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## Inheritance of a mutation causing neuropathy with splayed forelimbs in Jersey cattle

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### ABSTRACT

A new undesirable genetic factor, neuropathy with splayed forelimbs (JNS), has been identified recently in the Jersey breed. Calves affected with JNS are unable to stand on splayed forelimbs that exhibit significant extensor rigidity and excessive lateral abduction at birth. Affected calves generally are alert at birth but exhibit neurologic symptoms, including spasticity of head and neck and convulsive behavior. Other symptoms reported include dislocated shoulders, congenital craniofacial anomalies, and degenerative myelopathy. Inheritance of an undesirable genetic factor was determined from a study of 16 affected calves reported by Jersey breeders across the United States. All of their pedigrees traced back on both paternal and maternal sides to a common ancestor born in 1995. Genotypes revealed that JNS is attributable to a specific haplotype on *Bos taurus* chromosome 6. Currently 8.2% of the genotyped US Jersey population are carriers of the haplotype. Sequencing of the region of shared homozygosity revealed missense variant rs1116058914 at base 60,158,901 of the ARS-UCD1.2 reference map as the most concordant with the genetic condition and the most likely cause. The single-base G to A substitution is in the coding region of the last exon of *UCHL1*, which is conserved across species. Mutations in humans and gene knockouts in mice cause similar recessive symptoms and muscular degeneration. Since December 2020, carrier status has been tracked using the identified haplotype and reported for all 459,784 genotyped Jersey animals. With random mating, about 2,200 affected calves per year with losses of about \$250,000 would result from the 1.3 million US Jersey cows in the national population. Selection and mating programs can reduce numbers of JNS-affected births using either the haplotype status or

a direct gene test in the future. Breeders should report calf abnormalities to their breed association to help discover new defects such as JNS.

**Key words:** genetic defect, lethal recessive, carrier, *UCHL1*, Jersey neuropathy with splayed forelimbs (JNS)

### INTRODUCTION

Genomic testing of the Jersey breed has allowed accurate and inexpensive tracking of both deleterious and beneficial haplotypes for economically important traits. The recessive *CWC15* mutation in haplotype JH1 (Sonstegard et al., 2013) is associated with reduced fertility, whereas dominant mutations for polledness (Medugorac et al., 2012) can be tracked using the JHP haplotype (Cole et al., 2020). For recessive defects identified before the availability of genomic testing, such as limber legs (**LL**) and recto-vaginal constriction discovered in the Jersey breed in the 1970s and 1980s (Lamb et al., 1976; Leipold et al., 1990), carriers are labeled to reduce their use. Many other recessive or dominant conditions are now tracked using genomic tools as reported in other breeds (Nicolas and Hobbs, 2014; Cole et al., 2020).

A new abnormal phenotype condition in 16 newborn calves born since 2008 was reported to the American Jersey Cattle Association (2020a,b) by Jersey breeders. The condition was named Jersey neuropathy with splayed forelimbs (**JNS**) because affected calves are unable to stand on splayed forelimbs that exhibit significant extensor rigidity and excessive lateral abduction at birth (Figure 1). Affected calves generally were alert at birth but exhibited neurologic symptoms, including spasticity of head and neck and convulsive behavior. Other symptoms included dislocated shoulders, congenital craniofacial anomalies, and degenerative myelopathy. Sires and dams of affected calves had a normal appearance, which indicated recessive inheritance of the defect. Necropsies performed on some affected calves showed no evidence of bacterial or viral infections that might contribute to the phenotype,

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**Figure 1.** A homozygous Jersey calf affected with neuroathy with splayed forelimbs. Photograph courtesy of the American Jersey Cattle Association (Reynoldsburg, OH). Photograph used with permission.

which supports a genetic etiology. The objective of this study was to determine the genetic basis for JNS.

