

The impact of DNA gain or loss

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Seminar Göttingen, 27-05-2021



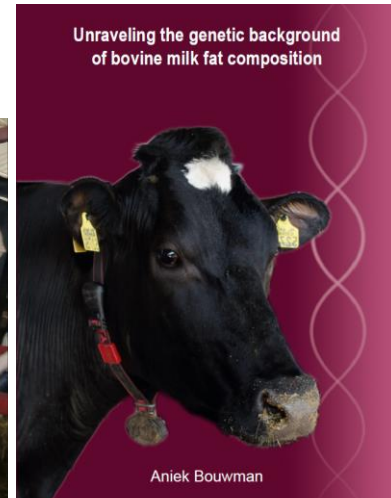
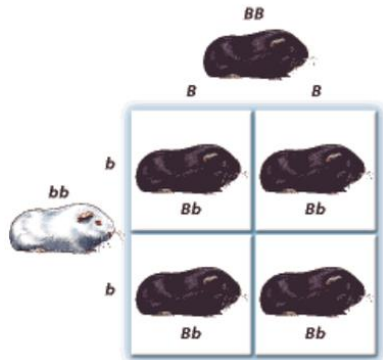
About me

BSc Animal Husbandry, HAS Den Bosch (2006)

MSc Animal Science, Wageningen University (2008)

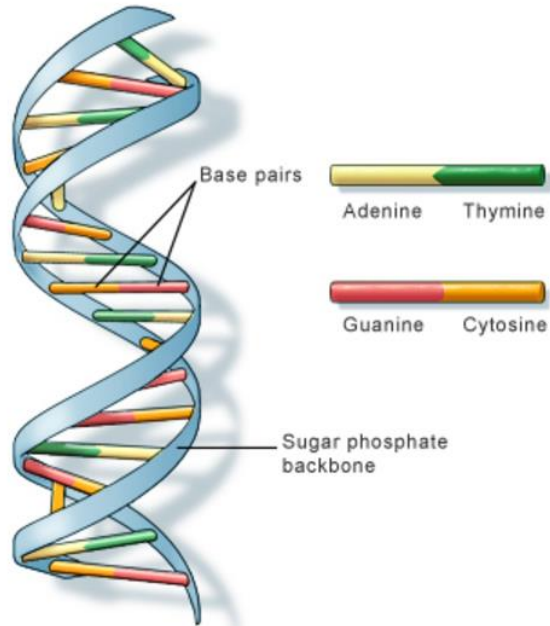
PhD Animal Breeding & Genetics, Wageningen University (2014)

2012-now: Wageningen Livestock Research

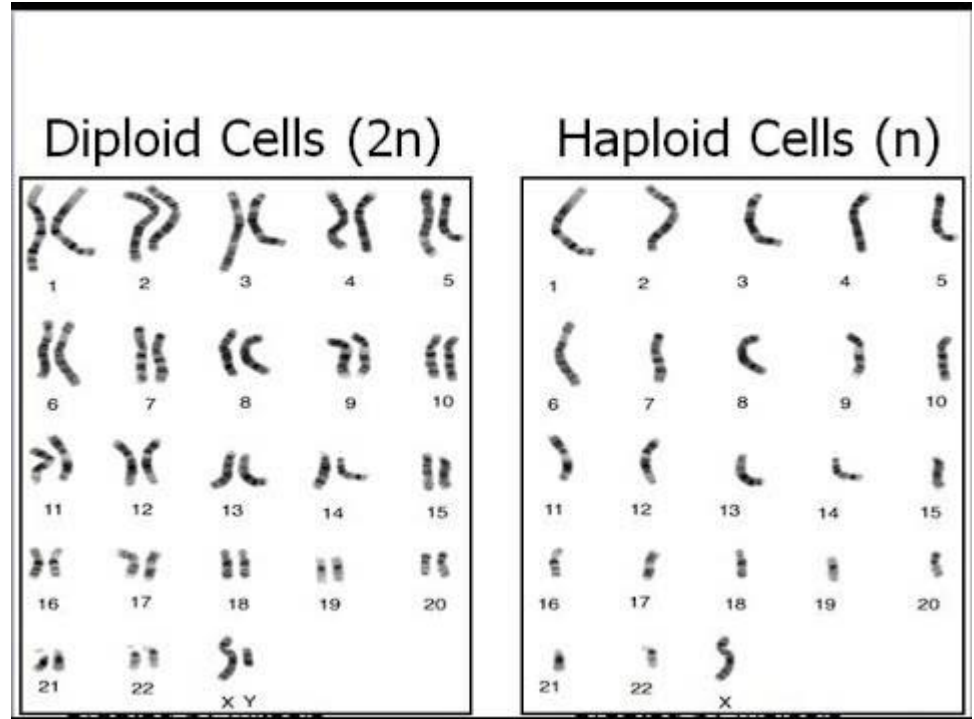




DNA & chromosomes



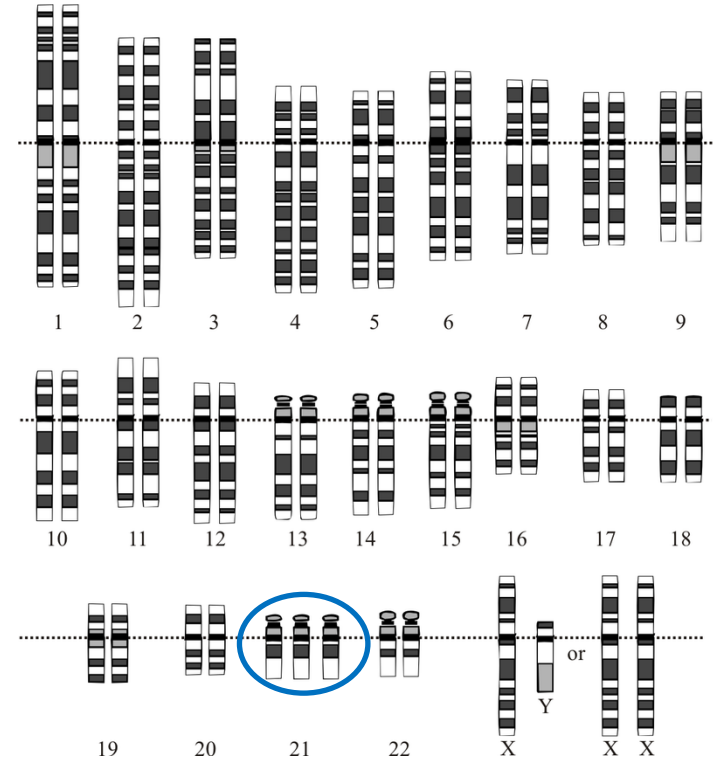
U.S. National Library of Medicine



Content

- Loss or gain of **full chromosome**
 - Aneuploidy in cattle embryos
- Loss or gain of **part of chromosome**
 - Reciprocal translocations in pigs
- Loss or gain of **kilo base pairs**
 - Duplication in cattle

