Novel harmful recessive haplotype identified for fertility traits in Nordic Holstein cattle

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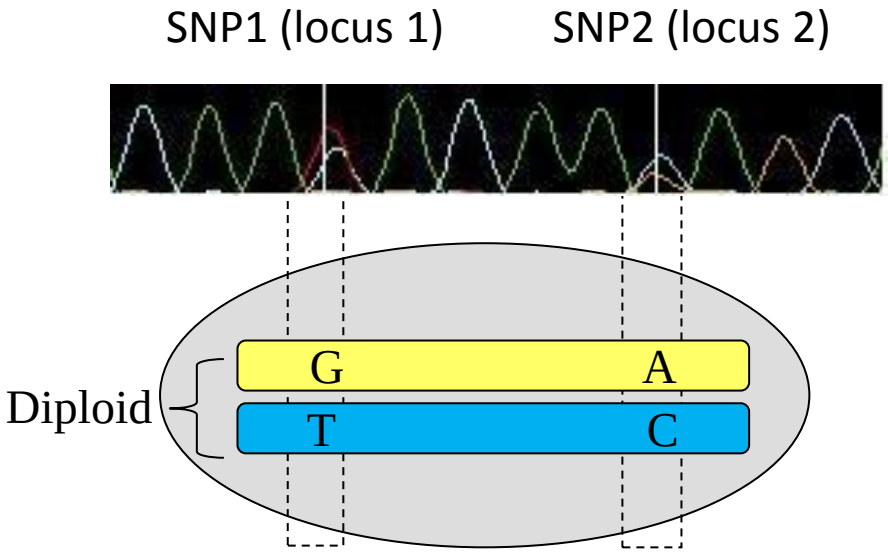
Recessive lethals

- Defects that cause embryo loss are difficult to detect even with large set of phenotypic and pedigree data
  - Too few observations
- Genomic data can help
  - Haplotype is common but never homozygous in live animals
- Requires genotypes only from normal individuals
  - Not from affected embryos
  - Opposite to ‘previous strategies’

Haplotype



Genotyping

SNP1	SNP2
G/T	A/C

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

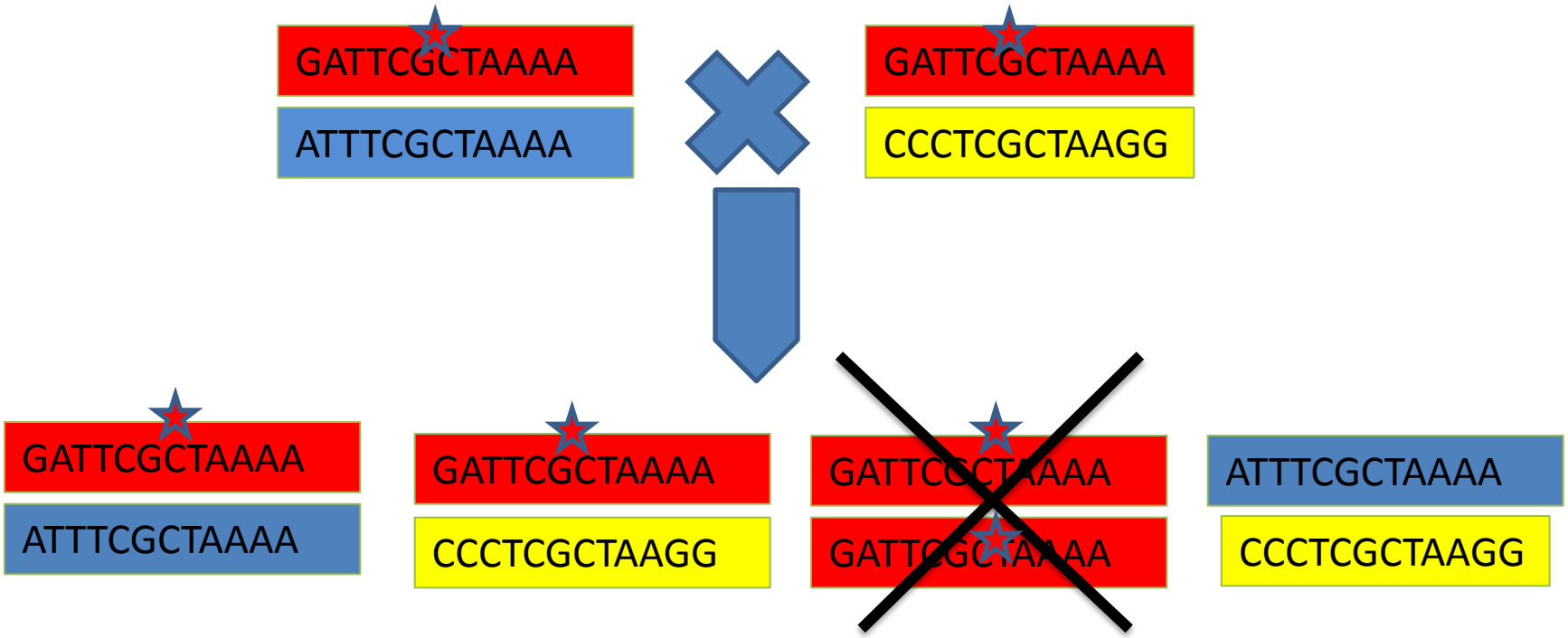
?

