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: **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.**

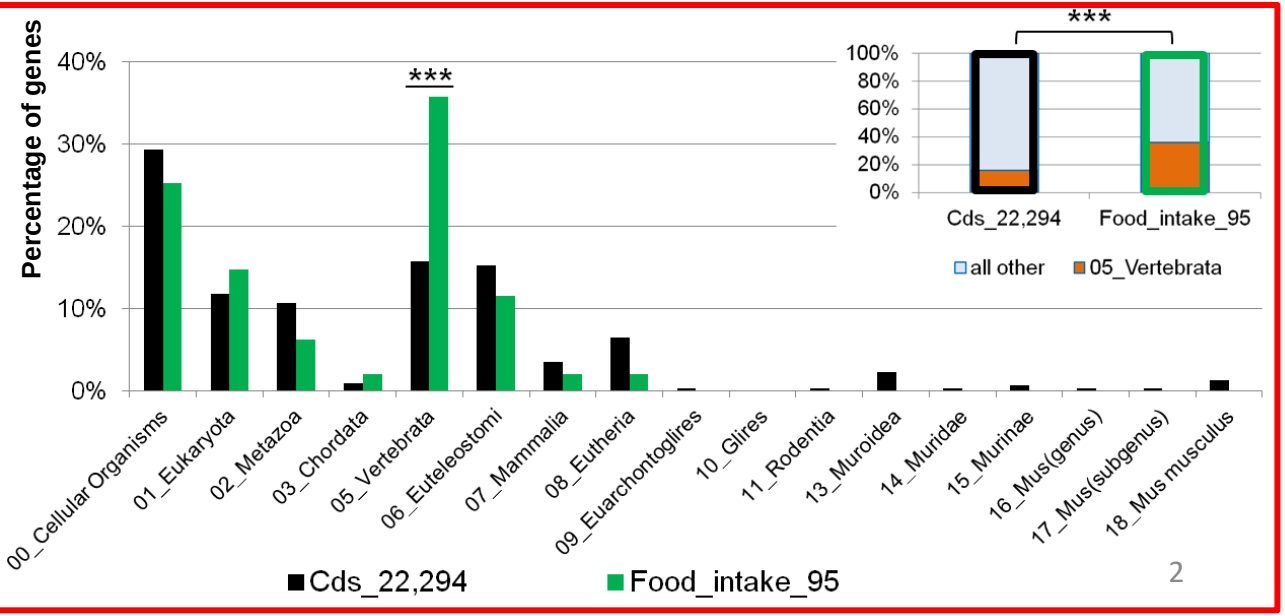
Methods and Algorithms: **Data on genes regulating appetite were collected, performing queries to PubMed using such terms as "knockout" or "knockdown" and terms designating appetite manifestations or disorders. Gene network was reconstructed using computer systems STRING, GeneMania, ANDVisio and Cytoscape. Evolutionary characteristics of genes (phylostratigraphic age index (PAI) and divergence index (DI)) have been calculated as it is described in [Mustafin Z.S. et al. 2021] taking into account sequences of orthologous genes that are 50% or more identical to one under consideration.**

Results: **Data on 96 genes regulating food intake has been collected, of them 95 genes are protein-coding genes.**

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

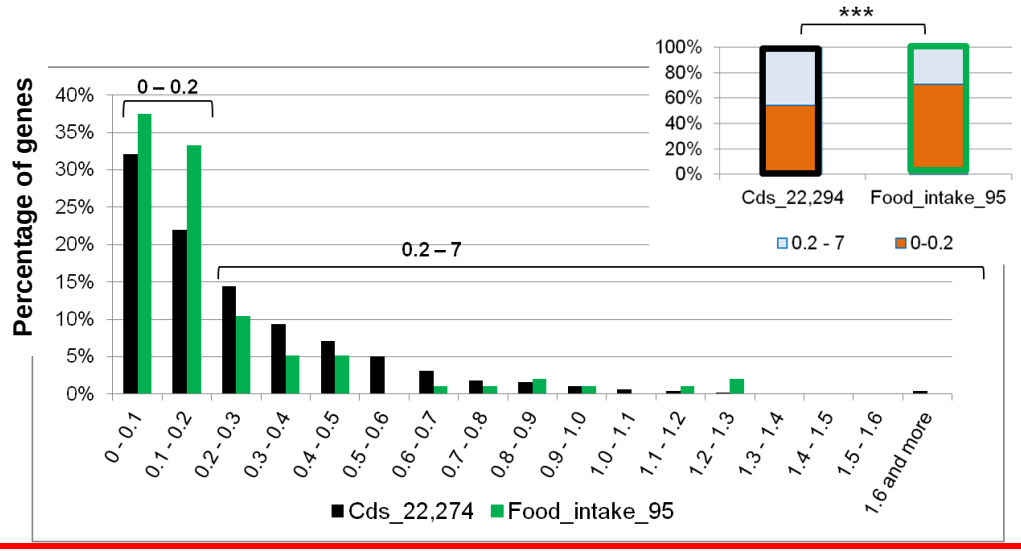
The distribution of the whole set of mouse protein-coding genes (*Cds_22,294*) and protein-coding genes controlling food intake (*Food_intake_95*) according to PAI values. Inset on the right shows portions of genes with PAI = 05 (05_Vertebrata) and portions of all other genes for protein-coding genes (*Cds_22,294*) and genes controlling food intake (*Food_intake_95*).
*****p < 0.001 (χ2-test).**



