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The genetics of adiposity

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Abstract

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 which 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.

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- 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

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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 ≥ 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 WHRadjBMI [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. However, despite much smaller sample sizes, GWASs of exclusively Asian or African ancestry populations have identified at least 64 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 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 and memory)

[9,12,15,17] (Figure 3). Analyses that include the most recent BMI-associated loci have also provided support for a role of immune-related cells (lymphocytes, B cells) in the etiology of obesity [12,15]. Similar analyses based on the WHR_{adjBMI}-associated loci have revealed a different biology, implicating adipogenesis, angiogenesis, and insulin resistance as processes affecting fat distribution [9,13].

While some of these pathways overlap with the broad biology already established by human and animal models of extreme obesity and fat distribution, GWAS loci reveal genes that have not previously been implicated in known and novel pathways. Pinpointing the causal gene/variant in loci remains a major challenge. For example, over the past 10 years, the *FTO* locus has been studied in great depth [18], but the mechanisms through which it affects body weight are still not fully understood. Recent studies suggest that *FTO*'s BMI-associated variants mediate their effect not (only) through *FTO*, but also by influencing nearby genes. A study that used an extensive battery of tests, including epigenomic analyses, allelic activity, motif conservation, regulator expression, and gene coexpression patterns, suggested that rs1421085 in *FTO* is the causal variant that disrupts the ARID5B-mediated repression of IRX3 and IRX5 in preadipocytes, thereby suppressing white adipocyte browning, reducing thermogenesis and promoting lipid storage in a brain-independent way [19]. However, an earlier study, which used chromosome conformation capture, evolutionary conservation, tissue-specific gene-expression and a transgenic mouse model also proposed a role for IRX3 in the regulation of energy homeostasis and body composition, but through hypothalamic-mediated pathway [20]. Others found that the BMI-increasing alleles of *FTO*'s rs1421085/rs8050136 affect the binding affinity of transcription factor *CUX1*, suppressing the neuronal expression of *FTO* and nearby *RPGRIP1L*, which results in increased food intake and adiposity in mice [21,22]. Thus, current studies suggest that multiple pathways in multiple tissues may link the *FTO*-locus and body weight. Slowly, more GWAS-identified loci are undergoing in-depth analyses to elucidate their biology (*TMEM18* [23,24], *CADM2* [25,26], *LYPLAL1* [27], *ADCY3* [28]), but many more are waiting to be scrutinized.

Alternative approaches for gene discovery

Conventional GWAS, described above, have been very fruitful, not only because of the large sample, but also because studied variants are common (MAF>5%); both are contributors to increased statistical power for discovery. However, several other approaches have identified new loci through leveraging specific phenotypic and genotypic features.

Refined adiposity phenotypes

While BMI and WHR are easily obtained phenotypes, they are rather crude and heterogeneous indices to capture adiposity; e.g. individuals with the same BMI may still differ substantially in body composition and fat distribution. Therefore, recent gene discovery efforts have focused on more refined adiposity phenotypes, such as body fat percentage (BFP), lean mass, adipose tissue depots, and circulating leptin level, and have identified several new loci that point to new aspects of biology.

The most recent GWAS meta-analysis for BFP (N_{max}~100,000) identified five novel loci that had not been reported by much larger GWAS for BMI or WHR_{adjBMI} [29]. Most notable is a locus near *IRS1*, of which the BFP-*increasing* allele protects against type 2 diabetes and cardiovascular disease–an unexpected association mediated through an effect on fat deposition [29]. Specifically, the BFP-increasing allele favors fat deposition in subcutaneous fat depots, but not the metabolically harmful visceral depots [30]. These findings mirror *Irs1* knockout mice that are lean but insulin resistant [31,32], and whose cell lines suggest a role in adipocyte differentiation [33,34]. Several other BFP-associated loci (in/near *COBLL1*, *TOMM40*, *PLA2G6*) stand out because of cross-trait associations similar to the near-*IRS1* locus [29].

A GWAS meta-analysis of lean mass (N_{max}~100,000) identified two novel loci; both of which are missense variants (p.Gly428Asp in *VCAN*, p.Gln283Arg in *HSD17B11*) in genes previously implicated in musculoskeletal health [35].

To more accurately assess fat distribution, a GWAS meta-analysis was performed on various adipose tissue depots, quantified using computed tomography and magnetic resonance imaging [36]. Despite a relatively small sample size (N_{max}~18,000), seven new loci associated with various ectopic-adiposity traits were identified [36]. Functional analyses in mice showed that two loci (*ATXN1*, *UBE2E2*) play a role in adipogenesis [36].