## MATERIALS AND METHODS

### *Affected Calves*

The study population consisted of 16 calves born in the time frame of July 2008 to October 2020 that exhibited symptoms of JNS. Physical examination of the affected calves at birth by local veterinarians confirmed the inability to stand on splayed forelimbs that exhibit significant extensor rigidity, excessive lateral abduction, or both. Other neurologic symptoms were seen, including spasticity of head and neck and convulsive behavior. The necropsy examination of the affected calves ruled out a possible bacterial or viral infection that can cause similar phenotypes. One additional calf born April 2021 was examined in greater detail at the University of Nebraska–Lincoln. A recessive genetic etiology was proposed for the JNS disorder as the calves' parent sires and dams all had a normal appearance.

### *Array Genotypes and Pedigrees*

Genotypes in the national cooperator database of the Council on Dairy Cattle Breeding (Bowie, MD) were

available for 459,784 Jerseys (37,084 males and 422,700 females) including 17,963 foreign Jerseys from 21 countries on 6 continents. The genotypes were from 45 different SNP arrays. All genotypes were imputed using Findhap version 3 (VanRaden et al., 2011; <https://aipl.arsusda.gov/software/findhap/>) to the 79,060 SNP used routinely in genomic predictions of the Council on Dairy Cattle Breeding. The genotype file had already been restricted to include only animals with at least 90% Jersey inheritance using estimates of genomic breed composition (VanRaden et al., 2020). The pedigree file for this genotyped population included a total of 983,234 animals.

The imputation process divided the genome into haplotype segments of maximum length 100 SNP. Among all haplotypes within all segments across the genome, those with highest frequency in the affected calves were examined. Haplotypes potentially carrying the JNS mutation were identified that were homozygous in the affected calves and were also heterozygous in the oldest genotyped common ancestor. A target region to search for the causal mutation was obtained by visually inspecting the JNS associated haplotype segments of shared homozygosity for the imputed genotypes of the affected calves. Whole-genome sequence data of the affected calves were used to identify the likely causative mutation after narrowing the suspect region using the

JNS-associated haplotypes. Carrier status for JNS of all animals in the population was determined using the haplotype containing the putative mutation. The available Jersey pedigree information allowed us to identify recombinant haplotypes also containing the mutation using the methods described in Sonstegard et al. (2013).

Pedigrees of affected animals and their carrier ancestors were visualized using PyPedal version 2.0.4 (Cole, 2007; <https://github.com/wintermind/pypedal>) and examined to ensure reporting consistency. The plausibility of the candidate founder animal was confirmed by using PyPedal to find the intersection of common ancestors in the pedigrees for the 16 affected calves. Two of these affected calves were not yet included in the December 2020 imputation file used for the homozygosity mapping.

The effect of JNS on stillbirth rate was estimated using 933 calving reports from carrier sire by carrier maternal grandsire matings compared with 242,020 other calving reports for Jerseys in the national database as of December 2020. Any detected stillbirths would be a subset of the expected calf losses because calves born dead or born and euthanized could both be coded as stillbirths. Evaluations are provided routinely only for Holsteins but have been investigated for US Jerseys (Yao et al., 2014). The effect of JNS on conception rate was estimated using 3,599 inseminations of carrier service sires to daughters of carrier sires compared with 224,421 noncarrier matings. This trait is defined to include all conception losses before the next calving and routinely evaluated for all breeds.

### Sequence Data

Whole genomes were sequenced for 8 of the 16 affected calves as well as 9 close relatives (3 sires, 4 dams, and 2 unaffected siblings). Sequencing depth ranged from 6.2× to 44.6×, and genotype call rates averaged 93.5%. The variant analysis included 17 Jerseys (affected calves and close relatives) plus 477 other Ayrshires, Brown Swiss, Guernseys, Holsteins, Jerseys, and Milking Shorthorns for a total of 494 sequenced animals from the Animal Genomics and Improvement Laboratory (Beltsville, MD) and the Collaborative Dairy DNA Repository (Madison, WI). All of the close relatives and 9 of the Jerseys included among the other animals were determined to be carriers of the suspect haplotype based on their array genotypes.

