the disease," says Professor Markku Laakso, one of the senior authors of the article.

"We found new genes that can help us understand the regulation mechanisms of insulin synthesis and insulin secretion."

This was the first time an exome chip was used in genetics research and, compared to traditional sequencing, it constitutes a considerably more cost-effective alternative. This method enables a speedy analysis of DNA samples, allowing researchers to access more than 200,000 markers representing diverse populations and conditions. Furthermore, the method is particularly well-suited for studying rare gene mutations.

"By using an exome chip, it was possible to analyse a total of 8,229 subjects in a small amount of time."