Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

The genetics of adiposity

Ruth JF Loos[1,2]

Genome-wide discovery efforts have identified more than 500 genetic loci associated with adiposity traits. The vast majority of these loci were found through large-scale meta-analyses for body mass index (BMI) and waist-to-hip ratio (WHR), and in European ancestry populations. However, alternative approaches, focusing on non-European ancestry populations, more refined adiposity measures, and low-frequency (minor allele frequency (MAF) < 5%) coding variants, identified additional novel loci that had not been identified before. Loci associated with overall obesity implicate pathways that act in the brain, whereas loci associated with fat distribution point to pathways involved in adipocyte biology. Pinpointing the causal gene within each locus remains challenging, but is a critical step towards translation of genome-wide association study (GWAS) loci into new biology. Ultimately, new genes may provide pharmacological targets for the development of weight loss drugs.

Addresses
[1] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[2] The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Corresponding author: Loos, Ruth JF (ruth.loos@mssm.edu)

Current Opinion in Genetics & Development 2018, **50**:86–95

This review comes from a themed issue on **Molecular and genetic basis of disease**

Edited by **Ines Barroso** and **Jose Florez**

https://doi.org/10.1016/j.gde.2018.02.009

Introduction

Obesity is a major risk factor of disease, not only posing an enormous burden on people's personal health [1], but also on societies as a whole [2,3]. Over the past four decades, the prevalence of obesity among adults has nearly quadrupled worldwide [4,5]. While in most high-income countries the rise in BMI seems to have slowed down as of late, albeit at a high level, in many low-income and middle-income countries the increase continues. Particularly alarming is the global rise in obesity among children and adolescents [4–6].

Initiatives to prevent obesity or promote weight loss through lifestyle changes have limited success and are often short-lived, both at the community and individual levels [7,8], suggesting that innate mechanisms, encoded by the genome, also contribute to energy homeostasis [9••]. Estimates of genetic contribution vary by study design and adiposity outcome, but are sufficiently high to warrant gene discovery studies (Table 1).

In the past 10 years, genome-wide association studies (GWASs) have been particularly effective in the identification of genetic loci associated with adiposity outcomes. However, translation of these loci into new biology has been challenging. Here, I review recent progress and insights gained from these discoveries.

Conventional GWAS — Common (MAF $\geq$ 5%) variants for commonly studied adiposity phenotypes

In 2007, GWASs discovered the first genetic locus in *FTO* that showed robust association with BMI and obesity risk [10,11]. More than 500 genetic loci, for a range of adiposity traits, have since been identified (Figure 1). The vast majority of these (92%) were first identified for body mass index (BMI; $n = 341$ loci), a proxy for overall adiposity, and for BMI-adjusted waist-to-hip ratio (WHR_{adjBMI}; $N = 129$), a proxy for body fat distribution. Because data on BMI and WHR are easily obtained, sample sizes have grown rapidly, resulting in a steep increase of new discoveries over the past 10 years. For example, the most recent GWAS meta-analyses by the GIANT (Genetic Investigation of Anthropometric Traits) Consortium included data from 339,224 individuals and 125 GWAS studies on BMI [12] and 210,088 individuals from 101 studies on WHR_{adjBMI} [13]. In the latest GWAS for BMI, data from the Biobank Japan Project ($N = 173,430$) was combined with the BMI summary statistics from the GIANT Consortium [14] for a total sample size of >512,000 individuals [15•].

More than 80% of loci were first identified in populations that were exclusively or predominantly of European ancestry. Despite much smaller sample sizes, GWASs of exclusively Asian or African ancestry populations have identified at least 64 additional loci for BMI and 18 for WHR that had not been identified in much larger European ancestry GWASs [12,13,15•,16]. For most loci, associations are directionally consistent across ancestries, but allele frequencies and/or effect sizes may differ.