The mpileup command from BCFtools version 1.9 (Danecek and McCarthy, 2017) was used to create the variant calling format file with flags to exclude low-quality sites, and results were annotated using SnpEff version 4.3 (Cingolani et al., 2012). Genotypes were set to missing if Phred score was <20. The number

of variants across all chromosomes before edits was 266,411,368, with 12,825,486 on BTA 6 and 36,986 in the target region of 59 to 62 Mb. Further edits removed 34 noncarrier animals with <10× coverage or <90% concordance for sequence and chip genotypes. From the remaining 460 animals (8 affected, 18 carriers, 434 noncarriers), concordances of sequence variants with affected status and with JNS haplotype status were determined, and any discordances were examined. Raw variant calls from Run 8 of the 1000 Bull Genomes Project (Hayes et al., 2014) were examined for 89 sequenced Jersey bulls who also had array genotypes from CDCB and JNS carrier status determined from haplotypes. Concordances of those sequence variants with array haplotype status were also examined.

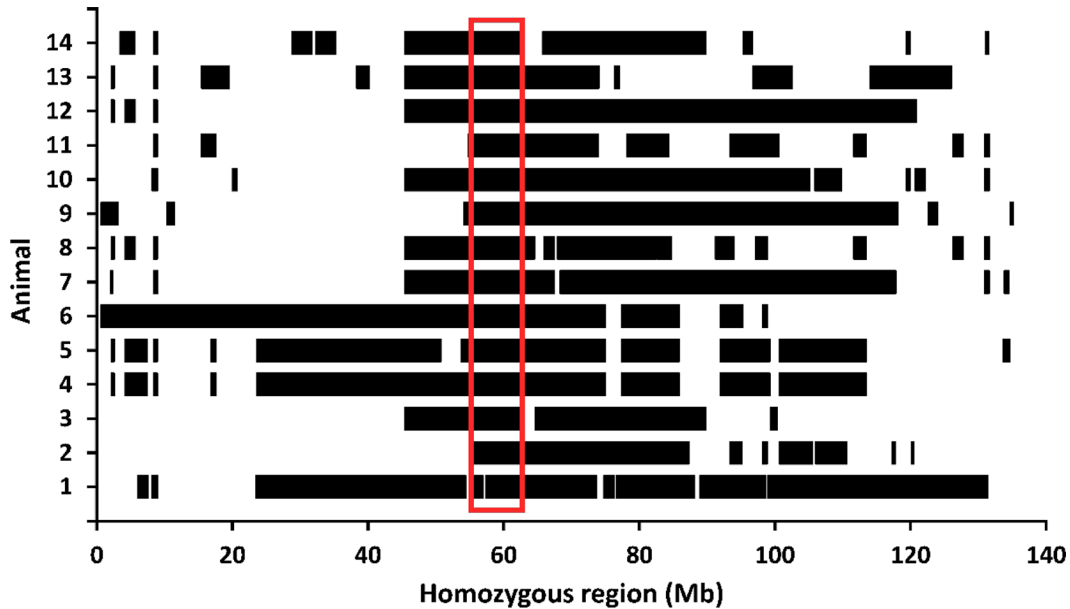
## RESULTS AND DISCUSSION

### Affected Calves

The symptoms and pathology for JNS-affected calves were not the same as those for LL-affected calves. The genotypes of known LL carriers did not include the same haplotype attributed to JNS. The genetic variants associated with LL and JNS were located on 2 different chromosomes. No clear pedigree connection was found between known LL and JNS carriers, and no common candidate haplotypes were discovered between the 2 conditions. Thus, LL and JNS appear to be distinctly different conditions with different underlying mechanisms.

