Monogenetic traits in the Jersey breed and how to handle these

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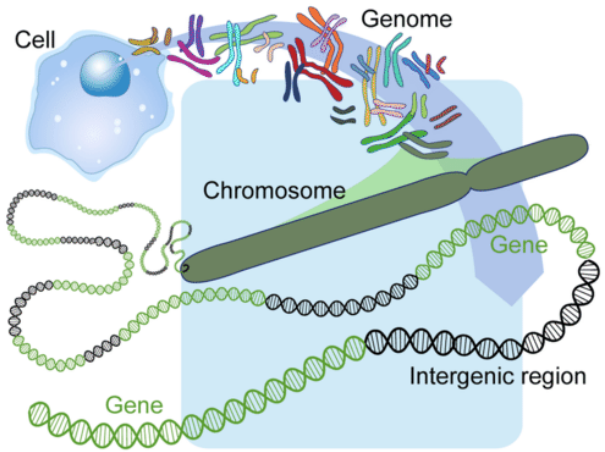
GENETIC MUTATION

- Heritable changes within DNA; a natural process
- Majority of the mutations are neutral
- A small fraction of mutations changes gene function
  - Some are useful
  - Majority are harmful
- Purifying selection eliminates harmful mutations



https://www.ck12.org/book/cbse_biology_book_class_xii/section/8.4/

MUTATION: SEVERAL TYPES

Point mutation

T G C A T T G C G T A G G C

T G C A T T C C G T A G G C

Insertion

T G C A T T T A G G C

T G C A T T C C G T A G G C

