Molecular genetics of Adiposeness

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Evidently obesogenic environment has resulted in major healthcare problem of obesity, but there is substantial evidence for the heritability of obesity, and research in both rare and common forms of obesity has identified genes with significant roles in its etiology.
In the 1960s, the 'thrifty gene' hypothesis was proposed by Neel, whereby genes that predispose to obesity would have had a selective advantage in populations that possess the gene that they 'overreact'— not just becoming slightly overweight, but extremely obese. Recent reports support that many genes involved in the glucose and lipid metabolism have been subject to positive selection in the last 10 000 years, especially in Asian and African ethnic groups. For over a decade, most of the research focused on monogenic or syndromic obesity. The cloning of the mouse*ob* gene and its human homologue, leptin, proved to be a paradigm for the field that resulted in the identification of many genes involved in the regulation of appetite via the leptin–melanocortin pathway. These variants account for ~5% of morbid human obesity and include leptin and its receptor, the α-melanocortin-stimulating hormone receptor (MC4R), pro-opiomelanocortin (POMC) and prohormone convertase-1.

Alongside these 'pure' forms of obesity, where the gene defect is in appetite regulation and the disease is characterized by severe early onset obesity because of hyperphagia, syndromic forms have provided additional insights into the mechanisms underlying obesity. There are around 30 different Mendelian disorders that have obesity as a significant clinical feature

As result of Genome Wide Association studies (GWAS), the Human Obesity Gene Map summarizes the present situation in the field of common polygenic obesity. There are currently 22 gene associations supported by at least five positive studies. The glutamic acid decarboxylase gene (GAD2) was first reported to be associated with obesity and feeding behaviours in morbidly obese adults. Ghrelin, ghrelin receptor and Obestatin gene also play role in obesity. Bardet-Beidl syndrome gene, the BBS6 variants showed some association with quantitative traits associated with the metabolic syndrome such as dyslipidaemia and hyperglycaemia. It is also becoming clear, in both rare and common forms of obesity, that epigenetic influences, defined as any heritable influence on genes that occurs without a change in the DNA sequence, are also important.

The fat has several protective functions and its evolution in mankind has been shown to be having selection advantage against adversities. The aberrant fat content strongly correlates with severe generalized insulin resistance and the development of a chronic inflammatory state, partly due to the infiltration of the adipose tissue by macrophages and results in metabolic syndrome.