Journal of Genetics (2021)100:32
https://doi.org/10.1007/s12041-021-01281-7

REVIEW ARTICLE

Genomics of body fat distribution

SIMMI SAINI[1], GAGANDEEP KAUR WALIA[2], MOHINDER PAL SACHDEVA[1] and VIPIN GUPTA[1]*

[1]*Department of Anthropology, University of Delhi, Delhi 110 007, India*
[2]*Public Health Foundation of India, Gurugram 122 002, India*
*For correspondence. E-mail: udaiig@gmail.com.

Received 1 May 2020; revised 10 November 2020; accepted 4 January 2021

Abstract. Central obesity and body fat distribution measured by waist circumference (WC) and waist hip ratio (WHR) are good predictors of cardio metabolic adversities independent of overall adiposity. There are substantial evidence that body fat distribution is controlled by genetic factors. Even after accounting for body mass index (BMI), individual variation in body fat distribution is heritable, with estimates ranging from 31–76%. Individuals genetically predisposed to store more fat in visceral depots are at higher risk of developing metabolic complications. Several linkage and genomewide association studies (GWAS) for measures of body fat distribution uncovered numerous loci harbouring genes potentially regulating body fat distribution. Additionally, genes with fat depot specific expression patterns (especially, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)) have provided plausible candidate genes involved in body fat regulation. Further, sexual dimorphism have revealed a remarkable heterogeneity in the genetic regulation of body fat distribution. More than hundred loci have been identified through GWAS, displaying more pronounced effect in females than males, suggesting that both sexes share potentially different biological architecture in traits related to body fat distribution. Moreover, the handful of genes identified by GWAS have been validated in different population groups. This article aims at reviewing the current knowledge of genomic basis of body fat distribution.

Keywords. body fat distribution; waist to hip ratio; genetics; genomewide association study; sexual dimorphism.

Introduction

Obesity is one of the major public health conditions that predispose population for the increased risk of type 2 diabetes, fatty liver disease, dyslipidemia, hypertension and cardiovascular disease (Van Gaal *et al.* 2006). The common measures of overall and regional adiposity, i.e. body mass index (BMI), and waist circumference (WC) and waist hip ratio (WHR), respectively, are well established risk factors for metabolic disorders (Carey *et al.* 1997; Wang *et al.* 2005; Canoy 2008). Moreover, the effect of central abdominal fat in visceral adipose depots make obese individuals more prone to metabolic complications than fat stored in subcutaneous adipose depots (Bjorntorp 1991; Cassano *et al.* 1992; Kissebah 1997; Wei *et al.* 1997; Folsom *et al.* 2000). Epidemiological evidence proposing the role of regional fat depots, as a mediator in causing metabolic disease risk is gradually accumulating in different human populations (Wang *et al.* 2005; Canoy 2008; Hardy *et al.* 2017; Lee *et al.* 2017).

There is a fair amount of literature that suggest the genetic underpinnings of body fat distribution independent of BMI and overall adiposity (Lindgren *et al.* 2009; Heid *et al.* 2010; Shungin *et al.* 2015). Twin and family aggregation studies have estimated the heritability levels of WC and WHR ranging from 31% to 76% (Selby *et al.* 1990; Nelson *et al.* 1999; Souren *et al.* 2007) even after adjusting for BMI (Rose *et al.* 1998; Nelson *et al.* 2002). Regional fat depots are also heritable, for instance, the heritability estimates of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were reported to be 40% and 50–55%, respectively (Pérusse *et al.* 1996).

Studies have shown that the genetic factors underlying adiposity traits detected through linkage and genomewide linkage studies (Pérusse *et al.* 2001; Do *et al.* 2008; González-Sánchez *et al.* 2009; Vaughan *et al.* 2015). Genomewide linkage studies have identified several chromosomal regions harbouring genes for obesity related traits using the linkage related genetic data (Pérusse *et al.* 2001; Rice *et al.* 2002; Aberg *et al.* 2009). Further, linkage studies have been

Published online: 24 May 2021

subsequently accompanied by large and statistically powerful genomewide association studies (GWAS), designed to dissect the genetic architecture of adiposity traits in hypothesis-free way (Manolio 2010; Lu *et al.* 2016; Rask-Andersen *et al.* 2019). GWAS have led to substantial discoveries of the genetic susceptibility loci for body fat distribution (Winkler *et al.* 2015; Ng *et al.* 2017). Genetic variants that reached genomewide significance level were further replicated to double ensure the statistical associations. These findings were further validated among different ethnic groups for the scientific credibility of genetic discoveries (den Hoed *et al.* 2010; Moore *et al.* 2012; Xi *et al.* 2013a). These detected genetic variants are important for unraveling biological mechanism and pathways involved in the regulation of body fat distribution.

A comprehensive understanding of the genetic architecture of body fat distribution is required to address the clinical and public health implications of alarming burden of obesity. Moreover, BMI as an imperfect proxy for the body fat with differential validity among populations highlight the importance of studying more accurate methods of quantifying regional adiposity levels. Therefore, the purpose of this review was to summarize the current knowledge and understanding of genomic basis of body fat distribution.

Linkage studies

We have identified five linkage-based studies which have primarily focussed on obesity related traits but were restricted to a few genetic markers (Norman *et al.* 1998; Lee *et al.* 1999; Norris *et al.* 2005; Voruganti *et al.* 2011; Gragnoli 2013). Two linkage studies have reported genetic association with body fat percentage (BF%) assessed by bioelectrical impedance. The first study (n = 451 sib-pairs and 362 siblings) found a strongest sib-pair-based multipoint linkage at 11q21-q22, near D11S2366, and the strongest sibling-based multipoint variance-components linkage at 18q21, near D18S877 for BF% with highest logarithm of the odds score (LOD = 2.1, 2.3, P = 0.001, 0.0006, respectively) in Pima Indians (Norman *et al.* 1998). Genes including *MMP1*, *MMP3*, *MMP8*, *GPDH-C* and *ATM* at chromosome 11 might influence adiposity through insulin resistance, lipid synthesis and insulin stimulated glucose transport (Hotamisligil *et al.* 1993; Evans *et al.* 1995; Edwards *et al.* 1996). The second study had revealed three peaks (D20S887, D20S120 and D20S149) at 20q13 for BF% (Lee *et al.* 1999), harbouring several genes such as *MC3R*, *MC4R* (Lu *et al.* 1994; Fong *et al.* 1997), *GNAS1* and *CEBPB* (Yeh *et al.* 1995) which might be candidates for obesity. Agouti-signalling protein (*ASIP*) belonged to the relevant region is a strong inhibitor of alpha melanocyte-stimulating-hormone receptors 3 and 4 (*MC3R* and *MC4R*) (Lu *et al.* 1994; Fong *et al.* 1997). Lack of functional *MC4R* gene resulted in obese mice (Huszar *et al.* 1997). However, mice homozygous for knockout mutations in *MC3R* gene had increased body fat and decrease lean mass not caused by increased food intake but due to increase food efficiency (Chen *et al.* 2000). The other candidate gene mapped in this region was CAAT/enhancer-binding-protein beta (*CEBPB*), having significant contribution in differentiation of adipocytes (Yeh *et al.* 1995).

Studies on refined measures of body fat distribution had identified a wide linkage peak on 12q13-q24 among Hispanic American families for WHR (D12S297 (LOD = 2.67), D12S1052 (LOD = 2.60) after adjusting with BMI (Norris *et al.* 2005). The potential candidate genes in this region such as *VDR*, *CD36L1* and *IGF1* are significantly involved in the mechanism of insulin release and glucose tolerance maintenance (Ye *et al.* 2001), high density lipoprotein metabolism (Acton *et al.* 1999) and insulin sensitivity (Sun *et al.* 1999), respectively. However, a linkage signal for BMI-adjusted with VAT was observed at 11q13 D11S2006 (LOD = 2.36) (Norris *et al.* 2005). Genes (*UCP2/UCP3*) identified in this location are actively involved in metabolism (Rodríguez *et al.* 2002). Moreover, genes mapped near 5q33 region for BMI-adjusted with SAT (D5S820, LOD = 2.64) include the glucocorticoid receptor (*GRL*) and *β2*-adrenoreceptor genes (Norris *et al.* 2005). The *β2*-adrenoceptor are the most abundant lipolytic adrenoceptor subtype and found to be linked with obesity due to accumulation of subcutaneous fat in Japanese men (Mori *et al.* 1999). In Quebec family study, *β2*-adrenoceptor genes have shown notable interactions with *GRL* gene, when their influence was evaluated on total abdominal fat area (Ukkola *et al.* 2001).

Voruganti *et al.* (2011) detected the evidence of linkage between D19S414 and D19S220 on chromosome 19 for WC (LOD = 3.5), BF% (LOD = 1.7), WHR (LOD = 2.5), subscapular (LOD = 2.1) and triceps skinfolds (LOD = 1.9) in 1214 Alaskan Eskimos. Important candidate genes in this region are *TGFB1*, *GYS1*, *LIPE*, *APOE*, *GIPR* and *LSR* which are functionally associated with growth and differentiation (Dickinson *et al.* 1990) and clearance of very low density lipoproteins and chylomicron remnants (Mooijaart *et al.* 2006). In addition, these genes also participate in insulin and glucocorticoid metabolism (Usdin *et al.* 1993), mobilization of free fatty acids from adipose tissue (Holm *et al.* 1988) and lipid transporter activity and clearance of dietary triglyceride (Yen *et al.* 1999). Moreover, the linkage of *PSMD9* (LOD = 0.93, P = 0.023) was observed with WC in 108 Italian families (Gragnoli 2013). This gene may contribute to type-2 diabetes, obesity, overweight and visceral obesity (Thomas *et al.* 1999).

Genomewide linkage studies

Before the advent of GWAS, genomewide linkage study was the primary approach for genetic mapping of Mendelian and complex traits with familial aggregation through linked markers (Dickinson *et al.* 1990). We have identified six

genomewide linkage studies on obesity related traits (Hsueh *et al.* 2001; Sutton *et al.* 2006; Dong *et al.* 2011; Kim *et al.* 2013; Liu *et al.* 2014; Vaughan *et al.* 2015), while additional six have focussed on body fat distribution as an independent phenotype (Pérusse *et al.* 2001; Rice *et al.* 2002; Fox *et al.* 2004; Aberg *et al.* 2009; Feitosa *et al.* 2009; Chiu *et al.* 2010) (table 1).

The first genomewide linkage study of obesity-related traits conducted on Old Order Amish population had reported linkage with maximum LOD scores for BF% (LOD = 1.61) and WC (LOD = 1.80) occurring on chromosomes 3p and 14q, respectively mapped near *PPARG* or *PPARγ* (Hsueh *et al.* 2001). *PPARγ* is actively involved in differentiation of adipocytes and glucose metabolism. Further, a genomewide linkage study on visceral fat assessed by CT scan in the Quebec family cohort revealed the strongest evidence of linkage on chromosome 12q24.3 between marker D12S2078 and abdominal subcutaneous fat (LOD = 2.88) (Pérusse *et al.* 2001). Three loci (1p11.2, 9q22.1 and 17q21.1) were in close proximity to the genes involved in regulation of sex steroid levels (*NHLH2*, *HSD17B3* and *HSDB3*), whereas other two loci (4q32.1 and 17q21.1) were close to the genes involved in regulation of food intake (*NPY* and *NPY2R*) (Pérusse *et al.* 2001). Moreover, the best evidence for abdominal visceral fat was found on 2q22.1 and 2q33.2-q36.3 (including the *IRS1* locus) in whites and suggestive findings on 7q22.2-q31.3 (including the *LEP* locus) in blacks of HERITAGE family cohort (Rice *et al.* 2002). *IRS1* is a cornerstone factor in insulin-signalling pathways and mediates the control of various cellular processes by insulin (Asano *et al.* 2007). Studies on humans and knockout mice have shown association of leptin gene with BMI, weight loss and body weight (Shintani *et al.* 1996; Li *et al.* 1999).

The significant linkage signal for WC were also attained at 1q32 (near *PROX1* gene marker rs1704198) in an Asian population (Kim *et al.* 2013). The biological role of *PROX1* gene was previously studied in a mouse model, where heterozygosity in *PROX1* gene causes adult-onset obesity and heavier adipocytes with large circumference as compared to wild-type animals. In addition, mice with *PROX1* heterozygosity had also developed impaired hepatic lipid accumulation along with increased levels of leptin and insulin (Harvey *et al.* 2005).

Candidate gene association studies

Candidate gene approach is hypothesis driven. Genes which have been previously implicated in pathways controlling energy intake and expenditure have been selected as important candidates and analysed (Tabor *et al.* 2002). Thus, this approach relies upon the existing knowledge of the biology and pathophysiology of the disease. A total of 14 candidate gene association studies have been conducted with respect to body fat distribution (table 2). Some of these genes were previously belonged to body mass and adiposity measures while others are involved in energy intake and energy expenditure.

Since from the discovery of *FTO* gene, an association of single-nucleotide polymorphisms (SNPs) with obesity and BMI was reported in number of populations, making *FTO* the first candidate gene associated with obesity (Yajnik *et al.* 2009; Vasan *et al.* 2013). Gene expression studies in animal models suggested that *FTO* is actively involved in controlling feeding behaviour and energy expenditure (Fawcett and Barroso 2010). It had been reported that the genetic variants of *FTO* influence obesity, and also associated with body fat distribution independent of BMI and sex (Do *et al.* 2008; González-Sánchez *et al.* 2009; Pausova *et al.* 2009; Yajnik *et al.* 2009; Liu *et al.* 2010a; Dwivedi *et al.* 2012; Vasan *et al.* 2013). Another candidate gene for obesity is *MC4R,* which play a significant role in the regulation of body weight and appetite (Huszar *et al.* 1997). The importance of *MC4R* in body weight regulation is apparent but studies have also reported its association with WC, WHR and BF% (Dwivedi *et al.* 2013; Evans *et al.* 2014). In addition, *PPARγ* was found to be an important candidate gene, actively involved in adipocyte differentiation (Passaro *et al.* 2011; Bhatt *et al.* 2012). Animal studies showed that the adipose-specific *PPARγ* knockout mice showed diminished weight gain on feeding with high-fat diet despite hyperphagia and also had diminished serum concentrations of leptin and adiponectin, and did not develop glucose intolerance or insulin resistance (Jones *et al.* 2005). In humans, of the three *PPARγ* isoforms, *PPARγ2* mRNA is the most abundantly and relatively specifically expressed in adipose tissue. It has been reported that *PPARγ2* mRNA levels were increased in adipocytes from morbidly obese subjects (Auwerx 1999). Further, investigators have explored the role of variants in *SIRT1* gene, previously known to be an important regulator of energy metabolism via its influence on glucose and lipid metabolism (Peeters *et al.* 2008). Moreover, variants in *LPL* and *IL6* genes might regulate body fat distribution through their contribution in ectopic visceral storage (Parikh and Groop 2004; Radha *et al.* 2007; Gupta *et al.* 2011).

