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REVIEW

Sex Disparities in Obesity: A Comprehensive Review of Hormonal and Genetic Influences on Obesity-Related Phenotypes

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ABSTRACT

The Worldwide Incidence of Obesity, which tripled in 2016 from 1975, is a leading risk factor for chronic diseases. The presence of sex-dependent disparities in obesity has spurred increased interest in understanding the diverse environmental and genetic factors influencing this condition. Typically, men tend to have more visceral adipose tissue (VAT), while women generally have higher amounts of subcutaneous adipose tissue (SAT). These differences have been largely attributed to the effects of sex hormones, particularly estrogen. However, large-scale genome-wide association studies (GWAS) have identified genetic factors associated with sex-dependent disparities in obesity-related traits, which revealed that the role of estrogen may have been overemphasized. This review aims to summarize sex-specific differences in adipose tissue distribution and adipose tissue type such as white adipose tissue (WAT) and brown adipose tissue (BAT). Additionally, the mechanisms underlying the development of sex-specific characteristics are explained, with a focus on estrogen and obesity-associated genes. Specifically, we propose a list of GWAS-derived genes that may be responsible for the observed sex differences in obesity, which could significantly contribute to the existing literature.

1 | Introduction

The World Health Organization (WHO) has reported that the worldwide incidence of obesity (BMI > 30) has tripled since 1975 [1]. Because individuals with obesity are at a higher risk of developing Type 2 diabetes (T2D), cardiovascular disease (CVD), and cancers of the esophagus, liver, breast, and colon than individuals with normal weight, effective weight reduction interventions are critical [2, 3]. Notably, the incidence of obesity is higher in women than in men. According to a WHO report published in 2021, the global obesity rate is 26%, comprising 15% of women and 11% of men [1], thus suggesting that sex disparities in obesity and obesity-associated diseases require special attention. Sex-associated disparities in obesity are influenced by many environmental factors and genetic factors, including those on the X chromosome and autosomes [4]. Among them, gonadal hormones and chromosomal gene expression are the main drivers of biological sex differences.

Within the many features of sex disparities in obesity, research attention has focused on the distribution of adipose tissue as excess abdominal fat accumulation is known to trigger systemic

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inflammation [5]. In general, men have a higher percentage of VAT to body weight than women, and women have a higher percentage of SAT to body weight than men [6, 7]. Estrogen is a major gonadal hormone responsible for these sex differences in fat deposition, protecting women from detrimental metabolic consequences [8]. Hence, the increased CVD risk among postmenopausal women has been explained by accelerated visceral fat deposition. Estrogen also plays a pivotal role in BAT thermogenesis [9]. BAT has a higher metabolic rate than WAT, and the volume of BAT is associated with increased whole-body lipolysis, free fatty acid (FFA) cycling, FFA oxidation, and adipose tissue insulin sensitivity [10].

Recently, GWAS has been facilitated by advances in genetic analysis technology with the completion of the human genome project. In fact, there are hundreds of sex-specific genetic loci associated with obesity, which are located not only on the sex chromosome but also on other chromosomes [11]. However, the genetic links to the molecular mechanisms underlying sex specificity are still not fully understood. This systematic review aims to pinpoint biological factors, including a sex hormone, estrogen, as well as genes located on both autosomes and sex chromosomes, in association with sex differences in obesity and its metabolic outcomes.

The initial PubMed search using the keyword "sex differences" yielded 247,761 records. To narrow the selection, only articles published between 2013 and 2023 were included, eliminating 128,366 records and leaving 119,395 for screening. Next, filtering by article type (classical article, clinical study, clinical trial, controlled clinical trial, meta-analysis, observational study, randomized controlled trial, review, and systematic review) further reduced the dataset, excluding 102,334 articles and resulting in 17,061 for retrieval. The search terms "sex differences & fat distribution" "fat metabolism" "WAT" "BAT" "sex differences & obesity & estrogen" "estrogen receptor α" "estrogen receptor β" "male hormones" "gene expression" "GWAS" "X chromosome" "autosome" were applied to identify relevant studies. An additional screening excluded 34 articles that did not meet the inclusion criteria, which were: (1) peer-reviewed original research articles and systematic review articles investigating the relationship between obesity or obesity-related metabolic indicators and genes, (2) studies using either human subjects or animals, (3) articles with clearly defined methodology, and (4) articles reporting key outcomes associated with obesity. This process yielded 119,395 eligible articles, of which 154 were cited. Gene single nucleotide polymorphism (SNP) information was derived from GWAS references, which used the data-driven expression-prioritized integration for complex traits (DEPICT) method to select responsible genes. The initial screening was independently conducted by two authors. The search results were then reviewed by another author to confirm they met the predefined inclusion criteria.

2 | Sex Disparities in Obesity Prevalence: Insights From Population-Based Studies

Differences in adipose tissue distribution between men and women have been extensively demonstrated, and those differences have been shown to have close linkages to metabolic diseases. Sex differences in the quantitative ratio of WAT and BAT have also been noted. Molecular mechanisms relating these sex-specific differences to metabolic phenotypes are the focus of interest to understand the sex-specific characteristics of lipid metabolism and associated disease incidences.

2.1 | Adipose Tissue Distribution and Associated Metabolism

Body fat is generally categorized as either essential or storage fat. Essential fat compartments are distributed in the central nervous system, bone marrow, heart, lungs, liver, kidneys, spleen, and muscles, contributing to total body fat mass [12]. Storage fat, including SAT and VAT, is accumulated in the subcutaneous or abdominal region to protect internal organs from external influences and serve as an energy reservoir.

The difference in body composition between men and women becomes evident during puberty when circulating estrogen surges in women. This results in distinct disparities in muscle mass and body fat mass between the sexes [13]. Women tend to have higher fat mass and lower muscle mass [14]. Consequently, the rate of women with obesity remains elevated throughout their lifespan. Nevertheless, in women, estrogen inhibits fat accumulation associated with metabolic diseases by promoting SAT accumulation and increasing BAT activity [15]. In particular, SAT exhibits a lower rate of lipolysis compared to VAT [16] and is notably associated with less inflammation during obesity [17]. In addition, SAT is more active in the absorption of circulating FFAs and triglycerides (TGs) and may actually provide a protective effect against obesity-related diseases [17]. Estrogen may additionally modulate appetite-related hormones, including leptin [18], brain-derived neurotrophic factor (BDNF) [19, 20], melanin-concentrating hormone [21], and ghrelin [22], while also stimulating energy expenditure. These effects contribute to reducing body weight gain and inhibiting the development of obesity [23].

