



Obesity gene associated with susceptibility to polycystic ovary syndrome (PCOS)

Researchers have shown that a gene implicated in the development of obesity is also associated with susceptibility to polycystic ovary syndrome (PCOS). The *FTO* gene has recently been shown to influence a person's predisposition to obesity, and is now the first gene to be associated convincingly with susceptibility to PCOS¹. Carried out by Dr Tom Barber and colleagues from the Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford and Imperial College London, this research is the first evidence to show a genetic link between obesity and PCOS. The results are being presented at the annual Society for Endocrinology BES meeting in Harrogate.

PCOS is a common condition affecting up to 1 in 10 women of child-bearing age. PCOS affects the ovaries and is characterised by irregular periods, excessive hair growth and is a common cause of infertility. PCOS is strongly associated with obesity, and it is thought that the prevalence of PCOS will increase with rising levels of obesity. The *FTO* gene is known to influence weight. There are two versions of this gene, one of which is associated with increased weight gain and susceptibility to development of obesity².

Dr Tom Barber and colleagues are interested in working out the genetic causes of PCOS and its metabolic consequences. Given the association between PCOS and obesity, they investigated whether variants of the *FTO* gene also influence susceptibility to PCOS. To this end, they analysed the type of *FTO* gene carried by 463 PCOS patients and 1336 female population controls. They found that the type of *FTO* gene a person carried significantly influenced their susceptibility to PCOS. In fact, the version of the gene which is associated with increased weight gain is also associated with PCOS. The data suggest that *FTO* variants influence PCOS-susceptibility via an effect on fat mass. This is the first gene to be associated convincingly with susceptibility to PCOS and provides genetic evidence to corroborate the well established link between PCOS and obesity.

Researcher Dr Tom Barber said:

*"Polycystic ovary syndrome is an incredibly common condition affecting 1 in 10 women of reproductive age and is a leading cause of infertility. It is a genetic condition and one that is strongly associated with obesity; it is therefore of huge relevance for women given today's obesity epidemic. Our research shows that a variant of the *FTO* gene that has previously*

been shown to be associated with obesity also influences susceptibility to polycystic ovary syndrome. These data provide the first genetic evidence to corroborate the well documented association between these two conditions. Our future work will focus on elucidating the underlying mechanisms of polycystic ovary syndrome and its metabolic consequences with the hope of understanding how this common condition develops. This in turn will instruct future therapeutic developments for women who suffer from polycystic ovary syndrome.”

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Notes for editors

1. Barber TM, Bennett AJ, Groves CJ et al. (2008) Association of variants within the fat mass and obesity-associated (*FTO*) gene and polycystic ovary syndrome. *Diabetologia* 51:1153-1158.
2. Frayling TM, Timpson NJ, Weedon MN et al. (2007) A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 316:889-894.

The paper will be presented at the Society for Endocrinology BES meeting at 17:45 on Monday 16 March 2009. The abstract for this work is reproduced below: see <http://www.endocrine-abstracts.org/ea/0019/ea0019s71.htm> Note, this presentation has won the Society for Endocrinology Young Endocrinologist Clinical Prize Lecture 2009.

The Society for Endocrinology BES 2009 is Britain's biggest scientific meeting on hormones, and is taking place at the Harrogate International Centre, Harrogate, from 16-19 March 2009. For the full programme, please see <http://www.endocrinology.org/meetings/2009/sfebes2009/prog/prog.aspx>

Please mention the Society for Endocrinology BES meeting in any story

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ABSTRACT

In search of the genetic basis of polycystic ovary syndrome and its metabolic consequences

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Polycystic ovary syndrome (PCOS) is characterised by reproductive, hyperandrogenic and

dysmetabolic features (including insulin resistance). There remain major questions about the basis of the metabolic dysfunction in PCOS and about its genetic aetiology. Having genotyped samples from >460 PCOS cases and >1300 female controls, I recently successfully identified the first genome-sequence variant (the *FTO* gene) to be implicated in susceptibility to PCOS [Barber et al., 2008, *Diabetologia*, 51, 1153-1158], providing the first genetic corroboration of the link between PCOS and obesity. Within the same cohort, I have also shown that variants implicated in T2D-susceptibility acting through adverse effects on beta-cell function, do not associate with PCOS. This is not consistent with the notion of a primary role of the beta-cell in the establishment of hyperinsulinaemia in PCOS.

Established dogma dictates that body fat distribution (*visceral* adiposity) is implicated in the inherent, fat-mass independent insulin resistance that characterizes many women with PCOS. Using axial MRI images, I recently demonstrated that groups of PCOS cases and BMI/fat mass-matched control women are indistinguishable with respect to distribution of fat within visceral, abdominal and gluteo-femoral subcutaneous depots, despite significant differences in measures of insulin resistance between the groups [Barber, 2008, *JCEM*, 93, 999-1004]. Therefore, insulin resistance in PCOS is less closely linked to *eutopic* fat distribution than has previously been thought, and *ectopic* fat may play an important role. To corroborate the notion of adipo-normality in PCOS, I have shown that adipokine levels (adiponectin and retinol-binding protein 4) are indistinguishable between PCOS cases and BMI/fat mass-matched control women [Barber, 2008, *JCEM*, 93, 2859-2865].

In conclusion, adipose tissue (both distribution and function) appears to behave normally in women with PCOS. Although the link between obesity and PCOS (probably mediated via effects on insulin resistance) has been genetically corroborated for the first time recently, our understanding of this association remains incomplete.