BIOINFORMATICS ANALYSIS OF SOME FUNCTIONAL GENES AND PROTEINS INVOLVED IN OBESITY-INDUCED TYPE 2 DIABETES

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ABSTRACT

The incidence of type-2 diabetes is rising rapidly worldwide, mainly because of the increase in the incidence of obesity, which is an important risk factor for this condition. Both obesity and type-2 diabetes are complex genetic traits but they also share some nongenetic risk factors. Differences among individuals in their susceptibility to both these conditions probably reflect their genetic constitutions. The dramatic improvements in genomic and bioinformatic resources are accelerating the pace of gene discovery. It is tempting to speculate the key susceptible genes/proteins that bridges diabetes mellitus and obesity. In this regard, we evaluated the role of several genes/proteins that are believed to be involved in the evolution of obesity associated diabetes through thorough literature search. Also we analyzed the data pertaining to genes of these proteins extracted from the databases that are available online for free access. The functional cDNA sequences of these genes/proteins are extracted from National Center for Biotechnology Information (NCBI) and Ensembl Genome Browser. Our bioinformatic analysis reports 21 genes as ominous link with obesity associated diabetes. Also this study indicated that, adipose tissue is now known to express and secrete a variety of metabolities, hormones and cytokines that have been implicated in the development of insulin resistance. This bioinformatic study will be useful for future studies towards therapeutic inventions of obesity associated type-2 diabetes.

Keywords: Bioinformatics, Functional Genes, Obesity and Type Two Diabetes

1. INTRODUCTION

Type 2 diabetes and its complications may be prevented by either avoiding factors that trigger the disease process (primary prevention) or using therapies that modulate the disease process before the onset of clinical symptoms (secondary prevention). Accurate prediction and identification using biomarkers will be useful for disease prevention and initiation of proactive therapies to those individuals who are most likely to develop the disease. Recent technological advances in genomics, genomics, proteomics and bioinformatics offer great opportunities for biomarker discovery (Gedela et al., 2007).

Obesity and its pathological complications, including atherosclerosis, hypertension and insulin resistance, have increased to reach epidemic dimensions nowadays (Bray, 2004). Some important factors for the development of these disorders are excessive accumulation of abdominal fat, which is known to play an important role in development of chronic inflammation; deposition of lipids into non-adipose tissues such as liver and muscles; atherosclerosis and chronic inflammation that increase risk in cardiovascular disorders and diabetes (Rajala and Scherer, 2003).

Adipose tissue is not just a site of energy storage but also behaves as a dynamic endocrine organ (Kershaw and Flier, 2004). It also plays an important role in energy expenditure, both as depot for energy-rich triglycerides and as a source for metabolic hormones as well (Bastard et al.,...
Adiponectin, Interleukin (IL)-1β, IL-6 and Tumor Necrosis Factor-alpha (TNF-α). Some of these molecules affect energy metabolism and insulin sensitivity in other tissues such as muscle and liver (Guilherme et al., 2008). During obesity, lipid storage in adipocytes is increased, which triggers the release of adipokines (Hotamisligil, 2006; Lupinacci et al., 2009). During inflammation, the mature adipocytes of the adipose tissue are responsible for increasing production of pro-inflammatory adipokines (Simons et al., 2005), including mentioned TNF-α, IL-1β, IL-6. That disregulation contributes to obesity and chronic inflammation (Ouchi et al., 2003). The local increase of these adipokines have been directly related to insulin resistance, increasing lypolisis and increasing leptin levels (Desruisseaux et al., 2007).

