Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Genetic diagnosis and therapeutic intervention in patients with severe early onset obesity

1. Summary of the impact (indicative maximum 100 words)

Professors O'Rahilly and Farooqi were the first to identify monogenic causes of severe childhood obesity, leading the way for identification of additional genetic causes by their group and others. Their research led to the development of diagnostic tests for these conditions, which are now an accepted element of clinical guidelines around the world. This work led to the understanding that inherited disorders of appetitive drive can underlie human obesity which has altered attitudes to obesity and had an impact on the management of families with these conditions. Their research also led directly to a highly effective therapy for congenital leptin deficiency which reverses the severe obesity associated with this condition and associated endocrine and immunological deficiencies. This treatment is now available throughout the UK and in specialist centres worldwide.

2. Underpinning research (indicative maximum 500 words)

Obesity represents one of the major challenges to public health in the developed world due to increased morbidity and mortality associated with cardiovascular disease, Type 2 diabetes and some forms of cancer, and results in annual healthcare costs in excess of £1.0 billion in the UK alone. Whilst public health initiatives to improve diet and promote exercise play a role, these have proved largely ineffective particularly in patients with severe obesity, highlighting the need for improved therapeutic strategies. The success of such strategies relies upon understanding the mechanisms involved in regulating body weight and how their disruption leads to obesity.

This research has been led by Professor S O'Rahilly (University employed from 1/8/1991) and Professor IS Farooqi (University employed from 1/12/2002; both University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital). Given the strong evidence that weight is highly heritable, they used genetic approaches to investigate patients with severe, early onset obesity. This work led to the discovery, by O'Rahilly and Farooqi, of the first two single-gene defects causing human obesity in 1997 (1, 2) involving the genes encoding leptin and prohormone convertase 1. In collaboration with the pharmaceutical company AMGEN, O'Rahilly and Farooqi were responsible for co-ordinating the first clinical trial of recombinant human leptin in patients with severe obesity due to congenital leptin deficiency (3). Treatment with recombinant human leptin was safe and efficacious and provided the first proof-of-principle that leptin is an essential regulator of body weight, T-cell-mediated immunity and the onset of puberty in humans. In 2007, in collaboration with Professor Paul Fletcher (Department of Psychiatry, University of Cambridge, University employed from 1/11/1998), they used functional MRI to demonstrate that leptin regulates the liking of food, a response that is mediated by activation of mesolimbic areas of the brain. These studies constitute a body of work that provides seminal insights into the role of leptin in human physiology.

O'Rahilly and Farooqi's research strategy has focussed on a cohort of over 4000 patients with severe, early onset obesity recruited to the Genetics of Obesity Study (GOOS) in Cambridge in collaboration with multiple centres in the UK and worldwide. They showed that loss-of-function mutations in the melanocortin 4 receptor (MC4R) cause a dominantly inherited obesity syndrome which is the most common genetic cause of obesity identified to date, occurring in 5-6% of severely obese children (4). They went on to characterise the phenotype of MC4R deficiency, demonstrate a genotype-phenotype correlation (4), and establish the role of central melanocortin signalling in regulating blood pressure (5). Additional findings of patients with mutations in the leptin receptor, POMC, BDNF and TrkB demonstrated the critical role of the hypothalamic melanocortin pathway in regulating human appetite and body weight, and that a range of single-gene defects can cause severe early onset obesity.

In 2010, they used a hypothesis-free approach to show that copy number variants contribute to the aetiology of severe childhood obesity, highlighting the role of the signalling molecule SH2B1 in human obesity and insulin resistance (6).

3. References to the research (indicative maximum of six references)

1: Montague CT*, Farooqi IS*, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903-8. PMID: 9202122.
Citations, 1356. Journal impact factor, 34.
2: Jackson RS, Creemers JW, Ohagi S, Raffin-Sanson ML, Sanders L, Montague CT, Hutton JC, O'Rahilly S. Obesity and impaired prohormone processing associated with mutations in the human prohormoneconvertase 1 gene. Nature Genetics 1997;16:303-6. PMID: 9207799.
Citations, 476. Journal impact factor, 34.
3. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med. 1999;341:879-84 PMID: 10486419.
Citations, 638. Journal impact factor, 47.
4: Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003;348:1085-95. PMID: 126466655:
Citations, 427. Journal impact factor, 47.
5. Greenfield JR, Miller JW, Keogh JM, Henning E, Satterwhite JH, Cameron GS, Astruc B, Mayer JP,Brage S, See TC, Lomas DJ, O'Rahilly S, Farooqi IS. Modulation of blood pressure by central melanocortinergic pathways. N Engl J Med. 2009;360:44-52.
Citations, 47. Journal impact factor, 47.
6. Bochukova EG, Huang N, Keogh J, Henning E, Purmann C, Blaszczyk K, Saeed S, Hamilton-Shield J, Clayton-Smith J, O'Rahilly S, Hurles ME, Farooqi IS. Large, rare chromosomal deletions associated with severe early-onset obesity. Nature 2010;463:666-70. PMID: 19966786.
Citations, 41. Journal impact factor, 34.