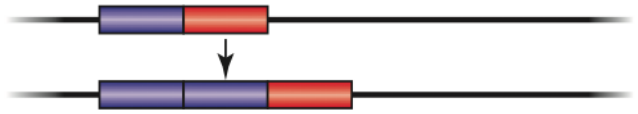
C C G

Deletion

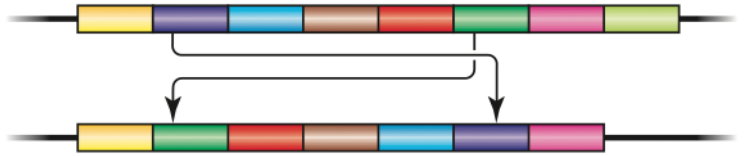
T G C A T T C C G T A G G C

T G C A T T T A G G C

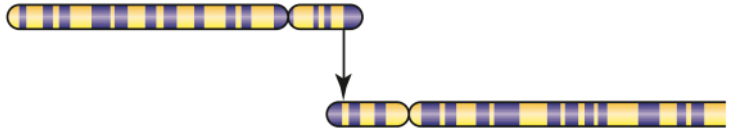
Gene duplication



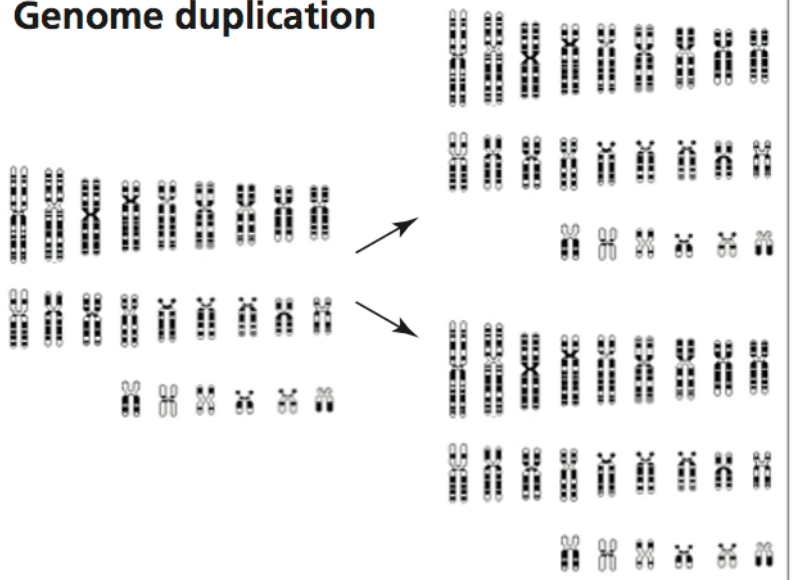
Inversion



Chromosome fusion



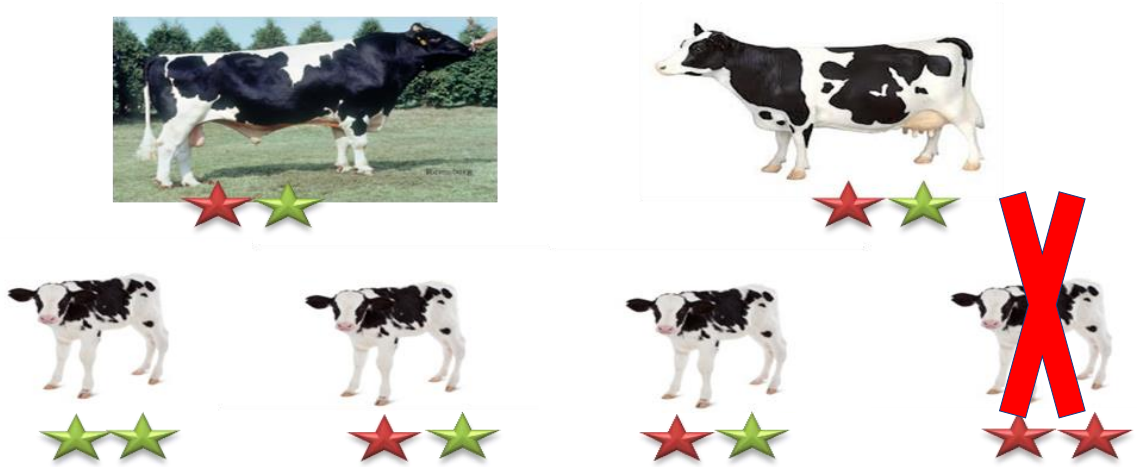
Genome duplication



RNF11 gene mutation in Belgian Blue Cattle
doi:10.1371/journal.pgen.1002581

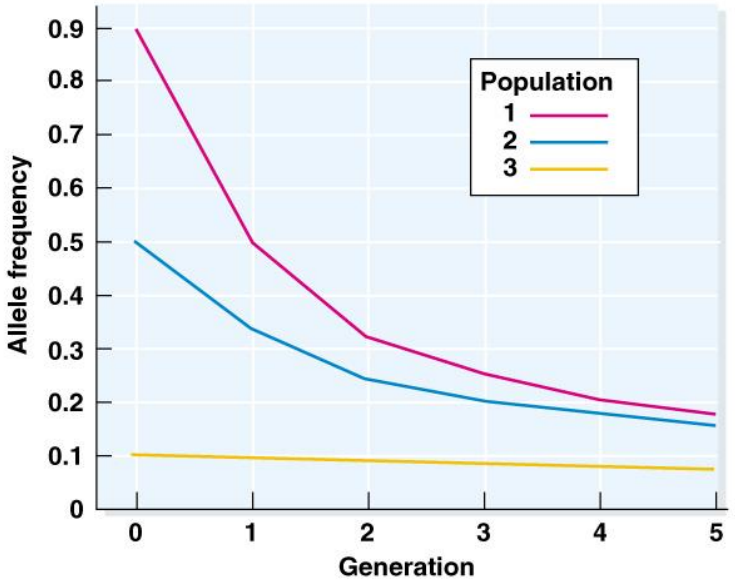
RECESSIVE LETHAL MUTATION

- Lethal mutation produces a non-functional version of an essential protein
- Individual inherits a lethal combination of mutated alleles, will die before or after birth



