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REVIEW ARTICLE

Genetics of obesity and its measures in India

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Abstract. Obesity is one of the largest global health problems associated with increased morbidity and mortality mediated by its association with several other metabolic disorders. The interaction between the genes and environment plays an important role in the manifestation of obesity. Despite a high heritability (40–70%) of obesity, the search for genetic variants associated with obesity susceptibility has been a challenging task. To date, limited studies have been conducted in India, restricted to the validation of few genetic variants identified by genomewide association studies. In this critical review, we sought to examine the current knowledge of genetic basis of obesity and its measures in the Indian population. A comprehensive literature search was performed using 'PubMed', 'Medline' and 'IndMed' databases to search for citations published until 31st May 2017, using the key terms as 'Genetics' AND 'obesity' AND 'India'. We identified 48 potential studies which fulfilled the eligibility criteria. The findings indicated that *FTO*, *MC4R*, *TNF-α*, *PPAR-γ*, *UCP1*, *UCP2*, *LPL*, *LEPR*, *AMD1*, *IL6*, *APOE*, *ADIPOQ*, *DOK5*, *INSIG2*, *PBEF1*, *IL6R*, *Myostatin*, *CXCR4*, *HHEX*, *IRX3*, *POMC*, *NGN3*, *FOXA2*, *MTR*, *TCN* and *CHDH* are some of the important genes studied among the Indian population. Importantly, the role of sexual dimorphism in the genetic regulation of obesity and body fat distribution was also reported in a few studies. Further, seven biological pathways have been identified that contribute to obesity pathogenesis in India. In conclusion, further exploration of pathway-based research on genetics of obesity can be useful for better understanding the pathophysiology of obesity in India.

Keywords. obesity; body fat distribution; genetics; genomewide association study; India.

Introduction

Obesity is one of the common public-health conditions that has a huge epidemiological burden across low-, middle-income and high-income countries. The global burden of overweight/obesity increased to 36.9% in men and 38% in women in 2013 (Ng *et al.* 2014). Rising prevalence of overweight and obesity is the major driving factor of noncommunicable chronic diseases (NCDs), accounting for 44% of diabetes, 23% of ischaemic heart disease and between 7 and 41% of certain cancer burden (WHO 2013). The prevalence of overweight/obesity range from 1.50 to 45.6% among the Indian population (Kshatriya and Acharya 2016; NFHS-4 2016, http://rchiips.org/NFHS/factsheet_NFHS-4.shtml).

Childhood obesity is another rapidly growing public health concern worldwide (Lobstein *et al.* 2004) and is one of the major determinants of onset of NCDs in adulthood (Biro and Wien 2010). It has been estimated that 10% of school-aged children worldwide, between 5 and 17 years, are either overweight or obese (Kalra and Unnikrishnan 2012). A recent systematic review has reported a combined prevalence of 19.3% of childhood overweight and obesity in India which is a significant increase from the earlier prevalence of 16.3% reported in 2001–2005 (Ranjani *et al.* 2016).

Obesity is broadly measured through body mass index (BMI), which is a composite parameter of weight–height that indicates the amount of body fat and also used to classify overweight and obesity in adults (Chris 2004). In comparison with Western countries, a lower cut-off for BMI ($\geq$23 kg/m^2 instead of $\geq$25 kg/m^2) has been proposed to define overweight/obesity in South Asians including Indians (Misra and Khurana 2011). The risks for type-2 diabetes (T2D) and cardiovascular diseases (CVDs) are associated with a lower BMI among South Asians as they have a higher total and central adiposity for a given body weight when compared with matched white populations

(Sniderman *et al.* 2007; Misra and Khurana 2011). Further, higher rate of metabolic syndrome in South Asians is mostly attributed to the increased prevalence of central adiposity (Ramachandran and Snehalatha 2010). Waist circumference (WC), hip circumference (HC) and waist–hip ratio (WHR) are the other indicators which measure regional fat distribution (Avenell *et al.* 2004). A higher prevalence of T2D and CVDs in Asian populations, especially in women could be attributed to the higher WC (Sniderman *et al.* 2007; Kaur *et al.* 2012).

Obesity is an outcome of complex, heritable and multifactorial interactions of multiple genes, environmental factors and behavioural traits that make the management and prevention challenging in human populations (Rao *et al.* 2014). Globally, the changing patterns of food intake, both in quality and quantity (nutrition transition), an increase in physical inactivity due to increasing sedentary lifestyle, changing modes of transportation and increasing urbanization (WHO 2013) are contributing to the rising burden of obesity. Biologically, obesity is an adverse consequence of energy imbalance between the calories consumed and calories expended. Family studies including twin and adoption studies indicated that adiposity is highly heritable with the estimated genetic contribution ranging from 65 to 80% for body weight (Stunkard *et al.* 1986; Malis *et al.* 2005), 40–77% for BMI (Maes *et al.* 1997; Atwood *et al.* 2002; Schousboe *et al.* 2003; Wardle *et al.* 2008) and 31–76% for WC and WHR (Selby *et al.* 1990; Nelson *et al.* 1999; Souren *et al.* 2007) even after accounting for the BMI (Rose *et al.* 1998; Nelson *et al.* 2002).

Genomewide association studies (GWASs) have changed the genetic landscape of common traits which were earlier restricted to the linkage and candidate gene-based association studies. More than 80 genomewide linkage studies have been carried out so far, identifying more than 300 chromosomal loci showing some evidence of linkage with obesity (Loos 2012). On the other hand, since 2007, several waves of GWASs have been conducted in Western countries, and have discovered more than 100 loci associated with obesity and related traits (Frayling *et al.* 2007; Scuteri *et al.* 2007; Chambers *et al.* 2008; Heid *et al.* 2010; Speliotes *et al.* 2010; Locke *et al.* 2015; Shungin *et al.* 2015). Indian-specific GWASs related to obesity and its measures are absent and to date no published findings are available. To address the clinical and public health implications of the alarming obesity epidemic in India, a comprehensive understanding of the genetic architecture of obesity and related traits is demanded. Therefore, the purpose of this review is to assess the current knowledge and understanding of genetics of obesity and its measures in the Indian population.

Search strategy

A comprehensive search was conducted using 'PubMed', 'Medline' and 'IndMed' databases using a combination of relevant search terms such as: 'genetics' OR 'genetic association studies' OR 'single-nucleotide polymorphisms' AND 'obesity' OR 'adiposity' OR 'body fat' OR 'segmental body fat' OR 'central obesity' AND 'measures' OR 'body mass index' OR 'waist circumference' OR 'hip circumference' OR 'waist hip ratio' OR 'skinfolds' AND 'risk' AND 'India'. We included all the studies that were published until 31st May 2017. Bibliographies and citation sections of the retrieved articles were also reviewed for additional related studies.

Selection strategy

The inclusion criteria followed were: (i) studies published in English language journals, (ii) studies related to humans, (iii) original research studies and (iv) studies conducted exclusively in India. Studies were excluded if they were (i) duplicated studies, (ii) reviews (iii) based on gene expression, (iv) methylation and (v) case only studies (in the case of other metabolic phenotypes such as T2D, insulin resistance and hyperinsulinaemia).

As a result of the initial search, we identified 919 potential articles for inclusion. After excluding articles not related to humans, 628 papers were left for examination. Further, screening for duplicates left a total of 133 studies. Preliminary assessment of titles and abstracts was carried out to determine the objectives and relevance of studies, which resulted in the exclusion of 70 articles. The full texts of 63 articles were read to extract information on the topic of interest, of which 15 articles were excluded. The excluded articles did not fit the inclusion criteria. The remaining 48 articles fulfilled eligibility criteria.

