Genome-Wide Association and Functional Annotation of Positional Candidate Genes for Immune Response in Canadian Holstein Cattle

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Disease Resistance, Theatre Presentation
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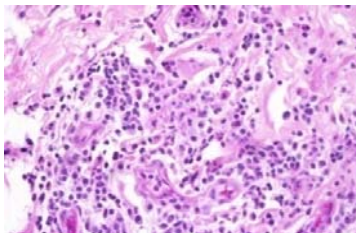# Could Immuno-Genetic Approaches be used to Improve Immunity in Livestock

We focussed on selecting for **broad-based** disease resistance (rather than on single diseases)

based on **Estimated Breeding Values** (EBVs)

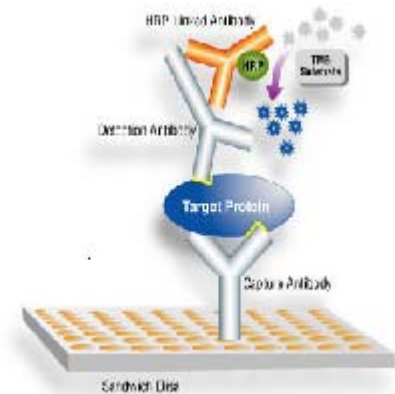of immune response traits used in a **Selection Index**

Performance of Two Tests

+

CELL-MEDIATED IMMUNE RESPONSE (CMIR)

ANTIBODY-MEDIATED IMMUNE RESPONSE (AMIR)
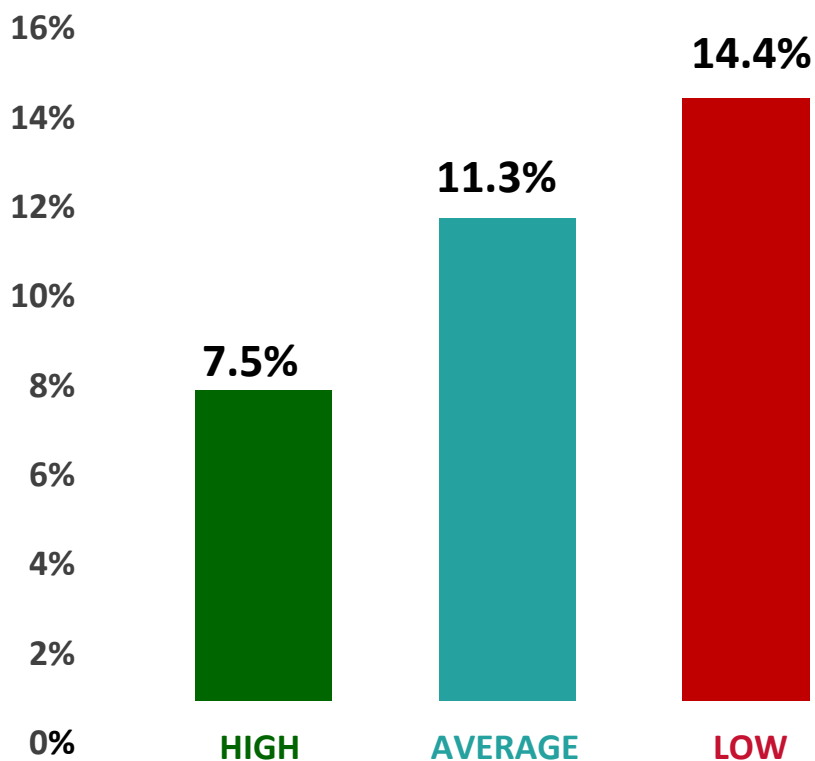

Photos and figures courtesy of Dr. B. Mallard
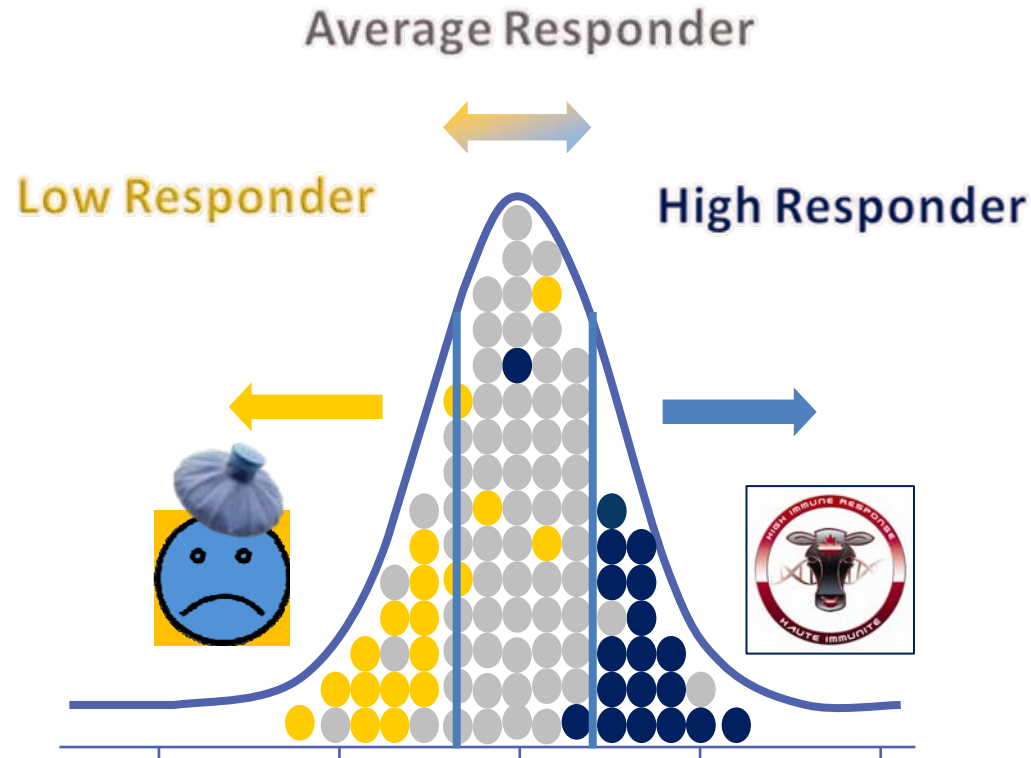
Selection for Immune Response is Based on

