Management of genetic trait information in the genomic era

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World Holstein Friesian Federation (WHFF)
Registration Working Group

WCGALP, ICAR and Interbull February 11, 2018

Outline of Talk

- Current WHFF activities and codes.
- Handling of new information.
- Personal thoughts on where the recording of genetic traits may be heading.

WHFF - Working Group

- Reviews the recording of Genetic Traits prevalent in the Holstein breed with emphasis on harmonization and exchange of data.

- Genetic Traits: phenotype can be described by a limited number of distinct categories and is under genetic control.

List of Genetic Traits

- Official Genetic traits for the Holstein breed are listed on the WHFF website for easy reference for all International Holstein Association and their respective Herdbooks.

WHFF - RECESSIVE/DOMINANT PROFILE GENES CODES

MASTER LIST

Expression Code: F = tested and noncarrier, C = Tested carrier

Name of abnormality or gene	Description	Gene Codes	Gene and Expression codes
BLAD	Bovine Leucocyte Adhésion Deficiency	BL	BLC = Tested carrier of BLAD; BLF = Tested noncarrier of BLAD
MULEFOOT	Mule-Foot	MF	MFC = Tested carrier of Mulefoot ; MFF = Tested noncarrier of Mulefoot
DUMPS	Deficiency of Uridine Monophosphate Synthase	DP	DPC = Tested carrier of Dumps ; DPF = Tested noncarrier of Dumps
CVM	Complex Vertebral Malformation	CV	CVC = Tested carrier of CVM; CVF = Tested noncarrier of CVM

- When newly observed or previously unknown Genetic Traits are discovered, they should be reported to WHFF for the classification.

Standardized Labelling for Genetic Trait Coding

Direct Tests	
F	Tested Free
C	Tested Carrier / Heterozygous
S	Tested / Homozygous
Phenotypically Observed	
R	Recorded

	Indirect Tests
0	Tested Free / non-carrier
1	**Tested Carrier / Heterozygous / confirmed with pedigree info**
2	**Tested / Homozygous / confirmed with pedigree info**
3	Suspected Carrier / could not be confirmed from pedigree
4	Suspected Homozygous/ could not be confirmed from pedigree

Standardized Labelling for *Direct Tests*

One gene, two alleles, recessive inheritance

Gene:APOB Common Name: Cholesterol Deficiency			
Genotype	Phenotype	WHFF Codes	
C C	Normal	CDF	Free
C c	Normal	CDC	Carrier
c c	Cholesterol Deficient	CDS	Homozygous

Standardized Labelling for *Direct Tests*

One gene, two alleles, dominance inheritance

Gene: COPA	**Common Name: Variant Red or Dominant Red**		
Genotype	Phenotype	WHFF Codes	Designation in Name
D D	Red	VRS	RED
D d	Red	VRC	RED
d d	Black	VRF	
	Red	VRR*	RED
* Not genotyped, Recorded and confirmed by pedigree			

One gene, four alleles, recessive inheritance

Gene: MC1R Traditional Red or Recessive Red			
Genotype	Phenotype	WHFF Codes	Designation in Name
E^D E^D	Black	BKS	
E^D E^{BR}	Black	BRC BKC	
E^D E^+	Black	RDC BKC	
E^D e	Black	RDC BKC	
E^{BR} E^{BR}	Black / Red	BRS	
E^{BR} E^+	Black / Red	BRC RDC	
E^{BR} e	Black / Red	BRC RDC	
E^+ E^+	Red	RDS	RED
E^+ e	Red	RDS	RED
e e	Red	RDS	RED

Codes should describe the primary biological effect

Genotype	Phenotype	WHFF Codes	Designation in Name
E^+ E^+	Red	RDS	RED
E^+ e	Red	RDS	RED
e e	Red	RDS	RED

The primary biological effect is RED coat color

All Reds are grouped together as **RDS**,
ignoring their different shades, they're red

One gene, three alleles, dominance inheritance

Friesian (P_f) and Celtic (P_c) alleles grouped together,
Primary biological effect: polled cattle

Gene: POLLED	Common Name: Polled	
Genotype	Phenotype	WHFF Codes
P* P*	Polled	POS
P* p	Polled	POC
p p	Horns	POF
recorded	Polled	POR

* Either P_f or P_c

WHFF codes: genetic information is reduced to its primary biological effect

WHFF interprets the scientific results.