Leptin is a hormone, predominantly secreted by adipocytes that plays a key role in food intake and energy-balance. A GWAS meta-analysis (N_{max}=52,126) identified four loci (in/near *LEP*, *SLC32A1*, *GCKR*, *CCNL1*) associated with circulating leptin levels [37]. Functional follow-up of candidate genes in each locus, using an adipose tissue explant model in mice, showed that knockdown of *Adig*, located near *Slc32a1*, influences leptin release and secretion [37]. *ADIG* encodes adipogenin, known to be a potent regulator of adipogenesis [38,39], plays possibly also a role in leptin regulation [37].

Taken together, GWAS meta-analyses for more refined adiposity traits have identified loci that were not revealed in much larger BMI and WHR_{adjBMI} discovery efforts. Furthermore, the interpretation of these loci may have been facilitated by the fact that phenotypes were less heterogeneous and more closely related to adiposity biology.

Low frequency (MAF:1<5%) and rare (MAF<1%) (coding) variants

GWAS-identified loci are typically common, non-coding and often intergenic, mainly because discovery has been limited by array design and available imputation reference panels. To further characterize the genetic architecture of adiposity traits, recent gene-discovery efforts have focused on low-frequency and rare variants. It had been speculated that such variants have larger effects and can therefore be identified with smaller sample sizes. However, recent whole genome and whole exome sequence based efforts did not identify novel low-frequency variants for adiposity traits [40,41], suggesting that their effects may not be as pronounced as expected and that larger sample sizes are needed for their discovery.

In a large-scale effort by the GIANT Consortium, BMI association summary statistics of 718,734 individuals from 125 studies with ExomeChip genotype data were combined, focusing on ~216,000 low-frequency (MAF:1<5%) and rare (MAF<1%) coding variants, which may alter gene function [42]. Four rare and 10 low-frequency variants in 13 genes were identified, eight of which were in genes (*ZBTB7B*, *ACHE*, *RAPGEF3*, *RAB21*, *ZFHX3*, *ENTPD6*, *ZFR2*, *ZNF169*) newly implicated in human obesity (Figure 2). Two rare variants (*MC4R*, *KSR2*) had been observed previously in extreme obesity [43–45], and two were found in *GIPR*, a gene previously implicated in common obesity and glycemic traits [12,46]. Effect sizes of low-frequency and, in particular, rare variants were larger than for common variants. Nevertheless, very large sample sizes were still needed for their discovery. The largest effect was observed for the *MC4R* stop-codon (p.Tyr35Ter); carriers (1 in 5,000 people) weigh on average ~7kg more than non-carriers. p.Tyr35Ter results in MC4R-deficiency and was one of the first mutations discovered in monogenic cases of obesity [43]. However, not all mutation carriers are obese; e.g. of 30 carriers in the UK Biobank, six were of normal weight, suggesting incomplete penetrance and compensation by other genetic or environmental factors [42]. Pathway analyses based on low-frequency and rare variants confirm a key role for the CNS in body weight regulation and provide new evidence for adipocyte and energy expenditure biology. Enrichment analyses based on low-frequency/rare variants provided more robust results than those based on common variants [42].

Interactions with lifestyle and demographics

Obesity is a multifactorial condition, resulting from an intricate interaction between genetic and non-genetic factors. Gene-by-environment (GxE) interaction studies show that some previously identified GWAS loci have indeed sex-specific and/or lifestyle-specific effects on adiposity outcomes. For example, effects of WHR_{adjBMI}-associated loci are generally more pronounced in women than in men [13] and the genetic susceptibility to obesity, assessed by a genetic risk score of multiple BMI-associated loci, was higher among individuals who lived unhealthy lives [47–50].

However, genome-wide searches to discover novel loci that interact with lifestyle and demographic factors has proven to be challenging. A large-scale GWAS (N_{max}~320,000) that examined the effect of age and sex on genetic associations with adiposity traits confirmed previously observed sex-specific effects for WHR_{adjBMI}-associated loci (mostly larger in women), and newly reported age-specific effects for BMI-associated loci (mostly larger among younger adults (age<50yrs)), but found few new loci [51]. Two GWASs that aimed to identify loci of which the association depends on physical activity or smoking status found no new loci for BMI and WHRadjBMI [52,53]. Despite the large sample size, it seems that current genome-wide GxE interaction studies do not have sufficient statistical power, suggesting that interaction effects are likely small, and/or the precision and accuracy with which non-genetic (lifestyle) factors are assessed is low. In addition, non-genetic factors are often not measured in a uniform manner and, despite rigorous efforts to harmonize across studies, this may increase heterogeneity and further reduce statistical power.