Data extraction

After the final inclusion, identifying information (such as research setting, study design, phenotype, gene, genetic variant and effect size) was extracted from each article and is presented in tables 1–4.

Genetic associations with obesity

Of the 25 genetic studies exclusively on obesity in the Indian population only 15 had observed significant associations of genetic variants with obesity in pooled sample size of 22,383 participants (table 2). Similar to the studies on Western populations (Frayling *et al.* 2007; Loos *et al.* 2008; Lindgren *et al.* 2009), *FTO* and *MC4R* loci have been widely studied in India (table 2) as they are the major obesity determining genes even in younger age groups (Zhao *et al.* 2011; Melka *et al.* 2012). Both the genes are highly expressed in the central nervous system that has shown to play a significant role in control of the well-known regulatory pathways of energy homeostasis (Beckers *et al.* 2009).

Table 1. Study designs adopted for studying obesity and its measures in India.

Study design	No. of studies ($n = 48$)	Areas covered	References
Population-based cross-sectional	2	Chennai	Cassell *et al.* (1999); Vasan *et al.* (2012)
	1	Delhi and Trivandrum	Moore *et al.* (2012)
	2	Lucknow, Nagpur, Hyderabad and Bengaluru (Indian Migration Study Sites)	Taylor *et al.* (2011); Gupta *et al.* (2013)
	7	New Delhi	Kumar *et al.* (2007); Bhatt *et al.* (2012a); Bhatt *et al.* (2012b) Sharma *et al.* (2013); Dhall *et al.* (2012) Sharma *et al.* (2011) Vikram *et al.* (2011)
	1	South India (area not specified)	Vasan *et al.* (2013)
School-based case control	3	Delhi	Dwivedi *et al.* (2012), Tabassum *et al.* (2012a); Tabassum *et al.* (2012b)
Population-based case control	1	South India (Kota tribe)	Bhaskar *et al.* (2010)
	1	Pune	Janipalli *et al.* (2012)
	2	Lucknow	Gupta *et al.* (2012); Kumar *et al.* (2014)
	1	North India (area not specified)	Gupta *et al.* (2011)
	1	Punjab	Bhagat *et al.* (2010)
	1	Mysuru, Karnataka	Dasgupta *et al.* (2014)
	5	Delhi, Haryana and Jammu and Kashmir Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand	Dwivedi *et al.* (2013); Prakash *et al.* (2016) Srivastava *et al.* (2016a); Srivastava *et al.* (2016b) Prakash *et al.* (2017)
	6	Chennai urban and rural Epidemiology Study (CURES)	Vimaleswaran *et al.* (2006a, b) Radha *et al.* (2007); Ramya *et al.* (2011) Ramya *et al.* (2013), Vimaleswaran *et al.* (2008)
	3	Punjab (Sikh Diabetes Study)	Been *et al.* (2012); Sanghera *et al.* (2010) Been *et al.* (2010)
Hospital-based case control	1	Lucknow	Madeshiya *et al.* (2015)
	1	Pune and Mysuru	Yajnik *et al.* (2009)
Hospital-based cases and population-based controls	5	Delhi	Tabassum *et al.* (2010); Chauhan *et al.* (2011) Mahajan *et al.* (2010); Chauhan *et al.* (2012) Tabassum *et al.* (2008)
	4	Lucknow	Srivastava *et al.* (2008); Prakash *et al.* (2011) Srivastava *et al.* (2010); Prakash *et al.* (2012)

Table 2. Genetic variants associated with obesity in India.

Authors (year)	Study design	Location	Sample size total (M/F)	Age in years (range/mean/mean ± SD)	Phenotype (obesity cut-off)	Genes	SNPs studied	OR (95% CI)	*P* value
Radha *et al.* (2007)	Population-based case control*	Chennai	731	49 ± 12	Obesity/T2D (≥25 kg/m^2)	*LPL*	–T93G	1.77 (1.19–2.63)	0.005
							–53G-C	0.561 (0.03–0.99)	0.05
Vimaleswaran *et al.* (2008)	Population-based case control*	Chennai	2000 (843/1157)	39 ± 12	Obesity/T2D (≥25 kg/m^2)	*ADIPOQ*	(+10211) T/G	1.57 (1.34–1.84)	10^{-7}
Been *et al.* (2010)	Population-based case control*	North India	783 (392/391)	51.5 ± 14.0	Obesity/T2D (>23 kg/m^2)	*MC4R*	rs12970134	1.24	0.012
Tabassum *et al.* (2010)	Hospital-based cases and population-based controls*	Delhi	1006 (606/400)	50	Obesity/T2D (≥23 kg/m^2)	*DOK5*	rs6064099	NR	9.8×10^{-3}
Srivastava *et al.* (2010)	Hospital-based cases and population-based controls*	Lucknow	440 Obese: 200 Nonobese: 240	Not specified	Obesity/ hyperinsulinaemia (>25 kg/m^2)	*UCP2*	-866 G/A	2.84 (1.55–5.19)	0.001
Mahajan *et al.* (2010)	Hospital-based cases and population-based controls*	Delhi	1006	50	T2D/obesity (≥25 kg/m^2)	*TNF-α*	rs2229094	1.3 (1.1–1.6)	0.005
							rs1800630	1.3 (1.1–1.6)	0.004
Bhagat *et al.* (2010)	Population-based case control	Punjab	344 Obese: 201 Thin: 143	Cases: 48.1 ± 12.9 controls: 39.5 ± 17.7	Obesity (≥30 kg/m^2)	*TNFA*	Gly318Ala	1.46 (1.05–2.03)	0.024
						PPARG	Pro12Ala	1.74 (1.03–2.93)	0.038

Table 2 (*contd*)

Authors (year)	Study design	Location	Sample size total (M/F)	Age in years (range/mean/mean ± SD)	Phenotype (obesity cut-off)	Genes	SNPs studied	OR (95% CI)	*P* value
Prakash *et al.* (2011)	Hospital-based cases and population-based controls	Lucknow	642 Nonobese subjects: 333 Obese subjects: 309	Not specified	Obesity (>30 kg/m^2)	*FTO*	rs17817449 (G>T)	1.75 (1.16–2.64)	0.008
Sharma *et al.* (2011)	Population-based cross-sectional	New Delhi	529 (269/260)	Obese: 40.2 ± 8.7 Non obese: 38.9 ± 8.7	Obesity (≥25 kg/m^2)	*LMNA*	1908C>T	5.6 (2.5–12.2)	0.001
Taylor *et al.* (2011)	Population-based cross-sectional	Lucknow, Nagpur, Hyderabad and Bengaluru	6780 (4301/2479)	40.7 ± 0.13	Obesity (>25 kg/m^2)	*MC4R*	rs17782313	1.19 (1.00–1.40)	0.05
Ramya *et al.* (2011)	Population-based case control*	Chennai	1001 (418/583)	43 ± 14	Obesity/T2D (≥25 kg/m^2)	*FTO*	rs8050136 rs1588413	NR 1.53 (1.05–2.22)	0.0001 0.002
Chauhan *et al.* (2011)	Hospital-based cases and population-based controls*	North India (areas around Delhi)	2854 Stage 1: 1006 (606/400) Stage 2: 1848 (1017/831)	Stage 1: 50 Stage 2: 52	Obesity/T2D (≥25 kg/m^2)	*FTO*	rs1421085 rs8050136	1.22 (1.05–1.41) 1.17 (1.01–1.36)	0.009 0.04
Bhatt *et al.* (2012a)	Population-based cross-sectional	New Delhi	335 (238/97)	Males: 38.2 ± 7.0 Females: 38.0 ± 6.9	Obesity (≥23 kg/m^2)	*Myostatin*	K153R	3.2 (1.2–12.9)	NR
Bhatt *et al.* (2012b)	Population-based cross-sectional	New Delhi	495 (279/216)	Obese: 38.4 ± 9.1 Nonobese: 40.8 ± 8.3	Obesity (≥25 kg/m^2)	PPAR-γ2	Pro12Ala	3.2 (1.2–12.9)	NR