Estimated Breeding Values

IR higher heritability (25-35%) than conventional health traits

IR vs Disease Incidence (Combined Diseases)

Recorded Diseases Include:

Mastitis, Metritis, Ketosis, Retained Placenta, Respiratory, Lameness

> than 100 herds tested in our research

Disease data from: Wagter, et al. 2000 J. Dairy Sci. 83:488-498; Thompson-Crispi, et al. 2012. J. Dairy Sci. 95:3888-3893; Thompson-Crispi, et al. 2013. Clin Vacc Immuno. 20:106-112.
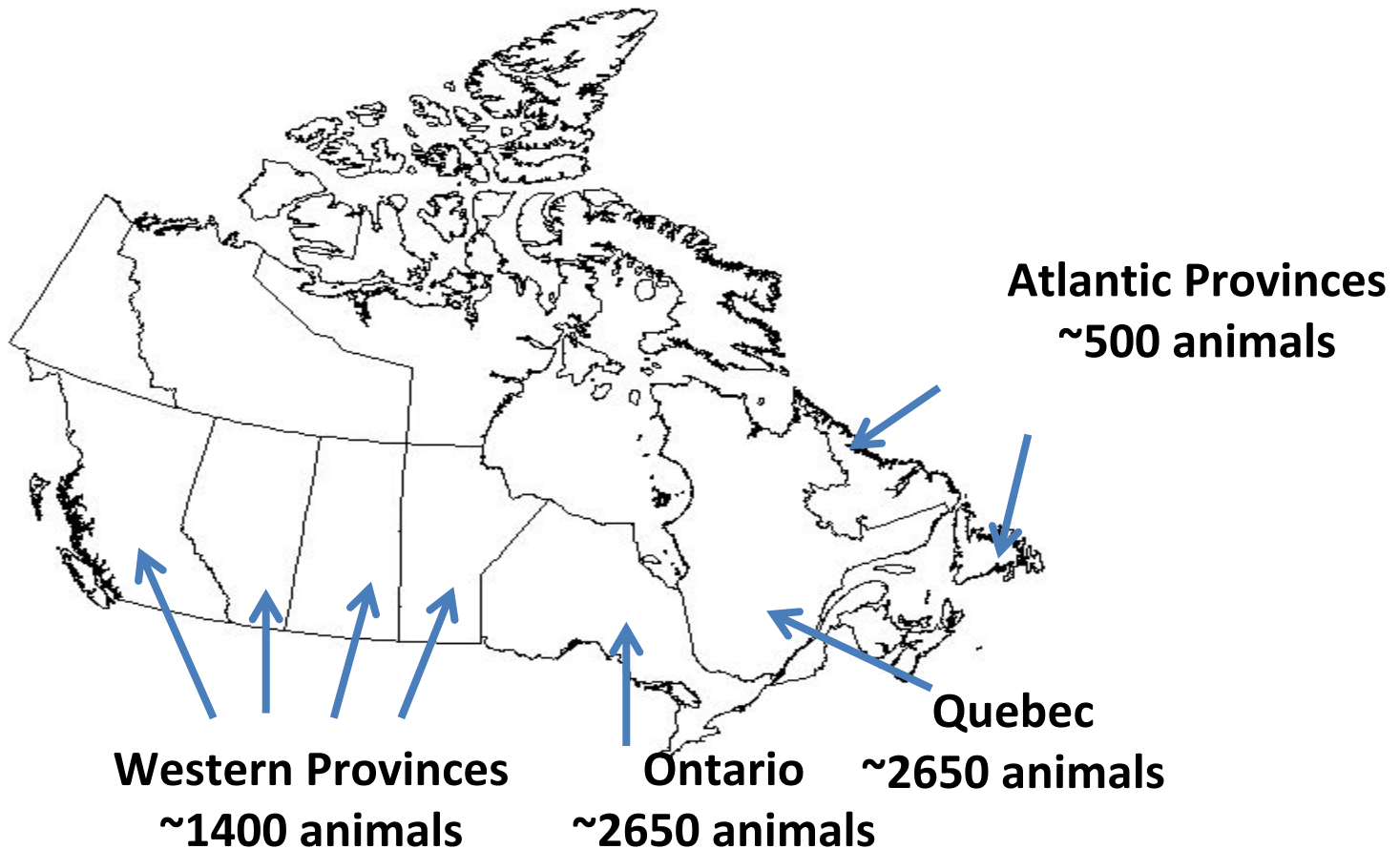
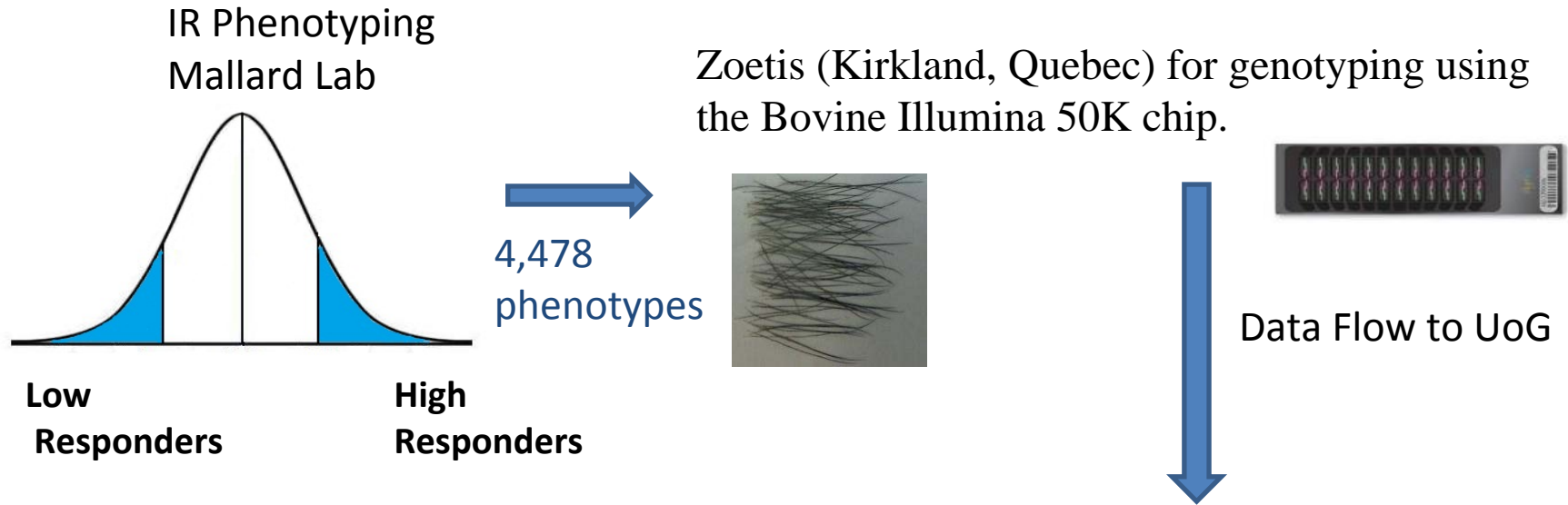# Is a Genomics Test based on HIR™ Test System Possible?

