

Genetic Mapping of Canine Multiple System Degeneration and Ectodermal Dysplasia Loci

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Abstract

We characterized a movement disorder of Chinese Crested dogs clinically and pathologically indistinguishable from canine multiple system degeneration (CMSD) previously recognized in Kerry Blue Terriers. This fatal disease segregated as an autosomal recessive in a 51-dog pedigree of both breeds and their crosses. The occurrence of affected dogs among first-generation crosses demonstrated that the mutations causing multiple system degeneration in these breeds are allelic. The *CMSD* locus maps to CFA1 (LOD > 18) and haplotype analysis narrowed the CFA1 target region to a 15-Mb segment that contains orthologs of genes on HSA6, including *PARK2*, the gene for the ubiquitin ligase parkin. Mutations in human *PARK2* cause the most common form of familial Parkinson's disease, autosomal recessive juvenile parkinsonism, which has clinical and pathological similarities to canine multiple system degeneration. A second phenotype, canine ectodermal dysplasia (CED), segregated in the pedigree as an autosomal dominant with homozygous lethality. Dogs with ectodermal dysplasia have a sparse hair coat and abnormal dentition that is characteristic of the "hairless" variety of Chinese Cresteds. *CED* mapped to a region of CFA17 (LOD > 14) containing orthologs from HSA2. *EDAR*, the gene for the ectodysplasin A1 receptor, occurs on HSA2 but was excluded as the cause of canine ectodermal dysplasia.

Introduction

Canine multiple system degeneration (CMSD) is a fatal, familial movement disorder of dogs (*Canis familiaris*) first described in Kerry Blue Terriers (deLahunta and Averill 1976; Metler and Goss 1946). Affected dogs are normal until 3–6 months of age, when they develop cerebellar ataxia. This progresses to akinesia and severe postural instability necessitating euthanasia by 1–2 years of age. Histologically, CMSD is characterized by initial loss of cerebellar Purkinje cells followed by degeneration of the olivary nucleus, substantia nigra, putamen, and caudate nucleus (deLahunta and Averill 1976; Montgomery and Storts 1983). In this article, we describe a CMSD-like disease in Chinese Crested dogs, demonstrate that the gene is allelic in Chinese Cresteds and Kerry Blue Terriers, and genetically map the *CMSD* locus in a pedigree of both breeds and their crosses.

A second phenotype, canine ectodermal dysplasia (CED), was independently segregating in this canine pedi-

gree. Chinese Crested breed standards recognize both a normal hair coat called "powderpuffs" and a "hairless" variety presenting CED, which is inherited as autosomal dominant. Dogs heterozygous for the *CED* mutation have a very sparse coat and poor dentition. Pups homozygous for the *CED* mutation are born with severe oro-buccal malformations and are not viable (Letard 1930). In addition to *CMSD*, we were also able to map *CED*.

Materials and Methods

Fifty-one dogs from a three-generation pedigree were studied. The Chinese Crested and Kerry Blue Terrier probands were presented to the University of Missouri Veterinary Medical Teaching Hospital for evaluation of their movement disorders. Subsequent test breedings were conducted either with the cooperation of private breeding kennels or at the University of Missouri in compliance with

Table 1. Primer sequences for new microsatellite markers

Marker	Primer sequences		Chromosome
UMC0001	agcccacaaggagaagtcaa	attgaggtttggcttcagga	CFA1
UMC0003	tgagatcattgctgagctg	aaagcaagtcagccaattt	CFA1
UMC0005	gccctgagaaaagtttacagca	tcccccaagtccttcttttc	CFA17
UMC0006	tgcataaaaaaccatttcttct	ttctccctctgctgtgtct	CFA 1
UMC0007	tggggaagaacgtatgagga	gaagccaggctcaaaatctg	CFA1
UMC0045	ccattcctcagtcaccctgt	ggtccaggctctgttctgag	CFA10
UMC0046	ggctccactcagcacagaat	acaatgtgacaagccaacca	CFA10

Animal Care and Use Committee guidelines. Magnetic resonance imaging (MRI) was performed using a Siemens Magnetom Symphony 1.5 T magnet. T1 weighted images with and without IV gadolinium contrast and T2 weighted images were obtained in sagittal and transaxial planes. A presumptive diagnosis of CMSD was based on characteristic clinical signs. Affected dogs were euthanized by an overdose of barbiturates, and the diagnosis confirmed by histopathology. Dogs were classified as CED or powderpuff based on their coat density. DNA was extracted from whole blood as previously described (Katz et al. 2005).