The growing incidence of type 2 diabetes with increasing obesity reflects that obesity is an emerging risk factor for the progression of insulin resistance and subsequently to overt type-2 diabetes. Both in normoglycemic and hyperglycemic states, obese people exhibit a higher degree of hyperinsulinemia that correlates with the degree of insulin resistance, in order to maintain normal glucose tolerance (Bonadonna et al., 1990). Following attainment of certain point, the progressive deterioration of the metabolic milieu leads to eventual failure of hyperinsulinemia to compensate fully for the insulin resistance and thereby produces impaired glucose tolerance that progress to overt diabetes (DeFronzo et al., 1992). It has been presumed from genetic studies that there could be subset of genes whose expression changes with obesity and those genes whose expression further changes in the progression to type-2 diabetes (Elbers et al., 2007; Wang and Eckel, 2009; Ocana et al., 2010). However, the molecular basis that links obesity and diabetes is still largely unknown.

Bioinformatics has been in the focus since recent years for unraveling the structure and function of complex biological mechanisms. The analysis of primary gene products has further been considered as diagnostic and screening tool for disease recognition. Such strategies aim at investigating all gene products simultaneously in order to get a better overview about disease mechanisms and to find suitable therapeutic targets. Recently Gerken et al. (2007) performed bioinformatics analysis and reported that the variants in the fat mass and obesity associated gene are associated with increased body mass index in humans. Although Elbers et al. (2007) identified five overlapping chromosomal regions for obesity and diabetes. These results illustrate the importance of proteomics and bioinformatics approaches for identify new therapeutic invention of obesity is a challenging subject.

This study will therefore focus on potential implications of bioinformatics as a tool to identify novel metabolic patterns or markers associated with disease status. We will exemplify the potential of this method using the association between specific fats and development of obesity associated diabetes as a test case. In the present study we have employed online bioinformatics tools for the analysis of 21 genes, which are expected to play major role in obesity and diabetes, we sought to identify the common central gene/protein that connects both the metabolic disorders such as obesity and diabetes.

2. MATERIALS AND METHODS

2.1. Methodology

The present research aims at finding the genes/proteins responsible for obesity associated diabetes in two phases. The first phase of the research attempts to identify the candidate genes/proteins which are involved in these disorders through thorough literature search. The second phase of the research analyzes the data pertaining to genes of these proteins obtained from the databases that are available online for free access. The functional cDNA sequences of these genes/proteins are extracted from: (1) National Center for Biotechnology Information (NCBI), (http://www.ncbi.nlm.nih.gov), (2) Rat Genome Database (RGD) (<http://rgd.mcw.edu/rgdweb/search/search.html>), (3) Online Mendelian Inheritance in Man (OMIM), which can be accessed with the Entrez database searcher of the National Library of Medicine, Ensembl Genome Browser (http://www.ensembl.org/index.html), (4) Mouse Genome Informatics (MGI) website is hosted by The Jackson Laboratory, (5) HomoloGene, a tool of the National Center for Biotechnology Information (NCBI), is a system for automated detection of homologs (similarity attributable to descent from a common ancestor) among the annotated genes of several completely sequenced eukaryotic genomes and (6) GeneCards is a database of human genes that provides genomic, proteomic, transcriptomic, genetic and functional information on all known and predicted human genes. GeneCards is being developed and maintained by the Crown Human Genome Center at the Weizmann Institute of Science.

3. RESULTS

3.1. First Phase (Literature Search)

From literature search several adipocyte-secreted factors has been demonstrated to potentially link obesity, insulin resistance and type 2 diabetes mellitus.
Table 1. Showing thorough literature search of the genes/proteins that have been studied in the present study, which are believed to be involved in type-2 diabetics and obesity

