Decoding the PROX1 gene

Targeting the mechanisms of metabolic disease, **Dr Aline Meirhaeghe** highlights her promising research developments into eating behaviours and the study of genetic factors linked with obesity and type 2 diabetes.

---

**How have your personal and professional experiences led you to focus your research on obesity and type 2 diabetes?**

Early in my career, I was attracted to gaining a more thorough understanding of obesity; why do some people gain weight while others do not? I joined the French National Institute of Health and Medical Research (Inserm) as a junior research associate when I was 30 to examine the molecular genetics of metabolic conditions in a laboratory working on the determinants of cardiovascular diseases (CVDs). Overweight people present with a greater risk of developing type 2 diabetes and, as both obesity and type 2 diabetes are major risk factors for CVDs, our team thought that studying these metabolic illnesses could help in the understanding of the aetiology of CVDs. Our strength is that we have multiple large human studies that enable the analysis of both environmental and genetic risk factors for these prevalent chronic diseases.

**Why is there a pressing need for research into the causes and mechanisms of obesity and type 2 diabetes?**

There is a marked rise in the prevalence of obesity and type 2 diabetes worldwide. These diseases are major public health problems due to their deleterious effects on health and health costs. They affect numerous organ systems involving the heart, liver, kidney and vascular system. Understanding the causes and mechanisms of obesity and type 2 diabetes would help to improve prevention and therapeutic strategies.

**Can you explain your decision to study the PROspero homeobox 1 (PROX1) gene?**

We chose the PROX1 gene as it was identified as a genetic risk factor for type 2 diabetes in genome-wide association studies, and very little was known about its function except that it was involved in lymphatic, hepatic and pancreatic development in mice models. Some data in the literature let us think that PROX1 could play a role in pancreas function that might explain its association with type 2 diabetes.

**What kind of eating behaviours do you investigate? Can you outline how each of them manifests?**

There are several types of eating behaviours: uncontrolled eating or hunger is the tendency to eat more than usual because of a loss of control over intake; emotional eating or disinhibition involves overeating during dysphoric mood states, eg. when feeling lonely, depressed or anxious; and cognitive restraint, which is conscious restriction of food intake to control body weight or to promote weight loss. Disinhibition and hunger are associated with an elevated body weight, whereas the relationship between cognitive dietary restraint and body weight is subject to debate.

**If obesity were found to be determined largely by genetic factors, would there still be a moral need to combat the environmental factors contributing to the disorder? How would such a discovery impact policy relating to obesity and healthcare?**

It is not because obesity is driven in part by our genes that one cannot prevent it. It is the combination between our genome and lifestyle that matters. Some genes, associated with a bad lifestyle, will have a more deleterious effect on weight gain than if associated with a healthier lifestyle. For example, our group showed in 1999 that physical activity could counterbalance the effect of a genetic predisposition to increased body weight, body fat and obesity. Obese individuals with this particular variant may especially benefit from physical activity to reduce their weight. This approach might lead to more effective personalised medicine.

**In what ways could your research inspire potential new strategies or treatments for reducing risk of, and managing, obesity and type 2 diabetes?**

This project should lead to the identification of new genetic determinants of eating behaviours and obesity, and to a better understanding of the mechanisms (both genetic and environmental) implicated in the onset of obesity. Better prevention and patient management strategies can then be implemented at the clinical level, once the individual’s susceptibility is better understood.
FAR MORE COMMON than type 1 diabetes and with no existing cure, type 2 diabetes is on the rise. In fact, over 439 million people worldwide are predicted to suffer from the disease by 2030. This metabolic illness has been linked to obesity and occurs when the body does not produce enough insulin to maintain a normal blood glucose level (insulin deficiency) or is unable to use the insulin produced effectively (insulin resistance).

Over the last few decades, there has been a considerable increase in the number of obese people of both genders across Europe – at present, almost 20 per cent of Europeans are considered to be obese. Searching for a solution, scientists are endeavouring to identify the environmental determinants and individual genetic susceptibility factors that cause obesity and type 2 diabetes through molecular and cellular explorations. A unifying aim among them is to develop new strategies for the diagnosis, prognosis, prevention and management of these conditions.

