Using genetically diverse mice to define transcript and protein dynamics in the aging heart

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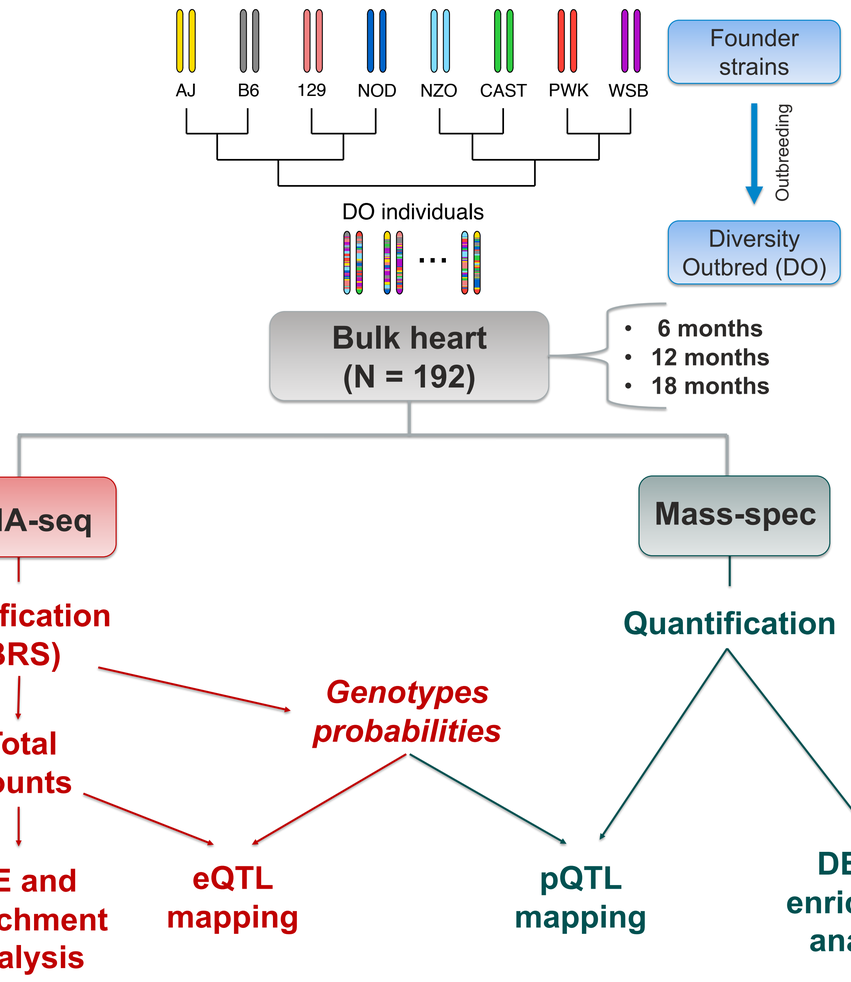
Introduction

Cardiovascular diseases (CVD) are the leading cause of death in elderly people. Better understanding of the molecular mechanisms underlying the age-related changes in the heart is needed for better prevention and treatment of CVD. In particular, the effect of environmental and genetic factors with aging are not known [1-4].

Mice models for aging recapitulate many phenotypes related to human cardiac aging, and the Diversity Outbred (DO) mouse population is a powerful resource with similar levels of genetic diversity to human populations [5].

We analyzed gene and protein expression data from DO mice at different ages to uncover the molecular changes associated with aging in the heart. We found three QTL hotspots in the genome associated with the muscle contraction apparatus, protein quality control system, and chromatin structure, showing that changes in these systems may explain some of the variability in the aging heart.