Candidate gene approach have been criticized because of its limited ability to include all possible causative genes, nonreplication of results and incapability to discover new genes (Tabor *et al.* 2002). All these limitations led to the establishment of more advanced tool, i.e. GWAS, which can pinpoint genes regardless of their unknown function.

GWAS

GWAS are the powerful tool for understanding the genetic basis of many complex traits (McCarthy *et al.* 2008). GWAS focussed on fat distribution traits including WC and WHR have generated genotyping data on thousands of samples and uncovered several loci (> 200) that harbour associations of common variants with adiposity traits (Shungin *et al.* 2015;

Table 1. Genes identified by genomewide linkage studies in context with body fat distribution.

Author (year)	Population	Sample size	Nearest gene	Position	Marker (EA)	Trait	Effect size, *P*-value
Pérusse *et al.* (2001)	Canadian families of French ancestry	496	*NHLH2, HSDB3*	1p11.2	D1S534	ASF	LOD = 2.07
			PPARGC1	4p15.1	D4S2397	ASF	LOD = 2.13
			NPY2R	4q32.1	D4S2417	ASF	LOD = 1.74
			LEP, CAV2	7q31.1	D7S1875	ASF	LOD = 2.01
			HSD17B3	9q22.1	D9S1122	ASF	LOD = 2.01
			–	–	D9S257	ASF	LOD = 1.69
			IGF1	12q22-q23	IGF1	ASF	LOD = 1.86
			HNF1	12q24.3	D12S2078	ASF	LOD = 2.53
			–	–	D12S1045	ASF	LOD = 1.09
			–	13q34	D13S285	ASF	LOD = 1.44
			HSD17B1	17q21.1-q21.3	D17S2180	ASF	LOD = 1.30
			PYY	–	D17S1290	ASF	LOD = 1.29
			PPY	–	D17S1301	ASF	LOD = 1.99
Hsueh *et al.* (2001)	Amish	672	–	14q	–	WC	LOD = 1.80
			PPARγ	3p	D3S3608	BF%	LOD = 1.61
Rice *et al.* (2002)	European ancestry	99 HERITAGE white families	–	2p14	D2S441	ASF	LOD = 1.88, *P* = 0.00164
			–	2q22.1	D2S1334	AVF	LOD = 1.97, *P* = 0.00131
			–	2q22.1	D2S1399	AVF	LOD = 2.33, *P* = 0.00053
			–	2q36.1	D2S434	AVF	LOD = 2.49, *P* = 0.00035
			IRS1	2q36.3	IRS1	AVF	LOD = 1.87, *P* = 0.00168
			–	5q31.2	D5S658	ASF	LOD = 2.06, *P* = 0.00104
			–	5q31.2	D5S658	ATF	LOD = 1.84, *P* = 0.00179
			–	5q31.3	D5S1480	ATF	LOD = 1.87, *P* = 0.00169
			–	22q11.23	D22S264	ASF	LOD = 1.96, *P* = 0.00132
		105 HERITAGE black families	–	3p26.3	D3S2387	ASF	LOD = 2.16, *P* = 0.00080
			–	3q29	D3S1311	ASF	LOD = 2.45, *P* = 0.00039
			–	4q31.22	D4S2431	ASF	LOD = 2.34, *P* = 0.00052
			–	7q36.3	D7S559	ASF	LOD = 1.74, *P* = 0.00230
			–	11p14.1	GATA34E08	ASF	LOD = 1.75, *P* = 0.00224
			–	14q24.1	D14S588	ASF	LOD = 2.38, *P* = 0.00047
			–	11p15.2	C11P15_3	ASF	LOD = 1.85, *P* = 0.00177
Fox *et al.* (2004)	European	2086	*ESR1, OPRM1* and *NMBR*	6	D6S1009	WC	LOD = 3.30
Sutton *et al.* (2006)	Hispanics	1425	–	–	D17S1301/D17S801	VAT	LOD = 3.05
			–	–	D17S1301/D17S801	WC	LOD = 1.92
Feitosa *et al.* (2009)	European	5076	*POMC, IRS1 and calpain 10*	2p25	GATA116B01	WC	LOD = 4.23
Aberg *et al.* (2009)	American Samoa and Samoa	1164	–	9p22.3– p21.3	D9S285	BF%	LOD = 2.48
					D9S157–D9S171	ABDCIR	LOD = 2.14
Chiu *et al.* (2010)	Chinese	1365	–	6p123	–	Hip	LOD = 2.39, *P* = 0.0018
				12q23.1	–	WC	LOD = 1.61, *P* = 0.0146
Dong *et al.* (2011)	Caribbean Hispanic	1390	–	16q23–24	D16S3091/D16S539	Average tricep skinfold	LOD = 2.32, *P* = 0.0008
			–	14q32	D14S1434	Abdominal thickness	LOD = 2.17, *P* = 0.001
Kim *et al.* (2013)	Mongolian and Korean	3106	*PROX1*	211977117	rs1704198 (A)	WC	$P = 4.11 \times 10^{-7}$
Liu *et al.* (2014)	Chinese	1791	*TBC1D22A*	22q13.31–13.33	rs16996195	WC	LOD = 3.13
Vaughan *et al.* (2015)	European	982	*SBSPON*	8	rs1007750	Thigh circumference	*P* = 0.0005
			–	5	rs878953	Thigh skinfold	*P* = 0.0004
			LUZP2	11	rs1596854	WC	*P* = 0.0003

ABDCIR, abdominal circumference; ASF, abdominal subcutaneous fat; AVF, abdominal visceral fat; ATF, abdominal total fat; BF%, body fat percentage; EA, effect allele; LOD, logarithm of the odds; VAT, visceral adipose tissue; WC, waist circumference.

Winkler *et al.* 2015; Wen *et al.* 2016) (table 3). A study conducted by Chambers *et al.* (2008) had reported an association of rs12970134 with WC (β = 0.88) among individuals of Indian-Asian and European ancestry. This genetic variant (rs12970134) have been mapped near *MC4R* gene and is known for their association with monogenic obesity (Hinney *et al.* 2010). Further, the association of a novel variant (rs10146997) of *NRXN3* with WC was discovered among Caucasians but this effect was reduced after adjusting for BMI, indicating the role of this locus in regulating overall adiposity rather than central obesity (Heard-Costa *et al.* 2009).

The first meta-analysis of GWAS related to two widely studied measures of body fat distribution, i.e. WC and WHR, was conducted among Europeans (Lindgren *et al.* 2009). Genetic variants within *TFAP2B* ($P = 1.87 \times 10^{-11}$) and near *MSRA* ($P = 8.89 \times 10^{-9}$) were found to be strongly associated with WC and a third locus, near *LYPLAL1* (β = 0.040, $P = 2.6 \times 10^{-8}$), was associated with WHR in women only (Lindgren *et al.* 2009). Second meta-analysis have included 32 GWAS to detect other genetic variants associated with WHR adjusted for BMI (WHRadjBMI) (n = 77,167). They have also followed up 16 loci in additional 29 studies (n = 113,636). Thirteen novel loci in or near *VEGFA*, *RSPO3*, *NISCH-STAB1*, *TBX15-WARS2*, *LY86*, *NFE2L3*, *GRB14*, *ITPR2-SSPN*, *HOXC13*, *ADAMTS9*, *ZNRF3-KREMEN1*, *DNM3-PIGC* and *CPEB4* genes were uncovered and confirmed association signal at *LYPLAL1* (Heid *et al.* 2010).

Several studies have used more precise techniques (CT scan) for measuring body fat distribution (Norris *et al.* 2009; Fox *et al.* 2012a; Plourde *et al.* 2013). GWAS focussing on more accurate methods for quantifying body fat had uncovered additional variants contributing to genetic control of body fat distribution. A novel locus near *THNSL2* was identified in association with VAT among women of European ancestry (Fox *et al.* 2012a). For the VAT/SAT ratio, the most significant *P*-value was attained at *LYPLAL1* gene ($P = 3.1 \times 10^{-9}$), previously identified in association with WHR. The genetic associations of seven loci were observed with VAT/SAT ratio (Fox *et al.* 2012a) after interrogating data for the 14 previously identified loci for WHRadjBMI (Heid *et al.* 2010). Findings of these studies have suggested that phenotyping using imaging techniques is better than typical anthropometric measures as imaging have the ability to partition subcutaneous fat depots from visceral fat depots (Fox *et al.* 2012a).

Further, six new loci near *IRS1*, *SPRY2*, *PLA2G6*, *IGF2BP1*, *COBLL1*/*GRB14* and *CRTC1* were identified for BF% (Kilpeläinen *et al.* 2011; Lu *et al.* 2016). The body fat decreasing allele of *IRS1* (rs2943650) and *SPRY2* (rs534870) were associated with 0.16% and 0.14%, respectively, decrease in BF% (Kilpeläinen *et al.* 2011). Additionally, four novel loci near *EFEMP1*, *ADAMTSL3*, *CNPY2*, *GNAS* with WC adjusted for BMI (WCadjBMI), two loci near *NID2*, *HLA-DRB5* with WHRadjBMI, and three novel loci near *CEP120*, *TSC22D2* and *SLC22A2* genes with WC not adjusted for BMI (WCnoBMI) were identified at the genome-wide significance level among individuals of East Asian ancestry (Wen *et al.* 2016). Moreover, the only GWAS conducted on pericardial fat identified a novel locus (rs10198628) near *TRIP2* showing significant association ($P = 2.7 \times 10^{-8}$) among individuals of European ancestry. This gene is exclusively associated with pericardial fat suggestive of unique genetic underpinnings for ectopic fat distribution (Fox *et al.* 2012b).

Recently, the largest GWAS (n = 362, 499) conducted on proportions of body fat distributed to arms, trunk and legs assessed through segmental bioelectric impedance analysis had identified 98 independent associations with body fat distribution. Of these, 29 associations were previously established for anthropometric traits. A total of 37 loci showed more pronounced effect in females than males, indicated a high level of sex heterogeneity (Rask-Andersen *et al.* 2019) (table 3). Moreover, Pulit *et al.* (2019) had performed a GWAS meta-analysis for WHRadjBMI in up to 694,649 individuals of European ancestry and identified 436 independent signals in 346 loci ($P < 5 \times 10^{-9}$). All these variants explained nearly 3.9% of the overall phenotypic variance in WHRadjBMI. On constructing the polygenic risk score, 5% of the individuals carrying WHRadjBMI increasing alleles were 1.62 times more expected to meet WHR threshold used for defining metabolic syndrome. Additionally, the WHRadjBMI of the individuals in the top 5% of the polygenic risk score was 1.05 and 1.06 times higher in males and females, respectively, as compared to individuals in the bottom 5% of the polygenic risk score (Pulit *et al.* 2019).

Sexual dimorphism

Sexual dimorphism is a well characterized feature of body fat distribution. Unlike BMI, both males and females tend to have different levels of fat depots that define body shape (Pulit *et al.* 2017). Studies focussed on the biology of body fat distribution considered WHR as the main phenotype since it indicates the amount of fat located in the visceral part of an individual (Heid *et al.* 2010). Our search for GWAS uncovering sexually dimorphic loci associated with fat distribution yielded limited number of studies and most of them have identified sexually dimorphic loci for WHRadjBMI.

Firstly, Heid *et al.* (2010) had conducted a sex stratified meta-analyses for the 14 WHR associated loci within the GIANT consortium included up to 108,979 women and 82,483 men (mean age range: 16.0–76.52 years) of European ancestry. They have identified seven loci (near *RSPO3*, *VEGFA*, *GRB14*, *LYPLAL1*, *HOXC13*, *ITPR2-SSPN* and *ADAMTS9*) which showed significant differences in sex-specific effect sizes (P ranging from 1.9×10^{-3} to 1.2×10^{-13}) in joint analyses. All these 14 loci explained 0.46% of the variance in WHR (adjusted for BMI and age) in men and 1.34% in women (Heid *et al.* 2010). Another sex-

Table 2. Candidate gene association and validation of GWAS identified genes in context with body fat distribution.

