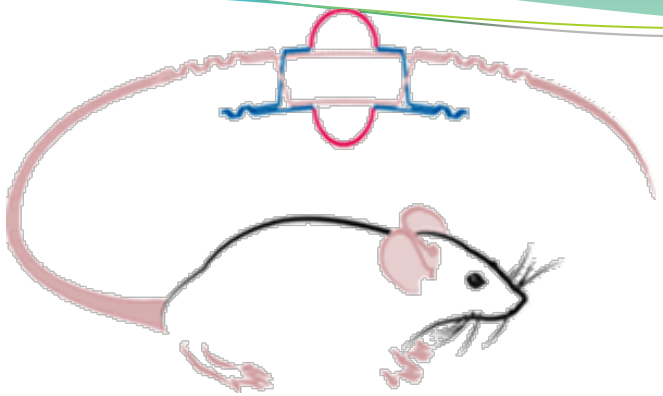


Knockout Mouse Production and Phenotyping (KOMP^2): Update and Envisioning a Possible Second Phase

National Institutes of Health
Division of Program Coordination, Planning, and Strategic Initiatives

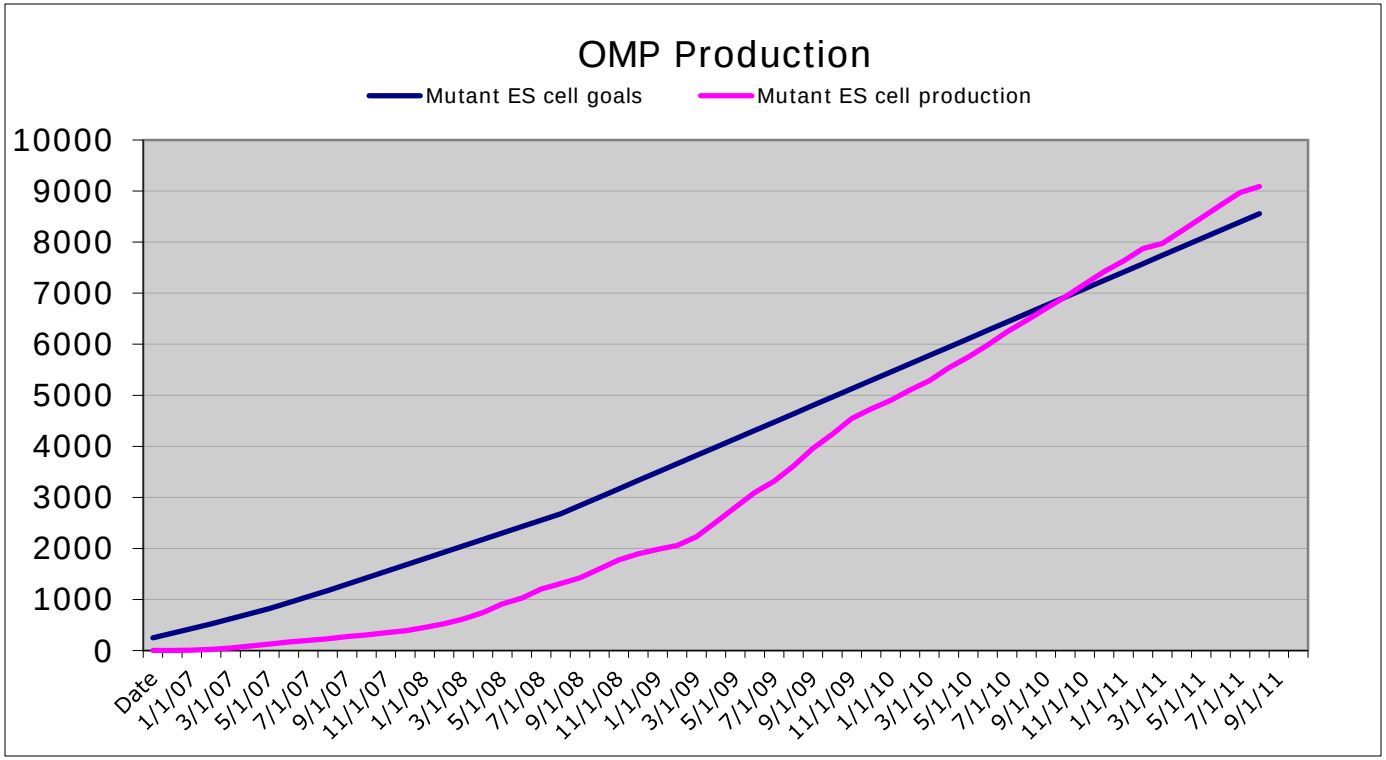
Council of Councils
September 5, 2014

National Institute on Deafness and Other Communication Disorders

KOMP (2006-2011)

- *"…a high-throughput international effort to produce…knockouts for all mouse genes, and place these resources into the public domain."*
- The KOMP was launched in 2006 by NIH
  - $56.6 million over 5 years from the ICs
  - a goal of creating 8,500 ES cell lines
  - alleles are nulls or conditional-ready, contain reporter
- The EC launched EUCOMM, the European Conditional Mouse Mutagenesis Program in October 2005 (funded in Feb 2005)
  - 13 M Euros over 3 years
  - a goal of creating 8,000 mutants.
- KOMP and EUCOMM along with other international efforts formed the International Knockout Mouse Consortium (IKMC) and have jointly produced > 17,000 mutant ES cell lines and made them available from public repositories.

KOMP - Goals and Progress



9090 KO lines produced and being distributed from the KOMP repository

Community uptake:

1250 orders for vectors
2512 orders for ES cells
980 orders for mice or germplasm