Experimental design and data analysis



Results

Functional enrichment in transcript and protein dynamics with age

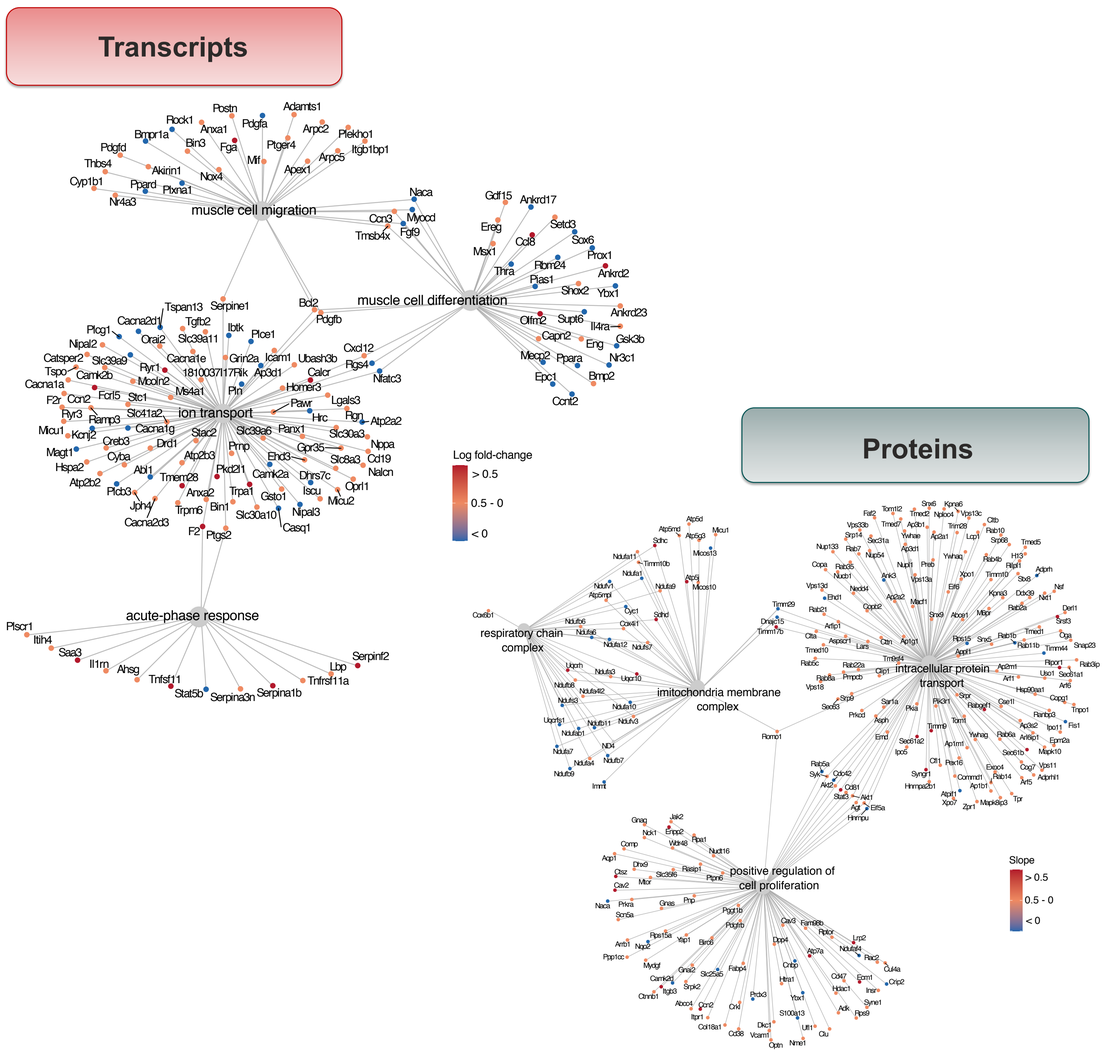


Figure 1. Enriched pathways for transcripts (top) and proteins (bottom) that change with age. Each cluster represents an enriched pathway with nodes representing the transcripts/proteins. The color indicates the estimated change for each transcript/protein with age.

QTL mapping for age-interactive scans

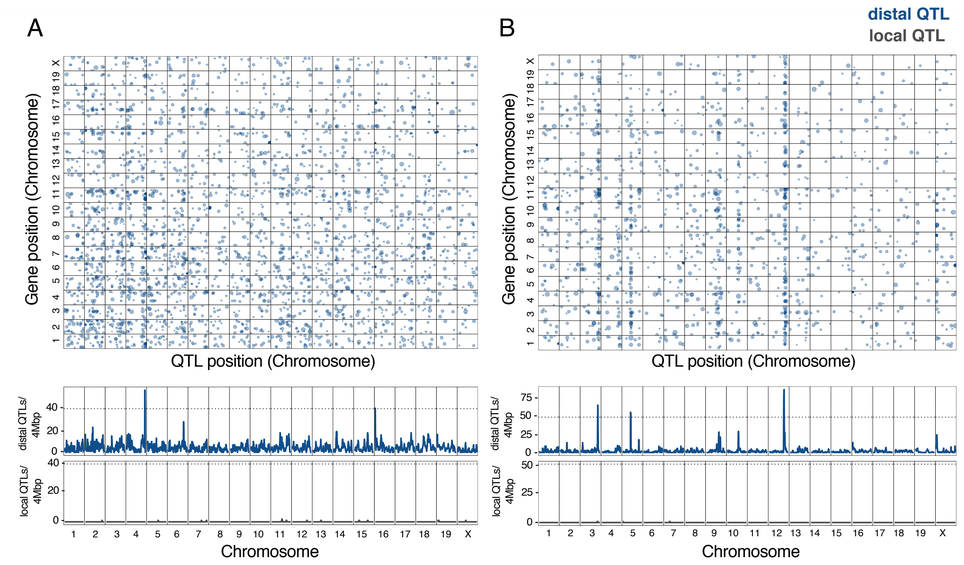


Figure 2. Distal QTLs hotspots are discernable as vertical bands in the QTL grids (upper panel) for eQTL (A) and pQTL (B). A high density of distal QTLs is found on chromosomes 4 and 16 for eQTL analysis (LOD > 7), and on chromosomes 3, 5 and 12 for pQTL analysis (LOD > 6).

