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Choice of Strains,
Strain Genetic-Differences, Modifiers

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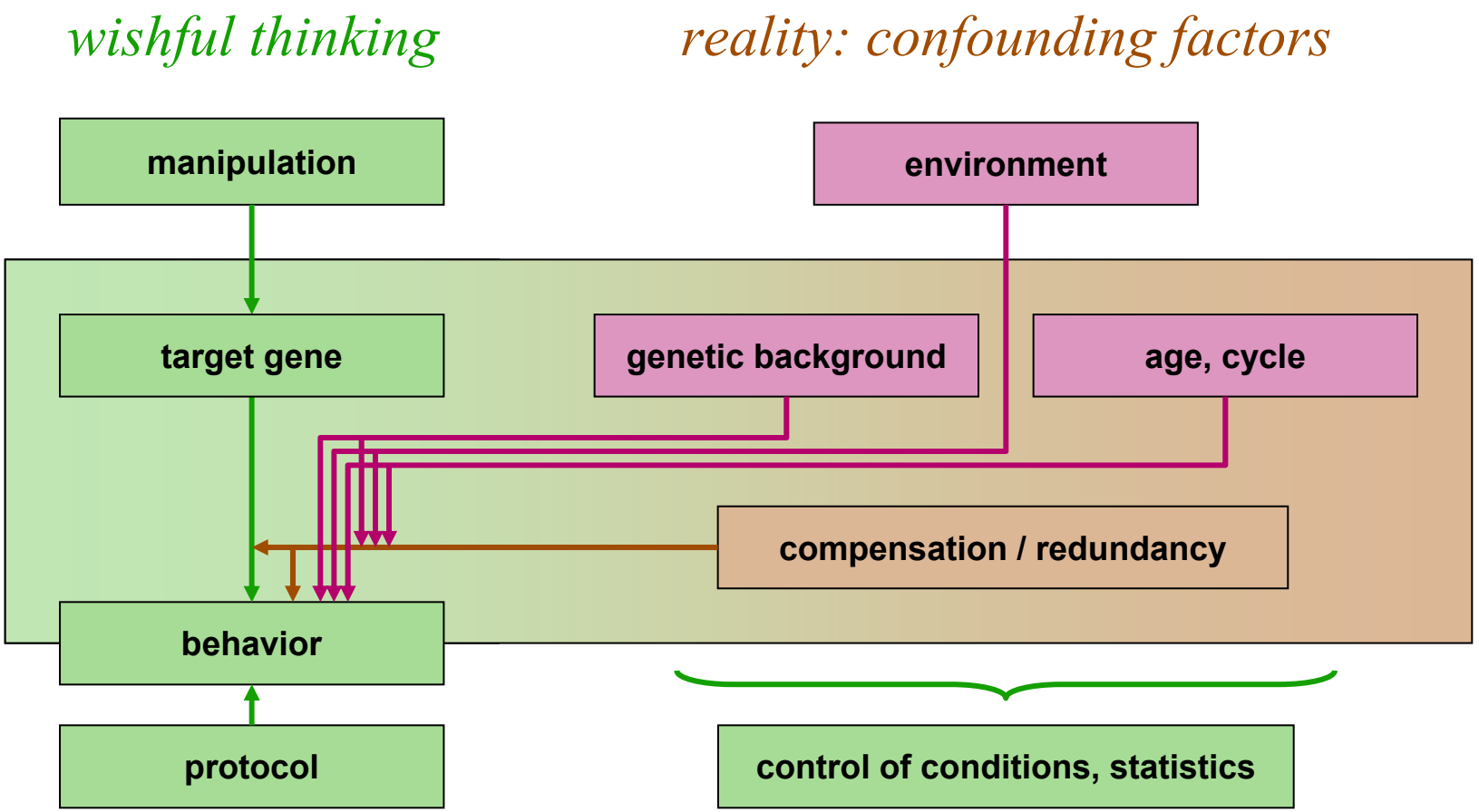
Gene targeting and behavior

