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Molecular pathways related to differential genotype/phenotype-interaction in non-inbred mouse strains

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In order to identify molecular pathways related to genotype/phenotype interactions in non-inbred mouse strains, we used mice long-term selected for high treadmill performance (DUhTP mice) and unselected controls (DUC mice), both originating from same genetic pool. As environmental factors we tested the effects of diet and training on growth, development and metabolism in both mouse strains. For the genome-wide assessment of molecular pathway regulation we performed RNAseq in muscle, liver, fat, and brain in all experimental groups.

In the first study, both lines received two commercial standard chows (A and S) with similar composition to compare parameters of food intake, growth, fat accretion, physical activity and reproduction. In a separate study, DUC and DUhTP mice completed three weeks of treadmill training for tissue analysis and NGS sequencing.

Despite similar diet composition in the 1st study, diet A resulted in weight reduction in DUC mice (day 21: ♂: -21.6%, $P<0.0001$; ♀: -15.6%, $P<0.05$) while the weight of DUhTP mice remained unaffected. Liver, epididymal and renal fat mass decreased by diet A in 21d old mice of both lines. There were no changes in food consumption, energy intake and physical activity between both diets. In female DUC, but not DUhTP mice, diet S accelerated reproductive development (e.g. age at vaginal opening: 21.7±0.8 d) compared to diet A (23.5±1.3 d, $P<0.0001$). NGS sequencing in the 2nd trial revealed strong line-specific differences. In particular, lipid metabolism and oxidative phosphorylation were increased in different tissues from DUhTP mice when compared to controls.

Because we have developed a non-inbred model for the assessment of genotype/phenotype/environment interactions, we may identify more general mechanisms for the control of energy metabolism and body weight. Our results further demonstrate the importance of environmental factors in functional genome analysis.