Search for single nucleotide polymorphisms (SNPs) associated with hypertension in the genome of senescence-accelerated OXYS rats

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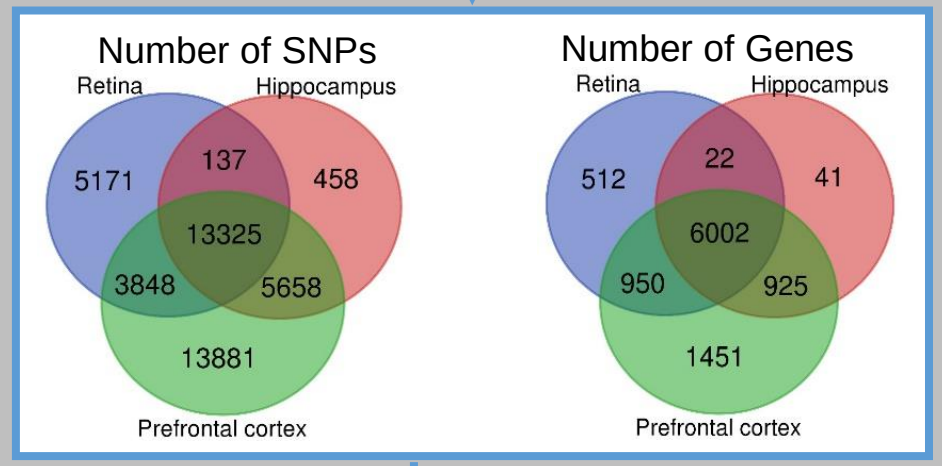
Motivation and aim: Aging is the largest risk factor for many diseases. Adverse genetic variants may contribute to multiple manifestations of aging and increase the number of comorbid conditions. The senescence-accelerated OXYS rats selected in the ICG SB RAS (Novosibirsk) are a unique model to identify 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, cardiomyopathy, hypertension, retinopathy and neurodegenerative pathology of the brain with features of Alzheimer's disease. There is evidence of links between hypertension and age-related diseases, although the genetic relationships are insufficiently studied. The aim of our work was to investigate the transcriptome of OXYS rats and to determine the contribution of hypertension to the development of accelerated-senescence syndrome in OXYS rats.

Methods and Algorithms: The RNA-Seq data were obtained from sequencing of prefrontal cortex, retina and hippocampus of senescence-accelerated OXYS rats. The effect of an amino acid substitution on protein function was predicted by the Variant Effect Predictor Web service (https://www.ensembl.org/vep); the consequence type, SIFT score and prediction were obtained for each variant. The SNPs found in OXYS rats were compared with the data of genomic and transcriptomic sequencing of 45 other rat strains, 12 of which simulate different forms of hypertension, 11 strains are used as a normotensive control, and the rest are used as experimental or control strains to study diseases not related to hypertension or aging.

Study design

Prefrontal cortex | Retina | Hippocampus

RNA-Seq



Exclusion of SNPs present in control strains*

2105 SNPs presumably related to the development of senescence-accelerated phenotype in OXYS rats

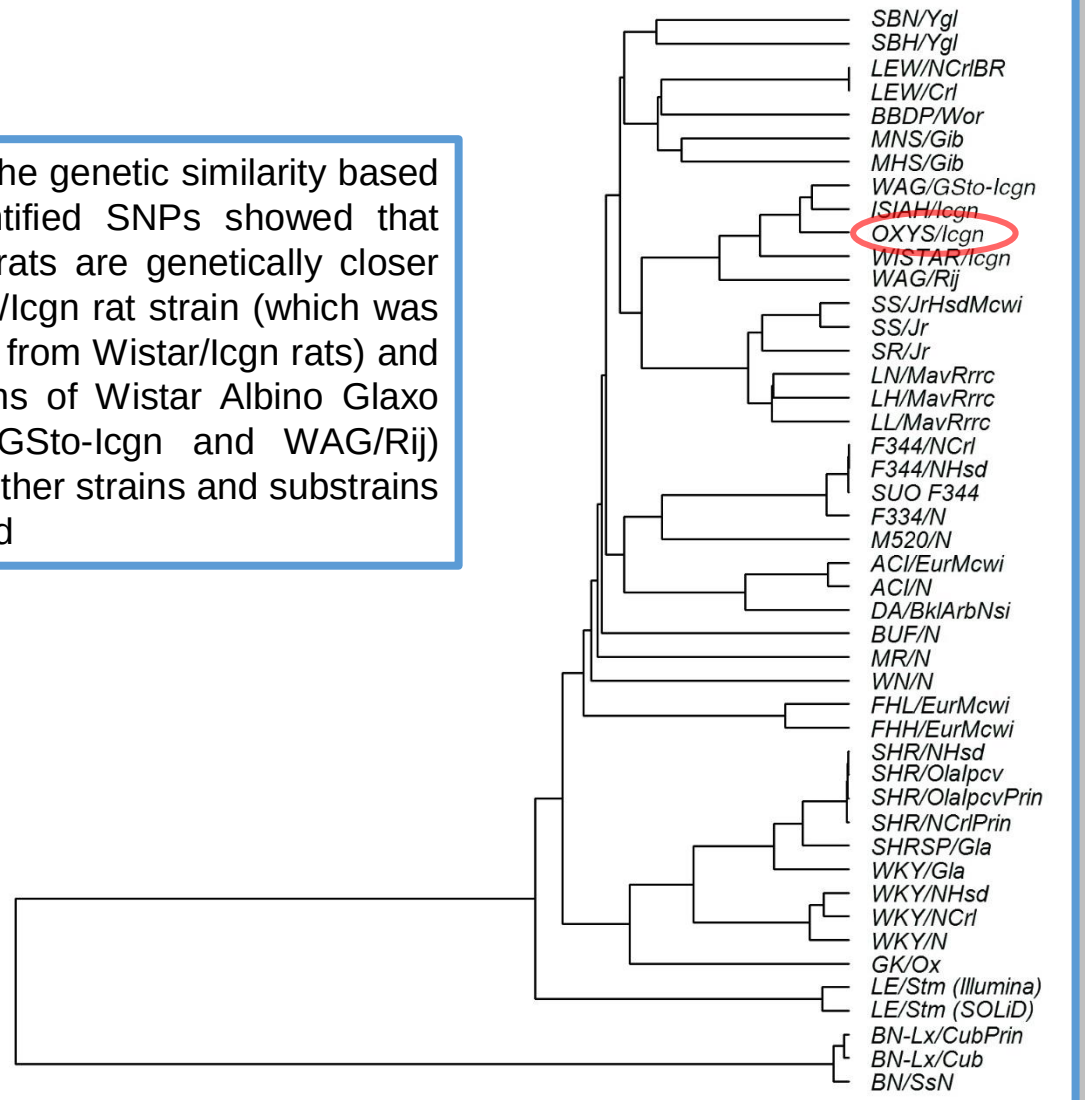
Comparison with hypertensive rat strains

