Phenotyping of genetically modified mice: important considerations regarding genetic background

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Increasingly sophisticated molecular genetic tools are used to generate mutant mouse models for the study of human biology and disease, including higher brain function and mental illness. The phenotyping of these mouse models, in particular at the level of behavior, requires careful consideration of genetic background. Because many inbred laboratory mouse strains are the result of selective breeding for extreme behavioral or morphological traits, genetic background alone can produce sufficient variation to span the range of behavioral variables in many tests and may mask or fake mutation effects if genetic studies are not designed properly. Mutation effects must be contrasted statistically against the influences of genetic background. In most situations, this is most efficiently and reproducibly achieved if (i) mutations are backcrossed to and maintained in one or (if possible) two well-characterized, commonly available inbred strains as congenic lines and (ii) if mutant and wild-type littermates are analyzed on a well defined genetic background that can be reproduced at any time from the inbred stocks. This may be inbred mice, F1 hybrids or a F2 generation, depending on the genetic model and the hypothesis being tested. Double and triple mutant models may require custom solutions. 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.

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