Impact gain or loss whole chromosome



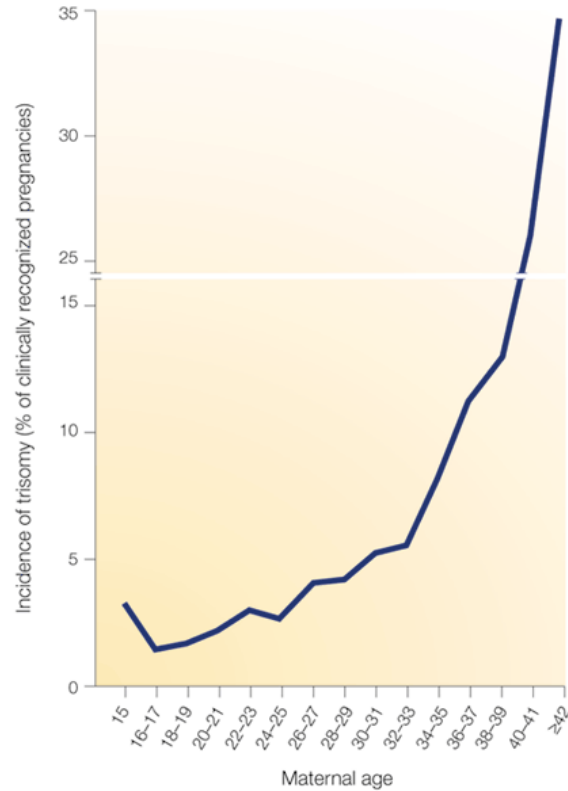
Incidence in humans

Table 1 | **Incidence of aneuploidy during development**

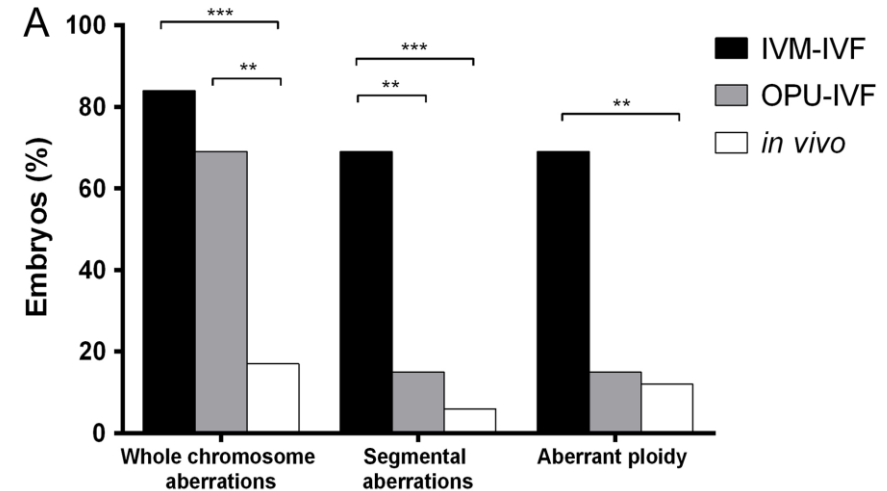
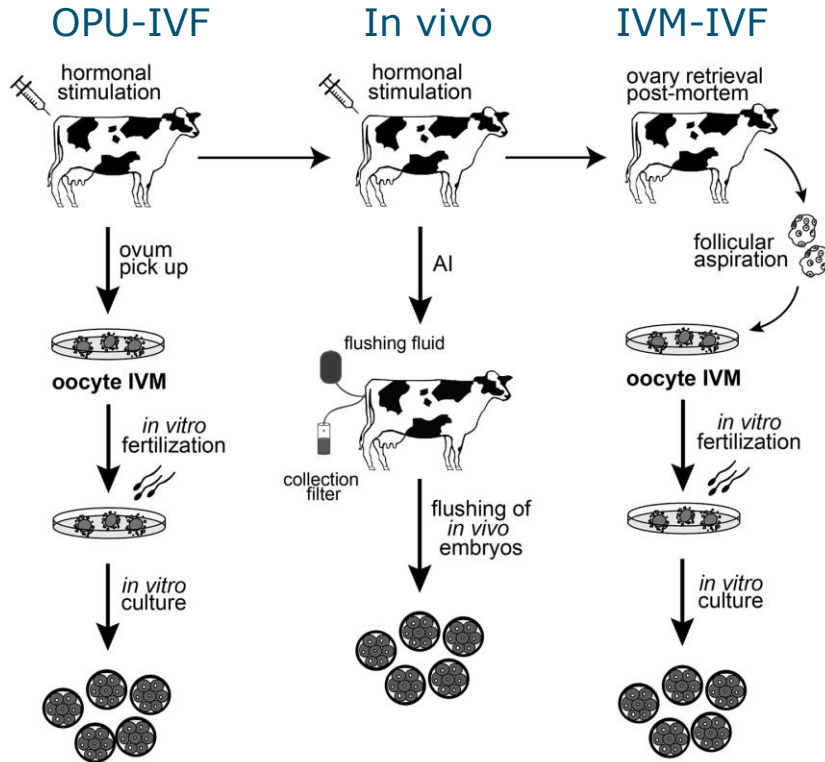
Gestation (weeks)	<div> <div>0</div> <div>6-8</div> <div>20</div> <div>40</div> </div>						
	Sperm	Oocytes	Pre-implantation embryos	Pre-clinical abortions	Spontaneous abortions	Stillbirths	Livebirths
Incidence of aneuploidy	1-2%	~20%	~20%	?	35%	4%	0.3%
Most common aneuploidies	Various	Various	Various	?	45,X; +16; +21; +22	+13; +18; +21	+13; +18; +21 XXX; XXY; XYY

- Higher incidence in early stages > mostly lethal
- Can occur in all chromosomes, gains and losses
- Only **gain of certain chromosomes** can survive longer

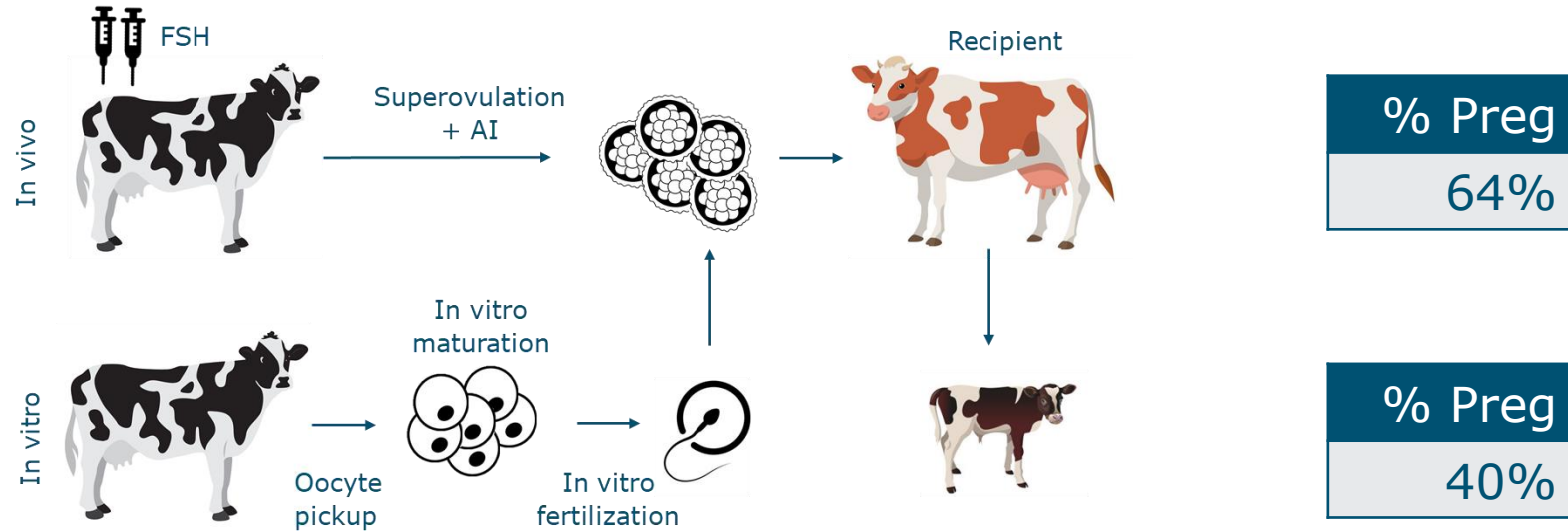
Maternal age



Cattle embryo aberrations



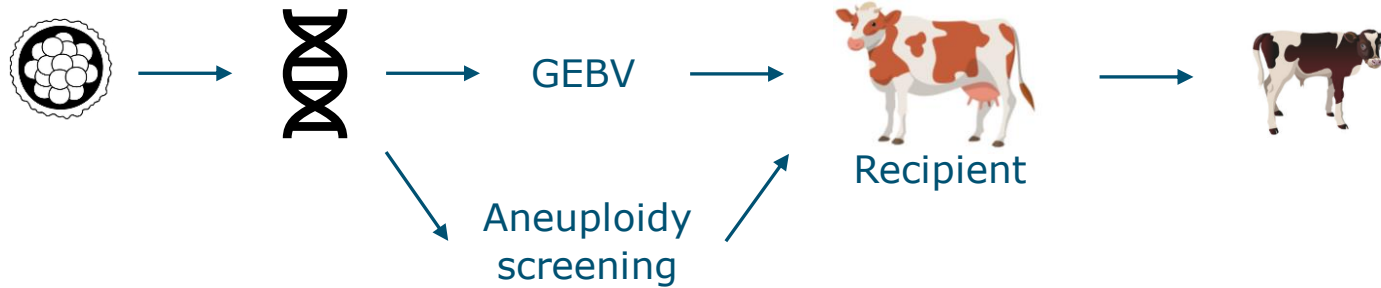
Cattle embryo pregnancy rate



Cattle breeding program

- Nucleus breeding programs produce top AI sires
- *In vitro* embryo production allows for optimal use of elite dams
- Oocytes matured and fertilized in lab, embryo cultured to day 7
- Embryos are genotyped to determine sex and breeding values
- Only top ranked embryos are transferred

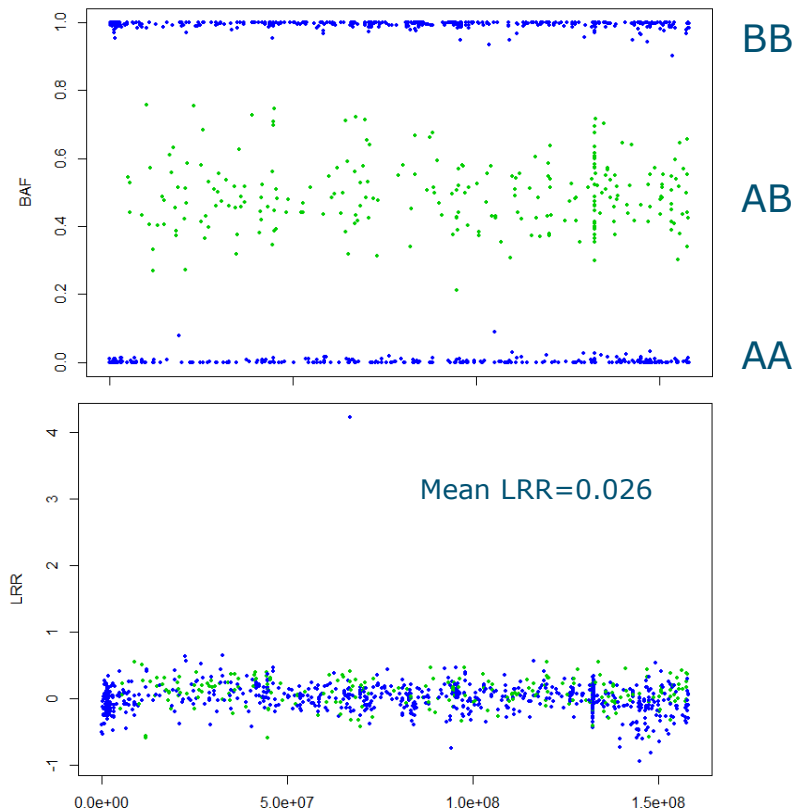
Cattle pre-screening



Genotyping embryos

- 10-15 cells at blastocyst stage
- DNA amplification
- Genotype with SNP array (10K-50K DNA markers)

