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Detection of haplotypes responsible for prenatal death in cattle

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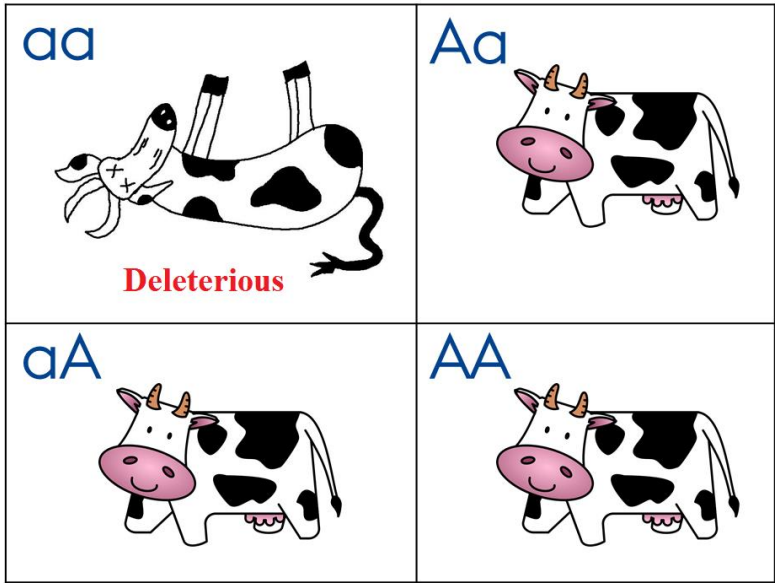
Recessive deleterious alleles

High frequency

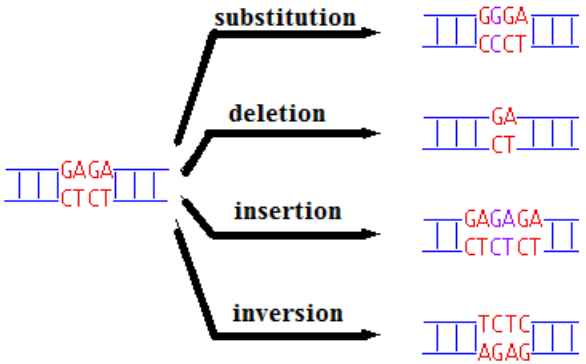
- by chance ~ genetic drift
- due to selection ~ linked to something valuable



Use of a limited number of elite sires ~ increase the risk of deleterious allelic variants being homozygous

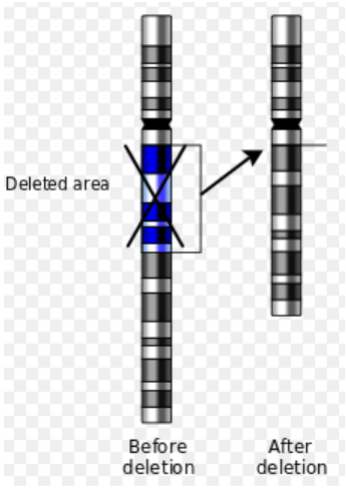
Type of variants

- **Point mutations**



http://carolguze.com/text/442-2-mutations.shtml

- **Chromosomal deletions**



National Human Genome Research (USA)

