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Genetic Determinants of Cardio-Metabolic Risk: A Proposed Model for Phenotype Association and Interaction

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Abstract

This review provides a translational and unifying summary of metabolic syndrome genetics and highlights evidence that genetic studies are starting to unravel and untangle origins of the complex and challenging cluster of disease phenotypes. The associated genes effectively express in the brain, liver, kidney, arterial endothelium, adipocytes, myocytes and β cells. Progression of syndrome traits has been associated with ectopic lipid accumulation in the arterial wall, visceral adipocytes, myocytes, and liver. Thus it follows that the genetics of dyslipidemia, obesity, and non-alcoholic fatty liver (NAFLD) disease are central in triggering progression of the syndrome to overt expression of disease traits, and have become a key focus of interest for early detection and for designing prevention and treatments. To support the "birds' eye view" approach we provide a road-map depicting commonality and interrelationships between the traits and their genetic and environmental determinants based on known risk factors, metabolic pathways, pharmacological targets, treatment responses, gene networks, pleiotropy, and association with circadian rhythm. Although only a small portion of the known heritability is accounted for and there is insufficient support for clinical application of gene-based prediction models, there is direction and encouraging progress in a rapidly moving field that is beginning to show clinical relevance.

Introduction

There is accumulating evidence that insulin resistance and associated biochemical derangements precede atherogenesis and beta cell failure by several years[1], indicating that there is a window of time during which prediction would be useful. The window extends further, since many of the traits have been identified in childhood and adolescence suggesting that early recognition of genotypes may precede disease progression and enable institution of preventive measures before the traits develop into overt disease. Even when the syndrome presents at an early age, it is more usual for more than one trait to be present, so it is realistic to approach the problem by recognizing the cluster in childhood and adolescence [2]. Since gene-gene and gene-environment interaction occurs with time, study of

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young age groups is less likely to have confounding effects and a popular strategy has been to search for novel loci in pediatric cohorts and to attain replication of the findings[3].

The cluster of three or more out of five criteria of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP), is predictive of both cardiovascular disease and type 2 diabetes and has been recommended for clinical use [4]. However, it is uncertain whether the syndrome is best represented by dichotomization of the variables or whether they should be assessed as continuous variables which have provided better prediction when used with the Framingham Risk Equation [5, 6]. It is also proposed that the syndrome contains four clusters with latent underlying linking factors, but it remains uncertain whether clinical identification of the syndrome has any advantages over separate evaluation of each component [7]. Blood pressure and hyperglycemia have been linked separately from the remaining factors such as waist circumference, triglyceride, and HDL-C [8]. The presence of hypertriglyceridemia with increased waist circumference has been identified as a strong predictor of coronary artery disease (CAD)[9] and has been recommended as a screening phenotype [10]. However, it has been debated whether obesity is a stronger underlying factor than insulin resistance since obese individuals can escape the metabolic syndrome and remain metabolically healthy, whereas lean individuals can be insulin resistant with increased cardio-metabolic risk, particularly if they have a first degree relative with type 2 diabetes [11]. Also the hypothesis that insulin resistance is the main underlying factor has been challenged, since many cases with the syndrome have insulin resistance measures below the first quartile [12].

To account for the rapid and variable increase in obesity and metabolic syndrome prevalence, the argument for gene-environment interaction has gained momentum. It was originally proposed that phenotype expression may occur when conditions of nutritional excess prevail, supporting the concept that the metabolic syndrome results from an array of “thrifty” genes that are latent in the normal state but manifest after prolonged nutritional excess often associated with obesity [13]. It is possible that efficient storage of nutrients had a selective advantage but the subsequent effects such as obesity and ectopic fat accumulation are deleterious. In some areas of metabolic syndrome research the concept is viable and supports lifestyle intervention. The mechanism that promotes accumulation of fat and lipid metabolites in liver and muscle resulting in insulin resistance has been defined by Shulman et al and has been recently reviewed [14] and the process can potentially be reversed with exercise [15]. These observations support the role of excessive organ fat storage in the progression of insulin resistance to diabetes and fatty liver disease. However, each of the criteria have been shown to be associated with several genes and SNPs within each gene resulting in complex polygenic inheritance that, as a whole would have been less likely to have provided selective advantage. Consequently alternative hypotheses favoring more direct gene-environment interaction have been proposed [16], but current approaches have involved gene association methods, particularly genome-wide association scanning (GWAS), requiring large populations with replication, since the traits are variable and interactive resulting in variable association. Because of the complexity of the cardio-metabolic phenotype, most reviews and studies, including GWAS, have preferred to use single traits and not the cluster of traits as a syndrome or score as the phenotype. However, to obtain a clinical perspective of the syndrome’s complex genetic inheritance, the traits will be reviewed in a sequence corresponding to three main anatomic locations of their expression and modulation of cardio-metabolic effects; hypothalamic genes modulating obesity, hepatic genes with effects on dyslipidemia and excessive hepatic fat deposition, hepatic, renal and possibly endothelial genes on blood pressure and the beta cell genes modulating the impairment of insulin secretion. Genes that express in more than one location such as the *FTO* in the hypothalamus and adipocyte are discussed under the organ where the effect appears most prominent. However there are examples of pleiotropic effects

and effects acting via gene networks and interacting metabolic pathways that can have significant effects on more than one trait. Circulating hormones, cytokines and lipoproteins that change with obesity and insulin resistance also can modulate traits associated with gene interaction in the target organ. In this regard recent evidence for the effects of lipoproteins on the β-cell is included. Effects of age and interrelationships between the traits and their genetic determinants are discussed, and a model of how interaction may occur is presented in Figures 1–2.

Hypothalamic Genes

Obesity measures such as waist or body mass index (BMI) are components of most childhood and adult definitions of the metabolic syndrome and both have strong association with insulin resistance [17] and are highly correlated, however BMI has been used in most genetic studies because of its availability and widespread acceptance.

Rare monogenic forms of obesity have clearly provided insight on possible mechanisms for the development of severe obesity [18] and has led to the question whether polymorphisms within these known genes are involved in polygenic inheritance of obesity in the general population, since 60–90% of the BMI variance within a population is accounted for by inheritance [19]. The discoveries lead to definition of energy homeostasis pathways in animal models; in particular the leptin-melanocortin pathway responsible for satiation [20]. *MC4R* deficiency, the commonest of the clinically occurring monogenic forms, has been described in association with severe obesity, increased lean mass, increased linear growth, hyperphagia beginning in childhood, and severe hyperinsulinemia in heterozygous carriers but with greater severity in homozygotes [21]. The increased linear growth has been associated with incomplete growth hormone suppression consistent with possible interference with somatostatin suppression of growth hormone pulsatility [22]. Several functional polymorphisms in the gene have been detected and some have protected against obesity, but larger scale GWAS have identified positive association. BMI association with 2.8 million single nucleotide polymorphisms (SNPs) in 123,865 individuals with follow-up in a significant number revealed 14 known obesity susceptibility loci and identified 18 new loci. Some of the loci such as *MC4R, POMC, SH2B1* and *BDNF* mapped near key hypothalamic regulators of energy balance. One of the loci was near *GIPR*, an incretin receptor [23] supporting a predisposition to type 2 diabetes with pleiotropic effects in the hypothalamus and β-cell.

