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SNPs associated with accelerated senescence in OXYS rats

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Motivation and Aim: Aging is the single largest risk factor for chronic diseases. However, little is known about a genetic overlap between complex age-related diseases. The senescence-accelerated OXYS rats selected in the ICG SB RAS (Novosibirsk) are a good model to identify the pathways that modulate the onset and progression of multiple age-related diseases as these rats develop a phenotype similar to human geriatric disorders including cataract, age-related macular degeneration-like retinopathy and neurodegenerative pathology of the brain with features of Alzheimer's disease. We hypothesize that the senile cataract development can serve as a biomarker of systemic changes associated with aging. The aim of our work is to investigate the transcriptome of OXYS rats and to identify the mutations (SNPs) in genes associated with cataract, which can potentially contribute to the development of accelerated aging.
Methods and Algorithms: We used the RNA-Seq data obtained from sequencing of prefrontal cortex, retina and hippocampus of senescence-accelerated OXYS and WAG (control) rats. Positions of SNPs within the aligned reads relative to the reference genome (Rnor 6.0) were identified using SAMtools (v. 0.1.17) utilities. The mutation was considered as reliable SNP if it was detected in at least 3 OXYS rats in homozygous state and was not present in any of the WAG rats. The effect of an amino acid substitution on protein function was predicted by the Variant Effect Predictor Web service; the consequence type, SIFT score and prediction were obtained for each variant. The list of genes associated with cataracts was compiled according to NCBI, Cat-Map, and KEGG Disease databases.
Results: In the genome of OXYS rats 52539 SNPs overlapped with 11684 transcripts representing 8012 genes. In 328 cases the substitutions can result in significant structural rearrangements (high impact effect) of the transcripts. Among the non-synonymous substitutions 254 have a deleterious effect on the structure or function of the protein product according to the SIFT algorithm. We revealed 543 described and 614 novel SNPs related to 255 genes that can be associated with cataract development in OXYS rats. 4 of this genes, *Pex2*, *Nbn*, *Rab18* and *Prss56* have SNPs (rs198310567, rs105362013, rs106234270 and rs106604882, respectively), which are expected to exert a deleterious effect on the structure or function of the encoded proteins. These polymorphisms are also described for SHR/OLAIPCV and SD rat strains, which were not earlier tested for signs of cataract. It is known that mutations in these genes are associated with mitochondrial diseases, nervous and cardiovascular disorders, consistent with the complex manifestation of the senile phenotype in OXYS rats.
Conclusion: The results of the study may serve as a background for further verification of SNPs contribution to the development of complex age-related diseases.
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