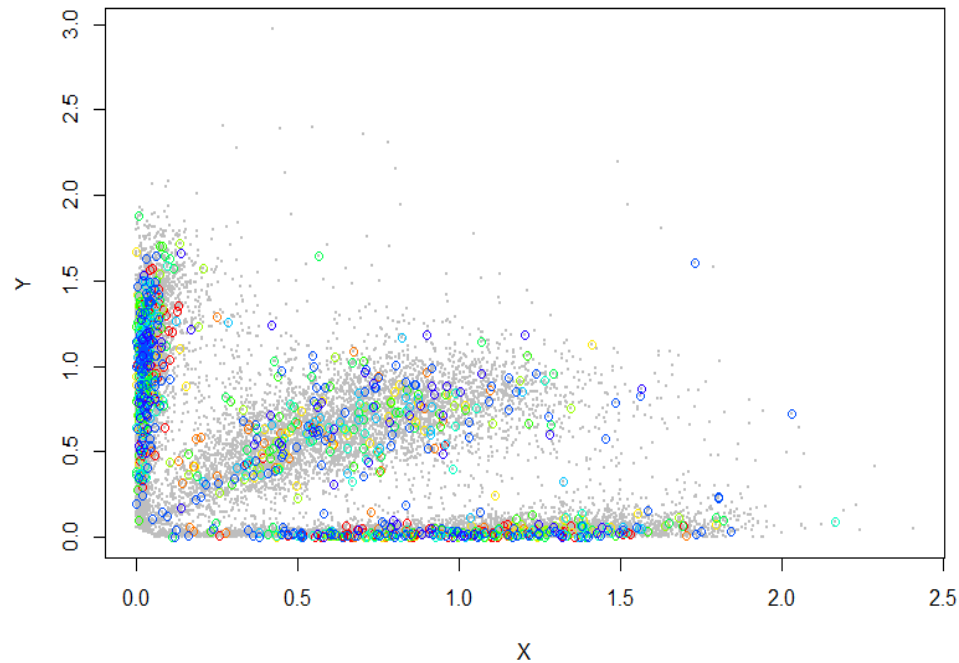
Normal example



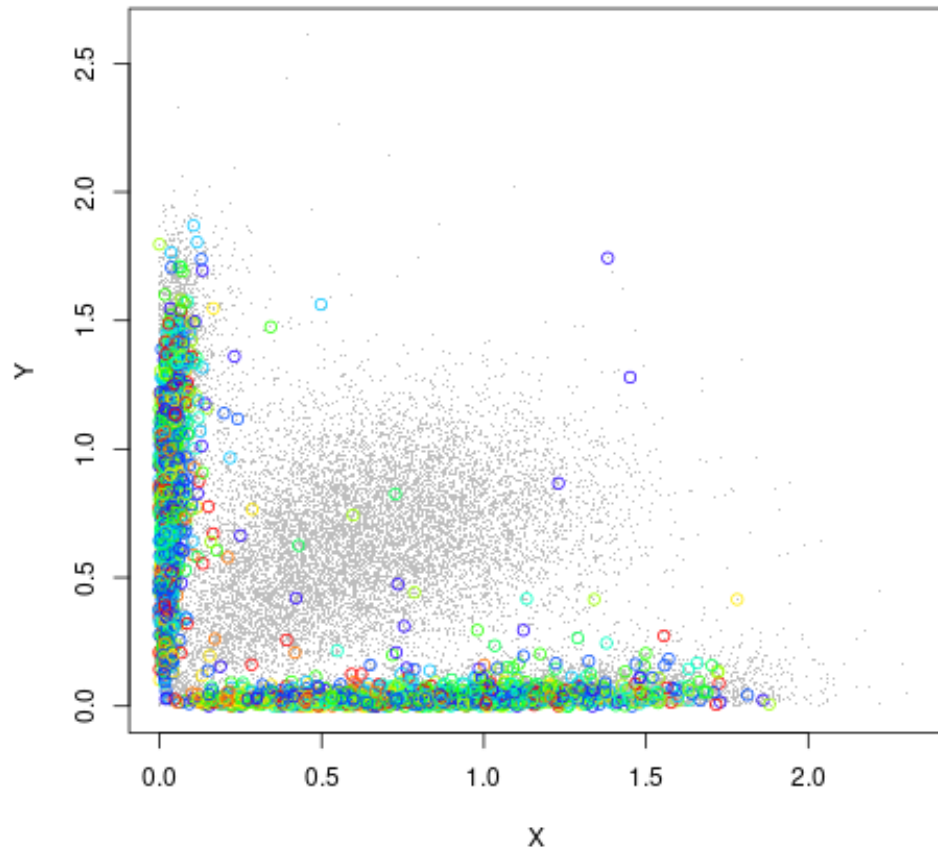
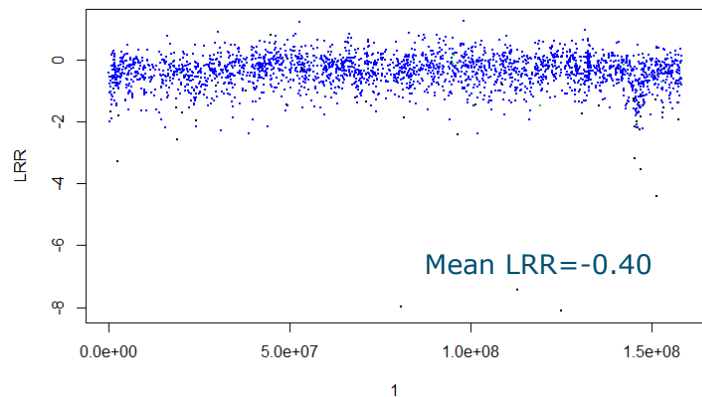
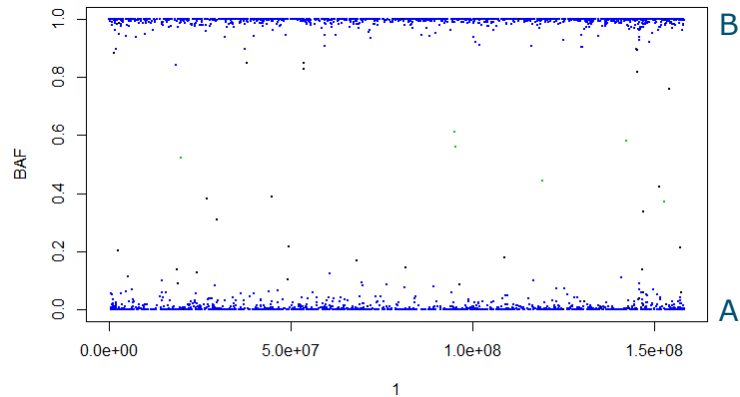
BB