A single common variant in intron 1 of the *FTO* (fat mass and obesity-associated) gene (rs9939609) was identified in association with type 2 diabetes, and further analysis revealed that the higher BMI in individuals with diabetes accounted for the association [24]. The analysis included 7477 UK children from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who had anthropometric measures at birth and at 7, 8, 9, 10, and 11 years of age and 4320 children from the Northern Finland 1966 birth cohort, leading to the conclusion that the *FTO* allele is not associated with changes in fetal growth as reflected by birth weight, but is associated with changes in BMI in children by the age of 7, and persisting to puberty [24]. The association with obesity has been confirmed in other longitudinal studies in childhood [25, 26] including a Dutch study showing association with higher BMI, fat mass index, and leptin concentrations during puberty but declining at ages 13–14 years, a finding thought to be consistent with hormonal effects of puberty [27]. The association of severe obesity with *FTO* has been studied using a haplotype approach. The investigators examined the linkage disequilibrium (LD) block structure of a region surrounding the candidate *FTO* rs9939609 SNP and determined the best haplotype composed of a three SNP combination associated with severe obesity. The calculation of a

risk score based on the haplotype yielded an attributable risk of 34% for severe obesity suggesting that the approach has clinical use for examining risk in predisposed families [28].

The finding that *FTO* mRNA is abundant in mouse hypothalamic nuclei and codes for 2-oxoglutarate-dependent nucleic-acid demethylase, supports a regulatory role in energy balance, appetite and sympathetic outflow to the circulatory system [29]. The *FTO* variants have early effects on obesity since they affect the rate of weight gain in African and European American youth [26]. These observations are consistent with the finding that high fat intake and low physical activity modify the association between genetic variation in the *FTO* genotype and obesity [30]. Since the common intron 1 *FTO* variant was initially associated with diabetes, and phenotypic interactions appear to be diabetogenic, the association with diabetes appears likely. The question has been explored in a meta-analysis of South Asian populations in whom BMI and waist association with *FTO* is similar to that seen in Europeans but a strong association with diabetes is only partly accounted for by BMI [31]. A recent large scale meta-analyses study conducted on 96,551 individuals from East and South Asia confirmed the association of rs9939609 with type 2 diabetes independent of obesity [32]. Also the *FTO* gene has been associated with hypertension and obesity in adolescents within a French Canadian founder population supporting pleiotropy [33].

Hepatic Genes

a. Dyslipidemia

Since, not all obese individuals have elevated triglycerides, and non-obese cases can present with elevated levels [34, 35], there is support for genetic predisposition for explaining abnormal levels and for gene-environment interactions with obesity and dietary intake as the main modifiers. Four classic Frederickson phenotypes (IIb, III, IV and V) originally described at the National Institutes of Health have been characterized as having an elevated triglyceride. With the exception of Type III hyperlipidemia, which has a distinct monogenic association with *APOE* polymorphism coding for homozygous apolipoprotein E_2 and expressing when the individual becomes obese, the remaining three phenotypes were found to have overlapping genotypes [36]. Interestingly, the genotypes had previously been identified in GWAS performed on subjects with mild triglyceride elevations. Thus clinically relevant dyslipidemia with high triglyceride as a component, can often be associated with triglyceride-associated polymorphisms. SNPs in genes such as *APOAV* and *APOE*, can result in severely increased triglyceride [37] and many cases were found to be carriers of *APOAV* variants (S19W or −1131 T>C). Studies on *APOAV* polymorphisms have consistently shown association with triglyceride elevation following the discovery that homozygous apoA-V deficiency results in severe hypertriglyceridemia. Also the −455 T>C polymorphism in the *APOCIII* gene promoter region is associated with increased triglyceride levels. The −455C and −482T alleles fail to respond to insulin-mediated down-regulation so that transcription remains active and plasma apoC-III is increased [38]. The activated state for apoC-III transcription occurs in insulin resistance, which accounts for increases in plasma apoC-III and triglyceride in obesity and in the metabolic syndrome [39]. In a multi-ethnic population sample, the triglyceride was 20% higher for −455C carriers, particularly in females who were also shown to have low HDL-C[40]. Findings in GWAS and meta-analysis studies have reported a strong association of common variants near *APOAV-AIV-CIII-AI* gene cluster with serum triglycerides [41] suggesting influence of polymorphisms on expression of apoC-III and apoA-V.

Although cultural, environmental and hormonal factors determine HDL-C, a genetic component accounts for up to 76% of the variation in HDL-C [42]. High heritability of HDL-C and HDL-associated traits provide a strong rationale for identifying loci that may uncover pathways crucial for HDL regulation and treatment design. Regulatory genes involved in

HDL metabolism mediated by apoA-I, LCAT, endothelial lipase and ABCA1 have been associated with severe HDL deficiencies [43]. However, the population frequencies of the major gene abnormalities are small and association with disease has been ambivalent [44], supporting a case for functional assays to represent the HDL phenotype, such as apoA-I and measures of cholesterol efflux [45]. Candidate gene association studies provide evidence that variation in HDL-regulatory genes have an effect on HDL which is dependent on environment [46] and as many as 20% of cases with a low HDL-C have known mutations.

GWAS using apoA-I and HDL-C as phenotypic markers, done in a predominantly American Indian population, located quantitative trait loci in regions of the genome that contain known candidate genes located in 6p, 9q and 15q regions [47], findings which could lead to further investigation to identify association with single nucleotide polymorphisms. The 15q region has been recognized to have a significant interaction with diabetes, BMI, smoking, alcohol intake and gender [48]. After serial adjustments, the LOD score increased from 1.75 to 4.52, supporting multiple endogenous and environmental influences including obesity. The region contains the gene for hepatic lipase suggesting that it has HDL-determining polymorphisms. The 9q locus contains the *ABCA1* gene, coding for the cholesterol transporter regulating efflux from cells to HDL, and located at 9q31.1. Moreover, the *ABCA1*-C230 allele was associated with low HDL-C in exclusively American Indian populations [49]. This is important since carriers of loss of function mutations in *ABCA1* display pancreatic beta-cell dysfunction supporting a role for *ABCA1* in removing cholesterol from beta cells [50].

Susceptibility to changes in HDL composition and function occur in obesity in part due to triglyceride elevation, triglyceride-enrichment of HDL mediated by cholesterol ester transfer protein (CETP) is followed by degradation of HDL by hepatic triglyceride lipase, dissociation of apoA-I and subsequent renal catabolism[51]. It follows that in hypertriglyceridemic conditions CETP activity has an HDL-reducing role. Conversely, CETP deficiency secondary to a gene defect results in extreme elevations in HDL-C [52], but there has been controversy on whether the large HDL particles formed in CETP deficiency perform an adequate protective function. Nevertheless, CETP inhibition is the basis for a series of pharmaceutical agents designed to raise HDL-C, although the initial ILLUMINATE trial was abruptly terminated when a disproportionate number of deaths occurred in the treatment arm. Hypertension, attributed to an off-target effect of Torcetrapib on increasing aldosterone, was a recognized problem which has been eliminated in newer compounds.

