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Network analysis identifies common genes associated with obesity in six obesity-related diseases*#

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Obesity has been reported to be associated with many diseases. However, common obesity-induced biological processes have not been evaluated across these diseases. We identified genes associated with obesity and obesity-related diseases, and used them to construct protein–protein interaction networks. We also analyzed gene ontology (GO) in those genes overlapping between obesity and disease. Our work identifies gene modules common to obesity and obesity-related diseases, which can provide a basis for understanding the process of how obesity induces disease.

Obesity is a global epidemic recognized as a public health problem that influences multiple systems. Obesity has been reported to be associated with many diseases. Studies of molecular mechanisms show that obesity is tightly linked with diseases such as cardiovascular events (Rogge *et al*., 2013; Eckel *et al*., 2016), diabetes (Hwang *et al*., 2016; Vilarrasa *et al*., 2017), gynecological disease (Gateva and Kamenov, 2012; Gateva *et al*., 2013), and cancer (Gao *et al*., 2016; Nagrani *et al*., 2016).

Although a strong association between obesity and these diseases is apparent, it is not clear whether obesity-induced biological processes are common across these diseases. Therefore, this research selected six obesity-related diseases: coronary artery disease (CAD), diabetes, hypertension, breast cancer, polycystic ovarian syndrome (PCOS), and kidney cancer, and then used genes from six obesity-related disease databases and one obesity database to construct networks to explore the relationship between these diseases. CAD is the most common type of cardiovascular disease, which has many common risk factors including obesity, hypertension, diabetes, family history, lack of exercise, stress, and high blood lipids (Mehta *et al*., 2015). Obesity is associated with about 20% of CAD cases (Kivimäki *et al*., 2012). Diabetes, a group of metabolic diseases, can double the risk of cardiovascular disease (Sarwar *et al*., 2010). Long-term hypertension increases the risk of CAD, stroke, heart failure, and chronic kidney disease (Lackland and Weber, 2015). Many reports have shown that hypertension can be influenced by both genetic and environmental factors including high salt intake, lack of exercise, obesity, and depression (Poulter *et al*., 2015). Breast cancer occurs in breast tissue. The risk factors for breast cancer include smoking, lack of physical exercise, a high-fat diet, drinking alcohol, and obesity-related high cholesterol levels (Boffetta *et al*., 2006; Blackburn and Wang, 2007; Johnson *et al*., 2011; Kaiser, 2013). PCOS is a hormonal problem that occurs in 5% to 10% of women and includes signs and symptoms such as menstrual disorders, infertility, high levels of masculinizing hormones and metabolic syndrome (Nafiye *et al*., 2010). PCOS is associated with obesity and

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there is some evidence that weight loss can restore normal ovulation (Moran *et al*., 2013). Kidney cancer has also been linked to adult obesity and hypertension (Wilson and Cho, 2016) and the incidence rate of this type of cancer is higher in men than in women (Hancock and Georgiades, 2016).

Our research identifies gene modules common to obesity and obesity-related diseases that can provide a basis for understanding the processes by which obesity induces disease. Our research found that the six obesity-related disease gene sets included 2499 genes (summarized in Table 1), of which some overlapped between sets. The obesity gene set included 835 genes (Table 1). A total of 3275 disease or obesity genes were found in the STRING 10.0 database (Table 1). Table 2 lists the genes that were present in not less than three gene sets. Five genes in the obesity gene set were shown to overlap: estrogen receptor 1 (*ESR1*), phosphatase and tensin homolog (*PTEN*), serine/threonine kinase 1 (*AKT1*), phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*), and E1A binding protein p300 (*EP300*). Although no genes were present in all six disease sets, ten genes, including five obesity genes, were present in not less than three obesity-related disease gene sets.

In this study we constructed six obesity-related disease gene networks. Table 3 shows the average degrees of the six disease gene sets. With thresholds of betweenness centrality (BC) >0.05 and degrees above the average value of each network (P<0.05), a total of 31 genes were identified as hub genes for six diseases, of which 17 were included in the obesity gene set, such as *ESR1*, coagulation factor II (*F2*), nuclear factor κB subunit 1 (*NFKB1*), prostaglandin-endoperoxide synthase 2 (*PTGS2*), interleukin 6 (*IL6*), peroxisome proliferator activated receptor α (*PPARA*), tumor protein p53 (*TP53*), Jun proto-oncogene (*JUN*), *AKT1*, insulin (*INS*), *EP300*, breast cancer 1 (*BRCA1*), vascular endothelial growth factor A (*VEGFA*), insulin like growth factor 1 (*IGF1*), transforming growth factor β 1 (*TGFB1*), proopiomelanocortin (*POMC*), and *PTEN*. Genes *ESR1*, SRC proto-oncogene (*SRC*), *IL6*, *TP53*, *JUN*, *INS*, and *AKT1* were hub genes for more than one disease. Because most hub genes are included in the obesity gene set, obesity may affect the occurrence and development of these obesity-related diseases.