Research Grant support

MRC Programme Grant funding held continually by O'Rahilly since 1999
Most recent renewal: Co-applicants, AP Coll, IS Farooqi, S O'Rahilly, G Yeo
Title: Molecular Mechanisms in Human Obesity
Amount awarded: £2,475,269; Oct 2009 – Oct 2014

MRC Centre for Obesity and Related Metabolic Diseases (CORD)
Director S O'Rahilly, Co-applicants 17 other PIs from Cambridge and Oxford.
Amount awarded: £2,149,149; June 2007- March 2013

MRC/University Metabolic Disease Unit
Director, S O'Rahilly
Amount Awarded: £10,482,000, April 2013-March 2018

Wellcome Trust Strategic Award for Institute of Metabolic Science
Allocation for Clinical Metabolic Research Facilities
Amount Awarded: £5,000,000, April 2013-March 2018

Wellcome Trust Senior Research Fellowship in Clinical Science
Applicant: IS Farooqi (PI)
Title: The pathophysiology and genetics of human early onset obesity
Amount awarded: £1,551,212; Dec 2007 – Dec 2012
Renewed: £2,080,343; Dec 2012 – Dec 2017

National Institute for Health Research – Cambridge Biomedical Research Centre
Applicants: IS Farooqi, S O'Rahilly
Title: Metabolism theme - Obesity allocation
Amount awarded: £1,615,000; Apr 2007 – Apr 2012

4. Details of the impact (indicative maximum 750 words)

New clinical intervention and impact on health outcomes

The research described here has led to the development of an entirely new therapeutic approach to patients with severe obesity due to congenital leptin deficiency. This was a life threatening disorder which their research demonstrated could be fully treated with injections of recombinant human leptin which were safe and well tolerated. Addenbrooke's Hospital is internationally recognised for pioneering treatment of this condition which has been provided to 22 patients worldwide on a named patient basis since 1997. Following treatment, patients undergo normal progression though puberty, have a significant improvement in quality of life and all adults are in full time education or employment (personal testimonies; www.goos.org.uk)**.**

Development of diagnostic tests and clinical guidelines for investigation

O'Rahilly and Farooqi's demonstration in 2000 that pathogenic MC4R mutations are found in up to 5-6% of children with severe obesity led to the evaluation of MC4R sequence as a routine part of the diagnostic evaluation of the severely obese child since 2006 (1). The impact of this pioneering Cambridge research and the replication of these findings by groups worldwide, has led to the development of new genetic tests, guidelines and policies established in the UK and in many European and US healthcare systems and commercial laboratories (1-3; *www.orpha.net/, www.athenadiagnostics.com, www.correlagen.com).*

Diagnostic testing for the monogenic obesity syndromes became available to Physicians in the UK and worldwide in 2007 through links between the GOOS study and the NHS Clinical Genetics Service at Addenbrooke's Hospital. Several centres across Europe and North America have offered testing for genetic obesity syndromes since 2010 (www.kumc.edu/gec/prof/labs.html, www.ncbi.nlm.nih.gov/sites/GeneTests/), many of which were discovered in Cambridge. These practical advances have led to the development of international guidelines in relation to the assessment of severe early onset obesity and University of Cambridge researchers have played a leading role in many of these initiatives (1-3).

Public debate and attitudes

The stigma associated with obesity in domains of employment, health care and education has been well documented, as has its impact on the quality of life of obese individuals and their willingness to approach health care professionals (Puhl and Heuer, Obesity 2009). Evidence is emerging that the comprehensive descriptions of the world's largest cohorts of patients with MC4R and leptin receptor deficiency in high impact medical journals have altered approaches and attitudes to severe obesity among medical professionals (4. personal testimonies). For example, in a recent study of medical students, reading about the genetic basis of obesity significantly reduced negative stereotyping of obese patients (Persky et al, Ann Behav Med 2011).

