AIP RESEARCH REPORT
GENOMIC5 (8-24)

Haplotype tests for economically important traits of dairy cattle

A.S. Al-Khudhair, J.B. Cole, P.M. VanRaden, D.J. Null, J.L. Hutchison, and S.M. Hubbard
Animal Genomics and Improvement Laboratory, Agricultural Research Service, USDA, Beltsville, MD 20705-2350
301-504-8334 (voice) • 301-504-8092 (fax) • daniel.null@usda.gov • http://go.usa.gov/xybuq

Haplotype tests are used routinely to identify animals with desirable traits of economic importance, discover new genetic disorders, and track carrier status of genotyped animals. Recessive haplotypes that affect fertility and stillbirth in dairy cattle (haplotypes BH1–BH2, HH1–HH5, and JH1–JH2 were described in detail by VanRaden et al. (2011, 2013, 2014). A recessive mutation that causes embryo death (haplotype HH6) was discovered by Fritz et al. (2018). Carrier status for Holstein haplotypes with mutations for brachyspina (haplotype HH0), bovine leucocyte adhesion deficiency (BLAD; haplotype HHB), complex vertebral malformation (CVM; haplotype HHC), deficiency of uridine monophosphate synthase (DUMPS; haplotype HHD), mulefoot (syndactyly; haploptype HHM), polledness (haplotype HHP), red coat color (haplotypes HBR, HDR, and HHR), and cholesterol deficiency (HCD) are reported by the Council on Dairy Cattle Breeding (Bowie, MD). Brown Swiss haplotype tests for spinal dismyelination (SDM; haplotype BHD), spinal muscular atrophy (SMA; haplotype BHM), and Weaver Syndrome (haplotype BHW) also are provided. Polledness haplotypes are reported for Brown Swiss (BHP) and Jerseys (JHP). A haplotype that affects conception rate in Ayrshires (AH1) was reported by Cooper et al. (2014), an Ayrshire haplotype that affects fertility (AH2) was discovered by Null et al. (2017), and a haplotype that results in curly calves in Ayrshires (AHC) as reported by Agerholm et al. (2016). A haplotype associated with Jersey neuropathy with splayed forelimbs (JNS) has been identified (Al-Khudhair et al., 2022). Haplotypes BH1 and JH2 were discontinued in December 2018 (VanRaden and Null, 2018).

The table below lists all of the haplotypes currently tracked in the U.S. genomic evaluation system, the frequency of the minor (less common) haplotype, and the location in base pairs (bp) of the haplotype based on the 2018 ARS-UCD1.2 genome assembly (www.ncbi.nlm.nih.gov/assembly/GCF_002263795.1/reference; Rosen et al., 2018). Locations are exact (single bp) when the causative mutation is known and approximate (range of bp) when it is unknown, a duplication, a deletion, or multiple mutations. The frequency of carriers in the population is generally twice the haplotype frequency because carriers have 1 defective and 1 normal haplotype.

Recessives with very low frequencies (e.g., HH4) can be identified because many Holsteins have been genotyped (current exact counts of genotyped animals are shown in the Council on Dairy Cattle Breeding's "Genotype Counts by Chip Type, Breed Code, and Sex Code"). Generally, recessives in breeds with fewer genotyped animals and smaller populations will not be detected until they have a high frequency in the population. Haplotype tests are less accurate than loss-of-function (LOF) mutation tests, and retesting valuable animals that have been identified as carriers using a haplotype test is recommended if an exact test is available. Further information on combining LOF mutation tests with haplotype tests is available (VanRaden et al., 2012) as is further detail on genetic defects (Nicholas and Hobbs, 2014; OMIA - Online Mendelian Inheritance in Animals, 2014).

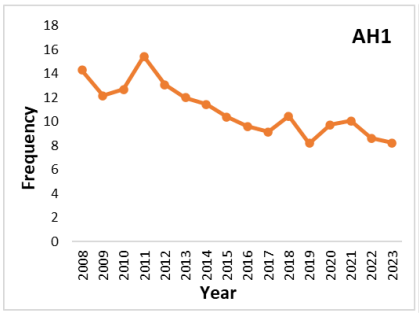
Breed	Haplotype	OMIA 9913 ID[1]	Functional/ *gene* name	Original and current haplotype frequencies		ARS-UCD (Chromosome: position)	Reference
				% (Year)	% (2023)		
Ayrshire	AH1	001934	PIRM/ *UBE3B*	11.4 (2014)	8.23	17:63,668,380	Cooper et al. (2014), Venhoranta et al. (2014)
	AH2	002134	*RPAP2*	12.25 (2017)	6.58	3: 51,108,622	Null et al. (2017)
	AHC	002022	*CHRNB1*	7.79 (2016)	5.81	19: 27,122,027	Agerholm et al. (2016)
Brown Swiss[2]	BH2	001939	*TUBD1*	5.13 (2016)	2.11	19:10,833,921	Schwarzenbacher et al. (2016)
	BHD	001247	SDM/ *SPAST*	2.52 (2010)	0.71	11: 14,742,184	Hafner et al. (1993), Thomsen et al. (2010)
	BHM	000939	SMA/ *KDSR*(*FVT1*)	2.01 (2007)	0.33	24:61,620,374	El-Hamidi et al. (1989), Krebs et al., 2007

