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Exploring Genetic Susceptibility to Obesity through Genome Functional Pathway Analysis

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Abstract

Objectives—Obesity is reaching epidemic levels in recent decades with a growing body of research identifying predisposing genetic components. To explore the relationship of genetic factors contributing to obesity, we undertook an analytical computer-based gene profiling approach utilizing an updated list of clinically relevant and known obesity-related genes.

Methods—We compiled an updated list of 494 genes reportedly associated with obesity and utilized the GeneAnalytics profiling software and interrogated genomic databases from GeneCards to cross-reference obesity gene-sets against tissues and cells, diseases, genetic pathways, Gene Ontology (GO)-biological processes and GO-molecular functions, phenotypes and compounds.

Results—Obesity-related fields identified by GeneAnalytics algorithms included 8 diseases, 46 pathways, 62 biological processes, 22 molecular functions, 148 phenotypes, and 286 compounds impacting adipogenesis, signal transduction by G-protein coupled receptors and lipid metabolism involving insulin-related genes (*IGF1*, *INS*, *IRS1*). GO-biological processes identified feeding behavior, cholesterol metabolic process, glucose and cholesterol homeostasis pathways while GO-molecular processes pertained to receptor binding affecting glucose homeostasis, body weight and circulating insulin and triglyceride levels.

Conclusions—The gene-profiling model suggests that pathogenesis of obesity relates to the coordination of biological responses to glucose and intracellular lipids possibly through a disruption of biochemical cascades and cellular signaling arising from affected receptors.

Keywords

Obesity; Genetics; functional analysis; pathways; gene interaction

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Introduction

Obesity is a prevalent physiological condition with growing public health concerns afflicting both adults and children worldwide. Obesity is functionally defined in adults by the World Health Organization (WHO) as a BMI of 30 kg/m².¹ Obesity levels increased by 2.5% from 1990 to 2010 and as of 2010, impacts an estimated 35.7% of adults (aged 20 years and over) in the United States.^{2,3} Obesity has also been associated with a variety of adverse conditions such as heart disease (coronary artery disease), hypertension, pulmonary embolism, cerebrovascular disease, diabetes, sleep apnea, cholelithiasis, arthritis, psychiatric conditions and certain malignancies. In 2008 an estimated 2.4% of national health care expenditure, or about \$1.8 billion, was spent due to obesity and related diseases.¹

Obesity has been attributed to certain environmental and lifestyle factors such as poor diet and nutrition, sedentary lifestyle, gut bacteria, and a number of medications have been found to contribute to obesity by impacting metabolic pathways and hormones with adipocytes playing a key role in regulating metabolic activity and feeding behavior through the secretion of leptin, a satiety hormone. Subsequently, the release of CART and ACTH amplifies the response to satiation.^{1,4,5} Leptin is important in managing long-term feeding behavior by mitigating hunger and maintaining energy homeostasis.^{1,6} Short term feeding behavior is mediated in part by ghrelin, an orexigenic peptide hormone secreted by ghrelinergic cells in the gastrointestinal tract following gastric emptying.⁷ Activated ghrelin receptors in the hypothalamus secrete NPY and AgRP lead to physiological characteristics associated with appetite.⁷ Defects in production or reception of both hormones can play a role in obesity due to their respective roles in dampening and stimulating appetite.^{1,8} Desensitization to leptin has been postulated as a major contributor to obesity due to leptin's role in managing appetite.⁹ While hormones seem to play a significant part, the direct physiological basis of obesity arises from a sustained positive energy balance and the storage of excess dietary lipids in adipocytes.¹⁰

Many genes have been implicated in the obesity epidemic with individuals and populations having genetic predisposition to the emergence of obesity. Locke et al.¹¹ stated that 40–70% of inter-individual variability in BMI (body mass index), which is a physiological measure used to assess obesity, can be attributed to genetics. We carried out genetic profiling using GeneAnalytics software as previously described^{12–14} to characterize the core processes underlying the development of obesity. We hypothesized that the functional impact of genes influencing obesity will converge on a common set of biological and molecular pathways influencing cellular metabolism, energy production and regulation. Recently, a review of the medical literature and genetic databases searching for obesity-related genes led to a compilation of 370 clinically relevant and known genes for obesity³ and used as the primary reference source for updating the current list of obesity-related genes required for a gene profiling approach utilizing the GeneAnalytics software program.