Table 1 Genes in the gene sets and networks

Set name	Gene number	Seed gene number (in STRING 10.0)
Coronary artery disease (CAD)	604	599
Diabetes	703	682
Hypertension	837	828
Breast cancer	80	78
Polycystic ovary syndrome (PCOS)	208	195
Kidney cancer	67	67
Obesity	835	826

Table 2 Genes present in not less than three obesity-related diseases

Gene symbol	Disease count
ESR1	5
PTEN	4
AKT1	3
PIK3R1	3
CDKN2A	3
EP300	3
CHEK2	3
RYR2	3
CASP8	3
EPHX1	3

ESR1: estrogen receptor 1; *PTEN*: phosphatase and tensin homolog; *AKT1*: serine/threonine kinase 1; *PIK3R1*: phosphoinositide-3-kinase regulatory subunit 1; *CDKN2A*: cyclin-dependent kinase inhibitor 2A; *EP300*: E1A binding protein p300; *CHEK2*: checkpoint kinase 2; *RYR2*: ryanodine receptor 2; *CASP8*: caspase 8; *EPHX1*: epoxide hydrolase 1

Table 3 Hub genes in six obesity-related disease/system networks

Network name	Seed node average degree	Hub gene
Coronary artery disease (CAD)	11.03	*ESR1*, *F2*, *NFKB1*, *SRC*, *PTGS2*, *IL6*, *PPARA*, *TP53*
Diabetes	13.17	*TP53*, *JUN*, *AKT1*, *INS*
Hypertension	17.71	*SRC*, *JUN*, *AKT1*
Breast cancer	4.28	*RUNX1*, *PIK3CA*, *EP300*, *BRCA1*, *SMARCD1*, *SMAD4*, *AKT1*, *TP53*
Polycystic ovary syndrome (PCOS)	8.65	*CYP17A1*, *AR*, *BMP2*, *VEGFA*, *IGF1*, *IL6*, *TGFB1*, *ESR1*, *AKT1*, *POMC*, *JUN*, *INS*
Kidney cancer	1.01	*TSC2*, *MTOR*, *PTEN*, *TP53*, *SMARCB1*, *ERCC2*, *KDM6A*

To explore the relationship between obesity and obesity-related diseases, the nodes of the six diseases and obesity were compared. The diabetes gene set includes 325 members of the obesity gene set, the hypertension gene set includes 283, the CAD gene set includes 234, the breast cancer gene set includes 15, the PCOS gene set includes 5, and the kidney cancer gene set includes 4 (Table S1).

GO enrichment analyzed using DAVID software revealed that genes overlapping both obesity and diabetes were significantly enriched in the biological processes of response to organic substances (GO: 0010033), response to hormonal stimuli (GO:0009725), response to endogenous stimuli (GO:0009719), homeostatic processes (GO:0042592), and chemical homeostasis (GO:0048878) (Table S2). The cellular component and molecular function cluster of the genes that overlap both obesity and diabetes are shown in Table S2. The biological process cluster, cellular component cluster, and molecular function cluster of the genes that overlap both obesity and hypertension are shown in Table S3. The biological process cluster, cellular component cluster, and molecular function cluster of the genes that overlap both obesity and CAD are shown in Table S4. The biological process cluster and cellular component cluster of the genes that overlap both obesity and breast cancer are shown in Table S5.

Obesity-related diseases are influenced by genes and the environment, so these pathway clusters could indicate specific potential targets for disease research. As shown in Tables S2–S4, cellular component clusters showed that the genes overlapping the diabetes, hypertension or CAD diseases and the obesity gene set are located in extracellular spaces and regions, whereas those overlapping both breast cancer and the obesity gene set are located in the nucleoplasm and cytosol. The biological processes (Tables S2–S5) provide candidate targets for research into disease mechanisms, such as processes related to responses to organic substances, hormonal stimuli, and endogenous stimuli. Moreover, clusters enriched in molecular functions, such as hormone activity, identical protein binding, and cytokine activity, provide potential drug targets (Tables S2–S5). These results imply that some obesity genes affect different diseases in the common GO pathway.

In the present study, we investigated the relationship between genes associated with obesity and obesity-related diseases. We identified hub genes included in diseases. These hubs may play important regulatory roles in these obesity-related diseases. For example, ESR1, an essential member of the nuclear hormone receptor super family, plays significant roles in vascular wall physiology and function (Gao *et al*., 2014). ESR1 is also involved in pathological processes including breast cancer, endometrial cancer, and diabetes (Jiang *et al*., 2015). Single-nucleotide polymorphisms in the *ESR1* gene were related to hypertension, CAD, and diabetes (Jiang *et al*., 2015). Previous studies showed that *ESR1* polymorphisms *Pvu*II (rs2234693T>C) and *Xba*I (rs9340799A>G) predicted the risk of CVD (Jiang *et al*., 2015). In hypogonadal men, the rs2207396 variant in *ESR1* gene was strongly correlated with diabetes susceptibility (Linnér *et al*., 2013). Numerous studies have shown that *Pvu*II polymorphism in *ESR1* gene was a risk factor for breast cancer (Zhang *et al*., 2015). AKT1 has been functionally regulated by many pathologies such as cancer and diabetes. AKT1 regulates insulin-induced glucose uptake by two phosphorylation events at threonine 308 (T308) and serine 473 (S473) (Kumar *et al*., 2007). Recent reports have also showed that overexpression of microRNA-409-3p induced downregulation of AKT1 protein to inhibit breast cancer cell proliferation (Zhang *et al*., 2016).

