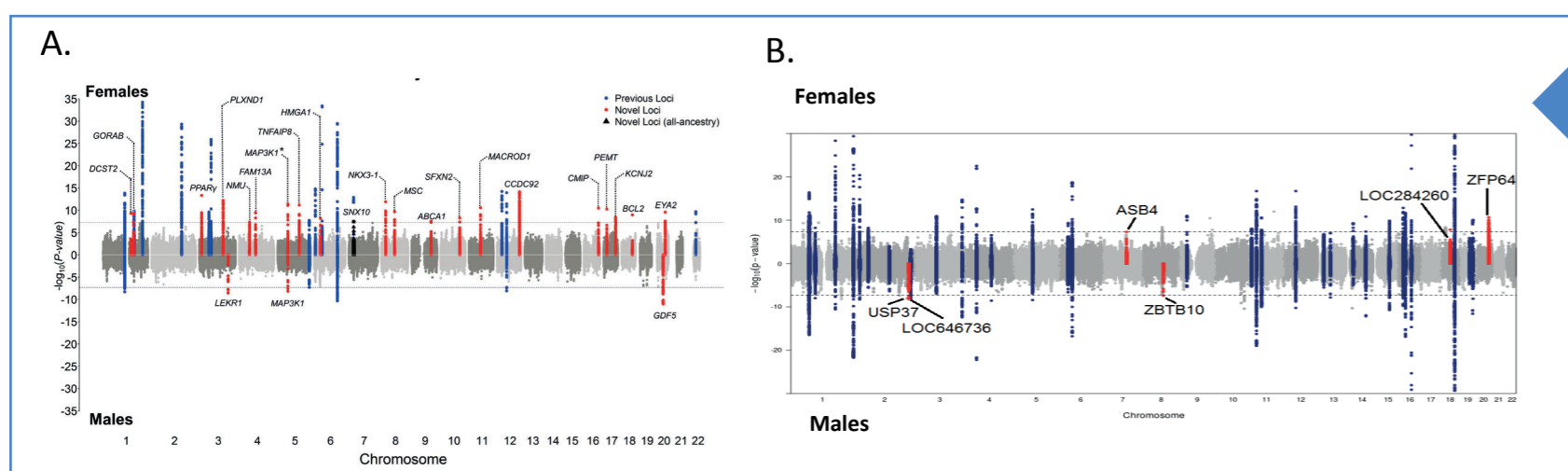


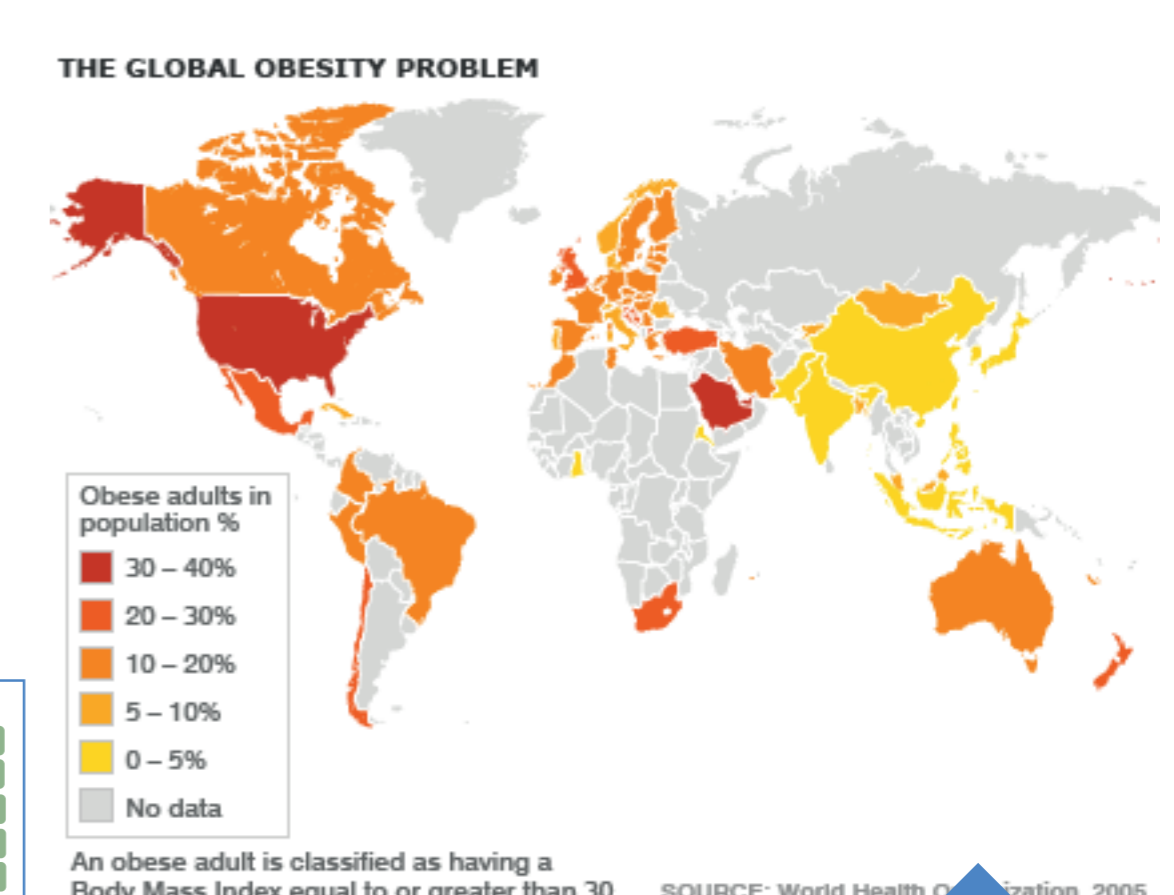
The Wellcome Trust Centre for Human Genetics