Methods

We used a variety of medical and genetic databases to research the genetics of obesity and to update the master list of obesity-related genes. We searched for key words such as “obesity,”

“genes,” “adiposity,” and “body mass index.” An assortment of genome-wide association studies (GWAS) and candidate gene studies identified novel genes and polymorphisms implicated in the pathogenesis of obesity. These literature sources included review articles with meta-analyses and primary research articles. Databases and catalogues included Online Mendelian Inheritance in Man (OMIM) (www.OMIM.org), PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), National Center for Biotechnology Information (NCBI) (<http://www.ncbi.nlm.nih.gov/>) and GeneCards (<https://www.genecards.org>). Our research update identified 124 additional obesity genes in addition to the 370 genes previously reported accounting for a total of 494 genes.³ Of the 494 genes, 462 were recognized by the GeneAnalytics program (see Supplemental Table 1).

This updated master list of genes was analyzed using the GeneAnalytics (<http://geneanalytics.genecards.org/>) program. GeneAnalytics is a commercial software developed by LifeMap Sciences, as part of the GeneCards Suite (<http://www.lifemapsc.com/products/genecards-suite-premium-tools/>) to generate a comprehensive, easy-to-apply gene-set analysis tool to contextualize expression patterns and functional signatures embedded in advanced genomic expression, sequencing and microarray datasets.¹⁵ Other databases included MalaCards (<http://www.malacards.org/>) – human disease database and PathCards (<http://pathcards.genecards.org/>) – biological pathways database and expression-based analyses including manually curated expression data from normal and diseased tissues to study for gene-tissue association relationships.

The GeneAnalytics program aggregated the obesity-related gene sets and cross-referenced them against various tissues and cells, diseases, pathways, gene ontology (GO)-biological processes, GO-molecular functions, phenotypes and compounds following established protocols reported previously.^{12–14} Scores were assigned to each of the above categorized fields using an algorithm native to GeneAnalytics which interrogates the number of “matched” genes (between our master list and those found in GeneCards) and the total number of genes identified by GeneCards for that particular category. Matching genes from the obesity-associated diseases category were then cross-checked against the pathways category and the corresponding frequencies were recorded including the number of times each gene appeared in a separate pathway. The results of this assessment can be found in Table 1 which isolates fifteen obesity-related genes implicated in a variety of pathways that may be considered prime candidates in the pathogenesis of obesity.

Results

We identified a number of obesity-related fields with high scores according to GeneAnalytics algorithm including 8 diseases, 46 pathways, 62 GO-biological processes, 22 GO-molecular functions, 148 phenotypes, and 286 compounds. As expected, obesity (high match score=84; 107 matched genes of 494 total genes in obesity pathway) was the top scoring disease associated with the surveyed genes (see Table 2) followed by noninsulin dependent (type 2) diabetes mellitus (74 out of 226 total genes in pathway). These were followed by related conditions such as acquired metabolic disease, overnutrition, and disease of glucose metabolism, and an association between obesity and certain cancers, such as prostate and colorectal.

Forty-six obesity-related pathways were identified that prominently featured adipogenesis (high match score = 95, 40 matches of 149 total genes) as the highest matching score and included intracellular signaling (e.g., G-protein coupled receptors), cholesterol and lipid biology (e.g., statin pathways), longevity, metabolism, and immune mediators (e.g., IL-7 signaling; see Table 3). Sixty-two GO-biological processes were identified that pertained to feeding behaviors (high match score = 73, 22 matches of 42 total genes) as the highest matching score followed by cholesterol metabolic process, glucose and cholesterol homeostasis, regulation of blood pressure and small molecule metabolic process (see Table 4). Twenty-two GO-molecular processes were identified that pertained to protein binding (high match score = 18, 18 matches of 82 total genes) including peptide hormone binding, hormone activity, protein binding, steroid hormone receptor activity, insulin receptor binding and enzyme binding (see Table 5).

