What we know about the genetics of reproduction

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What we know…

- Assisted Reproductive Technologies (ART)
  - Increase the rate of genetic improvement
  - Reduce the number of influential parents
    - Can increase the risk of propagating a lethal recessive gene
  - In Vitro Fertilization (IVF)
    - Culture media can influence the embryo – large calf syndrome
    - Modification of the function of the embryonic genome
  - These are not reasons to fear ART; they are reasons to incorporate genomic technologies into ART.

What we know…

- Reproductive traits are lowly heritable.
  - Polygenic – many genes with small effects
  - Environmental effects are big
- Culling every open heifer in your herd every year will not create a herd with 100% pregnancy rates.
- Only about 1% of heifers will fail to conceive in two consecutive breeding seasons.

What we know…

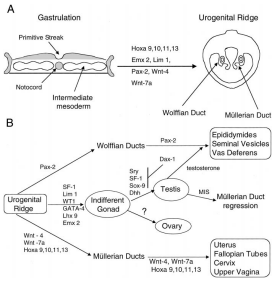
- Genetic Markers
  - Probably adopted for production traits first
    - Fastest economic benefit
  - ***However***, we need to insure that we do not negatively impact fertility
    - Holsteins
    - Selection index

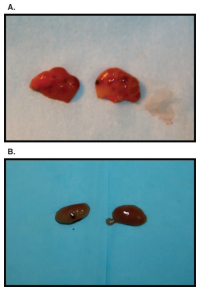
Genetics - not easy

Trait	*Heritability*	*References*
Age at First Ovulation	0.28	(Mialon et al., 2001)
Age at First Progesterone	0.38	(Mialon et al., 2001)
Age at Puberty	0.14	(Snelling et al., 2012)
	0.24	(Morris et al., 2000)
Reproductive Tract Score	0.30	(Martin et al., 1992)
Yearling Uterine Horn Diameter	0.20	(Johnston et al., 2009)
Antral Follicle Count	0.44	(Snelling et al., 2012)
Age at First Calving	0.28	(Minick Bormann and Wilson, 2010)
Heifer Pregnancy Rate	0.21	(Doyle et al., 2000)
	0.28	(Thallman et al., 1999)
Pregnancy Rate	0.07	(MacNeil et al., 2006)
Stayability	0.15	(Doyle et al., 2000)

Cushman et al., 2008. R Bras Zootec 37:116
Cammack et al., 2009. PAS. 25:515

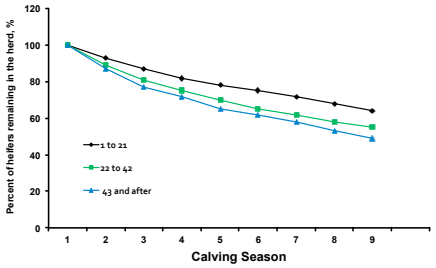
Differences in ovarian morphology exist at birth





MacLaughlin et al., 2001. Endo 142:2167
Cushman et al., 2009. JAS 87:1971

Advantages of calving early as a heifer



Kill et al., 2012. JAS 95(suppl 2):131
Cushman et al., 2012. JAS (in preparation)

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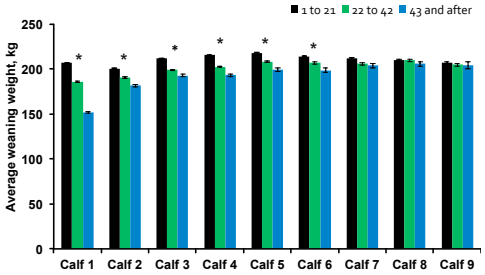

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Reproductive tract scoring

Table 1. Reproductive tract score (RTS) system

RTS	Uterine horn	Ovary: Length, mm	Ovary: Height, mm	Ovary: Width, mm	Ovarian structures
1	Immature <20-mm diameter, no tone	15	10	8	No palpable structures
2	20- to 25-mm diameter, no tone	18	12	10	8-mm follicles
3	25- to 30-mm diameter, slight tone	22	15	10	8- to 10-mm follicles
4	30-mm diameter, good tone	30	16	12	>10-mm follicles, corpus luteum possible
5	>30-mm diameter, good tone, erect	>32	20	15	>10-mm follicles, corpus luteum present

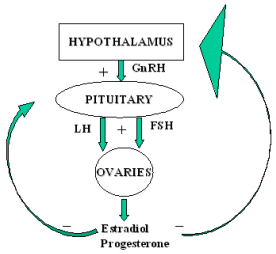
Table 4. Summary of reproduction and production outcomes by reproductive tract score (RTS) category in beef heifers

RTS	Pregnancy rate (%) to AI period	Final pregnancy rate, %	Median days to calving, d	Mean calf weaning weight, kg	Proportion of heifers present at start of subsequent season, %	Pregnancy rate (%) to subsequent AI period
1	31[a]	56[a]	53.5[ab]	194[ab]	50[a]	63[ab]
2	40[a]	76[a]	52[a]	186[a]	51[a]	61[a]
3	53[a]	81[ab]	28[bc]	213[b]	57[a]	72[b]
4	70[b]	92[b]	15[c]	207[b]	80[b]	85[b]
5	80[b]	93[b]	18[c]	213[b]	70[bc]	90[b]

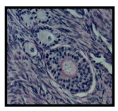
[a,b,c]Values within columns with no superscripts in common differ significantly ($P < 0.05$).

