From Linkage to Gene Detection

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Why detect QTL?

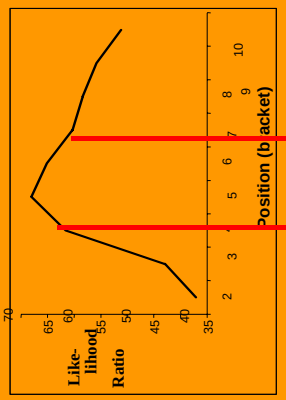
- Use markers linked to QTL in MAS
  - > genetic gain (esp. hard to select for traits)
- Use markers/ marker haplotypes in LD with QTL in MAS
  - >> genetic gain
- Find genetic mutation underlying QTL effect
  - patent = $$$$ (maybe)

Pathway for gene mapping

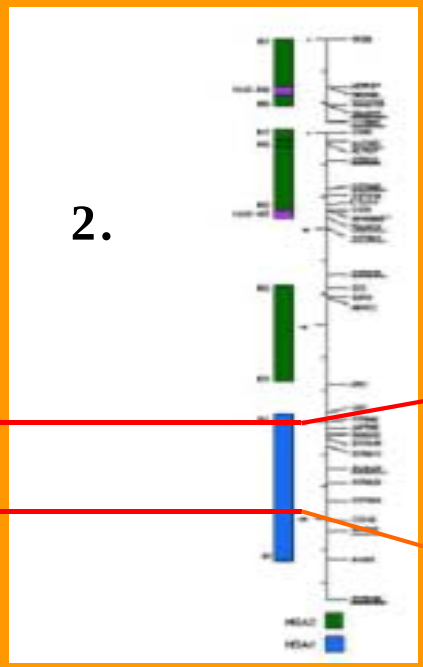
- If human genome ~ 3000cM long
- And there are between 30 000 and 100 000 genes
- 3cM segment contains between 30 and 100 genes
  - but don’t know what these genes are in livestock, no livestock genome project completed (yet)
  - even if we did know what genes were, too many genes to evaluate/sequence for causative mutation

Pathway for gene discovery

1.



2.



3.

25DAP 4EBP1
6P2ase ABF1
ACT ACTH actin
ADCC adrenaline
Af1 AF2 Ag
aIIbb3 AKT AP1
Apaf1 Apaf3

4.

5.

ACTGGGTCCCG
ACTGGGACCCG

6.