We consolidated the obesity-related gene list based on the number of pathways in which they appeared as a means to identify the most impactful gene linkages influencing the expression of obesity (see Table 1). Fifteen genes were overrepresented in obesity-related pathways including the genes for insulin (*INS*), several key insulin receptors (e.g., *IRS1*, *INSR*) and several growth factors (e.g., *IGF1*, *TGFB1*, *TNF*). The top four genes enumerated with their key pathways will follow: *CREB1* (cAMP Responsive Element Binding Protein 1) codes for a phosphorylation-dependent transcription factor, which promotes transcription when bound to the DNA cAMP response element and appeared in 59 high match pathways. Notable pathways that were associated include adipogenesis; signaling by G-protein coupled receptor (GPCR); longevity-regulating pathway and translation; insulin regulation of translation, and adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. *CREB1* appeared in 16 GO-biological processes, such as Positive Regulation of Transcription from RNA Polymerase II Promoter, Positive Regulation of Multicellular Organism Growth, Response to Drug, Positive Regulation of Transcription: DNA-templated; and Mammary Gland Development. *CREB1* appeared in seven GO-molecular functions including protein binding, enzyme binding, and sequence-specific DNA binding.

IGF1 (Insulin Like Growth Factor 1) appeared in 59 pathways, and represented by 18 high match scores, including adipogenesis, signaling by GPCR, longevity-regulating pathway, translation: insulin regulation of translation, and the AMPK signaling pathway. Insulin-like growth factor is a protein structurally and functionally similar to insulin and is involved in regulation of growth and development.¹⁶ *IGF1* appeared in 32 GO-biological processes including Positive Regulation of Transcription from RNA Polymerase II Promoter; Positive Regulation of Transcription: DNA-templated; Positive Regulation of Cell Proliferation, Mammary Gland Development, and Positive Regulation of Glucose Import. *IGF1* was also involved in eight GO-molecular functions including hormone activity, protein binding, and insulin receptor binding.

INS (Insulin) is a peptide hormone produced by the pancreas and is responsible for the increased uptake of glucose in cells via the Glut-4 transporter. The gene appeared in 59 pathways with 27 high match scores including Adipogenesis; Signaling by GPCR; Longevity Regulating Pathway; Translation: insulin Regulation of Translation, and

Metabolism. Insulin resistance is the cause of type II diabetes mellitus and resistance is positively correlated with increased severity of obesity.¹⁷ INS appeared in 43 GO-biological processes such as Cholesterol Metabolic Process; Glucose Homeostasis; Small Molecule Metabolic Process; Positive Regulation of Transcription: DNA-templated; and Energy Reserve Metabolic Process. INS was implicated in 10 functions including hormone activity, protein binding, and insulin receptor binding.

IL6 (Interleukin 6) is a cytokine involved in immunoregulation and management of inflammation.¹⁸ IL6 and other proinflammatory cytokines have been implicated in type 1 diabetes due to their proposed role in eliciting the apoptosis of pancreatic β cells and consequent insulin deficiency.¹⁹ IL6 has also been shown to inhibit insulin receptor signal transduction in liver cells, thereby increasing the circulation of free fatty acids and diminishing adiponectin secretion.¹ IL6 appeared in 49 pathways affiliated with obesity with 13 high score matches including Adipogenesis; Signaling by GPCR, Translation Insulin Regulation of Translation; Interleukin-3,5 and GM-CSF Signaling; and Activation of Camp-Dependent PKA. IL6 appeared in 40 GO-biological processes including Positive Regulation of Transcription from RNA Polymerase II Promoter; Response to Drug; Positive Regulation of Transcription: DNA-templated; Positive Regulation of Cell Proliferation; and Response to Glucocorticoid.

Discussion

The relationship between obesity and type 2 diabetes is well-documented with a number of possible pathways identified. Das et al.²⁰ found a positive correlation between obesity (especially central adiposity) and elevated levels of insulin resistance. In addition, plasma malondialdehyde was identified at higher levels of oxidative stress with increasing abdominal circumference and visceral fat content, suggesting that oxidative stress may be a link between obesity (especially central obesity) and noninsulin dependent diabetes mellitus.²⁰ As with obesity, the onset of type 2 diabetes is mediated by genetics and can be influenced by environmental factors including heavy metal exposure. For example Butler et al.²¹ reported disturbances of metallothionein gene patterns involved in detoxification indicating environmental exposure in coding and non-coding expression studies in lymphoblastoid cells in non-syndromic obese vs non-obese control subjects. Furthermore, a crucial link between obesity and the onset of type 2 diabetes is lipotoxicity, or the accumulation of fatty acids in non-adipose tissues from mature adipocytes, leading to the development of insulin resistance.¹⁰ In addition, Das et al.²² used an integrative genomics approach and identified activation of thioredoxin/thioredoxin reductase-1-mediated oxidative stress defense pathway and inhibition of angiogenesis in obese non-diabetic subjects utilizing expression of adipose tissue transcripts suggesting a novel interaction of up-regulated oxidative stress defense mechanisms and down-regulated angiogenesis pathways.

