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Metabolic syndrome components in murine models

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1. Abstract

Animal models have enriched understanding of the physiological basis of metabolic disorders and advanced identification of genetic risk factors underlying the metabolic syndrome (MetS). Murine models are especially appropriate for this type of research, and are an excellent resource not only for identifying candidate genomic regions, but also for illuminating the possible molecular mechanisms or pathways affected in individual components of MetS. In this review, we briefly discuss findings from mouse models of metabolic disorders, particularly in light of issues raised by the recent flood of human genome-wide association studies (GWAS) results. We describe how mouse models are revealing that genotype interacts with environment in important ways, indicating that the underlying genetics of MetS is highly context dependant. Further we show that epistasis, imprinting and maternal effects each contribute to the genetic architecture underlying variation in metabolic traits, and mouse models provide an opportunity to dissect these aspects of the genetic architecture that are difficult if not impossible to ascertain in humans. Finally we discuss how knowledge gained from mouse models can be used in conjunction with comparative genomic methods and bioinformatic resources to inform human MetS research.

Keywords

Metabolic Syndrome; hypertension; obesity; type-2 diabetes; cardiovascular disease; murine models; bioinformatics; comparative genomics; genome-wide association studies

2. Overview

The metabolic syndrome (MetS) is a suite of conditions, including impaired glucose tolerance, dyslipidemia, high blood pressure and central obesity that tend to occur in conjunction. This suite of conditions puts an individual at risk for developing type-2 diabetes (T2D) and cardiovascular disease (CVD) [1]. As such, the MetS classification is of great epidemiological interest: T2D has increased in prevalence and currently afflicts ~7% of the US adult population [2]. Approximately 90% of individuals with T2D are considered overweight, and ~ 70% will develop cardiovascular disease [2–4]. In the US alone, the prevalence of MetS exceeds 20%, and it is becoming more and more common in developing countries [5,6]. Many hypotheses have been proposed to explain this epidemic in terms of environmental factors, for example the thrifty gene and the sedentary lifestyle hypotheses, which posit that over-consumption of high caloric foods and inactive lifestyles are major causes of the metabolic disorders that comprise MetS [7]. Indeed, dietary and lifestyle modification have proven therapeutic [8]. However, it is becoming increasingly evident that some populations are more prone to metabolic disorders than others and, in general, that women are less prone than men of the same body mass [1,9]. Clearly there is a genetic component to MetS. Yet therapeutic dietary

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and lifestyle guidelines generally do not take into account underlying genetic variation, which can effect an individual's response to treatment [10]. Understanding the pathogenesis of the metabolic disorders comprising MetS is an enormous biomedical challenge because phenotypic variation is caused by complex interactions of many genes of small effects, by environmental factors, and by the interplay between the two. Thus animal models are particularly important because both genetic and environmental influences can be controlled for and monitored in a population of known genetic structure.

2.1 Murine models for human disease

Animal models have enriched understanding of the physiological basis of complex disease and advanced identification of genetic risk factors. In using animal models, a researcher is able to plan crosses between animal strains with measurable phenotypic differences and to generate large numbers of offspring from a single set of founders of known genomic background, overcoming the confounding factor of genetic heterogeneity present in human studies. In genetic mapping studies, this increases the power to detect quantitative trait loci (QTL) having small effects, those that are most likely to underlie complex disease and that are difficult to identify in human studies. Additionally, because phenotypes are ascertained in a controlled environment, animal models allow for detailed analysis of the architecture of gene-by-environment interactions, which for both practical and ethical reasons is not possible in human studies. Once a QTL has been identified in an animal model, fine-scale mapping of the genomic region can break a locus down into the quantitative trait genes (QTG) or the quantitative trait nucleotides (QTN) responsible for the QTL effect [11]. When an animal's DNA sequence has been identified, the human homolog can be isolated by DNA hybridization or by homology alignment to the human genome, and research can be conducted to determine if variation in the candidate sequence is associated with variation in the same phenotype in humans. Finally, returning to the animal model to obtain experimental proof through expression or intervention analysis can determine if and how the variants identified contribute to the disease.

Mouse models are especially appropriate for this type of research, and mouse studies have made major contributions to our knowledge of complex disease etiology [12]. This is, in part, because mice have relatively short gestation times and are relatively cheaper to breed and maintain than other mammalian models. In addition, mouse development and physiology is very well characterized and dense panels of polymorphic genetic markers are readily available. The initial sequence of the mouse genome was released in 2002 and, as of July 2007, is considered "essentially complete" with NCBI build 37 [13]. The only other species' genome that is considered "complete" is human [14]. Mouse–human chromosomal homology is well characterized and syntenic maps are available allowing for easy translation of linkage maps between the species. The Jackson Laboratories house the world's largest repository of inbred laboratory mouse strains and genetically engineered mouse stocks, including a large subset used in research of MetS components: T2D, obesity, hypertension, and cardiovascular disease [15]. Online resources are freely available for mouse queries, ranging from biology to genomic sequence to expression, providing valuable information for study design and potential generation of new mouse models that recapitulate the pathology of human diseases (see Table 1). In many instances mouse models represent monogenic changes with major effects for a disease, despite the fact that a common disease is generally the result of contributions from multiple genes. To circumvent this problem, different teams have worked with mice to combine recombinant congenic strains with multiple contributing genes for a disease. Consequently, existing mouse models have evolved to better approximate human disease models, and have become ideal tools for the genetic dissection of complex traits.

2.2 The search for a murine model of metabolic syndrome

The physiological features of MetS components vary across species and MetS is not well defined in mouse models. For example, absolute criteria for defining extreme blood serum levels in mice do not exist, and mice transport most of their cholesterol in high density lipoprotein cholesterol (HDLC) rather than in low-density lipoprotein cholesterol (LDLC) as humans do [1]. Mouse models for diabetes are generally resistant to many of the complications common to humans, e.g. diabetic neuropathy, nephropathy and retinopathy. When such complications do occur in mice, they do not reflect all the characteristics seen in human pathology [16–18]. Further, mice do not express certain genes affecting development of diabetic complications in humans, such as cholesterol ester transport protein [15]. Moreover, despite humans and mice sharing most of the same transcription factors, there are significant differences in the targets with which they bind [19]. These dissimilarities reflect genus-specific metabolic differences resulting from 65–85 million years of divergent evolution to fill different ecological niches [13,20]. Nevertheless, mouse models have expanded our understanding of MetS pathophysiology and have highlighted genomic regions that are fruitful candidates for further study.

