Host genetics of resistance to bovine tuberculosis infection in dairy cattle.

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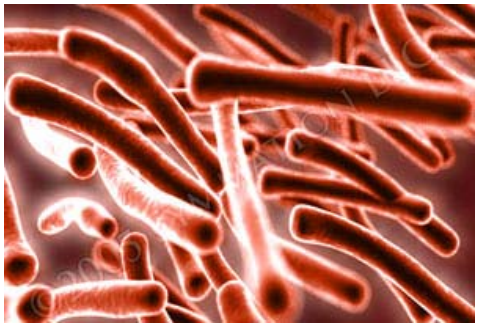
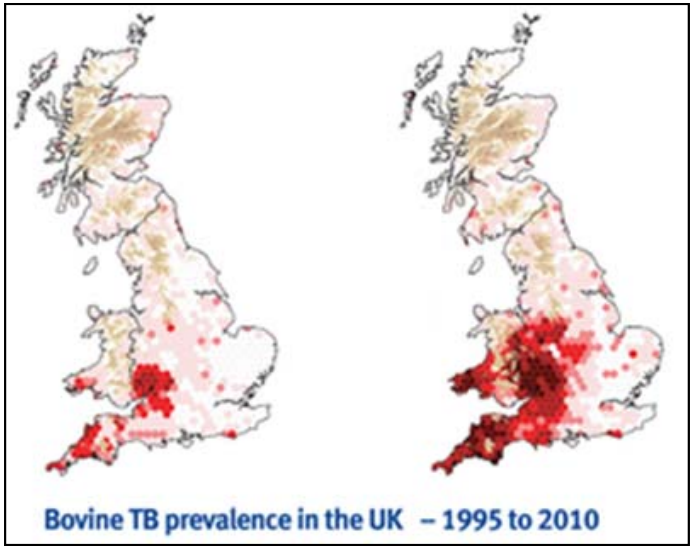
Bovine Tuberculosis (bTB)



- Caused by – *Mycobacterium bovis.*
- Primary host – cattle (badger involvement).
- Eradication scheme:
  - tuberculin testing and culling
  - abattoir surveillance
  - movement restriction.

- **Despite best efforts** – TB is persisting.
  - Increased incidence in GB and NI.
  - Much focus on wildlife control.
  - Vaccines and DIVA testing.



What other measures can be put in place?

There is no silver bullet for TB.

Can something that complements and enhances current schemes be used?

Is there a genetic component to bTB susceptibility?

Yes, there is.

Quantitative genetic studies of bTB resistance

- Heritability of bTB resistance = 0.18 (Bermingham et al. 2009; Brotherstone et al. 2009)

- Exploitable genetic variation in bTB resistance exists in dairy cattle

This raises the possibility of breeding cattle with enhanced resistance to bTB.

Genetic architecture underlying bTB resistance

- **Informs on genes and biological mechanisms underlying resistance**

  e.g. genome scan to identify candidate genomic regions (QTLs) associated with bTB resistance

There are at least two bTB infection outcomes – Phenotypes.

Phenotypes aid design of case / control studies to investigate genetic architecture of resistance.

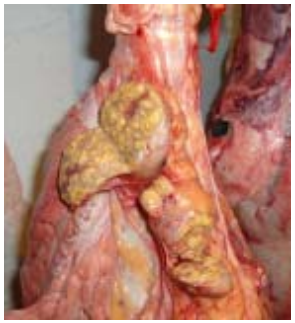
Phenotypes are defined by:

1 – Diagnostic skin test result

Positive test = **case**

Positive predictive value: average 91%, suggests majority of skin test positive animals are infected