NATURAL SELECTION AGAINST HARMFUL MUTATIONS

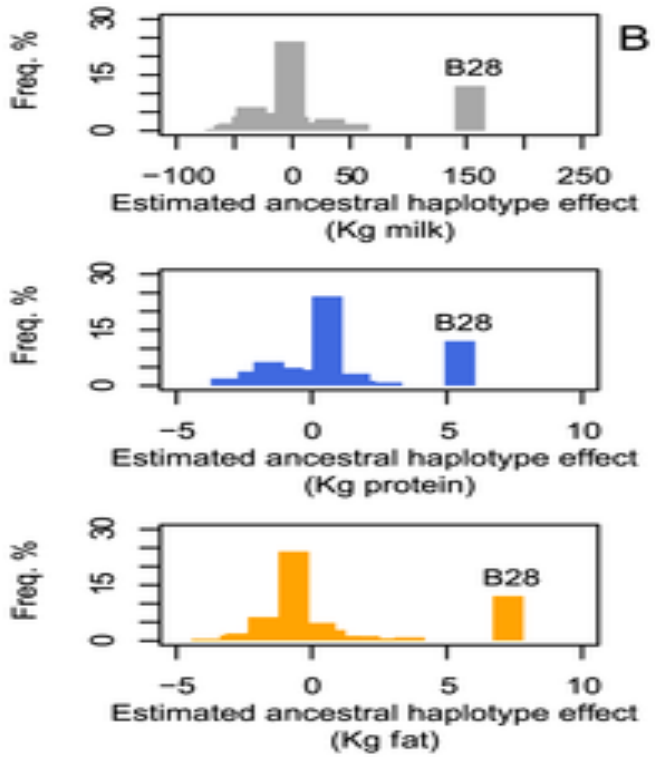
- Often result in reduced fitness
- Selection reduces the frequency
- Usually not eliminated completely
  - remains in heterozygote
- If a bull is a carrier, frequency can increase quickly
  - becomes a more serious issue



HETEROZYGOTE ADVANTAGE

7 bp duplication in FOX13 gene Heterozygous – hairlessness Homozygote – embryonic lethal

Hedrick 2015



0.6 MbP deletion on chromosome 12 is embryonic lethal in Nordic Red cattle

Kadri et al. 2014

RECESSIVE LETHALS – WHY A PROBLEM IN CATTLE

- All populations have recessive alleles segregating
- But is critical in highly specialized dairy breeds- given their specific population structure:
  - high inbreeding
  - small number of founder animals
  - declining effective population size
  - widespread use of artificial insemination
- All contribute to making modern dairy cattle breeds particularly susceptible to recessive genetic disorders

RECESSIVE LETHAL - DETECTION

- Many at low carrier frequencies

  If carrier frequency is <2% than 1 of 10,000 pregnancies affected

Almost impossible to identify

- Some occur at larger frequencies
  - either by chance - due to genetic drift
  - or due to selection - linked to something desirable