Results:

2 The set of mouse appetite-controlling genes contains an increased proportion of genes with low DI(< 0.2)

The distribution of the mouse protein-coding genes (*Cds_22,294*) and genes from the catalog (*Food_intake_95*) according to DI values (OX-axis). Inset on the right shows portions of genes with DI from 0 to 0.2 (0 – 0.2) and portions of genes with DI from 0.2 to 7 (0.2 – 7) for protein-coding genes (Cds_22,294) and genes from the catalog (Food _intake_95). ***p < 0.001 (χ2- test).



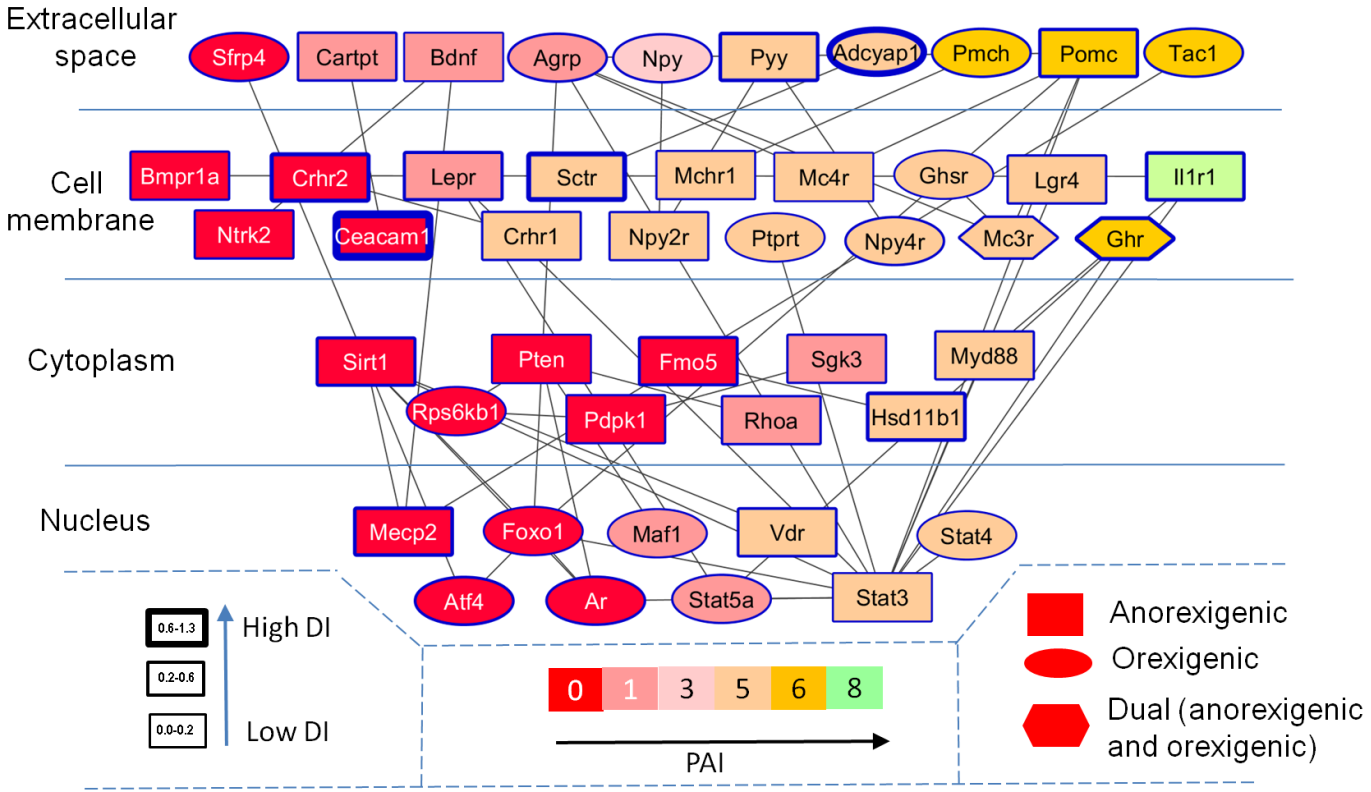
3 The whole-genome set of mouse genes contained 6.1% of young genes (that had PAI values from 09 to 18) while the set of appetite-controlling genes did not contain such genes.