GWAS of Immune Response

Thompson-Crispi et al 2014, BMC Genomics
Initial Publication

Establish a large reference population of 5000 cows and 2000 Semex bulls within Canada

Atlantic Provinces
~500 animals

Quebec
~2650 animals

Western Provinces
~1400 animals

Ontario
~2650 animals

IR Phenotyping
Mallard Lab

Zoetis (Kirkland, Quebec) for genotyping using the Bovine Illumina 50K chip.

4,478
phenotypes

Data Flow to UoG

Low
Responders

High
Responders
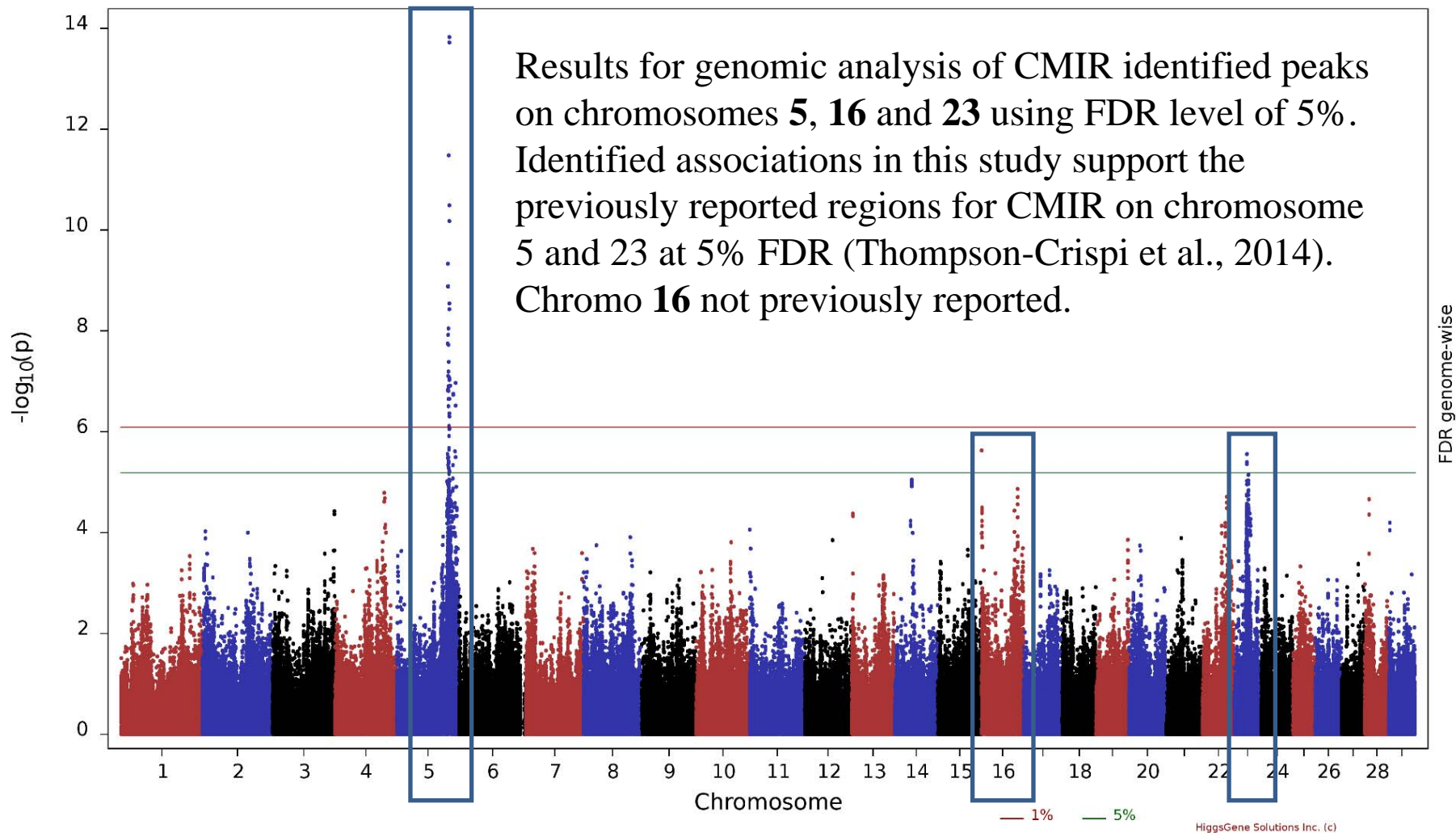
After performing genomic quality control, the 50k genotypes on autosomes were **imputed to HD (i.e. 777k panel)** using another 2,998 reference animals by FImpute (*Sargolzaei et al., 2014*). **GWAS was carried out on 604k SNPs** using single SNP mixed linear model implemented in snp1101 software (*Sargolzaei, 2014*).