In conclusion, this research identified genes associated with obesity and obesity-related diseases, and then used them to construct protein–protein interaction networks. This research identified hub genes including most obesity genes. A total of 31 hub genes were identified from six networks as potential key genes, of which 17 were included in the obesity gene set. Genes identified as common between gene sets included 325 between obesity and diabetes, 283 between obesity and hypertension, 234 between obesity and CAD, 15 between obesity and breast cancer, 5 between obesity and PCOS, and 4 between obesity and kidney cancer. This research also analyzed GO in those genes overlapping both obesity and disease. The common genes were enriched in some of the same GO functional clusters, which indicates that different obesity-related diseases share some common GO pathway clusters that may be influenced by the environment of obesity. The analysis of these pathways could identify the mechanisms by which obesity induces disease, but additional studies are required to confirm these results in humans.

Materials and methods

Gene sets of obesity-related disease

Genes from databases of obesity-related diseases were obtained and used for network analyses. Genes from the CAD gene database (Liu *et al*., 2011) were selected to form gene sets for CAD. Genes from the T-HOD database (Dai *et al*., 2013) were selected to form gene sets for diabetes and hypertension. Genes from the NCG5.0 database (An *et al*., 2016) were selected to form gene sets for breast cancer, PCOS, and kidney cancer. Human obesity genes in the T-HOD (Dai *et al*., 2013) database were selected to form a gene set for fatty metabolism. Overlaps were compared among the gene sets of obesity-related diseases.

Protein–protein interaction networks

The STRING 10.0 (Snel *et al*., 2000) database lists known and predicted protein–protein interactions based on their confidence scores. Genes in obesity-related disease gene sets or obesity datasets were used to construct interaction networks using STRING 10.0 with the highest confidence (score >0.9) and the genes found in the interaction networks were considered to be seed nodes. All networks were visualized by Cytoscape v3.4.0 (Kohl *et al*., 2011) software and calculated using the Network Analyzer tool (Assenov *et al*., 2008) based on parameters of BC and node degree. BC indicates the number of the shortest paths that pass one node. Degree reflects the number of interactions of one node. Nodes with thresholds of BC >0.05 and degrees above the average value of each network were considered to be hub genes.

Common gene ontology functional clusters

To examine whether biological processes are common between different obesity-related diseases and obesity, the DAVID (Sherman *et al*., 2007) gene annotation tool was used to analyze GO enrichment in the genes that overlap both obesity and obesity-related diseases. Values of $P<0.05$ and false discovery rate <0.05 were used as cutoff criteria.

Compliance with ethics guidelines

Li-ning SU, Yan-bing WANG, Chun-guang WNAG, and Hui-ping WEI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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List of electronic supplementary materials

Table S1 Overlapped genes between obesity and obesity-related diseases

Table S2 GO pathway clusters associated with common genes among obesity gene set and diabetes

Table S3 GO pathway clusters associated with common genes among obesity gene set and hypertension

Table S4 GO pathway clusters associated with common genes among obesity gene set and CAD

Table S5 GO pathway clusters associated with common genes among obesity gene set and breast cancer

中文概要

题　目：网络分析筛选六种与肥胖相关疾病的共同的肥胖基因

目　的：通过筛选在六种与肥胖相关疾病中发挥作用的共同的肥胖基因，阐明肥胖在疾病发生及发展中的作用，为预防及治疗肥胖相关的一系列疾病提供参考。

创新点：首次分析了与肥胖相关疾病的共同的肥胖基因，为解释肥胖与疾病的关系提供理论支持。

方　法：从疾病及肥胖数据库中获得与疾病和肥胖相关的基因，利用生物信息学软件进行蛋白互作网络分析和中心基因分析，筛选中心基因；对疾病与肥胖数据库中的重叠基因进行 GO（Gene Ontology, 基因本体）功能富集，获得在疾病中发挥作用的共同的基因本体功能集群。

结　论：通过分析初步推测六种与肥胖相关疾病中的 31 个中心基因中包括 17 个肥胖基因，每种疾病与肥胖的重叠基因具有一些相同的基因本体功能集群。

关键词：肥胖；肥胖相关疾病；冠状动脉疾病；高血压；糖尿病；乳腺癌；肾癌；多囊综合症