Interview

Obesity and Genetics: An Interview with
Dr. David Meyre

Interview conducted by
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Dr. David Meyre is an associate professor in the Department of Clinical Epidemiology and Biostatistics at McMaster University. Dr. Meyre completed his PhD in the field of quantitative plant genetics in France. He has been working on understanding the genetic basis of human obesity and type 2 diabetes for the last 12 years. He has a strong desire to better understand the interaction between genes and high risk environments, and their relative impact on obesity. Dr. Meyre has over 110 publications, and is recognized internationally as an expert in the genetic epidemiology of metabolic diseases. His expertise in the field has earned him the title of Canada Research Chair in Genetic Epidemiology. His interests for current and future research include understanding the genetics of obesity among different ethnic groups, better understanding the physiological and molecular mechanisms involved in metabolic diseases, identifying the interactions between genes and specific environmental exposures, and the usefulness of genetic information in clinical applications.

UTMJ: Can you tell us a little about yourself and the work you do?

DM: My field of research is the genetics of obesity and type 2 diabetes. Obesity is becoming a worldwide epidemic and according to the World Health Organization the prevalence of obesity has nearly doubled between 1980 and 2008. In some countries, close to 50% of adults are overweight or obese and the previsions for the coming years are worrisome, especially in low and middle income countries. We therefore need to better understand the disease to find efficient ways to curb the current obesity trend.

Is it really so bad to be obese? Obesity by itself does not necessarily lead to health complications and obese but metabolically healthy people have been well described in the literature. However, on average, 44% of diabetes, 23% of ischaemic heart disease, and 7–41% of certain cancers are attributable to overweight and obesity. Adiposity is also associated with early osteoarthritis and joint injury. It is also not good for your mood, and on average obese people have a lower self-esteem and a higher risk of depression. There is also strong discrimination against obese people, especially in Western societies. Our societal model is schizophrenic, in the sense that our everyday lifestyle (including high-fat high carb processed food, lack of physical activity, air conditioning) is pushing us to become obese, but when you do become obese you are discriminated against.

Environmental factors are really important in the onset of disease. High fat diet, lack of physical activity, lack of sleep, multiple pregnancies, smoking cessation, use of antidepressant drugs, and lack of education are established risk factors. We may naively think that obesity is just an environmental disease, but the story is more complex. It is clear that environment plays a role in causing obesity, but who becomes obese in this obesity-prone environment is determined by genes. If you have two obese parents, your risk of developing obesity is increased by 10-fold. Family history is the main risk factor for obesity. Even in the United States, we forget that 50% of people stay lean despite an obesity-prone environment. We can imagine that these people have a healthier lifestyle, but another plausible explanation is that they do not have the predisposing genes for obesity.

Obesity can therefore be considered an inherited disease, where 50-80% of risk is genetic and the remainder is determined by environment. As heredity plays an important role in obesity, it is critical to identify the genes responsible for this condition. First, you need to make an important distinction between the different forms of genetic obesity. The first form is termed the Mendelian or monogenic obesity. This means that one gene is responsible for the disease. If you have the mutation in one gene then you have the disease, and if you do not have the mutation then you do not have the disease.
Within monogenic obesity you can distinguish between monogenic syndromic and non-syndromic forms of obesity. Syndromic obesity means that obesity is just one feature among many others. People with Bardet-Biedl syndrome are obese but show additional features such as learning disabilities, retinopathy, renal defects, and polydactyly. These forms of obesity are extremely rare. Bardet-Biedl syndrome has a prevalence of only 1 in 140,000 to 1 in 160,000 newborns in North America. Despite these diseases being rare, it is valuable to understand the genetic cause of syndromic obesity in order to manage the care of these patients. Fifteen genes responsible for Bardet-Biedl syndrome have been identified these last 15 years changing drastically our understanding of this syndrome.

