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National Toxicology Program

NTP BSC

December 1, 2006

Multiple-Mouse Strain Studies of Genetic Variation and Host Susceptibility to Toxicity

HSI Concept Review

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Prior Public Discussions/Reviews

- NTP BSC 13 June 2006
- Extramural Experts (Mouse Genomics) 21 July 2006
- Intramural Research Scientists (Series)
- NTP Retreat 18-19 October 2006

A new (non-GLP) research contract is required to study -

- Gene-Environment Interaction

- Focus - individual susceptibility to environmental agents of public health importance

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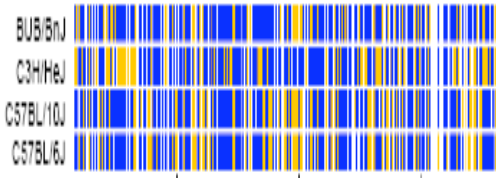
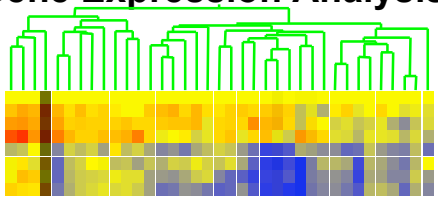
Cho et al. AJRCMB 24:42 (2002)

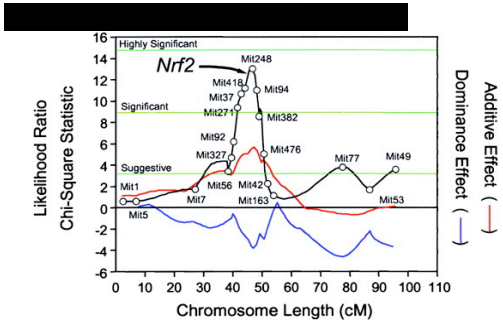
Haplotype Mapping



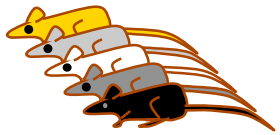
Gene Expression Analysis



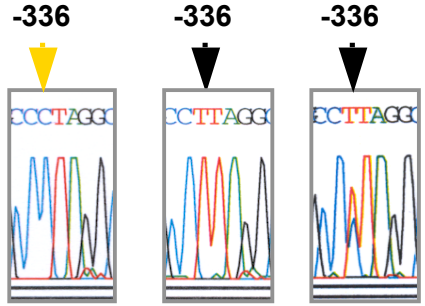
Candidate QTL

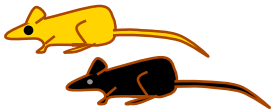


Phenotype isogenic strains



Susceptibility Gene





- Back-cross, F_2 cohorts Genetic markers
- Recombinant inbred mice

Meiotic Mapping

ctccatgcccttgtcctgcctctggccc
ttgcctcttgccctagccttttctccgcct
ctaagttcttgtcccgtccctaggtcctt
gttccgcccccggggcgggggcgg