Most candidate genomic regions are identified in mice by crossing two phenotypically distinct inbred strains, within each of which animals are genetically identical, and then intercrossing the resulting F_1 hybrid offspring to create an F_2 generation where all possible combinations of genotypes (homozygotes for each parental allele and the heterozygote) have the potential to be represented at each locus. This method facilitates QTL mapping and when matings are carried out to the F_{10} generation or beyond to create an advanced intercross line (AIL), resolution improves due to the accumulation of recombination over generations (e.g. an F_{10} generation has approximately 5 times the recombination of an F_2 generation). For example, Ehrich *et al*. (2005) identified several QTL affecting serum glucose and insulin levels in an F_{16} AIL of LG/J x SM/J (Wustl:LG,SM-G16) [21], and recently Fawcett *et al*. (2009) fine-mapped QTL contributing to obesity and organ weights using a combined F_9/F_{10} population (Wustl:LG,SM-G19 and Wustl:LG,SM-G10) [22]. A key advantage of using inbred crosses and AILs is that the architecture of genetic by environment interactions can be fully explored, and this is discussed further in Section 4.

Another common method for identifying candidate genomic regions is the use of recombinant inbred lines (RIL), which are produced by brother-sister mating F_2 intercross offspring for at least 20 generations. At this point all individuals are genetically identical and homozygous across the genome with a unique mosaic of fixed random alleles from the original parental genomes. Cheverud *et al*. (2004) demonstrated genetic independence of some diabetes and obesity related traits in a study of genetic correlations among LGXSM RILs [23]. Recently, Koutnikova *et al*. (2009) identified a QTL for hypertension in a BXD RILs, and subsequent association studies confirmed the human syntenic region's involvement in both systolic and diastolic blood pressure [24]. An advantage of using RILs is that results are replicable because the panel needs only to be genotyped once, yet the strains can be phenotyped across time by a diverse group of researchers.

The Jackson Laboratories provide catalogs of commonly used laboratory mouse models for T2D, obesity and cardiovascular research. As of this writing, 53 strains are used frequently to model T2D and obesity, and 48 to model diabetes without obesity. Approximately 250 mouse strains are used in CVD research, including 27 to model hypertension, 57 to model hypercholesterolemia, and 17 to model hypertriglyceremia (www.jaxmice.org/research/index/html). C57BL/6J features prominently in each of these research areas due to its physiological sensitivity to experimental diets, and much recent research has utilized this strain to explore MetS components [25–28]. Additionally, there are 10 strains that display a suite of characteristics resembling MetS. For example, studies indicate

that low-density lipoprotein receptor-deficient mice, B6.129S7-Ldlrtm1Her/J, may be a good model of dietary induced MetS [5,29–33]. Leiter (2009) discusses how one could go about selecting a mouse model when designing a T2D and/or MetS study [15].

3. Murine models of metabolic disorders

Figure 1 shows the number of unique genes found associated with one or more components of MetS for humans, for mice, and for their intersection. These numbers were ascertained for mouse by utilizing the "Phenotype/Human Disease" section of the advanced search for "Genes/Markers" and conditioning on "Gene" through the Mouse Genome Informatics database. For human, these numbers were obtained through the "Entrez Gene" database at the National Center for Biotechnology Information website. Both databases were queried on October 10, 2009 with keywords: "obesity", "type-2 diabetes", "insulin resistance", "impaired glucose tolerance", "hypertension", "dislipidemia", "cholesterol", "triglycerides", and "free-fatty acids". Supplemental Table 1 provides the gene names for the three full sets of these genes. Table 2 presents a list of the 28 genes out of the 512 that intersect in which mutations in both human and mouse orthologs are associated with phenotypes diagnostic of the risk factors of MetS in humans.

This illustrates that mouse models generally do not point to the same genes affecting the same phenotype in the same way in humans. Rather, their power lies in that they can aid in identification of genes acting in the same pathway and/or physiological system. As such, mouse models are an excellent resource not only for identifying candidate genomic regions, but also for illuminating the possible molecular mechanisms or pathways affected in individual components of metabolic disease. For example, the leptin pathway was first characterized in studies of the *ob* [34] and *db* [35] genes in mice. Subsequent studies in leptin (LEP)[36] and the leptin receptor (LEPR)[37] in humans revealed mutations in these genes underlie obesity [38]. Additionally, characterization of the melanocortin-AGRP pathway in studies of the mouse *agouti* gene[39] led to the discovery of mutations in MC4R, shown to similarly affect body fat content in mice and humans [40]. Recently, the T2D susceptibility gene sortilin-related domain containing receptor1 (SORCS1) was identified in humans based on candidate status from mouse studies [41], joining the ranks of calpain-10 (CAPN10) [42], peroxisome proliferator-activated receptor γ (PPARG), and transcription factor 7-like 2 (TCF7L2) [43] as genes that confer diabetes risk. Kraja *et al*. (2008) constructed gene networks for both humans and mouse models and identified 859 mouse genes with a corresponding human counterpart in one or more MetS components [44]. Further analysis of the interconnection of these genes in pathways, especially those affecting multiple disease components, could prove effective in identifying new genetic associations with MetS in humans.

In the following sections we briefly review QTL findings from mouse models of disease components of MetS, particularly in light of issues raised by the recent flood of human genome-wide association studies (GWAS) results. We also discuss how such mouse models have illuminated gene-by-environment interactions contributing to metabolic disease. Finally, we reflect on how these findings can be used in conjunction with genomic and bioinformatic resources to inform future study design.

3.1 Obesity

The overall prevalence of the MetS has increased in parallel with increases in obesity. The prevalence rate of obesity has increased steadily among US adults (>20 years of age) since 1960 from 13.3 to 32.1 percent [3]. Twin studies reveal estimates of broad sense heritability of BMI to be up to 70% in both children and adults, and admixture mapping shows that obesity is highly correlated with an individual's relative percentages of ethnic ancestries [7,45]. Mouse models have aided in identification of major variants in single genes underlying the obese

phenotype in humans, for example proopiomelanocortin (POMC) [46], and the LEP [36], LEPR [37], and MC4R [47] genes discussed above. Genome-wide linkage analysis and positional cloning have identified several other genes contributing to obesity in human populations, for example CAPN10, also associated with T2D [42], and PPARG [43], ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) [48], also associated with T2D, as well as solute carrier family 6 (SLC6A14) [49], and glutamate decarboxylase 2 (GAD2) [50].