- Putative haplotypes identified through loss of homozygosity

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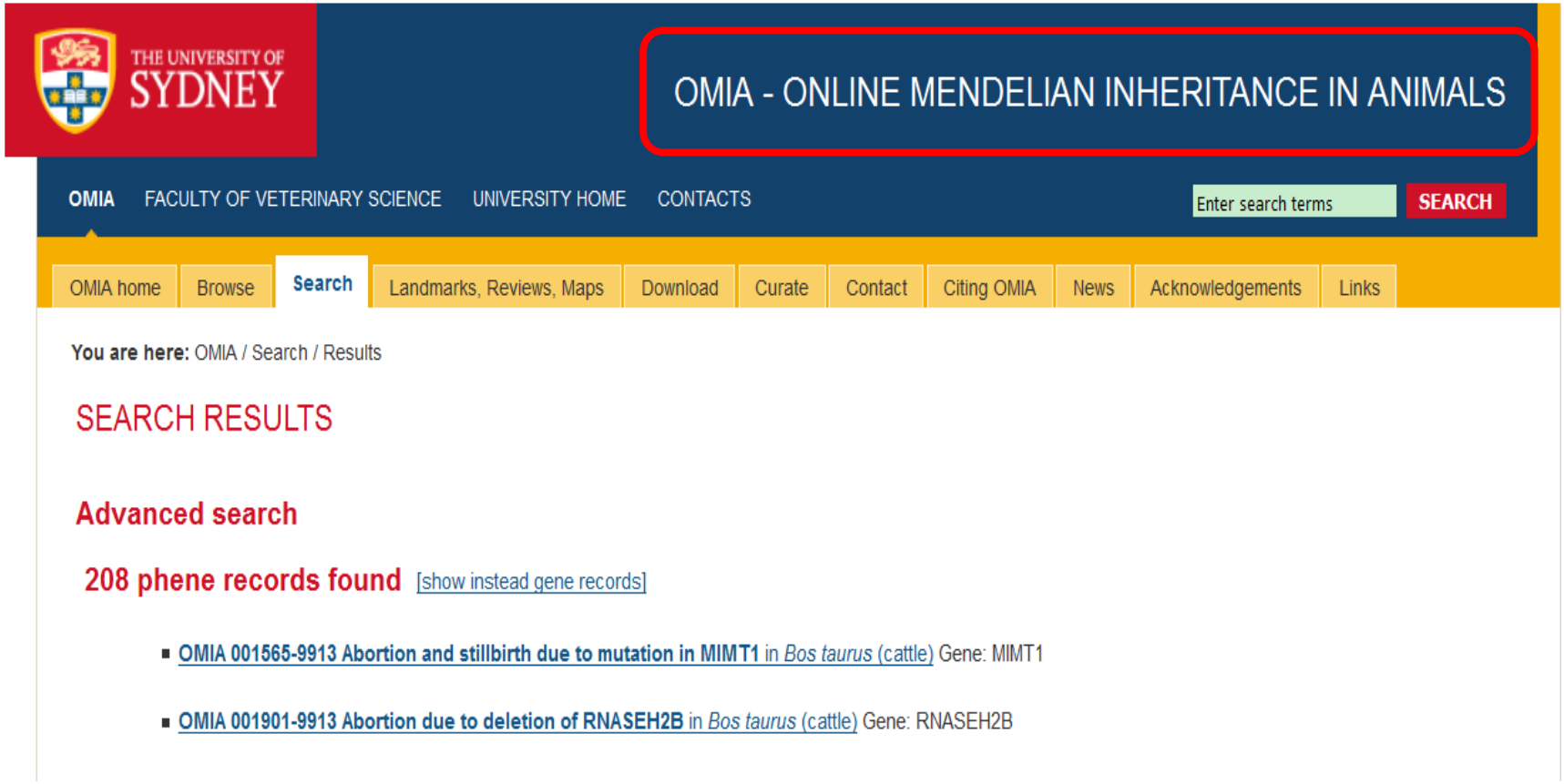
Recessive deleterious alleles database

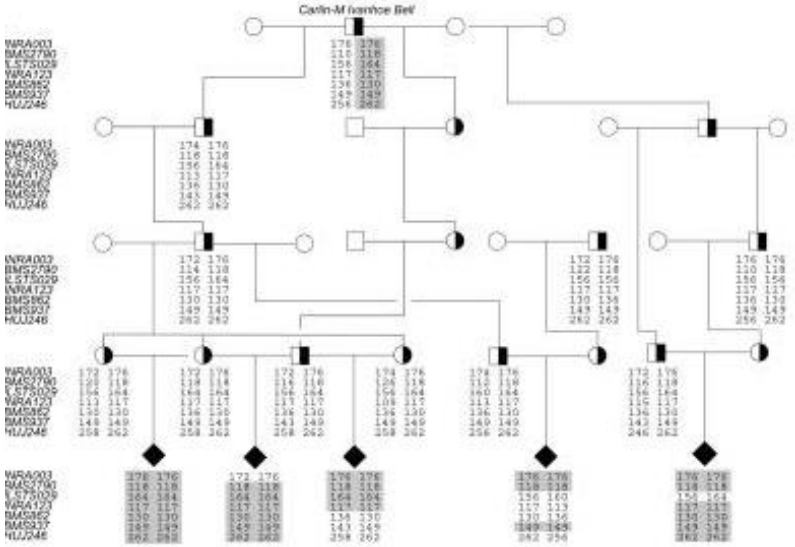


Conventional detection approach

From phenotype to genotype

- Tracing Pedigree
- Finding chromosome segments where defect calves are homozygotes for an allele in common ancestor
- Live-born calves are never homozygotes