Author (year)	Population	Sample size total (M/F)/range	Gene	SNPs studied (EA)	Trait	Effect size (S.E.)	95% CI	*P* value
Radha *et al.* (2007)	Indians	731	*LPL*	-93 T to G (G)	WC	–	–	0.03
Marvelle *et al.* (2008)	Philipines	1,886 Cebu Filipino female	*FTO*	rs9939609 (A)	WC	–	–	0.0094
Peeters *et al.* (2008)	Belgian	Obese cases, 1068; controls, 313	*SIRT1*	rs7069102 (C)	WC	–	–	0.04
					WHR	–	–	0.02
					VFA	–	–	0.005
				rs3818292 (G)	VFA	–	–	0.005
Do *et al.* (2008)	European	908	*FTO*	rs17817449 (G)	WC	–	–	0.00021
					HC	–	–	0.0014
					WHR	–	–	0.0013
					BF%	–	–	0.0023
					Sum of six skin-folds	–	–	0.0013
				rs1421085	WC	–	–	0.00059
					HC	–	–	0.0025
					WHR	–	–	0.0029
					BF%	–	–	0.0095
					Sum of six skin-folds	–	–	0.0019
Bauer *et al.* (2009)	European	1700 females	*NEGR1*	rs2568958 (A)	WC	$\beta = -0.43$	–0.76, –0.10	0.0100
Bressler *et al.* (2009)	African-American	3869	*INSIG2*	rs7566605 (C)	WHR	–	–	0.01
Yajnik *et al.* (2009)	Indians	960	*FTO*	rs9939609 (A)	HC	–	–	0.02
González-Sánchez *et al.* (2009)	European	80/127	*FTO*	rs9939609 (A)	WC	–	–	0.011
Pausova *et al.* (2009)	Americans	485 adolescents	*FTO*	rs9939609 (A)	WC	$\beta = 2.9$	0.2, 5.7	0.04
					Intra-abdominal fat	$\beta = 0.5$	0.1, 0.8	0.007
					Subcutaneous fat	$\beta = 0.5$	0.2, 0.8	0.0008
den Hoed *et al.* (2010)	European	2042	*SEC16B*	rs10913469	Sum of skinfolds	$B = 0.126$ (0.03)	–	2.5×10^{-4}
					Wc	$\beta = 0.075$ (0.03)	–	6.8×10^{-3}
			LYPLAL1	rs2605100	Sum of skinfolds	$\beta = 0.060$ (0.03)	–	3.9×10^{-2}
					Wc	$\beta = 0.060$ (0.02)	–	1.0×10^{-2}
			TMEM18	rs6548238	Sum of skinfolds	$\beta = 0.150$ (0.04)	–	2.5×10^{-5}
			TMEM18	rs6548238	WC	$\beta = 0.068$ (0.03)	–	1.6×10^{-2}
			NEGR1	rs2815752	WC	$\beta = 0.062$ (0.02)	–	4.8×10^{-3}
			GNPDA2	rs10938397	Sum of skinfolds	$\beta = 0.061$ (0.03)	–	2.5×10^{-3}
			BDNF	rs925946	Sum of skinfolds	$\beta = 0.065$ (0.03)	–	2.7×10^{-3}
			TFAP2B	rs987237	WC	$\beta = 0.056$ (0.03)	–	3.5×10^{-2}
Li *et al.* (2010)	European	20,125	*NEGR1*	rs3101336	WC	$\beta = 0.022$ (0.010)	–	0.027
			TMEM18	rs6548238	WC	$\beta = 0.050$ (0.013)	–	1.50×10^{-4}
			GNPDA2	rs10938397	WC	$\beta = 0.039$ (0.010)	–	1.69×10^{-4}
			KCTD15	rs368794	WC	$\beta = 0.024$ (0.011)	–	0.023
			MC4R	rs17782313	WC	$\beta = 0.042$ (0.012)	–	3.48×10^{-4}
			FTO	rs1121980	WC	$\beta = 0.080$ (0.010)	–	2.04×10^{-15}
			BDNF	rs925946	WC	$\beta = 0.049$ (0.011)	–	8.47×10^{-6}
			SH2B1	rs7498665	WC	$\beta = 0.024$ (0.010)	–	0.015
			FAIM2	rs7132908	WC	$\beta = 0.040$ (0.010)	–	8.43×10^{-5}

Table 2 (*contd*)

Author (year)	Population	Sample size total (M/F)/range	Gene	SNPs studied (EA)	Trait	Effect size (S.E.)	95% CI	*P* value
Liu *et al.* (2010a)	European and African ancestry	1975	*FTO*	rs9939609 (A)	WC	–	–	0.04
Haupt *et al.* (2010)	European	1469 nondiabetic white subjects	*TMEM18*	rs6548238 (T)	WC	–	–	0.03
			SH2B1	rs7498665 (G)	VAT	–	–	0.009
			NEGR1	rs2815752 (C)	VAT	–	–	0.02
					TAT	–	–	0.03
Gupta *et al.* (2011)	Indians	178	*IL6*	G-174C (C)	WHR	–	–	< 0.001
Liu *et al.* (2010b)	European Americans & African Americans	395–1652 European Americans & African Americans	*MC4R*	rs17782313 (C)	WC	–	–	0.03
				rs17700633 (A)	BF%	–	–	0.001
					VAT	–	–	<0.001
					SAAT	–	–	<0.001
Hotta *et al.* (2011)	Japanese	1279 (556/723)	*SH2B1*	rs7498665 (G)	VFA	–	–	0.00047
Klimentidis *et al.* (2011)	European	298 (children)	*FTO*	rs8050136 (A)	WC	–	–	0.0168
				rs9939609 (A)	WC	–	–	0.0197
			TMEM18	rs7561317 (G)	WC	–	–	0.042
Bille *et al.* (2011)	European	6038	*LYPLAL1*	rs2605100 (G)	WC	β = –0.08	–0.29, 0.13	0.04
			NRXN3	rs10146997 (G)	WC	β = 0.55	0.20, 0.89	0.02
Passaro *et al.* (2011)	Caucasians	364	*PPARγ*^{2}	Pro12Ala (Ala)	WC	β = 2.03	–	0.001
Bhatt *et al.* (2012)	Indians	495	*PPARγ*^{2}	Pro12Ala (Ala)	HC	–	–	0.03
Moore *et al.* (2012)	Indians	1129	*FTO*	rs3751812 (T)	WC	–	–	0.04
Dwivedi *et al.* (2012)	Indians	3126 children	*FTO*	rs8050136 (A)	WC	β = 0.12	0.07, 0.18	7.9×10^{-6}
					HC	β = 0.11	0.05, 0.16	1.5×10^{-4}
					WHR	β = 0.07	0.02, 0.13	9.2×10^{-3}
Hotta *et al.* (2012)	Japanese	1279	*CYP17A1*	rs1004467 (A)	SFA	β = −0.030 (0.008)	–	0.00011
			NT5C2	rs11191548 (T)	SFA	β = −0.026 (0.008)	–	0.0016
Dwivedi *et al.* (2013)	Indians	1362 children 2028 nondiabetic controls	*MC4R*	rs17782313 (C) (in children)	WC	β = 0.26	0.19, 0.34	3.8×10^{-12}
					WHR	β = 0.13	0.06, 0.20	2.0×10^{-4}
				rs12970134 (A) (in children)	WC	β = 0.24	0.16, 0.31	4.3×10^{-10}
					WHR	β = 0.11	0.04, 0.18	0.002
				rs17782313 (C) (In adults)	WC	β = 0.07	0.01, 0.14	0.034
				rs12970134 (A) (In adults)	WC	–	–	0.05
Gupta *et al.* (2013)	Indians	5056	*NGN3*	rs10823406 (A)	WHR	β = 0.08	–	0.01
Vasan *et al.* (2013)	Indians	1230	*FTO*	rs9939609 (A)	WHR	β = 0.006	0.001, 0.012	0.021
Xi *et al.* (2013a)	Chinese	2849	*SEC16B*	rs10913469 (C)	WC	β = 0.39	0.08, 0.7	0.014
Xi *et al.* (2013b)	Chinese	19593 children	*FTO*	rs9939609 (A)	WC	OR = 1.29	1.10, 1.50	0.001
					WHR	OR = 1.33	1.14, 1.56	3.56×10^{-4}
			MC4R	rs17782313 (C)	WC	OR = 1.27	1.12, 1.44	1.32×10^{-4}
					WHR	OR = 1.25	1.10, 1.42	4.71×10^{-4}
			BDNF	rs6265 (G)	WC	OR = 1.20	1.08, 1.34	8.86×10^{-4}
			GNPDA2	rs10938397 (G)	WC	OR = 1.22	1.09, 1.37	4.09×10^{-4}
					WHR	OR = 1.25	1.11, 1.39	1.32×10^{-4}
Evans *et al.* (2014)	African American white	1538–1616	*MC4R*	rs11152221 (T)	BF%	β = 0.75 (0.25)	–	0.003

Table 2 (*contd*)

Author (year)	Population	Sample size total (M/F)/range	Gene	SNPs studied (EA)	Trait	Effect size (S.E.)	95% CI	*P* value
Zhu *et al.* (2014)	Chinese	2894	*MTIF3*	rs4771122	BF%	β = 0.98 (0.34)	–	0.0047
			SH2B1	rs4788102	BF%	β = 0.55 (0.26)	–	0.033
			PCSK1	rs261967	BF%	β = 20.16 (0.08)	–	0.044
Nakayama *et al.* (2014)	Japanese	3013 (1,572/1339)	*GIPR*	rs55669001 (T)	VFA	β = 0.029	–	0.035
					WC	β = 0.046	–	0.008
				rs2287019 (C)	VFA	β = 0.031	–	0.023
					WC	β = 0.038	–	0.028

BF%, body fat percentage; β, beta coefficient; CI, confidence interval; EA, effect allele; HC, hip circumference; OR, odds ratio; SAT, subcutaneous adipose tissue; SFA, subcutaneous fat area; SAAT, subcutaneous abdominal adipose tissue; TAT, total adipose tissue; VFT, visceral fat area; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist hip ratio.

specific meta-analyses have identified four previously established and three novel anthropometric trait loci (near *MAP3K1*, *HSD17B4*, *PPARG*) exhibiting significant sex-differences for WHRadjBMI in European population (mean age range: 40.9–74.3 years). All these loci reached genomewide significant level only in women (joint *P*-women: 3.4 $\times$ 10^{-9} to 4.2 $\times$ 10^{-14}) (Randall *et al.* 2013).

The sexual dimorphism in body fat distribution gained further support from a recent large scale GWAS meta-analyses (>320,000 individuals of European descent; mean age range: 18.9–69.1 years) identified 44 loci displaying significantly distinct effects on WHRadjBMI between male and female, of which 17 were novel (near *TTN*, *IRS1*, *CDH10*, *IQGAP2*, *SIM1*, *ISPD*, *KLF14*, *SGCZ*, *PTPRD*, *RXRA*, *GANAB*, *SLC2A3*, *LEMD3*, *GNPNAT1*, *RPS6KA5*, *CECR2*, *HMGXB4*) and 27 loci had been confirmed in earlier study (Winkler *et al.* 2015). Of these 27 loci, sex-specific effects on WHRadjBMI for 10 of the previously established loci (near *GORAB*, *LY86*, *ITPR2*, *PIGU*, *EYA2*, *KCNJ2*, *MEIS*, *EYA1*, *CCDC92*, *NSD1*) were also reported. A total of 28 loci P_{binomial} = 3.3 $\times$ 10^{-5}) have shown more pronounced effects in females than in males (Winkler *et al.* 2015).

Another largest meta-analysis on 224,459 European individuals (mean age range: 18.90–73.90 years) have discovered 49 loci associated with WHRadjBMI, of which 20 loci showed significant sexual differences (Shungin *et al.* 2015). A total of 19 loci (11 new) near *PLXND1*, *NMU*, *FAM13A*, *MAP3K1*, *HMGA1*, *NKX2-6*, *SFXN2*, *MACROD1-VEGFB*, *CMIP*, *BCL2*, *SNX10*, *LYPLAL1*, *GRB14-COBLL1*, *PPARG*, *ADAMTS9*, *TNFAIP8-HSD17B4*, *VEGFA*, *RSPO3*, *HOXC13* displayed a stronger effect in women while only loci that showed a larger effect in men mapped near *GDF5* (rs224333, β_{men} = 0.036 and *P* = 9.0 $\times$ 10^{-12}, β_{women} = 0.009 and *P* = 0.074, $P_{\text{difference}}$ = 6.4 $\times$ 10^{-5}). Further, on conditional analysis, in *HOXC6–HOXC13* region, one loci was found to be female-specific (rs1443512, $P_{\text{conditional}}$ = 1.1 $\times$ 10^{-14}), similarly, in *TBX15–WARS2–SPAG17* region, one signal was male-specific (rs1106529, $P_{\text{conditional}}$ = 4.8 $\times$ 10^{-9}) (Shungin *et al.* 2015).

The association of rs3791679 near *EFEMP1* gene with WCadjBMI was significantly stronger in men than in women (effect size: 4.04 vs 2.43), whereas the association of rs1982963 near *NID2* gene with WHRadjBMI was significantly weaker in men than in women (effect size: 2.88 vs 6.26) (Wen *et al.* 2016) among individuals of East Asian ancestry (mean age range: 36.5–66.0 years). Two novel loci (*SSX2IP*, *PDE3B*) with WHRadjBMI were identified among women of African ancestry. On combining the GWAS of African and European ancestry, two more novel loci (*CASC8*, *ZDHHC1/HSD11B2*) for WHRadjBMI were identified in African and European ancestry (mean age range: 9.3–73.5 years) (Ng *et al.* 2017).

The only GWAS focussed on sexual dimorphic loci in BF% among individuals of European and Asian Indians

ancestry (mean age range: 43.4–75.5 years) have identified the association of locus near *IRS1* with BF% ($P_{\text{sex-difference}}$ = 0.02) and this effect was more pronounced in men ($P = 3 \times 10^{-11}$) than in women ($P = 9 \times 10^{-3}$) (Kilpeläinen *et al.* 2011). The *IRS1* locus was found to be associated with an adverse distribution of body fat in men as the BF% decreasing allele of rs2943650 near *IRS1* was associated with reduced subcutaneous fat in men ($P = 1.8 \times 10^{-3}$) but not in women ($P = 0.063$), implying that there may be sex differences in the effects of near *IRS1* locus on the function of gene itself (Kilpeläinen *et al.* 2011).

The above findings of GWAS have suggested that the contribution of women to genetic variance is significantly higher as compared to men.

Validation of GWAS identified genes

Our search yielded 17 validation studies of previously identified GWAS hits which have shown significant associations with body fat distribution in pooled sample size of 75,776 participants. Most of the validation studies ($n = 9$) have been conducted on WC and WHR and found significant associations (Marvelle *et al.* 2008; Bauer *et al.* 2009; Bressler *et al.* 2009; den Hoed *et al.* 2010; Bille *et al.* 2011; Klimentidis *et al.* 2011; Liu *et al.* 2012b; Moore *et al.* 2012; Xi *et al.* 2013a). The largest study (n = 20,125) conducted on European population have validated 12 loci, previously identified from GWAS on BMI. Of these, nine loci have shown significant association with WC with an effect size range from 0.010 to 0.013 cm per allele change for WC (Li *et al.* 2010). Second largest study performed on 19,593 Chinese children have validated 11 BMI associated loci in GWAS for associations with central obesity. It was found that four loci have shown significant association with central obesity assessed through WC (odds ratio (OR) range: 1.20–1.29) and WHR (OR range: 1.25–1.33) (Xi *et al.* 2013b). In addition, a validation study on Indian population have identified a locus (*NGN3*), previously established in GWAS for type-2 diabetes, in association with WHR (P = 0.01), suggestive of a common underlying biological mechanism (Gupta *et al.* 2013).

