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Obesity Genetics and Cardiometabolic Health: Potential for Risk Prediction

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Abstract

Increasing burden of obesity world-wide and its effect on cardiovascular disease (CVD) risk is an opportunity for evaluation of preventive approaches. Both obesity and CVD have a genetic background and polymorphisms within genes that enhance expression of variant proteins that influence CVD in obesity, thus genome-based prediction may be a feasible strategy. However, identification of genetically driven risk factors for CVD manifesting as clinically recognized phenotypes is a major challenge. Clusters of such risk factors include hyperglycemia, hypertension, ectopic liver fat, and inflammation. All involve multiple genetic pathways having complex interactions with variable environmental influences. The factors that make significant contributions to CVD risk include altered carbohydrate homeostasis, ectopic deposition of fat in muscle and liver, and inflammation with contributions from the gut microbiome. Futuristic model depends on harnessing the predictive power of plausible genetic variants, phenotype reversibility, and effective therapeutic choices based on genotype–phenotype interactions. Inverting disease phenotypes into ideal cardiovascular health metrics could improve genetic and epigenetic assessment, and form the basis of a futuristic model for risk detection and early intervention.

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Conflict of interest

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Keywords

Obesity; Cardiometabolic disease; Genetics; Microbiome; Gene Environment Interactions

INTRODUCTION

The prevalence of obesity and its associated co-morbidities have increased world-wide over the past three decades. Further increases are predicted by 2030.[1] Both, overweight and obesity continue to have serious implications for health[2] including excess mortality and costs,[3] in large part attributable to excess cardiovascular disease (CVD) in both men[4] and women.[5] Currently, over 78 million US adults (~one third of the US population) are obese, and 82 million are overweight. Obesity-associated morbidity is dependent on the rate at which midlife adults attain an increased body mass index (BMI) [6], suggesting that intervention to offset obesity-related disease early in life may help prevent its medical and economic consequences.[7] Since an expanding role for preventative CVD medicine has been increasingly recognized,[8,9]an emphasis on earlier risk factor (biomarkers) identification is reasonable and could begin in children, adolescents or young adults especially before manifestation of the risk factors[10,11].

This review highlights: molecular and genetic aspects of obesity and cardio-metabolic traits that are significantly associated with CVD, and mechanisms for the adverse metabolic effects of obesity on CVD. A futuristic screening model for effective and individualized interventions based on the degree of obesity, severity of the cardiovascular (CV) phenotype and response to available lifestyle and medical interventions has also been proposed.

GENETICS OF OBESITY

Obesity precedes the development of much of the CV risk[4,5,12] and the early manifestation and progression of obesity due to genetic predisposition provides the environment for adverse CV outcomes. Genetically driven phenotypes of obesity have been sub-classified into three main types: syndromic, non-syndromic and polygenic obesity.[13] All these have variable effects on body fat mass. Of the 79 forms of identified obesity syndromes, 19 have been fully elucidated, 11 have been partially elucidated, while 27 have been mapped to a chromosomal region but not characterized.[14] Monogenic obesity presents as a rare condition with severe obesity due to recessive mutations coding for key metabolites in pathways for the hypothalamic control of appetite. Studies on animal models and on families carrying these genetic alterations have provided significant insights into mechanisms for the development of obesity in the general population[15,16] such as the identification of the leptin-melanocortin pathway involved in monogenic obesity and satiation. [17]

Large genome-wide association studies (GWAS) have helped in the identification of more than 250 genes/loci important in the biology of obesity[18,19]. These studies have led to the discovery of several new genes with previously unknown function. Detailed discoveries of GWAS identified obesity loci that have been reviewed previously. A summary of the association of common variants in major obesity loci and their pleiotropic effects on other cardiovascular risk factors (traits) is included in Table 1 and Figure 1. Discovery of *FTO* (fat

mass and obesity-associated) gene by GWAS with robust replication of an intronic variant (rs9939609) in multiple independent studies, show that *FTO* variants have an important role in obesity and possibly in the pathogenesis of type 2 Diabetes (T2D). The association was abolished when adjusting for BMI suggesting that the *FTO* variant influences T2D via its effect on obesity [20]. The associations of the same *FTO* variant (rs9939609) with obesity and T2D were explored in a large-scale meta-analyses study conducted on 96,551 individuals from East and South Asia, which suggested that the association of FTO with T2D was independent of obesity.[21] Because of the strong association of *FTO* with T2D and its associated risk with CVD, the *FTO* gene has assumed priority for further studies beginning early in life. Indeed, the association of *FTO* with obesity has been replicated in longitudinal studies in childhood [22,23]. Additionally, a Dutch study reported association of *FTO* variants with higher BMI, fat mass index, and leptin concentrations during puberty but declining at ages 13–14 years; a finding presumed to be consistent with hormonal effects at pubertal onset [24]. Although considered a strong effect variant in polygenic obesity, the *FTO* gene has been predominantly associated with appetite regulation [25], as has been the case for most monogenic obesity genes. *FTO* mRNA transcripts have been observed in mouse hypothalamic nuclei encoding 2-oxoglutarate-dependent nucleic acid demethylase that supports a regulatory role in appetite and possibly energy balance and sympathetic outflow to the circulatory system [26]. The mouse model studies further validated the role of *FTO* in controlling food intake, energy homeostasis, and energy expenditure [27] possibly via nearby genes such as *RPGRIP1L* and *IRX3*.[25]

Another BMI locus detected by GWAS was near *GIPR,* the incretin receptor, which may indicate a causal contribution of variation in postprandial insulin secretion to the development of obesity.[28] This is important because there is accumulating evidence that the gut microbiome is increasingly involved in obesity, and could interact with intestinal functions such as absorption, neural control and appetite.[29] Most commonly encountered obese cases have a polygenic background. This accounts for about 60% of the BMI variance[30] and suggests that polygenic obesity is also dependent on the genetic interactions with environmental, lifestyle and cultural factors. This argument is consistent with Mendelian randomization studies that have reported that BMI-associated increase in CVD risk is attributable to genetic variation. [31,32] A variant or combination of variants can be used as an instrumental variable for disease traits such as ‘BMI’ to evaluate a causal relationship of obesity to an outcome variable such as a ‘CV event’ or disease onset. Importantly, as gene variants have a lifetime effect, influence on the respective CV phenotypes would be of long duration, although this could be confounded by environment and lifestyles.[33,34] Interestingly, these studies have also identified polymorphisms, within genes earlier known to be involved in monogenic obesity that also contribute to polygenic obesity.[15,17] For instance, polymorphisms in *PCSK1* contribute to extreme (monogenic) obesity (defined as having a BMI >40 kg/m^2) in addition to common obesity (defined as a BMI ranging from 30 to 40), which was reported in a large size meta-analysis study including up to 331,175 individuals from diverse ethnic groups, suggesting that ethnicity, age and study design modulate the association of *PCSK1* polymorphisms with obesity. Additionally, the study demonstrated the contribution of common variants in *PCSK1* to contribute to BMI variation and obesity.[35] One recent meta-analysis GWAS of BMI conducted on 123,865 individuals

using 2.8 million single nucleotide polymorphisms (SNPs), and follow-up in significant numbers, identified 18 new obesity susceptibility loci and confirmed 14 known genes associated with obesity.[28] Some variants identified by GWAS are near monogenetic loci, such as *MC4R*, *POMC*, *SH2B1* and *BDNF,* and are hypothalamic regulators of energy balance.[15,17]

