



Genetic Quality Control of Inbred and F1 Hybrid Rodent Strains

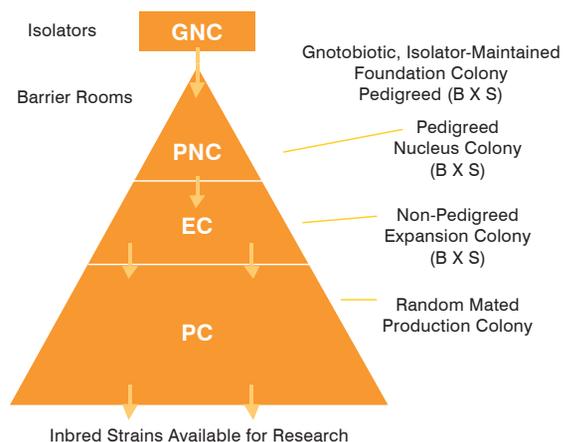
Genetically defined inbred and F1 hybrid strains are frequently the models of choice for research because of their unique and stable phenotypic traits, and hence, uniform and predictable experimental responses. The genetic attributes that underpin these desirable qualities are the homozygosity that results from brother x sister mating and isogenicity, i.e., that individuals of an inbred or F1 hybrid strain are essentially the same genetically. The loss of these properties is termed substrain (or subline) divergence, the most significant cause of which is the genetic contamination that occurs when one strain is unintentionally outcrossed to another. The residual heterozygosity that exists also contributes to subline divergence and the mutations that accumulate when a strain is separated into subpopulations. The Charles River Inbred Genetic QC Program is comprised of: (1) rigorous colony management practices to prevent, limit, and detect subline divergence and (2) routine genetic monitoring to verify that genetic contamination has not occurred.

I. Colony Management

Colony management for inbred rodent strains includes a pyramidal, multi-colony structure and the maintenance of detailed breeding records. At the apex of the pyramid is the foundation colony, which is sustained by brother x sister mating, with pedigree records of all matings. Foundation colonies, housed in isolators at our facility in Wilmington, MA, are the source of founder breeders for the brother x sister mated, pedigreed nucleus colonies in barrier rooms. Foundation breeders are reintroduced to each barrier room nucleus colony every three to five

years (within 10 generations) to control genetic drift. The nucleus provides breeders to an optional expansion colony or directly to the production colony. All expansion colony matings are between siblings, but pedigree records are not kept. The nucleus and expansion colonies are the source of all production colony breeders, which are randomly mated. An important aspect of this scheme is that all breeders are the offspring of brother x sister matings. This increases the likelihood that new recessive alleles, possibly originating from an unintentional outcross, will recombine and recessive phenotypes will be observed.

Production records and observations made by animal care technicians are the front line for detection of genetic contamination. For example, an increase in litter size may be an indication of heterosis, or hybrid vigor, due to genetic contamination, as might a coat color change.



EVERY STEP OF THE WAY

II. Genetic Monitoring

A. Overview

As genetic contamination is often inapparent, genetic monitoring of qualitative genetic markers is required to verify the authenticity of inbred and F1 hybrid strains. In association with advances in molecular genetics, the phenotypic biochemical and immunologic protein markers, once the mainstay of genetic monitoring, have been supplanted by gene sequence polymorphisms, including variations in the number of tandem repeats in mini- and microsatellite DNA, and most recently, single nucleotide polymorphisms (SNPs) found in large numbers across the genome.

Irrespective of type, qualitative markers for genetic monitoring are chosen to be distributed across the species genome and to distinguish among common research models. The allelic profiles generated by genetic monitoring are compared to established strain profiles.

B. The Charles River Program

Our mouse and rat panels for genetic monitoring each consist of 32 SNP loci on the autosomal and X chromosomes. The SNPs in these limited panels were chosen to differentiate strains rather than substrains and, hence, to detect genetic contamination rather than drift.

Genetic monitoring of nucleus colony animals in each inbred mouse and rat strain, as well hybrid F1 offspring or parental breeders, is performed once quarterly. The results of genetic testing are compared to established reference strain profiles to confirm genetic authenticity.