And then provides meaningful information for actionable data solutions

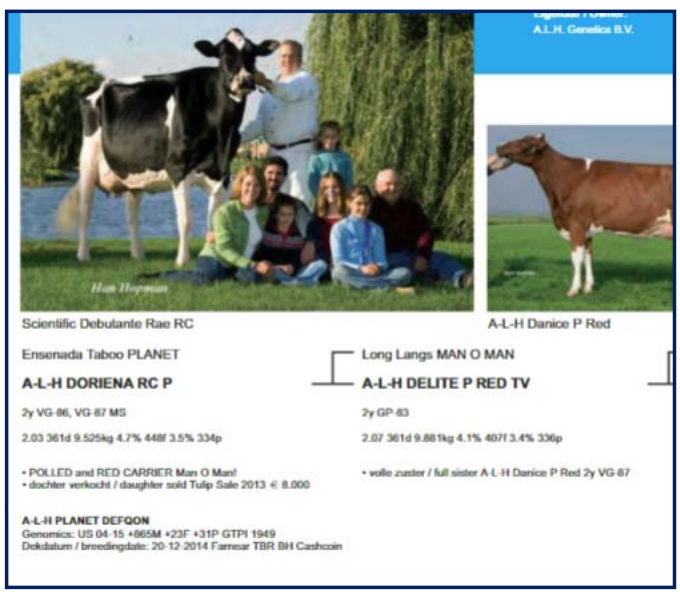
e.g. Buying, culling, mating

Domestic publication codes: information for the business part of dairy genetics

Provides a quick description

Allows animals to be categorized

- Carrier vs. Non-carrier



Publication codes
Maximum info – Limited space

Genotype	Phenotype	WHFF Codes	Publication Codes
P P	Polled	POS	PP
P p	Polled	POC	PC
p p	Horns	POF	PF
recorded	Polled	POR	PO

Publication code must cross reference to WHFF codes

Convey the most meaningful information
Reductionism

Gene: MC1R	Common Name: Traditional Red or Recessive Red		
Genotype for MC1R gene	Phenotype	Designation in Name	WHFF Direct Test Codes
E^D E^D	Black		
E^D E^{BR}	Black		B/R
E^D E^+	Black		RC
E^D e	Black		RC
E^{BR} E^{BR}	Black / Red		B/R
E^{BR} E^+	Black / Red		B/R RC
E^{BR} e	Black / Red		B/R RC
E^+ E^+	Red	RED	
E^+ e	Red	RED	
e e	Red	RED	

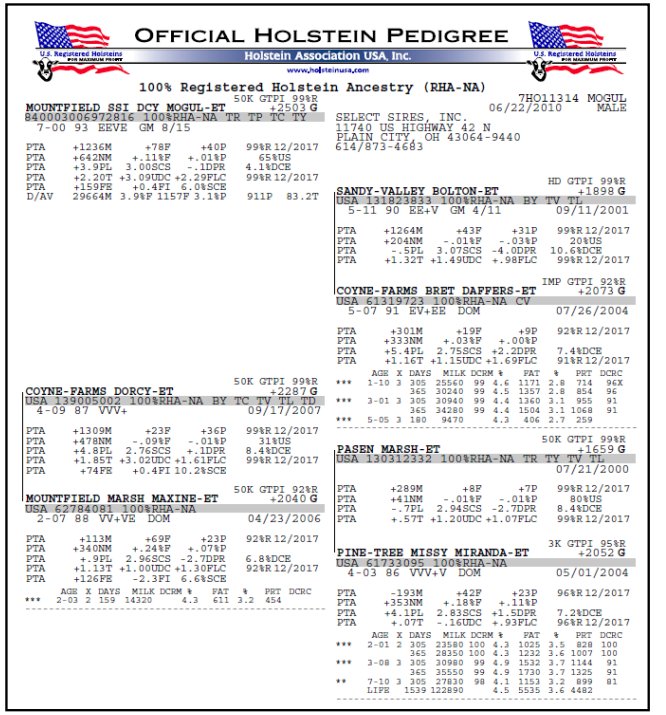
Publication Code
Not Red and it's not a carrier Homozygous Black
Carriers
RED in the Name Homozygous RED