Table 2 (*contd*)

Authors (year)	Study design	Location	Sample size total (M/F)	Age in years (range/mean/mean ± SD)	Phenotype (obesity cut-off)	Genes	SNPs studied	OR (95% CI)	*P* value
Dwivedi *et al.* (2012)	School-based case control	Delhi	3126 (NW: (789/1441) OW and OB: (305/591))	13.50	Obesity (IOTF criteria, Cole *et al.* 2000)	*FTO*	rs9939609 rs8050136	1.21 (1.07–1.37) 1.19 (1.05–1.35)	2.5×10^{-3} 5.0×10^{-3}
Chauhan *et al.* (2012)	Hospital-based case control	New Delhi	998 Obese: 562 Normal weight: 436	Obese and normal weight: 50	Obesity/T2D ($\geq$23 kg/m^2)	*TCN2* *MTR* *CHDH*	rs1801198 rs16834521 rs4563403	1.24 (1.04–1.48) 0.82 (0.68–0.99) 0.69 (0.52–0.92)	0.02 0.04 0.01
Tabassum *et al.* (2012a)	School-based case control	Delhi	3168 Stage 1: NW: (370/464) OW and OB: (173/279) Stage 2: NW: (420/979), OW and OB: (132/312)	Stage 1: NW: 14.00 OW/OB children 13.00 Stage 2: NW: 13.00 OW/OB children: 13.2	Obesity (IOTF criteria, Cole *et al.* 2000)	*IL6R* *IL6* *LEPR* *PBEF1*	rs7514452 rs2069845 rs1137100 rs3801266	1.19 1.37 1.39 1.35	0.011 2.3×10^{-5} 3.9×10^{-5} 4.3×10^{-4}
Tabassum *et al.* (2012b)	School-based case control	Delhi	3168 Stage 1: NW children: (370/464) OW and OB: (173/279) Stage 2: NW: (420/979) OW and OB: (132/312)	Stage 1: NW: 14.00. OW/OB: 13.00 Stage 2: NW: 13.00 OW/OB: 13.2	Obesity (IOTF criteria, Cole *et al.* 2000)	*AMD1*	rs2796749	1.35 (1.19–1.52)	1.9×10^{-6}

Table 2 (*contd*)

Authors (year)	Study design	Location	Sample size total (M/F)	Age in years (range/mean/mean ± SD)	Phenotype (obesity cut-off)	Genes	SNPs studied	OR (95% CI)	*P* value
Prakash *et al.* (2012)	Hospital-based cases and population-based controls	Lucknow	642 Obese: 309 Nonobese: 333	19-60	Obesity (>30 kg/m^2)	*PPAR-γ*	Pro12Ala rs1801282	1.65 (1.155–2.370)	0.006
Dwivedi *et al.* (2013)	Population-based case control*	Delhi	Children: 1362 (620/742) Nondiabetic patient (adults): 2028 (1111/917)	Children: 13.96 ± 1.81 Nondiabetic patient (adults): 53.65 ± 10.60	Obesity/T2D (≥25 kg/m^2)	*MC4R*	rs17782313 (in children)	1.73 (1.36–2.19)	6.9×10^{-6}
							rs12970134 (in children)	1.62 (1.27–2.05)	7.6×10^{-5}
							rs17782313 (in adults)	1.27 (1.09–1.48)	0.003
							rs12970134 (in adults)	1.24 (1.07–1.44)	0.005
Dasgupta *et al.* (2014)	Population-based case control	Mysuru, Karnataka	613 Obese: 304 Nonobese: 309	Obese: 46.37 ± 11.96 Nonobese: 46.88 ± 16.03	Obesity (≥27.5 kg/m^2)	*LEPR*	rs7799039	1.837 (1.035–3.261)	0.03775
							rs2167270	3.243 (1.352–7.78)	0.008391
							rs4731426	5.63 (2.701–11.74)	4.016×10^{-6}
Prakash *et al.* (2016)	Population-based case control	Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand	642 Obese cases: 309 Nonobese controls: 333 (347/295)	Obese: 36.8 ± 2.4 Nonobese: 35.4 ± 2.2	Obesity (≥30 kg/m^2)	*FTO*	rs9939609	1.71 (1.11–2.65)	0.015

Table 2 (*contd*)

Authors (year)	Study design	Location	Sample size total (M/F)	Age in years (range/mean/mean ± SD)	Phenotype (obesity cut-off)	Genes	SNPs studied	OR (95% CI)	*P* value
Srivastava *et al.* (2016a)	Population-based case control	Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand	600 (350/250)	20–42	Obesity (≥30 kg/m^2)	*FTO*	rs8050136	3.1 (1.9–5.2)	0.0001
							rs1421085	3.0 (1.8–5.0)	0.0001
							rs9939609	4.2 (2.5–7.3)	0.0001
						IRX3	rs17817449	3.8 (1.2–11.8)	0.021
							rs3751723	3.3 (1.8–3.6)	0.012
Srivastava *et al.* (2016b)	Population-based case control	Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand	696 Obese cases: 396 Nonobese controls: 300 (375/321)	20-42	Obesity (≥30 kg/m^2)	*MC4R*	rs17782313	2.9 (1.8–4.7)	0.0001
						POMC	rs1042571	4.0 (1.1–14.1)	0.03
						APOE	Hha1	5.0 (1.4–17.2)	0.011
Prakash *et al.* (2017)	Population-based case control	Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand	642 Obese cases: 309 Nonobese controls: 333 (347/295)	Obese: 36.78 ± 2.39 Nonobese: 35.44 ± 2.15	Obesity (≥30 kg/m^2)	*INSIG2*	rs7566605	3.82 (1.95–7.48)	<0.001

F, female; M, male; IOTF, International Obesity Task Force; NW, normal weight; NGT, normal glucose tolerant; OW/OB, overweight/obese; OR, odds ratio; 95% CI, 95% confidence interval; NR, not reported.

*In case–control design based on metabolic disorders other than obesity, effect sizes noted from control participants only.

Table 3. Genetic variants associated with BMI in India.