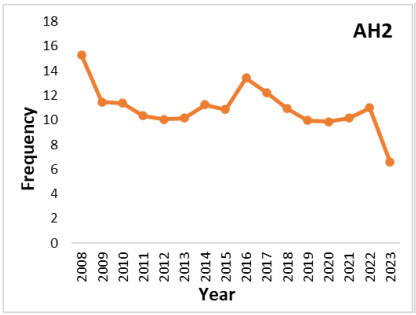
	BHP	000483	Polledness/ *POLLED*	4.91 (2014)	4.26	1:2,578,598	Medugorac et al. (2012), Rothammer et al. (2014)
	BHW	000827	Weaver/ *PNPLA8*	0.39 (2013)	0.08	4:49,339,002–49,461,342	McClure et al. (2013), Kunz et al., 2016
Holstein	HBR	001199	Black/red coat color/ *MC1R*(*MSHR*)	0.96 (2014)	0.23	18:14,705,501	Lawlor et al. (2014)
	HCD	001965	Cholesterol deficiency/*APOB*	0.90 (2015)	0.34	11:77,872,709	Kipp et al. (2015), Charlier (2016), Menzi et al. (2016), Schütz et al. (2016)
	HDR	001529	Dominant red coat color	0.01 (2003)	0.00	3:9,361,962	Capitan et al. (2014), Lawlor et al. (2014), Dorshorst et al., 2015
	HH0	000151	Brachyspina/ *FANCI*	4.85 (2007)	0.28	21:20,775,563	Agerholm et al. (2006), Charlier et al. (2012)
	HH1	000001	*APAF1*	1.84 (2012)	0.40	5:62,810,245	Adams et al. (2012)
	HH2	001823	*IFT80*	1.79 (2011)	0.68	1: 107,172,615	VanRaden et al. (2011), McClure et al. (2014), Ortega et al. (2022)
	HH3	001824	*SMC2*	3.19 (2014)	0.65	8:93,753,358	Daetwyler et al. (2014), McClure et al. (2014)
	HH4	001826	*GART*	0.27 (2013)	0.09	1:1,997,582	Fritz et al. (2013)
	HH5	001941	*TFB1M*	2.05 (2013)	2.50	9:91,847,117–91,937,003	Cooper et al. (2013), Schütz et al. (2016)
	HH6	002149	*SDE2*	0.30 (2018)	1.14	16: 29,020,700	Fritz et al. (2018)
	HHB	000595	BLAD/ *ITGB2*	0.39 (1993)	0.03	1:144,770,078	Shuster et al. (1992)
	HHC	001340	CVM/ *SLC35A3*	2.89 (2001)	0.25	3:43,261,946	Agerholm et al. (2001)
	HHD	000262	DUMPS/ *UMPS*	1.93 (1981)	0.00	1:69,151,931	Shanks et al. (1984)
	HHM	000963	Mulefoot/ *LRP4*	0.11 (2006)	0.00	15:76,807,960	Eldridge et al. (1951), Duchesne et al. (2006)
	HHP	000483	Polledness/ *POLLED*	1.08 (2014)	1.86	1:2,578,598	Medugorac et al. (2012), Rothammer et al. (2014)
	HHR	001199	Red coat color/ *MC1R*(*MSHR*)	5.21 (1996)	3.02	18:14,705,965	Joerg et al. (1996)
	HMW	002819	*CACNA1S*	2.04 (2014)	2.04	16:79,613,592	Al-Khudhair et al. (2024)
Jersey[2]	JH1	001697	*CWC15*	11.00 (2013)	3.47	15:15,449,431	Sonstegard et al. (2013)
	JHP	000483	Polledness/ *POLLED*	2.71 (2014)	1.95	1:2,578,598	Medugorac et al. (2012), Rothammer et al. (2014)
	JNS	002298	*UCHL1*	2.90 (2022)	4.08	6:60,158,901	Al-Khudhair et al. (2022)