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Biological processes</th>
</tr>
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<tbody>
<tr>
<td>Adiponectin</td>
<td>It enhances insulin resistance through activation of AMP protein kinase (AMPK). In addition, it also affects hepatic glucose production by decreasing the mRNA expression of two essential gluconeogenic enzymes, phosphoenol pyruvate, carboxykinase and glucose-6-phosphate (Kadowaki and Yamauchi, 2005; Antunna-Puente et al., 2008).</td>
</tr>
<tr>
<td>Resistin (RETN)</td>
<td>It links obesity to type-2 diabetes. Several studies showed that resistin expression was increased in obese animals and decreased in the presence of thiazolidinediones. A recent study revealed a decrease in fasting glucose, improved glucose tolerance and enhanced insulin sensitivity in resistin gene knockout mice (Antunna-Puente et al., 2008). Moreover, resistin inhibits adipocyte differentiation (Kim et al., 2001). In addition, the absence of resistin could allow activation of AMPK and reduce gene expression encoding for hepatic gluconeogenic enzymes. On the other hand, resistin has a role in inflammatory processes. It was associated with many inflammatory markers including C-reactive protein, TNF-α and IL-6. Thus, resistin may represent a link between inflammation and metabolic signals (Rabe et al., 2008).</td>
</tr>
<tr>
<td>Leptin (Obesity factor)</td>
<td>It adipocytes, suggesting reduced hormone and cytokine that regulates energy balance through a wide range of functions, fatty acid metabolism and energy homeostasis. Several studies showed that leptin play an important role in the central regulation of body weight. It is now apparent that leptin also has important functions as a metabolic and neuroendocrine hormone. Interestingly, plasma leptin levels correlate positively with body weight and it has been proposed that hyperleptinemia may be important in the development of insulin resistance associated with type 2 and gestational diabetes (Kahn and Flier, 2000).</td>
</tr>
<tr>
<td>TNF-α</td>
<td>It is a proinflammatory cytokine with a wide range of biologic effects including the stimulation of the production of prostaglandins, platelet-activating factor and plasminogen activator inhibitor; chemotaxis; the induction of adhesion molecules expression; the synthesis of other inflammatory mediators, inhibits lipolysis and impairs insulin-induced glucose uptake, thus leading to insulin resistance and weight loss (Antunna-Puente et al., 2008).</td>
</tr>
<tr>
<td>IL-6</td>
<td>Cytokines appear to be major regulators of adipose tissue metabolism. Expression studies show that adipocytokines can synthesize Tumor Necrosis Factor Alpha (TNF-α) and several Interleukin (IL) notably IL-1β and IL-6. IL-1β is well known to suppress adipocyte differentiation and lipoprotein lipase expression and activity by inhibiting the expression of fatty acid transport protein in adipose tissue. In addition, it is an important regulator of adipogenesis, food intake and energy expenditure (Carey et al., 2008; Wang et al., 2010).</td>
</tr>
<tr>
<td>RBP-4</td>
<td>Recent studies indicated that RBP-4 serum level was elevated in insulin-resistant rodents and in obese or type 2 diabetic humans. In fact, there is a positive correlation between RBP-4 plasma levels and insulin resistance severity in obese, glucose intolerant, type 2 diabetics and in non-obese subjects with strong family background (Yang et al., 2005; Antunna-Puente et al., 2008).</td>
</tr>
<tr>
<td>Adipsin</td>