Sequence Analysis

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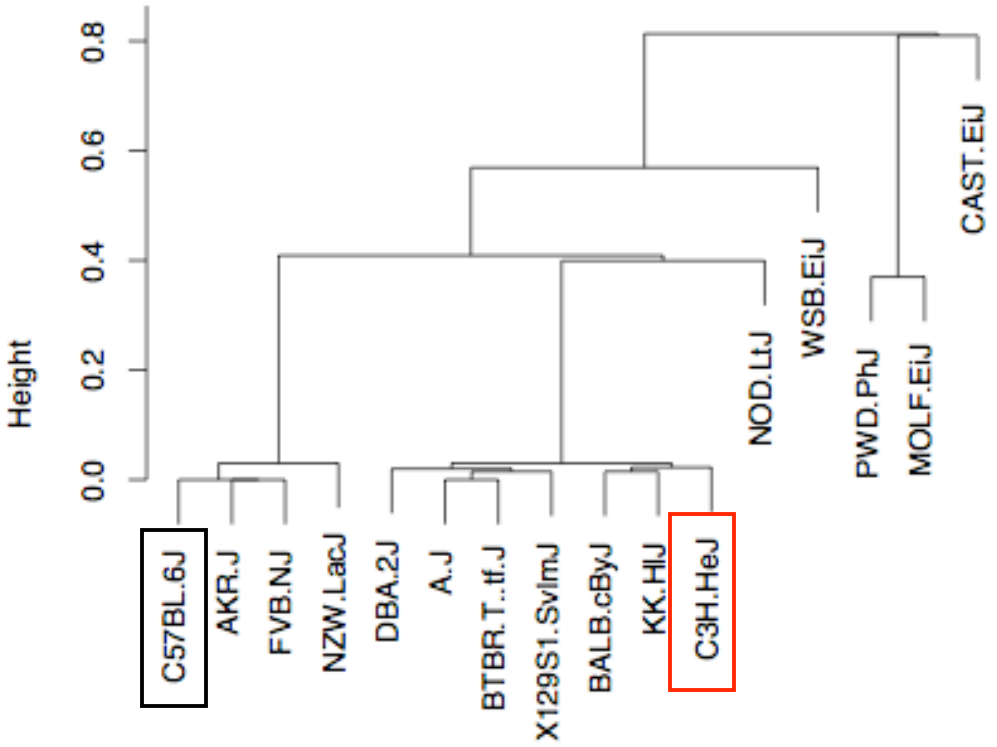
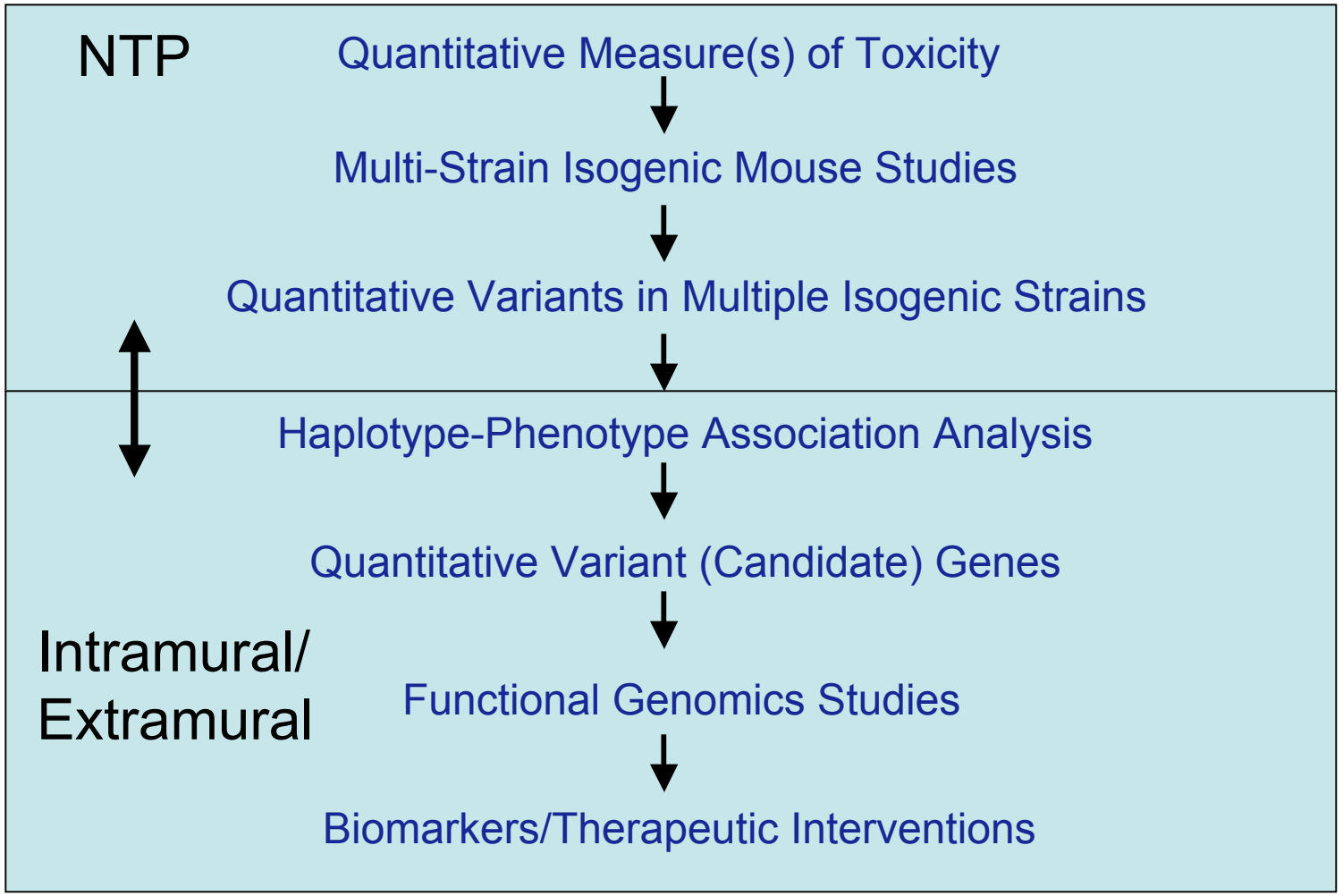
Nuclear factor, erythroid derived 2, like 2 (Nfe2l2)