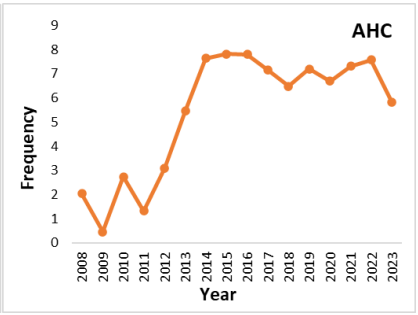
[1]Online Mendelian Inheritance in Animals (OMIA) identification number for *Bos taurus* (National Center for Biotechnology Information species code 9913).
[2]Discontinued haplotypes: BH1, JH2.

Haplotype frequency by year (2008-2023) for the recessively inherited conditions above.

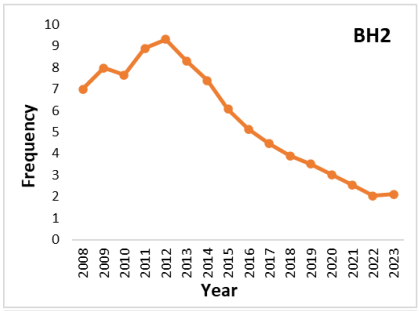
Ayrshire

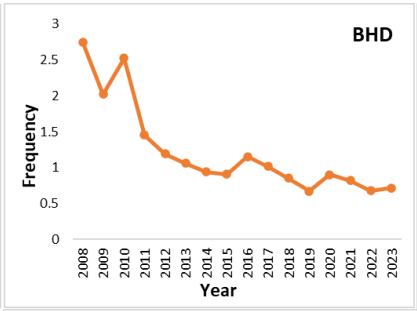


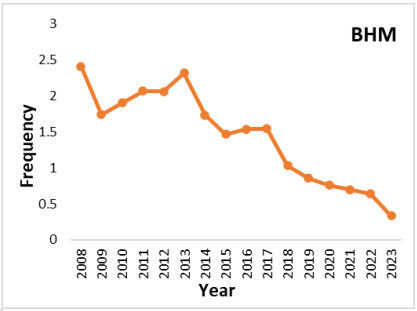


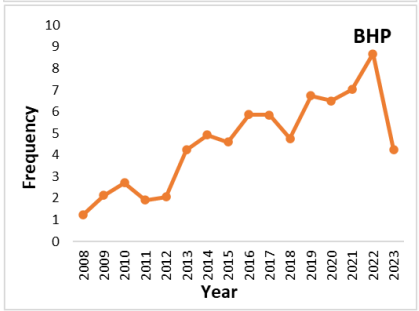


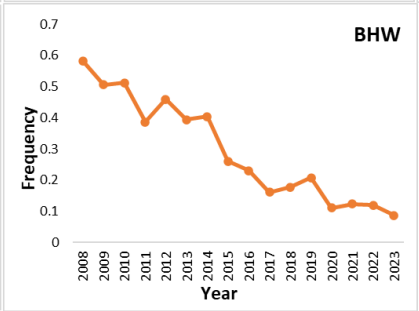
Brown Swiss



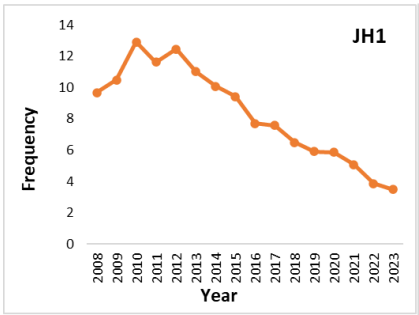


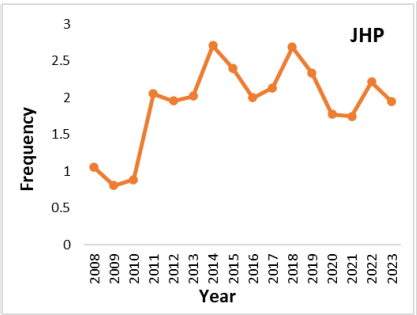


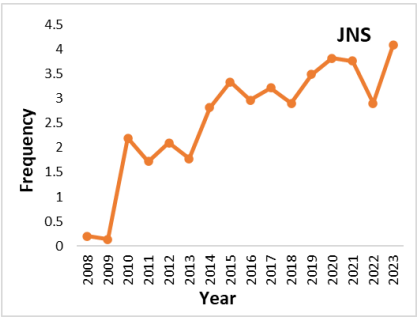




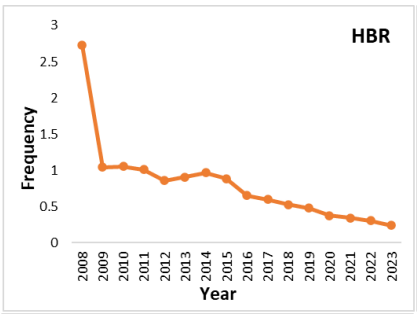
Jersey

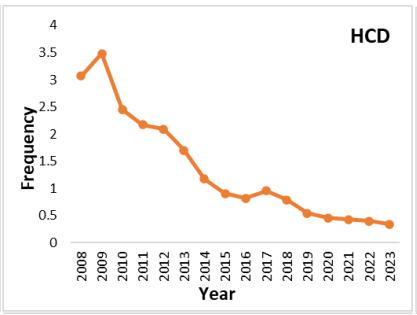


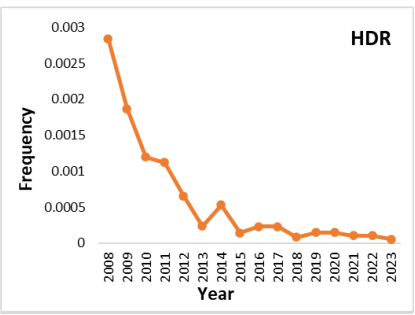


