Novel genetic mutations cause low metabolic rate and obesity

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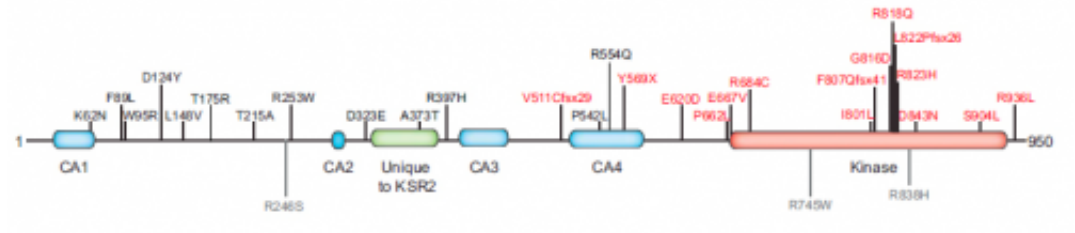

Schematic representation of full length KSR2 (Q6VAB6), indicating the location of each of the mutations identified in individuals with severe early-onset obesity and those found in controls (shown in grey). Credit: dx.doi.org/10.1016/j.cell.2013.09.058

Researchers from the University of Cambridge have discovered a novel genetic cause of severe obesity which, although relatively rare, demonstrates for the first time that genes can reduce basal metabolic rate – how the body burns calories.

Previous studies (performed by David Powell and colleagues at Lexicon Pharmaceuticals in Texas) demonstrated that when the gene KSR2 (Kinase Suppressor of Ras 2) was deleted in mice, the animals became severely obese. As a result of this research, Professor Sadaf Farooqi from the University of Cambridge's Wellcome Trust-MRC Institute of Metabolic Science decided to explore whether KSR2 mutations might also lead to obesity in humans.

In collaboration with Dr Ines Barroso's team at the Wellcome Trust Sanger Institute, the researchers sequenced the DNA from over 2,000 severely obese patients and identified multiple mutations in the KSR2 gene. The research was published online today, 24 October, in the journal *Cell*.

KSR2 belongs to a group of proteins called scaffolding proteins which play a critical role in ensuring that signals from hormones such as insulin are correctly processed by cells in the body to regulate how cells grow, divide and use energy. To investigate how KSR2 mutations might lead to obesity, Professor Farooqi's team performed a series of experiments which showed that many of the mutations disrupt these cellular signals and, importantly, reduce the ability of cells to use glucose and fatty acids.

Patients who had the mutations in KSR2 had an increased drive to eat in childhood, but also a reduced metabolic rate, indicating that they have a reduced ability to use up all the energy that they consume. A slow metabolic rate can be found in people with an underactive thyroid gland, but in these patients thyroid blood tests were in the normal range - eliminating this as a possible explanation for their low metabolic rate. People have speculated for a long time that some individuals may burn calories more slowly than others. The findings in this study provide the first evidence that defects in a particular gene, KSR2, can affect a person's metabolic rate and how their bodies processed calories.

Professor Farooqi said: "Up until now, the genes we have identified that control body weight have largely affected appetite. However, KSR2 is different in that it also plays a role in regulating how energy is used in the body. In the future, modulation of KSR2 may represent a useful therapeutic strategy for obesity and type 2 diabetes."

Changes in diet and levels of physical activity underlie the recent

increase in obesity in the UK and worldwide. However, there is a lot of variation in how much weight people gain. This variation between people is largely influenced by genetic factors, and many of the genes involved act in the brain. The discovery of a new obesity gene, KSR2, adds another level of complexity to the body's mechanisms for regulating weight. The Cambridge team is continuing to study the genetic factors influencing obesity, findings which they hope to translate into beneficial therapies in the future.

More information: The paper 'KSR2 Mutations Are Associated with Obesity, Insulin Resistance and Impaired Cellular Fuel Oxidation' will be published in the 24th October 2013 online edition of *Cell*. dx.doi.org/10.1016/j.cell.2013.09.058

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