### Array Genotypes and Pedigrees

The region of shared homozygosity among the affected calves (Figure 2) spans the region from 55.1 to 62.8 Mb on BTA 6 of the ARS-UCD1.2 reference map (Rosen et al., 2020). For all animals, JNS carrier status was determined using a 98-SNP haplotype (base-pair coordinates from 59,612,719 to 64,087,802) on BTA 6 that had been defined during imputation while dividing the genome into equal-length haplotype segments as in previous studies (VanRaden et al., 2011; Sonstegard et al., 2013). Among genotyped Jerseys, 36 were homozygous for JNS, and 26,064 (5.74%) were carriers. Pedigrees of all JNS-affected calves were traced on both paternal and maternal sides and found to be related to a common ancestor born in 1995 (Figure 3; Supplemental Table S1; [https://www.ars.usda.gov/arsuserfiles/80420530/publications/scientific/journals/JDS\\_JNS\\_SupplTableS1.pdf](https://www.ars.usda.gov/arsuserfiles/80420530/publications/scientific/journals/JDS_JNS_SupplTableS1.pdf)). The occurrence of JNS carriers in the population increased rapidly from 0.2% in 2009 to the current frequency of 8.2% (Figure 4), driven in large part by the heavy use of some carriers as AI sires.



**Figure 2.** Homozygous regions of BTA 6 on the ARS-UCD1.2 reference map (Rosen et al., 2020) for 14 Jersey calves affected with neuropathy with splayed forelimbs. The region of shared homozygosity, which spans the region from 55.1 to 62.8 Mb, is indicated by the red rectangle.

The bulls River Valley CeCe Chrome-ET (7JE5004, born 2013) and Hillview Listowel-P (200JE01045, born 2015) are largely responsible for this increase; Chrome was an extremely popular bull (6,322 daughters), and Listowel was often bred to those daughters.

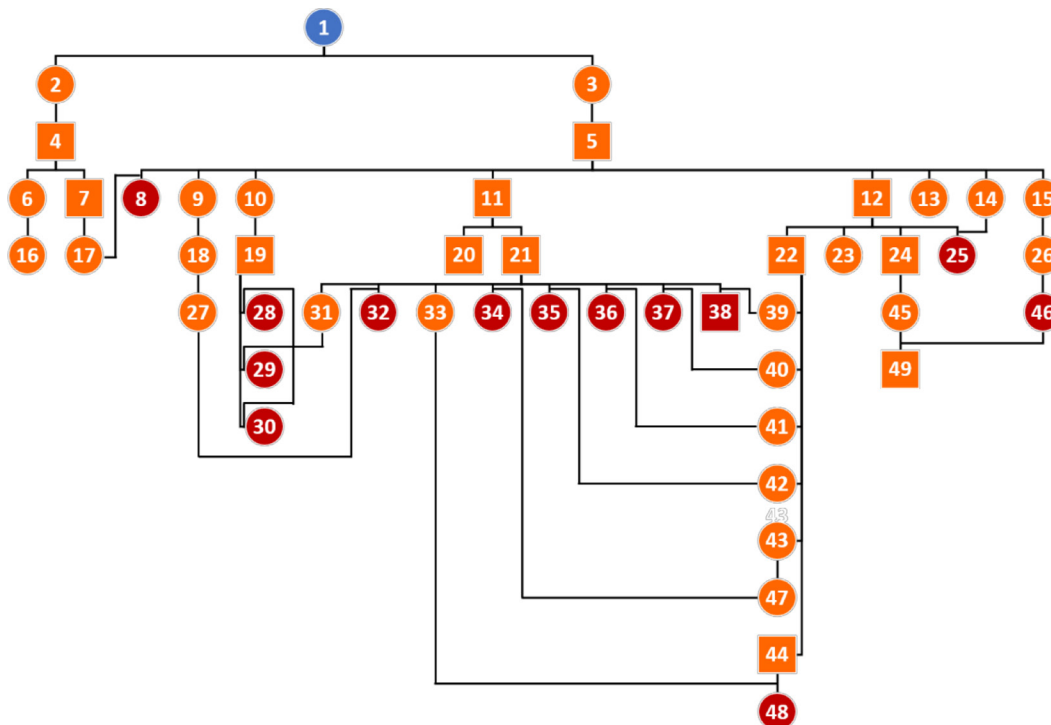
The economic loss of each affected Jersey heifer due to JNS is estimated to be \$225 based on current prices for young calves. The 360,000 Jersey cows with records used in the national genetic evaluations (Norman et al., 2020) are 14% of the cows enrolled in the national milk recording system. If the breed makes up the same proportion of the 9.4 million cow national herd then there are ~1.3 million Jersey cows in the United States. The current JNS allele frequency of 0.041 is half the carrier frequency of 0.082 and would be expected to result in 2,185 affected calves annually ( $1.3 \text{ million} \times 0.041^2$ ) with random mating. If half are bull calves, the national loss would be \$245,846 annually. Carrier status has not yet been determined for crossbred animals, and haplotypes were assumed to be homozygous normal for animals of other breeds.