The initial genotyping for the whole genome scan was performed at the Marshfield Clinic (www2.marshfieldclinic.org/research/genetics) using a panel of 247 multiplexed autosomal and X-linked canine microsatellites. Additional genotypes were generated at the University of Missouri for microsatellite markers from selected regions of the canine genome. Some of these markers were obtained from the NCBI *C. familiaris* genome view database (www.ncbi.nlm.nih.gov/mapview/map_search.cgi?taxid=9615). In addition, new marker assays were devised for microsatellites located in selected contigs from the first build of the canine genome (GenBank accession number AAEX01000000). Primer sequences for these new microsatellites are provided in Table 1. Microsatellite genotypes were examined for misinheritance and incorrect scoring using GENOPROB (Thallman et al. 2001a,b) and genotypes with low probability ($p_{Gmx} < 0.95$) were excluded from further analysis. Inheritance of CMSD was consistent with a fully penetrant autosomal recessive and of CED as a fully penetrant autosomal dominant with the *CED* homozygote being lethal. Twenty-seven *CMSD* genotypes (41 informative meioses) and 51 *CED* genotypes (46 informative meioses) were unequivocally inferred from the phenotypes and pedigree under these models of inheritance. Linkage analysis was performed using Cri-map v2.4 (Green et al. 1990).

Results

Eleven Chinese Crested dogs were diagnosed with CMSD. Affected Chinese Cresteds developed normally until 3–6 months of age. The first clinical sign was typically an intention tremor of the head, most prominent when dogs attempted to eat. Soon afterward, dysmetria became apparent as a goose-stepping gait, most noticeable in the thoracic limbs. Due to the inherent stability of a quadruped,

falls were infrequent at this stage of disease in spite of marked dysmetria. On midsagittal MRI, atrophy of the cerebellum was apparent as widening of the space between the folia (Figure 1A). Two dogs were euthanized during this stage of cerebellar ataxia. Light microscopy showed dramatic reductions in Purkinje cells in the cerebellum (Figure 1B) but no other histological changes.

Beginning at 6–8 months of age, the character of the movement disorder changed. Falls became more frequent. The gait changed to what can best be described as festination with dysmetria. The dogs shifted their body weight until they began to lurch forward. They then ran forward for a variable period until they fell. By 12–18 months of age, the dogs developed severe postural instability and fell frequently. When placed on the ground, they were akinetic, especially of the thoracic limbs. The dog would rock forward onto the thoracic limb, adopting a hunched, frozen posture (Figure 2) for a few minutes before losing balance and falling, though occasionally they could festinate forward. When lifted off the ground, they either adopted a saluting posture with the thoracic limbs raised above the head, or showed spontaneous slow dog-paddling movements. On MRI, increased signal on T2 weighted images was apparent in the caudate nucleus and substantia nigra (Figure 1C and D) as previously described in Kerry Blue Terriers (Vite et al. 1996).

Most dogs were euthanized before 18 months of age, but one was intensively nursed and survived to 29 months. All affected dogs showed normal mentation and social behavior. No autonomic dysfunctions were identified except regurgitation in one dog, and the oldest dog was capable of erection and ejaculation until at least 18 months of age, when it was determined that he was infertile in spite of normal sperm motility, and no further collections were performed. Affected dogs showed no evidence of gaze palsy, although downbeat nystagmus typical of cerebellar disease was occasionally seen. At the terminal stages of the disease, there was marked cavitation of the caudate nucleus and degeneration of the substantia nigra with milder degenerative changes in the putamen at necropsy (Figure 1E and F).