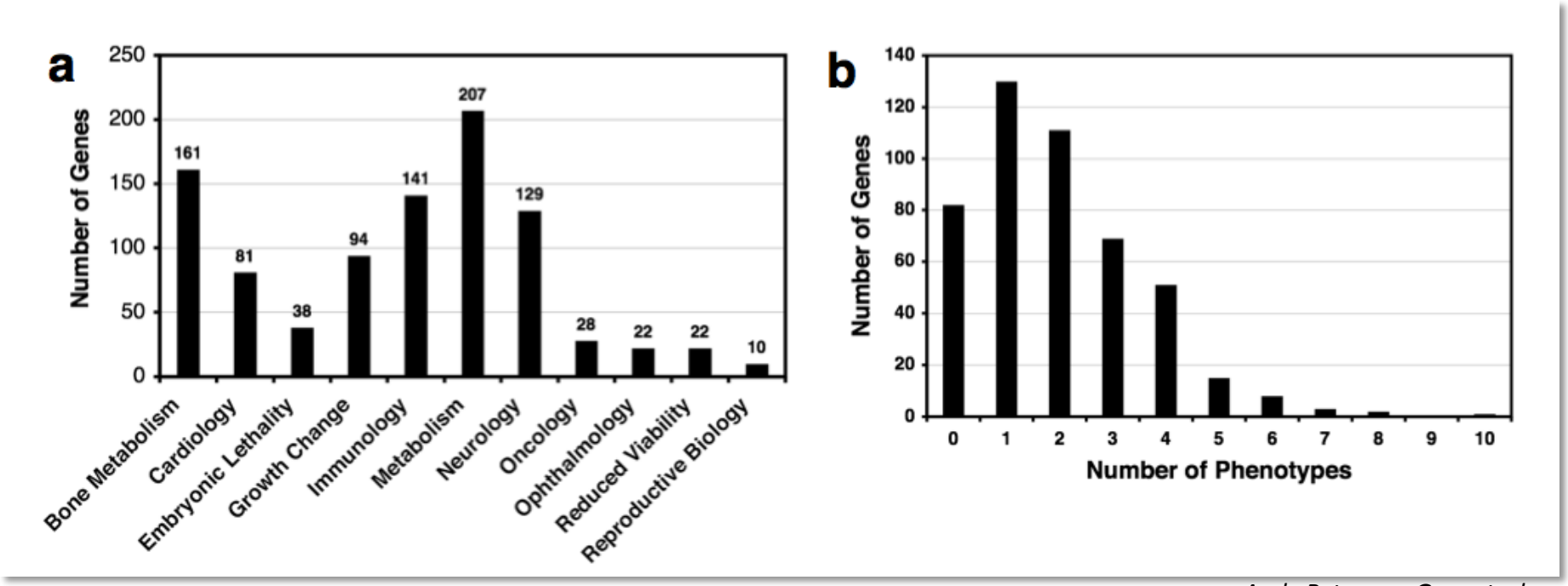
Rationale for Large-scale Phenotyping

Supporting a broad phenotyping effort would provide the following advantages:

- Eliminate the redundancy and waste inherent in the “cottage industry” approach
- Each mutant mouse will be characterized for a broad set of phenotypes to allow direct comparisons & result in a thorough description of gene function.
- Novel genes will be brought to light that would otherwise be ignored
- Quality standards will be established and maintained, so the data will be of the highest reliability.
- The risk of not finding a phenotype will be greatly reduced.
- Important, but unpublishable, negative results will be captured.
