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RATTACA: a new paradigm for examining genetic correlations in outbred rats

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Genetic correlations between traits are frequently studied in humans and model systems as a first step towards identifying causal pathways and mechanisms. In model systems, genetic correlations have been studied using several approaches. One of the simplest but also most prone to misinterpretation are correlations observed in pairs of inbred strains. Using this approach, a pair of strains that is divergent for one trait might be examined to determine if a second putatively causal factor also differs between the two strains. Such an approach can be misleading because numerous traits may differ between a pair of strains without having any causal relationship. Another approach would be to examine two factors in an outbred population; however, any observed correlations could be due to genetic or environmental causes. Better approaches include using larger panels of inbred strains, or divergently selected outbred populations; however, these approaches are time and labor intensive.

Here we introduce a novel experimental paradigm that we are calling RATTACA, in which phenotypes are predicted in naïve rats using extant rat GWAS data. Prediction is based on standard polygenic methods (e.g. BLUP) that are already widely used in agricultural and human genetics. Performance improves with the heritability of the trait and with sample size of the GWAS training data. RATTACA allows us to produce cohorts of rats that are predicted to be divergent for a trait. These divergent cohorts can be examined for a second putatively correlated trait to see if the second trait is genetically correlated with the first trait that used for prediction. One critical advantage of this approach is that by using prediction rather than directly measuring the first trait, the second trait can be measured in naïve rats. For example, we have examined slice electrophysiological traits in rats that were predicted to be divergent for cocaine self-administration. Because none of the rats were exposed to cocaine, electrophysiological differences are not secondary to differential cocaine exposure. This paradigm is especially attractive for lower throughput traits since they cannot be easily measured in large cohorts. We can also produce rats that are predicted to be divergent for multiple traits. Another possible application is to examine rats that are predicted to be divergent for the expression of one or more genes. Finally, for genes with LoF mutations, cohorts could be produced that resemble wild type, heterozygous and knock out populations, but with the benefit of an outbred genetic background, thus improving robustness. We are currently providing cohorts for free or at deeply subsidized prices to qualified investigators.