Sex differences in the above-mentioned adipose tissue distribution possibly affect the type and severity of metabolic diseases. Visceral adipocyte size is positively correlated with the levels of plasma apolipoprotein B (Apo B), total cholesterol, low-density lipoprotein (LDL) cholesterol, and triacylglycerol (TG), elevating the risk of CVD [24]. Subcutaneous adipocyte size is positively associated with insulin sensitivity [25]. Therefore, individuals with small subcutaneous adipocytes are more prone to T2D than those with large subcutaneous adipocytes [25]. Nevertheless, estrogen deprivation in women is associated with an increased risk of T2D [26], suggesting that estrogen plays an important role in sex-associated differences in adiposity-related clinical manifestations.

While congenital sex differences play a role in adipose tissue distribution and related metabolism, a few environmental factors, including sleep and exercise, influence body adipose tissue distribution in a sex-dependent manner. Recent research indicates that sleep disturbance accelerates weight gain and VAT accumulation in both premenopausal and postmenopausal women [27, 28]. Additionally, exercise intervention has revealed variations in VAT reduction based on the intensity of aerobic exercise,

including full-speed sprint interval training, high-intensity interval training, moderate-intensity continuous training, and no training [29].

2.2 | Types of Adipose Tissue: WAT and BAT

In humans, there are two main types of adipose tissue: WAT and BAT. WAT is anatomically divided into two main depots: SAT and VAT. SAT is located beneath the skin, while VAT surrounds internal organs. Functionally, WAT primarily stores excess energy in the form of TGs, whereas BAT is specialized in thermogenesis, converting stored energy into heat [30].

The expansion of WAT is associated with obesity and the development of obesity-related complications [31]. Most of the relevant WAT depots are located within the visceral cavity and include intrahepatic fat (fat accumulated within hepatocytes), epicardial WAT (epiWAT, located between the heart and the pericardium), perivascular WAT (PVAT, surrounding major blood vessels), mesenteric WAT (MWAT, adjacent to digestive organs in the mesentery), omental WAT (OWAT, forming a fat apron extending over the intestines, liver, and stomach), and retroperitoneal WAT (RWAT, surrounding the kidneys) [32]. The last three depots (MWAT, OWAT, and RWAT) are collectively classified here as VAT [32]. Additionally, the body distribution of WAT differs between men and women [31].

Unlike WAT, the body distribution of BAT is similar in men and women, predominantly located in the cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal areas, with the supraclavicular regions being the most common sites of active BAT [33]. Women tend to exhibit higher BAT activity and BAT mass compared to men [34]. Due to this heightened activity, women more frequently demonstrate detectable BAT when assessed using 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) [34, 35]. 18F-FDG-PET/CT has been used to quantify and visualize BAT with the ability to absorb 18F-FDG, allowing for precise localization [36, 37]. 18F-FDG PET/CT is a technique utilizing the principle that the metabolically active tissues, such as BAT, absorb deoxyglucose. On the other hand, imaging techniques such as magnetic resonance imaging are more suitable for analyzing the anatomical structure and composition of WAT, exerting low metabolic rates with minimal deoxyglucose uptake [38, 39].

Uncoupling protein-1 (UCP1) is a mitochondrial protein primarily expressed in brown and beige adipose tissue, where it facilitates thermogenesis by uncoupling oxidative phosphorylation, thereby dissipating energy as heat instead of storing it as ATP. A study on BAT activity in peripheral adipose tissue found that women exhibited a greater presence and expression of BAT expressing UCP1 compared to men [40]. Additionally, in one animal study, female mice fed a high-fat diet (HFD) exhibited greater vascularization of perigonadal WAT than male mice, and adipocytes in female mice showed a browning phenotype characterized by increased UCP1 expression [41]. These disparities resulted in sex-specific differences in adipose dysfunction (leptin and adiponectin expression ratio) and the development of obesity-related metabolic dysfunction such as alterations in insulin sensitivity [41].

In a clinical study, the presence of BAT inversely correlated with the prevalence of CVD, while higher BAT expression was associated with improved levels of blood glucose, TG, and high-density lipoprotein (HDL) levels [42]. Overall, BAT activity may vary between men and women based on its distribution, and sex differences in obesity-induced metabolic disorders may be elucidated by BAT activity. Nevertheless, we recommend further molecular biological studies to analyze specific contributing factors.

3 | Estrogen Plays a Pivotal Role in Sex-Dependent Differences in Obesity: Mechanistic Insights

Sex differences in the distribution and the type of adipose tissue have mostly been explained by sex hormones, particularly by the availability of estrogens. Sex hormones, in conjunction with sex hormone receptors, regulate lipid metabolism, appetite, and energy homeostasis. In this section, the mechanistic role of estrogen and its receptors in adipogenesis and related metabolic consequences are discussed.

3.1 | Estrogen and Adipose Tissue Distribution

Both genetic factors and environmental factors including physical activity and diet, and stress, influence the volume of total body fat, VAT, and SAT. However, the most significant factor driving sex-specific differences in adipose tissue distribution between men and women is estrogen [43]. In a murine model, tissue 17β-estriol level was 1.5–2 times higher in SAT compared to VAT depots, suggesting SAT depots are more sensitive to the action of estrogen [44]. In premenopausal women, estrogen receptor-1 gene (*ESR1*) expression was higher in VAT than in SAT, while estrogen receptor-2 gene (*ESR2*) expression was lower in VAT than in SAT in both premenopausal and postmenopausal women [45]. *ESR1* polymorphisms were associated with body weight, adipose tissue distribution, and total cholesterol levels, whereas *ESR2* polymorphisms were related to total cholesterol, TG levels, and body fat percentage [45].

Estrogen binds to estrogen receptors (ERs) to regulate the expression of genes involved in adipose tissue accumulation and distribution [45, 46]. A previous study showed that the lower expression of ERα in male VAT upregulates autophagy activity, thereby accelerating VAT lipogenesis [47]. When fed a HFD, ERα-knock out female mice exhibited an increase in VAT compared to control mice, along with increased body weight [38]. These results clearly suggest that estrogen interacts with its receptor to inhibit VAT accumulation. In another animal study, ovariectomized female mice exhibited an increase in VAT compared to the control group. However, when treated with estrogen, VAT volume returned to those observed in females with a normal cycle [48]. Interestingly, estrogen-treated male mice showed an increase in SAT volume and an overall increase in body fat [48]. These findings were also observed in transgender individuals transitioning from male to female, where estrogen treatment resulted in greater SAT accumulation compared to VAT [49].

ERα primarily influences fat distribution through metabolic signaling rather than directly altering fat cell lineage or type.