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

Reconstruct haplotypes

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

Haplotypes to trace recessive lethal



Hap freq. = q → Exp. Homozygous freq. = q^2

VanRaden et al. JDS 2011, 94:6153

- Analyzed Holstein (58,453), Jersey (5,288) and Brown Swiss (1,991)
- BovineSNP50 for genotyping
- Haplotypes ≤ 75 markers
- Traits
  - Sires conception rate
  - Stillbirth rate

VanRaden et al.

- Selected 11 haplotypes
  - expected 7 to 90 homozygotes, none observed
  - 0.0002 to 10^{-45}, probability of not observing
- Model: Routine model + carrier interaction

Carrier SS / Carrier MGS	Carrier	Non-carrier	Not-genotyped
Carrier	14,114	350,271	267,542
Non-carrier	365,594	6,880,546	6,283,334
Not-genotyped	13,655	285,967	450,364

Results from VanRaden et al.

- 5 haplotypes for large harmful effects (-3.0 to -3.7 percentage points)
- Confirmed known defects
  - CVM (Hol), Brachyspina (Hol), SMA (BS) etc.

Hap	Chr	Mb	Carrier freq.	Effect on CR
HH1	5	58-66	4.5	-3.1
HH2	1	92-97	4.6	-3.0
HH3	8	90-95	4.7	-3.2
JH1	15	13-18	23.4	-3.4
BH1	7	41-47	14.0	-3.7

Nordic Holsteins

Data and methods

- 7,937 Nordic Holsteins
- BovineSNP50 BreadChip
- Search for haplotypes from VanRaden et al. (2011)
  - HD imputed data for Nordic Holsteins
  - 50 kb region
  - Haplotype effect
    - Compare BVs of carriers and non-carrier bulls
- Genome scan
  - Two haplotype lengths: 25 and 75
  - Haplotype effect
    - Estimated from the phenotypes of the cows

BTA5:62-68 MB – HH1

Region (Mb)	Haplotype	Carrier freq. (%)
63.55 – 63.60	1311311311131112	4.5
63.70 -63.75	13311322332	4.3

chr	position	trait	carrier	non-carrier
5	63.55	iflc	102.263	112.085
5	63.55	iflh	95.071	100.704
5	63.55	nrrc	101.276	103.343
5	63.55	nrrh	97.6987	101.300
5	63.70	iflc	100.028	112.097
5	63.70	iflh	95.329	100.697
5	63.70	nrrc	101.035	103.343
5	63.70	nrrh	97.056	101.303

BTA1:93-98 MB – HH2

Region (Mb)	Haplotype	Carrier freq. (%)
95.00 – 95.05	1211233111	4.2

chr	position	trait	carrier	non-carrier
1	95.00	iflc	104.562	112.069
1	95.00	iflh	102.314	100.627
1	95.00	nrrc	100.266	103.355
1	95.00	nrrh	102.201	101.252

BTA8:92-97 MB – HH3

Region (Mb)	Haplotype	Carrier freq. (%)
93.10 – 93.15	2111111	4.2
93.30 – 93.35	31313111121313	4.2
95.10 – 95.15	111131113311	4.5

chr	position	trait	carrier	non-carrier
8	93.10	iflc	108.395	112.026
8	93.10	iflh	101.712	100.634
8	93.10	nrrc	101.934	103.336
8	93.10	nrrh	101.071	101.265
8	93.30	iflc	108.157	112.028
8	93.30	iflh	101.842	100.633
8	93.30	nrrc	102.183	103.334
8	93.30	nrrh	101.380	101.262
8	95.10	iflc	108.453	112.029
8	95.10	iflh	103.241	100.615
8	95.10	nrrc	104.876	103.307
8	95.10	nrrh	103.891	101.232