Moreover, the genetic associations were also validated for VAT (*NEGR1*, *SH2B1*), leg fat percentage (*PCSK1*, *MSRA*, *TFAP2B*), BF% (*FTO*, *MC4R*, *MTIF3*), trunk fat percentage (*TFAP2B*), visceral fat area (*GIPR*, *SH2B1*), subcutaneous fat area (*CYP17A1*, *NT5C2*), sum of skinfolds (*GNPDA2*, *BDNF*, *LYPLAL1*, *TMEM18*, *SEC16B*) (den Hoed *et al.* 2010; Liu *et al.* 2010b; Haupt *et al.* 2010; Hotta *et al.* 2011, 2012; Zhu *et al.* 2014; Nakayama *et al.* 2014). A total of 30 genetic variants in 20 genes have been validated in association with body fat distribution (table 2).

Biological functions of genes

Several genes have been identified through GWAS but the functional role could be allocated to a few of the candidate genes. For instance, the *cis*-expression quantitative trait loci (eQTL) data implicated *GRB14* as a potential candidate gene for WHR association (Heid *et al.* 2010). The *GRB14* variant (rs10195252) was also studied in association with insulin and triglyceride levels. These findings were supported by evidence that mice deficient with *Grb14* displayed improved glucose homeostasis despite having less circulating insulin levels, and increased insulin signalling in skeletal muscle and liver (Cooney *et al.* 2004). *VEGFA* is another candidate gene identified through GWAS, having a significant role as a mediator in adipogenesis (Nishimura *et al.* 2007). Given evidence that serum levels of *VEGFA* are correlated with obesity (Silha *et al.* 2005). Further, *TBX15* emerged to be a strongest candidate gene through *cis*-eQTL in omental fat with significant depot specific differences in expression of adipose tissue in mice and humans and associations between WHR and *TBX15* expression in visceral fat (Gesta *et al.* 2006, 2007). Developmental gene (*HOX13*) may determine the pattern of adipocyte specific expression which have been observed in different fat depots (Gesta *et al.* 2006; Lanctot *et al.* 2007). The signal near *ADAMTS9* showed overlapping with previously associated type-2 diabetes locus (Zeggini *et al.* 2009). The type-2 diabetes risk alleles of *ADAMTS9* locus were found to be associated with insulin resistance in peripheral tissue (Boesgaard *et al.* 2009). Moreover, the mRNA of the five potential body fat distribution related genes (*ITPR2*, *RSPO3*, *TBX15*, *WARS2* and *STAB1*) was differentially expressed between gluteal and abdominal subcutaneous adipose tissue (Heid *et al.* 2010).

Some of the validated genes such as *LYPLAL1* which encodes a lysophospholipase-like protein might acts as a triglyceride lipase and was reported to be upregulated in SAT of obese subjects (Steinberg *et al.* 2007). *TFAP2B* is another validated gene which encodes a transcription factor preferentially expressed in adipose tissue. Over expression of *TFAP2B* downregulates the expression of insulin sensitizing hormone adiponectin by direct transcriptional repression (Ikeda *et al.* 2006). Further, *CYP17A1* gene is involved in the biosynthesis of androgens, oestrogens, mineral corticoids and glucocorticoids (Gilep *et al.* 2011).

Moreover, other identified genes were involved in adipogenesis (*ZNF423*, *CEBPA*, *PPARG*, *BMP2*, *HOXCmir196*, *SPRY1* and *PEMT*), angiogenesis (*VEGFB*, *PLXND1*, *CALCRL*, *MEIS1*, *FGF2*, *SMAD6*), and inflammation (*NLRP3*) (Heid *et al.* 2010). Some of the transcriptional regulators at WHRadjBMI loci include *CEBPA*, *PPARG*, *MSC*, *SMAD6*, *HOXA*, *HOXC*, *ZBTB7B*, *JUND*, *KLF13*, *MEIS1*, *RFX7*, *NKX2-6* and *HMGA1* (Shungin *et al.* 2015). Deficiency of a few candidate genes including *NMU* (Hanada *et al.* 2004), *FGFR4* (Huang *et al.* 2007) and

Table 3. Summary of the genes identified by GWAS in context with body fat distribution.

Author (year)	Population	Sample size total (M/F)/ range	Gene	Chr	SNP studied (EA)	Phenotype	Effect size (S.E.)	*P* value
Scuteri *et al.* (2007)	Sardinian population	6148	*FTO*	16	rs9930506 (A)	HC	β = –0.157	3.4×10^{-8}
Chambers *et al.* (2008)	European ancestry or Indian Asians from UK	14,639	*MC4R*	18	rs12970134 (A)	WC	β = 0.88	1.7×10^{-9}
Norris *et al.* (2009)	Hispanic Americans	229	–	13	rs4541696	VSR	–	6.1×10^{-6}
			–	5	rs4134351	VSR	–	1.6×10^{-6}
			–	1	rs7543757	VAT	–	4.6×10^{-6}
			–	11	rs4754373	SAT	–	9.5×10^{-7}
			–	11	rs11212913	SAT	–	6.5×10^{-6}
Lindgren *et al.* (2009)	European	118,691	*TFAP2B*	17	rs987237 (G)	WC	–	1.87×10^{-11}
		80,210	*MSRA*	8	rs7826222 (G)	WC	–	8.89×10^{-9}
		47633	*LYPLAL1*	1	rs4846567 (G)	WHR	β = 0.040 (0.007)	2.6×10^{-8}
Polašek *et al.* (2009)	European	898	*ZNF498*	7	rs7792939	Brachial circumference	β = 0.255 (0.056)	4.90×10^{-6}
						HC	β = 0.256 (0.056)	5.73×10^{-6}
			SGCD	5	rs157350	Brachial circumference	β = −0.311 (0.067)	3.70×10^{-6}
						HC	β = −0.306 (0.068)	6.08×10^{-6}
			CRIM1	2	rs1863080	Brachial circumference	β = 0.307 (0.069)	7.82×10^{-6}
			ITGA1	5	rs7723398	Brachial circumference	β = 0.191 (0.043)	9.68×10^{-6}
			MAX	14	rs7158173	WC	β = −0.114 (0.025)	3.93×10^{-6}
			SEZ6L2	16	rs4787483	WC	β = 0.164 (0.035)	2.10×10^{-6}
Heid *et al.* (2010)	European	113,582	*RSPO3*	6	rs9491696 (G)	WHRadjBMI	β = 0.042	1.84×10^{-40}
		95,430	*VEGFA*	6	rs6905288 (A)	WHRadjBMI	β = 0.036	5.88×10^{-25}
		109,623	*TBX15-WARS2*	1	rs984222 (G)	WHRadjBMI	β = 0.034	8.69×10^{-25}
		113,636	*NFE2L3*	7	rs1055144 (T)	WHRadjBMI	β = 0.040	9.97×10^{-25}
		102,449	*GRB14*	2	rs10195252 (T)	WHRadjBMI	β = 0.033	2.09×10^{-24}
		91,820	*LYPLAL1*	1	rs4846567 (G)	WHRadjBMI	β = 0.034	6.89×10^{-21}
		92,018	*DNM3-PIGC*	1	rs1011731(G)	WHRadjBMI	β = 0.028	9.51×10^{-18}
		102,189	*LY86*	6	rs1294421 (G)	WHRadjBMI	β = 0.028	1.75×10^{-17}
		112,353	*HOXC13*	12	rs1443512 (A)	WHRadjBMI	β = 0.031	6.38×10^{-17}
		84,480	*ADAMTS9*	3	rs6795735 (C)	WHRadjBMI	β = 0.025	9.79×10^{-14}
		107,503	*ITPR2-SSPN*	12	rs718314 (G)	WHRadjBMI	β = 0.030	1.14×10^{-17}
		85,722	*CPEB4*	5	rs6861681 (A)	WHRadjBMI	β = 0.022	1.91×10^{-9}
		109,028	*NISCH-STAB1*	3	rs6784615 (T)	WHRadjBMI	β = 0.043	3.84×10^{-10}
		93,911	*ZNRF3-KREMEN1*	22	rs4823006 (A)	WHRadjBMI	β = 0.023	1.10×10^{-11}
Wang *et al.* (2011)	NonHispanic Caucasians	1060	*NRXN3*	14	rs11624704	WHR	–	2.67×10^{-9}
Croteau-Chonka *et al.* (2011)	Philippines	1792 adult women	*KCNE4*	9	rs1440072 (C)	WC	–	7.87×10^{-7}
Kilpeläinen *et al.* (2011)	Europeans and Indian Asians	76,150	*IRS1*	2	rs2943650 (T)	BF%	β = −0.16	3.8×10^{-11}
		70,831	*SPRY2*	13	rs534870 (A)	BF%	β = *−0.14*	6.5×10^{-8}
		70,642	*FTO*	16	rs8050136 (C)	BF%	β = −0.33	2.7×10^{-26}
Fox *et al.* (2012a)	European	4997/5560	*LYPLAL1*	1	rs11118316 (A)	VAT/SAT ratio	–	3.13×10^{-9}
		In women	*THNSL2*	2	rs1659258 (A)	VAT	–	1.58×10^{-8}
Liu *et al.* (2013)	African	33591	*LHX2*	9	rs2075064 (C)	WC	β = -0.07 (0.01)	2.24×10^{-8}
		27350	*RREB1*	13	rs6931262 (C)	WHR	β = 0.06 (0.01)	2.48×10^{-8}
Urbanek *et al.* (2013)	European	4281 newborns	*LEKR1/CCNL1*	3	rs17451107 (T)	Sum of skinfolds	–	1.90×10^{-13}
Randall *et al.* (2013)	European	98,321	*GRB14/COBLL1*	2	rs6717858 (T)	WHRadjBMI	–	1.99×10^{-29}
		98,352	*LYPLAL1/SL30A10*	1	rs2820443 (T)	WHRadjBMI	–	4.62×10^{-37}
		97,269	*VEGFA*	6	rs1358980 (T)	WHRadjBMI	–	2.41×10^{-31}
		95,325	*ADAMTS9*	3	rs2371767 (G)	WHRadjBMI	–	7.07×10^{-23}
		73,066	*HSD17B4*	5	rs10478424 (A)	WHRadjBMI	–	3.45×10^{-9}
		96,472	*PPARG*	3	rs4684854 (C)	WHRadjBMI	–	4.17×10^{-14}
		107,403	*MAP3K1*	5	rs11743303 (G)	WHRadjBMI	–	2.69×10^{-11}

Table 3 (*contd*)

Author (year)	Population	Sample size total (M/F)/ range	Gene	Chr	SNP studied (EA)	Phenotype	Effect size (S.E.)	*P* value
Plourde *et al.* (2013)	European	926	*LRRFIP1*	2	rs3769053 (C)	TAT	$\beta = 0.402$	1.1×10^{-4}
						VAT	$\beta = 0.321$	3.7×10^{-4}
					rs11680012 (C)	BF%	$\beta = 0.388$	2.7×10^{-4}
						TAT	$\beta = 0.581$	3.8×10^{-6}
						SAT	$\beta = 0.537$	1.6×10^{-5}
						VAT	$\beta = 0.450$	3.5×10^{-5}
					rs3806505 (G)	TAT	$\beta = 0.398$	1.7×10^{-4}
						VAT	$\beta = 0.329$	3.4×10^{-4}
Yoneyama *et al.* (2014)	European	48,549	*TMCC1*	3	rs2811337 (G)	WHR	$\beta = 0.048$ (0.008)	7.7×10^{-9}
		48,548	*HOXC10*	12	rs7302703 (G)	WHR	$\beta = 0.044$ (0.008)	2.9×10^{-7}
		35,827	*PEMT*	17	rs936108 (C)	WHR	$\beta = 0.035$ (0.007)	1.9×10^{-6}
		13,532 Females	*SHC1*	1	rs12076073 (A)	WHR	$\beta = 0.10$ (0.02)	1.9×10^{-6}
		15,207 Females	*ATBDB4*	15	rs1037575 (A)	WHR	$\beta = 0.046$ (0.01)	2.2×10^{-6}
Gao *et al.* (2015)	Hispanic-American	1257	*IDH1*	2	rs34218846 (T)	WC	$\beta = -0.080$ (0.010)	1.62×10^{-8}
		1034	*ZGRF1*	4	rs1471880 (C)	WHR	$\beta = -0.027$ (0.0047)	1.00×10^{-8}
					rs13144672 (C)	WHR	$\beta = -0.027$ (0.0047)	3.15×10^{-8}
					rs12054518 (A)	WHR	$\beta = 0.027$ (0.0048)	3.23×10^{-8}
					rs7696816 (C)	WHR	$\beta = 0.027$ (0.0048)	4.35×10^{-8}
Shungin *et al.* (2015)	European	207,867	*DCST2*	1	rs905938 (T)	WHRadjBMI	$\beta = 0.025$	7.3×10^{-10}
		181,049	*GORAB*	1	rs10919388 (C)	WHRadjBMI	$\beta = 0.024$	3.2×10^{-9}
		206,619	*MEIS1*	2	rs1385167 (G)	WHRadjBMI	$\beta = 0.029$	1.9×10^{-9}
		209,906	*CALCRL*	2	rs1569135 (A)	WHRadjBMI	$\beta = 0.021$	5.6×10^{-10}
		209,921	*PLXND1*	3	rs10804591 (A)	WHRadjBMI	$\beta = 0.025$	6.6×10^{-9}
		207,795	*LEKR1*	3	rs17451107 (T)	WHRadjBMI	$\beta = 0.026$	1.1×10^{-12}
		209,218	*NMU*	4	rs3805389 (A)	WHRadjBMI	$\beta = 0.012$	1.5×10^{-3}
		209,925	*FAM13A*	4	rs9991328 (T)	WHRadjBMI	$\beta = 0.019$	4.5×10^{-8}
		209,941	*SPATA5FGF2*	4	rs303084 (A)	WHRadjBMI	$\beta = 0.023$	3.9×10^{-8}
		208,181	*MAP3K1*	5	rs9687846 (A)	WHRadjBMI	$\beta = 0.024$	7.1×10^{-8}
		178,874	*FGFR4*	5	rs6556301 (T)	WHRadjBMI	$\beta = 0.022$	2.6×10^{-8}
		208,263	*BTNL2*	6	rs7759742 (A)	WHRadjBMI	$\beta = 0.023$	4.4×10^{-11}
		177,879	*HMGA1*	6	rs1776897 (G)	WHRadjBMI	$\beta = 0.030$	1.1×10^{-5}
		195,215	*HOXA11*	7	rs7801581 (T)	WHRadjBMI	$\beta = 0{,}027$	3.7×10^{-10}
		209,766	*NKX2-6*	8	rs7830933 (A)	WHRadjBMI	$\beta = 0.022$	7.4×10^{-8}
		203,826	*MSC*	8	rs12679556 (G)	WHRadjBMI	$\beta = 0.027$	2.1×10^{-11}
		209,941	*ABCA1*	9	rs10991437 (A)	WHRadjBMI	$\beta = 0.031$	1.0×10^{-8}
		209,642	*SFXN2*	10	rs7917772 (A)	WHRadjBMI	$\beta = 0.014$	5.6×10^{-5}
		209,807	*CCDC92*	12	rs4765219 (C)	WHRadjBMI	$\beta = 0.028$	1.6×10^{-15}
		208,255	*KLF13*	15	rs8042543 (C)	WHRadjBMI	$\beta = 0.026$	1.2×10^{-9}
		208,374	*RFX7*	15	rs8030605 (A)	WHRadjBMI	$\beta = 0.030$	8.8×10^{-9}
		207,447	*SMAD6*	15	rs1440372 (C)	WHRadjBMI	$\beta = 0.024$	1.1×10^{-10}
		198,072	*MACROD1VEGFB*	11	rs11231693 (A)	WHRadjBMI	$\beta = 0.041$	2.7×10^{-11}
		207,828	*CMIP*	16	rs2925979 (T)	WHRadjBMI	$\beta = 0.018$	1.2×10^{-6}
		198,196	*PEMT*	17	rs4646404 (G)	WHRadjBMI	$\beta = 0.027$	1.4×10^{-11}
		169,793	*BCL2*	18	rs12454712 (T)	WHRadjBMI	$\beta = 0.016$	1.0×10^{-4}
		209,990	*JUND*	19	rs12608504 (A)	WHRadjBMI	$\beta = 0.022$	8.0×10^{-10}
		209,977	*KCNJ2*	17	rs8066985 (A)	WHRadjBMI	$\beta = 0.018$	1.4×10^{-7}