More concise,
blank conveys homozygous animal

Publish the most meaningful information

Transparency without clutter

Due to limited space, genetic traits must be prioritized for publication



OFFICIAL HOLSTEIN PEDIGREE

Holstein Association USA, Inc.

www.holsteinusa.com

100% Registered Holstein Ancestry (RHA-NA)

50K GTPI 99%R

MOUNTFIELD SSI DCY MOGUL-ET +2503 G

840003006972816 100%RHA-NA TR TP TC TY

7-00 93 EEVE GM 8/15

PTA	+1236M	+78F	+40P	99%R	12/2017
PTA	+642NM	+.11%F	+.01%P	65%US	
PTA	+3.9PL	3.00SCS	-.1DPR	4.1%DCE	
PTA	+2.20T	+3.09UDC	+2.29FLC	99%R	12/2017
PTA	+159FE	+0.4FI	6.0%SCE		
D/AV	29664M	3.9%F	1157P	3.1%P	911P 83.2T

50K GTPI 99%R

COYNE-FARMS DORCY-ET +2287 G

USA 139005002 100%RHA-NA BY TC TV TL TD

4-09 87 VVV+ 09/17/2007

PTA	+1309M	+23F	+36P	99%R	12/2017
PTA	+478NM	-.09%F	-.01%P	31%US	
PTA	+4.8PL	2.76SCS	+.1DPR	8.4%DCE	
PTA	+1.85T	+3.02UDC	+1.61FLC	99%R	12/2017
PTA	+74FE	+0.4FI	10.2%SCE		

50K GTPI 92%R

MOUNTFIELD MARSH MAXINE-ET +2040 G

USA 62784081 100%RHA-NA

2-07 88 VV+VE DOM 04/23/2006

PTA	+113M	+69F	+23P	92%R	12/2017
PTA	+340NM	+.24%F	+.07%P		
PTA	+.9PL	2.96SCS	-2.7DPR	6.8%DCE	
PTA	+1.13T	+1.00UDC	+1.30FLC	92%R	12/2017
PTA	+126FE	-2.3FI	6.6%SCE		

	AGE	X	DAYS	MILK	DCRM %	FAT	%	PRT	DCRC
***	2-03	2	159	14320	4.3	611	3.2	454	

7HO11314 MOGUL

06/22/2010 MALE

SELECT SIRES, INC.
11740 US HIGHWAY 42 N
PLAIN CITY, OH 43064-9440
614/873-4683

HD GTPI 99%R

SANDY-VALLEY BOLTON-ET +1898 G

USA 131823833 100%RHA-NA BY TV TL

5-11 90 EE+V GM 4/11 09/11/2001

PTA	+1264M	+43F	+31P	99%R	12/2017
PTA	+204NM	-.01%F	-.03%P	20%US	
PTA	-.5PL	3.07SCS	-4.0DPR	10.6%DCE	
PTA	+1.32T	+1.49UDC	+.98FLC	99%R	12/2017

IMP GTPI 92%R

COYNE-FARMS BRET DAFFERS-ET +2073 G

USA 61319723 100%RHA-NA CV

5-07 91 EV+EE DOM 07/26/2004

PTA	+301M	+19F	+9P	92%R	12/2017
PTA	+333NM	+.03%F	+.00%P		
PTA	+5.4PL	2.75SCS	+2.2DPR	7.4%DCE	
PTA	+1.16T	+1.15UDC	+1.69FLC	91%R	12/2017

	AGE	X	DAYS	MILK	DCRM %	FAT	%	PRT	DCRC
***	1-10	3	305	25560	99 4.6	1171	2.8	714	96X
			365	30240	99 4.5	1357	2.8	854	96
***	3-01	3	305	30940	99 4.4	1360	3.1	955	91
			365	34280	99 4.4	1504	3.1	1068	91
***	5-05	3	180	9470	4.3	406	2.7	259	