- Potential for breakthrough discoveries

Genentech/Lexicon Mouse Phenotype Project

472 Mouse knockouts were broadly phenotyped



Andy Peterson, Genentech

130 (27%) strains had 1 phenotype
245 (52%) strains had 2-5 phenotypes

Similar findings in EUMODIC and Sanger Mouse Phenotyping Program

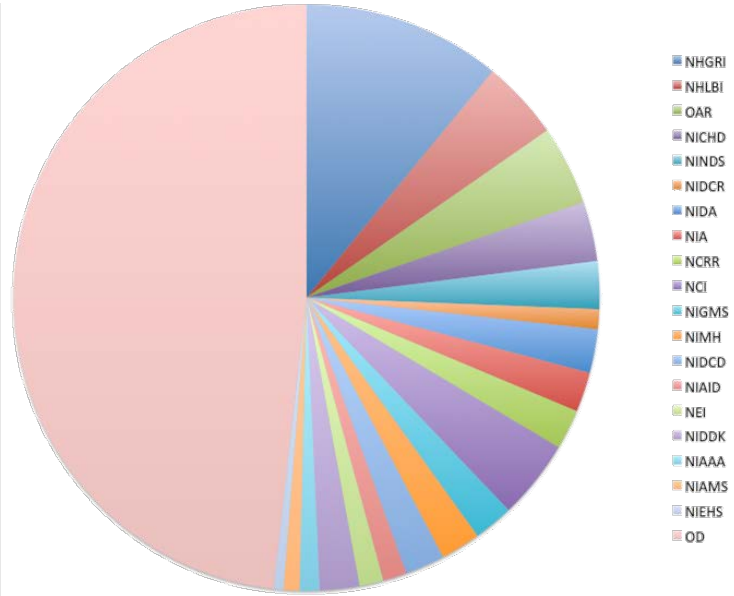
Co-Funding from Common Fund and ICs

Funding:

NIH Common Fund – 50%

Participating NIH ICs – 50%

$110M over five years



Project Awards:

Mouse Production and Phenotyping:

The Jackson Labs

Baylor College of Medicine

University of California, Davis

Data Coordination Center and Database:

European Bioinformatics Institute

KOMP2 Project Goals - (2011-2021)