Genetic variation in the *CETP* gene has been extensively studied for association with variation in HDL-C in different populations [53, 54]. A meta-analysis reported *CETP* genotypes to be associated with moderate inhibition of CETP activity and inverse association with CAD or no increased risk [55]. Other studies have reported greater risk associated with low CETP activity secondary to severe genetic deficiency[56]. A recent prospective study from the community-based Framingham Heart Study also reported greater risk with low CETP activity[57]. More recently it has been shown that polymorphisms in the *CETP* promoter region determine activity. GWAS in Caucasians has revealed association of the variant -2568 C/A (rs3764261) with HDL-C variation and the finding has been replicated in different ethnic groups [58, 59].

The role of three SNPs in the promoter region (−2568 C/A, −1700 C/T), −998 A/G) and the well-known non-coding SNP (397 A/G) identified as a restriction fragment (Taq1b) in the first intron, were studied in the unique Sikh population of Northern India who are known to have a high prevalence of type 2 diabetes and CAD despite much lower obesity rates [60]. The −2568 C/A allele showed a strong association with increased HDL-C and decreased blood pressure. Although none of the SNPs were individually associated with CETP activity, low

activity was associated with greater CAD risk and there was significant interaction between the *CETP* SNPs studied as haplotypes and CETP activity for affecting HDL-C [61]. These results suggest that more complete genotyping could serve to define individual risk and response to therapies designed to raise HDL-C by inhibiting CETP.

b. Hepatic Fat and NAFLD

The NAFLD begins as simple steatosis and progresses to inflammation with risk for cirrhosis and liver cancer and is independently associated with increased risk of CAD [62]. It has been proposed as a pre-diabetes phenotype and as a component of the metabolic syndrome [63]. When fatty acids are mobilized from peripheral adipocytes in obese individuals, they are delivered to the liver and serve as a source for triglyceride which can either be stored or become incorporated into VLDL [64]. It has been proposed that adipocytes become abnormal in obesity and that fatty acid release is excessive, particularly in Asian Indians who tend to be insulin resistant despite being relatively non-obese [65]. Adipocyte dysfunction results in part from ectonucleotide pyrophosphate phosphodiesterase (*ENPP1*) over-expression, which may account for excessive mobilization of fatty acids leading to ectopic fat deposits as well as increases in VLDL triglyceride formation [66]. In the multi-ethnic Dallas Heart Study, logistic regression analysis revealed significant interactions between the *ENPP1* genotype, age, and body mass index (BMI) within each ethnic group and an *ENPP1* allele predicted diabetes when a recessive model was tested. Consequently it was speculated that ethnic differences in the allele frequency could contribute to susceptibility to type 2 diabetes in African Americans and Hispanics [67].

Defective maturation of the VLDL particle in the golgi at the stage when triglyceride is transferred to apoB by microsomal triglyceride transfer protein coded for by *MTTP* [68], could account for excess liver fat storage leading to non-alcoholic fatty liver disease. This concept is supported by observations that *MTTP* polymorphism may impact non-alcoholic steatohepatitis by modulating lipoprotein metabolism and post-prandial lipemia. Carriers of the −493 G/T allele have a more atherogenic lipid profile [69], which also has a deleterious effect on beta cell function [70]. Genetic determinants of VLDL formation as a cause of both atherosclerosis and fatty liver disease are supported by association of apoC-III polymorphisms with NAFLD. Asian Indian carriers of the *APOCIII* variant alleles (C-482T, T-455C, or both) had a 30% increase in apoC-III levels and a 60% increase in triglyceride, as compared with the wild-type homozygotes. The prevalence of NAFLD was 38% among variant-allele carriers compared to 0% among wild-type homozygotes, and association with insulin resistance was significant [71] Furthermore, apo-CIII overexpressing mice are predisposed to diet-induced hepatic steatosis and hepatic insulin resistance [72]. These observations are explained by the dual role of apoC-III in VLDL assembly in the liver and in inhibiting VLDL lipolysis [73]. Missense mutation in *APOCIII* within the C-terminal lipid binding domain of human apoC-III results in impaired assembly and secretion of VLDL providing evidence that apoC-III plays a role in the formation of lipoproteins [74], whereas apoC-III non-competitively inhibits activity by direct interaction with lipoprotein lipase [75]. It is possible that a combination of polymorphisms could result in large sized VLDL as has been observed in NAFLD in an adolescent population independent of adiposity and insulin resistance, and interestingly the NMR lipid profile was characterized as having increased small dense LDL and a decrease in the number of large HDL particles [76], supporting the association of NAFLD with increased risk for atherosclerosois in adults [77] and with increased IMT in adolescents [78]. These findings support the concept that NAFLD genotypes have pleiotropic effects, or alternatively the effects arise from a biochemical cascade leading to excessive hepatic fat storage.

GWAS of 2111 participants of the Dallas Heart Study revealed a robust association of liver fat defined by magnetic spectroscopy with the I148M allele of the *PNPLA3* gene [79] and the

association also occurs in children and adolescents[80]. Furthermore a meta-analysis of 16 studies showed association with disease severity. *PNPLA3* has a strong effect on susceptibility to more aggressive disease with higher necroinflammatory scores and progression to fibrosis [81]. The gene *PNPLA3* codes for patatin-like phospholipase domain-containing a protein known as adiponutrin which plays a role in hepatic triglyceride hydrolysis, but the specific function is being investigated. It has been associated with increased alanine transaminase level, a marker of fatty liver disease, in Hispanics, Europeans, and Asian Indians [82, 83]. Interestingly the S453I allele was associated with lower hepatic fat content and was more frequent in African Americans who had the lowest hepatic fat content, suggesting a protective effect [79]. Although hepatic fat accumulation has been associated with insulin resistance there has been no association of the *PNPLA3* allele with glucose intolerance, however associated obesity and alcohol consumption act independently with the *PNPLA3* allele to increase serum transaminases [84].

Hypertension

Insight into the field of hypertension genetics has been provided by previous reviews[85, 86]. As with the other syndrome traits, the heritability of blood pressure is high ranging from 30–40% [87]. Furthermore, systolic blood pressure has been associated with greater risk of mortality from CAD and stroke than diastolic with strong relationships to dietary salt intake [88] and ingestion of sugars and sugar-sweetened beverages [89] supporting gene-environment interactions. An increase in systolic blood pressure precedes diastolic and both are associated with obesity [90] with an abundance of evidence to support the associated effect of insulin resistance. Rare 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. Using such an approach, 24-hour ambulatory blood pressure has been associated with five polymorphisms in the *KCNJ1* gene coding for an inward-rectifying apical potassium channel expressed in the thick ascending limb of Henle and throughout the distal nephron of the kidney. It has the potential to cause expression of antenatal Bartter Syndrome Type 2 when the abnormal allele is inherited [91]. Also ambulatory blood pressure is associated with common variations in the *WNK1* gene known to cause pseudohypoaldosteronism type 2 or Gordon syndrome[92]. Furthermore, association of *WNK1* with blood pressure in childhood underscores its possible association with evolving hypertension at young ages[93]. Additional association with variants in *CASR, NR3C2, SCNN1,* 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 [91]. However, GWAS has shown that only some of the associations are in or near genes involved in known hypertension-related metabolic pathways. The International Consortium for Blood Pressure GWAS studied 200,000 individuals of European descent and identified sixteen loci of which only six contained genes that are known or suspected to regulate blood pressure, which include *NPR3, GUCY1A3- GUCY1B3, ADM, GNAS-EDN3, NPPA-NPPB,* and *CYP17A1* and their known metabolic roles have been have been comprehensively reviewed [94]. Interestingly *CYP17A1* achieved the most 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.