<td>It is a serine protease and part of alternative complement pathway (complement factor D). It is discovered as a factor expressed in a differentiation-dependent manner in adipocyte cell lines and its expression was greatly reduced in animal models of obesity. Thus this polypeptide may act as a lipoatopic signal and may have a role linking insulin resistance with obesity (Trayhum and Beattie, 2001; Fruehbeck et al., 2004).</td>
</tr>
<tr>
<td>LPL</td>
<td>It plays a major role in the metabolism and transport of lipids. It is the enzyme responsible for the hydrolysis of core Triglycerides (TGs) in chylomicrons and very Low-Density Lipoproteins (VLDLs), producing chylomicron remnants and Intermediate-Density Lipoproteins (IDLs), respectively (Wang and Eckel, 2009). Besides its hydrolytic activity, LPL can interact with lipoproteins to anchor them to the vessel wall and facilitate lipoprotein particle uptake (Rinninger et al., 1998; Strauss et al., 2001; Long et al., 2006).</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>It is a novel 28-amino-acid peptide esterified with octanoic acid on Ser 3 that is principally released from Gt cells in the oxyntic mucosa of the stomach (Chung et al., 2007). Ghrelin has been identified as an endogenous ligand for the GH Secretagogue Receptor (GHS-R) (Kojima et al., 1999). Ghrelin stimulates GH release via the hypothalamus and direct pituitary pathways and induces a positive energy balance by stimulating food intake while decreasing fat use through GH-independent mechanisms (Nakazato et al., 2001). Ghrelin also has numerous peripheral actions including direct effects on exocrine and endocrine pancreatic functions, carbohydrate metabolism, the cardiovascular system, gastric secretion, stomach motility and sleep (Kojima and Kangawa, 2005; Ghigo et al., 2005).</td>
</tr>
<tr>
<td>Chemerin</td>
<td>It is crucial for normal adipocyte differentiation and modulate the expression of adipocyte gene involved in glucose and lipid homeostasis by affecting glucose transporter-4, fatty acid synthase and adiponectin via its own receptors. In addition, it enhances insulin stimulated glucose uptake and Insulin Receptor Substrat-1 (IRS-1) tyrosin phosphorylation in 3T3-L1 adipocytes, suggesting that chemerin may increase insulin sensitivity in adipose tissue (Roh et al., 2007; Cash et al., 2008; Takahashi et al., 2008).</td>
</tr>
<tr>
<td>Visfatin</td>
<td>It was recently discovered as a new adipokines. Similarly to insulin, visfatin in vitro enhanced glucose uptake by monocytes and adipocytes and inhibited hepatocytes glucose release (Gualillo et al., 2007). In addition, visfatin amplifies adipocyte differentiation. Also, it has insulin mimetic effects can bind to and activate insulin receptors. This hormone also affects insulin-transduction pathway as it induces tyrosine phosphorylation of insulin receptor substrate-1 and -2 and activate phosphorylnositol-3 kinase B and MAP kinase (Antunna-Puente et al., 2008).</td>
</tr>
<tr>
<td>Omentin</td>
<td>Plasma omentin-1 levels were inversely correlated with obesity and insulin resistance and positively correlated with adiponectin and HDL-levels (De Souza et al., 2007; Rabe et al., 2008). Interestingly, omentin increases insulin-stimulated glucose uptake in both omental and subcutaneous adipocytes and promotes AKT phosphorylation (Yang et al., 2006; Antunna-Puente et al., 2008).</td>
</tr>
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</table>
are activated by the peptide hormone fasting. It has been found that AgRP stimulates the hypothalamic-pituitary-adrenocortical axis to release ACTH, cortisol.

