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Genetics of fat deposition

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Abstract. – Adipose tissue distribution usually varies among men and women. In men, adipose tissue is known to accumulate in the abdominal region surrounding the visceral organs (android fat distribution) whereas, in women, the accumulation of adipose tissue generally occurs in the gluteal-femoral regions (gynoid fat distribution). In some cases, however, android distribution can be found in women and gynoid distribution can be found in men. The regulation of adipose tissue accumulation involves interaction of a variety of genetic and environmental factors. This review examines genetic factors that cause differential distribution of adipose tissue in different depots of the body, between men and women and between different ethnicities. Genome-wide association studies can be used to identify genetic associations with the distribution and accumulation of adipose tissue. Insight into adipose tissue accumulation and distribution mechanisms could lead to development of personalized interventions for people who develop increased fat mass.

Key Words:
Adipose tissue distribution, Fat tissue accumulation, GWAS.

Introduction

Body fat distribution differs between sexes. After puberty, women accumulate fat in the limbs to a proportionally greater extent compared to other parts of the body (gynoid fat distribution), while men accumulate a greater extent of fat in the trunk (android fat distribution)[1]. In some cases, however, android distribution can be found in women and gynoid distribution can be found in men. The differential distribution of body fat between sexes has been attributed to downstream effects of sex hormone secretion[1-3].

Among overweight or obese individuals, those with higher central adiposity show a greater risk of developing cardiometabolic disorders. In contrast, those with higher gluteal adiposity exhibit lower risk of type 2 diabetes, hypertension, dyslipidemia, and mortality[4-6]. The genetic studies of distribution of body fat in middle age women have identified single nucleotide polymorphisms (SNPs) associated with a favorable body fat distribution. This distribution depends on the storage capacity of the subcutaneous adipose tissue[2].

Body mass index (BMI) is commonly used as a proxy measurement of body adiposity in epidemiological studies and in clinical practice. However, BMI is unable to discriminate between adipose and lean mass, and fat stored in different compartments of the body. Other proxies that better represent distribution of body fat have also been utilized, such as waist circumference, hip circumference, and the waist-to-hip ratio (WHR). Recently, a genome-wide association study (GWAS) identified hundreds of loci associated with body fat distribution determined by segmental bio-electrical impedance analysis, revealing a genetic architecture influencing the distribution of adipose tissue to the arms, legs, and trunk[5]. Sex-stratified analyses have revealed sexual dimorphic effects at twenty WHR associated loci and 19 of these loci displayed stronger effects in women[7]. Resolving genetic determinants and mechanisms that lead to distinct regulation of

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regional fat depots may help in risk assessment and in identifying novel venues for intervention to prevent or treat obesity-related diseases. In this review, we discuss the importance of the genetics of adiposity, with a focus on body fat distribution, and ethnic and sexual differences[4].

Adipogenesis- and Metabolic Disease-Associated Genes

A research study[8] presented a GWAS, and meta-analysis of adipose tissue traits derived from imaging biomarkers from 2.6 million SNPs in up to 9594 women and 8738 men of European, African, Hispanic and Chinese ancestry and used mouse models to characterize selected loci. Seven loci associated with adipocyte development and differentiation, *ATXN1, UBE2E2, EBF1, RREB1, GSDMB, GRAMD3* and *ENSA,* were identified. Functional analysis of these genes revealed that loss of function of both *ATXN1* and *UBE2E2* in primary mouse adipose progenitor cells impaired adipocyte differentiation, suggesting a physiological role for *ATXN1* and *UBE2E2* in adipogenesis[8].

These results established that out of these 7 novel loci, 3 were associated with volumetric subcutaneous (*GSDMB*) and visceral fat traits (*GRAMD3* and *RREB1*) while 2 were associated with pericardial fat (*ENSA* and *EBF1*), 1 was associated with fat attenuation (*ATXN1*), and 1 was associated with VAT/SAT ratio (*UBE2E2*)[8,9].