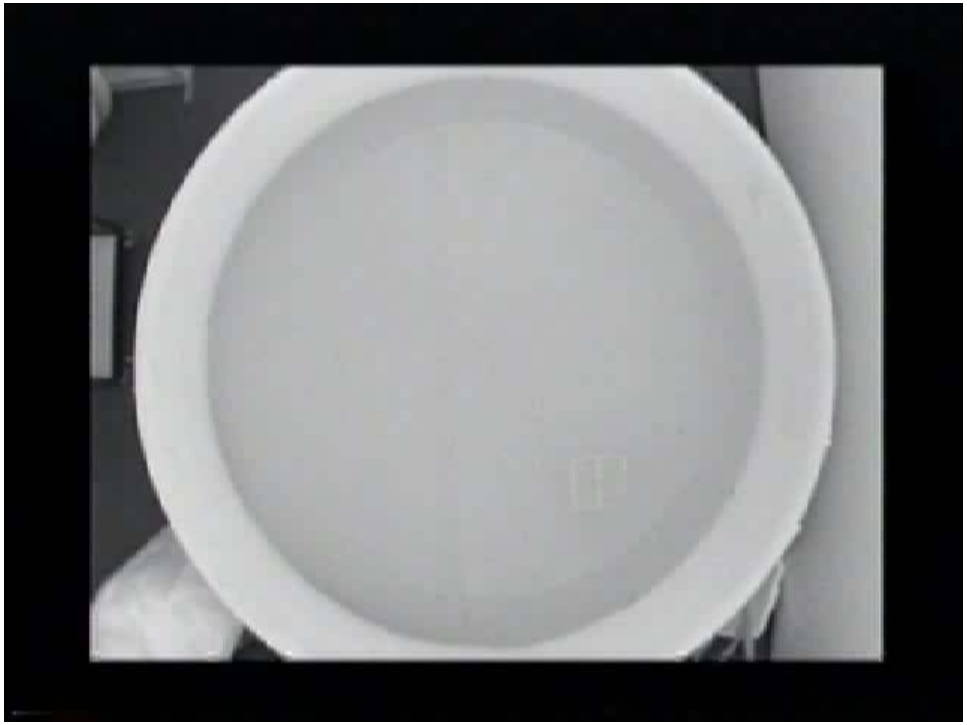


Genetic background:

Does it need consideration? YES!

Is it a hopeless issue? NO!

The place navigation task: testing spatial memory in a swimming pool



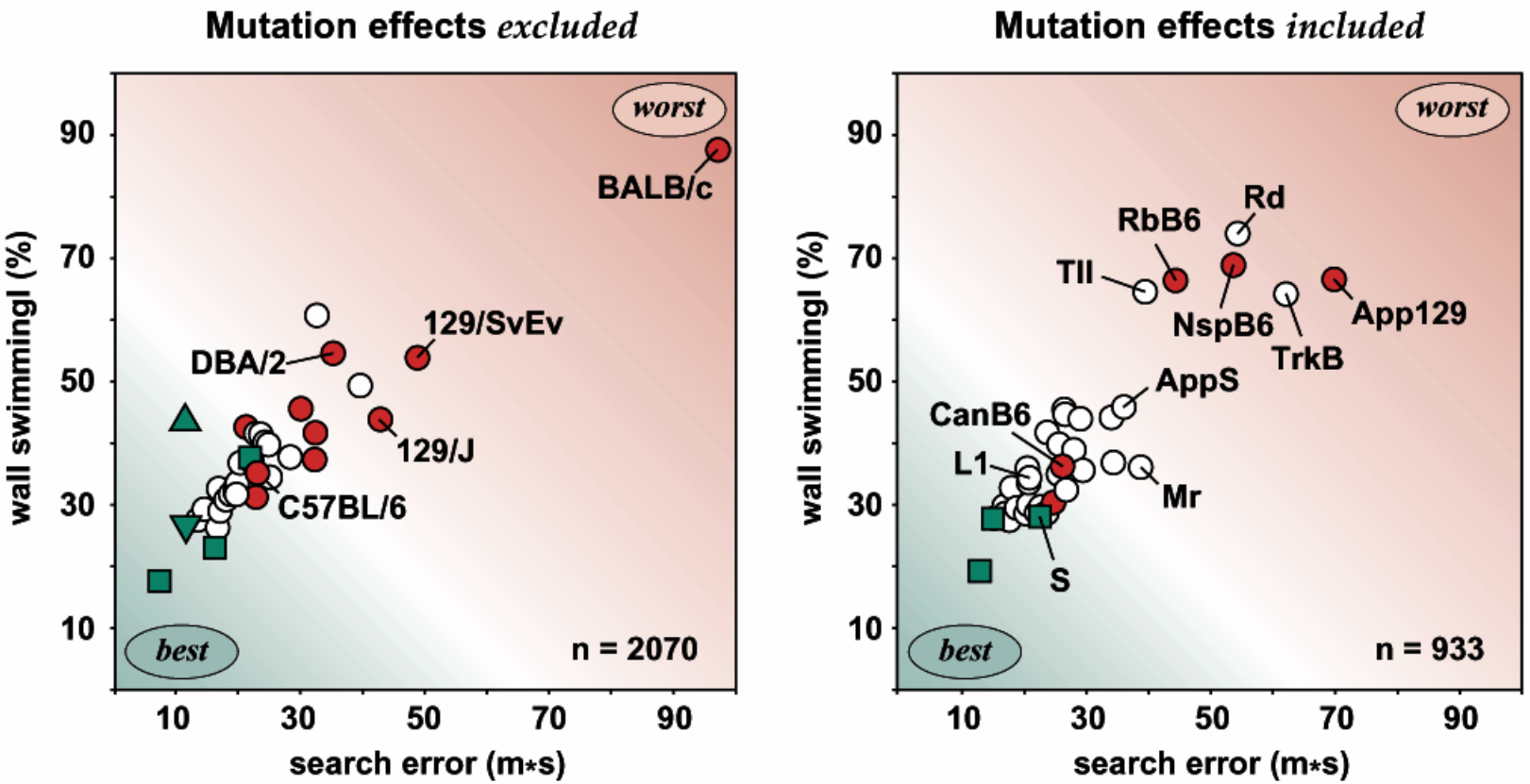
Morris RGM,
Learn Motiv, 12:239-260, 1981