Based upon Perlegen-NIEHS Resequencing

1 – simMat
Hap Size = 3

The Approach (Non-GLP)



Objective: **The purpose of this contract is to provide the capacity to use multiple isogenic mouse strains to study the genetic basis for variation in quantitative measures of chemical toxicity *in vivo*.**

AIMS

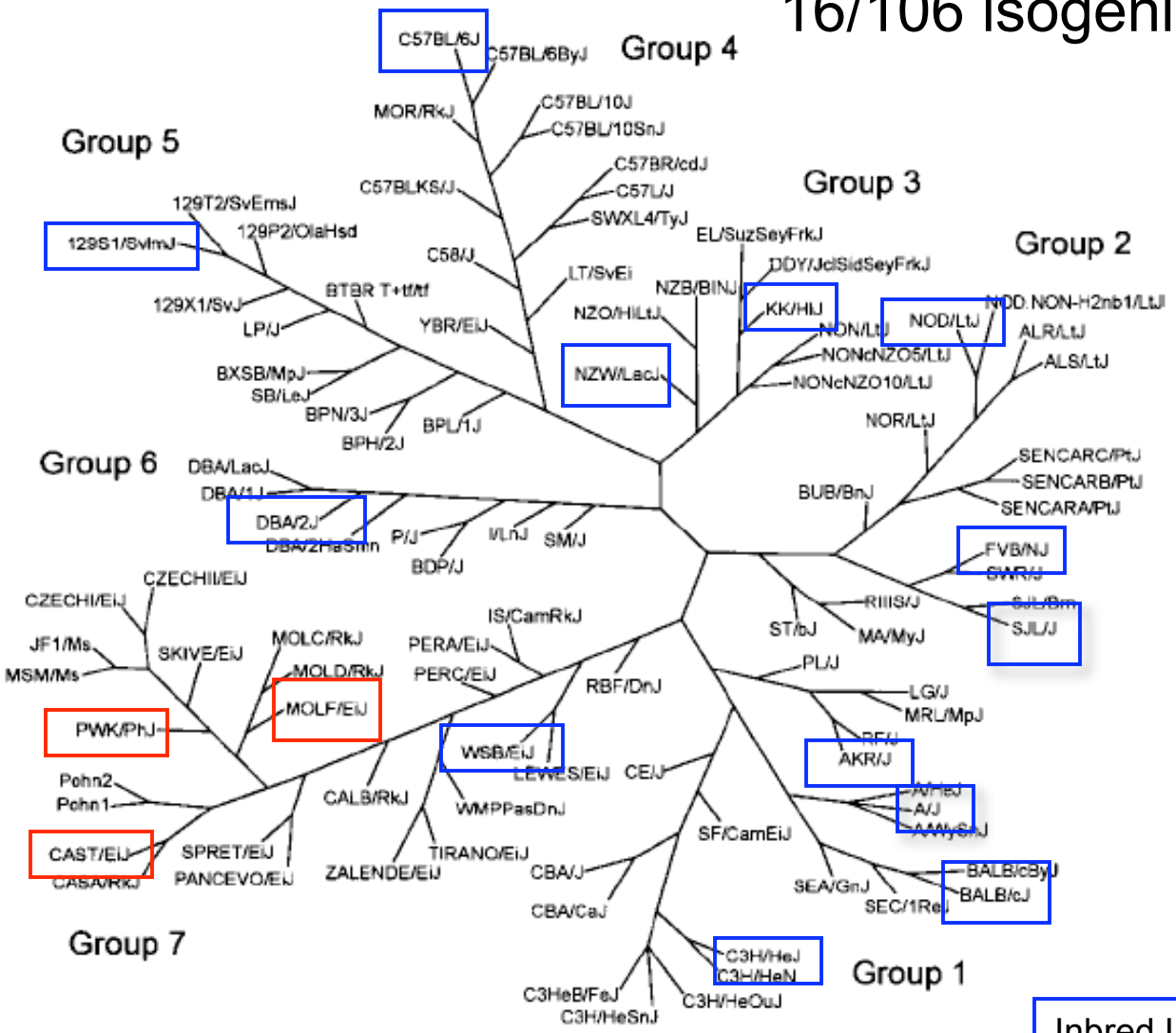
- To use the significant genetic diversity within different laboratory and/or wild-derived (isogenic) mouse strains to model and predict potential population-level ranges of response to toxicant exposure.
- To identify and to understand the functional characterization of specific genes and their allelic variants that are associated with individual differences in response to toxicant exposure.
- To use comparative genetic analysis of susceptibility genes discovered in individual strains of mice to identify risks specific to susceptible human populations harboring genetic variations in orthologous genes and pathways (NIEHS Environmental Genome Project).