GWAS have successfully identified novel loci associated with obesity, for example the fat mass and obesity associated gene (FTO) [51], catenin beta-like 1 (CTNNBL1) [52], and fibrillin 2 (FBN2) [53]. More recent GWAS have found novel chromosomal loci in addition to replicating previous obesity associations with genes such as FTO, MC4R [54] and brain-derived neurotrophic factor (BDNF) [55]. The office of population genomics at the National Human Genome Research Institute has made available a hand-curated catalog of published human genome-wide association studies (www.genome.gov/gwastudies) [56]. As of this writing, there are 19 unique GWAS reported loci associated with obesity.

While GWAS have successfully identified some obesogenic genes, these genes account for a very small percentage of the overall heritable variation of obesity in humans. For example FTO variants reported explain only ~1% of the heritability of BMI, despite having been identified as an obesogenic gene in multiple ethnic populations [51,57], and despite obesity's high heritability [45]. This is a common result in GWAS of complex traits and the paucity of results is due to a lack of power to detect genes of small effect. Indeed, the The Wellcome Trust Case Control Consortium recently demonstrated that enormous sample sizes are required to have adequate power to detect genomic regions having even large disease effects [58]. This is partly because GWAS were designed with the common disease–common variant hypothesis in mind [59–61]. While the method is successful at identifying associations between common phenotypes and common allelic variants in homogeneous populations, GWAS lack of power is reflective of humans' heterogeneity in both genotypic and environmental influences. McCarthy *et al*. (2008) provide a good review of issues related to GWAS [62]. Although obesity is a common disease, the alleles underlying the phenotype are many and relatively rare, and most will not pass the stringent multiple testing criteria necessary to claim association, hence the "missing" heritability. The same holds true for other metabolic disorders: T2D, CVD and hypertension. Thus a candidate gene approach, where candidates are identified independently in mouse models, can be used to protect genomic regions from strict thresholds and increase the power of these studies.

There have been a great many studies of the genetics of obesity and body weight in mice, spanning over a century [63], and mice have proven to be excellent models for complementing our understanding of the biology of obesity in humans. Several papers provide good reviews of single mutant mouse models of obesity [64–66]. However, polygenic obesity is the most common pattern of inheritance, and the most relevant in terms of modeling a component of MetS. A total of 536 records are produced when one searches the term "obesity" in the "Mouse Phenotypes and Models of Human Disease" section of the "Genes and Markers" query form in the Mouse Genome Informatics Database (Accessed October 9, 2009) [67]. Of these records, 172 are for genes identified in studies of major mutants and transgenics, and 326 are for QTL that have been mapped in many different inbred strain crosses, each segregating for its own unique set of obesity QTL. Most of these QTL were identified in F_2 populations and Brockmann and Bevova (2002) provide a good review [68] of the most common strains used in these crosses. Wuschke *et al*. (2007) report results of a meta-analysis of QTL associated with obesity in mice, wherein they compiled a list of candidate regions comprised of 162 non-redundant QTL for body weight and 117 QTL for adiposity (measured as fatpad weight) [69].

The largest number of obesity and body size QTL mapped in any single cross is in the LG/J x SM/J advanced intercross line [21–23,70–76]. LG/J and SM/J differ genetically for a number of MetS related phenotypic traits, described in Ehrich *et al*. (2003), and genome-wide scans in the F_2 generation identified eight QTL for adiposity (*Adip1–Adip8*)[71,72]. Fine-mapping efforts, which combined the F_2/F_3 generations, confirmed seven of these eight original QTL (*Adip1–Adip6* and *Adip8*), and found eleven more loci affecting adiposity (*Adip9–Adip20*) [70]. Further mapping of the F_9/F_{10} generations of the LG/J x SM/J AIL identified 31 adiposity QTL, 13 of which replicated from previous generations [22]. Additional mapping efforts in the F_{16} LG/J x SM/J AIL are ongoing, and preliminary results not only replicate previously identified adiposity QTL, but also identify novel locations at high resolution because the genetic map is 8 times that of the original F_2 map due to accumulated recombination (Cheverud et al. *in preparation*).

3.2 Type-2 diabetes

Like obesity, T2D is highly heritable, ranging from ~50–90% in twin studies, and disease incidence varies with an individuals' percent ethnic ancestry [77,78]. Linkage analysis and positional cloning have led to identification of monogenic forms of T2D, generally through studies of relevant phenotypes such as pancreatic β-cell function, for example the ATP-binding cassette (ABCC8) [79], insulin resistance, for example insulin-degrading enzyme (IDE) [80], and obesity, for example PPARG [81]. However, most cases of T2D do not exhibit Mendelian inheritance and GWAS attempt to identify common variants through hypothesis-free testing [82]. As of this writing, there are 30 unique GWAS reported loci associated with T2D [56].

A total of 212 QTL are associated with "type 2 diabetes" in the Mouse Genome Informatics Database (Accessed October 9, 2009) [67]. Of these, 56 QTL are also retrieved when "obesity" is queried, demonstrating the strong genetic association between these two components of MetS. Clee and Attie (2007) provide an excellent review of the genetic and physiological background of various mouse strains used to model T2D and its co-morbidities such as obesity [78].

While C57BL/6 is the most commonly used and, hence best characterized, mouse strain used in T2D research, results generated, whether "T2D-susceptible" or "T2D-resistant", are contingent on the strain it is being compared with, because it shows intermediate glucose and insulin levels compared with other strains [15]. Mice do not get diabetes *per se* therefore it is important to understand both the physiology and the genetic background of the inbred strains when evaluating a mouse model of T2D. The LG/J and SM/J have been well characterized with respect to T2D related traits and compared with SM/J, LG/J animals have lower basal glucose levels and respond better to a glucose challenge [72]. Strains from a set of LGXSM RILs show variation in development of hyperglycemia and hyperinsulinemia [83]. Additionally, ninety-one QTL mapping to 39 unique genomic locations were identified for obesity, glucose response, and serum glucose and insulin levels in an LGXSM RIL [23]. Cheverud *et al*. (2004) found discordance among the loci affecting obesity, insulin and glucose, suggesting there are genotypes that are protective for T2D in the presence of obesity [84]. While obesity is a major risk factor for T2D, approximately 20% of individuals with T2D are not obese [82], and Cheverud *et al*.'s results suggest it is possible to dissect the relationship between these two components of MetS. Ongoing research using an LG/J x SM/J F_{16} AIL is mapping QTL for serum glucose and insulin levels as well as response to a glucose challenge. Preliminary results identify 70 QTL mapping to 64 unique genomic locations (Lawson *et al.*, *in preparation*).