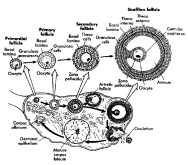
Holm et al., 2009. JAS 87:1934

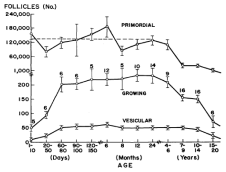
The Mammalian Ovary

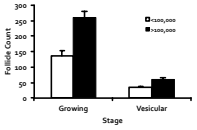


Variation in the ovarian reserve



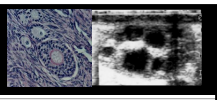






Erickson, 1966. JAS 25:800; Cushman et al. 1999. BOR 60:349; Ireland et al. 2008. BOR 79:1219

Antral Follicle Count



Item	Low AFC, n	High AFC, n	*P*-value
Ovary height,[1] mm	12.4 ± 0.18 (14)	14.3 ± 0.04 (41)	0.07
Ovary length,[2] mm	22.0 ± 0.13 (14)	26.6 ± 0.05 (41)	0.001
RTS[3]	4.1 ± 0.29 (14)	4.5 ± 0.08 (44)	0.13
Birth weight, kg	35.8 ± 0.57 (84)	38.7 ± 0.38 (178)	0.003
Age, d	406.9 ± 1.55 (84)	408.2 ± 1.30 (178)	0.59
Percentage pregnant	85.5 ± 3.4 (84)	94.3 ± 2.3 (178)	0.05

[1]Average height of the 2 ovaries within a heifer.
[2]Average length of the 2 ovaries within a heifer.
[3]RTS = reproductive tract score (Martin et al., 1992).

Cushman et al., 2009. JAS 87:1971

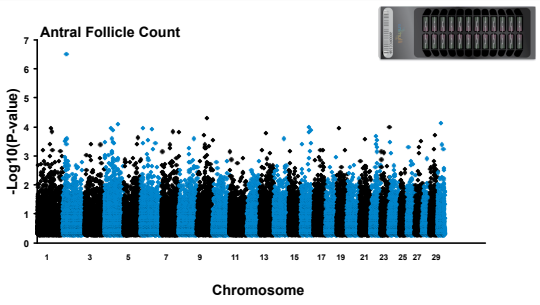
Antral Follicle Count and Calving Day

	Calving Period			
	1	2	3	*P*-value
Heifers	222	129	67	-
Age at puberty, d	315.2 ± 2.8	318.3 ± 3.6	317.9 ± 5.2	0.76
Antral Follicle Count	23.0 ± 0.5[a]	21.7 ± 0.7[ab]	20.6 ± 0.9[b]	0.05

Limitations to palpation

- Numbers that can be evaluated in a day.
- Cannot palpate until about 10 months of age.
  - Weaning optimal time to sort
- Antral follicle count only predicts about 30% of the variation in ovarian reserve.

USMARC genome wide association study for antral follicle count

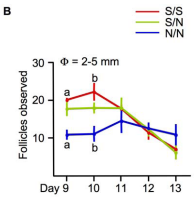


Snelling et al., 2012. JAS 90:1152

Ionotropic glutamate receptor AMPA 1 (GRIA1)

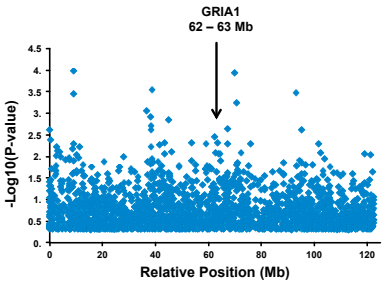
GRIA1 [G/A]

- Polymorphism associated with follicle numbers
- Serine to asparagine in the amino terminus
- Proposed to change binding affinity of receptor
- Decreased GnRH secretion from transfected immortalized hypothalamic cells
- LH surge decreased in vivo
- Decreased AI conception rates



Sugimoto et al., 2010. PLOS: e13817

USMARC genome wide association study for antral follicle count – Chomosome 6



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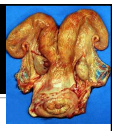
Sugimoto et al., 2010. PLOS: e13817