As indicated in the canine family pedigree (Figure 3), 11 Chinese Cresteds, 3 Kerry Blue Terriers, and 2 Chinese Crested/Kerry Blue Terrier crosses were diagnosed with CMSD. CMSD segregated in this family in a pattern consistent with an autosomal recessive mode of inheritance. Two point analysis provided maximum LOD scores of 4.20, 9.03, and 5.03 between *CMSD* and *C01.673*, *FH3370*, and

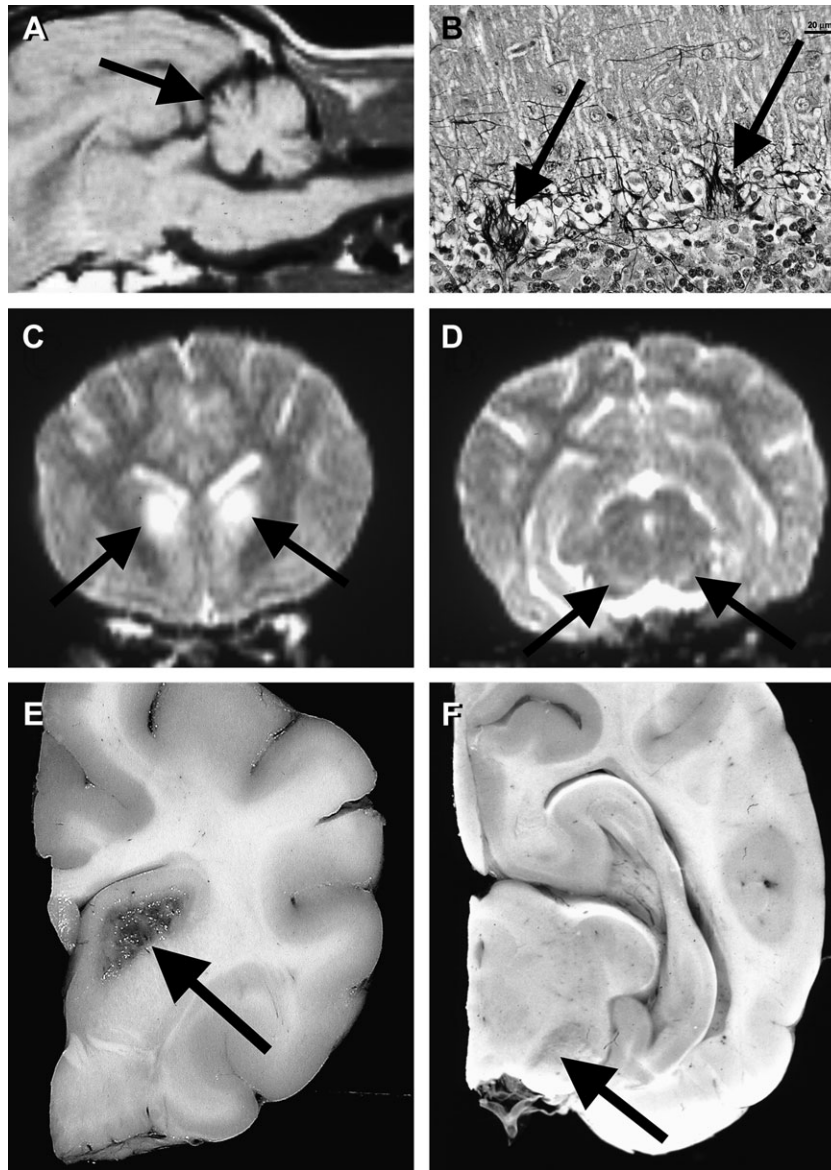


Figure 1. Degeneration of the cerebellum (**A** and **B**), caudate nucleus (**C** and **E**), and substantia nigra (**D** and **F**) in canine multiple system degeneration. On sagittal, T1 weighted MRI (**A**), atrophy is apparent in the cerebellum (arrow) as widening of the space between the folia. On light microscopy (**B**), Purkinje cells are lost, and basket cell dendrites collapse to form “empty baskets” (arrows, Bielschowsky stain, bar = 20 μ m). On transaxial T2 weighted MRI (**C** and **D**), increased signal intensity (arrows) reflects increased water density in the caudate nucleus (**C**) and substantia nigra (**D**). At necropsy, degeneration is visible grossly (arrows) in the caudate nucleus (**E**) and substantia nigra (**F**) on brain sections. Note that the substantia nigra is not pigmented in dogs and thus not normally distinguishable on gross sections.