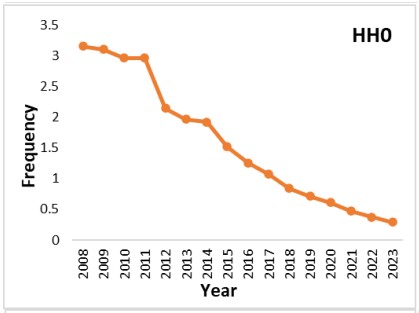


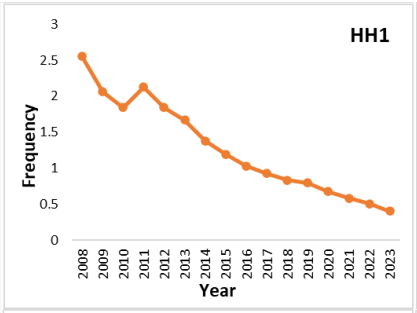
Holstein

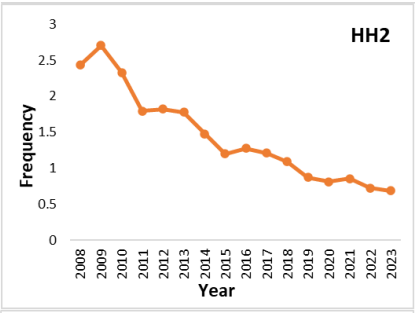


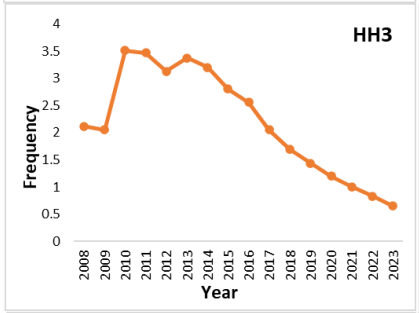


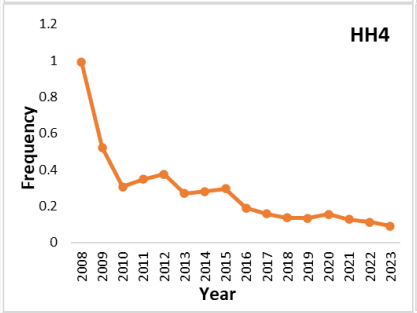


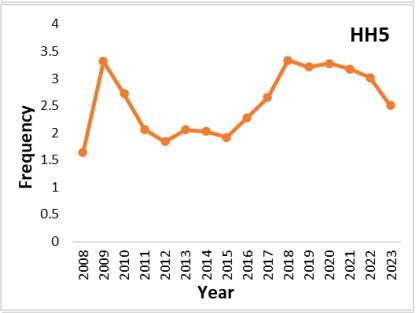

HH0
Frequency
Year

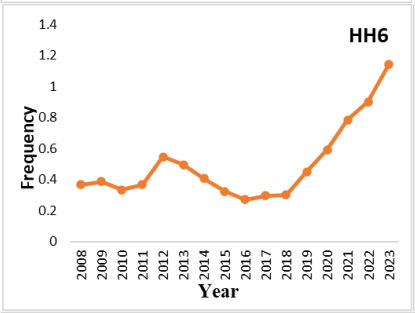

HH1
Frequency
Year

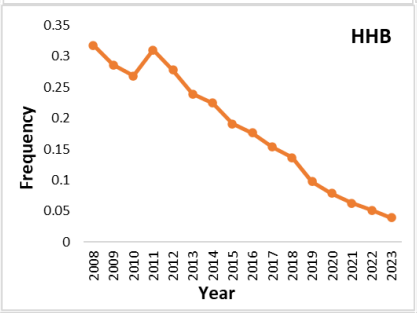

HH2
Frequency
Year

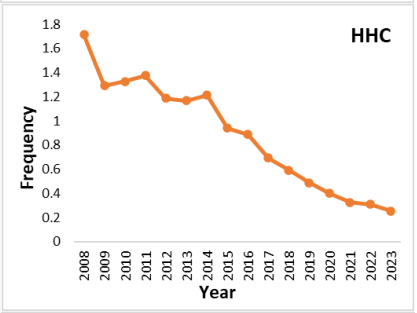

HH3
Frequency
Year

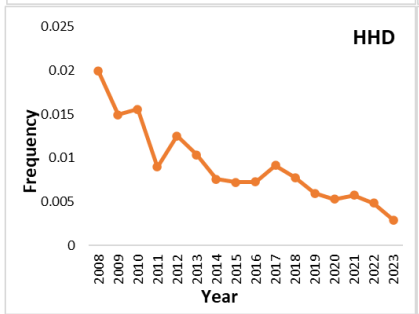

HH4
Frequency
Year

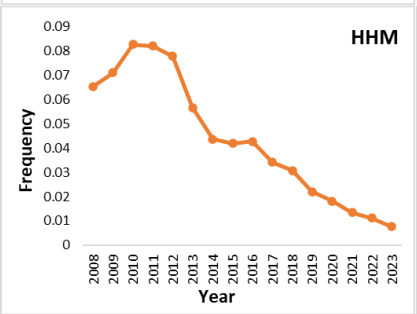

HH5
Frequency
Year

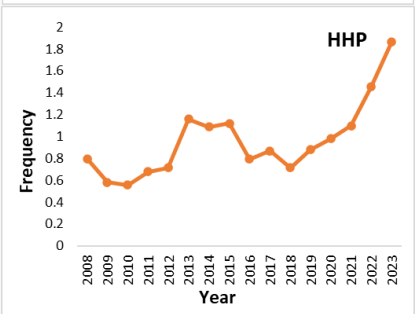

HH6
Frequency
Year

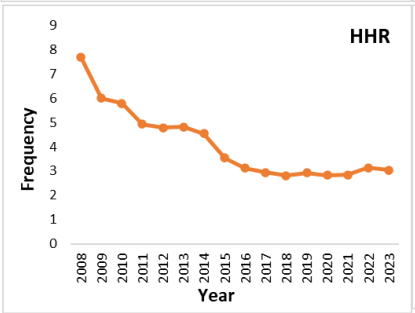

HHB
Frequency
Year

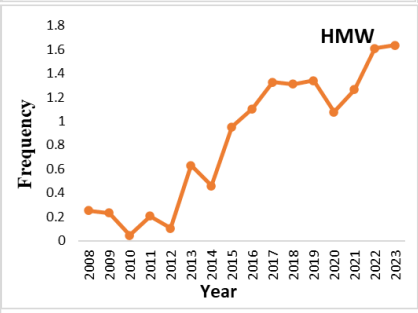

HHC
Frequency
Year


HHD
Frequency
Year


HHM
Frequency
Year


HHP
Frequency
Year


HHR
Frequency
Year


HMW
Frequency
Year

References

Adams, H.A., T. Sonstegard, P.M. VanRaden, D.J. Null, C. Van Tassell, and H. Lewin. 2012. Identification of a nonsense mutation in APAF1 that is causal for a decrease in reproductive efficiency in dairy cattle. Plant Anim. Genome XX Conf., abstr. P0555.

Agerholm, J.S., C. Bendixen, O. Andersen, and J. Arnbjerg. 2001. Complex vertebral malformation in Holstein calves. J. Vet. Diagn. Invest. 13:283–289.

Agerholm, J.S., F. McEvoy, and J. Arnbjerg. 2006. Brachyspina syndrome in a Holstein calf. J. Vet. Diagn. Invest. 18:418–422.

Agerholm J.S., F.J. McEvoy, F. Menzi, V. Jagannathan, C. Drögemüller . 2016. A *CHRNB1* frameshift mutation is associated with familial arthrogryposis multiplex congenita in Red dairy cattle. BMC Genomics 17:479.

