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Implications of mosaicism for deleterious *de novo* mutations in artificial insemination bulls

Genetic defects in cattle – identification, finding the mutation and managing it in breeding plans

The number of genetic defects is increasing constantly ...

OMIA - ONLINE MENDELIAN INHERITAN								HERITANCE	IN AN	NIMALS		
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Summary

	dog	cattle	cat	pig	sheep	horse	chicken	rabbit	goat	Japanese quail	golden hamster	Other	TOTAL
Total traits/disorders	<u>700</u>	<u>513</u>	<u>337</u>	<u>248</u>	<u>242</u>	<u>229</u>	<u>218</u>	<u>91</u>	<u>82</u>	<u>46</u>	<u>41</u>	<u>591</u>	3338
Mendelian trait/disorder	<u>299</u>	<u>237</u>	<u>95</u>	<u>67</u>	<u>101</u>	<u>54</u>	<u>129</u>	<u>55</u>	<u>16</u>	<u>34</u>	<u>29</u>	<u>205</u>	<u>1321</u>
Mendelian trait/disorder; key mutation known	<u>227</u>	<u>139</u>	<u>62</u>	<u>31</u>	<u>48</u>	<u>40</u>	<u>44</u>	<u>11</u>	<u>10</u>	<u>10</u>	<u>4</u>	<u>97</u>	<u>723</u>
Potential models for human disease	<u>405</u>	<u>197</u>	<u>204</u>	<u>104</u>	<u>105</u>	<u>127</u>	<u>47</u>	<u>47</u>	<u>36</u>	<u>15</u>	<u>16</u>	<u>310</u>	<u>1613</u>

The number of genetic defects is increasing constantly ...



- Increasing levels of inbreeding result in the phenotypic manifestation of recessive alleles (Garcia-Ruiz et al. PNAS. 2016)
- Genome-wide association and homozygosity analyses enable the rapid mapping of inherited disorders (Charlier et al. Nat Genet. 2008)
- Large-scale genotype data uncover homozygous haplotype deficiency (Vanraden et al. J Dairy Sci. 2011)
- The analysis of sequencing data using bioinformatics approaches reveals putatively deleterious sequence variants (Charlier et al. Genome Res. 2017)

... and so is the number of approaches to account for them in breeding programs

- Avoid the mating of closely related individuals
- Exclude carrier animals from breeding (Jung et al. BMC Genomics. 2014)
- Avoid matings between carrier animals (Vanraden et al. J Dairy Sci. 2011)
- Consider a selection index of genetic properties (Cole. Genet Sel Evol. 2015)
- Use pre-implantation genetic diagnosis (Kasinathan et al. Sci Rep. 2015)
- Apply genome-editing technologies (Hoyos-Flight et al. Transgenic Res. 2017)



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Dominant genetic traits aren't a threat to livestock breeding, are they?



The case «Energy P»

STANTONS EARN ENERGY P

K-Cn: AA

000011696813 • German Reg. No. 10.507450 born: 08/03/2013 Breeder: Stantons Bros. Limited, Ilderton, ON, CAN





TREMENDOUS POLLED SIRE · HIGH PRODUCTION FROM LEAD MAE FAMILY

Sire Summary 04/2017

Milk Production - Dtrs. / - Hrds.		Rel. 73 9	%	gRZM	135
Milk kg	Milk kg Fat %		Protein %	Proteir	n kg
+1789	-0.25	+42	-0.06	+53	;
Total Conformation - Dtrs. / - Hrds.	ı	Rel. 62 9	6	gRZE	117
Dairy Type	Body	Feet	& Legs	Udder	
127	114		110	107	
Functional Herd Life	I	Rel. 61 9	%	gRZN	100
Somatic Cell Count		Rel. 77 9	%	gRZS	101
Milking Speed		Rel. 70 9	%	gRZD	100
Daughter Fertility		Rel. 54 9	%	gRZR	95
Robot Index		Rel %	gR	ZRobot	-
Fitness Index		Rel. 61 9	%	gRZFit	113
Calving Ease		gRZKn 109	n gRZKd 80	gCEd	86

Total Merit Index			gRZ	G	131	
Linear Profile		88	100	112	124	
Stature	small				tall	137
Dairy Character	tight rib				open rib	126
Body Depth	shallow				deep	120
Strength	frail				strong	105
Rump Angle	ascending				sloped	115
Rump Width	narrow				wide	112
Rear Leg Set Side View	posty				sickled	105
Foot Angle	low angle				posty	107
Hock Quality	swollen				dry	107
Rear Leg Rear View	hock-in		•		parallel	99
Locomotion	bad				good	106
Rear Udder Height	low				high	114
Suspensory Ligament	weak				strong	111
Teat Placement Front	wide				close	114
Teat Placement Rear	wide				close	109
Fore Udder Attachment	loose				tight	97
Udder Depth	deep				shallow	99
Teat Length	short				long	110

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4900 inseminations before the first descendants were born

1700 pregnancies

The case «Halvar PP»