Table 3 (*contd*)

Author (year)	Population	Sample size total (M/F)/ range	Gene	Chr	SNP studied (EA)	Phenotype	Effect size (S.E.)	*P* value
Shungin *et al.* (2015)	European	207,418	*CEBPA*	19	rs4081724 (G)	WHRadjBMI	$\beta = 0.035$	7.4×10^{-12}
		209,941	*BMP2*	20	rs979012 (T)	WHRadjBMI	$\beta = 0.027$	3.3×10^{-14}
		208,025	*GDF5*	20	rs224333 (G)	WHRadjBMI	$\beta = 0.020$	2.6×10^{-8}
		209,435	*EYA2*	20	rs6090583 (A)	WHRadjBMI	$\beta = 0.022$	6.2×10^{-11}
		209, 808	*TBX15-WARS2*	1	rs2645294 (T)	WHRadjBMI	$\beta = 0.031$	1.7×10^{-19}
		203,401	*DNM3-PIGC*	1	rs714515 (G)	WHRadjBMI	$\beta = 0.027$	4.4×10^{-15}
		209,975	*LYPLAL1*	1	rs2820443 (T)	WHRadjBMI	$\beta = 0.035$	5.3×10^{-21}
		209,395	*GRB14-COBLL1*	2	rs10195252 (T)	WHRadjBMI	$\beta = 0.027$	5.9×10^{-15}
		208,809	*PPARG*	3	rs17819328 (G)	WHRadjBMI	$\beta = 0.021$	2.4×10^{-9}
		208,901	*PBRM1*	3	rs2276824 (C)	WHRadjBMI	$\beta = 0.024$	3.2×10^{-11}
		194,506	*ADAMTS9*	3	rs2371767 (G)	WHRadjBMI	$\beta = 0.036$	1.6×10^{-20}
		209,710	*TNFAIP8-HSD17B4*	5	rs1045241 (C)	WHRadjBMI	$\beta = 0.019$	4.4×10^{-7}
		209,827	*CPEB4*	5	rs7705502 (A)	WHRadjBMI	$\beta = 0.027$	4.7×10^{-14}
		209,830	*LY86*	6	rs1294410 (C)	WHRadjBMI	$\beta = 0.031$	2.0×10^{-18}
		206,862	*VEGFA*	6	rs1358980 (T)	WHRadjBMI	$\beta = 0.039$	3.1×10^{-27}
		209,859	*RSPO3*	6	rs1936805 (T)	WHRadjBMI	$\beta = 0.043$	3.6×10^{-35}
		210,008	*NFE2L3*	7	rs10245353 (A)	WHRadjBMI	$\beta = 0.035$	8.4×10^{-16}
		210,023	*ITPR2-SSPN*	12	rs10842707 (T)	WHRadjBMI	$\beta = 0.032$	4.4×10^{-16}
		209,980	*HOXC13*	12	rs1443512 (A)	WHRadjBMI	$\beta = 0.028$	6.9×10^{-13}
		209,454	*ZNRF3*	22	rs2294239 (A)	WHRadjBMI	$\beta = 0.025$	7.2×10^{-13}
		140,515	*OR2W5-NLRP3*	1	rs10925060 (T)	WCadjBMI	$\beta = 0.017$	2.2×10^{-5}
		231,284	*ITGB6*	2	rs2124969 (C)	WCadjBMI	$\beta = 0.020$	7.1×10^{-9}
		217,564	*CCNJL*	5	rs17472426 (T)	WCadjBMI	$\beta = 0.014$	3.1×10^{-2}
		63,892	*KIAA1731*	11	rs1784203 (A)	WCadjBMI	$\beta = 0.031$	1.3×10^{-8}
		231,009	*ZNF423*	16	rs2047937 (C)	WCadjBMI	$\beta = 0.019$	4.7×10^{-8}
		210,935	*KLF14*	7	rs13241538 (C)	HIPadjBMI	$\beta = 0.017$	1.6×10^{-6}
		210,737	*VPS53*	17	rs2034088 (T)	HIPadjBMI	$\beta = 0.021$	4.8×10^{-9}
		202,070	*HMGXB4*	22	rs1053593 (T)	HIPadjBMI	$\beta = 0.021$	3.9×10^{-8}
		131,877	*KLHL31*	6	rs7739232 (A)	HIPadjBMI	$\beta = 0.037$	5.4×10^{-5}
		207,648	*SOX11*	2	rs10929925 (C)	HIP	$\beta = 0.020$	4.5×10^{-8}
		143,412	*C5*	9	rs7044106 (C)	HIPadjBMI	$\beta = 0.023$	4.1×10^{-5}
		212,815	*MYEOV*	11	rs11607976 (C)	HIP	$\beta = 0.022$	4.2×10^{-8}
		144,349	*CNTN5*	11	rs1394461 (C)	WHR	$\beta = 0.017$	4.7×10^{-4}
		212,137	*GPC6*	13	rs319564 (C)	WHR	$\beta = 0.014$	3.4×10^{-5}
	European, east Asian, south Asian and African-American ancestry	244,110	*ARL15*	5	rs1664789 (C)	WCadjBMI	$\beta = 0.014$	2.6×10^{-5}
		239,342	*SRPK2*	7	rs1144 (C)	WCadjBMI	$\beta = 0.019$	3.1×10^{-8}
		205,815	*GMDS*	6	rs722585 (G)	HIPadjBMI	$\beta = 0.015$	2.1×10^{-4}
		226,572	*PTPDC1*	9	rs2398893 (A)	WHR	$\beta = 0.020$	4.0×10^{-8}
		212,501	*SNX10*	7	rs1534696 (C)	WHRadjBMI	$\beta = 0.011$	1.3×10^{-3}
		227,296	*PDXDC1*	16	rs4985155 (A)	HIP	$\beta = 0.018$	4.5×10^{-7}
Lu *et al.* (2016)	European ancestry, South Asian ancestry, East Asian ancestry, African Americans	80,196	*COBLL1/ GRB14*	2	rs6738627 (A)	BF%	$\beta = 0.030$ (0.005)	5.7×10^{-9}
		74,338	*IGF2BP1*	17	rs9906944 (C)	BF%	$\beta = 0.033$ (0.006)	2.9×10^{-8}
		51,687 Men	*PLA2G6*	22	rs3761445 (G)	BF%	$\beta = 0.037$ (0.0063)	2.5×10^{-9}
		47,986 Women	*CRTC1*	19	rs757318 (C)	BF%	$\beta = 0.037$ (0.0067)	4.8×10^{-8}
		99,328	*FTO*	16	rs1558902 (A)	BF%	$\beta = 0.051$ (0.005)	3.8×10^{-27}
		99,323	*IRS1*	2	rs2943652 (C)	BF%	$\beta = 0.034$ (0.005)	1.5×10^{-12}
		100,642	*MC4R*	18	rs6567160 (C)	BF%	$\beta = 0.034$ (0.005)	1.3×10^{-10}
		99,855	*TMEM18*	2	rs6755502 (C)	BF%	$\beta = 0.039$ (0.006)	1.4×10^{-10}
		100,190	*SPRY2*	13	rs693839 (C)	BF%	$\beta = 0.028$ (0.005)	6.6×10^{-9}
		68,857	*TOMM40*	19	rs6857 (C)	BF%	$\beta = 0.048$ (0.008)	6.6×10^{-9}
		100,659	*TUFM*	16	rs4788099 (G)	BF%	$\beta = 0.027$ (0.005)	1.2×10^{-8}
		100,705	*SEC16B*	1	rs543874 (G)	BF%	$\beta = 0.032$ (0.006)	4.5×10^{-8}

Table 3 (*contd*)

Author (year)	Population	Sample size total (M/F)/ range	Gene	Chr	SNP studied (EA)	Phenotype	Effect size (S.E.)	*P* value
Wen *et al.* (2016)	East Asian ancestry	64,454	*EFEMP1*	2	rs3791679 (A)	WCadjBMI	β = 2.87 (0.38)	4.86×10^{-14}
		49,519	*HLA-DRB5*	6	rs5020946 (T)	WHRadjBMI	β = 3.15 (0.52)	1.30×10^{-9}
		60,909	*CEP120*	5	rs10051787 (T)	WCnoBMI	β = 3.96 (0.58)	7.2×10^{-12}
		36,247	*TSC22D2*	3	rs1868673 (C)	WCnoBMI	β = 4.36 (0.77)	1.49×10^{-8}
		62,430	*SLC22A2*	6	rs368123 (G)	WCnoBMI	β = 3.16 (0.57)	2.64×10^{-8}
		50,668	*ADAMTSL3*	15	rs8030379 (A)	WCadjBMI	β = 2.46 (0.41)	1.62×10^{-9}
		30,368	*CNPY2*	12	rs3809128 (C)	WCadjBMI	β = 3.69 (0.63)	3.74×10^{-9}
		38,613	*GNAS*	20	rs2057291 (G)	WCadjBMI	β = 2.52 (0.46)	4.02×10^{-8}
		56,208	*NID2*	14	rs1982963 (A)	WHRadjBMI	β = 4.82 (0.62)	1.07×10^{-14}
Ng *et al.* (2017)	African ancestry	23,095	*TCF7L2/HABP2*	10	rs116718588 (A)	WHRadjBMI	β = 0.134 (0.024)	3.22×10^{-8}
		12,148 (women)	*SSX2IP*	1	rs140858719 (G)	WHRadjBMI	β = 0.502 (0.091)	3.69×10^{-8}
		17,331 (women)	*PDE3B*	11	rs185693786 (G)	WHRadjBMI	β = 0.125 (0.023)	2.98×10^{-8}
	African and European ancestry	102,655 (women)	*CASC8*	8	rs378854 (C)	WHRadjBMI	–	3.26×10^{-8}
		103,646 (women)	*ZDHHC1/ HSD11B2*	16	rs6499129 (A)	WHRadjBMI	–	4.84×10^{-8}
		162,962	*SPRYD7/ DLEU2*	13	rs2472591 (T)	WHRadjBMI	–	3.53×10^{-8}
		168,351	*ADAMTS9-AS2*	3	rs2371767 (G)	WHRadjBMI	–	9.13×10^{-27}
Graff *et al.* (2017)	European ancestry	130,413	*ZSCAN2*	15	rs7176527 (C)	WCadjBMI	β = 0.0317 (0.0054)	5.98×10^{-9}
		113,963	*PAPPA2*	1	rs4650943 (A)	WHRadjBMI	β = 0.0267 (0.0048)	2.34×10^{-8}
		110,881	*MEIS1*	2	rs2300481 (T)	WHRadjBMI	β = 0.0267 (0.0048)	2.41×10^{-8}
		46,591 (men)	*ARHGEF28*	5	rs167025 (A)	WHRadjBMI	β = 0.0427 (0.0074)	6.24×10^{-9}
		64,138 (men)	*HCP5*	6	rs3094013 (G)	WHRadjBMI	β = 0.0494 (0.009)	4.51×10^{-8}
		145,913	*BAZ1B*	7	rs6976930 (G)	WHRadjBMI	β = 0.0294 (0.0051)	1.03×10^{-8}
		147,123	*PLCE1*	10	rs10786152 (A)	WHRadjBMI	β = 0.0224 (0.004)	1.79×10^{-8}
		70,315 (women)	*CTRB2*	16	rs889512 (C)	WHRadjBMI	β = 0.0506 (0.0091)	2.87×10^{-8}
Yoneyama *et al.* (2017)	African	Total =15945	*TBX15-WARS2*	1	rs12096179 (G)	WHR	β = 0.0044	2.24×10^{-6}
		In women	*TBX15-WARS2*	1	rs6701378 (A)	WHR	β = 0.0054	3.07×10^{-5}
		In men	*TBX15-WARS2*	1	rs7412918 (G)	WHR	β = 0.0054	2.47×10^{-5}
		Total =15945	*GRB14*	2	rs10195252 (A)	WHR	β = 0.0025	3.69×10^{-6}
		In women	*GRB14*	2	rs6717858 (A)	WHR	β = 0.0071	3.49×10^{-7}
		Total =15945	*ADAMTS9*	3	rs2059092 (A)	WHR	β = 0.0049	5.897×10^{-6}
		In women	*ADAMTS9*	3	rs2059092 (A)	WHR	β = 0.0072	9.98×10^{-8}
		Total =15945	*RSPO3*	6	rs9321069 (G)	WHR	β = 0.0042	1.35×10^{-5}
		In women	*RSPO3*	6	rs9491696 (G)	WHR	β = 0.0053	2.58×10^{-5}
Rask-Andersen *et al.* (2019)	Data taken from UK biobank	362,499	*KRTCAP2*	1	rs4971091	AFR	–	3.62×10^{-11}
			THBS3	1	rs180921974	TFR	–	7.52×10^{-35}
			NSD1	5	rs34022431	AFR	–	1.67×10^{-11}
			VRK2	2	rs13011472	AFR	–	1.17×10^{-11}
			MAP4K5	14	rs71420186	LFR	–	2.47×10^{-18}
			WDR6	3	rs4521268	TFR	–	1.46×10^{-18}
			ASB16	17	rs2071167	LFR	–	1.58×10^{-10}
			RFTN	2	rs148812496	AFR	–	8.07×10^{-11}
			KCNH2	7	rs56282717	AFR	–	3.03×10^{-15}
			BNC2	9	rs10962638	TFR	–	4.50×10^{-10}
			RALGPS1	9	rs3780327	LFR	–	3.40×10^{-13}
			PLCE1	10	rs11289753	AFR	–	1.22×10^{-22}
			AP006621.1	11	rs1138714	AFR	–	6.65×10^{-11}
			ORAOV1	11	rs1789166	AFR	–	4.92×10^{-12}
			FAMBS3	2	rs62107261	AFR	–	1.80×10^{-38}