The stillbirth rate was estimated to increase by  $2.4 \pm 1.2\%$ , which was significant ( $P = 0.05$ ) but small compared with the 12.5% expected increase for sire-by-MGS (maternal grandsire) carrier matings. Thus, most of the affected calves are likely coded as born alive before being euthanized. The conception rate decrease was only  $-1.3 \pm 0.8\%$ , which was small and not significant, consistent with the calves appearing to be healthy except for the inability to stand.

### Sequence Analysis

The most likely biological cause for JNS within the region of common homozygosity on BTA 6 is the variant rs1116058914 (G to A substitution) located in the coding region of the last exon of the ubiquitin C-terminal hydrolase L1 (*UCHL1*) gene. This variant's exact position is at base 60,158,901; full *UCHL1* variant annotation is in Supplemental Table S2 ([https://www.ars.usda.gov/arsuserfiles/80420530/publications/scientific/journals/JDS\\_JNS\\_SupplTableS2.csv](https://www.ars.usda.gov/arsuserfiles/80420530/publications/scientific/journals/JDS_JNS_SupplTableS2.csv)). In cattle, *UCHL1* extends from 60,147,511 to 60,159,287 bp.

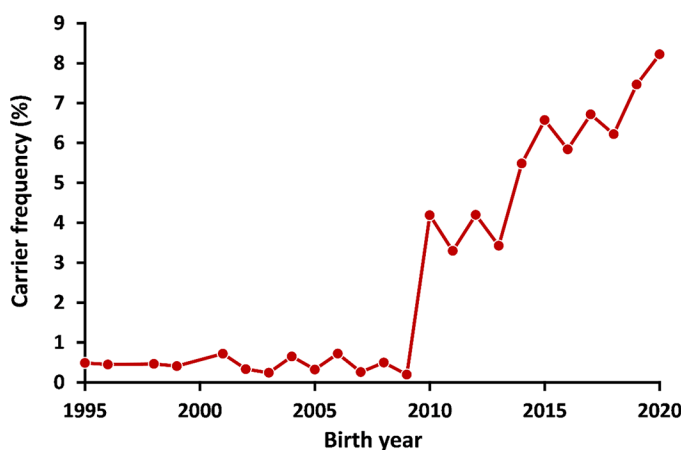
The multiple-sequence alignments of the 5 possible transcripts of the *UCHL1* gene (Figure 5) show that the sequence is conserved across all 5 transcripts. From its location in each of the *UCHL1* transcripts, the rs1116058914 variant is predicted to have a missense consequence in all 5 transcripts by modifying the codon from GAG to AAG, which gives rise to lysine AA recruitment instead of glutamic acid. The normalized probabilities calculated by SIFT (sorting intolerant from tolerant) software ranged from 0 to 0.04 for all of the aligned transcripts of *UCHL1* (Table 1). The SIFT probabilities threshold greater than or equal to 0.05 indicates a tolerated AA substitution, whereas the SIFT scores for all *UCHL1* transcripts were less than 0.05, which favors a deleterious effect of the AA substitution caused by the rs1116058914 variant. Also, variant rs1116058914 (G to A substitution) in