GS HALVAR PP*	AT 070.213.719, geb. 09.04.2012, Stat.Nr Zü: Pirker Franz, Di., St.Mi Bes: GENO	: 4048 lichael OSTAR		F١	/-Be	ef	
	TELS	STAR 1 PpU	IK 542.191.	201.154	PANACHE POLARINE	UK 502.9 Pp UK 542.1	18.600.053 91.700.725
	ELEP	KTRA PP*	AT 566.	600.717	VITO PP	DK 5	1546-02044
	мм	IV: RONNI I	PP A A	A. A. A. A. A. A.	k pik pik p na na na	* * * *	
	В	BEEF - B	BREEDI	NG VA	ALUE: 1	22 (67%	6)
and a second	N	NTZ	116	AUS	116	HKL	119
	CIZ7112	ITNESS	S – BRE	EDIN	G VALI	JES	
HARA	M G K Z I I Z M - K	(V pat.	112	KV ma	t.	VIW	

The case «Halvar PP»



GS HALVAR PP*	AT 070.213.719, geb. 09.04.2012, Stat.Nr: 40 Zü: Pirker Franz, Di., St.Micha Bes: GENOSTA	48 ael AR	F	V-Be	ef	
	TELSTAR	1 PpUK 542	.191.201.154	PANACHE POLARINE	UK 502.9 Pp UK 542.1	18.600.053 91.700.725
	ELEKTRA	A PP* AT	566.600.717	VITO PP	DK 51	1546-02044
	MMV: R	ONNI PP				
	BEE	F - BREI	EDING V	ALUE:	122 (67%	()
	NTZ	116	AUS	116	HKL	119
Hall	GK7112	NESS – E	BREEDIN	IG VALU	JES	
	VINZIIZ KV	pat. 112	KV m	at.	VIW	

1394 inseminations before the first descendants were born

731 pregnancies

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An accumulation of «Bulldog»-calves among the progeny of «Energy P»



Progeny	Number
Stillborn	57 (20.7%)
Normal	218 (79.3%)
Total	275 (100%)

An accumulation of calves with osteogenesis imperfecta among the progeny of «Halvar PP»



Progeny	Number
Stillborn or died within 48 h	254 (34.7%)
Normal	477 (65.3%)
Total	731 (100%)

Mining sequencing data to pinpoint causal mutations

- One affected calf per condition and both sires were sequenced at between 10and 20-fold coverage
- Assuming dominant inheritance, the mutations are expected to be heterozygous in affected calves and not present in 1150 unaffected animals from the 1000 bull genomes reference panel
- Osteogenesis imperfecta COL1A1: p.Ala1049_Pro1050delinsSer
- Bulldog
 COL2A1: p.G996S

Detection of mosaicism for both mutations in the sires using Sanger and pyro-sequencing



Detection of mosaicism for both mutations in the sires using Sanger and pyro-sequencing



Mosaicism for deleterious *de novo* mutations is not a new phenomenon – why bother?

- Epidermolysis bullosa in the progeny of a Jer x Hol bull (Ford et al. J Invest Dermatol. 2005)
- Lethal chondrodysplasia in French Holstein cattle (Daetwyler et al. Nat Genet. 2014)
- Lethal chondrodysplasia in Danish Holstein cattle (Agerholm et al. BMC Vet Res. 2016)
- Facial dysplasia in Danish Holstein cattle (Agerholm et al. BMC Genet. 2017)
- Young bulls with excellent genomic profiles are used for more than 10.000 inseminations before the first descendants are born

Mosaicism for deleterious *de novo* mutations is not a new phenomenon – why bother?

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- Young bulls with excellent genomic profiles are used for more than 10.000 inseminations before the first descendants are born
- Can mosaicism for deleterious *de novo* mutations be detected before affected calves are born?

The early detection of mosaicism for deleterious *de novo* mutations is a difficult task at best

- Bulls are not routinely sequenced before they are used in artificial insemination
- The reliable prediction of the deleteriousness of new mutations with e.g., SIFT or PolyPhen is not possible

Comparison of predicted and actual consequences of missense mutations. Vicky Cho ^{a,b} , Simon Johnson ^{a,b} , Anna Palkova ^{a,b} , Shavani Balakishnan ^b , Rong Liang ^b , Yafei Zhang ^b , Stephen Lyon ^c , Bruce Beutler ^c , Belinda Whittle ^b , Edward M. Bertram ^b , Anselm Enders ^d , Christopher C. Goodnow ^{a,e,2,3} , and T. Daniel Andrews ^{a,2,3} .	SEE COMMENTARY PLUS	«We conclude that for de novo […] mutations found by genome sequencing, half those inferred as deleterious correspond to nearly neutral mutations that have little impact on the clinical phenotype […]»
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Conclusions and implications for breeding programs

- Mosaicism for *de novo* mutations is pervasive¹ and can be a serious threat to livestock breeding
- Mosaic carriers of deleterious dominant mutations can be used for (tens of) thousands of inseminations before the first affected calves are born
- Reliably classifying the deleteriousness of *de novo* mutations is (currently) not possible
- The heavy use of individual sires in artificial insemination seems inappropriate (and irresponsible?)

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Collaborators ...

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- Chair of Animal Biotechnology TU München Krzysztof Flisikowski
- Vit Verden w.V. Dierck Segelke
- ZuchtData Dienstleistungen GmbH Hermann Schwarzenbacher
- University of Veterinary Medicine Vienna Johann Burgstaller
- Lower Saxony State Office for Consumer Protection and Food Safety Michael Brügemann
- INRA, ALLICE Aurélien Capitan













Thank you for your attention!

I'm hiring PhD students and PostDocs!

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