Towards 2020:
The genetic influence on obesity and associated disease

Thursday, 25 April 2013

The Royal College of Pathologists. 2 Carlton House Terrace. London. SW1Y 5AF, United Kingdom

Obesity: a multi disciplinary approach to the genetic influence on this global epidemic. After hearing an overview of the problem, speakers will give evidence based on the genetics of eating behavior, its influence on childhood obesity and treatment ; genome wide association studies identifying genes with a role in obesity, molecular mechanisms underlying the central control of food intake and body weight; and an appreciation of genetic factors over the environment in obesity. Speakers will also inform us of diseases associated with obesity.

This event has CPD accreditation

9:00 – 9:45 **Registration**

9:45 – 10:00 **Introduction by the Chair: Jane Cutler,** UK

10:00 – 10:30 **Gene-environment interactions in obesity**
Dr Clare Llewellyn , University College London and King's College London, UK
Despite the ubiquitous 'obesogenic' food environment, not everyone is overweight. Genetic susceptibility to the environment is thought to explain some of the individual differences in weight, with differential appetitive responses to food, being implicated as the mediating mechanism. It has been hypothesised that individuals who inherit a more avid appetite, lower sensitivity to satiety and preference for energy dense foods, are more likely to overeat in response to the modern food environment and gain weight – i.e. 'obesity genes' influence adiposity partly through appetitive mechanisms. This talk summarises the evidence for genetic regulation of appetitive behaviours.

10:30 – 11:00 **Candidate gene studies in obesity and related traits**
Dr. Vimal Karani S, Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health
Obesity is an heritable trait that arise from the interactions between multiple genes and lifestyle factors such as diet and physical inactivity. Hundreds of candidate genes for obesity-susceptibility had been identified through various approaches. With genome-wide association study (GWAS) data now available on numerous large cohorts, it has become possible to embed candidate gene studies within GWASs, testing for association on a much larger number of candidate genes than previously possible. The talk will highlight three main aspects: 1.Gene x environment interactions, 2.Candidate gene analysis using GWAS datasets and 3.Use of Mendelian Randomization approach to obesity traits.

11:00 – 11:30 **Speakers' photo then mid-morning break and trade show/poster viewing**
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11:30 – 12:00 **Genetic studies of metabolic disease - extreme phenotypes and common disease**
Dr Inês Barroso, Wellcome Trust Sanger Institute, Cambridge
In recent years, genome-wide association studies (GWAS) have led to a rapid increase in the number of loci known to influence type 2 diabetes and obesity risk. This has highlighted particular pathways and genes, previously unsuspected, as having an important role in disease predisposition. Further important insights are also emerging from whole-exome sequencing studies of more severe phenotypes where rare mutations can reveal important pathways that when malfunctioning can lead to disease. Insights from these approaches and future directions will be highlighted during the talk.

12:00 – 12:30 **Considering obesity as a chronic brain disease**
Dr Giles S.H. Yeo, *University of Cambridge Metabolic Research Labs*, Institute of Metabolic Science, Addenbrookes Hospital, Cambridge, UK
It is an inescapable fact that the underlying cause of obesity is a result of consuming more energy than you burn. The question that is more complex to answer is why some people eat more than others. Over the past 15 years, insights from human and mouse genetics have illuminated multiple pathways within the hypothalamus, brainstem and higher brain regions that play a key role in the control of food intake. We now know for example, that the brain leptin-melanocortin signalling pathway is central to the control of mammalian food intake. Intriguingly, it is becoming clear that in addition to engaging classical "neuropeptide/receptor" systems within the brain, leptin also rapidly modifies synaptic connections between neurons. There is also evidence for neurotrophins, which are critical in the development and maintenance of neuronal connections, playing a role in the control of energy homeostasis. However, although monogenic alterations in these pathways result in extreme Mendelian obesity, these remain

incredibly rare. The major burden of disease is carried by those of us with "common obesity," which to date has resisted yielding meaningful biological insights. Progress however, has been made with genomewide association studies. For example, sequence variants in the first intron of *FTO* (Fat mass and Obesity related) are strongly associated with human obesity and carriers of the risk alleles show evidence for increased appetite and food intake. Although global FTO null mice display decreased fat and lean body mass, increased metabolic rate and food intake, this is seen against a complex phenotype of postnatal growth retardation and mortality. In contrast, when we modulated FTO levels discretely in the hypothalamic arcuate nuclei of adult animals, we were able to influence food intake, suggesting tissue specific functions for FTO. FTO's physiological role and how it influences bodyweight is yet to be determined. Using a variety of *in vivo, in vitro* and biochemical methods, we are currently characterising the molecular mechanism by which *FTO* controls of energy balance. Further GWAS have now revealed more than 30 different candidate genes, most of which are highly expressed or known to act in the CNS, emphasizing, as in rare monogenic forms of obesity, the role of the brain in predisposition to obesity.