C01.424, respectively, which span a 28-Mb region of CFA1 and contains orthologs of genes on HSA6 and HSA18. Seventeen additional microsatellites were incorporated into the map of CFA1, including eight within the region from *C01.673* to *C01.424* which is the LOD > 3 interval for *CMSD*. Moving *CMSD* anywhere on CFA1 outside of this interval decreases support for location of the locus by LOD > 3 (Figure 4A). The multipoint analysis, in which the location of *CMSD* was sequentially moved along the chromosome,

produced LOD scores above 18.0 for the location of *CMSD* between *FH3300* and *DGN3*. The LOD scores in Figure 4 provide support for *CMSD* at any given position on the chromosome when tested against the least likely position on the chromosome (99.39 Mb).

We examined CFA1 haplotypes of the canine family members for 11 markers in the region of maximum LOD score. Five distinct parental haplotypes (one disease and four wild type) were present within the Chinese Crested parents



Figure 2. Chinese Crested dog with the multiple system degeneration and ectodermal dysplasia phenotypes. Note the hunched posture characteristic of the akinetic, terminal stage of the movement disorder and the sparse coat characteristic of the hairless variety.

and three (one disease and two wild type) in the Kerry Blue Terrier parents. The Chinese Crested disease haplotype (Chinese Crested 1 in Figure 5) was present on 27 progeny chromosomes in association with the *CMSD* disease allele in affected Chinese Cresteds, Chinese Crested obligate carriers, and affected Chinese Crested/Kerry Blue Terrier crosses. A recombinant haplotype (Chinese Crested 2) occurred in an obligate carrier and two affected progeny placing *CMSD*

centromeric of *C01.424*, whereas another recombinant haplotype (Chinese Crested 3) in an affected progeny places *CMSD* telomeric of *UMC0003*. The disease haplotype in Kerry Blue Terriers (Kerry Blue Terrier 1) was present on 10 progeny chromosomes in association with the *CMSD* disease allele in affected Kerry Blue Terriers, Kerry Blue Terrier obligate carriers, and affected Chinese Crested/Kerry Blue Terrier crosses. One phenotypically normal Kerry Blue Terrier inherited a Kerry Blue Terrier 1 disease haplotype from its obligate carrier mother and a recombinant haplotype (Kerry Blue Terrier 2) from its obligate carrier father that contained disease haplotype alleles at *DGN3*, *FH3284*, and *C01.424*. This dog's phenotype and genotype place *CMSD* centromeric of *DGN3*. The combined phenotype and haplotype information in Figure 5 indicate that the target region harboring the *CMSD* mutation is the 15-Mb region between *UMC0003* and *DGN3*.

Twenty dogs exhibited the CED phenotype. CED segregated as an autosomal dominant trait, and two matings among *CED* heterozygotes produced 7 CED pups out of 10 total pups (Figure 3). All 7 of these pups were assigned heterozygous *CED* genotypes based on the model of homozygous lethality that was subsequently confirmed by their flanking marker haplotypes after integration of the *CED* locus into the CFA17 genetic map.

Two point analysis provided LOD scores of 7.02, 6.71, and 3.19 between *CED* and *FH2847*, *REN310J13*, and *PEZ8*, respectively, on CFA17. Two additional markers were scored in the pedigree resulting in the genetic map of 11 CFA17 markers shown in Figure 4B. LOD scores above 14.0 were obtained between *REN294E18* and *UMC0005* in the multi-point analysis of CFA17. This segment of CFA17 contains genes with orthologs from HSA2, including some HSA2 genes located near candidate gene *EDAR*. Nonetheless, a MegaBlast