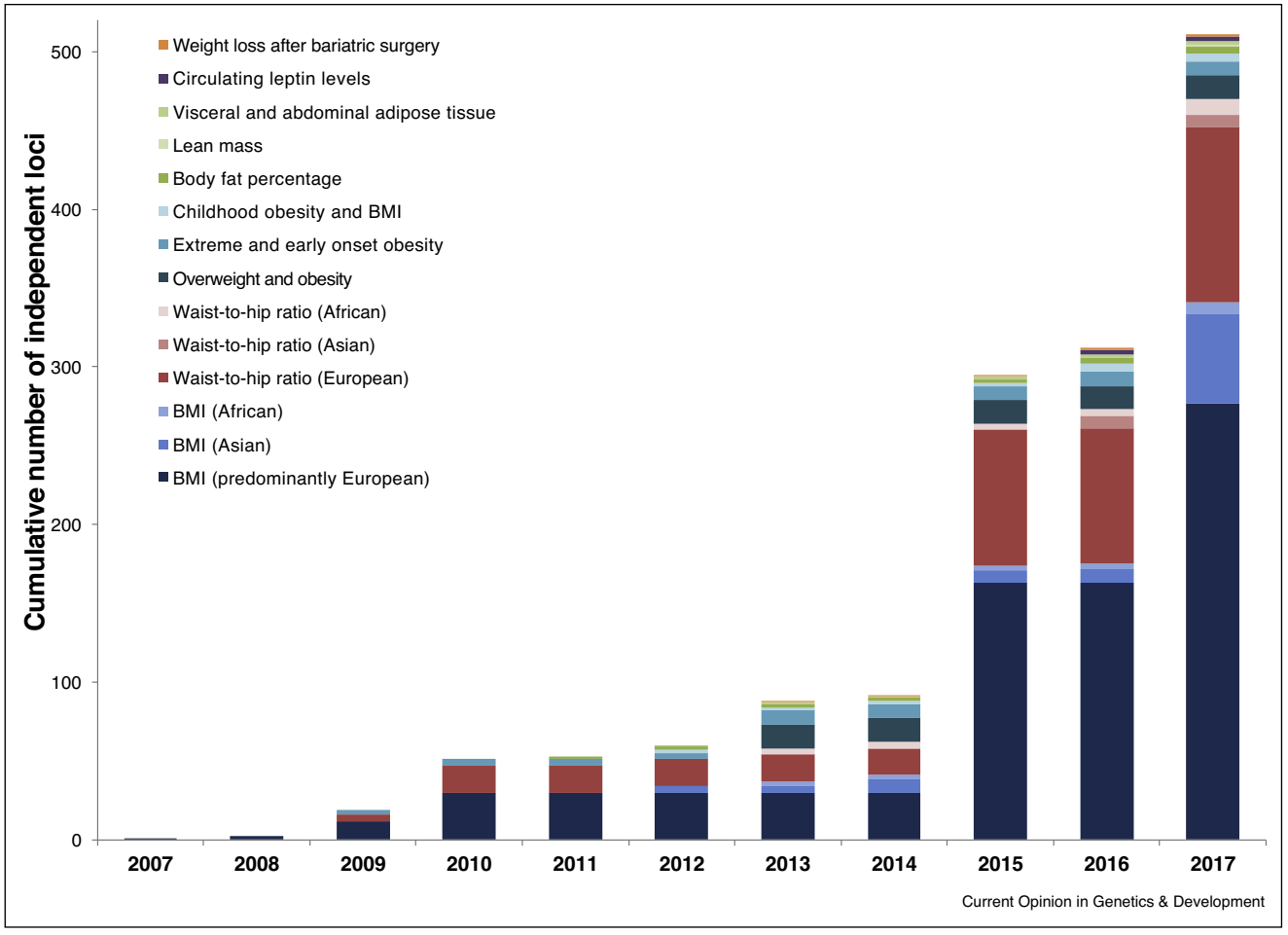
Loci discovered in the earliest, and thus smallest, meta-analyses tend to have the largest (albeit modest) effect

Table 1

Heritability estimates for body mass index (BMI) and waist-to-hip ratio (WHR), by study design

Study design	BMI		WHR	
	h^2 estimate	Reference	h^2 estimate	Reference
Twin-based	60–75%	[91,92]	30–60%	[13,93]
Family-based	40–45%	[91]	20–50%	[13,94]
Population-based	20–40%	[12,15•,95,96]	~10%	[13,97]

Figure 1



Cumulative number of loci identified since 2007. Color coding and shading corresponds to adiposity trait (and population ancestry) for which the initial discovery was made.

sizes (Figure 2). As sample sizes increase with each new meta-analysis, the power to identify variants with smaller effect sizes and/or lower minor allele frequencies (MAFs) increases and the variance explained by each new locus becomes incremental (Figure 2). Current GWAS-identified loci combined explain ~4% of the phenotypic variation of BMI. For WHR_{adjBMI}, effect sizes and variance explained tend to be larger for women (~2.7%) than for men (~1.4%).

GWASs have been successful in identifying numerous novel adiposity loci, but the ultimate goal is to elucidate the biology that these loci represent. Gene set, tissue, and functional enrichment analyses based on BMI-associated loci have implicated the central nervous system (CNS) as a key organ in the regulation of energy balance, highlighting not only the hypothalamus and pituitary gland (known appetite regulation sites), but also the hippocampus and limbic system (involved in learning, cognition, emotion