12: 30 – 13: 30 **Lunch and trade show/poster viewing**

13:30– 14:30 **Question and Answer Session**
Delegates will be asked to submit questions to a panel of experts. Questions can be submitted before the event or on the day

14:30 – 15:00 **Genetics of obesity: A low- and middle-income country perspective**
Dr Branwen Hennig, MRC International Nutrition Group at the London School for Hygiene & Tropical Medicine, UK and MRC Keneba, The Gambia
Epidemiology of obesity varies in different regions of the world. Rapid changes occur in particular in low- and middle-income countries where development, urbanization and investment act as drives of an epidemic of non-communicable diseases including obesity and associated diseases.
Most low- and middle-income countries have been left behind in the 'genomic revolution' seen in higher income countries. However, there is a need for population-specific and comparative studies due to significant differences in environmental risk factors and genetic backgrounds affecting disease outcomes. Studies in diverse populations will help test biologically functional variants of known obesity risk genes as well as identify novel susceptibility loci.

15:00 – 15:30 **Afternoon Tea**

15:30– 16:00 **Associations between genes, lifestyle factors and glucose metabolsim in adolescents**
Dr Alice Kong, The Chinese University of Hong Kong, Hong Kong
Type 2 diabetes is a multifactorial disease involving the interplay between gene and environment. We aimed to investigate the associations between dietary intake of vegetables, exercise, combined genetic risk score (CGS) and glucose metabolism in a community recruited cohort of adolescents. From 270 subjects who had undergone oral glucose tolerance test (OGTT) and genetic studies, we found a linear relationship between CGS and 2-hour post OGTT plasma glucose values. However, when these adolescents were stratified by their exercise levels and consumption of vegetables and fruits, the linear relationship was attenuated. Our results suggest that high exercise level and increased dietary consumption of vegetables reduce the risk of having high post-prandial glycemia which might be conferred by the genetic variants.

16:00 – 16:30 **Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome**
Dr J. Bernadette Moore, University of Surrey
Non-alcoholic fatty liver disease (NAFLD) is now the most common liver disease in both adults and children worldwide. A disease spectrum, NAFLD may progress from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis. Development of NAFLD is strongly linked to components of the metabolic syndrome including obesity, insulin resistance, dyslipidaemia and type 2 diabetes. The cellular and molecular aetiology of NAFLD is multi-factorial; genetic polymorphisms influencing NAFLD have been identified and nutrition is a modifiable environmental factor influencing NAFLD progression

16:30 – 17:00 **A Meta-analysis including 18,290 individuals confirms an interaction effect between depression and FTO genotype on BMI**
Dr Margarita Rivera Sanchez, MRC SGDP Centre, Institute of Psychiatry, King's College London
This work focuses on exploring the influence of the FTO gene, BMI and depression concurrently in a meta-analysis including 18,290 individuals. A history of depression moderates the effect of FTO on BMI, such that the BMI-increasing effect is significantly enlarged. This meta-analysis demonstrates a consistent effect of the interaction between FTO, depression and BMI, and suggests that FTO is involved in the mechanism underlying the reported association between obesity and depression. It will also have implications for predicting which patients with depression are at risk of high-BMI related disorders and potentially highlights how to improve prevention, management and treatment programs.

17:00 **Chairman's summing up**

About the Speakers

Jane Cutler
After taking early retirement from a career in commerce and local government, Jane pursued her interest in cell biology, first awakened in Adelaide, by taking a BSc in Cell and Molecular Biology at Oxford Brookes University. On graduation she was a committed student and eagerly waited for an opportunity to take a second degree. She studied an MSc in Bioinformatics at Cranfield University at an exciting time when the human genome was first published. Having achieved the MSc, her inquisitive nature was still not satisfied and she took a further MSc, this time in Molecular Medicine, again at Cranfield University. She welcomes the opportunity to chair this meeting for Euroscicon and appreciate the latest developments in the study of obesity

Alice Kong graduated from The Chinese University of Hong Kong and had her overseas training as postdoctoral fellow at the Division of Endocrinology, Department of Medicine at University of California, San Diego, United States. Her research has focused on type 2 diabetes and obesity with particular focus on lifestyle factors and cardiovascular risk factors clustering in adults and adolescents. A fellow of the Royal College of Physicians and Surgeons of Glasgow and Royal College of Physicians of Edinburg, United Kingdom and fellow of the Hong Kong Academy of Medicine, Dr. Kong also holds membership in other professional societies, including the American Diabetes Association. In 2007, she has received the Hong Kong College of Physicians Distinguished Research Award for Young Investigators.