3.3 Cardiovascular disease

CVD has a multifactorial etiology involving metabolic, neuro-endocrine and genetic interactions [85]. It shares many common risk factors with obesity and T2D, including dyslipidemia and elevated blood pressure, and it is the leading cause of death in the United States [86]. Heritability estimates for risk factors of CVD are variable among studies across populations dependent on whether they are twin studies or family based studies. For example estimates range from 20–66% for diastolic blood pressure, from 8–72% for fasting total cholesterol, from 21–79% for fasting HDLC, from 31–68% for fasting LDLC, and from 19–72% for fasting triglycerides [87]. After the leptin and the leptin receptor pathways were characterized in mouse models, studies in human families have found >600 mutations in the LDLR gene [88], and mutations in genes in the LDL and LDLR pathways, such as apolipoprotein B (APOB) [89] and the ATP-binding cassette (ABCG5) [90] account for a large majority of monogenetic dyslipidemia [91]. However, as with obesity and T2D, single genes with large effects account for a small minority of cases of CVD, and most of the genes underlying CVD remain unknown. As of this writing, there are 114 unique GWAS reported loci associated with the CVD domains of total cholesterol, HDLC, LDLC, triglycerides, blood pressure and systolic blood pressure [56].

A total of 340 QTL are associated with “cholesterol”, “triglycerides” and “blood pressure” in the Mouse Genome Informatics Database (Accessed October 9, 2009) [67]. Of these, 99 are also associated with obesity, 34 with diabetes and 18 with all three components of MetS. Mouse models have significantly contributed to our knowledge of CVD and, despite being characteristically resistant to CVD *per se*, many genetically altered strains respond to high-cholesterol feeding with CVD pathologies [92]. The body of literature on this topic is rich: a search of PubMed for “mouse models” and “cardiovascular disease” limited to the last five years yields 4,672 results (www.ncbi.nlm.nih.gov/sites/entrez; Accessed October 17, 2009), entire books are dedicated to the role of the laboratory mouse in CVD research [93], and the Jackson Laboratories currently offer 250 mouse strains appropriate for CVD studies. Again the most commonly referenced strain is C57BL/6 [1,27,94], and the Mouse Phenome Database provides complete blood serum lipid profiles as well as atherosclerotic phenotypes characterized for this strain [95]. The LG/J and SM/J strains have also been well characterized with respect to CVD related traits. Compared with SM/J, LG/J animals have higher cholesterol and free fatty acid levels [72]. Ongoing research using an LG/J x SM/J F_{16} AIL is mapping QTL for variation in cholesterol, free fatty acid and triglyceride levels, and their variation in response to dietary fat. Preliminary results identify 25 trait-specific QTL mapping to 24 unique genomic locations (Lawson *et al.*, *in preparation*).

3.4 Hypertension

Hypertension is the most common CVD risk factor, with an approximate 27% world-wide prevalence [96]. Estimates of heritable variation vary, as discussed above, and while some genes associated with hypertension have shown Mendelian patterns of inheritance, for example mineralocorticoid (NR3C2) [97] and PPARG (also associated with obesity and T2D)[98], relatively fewer causal genes than other risk factors have been identified. As of this writing, there are 23 unique GWAS reported loci associated with hypertension [56]. Cowly (2006) provides a good review of the genetic analysis of the etiology of hypertension [99].

Historically, the rat has been the preferred rodent model for the genetics of hypertension, however the mouse is beginning to take a prominent role with the development of equipment capable of measuring blood pressure in small animals [100]. Recently, a QTL associated with blood pressure was identified in a mouse BXD RIL panel, and this candidate genomic region was used to identify the gene ureidopropionase (UPB1). Subsequent analysis in humans revealed the syntenic region to be a determinant of both systolic and diastolic blood pressure

[24]. A total of 33 QTL are associated with "hypertension" in the Mouse Genome Informatics Database (Accessed October 9, 2009) [67]. Of these, 9 are also associated with obesity, 3 with diabetes, and 7 with CVD. Three QTL, *Bpq21–Bpq23*, are associated with all four components of MetS. These three loci were identified in the males of an F_2 generation NZO/HILtJ x C3H/HeJ intercross [101]. However, a previous analysis of the F_2 progeny of this same intercross found no relation between blood pressure and other MetS components [102]. Supplementary Table 2 lists the mouse QTL identified for each of the metabolic disorders discussed above.

4. Metabolic syndrome components: gene-by-gene and gene-by-environment interactions

The genetic effects of most of these individual QTL discussed above are predominantly additive, where the combined phenotypic effects of two alleles at a locus is equal to the sum of their individual effects, and dominance deviations, where the heterozygote phenotype at a locus deviates from the midpoint of the two homozygotes, i.e. due to interaction between alleles at the same locus, also occur quite frequently. However, mouse-based QTL studies of MetS components are uncovering a more complex genetic architecture, wherein QTL effects are modified by diet and by sex [23,103]. Further, other characteristics such as epistasis [22,70], imprinting [104], and maternal effects [105], each of which are difficult to ascertain in human populations, are being illuminated through mouse models.

4.1 Gene-by-diet and gene-by-sex effects

Characterizing variation in response to diet is essential for testing hypotheses of the environmental contribution to metabolic disorders and to understanding the etiology of MetS. This is a challenging endeavor in studies of human populations because it is difficult to control and/or record diet over time. Some human population studies have successfully examined gene-by-environmental interactions [106–108], but typically, gene-by-environmental interactions are regarded as nuisance factors, despite the fact that they may underlie the increasing worldwide prevalence of MetS. Hence mouse models can be used to elucidate gene-by-environmental effects that can be further extrapolated to humans. Svenson *et al*. (2007) present results of a study assessing response to a high-fat diet in 43 inbred strains for 10 traits, including blood serum levels and body composition including weight and adiposity [109]. The Mouse Phenome Database [95] has compiled an inventory of high-fat diet intervention studies, including sex effects where applicable.