The majority of high-ranking pathways and genes, according to our analysis, involved insulin production, signaling or related metabolic functions involving IGF1, IRS1 and INS. Polymorphisms of the INS (insulin) gene can render an individual vulnerable to increases in insulin resistance or diminished insulin production. The frequency of overlap in insulin and insulin-related genes for both diabetes and obesity-associated pathways may be emblematic

of an intrinsic physiological linkage between the two diseases. The potential role for insulin sensitivity in the pathogenesis of obesity is reiterated by the fact that GeneAnalytics software program (geneanalytics.genecards.org) designated abnormal glucose homeostasis and increased insulin circulation levels as high-scoring phenotypes (see Table 6). The results emphasize the need to further elucidate the relationship between insulin sensitivity and the development of obesity.

Obesity has been associated with increased risk of certain malignancies such as colorectal and prostate cancer; however, the precise mechanism of the linkage is not fully understood. Oh et al.²³ noted a relationship between visceral obesity and increased risk of colorectal neoplasm, although no causal link was identified. Von Hafe et al.²⁴ also investigated visceral fat as a risk factor for prostate cancer and found a potential link in the form of steroid hormone imbalances, increased insulin levels, and the aberrant activity of adipocytokines secreted by visceral fat cells. GeneAnalytics profiling of obesity-associated genes further supported a link between key biological processes of obesity and prostate cancer possibly related to *AR* (androgen receptor), *CREB1*, and *CYP19A1* genes. The top scoring genes in terms of key pathway involvement included cytokines and growth factors implicated in tumorigenesis (see Table 1), particularly *CREB1*, *IGF1*, *INS*, and *IL6*. These four genes are all involved in the cAMP-dependent protein kinase pathway, instrumental in intracellular signal transduction and mediating glycogen, sugar, and lipid metabolism.²⁵

Another recurring pathway identified was the G-protein coupled receptor (GPCR) signaling pathway. The high frequency of genes involved in cell signaling and signal transduction encompassing molecular processes incorporating protein binding seems to reinforce the idea that the pathogenesis of obesity can be attributed, to a certain extent, to the failure of cells to properly coordinate blood-sugar content and intracellular lipid levels. It is likely that polymorphisms in these genes, which have been linked to cell signaling pathways, contribute to the development of obesity through modulation in the biochemical cascade of reactions arising from affected receptors. *LEP* (leptin) and *GHRL* (ghrelin), genes involved in the production of the hormones of the same name, were involved in only 20 and 5 pathways, respectively, although leptin and ghrelin are prominent factors in the behavioral foundation of obesity since they mediate appetite. These hormones do not appear to influence as many key biological pathways as *CREB1* and *IGF1* based upon the GeneAnalytics profile. However, the scope of our study is limited by current knowledge base and understanding of the physiological functions of the obesity-related genes modeled in our analysis. For example, the *FTO* gene (codes for the fat mass and obesity-associated protein) and is widely known as a gene playing a role in obesity. Yet, it did not appear in our list of key genes because the precise etiology is not known and could not be linked to a particular pathway, i.e. adipogenesis, GPCR or biological processes. Further, the actions of specific genes and their interactions in multiple pathways may limit the development of therapeutic interventions particularly if they have multiple effects or are widely pleiotropic. Thus, interventions may disrupt other important functioning pathways. Additional investigations are required to further address the genetic relationship utilizing the growing and broadly applicable post-genomics datasets to gain knowledge applicable to understanding and treating obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known about this subject?