Rats learn to swim to a hidden platform using cues located outside the pool.

Morris RGM et al.,
Nature, 297:681-683, 1982

Lesions of the hippocampus disrupt spatial navigation but not the ability to swim.

Place navigation in the water-maze: training performance of non/mutant mice

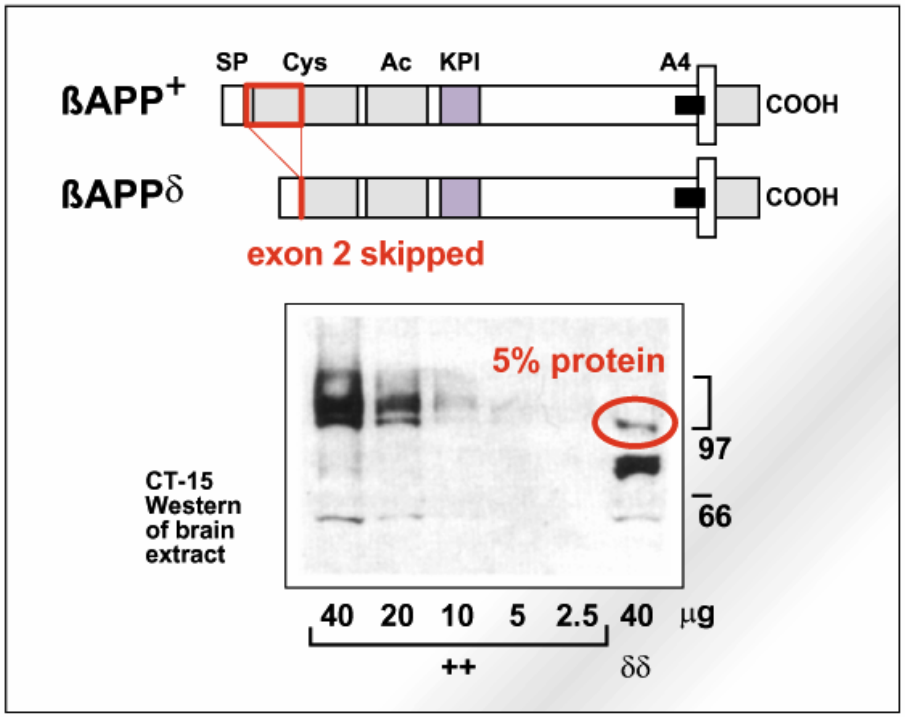


Exp Physiol 85:627-634, 2000

Genetic background effects

- Inconsistent or false negative results due to mutation-independent effects of genetic background:
  - baseline shift
  - ceiling/floor effects, non-performance of control animals
- Inconsistent results due to background x mutation interactions:
  - strain differences in ability to compensate
- False negative results due to large variability:
  - genetic noise in genetically inhomogeneous samples
- False positive results due to systematic differences in genetic background of mutant and control groups:
  - breeding of separate mutant and control lines
  - insertion effects
  - genetic linkage ("flanking gene problem")

βAPP-deficient mice



Phenotype of ßAPPδδ mice has been characterized in different genetic backgrounds:

Reduced body weight, impaired place navigation, abnormal openfield exploration, frequent agenesis of corpus callosum.