In animal studies, wild-type control male mice exhibited higher VAT volume than females. However, deletion of ERα normalized autophagic activity and eliminated sex differences in VAT accumulation [47]. Mechanistically, ERα signaling activated mammalian target of rapamycin (mTOR), which phosphorylated and inhibited unc-51 like autophagy activating kinase 1 (ULK1), leading to the suppression of autophagy and VAT accumulation [47]. Additionally, ERα signaling interfered with the peroxisome proliferator-activated receptor gamma (PPARγ) pathway by reducing DNA binding of PPARγ and inhibiting the recruitment of the PPARγ coactivator CREB-binding protein (CBP) [50]. In OVX mice, 17β-estradiol treatment significantly reduced VAT volume, adipocyte size, and adipogenic marker gene expression [50].

Although not as influential as ERα, estrogen receptor beta (ERβ) has also been shown to have a direct anti-adipogenic effect on adipocytes. In particular, animal studies have demonstrated that treatment with an ERβ-selective ligand in HFD-fed male mice resulted in an increase in SAT while VAT remained unchanged [51]. In contrast, treatment with an ERβ-selective ligand in female mice fed a HFD exhibited weight loss, along with a reduction in both VAT and SAT [52]. One possible mechanism for the action of ERβ in lipid homeostasis is through signaling between ERβ and PPARγ. In this process, ERβ inhibits ligand-mediated PPARγ activity, resulting in reduced adipogenesis [53].

3.2 | Estrogen and the Accumulation of White and Brown Adipose Tissues

The expansion and reduction of WAT are influenced by estrogen [54]. Elevated estrogen levels increased SAT while decreasing abdominal WAT [55]. Notably, a higher ERα to ERβ ratio is observed in premenopausal women compared to postmenopausal women [56], which was associated with an expansion of subcutaneous WAT and a decrease in abdominal WAT production [54].

BAT activity also exhibits sex differences in response to estrogen. Although BAT stores are similar in men and women [33], women respond faster and show higher BAT activity when exposed to cold than men [57]. Beta adrenergic receptors (ADRBs), especially ADRB1, induce UCP1 mRNA expression and lipolysis, releasing glycerol [58]. An observational study showed that BAT thermogenesis stimulated by either cold temperature or meal was greater in women than in men [59]. Regression analyses indicated stimuli-induced increases in BAT temperature correlated with 17β-estradiol concentrations [59, 60]. Animal studies further elucidated these mechanisms. ERα-knockdown male mice exhibited less FDG uptake and lower UCP1 expression in BAT when exposed to cold compared to wild-type male mice [61]. Moreover, male mice administered estrogen showed a simultaneous increase in both BAT and core temperature [62]. Although the ERβ-associated mechanisms are less understood compared to ERα, ERβ has been shown to increase the expression of BAT marker genes (*Ebf2, Foxc2, Pdk4, and Tbx2*) through the action of the estrogen receptor β-selective ligand (β-LGND) [63]. ERβ is proposed to inhibit preadipocytes and mesenchymal stem cells from differentiating into adipocytes, instead promoting their differentiation into BAT [63]. Also, infusion of an ERβ isoform-selective estrogen receptor ligand into ovariectomized female mice with overweight significantly increased the expression of UCP1, which decreased body weight and body fat mass, thus suggesting that ERβ is a potential target to control obesity [54].

4 | The Relationship Between Male Sex Hormones and Obesity in Men and Women

Androgen is a broad term referring to substances that function as male hormones, including testosterone, dehydroepiandrosterone (DHEA), and dihydrotestosterone (DHT). All male hormones interact exclusively with ARs and play a key role in various adipose tissue-related mechanisms, such as adipose tissue distribution, expansion, and lipid metabolism [64, 65].

Male sex hormones, particularly testosterone, play a significant but distinct role in obesity and fat metabolism in both men and women. In men, obesity is strongly associated with a decline in testosterone levels due to decreased sex hormone-binding globulin (SHBG) from obesity-induced hyperinsulinemia and increased aromatase activity in adipose tissue, which converts testosterone into estrogen [66]. This decline contributes to increased abdominal fat accumulation, reduced muscle mass, and a higher risk of metabolic syndrome [64]. Conversely, low testosterone itself can promote obesity, creating a bidirectional relationship [67]. A population study has shown strong negative correlations between testosterone levels and obesity-related markers, particularly VAT [68]. Testosterone also regulates fat metabolism by inhibiting lipoprotein lipase (LPL) [69] and reducing TG uptake in adipocytes while activating hormone-sensitive lipase (HSL), promoting fat breakdown [70]. Testosterone replacement therapy (TRT) in hypogonadal men has demonstrated benefits in reducing fat mass and improving metabolic parameters [71], though its effectiveness diminishes with age [72]. Androgen receptors (ARs) mediate the metabolic effects of testosterone [73]. In the Wnt signaling pathway, AR interacts with β-catenin to suppress fat accumulation [74]. According to animal studies, AR knockout (ARKO) male mice accumulate more VAT and exhibit metabolic dysfunction [75], which may influence WAT accumulation [76].

In women, androgens also influence adipose tissue distribution, though their role is more complex. The “backdoor” androgen synthesis pathway is particularly relevant in conditions like polycystic ovarian syndrome (PCOS), where excess androgens promote abdominal fat accumulation and metabolic disturbances [77]. In women with PCOS, resting metabolic rate (RMR) is comparable to controls, but those with high waist-to-hip ratios exhibit significantly lower RMR, suggesting that androgens may impact energy expenditure [78]. Postmenopausal women receiving androgen supplementation experience increased VAT and reduced SAT [79], an effect also observed in animal models and female-to-male transgender individuals undergoing androgen therapy [80, 81]. These findings indicate that while androgens contribute to obesity-related metabolic changes in women, their effects differ from those seen in men.

TABLE 1A | The list of obesity-associated genes on X chromosome with SNPs exhibiting sex differences.

	Gene	Associated traits	References (trait)
X-escape	*KDM5C*	(↑) Adipose tissue expansion.	[89, 93–95]
	DDX3X	(↓) Tumorigenesis/lipid accumulation/ApoB	[89, 93, 96–102]
	KDM6A/UTX	(↑) WAT differentiation/body weight/appetite (↓) BAT activity, leptin	[86, 89, 93, 103–105]
	EIF2S3X	(↑) Adipose tissue depot	[89, 93, 106]
	USP9X	(↑) Glucose uptake/glycolysis/lipogenesis	[89, 107, 108]
Putative-escape	*XIST*	(↑) Adiposity	[109–111]
	OGT	(↑) Food intake/hyperphagia/insulin/glucose/FFA/glucose uptake/glycolysis	[112–115]
	5-HTR2C	(↑) Food intake/hyperinsulinemia/obesity/lipogenesis (↓) BAT activity	[112, 116–119]
	TNMD	(↓) Insulin resistance	[120]

Note: (↑) positively associated traits; (↓) negatively associated trait.