Reproductive performance

	Repeat Breeder	Control	*P*-value
Cows	64	72	-
Age at first breeding, d	426.5 ± 2.1	425.5 ± 2.3	0.74
Age at first calving, d	758.8 ± 11.3	715.9 ± 10.6	0.006
Age at last calving, d	1710.9 ± 103.4	3467.2 ± 97.5	< 0.0001
Days post-partum, d	475.6 ± 18.9	249.1 ± 17.8	< 0.0001
Days post-weaning, d	325.24 ± 20.1	115.2 ± 18.9	< 0.0001

Cushman et al., 2012. JAS (In Revision)

Reproductive tract



	Repeat Breeder	Control	*P*-value
Cows	64	72	-
Day of the Estrous Cycle	5.9 ± 0.2	5.7 ± 0.2	0.44
Ovarian Length, mm	28.7 ± 1.8	34.7 ± 1.5	0.03
Ovarian Height, mm	18.2 ± 1.2	22.5 ± 1.0	0.02
Endometrial diameter, mm	11.5 ± 1.1	18.9 ± 1.0	< 0.0001

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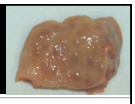
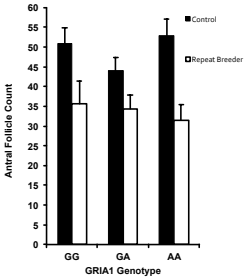
Cushman et al., 2012. JAS (In Revision)

Antral Follicle Count



- **GRIA1 genotype did not influence the number of 1-5 mm follicles (*P* = 0.43)**
- **Repeat Breeder cows had fewer 1-5 mm follicles than Control cows (*P* = 0.003)**



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GnRHr genotype

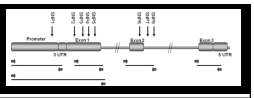

Table 1
Gene frequency, Hardy–Weinberg equilibrium (HWE), expected heterozygosities (h_e), and exclusion power estimated for GNRHR SNP5 alleles identified by pirosequencing analysis in seven bovine breeds.

Breed	*N*	Gene frequency		HWE	h_e	*Q*
		C	T			
Angus[1]	95	0.415	0.585	0.199	0.488	0.184
Holstein	28	0.518	0.482	1.000	0.508	0.187
Hereford	82	0.541	0.459	0.110	0.500	0.187
Angus[2]	19	0.583	0.417	0.011	0.500	0.184
Creolle	24	0.676	0.324	0.265	0.451	0.171
Wagyu	19	0.711	0.289	0.013	0.422	0.163
Brahman	18	0.722	0.278	1.000	0.413	0.160
Nelore	22	0.864	0.136	1.000	0.241	0.104

[1] Angus with American influence.
[2] Angus with low American influence and selected towards low timing of puberty during several generations.

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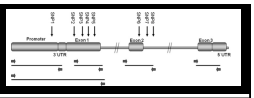
Liron et al., 2011. RVS 91:391
Cushman et al. 2012. JAS (In Revision)

GnRHr genotype



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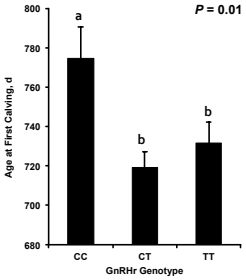

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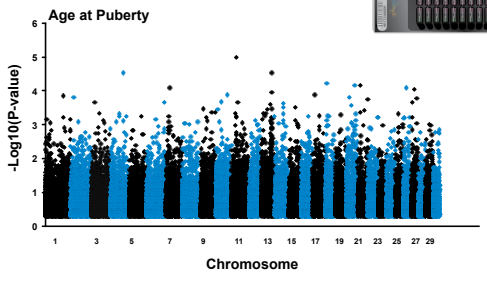
USMARC genome wide association study for age at puberty



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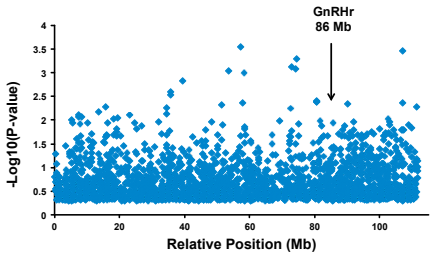

USDA ARS

Snelling et al., 2012. JAS 90:1152

What we know…

- **Age at first calving impacts lifetime productivity**
  - **Genes involved in development of the reproductive tract and puberty are key**
  - **Polygenic**
  - **Large environmental effects**
- **Functional polymorphisms make the best genetic markers**
  - **Very difficult to identify**
  - **Biomarkers are exaggerated 83% of the time (Ionnidis and Panagiotou, 2011)**
- **The GnRHr polymorphism was associated with age at first calving.**
  - **Not functional**
  - **Needs validation (Bos taurus vs. Bos indicus)**
  - **Probably not age at puberty**

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