A number of QTL have been found in crosses between inbred strains fed a high-fat diet [110–115], some of which showed sex-specificity [68,111,112,115]. While these studies are valuable in characterizing response to a high-fat environment, most do not examine this response relative to a low-fat diet. As such, the context dependence of genetic by environmental interactions is missed. Cheverud *et al*. have taken advantage of the genotypic and phenotypic differences between LG/J and SM/J to identify genetic variation in dietary response for multiple MetS component traits (obesity (adiposity), glucose tolerance, and serum insulin, glucose, cholesterol, free fatty acid, and triglyceride levels) both in the LGXSM RIL panel [84] and in the F_{16} LG/J x SM/J AIL, dividing litters into high- and low-fat diet treatments [21]. Of the 91 QTL mapped in the RIL, 34% were only observed in individuals fed a high-fat diet and, for 58% of the traits examined, having the LG/J allele led to higher values. Eight sex-specific QTL were found, and in general females showed a greater genetic response to high-fat diet for obesity related traits, whereas males showed a greater response in fasting glucose levels [23]. Ongoing QTL mapping efforts in the F_{16} LG/J x SM/J AIL for these same MetS component traits confirm that genotype interacts with environment in important ways, indicating that the underlying genetics of MetS is highly context dependant (Cheverud *et al., in preparation*; Lawson *et al., in preparation*).

4.2 Epistasis

Epistasis occurs when the interaction among the alleles at two or more loci cause a phenotypic effect. In humans, epistasis between genetic variants of PPARG2 and proprotein convertase subtilisin/kexin (PCSK1) effects individual susceptibility to insulin resistance [116]. Additionally, the contribution of the apolipoprotein epsilon locus (*ApoE*) to serum cholesterol levels is mediated by an individual's genotype at the LDLR locus [117]. However, in general, studies of the contribution of epistasis to components of MetS in humans are under-represented in the literature. Mouse models of MetS components are revealing that epistatic interactions among QTL are commonplace, and that even QTL having small individual effects contribute considerably to epistatic interactions [101,118–121]. Recently, Fawcett *et al*. (2009) found that epistasis contributed significantly to genetic variation in fatpad (8.1%) and body weight (12.3%) in an analysis of a combined F_9/F_{10} LG/J x SM/J AIL [22]. Sometimes, an individual QTL will interact with many others. For example, Brockman *et al*. (2000)found a QTL, *Lepq1*, on chromosome 14, interacting with seven other QTL associated with adiposity in an F_2 DU6i x DBA/2 intercross [118]. Cheverud *et al*. (2001) found that *Adip8*, on chromosome 18, interacted with all seven other adiposity QTL identified in a LG/J x SM/J intercross [71]. These results point to QTL that may contain major regulators of the genetic pathways underlying MetS.

4.3 Imprinting

Our knowledge of the influence of epigenetic factors, cell-specific heritable changes in gene expression occurring in the absence of DNA mutation, on metabolism is limited. However, the various disease components comprising MetS show non-Mendelian features, such as some discordance in twins, male and female differences in prevalence, and individual variation in both healthy and disease states, each of which are consistent with epigenetic mechanisms [122]. Genomic imprinting can be generally defined as the unequal expression of maternally and paternally derived copies of a gene, and it is becoming apparent that imprinting is an important aspect of the genetic architecture of many complex traits, including growth and metabolism [123]. More than 80 imprinted genes have been identified in humans and mice [124], and genome-wide bioinformatic analyses have trained algorithms with imprinting signatures, such as methylation and histone modification, to predict that several hundred genes are likely to be imprinted across the genome [125,126]. QTL mapping can also identify imprinted loci [104,127,128], and loci with imprinting effects on obesity have been mapped in human populations [129]. Using an F_{16} population of LG/J x SM/J AIL fed both high- and low-fat diet treatments, we have mapped genome-wide imprinting values for various MetS component traits (adiposity, serum lipid levels of cholesterol, free fatty acids, and triglycerides, serum insulin and glucose, and glucose tolerance). The imprinting genotypic value is defined as half the difference between the reciprocal heterozygotes, LS and SL, where the first allele is derived from the father and the second from the mother (Cheverud *et al., in preparation*; Lawson *et al., in preparation*).

In this study, one thousand two animals were partitioned by sex and fed low- (247 males; 254 females) and high- (253 males; 248 females) fat diets. Animals were scored at 1,402 autosomal SNPs using the Illumina Golden Gate Assay. Details of the pedigree and of the phenotyping and genotyping process are described in Ehrich *et al*., (2005) [21]. Additive, dominance, and imprinting scores were estimated at each marker and additional markers were imputed at 1 cM intervals. Analyses were performed using the SAS PROC mixed model with additive, dominance, and imprinting genotypic scores, their interactions with sex, diet, and with sex by diet as the fixed effects and with family, family by sex, diet and by sex and diet interactions as the random effects. Figure 2 shows the genotypic means for a significant QTL found on chromosome 8 for glucose tolerance, measured as the area under the curve (AUC) calculated from results of an intra-peritoneal glucose tolerance test performed at 10 weeks of age. This

QTL has significant additive effects in the full population, and significant additive and imprinting effects when the QTL is deconstructed into sex-by-diet cohort. In males fed a high-fat diet, there is paternal imprinting whereby individuals inheriting the SM/J allele from their father have a relatively poor response to glucose stress. The implications of this result are two-fold: genomic imprinting is not only a dynamic contributor to variation, but also an effect that is highly context dependent. These results support previous findings that imprinting patterns are labile [104,130] and not consistent across all genotypes and environments. Further, if sex-by-diet cohorts are not considered individually, the imprinting effect is washed out in the full population. Such context goes unmeasured in human GWAS and by not being considered, results are missing an important aspect of the genetic architecture underlying variation in metabolic traits.

4.4 Maternal effects

Maternal effects can be generally defined as the influence of a mother's phenotype on the phenotypes of her offspring [131], and human studies indicate that maternal BMI is significantly associated with MetS in offspring [132,133]. While maternal phenotype is considered environmental with respect to offspring genotype, there is a genetic basis to variation in the maternal generation including the mitochondria (that generate energy and are referred to as the "powerhouse" of the cells), transmitted by mother's ovum. Because it is difficult to quantify the genetic and environmental components of maternal phenotype on MetS in offspring in humans, the mouse has proved invaluable for illuminating this aspect of the genetic architecture. For example, Wolf *et al*. (2002) identified maternal effect QTL that accounted for 31.5% of among litter variance in offspring early growth in a cross-fostered F_3 LG/J x SM/J intercross [134]. Jarvis *et al*. (2005) measured genetic maternal effects on offspring lipid, obesity and diabetes related traits in reciprocal crosses between C57BL/6J and 10 LGXSM RILs [105]. The authors found that genetic maternal effects accounted for as much as 10% of the phenotypic variance in offspring at 17 or more weeks after weaning. These results indicate that variation in metabolic traits not only is dependent on an individual's own genotype, but also is independently influenced by the individual's mother's genotype.