GWASs have identified more than 400 SNPs implicated in metabolic diseases and traits. Some of these variants modulated the risk of type 2 diabetes through insulin secretion, either through direct effects on islet function (e.g., *KCNJ11*) or islet development (*HNF1A*, *WFS1*) or indirectly, through impact on incretin signaling (*GLP1R*). In contrast, a handful of type 2 diabetes associated loci seem to primarily operate through insulin resistance (*PPARG*, *IRS1*), adipogenesis (*KLF14*, *PPARG*) and obesity (*FTO*)[9].

These GWASs have helped identify further novel risk loci, for example, the *KCNQ1* locus in the Japanese population, *ZRANB3* locus in Africans, *SLC16A11* in Mexicans, *ZFAND3* in East Asians, *CREBRF* variant in Samoans, an *HNF1A* variant in Oji-Cree Indians and *ITGA1* and *TBC1D4* variants in the Greenlandic Inuit[9,10].

There is a genetic predisposition for adipose tissue expandability and fat storage capacity. The initial results from more than 160 subcutaneous fat biopsies provided evidence that three favorable adiposity variants (in or near *PPARG*, *KLF14* and *FAM13A*) are linked with adipose tissue function[9]. These results indicated that adiposity-increasing alleles at these variants possibly protect from type 2 diabetes by increasing the pool of small adipocytes in the subcutaneous fat depots. For other favorable adiposity variants, it is not known which genes they are acting through; however, the nearest genes are enriched in mechanisms related to adipogenesis and adipocyte differentiation (*IRS1, DNAH10* and *CCDC92*), insulin signaling (*FAM13A*), adipose tissue maintenance (*TRIB1*), triglycerides lipase (*LYPLAL1*) and insulin sensitivity (*GRB14*), all highly expressed in subcutaneous adipose tissue[9].

In addition, adipose tissue development, inflammation, and glucose homeostasis may be influenced by the adipocytokine chemerin, encoded by the retinoic acid receptor responder 2 (*RARRES2*) gene[11]. Circulating lipocalin 2 (*LCN*2) levels are positively associated with adiposity. Lipocalin 2 is a protein able to bind and transport lipophilic substances such as retinoids, arachidonic acid and steroids. The cell surface proteoglycan glypican-4 (*GPC4*) is released primarily by adipocytes following a proteolytic cleavage of the GPI anchor by lipases, such as the insulin-regulated glycosylphosphatidylinositol-specific phospholipase D (GPLD1). Omentin is another new adipocytokine that is secreted mainly by stromavascular cells[12]. A family of five secreted frizzled-related proteins, termed SFRP1-5, has been implicated in the regulation of adipogenesis. Vaspin (visceral adipose tissue-derived serine protease inhibitor, serpinA12), is another adipokine associated with insulin-sensitizing effects. In human studies, vaspin mRNA levels are not detectable in people with normal weight and in some obese subjects with insulin resistance[11]. Excess upper-body adipose tissue is strongly associated with insulin resistance and clinical conditions associated with cardiovascular risk, such as hypertension and dyslipidemia. The relative importance of abdominal visceral fat (AVF) and abdominal subcutaneous fat (ASF) in insulin resistance is under debate, with some studies reporting better insulin and glucose homeostasis with AVF and others favoring ASF[13].

Segregation analyses further suggest that the familial effect is primarily attributable to major recessive genes for AVF. Candidate gene studies have identified regions that may contribute to this variability. For example, there are reports of associations or linkages between AVF and the

glucocorticoid receptor gene, the β-3-adrenergic receptor gene, and the fatty acid binding protein 2 gene. The first genome-wide scan for abdominal adiposity was from the Québec Family Study, in which linkage was found primarily for ASF. As expected for complex traits, multiple linked regions were found[14].