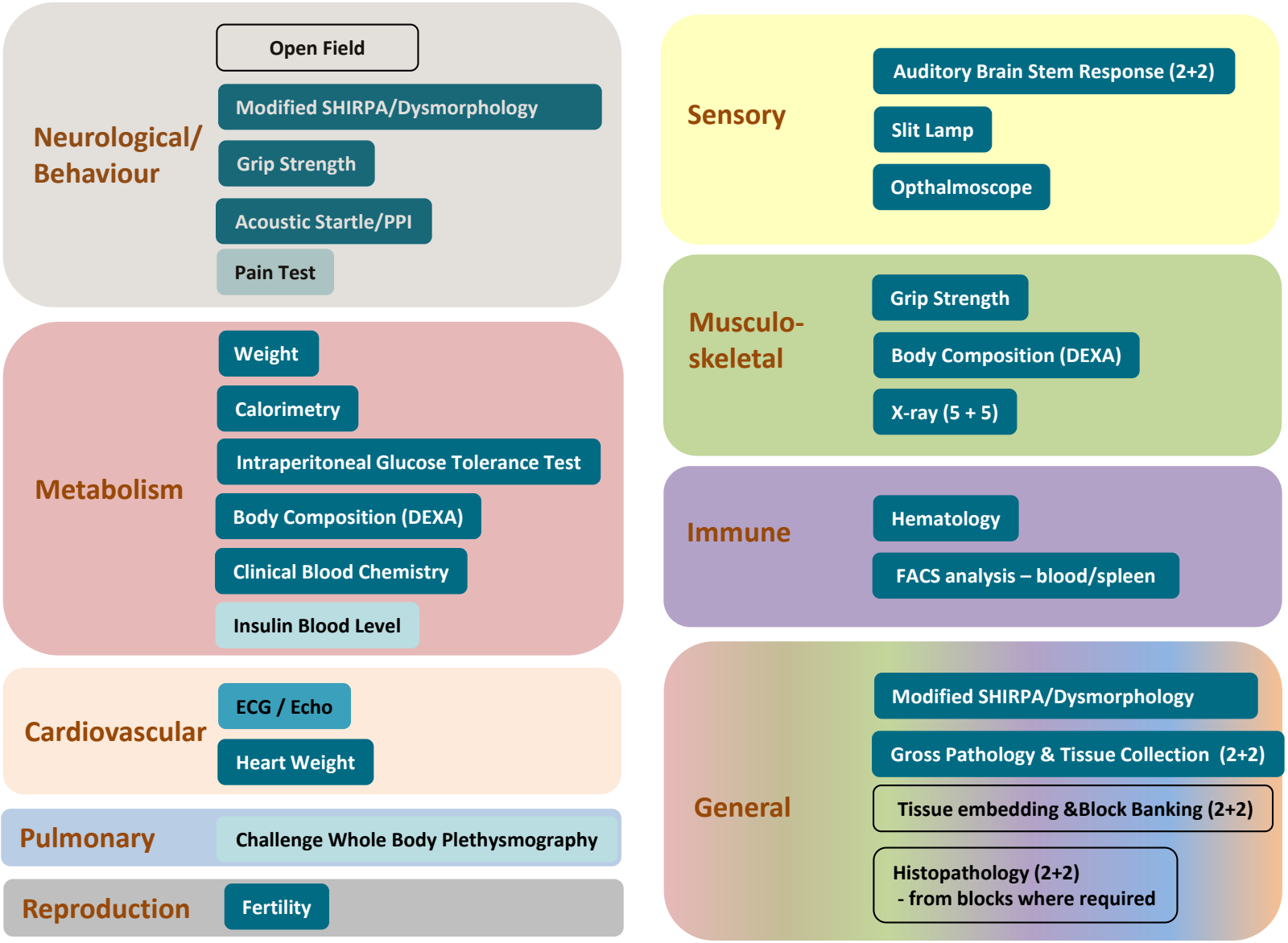
- **Phase 1 (2011-2016): Phenotype up to 2,500 lines**
  - Pipeline development, logistics
  - Phenotype technology developments
  - Economies of scale
- **Phase 2 (2016-2021): Phenotype 6,000 mutants**
  - Business plan in preparation

- **Data freely available through a Data Coordination Center**
  - "One stop shop" Web Portal

