PI profile

**Cecilia Lindgren**

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|  | **Professor Cecilia Lindgren** **Titles:** Professor of Genomic Endocrinology & Metabolism, Group Leader / PI and Fellow / BDI director**Location:** Big Data Institute **Department:** Big Data Institute, Wellcome Centre for Human Genetics **Group:** Genetics of Type 2 Diabetes **Webpage:** <https://www.bdi.ox.ac.uk/Team/celi> **Email:** celi@well.ox.ac.uk **PA:** Carol Mulligan-John < indgrenpa@bdi.ox.ac.uk>  |

### GMS themes:

[Please retain any that describe your research, deleting others:]

* Functional genomics
* Genome biology (genomes and genetic variation)
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)

**Research Overview**

Obesity is an urgent global health challenge with no imminent preventive solutions within reach. It is a heritable heterogeneous condition and a well-established predictor of adverse metabolic outcomes. Our research focuses on the integration of large-scale data sets of genomic sequence variation and transcriptional regulation (genetics and genomics) with phenotypic data to advance the understanding of the molecular pathogenesis of obesity and related traits. We have been playing a key role in the collaborative work that have brought forward over 7,000 loci associated with various obesity traits (body mass index, BMI, waist:hip ratio, WHR, fat% etc.) (GiANT – unpublished data). It is notable that many variants associated with overall obesity (BMI) are located near neuronal genes that affect appetite regulation and variants associated with fat distribution (WHR) are located near genes that affect insulin signalling, fat deposition and metabolic traits. My team is dedicated to translating genetic associations into functional and pathophysiological mechanisms, and establishing how this can improve our understanding of the physiology and biology underlying obesity traits.

Projects can be tailored to personal interests and can involve either a wet lab and/or a data analysis/bioinformatics component though the listed project is 100% dry lab, computer based.

Project areas: Electronic phenotyping, bioinformatics, computational biology, SNP typing and statistical genetics, genomics, obesity, fat distribution, meta-analysis, genetic association and gene expression.

### Specific project proposals:

* ‘’Accelerate the discovery of causal variant(s) associated with fat distribution and central obesity’

Please contact directly for further information.

*These pages were reviewed/updated:* ***[insert date]***

Project proposal

Title: **Accelerate the discovery of causal variant(s) associated with fat distribution and central obesity**

Supervisors: Prof Cecilia Lindren

Wet/dry lab mix (approx): 100% dry lab

### Description:

**Background**

Our research focuses on the integration of large-scale data sets of genomic sequence variation and transcriptional regulation (genetics and genomics) with phenotypic data to advance the understanding of the molecular pathogenesis of obesity related traits. We have been playing a key role in the collaborative work that have brought forward over 7,000 loci associated with various obesity traits (body mass index, BMI, waist:hip ratio, WHR, fat% etc.) (Ref below, and GiANT – unpublished data).

My team is dedicated to translating genetic associations into functional and pathophysiological mechanisms, and establishing how this can improve our understanding of the physiology and biology underlying obesity traits.

This project seeks to expand our previous efforts on using large-scale genomic approaches to identify causal genetic variants influencing fat distribution. It builds on the global collaboration I lead through the GiANT consortium and the International Common Disease Alliance, aimed at identifying the genetic determinants of obesity and fat distribution.

**Description of the work**

The first strand of genetic analysis in this project will identify and fine-map common/low frequency associations to fat distribution using large scale meta-analysis as well as exome sequencing analysis from UKBB.

In the second strand of this project, we will explore novel strategies to further accelerate the discovery of novel genetic loci for fat distribution (collaboration with the Neale lab – Broad Institute, and Kong lab – Big Data Institute).

Lastly, we will systematically identify which molecular, cellular, and physiological processes are relevant to genetic risk for central obesity and fat distribution (collaboration with Ebener group- TDI, Finucane lab – Broad Institute and Pers lab – Copenhagen university).

**We aim to answer the following questions:**

* What additional phenotypes can be derived out of electronic health records and images that paired with genetics can advance our understanding of the mechanisms underlying obesity, and its different facets?
* What are the causal variants in loci associated in genome wide association studies with these obesity traits?
* Which are the low-frequency and rare variants not picked up in genome wide association studies of obesity traits and how do we best detect them?
* Can we annotate these associated variants for fat distribution with rich regulatory information to elucidate likely effector genes (these will then be followed up functionally, both in our own budding wet lab as well as in large scale international collaborations, particularly with Claussnitzer lab – Broad Institute)?

### Training Opportunities:

The candidate will have ample in-house support for any necessary statistical, bioinformatics package/pipelines. The candidate will have the ability to go to relevant summer schools in the fields of (but not limited to): genetics, bioinformatics, statistical genetics and machine learning. The candidate will have the opportunity to present work in both national and internationally renowned conferences. The candidate will be exposed to a vast network of local, national and international collaborators across a range of areas and disciplines.

### Background reading / references:

* [Glastonbury CA, et al. Machine Learning based histology phenotyping to investigate the epidemiologic and genetic basis of adipocyte morphology and cardiometabolic traits. PLoS Comput Biol. 2020 Aug 14;16(8):e1008044.
* Censin JC, et al. Causal relationships between obesity and the leading causes of death in women and men. PLoS Genet. 2019 Oct 24;15(10):e1008405.
* Justice AE, et al. Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body-fat distribution. Nat Genet. 2019 Mar;51(3):452-469.
* Turcot V, et al. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. Nat Genet. 2018 Jan;50(1):26-41.
* Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, Yengo L, Ferreira T, Marouli E, Ji Y, Yang J, Jones S, Beaumont R, Croteau-Chonka DC, Winkler TW; GIANT Consortium, Hattersley AT, Loos RJF, Hirschhorn JN, Visscher PM, Frayling TM, Yaghootkar H, Lindgren CM. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet. 2019 Jan 1;28(1):166-174.
* Claussnitzer, Melina, et al. "FTO obesity variant circuitry and adipocyte browning in humans." *New Engl J Med* 2015.373 (2015): 895-907.
* Locke, Adam E., et al. "Genetic studies of body mass index yield new insights for obesity biology." Nature 518.7538 (2015): 197.
* Shungin, Dmitry, et al. "New genetic loci link adipose and insulin biology to body fat distribution." Nature 518.7538 (2015): 187.
* Heid IM, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010 Nov;42(11):949-960.
* Loos RJ, Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet. 2008 Jun;40(6):768-75.