Data from the National Health and Nutrition Examination Survey showed the prevalence of hypertension to be 40% in African Americans compared to 27% in European Americans [95] leading to the hypothesis that part of the excess burden in African Americans is due to genetic susceptibility [96]. Genome-wide and candidate gene associations have been examined in the Candidate Gene Association Resource Consortium consisting of 8591 African

Americans. Novel associations were detected for diastolic blood pressure on chromosome 5 near *GPR98* and *ARRDC3* and for systolic blood pressure on chromosome 21 in *C21orf91*. Two of the top SNPs were not replicated in previously studied independent African American cohorts. However, several European American SNPs in *SH2B3, TBX3-TBX5 and CSK-ULK3* did replicate supporting similarities in inheritance and associated complexities due to environmental and cultural factors [96].

The Beta Cell

a) Lipoproteins and the Beta Cell

Epidemiological observations supporting a role for HDL in the pathogenesis of diabetes have been supported by in vitro studies showing that addition of LDL to isolated human and rat islets decreases glucose stimulated insulin secretion and is attributed to cholesterol uptake by islet LDL receptors [97]. Furthermore, the effect of intracellular accumulation of cholesterol is strongly influenced by HDL-mediated cholesterol efflux via the ATP-binding cassette transporter A1 (ABCA1), since mice lacking the LDL receptor and the ABCA1 transporter were not protected from effects of added LDL on decreasing beta cell insulin secretion, suggesting that HDL-mediated efflux plays a critical protective role [98]. Further studies have revealed that high cholesterol content in the beta cell membrane down-regulates insulin secretion by influencing membrane depolarization, the signal for calcium influx and calcium-mediated insulin secretion [99]. These studies provide a plausible explanation for the role of HDL in protecting the beta cell from cholesterol-induced toxicity.

b) Intrinsic Beta Cell Genes

The majority of gene variants associated with type 2 diabetes such as *TCF7L2, CDKAL1, CDKN2A/B, HHEX-IDE, IGF2BP2, SLC30A8, KCNJ11, WFS1, JAZF1, TSPAN8, CD123/CAMK1D* and *MTNR1B*, are implicated in β-cell functions such as glucose-stimulated insulin secretion, incretin effects on β-cell stimulation, and proinsulin to insulin conversion [100, 101]. However the variants associated with fasting glucose levels in the normoglycemic population such as *GCK, GCKR, G6PC2* and *MTNR1B* [102], do not always influence risk for type 2 diabetes but may only influence fasting glucose homeostasis both individually and when combined [103, 104].

Since fatty acids, LDL and HDL interact with the beta cell, it is possible that the levels, function and corresponding lipoprotein metabolism-determining genotypes interact with known SNPs which determine beta cell function and survival, and have a compounding effect on the beta cell. If so, those populations that have very high diabetes incidence may be collectively predisposed by influx of cholesterol, fatty acids and genes coding for beta cell metabolism. For example the Khatri Sikhs in Northern India are very susceptible to both type 2 diabetes and cardiovascular disease. Four of six SNPs for the *TCF7L2* gene and two variants within the *KCNQ1* gene were associated with type 2 diabetes [105, 106]. Three of the four *TCF7L2* SNPs were associated with LDL-C levels [105]. In separate studies the *CDK5* gene contained an allele associated with decreased HDL-C [107]. In addition a GWAS performed in the same population has identified significant linkage signals for HDL-C at 10q21.2 and for LDL-C at 10p11.23 [108].

Effects of Age

The increasing presentation of the metabolic syndrome in children and adolescents observed over the past two decades has coincided with increasing prevalence in adults and descending age of onset for both obesity and type 2 diabetes [109]. Since the likelihood of risk factor appearance increases with age, most GWAS are adjusted for age. Although risk begins at birth most GWAS are done on large populations over age 18 years, however expression of

risk factors in childhood and adolescence may represent more significant lifetime effects than if they presented later. Longitudinal studies indicate association of risk with insulin resistance and obesity in youth with gender and ethnic differences with tracking of BMI, blood pressure, and lipids to middle age adulthood [110]. Analyses from 4 longitudinal cohorts beginning in childhood showed that the strength of the associations between baseline risk factors and adult carotid intima-media thickness is dependent on childhood age [111]. For the most part these studies indicate that phenotypes in adolescence are similar to those in adults, and GWAS have shown replication. The *PNPLA3* association with NAFLD is an example of replication of adult GWAS findings in youth, answering the question whether this association begins at early ages when preventive measures would be appropriate[80].

Thrifty Phenotype

Significantly, over the past two decades there has been accumulation of epidemiological data showing a relationship of low birth weight associated with relatively less nutrient supply for the fetus leading to metabolic syndrome traits in adulthood including obesity, hypertension and progression to type 2 diabetes. Based on their own and accumulating evidence, Hales and Barker proposed the thrifty phenotype hypothesis stating that "epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism"[112] (Figure 1).

It is also clearly evident that both nutritional excess and exposure to high maternal glucose during gestation can result in large babies and prediction of similar metabolic syndrome traits giving rise to the observation that the association with birth-weight is often u-shaped[113]. However, the relative roles of genes and environment to these relationships remains a focus of further study. A review of 11 animal models investigating glycemic control in offspring of mothers exposed to a high fat diet during gestation has identified risk for type 2 diabetes and obesity in the offspring especially in males, and the loss of glucose tolerance is independent of maternal obesity, birth weight, or post-weaning macronutrient intake[114]. The experiments elucidating mechanisms whereby fetal systems are modulated by hormones (cortisol, insulin and leptin) changes in blood supply, oxidative stress, transcription, DNA methylation and histone acetylation has been reviewed and could not only serve as a foundation for therapeutic strategy but also could lead to studies on interaction with genotypes[115].

Metabolic Pathways

Although investigations on genetic determinants of cardio-metabolic risk have progressed over the past decade following increased characterization of the genome and use of GWAS, a large portion of the heritability is unaccounted for and many of the genes commonly found in GWAS have small effects [81, 84, 116, 117]. Also the SNPs cannot yet be used to predict disease onset or response to treatment as can be done with monogenic forms of diabetes, dyslipidemia or hypertension [117]. Furthermore metabolic pathways that have been responsive to treatment with pharmaceutical agents or exercise, or have been associated with disease have rarely contained genes that have been identified by large scale studies such as GWAS. Therefore common pathways that may be responsive to treatments with pharmaceutical agents or exercise, may contain enzymes that are encoded by gene candidates for drug targets.