50K GTPI 99%R

PASEN MARSH-ET +1659 G

USA 130312332 100%RHA-NA TR TY TV TL

07/21/2000

PTA	+289M	+8F	+7P	99%R	12/2017
PTA	+41NM	-.01%F	-.01%P	80%US	
PTA	-.7PL	2.94SCS	-2.7DPR	8.4%DCE	
PTA	+.57T	+1.20UDC	+1.07FLC	99%R	12/2017

3K GTPI 95%R

PINE-TREE MISSY MIRANDA-ET +2052 G

USA 61733095 100%RHA-NA

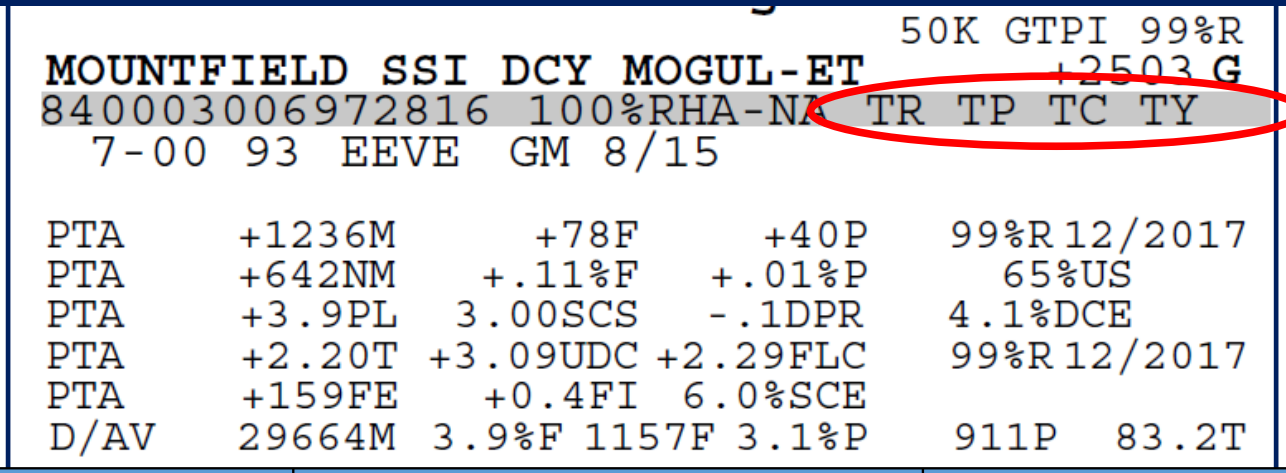
4-03 86 VVV+V DOM 05/01/2004

PTA	-193M	+42F	+23P	96%R	12/2017
PTA	+353NM	+.18%F	+.11%P		
PTA	+4.1PL	2.83SCS	+1.5DPR	7.2%DCE	
PTA	+.07T	-.16UDC	+.93FLC	96%R	12/2017

	AGE	X	DAYS	MILK	DCRM %	FAT	%	PRT	DCRC
***	2-01	2	305	23580	100 4.3	1025	3.5	820	100
			365	28350	100 4.3	1232	3.6	1007	100
***	3-08	3	305	30980	99 4.9	1532	3.7	1144	91
			365	35550	99 4.9	1730	3.7	1325	91
**	7-10	3	305	27830	98 4.1	1153	3.2	899	81
	LIFE		1539	122890	4.5	5535	3.6	4482	

Physical traits:	Coat Color, Horns
Carriers:	Confirmed Carriers
Tested Free:	Ordered Most Prevalent to least Prevalent

Actionable Data I want to use this bull if he has certain characteristics and he doesn't have others



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                                                    50K GTPI 99%R
MOUNTFIELD SSI DCY MOGUL-ET                              +2503 G
840003006972816 100%RHA-NA TR TP TC TY
  7-00 93  EEVE  GM 8/15

