



Obesity and Cardiovascular Health Award 2011

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“Apple-shaped or pear-shaped, it's partly down to your genes”

The work I will discuss focuses on waist-hip ratio (WHR), a common clinical measure of central adiposity and fat distribution.

WHR is of particular interest in diabetes, hypertension, cardiovascular disease and dyslipidemia because it integrates the well known adverse metabolic risk of abdominal fat with the more protective role of gluteal fat. WHR is heritable and to identify genetic variants influencing fat distribution, we conducted a meta-analysis of 32 genome-wide association studies (up to 77,167 participants) of WHR, where we adjusted for BMI to identify loci independent of overall obesity. We followed up 16 loci in a further 30 studies (up to 113,636 subjects). We identified 14 loci influencing WHR, including 13 novel loci and the known signal at *LYPLAL1*. We find evidence for sexual dimorphism at 7 of the 14 loci. We also identify strong candidate genes at several of the loci: a) using expression quantitative trait loci (eQTL) analysis, which identifies 6 transcripts with expression levels associated with WHR associated gene regions and b) investigating differing expression levels in subcutaneous abdominal as compared to gluteal fat at five genes. Further, our loci exhibit enrichment for metabolism-related associations, including the *ADAMTS9* locus, previously reported as associated with type 2 diabetes and the *GRB14* locus which was previously reported as associated with HDL-C, and is now also genome-wide significant in association with triglycerides.

Furthermore, *VEGFA* is the most apparent biological candidate in the associated region on chromosome 6, given the presumed role of *VEGFA* as a mediator of adipogenesis and evidence that serum levels of *VEGFA* are correlated with obesity. Through our research we hope to resolve the crucial underlying biological processes of fat distribution as well as related metabolic disturbances and cardiovascular disease. Understanding biology through finding genes is a first, but vital step, towards treatment.

As efforts to tackle obesity through changes in lifestyle or by different treatment options have proved extremely challenging, the potential to alter patterns of fat distribution may offer an alternative for future drug discovery.