5 | Sex Differences in Obesity-Associated Genes

While estrogen is traditionally regarded as the main biological factor underlying sex-specific adipose tissue distribution, emerging evidence underscores a significant role of sex chromosomes themselves. Male fetuses are consistently larger than female fetuses in both humans and mice [82, 83], and potential sex differences in body weight, height, lean mass, and total body fat mass are evident even before puberty [84, 85]. These findings indicate that sex hormones are not the only drivers of sex disparities in adiposity.

Recent epidemiological and experimental studies highlight that genes located on sex chromosomes contribute directly to the development of obesity-related traits in a sex-specific manner [86, 87]. Thus, understanding chromosomal gene expression is essential to fully explain sex-based differences in obesity phenotypes.

As genome-wide association studies (GWAS) continue to expand, increasing evidence indicates that, beyond sex chromosomes, autosomal genes also play a role in mediating sex differences in obesity. In this section, we systematically categorize these genes and describe the obesity-related traits they influence.

5.1 | Evidence From Animal Models: The Role of Sex Chromosomes

To distinguish the independent contributions of sex hormones and sex chromosomes, the Four Core Genotype (FCG) mouse model has been instrumental [86, 88]. This model separates chromosomal sex (XX vs. XY) from gonadal sex (male vs. female), creating four combinations: XX with female or male gonads, and XY with female or male gonads [86].

In response to HFD, XX mice—regardless of gonadal sex—demonstrated approximately double the fat accumulation, higher weight gain, dyslipidemia, and hyperinsulinemia compared to XY mice [89, 90]. These findings suggest that the presence of two X chromosomes confers a greater susceptibility to diet-induced obesity and metabolic disturbances [86, 89].

To discern whether this effect is due to the presence of two X chromosomes or the absence of the Y chromosome, further experiments compared XX, XO, XXY, and XY genotypes [86]. Mice with two X chromosomes (XX and XXY) had higher body weight and HDL cholesterol than those with one X chromosome (XO and XY) [76, 77], supporting the notion that X chromosome dosage, not the absence of the Y, influences metabolic risk.

5.2 | Obesity-Associated Genes on the X Chromosome

Several genes located on the X chromosome have been identified as contributors to sex differences in obesity [91, 92]. Table 1A summarizes X chromosome-linked escape or putative escape genes. Although the difference between XX and XY cells is mitigated by the transcriptional inactivation of one copy of the X chromosome in each cell of an XX individual, approximately 15% of genes escape X-chromosome inactivation [93, 121]. This table also lists key obesity-related traits and corresponding references to aid the interpretation of these sex-related genetic differences in obesity.

5.2.1 | X-Escape Genes

Kdm5c (Lysine demethylase 5C) is found in both mice and humans, and its expression levels in metabolic tissues, including adipose, liver, skeletal muscle, pancreas, hypothalamus, and small intestine [89, 94], are two times higher in female mice than in male mice [91, 94, 95], potentially contributing to sex differences. Recently, body weight gain and body fat content of reduced dosage of ***Kdm5c*** in female mice were reported to be similar to those in male mice [94].

DDX3X (dead-box helicae 3 X-linked) [89, 91], is thought to play a role in both the nucleus and cytoplasm [97]. In the nucleus, ***DDX3X*** is involved in transcriptional regulation, pre-mRNA splicing [97], and mRNA export [98], while in the cytoplasm, it regulates translation, cellular signaling [99], and viral replication [100]. In addition, dysregulation of this gene has been implicated in tumorigenesis [99]. Although the precise mechanistic association between *DDX3X* and adiposity has not yet been revealed, *DDX3* inhibits microsomal triglyceride transfer protein (MTP), which resulted in lipid accumulation and affected ApoB secretion in the liver [101]. The expression of ***DDX3X*** is upregulated when obesity-induced translocation of lipopolysaccharide (LPS) occurs, thus stimulating pro-inflammatory cytokine production [102].

KDM6A (lysine demethylase 6A) is also known as ***UTX*** [86, 89, 91, 103]. ***KDM6A*** is associated with obesity, accelerating WAT differentiation while suppressing BAT activity [104]. A recent study using Kdm6a-knockout mice found that ***KDM6A*** is associated with body weight gain in diet-induced obesity by suppressing leptin signaling that activates signal transducer and activator of transcription 3 (STAT3) and stimulates appetite [105].

Another X-escape gene known to be associated with adiposity is ***EIF2S3X*** (eukaryotic translation initiation factor 2 subunit 3 X-linked) [89, 91, 106]. The adipose transcriptome of offspring from dams consuming either a control or HFD exhibited higher ***EIF2S3X*** expression in females compared to males across all adipose tissue depots—SAT, VAT, and BAT—regardless of the dam's diet [106]. Furthermore, the expression of ***EIF2S3X*** was even higher in female offspring of dams consuming HFD [106].

USP9X (ubiquitin specific peptidase 9 X-linked) [89, 107, 108] is known to be associated with mechanistic target of rapamycin complex 2 (mTORC2) signaling [107]. Depletion of *USP9X* decreases mTORC2 signaling [107], which is associated with increased glucose uptake, glycolysis, and lipogenesis [108]. Therefore, increased expression of *USP9X* induces obesity by stimulating mTORC2 signaling.

5.2.2 | Putative-Escape Genes

XIST (X-inactive specific transcript), an X chromosome inactivating factor [109], exists only on the X chromosome and is present in both males and females, with a higher expression in females [110]. Although the precise mechanisms remain unclear, higher expression of *XIST* has been positively correlated with increased adiposity [111]. However, ***OGT (o-linked N-acetylglucosamine transferase)*** is a gene on the X chromosome that is involved in the regulation of food intake [112, 113]. Interestingly, HFD intake activates the expression of ***OGT***, which leads to hyperphagia, and ***OGT*** deficiency reduces the levels of serum insulin, glucose, and FFA [114]. In addition, the activation of ***OGT*** increased glucose uptake and glycolysis by regulating the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway [115]. ***5-HTR2C*** (5-hydroxytryptamine receptor 2C) [112, 116] is an X chromosome gene known as the serotonin receptor [117]. It is associated with increased food intake, leading to hyperinsulinemia and obesity [116]. In addition, ***5-HTR2C*** is upregulated in individuals and mice with obesity, stimulating its binding to serotonin, which in turn activates the extracellular-signal-regulated kinase (ERK)/c-Fos pathway and accelerates food intake [116]. Serotonin secretion also reduces BAT activity [118] and exacerbates lipogenesis in WAT [119], ultimately contributing to the development of obesity. Finally, although the precise mechanism remains unclear, ***TNMD*** (tenomodulin) is known to play a role in ameliorating insulin resistance in obesity [120].