However, despite these successes, the common non-coding variants discovered using the GWAS approach explain only a small fraction of total genetic variance and these studies are often underpowered to locate those less common coding variants with a frequency of <5% [57]. Whole genome exome-wide sequencing or targeted sequencing studies have discovered low-frequency / rare variants with larger effect sizes within the earlier known obesity genes. A large meta-analysis study of exome and targeted sequence data using 718,734 individuals (80% Caucasians) discovered rare functional coding variants in 13 genes, including 5 known and 8 new obesity genes, and *in silico* gene set enrichment analysis predicted a strong role for neurobiology in body weight regulation. The effect sizes of rare variants were ~10 times larger than those observed in common variants. The carriers of a rare (MAF 0.01) *MC4R* mutation (Tyr35Ter) weighed 7 kg more than the non-carriers in this study[36]. Exome sequencing in a family-based design has detected novel functional variants for predicting childhood obesity in peroxisome biogenesis factor (PEX-1). *PEX-1,* an earlier identified gene by GWAS, is involved in childhood obesity through a novel mechanism of peroxisomal biogenesis and metabolism.[37] Importantly, by far, the vast majority of whole genome, exome-wide, or targeted sequencing studies have been predominantly performed on Caucasian populations, more investigations on other major ethnic groups would be needed to identify causal variants with population-specific effects.

OBESITY AND CARDIOMETABOLIC RISK PHENOTYPES

Hyperglycemia

Hyperglycemia, a known cardiovascular risk factor and component of the metabolic syndrome joins other traits in preceding both diabetes and cardiovascular disease. Detectable changes in glucose and insulin metabolism precede T2D and have been studied as quantitative traits (QTs) in genetic studies and as targets for reversal or prevention of T2D onset. Therefore, there has been interest not only in searching for genetic association but also in finding the glucose levels which accurately reflect T2D and preceding risk. It is known that progression of IGT (Impaired glucose tolerance) to T2D is potentially reversible with lifestyle.[36] The American Diabetes Association Expert Committee established the impaired fasting glucose and impaired glucose tolerance range.[38] These cut-off points were selected to facilitate early diagnosis of risk and to initiate lifestyle interventions known to reduce risk.[36] Approximately 60% of people who develop diabetes have either IGT or IFG (impaired fasting glucose) about 5 years before T2D onset, while 40% have normal glucose tolerance.[39]

Studies also suggest that IGT is strongly associated with hypertension, dyslipidemia and worse cardiovascular outcomes.[38] The rs553668 of the *ADRA2A* gene predicts worsening of fasting glucose values in a prediabetic cohort.[39] Variants associated with fasting glucose discovered through GWAS such as *GCK*, *G6PC2*, *MTNR1B*, and *DGKB- TMEM195*[40] in

the normoglycemic population do not always influence risk for T2D (in contrast to *TCF7L2* and *SLC30A8*), but their effect appears confined to fasting glucose homeostasis.[40,41] The data support recognition of early hyperglycemic phenotypes derived from regulatory polymorphisms on the genes affecting interacting pathways leading to T2D. Meta-analysis of 21 GWA studies identified nine new loci influencing fasting blood glucose: *ADCY5, MADD, ADRA2A, CRY2, FADS1, GLIS3, SLC2A2, PROX1 and C2CD4B*. However, of these, only *ADCY5* and *PROX1* were associated with T2D. These data suggest that although there is overlap, the genetic background for fasting glucose is different from that for the T2D phenotype.[42] Similarly, the 2-h glucose levels after a standard oral glucose load, can be defined as a separate trait to T2D with overlapping associated variants. Meta-analysis identified new loci, *GIPR* and *UPS13C*, uniquely influencing 2-h glucose [43] supporting the hypothesis that there are separate glucose-related QTs representing specific modes of carbohydrate metabolism.[44]

Based on population studies and animal models, it has been proposed that T2D has a progressive pathogenesis beginning with insulin resistance and advancing to β-cell failure [45], and that it may involve several genes, sometimes with significant epistatic interactions.[46] For example, using knockout models for both *IRS- 1* and the insulin receptor, it was shown that neither model alone had much effect on T2D onset, but the combined effect resulted in more than a 50% chance of developing diabetes at young ages.[44] A recent study compared loci associated with multiple glycemic traits with those for T2D. Amongst 88 T2D risk loci and 72 glycemic trait loci, only 29 were shared and showed disproportionate magnitudes of phenotypic effects. These results lead to important insights regarding the role of T2D loci in disease predisposition through their contribution to glycemic trait variability.[48]

Hypertension

Obesity has been identified as an important risk factor for hypertension.[49] The association of insulin resistance with high blood pressure [47] is one of several independent risk factors for CVD.[48] However, evidence from genetic studies, specifically from GWAS, points to largely separate genetic backgrounds for hypertension and T2D. Because hypertension is attributed to enhanced sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activity,[47,49] cardiovascular effects are likely disparate.

Several studies have reported the association of genetic variation in RAAS with CVD risk factors, hypertension and coronary artery disease.[50,51] The relationship of CVD with RAAS variants has been investigated and shows that multiple variants are associated with greater risk. Angiotensin II is also involved in triggering vascular inflammation and oxidative stress in the endothelium by stimulating NAPH/NADPH oxidase, protein kinase C, and mitogen-activated protein kinase (MAPK).[52,53] It also has a direct effect on increasing insulin resistance independent of alterations in blood flow and interstitial insulin concentration,[54] but angiotensin II is equally responsible for influencing the arterial wall through vascular inflammation.[55,56] The insulin resistance is reversible by selective inhibitors of angiotensin II at AT1 receptors.[58] Similar selective antagonism using irbesartan, an AT1 receptor blocker (ARB), has been shown to improve insulin action in the obese rat model associated with upregulation of GLUT4, the main glucose transporter in skeletal muscle.[59] On investigating

the association of common variants such as *ACE* (angiotensin-converting enzyme) and *AGT* (angiotensinogen) with hypertension, results have been inconclusive [57] and they have not been associated with T2D.[61] However, variants in *ACE* and *CYP11B2* genes have been associated with insulin resistance in hypertensive families in Taiwan.[58]