Sookoian et al have reviewed the question whether SNPs identified by GWAS are related to metabolic pathways [81]. They used GWAS data and gene enrichment analysis based on neighboring genes and protein interaction networks. Results of the analysis support evidence

for a network regulated by nuclear receptor proteins including retinoid X receptor (*RXR*) and farnesoid x receptor (*FXR*). They may be driving the expression of metabolic syndrome traits by their interaction with genes associated with metabolic pathways, cell differentiation and oxidative stress. *KLF14* which encodes the transcription factor Kruppel-like factor 14, is an example of a gene located by GWAS, which has a central role in a regulatory network involving ten genes identified by gene expression profiling [118]. The studies identified a single locus associated with a variety of metabolic syndrome traits including obesity, dyslipidemia and measures of insulin resistance. The method provides a way to identify variability in gene expression and to distinguish whether factors regulate the transcript level of the gene itself, known as cis-regulated expression quantitative trait loci (cis eQTLs) or transcripts of other genes (trans eQTLs). Spector et al have identified ten genes that have trans association with the same SNP that regulates *KLF14* expression in the cis mode. One of the genes, SLC7A10, is associated with mediating neutral amino acid transport and has been associated with HDL and obesity [118]. Further studies identifying a gene network of variants related to obesity and the metabolic syndrome has been conducted by Monda et al [119] who extracted and compiled data from GWAS and gene networks using the National Center for Biotechnology Information (NCBI). Based on the reported phenotypes, the results were grouped into six domains (obesity, dyslipidemia, type 2 diabetes, glucose, blood pressure and inflammation) that had been reported in GWAS. There were no apparent network drivers, but *APOE, APOC1, CETP, GCKR, LPL, FADS1, FTO, MADD, HNF1A, SLC30A8 and TCF7L2* had inter-connections.

Maury et al [120] have proposed that mechanisms regulating sleep play a central role in the pathogenesis of the metabolic syndrome and have reviewed the influence of genotype and environment on sleep and circadian rhythms and the effects of sleep rhythm disruption. Based on evidence that both environmental effects or social factors resulting in sleep disruption and abnormal metabolic regulation of the internal clock system have been associated with obesity, diabetes, cardiovascular disease, thrombosis and inflammation, it is feasible that studies of sleep-regulated effects could lead to effective treatments. *CLOCK, BMAL1, PER2, NNAS2* and *MTNR1B* encode proteins that function to regulate the mammalian clock and have been linked to features of the metabolic syndrome such as obesity, diabetes and hypertension [120]. Furthermore differences in circadian gene expression in adipose tissue may influence the rate of fatty acid overflow resulting in deposition in liver, muscle and islets leading to NAFLD and diabetes.

Resistance to insulin action occurring in the liver fat cells and muscle is associated with many of the metabolic syndrome characteristics. This observation has led to the hypothesis that insulin resistance regulates the metabolic syndrome [121] which has been used to test for associations among components by factor analysis using insulin resistance as the central component [122], but the theory has often been questioned [123–125]. Alternatively, it is possible that obesity is the factor driving the appearance of the syndrome and its progression, particularly blood pressure [124]. However the opposing views may not be incompatible since both mechanisms may strain metabolic pathways and trigger disruption, and polymorphisms that involve pathways regulating expression of metabolic syndrome traits may accelerate the disruption. Since the metabolic syndrome is a strong predictor of type 2 diabetes [4, 126], it follows that predictive gene polymorphisms overlap; however, many of the mutations predicting monogenic diabetes have largely involved the β-cell and polymorphisms that have predicted the type 2 diabetes phenotype have often been β-cell-specific. Based on these observations Doria et al have concluded in an insightful review that type 2 diabetes has a progressive pathogenesis beginning with insulin resistance and progressing to β-cell failure [117]. Furthermore, the authors emphasize that genes interact with one another and with the environment. The same group headed by Ronald Kahn have shown that a compound effect of gene interaction in a rodent model with separate and combined knockouts of the

insulin receptor and *IRS-1* genes results in a compounding effect of the two genes. However, neither gene defect alone could produce diabetes in more than 10% of the mice but when combined more than 50% developed diabetes at young ages [127]; a phenomenon known as epistasis. It has been established that environmental effects modify the expression of insulin resistance via effects on post-receptor metabolic pathways [117] including epigenetic modifications such as DNA methylation. This effect can occur in the fetus [128], in peripheral white blood cells in adolescents [129], and involves the peroxisome proliferator-activated receptor gamma coactivator 1alpha (PGC-1α or *PPARGC1A* gene) promoter in NAFLD in association with insulin resistance [130], which is also an important coactivator and major regulator of exercise-induced adaptation within physiological ranges [131].

Drug Targets and Genes that Predict Treatment Response

Since the enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyses intracellular conversion of inert 11-ketosteroids to cortisol and corticosterone and has been identified as being increased in obese human and rodent adipose tissue, it has been a focus of investigation [132]. Transgenic mice selectively overexpressing the enzyme in adipose tissue show many of the metabolic syndrome traits [133]. Conversely knock-out 11β-HSD1 mice showed cardio-protective traits including an improved lipid and lipoprotein profile [134]. Human studies have shown increased activity in subcutaneous fat tissues [135], suggesting that the enzyme might be a suitable selective target for pharmaceutical intervention that not only influences activity in the fat cell by down-regulating harmful glucocorticoid effects but also has beneficial pleiotropic effects on syndrome traits [136]. Emodin, an active ingredient of Chinese herbs has been show to selectively inhibit 11β-HSD1 in mice suggesting that analogues might be developed for therapeutic use [136]. Studies in identical twins have shown association enzyme activity with environmental factors but not genotype [137], however, polymorphisms of *11β-HSD1* have been associated with diabetes, hypertension and apolipoprotein levels [138–140] and the rs3753519 polymorphism has been associated with pediatric-onset obesity in Spanish children [141].

Adenosine-monophosphate-activated kinase (AMPK) is a key regulator of metabolism involving pathways central to regulation of obesity and the metabolic syndrome [142], consequently it has emerged as a drug target [143]. It is a large heterotrimeric enzyme composed of a catalytic and two regulatory subunits encoded by separate genes. AMPK serves as a central metabolic switch sensing cellular energy status through modulation via its phosphorylation and activation. Liver AMPK controls hepatic glucose production by inhibiting expression of the gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. The AICAR (5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside) and metformin down-regulate both enzymes. Furthermore AMPK is activated by several stimuli, including exercise, hypoxia, hypoglycemia, calcium, hormones (adiponectin, leptin, ciliary neurotrophic factor, ghrelin), interleukin-6, α-lipoic acid and resveratrol [143]. It follows that genes encoding enzymes, cofactors and transcription factors involved in AMPK-associated pathways could represent significant candidate genes for prospective studies with both predictive and therapeutic implications. AREBP (AICAR response element binding protein) is an example of a transcription factor that binds to the PEPCK promoter and represses translation in a phosphorylation-dependent manner. When overexpressed in mice, investigators were able to show that AICAR could reduce fasting-induced upregulation of PEPCK [144] supporting PEPCK activation by AMPK as a target.