Enrichment analysis for QTLs hotspots

We filtered out transcript/proteins that mapped to a QTL hotspot but had a mean absolute correlation value lower than 0.3. For eQTL, none of the genes matched this criterion, suggesting the eQTL hotspots were complex.

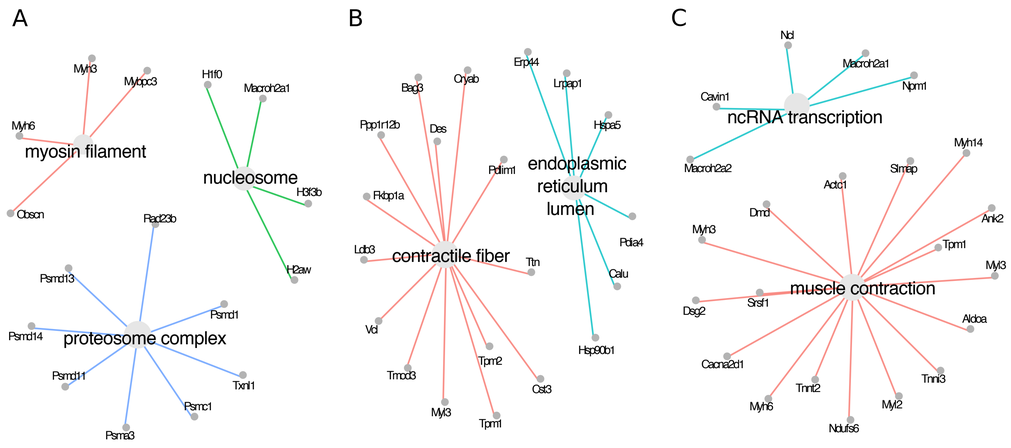


Figure 3. Enriched pathways for proteins that mapped on chromosome 3 (A), chromosome 5 (B) and chromosome 12 (C) pQTL hotspots.

Candidate driver SH3GLB1 on chromosome 3

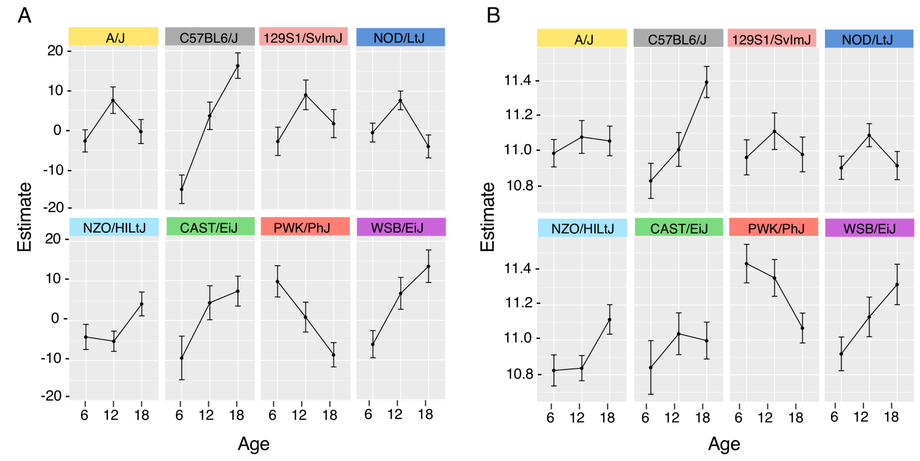


Figure 4. Founder allele effects for the PC1 computed for proteins that mapped on chromosome 3 (A) and for the expression of the candidate driver SH3GLB1 (B) showing the similarities of the effects for each founder haplotype.

Conclusions

We detected large-scale changes in transcript and protein levels with age in the hearts of DO mice. These dynamics are consistent with mitochondria dysfunction and physiological hypertrophy. We also mapped three distal age-interactive pQTL hotspots, revealing that genetic variation at different loci may regulate protein dynamics with age related to common processes, such as muscle contraction, protein quality control system, and chromatin structuring. Finally, we suggest that genetic variation at the autophagy regulator, SH3GLB1, may be a potential candidate driver for the chromosome 3 hotspot.

References

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