It appears likely that variation in genetic background for hypertension according to race is important since differences have provided insight on possible mechanisms and responses to treatments. Fine mapping of GWAS determined loci have revealed association of novel variants with blood pressure in Hispanics and African Americans, and were similar to variants such as *KCNK3* and *HOTTIP* in populations of European descent.[59] Data from the National Health and Nutrition Examination Survey (NHANES) showed the prevalence of hypertension to be 40% in African Americans compared to 27% in European Americans [60,61], leading to the hypothesis that part of the excess burden in African Americans suggests implication of genetic susceptibility that potentially manifests with the influence of environment (i.e. gene x environmental interactions).[62] GWAS and candidate genes examined in the Candidate Gene Association Resource Consortium consisting of 8,591 African Americans identified novel associations for diastolic blood pressure on chromosome 5 near *GPR98* and *ARRDC3,* and for systolic blood pressure on chromosome 21 in *C21orf 91*. However, none of these variants were associated with T2D.[62]

Certain blood pressure and hypertension loci under selective pressure or adaptation in some African American populations, and were likely advantageous in dry and/or salty environments. For instance, the CYP3A5 enzyme polymorphism *CYP3A5*3* (which influences salt and water retention), showed extreme variation in allele frequency even within African populations, and correlated with the distance from the equator [63]. Monogenic forms of hypertension have provided evidence for a regulatory role of key metabolic pathways and have been the basis for candidate gene population studies, but none have involved carbohydrate metabolism or insulin action. Using such an approach, 24-hour ambulatory blood pressure has been associated with five polymorphisms in the *KCNJ1* gene, which has the potential to cause Bartter syndrome Type 2 when the abnormal allele is inherited.[64] Ambulatory blood pressure is also associated with common variations in the *WNK1* gene known to cause pseudohypoaldosteronism Type 2 or Gordon syndrome. Association of *WNK1* with blood pressure in childhood underscores its possible association with evolving hypertension at young ages and emphasizes the role of WNK signaling pathways in blood pressure regulation.[68] Additional association with variants in *CASR*, *NR3C2, and SCNN1B*, all of which are known to have had mutations causing rare Mendelian defects in blood pressure regulation, provide support for the hypothesis that relevant polymorphisms influence conventional pathways involved in blood pressure regulation.[65] However, only a few variants have been discovered in GWAS in the earlier known genes, suggesting new pathways involved in hypertension.

A large meta-analysis performed by the International Consortium for Blood Pressure on 200,000 individuals of European descent, identified 16 loci of which only 6 contained genes that are known or suspected to regulate blood pressure, which include *NPR3*, *GUCY1A3-GUCY1B3*, *ADM*, *GNAS- EDN3*, *NPPA- NPPB*, and *CYP17A1* [66]. *CYP17A1* achieved the most robust GWAS significance and is the site for a known Mendelian-inherited mutation

causing hypertension by increasing mineralocorticoids in the adrenal steroid pathway and causing a rare form of congenital adrenal hyperplasia attributed to 17-hydroxylase deficiency. Since diabetes and hypertension share common pathways there might be interaction with other genes and lifestyle factors. When the association of RAAS variants with CVD was scored by the Gensini system, multiple variants were associated with CVD and an *AGTR1* variant encoding for the angiotensin II type 1 receptor was associated with CVD severity. There was gene-environment interaction for smoking status with an aldosterone synthase variant *(CYP11B2)* and CVD[67].

Ectopic Liver Fat

The buildup of extra fat in liver cells that is not caused by alcohol or other drugs is termed non-alcoholic fatty liver disease (NAFLD) and has been defined as accumulation of fat in the hepatocyte exceeding 5%. The increase of the obesity epidemic parallels the rise in obesity associated insulin resistance[68], which plays a role in the pathogenesis of NAFLD.[69] Furthermore, it is associated with increased CVD risk over and above that attributed to obesity.[70] This is also a risk factor for progression from a metabolically normal to abnormal state in obese and non-obese individuals[71], supporting the need for early detection and prediction of severity.

Prevalence of NAFLD is dependent on the detection method and the study population. Serum aminotrasferases--ALT and AST levels are typically used to screen for the condition but are non-specific markers; liver scanning or biopsy, the gold-standard, is preferred. The mean prevalence in pediatric populations exceeds 7% but increases to above 30% in studies based on children attending obesity clinics.[72] The prevalence varies dramatically among different ethnic groups despite similar rates of the metabolic syndrome and related risk factors, and there are possible environmental and genetic reasons.[73] Male gender and Hispanic background increase risk [68], but African Americans are relatively spared.[73]

Accumulation of excessive diacylglycerol in the liver is associated with accumulation of liver fat leading to defective insulin action [74], particularly in genetically susceptible populations such as Asian Indian men. [75] Ectopic liver fat is highly associated with atherogenic dyslipidemia, even in adolescents. [76,77] Adiponectin, a fat cell hormone involved in lipid metabolism, is a possible mediator. Both +45T>G (rs2241766) and −11377C>G (rs577853790) have shown association with NAFLD in a meta-analysis,[78] a finding that supports the hypothesis that overlapping genetic backgrounds contribute to both NAFLD and CVD, since the adiponectin +45T>G genotype has shown association with CVD in a separate meta-analysis.[79] Increased visceral fat is associated with low adiponectin in adolescence[80], supporting association with adiponectin action via adiponectin receptor 2 (*ADIPOR2*) in three independent Finnish cohorts.[81] However, among Asians, a meta-analysis suggests that adiponectin variants might be risk factors for NAFLD while the *+276G>T* variant is protective.[78] Simple steatosis progresses to inflammation with risk for cirrhosis and liver cancer [82], and is independently associated with increased risk of coronary artery disease (CAD).[83] Large-sized VLDL has been observed in NAFLD in an adolescent population independent of adiposity and insulin resistance, and the NMR (nuclear magnetic resonance) lipid profile was characterized by small dense LDL and reduced number of large

HDL particles. [84] An association of NAFLD with a lipid profile predisposing to atherosclerosis in adults [70], and with increased intima-media thickness (IMT) in adolescents [85], has been revealed. These data suggest pleiotropic effects, or alternatively, the effects arise from a biochemical cascade leading to excessive hepatic fat storage, inflammation, and lipoprotein abnormalities. Maturation of the VLDL particle in the Golgi, at the stage when triglyceride is transferred to apoB by microsomal triglyceride transfer protein encoded by *MTTP*, determines liver fat storage and if defective may lead to NAFLD.[86] Carriers of the −493 G/T allele also have a more atherogenic lipid profile and the homozygous genotype of the less common T allele was associated with subclinical proinflammatory markers and CVD.[87] The same genotype was also predicted to have a deleterious effect on β-cell function.[88] Furthermore, the - I128T variant is associated with central obesity, elevated liver enzymes in fatty liver disease with and without association with alcoholism.[89] In addition, a manganese superoxide dismutase (*MnSOD*) variant was associated, possibly working by reducing mitochondrial fatty acid oxidation. Genetic determinants of VLDL formation and disposal may result in both atherosclerosis and fatty liver disease. A study conducted on Asian Indian men revealed that the carriers of minor alleles of two *APOCIII* variants rs2854117 (C-482T), rs2854116 (T-455C), or both had a 30% increase in apoC-III levels and a 60% increase in serum triglyceride, as compared with the wild-type homozygotes. The prevalence of NAFLD was 38% among variant T allele of rs2854117 and C allele of rs2854116 carriers compared to 0% among wild-type carriers showing a significant correlation with insulin resistance.[90] Furthermore, the apoC-III overexpression model is predisposed to diet-induced hepatic steatosis and hepatic insulin resistance.[91]