AB

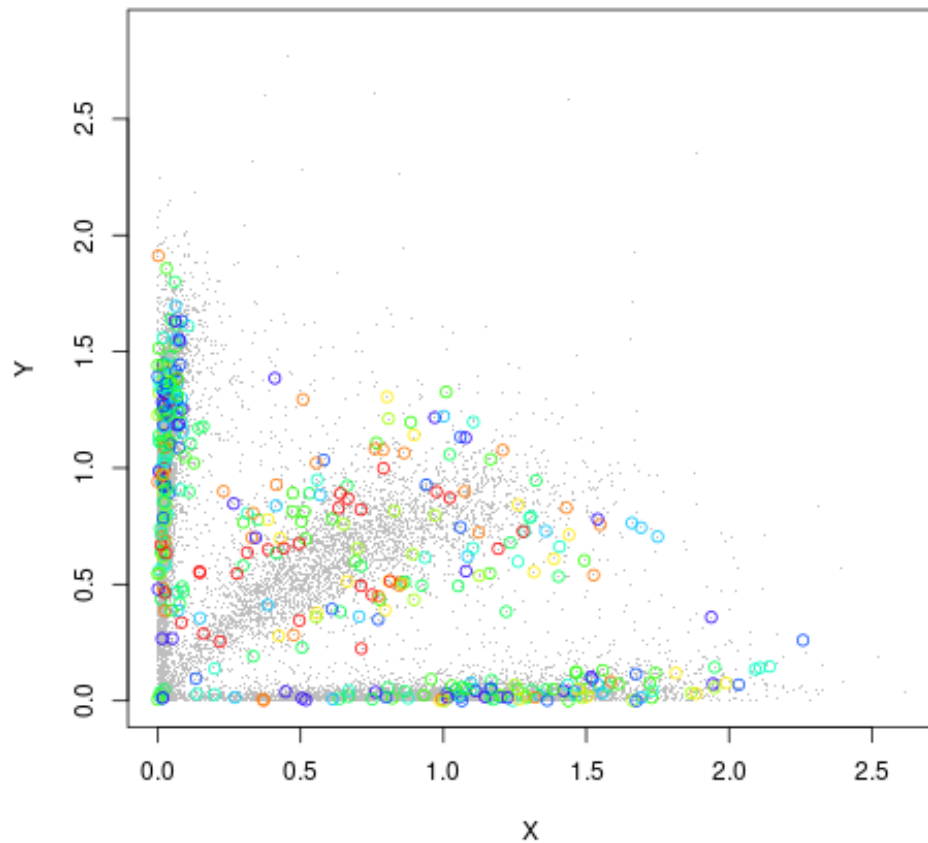
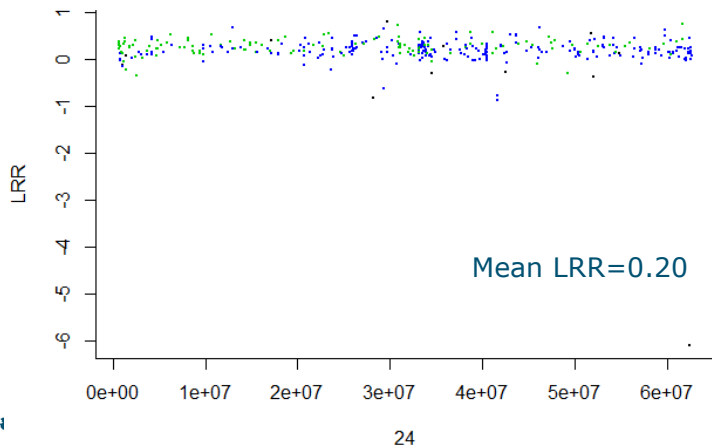
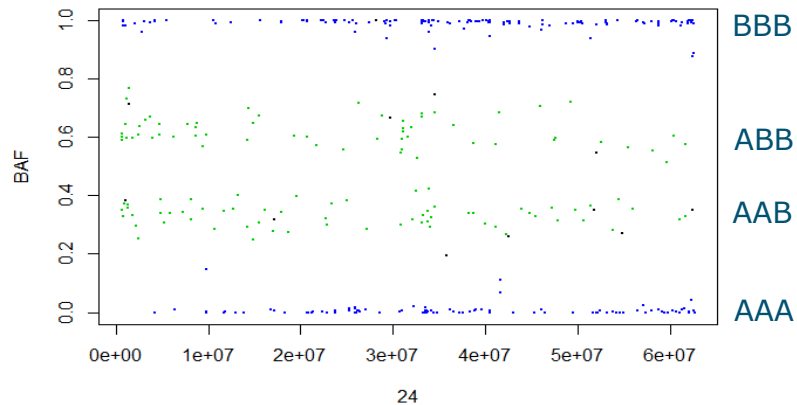
AA



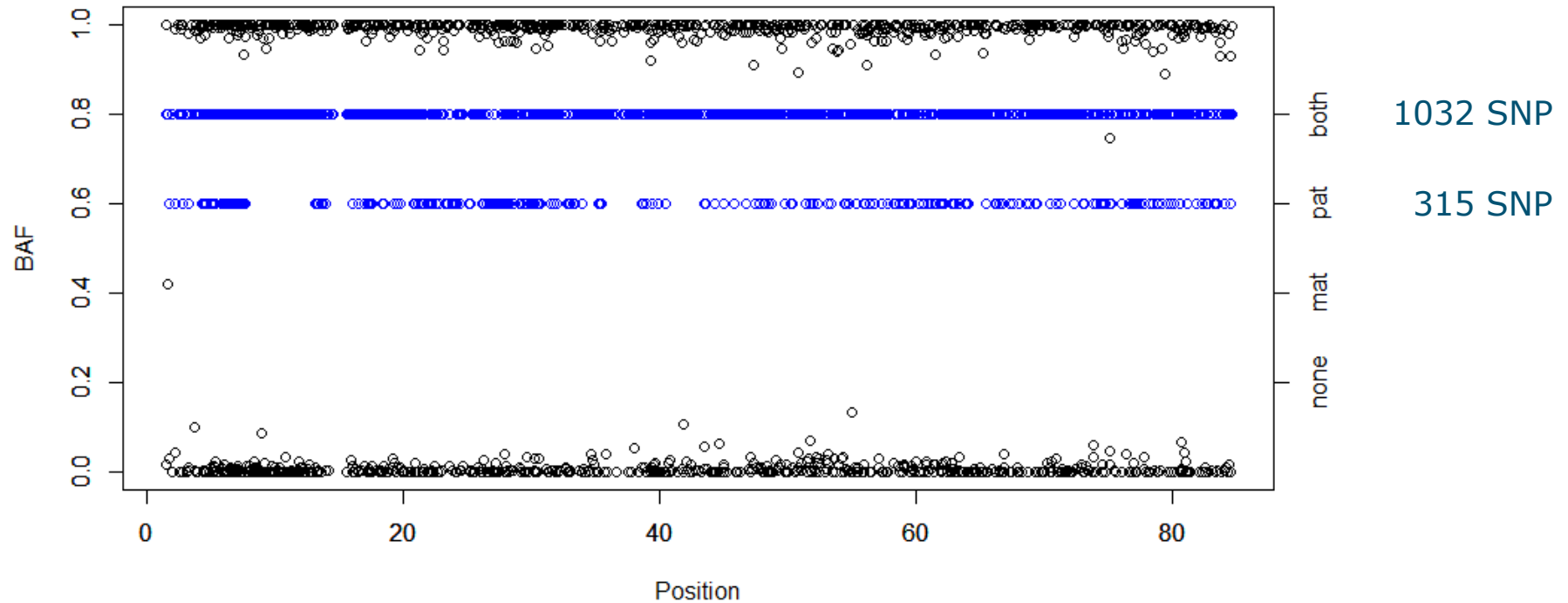
Monosomy example



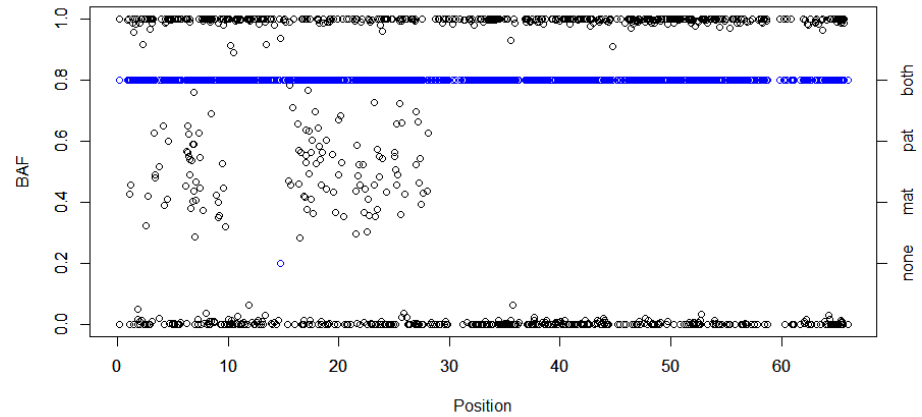
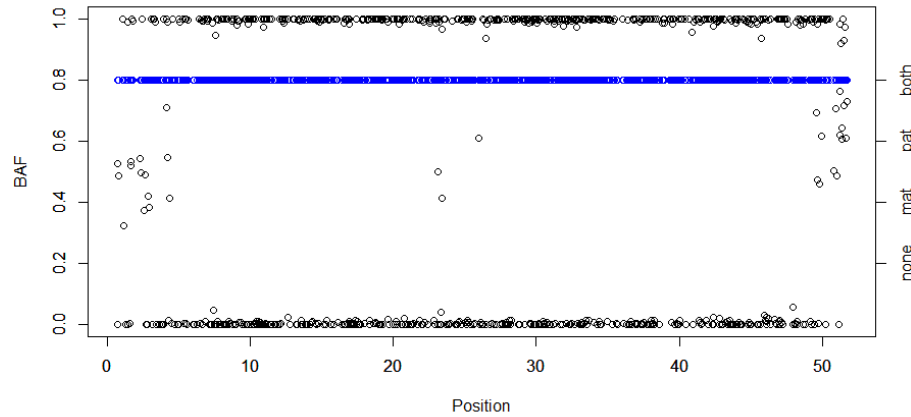
Trisomy example



Monosomy – paternal present



ROH(s) instead of monosomy



■ Inbreeding

Parental origin

- 11 monosomy
 - 4 paternal chromosome absent
 - 7 maternal chromosome absent
- 1 haploidy
 - Maternal genome absent
- Trisomy
 - Under investigation

Impact gain or loss whole chromosome

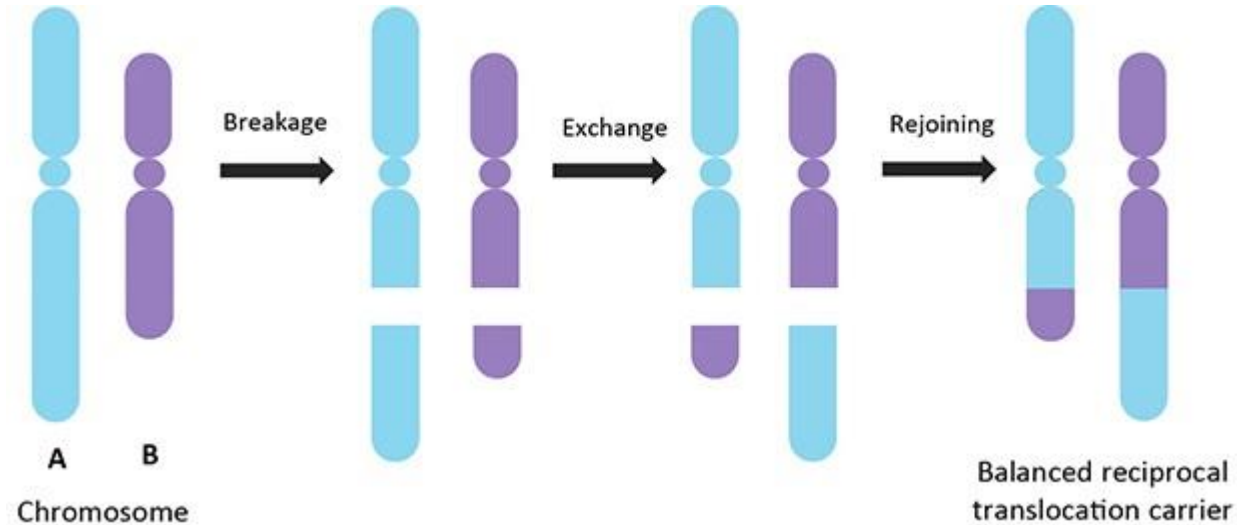
- Embryo losses
- Reduced pregnancy rates
- Screening genotype intensity data
- Implementing embryo selection before transfer
- Test lab protocols that reduce incidence

Questions?