**Figure 3.** Pedigree of 16 Jersey calves affected with neuropathy with splayed forelimbs (red), their carrier ancestors (orange), and the earliest known carrier (blue); the animal identification key is given in Supplemental Table S1 ([https://www.ars.usda.gov/arsuserfiles/80420530/publications/scientific/journals/JDS\\_JNS\\_SupplTableS1.pdf](https://www.ars.usda.gov/arsuserfiles/80420530/publications/scientific/journals/JDS_JNS_SupplTableS1.pdf)).

the ENSBTAT0000072142.1 transcript of *UCHL1* is extremely close to the end boundary of the exon, which also predicts a possible disruption of the alternative splicing region and could result in potential variation of proteome diversity (Figure 5; Table 1). Predicted modulation (physical and quantitative) of each transcript alteration is hypothetical and requires additional molecular level experimentation for validation.

The *UCHL1* gene is conserved in human, mice, rats, swine, cattle, equine, and sheep, with similar expression in many species (Supplemental Figure S1; <https://mfr.osf.io/render?url=https://osf.io/6bfm5/?direct%26mode=render%26action=download%26mode=render>). In humans, mutations in *UCHL1* can cause the autosomal recessive disorder spastic paraplegia-79 (also known as childhood-onset neurodegeneration with optic atrophy); symptoms include head tremors, loss of muscle control, and gradual inability to stand (Bilguvar et al., 2013; Rydning et al., 2017; Online Mendelian Inheritance in Man, 2021). In mice, homozygous gene knockout of *UCHL1* caused denervation of muscles and progressive paralysis of hind and forelimbs from ages 4 to 8 mo and death by 10 mo; in contrast, parents and siblings heterozygous for the knockout were normal (Chen et al., 2010). Affected mice displayed a pattern of splayed limbs (Chen et al., 2010) like that of the affected Jersey calves. For the JNS-affected calf examined at the University of Nebraska and compared with normal calves, histology of nerve, spinal cord, and nerve rootlet did not reveal any observable difference or degeneration of myelin as has been reported in mice (Chen et al., 2010). This can be explained as the vital damage and impairment of the synaptic transmission at the neuromuscular junction that happens in the early