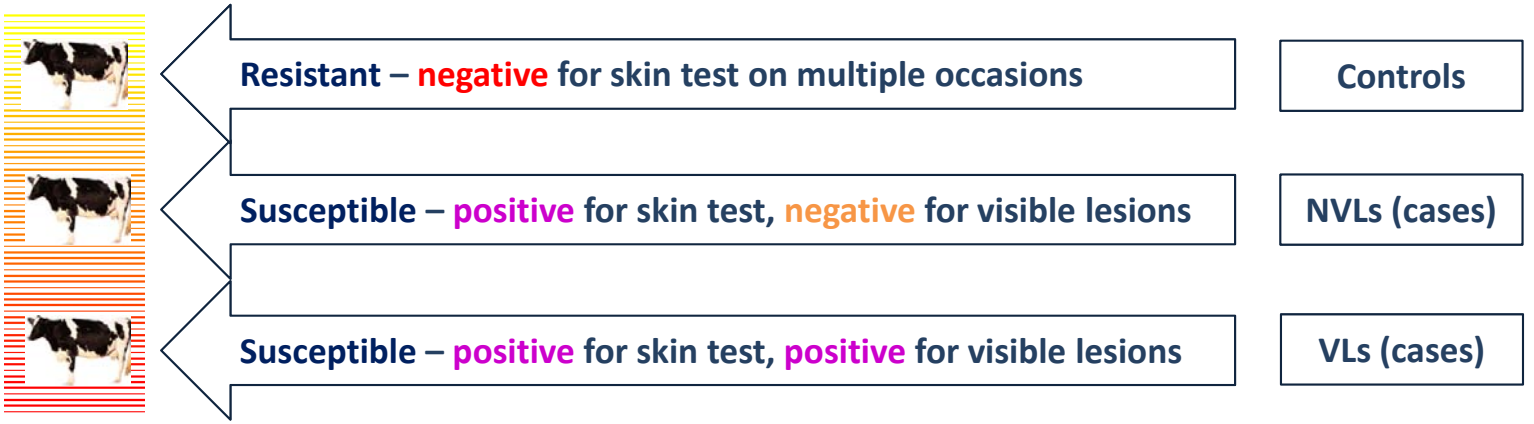
Negative test on multiple occasions = **control**.



2 – Abattoir inspection and bacteriology.

Positive animals = approx. 40% **visibly lesioned**. Remainder, **no visible lesions**.

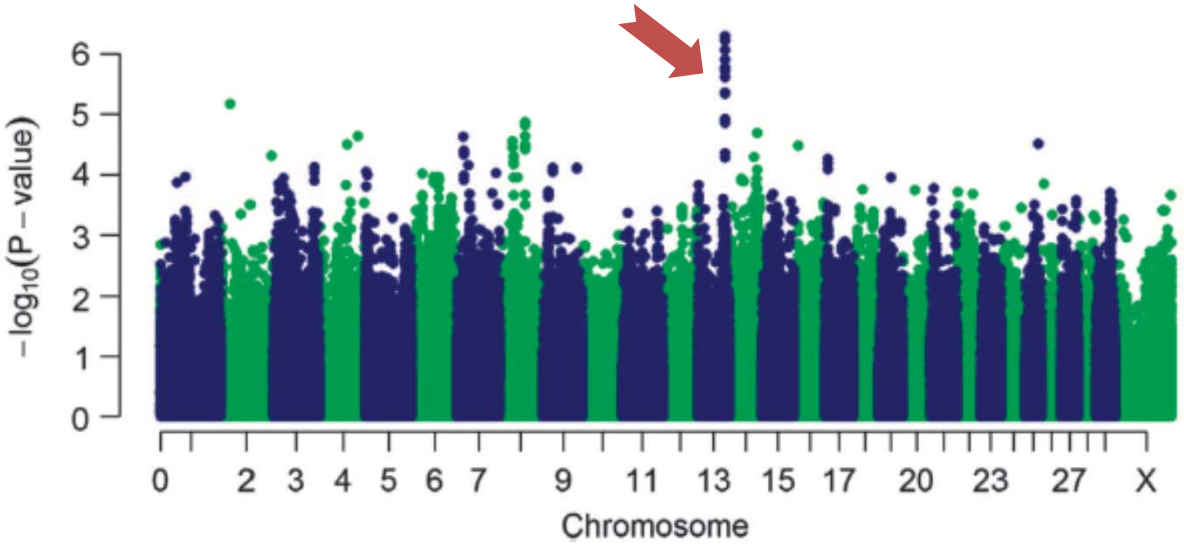
All lesioned case animals confirmed as *M. bovis* infected by culture.



Genome wide association study (GWAS) – Controls vs VL cases

- Northern Ireland dairy cows
  - **Cases** = VLs
  - **Controls** = negative for skin test multiple times and age- and herd-matched to cases and high prevalence herds

➢ 1200 cases and controls genotyped at ~500,000 SNPs



Bermingham et al 2014 - ***Genome-wide association study identifies novel loci associated with resistance to bovine tuberculosis. Heredity 112(5):543-51***

NVL phenotype <u>not</u> included in this previous study.