5.3 | Sex-Dimorphic Autosomal Genes in Obesity

Genetic factors that affect sex differences in obesity exist not only on sex chromosomes but also on autosomes. GWAS have identified more than 100 genetic variants that contribute to body mass index (BMI) or WHR [11, 122]. In this review, we referred to several GWAS that provide a list of genes related to WHR adjusted with BMI (WHRadjBMI) [122–124]. WHRadjBMI is an easily measurable adipose tissue distribution phenotype that correlates with imaging-based adipose tissue distribution measures [125], reflects physiological differences in body fat and muscle mass between males and females [126], and is well established as a sex-specific marker of abdominal fat and adiposity [127]. WHRadjBMI has shown twin-based heritability estimates ranging from 30%–60% [123] and narrow-sense heritability estimates of ~50% in females and ~20% in males [123]. In addition, it is a predictor of T2D and coronary heart disease (CHD) risk through intermediates of blood lipids and glycemic phenotypes [127].

Table 1B summarizes autosomal genes classified based on whether their associations are stronger in one sex, opposite between sexes, or exclusive to males or females. Key obesity-related traits and supporting references are also included, offering a concise overview of sex-specific genetic contributions to obesity.

5.3.1 | Autosomal Genes With Stronger Obesity Links in Females

Large-scale human genetic studies have identified many sexually dimorphic loci for central obesity and adipose tissue distribution, with most loci showing stronger effects in women than in men [11]. In these studies, DEPICT was used to map genes associated with WHRadjBMI [122, 123]. DEPICT is a computational tool used in genetic studies such as GWAS to prioritize genes, biological pathways, and tissues that are likely involved in complex traits and diseases [182]. It uses expression data to reconstitute protein–protein interaction gene sets, mouse phenotype gene sets, Reactome pathway gene sets, Kyoto Encyclopedia of Genes (KEGG) pathway gene sets, and Gene Ontology (GO) term gene sets [182].

Fifteen genes are identified with heritability and variant effects that are generally stronger in females with obesity than in males with obesity [11]. Among them, 11 genes are reported to have specific functions in adipogenesis and related metabolism.

Vascular endothelial growth factor A (***VEGF-A***) is located on chromosome 6 [128]. Its association with obesity has been

TABLE 1B | The list of obesity-associated autosomal genes with SNPs exhibiting sex differences.

	Gene		Associated traits	References (trait)
Stronger links in females	*VEGF-A/VEGF-B*		(↑) Thermogenesis/insulin sensitivity	[122, 123, 128–130]
	PLXND1		(↑) WHR, T2D, VAT accumulation/ insulin resistance	[122, 123, 131–133]
	HOXC13		(↓) Obesity/triglyceride	[122, 123, 134, 135]
	BCL2		(↑) Leptin, Insulin/lipogenesis/food intake/ insulin resistance/adipogenesis/lipolysis	[123, 136–138]
	GDF5		(↑) Thermogenesis/insulin sensitivity/ differentiation into BAT (↓) Body fat	[123, 139, 140]
	SNX10		(↓) Lipolysis	[123, 141, 142]
	LY86/MD1		(↓) BMI/Adiposity/insulin resistance	[122, 143]
	CCDC92		(↑) Insulin sensitivity (↓) Obesity	[122, 144]
	ITPR2		(↑) Fasting condition (↓) Obesity	[122, 145, 146]
	GRB14		(↑) Obesity/WHR	[123, 147–149]
Opposite links in males vs. females	Positively associated in females and negatively in males	*SIM1*	(↑) Obesity/thermogenesis/ energy expenditure (↓) Food intake	[122, 150–152]
		NMU	(↑) Obesity/energy expenditure/ beiging of WAT/glucose tolerance (↓) Food intake/body weight/ eating behavior (dark-phase food intake) /leptin signaling	[122, 123, 150, 151, 153, 154]
	Positively associate in males and negatively in females	*GNPNAT1*	(↑) Diabetes/fatty acid oxidation/TCA cycle	[122, 155–158]
		SLC2A3	(↑) Obesity/glucose transport	[122, 159, 160]
		IRS1	(↑) Lipogenesis (↓) Diabetes	[122, 161]
		RXRA	(↑) Fatty acid oxidation (↓) Fatty acid synthesis	[122, 162]
		TTN	(↓) Total body fat mass/SAT and VAT mass	[122, 163]
Female-exclusive	*LYPLAL1*		(↑) WHRadjBMI/Lipogenesis/weight gain/body fat/adipocyte size	[122, 123, 147, 164–168]
	COBLL1		(↑) SAT accumulation	[122, 123, 147, 164, 169]
	PPARG		(↑) Adipogenesis/thermosensing response/beige adipocyte formation/energy expenditure	[122, 123, 147, 164, 170, 171]
	CMIP		(↑) T2D/Obesity	[122, 123, 172, 173]
	MEIS1		(↓) Adipogenesis/adipocyte differentiation	[122, 123, 174]
	KLF14		(↓) T2D/Fat mass/fat deposition in VAT	[122, 123, 175, 176]
	FAM13A		(↑) VAT/SAT ratio/adipocyte differentiation/ fasting insulin/WHRadjBMI/fatty liver (↓) Number of small adipocytes/ mitochondrial respiration	[122, 123, 177, 178]
	PDE3B		(↓) Insulin sensitivity	[124, 179]
Male-exclusive	*EDEM2*		(↑) Insulin secretion	[123, 180, 181]

Note: (↑) positively associated traits; (↓) negatively associated trait.

reported in studies of 210,088 individuals of European ancestry [123] and 320,485 individuals of European descent [122]. ***VEGF-B***, located on chromosome 11, was found to be associated with obesity in a study of 210,088 individuals of European ancestry [123]. Upon activation, ***VEGF-A*** and ***VEGF-B*** increase thermogenesis and insulin sensitivity [129, 130].

Plexin d1 (***PLXND1***), located on chromosome 3, was found in studies of 320,485 individuals of European descent [122] and 210,088 individuals of European ancestry [123], and it is positively correlated with WHR, T2D, and VAT accumulation [131]. Activation of ***PLXND1***, the receptor for Sema3E, promotes semaphorin 3E (Sema3E)-induced macrophage migration and pro-inflammatory cytokine expression [132]. The activation of Sema3E also inhibits the Akt signaling pathway, thereby interfering with insulin signaling, which results in increased insulin resistance [133].