GENETIC AND MOLECULAR STUDIES

The introduction of genome-wide association studies (GWAS) in the early 2000s has enabled scientists to identify 52 loci associated with type 2 diabetes-related phenotypes. Research projects carrying out GWAS were able to screen millions of genetic polymorphisms at a time, with scientists combining their cohorts to increase statistical power. Although this represents a big step forward, it has also raised the following question: what function do these genes play in humans to lead, when mutated, to diseases? “My group tries to decipher the physiological functions of some of the proteins encoded by these genes,” Dr Aline Meirhaeghe, Senior Research Associate at the Institut Pasteur de Lille in France elucidates.

There had been no link established between the PROspero homeoboX 1 (PROX1) gene and type 2 diabetes until researchers carried out GWAS showing that the rs340874 single nucleotide polymorphism (SNP) in PROX1 is a genetic susceptibility factor for type 2 diabetes. Located on human chromosome 1, the PROX1 gene encodes a key transcription factor implicated in the development of various tissues such as lymph, liver, retina and pancreas, playing a significant role in maintaining glycaemic control in pancreatic beta cells.

HELENA

Participating in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional project, Meirhaeghe’s team...
The PROX1 gene encodes a key transcription factor implicated in the development of various tissues, playing a significant role in pancreatic beta cells in maintaining glycaemic control.

Although diabetes has been recognised as a distinct disease for over 2,000 years, it was only in 1935 that Roger Hinsworth established that there were two types of diabetes.

assessed the impact of the whole common genetic variability of PROX1 (80 variants) on type 2 diabetes-related biochemical traits in adolescents.

Indeed, HELENA involved a total of 2,865 adolescents aged 12-18 randomly selected from nine European countries. HELENA’s main objective was to obtain reliable and comparable data of a representative sample of European adolescents about: food and nutrients intake, food choices and preferences, obesity prevalence, dyslipidaemia, insulin resistance, vitamin and minerals status, immunological markers for subclinical malnutrition, physical activity and fitness patterns, and variations of the nucleotide sequence in selected genes. A general linear regressions model (GLM) was used to compare mean values of anthropometric and biological markers for various genotypes. The GLM was then adjusted for age, gender, centre and body mass index.

Meirhaeghe and her colleagues observed that among 80 variants in PROX1, nine were significantly associated with fasting plasma insulin levels in adolescents. They performed specific functional studies on 11 polymorphisms in order to identify polymorphisms causally related to this association. The insulin-lowering alleles of three variants were associated with lower PROX1 expression in mice pancreatic cells. Moreover, in rat pancreatic cells, the knockdown of PROX1 expression resulted in an approximate two-fold reduction in glucose-stimulated insulin secretion leading the researchers to the conclusion that reduced expression of PROX1 by regulatory variants results in altered β-cell insulin secretion and thereby confers susceptibility to type 2 diabetes. The results suggested that liver and pancreas expression levels of PROX1 may be lower in diabetics [compared with non-diabetics] and in subjects carrying at-risk alleles.

INSIGHTFUL GENES

In addition to her work on diabetes, Meirhaeghe has been looking at the role of eating behaviours in the development of obesity by using her expertise in genetics and molecular biology to create the Gene and Environment Case Control study of ObeSity (GECCOS). Although almost a hundred genetic factors associated with fat mass or obesity have previously been discovered, these factors explain a minor fraction of the heritability of these phenotypes – other loci still remain to be determined. GECCOS aims to help in finding part of the missing heritability: “Indeed, eating behaviours may explain an excess of energy intake,” reveals Meirhaeghe. “The association between some genes and obesity may be seen only in individuals with a particular eating behaviour [interaction]. In that case, this effect will be diluted or hidden if we take obesity as the sole criterion of study.”

The group has directed some of its studies to the identification of genetic determinants of eating behaviour and, subsequently, to the examination of whether these determinants increase the risk of obesity. Estimations of genetic heritability vary greatly from one study to another and several questionnaires can be used to assess eating behaviours. For GECCOS, the team used the Three-Factor Eating Questionnaire, which measures the three dimensions of human eating behaviour. To date, very few genetic susceptibility factors for eating behaviour have been identified. “I set up collaborations with several other teams in Europe and the US who have similar data in order to perform the first GWAS on eating behaviours and obesity,” Meirhaeghe reveals. Following encouraging results for the PROX1 gene, the team wants to further develop these results: “We plan to perform in vitro experiments in order to identify the functional variants in the genes we will find associated with eating behaviours and understand the physio-pathological processes,” Meirhaeghe concludes.