Accumulation of VAT is clearly associated with an increased risk of obesity-related diseases and all-cause mortality, whereas gluteal subcutaneous fat accumulation (g-SAT) is associated with a lower risk. There is recent evidence that differentiation between upper-body and lower-body adipose tissues might be under control of site-specific sets of developmental genes, such as Homeobox (HOX) genes, a group of related genes that control the body plan of an embryo along the anterior-posterior axis. However, the possible heterogeneity between different subcutaneous regions has not been extensively investigated. Different expression of HOX genes, fundamental during the embryo development, suggests an early regional differentiation of subcutaneous adipose depots. Moreover, the higher expression of *HOXA5* and *NR2F1* in abdominal SAT, two molecular signatures of visceral adipocytes, suggests that this subcutaneous adipose depot could be more similar to VAT than g-SAT[15].

Genetics of Fat Distribution

Body mass index is a measure commonly used to identify people as having obesity without regional specification or sex specificity[16]. Familial aggregation analysis, including twin and adoption studies, consistently estimate the heritability of BMI to be approximately 40-70%. There is compelling evidence[4,17] supporting that the genetic control of regional fat deposition is distinct from overall adiposity. Several lines of evidence suggest a unique genetic component to body fat distribution. For example, certain SNPs are associated with pericardial fat but are not associated with visceral fat, BMI or WHR[18,19].

The most recent meta-analysis of GWAS identified 941 independent SNPs associated with BMI. Collectively, these genome-wide significant SNPs explain ~6% of the variance of BMI[20]. Interestingly, many of these loci were found to be heavily involved in pathways of the central nervous system, such as regulation of appetite and food intake[21].

The heritability of waist circumference and WHR is estimated to be 30-45%, even after adjusting for BMI. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), other regional measures of adiposity, when measured by computed tomography scans, are demonstrated to be 36% and 57% heritable, respectively[4].

A research study[22] presented a study of the role of coding genetic variants on fat mass in six distinct regions of the body, based on dual-energy X-ray absorptiometry imaging on more than 17000 participants. The missense variant in the protein coding gene, coiled-coil domain containing 92 (*CCDC92*), p.Ser70Cys, previously associated with WHR, is specifically associated with increased fat mass in the legs and reduced visceral but not subcutaneous central fat[22]. Confirming the importance of this gene in adipose tissue, the minor allele-carrying transcript of *CCDC92*, which shows significant opposing effects on android, specifically visceral fat mass, and lower body fat, is constitutively more expressed than the major allele in adipose tissue samples[22]. In the same study, the authors identified two coding variants in the spermatogenesis associated 20 (*SPATA20*) gene and the ubiquinol-cytochrome C reductase complex assembly factor 1 (*UQCC1*) gene, both associated with arm fat mass. The variant p.Lys422Arg in SPATA20 has a low frequency with a large effect on arm fat only, and the p.Arg51Gln variant in UQCC1 is a common variant reaching significance for arm subcutaneous fat depots[22]. For a more comprehensive list of SNPs involved in the subcutaneous fat tissue accumulation, retrieved from the GWAS Catalog (https://www.ebi.ac.uk/gwas/), see Table I.

Gene-Environment Interaction and Body Fat Distribution

Body fat distribution is determined by both genetic and environmental factors. Recently emerged omics studies, such as metabolomics and microbiomics, are generating novel data regarding factors affecting body fat distribution[4].

The continual increase in obesity and obesity-related disorders is paralleled by dramatic changes from "traditional" to "obesogenic" living environments[18]. However, it has long been noted that substantial inter-individual variability exists in response to diet/lifestyle modifications, and that genetic factors play a fundamental role[28]. The ways in which genetic variants interact with environmental factors may provide new insights into the biology of body fat distribution, and the development of personalized intervention strategies to reduce the risk of obesity-related disorders[29].

Table I. SNP association with subcutaneous adipose tissue measurements.

