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Search of single-nucleotide polymorphisms associated with accelerated senescence in OXYS rats

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Motivation and Aim: Aging is the single largest risk factor for chronic disease, still little is known about a genetic overlap between complex age-related diseases. For search pathways that modulate the onset and progression of multiple age-related diseases here we used senescence-accelerated OXYS rats derived from Wistar rats in the ICG SB RAS (Novosibirsk) and developing 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 purpose of our work is to identify in the genome of OXYS rats mutations in genes associated with cataract, which can potentially contribute to the development of signs of accelerated aging.
Methods and Algorithms: We used the data of RNA-Seq from 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. Each mutation was present 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, KEGG Disease databases.
Results: In the genome of OXYS rats 52539 SNPs in the homozygous state, not presented in the genome of Wag rats, overlapped with 8012 genes and 11684 transcripts were revealed. 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 SNPs in 255 genes that can be associated with cataract development in OXYS rats and contained 543 described and 614 novel SNPs. 4 of this genes, *Pex2*, *Nbn*, *Rab18* and *Prss56* have SNPs (rs198310567, rs105362013, rs106234270 and rs106604882, respectively) with a deleterious result according to SIFT, although these polymorphisms are described for SHR/OLAIPCV and SD rat strains without signs of cataracts. However, it is known that mutations in these genes are associated with a number of mitochondrial diseases, nervous and cardiovascular disorders, consistent with the complex manifestation of the senile phenotype in OXYS rats against the background of cataract development.
Conclusion: Genes with mutations revealed in OXYS rats are promising for further verification of the contribution of found polymorphisms to the development of complex age-related diseases.
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