Table 3. *(contd)*

Author (year)	Population	Sample size total (M/F)/range	Gene	Chr	SNP studied (EA)	Phenotype	Effect size (S.E.)	*P* value
		195,068 (females)	*CPZ*	4	rs2241069	TFR	–	3.97×10^{-13}
			RP11-32D16	5	rs1317415	LFR	–	4.71×10^{-11}
			ERI1	8	rs2044387	AFR	–	1.69×10^{-16}
			XKR6	8	rs12546366	AFR	–	8.23×10^{-14}
			RMI1	9	rs7039458	TFR	–	7.20×10^{-17}
			ADAMTS14	10	rs34821335	TFR	–	2.89×10^{-14}
			TSGA10IP	11	rs71455793	TFR	–	8.29×10^{-12}
			LARP4	12	rs11614785	TFR	–	1.15×10^{-18}
			SMAD3	15	rs35874463	TFR	–	3.10×10^{-21}
			RP11-343B18.2	15	rs8026676	TFR	–	6.37×10^{-14}
			RP11-419C5.2	16	rs80257620	AFR	–	1.79×10^{-17}
			C16ORf3	16	rs10584116	TFR	–	1.20×10^{-12}
			ZNF652	17	rs28394864	TFR	–	3.51×10^{-17}
			ADAMTS10	19	rs62621197	TFR	–	8.33×10^{-46}

AFR, arm fat ratio; β, beta coefficient; Chr, chromosome; EA, effect allele; HC, hip circumference; HIPadjBMI, hip adjusted with body mass index; LFR, leg fat ratio; OR, odds ratio; BF%, body fat percentage; SAT, subcutaneous adipose tissue; S.E, standard error; TFR, trunk fat ratio; TAT, total adipose tissue; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist hip ratio; WHRadjBMI, waist hip ratio adjusted with body mass index; WCadjBMI, waist circumference adjusted with body mass index; WCnoBMI, waist circumference not adjusted for BMI.

HMGA1 (Foti *et al.* 2005) exhibit obesity, glucose intolerance and insulin resistance in mice.

Overlapping signals with BMI

The era of large scale GWAS have identified several loci influencing overall obesity through BMI (Thorleifsson *et al.* 2009; Speliotes *et al.* 2010). The first obesity GWAS identified a strongest association of rs9930506 with BMI ($P = 8.6 \times 10^{-7}$) and HC ($P = 3.4 \times 10^{-8}$) in the first intron of the *FTO* gene among Sardinian population (Scuteri *et al.* 2007). In line with this, a strong and replicated association between variants in *MC4R* and BMI was reported among Asian Sikh and European population (Been *et al.* 2010; Locke *et al.* 2015). The effect of *MC4R* variant was also reported with WC ($P = 1.7 \times 10^{-9}$) among Europeans and Indian Asians living in UK, suggesting the role of *MC4R* loci in mediating susceptibility to obesity by influencing overall body size (Chambers *et al.* 2008). In addition, associations of 12 loci (*NEGR1*, *BDNF*, *SH2B1*, *GNPDA2*, *FAIM2*, *TMEM18*, *ETV5*, *MTCH2*, *KCTD15*, *TFAP2B*, *NRXN3*, *GIPR*) previously established by GWAS for BMI (Thorleifsson *et al.* 2009; Speliotes *et al.* 2010; Wen *et al.* 2014) were found to overlap with WC (Heard-Costa *et al.* 2009; Li *et al.* 2010; Wang *et al.* 2011; Nakayama *et al.* 2014).

Moreover, few other loci (*SEC16B*, *INSIG2*, *GPRC5B*, *PCSK1*, *MTIF3*, *TOMM40*, *TUFM*, *NT5C2*, *IRS1*) associated with BMI (Zhao *et al.* 2009; Speliotes *et al.* 2010; Wen *et al.* 2014; Locke *et al.* 2015), also revealed evidences of their association with BF%, leg fat percentage, subcutaneous fat area and WHR (Talbert *et al.* 2009; Hotta *et al.* 2012; Murphy *et al.* 2013; Zhu *et al.* 2014; Lu *et al.* 2016).

Conclusion

The compilation of genetic studies related to body fat distribution, summarized in our critical review provides a comprehensive update on the current knowledge of genomic basis of body fat distribution among different ethnic groups. Several linkage scans and association studies, as well as many candidate gene studies have yielded numerous loci associated with body fat distribution. Nevertheless, given the high heritability estimates for body fat distribution, only a small proportion of the variance can be explained by the existing knowledge of identified variants associated with body fat distribution. Further, the genetic heterogeneity of variants associated with fat distribution has not been well documented among different ethnic groups. Majority of the GWAS have focussed on samples with European ancestry while gene mapping findings among Asian populations remain rare. Moreover, the use of GWAS has increasingly gained importance for uncovering the genetics of complex traits and diseases. Despite their value, problems to confirm the findings of GWAS are rather common; therefore, there is

a need to validate these discoveries in distinct human populations using appropriate study design and large sample size for further confirmation. This review emphasized not only the need for more genetic studies to explore missing heritability using more accurate methods (DEXA and CT scan) but also dissecting the precise biological functions of these genes in the regulation of body fat, which could be helpful in developing better disease management strategies.

Acknowledgement

The authors would like to acknowledge Science and Engineering Research Board (SB/YS/ LS-173/2014) for financial assistance.

References

Aberg K., Dai F., Sun G., Keighley E. D., Indugula S. R., Roberts S. T. *et al.* 2009 Susceptibility loci for adiposity phenotypes on 8p, 9p, and 16q in American Samoa and Samoa. *Obesity* (Silver Spring) **173**, 518–524.

Acton S., Osgood D., Donoghue M., Corella D., Pocovi M., Cenarro A. *et al.* 1999 Association of polymorphisms at the SR-BI gene locus with plasma lipid levels and body mass index in a white population. *Arterioscler. Thromb. Vasc. Biol.* **19**, 1734–1743.

Asano T., Fujishiro M., Kushiyama A., Nakatsu Y., Yoneda M., Kamata H. *et al.* 2007 Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions. *Biol. Pharm. Bull.* **30**, 1610–1616.

Auwerx J. 1999 PPAR gamma, the ultimate thrifty gene. *Diabetologia* **42**, 1033–1049.

Bauer F., Elbers C. C., Adan R. A., Loos R. J., Onland-Moret N. C., Grobbee D. E. *et al.* 2009 Obesity genes identified in genome-wide association studies are associated with adiposity measures and potentially with nutrient-specific food preference. *Am. J. Clin. Nutr.* **90**, 951–959.

Been L. F., Nath S. K., Ralhan S. K., Wander G. S., Mehra N. K., Singh J. *et al.* 2010 Replication of association between a common variant near melanocortin-4 receptor gene and obesity related traits in Asian Sikhs. *Obesity* (Silver Spring) **18**, 425–429.

Bhatt S. P., Misra A., Sharma M., Luthra K., Guleria R., Pandey R. M. *et al.* 2012 Ala/Ala genotype of Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-γ2 gene is associated with obesity and insulin resistance in Asian Indians. *Diabetes Technol. Ther.* **14**, 828–834.

Bille D. S., Banasik K., Justesen J. M., Sandholt C. H., Sandbæk A., Lauritzen T. *et al.* 2011 Implications of central obesity-related variants in LYPLAL1, NRXN3, MSRA, and TFAP2B on quantitative metabolic traits in adult Danes. *PLoS One* **6**, e20640.

Bjorntorp P. 1991 Metabolic implications of body-fat distribution. *Diabetes Care* **14**, 1132–1143.

Boesgaard T. W., Gjesing A. P., Grarup N., Rutanen J., Jansson P. A., Hribal M. L. *et al.* 2009 Variant near ADAMTS9 known to associate with type 2 diabetes is related to insulin resistance in offspring of type 2 diabetes patients–EUGENE2 study. *PLoS One* **4**, e7236.

Bressler J., Fornage M., Hanis C. L., Kao W. H., Lewis C. E., McPherson R. *et al.* 2009 The INSIG2 rs7566605 genetic variant does not play a major role in obesity in a sample of 24,722 individuals from four cohorts. *BMC Med. Genet.* **10**, 56.

Canoy D. 2008 Distribution of body fat and risk of coronary heart disease in men and women. *Curr. Opin. Cardiol.* **23**, 591–598.

Carey V. J., Walters E. E., Colditz G. A., Solomon C. G., Willett W. C., Rosner B. A. *et al.* 1997 Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am. J. Epidemiol.* **145**, 614–619.

Cassano P. A., Rosner B., Vokonas P. S. and Weiss S. T. 1992 Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. A prospective cohort study of men in the normative aging study. *Am. J. Epidemiol.* **136**, 1474–1486.

Chambers J. C., Elliott P., Zabaneh D., Zhang W., Li Y., Froguel P. *et al.* 2008 Common genetic variation near MC4R is associated with waist circumference and insulin resistance. *Nat. Genet.* **40**, 716–718.

Chen A. S., Marsh D. J., Trumbauer M. E., Frazier E. G., Guan X. M., Yu H. *et al.* 2000 Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. *Nat. Genet.* **26**, 97–102.

Chiu Y. F., Chuang L. M., Kao H. Y., Shih K. C., Lin M. W., Lee W. J. *et al.* 2010 Sex-specific genetic architecture of human fatness in Chinese: the SAPPHIRe Study. *Hum. Genet.* **128**, 501–513.

Cooney G. J., Lyons R. J., Crew A. J., Jensen T. E., Molero J. C., Mitchell C. J. *et al.* 2004 Improved glucose homeostasis and enhanced insulin signalling in Grb14 deficient mice. *EMBO J.* **23**, 582–593.

Croteau-Chonka D. C., Marvelle A. F., Lange E. M., Lee N. R., Adair L. S., Lange L. A. *et al.* 2011 Genome-wide association study of anthropometric traits and evidence of interactions with age and study year in Filipino women. *Obesity* (Silver Spring) **19**, 1019–1027.

den Hoed M., Ekelund U., Brage S., Grontved A., Zhao J. H., Sharp S. J. *et al.* 2010 Genetic susceptibility to obesity and related traits in childhood and adolescence: influence of loci identified by genome-wide association studies. *Diabetes* **59**, 2980–2988.

Dickinson M. E., Kobrin M. S., Silan C. M., Kingsley D. M., Justice M. J., Miller D. A. *et al.* 1990 Chromosomal localization of seven members of the murine TGF-beta superfamily suggests close linkage to several morphogenetic mutant loci. *Genomics* **6**, 505–520.

Do R., Bailey S. D., Desbiens K., Belisle A., Montpetit A., Bouchard C. *et al.* 2008 Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec family study. *Diabetes* **57**, 1147–1150.

Dong C., Beecham A., Slifer S., Wang L., McClendon M. S., Blanton S. H. *et al.* 2011 Genome-wide linkage and peak-wide association study of obesity-related quantitative traits in Caribbean Hispanics. *Hum. Genet.* **129**, 209–219.

Dwivedi O. P., Tabassum R., Chauhan G., Ghosh S., Marwaha R. K., Tandon N. *et al.* 2012 Common variants of FTO are associated with childhood obesity in a cross sectional study of 3,126 urban Indian children. *PLoS One* **7**, e47772.

Edwards D. R., Beaudry P. P., Laing T. D., Kowal V., Leco K. J., Leco P. A. *et al.* 1996 The roles of tissue inhibitors of metalloproteinases in tissue remodelling and cell growth. *Int. J. Obes.* **20**, S9–S15.

Evans D. S., Calton M. A., Kim M. J., Kwok P. Y., Miljkovic I., Harris T. *et al.* 2014 Genetic association study of adiposity and melanocortin-4 receptor (MC4R) common variants: replication and functional characterization of non-coding regions. *PLoS One* **9**, e96805.

Evans J. L., Honer C. M., Womelsdorf B. E., Kaplan E. L. and Bell P. A. 1995 The effects of wortmannin, a potent inhibitor of phosphatidylinositol 3-kinase, on insulin-stimulatedglucose transport, GLUT4 translocation, antilipolysis, and DNA synthesis. *Cell Signal.* **7**, 365–376.

Fawcett K. A. and Barroso I. 2010 The genetics of obesity: FTO leads the way. *Trends Genet.* **26**, 266–274.

Feitosa M. F., North K. E., Myers R. H., Pankow J. S. and Borecki I. B. 2009 Evidence for three novel qtls for adiposity on chromosome 2 with epistatic interactions: the nhlbi family heart study. *Obesity* (Silver Spring) **17**, 2190–2195.

Folsom A. R., Kushi L. H., Anderson K. E., Mink P. J., Olson J. E., Hong C. P. *et al.* 2000 Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch. Intern. Med.* **160**, 2117–2128.