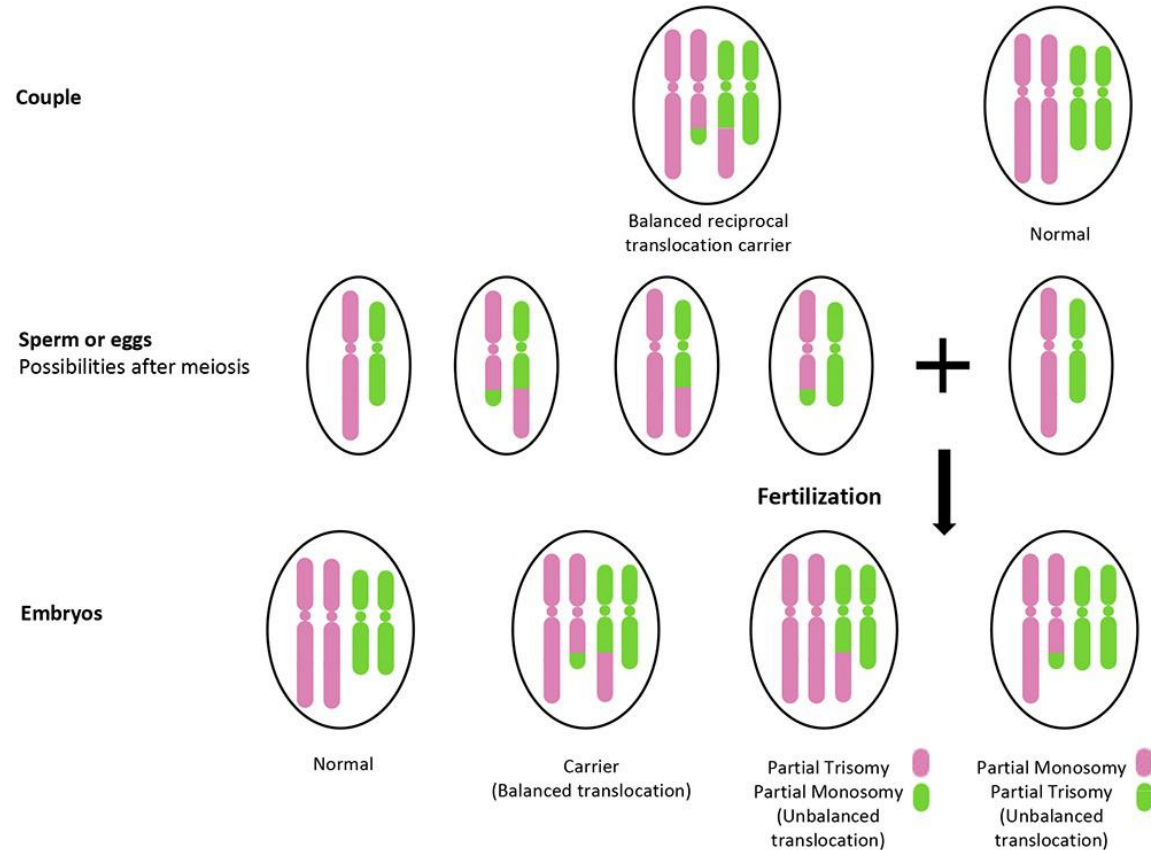


Gain or loss of part of chromosome

Balanced Reciprocal Translocation

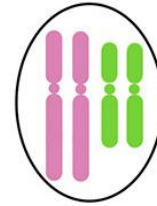


Gain AND loss of part of two chromosomes



In human

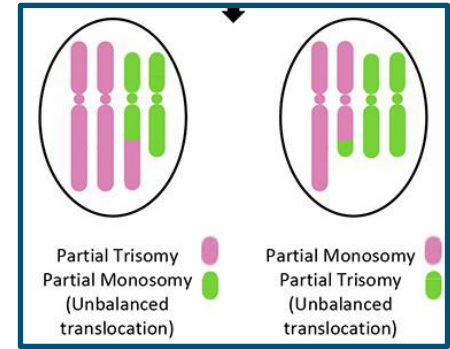
Embryos



Normal



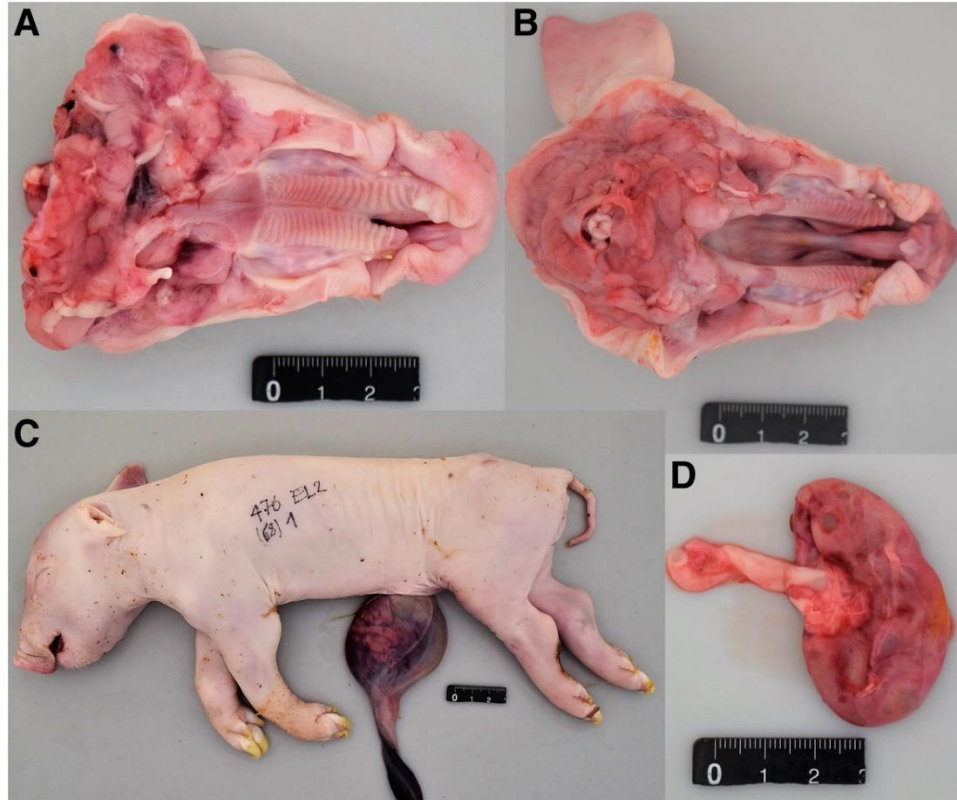
Carrier
(Balanced translocation)



- Occurrence $\sim 0.2\%$
- Carriers
 - Recurrent miscarriages
 - Child with congenital abnormalities and/or learning difficulties
- Pre-screening of embryos