Thomsen et al., 2006



Complex vertebral malformation (CVM)

‘New’ detection approach

From genotype to phenotype

- Using genotype data (VanRaden et al. 2011)
- Haplotypes common in population, but no homozygous among live animals
- Requires genotypes only from live animals, but not from affected embryos/calves

Aim and objectives

To avoid loss due to recessive lethal carriers in cattle industry

Objectives:

- To detect the recessive lethal haplotypes in three cattle breeds
- To identify casual genetic factors underlying these haplotypes

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Data

Bovine 50k

- HOL 26,312
- RDC 19,309
- JER 4,291

Full sequence

- HOL 57
- RDC 56
- JER 27

Method

From genotype to phenotype

- Phased, 47k SNPs
- Window: 25 markers
- Compared Obs. homozygotes vs. Exp. homozygotes
- Exp. =(genotyped individuals No.)*H^2 ,

  H is haplotype frequency (assume random mating)
- Chi-square test

Method

- **Whole genome sequence variants**
  - Sequence depth
  - Concordance among carrier and non-carrier

- **Phenotype: Reproductive failure**

  Carrier-sire by carrier-dam mating vs. other matings

Detected haplotypes for HOL

Chr.	Freq.	Obs.	Exp.	P-value	Reported
4	0.028	2	15	7.89E-04	New
6	0.069	87	124	8.92E-04	HH7
7	0.086	141	193	1.82E-04	HH8
8	0.025	0	17	3.74E-05	HH3
9	0.028	2	20	5.70E-05	HH5
11	0.105	183	291	2.43E-10	11-926
15	0.040	21	43	7.94E-04	HH12
19	0.020	0	11	9.11E-04	19-151
21	0.029	0	22	2.73E-06	Brachyspina
26	0.025	1	16	1.77E-04	New

CVM, BLAD… not detected

Detected haplotypes for RDC

Chr.	Freq.	Obs.	Exp.	P-value	Reported
1	0.028	1	15	3.01E-04	New
1	0.026	0	13	3.11E-04	New
1	0.025	0	12	5.32E-04	New
4	0.027	0	14	1.83E-04	New
7	0.027	1	14	5.12E-04	New
12	0.051	0	50	1.54E-12	LH12(660kb)
17	0.024	0	11	9.11E-04	PIRM
21	0.027	1	14	5.12E-04	New
21	0.027	1	14	5.12E-04	New
23	0.029	0	16	6.33E-05	New

Detected haplotypes for JER

Chr.	Freq.	Obs.	Exp.	P-value	Reported
1	0.053	0	12	5.32E-04	New
3	0.061	1	16	1.77E-04	New
5	0.067	1	19	3.64E-05	New
8	0.058	1	14	5.12E-04	New
20	0.061	1	16	1.77E-04	New
22	0.055	1	13	8.74E-04	New