Homeobox C13 (***HOXC13***), located on chromosome 12, has been suggested to be associated with obesity in studies of 320,485 individuals of European descent [122] and 210,088 individuals of European ancestry [123]. In fat mass and obesity-associated protein (*FTO*) deficiency, ***HOXC13*** is activated [134]. *FTO* was the first obesity-related gene identified through GWAS, and its expression is positively related to obesity, especially by increasing triglyceride levels in the liver [135].

The expression of B-cell lymphoma 2 (***BCL2***) located on chromosome 18 was found in a study of 210,088 individuals of European ancestry [123]. It is also increased in mice with obesity, stimulating the secretion of leptin, insulin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNFα), which activate the PI3K/Akt signaling pathway [136]. Activation of ***BCL2*** and the PI3K/Akt signaling pathway stimulates the mTOR pathway [137], resulting in increased lipogenesis, food intake, insulin resistance, adipogenesis, and lipolysis in metabolic tissues such as adipose tissue, liver, pancreas, and skeletal muscle [138].

Growth differentiation factor 5 (***GDF5***), located on chromosome 20, is found in 210,088 individuals of European ancestry [123] and is a member of the transforming growth factor-β (TGF-β) superfamily [139]. ***GDF5*** is known to mitigate excess body fat by increasing thermogenesis and insulin sensitivity through the activation of the p38/mitogen-activated protein kinase (MAPK) signaling pathway in WAT [140]. It also promotes differentiation of pre-brown adipocytes into BAT by increasing the expression of its gene in pro-brown adipocytes [139].

An autosomal gene on chromosome 7, sorting nexin 10 (***SNX10***) deficiency, activates lipolysis [141]. ***SNX10*** was also found in a study of 210,088 individuals of European ancestry [123]. In mice fed a HFD, CD36 expression increases [142], and the binding of CD36 to ***SNX10***/Akt leads to the formation of atherosclerotic plaques [141]. Concurrently, ***SNX10*** deficiency results in increased lipolysis through lysosomal acid lipase (LAL), leading to plaque regression via M2 cells [141].

Lymphocyte antigen 86 (***LY86***/***MD1***), located on chromosome 6, was found in a study of 320,485 individuals of European descent [122] and is downregulated in obesity [143]. In addition, the methylation level of the *LY86* gene is associated with BMI and shows positive correlations with adiposity, insulin resistance, and inflammatory markers [143].

Deficiency of coiled-coil domain containing 92 (***CCDC92***) found in a study of 320,485 individuals of European descent [122], located on chromosome 12, is negatively associated with obesity and positively associated with insulin sensitivity through inhibiting activation of nuclear factor kappa B (NF-κB) and NLR family pyrin domain containing 3 (NLRP3) inflammasome in a HFD-fed mice study [144].

Inositol 1,4,5-trisphosphate receptor type 2 (***ITPR2***) located on chromosome 12, which is also suggested in a study of 320,485 individuals of European descent [122], was shown to be decreased in mice with HFD-induced obesity [145], while its expression was increased in fasting conditions [146]. Growth factor receptor bound protein 14 (***GRB14***), found in studies of 210,088 individuals of European ancestry [123] and over 270,000 individuals with anthropometric traits [147], is located on chromosome 2 and has a stronger correlation in females with obesity compared to males with obesity [148]. In addition, ***GRB14*** is positively associated with WHR [149].

5.3.2 | Autosomal Genes With Opposite Obesity Links in Males vs. Females

1. Genes positively associated with obesity in females and negatively in males

SIM bHLH transcription factor 1 (***SIM1***) located on chromosome 6 was found in a study of 320,485 individuals of European descent [122]. Neuromedin U (***NMU***) located on chromosome 4 was found in studies of 320,485 individuals of European descent [122] and 210,088 individuals of European ancestry [123]. Both ***SIM1*** and ***NMU*** were positively associated with obesity in females but negatively associated with obesity in males [150, 151]. ***SIM1***, a transcription factor required for the development of the paraventricular nucleus of the hypothalamus, is known to reduce food intake and increase the energy expenditure [183]. In addition, ***SIM1*** deficiency is known to reduce the expression of UCP1 in BAT, leading to impaired thermogenesis [152]. ***NMU*** is a gene involved in the negative regulation of food intake, body weight, eating behavior (dark-phase food intake), and the leptin signaling pathway [153]. In both ***NMU***-deficiency female and male mice, energy expenditure and UCP1 expression are suppressed, whereas the increased expression of ***NMU*** has been shown to decrease food intake and increase energy expenditure [153]. In addition, peripheral administration of ***NMU*** promotes beigeing of WAT and improves glucose tolerance [154].

2. Genes positively associated with obesity in males and negatively in females

All five genes in this part were identified in 320,485 individuals of European descent [122]. A gene located on chromosome 14, glucosamine-phosphate N-acetyltransferase 1 (***GNPNAT1***), is known to be upregulated in diabetes and cancers of the lung, breast, and prostate [155–157]. It is also activated by acetyl-CoA,

a product of fatty acid oxidation or the tricarboxylic acid cycle (TCA) cycle [157]. Diet-induced increases in acetyl-CoA increase the expression of ***GNPNAT1***, and ***GNPNAT1*** activates tumor cell metabolism and promotes cancer progression [157, 158]. Solute carrier family 2 member 3 (***SLC2A3***), located on chromosome 12, is positively correlated with hypoxia-inducible factor 1 (HIF-1), which is increased in obesity [159] and is known to be involved in glucose transport [160]. Another autosomal gene located on chromosome 2 is insulin receptor substrate 1 (***IRS1***). In human adipocytes, the expression of ***IRS1*** is reduced in diabetes mellitus, while in non-alcoholic fatty liver disease (NAFLD) patients, liver ***IRS1*** is known to promote lipogenesis by activating FAS [161]. A gene located on chromosome 9 is retinoid X receptor alpha (***RXRA***). It is known to activate the AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor (PPAR) pathway, suppressing fatty acid synthesis and promoting fatty acid oxidation [162]. Titin (***TTN***) has been associated with decreased total body fat mass, SAT, and VAT, and increased risk of cancer cachexia [163]. The precise mechanisms by which this gene reduces fat mass are not well understood.

Other autosomal genes including IQ motif containing GTPase activating protein 2 (***IQGAP2***), protein tyrosine phosphatase receptor type D (***PTPRD***), sarcoglycan zeta (***SGCZ***), and CECR2 histone acetyl-lysine reader (***CECR2***) are located on chromosomes 5, 9, 8, and 22, respectively [122]. Although these have been shown to be associated with obesity through GWAS studies, their functions related to adipogenesis are unclear.

5.3.3 | Obesity-Associated Autosomal Genes Identified Exclusively in Females

These 22 genes were those whose expression changes were significantly associated with WHRadjBMI specifically in females based on the GWAS analyses.