1. Obesity arises from a sustained energy imbalance and the storage of excess dietary lipids in adipocytes under genetic control
2. Certain individuals and populations appear to have a genetic predisposition to the emergence of obesity
3. About 500 genes have been implicated in the pathophysiology of obesity stemming from multiple functional domains.

What does our study add to the current literature?

1. We provide a novel molecular pathway analysis using GeneAnalytics programs to characterize the functional domains related to genes implicated in the development of obesity.
2. GeneAnalytics algorithm converged on 8 diseases, 46 pathways, 62 biological processes, 22 molecular functions, 148 phenotypes, and 286 compounds significantly linked to our list of obesity-related genes.
3. GeneAnalytics profiling identified pathways affecting biological responses to glucose and lipids, biochemical cascades and cellular signaling arising from affected receptors which may serve as therapeutic targets for intervention.

Table 1

Frequency of Individual Obesity-Related Genes Associated with Pathways Using GeneAnalytics

Symbol	Name	Location	Number of High-Scoring Obesity-Related Pathways Featuring This Gene
<i>CREB1</i>	cAMP Responsive Element Binding Protein	2q34	59
<i>IGF1</i>	Insulin Like Growth Factor 1	12q23.2	59
<i>INS</i>	Insulin	11p15.5	59
<i>IL6</i>	Interleukin 6	7p21	49
<i>IRS1</i>	Insulin Receptor Substrate 1	2q36	47
<i>TGFB1</i>	Transforming Growth Factor Beta 1	19q13	46
<i>TNF</i>	Tumor Necrosis Factor	6p21.3	46
<i>INSR</i>	Insulin Receptor	19p13.2	42
<i>GNB3</i>	G Protein Subunit Beta 3	12p13	36
<i>PRKARIA</i>	Protein Kinase CAMP-Dependent Type 1 Regulatory Subunit Alpha	17q24	31
<i>FASN</i>	Fatty Acid Synthase	17q25	29
<i>IRS2</i>	Insulin Receptor Substrate 2	13q34	29
<i>VEGFA</i>	Vascular Endothelial Growth Factor A	6p12	29
<i>PPARG</i>	Peroxisome Proliferator Activated Receptor Gamma	3p25	27
<i>GH1</i>	Growth Hormone 1	17q24.2	25

Table 2

Profiling of the High Scoring Obesity-Associated Diseases Using GeneAnalytics

Score	Disease	Total Genes in Disease	Matched Obesity-Related Genes (%)
84.01	Obesity	562	107 (19%)
70.31	Diabetes Mellitus, Noninsulin-Dependent	226	74 (33%)
37.18	Diabetes Mellitus, Insulin-Dependent	160	42 (26%)
33.99	Acquired Metabolic Disease	57	34 (60%)
31.53	Overnutrition	42	30 (71%)
29.66	Prostate Cancer	682	46 (7%)
28.50	Glucose Metabolism Disease	51	28 (55%)
25.33	Colorectal Cancer	802	39 (5%)

Table 3

Profiling of the High Scoring Obesity-Associated Pathways Using GeneAnalytics

Score	Pathway	Total Genes in Pathway	Matched Obesity-Related Genes (%)
94.78	Adipogenesis	149	40 (27%)
54.50	Signaling By GPCR	2661	130 (5%)
49.42	Statin Pathway	37	16 (43%)
48.25	Regulation of Lipid Metabolism By Peroxisome Proliferator-activated Receptor Alpha (PPARalpha)	268	34 (13%)
46.73	Lipoprotein Metabolism	79	20 (25%)
46.49	Peptide Ligand-binding Receptors	710	55 (8%)
45.66	Longevity Regulating Pathway - Multiple Species	144	25 (17%)
43.31	Translation Insulin Regulation of Translation	359	37 (10%)
42.68	Metabolism	2472	115 (5%)
38.89	PPAR Signaling Pathway	82	18 (22%)
36.70	AMPK Signaling Pathway	145	22 (15%)
34.71	Prolactin Signaling Pathway	172	23 (13%)
34.37	Interleukin-3, 5 and GM-CSF Signaling	1382	73 (5%)
32.65	Monoamine GPCRs	47	13 (28%)
32.56	Activation of CAMP-Dependent PKA	656	45 (7%)
31.75	Adipocytokine Signaling Pathway	72	15 (21%)
30.49	NFAT and Cardiac Hypertrophy	337	30 (9%)
30.18	SIDS Susceptibility Pathways	185	22 (12%)
28.88	Development Ligand-independent Activation of ESR1 and ESR2	143	19 (13%)
28.74	Peptide Hormone Metabolism	98	16 (16%)
27.35	Mesenchymal Stem Cell Differentiation Pathways and Lineage-specific Markers	105	16 (15%)
27.10	IL-7 Signaling Pathways	172	20 (12%)
26.80	CAMP Signaling Pathway	211	22 (10%)
26.71	Metabolism of Fat-soluble Vitamins	124	17 (14%)
26.58	Alzheimers Disease	252	24 (10%)
26.26	Ovarian Steroidogenesis	56	12 (21%)
25.85	Wnt Signaling Pathways: Beta-Catenin-independent Wnt/PCP Signaling Pathways	200	21 (11%)
25.72	Nuclear Receptor Transcription Pathway	58	12 (21%)
25.63	Insulin Secretion	165	19 (12%)