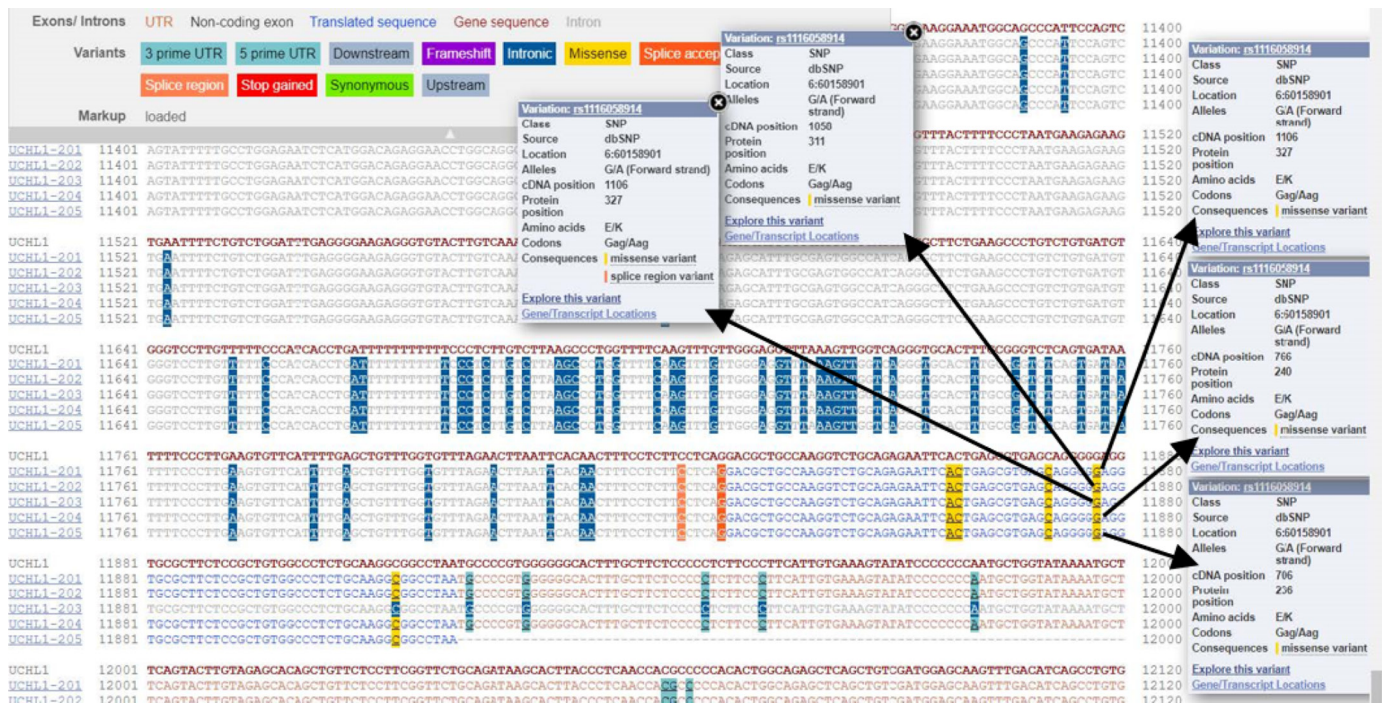
**Figure 4.** Trend of the increase per year of carriers of Jersey neuropathy with splayed forelimbs.

stages of birth and is only seen on the electrophysiological, molecular level. Morphological structural damage of the muscle fibers and nerves would progressively develop and worsen by age, markedly seen at the 5-month age in the homozygous gene knockout of *UCLH1* mice (Chen et al., 2010). Thus, no direct diagnostic test for JNS was found other than the initial symptoms reported by owners.

The most abundant expression of *UCLH1* in *Bos taurus* is found in the brain, particularly the hypothalamus, as well as many other tissues according to the Gene Expression Atlas Database ([https://www.ebi.ac.uk/gxa/genes/ensbtg00000005078?bs=%7B%22bos%20taurus%22%3A%5B%22ORGANISM\\_PART%22%5D%7D&ds=%7B%22kingdom%22%3A%5B%22animals%22%5D%7D#baseline](https://www.ebi.ac.uk/gxa/genes/ensbtg00000005078?bs=%7B%22bos%20taurus%22%3A%5B%22ORGANISM_PART%22%5D%7D&ds=%7B%22kingdom%22%3A%5B%22animals%22%5D%7D#baseline)). Baseline expression is also found in the kidney, testis, adipose tissue, colon, duodenum, skeletal muscles tissue, heart, spleen, liver, lung, and muscle tissue (Merkin et al., 2012; Liao et al., 2014).

