Gene produces hormones that lead to obesity

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(PhysOrg.com) -- Obesity and common weight gain share a genetic basis. Professor Philippe Froguel, from Imperial College in Great Britain, and his team from the laboratoire Génomique et physiologie moléculaire des maladies métaboliques (CNRS/ Université Lille 2 / Institut Pasteur de Lille), in collaboration with teams from Inserm and Danish, Swiss and German partners, have discovered a new obesity gene that plays an essential role in the maturation of several key hormones that control food intake.

Mutations in this gene increase the risk of severe obesity and can lead to excessive weight. These results were published online in the journal *Nature Genetics.*

The gene PCSK1 produces an enzyme called proconvertase 1 which activates several hormones and circulating peptides that are essential to life and are involved in controlling appetite – examples include insulin, glucagon (and derivatives such as GLP1, a new treatment for type 2 diabetes) and proopiomelanocortin (which makes a person feel full).

This enzyme had been previously identified as being almost completely ineffective in three obese patients with abnormalities in intestinal functioning.

The French-British team became interested in the frequent mutations in the gene PCSK1 which modify the structure of proconvertase 1. They showed that the enzyme activity in the mutated gene is intermediate between what was seen in the three obese patients and that of a non-

mutated gene. These mutations increase the risk of becoming severely obese and have contributed to weight gain in, among others, French, Swiss, and Danish populations. Carriers of mutations of the PCSK1 gene also have a tendency to be hypoglycemic after meals due to insulin abnormalities linked to this mutation.

This discovery shows that apparently minor abnormalities in a key enzyme for the maturation of several hormones involved in controlling appetite (insulin, GLP1, melanocortin) are enough to significantly increase the risk of severe obesity and to lead to excessive weight in the general population.

After the early 2008 discovery that frequent variants in the melanocortin 4 receptor play a role in obesity (also published in *Nature Genetics*), the French-British team demonstrated that severe obesity and common weight gain have a common genetic base principally linked to defects in the complex hormone system (including some hormones produced by the intestine) and in specific receptors in certain areas of the brain that regulate food intake and satiation. At a time when the prevalence of morbid obesity (body-mass index greater than 40 kg/m2) has doubled in the past decade, these results highlight the importance of early dietary control to prevent and reduce obesity.

This study was carried out thanks to volunteers from families with obese children.

Citation: Common nonsynonymous variants in PCSK1 confer risk of obesity, Michael Benzinou et al. *Nature Genetics*, July 6, 2008.

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