		N	*N (PAI < 08)*	*N (PAI > 09)*	*p*
Whole genome	Detected	22,294	20,920 (93.9%)	1,374 (6.1%)	
Appetite-controlling	Detected	95	95 (100%)	0 (0%)	
	Expected	95	89.15[a]	5.85[b]	< 0.05

N: The total number of protein-coding genes in the considered set of genes.
N (PAI < 08): the number of genes with PAI less than 09 (from 00 to 08).
N (PAI > 09): the number of genes with PAI more than 08 (from 09 to 18).
p - probability rate calculated according to χ2-test.
[a] = N * (20,920/22,294) ; [b] = N * (1,374/22,294)

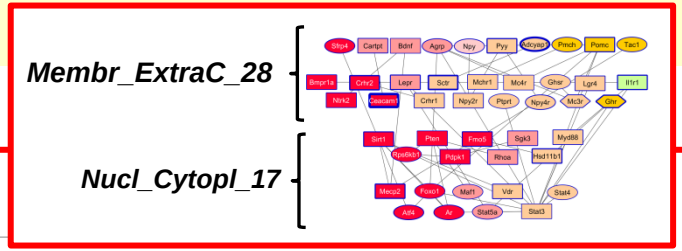
Results:

Gene network comprising genes/proteins involved in physical interactions with each other has been constructed . The network includes 45 nodes and 50 edges. The highest number of interactions have *Stat3*, *Foxo1*, *Pomc*, and *Sirt1*. Most genes (71%) involved in the network have low DI (below 0.2), indicating that these genes are under high selection pressure.

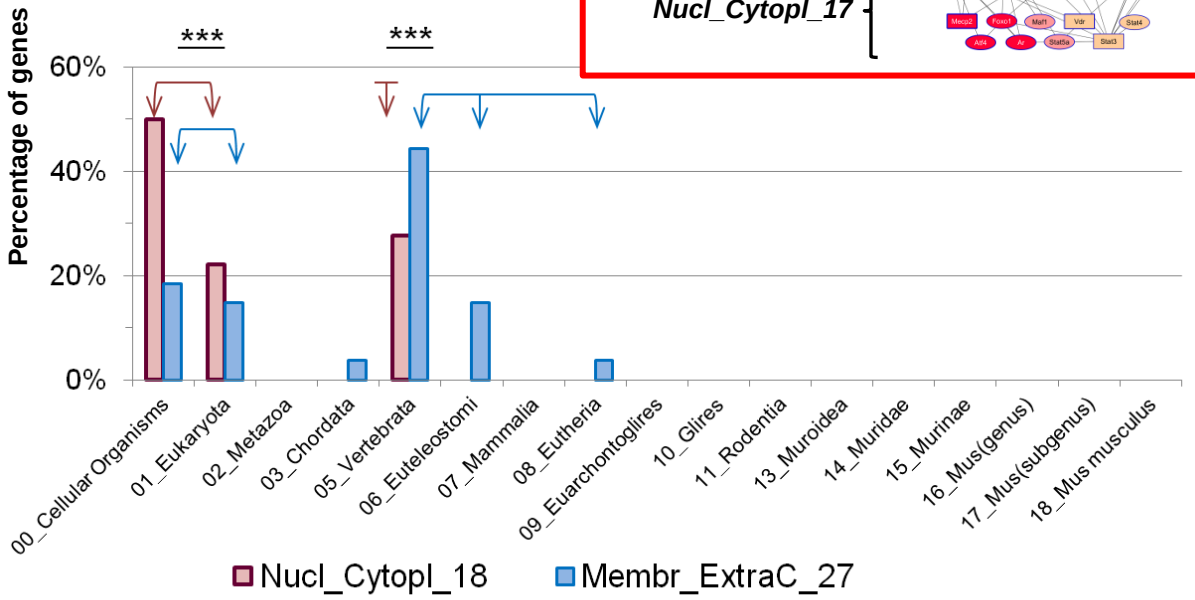


Results:

Within the gene network the set of genes encoding proteins located in nucleus and cytoplasm contains increased portion of genes with PAI ≤ 1.
The set of genes encoding proteins located on membrane and extracellular space contains increased portion of genes with PAI ≥5



The distributions of PAI values for the sets of genes involved in the network encoding proteins located in nucleus or cytoplasm (*Nucl_Cytopl_17*) and located on membrane and extracellular space (*Membr_ExtraC_28*).
*****p < 0.001 (χ^2- test).**



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 distinctive evolutionary features 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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The end !!!