Of the sequenced Jerseys, all 8 affected calves that were sequenced were homozygous for the alternate allele in variant rs1116058914 and 18 were heterozygous. The other 468 sequenced animals were homozygous reference including the animals of all other breeds, as expected. Concordance of haplotype status with genotype status for this variant across the 460 animals that had

both sequence and array genotypes was 99.3%, whereas all other variants in the 3-Mb target region had concordances of <96.2%. One animal that was homozygous for the JNS haplotype was heterozygous for the sequence variant and was unaffected, and 2 of the affected calves had only heterozygous haplotype status. Those results indicate that true JNS status is tracked more precisely by the sequence variant than by the haplotype status. Some sires or dams were not genotyped, which reduced the accuracy of phasing and tracking the haplotype's inheritance; however, the genotype call rate from sequence data for the candidate variant was only 92.4%. For the 89 Jersey bulls with 1000 Bull Genomes data and JNS haplotype status, concordance of the 60,158,901 locus (rs1116058914) variant in *UCLH1* was 100%, and the call rate from the sequence for that variant was also 100%. Concordance for 8 other variants on BTA 6 in the range of 57 to 68 Mb was also 100%, but the call rates for those variants were much lower (Supplemental Table S3; <https://mfr.osf.io/render?url=https://osf.io/xm7sr/?direct%26mode=render%26action=download%26mode=render>). A frameshift variant at 65,420,916 Mb had high priority but only a 30% call rate and was in transcript ENSBTAG00000039213 rather than within a named gene with a known effect on limb control. The causal mutation identified in this study using



**Figure 5.** Multiple-sequence alignment in the proximity of rs1116058914 for 5 possible transcripts (last exon region) of *UCLH1* and predicted consequences of variant alteration. The *UCLH1-203* sequence (transcript ENSBTAT00000072142.1) is predicted to be a missense/splice variant because it is located at the end boundary of the coding sequence (indicated by blue DNA bases). Full sequence alignment of *UCLH1* gene transcripts is available through Ensembl at [https://useast.ensembl.org/Bos\\_taurus/Share/f5768d6fe82152151d906501a41a1938](https://useast.ensembl.org/Bos_taurus/Share/f5768d6fe82152151d906501a41a1938).



**Table 1.** Predicted consequences of the rs1116058914 (G to A substitution; bolded) variant based on overlapping 5 transcripts of *UCHL1* (ENSEBTAG00000005078)

Transcript identification (strand)	Consequence	Position			Reference/alternate			SIFT <sup>1</sup>
		Transcript	Coding sequence	Protein	AA	Codons		
ENSEBTAT00000046823.2 (+)	Missense	766 (out of 1,134)	718 (out of 759)	240 (out of 252)	Glu/Lys	GAG/AAG	0.00	
ENSEBTAT00000074165.1 (+)	Missense	706 (out of 747)	706 (out of 747)	236 (out of 248)	Glu/Lys	GAG/AAG	0.00	
ENSEBTAT00000072142.1 (+)	Missense, splice region	1,106 (out of 1,329)	979 (out of 1,047)	327 (out of 348)	Glu/Lys	GAG/AAG	0.01	
ENSEBTAT00000066434.1 (+)	Missense	1,058 (out of 1,444)	931 (out of 972)	311 (out of 323)	Glu/Lys	GAG/AAG	0.04	
ENSEBTAT00000072800.1 (+)	Missense	1,106 (out of 1,492)	979 (out of 1,020)	327 (out of 339)	Glu/Lys	GAG/AAG	0.04	

<sup>1</sup>SIFT = score that predicts if a missense variant is likely to affect protein function based on sequence homology and physico-chemical similarity between alternate AA.

the sequence data is not yet included in genotyping arrays. Polymerase chain reaction-based diagnostic tests are currently under development by commercial laboratories.

## CONCLUSIONS

Jersey neuropathy with splayed forelimbs is a recessive genetic condition that results in an affected calf that is unable to stand when the recessive allele is inherited from both parents. Inheritance of the defect began to be tracked and reported in December 2020 by the Council on Dairy Cattle Breeding (Bowie, MD) using a haplotype test, and direct genotype tests for the *UCHL1* missense variant at 60,158,901 bp on BTA6 are becoming available (Jiang et al., 2021). Jersey owners should select against JNS and limit carrier-to-carrier matings to manage the effect on potential calf loss. Annual losses near \$250,000 nationally would result without management of JNS given the current 8.2% carrier frequency.

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