Malformed piglet: Cleft plate

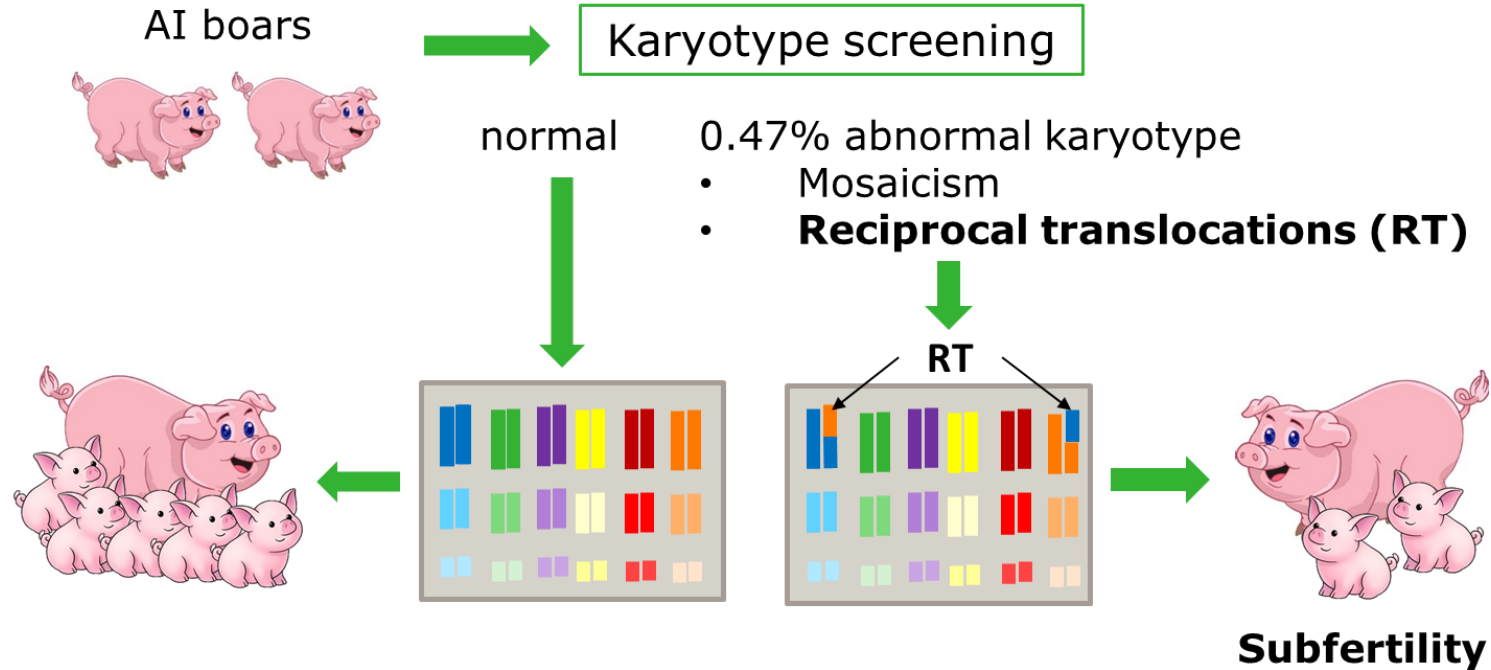
Malformed snout



Also a hernia

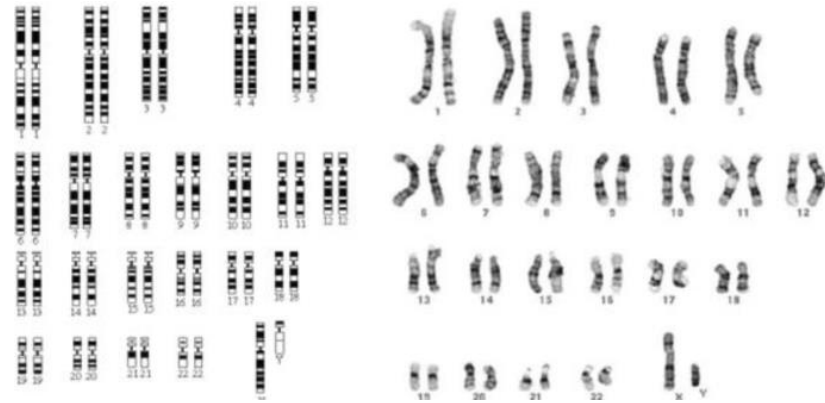
Renal cyst
(fluid in
kidneys)

Routine karyotype screening AI boars



How to screen for carriers

- Carrier has no gain or loss of DNA, it is just in the wrong place
- Karyotyping: staining of chromosomes
- Requires fresh blood and a skilled lab
- Can only detect if exchanged part is larger than bandsize ($\sim 5\text{Mb}$)
- Genotype data no order of markers
- Whole genome sequence data



Litter sizes

- Average reduction 40%, range 10-100% (Ducos *et al.* 2007)

		Individual		Sire		Dam	
	RT	Litter size ^a	N ^b	Litter size	N	Litter size	N
Pig1	T(2,4)	–	0	12.2 (± 3.7)	174	10.4 (± 3.3)	5
Pig2	T(6,8)	–	0	14.0 (± 3.9)	275	8 (± 7.1)	2
Pig3	T(2,4)	–	0	14.4 (± 3.9)	211	10.5 (± 2.4)	6
Pig4	T(2,4)	–	0	14.4 (± 3.9)	211	10.5 (± 2.4)	6
Pig5	T(7,14)	–	0	6.6 (± 2.9)	13	9.4 (± 1.6)	7
Pig6	T(2,4)	–	0	12.0 (4.0)	55	10.5 (± 2.4)	6
Pig7	T(1,16)	5 (± 2.6)	6	6.5 (± 2.4)	6	8.5 (± 1.7)	4

^a Litter size based on liveborn piglets only

^b N is the number of litters with recorded litter size

Littersize

- Average reduction 40%, range 10-100% (Ducos *et al.* 2007)

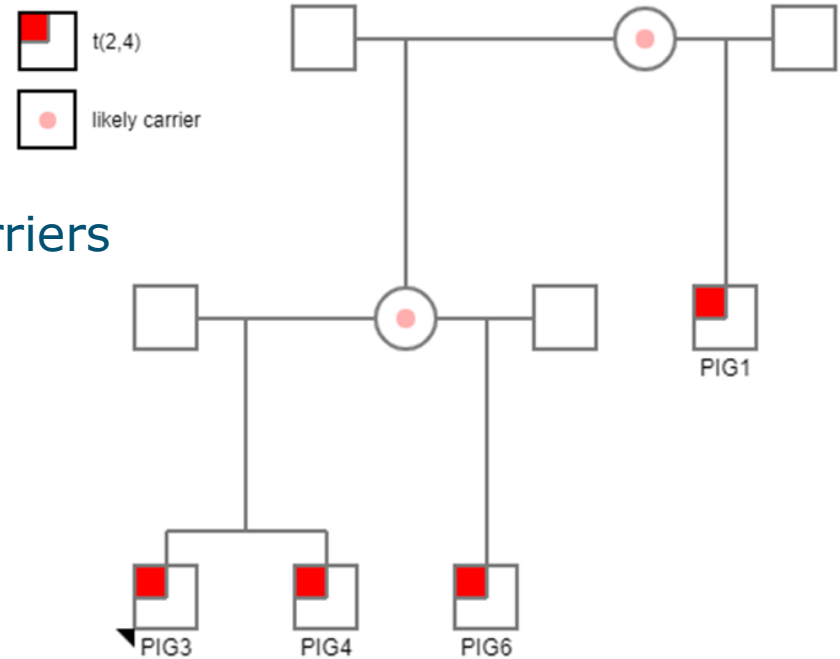
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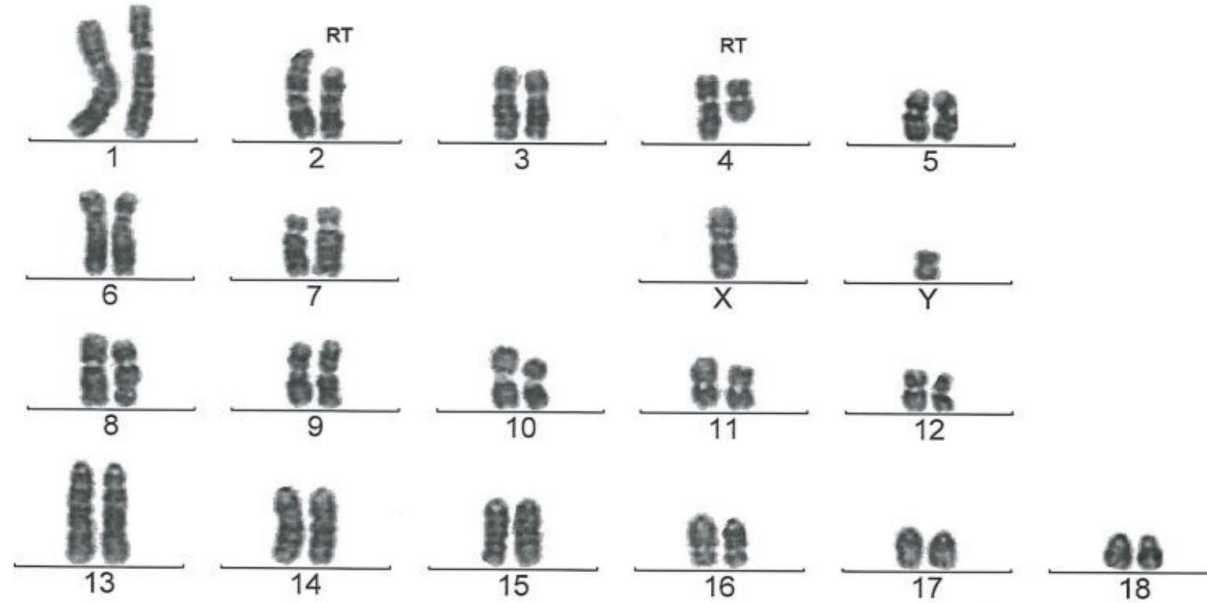
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Pedigree