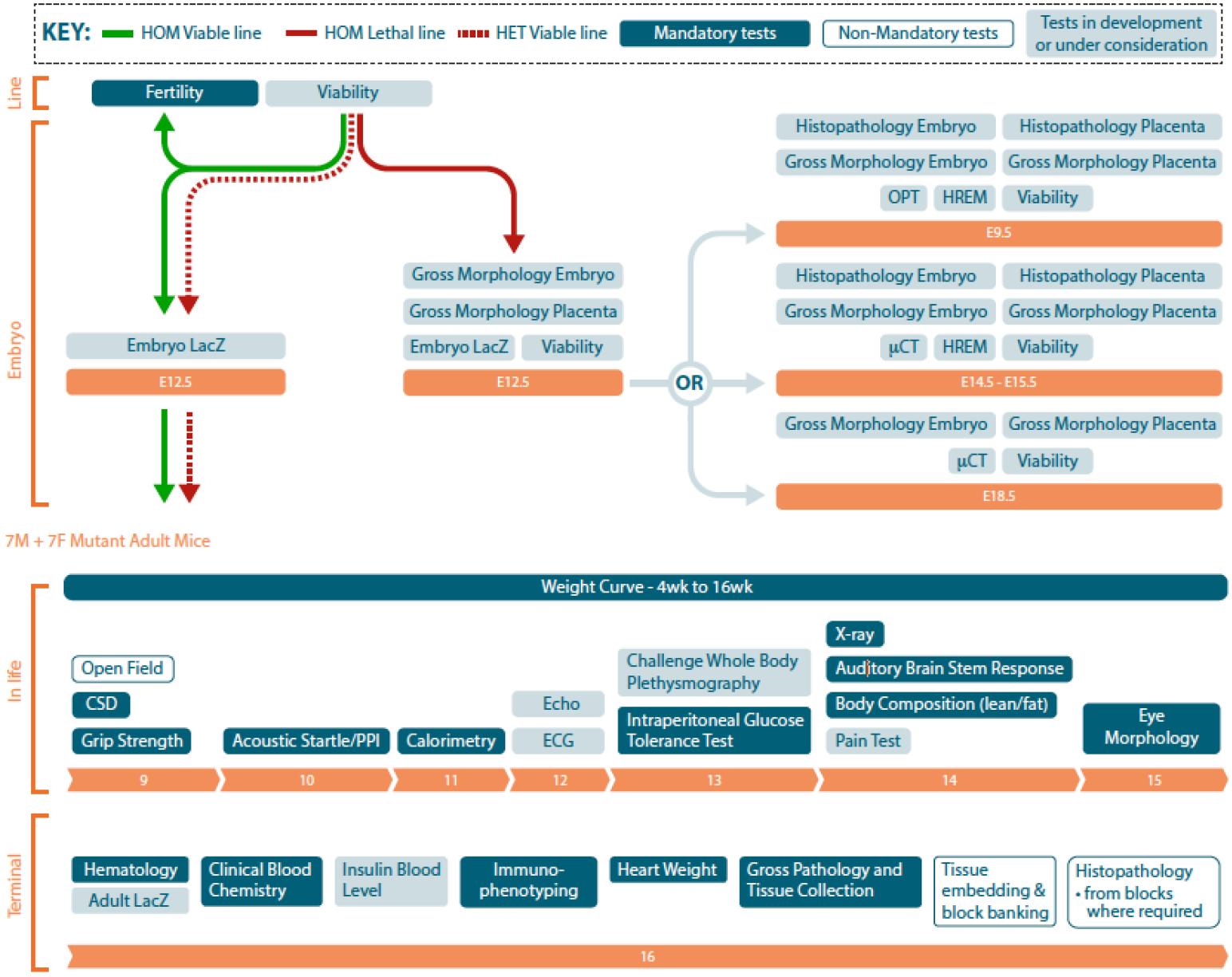
- **Mice available through the global network of mouse repositories**

- **Coordinate with IMPC to achieve broad-based phenotyping of 20,000 mutants from the IKMC resource**
  - A collaborative activity of mouse centers worldwide