Statistical models for AMIR and CMIR were as described in the manuscript.

CMIR (HD)

Results for genomic analysis of CMIR identified peaks on chromosomes **5**, **16** and **23** using FDR level of 5%. Identified associations in this study support the previously reported regions for CMIR on chromosome 5 and 23 at 5% FDR (Thompson-Crispi et al., 2014). Chromo **16** not previously reported.

Figure 2. Manhattan Plots for AMIR trait

AMIR (HD)

The genomic analysis for AMIR detected four significant SNPs on chromosomes **2** and **14** (5% FDR), and associations on chromosomes **21** and **23** (1% FDR)
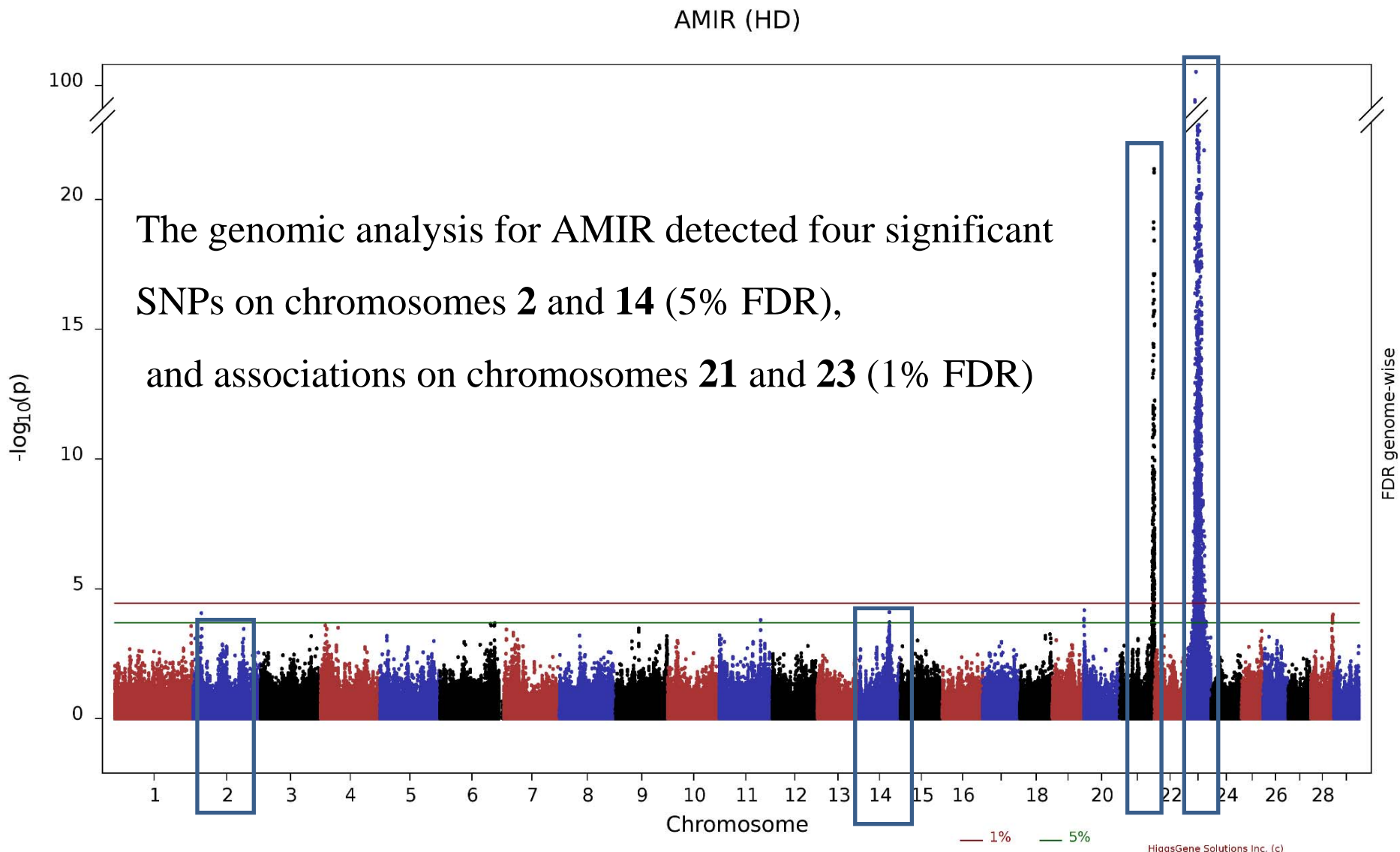
Functional Analysis: Ingenuity Pathway CMIR

Table 1. Top <u>disease and functions enriched </u>in Ingenuity Pathway Analysis for cell-mediated immune response