Discovering the genetic variation contributing to obesity traits

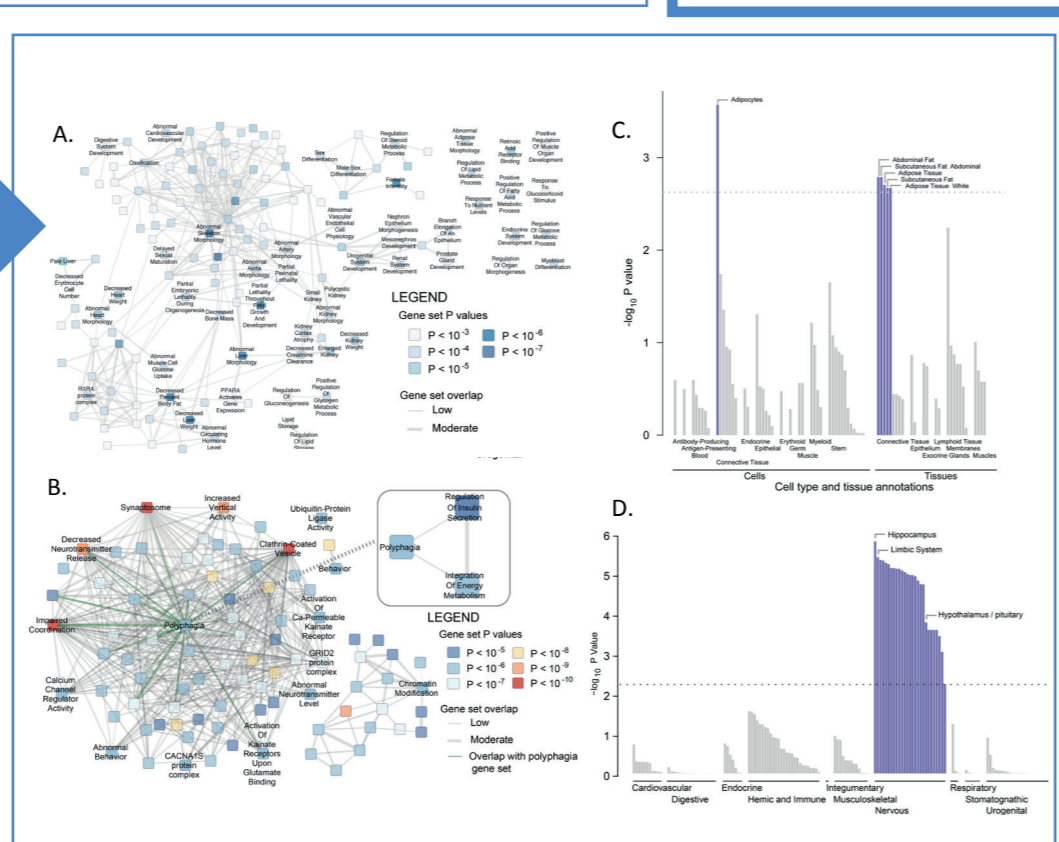


Our results emphasize the strong sexual dimorphism in the genetic regulation of fat distribution traits (A.), a characteristic not observed for overall obesity as assessed by BMI (B.)