Populations with specific genomic features

While increasing sample size has been a major driver for continued discovery in traditional GWAS, recent studies have taken advantage of specific demographic, evolutionary and/or genomic features of relatively small populations. For example, a recent GWAS of BMI in Samoans (N_{max}=3,072), a unique founder population with a high prevalence of obesity, identified a coding variant (p.Arg457Gln) in *CREBRF* that is common among Samoans (MAF=26%) and other Pacific populations, but practically non-existent in other populations [54,55]. The Gln-allele is associated with a 1.4 kg/m^2 higher BMI (equivalent to ~4kg for a 1.7m tall person) and was found to reduce energy use and promote fat storage in an adipocyte model [55]. Particularly intriguing is that the Gln-allele protects significantly against type 2 diabetes [55].

A study in a Greenlandic Inuit population (N~4,000) characterized by an extreme demographic history [56], identified a functional variant in *ADCY3* (c.2433-1G>A) [57], a gene located in a locus previously identified by GWAS in which common variants were found to associated with BMI [58]. While relatively common in the Greenlandic population (~3%), the variant is monomorphic in other populations [57]. Other mutations in *ADCY3* were found to cause monogenic obesity in a consanguineous population from Pakistan [59]. Functional follow-up analyses showed that *ADCY3* co-localizes with *MC4R* at the primary cilia of a subset of hypothalamic neurons, previously implicated in body weight regulation [28].

While the identified variants were population-specific, the genes (and encoded proteins) may have a role in energy-homeostasis across all ancestries.

Genetic correlation and Mendelian randomization

Genetic correlation and Mendelian randomization are complementary approaches to assess shared etiology and causal relationships between adiposity and other traits.

Genetic correlation studies correlate SNP-association effects of one trait with those of another trait. SNP-association effects of BMI and WHR_{adjBMI} were found to positively correlate with those of cardiometabolic traits, excessive daytime sleepiness, sleep duration [60–62], and negatively with those for anorexia nervosa, age at menarche, years of education, alcohol use, and self-rated health [60,63,64].

Mendelian randomization, also dubbed nature's randomized trial, relies on the fact that SNPs, associated with a trait or biomarker, "randomize" a population – in an unbiased way – into low-to-highly exposed individuals. For example, the *FTO* genotype randomizes the population in three groups (by genotype); those with a low obesity risk (homozygous for the protective allele), intermediate risk (heterozygous) and high obesity risk (homozygous for the risk allele). This design allows testing whether BMI is causally associated with other traits. Consistent with findings from observational studies, Mendelian randomization studies have reported that increased BMI is causally related to higher risk of metabolic and cardiovascular diseases [65–70], higher risk of pancreatic, gastric, colorectal and breast cancer [71–76], lower risk of lung and skin cancer [76], higher risk of asthma [77], and

increased bone mineral density [78]. Furthermore, they have also provided evidence of lesser-known causal effects; i.e. of increased BMI on higher risk of multiple sclerosis [79,80] and lower risk of Parkinson's disease [81], and of increased childhood adiposity on higher risk of type 1 diabetes [82] and of disordered eating in adolescence [83].

Genetic information to predict obesity

Historically, genetic tests have been used to provide a genetic diagnosis to patients with rare forms of extreme and early-onset obesity that may be due to a single mutation [84]. For some patients, such a genetic diagnosis has been instrumental in their treatment [85,86]. As more variants are being discovered and genome sequencing is becoming mainstream, there is a growing expectation that genetic tests will help clinicians predict and diagnose patients' risks of complex disease, such as common forms of obesity. However, unlike monogenic forms, common obesity is polygenic and multifactorial; i.e. numerous genetic variants, and also lifestyle and demographic factors contribute to a person's obesity susceptibility. Therefore, it is no surprise that genetic prediction of obesity, even when based on nearly 100 GWAS-identified common variants, is poor (AUC_{ROC}~0.60) and unfit for use in clinical settings [12,87]. Because the heritability is modest, a test based solely on genetic variants will never accurately predict common obesity.

