doi 10.18699/bgrs2024-1.4-25

Differentially expressed genes and molecular susceptibility to human age-related diseases

Oshchepkov D.[1, 4]*, Shikhevich S.[1], Chadaeva I.[1], Khandaev B.[1, 2], Kozhemyakina R.[1], Zolotareva K.[1, 2], Kazachek A.[1, 2], Bogomolov A.[1, 2], Klimova N.V.[1], Ivanisenko V.A.[1, 2], Demenkov P.[1], Mustafin Z.[1, 2], Markel A.[1, 2], Savinkova L.[1], Kolchanov N.A.[1, 2], Kozlov V.[3], Ponomarenko M.[1]

[1] *Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

[2] *Novosibirsk State University, Novosibirsk, Russia*

[3] *Research Institute of Fundamental and Clinical Immunology (RIFCI), SB RAS, Novosibirsk, Russia*

[4] *Kurchatov Genomic Center of the Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

* *diman@bionet.nsc.ru*

Key words: RNA-seq; *Rattus norvegicus*; age-related disease; bootstrap; correlation; differentially expressed gene; human; meta-analysis; molecular marker; principal component; qPCR

Motivation and Aim: Mainstream transcriptome profiling of susceptibility versus resistance to age-related diseases (ARDs) is focused on differentially expressed genes (DEGs) specific to gender, age, and pathogeneses. This approach fits in well with predictive, preventive, personalized, participatory medicine and helps understand how, why, when, and what ARDs one can develop depending on their genetic background. Within this mainstream paradigm, we wanted to find out whether the known ARD-linked DEGs available in PubMed can reveal a molecular marker that will serve the purpose in anyone's any tissue at any time. Recently we have obtained and compared transcriptomes of the midbrain tegmentum [1] in gray rats of a tame and an aggressive outbred strain; this allowed us to identify, in *in silico* settings, potential molecular markers for neoteny, which has a power to reverse ARDs. Furthermore, we have recently profiled transcriptomes in the hippocampus [2] of tame versus aggressive rat strains, in which deficient beta-protocadherins and beta-hemoglobin were found to be the statistically significantly most common theranostic molecular markers for ARD-related hypertension. That is why we sequenced, in the same way, one more transcriptome, that of the periaqueductal gray matter (PAG), in the tame versus aggressive rats, identified the corresponding behavior-related PAG-associated DEGs in them. We compared these DEGs with their homologous PubMed-based ARD-linked DEGs in animals and humans to find out whether there are invariant molecular markers for such diseases among them. *Methods and Algorithms*: We retrieved all PubMed-based ARD-linked DEGs in animals and humans, 37834 and 14535 DEGs respectively. We sequenced PAG transcriptome of tame versus aggressive rats, identified rat-behavior-related DEGs, and compared them with their known homologous animal ARD-linked DEGs. This analysis yielded statistically significant correlations between behavior-related and ARD-susceptibility-related fold changes (log2 values) in the expression of these DEG homologs. We found principal components, PC1 and PC2, corresponding to the half-sum and the half-difference of these log2 values, respectively. With the DEGs linked to ARD susceptibility and ARD resistance in humans used as controls, we verified these principal components. Finally, for each of the identified 39 DEGs in the PAG of tame and

aggressive rats and the corresponding homologous DEGs of humans and animals, we determined the number of homologous pairs of DEGs that have the same signs for the main components, calculated using the corresponding log2 values of changes expression, and their statistical significance.

Results: This analysis yielded only one statistically significant common molecular marker for ARDs: an excess of Fc receptor IIb suppressing immune cell hyperactivation. That is consistent with independent RNA-Seq data on the rise in the levels of murine Fcgr2b in astrocytes with age [4].

Conclusion: Finally, we propose the human immunoregulatory genes FCGR1A, FCGR2A, FCGR2B, FCGR2C, FCGR3A, and FCGR3B, homologous to the rat Fcgr2b gene and expressed in the majority of the human tissues, as theranostic molecular markers of age-related diseases.

Funding: The study is supported by the Government Budget Project FWNR-2022-0020 and computational resources of HPC facilities at collaborative center “Bioinformatics” ICG SB RAS.

References

1. Oshchepkov D., Chadaeva I., Kozhemyakina R., Shikhevich S., Sharypova E., Savinkova L., Klimova N.V., Tsukanov A., Levitsky V.G., Markel A.L. Transcription factors as important regulators of changes in behavior through domestication of gray rats: quantitative data from rna sequencing. *Int J Mol Sci.* 2022;23(20):12269. doi 10.3390/ijms232012269
2. Oshchepkov D., Chadaeva I., Kozhemyakina R., Zolotareva K., Khandaev B., Sharypova E., Ponomarenko P., Bogomolov A., Klimova N.V., Shikhevich S., Redina O., Kolosova N.G., Nazarenko M., Kolchanov N.A., Markel A., Ponomarenko M. Stress reactivity, susceptibility to hypertension, and differential expression of genes in hypertensive compared to normotensive patients. *Int J Mol Sci.* 2022;23(5):2835. doi 10.3390/ijms23052835
3. Shikhevich S., Chadaeva I., Khandaev B., Kozhemyakina R., Zolotareva K., Kazachek A., Oshchepkov D., Bogomolov A., Klimova N.V., Ivanisenko V.A., Demenkov P., Mustafin Z., Markel A., Savinkova L., Kolchanov N.A., Kozlov V., Ponomarenko M. Differentially expressed genes and molecular susceptibility to human age-related diseases. *Int J Mol Sci.* 2023;24(4):3996. doi 10.3390/ijms24043996
4. Clarke L.E., Liddelow S.A., Chakraborty C., Münch A.E., Heiman M., Barres B.A. Normal aging induces A1-like astrocyte reactivity. *Proc Natl Acad Sci USA.* 2018;115(8):E1896-E1905. doi 10.1073/pnas.1800165115