There also is evidence that inherited hepatic enzyme abnormalities are causative. *PNPLA3* and *TM6SF2* variants lower triglyceride[92,93] by decreasing intrahepatic lipolysis thus promoting hepatic fat storage. These variants are associated with a distinct form of NAFLD [94] that may also co-exist with insulin resistance.[95,96] Although, *PNPLA3*, *TM6SF2* and *GCK* genes have shown the strongest associations with NAFLD in genome-wide association scans (GWAS) accounting for 10% of heritability, multiple genes with small additive effects are also causative [96]. A GWAS of 2,111 participants in the Dallas Heart Study revealed a robust association of liver fat defined by magnetic spectroscopy with the I148M allele of the *PNPLA3* gene [97], this association was independently replicated in children and adolescents [98]. Another study investigated the effects of candidate gene SNPs and suggested joint effects between *PNPLA3* and *GCKR* SNPs, explaining 32% of fatty liver disease in Caucasian children.[99] A meta-analysis of 16 studies showed association of *PNPLA3* with disease severity with strong effect on more aggressive disease susceptibility indicated by higher inflammation indices and progression to fibrosis. [100] The gene *PNPLA3* codes for patatin-like phospholipase domain-containing protein 3, or adiponutrin, which plays a role in hepatic triglyceride hydrolysis catalyzing conversion of lysophosphatidic acid into phosphatidic acid, an important regulatory reaction in lipid synthesis. PNPLA3 is upregulated by sucrose feeding in the mouse model, and the l148M variant (rs738409 C/G) in *PNPLA3* results in increased cellular lipid accumulation providing a plausible mechanism for its impressive association with NAFLD.[101] In addition to *PNPLA3*, diet-induced obesity increases mRNA expression [102] which is associated with increased alanine amino transaminase (ALT), a marker of fatty liver disease, in Europeans, Hispanics, and Asian

Indians.[103,104] The homozygous carriers of the minor G allele of rs738409 C/G (I148M) variant showed increased fasting glucose levels[89], and the minor T allele of rs6006460 G/T (S453I) variant was associated with lower hepatic fat content and was more frequent in African Americans who had the lowest hepatic fat content, suggesting protection from NAFLD.[97]

Inflammation and Gut Microbiota

There is strong evidence that inflammation plays a key role in increasing insulin resistance in obesity [105] and in the molecular mechanism underlying atherosclerosis.[106] Presence of immune cells in adipose tissue suggests their major role in inflammation. Studies using genetic mouse models revealed key pathways in the immune process which ultimately led to the identification and targeting of key regulatory pathways.[107] It is also becoming evident that the intestinal microbiome regulates immune cells[108] and alters the permeability of the gut[109] secondary to degradation of endothelial tight junctions, and thereby allows inflammatory products to circulate and cause systemic inflammation and activate insulin resistance. Composition of gut microbiota in obesity affect the epigenetic regulation of genes via the action of bacteria-derived short chain fatty acids on free fatty acid receptors,[110] providing evidence for the hypothesis that dietary interventions to change microbial composition may ameliorate inflammation and insulin resistance. Experimental evidence has demonstrated that a high-fat diet increases expression of toll-like receptors (TLRs), mediators of chronic inflammation, and kruppel-like factors (KLFs) involved in adipocyte differentiation associated with an atherogenic lipid derangement[111], suggesting that appropriate dietary modification can change obesity-associated inflammation.

It is also possible that changes in the microbiome and specific amino acids influence nutrient-specific appetite regulation via hypothalamic receptors based on evidence derived from non-mammalian as well as several recent mammalian and human studies.[112] Recent metagenome-wide studies of gut microbiota were able to differentiate between useful and pathogenic microbes, and identified a set of bacteria associated with gut oxidative stress response linked with diabetes complications and inflammatory bowel disease[113,114]. Furthermore, evidence suggests that the severity of non-alcoholic fatty liver disease is influenced by a dysfunctional microbiome and that the dysbiosis is associated with hepatic inflammation leading to fibrosis[115]. These observations point to inflammation as being central to formation of metabolic traits that lead to atherosclerosis in obese individuals and are likely to have respective genetic interactions.

Endothelial Dysfunction

Endothelial dysfunction is characterized by impaired endothelium-dependent vasodilation and increased pro-coagulant and pro-inflammatory activity[116]. Vascular endothelial cells play a pivotal role in regulating blood flow in the entire circulatory system. Endothelial dysfunction has also been linked with obesity and elevated C-reactive protein (CRP). CRP is a pro-inflammatory marker whose concentrations are markedly increased in patients with T2D, hypertension and metabolic syndrome[117]. The development of atherosclerosis is considered to be a consequence of a chronic inflammatory process, perpetuated in part by LDL that is trapped and oxidized within the vessel wall[118]. Specifically, oxidative stress

increases vascular endothelial permeability and promotes leukocyte adhesion (Figure 2), which is coupled with alterations in endothelial signal transduction and redox-regulated transcription factors [119]. On the other hand, oxidized LDL may impair signal transduction activation of nitric oxide synthase, thus lowering the synthesis of nitric oxide. [120] Reduced nitric oxide could also stimulate the synthesis and release of endothelin, producing enhanced vasoconstrictor tone; promote the release and activity of growth factors, increasing smooth muscle cell migration into the intima and enhancing the synthesis and release of pro-inflammatory cytokines. Additionally, reduced nitric oxide could promote platelet attachment and release of growth factors in the vessel wall. These consequences of endothelial dysfunction such as lipid peroxidation along with reduced nitric oxide bioactivity, may be important in the initiation and progression of atherosclerosis and ultimately result in clinical manifestation of CVD. Angiotensin II is also involved in triggering vascular inflammation and oxidative stress in the endothelium by stimulating NAPH/NADPH oxidase, protein kinase C and mitogen-activated protein kinase (MAPK) [121,122]. Peripheral endothelial function correlates well with coronary endothelial vasodilation and is reduced in patients with CVD risk factors such as obesity, hypercholesterolemia, hypertension and diabetes[123].

Diet, Physical Activity and Gene-Environment Interactions

Dietary and physical activity interventions for promoting metabolic health and reducing development of CVD are important. The cumulative effects of common variants and interaction of genetic markers with diet and exercise are approaches used to study predictors of weight change. Based on accumulating evidence that appetite-determining genes play a role in obesity these are targets of investigation.