Müller et al. Cell 79:755-65, 1994

Retardation of neurological, behavioral, and somatic postnatal development. Permanent reduction of grip strength.

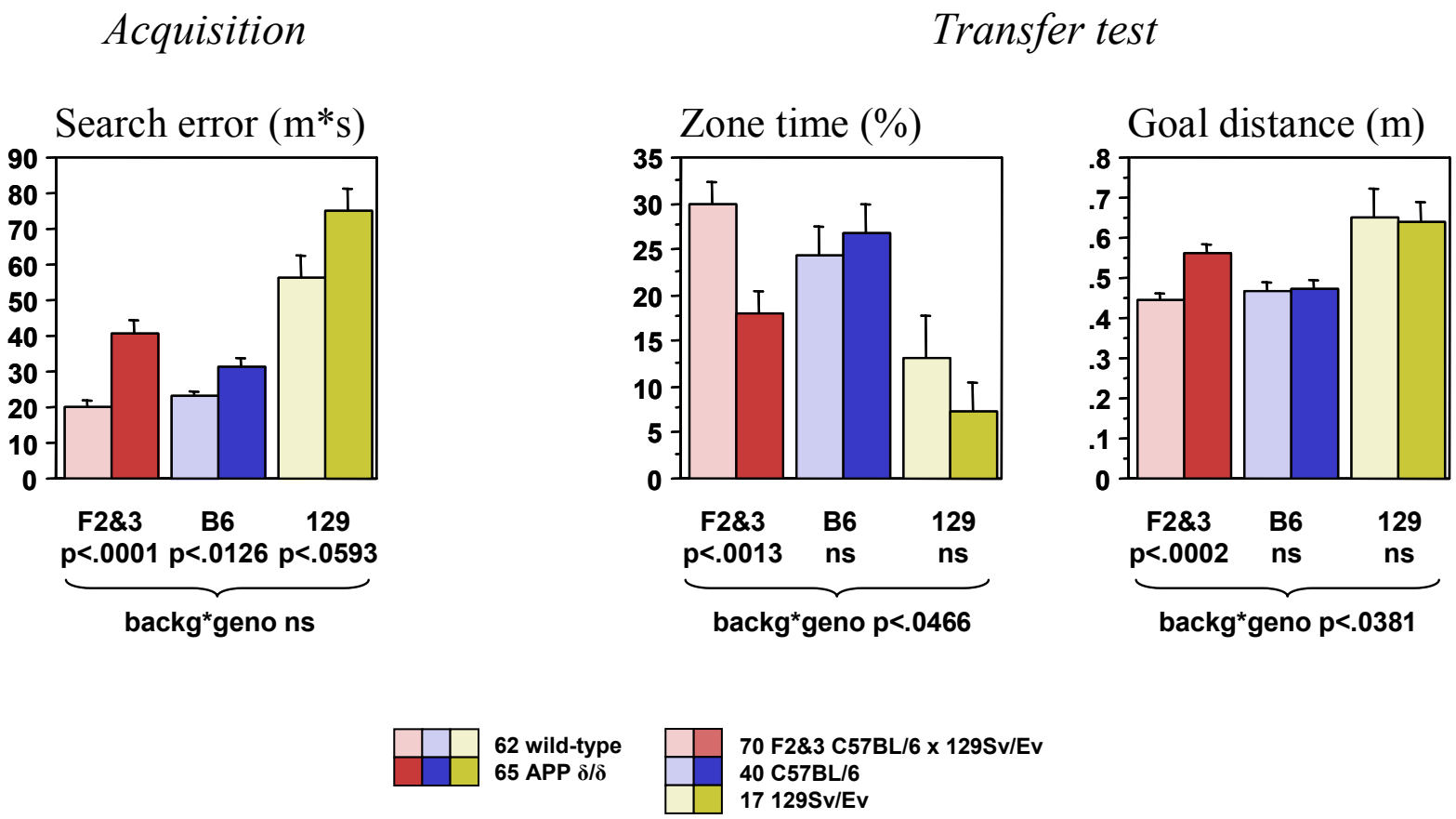
Tremml et al. BBR 95:65-76, 1998

Reduction of brain weight and forebrain commissure size. 100% corpus callosum agenesis in 129 background.