PTA      +1236M      +78F      +40P    99%R 12/2017
PTA      +642NM    +.11%F    +.01%P      65%US
PTA      +3.9PL   3.00SCS    -.1DPR    4.1%DCE
PTA      +2.20T +3.09UDC +2.29FLC    99%R 12/2017
PTA      +159FE    +0.4FI  6.0%SCE
D/AV    29664M  3.9%F 1157F 3.1%P    911P   83.2T
```

Category	Genetics	Comments
Physical traits	Black, Horned	Traditional Holstein
Carrier Status	None identified	No mating restrictions
Tested Free	Free of prevalent disorders	Can be used widely

ALL genetic codes and haplotype information is available upon request.

Sometimes it's a written document

Based on the SNP genotype for these bulls available at Canadian Dairy Network (CDN), these animals are not carriers of the HH1, HH2, or HH3 haplotypes.

NAME	SEMEN CODE	REGISTRATION #

Other times it's an on-line, searchable, database

Enlight™ POWERED BY CLARIFIDE.

Official ID	Brd	HH1	HH2	HH3	HH4	HH5	CD	BLAD	Citrullinemia	DUMPS	Factor XI	CVM	Brachy	Mulefoot	Recessive Red	Dominant Red
HO840003139068646	HO	HH1T	HH2T	HH3T	HH4T	HH5T		HHBT		HHDT		HHCT	HH0T	HHMT	ED ED	HDR0
HO840003139068578	HO	HH1T	HH2T	HH3T	HH4T	HH5T		HHBT		HHDT		HHCT	HH0T	HHMT	ED ED	HDR0
HO840003139068575	HO	HH1T	HH2T	HH3T	HH4T	HH5T		HHBT		HHDT		HHCT	HH0T	HHMT	ED ED	HDR0
HO840003139068573	HO	HH1T	HH2T	HH3T	HH4T	HH5T		HHBT		HHDT		HHCT	HH0T	HHMT	ED ED	HDR0
HO840003139068555	HO	HH1T	HH2T	HH3T	HH4T	HH5T		HHBT		HHDT		HHCT	HH0T	HHMT	ED ED	HDR0
HO840003139068540	HO	HH1T	HH2T	HH3T	HH4T	HH5T		HHBT		HHDT		HHCT	HH0T	HHMT	ED ED	HDR0

Haplotypes

GATTCACGCTTACTGTTTCACTGGAA

Causative variant is between SNPs

	Indirect Tests
0	Tested Free / non-carrier