Do the different bTB phenotypes exhibit differing genetic bases?

- Is response to TB a spectrum?
- Are non lesioned animals on their way to becoming lesioned?
- **OR**, are both phenotypes **distinct** & under differing genetic control?

Perform new analysis on all phenotype groups to address hypothesis.

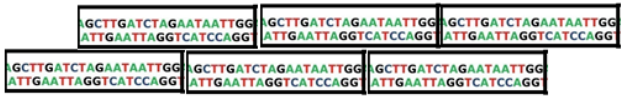
***Study design*:**

- Northern Ireland dairy cows from same herds
- Phenotype definitions using 2 diagnostic tests
  1. **560 Controls**
  2. **800 NVLs: POSITIVE ONLY for skin test**
  3. **610 VLs: DOUBLE POSITIVE for lesions and skin test**
- Genotyped with BovineHD Chip: ~500,000 SNPs

Methodology

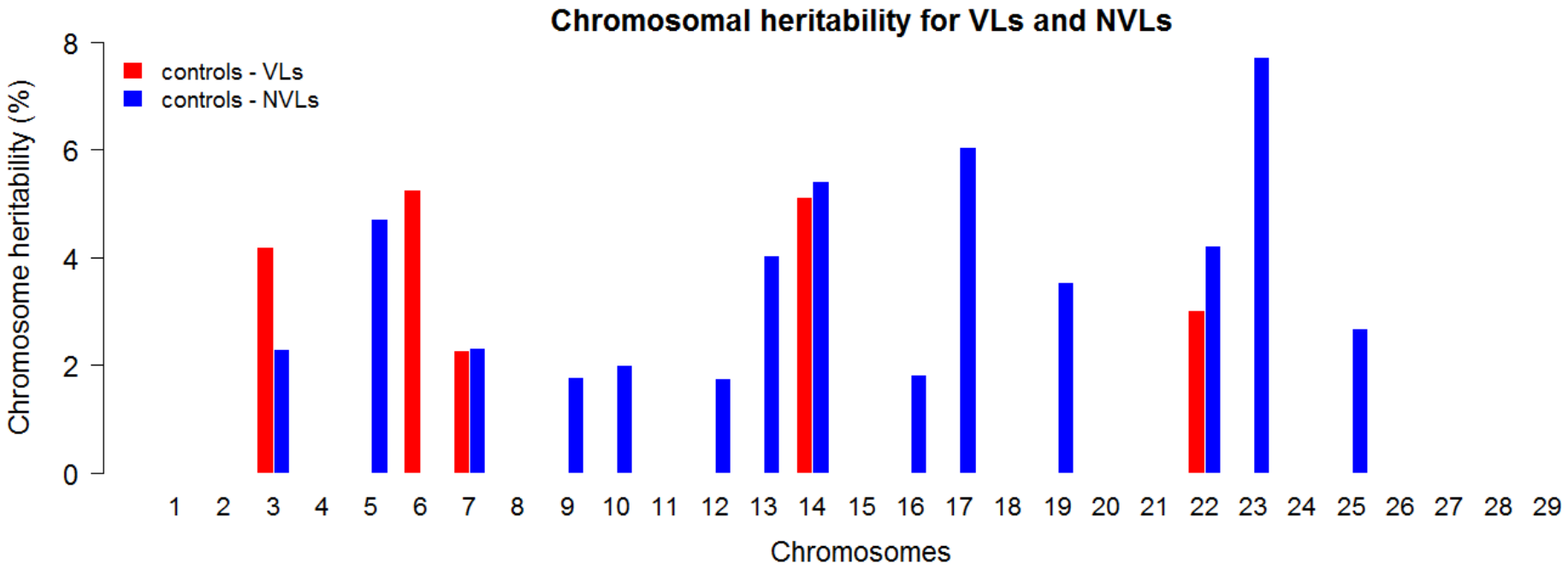
- **Chromosomal heritability analysis –** **to find which chromosomes are associated with bTB resistance, and what proportion of variance they account for.**

- **Regional heritability (RH) mapping** – **to find regions of genome associated with bTB resistance.**
  - Genome divided into 100-SNP overlapping windows and estimate genetic variance for each window



  - Likelihood ratio test computed against null hypothesis of no genetic variance for the window
  - Multiple testing Bonferroni correction:
    - genome-wide significance (one false positive association 0.05 times per genome scan)
    - suggestive significance (one false positive association per genome scan)