Name	P-value range	# Molecules
Inflammatory Response	3.75E-02 – 1.57E-04	10
Hematological Disease	5.23E-04 – 5.23E-04	3
Immunological Disease	5.23E-04 – 5.23E-04	3
Neurological Disease	4.84E-02 – 1.20E-03	4
Infectious Disease	1.99E-02 – 3.81E-03	3

Relevant biological functions, for example "disease" and "bio-functions" were over-represented among the positional candidate genes for CMIR

Table 2. Top <u>disease and functions enriched </u>in Ingenuity Pathway Analysis for antibody-mediated immune response

Name	P-value range	# Molecules
Infectious Disease	4.61E-02 – 2.67E-03	10
Inflammatory Response	4.80-02 – 2.67E-03	11
Immunological Disease	4.61E-02 – 1.1E-02	8
Respiratory Disease	4.39E-02 – 1.14E-02	5
Cancer	1.17E-02 – 1.17E-02	1

Relevant biological functions, for example "disease" and "bio-functions" were also over-represented among the positional candidate genes for AMIR
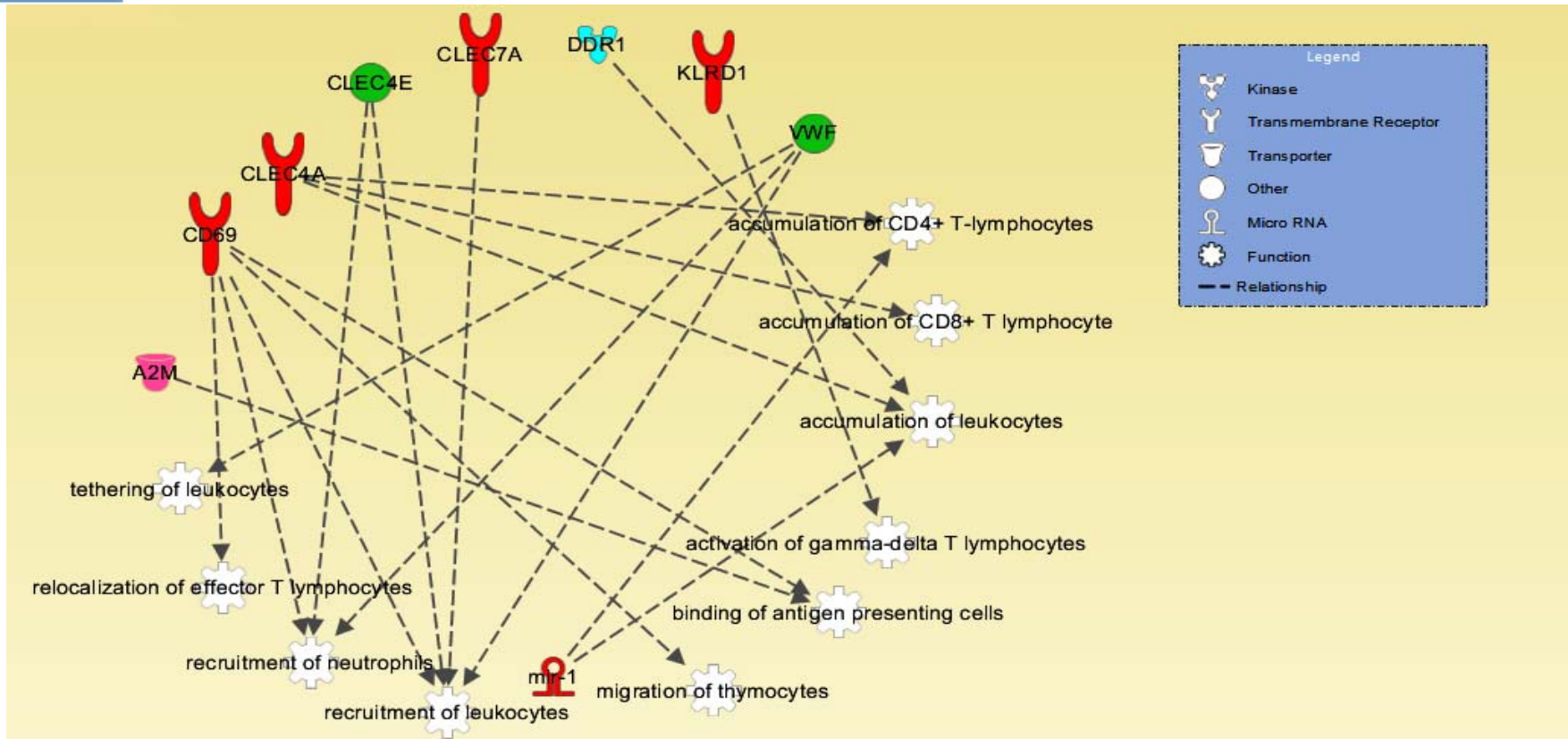
Fig 3. Immune cell trafficking pathways regulated by genes associated with CMIR emphasizes the relevance of T-lymphocytes in this response
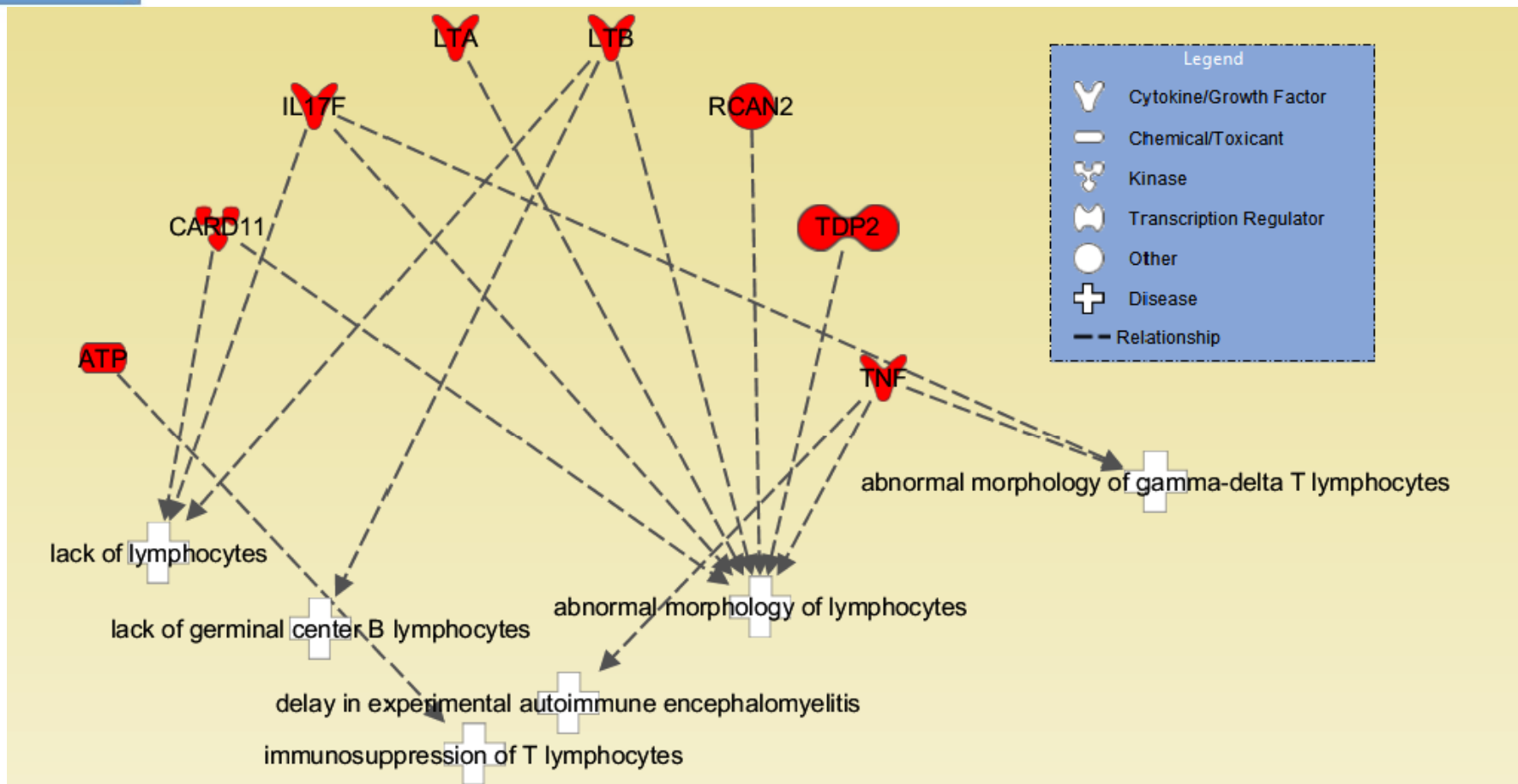
https://www.qiagenbioinformatics.com