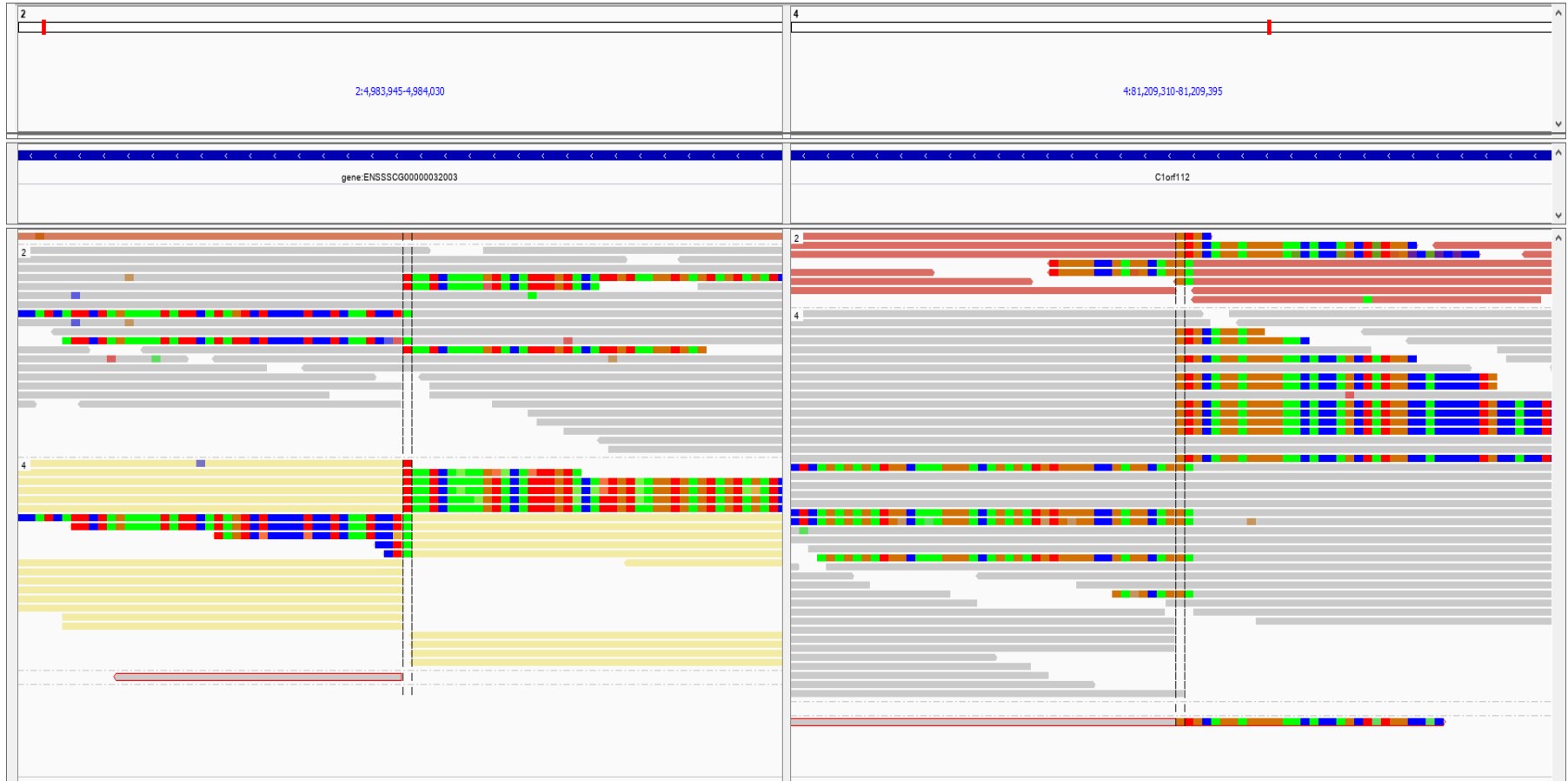
- Females are not tested
- Litter size not reduced
- Pedigree can identify potential carriers



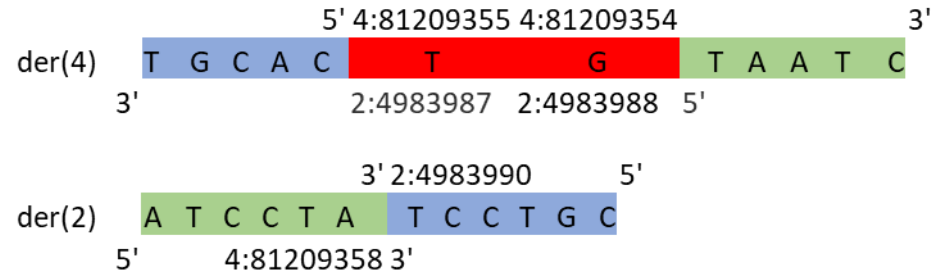
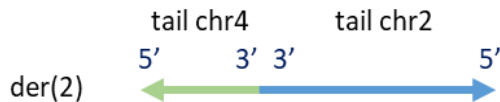
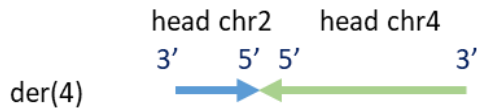
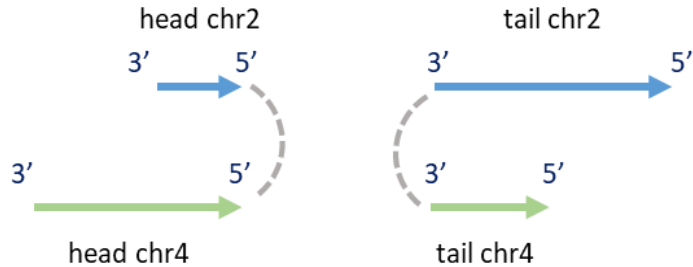
Case t(2,4)



Sequence reads t(2,4)

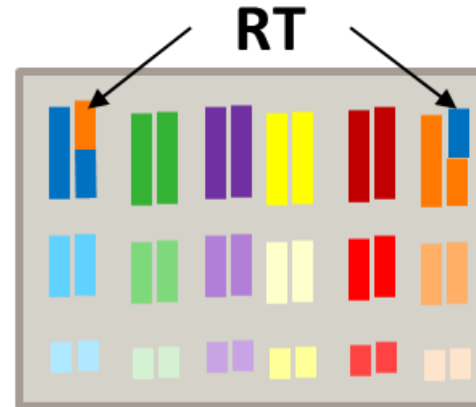


Breakpoint junction t(2,4)



Breakpoint junctions

- 6 out of 8 unique breakpoints **within gene**
 - No consequence because present in heterozygous state
 - Onset at later age?
- Similar to human studies




Detection using DNA sequence

- 6 out of 7 RTs detected (blinded)
- 7th detected after unblinding: was in repetitive area
- 15 controls negative for RTs
- Need at least 20x coverage

	PIG1	PIG2	PIG3	PIG4	PIG5	PIG6	PIG7
RT chr	2/4	6/8	2/4	2/4	7/14	2/4	1/16
Coverage	32.6	37.9	33.4	35.1	37.2	31.1	30.3
Final filt	30(15)	56(28)	34(17)	38(19)	68(34)	38(19)	44(22)
Visual insp	1(2,4)	1(6,8)	1(2,4)	1(2,4)	1(7,14)	1(2,4)	0(FN)

Impact gain or loss partial chromosome

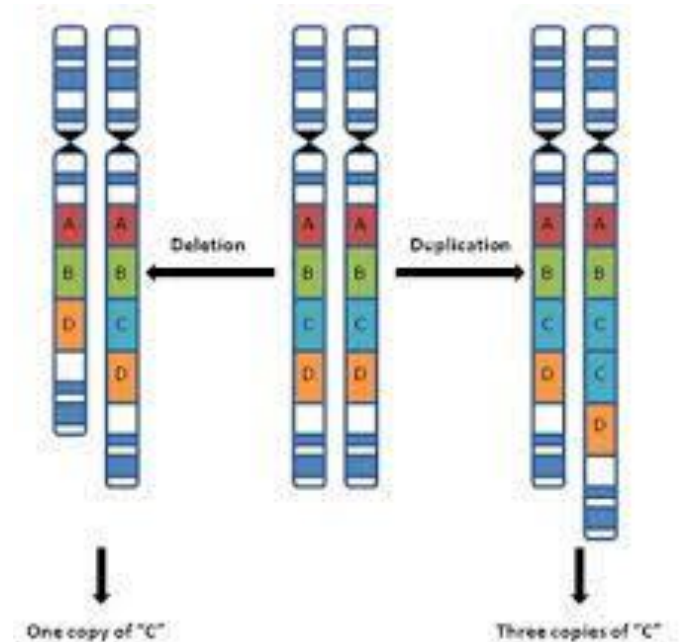
- Gain of part of chromosome AND loss of part of other chromosome
 - Unviable / malformed
 - Carrier: partial exchange between chromosomes
 - No gain or loss of DNA
 - Often genes interrupted, but in heterozygous state
 - Reduced fertility (~40% offspring unviable)
 - Screening of AI boars and tracing females through pedigree
- 

Questions?