Possible to identify

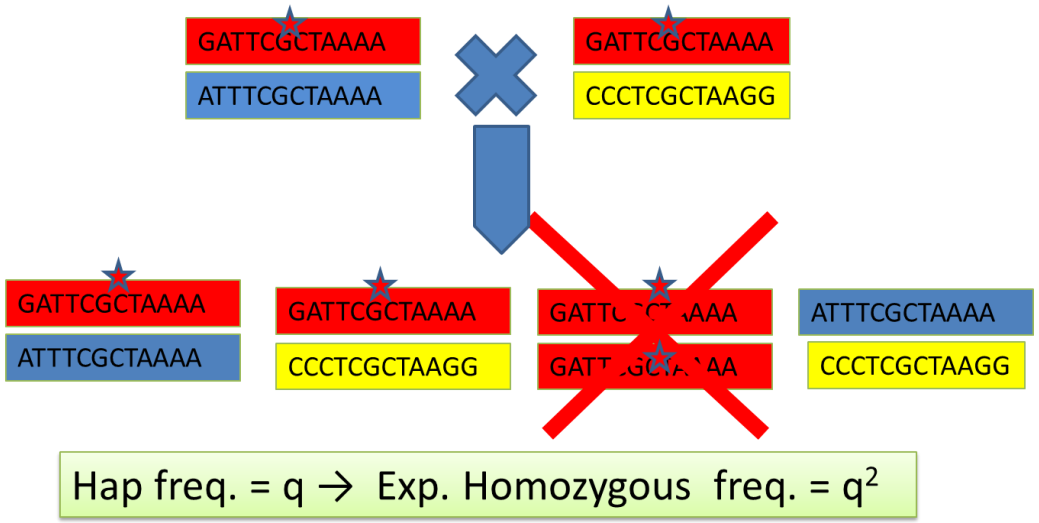
IN THE ‘OLD’ DAYS …

- Several calves with identical defect phenotypes (e.g. BLAD, CVM, BY)
- Finding common ancestor(s) in pedigrees of defect calves
- Finding chromosome segments where defect calves are homozygotes for an allele in common ancestor
- No live-born/normal homozygous calves

Most ‘old’ discoveries are affecting calf mortality

MANY ‘NEW’ MUTATIONS ARE IDENTIFIED RECENTLY

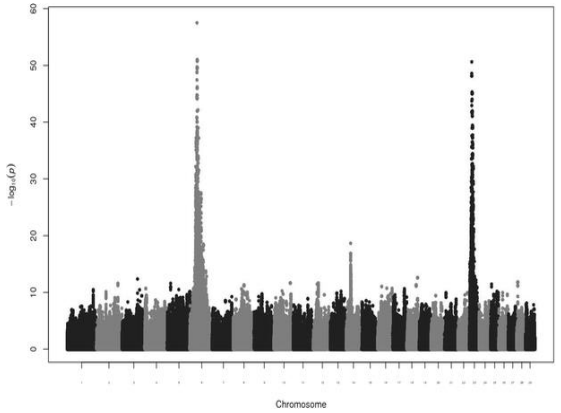
- Finding chromosome segments where homozygotes are missing

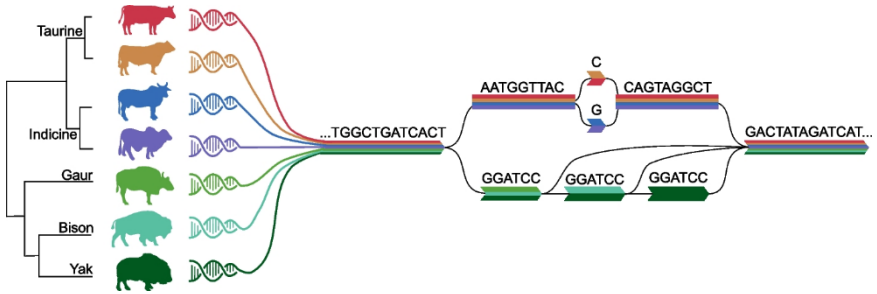


‘New’ alleles are affecting embryo survivability

APPROACHES TO MAP LETHAL MUTATIONS

1. Defect/dead calves
2. QTL approach
   - Chromosomes 12 and 23
3. Missing homozygous haplotype
   - HH1 (APAF1), HH3 (SMC2), and many more
4. Whole genome sequence data





Smith et al. 2023 https://doi.org/10.1186/s13059-023-02975-0

Sahana et al. 2016

IDENTIFYING CARRIERS IS ESSENTIAL

- Keep allele frequency low
  - remove them from the breeding population
  - apply effective mating strategies
- If causal mutation is known
  - laboratory assay
  - causal mutations in SNP chip
- If haplotype associated is known
  - infer haplotype from genotype data
  - haplotype-based tests can have errors