Fong T. M., Mao C., MacNeil T., Kalyani R., Smith T., Weinberg D. *et al.* 1997 ART (protein product of agoutirelated transcript) as an antagonist of MC-3 and MC-4 receptors. *Biochem. Biophys. Res. Commun.* **237**, 629–631.

Foti D., Chiefari E., Fedele M., Iuliano R., Brunetti L., Paonessa F. *et al.* 2005 Lack of the architectural factor HMGA1 causes insulin resistance and diabetes in humans and mice. *Nat. Med.* **11**, 765–773.

Fox C. S., Heard-Costa N. L., Wilson P. W., Levy D., D'Agostino R. B. Sr *et al.* 2004 Genome-wide linkage to chromosome 6 for waist circumference in the framingham heart study. *Diabetes* **53**, 1399–1402.

Fox C. S., Liu Y., White C. C., Feitosa M., Smith A. V., Heard-Costa N. *et al.* 2012a Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. *PLoS Genet.* **8**, e1002695.

Fox C. S., Massaro J. M., Hoffmann U., Pou K. M., Maurovich-Horvat P., Liu C. Y. *et al.* 2007 Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham heart study. *Circulation* **116**, 39–48.

Fox C. S., White C. C., Lohman K., Heard-Costa N., Cohen P., Zhang,Y. *et al.* 2012b Genome-Wide Association of Pericardial Fat Identifies a Unique Locus for Ectopic Fat. *PLoS Genet.* **8**, e1002705.

Gao C., Wang N., Guo X., Ziegler J. T., Taylor K. D., Xiang A. H. *et al.* 2015 A Comprehensive analysis of common and rare variants to identify adiposity loci in Hispanic Americans: the IRAS family study (IRASFS). *PLoS One* **10**, e0134649.

Gesta S., Blüher M., Yamamoto Y., Norris A. W., Berndt J., Kralisch S. *et al.* 2006 Evidence for a role of developmental genes in the origin of obesity and body fat distribution. *Proc. Natl. Acad. Sci. USA* **103**, 6676–6681.

Gesta S., Tseng Y. H. and Kahn C. R. 2007 Developmental origin of fat: tracking obesity to its source. *Cell* **131**, 242–256.

Gilep A. A., Sushko T. A. and Usanov S. A. 2011 At the crossroads of steroid hormone biosynthesis: the role, substrate specificity and evolutionary development of CYP17. *Biochim. Biophys. Acta.* **1814**, 200–209.

González-Sánchez J. L., Zabena C., Martínez-Larrad M. T., Martínez-Calatrava M. J., Pérez-Barba M. and Serrano-Ríos M. 2009 Variant rs9939609 in the FTO gene is associated with obesity in an adult population from Spain. *Clin. Endocrinol.* **70**, 390–393.

Graff M., Scott R. A., Justice A. E., Young K. L., Feitosa M. F., Barata L. *et al.* 2017 Correction: Genome-wide physical activity interactions in adiposity - A meta-analysis of 200,452 adults. *PLoS Genet.* **13**, e1006972.

Gragnoli C. 2013 Overweight condition and waist circumference and a candidate gene within the 12q24 locus. *Cardiovasc. Diabetol*. **12**, 2.

Gupta A., Gupta V., Singh A. K., Tiwari S., Agrawal S., Natu S. M. *et al.* 2011 Interleukin-6 G-174C gene polymorphism and serum resistin levels in North Indian women: potential risk of metabolic syndrome. *Hum. Exp. Toxicol.* **30**, 1445–1453.

Gupta V., Vinay D. G., Sovio U., Rafiq S., Kranthi Kumar M. V., Janipalli C. S. *et al.* 2013 Association study of 25 type 2 diabetes related loci with measures of obesity in Indian sib pairs. *PLoS One* **8**, e53944.

Hanada R., Teranishi H., Pearson J. T., Kurokawa M., Hosoda H., Fukushima N. *et al.* 2004 Neuromedin U has a novel anorexigenic effect independent of the leptin signalling pathway. *Nat. Med.* **10**, 1067–1073.

Hardy D. S., Stallings D. T., Garvin J. T., Xu H. and Racette S. B. 2017 Best anthropometric discriminators of incident type 2 diabetes among white and black adults: A longitudinal ARIC study. *PLoS One* **12**, e0168282.

Harvey N. L., Srinivasan R. S., Dillard M. E., Johnson N. C., Witte M. H., Boyd K. *et al.* 2005 Lymphatic vascular defects promoted by Prox1 haploinsufficiency cause adult-onset obesity. *Mech. Dev.* **122**, S77–S77.

Haupt A., Thamer C., Heni M., Machicao F., Machann J., Schick F. *et al.* 2010 Novel obesity risk loci do not determine distribution of body fat depots: a whole-body MRI/MRS study. *Obesity* (Silver Spring) **18**, 1212–1217.

Heard-Costa N. L., Zillikens M. C., Monda K. L., Johansson A., Harris T. B., Fu M. *et al.* 2009 NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE consortium. *PLoS Genet.* **5**, e1000539.

Heid I. M., Jackson A. U., Randall J. C., Winkler T. W., Qi L., Steinthorsdottir V. *et al.* 2010 Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat. Genet.* **42**, 949–960.

Hinney A., Vogel C. I. and Hebebrand J. 2010 From monogenic to polygenic obesity: recent advances. *Eur. Child Adolesc. Psychiatry.* **19**, 297–310.

Holm C., Kirchgessner T. G., Svenson K. L., Fredrikson G., Nilsson S., Miller C. G. *et al.* 1988 Hormone-sensitive lipase: sequence, expression, and chromosomal localization to 19cent-q13.3. *Science* **241**, 1503–1506.

Hotamisligil G. S., Shargill N. S. and Spiegelman B. M. 1993 Adipose expression of tumor necrosis factor - alpha: direct role in obesity-linked insulin resistance. *Science* **259**, 87–91.

Hotta K., Kitamoto A., Kitamoto T., Mizusawa S., Teranishi H., Matsuo T. *et al.* 2012 Genetic variations in the CYP17A1 and NT5C2 genes are associated with a reduction in visceral and subcutaneous fat areas in Japanese women. *J. Hum. Genet.* **57**, 46–51.

Hotta K., Kitamoto T., Kitamoto A., Mizusawa S., Matsuo T., Nakata Y. *et al.* 2011 Computed tomography analysis of the association between the SH2B1 rs7498665 single-nucleotide polymorphism and visceral fat area. *J. Hum. Genet.* **56**, 716–719.

Hsueh W. C., Mitchell B. D., Schneider J. L., St Jean P. L., Pollin T. I., Ehm M. G. *et al.* 2001 Genome-wide scan of obesity in the old order amish. *J. Clin. Endocrinol. Metab.* **86**, 1199–1205.

Huang X., Yang C., Luo Y., Jin C., Wang F. and McKeehan W. L. 2007 FGFR4 prevents hyperlipidemia and insulin resistance but underlies high-fat diet induced fatty liver. *Diabetes* **56**, 2501–2510.

Huszar D., Lynch C. A., Fairchild-Huntress V., Dunmore J. H., Fang Q., Berkemeier L. R. *et al.* 1997 Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* **88**, 131–141.

Ikeda K., Maegawa H., Ugi S., Tao Y., Nishio Y., Tsukada S. *et al.* 2006. Transcription factor activating enhancer-binding protein-2beta. A negative regulator of adiponectin gene expression. *J. Biol. Chem.* **281**, 31245–31253.

Jones J. R., Barrick C., Kim K. A., Lindner J., Blondeau B., Fujimoto Y. *et al.* 2005 Deletion of PPARγ in adipose tissues of mice protects against high fat diet-induced obesity and insulin resistance. *Proc. Natl. Acad. Sci USA***102**, 6207–6212.

Kilpeläinen T. O., Zillikens M. C., Stančákova A., Finucane F. M., Ried J. S., Langenberg C. *et al.* 2011 Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. *Nat. Genet.* **43**, 753–760.

Kim H. J., Yoo Y. J., Ju Y. S., Lee S., Cho S. I., Sung J. *et al.* 2013 Combined linkage and association analyses identify a novel locus for obesity near PROX1 in Asians. *Obesity* (Silver Spring) **21**, 2405–12.

Kissebah A. H. 1997 Central obesity: measurement and metabolic effects. *Diabetes Rev.* **5**, 8–20.

Klimentidis Y. C., Chen G. B., López-Alarcón M., Harris J. J., Duarte C. W. and Fernández J. R. 2011 Associations of obesity genes with obesity-related outcomes in multiethnic children. *Arch. Med. Res.* **42**, 509–514.

Lanctôt C., Kaspar C. and Cremer T. 2007 Positioning of the mouse Hox gene clusters in the nuclei of developing embryos and differentiating embryoid bodies. *Exp. Cell Res*. **313**, 1449–1459.

Lee J. H., Reed D. R., Li W. D., Xu W., Joo E. J., Kilker R. L. *et al.* 1999 Genome scan for human obesity and linkage to markers in 20q13. *Am. J. Hum. Genet.* **64**, 196–209.

Lee J. J., Pedley A., Therkelsen K. E., Hoffmann U., Massaro J. M., Levy D. *et al.* 2017 Upper body subcutaneous fat is associated with cardiometabolic risk factors. *Am. J. Med.* **130**, 958–966.e1.

Li S., Zhao J. H., Luan J., Luben R. N., Rodwell S. A., Khaw K. T. *et al.* 2010 Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. *Am. J. Clin. Nutr.* **91**, 184–190.

Li W. D., Reed D. R., Lee J. H., Xu W., Kilker R. L., Sodam B. R. *et al.* 1999 Sequence variants in the 5' flanking region of the leptin gene are associated with obesity in women. *Ann. Hum. Genet.* **63**, 227–234.

Lindgren C. M., Heid I. M., Randall J. C., Lamina C., Steinthorsdottir V. and Qi L. 2009 Genome-wide associations can meta-analysis identifies three loci influencing adiposity and fat distribution. *PLoS Genet.* **5**, e1000508.

Liu A. Y., Gu D., Hixson J. E., Rao D. C., Shimmin L. C., Jaquish C. E. *et al.* 2014 Genome-wide linkage and regional association study of obesity-related phenotypes: the gensalt study. *Obesity* (Silver Spring) **22**, 545–556.

Liu C. T., Monda K. L., Taylor K. C., Lange L., Demerath E. W., Palmas W. *et al.* 2013 Genome-wide association of body fat distribution in african ancestry populations suggests new loci. *PLoS Genet.* **9**, e1003681.

Liu G., Zhu H., Lagou V., Gutin B., Barbeau P., Treiber F. A. *et al.* 2010b Common variants near MC4R are associated with general and visceral adiposity in European- and African-American Youth. *J. Pediatr.* **156**, 598–605.

Liu G., Zhu H., Lagou V., Gutin B., Stallmann-Jorgensen I. S., Treiber F. A. *et al.* 2010a FTO variant rs9939609 is associated with body mass index and waist circumference, but not with energy intake or physical activity in European- and African-American youth. *BMC Med. Genet.* **11**, 57.

Locke A. E., Kahali B., Berndt S. I., Justice A. E., Pers T. H., Day F. R. *et al.* 2015 Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197–206.

Lu D., Willard D., Patel I. R., Kadwell S., Overton L., Kost T. *et al.* 1994 Agouti protein is an antagonist of the melanocyte-stimulating hormone receptor. *Nature* **371**, 799–802.

Lu Y., Day F. R., Gustafsson S., Buchkovich M. L., Na J., Bataille V. *et al.* 2016 New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. *Nat. Commun.* **7**, 10495.

Manolio T. A. 2010 Genomewide association studies and assessment of the risk of disease. *N. Engl. J. Med*. **363**, 166–176.

Marvelle A. F., Lange L. A., Qin L., Adair L. S. and Mohlke K. L. 2008 Association of FTO with obesity-related traits in the cebu longitudinal health and nutrition survey (CLHNS) cohort. *Diabetes* **57**, 1987–1991.

McCarthy M. I., Abecasis G. R., Cardon L. R., Goldstein D. B., Little J., Ioannidis J. P. *et al.* 2008 Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat. Rev. Genet.* **9**, 356–369.

Mooijaart S. P., Berbée J. F., van Heemst D., Havekes L. M., de Craen A. J., Slagboom P. E. *et al.* 2006 ApoE plasma levels and risk of cardiovascular mortality in old age. *PLoS Med.* **3**, e176.

Moore S. C., Gunter M. J., Daniel C. R., Reddy K. S., George P. S., Yurgalevitch S. *et al.* 2012 Common genetic variants and central adiposity among Asian-Indians. *Obesity* (Silver Spring) **20**, 1902–1908.

Mori Y., Kim-Motoyama H., Ito Y., Katakura T., Yasuda K. and Ishiyama-Shigemoto S. 1999 The Gln27Glu beta2adrenergic receptor variant is associated with obesity due to subcutaneous fat accumulation in Japanese men. *Biochem. Biophys. Res. Comm.* **258**, 138–140.

Murphy R. A., Nalls M. A., Keller M., Garcia M., Kritchevsky S. B., Tylavsky F. A. *et al.* 2013 Candidate gene association study of BMI-related loci, weight, and adiposity in old age. *J. Gerontol. A. Biol. Sci. Med. Sci.* **68**, 661–666.

Nakayama K., Watanabe K., Boonvisut S., Makishima S., Miyashita H. and Iwamoto S. 2014 Common variants of GIP are associated with visceral fat accumulation in Japanese adults. *Am. J. Physiol. Gastrointest. Liver. Physiol.* **307**, G1108–G1114.

Nishimura S., Manabe I., Nagasaki M., Hosoya Y., Yamashita H., Fujita H. *et al.* 2007 Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells, and blood vessels. *Diabetes* **56**, 1517–1526.

Nelson T. L., Brandon D. T., Wiggins S. A. and Whitfield K. E. 2002 Genetic and environmental influences on body-fat measures among African-American twins. *Obes. Res.* **10**, 733–739.

Nelson T. L., Vogler G. P., Pedersen N. L. and Miles T. P. 1999 Genetic and environmental influences on waist-to-hip ratio and waist circumference in an older Swedish twin population. *Int. J. Obes. Relat. Metab. Disord.* **23**, 449–455.