1	**Tested Carrier / Heterozygous / confirmed with pedigree info**
2	**Tested / Homozygous / confirmed with pedigree info**
3	Suspected Carrier / could not be confirmed from pedigree
4	Suspected Homozygous/ could not be confirmed from pedigree

Newer mutations

Can't tell Good haplotype **GATTCA**

From the Bad haplotype **GATTCA**

Do haplotypes simply bridge the time until the causative mutation is discovered?

OR

Do haplotypes represent a new class of undesirable genetic traits?

Even when the causative variant is known, a definitive SNP has not been added

	Causative Variant Known	Royalty fee	Used in SNP chip
Brachyspina	Yes	Yes	No
HH1	Yes	No	Yes
HH2	No		No
HH3	Yes	No	No
HH4	Yes	No	No
HH5	Yes	No	No

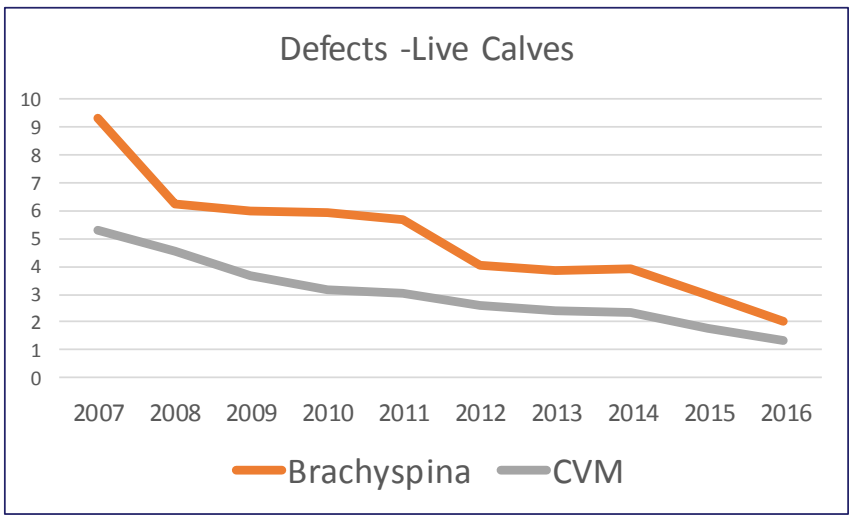
Timing

Population needs time for good and bad alleles to segregate

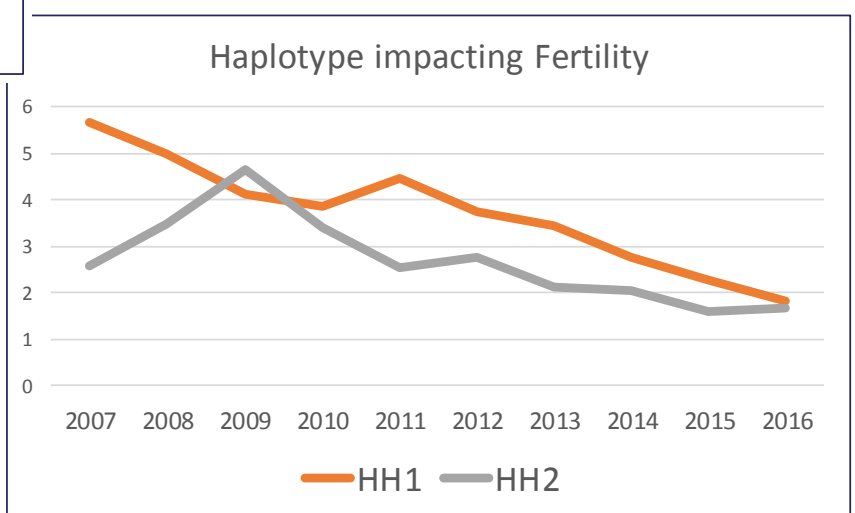
Then purge the undesirable alleles

	Announced	Prominent Bulls
HH1	August 2011	Past
HH2	August 2011	Past
HH3	August 2011	Current – O Man
HH4	August 2013	Current - Besne Buck
HH5	August 2013	Current - Shottle
HCD	August 2015	Current – Storm, Goldwyn

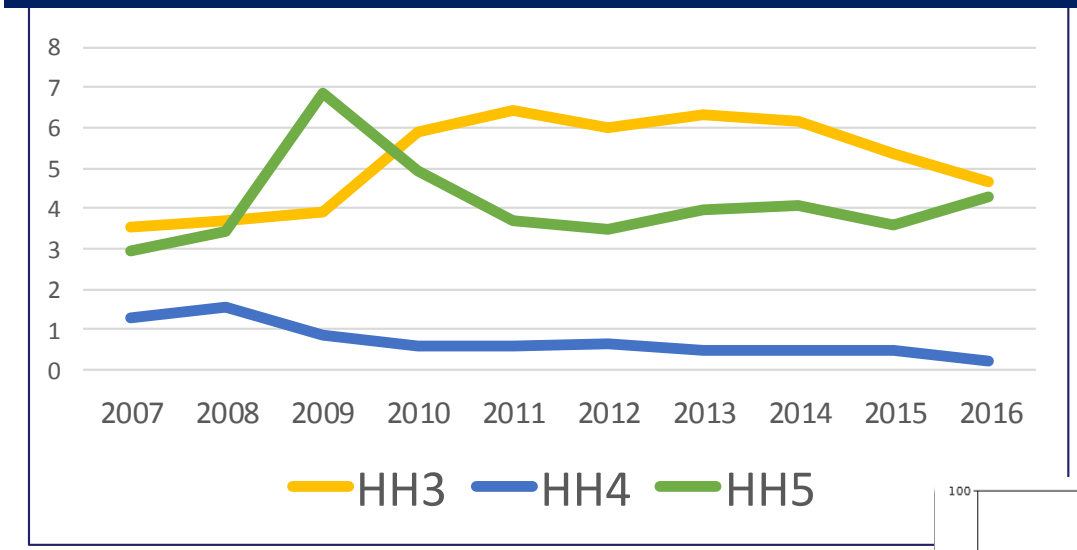
Balancing genetic gain and diversity with “time” to reduce frequency of undesirable alleles



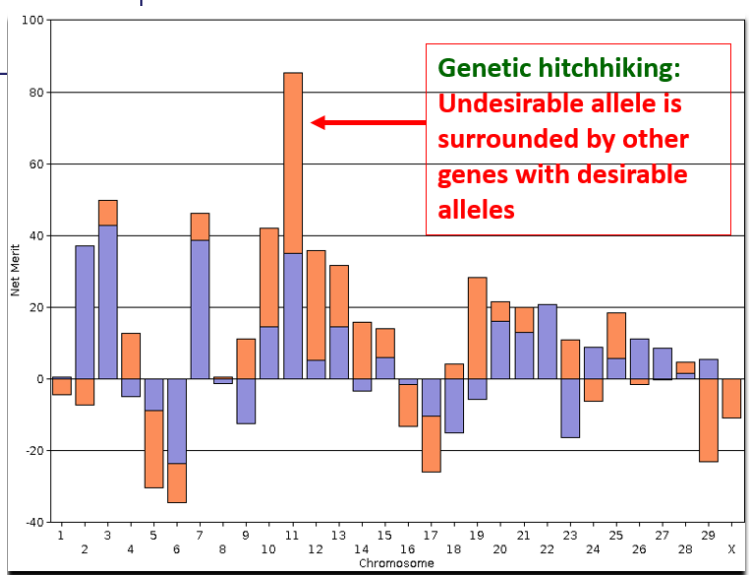
Older mutations



"Newer" mutations take longer to reduce in frequency



Newer mutations



We’re going to find more genetic traits

- Pre-genomics – farmer reported
- Genomics – wide scale genotyping
- Sequencing – find causative variants
- Improved phenotypes – actively looking
  - Heifer survival data, **French national observatory on genetic defects (ONAB)**

