Choice of Strains/Strain Genetic-Differences/Modifiers

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Increasingly sophisticated and precise molecular genetic tools are used to generate mutant mouse lines as models for the study of human biology and disease, including higher brain function and mental illness. However, despite such advanced technology many studies have produced unclear or conflicting results, especially at the level of behavioral analysis. Limitations of available testing procedures and interactions with poorly standardized laboratory environments are frequently discussed reasons for this. In my presentation, I will focus on the problem of genetic background. Inbred laboratory mouse strains often show extreme phenotypic profiles. Therefore, 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 (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 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. 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.