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β_{BMI}	95% CI	*P* value
Cassell *et al.* (1999)	Population-based cross-sectional*	Chennai	255 (45 ± 12)	BMI/T2D	*UCP2*	Exon 8	NR	NR	<0.001
Radha *et al.* (2007)	Population-based case control*	Chennai	731 (49 ± 12)	Obesity/T2D	*LPL*	−93 T to G	NR	NR	0.003
Been *et al.* (2010)	Population-based case control*	Sikh Diabetes Study (Punjab)	765 (51.5 ± 14.0)	Obesity/T2D	*MC4R*	rs12970134	NR	NR	0.002
Tabassum *et al.* (2010)	Hospital-based cases and population-based controls*	Delhi	1006 (50.0)	Obesity/T2D	*DOX5*	rs6064099	NR	NR	7.0×10^{-3}
Bhagat *et al.* (2010)	Population-based case control	Punjab	344 (39.5 ± 17.7)	Obesity	*PPARG* *TNFA*	Pro12Ala Gly318Ala	NR NR	NR NR	0.01 0.01
Mahajan *et al.* (2010)	Hospital-based cases and population-based controls*	Delhi	1006 (50.0)	Obesity/T2D	*TNF-α*	rs2229094 rs1800630	NR	NR	0.008 0.01
Taylor *et al.* (2011)	Population-based cross-sectional	Indian Migration study	6170 (40.7 ± 0.13)	Obesity	*FTO*	rs9939609	0.08	0.02–0.14	0.009
Sharma *et al.* (2011)	Population-based cross-sectional	New Delhi	529 Obese: (40.2 ± 8.7) Non obese: (38.9 ± 8.7)	Obesity	*LMNA*	1908C>T	NR	NR	0.001

Table 3 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β_{BMI}	95% CI	*P* value
Chauhan *et al.* (2011)	Hospital-based cases and population-based controls*	North India (areas around Delhi)	1627–1671 (52.0)	Obesity/T2D	*FTO*	rs1421085 rs8050136 rs9930506	NR NR NR	NR NR NR	0.0002 0.002 0.04
Tabassum *et al.* (2012a)	School-based cross-sectional	Delhi	3168 (13.0)	Obesity	*IL6* *LEPR* *PBEF1*	rs2069845 rs1137100 rs3801266	0.12 0.15 0.17	NR NR NR	5.7×10^{-5} 3.2×10^{-6} 1.7×10^{-4}
Tabassum *et al.* (2012b)	School-based case control	Delhi	3168 (13.0)	Obesity	*AMD1*	rs2796749	0.13	NR	2.5×10^{-6}
Vasan *et al.* (2012)	Population-based cross-sectional study	Vellore Tamil Nadu	2060 (28.3 ± 1.1)	Obesity	*FTO*	rs9939609	0.015	0.003–0.026	0.01
Dwivedi *et al.* (2012)	School-based case control	Delhi	3126 (13.50)	Obesity	*FTO*	rs9939609 rs8050136	0.14 0.14	0.09–0.19 0.08–0.19	1.6×10^{-7} 4.2×10^{-7}
Bhatt *et al.* (2012a)	Population-based cross-sectional	New Delhi	335 (38.0 ± 66.9)	Obesity	*Myostatin*	A55T	NR	NR	0.04

Table 3 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β_{BMI}	95% CI	*P* value
Bhatt *et al.* (2012b)	Population-based cross-sectional	New Delhi	495 Obese: (38.4 ± 9.1) Nonobese: (40.8 ± 8.3)	Obesity	*PPAR-γ2*	Pro12Ala	NR	NR	0.02
Moore *et al.* (2012)	Population-based cross-sectional	New Delhi and Trivandrum	1129 New Delhi: 511 (47.1 ± 9.9) Trivandrum: 618 (48.7 ± 9.2)	Obesity	*FTO*	rs3751812	0.55	0.14–0.96	0.008
Janipalli *et al.* (2012)	Population-based case control*	Pune	1549 (not specified)	T2D	*MC4R*	rs12970134	0.43	0.19–0.66	4.1×10^{-4}
						rs17782313	0.45	0.21–0.68	2.1×10^{-4}
Gupta *et al.* (2013)	Population-based cross-sectional	Indian Migration Study	5056 (39.6 ± 10.3)	Obesity	*CXCR4*	rs932206	0.13	NR	0.001
					HHEX	rs5015480	0.09	NR	0.002
Dwivedi *et al.* (2013)	Population-based case control	Delhi	Children: 1362 (13.96 ± 1.81) Nondiabetic patient (adults): 2028 (53.65 ± 10.60)	Obesity/T2D	*MC4R*	rs17782313 (in children)	0.24	0.17–0.32	8.5×10^{-11}
						rs12970134 (in children)	0.22	0.14–0.29	6.7×10^{-9}
						rs17782313 (in adults)	0.08	0.01–0.14	0.027
						rs12970134 (in adults)	0.08	0.01–0.14	0.018

Table 3 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β_{BMI}	95% CI	*P* value
Dasgupta *et al.* (2014)	Population-based case control	Mysuru, Karnataka	613 Obese: 304 (46.37 ± 11.96) Nonobese: 309 (46.88 ± 16.03)	Obesity	*LEPR*	rs7799039	0.604	NR	0.0501
						rs2167270	1.304	NR	0.0068
						rs4731426	1.46	NR	0.0001
Prakash *et al.* (2017)	Population-based case control	Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand	642 Obese cases: 309 (36.78 ± 2.39) Nonobese controls: 333 (35.44 ± 2.15)	Obesity	*INSIG2*	rs7566605	NR	NR	<0.001

T2D, type-2 diabetes; β, beta coefficient; NR, not reported.
*In case–control design based on metabolic disorders other than obesity, effect sizes noted from control participants only.

Table 4. Genetic variants associated with other obesity measures in India.

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β (95% CI), P value		
							WC	HC	WHR
Radha *et al.* (2007)	Population-based case control*	Chennai	731 (49 ± 12)	Obesity/T2D	*LPL*	−93 T to G	$P = 0.03$	NR	NR
Tabassum *et al.* (2008)	Hospital-based cases and population-based controls*	New Delhi	625 (50.0)	T2D	*FOXA2*	rs1055080	NR	NR	$P = 0.013$
Yajnik *et al.* (2009)	Hospital-based case control*	Pune and Mysuru	960 (37.0 ± 16.4)	Obesity/T2D	*FTO*	rs9939609	NS	$P = 0.02$	NS
Been *et al.* (2010)	Population-based case control*	Sikh Diabetes Study (Punjab)	765 (51.5 ± 14.0)	Obesity/T2D	*MC4R*	rs12970134	$P = 0.009$	$P = 0.03$	NS
Sanghera *et al.* (2010)	Population-based case control*	Sikh Diabetes study (Punjab)	500 (51.8 ± 15.6)	T2D	*ADIPOQ*	rs12495941	NS	$P = 0.040$	NR
Srivastava *et al.* (2010)	Hospital-based cases and population-based controls*	Lucknow	240 (not specified)	Obesity and hyperinsulinaemia	*UCP2*	−866 G/A	NR	NR	$P = 0.033$
Mahajan *et al.* (2010)	Hospital-based cases and population-based controls*	Delhi	1006 (50.0)	Obesity/T2D	*TNF-α*	rs2229094 rs1800630	$P = 4 \times 10^{-4}$ $P = 4 \times 10^{-4}$	NR NR	NR NR
Bhagat *et al.* (2010)	Population-based case control	Punjab	344 (39.5 ± 17.7)	Obesity	*PPARG* *TNFA*	Pro12Ala Gly318Ala	$P<0.01$ $P<0.05$	NR NR	$P<0.01$ $P<0.01$