GWAS including 320,485 individuals of European descent [122], 210,088 individuals of European ancestry [123], over 270,000 individuals with anthropometric traits [147], and 2958 subjects from Chinese community-based populations [164] concomitantly identified Lysophospholipase-like 1 (***LYPLAL1***), Cordon-bleu WH2 repeat protein like 1 (***COBLL1***), Peroxisome proliferator-activated-gamma (***PPARG***), C-maf inducing protein (***CMIP***), Meis homeobox 1 (***MEIS1***), Klf transcription factor 14 (***KLF14***), Families with sequence similarity 13 member A (***FAM13A***), and Phosphodiesterase 3 B (***PDE3B***) as female-specific obesity-associated genes.

LYPLAL1, located on chromosome 1, shows a strong association with WHRadjBMI and central obesity in females [165]. The exact functions in adipose tissue development and obesity are unknown; however, in a mouse model of HFD-induced obesity, this gene showed increased expression during lipogenesis and in mature adipocytes [165]. In addition, ***Lyplal1*** knockout mice on a high-fat high-sucrose (HFHS) diet had reduced weight gain, body fat percentage, and adipocyte size only in females [166]. In other studies, the expression of ***Lyplal1*** was negatively correlated with obesity only in females [167], and inhibition of this gene has been shown to increase glucose production in the liver [165, 168]. When fat depots of wild-type and ***Lyplal1***-knockout female mice were compared, the amount of ERα, which is a known obesity suppressor, was higher in wild-type females [166]. ***COBLL1***, located on chromosome 2, is shown to be increased in female SAT compared with that in VAT [169]; however, the precise mechanisms by which this gene is involved in obesity and why it is a sex-specific trait remain unclear. ***PPARG,*** located on chromosome 3, is known to promote adipogenesis by activating the obesity-susceptibility gene *TMEM18* [170]. ***PPARG*** serves as a crucial nuclear receptor necessary for the functionality of adipocytes, contributing to thermosensing responses and metabolic regulation while also promoting the formation of thermogenically proficient beige adipocytes to enhance energy expenditure [171]. ***PPARG*** target genes *LPL*, *FABP4*, *PLIN*, *ADIPOQ*, *LIPE*, and *SLC2A4* were downregulated in the later stages of adipocyte differentiation when ***PPARG*** expression was reduced [170].

CMIP, located on chromosome 16, has been found in studies of 320,485 individuals of European descent [122] and 210,088 individuals of European ancestry [123]. It is known to be positively associated with T2D risk only in females but not in males [172]. In a mouse study, ***CMIP*** expression in the liver tissue of ob/ob mice was significantly higher than in wild-type mice [173]. A gene identified in 320,485 individuals of European descent [122], ***MEIS1***, is located on chromosome 2. This gene is known to inhibit adipogenesis activated by SRY-box transcription factor 9 (Sox9) [174]. In Sox9 knockout 3T3-L1 cells, the expression of the adipogenic gene ***Meis1*** was significantly reduced compared to that in wild-type cells, and inhibition of ***Meis1*** expression by 90% accelerated adipocyte differentiation [174]. A study of 320,485 individuals of European descent [122] identified the gene ***KLF14***, located on chromosome 7, as being associated with an increased risk of T2D only in females [175]. ***Klf14*** deficiency has been shown to increase fat mass and shift fat deposition from subcutaneous to visceral fat deposits [176]. However, the mechanisms involved in its female-specific functions remain unclear. ***FAM13A***, located on chromosome 4, were found in studies of 320,485 individuals of European descent [122] and 210,088 individuals of European ancestry [123]. In mice fed HFD, ***FAM13A*** deficiency resulted in a decrease in the VAT/SAT ratio and an increase in the number of small adipocytes in the SAT [177]. In addition, ***FAM13A*** expression increases during adipose differentiation and is positively correlated with fasting insulin levels and WHRadjBMI [177]. Another study showed that ***FAM13A−/−*** mice are resistant to HFD-induced obesity and fatty liver, with increased mitochondrial respiration and AMPK activation [178]. ***PDE3B*** is located on chromosome 11 and was identified in a study of 23,095 African ancestry individuals [124]. ***PDE3B*** is known to regulate the NLRP3 inflammasome in adipose tissue and is negatively correlated with insulin sensitivity [179].

Other genes including tumor necrosis factor-alpha-induced protein 8 (***TNFA1P8)***, hydroxysteroid 11-beta dehydrogenase 2 (***HSD11B2***), glucosidase 2 alpha subunit (***GANAB***), potassium inwardly rectifying channel subfamily J member 2 (***KCNJ2***), CDP-L-ribitol pyrophosphorylase A (***ISPD/CRPPA***), and cancer susceptibility 8 (***CASC)***, NK2 homebox 6 (***NKX2–6***), EYA transcriptional coactivator and phosphatase 1/2 (***EYA1/2***), ribosomal protein S6 kinase A5 (***RPS6KA5***), golgin, RAB6 interacting (***GORAB***), HMG-box containing 4 (***HMGXB4***), sideroflexin