5. Promise of comparative genomics and bioinformatics

The wealth of information provided by recently available whole-genome sequences promises to expand our knowledge of MetS. Direct examination of the human syntenic regions for mouse QTL has already led to identification of QTG for plasma lipids [135–137] and hypertension [24,138,139]. Bioinformatic tools are developed that can aid this research [140], and several databases catalog positional information for human disease mutations, including both coding and non-coding variations [141]. For example, bioinformatic analysis of multiple-species protein coding sequence alignments finds that heritable human disease-associated mutations overwhelmingly occur at phylogentically conserved amino acid sites [142–144]. However, comparative genomic analyses of mammalian molecular evolution have also found evidence that genes related to some known Mendelian disorders have evolved differently in humans than in lineages leading to other closely related contemporary mammals [145,146]. Comparison among primates has identified several instances of a human disease-associated coding variant corresponding to the wild-type amino acid in the chimpanzee, the macaque, or the reconstructed ancestral primate genome [147], implying that the protective variant seen in humans is derived. Thus a non-trivial proportion of disease genetic risk is associated with ancestral alleles [148], and knowledge of a QTL associated with a disease phenotype in mouse can allow one to use whole genome multiple-species alignments to reconstruct the evolution of a genomic region and to make functional predictions, which, in a biomedical context, have obvious therapeutic implications.

Comparing multiple species' genomes has led to the discovery of polymorphisms and molecules that have been shown to contribute to disease risk. For example, copy number variants (CNVs), DNA segments that vary in number among individuals, are a recently identified source of genetic variation in mammals and have been shown to affect gene expression, presumably through altered gene dosage [149–151]. Recently, CNVs were found to be highly associated with variation in gene expression levels in mouse adipose tissue, and QTL for metabolic traits were identified at or near several CNV genes in an F_2 C57BL/6J x C3H/HeJ intercross [152]. Non-coding microRNAs have been shown to affect many biological processes, including metabolism [153,154], and mouse models have recently been used to characterize microRNA-dependent regulation of glucose homeostasis and lipid metabolism in mouse models of obesity and T2D [155,156].

A particularly promising area of research where mouse models are proving invaluable is the characterization of coding and non-coding DNA sequence in gene networks and regulatory pathways. Genes do not function singly, or singly affect a trait. A recent experiment that focused on susceptibility loci for metabolic disease traits to identify gene networks validated lipoprotein lipase (*Lpl*), lactamase beta (*Lactb*), and protein phosphatae 1-like (*Ppm1l*) as genes underlying obesity in mice [157]. Some recent bioinformatic approaches have taken advantage of genes and QTL found through mouse models to identify sequences affecting multiple components of MetS. Both these methods, experimental and bioinformatic, point to focal candidates for further analysis in human populations [44,69]. Further, under a comparative genomics framework, one could examine co-evolution of genes that interact within and between disease components to identify patterns that could guide future research into the etiology of MetS. Such an approach should incorporate insights gained from mouse models about the complexity and the context-dependency of gene-by-environment interactions if it is to lead to rational treatments and prevention strategies in humans.

Supplementary Material

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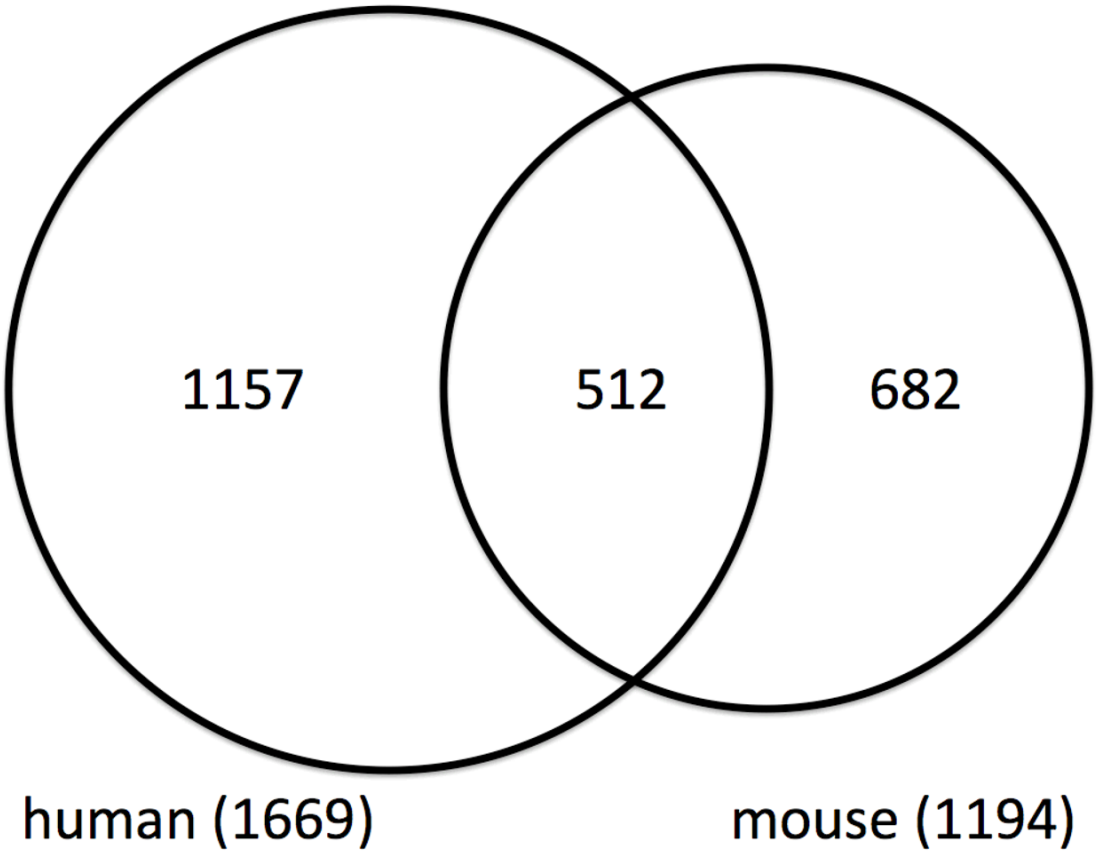