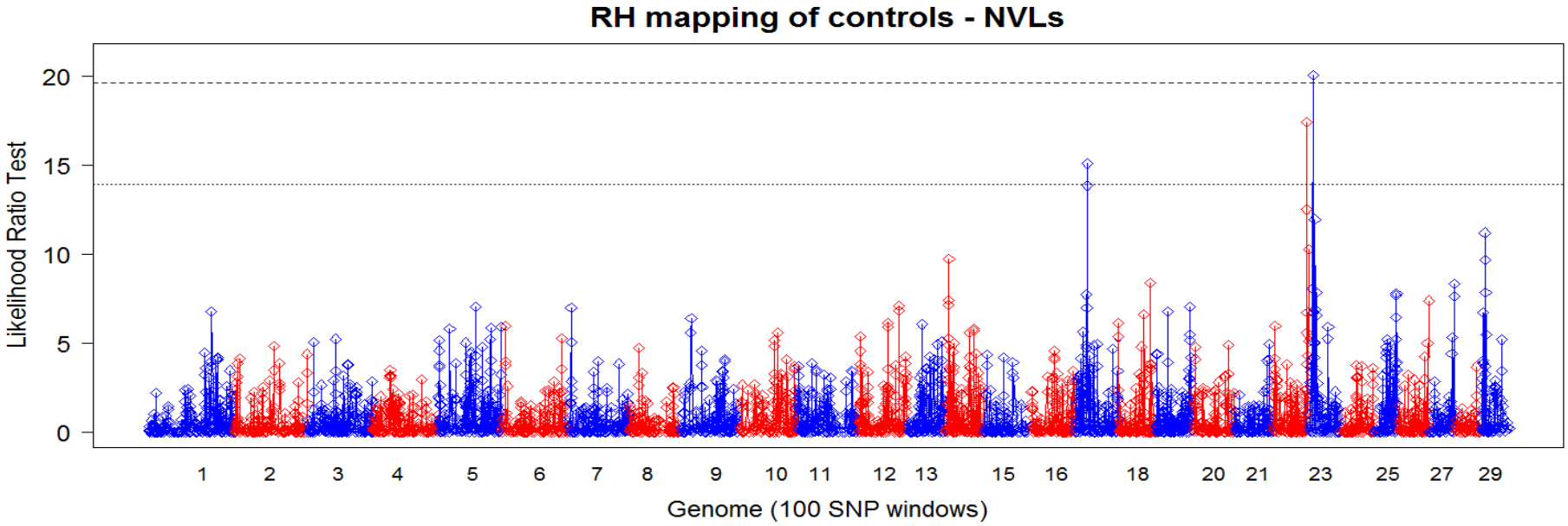
Results – Chromosomal Variation for bTB Phenotypes.



- 15 chromosomes contribute to both VL and NVL bTB phenotypes.
- Some shared chromosomal variation for the two case phenotypes
- Distinct chromosomal variation for case phenotypes – **1 VLs, 10 NVLs**
- **bTB resistance is polygenic – clusters of variants of small effect across whole genome.**

Results - Regional heritability mapping.

RH mapping of VLs vs Controls – found region on C'some 13 again – same as Bermingham et al 2014.



- **NVLs vs Controls** – Chromosome 13 not associated.
- Associated regions / QTLs:
  - Chromosome 17 – *SLC7A11* – solute carrier protein.
  - Chromosome 22 – PPARG – Peroxisome proliferator activated receptor gamma.
  - Chromosome 23 – *BoLA* – Bovine leucocyte antigen locus.

Conclusions

- Bovine TB – Complex disease with 2 phenotypes.
- Inherited TB resistance is real – breeding for resistance a definite possibility.
- TB advantage breeding index has already been released to industry.
- Overlap in chromosomal heritability of both phenotypes – combined EBVs.
- Resistance is a polygenic trait – many genes of moderate effect.
- bTB may not be blurred moving spectrum of phenotypes – NVLs become VLs.
- **Rather** – pathological outcomes of bTB infection may differ with host genetics.
- Some suggestion that NVL animals are less infectious than VLs – host pathogen interaction and adaptation to one another.
- QTLs identify targets involved in different TB outcomes – future cell biology work.
- May lead to novel intervention strategies.