How many inherited disorders do we expect to find?

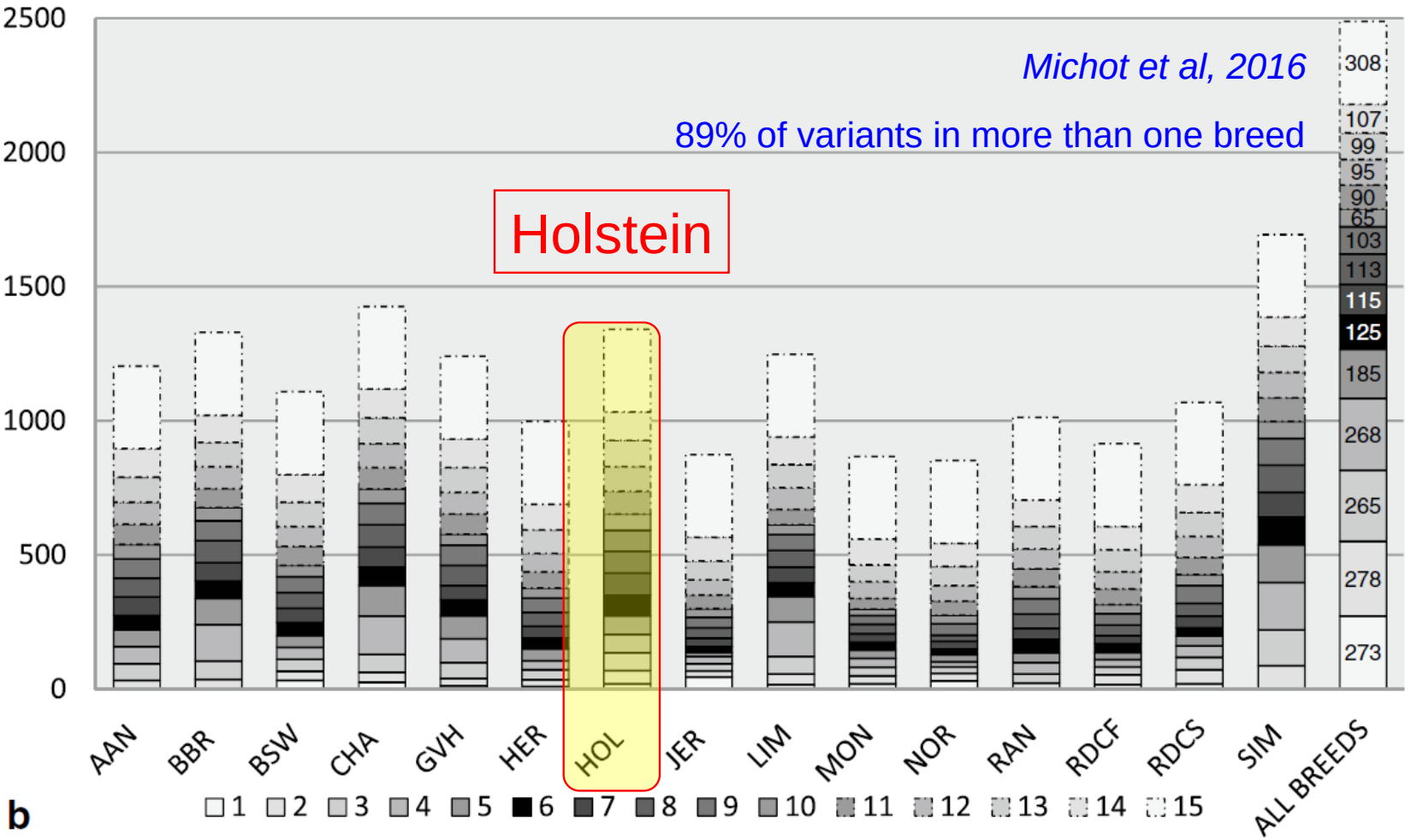
Using whole genome sequence data

Aim was to characterize the genetic load of 15 European breeds using data from the 1000 bull genomes consortium.

Michot et al, 2016

1,341 non-rare putative deleterious variants

Holstein, few are unique, most shared with other breeds



How often?
What do we do?

One in five animals are expected to be a carrier of a genetic defect causing early embryonic loss.

VanRaden and Miller, 2006

One in two: Estimated by simulation that cattle might carry, on average, ~0.5 recessive embryonic lethal mutation.

Charlier et al. 2016

What do we do?

Resulting information will be useful to avoid at-risk matings

Charlier et al. 2016

Broken genes: The sensible approach is to manage the matings in such a way as to avoid the pairing of carrier animals.

Dorian Garrick, 2013

Manage haplotype carriers or eliminate them?

- Provide breeders with information to maximize profitability in their herds through the use of superior genetics.
- We have very few policies restricting the use of superior genetics.*
- We do advise breeders to manage undesirable genetic conditions through a proper mating program.

*At least 19 countries have “health” laws excluding carriers of defects

Manage haplotype carriers

Holstein Association USA encourages breeders to pay attention to pedigrees, work to learn the status of their animals, be mindful of the status of service sires in their herd, and avoid mating carriers of individual haplotypes to carriers of the same haplotype.

