A University of Michigan Animal Care & Use Program initiative

MY STRAIN

WHAT'S IN A STRAIN?

Genetic quality control is one of many animal-related factors that can have wide-ranging, unexpected effects on research. Ever wonder what exactly makes a strain *a strain*? Is there a difference between a C57BL/6 mouse bred at a vendor versus one bred in your lab? Why do strains have such long names? Read on for a primer!

WHAT IS A STRAIN?

A **strain** is made by breeding brother and sister mice to one another for at least 20 generations. Mice in the same strain are considered genetically identical to each other, though residual heterozygosity can remain until the 60th filial generation.

Substrains are branches within a strain created by breeding separate lines for at least 20 generations. Substrains can also occur if genetic differences arise within a strain. Even if they are the same strain, animals of different substrains are not genetically or phenotypically identical.

Note that **generations are additive** – if you and a colleague separately breed the same strain for 10 generations, your mice have been separated for 20 total generations and are considered substrains.

The **background strain** is the strain on which a mutation was induced. Backcrossing may be used to transfer a mutation from one background strain to a new strain. The new mutant strain will never be fully genetically identical to the background strain because the mutant locus is surrounded by flanking DNA. Flanking DNA can have unexpected and significant effects on phenotype.

WHY DO STRAINS DIVERGE?

The most common reasons for strain divergence are **human** error and **genetic** drift.

- **Human error** is the most significant cause of divergence. Common sources of error include mis-marking cage cards, mis-recording identification numbers, or accidentally pairing the wrong animals. Careful recordkeeping and training can minimize this.
- **Genetic drift** occurs when random mutations occur during cell division, are passed on to offspring, and accumulate in the population. These changes can have unexpected effects on phenotype even if they are not obvious. Good breeding practices can minimize genetic drift.

The Jackson Labs reports that **12.5% of newly imported strains are not on the background described by the investigators importing them.**

Kelmenson, 2016

WHY IS GENETIC QUALITY CONTROL IMPORTANT?

Inbred animals should be as genetically homogenous as possible to minimize variability caused by unexpected phenotypes. Poor genetic quality control leads to contamination of strains. There are many published reports in the literature of contamination causing unexpected or invalid research results. This leads to wasted time, money, and animal lives.

WHAT ARE THE COMPONENTS OF A GENETIC QUALITY CONTROL PROGRAM?

A good genetic quality control program uses a combination of factors. These may include the following:

1) **Consistent phenotypes**: any change in phenotype should be investigated and mice exhibiting changes should be removed from the breeding colony. Changes may be noted on physical examination (body size, coat color, skeletal structure) or as part of your research (unexpected behavioral responses, changes in tumor susceptibility)

   - Using this method alone may cause you to miss contamination that is not phenotypically obvious. One example of this is *Nitzki, 2006* where contamination was not noted for years until the lab began working with F1 cross mice that yielded an unexpected coat color.

2) **Single nucleotide polymorphisms (SNP):** SNP panels may be performed by commercial vendors or within your lab. SNP analysis is especially helpful to ensure the integrity of newly created or acquired strains, to check that congenic strains have been appropriately back-crossed, and to evaluate founder mice before you start a breeding colony.

3) **Allele-specific genotyping:** this method is used for identifying mutant alleles within a strain and is especially useful for checking breeders.

In some situations, such as differentiating between closely related strains, more specialized techniques may be necessary to monitor your strains.

WHAT ARE SOME BEST PRACTICES FOR MAINTAINING INBRED AND MUTANT STRAINS?

- **For all strains:**
  - Use brother x sister mating schemes.
  - SNP analyze breeders prior to use.
  - Periodically refresh inbred lines. You should use pedigreed animals from a high-quality vendor or cryopreserved founders to refresh lines.

- **For mutant strains** (including those created with programmable endonucleases such as CRISPR), the following tips are especially important:
  - Back-cross to the parent strain every 10 generations to minimize drift.
  - Confirm the presence of mutant alleles with phenotyping and genetic testing.
  - Genetically test newly created lines.
  - Periodically monitor transgene copy number and expression.

- **For newly acquired strains** (whether purchased, donated, or self-created):
  - Validate both the background and mutations prior to beginning experiments.

HOW CAN WE MINIMIZE HUMAN ERROR?

