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The quest for candidate genes affecting the hypothalamic pituitary adrenal (HPA) axis: A linkage study in an F2 cross of mice bred for trait anxiety

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Despite years of extensive research on a common final pathway of anxiety and depression-related disorders, it is still a major issue to pinpoint the candidate genes involved in modulating the relevant phenotypes, among others, due to the complexity of the respective traits. Therefore, even large-sample clinical patient-control genome-wide association studies encounter difficulties to highlight genes that contribute a small, but nevertheless significant, effect to a specific phenotype.

To circumvent the pitfalls of analyzing a population with vast amounts of heterogenous variants, including rare ones, we followed a breeding strategy to select for genetic variants based on trait anxiety in mice. A commonly used parameter in antidepressant research, the percentage of time animals spend on the arms of the elevated plus-maze, was applied to select for high (HAB) and low (LAB) anxiety-related behavior mice over generations, starting from the outbred CD-1 mouse strain. After accumulating some of the genetic determinants, we crossbred HABxLAB animals to generate a population of HABxLAB-derived F2 mice that would already show free segregation of the previously inbred alleles, thus allowing us to calculate linkages based on the phenotypes of interest.

Applying genomic single-nucleotide polymorphism (SNP) screening in 521 of these F2 mice, with subsequent linkage analyses, we succeeded in highlighting a very strong effect of a 7.5cM locus on mouse chromosome 3 on HPA-axis responsiveness, which is known to be connected with anxiety and depression scale disorders. Indeed, the locus harbors genes relevant to corticosteroid synthesis, e.g. *Hsd3b1*.

Using this bottleneck breeding and subsequent segregating approach, we could also demonstrate that the effect sizes can be increased to a well-measurable size of true effects in complex traits, which seems to be acceptable even at the price of losing other potential loci.

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