Table 4 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β (95% CI), P value		
							WC	HC	WHR
Taylor *et al.* (2011)	Population-based cross-sectional	Indian Migration Study	6168 (40.7 ± 0.13)	Obesity	*MC4R*	rs17782313	NS	0.06 (0.01–0.12) $P = 0.03$	NS
Gupta *et al.* (2011)	Population-based case control*	North India	178 Nonobese: (28.04 ± 5.86) Obese: (29.12 ± 6.51)	Metabolic syndrome	*IL6*	G-174C	NS	NS	$P<0.001$
Sharma *et al.* (2011)	Population-based cross-sectional	New Delhi	529 Obese: (40.2 ± 8.7) Nonobese: (38.9 ± 8.7)	Obesity	*LMNA*	1908C>T	$P = 0.001$	$P = 0.002$	NS
Chauhan *et al.* (2011)	Hospital-based cases and population-based controls*	North India (places in and around Delhi)	1627–1671 (52.0)	Obesity/T2D	*FTO*	rs1421085	$P = 0.001$	NS	NS
						rs8050136	$P = 0.05$	NS	NS
						rs9930506	$P = 0.02$	NS	NS
						rs9939609	$P = 0.02$	NS	$P = 0.03$
Dwivedi *et al.* (2012)	School-based case control	Delhi	3126 (13.50)	Obesity	*FTO*	rs9939609	0.12 (0.07–0.17) $P = 1.7 \times 10^{-5}$	0.11 (0.05–0.16) $P = 1.3 \times 10^{-4}$	0.06 (0.01–0.12) $P = 0.02$
						rs8050136	0.12 (0.07–0.18) $P = 7.9 \times 10^{-6}$	0.11 (0.05–0.16) $P = 1.5 \times 10^{-4}$	0.07 (0.02–0.13) $P = 9.2 \times 10^{-3}$

Table 4 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β (95% CI), P value		
							WC	HC	WHR
Tabassum *et al.* (2012b)	School-based case control	Delhi	3168 (13.0)	Obesity	*AMD1*	rs2796749	0.14 $P = 3.2 \times 10^{-7}$	0.16 $P = 3.7 \times 10^{-7}$	0.06 $P = 0.05$
Moore *et al.* (2012)	Population-based cross-sectional	New Delhi and Trivandrum	1129 New Delhi: 511 (47.1 ± 9.9) Trivandrum: 618 (48.7 ± 9.2)	Obesity	*FTO*	rs3751812	$P = 0.04$	NR	NR
Bhatt *et al.* (2012a)	Population-based cross-sectional	New Delhi	335 (38.0 ± 66.9)	Obesity	*Myostatin*	K153R	$P = 0.04$	NS	NS
Bhatt *et al.* (2012b)	Population-based cross-sectional	New Delhi	495 Obese: (38.4 ± 9.1) Nonobese: (40.8 ± 8.3)	Obesity	*PPAR-γ2*	Pro12Ala	NS	$P = 0.03$	NS
Vasan *et al.* (2012)	Population-based cross-sectional	Tamil Nadu (Vellore)	2065 (28.3 ± 1.1)	Obesity	*FTO*	rs9939609	0.013 (0.005–0.021) $P = 0.002$	0.007 (0.002–0.013) $P = 0.011$	0.005 (0.001–0.0008) $P = 0.01$
					MC4R	rs17782313	NS	0.005 (0.002–0.012) $P = 0.039$	NS

Table 4 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β (95% CI), P value		
							WC	HC	WHR
Janipalli *et al.* (2012)	Population-based case control*	Pune	1549 (not specified)	T2D	*MC4R*	rs12970134	1.06 (0.38–1.74) $P = 2.0 \times 10^{-3}$	0.86 (0.31–1.41) $P = 2.0 \times 10^{-3}$	NR
						rs17782313	1.19 (0.52–1.87) $P = 1.0 \times 10^{-3}$	0.89 (0.34–1.44) $P = 1.0 \times 10^{-3}$	NR
Vasan *et al.* (2013)	Population-based cross-sectional	South India	1230 (17.1 ± 1.9)	Obesity	*FTO*	rs9939609	NS	NS	0.006 (0.001–0.012) $P = 0.021$
Gupta *et al.* (2013)	Population-based cross-sectional	Indian Migration study	5056 (39.6 ± 10.3)	Obesity	*NGN3*	rs10823406	NS	NS	0.08 $P = 0.01$

Table 4 (*contd*)

Reference	Study design	Location	Sample size/range (mean age)	Primary outcome	Gene	SNPs studied	β (95% CI), P value		
							WC	HC	WHR
Dwivedi *et al.* (2013)	Population-based case control	Delhi	Children: 1362 (13.96 ± 1.81) Nondiabetic patient (adults): 2028 (53.65 ± 10.60)	Obesity/T2D	*MC4R*	rs17782313 (in children)	0.26 (0.19–0.34) $P = 3.8 \times 10^{-12}$	NR	0.13 (0.06–0.20) $P = 2.0 \times 10^{-4}$
						rs12970134 (in children)	0.24 (0.16–0.31) $P = 4.3 \times 10^{-10}$	NR	0.11 (0.04–0.18) $P = 0.002$
						rs17782313 (in adults)	0.07 (0.01–0.14) $P = 0.034$	NR	NR
						rs12970134 (in adults)	$P = 0.05$	NR	NR
Ramya *et al.* (2013)	Population-based case control*	Haryana, Himachal Pradesh, Delhi and Jammu and Kashmir	1100 (41 ± 13)	Obesity/T2D	*ADIPOQ*	+276G/T (rs1501299)	NS	$P = 0.001$	NR
						11365C/G (rs266729)	NS	$P = 0.01$	NR
						–3971A/G (rs822396)	$P = 0.001$	NS	NR

WC, waist circumference; HC, hip circumference; WHR, waist–hip ratio; β, beta coefficient; NS, nonsignificant; NR, not reported.
*In case–control design based on metabolic disorders other than obesity, effect sizes noted from control participants only.

The associations of genetic variants of *FTO* (rs9939609 and rs8050136) and *MC4R* (rs17782313 and rs12970134) with obesity are relatively well studied in the Indian population. Fourteen studies have made an attempt to validate these genes in the Indian populations. Of these, 10 studies have found significant associations of *FTO* variants (OR range: 1.17–4.2) (Chauhan *et al.* 2011; Prakash *et al.* 2011; Ramya *et al.* 2011; Dwivedi *et al.* 2012; Janipalli *et al.* 2012; Moore *et al.* 2012; Vasan *et al.* 2012, 2013; Prakash *et al.* 2016; Srivastava *et al.* 2016a), and comparatively, only four studies identified associations of *MC4R* variants (OR range: 1.19–2.9) with obesity (Been *et al.* 2010; Taylor *et al.* 2011; Dwivedi *et al.* 2013; Srivastava *et al.* 2016b) (table 2).

Taylor *et al.* (2011) had conducted the largest population-based study on obesity and related traits on 3390 sib pairs from four Indian cities. They had reported weak evidence of association of *MC4R* (rs17782313) with obesity (OR=1.19, P=0.05) and no association was observed for *FTO* (rs9939609). Sib-pair design was the major strength of this study due to its resistance to population stratification which reduces the possibility of false-positive associations (Taylor *et al.* 2011). Further, Chauhan *et al.* (2011) had reported association of two variants of *FTO* (rs1421085 and rs8050136) with obesity after evaluating eight genetic variants of *FTO* (rs1421085, rs8050136, rs9939609, rs9930506, rs1861867, rs9926180, rs2540769 and rs708277) in 2854 nondiabetic control subjects from north India (table 2).

The studies with largest effect sizes for *FTO* and *MC4R* were primarily based on obesity and have used case–control study design with relatively small sample size (n range: 600–696) (table 2) (Srivastava *et al.* 2016a, b), indicating the need for larger sample size to observe an unbiased true effect size.