Conclusions and future perspectives

In the past decade, large-scale genome-wide discovery efforts have uncovered numerous new loci that harbor genetic variants associated with adiposity traits. With the advent of additional large population studies (e.g. UK Biobank, Million Veterans Project, All of Us), the number of loci will continue to increase rapidly in coming years. Preliminary analyses suggest that these loci highlight pathways that broadly overlap with the biology previously identified in extreme models of obesity in human and animals. However, the value of GWAS is that identified loci implicate new genes in both novel and known pathways. Pinpointing of these genes within each locus remains an important challenge, but may be sped up with the advent of novel approaches that integrate multiple sources of information [88,89]. The identification of the causal gene/variant is a critical step towards the translation of genetic loci into biology and requires close collaboration between geneticists and physiologists. Ultimately, new genes, even in known pathways, may provide new avenues for the development of obesity drugs, a field that had seen limited progress in the past four decades [90].

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*of special interest

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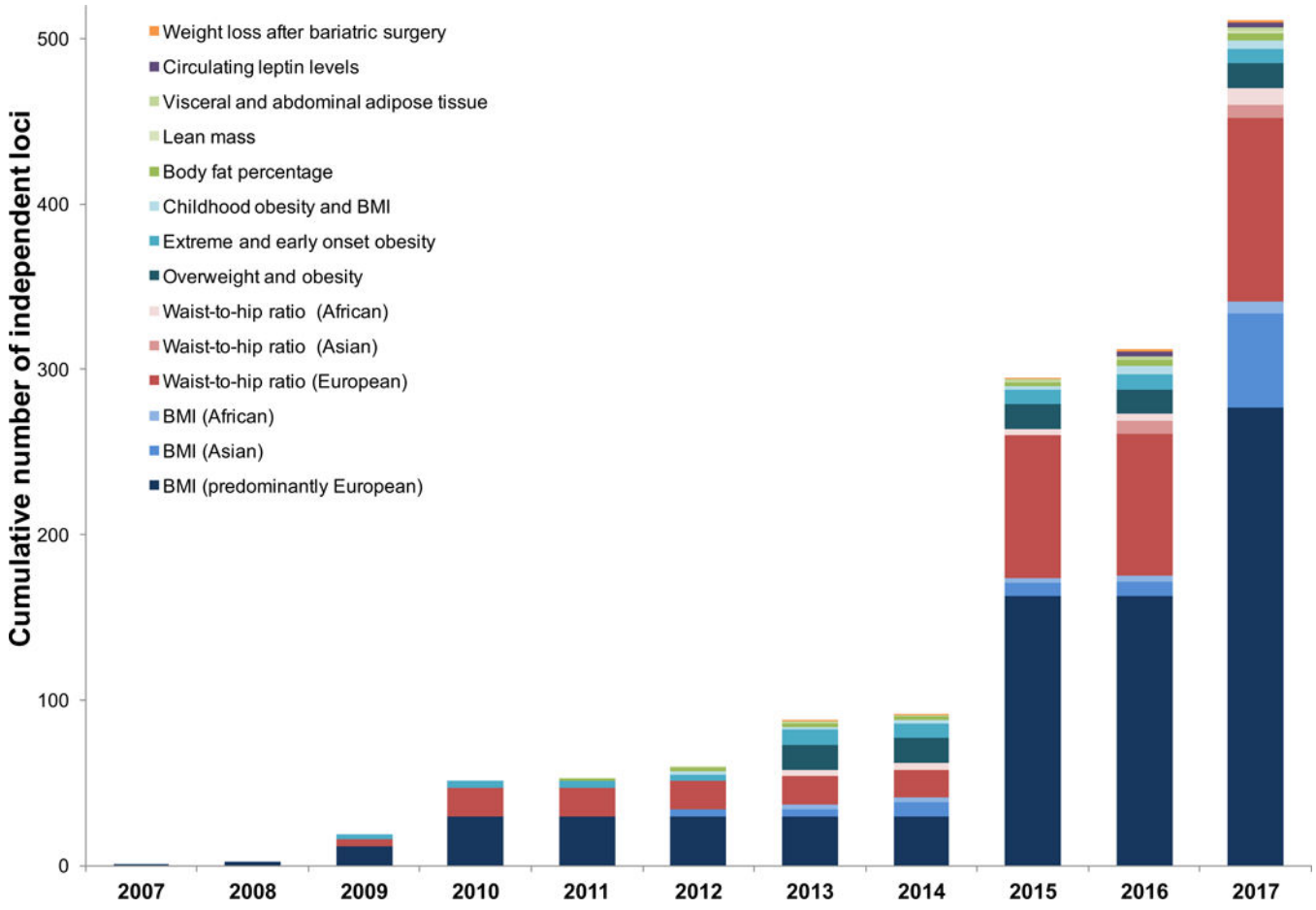

Figure 1.