Gene	Variant-Risk allele	Location	*p*-value	Reference
LINC01252, ETV6	rs10743966	12:11594182	3×10^{-8}	23
ITPKB, ITPKB-IT1	rs10916025-G	1:226668188	6×10^{-6}	24
RNF217-AS1	rs11154271-C	6:124835303	1×10^{-6}	24
NR3C2	rs11725509-A	4:148390576	1×10^{-6}	24
AC104119.1, NNT	rs117565216	5:43726698	3×10^{-7}	25
RNGTT, AL139042.1	rs11757661-A	6:88473861	8×10^{-6}	24
STXBP6	rs11850957-T	14:25010336	6×10^{-6}	24
SMAD6	rs11858577-T	15:66774225	9×10^{-6}	24
NSG2, AC025752.1	rs11952171-A	5:174268775	7×10^{-6}	24
PSMC1P10, RAD51AP2	rs12185578-A	2:17427972	9×10^{-6}	24
ADIPOR1P1, EBLN1	rs12257323-T	10:22205214	4×10^{-8}	26
MGAT5	rs12467609-T	2:134385716	7×10^{-6}	24
GNG5P5, HTR2A	rs12583882-G	13:46999481	6×10^{-6}	24
RORA	rs12591650-A	15:60768508	7×10^{-7}	24
AC092957.1	rs12629805-C	3:146914377	3×10^{-6}	24
LHPP	rs12773846-G	10:124587345	7×10^{-6}	24
RPL35P9, LINC00460	rs12866352-A	13:106392726	8×10^{-7}	26
AC044873.1, AC091027.2	rs12967884-A	18:78831635	7×10^{-6}	24
AC093298.2	rs13153333-G	5:91685570	8×10^{-6}	24
LINC02147, LINC02208	rs13166814-A	5:118002058	5×10^{-7}	24
RNA5SP30, PCDH17	rs1370053-T	13:57940531	6×10^{-7}	26
FTO	rs1421084-A	16:53723828	3×10^{-6}	24
KLF7, CPO	rs1453160-A	2:207012741	4×10^{-6}	24
SMC4P1, THSD7B	rs1582861-T	2:136733551	3×10^{-6}	24
AC022168.1	rs16951883	16:10224922	5×10^{-7}	27
AC097634.4, FOXP1	rs17008402-G	3:71251416	2×10^{-6}	24
RN7SL423P, AC009313.2	rs1722636-T	2:160925262	6×10^{-7}	24
PTPRD	rs17241164-T	9:9857448	7×10^{-7}	26
STAC, NBPF21P	rs17248901	3:36605969	2×10^{-7}	27
LINC01170	rs17501712-T	5:124235467	7×10^{-7}	24
AL136456.1	rs2025934-G	1:193765770	3×10^{-6}	24
RN7SL625P, SBDSP1	rs2058059-C	7:72841239	7×10^{-6}	24
ZPBP2, GSDMB	rs2123685-T	17:39897636	3×10^{-8}	8
AC091544.2	rs2173063-A	15:92588402	3×10^{-6}	24
TFAP2D	rs2223471	6:50765935	5×10^{-7}	25
ATXN1	rs2237199-A	6:16429790	1×10^{-7}	8
ATXN1	rs2237199-A	6:16429790	1×10^{-8}	8
CTLA4, RNU6-474P	rs231784	2:203832259	3×10^{-7}	25
AC107024.1, CADM2	rs2324999-T	3:86109735	4×10^{-6}	24
AC107024.1, CADM2	rs2324999-T	3:86109735	2×10^{-6}	24
HMGB3P18, RNU1-18P	rs2679649-A	6:122029239	2×10^{-7}	26
BDKRB2, C14orf132	rs4384548-A	14:96178806	5×10^{-8}	26
CTNNA3	rs4746598	10:66549410	6×10^{-6}	25
CTNNA3	rs4746598	10:66549410	2×10^{-7}	25
CTAGE16P, DNAJA1P1	rs4886088-A	13:58554392	8×10^{-6}	24
PMS1	rs5743030-A	2:189813819	5×10^{-6}	24
ZFP64, RNU7-6P	rs6013355-A	20:52021121	5×10^{-6}	24
LCN1, OBP2A	rs62577244	9:135536231	1×10^{-7}	25
LCN1, OBP2A	rs62577244	9:135536231	1×10^{-6}	25
SLC25A5P4, RPL31P53	rs6561930	13:57352300	3×10^{-7}	27
AL139130.1, RHBG	rs6686886-G	1:156386688	9×10^{-6}	24
AC009950.1	rs6727879-A	2:230161876	2×10^{-7}	26
FTO	rs7185735-A	16:53788739	1×10^{-9}	8
FTO	rs7193144	16:53776774	5×10^{-6}	27
SNRPD2	rs7245708-C	19:45692498	2×10^{-6}	24
SNRPD2	rs7245708-C	19:45692498	1×10^{-6}	24
CPHL1P	rs7617219-A	3:149259527	1×10^{-6}	24
STC1, RNU1-148P	rs7833268	8:23961174	6×10^{-7}	24
DNAJC1	rs7903144-A	10:21768476	1×10^{-8}	26
DNAJC1, MLLT10	rs7919823-A	10:21747562	1×10^{-8}	26
FTO	rs8050136	16:53782363	4×10^{-6}	27
KCNH5	rs869834-T	14:62710426	2×10^{-6}	24
RBFOX1	rs870288-A	16:5535851	9×10^{-6}	24
AL513166.1	rs990871-T	1:72358030	4×10^{-6}	24
FTO	rs9922619-T	16:53797859	6×10^{-8}	24