Indian genetic studies (n=4) with relatively large sample size (n range: 3126–3390) are actually related to childhood obesity (Dwivedi *et al.* 2012, 2013; Tabassum *et al.* 2012a, b). An attempt was made by Tabassum *et al.* (2012a) in assessing the association of 125 common variants from 21 genes, encoding adipocytokines and inflammatory markers in 1325 urban Indian children. They had replicated the top four loci in 1843 Indian children, and finally showed association of four variants: *PBEF1* (rs3801266, OR = 1.35), *IL6* (rs2069845, OR = 1.37), *LEPR* (rs1137100, OR = 1.39) and *IL6R* (rs7514452, OR = 1.19) after correction for multiple testing (Tabassum *et al.* 2012a). These loci are known to play an important role in energy homeostasis, metabolic processes and regulation of body (Tilg and Moschen 2006). They also examined the contribution of single-nucleotide polymorphisms (SNPs) to homocysteine pathway genes in relation to obesity susceptibility (Tabassum *et al.* 2012b) and identified association of the *AMD1* variant (rs2796749, OR = 1.35) with obesity in urban Indian children (table 2). It was proposed that *AMD1* influences the susceptibility to obesity by modulating either the polyamine metabolism or DNA (Park *et al.* 2011). In both studies, samples were collected from multiple ethnicities and using them for combined analysis was the major limitation.

Further, Dwivedi *et al.* (2012) had found the association of *FTO* (rs9939609, OR = 1.21 and rs8050136, OR = 1.19) with childhood obesity in urban India. They had also found age-dependent influence of *MC4R* (rs17782313 and rs12970134) with higher effect size in children compared with adults (Dwivedi *et al.* 2013) (table 2). The reported risk of obesity in Indian children for *MC4R* (rs17782313, OR = 1.73) was higher in comparison with European children (OR range: 1.20–1.40), in spite of a similar mean BMI in the obese category in both studies (29.5–33.0 kg/m^2 in European versus 30.14 kg/m^2 in Indians) (Loos *et al.* 2008; Dwivedi *et al.* 2013). Altogether, nine genetic variants in seven genes have shown associations with childhood obesity in India.

All the genetic studies which have been conducted so far in relation to childhood obesity have used case–control design and restricted to a single geographical location (i.e. Delhi) which may be biased given the high level of cultural and biological diversity in India. For better understanding, these loci need to be validated on children from different ethnic groups representing the socio-cultural diversity of India.

The obesity associated SNPs within *FTO* are functionally connected with regulation of *IRX3* expression which is an important determinant of body mass and composition (Ragvina *et al.* 2010; Smemo *et al.* 2014). Recently, Srivastava *et al.* (2016a) explored the associations of *FTO* (rs8050136, rs9939609, rs1421085 and rs17817449) and *IRX3* (rs3751723) variants with obesity in the north Indian population (table 2). They have found that these variants were associated with obesity risk and were in high linkage disequilibrium (r^2 = 0.81–0.91) with each other, supporting the concept of genetic connectivity between the *FTO* and *IRX3* loci (Srivastava *et al.* 2016a). Further studies with fairly large sample sizes are necessary to confirm these findings.

In India, research on genetics of obesity is generally performed along with other metabolic disorders. For example, eight studies have reported significant associations of SNPs with obesity when studied in samples primarily collected for T2D, hyperinsulinaemia and insulin resistance (Radha *et al.* 2007; Vimaleswaran *et al.* 2008; Been *et al.* 2010; Mahajan *et al.* 2010; Srivastava *et al.* 2010; Tabassum *et al.* 2010; Chauhan *et al.* 2011; Ramya *et al.* 2011; Chauhan *et al.* 2012; Ramya *et al.* 2013). Radha *et al.* (2007) had examined the association of the *LPL* variant (–T93G, OR=1.77, 95% CI: 1.19–2.63, P=0.005) with obesity, whereas the other variants (–G53C) of the same gene appears to be protective (OR = 0.561, 95% CI: 0.03–0.99, P=0.05) against obesity in a Chennai Urban Rural Epidemiology Study. Another study from Chennai showed association of a novel variant (+10211 T/G, OR = 1.57, 95% CI: 1.34–1.84, $P = 10^{-7}$) in the first

exon of *ADIPOQ* (Vimaleswaran *et al.* 2008). It was proposed that the *ADIPOQ* gene enhances insulin sensitivity and functions in regulating homeostatic control of glucose, lipids and energy metabolism (Hu *et al.* 1996; Díez and Iglesias 2003) (table 2). Further, Chauhan *et al.* (2012) had observed nominal associations of *CHDH* (rs4563403, OR = 0.69 (95% CI: 0.52–0.92), $P = 0.01$), *TCN2* (rs1801198, OR = 1.24 (95% CI: 1.04–1.48), $P = 0.02$) and *MTR* (rs16834521, OR = 0.82 (95% CI: 0.68–0.99), $P = 0.04$) in the discovery phase, but no association was observed after meta-analyses (table 2).

The associations of several other genes such as *PPARG*, *TNF-α*, *Myostatin*, *DOK5*, *UCP2*, *LMNA*, *IRX3*, *POMC*, *APOE* and *INSIG2* with obesity have been reported in studies with relatively small sample size (*n* range: 335–1006) with an OR range of 1.3–5.6 in different Indian population groups (Bhagat *et al.* 2010; Mahajan *et al.* 2010; Srivastava *et al.* 2010; Tabassum *et al.* 2010; Sharma *et al.* 2011; Bhatt *et al.* 2012a, b; Srivastava *et al.* 2016a, b; Prakash *et al.* 2017) (table 2). More comprehensive studies are needed before ruling out the role of these candidate genes in predisposition of obesity.

Genetic associations with BMI

The categories of BMI are widely used for assessing the obesity status. An elevated BMI increases the risk of mortality and is associated with several adverse health outcomes, like T2D, CVDs, and continues to remain as a significant public health problem (Misra and Shrivastava 2013). A total of 32 studies have made an attempt to examine the roles of previously known genetic polymorphisms in relation to BMI among Indians. Of these, 21 studies showed significant associations with BMI (table 3).

Taylor *et al.* (2011) had studied the effects of *FTO* and *MC4R* variants in 3390 sib-pairs recruited from four Indian cities, and showed associations of *FTO* (*Z* score=0.08, 95% CI: 0.02–0.14, $P = 0.009$) with BMI, and no such association was observed for *MC4R*. They had also performed an interaction analysis between the *FTO* and *MC4R* loci and rural/urban dwelling in association with BMI, but no strong evidence was detected (Taylor *et al.* 2011). In a population-based cross-sectional study from the rural and urban regions of south India, *FTO* (rs9939609) was shown to be associated with BMI only in adulthood, and not at younger ages (Vasan *et al.* 2012). On comparing the effect sizes of two SNPs of *FTO* (rs9939609 and rs17782313) on BMI in rural and urban groups, the carriers of *FTO* risk allele was associated with 1% increase in BMI ($\beta = 0.020$ SD/allele, $P = 0.026$) in the urban group than in the rural group, and were suggested to be influenced by urban living (Vasan *et al.* 2012). Interestingly, in a school-based case–control study, the *FTO* variant (rs9939609) showed 0.88% BMI variance in urban Indian children (Dwivedi *et al.* 2012) which is almost four times higher than that reported for adult BMI variance (0.20%) in South Asians (Li *et al.* 2012). These findings have clearly indicated higher impact of *FTO* variants in children than in adults.