PPAR-γ

The members of the PPAR-family, PPARα, PPARβ/δ and PPARγ play an important role in the regulation of lipid and glucose metabolism (Fliegel et al., 2006). Disturbance of PPAR pathways promotes the progression of diseases, such as obesity, type 2 diabetes, cardiovascular disease, cancer, neurodegenerative diseases, hypertension and chronic inflammation (Michalik et al., 2006; Hamblin et al., 2009; Khateeb et al., 2010). Once activated by a ligand, PPARs recruit transcriptional co-activators, which are necessary to initiate target gene transcription. The target genes are mainly involved in the energy homeostasis and include genes from the β-oxidation, the free fatty acid translocase (CD36), the Medium Chain Acetyl Dehydrogenase (MCAD), the Acetyl-CoA-Oxidase (ACO) and the carbohydrate oxidative pathways involved in the energy homeostasis and include genes from the β-oxidation, the free fatty acid translocase (CD36), the Medium Chain Acetyl Dehydrogenase (MCAD), the Acetyl-CoA-Oxidase (ACO) and the carbohydrate oxidative pathways.

Agouti (AgRP)

It has been demonstrated to be an inverse agonist of melanocortin receptors, specifically, MC3-R and MC4-R. The hypothalamic AgRP neurons that stimulate the secretion of NPY and AgRP to increase appetite. AgRP is stored in intracellular secretory granules and is secreted via a regulated pathway (Creemers et al., 2006). The transcriptional and secretory action of AgRP is regulated by inflammatory signals (Scarlett et al., 2008). Levels of AgRP are increased during periods of fasting. It has been found that AgRP stimulates the hypothalamic-pituitary-adrenocortical axis to release ACTH, cortisol and prolactin. It also enhances the ACTH response to IL-1-beta, suggesting it may play a role in the modulation of the regulation of glucose homeostasis and cardiac energy metabolism (Hamblin et al., 2009). So that, PPAR-γ ligand could potentiate the insulin effect and improve insulin signaling via increasing tyrosine phosphorylation of the insulin receptors.

FOXO1

It is a family of winged helix/forkhead box factors which are crucial for adipocyte differentiation and have prominent roles in insulin signaling pathways (Armoni et al., 2006). In addition, convergence of nuclear receptors and forkhead pathways in general and of FOXO1 and PPAR-γ in particular has been implicated in the pathophysiological states of insulin resistance and diabetes. Several studies showed that, FOXO1 also functions in adipose tissue to couple insulin signaling to adipogenesis, which involves switching pre-adipocytes from proliferation to terminal differentiation. Also, FOXO1 directly or indirectly represses expression of PPAR-γ gene which represses GLUT4 promoter activity.

11β-HSD-1

Data from rodents provide evidence for a causal role of 11β-HSD-1 in the development of obesity and its complications (Masaoka et al., 2001; Boullu-Ciocca et al., 2005). Recent studies indicated that, 11β-HSD-1 expression was increased in visceral adipose tissue in obese patients. However, 11β-HSD-1 inhibition had therapeutic effect in murine models of metabolic syndrome or type 2 diabetes (Hermanowski-Vosatka et al., 2005; Desbriere et al., 2006).

Apelin

Apelin is an active peptide regulate insulin resistance by influencing the circulating adiponectin level and the expression of brown adipose tissue uncoupling proteins and energy expenditure in mice (Gualillo et al., 2007; Higuchi et al., 2007). However, human mRNA was also expressed in subcutaneous adipose tissue (Rabe et al., 2008). Administration of recombinant human apelin to a mouse model of diet-induced obesity improved glucose tolerance and insulin sensitivity, suggesting that apelin may represent an insulin sensitizing adipokines (Antunna-Puente et al., 2008; Rabe et al., 2008).
These adipocytokines comprise mediators (Table 1) such as adiponectin, resistin, leptin (obesity factor), Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-6 (IL-6), Retinol Binding Protein-4 (RBP-4), adipisin, Lipoprotein Lipase (LPL), ghrelin, chemerin, visfatin, omentin, Plasminogen Activator Inhibitor-1 (PAI-1), Fatty Acid Binding Protein-2 (FABP2), Peroxisome Proliferators-Activated Receptor-γ (PPARγ), Aguti (AgRP), nuclear Sterol Regulatory Element-Binding Proteins-1c (nSREBP-1c), winged-helix-forkhead box class O-1 (FOXO-1), 11β-Hydroxysteroid Dehydrogenase type-1 (11β-HSD-1), apelin and vaspin. These adipose derived factors are presently subjected to intensive research concerning their involvement in the regulation of adipose tissue physiology and in particular, their potential implication in insulin resistance, obesity and diabetes. In addition, most of these mediators may directly or indirectly interact with insulin receptors and/or insulin signaling, leading to insulin resistance in liver and peripheral tissues, especially in visceral obesity. The roles and mechanisms of some of the most important adipokines were suggested by some publications illustrated in Table 1.
Table 3. Showing gene ontology data of the genes/proteins that have been studied in the present study, which are believed to be involved in type-2 diabetics and obesity