Magara et al. PNAS 96:4656-61, 1999

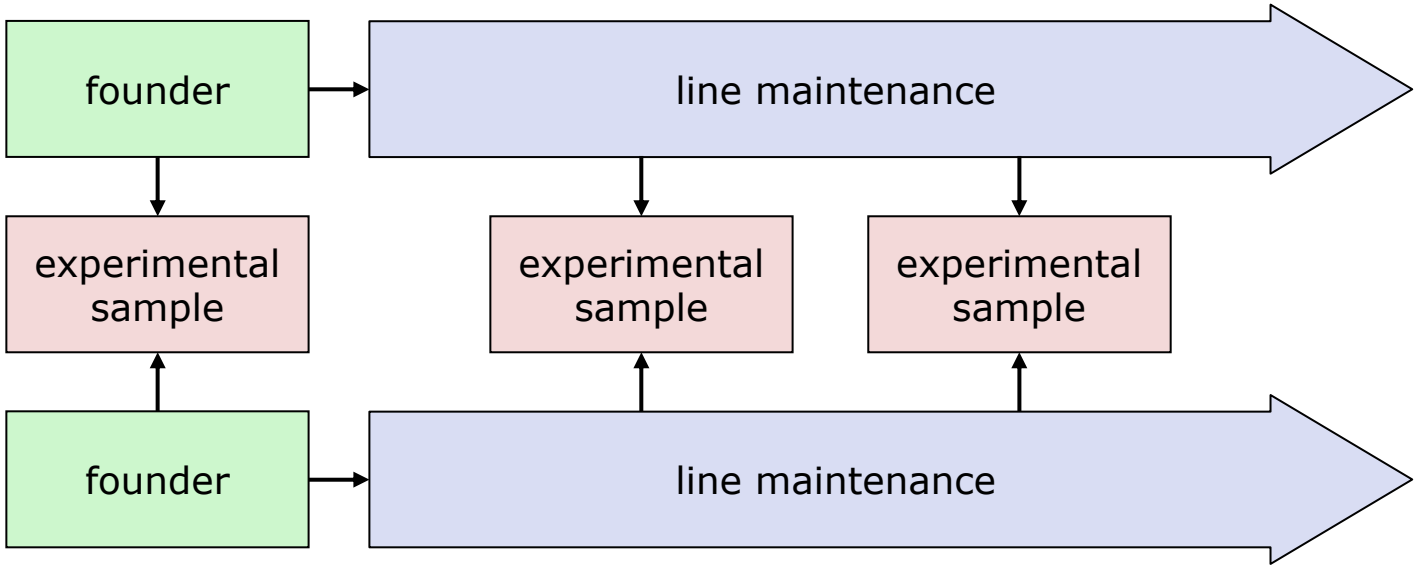
Cell 79:755, 1994

Genetic background modifies the impairment of βAPP-deficient mice in the water-maze task



Brain Res 771:1, 1997

Line generation, maintenance and analysis



Different genetic backgrounds may be appropriate for

- generation of founder animals
- long-term maintenance of mutant lines
- animals used for experimental investigation

Common choices of genetic background

Founder

Strain determined by requirements of transgenic technique:
- homologous recombination: 129- or C57BL/6- derived ES-cells
- random insertion transgenics: F1-hybrid oocytes

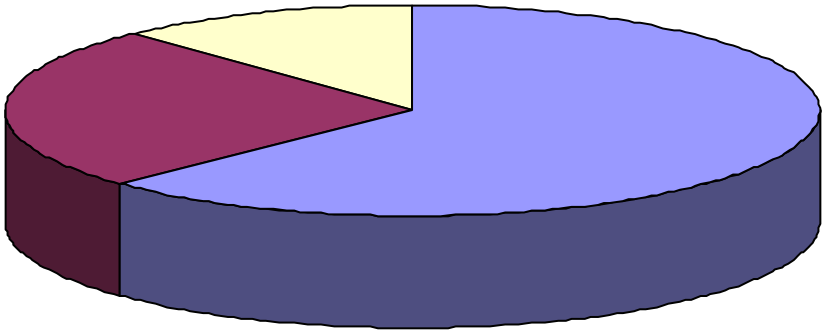
Line maintenance

Goal: efficient breeding, easy transfer between labs, repeated generation of experimental samples with same genetic background:
- backcross to ES-cell donor strain: *co-isogenic* line
- backcross to other commonly available strain: *congenic* line
- propagation of first test sample without control of background