The association of *MC4R* variant (rs17782313) with BMI is relatively well studied in Indian children and had shown ~2.5 kg/m^2 increased BMI in comparison with wild genotypes (Dwivedi *et al.* 2013). Similar association has been reported in adults, i.e. ~0.8 kg/m^2 increased BMI among homozygous adults for effect allele in comparison with common allele (Dwivedi *et al.* 2013). Indian children with risk allele of *MC4R* have ~2-fold higher BMI (*Z* score=0.24) when compared with European children (*Z* score=0.01–0.13) (Loos *et al.* 2008; Dwivedi *et al.* 2013). The risk alleles of *MC4R* variants (rs17782313 and rs12970134) are more prevalent in Indians (~36–40%) compared with Europeans (~27–31%), Asians (~18–24%) and Africans (~13–31%) (HapMap release no. 27), suggesting possible higher population attributable risk for obesity in Indians. Further, a school-based case–control study has evaluated the associations of variants in *PBEF1* (rs3801266, $\beta = 0.17$), *IL6* (rs2069845, $\beta = 0.12$) and *LEPR* (rs1137100, $\beta = 0.15$) with BMI in urban Indian children, suggesting the role of inflammatory genes in predisposition to obesity in childhood (Tabassum *et al.* 2012a) (table 3).

Gupta *et al.* (2013) conducted the second largest population-based study on obesity-related traits on 2528 sib-pairs recruited from four Indian cities. They had examined the influence of 25 T2D-associated loci on obesity risk using sib-pair design which is resistant to population stratification and decreases the likelihood of false-positive associations. They had found associations of *CXCR4* (rs932206, $\beta = 0.13$) and *HHEX* (rs5015480, $\beta = 0.09$) with higher BMI suggesting the role of T2D-associated loci in influencing the measures of obesity in the Indian population (Gupta *et al.* 2013) (table 3).

In studies primarily based on T2D samples, analysis for obesity traits was conducted on control samples. For instance, seven Indian studies have reported significant associations of SNPs with BMI in control subjects. The association of *FTO* with T2D is mediated through BMI is well-known among Europeans (Frayling *et al.* 2007). Yajnik *et al.* (2009) had reported weaker association between the *FTO* variant (rs9939609) and BMI (*Z* score=0.06, 95% CI: 0.01–0.10) among controls of Indo-European and Dravidian ancestry than the previously reported effect in Europeans (*Z* score=0.1, 95% CI: 0.09–0.12) (Frayling *et al.* 2007). Similarly, associations of SNPs near *MC4R* (rs12970134 and rs17782313) with BMI ($p = 4.1 \times 10^{-4}$ and 2.1×10^{-4}, respectively) was reported in 1549 control subjects of Indo-European ethnicity (Janipalli *et al.* 2012). Further, two studies with a relatively large sample size ($N = 1006$) had reported significant associations of variants in *DOX5* (rs6064099, $P = 7.0 \times 10^{-3}$) (Tabassum *et al.* 2010) and *TNF-α* (rs2229094, $P = 0.008$

and rs1800630, $P = 0.01$) (Mahajan *et al.* 2010) with BMI among controls of north India belonging to Indo-European ethnicity (table 3).

In addition, several studies with a relatively small sample size (n range: 255–642) had reported the associations of genetic variants of *UCP2*, *LPL*, *LMNA*, *Myostatin*, *PPAR-γ2* and *INSIG2* (Cassell *et al.* 1999; Radha *et al.* 2007; Sharma *et al.* 2011; Bhatt *et al.* 2012a, b; Prakash *et al.* 2017) with BMI in different population groups of India. A total of 23 variants in 16 genes have reported associations with BMI in the Indian population (table 3). More studies with large sample size are needed to validate these loci on anthropologically well-defined populations of India.

GWASs conducted in European populations have identified more than 100 genetic variants that influence BMI (Locke *et al.* 2015). Of these, only very few have been validated in Indian populations. Since the distribution of body fat in India is different from Europeans (Rush *et al.* 2009), the identification of genetic variants related to BMI at a genomewide scale is required for the Indian population with emphasis on exploring gene environmental interactions in predisposing increased adiposity levels.

Genetics of body fat distribution

Genetics of body fat distribution is relatively less investigated, around the world, in comparison with obesity and BMI, and generally restricted to two measures, i.e. WC and WHR and only a few attempts have been made to study genetic variants of HC and body composition measures. A total of 23 genetic studies in India had reported the association of studied markers with WC or WHR (table 4).

Association of the *FTO* locus has been studied in different Indian populations, not only with BMI but also with other measures of adiposity. The observed effect sizes of *FTO* variants (rs9939609 and rs8050136) and their contribution to variance of adiposity traits (WC, HC and WHR) in Indian children are higher than adults (Li *et al.* 2012). For adiposity parameters (WC and WHR), age-dependent effects of *FTO* have been suggested with higher contribution to the variance in children (0.54–0.65%) than South Asian adults (0.03–0.10%) (Dwivedi *et al.* 2012). The effect of rs9939609 was also examined in Indian adolescents and was found that carriers of homozygous risk allele displayed a 0.007 unit increase in the WHR with each copy of the *FTO* risk allele (Vasan *et al.* 2013) even after adjusting for BMI ($\beta = 0.006$, 95% CI: 0.001–0.012, $P = 0.021$) which may predispose to future metabolic risk in adulthood (Vasan *et al.* 2013) (table 4). The WHR also correlates strongly with insulin resistance and dyslipidaemia among Indians and other ethnic groups independent of overall obesity (Dhawan *et al.* 1994).

The widely studied *FTO* variant (rs9939609) is not only associated with WC and WHR but evidence of its association was also found with skinfold measures: abdomen ($P = 0.014$), triceps ($P = 0.003$), biceps ($P = 0.004$), subscapular ($P = 0.003$), thigh ($P = 0.042$) and body fat percentage (BF%) ($P = 0.005$) in individuals recruited from the Vellore birth cohort (Vasan *et al.* 2012). Other variants of *FTO* (rs1421085, rs9930506 and rs3751812) are not well studied in the Indian population, only a few studies have shown significant associations of these variants with WC (Chauhan *et al.* 2011; Moore *et al.* 2012) (table 4).

Further, association of *MC4R* (rs17782313 and rs12970134) with adiposity measures has been indicated that these variants might mediate susceptibility to obesity through overall body size (Hardy *et al.* 2010). In comparison with wild genotypes, both homozygous children and adults for effect allele (rs17782313) had ∼6.4 and ∼1.5 cm increased WC, respectively (Dwivedi *et al.* 2013). In contrast, Vasan *et al.* (2012) failed to detect any association of variants near *MC4R* with adiposity measures (WC and HC) after adjusting for height, suggesting an association with a larger body frame than obesity related traits in younger age groups. In comparison with WC and WHR, very few studies ($n = 11$) have shown genetic associations with HC (Yajnik *et al.* 2009; Been *et al.* 2010; Sanghera *et al.* 2010; Sharma *et al.* 2011; Taylor *et al.* 2011; Bhatt *et al.* 2012b; Dwivedi *et al.* 2012; Janipalli *et al.* 2012; Tabassum *et al.* 2012b; Vasan *et al.* 2012; Ramya *et al.* 2013). It was reported that each additional copy of the risk allele at the rs17782313 of the *MC4R* gene was associated with a 0.06 Z score increase in HC among the individuals recruited from four Indian cities (Taylor *et al.* 2011) (table 4).