Multiple Physiological Domains



Phenotyping Pipeline



Embryo

In Vivo

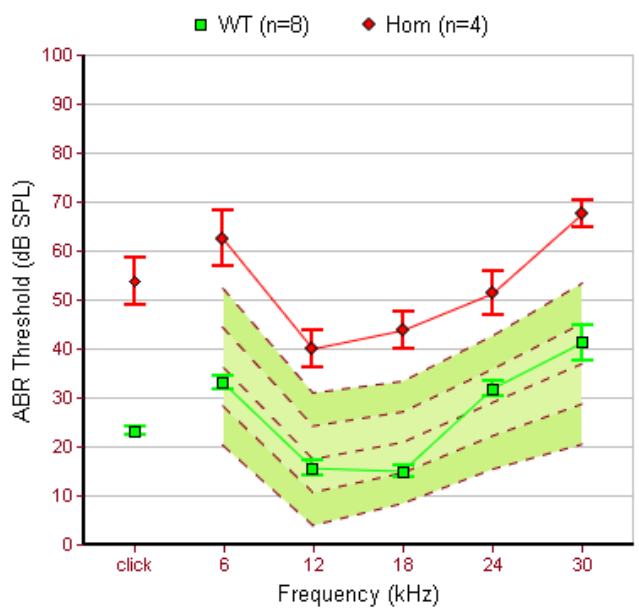
Terminal

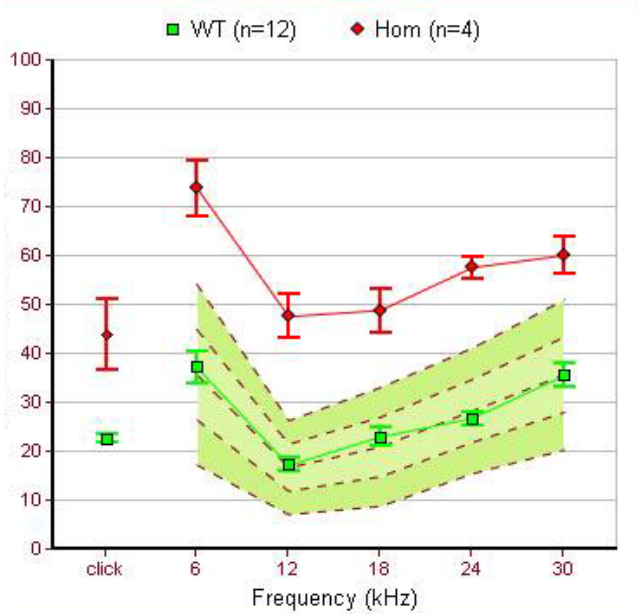
Three new genes involved in deafness

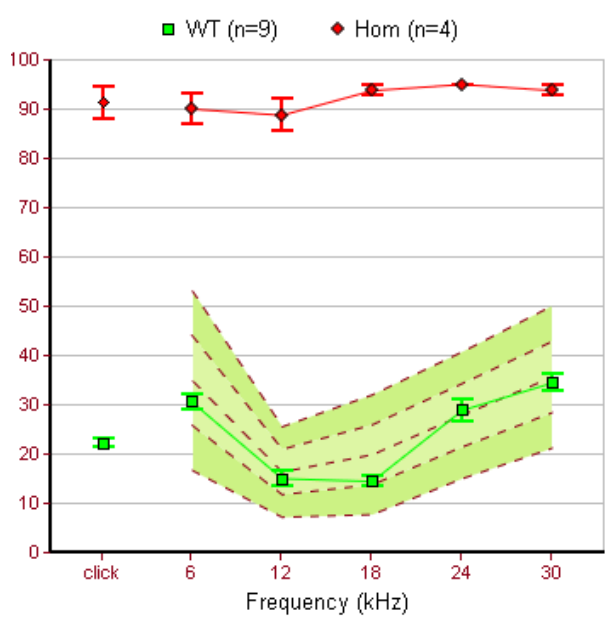
Lrig1 has moderate deafness (20-30 dB)

Mcph1 has moderate deafness (25-30 dB)

Spns2 has severe deafness (60-80 dB)







Plus: 9 further genes with possible mild hearing impairment (5-15 dB) and 20+ genes with possible amplitude or latency defects but normal thresholds

KOMP/KOMP^2 Timeline