With the hypothesis that polymorphisms in metabolic pathways involving metformin's action may determine treatment responses, investigators in the United Kingdom conducted a meta-analysis using the glycemic response to metformin as the phenotype. A SNP at a locus containing *ATM*, the ataxia telangiectasia mutated gene (rs11212617) was associated with

the response [145]. In a rat hepatoma cell line, specific inhibition of ATM attenuated the phosphorylation and activation of AMPK in response to metformin [145]. The data suggest that *ATM*, a gene known to be involved in DNA repair and cell cycle control, plays a role in the effect of metformin upstream of AMP-activated protein kinase. Although the effect attributed to the polymorphism is small, the study identified an important upstream AMPK regulator adding information to how metformin works, and also identifies a possible mechanistic link with DNA repair and cancer prevention. Shu et al have investigated polymorphisms in *SLC22A1* which encodes organic cation transporter 1(OCT-1) functions to facilitate absorption of metformin into hepatocytes and identified association with reduced responsiveness to metformin's effect on glucose levels during an oral glucose tolerance test [146]. Also association with HbA1c was shown with a variant in *SLC47A1* encoding the multidrug and toxin extrusion protein 1 involved in the excretion of metformin into bile and urine [147]. Furthermore, the two genes both acting to increase intracellular metformin, have an interactive effect [148]. The roles of both genes were supported by the Diabetes Prevention Program investigators [149] who confirmed association of the glucose-lowering response to metformin and variants in *SLC47A1*, and interactions with *SLC22A1* and the AMPK genes *STK11, PRKAA1* and *PRKAA2.*

The pharmacogenetics of other anti-diabetes drugs has been well reviewed [150]. Besides metformin, it is likely that genes encoding the receptor and pathways for PPARG agonists constituting the thiozolidinediones, are most likely to be associated with the metabolic syndrome because of their role in insulin sensitivity. Of 133 *PPARG* SNPs tested in the TRIPOD study, eight showed evidence for association with response to Troglitazone therapy defined as change in tolerance to intravenous glucose (IVGTT) [151]. However there was no association with fasting glucose suggesting that response in confined to measures of insulin resistance such is the minimal model IVGTT whereas fasting glucose is more likely to be a measure of β-cell failure. In studies where overt type 2 diabetes has been the phenotype the majority of associated polymorphisms have encoded proteins known to be involved in β-cell metabolism; for example *TCF7L2, KCNJ11* and *HHEX* have shown robust association [152, 153]. The *HHEX* gene was shown to be associated with increased risk for type 2 diabetes in mainly Asians and Caucasians by meta-analysis [154], and is involved in β-cell development and function via interaction with hepatic nuclear factor 1α (HNF1α) [155]. Similarly the c-allele of rs13266634 located in S*LC30A8* (ZNT8) has been associated with insulin and glucagon levels and type 2 diabetes in East Asians and Europeans in a meta-analysis [156]. Interestingly the glucokinase gene (GCK) has activating mutations causing hypoglycemia that might provide structural and functional models leading to drug targets for treating type 2 diabetes [157]. In GoDARTs study, investigators examined the medication response of metformin and sulphonylurea based on the *TCF7L2* genotypes. The carriers of the at risk 'T' allele responded less well to sulphonylurea therapy than metformin[158]. In the Diabetes Prevention Program (DPP), the lifestyle modifications were shown to reduce the risk of diabetes conferred by risk variants of *TCF7L2* at rs7093146. In placebo participants who carried the homozygous risk genotype (TT), had 80% higher risk for developing diabetes compared to the lifestyle intervention group carrying the same risk genotypes [159].

Statins and fibrates alone or in combination are frequent choices for treatment of the metabolic syndrome dyslipidemia indicating a need for genetic prediction of treatment response so that effective lipid lowering can be attained by tailoring treatment to individual requirements. Brautbar et al have recently identified lipoprotein lipase gene variants that affect apoC-III lowering by paradoxically increasing apoC-III levels [160]. The study offers a feasible explanation for disappointing clinical outcomes in trials that evaluated the efficacy of fibrates such as FIELD and ACCORD [161–163]. The importance of apoC-III is underscored by association of polymorphisms in the promoter with coronary heart disease, particularly in the insulin response element [164]. There is strong association of apoC-III bound to apoB-

containing lipoproteins with the number of metabolic syndrome criteria [165], coronary heart disease events in the CARE trial [166], whereas apoC-III bound to apoA-I-containing particles was a predictor of angiographic change in the Cholesterol Lowering Atherosclerosis Study in response to colestipol and niacin [167]. It is unknown how apoC-III, an LPL inhibitor, may interact with LPL to determine the response to fibrates. ApoB and the LDL receptor may also determine response to therapy such as statins in familial hypercholesterolemia [168] and anti-hypertensive medications [169].

Proposed Model for Phenotype Interaction

Monogenic models such as the lipodystrophy syndromes could serve as a model [170.] but there has been accumulating evidence for multigenic origin, and changes in the traits throughout life. Therefore the serial nature of the syndrome should be taken into account since the traits are susceptible to interaction both at the gene level as shown by epigenetic modifications and at the pathway level as shown by modifications coinciding with the development of insulin resistance and obesity (Figure 1). Based on known metabolic pathways, genotype and phenotype associations and epidemiological studies, we propose an outline for genetic modulation of clinical cardio-metabolic phenotypes such as obesity, hypertension, dyslipidemia, NAFLD, and glucose intolerance leading to atherosclerosis and type 2 diabetes (Figure 2).

In addition to the standard five criteria, NAFLD, a newly recognized addition to the metabolic syndrome, appears to have a central predisposing role for cardiovascular disease and type 2 diabetes. There is evidence, cited in the text, to support inter-relationship in regard to progression to atherosclerosis and diabetes phenotypes. The classic lipid derangement observed in insulin resistance consisting of elevated triglyceride, small LDL particles in increased numbers and low HDL-C has significant association with genotype and risk prediction. Cross-sectional and sequential clinical investigations beginning at early phases of the pathogenesis are needed to determine more precise inter-relationship of phenotypes to each other and to the respective genotypes while contributing to improved characterization. In addition improved phenotypic characterization and relationship to genotypes is needed to uncover new pathways and targets for intervention [171]. To achieve this goal it will be necessary to understand overlapping relationships of polymorphisms with traits, their expression during the lifespan and interrelationships either by pleiotropism or common pathways. We propose beginning this process by sorting the genes by their respective metabolic functions (Table 1, Figure 3).

Conclusions

This review summarizes the rapidly moving field of metabolic syndrome genetics by covering advances in the commonly encountered clinical traits as opposed to a more specialized focus on one trait. The evidence supports progress in unraveling the origins of a complex and interrelated cluster, and provides insight on how each of the traits may relate to one another, either through common genes, common and overlapping pathways or by shared end-points. We propose commonality and interrelationships between the traits and their genetic and environmental determinants, which includes sequential development from conception through gestation, childhood and adolescence. Progress in the field is encouraging and is beginning to show some potential for clinical prediction and identification of drug targets. Reviewing progress in genetics of the syndrome as a whole does not argue against coning down on individual components in studies that provide insight and have made significant discoveries of genes for which key functions can be determined. Since understanding biochemical mechanisms and interactions between pathways is central to unveiling the cluster, key questions relate to the small effect size of multiple common

mutations when assessed in a multi-genic background, making it difficult to support successful pathway-based pharmaceutical interventions. However, discovery of missing heritability from rare variants with larger effects and genes coding for novel drug targets together with gene-gene and gene-environmental interactions and effects of lifestyle interventions are important considerations in actively investigated approaches.