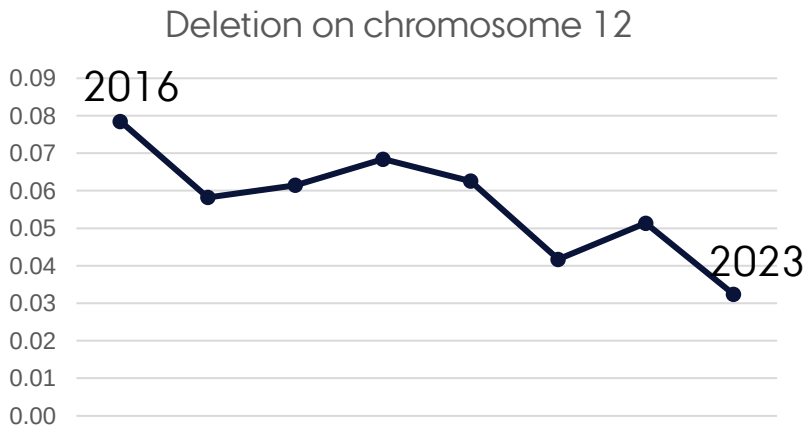
MANAGING RECESSIVE LETHAL MUTATIONS

Managing genetic defects is a trade-off between avoiding matings between carriers in the short-term and eliminating defects in the long run

Penalty on carriers: lethal score

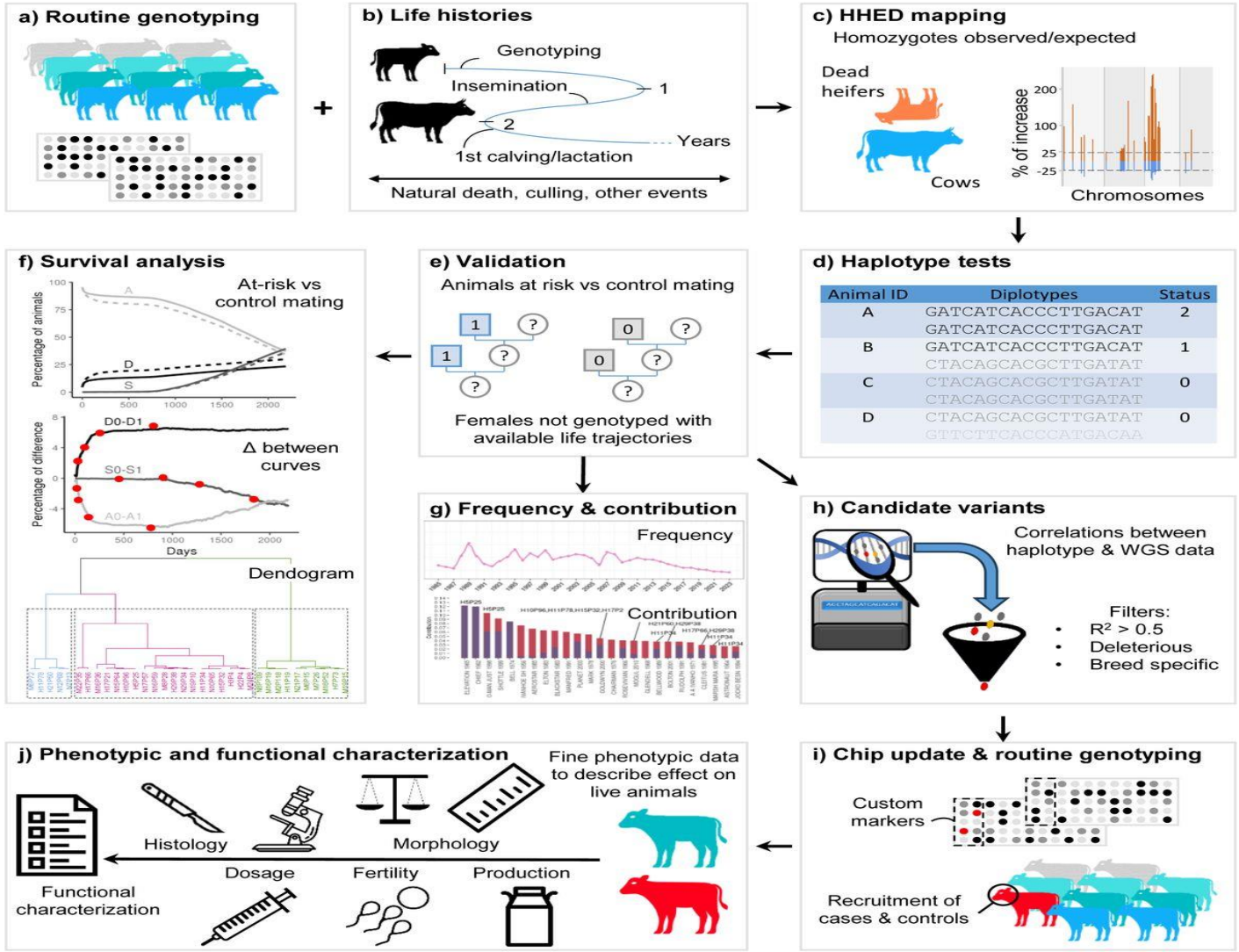
$$l = \sum_{i=1}^{k} \pi_i \delta_i q_i C_i$$