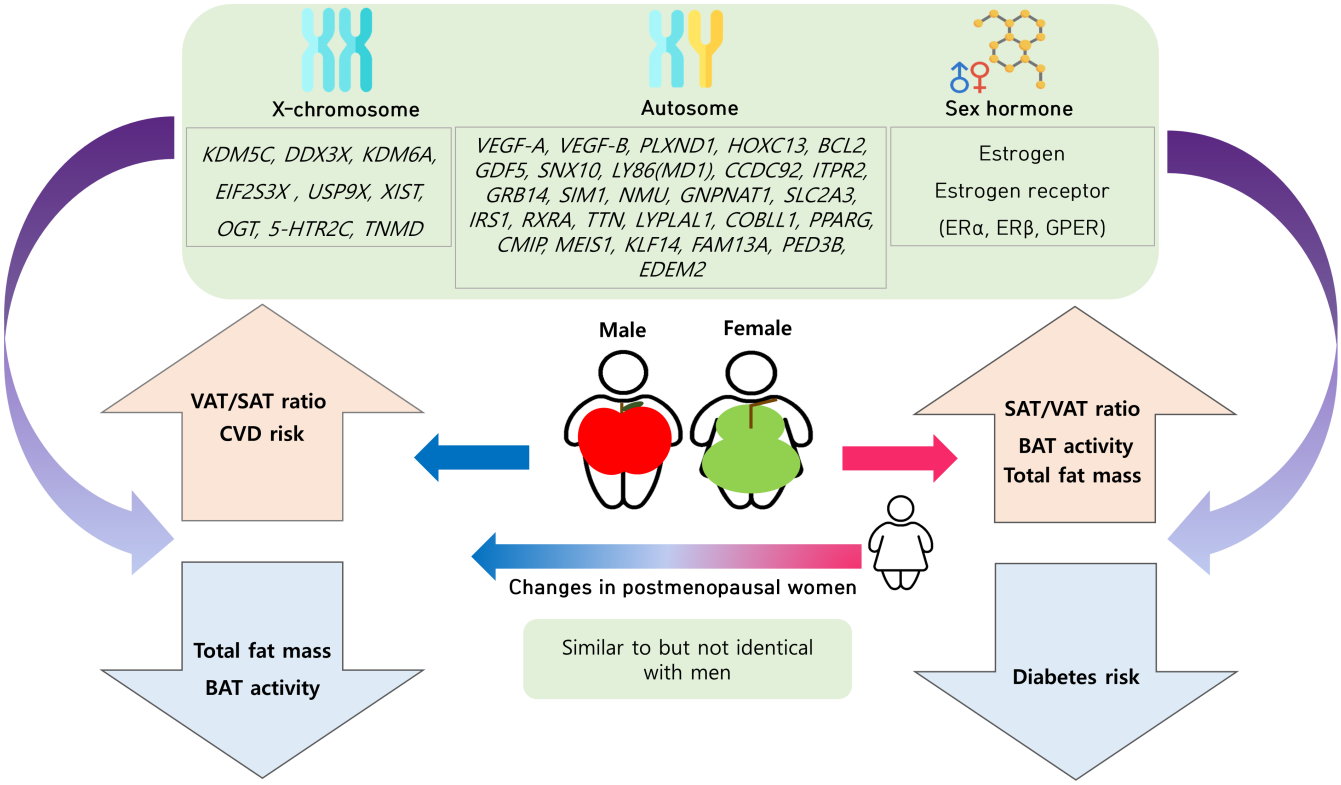

FIGURE 1 | Drivers of sex disparities in obesity In general, females tend to have a higher proportion of body fat compared to males, which can attribute to the greater accumulation of essential fat in major organs. Body fat distribution and BAT activity, both of which may influence disease development, are regulated by estrogen, its receptors, androgen, androgen receptor, and certain genes. The depletion of estrogen in postmenopausal females leads to a metabolic profile resembling, but not identical to, that of males. ERα, estrogen receptor α; ERβ, estrogen receptor β; AR, androgen receptor; BAT, brown adipose tissue; CVD, cardiovascular disease.

(***SFXN2***), SSX family member 2 interacting protein (***SSX2IP***), and zinc finger DHHC-type containing 1 (***ZDHHC1***) are found in GWAS analyses as female-specific WHRadjBMI-associated genes; however, their functions in obesity are not reported [122–124].

5.3.4 | Obesity-Associated Autosomal Genes Identified Exclusively in Males

As opposed to female-specific genes, five genes, including ER degradation enhancing alpha-mannosidase like protein 2 (***EDEM2***), phosphatidylinositol glycan anchor biosynthesis class U (***PIGU***), cadherin 10 (***CDH10***), nuclear receptor binding SET domain protein 1 (***NSD1***), and LEM domain containing 3 (***LEMD3***), are reported to have significant associations with WHRadjBMI only in males [180]. ***EDEM2***, located on chromosome 20, was identified in a study of 210,088 individuals of European ancestry [123]. It is also associated with insulin secretion [181]. In rat RIN-m β-cells, downregulation of ***EDEM2*** decreased insulin secretion by decreasing the expression of insulin 1 (***Ins1***) and ***Ins2*** and was reported to cause impaired insulin secretion by suppressing the expression of pancreas-specific genes solute carrier family 2 member 2 (***Glut2***/***Slc2a2***) and pancreatic and duodenal homeobox 1 (***Pxd1***) [181]. Although other genes are associated with WHRadjBMI in GWAS, their functions in obesity remain unclear.

We have summarized the key findings of our study in a graphical representation in Figure 1. While hormonal and genetic factors contribute to sex differences in obesity, it is clear that there are still unknown causes and mechanisms yet to be uncovered. In this study, the review was limited to articles indexed in the PubMed database. A broader search using EMBASE or the Cochrane Library may be necessary in future research to capture a wider range of studies.

6 | Conclusion

There are distinct sex differences in the incidence, distribution, and types of adipose tissue related to obesity. Women generally maintain a higher percentage of body fat than men; however, their fat is predominantly stored in SAT and is associated with higher BAT activity, which may reduce the risk of metabolic diseases such as CVD and T2D. In contrast, postmenopausal women experience a sharp increase in obesity-related metabolic diseases, highlighting the significance of sex differences in obesity and its health implications.

Traditionally, these sex differences have been primarily attributed to sex hormones such as estrogen and testosterone. However, with the advent of large-scale GWAS, there is growing recognition that genetic factors—beyond hormonal influences—also play a critical role. GWAS have identified numerous

obesity-associated genes located on both autosomes and sex chromosomes, suggesting that the observed sex differences in adiposity are influenced by a complex interplay between genetic loci and endocrine signals.

Although many studies have focused on sex hormones as unilateral determinants of metabolic outcomes, emerging evidence supports the concept of multifactorial regulation, where sex-specific genetic variants interact dynamically with hormonal milieus to influence fat distribution, energy metabolism, and disease susceptibility. These findings underscore the importance of moving beyond a one-size-fits-all model toward more nuanced, stratified approaches to obesity research and clinical care.

Since the completion of the Human Genome Project, there has been increasing consensus that the prevention and management of metabolic diseases, including obesity, should be tailored to an individual's unique genetic and hormonal profile. Such a precision medicine approach holds promise for improving intervention efficacy, minimizing adverse outcomes, and promoting long-term metabolic health.

This review systematically examines genes that exhibit sex differences in obesity and highlights their roles in key regulatory pathways. By integrating genetic and hormonal perspectives, we aim to lay the groundwork for the development of personalized prevention and treatment strategies that address the unique physiological needs of both men and women. Future research should focus on validating these sex-specific mechanisms in diverse populations and translating molecular insights into clinically actionable interventions. Ultimately, understanding the biological basis of sex differences in obesity will be instrumental in reducing the global burden of obesity and its associated comorbidities through targeted, equitable, and effective healthcare strategies.

Author Contributions

Sung and Kim conceived the idea. Kang and Chang were responsible for the actual review of the literature. Kang, Lee, and Chang drafted the manuscript. Sung finalized the manuscript. All authors revised the manuscript, contributed intellectual content, and approved the final version.

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Conflicts of Interest

The authors declare no conflicts of interests.

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