Table 4

Profiling of the High Scoring Obesity-Associated GO-Biological Processes Using GeneAnalytics

Score	GO-Biological Process	Total Genes in GO-Biological Process	Matched Obesity-related Genes (%)
72.90	Feeding Behavior	42	22 (52%)
49.54	Cholesterol Metabolic Process	71	20 (28%)
44.15	Glucose Homeostasis	111	22 (20%)
44.05	Cholesterol Homeostasis	66	18 (27%)
43.68	Regulation of Blood Pressure	67	18 (27%)
41.57	Small Molecule Metabolic Process	1551	84 (0.01%)
40.56	Triglyceride Catabolic Process	30	13 (36%)
40.41	Lipoprotein Metabolic Process	38	14 (37%)
38.61	Positive Regulation of Transcription From RNA Polymerase II Promoter	970	61 (0.06%)
37.32	Positive Regulation of Multicellular Organism Growth	36	13 (43%)
37.09	Response to Drug	335	33 (10%)
36.56	Positive Regulation of Transcription, DNA-templated	578	44 (0.08%)
34.38	Temperature Homeostasis	19	10 (53%)
34.06	Energy Reserve Metabolic Process	101	18 (18%)
31.85	Retinoid Metabolic Process	60	14 (23%)
30.90	Response to Hypoxia	180	22 (12%)
30.74	Positive Regulation of Cell Proliferation	489	37 (0.08%)
30.70	Cellular Response to Insulin Stimulus	76	15 (20%)
30.69	Response to Glucocorticoid	89	16 (18%)
30.51	Reverse Cholesterol Transport	18	9 (50%)
30.27	Mammary Gland Development	34	11 (32%)
29.54	Cholesterol Efflux	27	10 (53%)
29.37	Adenylate Cyclase-modulating G-protein Coupled Receptor Signaling Pathway	46	12 (25%)
29.05	Positive Regulation of Glucose Import	28	10 (37%)
28.90	Glucose Metabolic Process	127	18 (14%)
28.78	Fat Cell Differentiation	71	14 (20%)
28.74	Positive Regulation of MAPK Cascade	98	16 (16%)
28.24	Response to Cold	39	11 (28%)
28.10	Regulation of Insulin Secretion	87	15 (17%)
28.06	Positive Regulation of Glycogen Biosynthetic Process	15	8 (53%)
28.06	Negative Regulation of Lipid Catabolic Process	15	8 (53%)
27.43	Generation of Precursor Metabolites and Energy	52	12 (23%)
27.24	Brown Fat Cell Differentiation	32	10 (31%)
26.95	Regulation of Vasoconstriction	24	9 (38%)
26.86	Response to Glucose	79	14 (18%)
26.86	Response to Insulin	66	13 (20%)

Score	GO-Biological Process	Total Genes in GO-Biological Process	Matched Obesity-related Genes (%)
26.44	Locomotory Behavior	95	15 (16%)
26.43	Activation of Adenylate Cyclase Activity	34	10 (29%)
26.25	Phototransduction, Visible Light	96	15 (16%)
26.15	Positive Regulation of CAMP Biosynthetic Process	45	11 (24%)
25.99	Steroid Hormone Mediated Signaling Pathway	57	12 (21%)
25.29	Triglyceride Metabolic Process	37	10 (27%)