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.

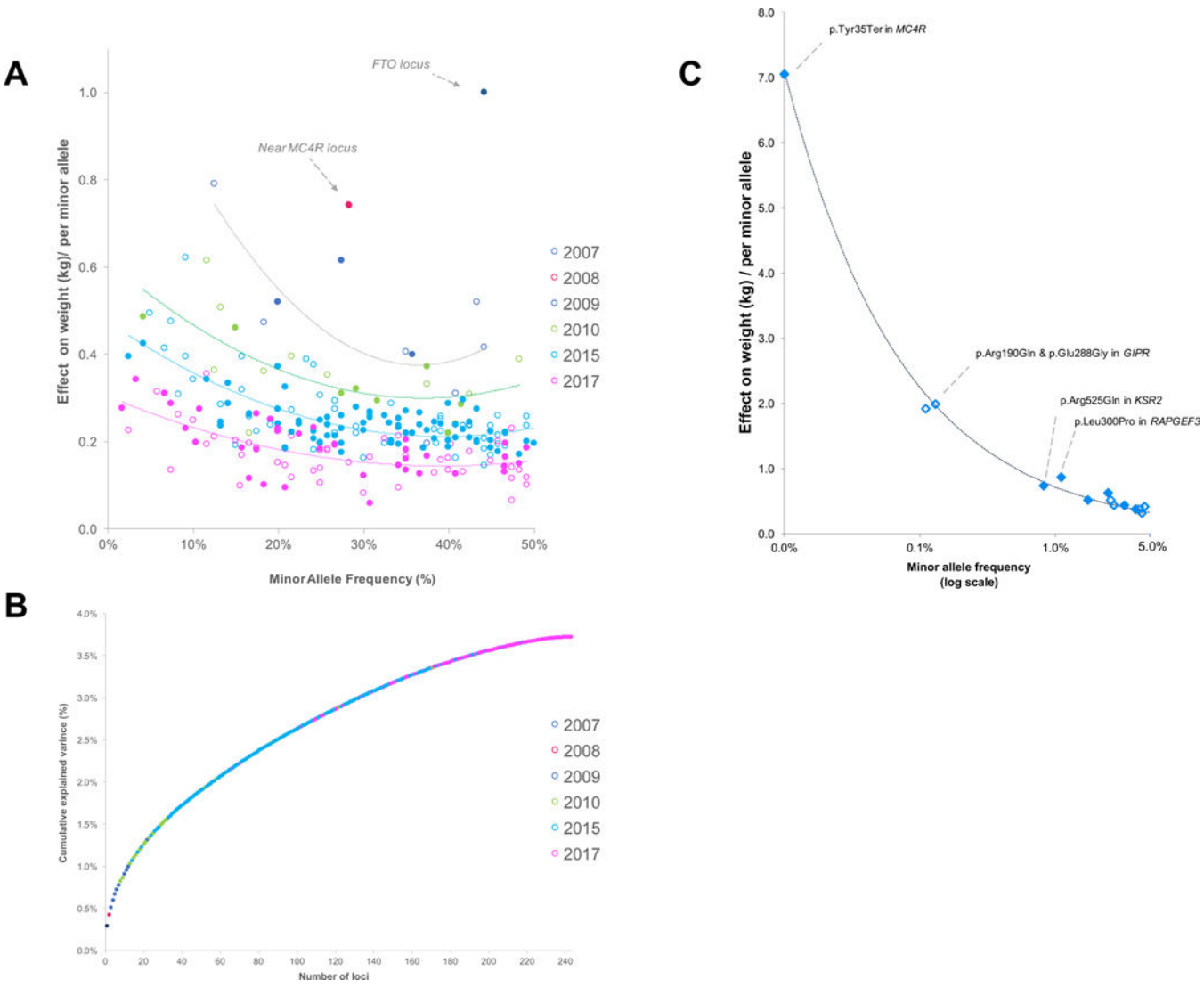

Figure 2.

Tissue expression of genes at BMI-associated loci (**Panel A**) and WHRadjBMI-associated loci (**Panel C**) [Adapted from Locke et al. [12] and Shungin et al. [13], respectively). Enrichment of BMI-associated variants included in the 99% credible sets for active enhancer in 10 cell groups (**Panel B**) [Adapted from Akiyama et al. [15]].