In addition, some studies have used more precise methods for assessing regional deposition of fat such as computed tomography scan (Vimaleswaran *et al.* 2006b), dual-energy X-ray absorptiometry scan (Vimaleswaran *et al.* 2006a; Sharma *et al.* 2011, 2013; Vikram *et al.* 2011; Bhatt *et al.* 2012a), magnetic resonance imaging (Sharma *et al.* 2011, 2013; Vikram *et al.* 2011) and bioelectric impedance (Bhagat *et al.* 2010; Dhall *et al.* 2012; Prakash *et al.* 2012). The first study quantifying regional fat deposition had reported the association of *PPARGC1A* variant (Gly482Ser) with visceral fat ($P = 0.001$), subcutaneous fat ($P = 0.001$), abdominal fat ($P = 0.004$), central abdominal fat ($P<0.0001$) and nonabdominal fat ($P<0.0001$) among the normal glucose tolerant (NGT) in the south Indian population (Vimaleswaran *et al.* 2006a). Vikram *et al.* (2011) had explored the association of *TNF-α* with body fat distribution among north Indians and failed to detect any relationship.

Variants in several other genes such as *FOXA2* (Tabassum *et al.* 2008), *UCP2* (Srivastava *et al.* 2010), *ADIPOQ* (Sanghera *et al.* 2010), *IL6* (Gupta *et al.* 2011), *LMNA* (Sharma *et al.* 2011), *Myostatin* (Bhatt *et al.* 2012a), *AMD1* (Tabassum *et al.* 2012b) and *NGN3* (Gupta

et al. 2013) were also associated with measures of body fat distribution (table 4).

Since body fat distribution reflects regional adiposity and its pattern is different in the Indian population when compared with Europeans (Sniderman *et al.* 2007), there is a need for genetic studies on body fat distribution measured in detail using advance imaging techniques in India.

Sexual dimorphism

To dissect the genetic architecture of sexual dimorphism in obesity, very few studies with obesity as a primary outcome of interest, have performed sex stratified analysis and showed different effect sizes in males and females. Gupta *et al.* (2013) had made an attempt to understand the genetics associated with sexual dimorphism in sib-pairs (males = 436 pairs and females = 331 pairs). They identified a variant in *CXCR4* (rs932206) showing association with overweight in both sexes (OR = 1.80), but the effect was observed only in males, which may be due to smaller sample size of females. Other variants in *TCF2* (rs757210, OR = 0.57) and *LOC646279* (rs1256517, OR = 0.29) were shown to be associated with protective effects against overweight in females with twice the effect size compared with males (Gupta *et al.* 2013).

Sexual dimorphism is a well-marked feature of body fat distribution. Both males and females have different patterns of body fat distribution which defines their body shape (Wells 2007). Genetic variants associated with sexual dimorphism play a vital role in regulation of body fat distribution traits (Heid *et al.* 2010; Shungin *et al.* 2015). Sexual dimorphism in body fat distribution is not well studied in the Indian population. Vikram *et al.* (2011) had investigated the association of variants in *TNF-α* (–308G>A) with subscapular skinfold in males and total BF% in females. It was found that the females with at least one single effect allele of *TNF-α* (–308G>A) had significantly high BF% and total skinfold, whereas higher values of WHR were observed in males, suggesting a gender-specific role of this polymorphism in body fat distribution (Sharma *et al.* 2013). Low statistical power due to small sample size make these studies inconclusive, and demands more research using large sample sizes to confirm these associations. For better understanding of adiposity, research exclusively based on sexual dimorphism in body fat distribution among Indians is needed as it can yield insights into the gender-specific risk factors and causes of overall obesity.

Lifestyle factors

Interplay between the genetic and environmental factors plays a vital role in modulating predisposition to obesity. In India, limited studies (n = 2) have investigated gene–environment (GxE) interactions. For instance, Taylor *et al.* (2011) had studied GxE interactions, among rural/urban dwellers of Indian Migration Study to investigate whether the urban or rural environment modifies genetic risk of obesity. They had found stronger association of *FTO* with weight in urban dwellers (Z scores=0.15, 95% CI: 0.01–0.29) as they were found to be physically inactive and consuming higher levels of dietary fat intake than rural dwellers. Bhagat *et al.* (2010) have also reported that subjects with *PPARG AB* allele were less physically active and had a greater intake of calories and fats.

Large-scale studies with detailed information on lifestyle and dietary intake are needed for identifying GxE interactions as this may facilitate the choice of more effective measures in prevention of obesity based on the individualized genetic make-up.

Biological pathways

The biological pathways related to genes studied in the Indian population supported strongly the role of central nervous system in obesity susceptibility. Several genes have been identified but the functional role could be assigned to handful of them involved in the central neuronal signalling pathway (*NPY* and *MC4R*) (Bhaskar *et al.* 2010; Dwivedi *et al.* 2013), energy metabolism and thermogenesis (*UCP1* and *UCP2*) (Srivastava *et al.* 2010; Dhall *et al.* 2012), homocysteine metabolism/one carbon metabolism (*AMD1*) (Tabassum *et al.* 2012b), adipogenesis (*LPL*, *LMNA*, *PPAR-γ2*, *ADIPOQ*, *APOE* and *INSIG2*) (Radha *et al.* 2007; Sharma *et al.* 2011; Bhatt *et al.* 2012b; Ramya *et al.* 2013; Srivastava *et al.* 2016b; Prakash *et al.* 2017), the insulin signalling pathway (*PPARGC1A*) (Vimaleswaran *et al.* 2006a), the leptin insulin signalling pathway (*LEPR* and *resistin*) (Gupta *et al.* 2011; Tabassum *et al.* 2012b; Dasgupta *et al.* 2014) and inflammatory cytokine (*TNF-α* and *IL6*) (Vikram *et al.* 2011; Tabassum *et al.* 2012a). To understand the biological processes controlled by other identified genes leading to obesity, there is a need for pathway-based validation of genetic polymorphisms, identified by GWASs related to obesity in the Indian population.

Limitations of the studies

Most of the studies conducted in India lack information on lifestyle risk factors like unhealthy dietary intake and physical inactivity which can influence the effects of genetic variants on obesity and its measures. A large number of studies have used case–control design, even for studying quantitative traits like BMI and WHR, where cases were defined as T2D or related metabolic disorders. For studying obesity, very few studies have taken cases defined by obesity which is why the majority of findings from Indian studies are based on control samples only, and may be considered as drastically biased. Two studies have not

reported whether the investigated polymorphisms were in the Hardy–Weinberg equilibrium or not, which is an important quality control measure (Cassell *et al.* 1999; Gupta *et al.* 2012). The availability of the limited number of large population-based resources in India is one of the reasons that very few studies have explored genetics of sexual dimorphism with body fat distribution. Moreover, validations of findings of GWASs conducted on Western populations are limited to few genetic variants in India. So far, there has been only a single meta-analysis related to obesity and its measures were published from India (Vasan *et al.* 2014). Differences in sample size, study design and SNPs studied made it difficult to perform meta-analyses for the *FTO* gene.

In conclusion, the compilation of genetic studies related to obesity and its measures summarized in our critical review provides a comprehensive update on the current knowledge on genetic basis of obesity and related measures among Indian populations. There are some research gaps which pose a challenge in understanding general pathways underlying obesity susceptibility such as small sample size, differences in methodology used across studies, limited information on obesity susceptibility loci and lack of validation studies that may reflect differences in the genetic background. Moreover, given the high heritability estimates for obesity and its measures, only a small proportion of variance can be explained by the existing knowledge of identified genetic variants associated with adiposity across the globe. We emphasize on the need for more genetic studies to explore the missing heritability and aetiology of obesity in the Indian subcontinent.

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