Figure 4. Immunological disease pathways regulated by genes associated with AMIR emphasizes the relevance of <u>cytokines</u> and <u>B-cell germinal centres</u>

https://www.qiagenbioinformatics.com

Pedigree-based and Genomic Heritability Estimates

Heritability	Pedigree-Based	Genomic
AMIR	0.45 (0.037)	0.37 (0.025)
CMIR	0.18 (0.032)	0.16 (0.021)

- Both h^2 were estimated using REML method with the same model

- The only difference between the two estimates was the use of pedigree-based or genomic-based relationship between individuals

- Genomic h^2 estimates are always lower than pedigree-based h^2, this may relate to Mendelian sampling making genomic estimates more accurate with the added marker information or some epigenetic effects captured in the pedigree estimate (Ann Rev Genet, 2013).

Summary

➤ Results of this study confirm there are significant markers associated with immune response traits

➤ And that these are associated with particular biological processes or functions of immune response relevant to either AMIR or CMIR or both.

➤ Taking into account the moderate to high estimates of heritability and existence of major genes, the results here demonstrate that a genomics test could be utilised for immune response

➤ This is leading to more accurate selection of IR traits that help improve overall resistance to disease in Holstein cattle.
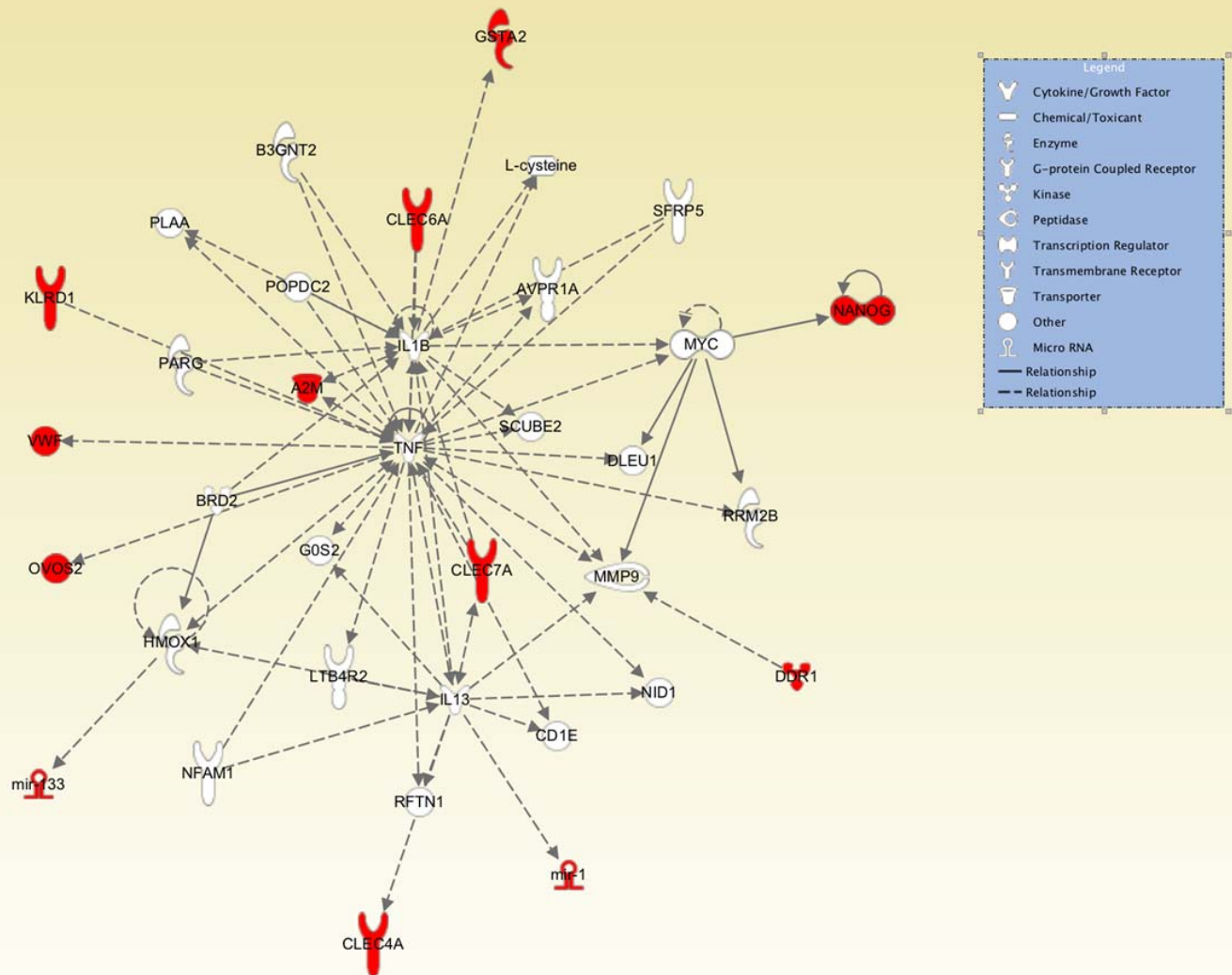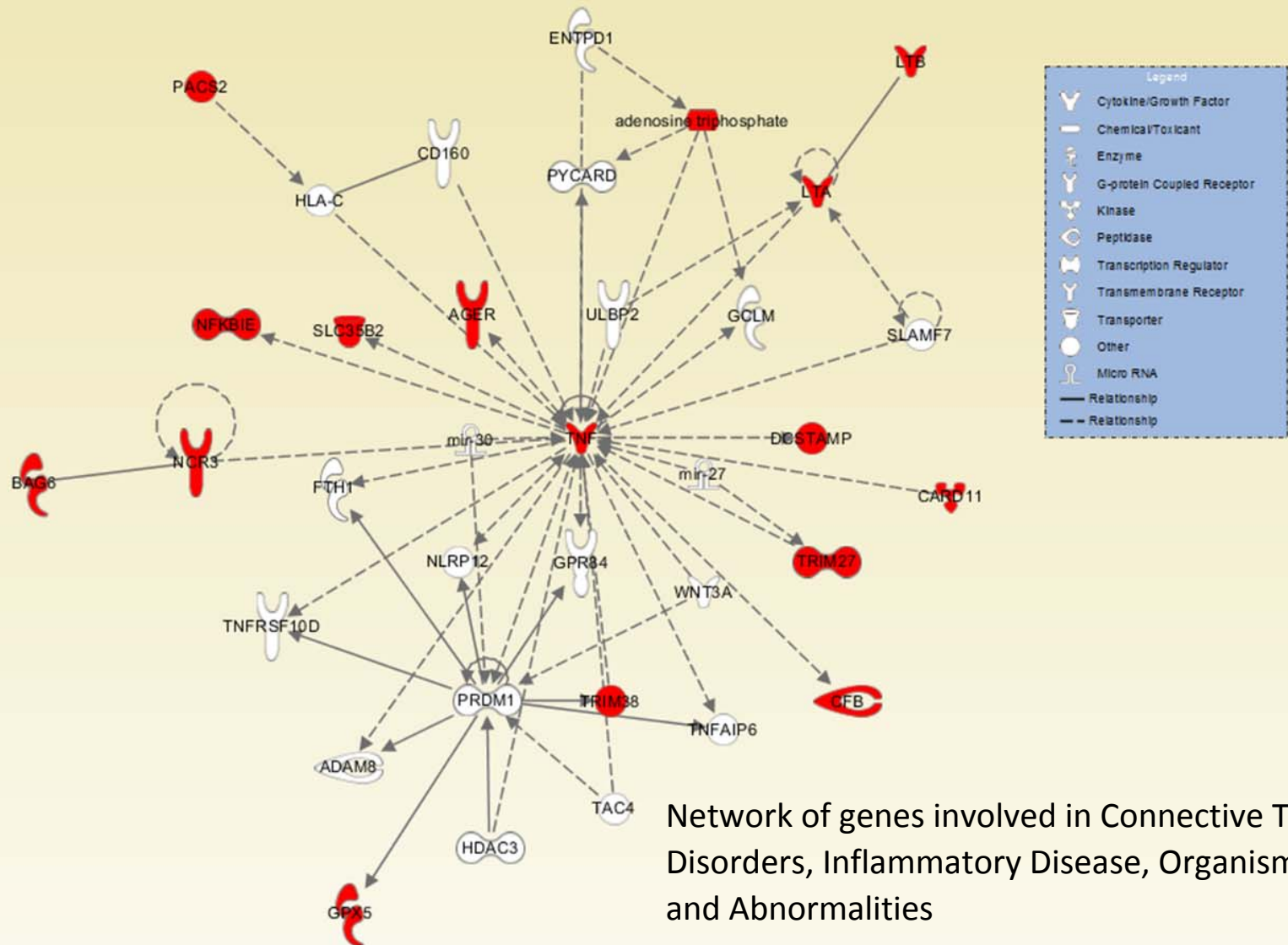
Questions

Thank you!