FHH/EurMcwi, LH/MavRrrc, MHS/Gib, SBH/Ygl, SHR/OlaIpcv, SHRSP/Gla, SHR/NCrlPrin, SHR/NHsd, SHR/OlaIpcvPrin, SS/Jr, SS/JrHsdMcwi and ISIAH/Icgn

1380 SNPs specific for OXYS rats

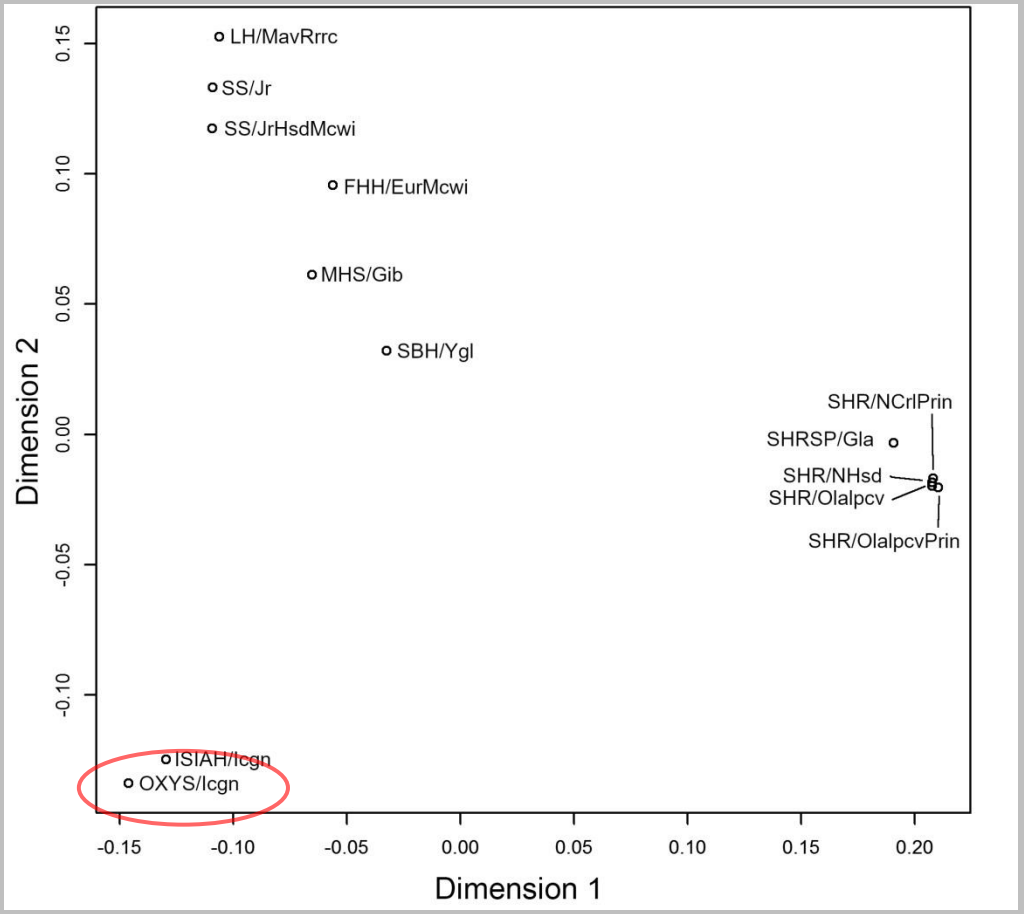
725 SNPs are present the both in OXYS rats and in one or several other hypertensive rat strains