The number of published, robust associations obesity traits has reached 163, with dozens more identified and in the pipeline to be published



Pathway analysis of fat distribution (WHR) and overall obesity (BMI) show enrichment of both fertility and insulin resistance related pathways (A.) for fat distribution and the central, neuroendocrine control of energy balance (B.) for overall obesity. Genes within WHR associated loci are enriched for expression in adipose cells and adipose tissue (C.) while BMI-associated loci are enriched for expression in the brain and central nervous system (D.)



Gene	Location	Association
SH2B3	11q24	WHR
FTO	16q12	BMI
MC4R	18q11	BMI
IRX3	10q26	WHR
IRX5	10q26	WHR
IRX6	10q26	WHR
IRX7	10q26	WHR
IRX8	10q26	WHR
IRX9	10q26	WHR
IRX10	10q26	WHR
IRX11	10q26	WHR
IRX12	10q26	WHR
IRX13	10q26	WHR
IRX14	10q26	WHR
IRX15	10q26	WHR
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IRX21	10q26	WHR
IRX22	10q26	WHR
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IRX92	10q26	WHR
IRX93	10q26	WHR
IRX94	10q26	WHR
IRX95	10q26	WHR
IRX96	10q26	WHR
IRX97	10q26	WHR
IRX98	10q26	WHR
IRX99	10q26	WHR
IRX100	10q26	WHR

WHAT WAS KNOWN

- Obesity is a worldwide epidemic associated with increased morbidity and mortality that imposes an enormous burden on individual and public health
- Family studies highlight a strong genetic contribution to individual risk of obesity traits
- Early efforts to identify genetic variants that were associated with obesity had been dominated by a large number of nominal associations generated from underpowered studies leaving almost all genetic variability and biological processes underlying obesity susceptibility remain unknown and hamper progression towards prevention and treatment
- The dawn of genome wide association studies changed the landscape of common, complex disease genetics completely

WHAT WE DID

- With a starting point of the Wellcome Trust Case Control Consortium we performed genome wide association analysis on all samples informative for obesity traits
- We quickly expanded into more well powered collaborations and this ended up to be the core of what was the GIANT (Genetic Investigation of Anthropometric Traits) consortium
- Within this setting we have contributed to analytical efforts that today involve over 1 million individuals and 10 million common genetic markers
- We are currently expanding the allelic spectra using both exome centric genotyping arrays designed to capture to low frequency markers and exome sequencing strategies

WHAT THIS ADDS

- During the last 9 years we have been integral to the work that set out with delivering the first, located in the first intron of the FTO gene and ~188kb upstream from MC4R
- These discoveries were recently followed by a second and third wave of discovery, which have brought the number of genetic variants that are involved in regulation of body weight and overall obesity up to ~100
- In parallel, we have shown that overall obesity is distinct from body fat distribution. In this setting, we have delivered the first 50 common variants that are involved in regulating where on the body fat accumulates
- In contrast to overall obesity and body weight, body fat distribution show a strong sexual dimorphism, where about 50 % of associated variants display a stronger effect in women
- The significance of our research is not limited to determining genetic associations; our findings have established the influence of neuronal pathways on body weight regulation and the importance of adipose tissue related pathways in fat distribution regulation
- We are currently working towards elaborating the specific mechanisms through which these variants exert their metabolic effects

REFERENCES

A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity.
 T M Frayling*, N J Timpson*, M N Weedon*, E Zeggini*, R M Freathy, C M Lindgren, [...], A T Hattersley* & M I McCarthy*. *Science*. 2007 May 11; 316(5826):889–94.

Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution.
 I M Heid*, A U Jackson*, J C Randall*, T W Winkler*, L Qi*, V Steinthorsdottir*, G Thorleifsson [470 authors], L A Cupples*, R J Loos*, I Barroso*, M McCarthy*, C S Fox*, K L Mohlke* & C M Lindgren*. *Nature Genetics* 2010 Nov; 42(11):949–960.

New genetic loci link adipose and insulin biology to body fat distribution
 D Shungin*, T W Winkler*, D C Croteau-Chonka*, T Ferreira*, A E Locke*, R Mägi*, [...] I M Heid, R J Loos, L A Cupples, A P Morris, C M Lindgren* & K L Mohlke*. *Nature* 2015 Feb 12; 518(7538):187–96.

Genome-Wide Association Scan Meta-Analysis Identifies Three Loci Influencing Adiposity and Fat Distribution.
 C M Lindgren*, [...], K L Mohlke, I Barroso, M I McCarthy for The Giant Consortium *PLoS Genetics* 2009 Jun; 5(6):e1000508.