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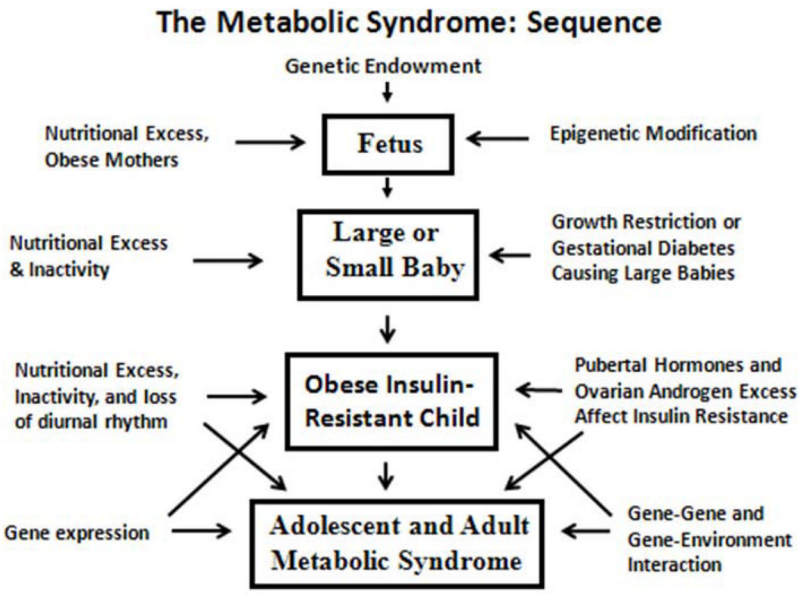

Figure 1.

The fetus, endowed with a genotype, becomes exposed to the maternal environment coinciding with susceptibility to metabolic programming by hormones, nutrients and stresses (see text). Programming continues during childhood leading to expression of metabolic syndrome traits.

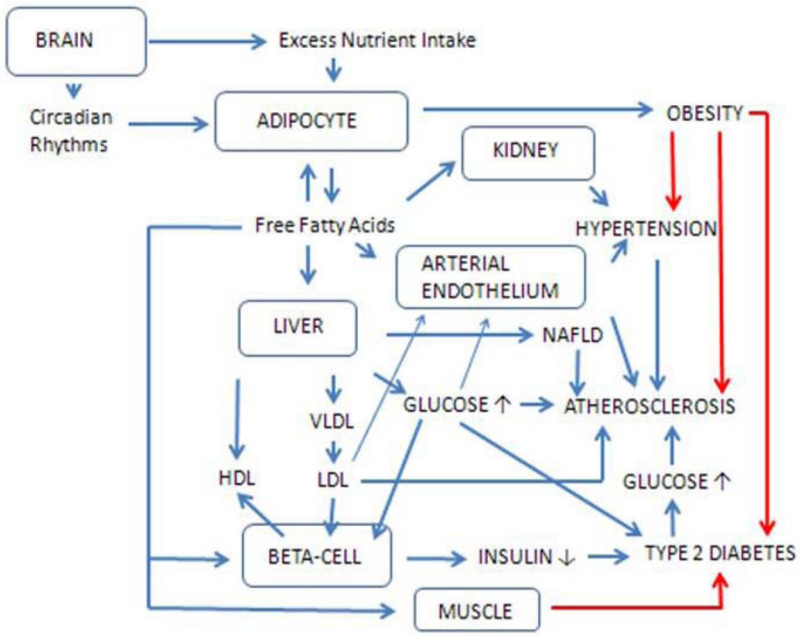

Figure 2.

The genes express in six main locations: in the brain, adipocyte, kidney, liver, arterial endothelium and β-cell. Perturbations in metabolic pathways programmed by the respective genes result in alterations in plasma metabolites (lipids carried in lipoproteins, glucose and fatty acids) and insulin, resulting in progression of metabolic syndrome traits leading to disease expression. Effects of insulin resistance are shown by the red lines.

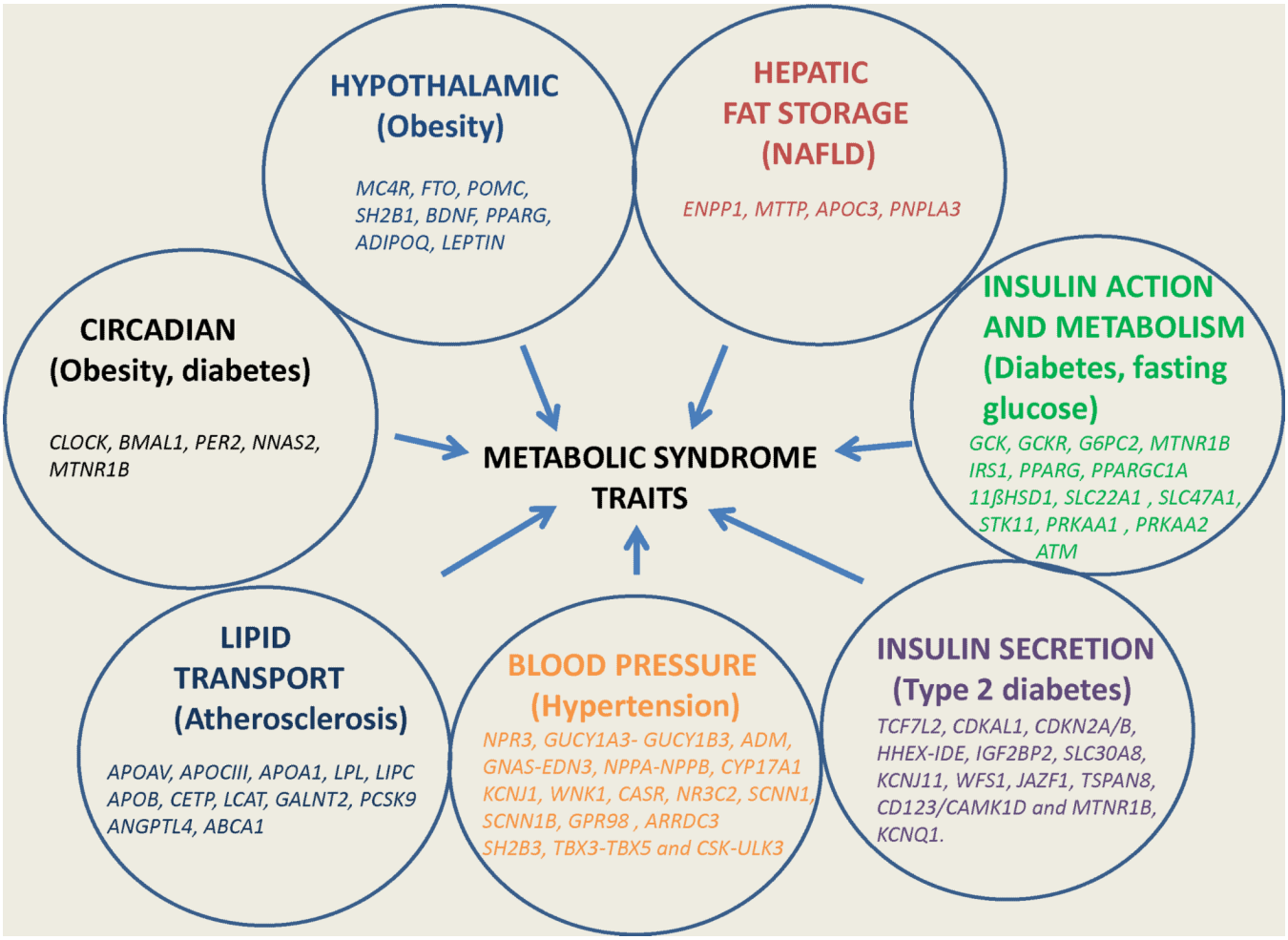

Figure 3.
Interrelationship between obesity, hepatic fat, insulin action, insulin secretion, blood pressure, dyslipidemia, and circadian clock with metabolic syndrome. Seven groups of genes that affect metabolic syndrome traits are summarized (see table for details).