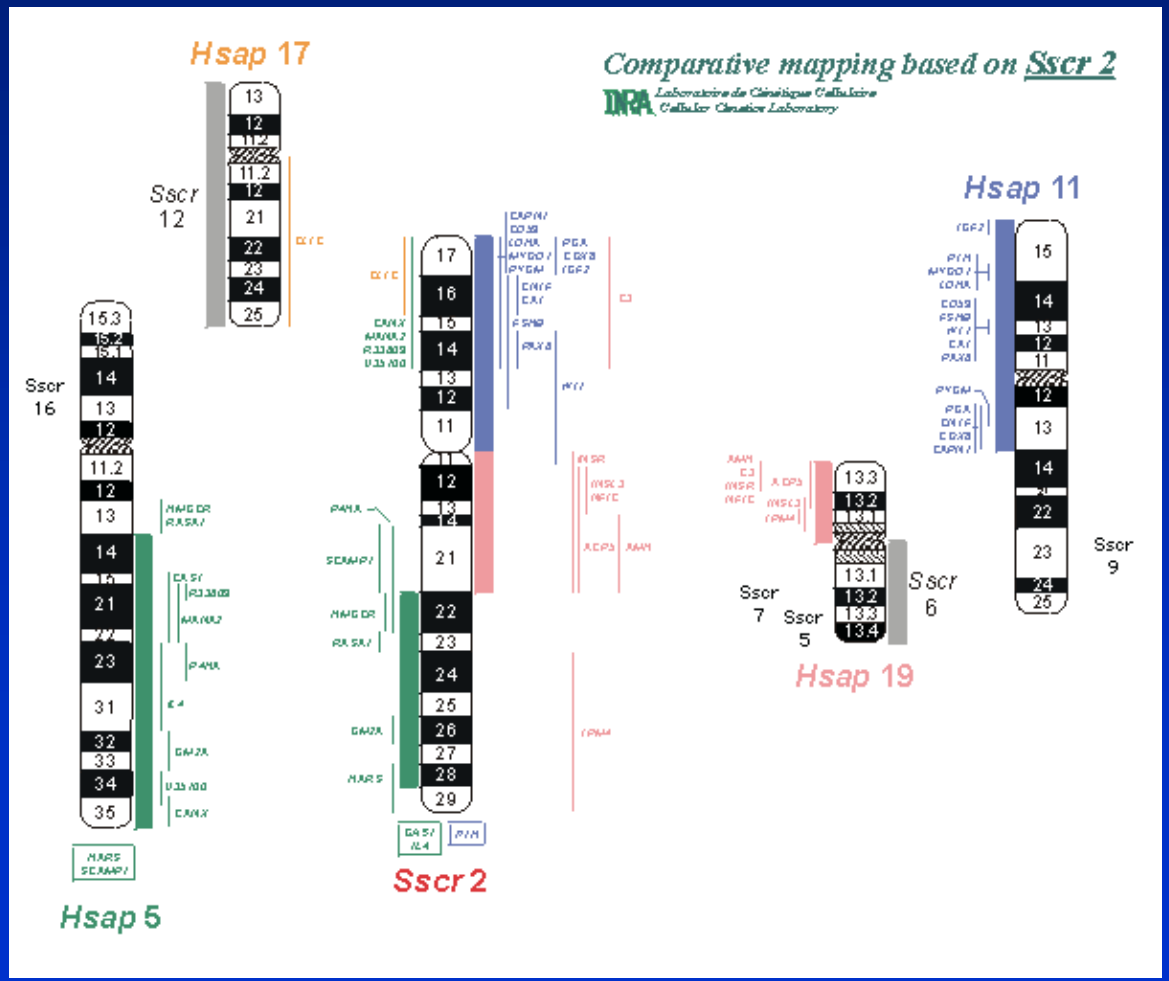
BLAST

Comparative mapping with humans

- Following human genome project, great deal of information about human genes
  - map livestock chromosome segment (C.I.) to corresponding human chromosomes
  - radiation hybrids, bi-directional painting