π is the probability that the zygote expresses its phenotype
δ is an indicator, 0 for non-carrier, 1 for carrier
q is the allele frequency
C is the cost associated with the occurrence of a homozygotes
k is the number of recessive alleles



STEPS TO DETECT RECESSIVE GENETIC DEFECTS

1. Genotypes from the routines
2. Correlate with phenotypes
3. Whole genome sequence
4. Functional information
5. Add on the SNP chip
6. Validation



Besnard et al. 2023 https://doi.org/10.1101/2023.09.22.558782

ONE JERSEY BULL CASE UNDER STUDY

Young stock survival

- Heifer calves, early period (day 1-30): 103
- Heifer calves, late period (day 31-458): 39
- Bull calves, early period (day 1-30): 102
- Bull calves, late periode (day 31-184): 42

	Bull's sire	Brother-1	Brother-2	Brother-3	Bull
Heifers, early	97	100	101	100	104
Heifers, late	83	88	100	101	54
Bulls, early	94	96	99	99	102
Bulls, late	83	87	98	100	55

JERSEY GENETIC CONDITIONS

https://uscdcb.com/haplotypes/

CODE	DESCRIPTION
LL	Limber leg
RVC	Rectovaginal constriction
JH1	First Jersey haplotype affecting fertility
JHP	Jersey haplotype for polledness
JNS	Jersey Neuropathy with Splayed Forelimbs