Al-Khudhair, A., D. J. Null, J. B. Cole, C. W. Wolfe, D. J. Steffen, and P. M. VanRaden. 2022. Inheritance of a mutation causing neuropathy with splayed forelimbs in Jersey cattle. J. Dairy Sci. 105: 1338-1345.

Al-Khudhair, A., VanRaden, P. M., Null, D. J., Neupane, M., McClure, M. C., & Dechow, C. D. (2024). New mutation within a common haplotype is associated with calf muscle weakness in Holsteins. *J Dairy Sci*. 107(6):3768-3779.

Capitan, A., P. Michot, F. Guillaume, C. Grohs, A. Djari, S. Fritz, S. Barbey, P. Otz, E. Bourneuf, D. Esquerré, Y. Gallard, C. Klopp, and D. Boichard. 2014. Rapid discovery of mutations responsible for sporadic dominant genetic defects in livestock using genome sequence data: Enhancing the value of farm animals as model species. Proc. 10th World Congr. Genet. Appl. Livest. Sci., Commun. 182.

Charlier, C. 2016. The role of mobile genetic elements in the bovine genome. Plant Anim. Genome XXIV Conf., abstr. W636.

Charlier, C., J.S. Agerholm, W. Coppieters, P. Karlskov-Mortensen, W. Li, G. de Jong, C. Fasquelle, L. Karim, S. Cirera, N. Cambisano, N. Ahariz, E. Mullaart, M. Georges, and M. Fredholm. 2012. A deletion in the bovine *FANCI* gene compromises fertility by causing fetal death and brachyspina. PLoS ONE 7:e43085.

Cooper, T.A., G.R. Wiggans, D.J. Null, J.L. Hutchison, and J.B. Cole. 2014. Genomic evaluation, breed identification, and discovery of a haplotype affecting fertility for Ayrshire dairy cattle. J. Dairy Sci. 97:3878–3882.

Cooper, T.A., G.R. Wiggans, P.M. VanRaden, J.L. Hutchison, J.B. Cole, and D.J. Null. 2013. Genomic evaluation of Ayrshire dairy cattle and new haplotypes affecting fertility and stillbirth in Holstein, Brown Swiss and Ayrshire breeds. Amer. Dairy Sci. Assoc.–Amer. Soc. Anim. Sci. joint annual meeting, Indianapolis, IN, July 9, poster T206.

Daetwyler,H.D., A. Capitan, H. Pausch, P. Stothard, R. van Binsbergen, R.F. Brøndum, X. Liao, A. Djari, S.C. Rodriguez, C. Grohs, D. Esquerré, O. Bouchez, M.-N. Rossignol, C. Klopp, D. Rocha, S. Fritz, A. Eggen, P.J. Bowman, D. Coote, A.J. Chamberlain, C. Anderson, C.P. Van Tassell, I. Hulsegge, M.E. Goddard, B. Guldbrandtsen, M.S. Lund, R.F. Veerkamp, D.A. Boichard, R. Fries, and B.J. Hayes. 2014. Whole-genome sequencing of 234 bulls facilitates mapping of monogenic and complex traits in cattle. Nature Genet. 46:858–865.

Dorshorst, B., C. Henegar, X. Liao, M. Sällman Almén, C.-J. Rubin, S. Ito, K. Wakamatsu, P. Stothard, B. Van Doormaal, G. Plastow, G.S. Barsh, and L. Andersson. 2015. Dominant red coat color in Holstein cattle is associated with a missense mutation in the coatomer protein complex, subunit alpha (*COPA*) gene. PLoS ONE 10:e0128969.

Duchesne, A., M. Gautier, S. Chadi, C. Grohs, S. Floriot, Y. Gallard, G. Caste, A. Ducos, and A. Eggen. 2006. Identification of a doublet missense substitution in the bovine LRP4 gene as a candidate causal mutation for syndactyly in Holstein cattle. Genomics 88:610–621.

El-Hamidi, M., H.W. Leipold, J.G.E. Vestweber, and G. Saperstein. 1989. Spinal muscular atrophy in Brown Swiss calves. J. Vet. Med. A. 36:731–738.

Eldridge, F.E., W.H. Smith, and W.M. McLeod. 1951. Syndactylism in Holstein-Friesian cattle: Its inheritance, description and occurrence. J. Hered. 42:241–250.

Fritz, S., A. Capitan, A. Djari, S. C. Rodriguez, A. Barbat, A. Baur, C. Grohs, B. Weiss, M. Boussaha, D. Esquerré, C. Klopp, D. Rocha, and D. Boichard. 2013. Detection of haplotypes associated with prenatal death in dairy cattle and identification of deleterious mutations in GART, SHBG and SLC37A2. PLoS ONE 8:e65550.