Widespread stigma towards obese patients also negatively impacts on public support for policies aimed at tackling obesity (4. personal testimonies; www.goos.org.uk). In studies of interventions that might reduce weight bias in the general public, a discussion of the multidimensional aetiology of obesity which includes genetic/biological factors, has been associated with less negative attitudes in several studies (reviewed in Sikorski et al. BMC Public Health 2011, 11:661). This work has also formed the basis for public engagement and debate on translational outcomes of genetics in medicine, on the causes of obesity and on the role of the brain in the regulation of appetite (5).

Social policy

Since 2000, identification of pathogenic mutations in 26 patients with leptin receptor, MC4R, SIM1 and SH2B1 mutations by the Cambridge group has prevented severely obese children from being taken away from their families and placed into the care of social services, under the assumption that a dysfunctional family environment was the cause of the child's obesity. This has major impact on the health and well-being of the families involved (4. personal testimonies).

Training

Since 2009, Professor Farooqi, with the Society for Endocrinology, has organised an annual symposium '*Obesity Management for the Endocrinologist*', for specialty registrars and consultants

with an interest in the practicalities of obesity management (6).

Drug development
Advances in understanding of the genetic and molecular basis of severe obesity, which have been ongoing since 1997, have informed drug development with the realisation that targeting central pathways involved in the regulation of appetite may have considerable benefit. Current collaborations with a number of biotechnology and pharmaceutical companies including GSK, Merck, Pfizer, Takeda, Astra Zeneca and Rhythm Pharmaceuticals are based on exploiting these observations for the development of novel drugs for the treatment of obesity and other disorders of weight regulation such as cachexia (CDAs and MTAs in place 2012; 7). A novel melanocortin receptor agonist targeted specifically at patients with MC4R deficiency is scheduled to enter Phase 2 studies in 2014, with Cambridge as the lead centre.

Awards and prizes based on this research and its impact
The achievements of Professor O'Rahilly and Professor Farooqi are recognised nationally and internationally. Prof O'Rahilly has received numerous awards relating to this work, including the 2010 InBev-BailletLatour Health Prize (value, EURO 250000) for '*his pioneering research in the field of human obesity and its relationship to type 2 diabetes. He was the first person to show that a change in one or two genetic factors may lead to serious forms of obesity and as a result he succeeded in negating the accepted hypothesis that obesity is mostly the result of individual behaviour*' (ref 8). He was elected to Fellowship of the Royal Society in 2003, membership of EMBO in 2009 and became a Foreign Associate of the National Academy of Sciences, USA in 2011. He gave the 2011 Croonian Lecture to the Royal College of Physicians, London. Additional to be added in late 2013.
Professor Farooqi received the European Society for Clinical Investigation Award for Excellence in Clinical Research in 2010, the Society for Endocrinology Medal (2012) and the Graham Bull Prize of the Royal College of Physicians in 2012 in recognition of this research.
She was elected to Fellowship of the Academy of Medical Sciences in 2013.

5. Sources to corroborate the impact (indicative maximum of 10 references)
Review that corroborates the impact of this research on clinical practice
1. Viner RM, White B, Barrett T, Candy DC, Gibson P, Gregory JW, Matyka K, Ong K, Roche E, Rudolf MC, Shaikh G, Shield JP, Wales JK. Assessment of childhood obesity in secondary care: OSCA consensus statement, Arch Dis Child EducPract Ed 2012;97:3 98-105**Guidelines that corroborate the impact of this research on clinical practice**
2. Scottish Intercollegiate Guidelines Network (SIGN). Management of obesity. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2010 Feb. (SIGN publication; no. 115).
3. The Endocrine Society (TES). Prevention and treatment of pediatric obesity: an Endocrine Society clinical practice guideline based on expert opinion. Journal of Clinical Endocrinology & Metabolism 2008 Dec;93(12):4576-99.
Personal testimonies to corroborate impact on patients and their families
4. http://www.goos.org.uk/patients-and-families/personal-experiences
Informing public debate
5. commentary in Newsweek; "The Real Cause of Obesity" Sep 9, 2009
http://www.thedailybeast.com/newsweek/2009/09/09/the-real-cause-of-obesity.html
Training
6. (http://www.endocrinology.org/meetings/2010/oms2010/index.html).
Drug Development
7. CDAs and MTAs available, University of Cambridge Clinical School.
Awards
8. http://www.mrl.ims.cam.ac.uk/documents/PR-100419-PrijsGezondheid2010-en-def1.pdf