A meta-analysis of 10 studies comprising 6,951 participants reported that individuals with heterozygous and homozygous *FTO* genotypes were predisposed to more weight loss during lifestyle intervention with a trend for a gene dose effect.[124] Although a small effect, the association of *FTO* with appetite and components of dietary intake[125] support the role of genotyping for predicting individual responses to dietary intervention. More recent studies show greater body weight and waist circumference reductions in individuals carrying a *FTO* risk variant in the Food4Me randomized control trial, adding support for the idea that gene-based advice can be helpful for weight loss.[121] Leptin receptor (*LEPR*) variants contribute to BMI, LDL-C and HDL-C responses to a high carbohydrate diet in healthy Chinese adults. [126] Adiponectin, a key regulator of appetite and food intake, has been studied using a genetic risk score with divergent results on the effect of weight loss diets on adiponectin levels,[127] suggesting that the levels could be a better predictor as shown in the POUNDS Lost Trial in which adiponectin increased in association with improved abdominal fat distribution and lipid metabolism independent of weight change.[128,129] Fibroblast growth factor 21 (*FGF21*), although not directly involved in appetite, may interact with response to interventions for obesity. A low-calorie high carbohydrate diet had beneficial effects on body composition and abdominal obesity in obese individuals carrying an *FGF21 'C' allele* in the 2-year POUNDS Lost Trial.[130]

A large body of data suggests strong interaction between obesity and 25 (OH)D deficiency. [131] Genetically determined vitamin D deficiency in certain populations has been reported to be linked with increased risk for obesity, diabetes, and cardiometabolic diseases. [132,133] Earlier it was speculated that the sequestration of vitamin D in adipose tissue reduces its bioavailability. [134] However, recent studies by Drincic et al. [135] could not find any evidence of sequestration of supplemental or endogenous 25(OH)D in fat cells. Their results suggested that the dosing for vitamin D in obese patients should be adjusted according to body size and not according to BMI to achieve desired serum 25(OH)D concentrations[136]. Additionally, hyperparathyroidism, secondary to hypovitaminosis D, augmented by obesity, could also be responsible for the observed association with obesity [137]. These findings highlight the need to develop strategies to detect individuals at risk for the cardiometabolic effects of vitamin D deficiency. Essentially, ethnic variation in vitamin D deficiency, e.g., American Indians and their children beginning in infancy, whose dietary intake tends to be deficient in vitamin D[138].

MC4R encoding the melanocortin-4 receptor has a common variant with a strong effect on obesity [139]. Qi et al. reported association of *MC4R* variant (rs17782313) with higher intake of total energy and higher intake of dietary fat and protein. [140] The 'C' risk allele was associated with a 14% increased risk of T2D. The *FGF21* polymorphism (rs838147) has been reported to interact with dietary carbohydrate/fat intake and changes with obesity.[130] Since physical activity is a major modality used to enhance metabolic health and modulate obesity, it is a target for genetic association studies. A meta-analysis has shown that exercise attenuates the weight-gain effect of an *FTO* variant[141] as shown in the Food4Me study.[142] *FTO* variants interact with physical activity and dietary intake in the form of carbohydrate and fiber intake in an Asian Indian population, which are factors that are likely to be long-term beginning in youth.[143] Since the MC4R receptor protein is a key step in the pathway for appetite control in the hypothalamus, it has been a target for studies on lifestyle interactions including physical activity. The effect of an MC4R variant on BMI was modified by physical activity in Chinese children[135], and cardiometabolic risk in metabolically healthy obese Chinese children was predicted by a *KCNQ1* variant, and it interacted with walking to school.[144] The attenuating effect of physical activity on the effect of the *FTO* risk variant on BMI and waist circumference adds support for the variant as being helpful for weight loss in the Food4Me trial.[145]

Several genetic variants have been shown to interact with the effects of obesity, smoking and/or exercise on increasing triglyceride and lowering HDL-C [146], highlighting the importance of interactive lifestyle factors and their potential use in enhancing prediction. The *LPL* S447S (rs328) and Hind III (rs320) variants modified the effect of a high carbohydrate diet on triglyceride and HDL-C in a young Chinese population, especially in females suggesting that lifestyle intervention strategies for dietary intervention could be targeted according to genetic variants and gender.[147]

CLINICAL RELEVANCE OF GENETIC MODEL IN RISK PREDICTION

Genetic risk predictors represent loci or variants that contribute to polygenic obesity or may increase the risk of obesity in individuals who are not yet obese or are below obesity

thresholds. Since over a hundred candidate genes have been linked to BMI, with most acting in the central nervous system and influencing food intake [148], identification of gene network pathways may facilitate prediction and can lead to therapies directed at modifying behaviors including appetite. However, existing literature suggests that predicting obesity using genetic models based on common variants (representing GWAS loci), still have poorer predictive value than traditional clinical predictors such as a family history or obesity in childhood.[149] Incomplete understanding of the human genetic variation due to population heterogeneity, admixture, lack of population specific SNP arrays, incomplete mapping of regulatory domains etc., could likely contribute to the poor performance of genetic models. As data from more and more global populations are being added to the GWAS catalogue and the variant repositories, it may improve predictive power of genetic scores. This includes data obtained from targeted and whole genome sequencing in high-risk or susceptible populations.[150] Furthermore, a potentially productive and accurate prediction strategy for complex traits like obesity or diabetes will only be accomplished when regulatory domains are identified.[151] Therefore, in the current scenario, genetic information can only supplement the clinical history but cannot replace it. However, considering the usefulness of genetic models in better predicting the weight gain before middle age provides rationale for early screening which will be important for timely interventions.[152] Also, the weight gain trajectory in early adult life is associated with greater risk for poor cardio-metabolic outcomes such as hypertension, diabetes and dyslipidemia, supporting the argument for using genetics for predicting weight gain [6], and degree of weight gain. However, identification of putative genetic predictors is still incomplete.

FUTURISTIC MODEL

Genetic variation collectively account for only 8–10 % of total heritability linked with cardiovascular traits in GWAS, hence efforts are needed to account for missing heritability using more biologically associated explanations. Accounting for the effects of environmental interactions in a time-sensitive manner may contribute to solving the problem. Ongoing research continues to improve design and tools for better evaluation of genetic and non-genetic factors. However, effective prediction early in the pathological sequence of atherosclerosis, is central to preventing or offsetting progression to recognized end-points. Obesity has a recognized benchmark, beginning with rapid weight gain clinically seen on childhood weight charts when percentiles are crossed with a trajectory towards overweight and obesity thresholds. This observation presents as an opportunity for detection of early obesity trends as signals for evaluation of genetic interaction. Similarly, insulin resistance has a progressive and graded presentation with corresponding effects on the risk factor cluster, including NAFLD and inflammation. Since genetic information on both monogenic and polygenic obesity has shown a predominance of appetite and brain-associated gene variants, intervention strategies have moved towards modifying the respective behaviors. Our futuristic model depends on knowing the predictive power of selected variants, phenotype reversibility and effective therapeutic choices based on genetic interactions. However, less is currently known about the role genes play in pathogenesis than how they predict treatment effects by interacting with nutritional, exercise and pharmacological interventions. Gene variants constitute the genetic background for obesity in part via the

brain and appetite centers, subsequent insulin resistance, and the cluster of metabolic pathways influencing glucose intolerance, dyslipidemia, blood pressure, hepatic fat deposition and inflammation influence CVD progression in four main stages. These pathways can provide a road-map for intervention by using information from genetic variation that interact with nutrition, exercise and pharmacological treatments (Figure 2).