Data from GWAS Catalog, https://www.ebi.ac.uk/gwas/. All SNPs are mapped to Genome Assembly GRCh38.p13 and dbSNP Build153.

Observational studies specifically investigated the interactions of body fat distribution-associated SNPs or genetic risk scores, with nutrients, foods, dietary patterns, physical activity and other lifestyle factors[30,31]. For example, in a cohort study[32], which included 334 female twins (57.7±6.7 years), it was found that, when carrying a low genetic risk of abdominal fat, women in the highest tertile of polyunsaturated fat intakes had about 50% less central abdominal fat than those in the lowest tertile of intakes[4,32].

Epigenetic Response to Parental Diet

Sex differences in epigenetic regulation by environmental and/or hormonal factors have been reported in both rodents and humans and greatly contribute to adipose tissue distribution and accumulation[33]. In fact, maternal malnutrition and/or over-nutrition during the pre-natal period are the main factors that may influence offspring and adult phenotypic consequences[34], by increasing the susceptibility to metabolic disease[35]. Furthermore, it was found that also epigenetic modifications in the sperm of obese glucose-intolerant males affect genes associated with obesity (*FTO*, *MC4R* and others) and it is possible that these modifications can be transmitted to the offspring, leading to paternal epigenetic inheritance of metabolic disorders[36].

Sex-Specific Adipose Tissue

Increasing evidence[37] has supported disease susceptibility heterogeneity related to adipose tissue depots; SAT is benign, while VAT is correlated with metabolic risks. In females there is a higher proportion of gluteal-femoral SAT, whereas males have more VAT, concentrated in the abdominal region[38]. Furthermore, there is great heterogeneity in lipolysis between adipose tissue depots of male and female. In fact, on average, adipose tissue lipolysis is substantially greater (~40%) in women than in men, even though metabolic health is typically better in women[25]. Unlike overall adiposity, genes related to regional fat distribution shows a high degree of sexual dimorphism. For example, Shungin et al[28] identified 49 loci associated with WHR adjusted for BMI, of which 20 showed high sexual dimorphism. Nineteen of the 20 loci displayed a stronger effect in females, while only one genetic variant located on *GDF5* gene was stronger in males[7]. In the recent GWAS meta-analysis of body fat distribution, measured by WHR adjusted for BMI, 346 loci were identified, with approximately one-third of them stronger among women than men[39].

Sex differences in the expression of homeobox genes have also been observed in adipose tissue. Gesta et al[40] reported that there is higher expression of the *HOXC9* gene in SAT than in VAT in males, but not in females. GWAS and meta-analyses of GWAS have also identified novel sexually-dimorphic genetic loci associated with upper- or lower-body fat distribution, including five genes (*RSPO3, TBX15, ITPR2, WARS2* and *STAB1*) that are differentially expressed between abdominal and gluteal SAT[41]. These studies[11,42] provide evidence for sexual dimorphism in the associations of certain genetic loci as effectors of adipose tissue distribution. Polymorphisms in the estrogen receptor α (*ESR1*) gene are also associated with body fat distribution in women.