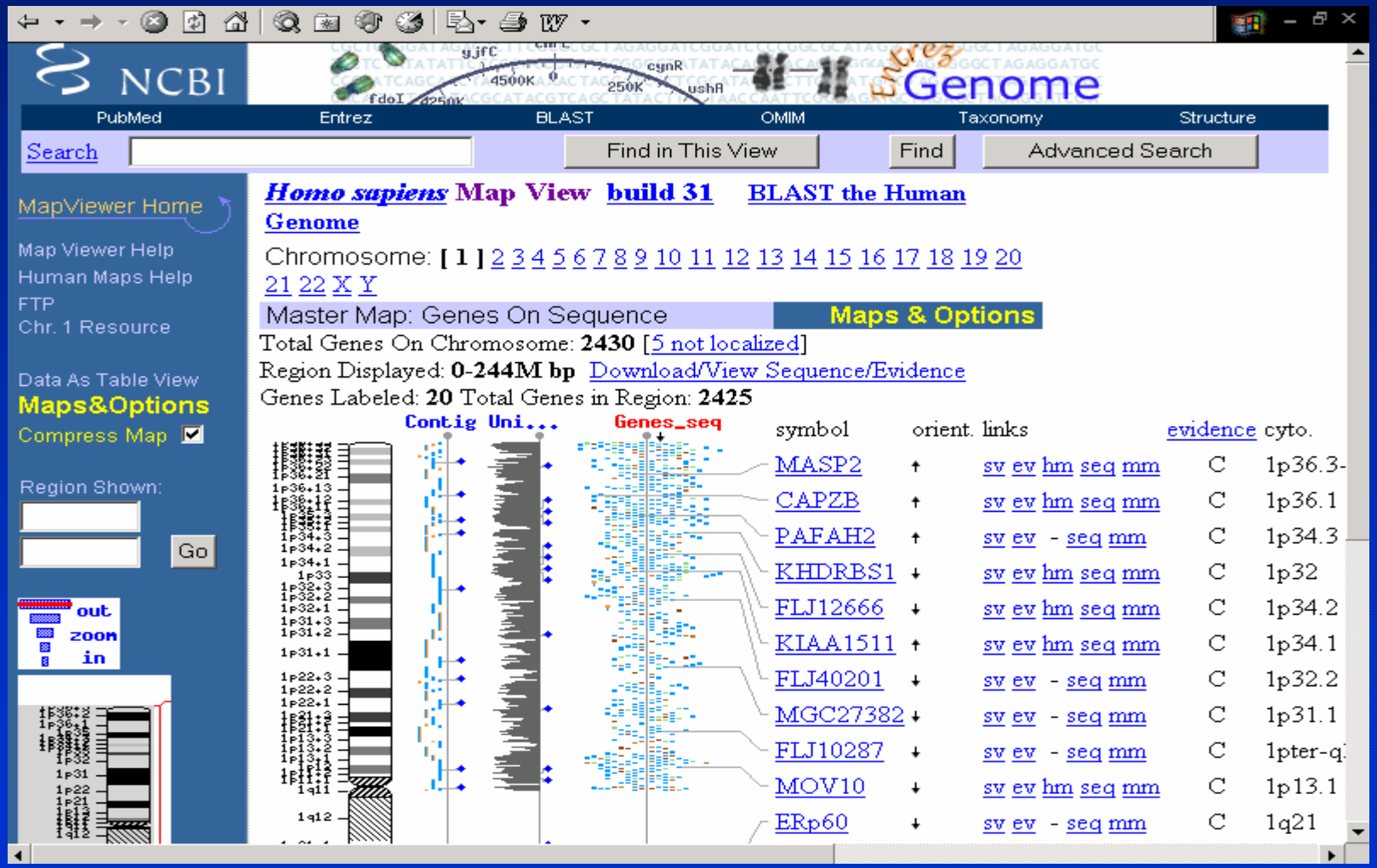
Comparative mapping with humans

Pig Chromosome 2



Selecting candidate genes in an interval

- For the segment of human chromosome, can return a list of genes on that segment



Selecting candidate genes in an interval

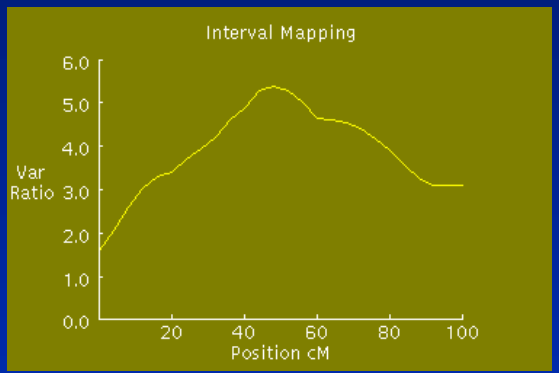
- Literature search (PubMed, etc) on key words (eg. “Lactation”)
  - record number of ‘hits’ to narrow list of candidates
- Next step: sequence heterozygous sires for candidate gene (or part thereof)
  - sequence of gene from NCBI
  - BLAST search to determine if any SNPS are function, eg change amino acids or insert stop codon

Selecting candidate genes in an interval

- Example of Inverdale gene (Galloway et al 2001)
  - July 2001, AgResearch (NZ) reported discovery of a mutation affecting litter size in sheep
  - Single copy of mutation in heterozygous ewes increased litter size by 0.6 lambs
  - Double copy small non-functional ovaries, infertile

Selecting candidate genes in an interval

- Example of Inverdale gene (Galloway et al 2001)



X chromosome

Candidate gene GDF9, selected, based on Inverdale like effects in mutant mice

But GDF9 not on X chromosome in humans, mice or sheep

Alternative candidate, GDF9B, does map to X chromosome

Point mutation discovered, use in sheep breeding schemes

Selecting candidate genes in an interval

- Example of Inverdale gene (Galloway et al 2001)
  - aided by unambiguous phenotype
- Nevertheless, this example and particularly DGAT1, prove it is possible to find the mutations which underlie variation in livestock production traits