<table>
<thead>
<tr>
<th>Gene</th>
<th>Secreted tissues</th>
<th>MGD</th>
<th>OMIM</th>
<th>Homologene</th>
<th>Array ID</th>
<th>Molecular function</th>
<th>Biological activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghrelin</td>
<td>produced by P/D1 cells lining the funds of stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hormone activity</td>
<td>- Positive regulation of appetite</td>
</tr>
<tr>
<td>Omentin</td>
<td>visceral adipose tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cytokine activity</td>
<td>- Regulation of intestinal cholesterol absorption</td>
</tr>
<tr>
<td>PPAR-g</td>
<td>vascular smooth muscle cells, endothelial adipocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>transcription factor activity</td>
<td>- Regulation of lipid metabolic process</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Numerous cells, but mainly macrophages and lymphocytes fibroblasts, adipose tissues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cytokine activity</td>
<td>- Induction of apoptosis via death domain receptors</td>
</tr>
<tr>
<td>Leptin</td>
<td>Adipocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hormone activity</td>
<td>- Positive regulation of lipolysis</td>
</tr>
<tr>
<td>Apelin</td>
<td>Adipocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>growth factor activity</td>
<td>- Regulation of cell proliferation</td>
</tr>
<tr>
<td>IL-6</td>
<td>macrophages, adipocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cytokine activity</td>
<td>- Positive regulation of cell proliferation</td>
</tr>
<tr>
<td>RBP-4</td>
<td>Adipocyte tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transporter activity</td>
<td>- Regulation of intestinal cholesterol absorption</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>cytokine activity</td>
<td>- Regulation of intestinal cholesterol absorption</td>
</tr>
<tr>
<td>LPL</td>
<td>Adipose tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lipid transporter activity</td>
<td>- Regulate fatty acid metabolic process</td>
</tr>
<tr>
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<td>produced by P/D1 cells lining the funds of stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hormone activity</td>
<td>- Positive regulation of lipolysis</td>
</tr>
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<td>- Regulation of lipid metabolic process</td>
</tr>
</tbody>
</table>

3.2. Second Phase (Databases Analysis)

The second phase of the research analyzes the gene orthologs and the gene ontology (Table 2 and 3 respectively) of the 21 detected genes. The data pertaining to these genes/proteins obtained from the databases that are available online for free access.

4. DISCUSSION

The emerging epidemic of diabetes in Egypt and around the world cannot be ignored. According to the World Health Organization, over 180 billion people now have diabetes worldwide and this number is expected to double by the year 2030 (WHO, 2008). Similarly alarming is the high prevalence of two factors closely linked with increased risk for diabetes: Metabolic Syndrome (MeS) and obesity (Pradhan, 2007). Several recent studies investigated that, a number of common factors including genetic predisposition, poor dietary patterns, increased physical inactivity and longer life expectancy contribute to the rising prevalence of these disorders; subclinical inflammation may represent an additional novel risk factor. In this regard, epidemiologic data suggest that inflammatory biomarkers
may serve as important risk indicators for the future development of diabetes (Moller et al., 2003; Ford et al., 2004; Chew et al., 2006; Ogden et al., 2006; Shoelson et al., 2006; Ocana et al., 2010).

Also, there is growing evidence that the insulin-resistance syndrome associated to obesity is mainly caused by excessive accumulation of fat in intra-abdominal adipocytes (Macor et al., 1997; Kahn and Flier, 2000). It has been observed that the surgical removal of visceral fat improves insulin effect on hepatic glucose production in animal models of obesity (Barzilai et al., 1999). Adipose cells from visceral or subcutaneous depots largely differ concerning their metabolic characteristics as the control of lipolysis and the sensitivity to insulin (Wajchenberg, 2000). Therefore, it would be interesting to define the regional adipose differences in the expression of the recently discovered proteins, which are candidate links between fat accumulation and insulin resistance.