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Table 5

Profiling of the High Scoring Obesity-Associated GO-Molecular Processes Using GeneAnalytics

Score	GO-Molecular Process	Total Genes in GO-Molecular Process	Matched Obesity-Related Genes (%)
38.89	Drug Binding	82	18 (22%)
35.75	Peptide Hormone Binding	31	12 (39%)
32.74	Hormone Activity	107	18 (17%)
30.38	Protein Binding	11034	319 (3%)
27.13	Steroid Hormone Receptor Activity	53	12 (23%)
26.83	Insulin Receptor Binding	33	10 (30%)
26.30	Enzyme Binding	339	28 (8%)
25.51	RNA Polymerase II Repressing Transcription Factor Binding	27	9 (33%)
25.22	Receptor Binding	374	29 (8%)
23.20	Sequence-specific DNA Binding	626	38 (6%)
22.51	Dopamine Binding	10	6 (60%)
21.68	Protein Homodimerization Activity	708	40 (6%)
21.36	Phosphatidylcholine-sterol O-acyltransferase Activator Activity	6	5 (83%)
21.36	Epinephrine Binding	6	5 (83%)
21.31	Lipid Binding	162	17 (10%)
21.23	Cholesterol Transporter Activity	19	7 (37%)
20.78	RNA Polymerase II Transcription Factor Activity, Ligand-activated Sequence-specific DNA Binding	40	9 (22%)
20.38	Transcription Factor Binding	297	23 (8%)
20.27	Lipid Transporter Activity	21	7 (33%)
19.43	G-protein Coupled Receptor Binding	58	10 (17%)
19.14	Insulin-like Growth Factor Receptor Binding	15	6 (40%)
19.14	Low-density Lipoprotein Particle Binding	15	6 (40%)

Table 6

Profiling of the High Scoring Obesity-Associated Phenotypes Using GeneAnalytics

Score	Phenotype	Total Genes in Phenotype	Matched Obesity-Related Genes (%)
127.46	Abnormal Glucose Homeostasis	182	52 (28%)
117.44	Decreased Body Weight	1146	108 (9%)
107.16	Increased Circulating Insulin Level	146	43 (29%)
101.46	Increased Body Weight	205	47 (23%)
94.99	Increased Food Intake	77	32 (42%)
93.38	Increased Circulating Triglyceride Level	123	37 (30%)
88.53	Decreased Circulating Glucose Level	179	41 (23%)
83.65	Decreased Circulating Insulin Level	184	40 (22%)
83.21	Increased Total Body Fat Amount	92	31 (34%)
81.86	Obese	70	28 (40%)
81.06	Decreased Circulating Leptin Level	88	30 (34%)
78.95	Polyphagia	53	25 (47%)
77.99	Insulin Resistance	114	32 (28%)
77.53	Increased Circulating Leptin Level	87	29 (33%)
75.77	Hypoactivity	314	47 (15%)
72.41	Abnormal Lipid Homeostasis	130	32 (25%)
71.69	Impaired Glucose Tolerance	205	38 (19%)
71.68	Hepatic Steatosis	167	35 (21%)
67.66	Decreased Circulating Triglyceride Level	134	31 (23%)
64.92	Hyperglycemia	80	25 (31%)
60.63	Improved Glucose Tolerance	147	30 (20%)
58.43	Increased Circulating Cholesterol Level	143	29 (20%)
57.86	Partial Postnatal Lethality	547	53 (10%)
57.57	Increased Circulating Glucose Level	134	28 (21%)
57.14	Increased Circulating HDL Cholesterol Level	62	21 (34%)
55.37	Decreased Circulating Cholesterol Level	130	27 (21%)
53.00	Premature Death	830	64 (8%)
53.00	Abnormal Epididymal Fat Pad Morphology	25	15 (60%)
53.00	Abnormal Circulating Cholesterol Level	25	15 (60%)
48.19	Increased Insulin Sensitivity	133	25 (19%)
46.75	Increased Fluid Intake	50	17 (34%)
46.73	Decreased White Adipose Tissue Amount	79	20 (25%)
45.85	Decreased Liver Triglyceride Level	52	17 (33%)
45.55	Increased Circulating Free Fatty Acid Level	62	18 (29%)