Breeding of constitutive and conditional mouse mutants: a pragmatic approach

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The genetic background of genetically modified mice can interfere with phenotypic characterization by direct effects or through interaction with the introduced mutation. An uncontrolled bias or shift of genetic background can severely confound the interpretation of results, particularly in behavioral studies. It has therefore repeatedly been suggested that phenotyping should exclusively be done in co-isogenic or at least congenic lines. However, because 129 strains are unsuitable for many behavioral and morphological analyses, generation of co-isogenic lines by backcrossing to the ES-cell donor strain is impractical as long as 129 strains remain the predominant source of embryonic stem (ES) cell lines. This limitation does not apply to congenic lines, but backcrossing to a strain other than the ES-cell donor strain takes a long time and is resource intensive. For these practical reasons it is often impossible to establish a homogeneous genetic background and many studies are conducted in a mixed genetic background, typically a combination of C57BL/6 with a substrain of 129. During the past decade, our laboratory has been involved in the phenotypic characterization of more than 60 different genetic mouse models with various genetic backgrounds. A meta-analysis of the accumulated data shows that experimental samples with mixed genetic background usually show better baseline performance than congenic lines and produce results of comparable reliability. Thus, samples with mixed genetic background are a valid alternative, especially if one takes into consideration that unlike inbred strains they can be used for any kind of analysis. However, according to the recommendations issued by the 1997 Banbury Conference on Genetic Background in Mutant Mice, the genetic background of such samples should always be well documented, easy to reproduce, and involve only commonly available strains. Here we propose a set of breeding strategies that implement these rules with a minimum of resources and can be used with constitutive or conditional targeted mutations.

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