Analysis of the genetic similarity based on the identified SNPs showed that OXYS/Icgn rats are genetically closer to the ISIAH/Icgn rat strain (which was also derived from Wistar/Icgn rats) and to two strains of Wistar Albino Glaxo rats (WAG/GSto-Icgn and WAG/Rij) than to the other strains and substrains being studied



* - 11 of these strains/substrains are commonly employed as a normotensive control (FHL/EurMcwi, LN/MavRrrc, LL/MavRrrc, MNS/Gib, SBN/Ygl, SR/Jr, WKY/N, WKY/Gla, WKY/NCrl, WKY/NHsd and WAG/GSto-Icgn), 22 rat strains/substrains serve as control or experimental animals in the studies on various pathological conditions that have no relation to hypertension or aging (ACI/N, ACI/EurMcwi, BBDP/Wor, BN-Lx/Cub, BN-Lx/CubPrin, BN/SsN, BUF/N, DA/BklArbNsi, F334/N, F344/NHsd, F344/NCrl, SUO_F344, GK/Ox, LE/Stm (SOLiD), LEW/Crl, LEW/NCrlBR, LE/Stm (Illumina), M520/N, MR/N, WAG/Rij, WN/N and Wistar)

Multidimensional scaling analysis of 12 hypertensive rat strains and substrains



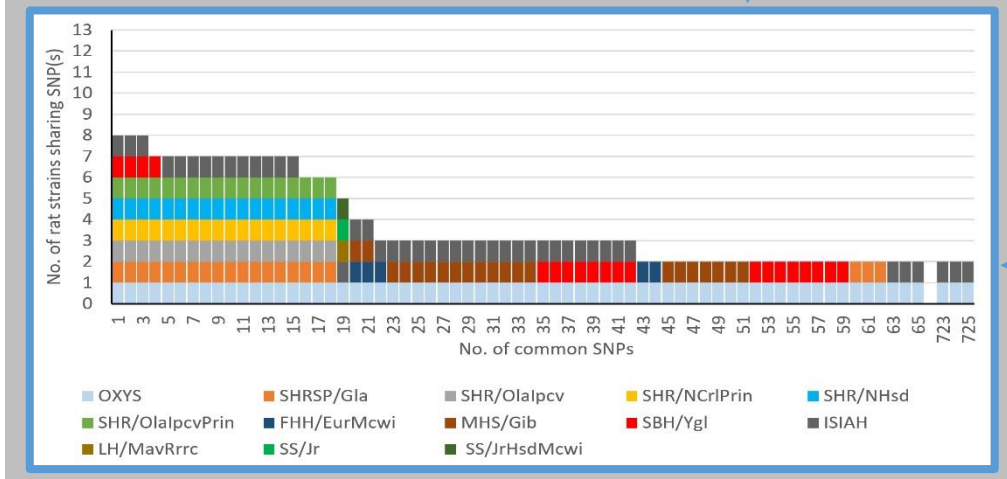
Analysis uncovered substantial similarity of genotypes between OXYS and ISIAH rats and substantial differences of these two strains from the rest of the hypertensive rat strains and substrains. Also rats with salt-sensitive hypertension (SS/Jr, SS/JrHsdMcwi, and SBH/Ygl) and rat strains developing spontaneous hypertension (SHR/OlaIpcv, SHR/NCrlPrin, SHR/NHsd, SHR/OlaIpcvPrin, and SHRSP/Gla) are genetically distant from each other.

SNPs presented in OXYS rats and in one or several other hypertensive rat strains

The SIFT algorithm detected 13 SNPs in genes ***Pla2r1, Spata2, Zmym6, Ccdc28b, Slc25a32, Trappc9, Mroh1, Kifc2, Ephx1, Nqo2, Gtpbp4, RT1-A1, Ostm1*** presumably having a significant negative effect on the structure and/or function of a protein

Four SNPs in genes ***Csnk1e, AABR07045405.1, Lemd2*** exert a high impact on transcript structure

Enrichment with such functional categories as GTP/ATP binding, various signaling systems and cell division



We did not find SNP common to all the 13 hypertensive rat under study. The highest frequency of an SNP among the hypertensive rat was eight out of 13 strains, and four out of these eight strains were represented by SHR substrains.

CONCLUSION: Transcriptome of OXYS rats contains 725 common SNPs with one or more hypertensive rat strains and substrains. Analysis of genes with SNPs showed that only one gene *Ephx1* annotated in RGD as associated with hypertension. In addition, *Ephx1*, as well as several other genes (*Pla2r1, Zmym6, Trappc9, Nqo2*) are associated with neurodegenerative diseases and/or mental disorders. Multidimensional scaling analysis showed that OXYS rats are genetically distant from other strains and presumably have their own basis for the development of hypertension, which may determine the absence of senile phenotype of OXYS rats in the hypertensive rat strains.

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