Non-syndromic Mendelian obesity means that hyperphagic obesity is the main feature observed in affected patients. Researchers have found nine genes involved in non-syndromic monogenic forms of obesity, but there are probably more genes involved and we are trying to make progress in this area. Non-syndromic Mendelian obesity may concern at least 10% of obese patients. All the associated genes identified to date are located in the leptin / melanocortin molecular pathway. Leptin is a key hormone that is produced by fat tissue and controls satiety via the brain. When leptin is high you feel full, and when leptin is low it is time to eat. A genetic defect in that molecular pathway invariably leads to lack of satiety and hyperphagic behavior.

There is a third form of obesity called polygenic obesity. In this case, several genes are involved in causing obesity, with each gene contributing to a small extent. We currently know about 80 of these polygenic obesity genes. Some people only carry a small number of these obesity predisposing gene variants, and these people have a low likelihood of being obese. Other people carry a large number of these obesity risk gene variants and these people are much more likely to be obese. My research focuses on these three forms of genetic obesity.

**DM:** One particular gene that is most commonly involved in monogenic obesity is the melanocortin receptor 4 gene, and we estimate that in Europe 2% of obese people carry mutations in this gene. Previous publications suggested that melanocortin receptor 4 genetic deficiency was a Mendelian form of obesity, but a few years ago I suspected that even in these high genetic risk people obesity may not be automatic depending on the environment. We sequenced the genes in 5,000 lean and obese subjects and we found 25 French pedigrees with kids, parents, and grandparents co-segregating for mutations in the melanocortin receptor 4 gene. We evaluated the percentage of people with the mutation who were obese depending on the generation. We found that 40% of the grandparents, 60% of parents, and 80% of the kids, who were 11 years of age on average, were obese. So even though all generations had the same extent of genetic risk, environment was playing a large role in the development of obesity.

Our explanation was that when the grandparents were young it was right after World War II, and this was a time when food was often scarce. These people were probably hungry all the time but there was not so much food available, and so only 40% of them developed obesity. The parents grew up during the 1960s and during this time there was access to more food, and so 60% of them developed obesity. The last generation involved kids growing in an ‘obesogenic’ environment, and 80% of these kids around 11 years of age have already become obese. This proves that even if you have a very high genetic risk for obesity, you can still avoid obesity since environment is still greatly involved.

When newspapers talk about obesity they communicate the message that obese people are lazy people who do not have the will to say ‘no’ to food. The research that we and others have done proves that in reality people with obesity are different, biologically speaking (we are not all equal before food!). In reality, hormones control your feeding behaviour and this changes the way obesity needs to be managed. To reiterate, obese people are not lazy, but rather biologically different. Even the decision making process of whether to eat or not is controlled biologically. Our study was important to show this, and we were able to prove that even with high genetic risk people can avoid obesity with strict diet control, which gives hope for the future of obesity prevention and management.

**DM:** Could you tell us how your research could apply to the medical field and impact it in the future?

**DM:** You mentioned that there is an environmental aspect to obesity but also a large influence through genetics. Could you tell us more about how genetic factors interact with the environment to induce obesity?
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Scientifically speaking, people with a genetic deficiency in the leptin-melanocortin pathway have a biological signal that pushes them to eat. Researchers are working hard to find drugs that can compensate for the leptin-melanocortin pathway deficiency, but it has not been really successful to date. However, when we practice sports, a lot of ‘well-being’ hormones such as endorphins or dopamine are produced and the hormonal balance changes drastically. My hope is that these hormones may, to a certain extent, help these patients to better cope with the frustrations induced by their genetic condition. Doctors working with monogenic obese patients frequently report that they tend to over-eat to relieve the stress in their lives, and we need to test if regular physical activity can have a positive impact.

Nutritional education is an important cornerstone in obesity management programs today but it may not work so well for monogenic obese patients. In the general population, the more educated you are, the less likely you are to become obese, but we were unable to find this trend in melanocortin 4 receptor deficient monogenic patients from 25 pedigrees. We did find a significant negative association between education and corpulence in the family members who did not carry mutations. This observation may signify that people carrying monogenic mutations in the melanocortin receptor 4 gene do not change their diet habits despite having all the knowledge about what food is healthy and what food is not.