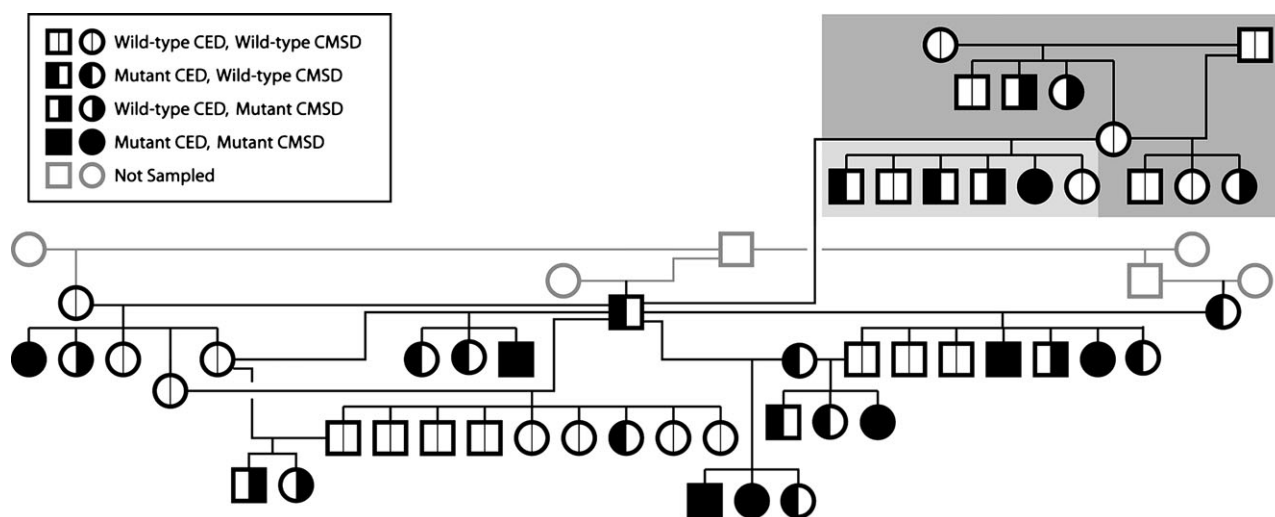


Figure 3. Pedigree showing segregation consistent with an autosomal recessive and autosomal dominant inheritance for multiple system degeneration and ectodermal dysplasia, respectively. The background is darkly shaded behind the Kerry Blue Terrier family, lightly shaded behind the cross-bred litter.

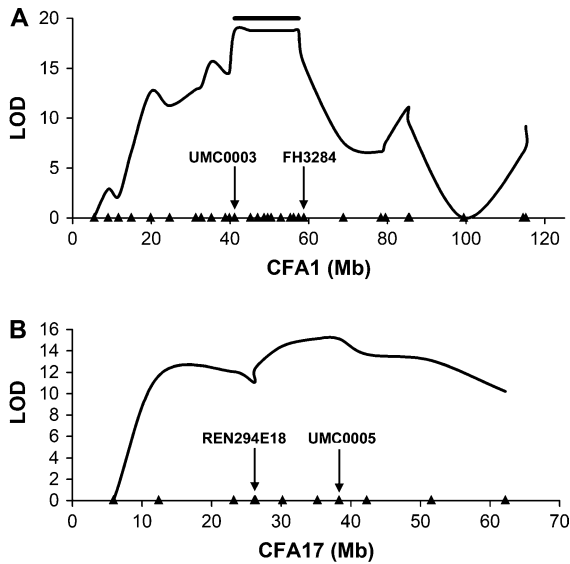


Figure 4. LOD score support for the location of the multiple system degeneration (A) and ectodermal dysplasia (B) on canine chromosome 1 and 17, respectively. Arrowheads on x-axis indicate location of markers, arrows indicate location of marker which delineated the region of maximal LOD score. The bar in Figure 1A indicates the region shown in Figure 5.

search of the first build of the canine whole genome sequence queried with human *EDAR* exonic sequences located the canine *EDAR* ortholog on contig AAEX01018667, which was assigned to CFA10. Canine microsatellites *UMC0045* and

UMC0046, located in AAEX01018667 less than 80 kb upstream from the first *EDAR* coding exon, segregated independently of *CED* in the Chinese Crested/Kerry Blue Terrier family and mapped between *FH2293* and *ZUBECA1* on CFA10.