Fritz, S., C. Hoze, E. Rebours, A. Barbat, M. Bizard, A. Chamberlain, C. Escouflaire, C. Vander Jagt, M. Boussaha, Baur, C. Grohs, A. AllaisBonnet, M. Philippe, A. Vallée, Y. Amigues, B.J. Hayes, D. Boichard, and A. Capitan. 2018. An initiator codon mutation in *SDE2* causes recessive embryonic lethality in Holstein cattle. PLoS ONE 8:e65550.

Hafner, A., E. Dahme, G. Obermaier, P. Schmidt, and G. Dirksen. 1993. Spinal dysmyelination in new-born Brown Swiss × Braunvieh calves. J. Vet. Med. B 40:413–422.

Joerg, H., H.R. Fries, E. Meijerink, and G.F. Stranzinger. 1996. Red coat color in Holstein cattle is associated with a deletion in the *MSHR* gene. Mamm. Genome 7:317–318.

Kipp, S., D. Segelke, S. Schierenbeck, F. Reinhardt, R. Reents, C. Wurmser, H. Pausch, R. Fries, G. Thaller, J. Tetens, J. Pott, M. Piechotta, and W. Grünberg. 2015. A new Holstein haplotype affecting calf survival. Interbull Bull. 49:49–53.

Krebs, S., I. Medugorac, S. Röther, K. Strässer, and M. Förster. 2007. A missense mutation in the 3-ketodihydrosphingosine reductase *FVT1* as candidate causal mutation for bovine spinal muscular atrophy. Proc. Natl. Acad. Sci. USA 104:6746–6751.

Kunz, E., S. Rothammer, H. Pausch, H. Schwarzenbacher, F. Seefried, K. Matiasek, D. Seichter, I. Russ, R. Fries, and I. Medugorac. 2016. Confirmation of a non-synonymous SNP in *PNPLA8* as a candidate causal mutation for Weaver syndrome in Brown Swiss cattle. Genet. Sel. Evol. 48:21.

Lawlor, T.J., P.M. VanRaden, D. Null, J. Levisee, and B. Dorhorst. 2014. Using haplotypes to unravel the inheritance of Holstein coat color. Proc. World Congr. Genet. Appl. Livest. Prod., Commun. 289.

McClure, M., E. Kim, D. Bickhart, D. Null, T. Cooper, J. Cole, G. Wiggans, P. Ajmone-Marsan, L. Colli, E. Santus, G.E., Liu, S. Schroeder, L. Matukumalli, C. Van Tassell, and T. Sonstegard. 2013. Fine mapping for Weaver Syndrome in Brown Swiss cattle and the identification of 41 concordant mutations across NRCAM, PNPLA8 and CTTNBP2. PLoS One 8:e59251.

McClure, M.C., D. Bickhart, D. Null, P. VanRaden, L. Xu, G. Wiggans, G. Liu, S. Schroeder, J. Glasscock, J. Armstrong, J.B. Cole, C.P. Van Tassell, and T.S. Sonstegard. 2014. Bovine exome sequence analysis and targeted SNP genotyping of recessive fertility defects BH1, HH2, and HH3 reveal causative mutation in *SMC2* for HH3. PLoS ONE 9:e92769.

Medugorac, I., D. Seichter, A. Graf, I. Russ, H. Blum, K.H. Göpel, S. Rothammer, M. Förster, and S. Krebs. 2012. Bovine polledness – An autosomal dominant trait with allelic heterogeneity. PLoS ONE 7:e39477.

Menzi, F., N. Besuchet-Schmutz, M. Fragnière, S. Hofstetter, V. Jagannathan, T. Mock, A. Raemy, E. Studer, K. Mehinagic, N. Regenscheit, M. Meylan, F. Schmitz-Hsu, and C. Drögemüller. 2016. A transposable element insertion in *APOB* causes cholesterol deficiency in Holstein cattle. Anim. Genet. 47:253–257.

Nicholas, F.W., and M. Hobbs. 2014. Mutation discovery for Mendelian traits in non-laboratory animals: A review of achievements up to 2012. Anim. Genet. 45:157–170.

Null, D.J., J.L. Hutchison, D.M. Bickhart, P.M. VanRaden, and J.B. Cole. 2017. Discovery of a haplotype affecting fertility in Ayrshire dairy cattle and identification of a putative causal variant. J. Dairy Sci.100(Suppl. 2):199(abstr. 206).

OMIA - Online Mendelian Inheritance in Animals. 2014. Fac. Vet. Sci., Univ. Sydney.