Ng M., Graff M., Lu Y., Justice A. E., Mudgal P., Liu C. T. *et al.* 2017 Discovery and fine-mapping of adiposity loci using high density imputation of genomewide association studies in individuals of African ancestry: African Ancestry Anthropometry Genetics Consortium. *PLoS Genet.* **13**, e1006719.

Norman R. A., Tataranni P. A., Pratley R., Thompson D. B., Hanson R. L., Prochazka M. *et al.* 1998 Autosomal genomic scan for loci linked to obesity and energy metabolism in Pima Indians. *Am. J. Hum. Genet.* **62**, 659–668.

Norris J. M., Langefeld C. D., Scherzinger A. L., Rich S. S., Bookman E., Beck S. R. *et al.* 2005 Quantitative trait loci for abdominal fat and BMI in Hispanic-Americans and African-Americans: the IRAS Family Study. *Int. J. Obes. (Lond).* **29**, 67–77.

Norris J. M., Langefeld C. D., Talbert M. E., Wing M. R., Haritunians T., Fingerlin T. E. *et al.* 2009 Genome wide association study and follow-up analysis of adiposity traits in Hispanic-Americans: the IRAS family study. *Obesity* (Silver Spring) **17**, 1932–1941.

Parikh H. and Groop L. 2004 Candidate genes for type 2 diabetes. *Rev. Endocr. Metab. Disord.* **5**, 151–176.

Passaro A., Dalla Nora E., Marcello C., Di Vece F., Morieri M. L., Sanz J. M. *et al.* 2011 PPARγ Pro12Ala and ACE ID polymorphisms are associated with BMI and fat distribution, but not metabolic syndrome. *Cardiovasc. Diabetol.* **10**, 112.

Pausova Z., Syme C., Abrahamowicz M., Xiao Y., Leonard G. T., Perron M. *et al.* 2009 A common variant of the FTO gene is associated with not only increased adiposity but also elevated blood pressure in French Canadians. *Circ. Cardiovasc. Genet.* **2**, 260–269.

Peeters A. V., Beckers S., Verrijken A., Mertens I., Roevens P., Peeters P. J. *et al.* 2008 Association of SIRT1 gene variation with visceral obesity. *Hum. Genet.* **124**, 431–436.

Pérusse L., Després J. P., Lemieux S., Rice T., Rao D. C. and Bouchard C. 1996 Familial aggregation of abdominal visceral fat level: results from the Quebec family study. *Metabolism* **45**, 378–382.

Pérusse L., Rice T., Chagnon Y. C., Després J. P., Lemieux S., Roy S. *et al.* 2001 A genome-wide scan for abdominal fat assessed by computed tomography in the Quebec family study. *Diabetes* **50**, 614–621.

Plourde M., Vohl M. C., Bellis C., Carless M., Dyer T., Dolley G. *et al.* 2013 A variant in the LRRFIP1 gene is associated with adiposity and inflammation. *Obesity* (Silver Spring) **21**, 185–192.

Polasek O., Marusić A., Rotim K., Hayward C., Vitart V., Huffman J. *et al.* 2009 Genome-wide association study of anthropometric traits in Korčula island, Croatia. *Croat. Med. J.* **50**, 7–16.

Pulit S. L., Karaderi T. and Lindgren C. M. 2017 Sexual dimorphisms in genetic loci linked to body fat distribution. *Biosci. Rep.* **37**, BSR20160184.

Pulit S. L., Stoneman C., Morris A. P., Wood A. R., Glastonbury C. A., Tyrrell J. *et al.* 2019 Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum. Mol. Genet*. **28**, 166–174.

Radha V., Vimaleswaran K. S., Ayyappa K. A. and Mohan V. 2007 Association of lipoprotein lipase gene polymorphisms with obesity and type 2 diabetes in an Asian Indian population. *Int. J. Obes.* **31**, 913–918.

Randall J. C., Winkler T. W., Kutalik Z., Berndt S. I., Jackson A. U., Monda K. L. *et al.* 2013 Sex-stratified genome-wide association studies including 270,000 individuals show sexual dimorphism in genetic loci for anthropometric traits. *PLoS Genet.* **9**, e1003500.

Rask-Andersen M., Karlsson T., Ek W. E. and Johansson Å. 2019 Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. *Nat. Commun.* **10**, 339.

Rice T., Chagnon Y. C., Pérusse L., Borecki I. B., Ukkola O., Rankinen T. *et al.* 2002 A genomewide linkage scan for abdominal subcutaneous and visceral fat in black and white families. The HERITAGE Family Study. *Diabetes* **51**, 848–855.

Rodríguez V. M., Macarulla M. T., Chávarri M. and Portillo M. P. 2002 Role of uncoupling proteins in obesity. *An. Sist. Sanit. Navar.* **25**, 65–77.

Rose K. M., Newman B., Mayer-Davis E. J. and Selby J. V. 1998 Genetic and behavioral determinants of waist-hip ratio and waist circumference in women twins. *Obes. Res.* **6**, 383–392.

Scuteri A., Sanna S., Chen W. M., Uda M., Albai G., Strait J. *et al.* 2007 Genome-wide association scan shows genetic variants in the fto gene are associated with obesity-related traits. *PLoS Genet.* **3**, e115.

Selby J. V., Newman B., Quesenberry C. P., Jr Fabsitz R. R., Carmelli D. and Meaney F. J. 1990 Genetic and behavioral influences on body fat distribution. *Int. J. Obes.* **14**, 593–602.

Shintani M., Ikegami H., Yamato E., Kawaguchi Y., Fujisawa T., Nakagawa Y. *et al.* 1996 A novel microsatellite polymorphism in the human OB gene: a highly polymorphic marker for linkage analysis. *Diabetologia* **39**, 1398–1401.

Shungin D., Winkler T. W., Croteau-Chonka D. C., Ferreira T., Locke A. E., Mägi R. *et al.* 2015 New genetic loci link adipose and insulin biology to body fat distribution. *Nature* **518**, 187–196.

Silha J. V., Krsek M., Sucharda P. and Murphy L. J. 2005 Angiogenic factors are elevated in overweight and obese individuals. *Int. J. Obes. (Lond)*. **29**, 1308–1314.

Snijder M. B., Dekker J. M., Visser M., Bouter L. M., Stehouwer C. D. and Kostense P. J. 2003 Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. *Am. J. Clin. Nutr.* **77**, 1192–1197.

Souren N. Y., Paulussen A. D., Loos R. J., Gielen M., Beunen G. and Fagard R. 2007 Anthropometry, carbohydrate and lipid metabolism in the East Flanders Prospective Twin Survey: heritabilities. *Diabetologia* **50**, 2107–2116.

Speliotes E. K., Willer C. J., Berndt S. I., Monda K. L., Thorleifsson G., Jackson A. U. *et al.* 2010 Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **42**, 937–948.

Steinberg G. R., Kemp B. E. and Watt M. J. 2007 Adipocyte triglyceride lipase expression in human obesity. *Am. J. Physiol. Endocrinol. Metab.* **293**, E958–E964.

Sun G., Gagnon J., Chagnon Y. C., Pérusse L., Després J. P., Leon A. S. *et al.* 1999 Association and linkage between an insulin-like growth factor-1 gene polymorphism and fat free mass in the HERITAGE Family Study. *Int. J. Obes. Relat. Metab. Disord.* **23**, 929–935.

Sutton B. S., Langefeld C. D., Campbell J. K., Haffner S. M., Norris J. M., Scherzinger A. L. *et al.* 2006 Genetic mapping of a 17q chromosomal region linked to obesity phenotypes in the IRAS family study. *Int. J. Obes.* **30**, 1433–1441.

Tabor H. K., Risch N. J. and Myers R. M. 2002 Candidate-gene approaches for studying complex genetic traits: practical considerations. *Nat. Rev. Genet.* **3**, 391–397.

Talbert M. E., Langefeld C. D., Ziegler J. T., Haffner S. M., Norris J. M. and Bowden D. W. 2009 INSIG2 SNPs associated with obesity and glucose homeostasis traits in Hispanics: the IRAS Family Study. *Obesity* (Silver Spring) **17**, 1554–1562.

Thomas M. K., Yao K. M., Tenser M. S., Wong G. G. and Habener J. F. 1999 Bridge-1, a novel PDZ domain coactivator of E2A-mediated regulation of insulin gene transcription. *Mol. Cell. Biol.* **19**, 8492.

Thorleifsson G., Walters G. B., Gudbjartsson D. F., Steinthorsdottir V., Sulem P., Helgadottir A. *et al.* 2009 Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat. Genet.* **41**, 18–24.

Ukkola O., Pérusse L., Chagnon Y. C., Després J. P. and Bouchard C. 2001 Interactions among the glucocorticoid receptor, lipoprotein lipase and adrenergic receptor genes and abdominal fat in the Quebec Family Study. *Int. J. Obes.* **25**, 1332–9.

Urbanek M., Hayes M. G., Armstrong L. L., Morrison J., Lowe L. P., Badon S. E. *et al.* 2013 The chromosome 3q25 genomic region is associated with measures of adiposity in newborns in a multi-ethnic genome-wide association study. *Hum. Mol. Genet.* **22**, 3583–3596.

Usdin T. B., Mezey E., Button D. C., Brownstein M. J. and Bonner T. I. 1993 Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. *Endocrinology* **133**, 2861–2870.

Van Gaal L. F., Mertens I. L. and De Block C. E. 2006 Mechanisms linking obesity with cardiovascular disease. *Nature* **444**, 875–880.

Vasan S. K., Fall T., Job V., Gu H. F., Ingelsson E., Brismar K., Karpe F. *et al.* 2013 A common variant in the FTO locus is associated with waist–hip ratio in Indian adolescents. *Pediatr. Obes.* **8**, e45–49.

Vaughan L. K., Wiener H. W., Aslibekyan S., Allison D. B., Havel P. J., Stanhope K. L. *et al.* 2015 Linkage and association analysis of obesity traits reveals novel loci and interactions with dietary n-3 fatty acids in an Alaska Native (Yup'ik) population. *Metabolism* **64**, 689–697.

Voruganti V. S., Diego V. P., Haack K., Cole S. A., Blangero J., Göring H. H. *et al.* 2011 A QTL for genotype by sex interaction for anthropometric measurements in Alaskan Eskimos

(GOCADAN study) on chromosome 19q12-1. *Obesity* (Silver Spring) **19**, 1840–1846.

Wang K., Li W. D., Zhang C. K., Wang Z., Glessner J. T., Grant S. F. *et al.* 2011 Genome-wide association study on obesity and obesity-related traits. *PLoS One* **6**, e18939.

Wang Y., Rimm E. B., Stampfer M. J., Willett W. C. and Hu F. B. 2005 Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am. J. Clin. Nutr.* **81**, 555–563.

Wei M., Gaskill S. P., Haffner S. M. and Stern M. P. 1997 Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans–a 7-year prospective study. *Obes. Res.* **5**, 16–23.

Wen W., Kato N., Hwang J. Y., Guo X., Tabara Y., Li H. *et al.* 2016 Genome-wide association studies in East Asians identify new loci for waist-hip ratio and waist circumference. *Sci. Rep.* **6**, 17958.

Wen W., Zheng W., Okada Y., Takeuchi F., Tabara Y., Hwang J. Y. *et al.* 2014 Meta-analysis of genome-wide association studies in East Asian-ancestry populations identifies four new loci for body mass index. *Hum. Mol. Genet.* **23**, 5492–5504.

Winkler T. W., Justice A. E., Graff M., Barata L., Feitosa M. F., Chu S. *et al.* 2015 The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. *PLoS Genet.* **11**, e1005378.

Xi B., Shen Y., Reilly K. H., Zhao X., Cheng H., Hou D. *et al.* 2013a Sex-dependent associations of genetic variants identified by GWAS with indices of adiposity and obesity risk in a Chinese children population. *Clin. Endocrinol. (Oxf).* **79**, 523–528.

Xi B., Cheng H., Shen Y., Chandak G. R., Zhao X., Hou D. *et al.* 2013b Study of 11 BMI-associated loci identified in GWAS for associations with central obesity in the Chinese children. *PLoS One* **8**, e56472.

Yajnik C. S., Janipalli C. S., Bhaskar S., Kulkarni S. R., Freathy R. M., Prakash S. *et al.* 2009 FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. *Diabetologia* **52**, 247–252.

Ye W. Z., Reis A. F., Dubois-Laforgue D., Bellanné-Chantelot C., Timsit J. and Velho G. 2001 Vitamin D receptor gene polymorphisms are associated with obesity in type 2 diabetic subjects with early age of onset. *Eur. J. Endocrinol.* **145**, 181–186.

Yeh W., Cao Z., Classon M. and McKnigh, S. 1995 Cascade regulation of terminal adipocyte differentiation by three members of the C/EBP family of leucine zipper proteins. *Genes. Dev.* **9**, 168–181.

Yen F. T., Masson M., Clossais-Besnard N., André P., Grosset J. M., Bougueleret L. *et al.* 1999 Molecular cloning of a lipolysis-stimulated remnant receptor expressed in the liver. *J. Biol. Chem.* **274**, 13390–13398.

Yoneyama S., Guo Y., Lanktree M. B., Barnes M. R., Elbers C. C., Karczewski K. J. *et al.* 2014 Gene-centric meta-analyses for central adiposity traits in up to 57 412 individuals of European descent confirm known loci and reveal several novel associations. *Hum. Mol. Genet.* **23**, 2498–2510.

Yoneyama S., Yao J., Guo X., Fernandez-Rhodes L., Lim U., Boston J. *et al.* 2017 Generalization and fine mapping of European ancestry-based central adiposity variants in African ancestry populations. *Int. J. Obes. (Lond)*. **41**, 324–331.

Zeggini E., Scott L. J., Saxena R., Voight B. F., Marchini J. L., Hu T. *et al.* 2008 Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat. Genet*. **40**, 638–645.

Zhao J., Bradfield J. P., Li M., Wang K., Zhang H., Kim C. E. *et al.* 2009 The role of obesity-associated loci identified in genome wide association studies in the determination of pediatric BMI. *Obesity* (Silver Spring) **17**, 2254–2257.

Zhu J., Loos R. J., Lu L., Zong G., Gan W., Ye X. *et al.* 2014 Associations of genetic risk score with obesity and related traits and the modifying effect of physical activity in a Chinese Han population. *PLoS One* **9**, e91442.

Corresponding editor: B. K. Thelma