Summary

- A new initiative to leverage NTP expertise and data to gain insight into critical genes and basic disease processes contributing to the individual response to environmental exposures.
- Intended to foster greater use of NTP data in the understanding of complex human disease.
- Ultimately, to increase our understanding of Gene-Environment interactions leading to: 1) identification of new biomarkers for detection of exposure and/or effect of environmental agents and 2) new candidate genes and signaling pathways for clinical intervention.

Discussion

16/106 isogenic strains

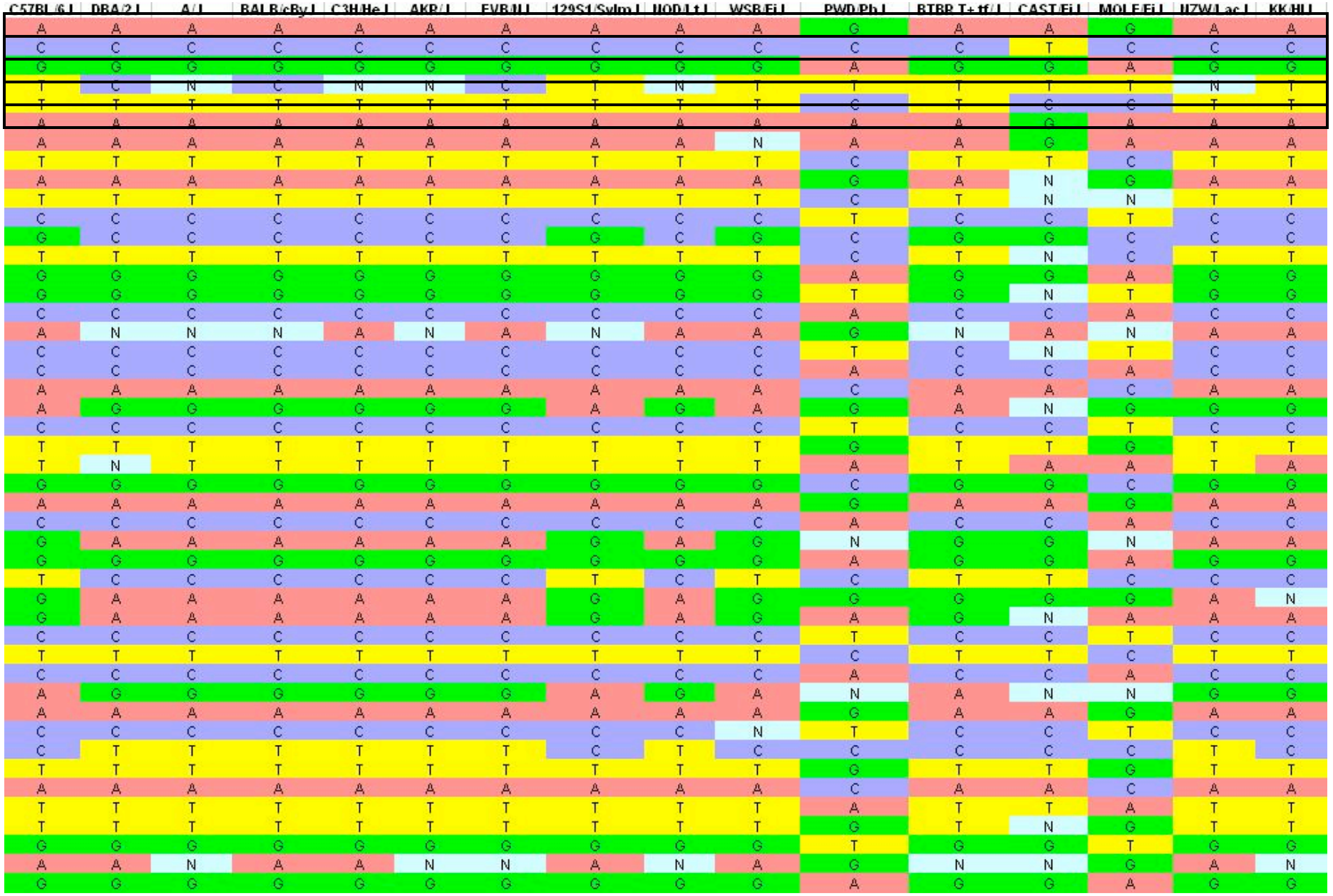


Inbred Laboratory

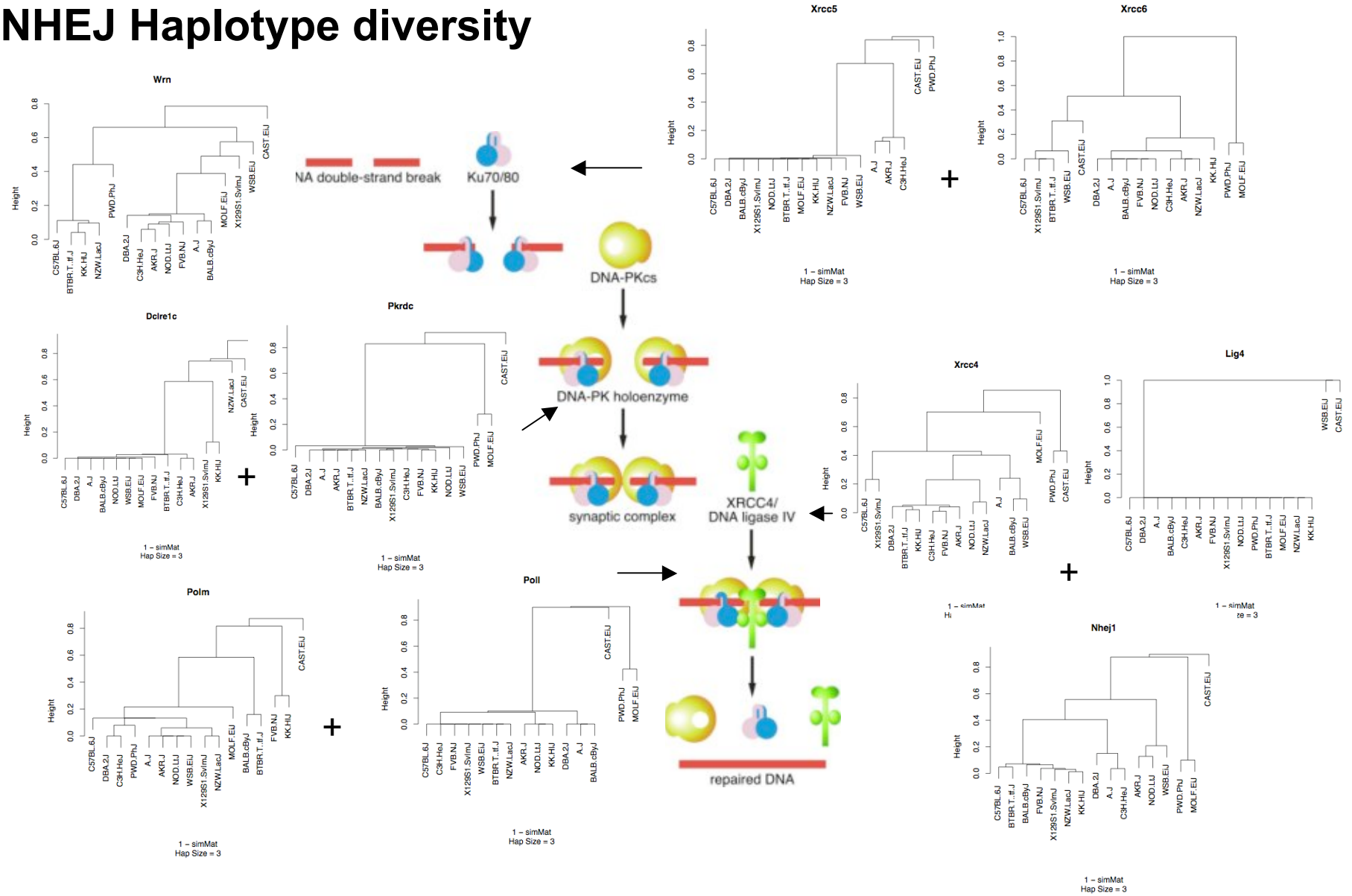
Inbred Wild-Derived

Petkov Genome Res 14:1806, 2004

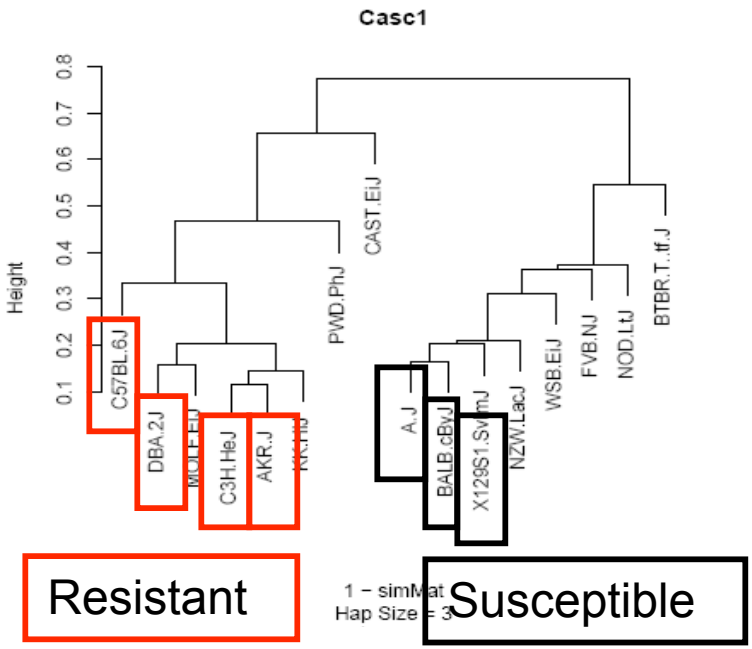
Xrcc6 (Ku70) Haplotype Map



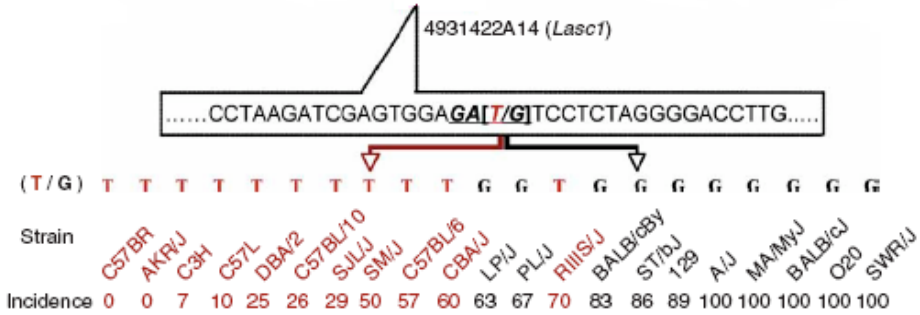
NHEJ Haplotype diversity



Casc1 susceptible haplotype segregation



Dendrogram for *Casc1*.



Identification of a nonsynonymous substitution (T>G = D102E) in the C*asc1* gene and its allelic distribution in laboratory inbred mice with different lung tumor incidence.

Liu et al. Nat Genet. 38:888-95 (2006)

- Over 100 B6xD2 RI lines have been created – if all were phenotyped and genotyped by SSLP, QTLs 1 cM apart could be identified by statistical association
- By SNP genotyping this could be reduced to 5000 base pairs or less