Ortega, M. S., D. M. Bickhart, K. N. Lockhart, D. J. Null, J. L. Hutchison, J. C. McClure, and J. B. Cole. 2022. Truncation of IFT80 causes early embryonic loss in Holstein cattle associated with Holstein haplotype 2. J. Dairy Sci.105(11):9001-9011.

Rosen, B.D., D.M. Bickhart, R.D. Schnabel, S. Koren, C.G. Elsik, A. Zimin, C. Dreischer, S. Schultheiss, R. Hall, S.G. Schroeder, C.P. Van Tassell, T.P.L. Smith, and J.F. Medrano. 2018. Modernizing the bovine reference genome assembly. Proc. World Congr. Genet. Appl. Livest. Prod., Vol. Molecular Genetics 3, p. 802.

Rothammer, S., A. Capitan, E. Mullaart, D. Seichter, I. Russ, and I. Medugorac. 2014. The 80-kb DNA duplication on BTA1 is the only remaining candidate mutation for the polled phenotype of Friesian origin. Genet. Sel. Evol. 46:44.

Schütz, E., C. Wehrhahn, M. Wanjek, R. Bortfeld, W.E. Wemheuer, J. Beck, and B. Brenig. 2016. The Holstein Friesian lethal haplotype 5 (HH5) results from a complete deletion of *TFB1M* and cholesterol deficiency (CDH) from an ERV-(LTR) insertion into the coding region of *APOB*. PLoS ONE 11:e0154602.

Schwarzenbacher, H., J. Burgstaller, F.R. Seefried, C. Wurmser, M. Hilbe, S. Jung., C. Fuerst, N. Dinhopl, H. Weissenböck, B. Fuerst-Waltl, M. Dolezal, R. Winkler, O. Grueter, U. Bleul, T. Wittek, R. Fries, and H. Pausch. 2016. A missense mutation in *TUBD1* is associated with high juvenile mortality in Braunvieh and Fleckvieh cattle. BMC Genomics 17:400.

Shanks, R.D., D.B. Dombrowski, G.W. Harpestad, and J.L. Robinson. 1984. Inheritance of UMP synthase in dairy cattle. J. Hered. 75:337–340.

Shuster, D.E., M.E. Kehrli Jr., M.R. Ackermann, and R.O. Gilbert. 1992. Identification and prevalence of a genetic defect that causes leukocyte adhesion deficiency in Holstein cattle. Proc. Natl. Acad. Sci. USA 89:9225–9229.

Sonstegard, T.S., J.B. Cole, P.M. VanRaden, C.P. Van Tassell, D.J., Null, S.G. Schroeder, D. Bickhart, and M.C. McClure. 2013. Identification of a nonsense mutation in CWC15 associated with decreased reproductive efficiency in Jersey cattle. PLoS ONE 8:e54872.

Thomsen, B., P.H. Nissen, J.S. Agerholm, and C. Bendixen. 2010. Congenital bovine spinal dysmyelination is caused by a missense mutation in the *SPAST* gene. Neurogenetics 11:175–183.

VanRaden, P., and D. Null. 2018. Changes in haplotype distribution in Holstein, Brown Swiss and Jersey. Changes to evaluation system (December 2018). Council on Dairy Cattle Breeding.

VanRaden, P., D. Null, J. Hutchison, D. Bickhart, and S. Schroeder. 2014. Jersey haplotype 2 (JH2). Changes to evaluation system (August 2014). Council on Dairy Cattle Breeding.

VanRaden, P., D. Null, J. Hutchison, and T. Cooper. 2013. New fertility and stillbirth haplotypes and changes in haplotype status. Changes to evaluation system (August 2013). Council on Dairy Cattle Breeding.

VanRaden, P.M., D.J. Null, T.S. Sonstegard, H.A. Adams, C.P. Van Tassell, and K.M. Olson. 2012. Fine mapping and discovery of recessive mutations that cause abortions in dairy cattle. J. Dairy Sci. 95(Suppl. 2):ii–iii(abstr. LB6).

VanRaden, P.M., K.M. Olson, D.J. Null, and J.L. Hutchison. 2011. Harmful recessive effects on fertility detected by absence of homozygous haplotypes. J. Dairy Sci. 94:6153–6161.

Venhoranta, H., H. Pausch, K. Flisikowski, C. Wurmser, J. Taponen, H. Rautala, A. Kind, A. Schnieke, R. Fries, H. Lohi, and M. Andersson. 2014. In frame exon skipping in *UBE3B* is associated with developmental disorders and increased mortality in cattle. BMC Genomics 15:890.