Genome scan

- HAP25
  - 17 haplotypes on 6 chromosomes
  - ~ 8 genomic regions

Rare haplotypes and their frequencies

Hap ID	Carrier frequency (%)	No. of homozygotes	
		Obs.	Exp.
05-826	3.4	1	9
05-1351	4.0	1	13
05-1476	3.2	1	8
07-126	6.8	0	36
07-476	3.8	0	12
08-1276	3.0	0	7
08-1301	3.0	0	7
08-1326	3.0	0	7
08-1351	3.1	0	7
11-926	2.8	0	6
11-976	2.8	0	6
11-1001	2.8	0	6
11-1026	2.7	0	6
19-151	3.8	0	11
21-276	4.0	0	13
21-301	4.1	1	13
21-326	3.9	1	12

Fertility traits

Trait	No. of records	Mean	Std. Dev.	Phenotypic correlations			
				NR56	NR100	NR150	CI
NR56	98,957	59.50	49.09	1.00			
NR100	99,239	48.79	49.99	0.81	1.00		
NR150	99,247	45.89	49.83	0.76	0.94	1.00	
CI	78,757	407.68	70.95	-0.21	-0.38	-0.45	1.00

NR – Non-return rate, CI – Calving interval

Model

Probability being homozygous ($P_{hom-foetus}$) for the recessively lethal allele:

$$P_{hom-foetus} = 0.5 \times P_{carr-sire} \times 0.5 \times P_{carr-dam}$$

Model:

$$Y_{ij} = \mu + \beta \times \left(P_{hom-foetus}\right) + Year \times Month_j + e_{ij}$$

Effects on fertility traits

Hap-ID	Effect of $P_{hom-foetus}$ on							
	NR56		**NR100**		**NR150**		**Calving interval**	
	Effect (%)	P-value	Effect (%)	P-value	Effect (%)	P-value	Effect (%)	P-value
05-826		N.S.		N.S.		N.S.		N.S.
05-1351		N.S.		N.S.		N.S.	**16.8**	0.02
05-1476		N.S.		N.S.		N.S.	**22.2**	0.003
07-126		N.S.		N.S.		N.S.		N.S.
07-476	**-6.07**	0.0001	**-6.7**	0.0001	**-6.2**	0.0001		N.S.
08-1276	**-15.3**	0.05		N.S.	**.**	N.S	**28.4**	0.02
08-1301	**-20.8**	0.003	**-20.1**	0.004	**-20.4**	0.004	**22.8**	0.04
08-1326	**-21.4**	0.002	**-21.3**	0.002	**-21.5**	0.002	**22.7**	0.04
08-1351	**-18.3**	0.008	**-18.1**	0.001	**-18.1**	0.001	**27.2**	0.01
11-926	**-14.1**	0.0008	**-16.5**	0.0001	**-17.1**	0.0001	**15.4**	0.02
11-976	**-13.7**	0.001	**-16.9**	0.0001	**-17.5**	0.0001	**15.4**	0.02
11-1001	**-13.5**	0.001	**-16.4**	0.0001	**-17.1**	0.0001	**15.7**	0.02
11-1026	**-14.7**	0.001	**-16.7**	0.001	**-17.0**	0.0001	**13.1**	0.02
19-151	**-14.4**	0.0001	**-11.1**	0.01	**-10.6**	0.02		N.S.
21-276	**-9.7**	0.01	**-24.4**	0.0001	**-25.0**	0.0001	**39.7**	0.0001
21-301	**-9.0**	0.01	**-23.6**	0.0001	**-25.7**	0.0001	**43.1**	0.0001
21-326	**-7.2**	0.06	**-22.3**	0.0001	**-25.0**	0.0001	**47.2**	0.0001

Summary

- Presence of HH1, HH2, and HH3 in Nordic Holsteins
  - Carrier frequencies between 4 – 5%
- Additional ’lethal’ haplotypes detected
- Confirmed Brachyspina on BTA21 (21 Mb)

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