Figure 1.
Venn diagram illustrating the number of unique genes associated with a MetS component for humans, for mice, and their intersection

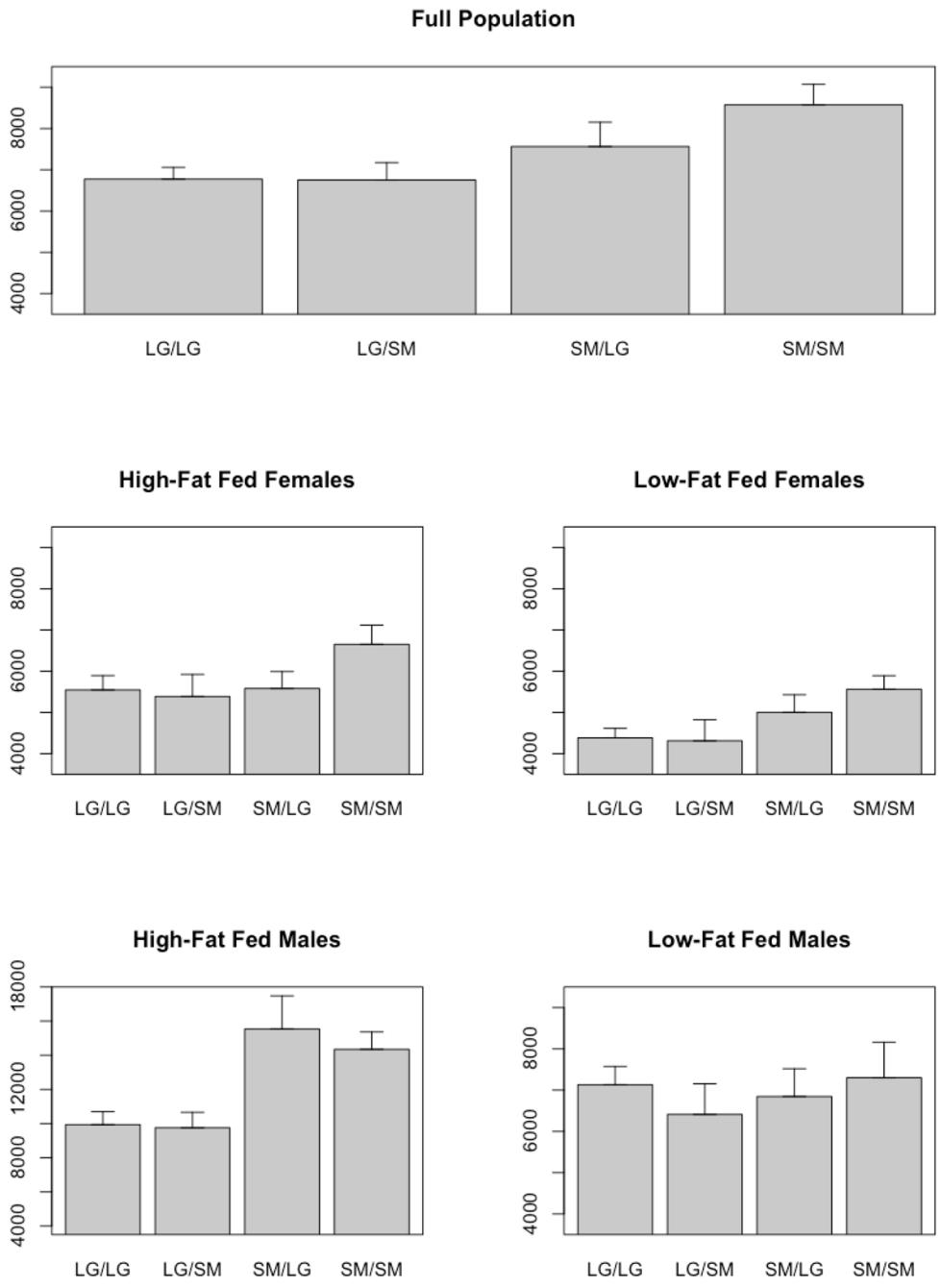

Figure 2.

Genotypic means for a significant QTL for glucose tolerance in an F_{16} LG/J and SM/J AIL (Wustl:LG,SM-G16). The QTL has significant additive effects in the full population, and significant additive and imprinting effects in males fed a high-fat diet. Note the scale is different in the high-fat fed males to accommodate that cohort's higher mean values.

Table 1

Useful online resources for mouse model study design.

Resource	Information
The Jackson Labs (http://www.jax.org/)	Repository of inbred laboratory mouse strains and genetically engineered mouse stocks
UCSC Genome Browser (http://genome.ucsc.edu/)	Sequence information, multi-species whole-genome alignments, tools for visualizing genome-wide data sets
Ensemble (http://www.ensembl.org/index.html)	Sequence information, data mining and exporting via BioMart
National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/)	Gateway to NCBI mouse genome resources including dbSNP, Clone Finder, Full-Length cDNAs, e-PCR and more
Mouse Genotype Informatics (http://www.informatics.jax.org/)	Integrated resource for molecular, genomic and biological data and their applications to human disease research
Mouse Phenome Database (http://phenome.jax.org/pub-cgi/phenome/mpdcgi)	Phenotype data organized by subject, by mouse strain and by project with the aim of enabling investigators to find research-appropriate mouse strains
Gene Paint (http://www.genepaint.org/)	Atlas of gene expression patterns in the mouse embryo
Galaxy (http://main.g2.bx.psu.edu/)	Online tool for retrieving sequences and alignments and performing simple statistics and evolutionary analyses

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Table 2

Genes where mutations in both human and mouse orthologs are associated with phenotypesdiagnostic of the human metabolic disorder.