Back up slides

Demonstration of the enriched associated gene networks and correlated genes for CMIR trait:

https://www.qiagenbioinformatics.com

Network of genes involved in Connective Tissue Disorders, Inflammatory Disease, Organismal Injury and Abnormalities

https://www.qiagenbioinformatics.com

Network of genes involved in: Cellular
Function and Maintenance, Infectious Disease,
Connective Tissue Disorders

https://www.qiagenbioinformatics.com

Canadian Reference Population -
so far is 2561 Cows (60 herds) and 1907 Bulls (4 Semex herds) in the Analysis

Trait	Animals	Panel	Ave increase in theoretical reliability
AMIR	n = 4006	S50K chip	30.4%
CMIR	n = 3041	S50K chip	29.4%

S50K = Selected 50K chip

Adding genomic information increases the accuracy of EBVs for immune response

Internal Report - M. Sargolzaei, M. Emam, S. Cartwright, J. Chesnais, B. Mallard
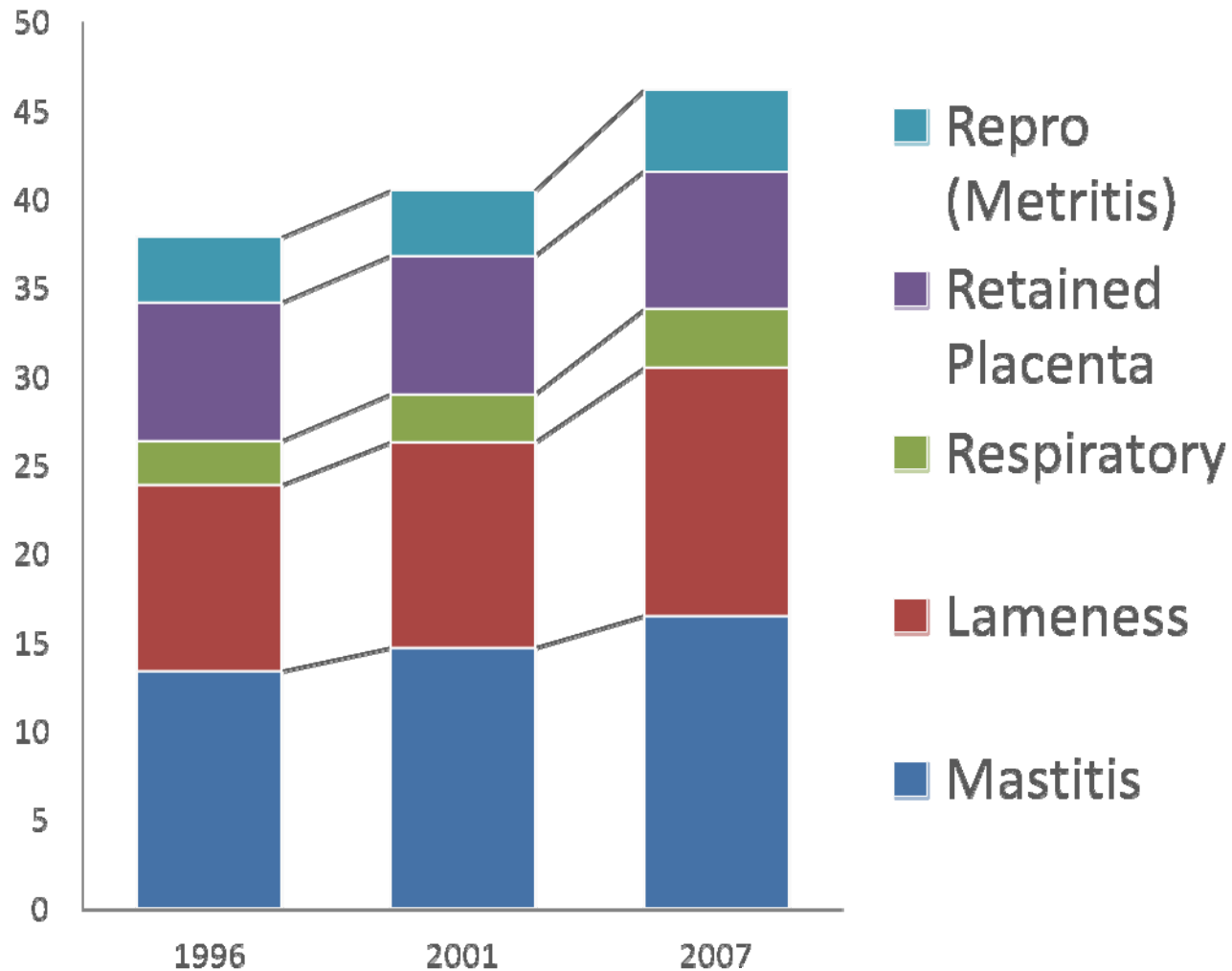
NAHMS Dairy 2007 Part II: Changes in the Dairy Cattle Industry 1991-2007