Margarita Rivera Sanchez is a BRC Postdoctoral Researcher at the MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry. Her work focuses on investigating the genetic relationship between psychiatric disorders, mainly depression and bipolar disorder, and obesity-related diseases (i.e. type 2 diabetes, metabolic syndrome, cardiovascular disorders, etc). The goal of her research is to get a better understanding of the molecular genetic basis of comorbidity between psychiatric disorders and obesity related diseases, both of which have major public health, clinical, economic, personal and social implications worldwide.

Clare Llewellyn's research interest is the elucidation of genetic susceptibility to the 'obesogenic' environment, with a focus on the role of appetite regulation. For her PhD at UCL she used data from large population-based twin cohorts (Gemini; the Twins Early Development Study), in combination with molecular genetic studies, to provide evidence for genetic influence on appetitive phenotypes in infancy and childhood. More recently, she is interested in characterising the neural correlates of appetitive phenotypes in early life.

Vimal Karani is a research scientist and the lead study co-ordinator of the D-CarDia Collaboration at the MRC Centre of Epidemiology for Child Health, Institute of Child Health (University College London). He is working on a collaborative project combining information from several large cohort studies around the world and the main aim of his research is to establish causal effects of vitamin D on cardiovascular disease related traits such as obesity, hypertension, type 2 diabetes and inflammation using Mendelian Randomization approach.

Dr. J Bernadette Moore is research scientist and a Lecturer in Molecular Nutrition within the Faculty of Health and Medical Sciences at the University of Surrey. Her research primarily focuses on the dietary, genetic and immune factors that influence non-alcoholic fatty liver disease development. Utilizing discovery-based proteomics, genomics and systems biology approaches alongside molecular cell biology techniques, her group aims both to identify disease biomarkers and characterize molecular mechanisms of NAFLD progression.

Inês Barroso is Joint Head of Human Genetics at the Wellcome Trust Sanger Institute (WTSI) where she leads a group interested in the genetic aetiology of type 2 diabetes, obesity and related traits. Her group combines large-scale genetic and genomic approaches, and studies in model organisms, to understand the aetiology of various metabolic diseases. She is also a Principal Investigator at the Metabolic Research Labs, within the Institute of Metabolic Science.

Inês graduated from Lisbon University in 1992 with a BSc degree (Licenciatura) in Biology. She earned her PhD in human molecular genetics from the University of Cambridge, Department of Pathology. Following a short period of postdoctoral work at the University of Cambridge in the lab of Professor Peter Goodfellow, she joined the newly formed company, Hexagen (a spin-off from the Goodfellow lab). Inês worked in the biotechnology sector for six years before joining WTSI in 2002, where she established the Metabolic Disease Group.

Branwen Hennig works within the MRC International Nutrition Group at LSHTM and MRC Keneba, The Gambia, heading the genetics programme. She is involved in various genetic epidemiology projects, with an emphasis on nutritional genetics and studies based in Africa. Prior to that she worked at LSHTM on a research project investigating the effect of host genetic factors on vaccine-induced immunity to hepatitis B and befor then was based at the Wellcome Trust Centre for Human Genetics in Oxford, where she was involved in studies assessing genetic susceptibility to hepatitis C and other infectious diseases. Her background is in human molecular genetics and she trained in epidemiology at LSHTM.

Registration Web Site: **www.regonline.co.uk/obesity2013**

Keywords: genetics, obesity, diabetes, cardiovascular, NAFLD,Nonalcoholic fatty liver disease; proteomics; iTRAQ; biomarkers, genome-wide association studies; whole-exome sequencing; genetics; type 2 diabetes; obesity, Africa, life-course anthropometry/obesity, nutrition, developmental origin of health and disease (DOHaD) hypothesis, Childhood obesity; twins; appetite; genetic; behaviour, Obesity, Body mass index, physical activity, interaction, Mendelian Randomization, Genes, Lifestyle factors, Glucose Metabolism, depression, obesity, BMI, FTO gene

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