Complex traits such as obesity and type-2 diabetes pose special challenges for genetic analyses because of gene–gene and gene-environment interactions, genetic heterogeneity and low penetrance of the individual genes. The heterogeneity means that it is difficult to generalize genome scan results over different populations and ethnicities. In addition, the exponential and alarming growth of the obesity epidemic has led scientists to begin to take advantage of proteomics to identify obesity molecular targets and to study the mechanisms of action of potential obesity therapies. Proteomics analyses have been proven useful in the characterization of the adipocyte proteome (Adachi et al., 2007), in the identification of obesity targets in different models of experimental obesity and to characterize targets of several agents such as the insulin sensitizser rosiglitazone (Sanchez et al., 2003). Although they are highly informative, these strategies often generate large amounts of data and long lists of proteins that are difficult to analyze and understand their biological importance.

The approach in this article is similar to the one in Rao et al. (2008) and Park et al. (2009), but it is more robust to the data here, which are more heterogeneous and encompassing the bioinformatic gene analysis of human, mouse and rat models in addition to other variables. The present bioinformatic analysis showed significant relationships between metabolic and obesity type-2 diabetes risk factors and abdominal subcutaneous adipose tissue gene expression.

Recently, You et al. (2005) investigated that, the quantity of visceral fat was negatively related to leptin and adiponectin abdominal adipose tissue gene expression. In addition, hyperinsulinemia, as indicated by fasting insulin and 2-h insulin during the Oral Glucose Tolerance Test (OGTT), was positively associated with adipose TNF-a and IL-6 gene expression. Also, Elbers et al. (2007) yielded an interesting list of candidate genes by investigating the overlapping chromosomal linkage regions for type-2 diabetes and obesity, using a combination of six computational disease gene identification methods. Many of these identified genes are excellent candidates to study further for their role in the shared disease aetiology between obesity and type-2 diabetes and a few have already been genetically or functionally associated with both disorders.

Current evidence supports that metabolic risk factors, including dyslipidemia, glucose intolerance and hyperinsulinemia, are linked with circulating levels of inflammatory and thrombotic cytokines (Chan et al., 2002; Bonora et al., 2003; Lyon and Hsueh, 2003). Relationships between cytokine gene expression in adipose tissue and metabolic risk and insulin resistance have been reported as well (Garaulet et al., 2004; Koistinen et al., 2000). Abdominal adipose gene expression levels of TNF-a (Koistinen et al., 2000), IL-6 (Rotter et al., 2003) and PAI-1 (Koistinen et al., 2000) are positively linked with insulin resistance and other cardiovascular risk factors, whereas adiponectin gene expression is negatively associated with metabolic variables (Garaulet et al., 2004). Our results were consistent with these previous findings and demonstrated that hyperinsulinemia was positively linked to adipose TNF-a and IL-6 gene expression and hyperinsulinemia and glucose intolerance were negatively linked to adipose adiponectin expression. Although these adipose-derived cytokines are traditionally viewed as the causes of the insulin resistance and metabolic risk (Rotter et al., 2003), recent evidence suggests that an elevated TNF-a and IL-6 expression (Krogh-Madsen et al., 2004) and a decreased adiponectin expression (Fasshauer et al., 2004) may also be a consequence of hyperinsulinemia. However, insulin infusion did not affect adiponectin gene expression in either healthy or type 2 diabetic individuals (Koistinen et al., 2004). Therefore, this study provides information from previous literatures and genome databases of different websites and act as a material for future studies to clarify the underlying mechanisms of these associations and finding of new therapies of obesity associated type2 diabetes mellitus.

5. CONCLUSION

In conclusion, any rigid assessment of disease patterns will need support from well documented and curated databases. However, there are also several practical and...
theoretical constraints known if applying bioinformatics as a tool for improved understanding and diagnostics of disease patterns. So that, the current study provides evidence that the quantity of visceral fat and glucose/insulin complications of obesity is related to abdominal subcutaneous adipose tissue cytokine gene expression. Moreover, additional research is needed to discern whether abdominal subcutaneous adipocyte gene expression is causative for these risk factors or whether there is compensatory regulation of adipose tissue gene expression as a result of elevated visceral fat and/or insulin resistance.

6. ACKNOWLEDGMENT

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