Leptin, an adipocyte-secreted factor, is predominantly expressed by isolated subcutaneous adipocytes as opposed to omental adipocytes, particularly in women[11]. Protein expression of dipeptidyl peptidase (DPP)-4, a novel adipokine previously studied for its role in the incretin system, is substantially elevated in VAT compared with SAT of obese individuals[43].

GWAS of subcutaneous and visceral adipose tissue reveals novel sex-specific adiposity loci in Mexican Americans[25]. These results provided genetic evidence for a differential basis of fat deposition between genders. Association analyses were computed for SAT, VAT, VAT adjusted for BMI, and visceral/subcutaneous ratio, adjusting for age, sex, recruitment center, and admixture[25]. In addition, as SAT and VAT distributions vary by sex, sex-stratified and SNP-sex interaction analyses were performed. Signals with significant sex-specific effects were identified[25]. The strongest signal identified in association with VAT was an intronic variant (rs2185405) of the GLIS family zinc finger 3 gene (*GLIS3*). Another intronic variant (rs12657394), located in the serum response factor binding protein 1 gene (*SRFBP1*) was associated with VAT in males. In this case, male carriers had increased VAT compared with non-carriers. Genome-wide SNP-sex interaction analysis revealed that the SNPs rs10913233 in the gene encoding pappalysin 2 (*PAPPA2*) and rs10923724 upstream of the gene encoding the T-Box transcription factor 15 (*TBX15*) were strongly associated with visceral/subcutaneous fat ratio[25].

Ethnic Differences in Adiposity

Genetic diversity can explain the differences in body fat distribution among populations of different ethnicity. These differences are also evident in ethnic disparity in risk of type 2 diabetes with the prevalence of the disease in the USA ranging from 17.7% in white European individuals to 22.5% in Asians, 30.6% in Hispanics and Africans, and 45.2% in American Indians/Alaska Natives in adults ≥ 75 years of age[9].

In a research study, multipoint variance components linkage analysis using a genome-wide scan of 344 markers was conducted separately by race using race-specific allele frequencies. Several promising results ($p<0.0023$) were obtained. For baseline AVF, the best evidence was on 2q22.1 and 2q33.2-q36.3 (including the *IRS1* locus) in whites, with suggestive findings on 7q22.2-q31.3 (including the *LEP* locus) in blacks[13].

South Asians have been reported to have higher waist circumference, WHR and 5-7% higher total body fat at any given BMI compared to white Europeans. This elevated central adiposity in South Asians has been linked to greater risk of developing type 2 diabetes, insulin resistance and cardiovascular disease at a lower BMI compared to white Europeans. Lean mass and the lean-to-fat-mass ratio are also lower in South Asians compared to white Europeans and East Asians. The combination of low muscle mass and high truncal fat (estimated by high subscapular skinfold thickness) has been detected in South Asian newborns and is presumed to predispose to insulin resistance later in life[9].

There are very few observational studies investigating the cellular characteristics of adipose tissue across ethnicities, but their results are consistent with the low frequency of favorable adiposity alleles in South Asians. Compared to white Europeans, South Asian men and women have been shown to have larger adipocytes. The study of type 2 diabetes risk factors in obese Pima Indians indicated the best predictive factor for the onset of diabetes was adipocyte size independent of age, sex and body fat percentage, suggesting difficulty in differentiating new adipocytes plays an important role in disease mechanism[44,45].

Conclusions

In this review, we examined genetic factors that are associated with a differential distribution of adipose tissue between men and women. The distribution of adipose tissue varies among males and females, as males have a greater tendency to accumulate in the abdominal region while females have a greater accumulation of adipose tissue in the gluteal-femoral regions. This fat distribution is regulated by genetic factors influenced by ethnicity and environment. Insight into adipose tissue accumulation and distribution mechanisms could lead to the development of personalized interventions in people with higher fat accumulation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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