Interaction of gene variants influences effective primary, secondary and tertiary preventive strategies and CVD reversal. The ultimate goal is to improve end-points enabling treatment planning for timely interventions (Figure 3). Novel variant discovery by fine mapping, use of gene scores, whole exome sequencing and accounting for gene-gene and gene-environment interactions might contribute to improvements in prediction. However, the wide spectrum of clinical presentations for obesity and related complications presents as an organizational challenge.

CONCLUSIONS

Adverse influence of obesity on CVD has the potential to be lowered by coordinated preventive approaches based on genetic prediction so that multiple risk factors can be simultaneously decreased. The genetic background of obesity and associated risk factors provides a basis for using genetic variants to offset their expression of CVD phenotypes and appears to be a feasible clinical strategy. The challenge is to select SNPs that can be identified as clinically recognized phenotypes. Altered carbohydrate homeostasis leading to insulin resistance and T2D appears to be central to this cluster that also includes hyperglycemia, hyperlipidemia and hypertension. Ectopic deposition of fat in muscle and in liver (manifesting as NAFLD), and inflammation with contributions from the gut microbiome are more recently recognized additions. Relatively little is known about the genetic background for inflammation and how it interacts with the microbiome, although they make significant contributions to CVD and present as possible therapeutic targets. Therefore, the plausible futuristic model would include the discovery of putative genetic and non-genetic factors that interact with phenotypes, and may help predict CVD risk and facilitate early detection, risk reversal, and effectual individualized intervention.

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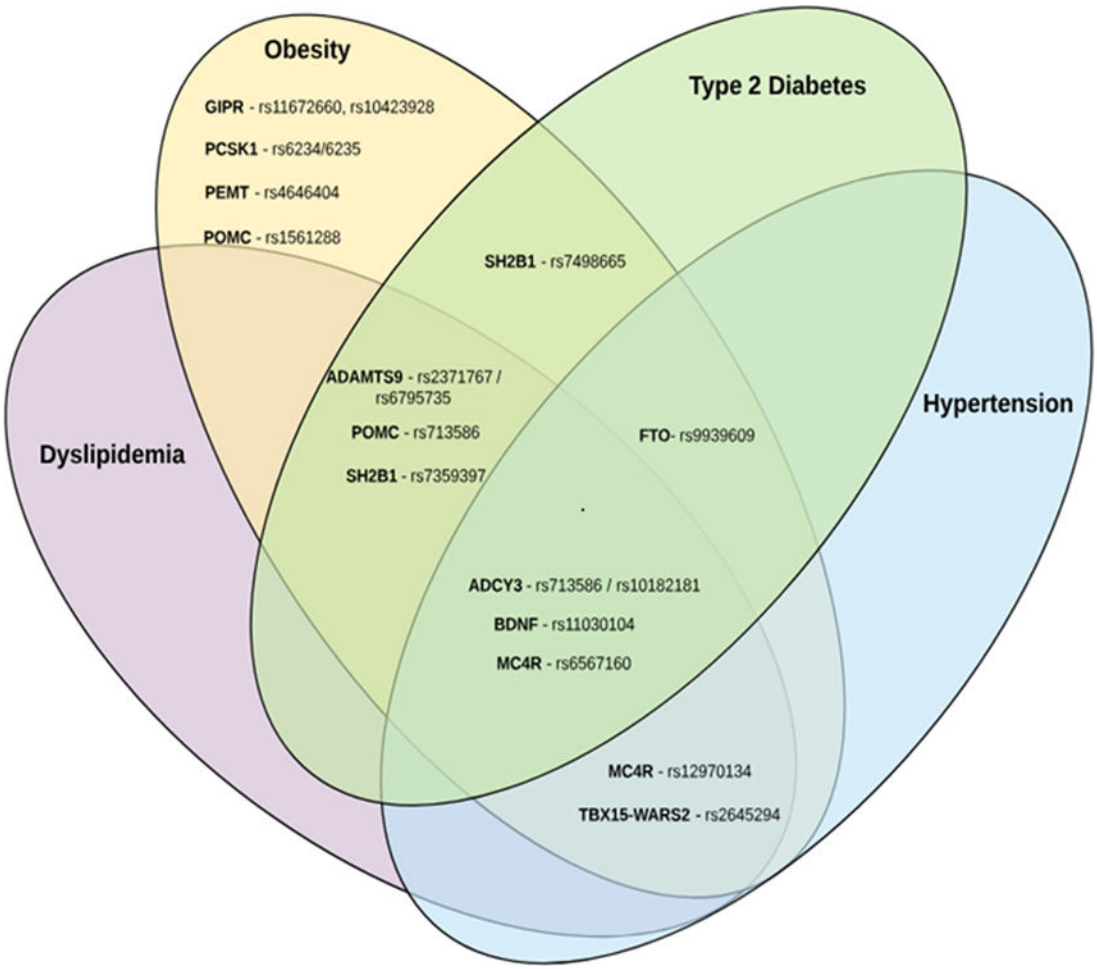

Figure 1.

Venn diagram showing the pleiotropic associations of common variants among the major obesity loci identified by GWAS. Genetic variants identified in the GWAS for obesity are classified based on the results of the pleiotropic association reported of the same loci/ variants with other cardiovascular traits. Each cardiovascular trait shown in different colors in the Venn diagram (yellow, purple, green, aqua) corresponds to each of the cardiovascular traits (obesity, dyslipidemia, type 2 diabetes, and hypertension), respectively. Effect sizes and pleiotropic association p-values are summarized in Table 1.

