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A pragmatic approach to genetic background problems in the analysis of genetically modified mice

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Increasingly sophisticated and precise molecular genetic tools are applied to mice in order to study the cellular mechanisms underlying higher brain functions, including learning and memory. However, despite such advanced technology several studies have produced unclear or conflicting results. One reason for this is that genetic background and environment alone produce sufficient variation to span the range of behavioral variables in many tests and can easily mask or fake mutation effects if genetic studies are not designed properly. Thus, mutation effects can only be contrasted statistically against the influences of genetic background and environment. In most situations, this is most efficiently and reproducibly achieved if (i) mutations are backcrossed to and *maintained* in one or (preferably) two well-characterized, commonly available inbred strains and (ii) if mutant and wild-type littermates are *analyzed* on a well defined genetic background that can be reproduced at any time form the inbred stocks. This may be inbred mice, F1 hybrids or a F2 generation, depending on the genetic model and the hypothesis being tested. However, these recommendations do not eliminate the so called “flanking allele problem”, genetic bias resulting from genetic linkage between the targeted locus and neighboring genes. If desired, such bias can be removed using simple modifications of the standard breeding schemes.