Reconstruction and analysis of the protein-protein interaction network involving GWAS genes associated with elevated body mass index

Elena V. Ignatieva

The Federal Research Center Institute of Cytology and Genetics of Siberian Branch of the Russian Academy of Sciences, Novosibirsk 630090, Russia; Novosibirsk State University, Novosibirsk 630090, Russia, eignat@bionet.nsc.ru

Elevated body mass index (BMI) is a substantial risk factor for human disease emergence. Feeding behavior and body weight (BW) are controlled by a complex network, which involves genes expressed in many organs and tissues. Genome-wide association studies (GWASs) have identified multiple genetic variants that are associated with elevated BMI or the risk of obesity. It is important to determine how genetic variants influence body weight, but most of them are non-coding, and there is little understanding of how these variants contribute to BW control. Moreover, in most cases GWAS papers register candidate genes, but biological functions of many of them revealed so far (especially for nearest genes or genes containing eQTL) remain unknown or poorly understood. Therefore, the explanation of biological functions of genes noted in GWAS in the context of BW regulation is a separate and essential task. In our recent research we created a compendium of human genes (578 genes) controlling feeding behavior and body weight [1]. Candidate genes were collected from various sources, including previously published original research and review articles, GWAS meta-analyses, and OMIM. We ranked genes from the GWAS meta-analysis set according to the number and quality of associations in the networks and then according to their involvement in the brain-specific PPI network. We proposed new regulatory schemes involving three GWAS genes (*ETV5*, *LRP1B*, and *NDUFS3*) in BW regulation.

In this work, we investigate the genetic basis of body weight regulation basing on theoretical analysis of the extended network involving additional portion of GWAS genes that were associated with elevated BMI at less stringent significance level of 10^{-5}. The objectives of this study were: (1) to compile an extended catalog of human genes controlling feeding behavior and body weight, incorporating additional new genes revealed at significance level of 10^{-5}; (2) to construct and analyze networks formed by associations between genes/proteins from the

catalog; (3) to prioritize additional GWAS genes according to the number of their neighbors in the network.

We created an extended catalog of human genes controlling feeding behavior and body weight using two data sources. The first data source was a compendium of 578 human genes (Sublist A) presented in our recent research [1]. Among other genes, this compendium included GWAS genes located in regions around lead SNPs associated with elevated BMI at significance level of 10^{-8}. The second data source was [2] providing data on additional 184 GWAS genes (Sublist B). These 184 genes were found in the vicinity of the SNPs revealed to be associated with elevated BMI at a less stringent significance level of 10^{-5}. Thus, an extended catalog included 762 genes.

At the next step we constructed network presenting pairwise physical interactions between proteins encoded by genes from the catalog. Data on pairwise physical interactions between proteins/genes from catalog were obtained from STRING [3] and uploaded into Cytoscape [4]. Only high-confidence edges with STRING scores greater than 0.4 were included. As a result, we obtained network involving 317 nodes and 578 edges. This network included 59 genes/proteins from the Sublist B.

To characterize the functional importance of genes from the Sublist B in the context of body weight regulation we ranked them according to the number of neighbors in the network. The top proteins were YWHAZ and MTOR (19 and 11 neighbors respectively).

Human YWHAZ gene encoding tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta was found to contain intronic SNP rs3134353 associated with elevated BMI at P value = 7.2×10^{-6}. YWHAZ is also known as 14-3-3 protein zeta/delta. According to UniProtKB annotation (Entry name: 1433Z_HUMAN), it is an adapter protein implicated in the regulation of a large spectrum of both general and specialized signaling pathways. 14-3-3 protein zeta/delta binds to a large number of partners, usually by recognition of a phosphoserine or phosphothreonine motif. Binding generally results in the modulation of the activity of the binding partner. It is also found that 14-3-3 protein zeta/delta interacts with IRS1 protein, suggesting a role in regulating insulin sensitivity [5].

Human MTOR gene encoding mechanistic target of rapamycin was found to contain intronic

SNP rs10779751 associated with elevated BMI at P value =$8.5x10^{-6}$. According to UniProtKB annotation (Entry name: MTOR_HUMAN), MTOR is a serine/threonine protein kinase which is a central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals. MTOR directly or indirectly regulates the phosphorylation of at least 800 proteins, including RPS6KB1 and RPS6KB2 that, according to KEGG Pathway (map04931), are important players of insulin resistance pathway.

Conclusion: An extended catalog comprising 762 human genes for which there are indications of their direct or indirect relevance to regulation of body weight was constructed. Basing on human protein-protein interaction network involving genes/proteins from the catalog we ranked GWAS genes according to the number of neighbors and revealed two top genes (*YWHAZ* and *MTOR*) among genes that were identified at a less stringent significance level of 10^{-5}. According to functional annotation, provided by UniProtKB, both genes encode proteins involved in insulin signaling, a key energy balance signaling pathway [6]. We propose to keep in mind these genes as potential candidates for investigating the genetic factors predisposing elevated BMI and as potential drug targets in obesity treatment.

This work was supported by the Federal Agency of Scientific Organizations, project 0324-2015-0003.

References

1. E.V.Ignatieva et al. (2016) A compendium of human genes regulating feeding behavior and body weight, its functional characterization and identification of GWAS genes involved in brain-specific PPI network, *BMC Genet*, **17(Suppl 3)**:158

2. A.E. Locke et al. (2015) Genetic studies of body mass index yield new insights for obesity biology, *Nature*, **518**:197-206

3. D.Szklarczyk, et al. (2011) The STRING database in 2011: Functional interaction networks of proteins, globally integrated and scored, *Nucleic Acids Res*, **39**:D561–D568.

4. M.E.Smoot et al. (2011) Cytoscape 2.8: new features for data integration and network visualization, *Bioinformatics* **27**:431-2.

5. T.Ogihara et al. (1997) 14-3-3 protein binds to insulin receptor substrate-1, one of the binding sites of which is in the phosphotyrosine binding domain, *J Biol Chem*, **272**:25267-74.

6. M.C.Vogt, J.C.Brüning (2013) CNS insulin signaling in the control of energy homeostasis and glucose metabolism - from embryo to old age, *Trends Endocrinol Metab*, **24**:76-84