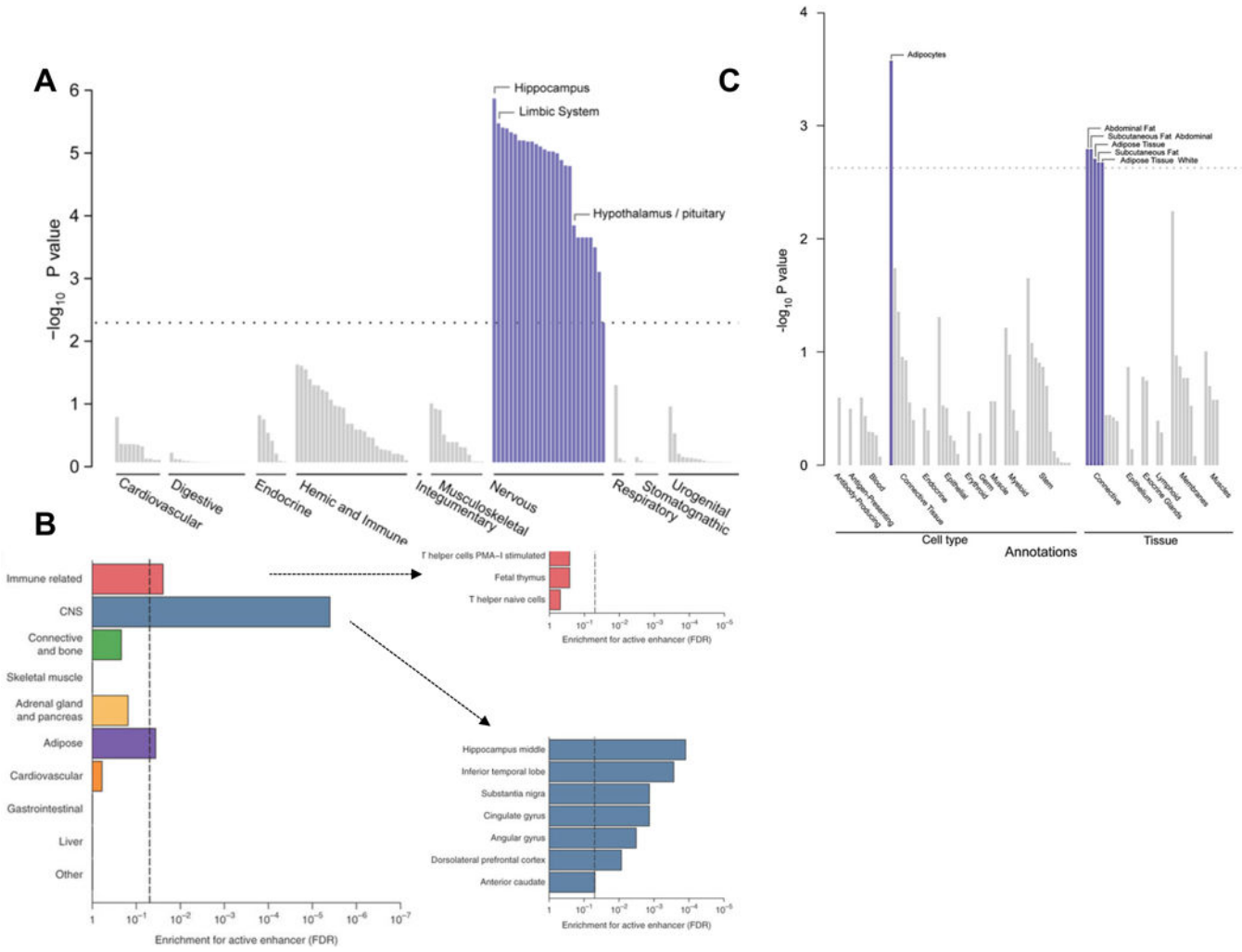

Figure 3.

Effect size (in kg, assuming a 1.7m tall person) by MAF for GWAS-identified BMI loci (**Panel A**) and their cumulative explained variance (**Panel B**). Color coding corresponds with year of discovery and dotted line represent trends of effect sizes by year. Effect size (in kg, assuming a 1.7m tall person) by MAF for low-frequency and rare exomechip-identified loci (**Panel C**) [Adapted from Turcot et al. [42]]. Filled markers indicate that the minor allele is associated with higher BMI, and unfilled markers indicate that the minor allele is associated with lower BMI. The dotted line represents 80% power.

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]