Breed associations need to categorize genetic traits

- Traditional: Traits with distinctive characteristics
  - Breed characteristics: Color, horns
  - Physical deformities: CVM, Brachyspina, CD
- Management Level
  - Embryonic mortality
  - Non-specific: Poor health, multiple pathways
  - Late onset: Vision loss, heart malformations
- Predicted loss-of-function
  - De-novo mutations in elite animals

Breed associations need databases to be cross referenced

Full on-line description and annotation

Genetic testing criteria

WHFF Codes – uniform description and transfer

Publication Codes – **actionable data**

Service requires financial support

For example: OMIM Donation Request

Dear OMIM User,

At the request of the NIH and to ensure long-term funding for the OMIM project, we must diversify our revenue stream. We are determined to keep this website freely accessible. Unfortunately, it is not free to produce. Expert curators review the literature and organize it to facilitate your work. Over 90% of the OMIM's operating expenses go to salary support for MD and PhD science writers and biocurators. Please consider making a donation now and again in the future. We need long-term secure funding to provide you the information that you need at your fingertips.

Thank you in advance for your generous support,
Ada Hamosh, MD, MPH
Scientific Director, OMIM

The future is not that much different than the past.

- What is the mode of inheritance for this trait?
- Is this genetic trait prevalent in my breed?

- What category of genetic trait is this?

How best can I get information on new genetic traits to the breeders?

Questions?