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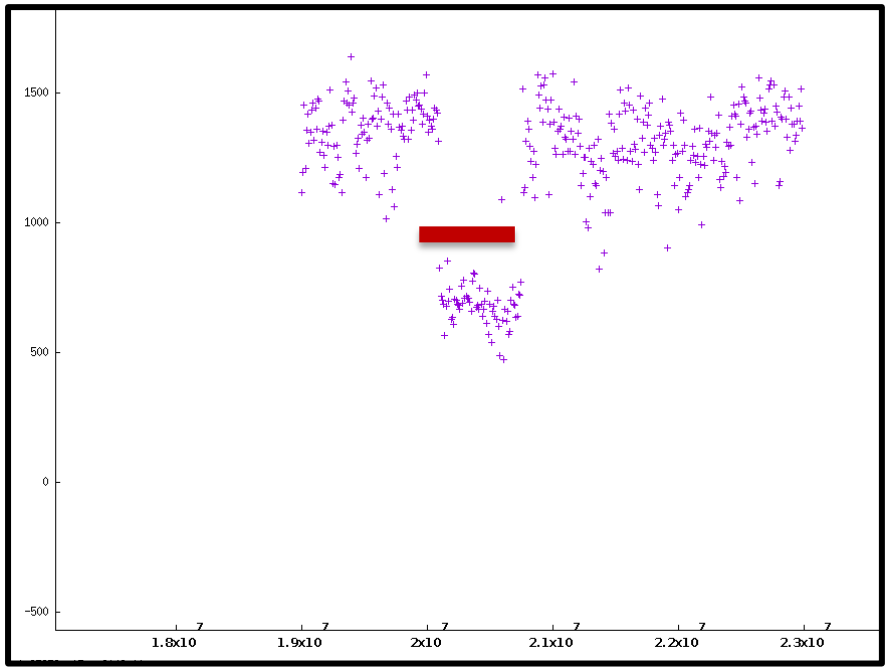
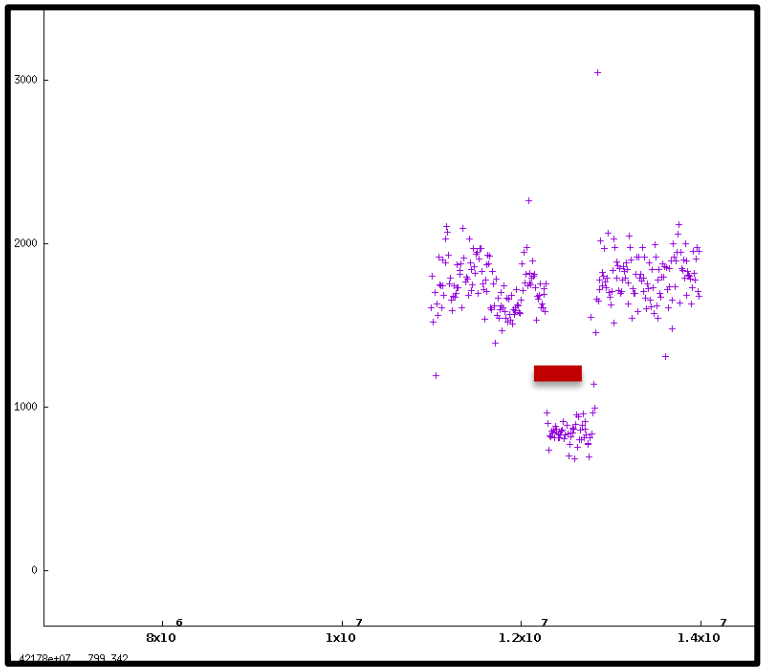
Large chomosomal deletions

Sequence depth



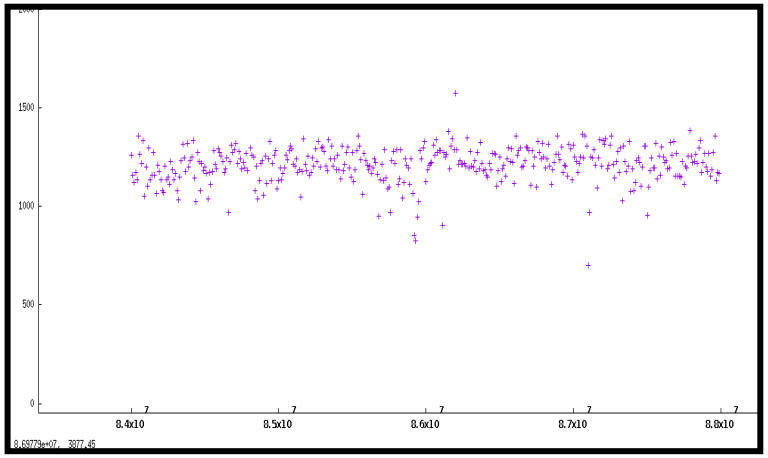
660kb deletion, Kadri et al, 2014



500kb deletion, Sahana et al, (under preparation)

Search for causative mutation

Sequence depth



Other detected haplotypes

- Not large deletion
- Could be small deletion, point mutation
- False positive

CCCGGATGCTGGA**G**GTGAGGAG

CCCGGATGCTGGA**A**GTGAGGAG

Future work plan

- **Phenotype: reproductive trait**

  Insemination outcome from carrier-sire by carrier-dam mating vs. other matings

- **Application: Following the carrier frequencies**
  - limited use of high-merit carriers as bull sires
  - Add the 'diagnostic' markers in LD-chip

Acknowledgement

- **Nordic Cattle Genetic Evaluation**
- **VikingGenetics**

THANK YOU FOR YOUR ATTENTION!