Table 1

List of Genetic loci in Metabolic Syndrome Pathway

Category	Gene Name	Chromosome	Entrez Gene ID	Role
Hypothalamic Genes	*FTO*†	16q12.2	79068	Severe obesity/insulin resistance
	MC4R†	18q21.32	4160	Member of G-protein coupled receptor family, signaling hormone involved in energy homoeostasis
	PPARG†	3p25.2	5468	Transcription factor involved in adipogenesis and type 2 diabetes risk
	ADIPOQ	3q27.3	9370	Adipose tissue specific protein involved in insulin sensitizing and anti-atherosclerotic properties
	LEPTIN	7q31.3	3952	Signaling hormone affects directly or indirectly on the central nervous system to inhibit food intake and/or regulate energy expenditure as part of a homeostatic mechanism
Hepatic Genes				
Dyslipidemia	*APOE-CI-CII-CIV*†	19q13.32	2282	Cluster of triglyceride-rich lipoprotein receptor ligands for LDL receptor –related proteins
	APOB†	2p24.1	338	Main apolipoprotein of chylomicrons and low density lipoproteins, functions as a recognition signal for the cellular binding and internalization of LDL particles
	APOAV-AIV-CIII-AI†	11q23.3	117536	Cluster of apolipoproteins plays an important role in regulating the plasma triglyceride levels
	GALNT2	1q42.13	2590	Catalyzes the initial reaction in O-linked oligosaccharide biosynthesis
	PCSK9	1p32.3	255738	Decreases plasma cholesterol and LDL cholesterol and provides protection from coronary artery disease
	CETP†	16q13	1071	Exchanges cholesterol esters for triglycerides from HDL and triglyceride rich lipoproteins
	LCAT†	16q22.1	3931	Required for remodeling HDL particles into their spherical forms
	ABCA1†	2p23.3	2646	Functions as a cholesteral efflux pump in the cellular lipid removal pathway. Mutations in this gene cause Tangier' disease and familial HDL deficiency.
	LPL†	8p21.3	4023	Catalyzes the hydrolysis of triglycerides to release free fatty acids into the circulation
	LIPC†	15q21.3	3990	Encodes hepatic triglyceride lipase in liver and hydrolyses triglycerides
	ANGPTL4†	19p13.2	51129	Plasma hormone directly involved in regulating glucose homeostasis, lipid metabolism, and insulin sensitivity and also acts as an apoptosis factor for vascular endothelial cells
NAFLD	*MTTP*	4q23	4547	Catalyzes the transport of triglyceride, cholesterol ester, and phospholipid between phospholipid surfaces

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Category	Gene Name	Chromosome	Entrez Gene ID	Role
	ENPP1	6q23.2	5167	Involved primarily in ATP hydrolysis at the plasma membrane. Appears to modulate insulin sensitivity
	APOCIII†	11q23.3	345	Inhibits lipoprotein lipase; it delays catabolism of triglyceride-rich particles, induces the development of hypertriglyceridemia
	PNPLA3†	22q13.31	80339	Triacylglycerol lipase that mediates triacylglycerol hydrolysis in adipocytes
Hypertension	WNK1	12p13.33	65125	A key regulator of blood pressure by controlling the transport of sodium and chloride ions
	KCNJ1	11q24.3	3758	Mutations in this gene have been associated with Bartter syndrome, which is characterized by salt wasting, hypercalciuria, and low blood pressure
	NPR3	5p13.3	4883	Encodes natriuretic peptides which regulate blood volume and pressure, pulmonary hypertension, and cardiac function
	GUCY1A3	4q32.1	2982	guanylyl cyclases are groups of enzymes that mediate important communication between the heart, intestine and kidney to regulate blood volume and Na+ balance.
	GNAS	20q13.32	4686	Guanine nucleotide-binding proteins (G proteins) are involved as modulators or transducers in various transmembrane signaling systems
	NPPA-NPPB	1q36.22	9757	Natriuretic peptide receptors are associated with intracellular guanylyl cyclase activity and involved in homeostasis of body fluid volume
	CYP17A1†	10q24.32	1586	Mono-oxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and lipids; gene variants associated with hypertension
	C21orf91†	21q21.1	54149	Gene variants associated with systolic blood pressure
	GPR98†	5q14.3	84059	Associated with Usher syndrome 2 and familial febrile seizures, gene variants associated with diastolic blood pressure
	ARRDC3	5q14.3	57561	Gene variants associated with diastolic blood pressure
β-cell function, insulin secretion and insulin resistance, and type 2 diabetes genes	*GCKR*†	2p23.3	2646	Enzyme regulators, controls activity of glucokinase in liver and brain
	G6PC2†	2q24.3	57818	Enzyme, transport channel, key role in glucose homeostasis
	CDKN2A-B†	9p21.3	1029	Enzyme, anti-oncogene involved in pancreatic carcinomas, type 2 diabetes
	GLUT4	17 p13.1	6517	Solute carrier family 2, mediates insulin-stimulation glucose uptake in adipocytes & muscles
	INSR	19 p13.3	3643	Signaling hormone receptor tyrosine kinase
	HNF4A†	20q12	3172	Transcription factor regulates genes required for glucose transport and metabolism
	ADAM 30†	1p12-p11	11085	Disintegrin and metalloproteinase domain-containing protein 30 has been implicated in a variety of biological processes and associated with type 2 diabetes risk
	NOTCH2†	1p13-p11	4853	Transcription regulator, type 2 diabetes

Category	Gene Name	Chromosome	Entrez Gene ID	Role
	THADA†	2p21	63892	Death receptor membrane protein, gene variants associated with type 2 diabetes
	ADAMTS9†	3p14.3	56999	Enzyme, anti-oncogene, associated with type 2 diabetes
	JAZF1†	7p15.2	221895	Transcription factor, increases risk for prostate cancer, type 2 diabetes
	TSPAN8†	12q14.1	7103	Regulatory protein involved in cell development, growth and motility, type 2 diabetes
	IGF2BP2†	3q27.2	10644	Regulatory enzyme influences insulin secretion
	CDKAL1†	6p22.2	54901	Variant confers risk through reduced insulin secretion
	GCK†	7p14	2645	Modulates insulin secretion, glucolysis, energy pathways
	SLC30A8†	8q24.11	169026	Facilitates transportation of zinc from cytoplasm into insulin containing vesicles
	TCF7L2†	10 q25.2	6934	Transcription regulator influences insulin secretion
	INS	11 p15.5	3630	Signaling hormone, increases cell permeability to monosaccharides, amino acids and fatty acids
	CDC123†	10p13	8872	Involved in transcription regulation, insulin secretion
	HHEX	10q23.33	3087	Transcription factor involved in hematopoietic differentiation, pancreatic development, insulin secretion
	KCNJ11†	11 p15.1	3767	Ion channel transporter

†Gene association detected in GWAS