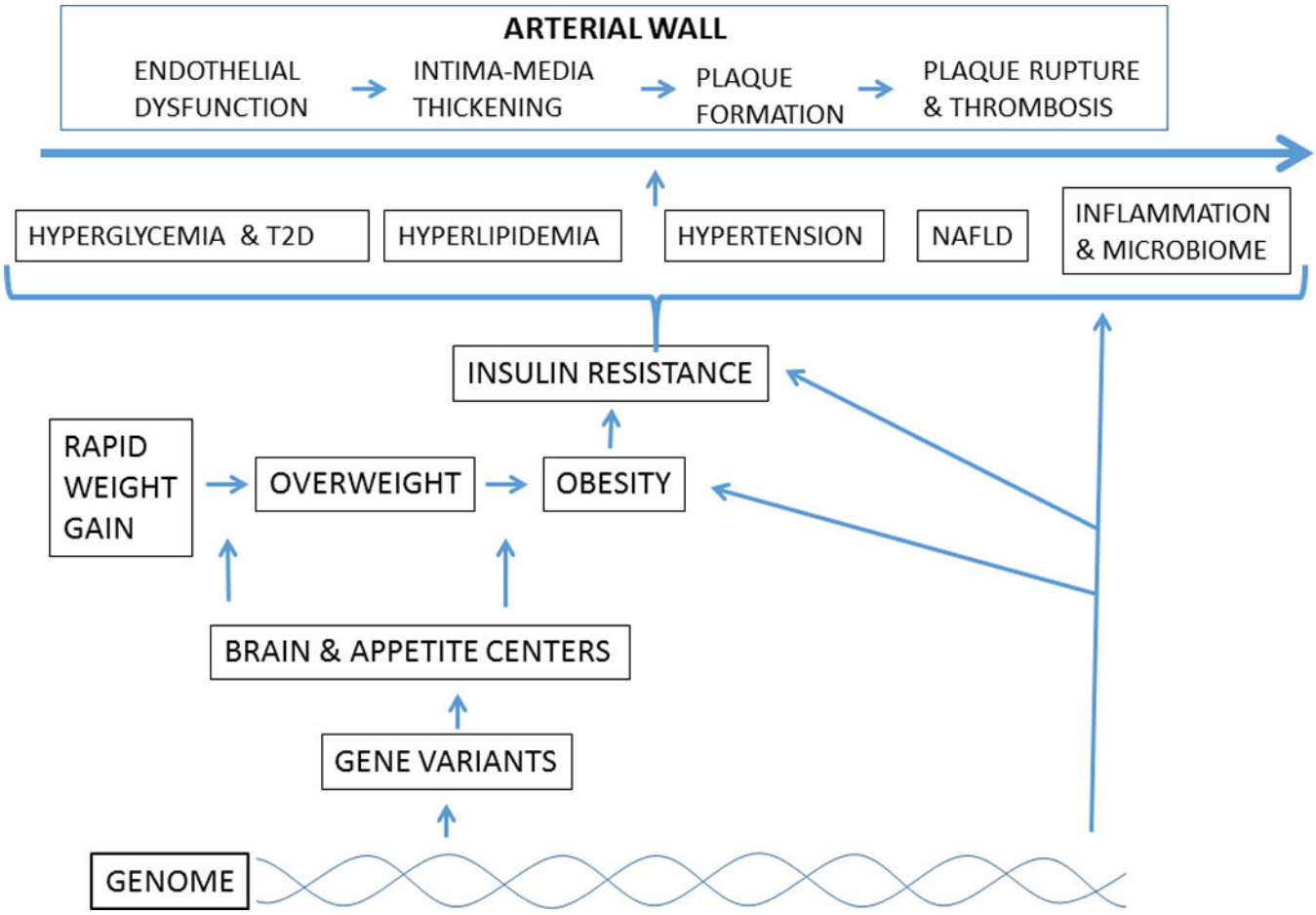

Figure 2.

Genetic background for obesity resulting in CVD progression in three main stages. These include metabolic derangements due to genetic, non-genetic, dietary and lifestyle interactions; the development of cardiometabolic syndromic traits leading to fatty liver disease and inflammatory microbiome; and ultimately leading to vascular dysfunction and atherosclerotic plaque formation.

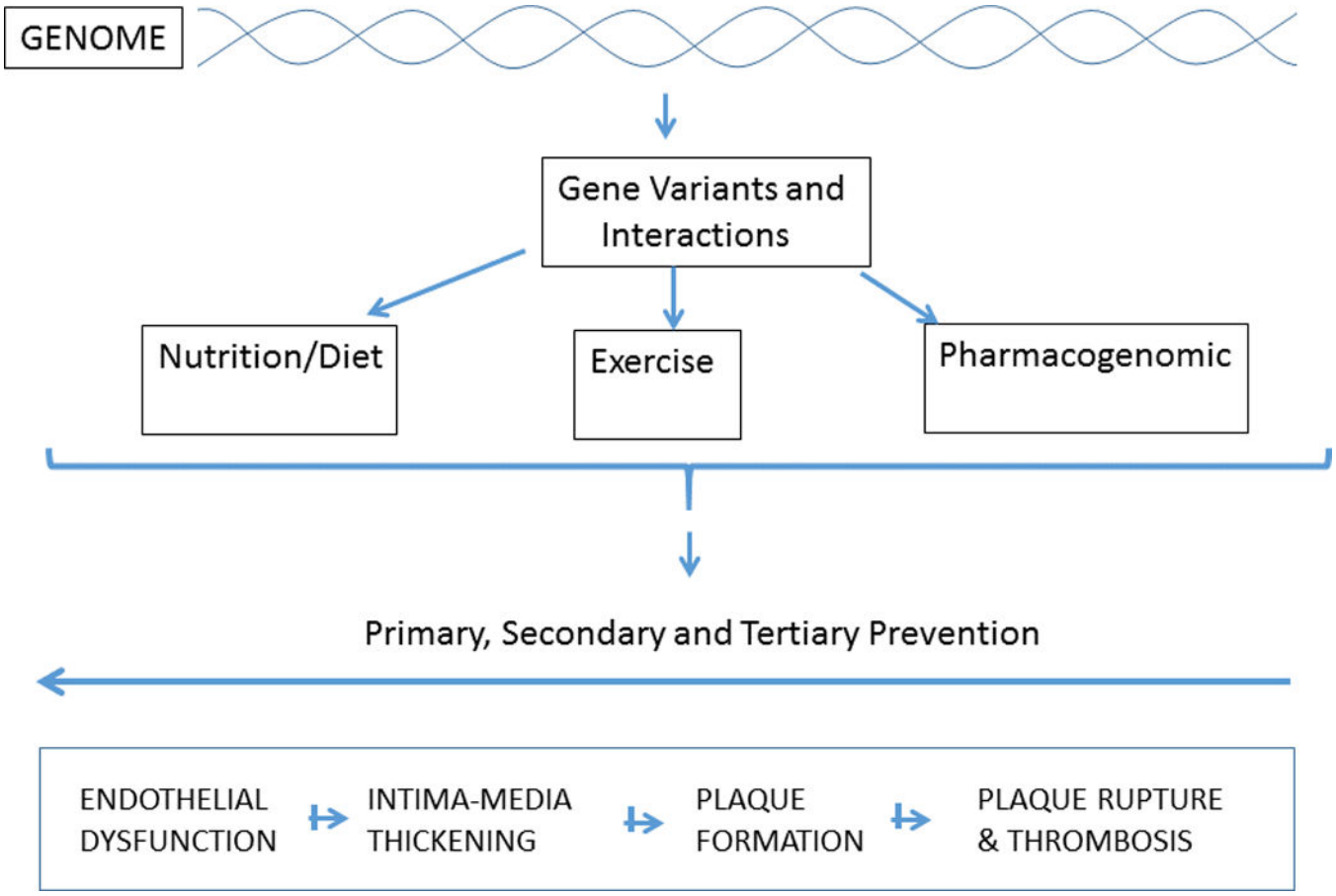

Figure 3.