Gain or loss of kilo bases

- Deletion or duplication affecting considerable number of bases
- Copy number variants
- Common in our genomes
- Segregating in populations



Deletions and duplications in cattle

Functional and population genetic features of copy number variations in two dairy cattle populations

[Young-Lim Lee](#) ✉, [Mirte Bosse](#), [Erik Mullaart](#), [Martien A. M. Groenen](#), [Roel F. Veerkamp](#) & [Aniek C. Bouwman](#)

[BMC Genomics](#) **21**, Article number: 89 (2020) | [Cite this article](#)



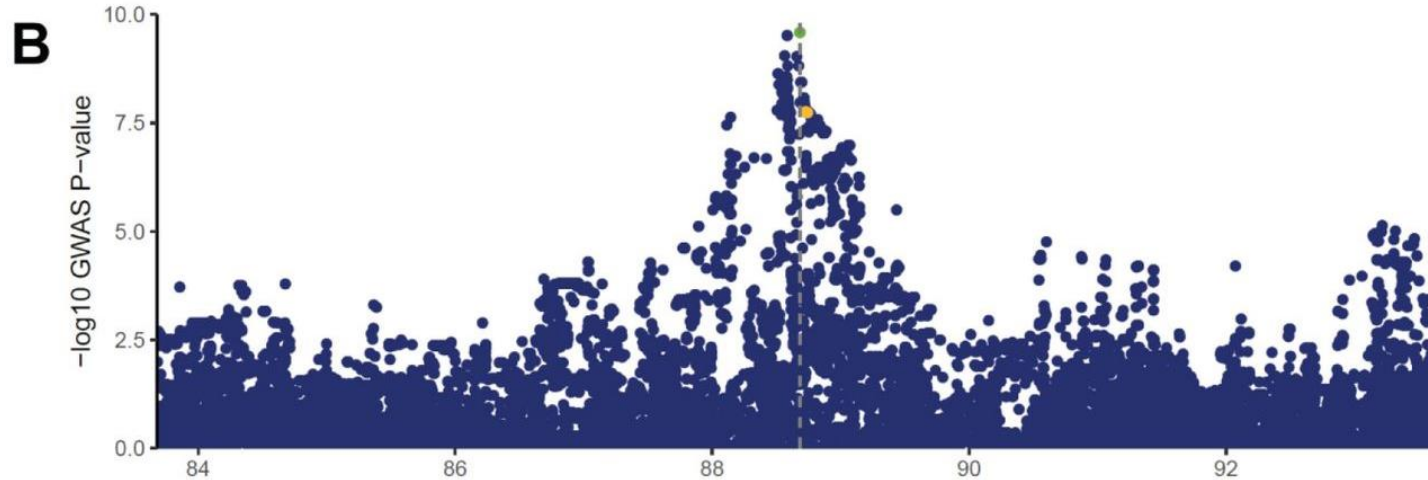
A 12 kb multi-allelic copy number variation encompassing a GC gene enhancer is associated with mastitis resistance in dairy cattle

Young-Lim Lee, Haruko Takeda, Gabriel Costa Monteiro Moreira, Latifa Karim, Erik Mullaart, Wouter Coppieters, The GplusE consortium, Ruth Appeltant, Roel F. Veerkamp, Martien A. M. Groenen, Michel Georges, Mirte Bosse, Tom Druet, Aniek C. Bouwman, Carole Charlier

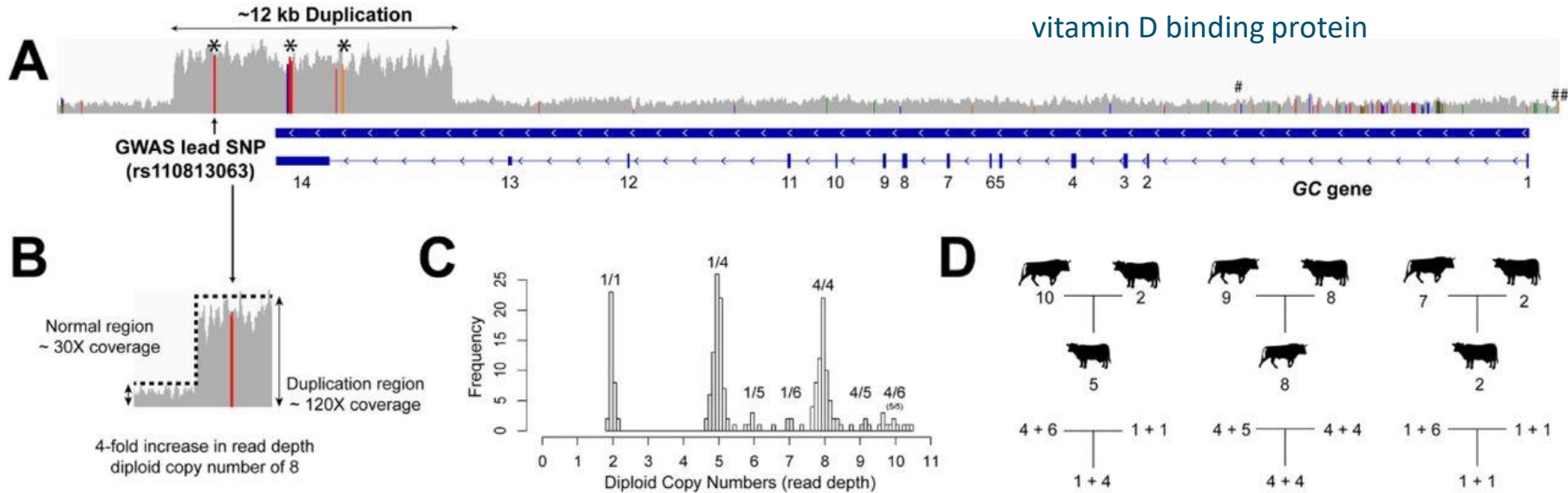
doi: <https://doi.org/10.1101/2021.01.08.425854>

This article is a preprint and has not been certified by peer review [what does this mean?].

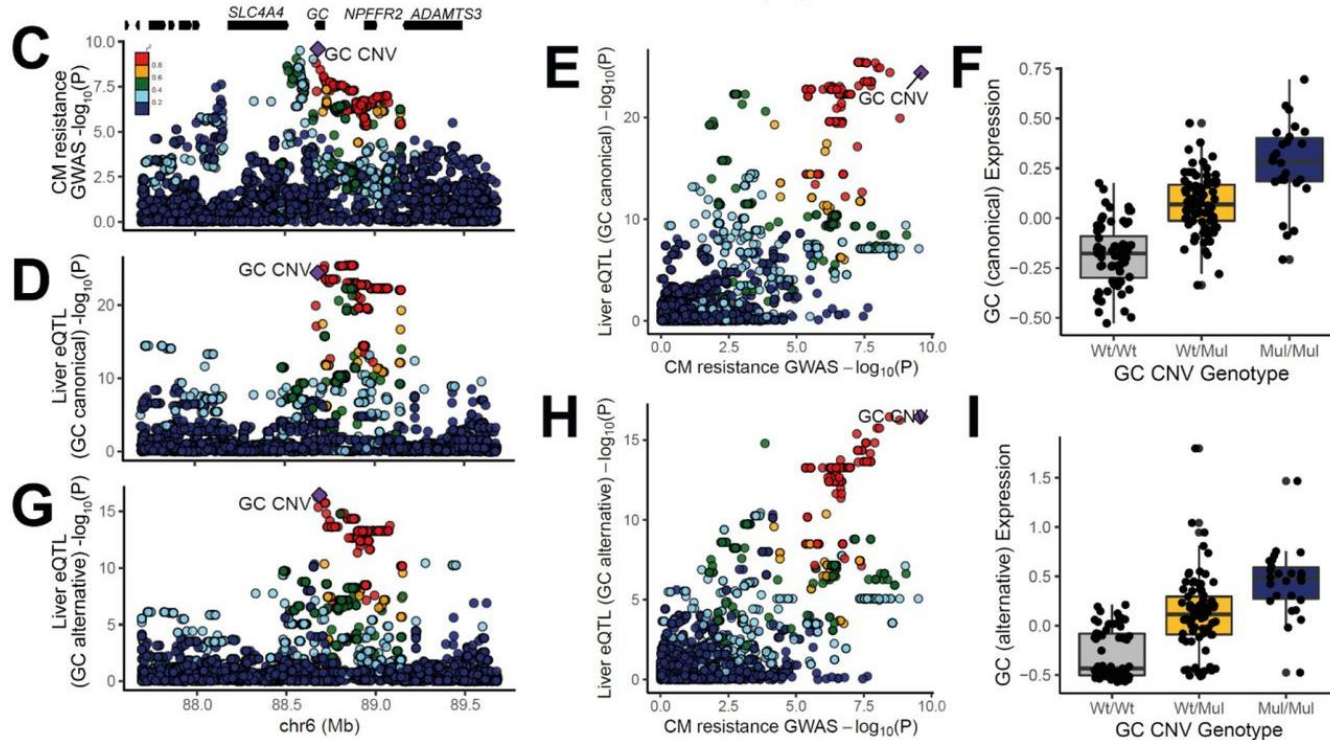
GWAS clinical mastitis Holstein cattle



GWAS lead SNP in Duplication



Gene expression higher for duplication



Impact of gain or loss of kilo base pairs

- Deletions and duplications
- If affects gene expression
 - Variation in traits or causal to disease
- Identify and genotype in populations
- Include in association studies and genomic prediction

In summary:

The impact of DNA gain or loss

Monitoring using advanced DNA technology

- Gain or loss of **whole chromosome**
 - (Mostly) unviable > embryo losses > reduce pregnancy rates
- Gain or loss of **large part of chromosome**
 - Unviable/Malformations
 - Carriers > reduced fertility
- Gain or loss of **kilo base pairs**
 - Reduced/increased gene expression > phenotypic variation

Questions?



World Congress on
Genetics Applied
to Livestock Production

Rotterdam | The Netherlands
3 - 8 July 2022

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IMPORTANT DATES

12 January 2022: Deadline abstract submission
1 March 2022: Deadline early bird registration

www.wcgalp2022.com