Metabolic Disorder (Human Disease Query)	OMIM ID	Human Gene RefSeq accession	Human Genome Coordinates (hg19; build 37.1)	Mouse Genome Coordinates (mm9; build 37)	Mouse Genetic Background (Strain)	Reference (First author)
Obesity	601665	MC4R NM_005912	chr18: 58038564-58040001	chr18: 67017362-67020126	129S4/SvJae*C57BL/6	Huszar D. *Cell*.1997;88:131–141
		SIM1 NM_005068	chr6: 100836751-100911551	chr10: 50615457-50708958	129/Sv*C57BL/6	Goshu E. *Mol Cell Biol*. 2002;22:4147–4157
	609734	POMC NM_000939	chr2: 25383722-25391559	chr12: 3954951-3960618	129S1/SvEv*129X1/SvJ	Yaswen L. *Nat Med*. 1999;5:1066–1077
Type-2 Diabetes/	125800	AQP2 NM_000486	chr12: 50344524-50352662	chr15: 99409487-99414976	C57BL/6*Aqp2^{cph}	McDill B. *Proc Natl Acad Sci USA*. 2006; 103:6952–6957
Insulin Resistance/	125700	AVP NM_000490	chr20: 3063203-3065370	chr2: 130406413-130408277	129S1/Sv*129X1/SvJ	Russell TA. *J Clin Invest.* 2003;112:1697–1706
Impaired Glucose	222100	HLA-DQB1 NM_002123	chr6: 32627657-32634466	chr17: 34401704-34404980	129S2/SvPas*C57BL/6*CBA*SJL	Wen L. *J Clin Invest.* 2001;107:871–880
Tolerance	125853	AKT2 NM_001626	chr19: 40736225-40791265	chr7: 28390879-28424472	129P2/O1aHsd*C57BL/6	Cho H. *Science*. 2001; 292:1728–1731
		GCK NM_000162	chr7: 44183870-44229022	chr11: 5800825-5849602	129X1/SvJ*C57BL/6*CBA*ICR	Toye AA. *Diabetes*. 2004; 111:1147–1160
		HNF1A NM_000545	chr12: 121416549-121440312	chr5: 115398370-115421047	129X1/SvJ*C57BL/6	Lee Y. *Mol Cell Biol*. 1998;18:3059–3068
		IRS1 NM_005544	chr2: 227304277-227371750	chr1: 82229680-82288014	129X1/SvJ*C57BL/6*CBA*ICR	Lin X. *J Clin Invest.* 2004; 114:908–916
		IRS2 NM_003749	chr13: 109204185-109236915	chr8: 10986964-11008430	129S1/Sv*129X1/SvJ*C57BL/6	Withers DJ. *Nature*. 1994; 372:182–186
		PDX1 NM_000209	chr13: 27392168-27398451	chr5: 148081707-148086725	129S6/SvEvTac*C57BL/6*129T/Sv	Kim SK. *Nat Genet*; 2002; 30:430–435
		SLC2A4 NM_001042	chr17: 7185054-7191366	chr11: 69755788-69761692	129/Sv*C57BL/6J*CD-1*SJL	Stenbit AE. *Nat Med*. 1997;3:1096–1101
	304800	AVPR2 NM_000054	chrX: 153170529-153172619	chrX: 71137441-71139766	129S1/Sv*129X1/SvJ*CF-1	Yun J. *J Clin Invest*. 2000;106:1361–1371
	610199	GLIS3 NM_001042413	chr9: 3824128-4300035	chr19: 28336938-28754567	C57BL/6*CBA	Watanabe N. *FEBS Lett*. 2009; 583:2108–2113
	226980	EIF2AK3 NM_004836	chr2: 88856261-88926994	chr6: 70794521-70855234	129S6/SvEvTac*Swiss Webster	Harding HP. *Mol Cell*. 2001; 7:1153–1163
	304790	FOXP3 NM_014009	chrX: 49106898-49121288	chrX: 7156819-7172360	101/RI*C3Hf/RI*STOCK MR	Wildin RS. *Nat Genet*. 2001; 27:18–20

Metabolic Disorder (Human Disease Query)	OMIM ID	Human Gene RefSeq accession	Human Genome Coordinates (hg19; build 37.1)	Mouse Genome Coordinates (mm9; build 37)	Mouse Genetic Background (Strain)	Reference (First author)
	125850	HNF4A NM_178849	chr20: 43029924-43060029	chr2: 163372924-163398643	129X1/SvJ*C57BL/6*DBA	Miura A. *J Biol Chem.* 2006;281:5246–5247
	249270	SLC19A2 NM_006996	chr1: 169433151-169455208	chr1: 166179186-166195499	129X1/SvJ	Oishi K. *Hum Mol Genet.* 2002;11:2951–2960
Hypertension	145500	NOS3 NM_000603	chr7: 150688144-150711686	chr5: 23870637-23890292	129P2/o1aHsd*C57BL/6	Duplain H. *Circulation*. 2001; 104:342–345
	178600	SMAD9 NM_001127217	chr13: 37422207-37494409	chr13: 54559504-54605179	129S4/SvJaeSor	Huang Z. *HumMol Genet.* 2009; 18:2791–2801
Dyslipidemia/	136120	LCAT NM_000229	chr16: 67973787-67978015	chr8: 108463452-108467282	129X1/SvJ*C57BL/6J	Sakai N. *J Biol Chem.* 1997; 272:7506–7510
	143890	LDLR NM_000527	chr19: 11200057-11244503	chr9: 21528038-21554362	129S7/SvEvBrd*C57BL/6 B6.Lg-Lep^{ob}Ldlr^{Tm1Her}	Hasty AH. *J Biol Chem*. 2001; 276:37402–37408
	603813	LDLRAP1 NM_015627	chr1: 25870076-25895375	chr4: 134301327-134323919	129S5/SvEvBrd*C57BL/6	Harada-Shiba M. *Circ Res.* 2004; 95: 945–952
Cholesterol/	200100	MTTP NM_000253	chr4: 100485240-100545153	chr3: 137752819-137794341	129S1/Sv*129X1/SvJ*C57BL/6	Chang BH. *J Biol Chem.* 1999; 274: 6051–6055
Triglycerides/	201470	ACADS NM_000017	chr12: 121163571-1221177810	chr5: 115560308-115569322	BALB/cByJ	Schiffer SP. *Biochem Genet*. 1989; 27:47–58
Free-Fatty Acids	301500	GLA NM_0000169	chrX: 100652779-100663001	chrX: 131122708-131135544	129S4/SvJae*C57BL/6	Ohshima T. *Proc Natl Acad Sci USA*. 1997; 94: 2540–2544
	144250	LPL NM_000237	chr8: 19796582-19824769	chr8: 71404454-71430831	129P2/O1aHsd	Xian X. *Biochem Biophys Res Commun*. 2009; 385:563–569

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