Experimental samples

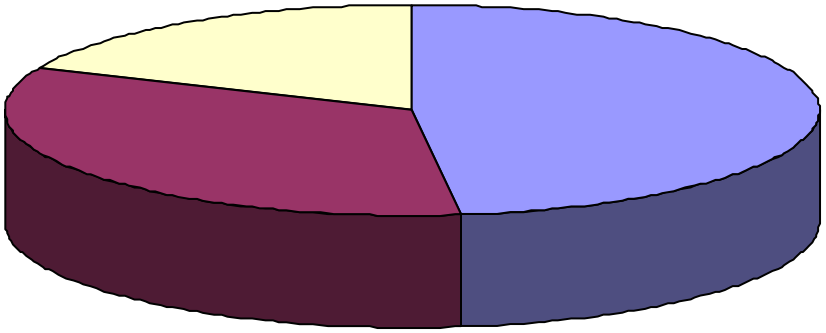
Goals: rapid and reproducible results, low variability, no ceiling or floor effects, suitability for wide range of investigations:
- F2/F3 crosses, inbred strains, F1 crosses

Genetic background of mouse lines tested in Zurich



1987-2004, 7167 mice

63% F2 / mixed
25% inbred
12% F1 hybrid

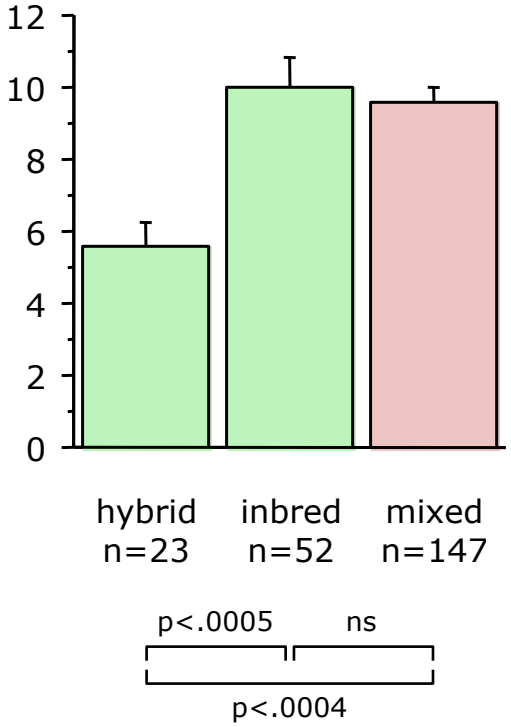


2002-2004, 2194 mice

48% F2 / mixed
34% inbred
18% F1 hybrid

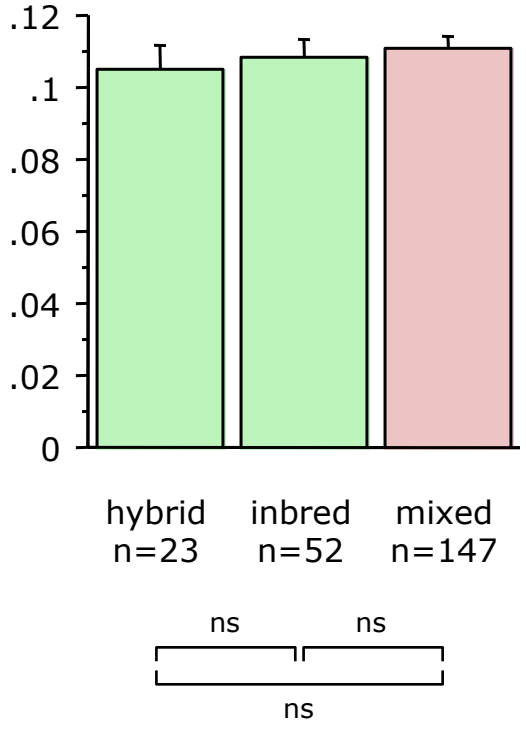
Inbreeding and variability of water-maze learning

Water-maze, training
SD search error (m,SE)



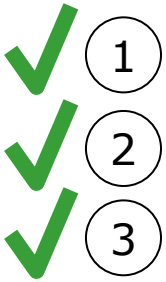
2989 mice,
average group
size 13.5
(non-mutants)

Water-maze, probe test
SD goal distance (m,SE)



Minimal requirements for genetic background

Check that genetic background in experiment is…



1. …free of bias between control and mutant groups
2. …well documented and easy to reproduce
3. …compatible with all experimental procedures, with controls producing a baseline that prevents ceiling or floor effects

Maintain mutation as congenic or co-isogenic line, e.g. by backcrossing to C57BL/6

Analyze mutation in inbred, F1 hybrid or F2 samples using littermate controls (at least for behavioral experiments)