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# Functional and evolutionary characteristics of the gene network controlling appetite in mice: lessons from knockout or knockdown animals

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*Motivation and Aim*: Appetite is a drive to consume food. It is one of the most primitive instincts promoting survival and exists in all higher life-forms. Appetite serves to regulate adequate energy intake to maintain metabolic needs, although it may be stimulated by appealing foods even when hunger is absent. Dysregulation of appetite can lead to human diseases (bulimia nervosa and overeating (both leading to obesity), anorexia nervosa, cachexia, etc.) [1]. In efforts to understand the molecular-genetic basis of appetite abnormalities and to collect data on potential targets for new therapies, we (1) have compiled a list of genes regulating food intake identified in experiments on knockout or knockdown animals; (2) have constructed gene network involving physical interactions between these genes or encoded proteins; (3) analyzed functional and evolutionary characteristics of genes in the network

*Methods and Algorithms*: Data on genes regulating appetite were collected with the use of text-mining-based approach, performing queries to PubMed using such terms as "knockout" or "knockdown" and terms designating appetite manifestations or disorders. If the genes have been identified in rats, zebrafish, etc., then an appropriate mouse ortholog has been identified too. To reconstruct the gene network comprising genes/proteins involved in physical interaction with each other we have used computer systems STRING [2], GeneMania [3] and ANDVisio [4]. Evolutionary characteristics of genes (phylostratigraphic age index (PAI) and divergence index (DI)) have been calculated as it is described in [5] taking into account sequences of orthologous genes that are 50 % or more identical to one under consideration.

*Results*: Data on 96 genes regulating appetite has been collected. Knockout or knockdown of these genes lead to hypophagia or hyperphagia in experimental animals (mainly in mice). The largest part of genes encoded cell surface receptors and signal molecules (hormones, neuropeptides), and about a quarter of all genes are genes encoding such regulatory proteins as transcription factors (TFs) and enzymes regulating protein activities. It has been found that the total number of anorexigenic genes significantly exceeds the total number of orexigenic genes. Vice versa, the number of genes encoding orexigenic TFs significantly exceeds the number of genes encoding anorexigenic TFs.

Using PAI and DI we have compared evolutionary characteristics of mouse appetite-controlling genes with the same characteristics defined for all protein-coding mouse genes. A number of distinctive features have been found: (1) the set of mouse appetite-

controlling genes is enriched with genes whose evolutionary age corresponds to the appearance of vertebrates; (2) this set of genes contains an increased proportion of genes with low DI (< 0.2). It has also been found that the distribution of PAI values for orexigenic genes has less variance than the distribution of PAI values of all protein-coding mouse genes, i.e., young genes (aged at time of *Mammalia* origin and later) are absent in the set of orexigenic genes.

Gene network comprising genes/proteins involved in physical interaction with each other has been constructed. The highest number of interactions have *Stat3*, *Foxo1*, *Pomc*, and *Sirt1*. All genes that make up this network have low DI (below 0.45), indicating that these genes are under high selection pressure.

*Conclusion*: Reviewing PubMed publications that present the results of knockout or knockdown experiments, we have collected data on 96 mouse genes regulating appetite. Analysis of the gene network involving these genes or encoded proteins has revealed a complex nature of the molecular-genetic mechanisms controlling appetite. We identified genes with the highest functional load in the gene network and revealed features of evolutionary characteristics of the appetite-controlling genes. Taking into account these findings may be useful in the search for new pharmacological targets for the treatment of appetite disorders.

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*References*

1. Mitchell J.E., Crow S. Medical complications of anorexia nervosa and bulimia nervosa. *Curr Opin Psychiatry*. 2006;19(4):438-43.
2. Szklarczyk D. et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res*. 2019;47(D1):D607-D613.
3. Warde-Farley D. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Res*. 2010;38(Suppl_2):W214-W220.
4. Ivanisenko V.A. et al. A new version of the ANDSystem tool for automatic extraction of knowledge from scientific publications with expanded functionality for reconstruction of associative gene networks by considering tissue-specific gene expression. *BMC Bioinformatics*. 2019;20(Suppl 1):34.
5. Mustafin Z.S. et al. Phylostratigraphic analysis of gene networks of human diseases. *Vavilov J Genet Breed*. 2021;25(1):46-56.