Beneficial variants

Kappa Casein – Cheese making quality

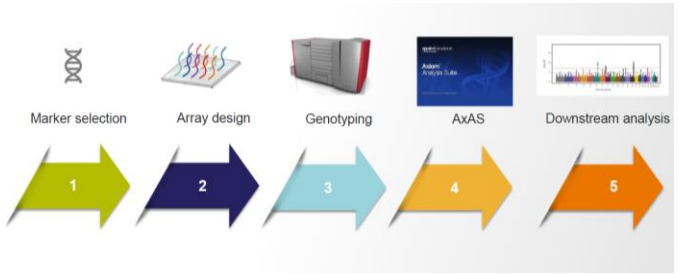
Beta Casein – A1 and A2 variety

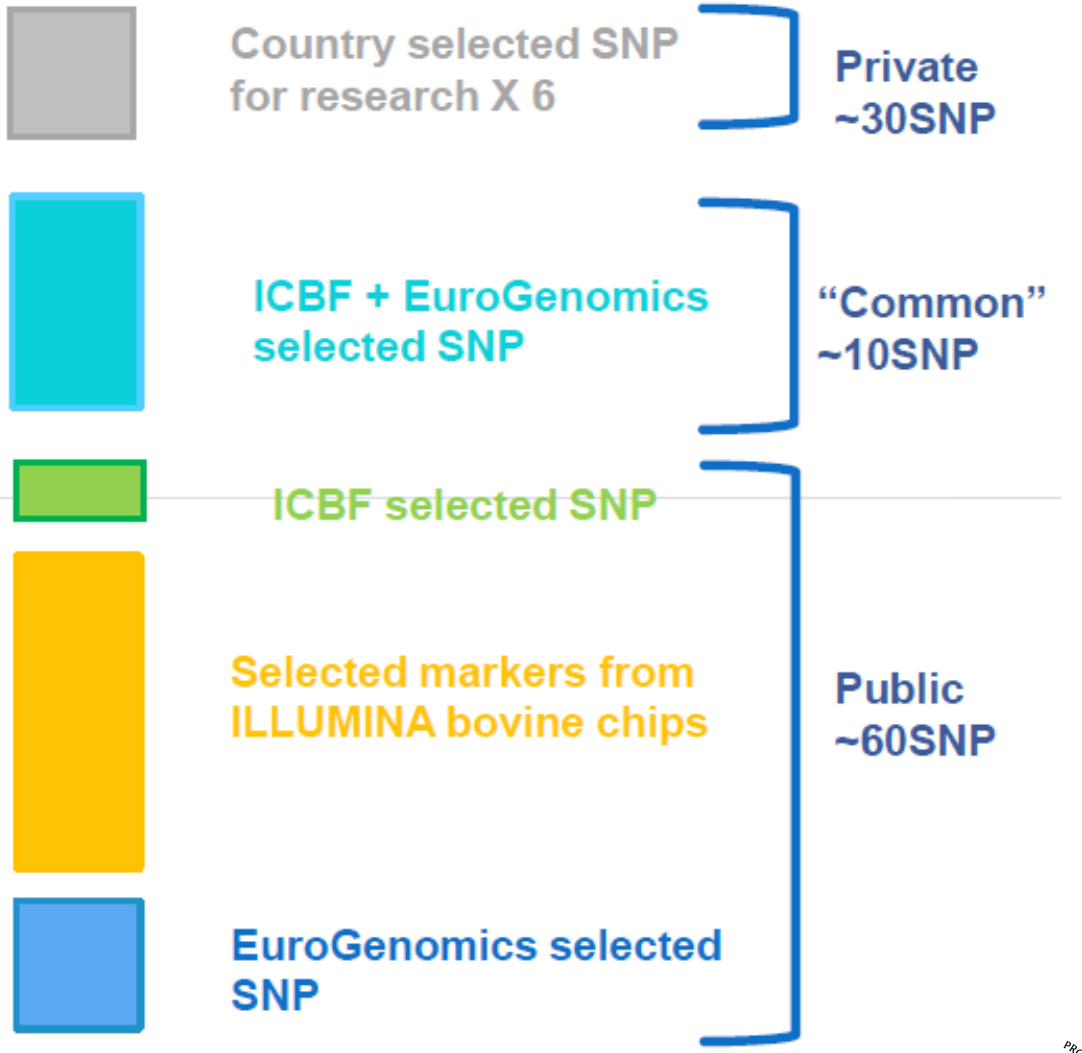
Beta Lactoglobulin – Whey content in milk protein

Polled – Polled–Friesian variant is segregating in Jersey

EUROGENOMICS SNP ARRAY

- EuroG MDv4 (~100,000 markers)
  - ~ 80,000 markers





SUMMARY- GENETIC DEFECTS SURVEILLANCE

1. **Forward genetics: phenotype to genotype**
   - Multiple animal with identical defect phenotype
   - Compare genotype/sequence of cases and controls
   - Study anatomy/pathology
2. **Reverse genetics: genotype to phenotype**
   - Common haplotype/allele but missing in homozygous state
   - Follow carrier x carrier matting for dead/defect calves
3. **QTL analysis** for stillbirth/mortality phenotypes
   - Follow the genome regions
4. **Semi-lethals** – linking genotypes/haplotypes to longevity
5. **Monitoring changes in frequency** of known defects from routine genotype data
   - Mating plan and strategy

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