Influence of genetic interactions with various treatment modalities. Futuristic screening model suggesting the usefulness of clinically relevant genetic information and their interactions with dietary and lifestyle factors to design effective primary, secondary and tertiary preventive strategies for effective interventions for CVD reversal.

Table 1.

Summary of common variants associations in major genes identified in GWAS of obesity showing pleiotropic association with two or more cardiovascular risk traits

			Obesity				Type 2 Diabetes				Fasting Blood Glucose				Dyslipidemia				Hypertension			
Gene/rs ID	**Popul ation**	**Effect Allele**	**Beta or OR**	**P value**	**N**	**PMID**	**OR**	**P value**	**N**	**PMID**	**Beta**	**P value**	**N**	**PMID**	**Beta**	**P value**	**N**	**PMID**	**Beta**	**P value**	**N**	**PMID**
ADAMTS9 rs6795735	EUR	C	0.025	9.8×10^{-14}	161,642	20935629	1.07	4.4×10^{-4}	69,033	24509480	2.03‡	0.042	77,167	20935629	−2.5‡	0.013	77,167	20935629	---	---	---	---
ADCY3 rs10182181	EUR	G	0.031	8.8×10^{-24}	322,154	25673413	1.0	0.89	86,188	25673413	6×10^{-4}	0.77	131,771	25673413	0.009	0.049	172,937	25673413	0.14	0.023	67,936	25673413
ADCY3/ POMC rs713586	EUR	C	0.14	6.2×10^{-22}	230,748	20935630	−	0.833	10,128	20935630	0.004	0.44	5,641	27530450	−	0.45	19,000	20935630	---	---	---	---
rs713586	EAS	C	0.025	4.9×10^{-13}	173,430	28892062	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
BDNF rs11030104	EUR	A	1.05†	1.3×10^{-34}	339,224	25673413	1.01	0.37	83,545	25673413	0.003	0.41	58,074	25673413	0.014	1.35×10^{-3}	163,969	25673413	0.23	2.1×10^{-3}	69,843	28135244
FTO rs9939609	EUR	A	0.10‡	3×10^{-35}	30,081	17434869	1.25	1×10^{-20}	63,961	22693455	0.69	0.012	9,618	27790247	---	---	---	---	0.28	0.163	9,618	27790247
rs9939609	SAS	A	1.25†	9×10^{-19}	39,774	22109280	1.15	5.5×10^{-8}	18,112	22109280	0.24	0.03	1,666	21294771	---	---	---	---	---	---	---	---
rs9939609	EAS	A	1.27†	1.2×10^{-13}	9,035	22109280	1.15	2.43×10^{-7}	59,106	22109280	---	---	---	---	---	---	---	---	---	---	---	---
GIPR rs11671664	EUR	A	0.029	0.0012	194,562	22344221	1.08	2.4×10^{-5}	20,298	28869590	---	---	---	---	---	---	---	---	---	---	---	---
rs11671664	SAS	A	---	---	---	---	1.08	1.29×10^{-2}	42,071	28869590	---	---	---	---	---	---	---	---	---	---	---	---
rs11671664	EAS	A	0.046	7×10^{-14}	62,245	22344221	1.08	6.3×10^{-7}	50,981	28869590	---	---	---	---	---	---	---	---	---	---	---	---
GIPR rs10423928	EUR	A	1.16†	4×10^{-13}	95,632	23563607	1.07	1.8×10^{-4}	57,599	20081857	0.08	2×10^{-15}	41,099	20081857	---	---	---	---	---	---	---	---
MC4R rs6567160	EUR	C	0.056	3.9×10^{-53}	321,958	25673413	1.07	6×10^{-7}	80,620	25673413	0.003	0.196	128,057	25673413	-0.03	2.9×10^{-9}	185,608	25673413	0	0.994	66,849	25673413
MC4R rs12970134	EUR	A	1.12†	9.9×10^{-16}	51,151	23049848	1.26	0.006	4,561	18454146	0.004	0.083	889	21372613	-1.34	0.01	4,561	18454146	0.11	0.64	4,561	18454146
rs12970134	SAS	A	0.004	6.8×10^{-4}	7,394	18454146	1.07	0.15	7,394	18454146	---	---	---	---	-0.76	0.03	7,394	18454146	-0.06	0.71	7,394	18454146
rs12970134	SAS- Sikhs	A	0.67	0.0005	1,528	19680233	---	---	---	---	---	---	---	---	0.01	0.97	1,528	19680233	---	---	---	---
PCSK1 rs6234/ rs6235	EUR	G	1.09†	1.25×10^{-5}	163,385	25784503	---	---	---	---	−0.01	1.4×10^{-6}	1,367	23903356	---	---	---	---	---	---	---	---
rs6234/ rs6235	EAS	G	1.0†	0.274	66,721	25784503	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
PEMT rs4646404	EUR	G	0.027	1.4×10^{-11}	198,196	27195708	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
rs4646404	SAS	G	-0.03	0.1	9,505	27195708	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
POMC rs1561288	EUR	C	0.055	5×10^{-8}	28,998	23669352	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
SH2B1 rs7359397	EUR	T	0.15	1.9×10^{-20}	204,309	20935630	+	0.306	10,128	20935630	0.018	9.8×10^{-4}	5,641	27530450	-	0.099	19,000	20935630	---	---	---	---
SH2B1 rs7498665	EUR	G	0.15	5.1×10^{-11}	86,677	19079261	1.09	2.5×10^{-6}	70,930	24528214	---	---	---	---	---	---	---	---	---	---	---	---

			Obesity				Type 2 Diabetes				Fasting Blood Glucose				Dyslipidemia				Hypertension			
Gene/rs ID	**Popul ation**	**Effect Allele**	**Beta or OR**	**P value**	**N**	**PMID**	**OR**	**P value**	**N**	**PMID**	**Beta**	**P value**	**N**	**PMID**	**Beta**	**P value**	**N**	**PMID**	**Beta**	**P value**	**N**	**PMID**
rs7498665	EAS	G	---	---	---	---	1.11	0.179	21,793	24528214	---	---	---	---	---	---	---	---	---	---	---	---
TBX15- WARS2 rs2645294	EUR	T	0.031	1.7×10^{-19}	209,808	25673412	---	---	---	---	-0.09	0.014	770	28257690	0.155	1.6×10^{-5}	770	28257690	-0.12	8.3×10^{-4}	770	28257690

+/−: Effect Direction

†OR Values

‡Z score

N: Sample Size; **PMID**: PubMed ID; **EUR**: European; **EAS**: East Asian; **SAS**: South Asian