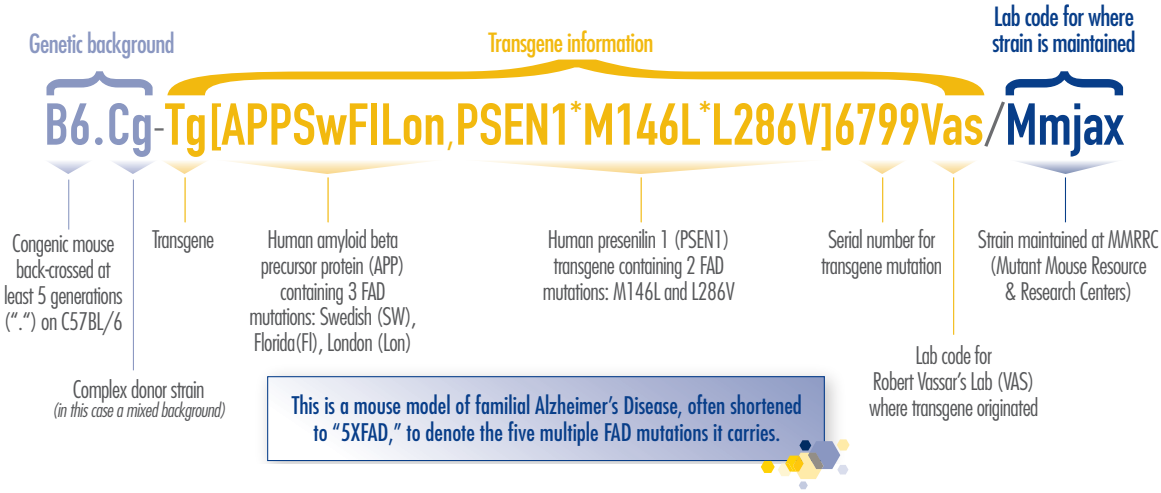
- Maintain consistent breeding and husbandry practices.
- Develop a clear colony management strategy.
- Provide frequent training opportunities for lab members.

- Keep detailed breeding records.
- Use clear cage labels with correct nomenclature.
- Use clear, consistent animal identification.

- Separate strains in the room or on the rack by observable phenotype such as coat color.
- When working with mice, only open one cage at a time.

WHY IS NOMENCLATURE SO IMPORTANT AND WHY ARE STRAIN NAMES SO COMPLEX?

Because there are so many strains, stocks, and mutant mice available, the *International Committee on the Standardized Genetic Nomenclature for Mice and Rats* developed a systematic naming scheme to reduce confusion. Under this system, every strain name will tell you the following information:



- Background strain
- Mutations
- Originating laboratory
- Where the strain is maintained
- How a mutant strain was created
- Whether a congenic strain has been fully back-crossed

Using and learning about proper nomenclature can, therefore, tell you a lot of information about the mouse strains you encounter. **Using standardized naming and abbreviations reduces confusion when animals are shared between labs or when scientists from outside of the university read papers you have published. Failure to use these conventions can have effects on your research**. Illustrations of this can be found in *Fontaine and Davis, 2016*.

I HAVE MORE QUESTIONS — WHERE CAN I GO FOR HELP?

Each ULAM Faculty Veterinarian is knowledgeable about rodent breeding and colony maintenance. We are always happy to answer any questions you may have!

Connect with your ULAM Faculty Veterinarian at
animalcare.umich.edu/faculty-vets

HOW ARE MOUSE STRAINS AND SUBSTRAINS NAMED?

Information about mouse nomenclature can be found at the following resources:

Mouse Genome Informatics (MGI) Nomenclature Home Page
informatics.jax.org/mgihome/nomen/index.shtml

FEATURED RESOURCE

The Jackson Laboratories Interactive Nomenclature Tutorial
jax.org/nomenclature-tutorial

The Jackson Laboratories Nomenclature Information
jax.org/jax-mice-and-services/customer-support/technical-support/genetics-and-nomenclature

FEATURED RESOURCE

The Jackson Laboratories Mouse Nomenclature Quick Guide
http://bit.ly/jax-nomenclature

REFERENCES AND ADDITIONAL READING

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MY STRAIN — A University of Michigan Animal Care & Use Program initiative

MY STRAIN IS A NEW INITIATIVE FROM THE UNIVERSITY OF MICHIGAN ANIMAL CARE & USE PROGRAM THAT AIMS TO PROMOTE INTERDISCIPLINARY RESEARCH COLLABORATION THROUGH THE RESPONSIBLE SHARING OF INFORMATION ABOUT TRANSGENIC MOUSE STRAINS.

LEARN MORE AT ANIMALCARE.UMICH.EDU/MY-STRAIN

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