Systems genetics approaches to explore mitochondria and aging

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Our understanding of genetic mechanisms that define complex traits has been hindered by the difficulty of obtaining comprehensive omics datasets across a broad range of biological “layers”. Complete data on the genome of individuals can be readily obtained, but the full complexity of the transcriptome, proteome, metabolome, and phenome have remained largely out of reach. This is, however, beginning to change, with the development of robust multi-layered omics strategies that are pioneered in model organisms. We here profiled the healthspan and lifespan in >80 cohorts of the BXD mouse genetic reference population. Large variability was observed across all omics layers; to understand how these differences stem from genetic variance, we exploited a multilayered set of molecular phenotypes—genomics, transcriptomics, proteomics, and metabolomics. With this multi-omics strategy, large networks of proteins could be analyzed and causal variants identified in proteins involved in determination of lifespan (e.g. *Mrps5, Jmjd3*), glucose homeostasis (e.g. *Dhtkd1*), hypertension (*Ubp1*) and mitochondrial supercomplex formation (*Cox7a2l*). These new candidates were then validated using cross-species genetic strategies in *C.elegans*, mouse, and human. Our large-scope multi-omics measurements in mouse populations combined with cross-species validation hence provided us with robust conserved and mechanistically defined pathways that underpin complex traits involved in metabolism and aging.