This project is primarily for kids, but for adults we have some ongoing projects based on obesity bariatric surgery. Bariatric surgery includes a variety of procedures where weight loss is achieved by reducing the size of the stomach with a gastric banding, or through more invasive procedures such as removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch) or by resecting and re-routing the small intestines to a small stomach pouch (gastric bypass surgery). Surgeons typically determine the type of surgery to be used for a patient depending on the degree of obesity and health-related complications. We and others recently proved that genetic information may help to better decide the type of surgery to apply. People with melanocortin 4 receptor monogenic mutations have a higher risk of post-surgery complications and reoperation after gastric banding and it may be very beneficial to orient them directly to bypass surgery. This is another application of genetic discoveries and although this process is not being routinely used today, it is likely that genetics will be used for such applications in the future. Information on genetic mutations can have a large positive impact in terms of health benefits, patient well-being, and economy. There is
definitely hope for patients whose mutations fall under the category of Mendelian genetics in terms of personalized medicine. Regarding polygenic forms of obesity, it is too early to think about genomic medicine because we do not have much information about the genes. I am confident that we will see clinical application coming in the long term, but a lot of genetic information needs to be discovered first.

UTMJ: It seems like there are a lot of barriers in the study of obesity. Could you tell us about general barriers in the field and barriers that you have come across personally in your research?

DM: For a long time obesity was not considered a disease, and this notion still is highly debated by specialists of the field even in 2013. Some researchers think that it does not make sense to class 35% of Americans as sick. This tells you a lot about the ambient psychological barriers in the perception of obesity as a disease. In my opinion, it is not really important to know if obesity is a disease, a pre-disease or not a disease at all. The only thing I know is that obesity is an important risk factor for many different health complications (diabetes, hypertension, cardiovascular diseases, cancers), that severe obesity reduces your life expectancy by 10 years, and that obesity costs 7 billion a year to the Canadian economy. This must be enough to push forward nation-wide obesity prevention programs, but unfortunately things move very slowly. For instance, we don’t need to find all of the obesity predisposing genes to know that sweetened beverages make us fat. One glass of sweetened beverage equals six cubes of sugar, and you need to run one hour to burn these calories! In my opinion sweetened beverages should be highly taxed or simply banned from our stores, but things are not as simple as large-scale obesity prevention programs may have important economic repercussions on agri-food industry. Agri-food industry is the number one economical player in the world, and politicians must carefully balance health concerns and the lobbying of agri-food industry. However, killing people and weakening our society to preserve an industry is not ethical in my view, especially because everyone knows that industry has an incredible ability to adapt to new rules. I would love to see more ambitious political initiatives to fight obesity in North America such as the ones applied in Finland a long time ago.

Another barrier is that genetic research has been mainly done in populations of European ancestry. This is probably because money is concentrated in Western countries. However, the genetic architecture of obesity varies with ethnicity and genetic research need to be undertaken in different ethnic groups. Certain ethnic groups are more predisposed to obesity than others and they probably have genetic specificities. For example, aboriginal and African populations have a higher risk of developing obesity. We need to invest more into learning about the ethnicity specific architecture of obesity.

Yet another barrier is the lack of research into finding genes that protect you from obesity. Very little research has been done in order to find such genes, and most research focuses on genes that cause obesity. Part of the explanation is that it is far more difficult to convince lean and healthy people to participate to genetic studies as compared to obese people. Obese people are generally very open to contribute to research studies because they want a different future for themselves and for their kids. There is a lot of scope for making new discoveries in this field and it is something that should be done in the future. Understanding the biological mechanisms that make you resistant to obesity even in an unfavorable environment may have exciting medical applications.

In addition, it is essential for research funding agencies to invest more in obesity research because the treatment for obesity is by essence very complex. You cannot treat obesity by just prescribing one pill that cures the disease, and this point will never be reached because obesity involves complex interplays between a multitude of genes and environments. We also need to invest more energy into translating information from basic research and applying them to medical applications. People are very good at basic research and a lot of things have been discovered, but it is difficult for basic researchers to translate their findings into clinical applications. Despite researchers talking a lot about genomic medicine, well-designed studies demonstrating the value of adding genetic information to medical practice using an evidence based medicine approach remain rare.