Discussion

The CMSD phenotype in Chinese Crested dogs was indistinguishable from that reported earlier for Kerry Blue Terriers (deLahunta and Averill 1976; Montgomery and Storts 1983). This disease segregates as an autosomal recessive trait in the combined Chinese Crested/Kerry Blue Terrier family. The occurrence of CMSD in the crossbred offspring confirms that the trait is allelic in the two breeds. The initial clinical signs of CMSD are cerebellar ataxia and intention tremors. Dogs euthanized at this stage of the disease process show only cerebellar Purkinje cell loss with later atrophy of the olivary nuclei (Montgomery and Storts 1983). In humans, Purkinje cell loss and atrophy of the olivary nucleus occurs in some of the hereditary spinocerebellar ataxias (Evidente et al. 2000) and in multiple system atrophy (MSA) (Wenning et al. 1997; Quinn 1989).

As CMSD progresses, dogs develop degeneration of the substantia nigra (deLahunta and Averill 1976; Montgomery and Storts 1983). Their gait becomes festinating, and sudden movements result in falls. At the terminal stages, affected dogs become akinetic with a hunched posture, and severe postural instability results in frequent falls. These signs are comparable to the akinesia, gait abnormalities, and postural instability seen in Parkinson's disease (Siderowf 1991),

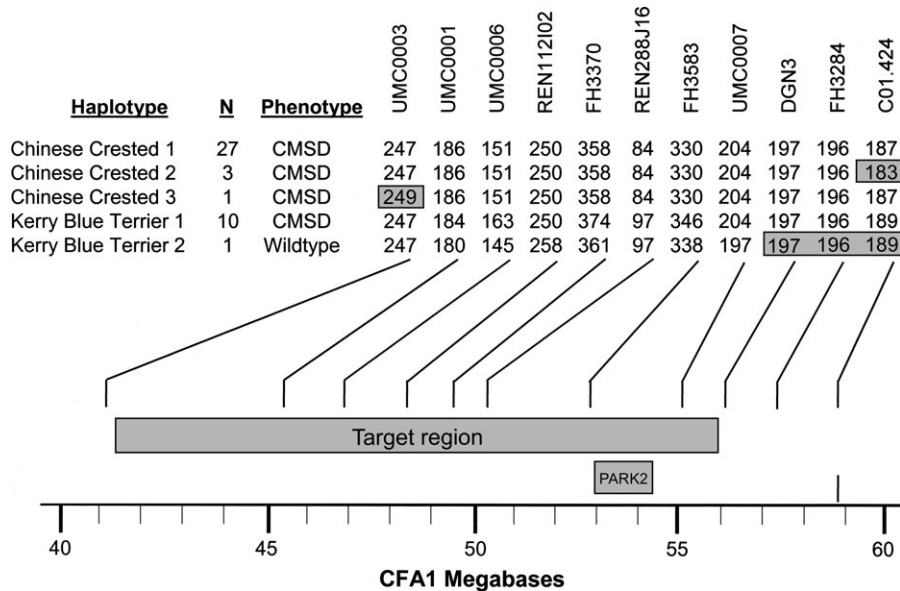


Figure 5. Haplotypes in Chinese Cresteds and Kerry Blue Terriers for 11 contiguous microsatellites on CFA1. Recombinant haplotypes (Chinese Crested 2 and 3 and Kerry Blue Terrier 2) detected in progeny define the 15-Mb target region harboring *CMSD* between *UMC0003* and *DGN3*, an area that includes the ortholog of *PARK2*. N indicates the number of times each haplotype occurs in the 51-member pedigree.

though the tremors seen in these dogs continue to be intention tremors characteristic of cerebellar disease. The pathology of Parkinson's disease is characterized by the loss of dopamine neurons in the substantia nigra, but degeneration in other brain areas also occurs (Braak et al. 2003; Jellinger 2003). Degeneration of the substantia nigra and clinical signs of parkinsonism can also occur in human as part of multiple system degenerations, conditions sometimes referred to as Parkinson plus syndromes (Mark 2001; Jellinger 1995). MSA is a sporadic, middle-age onset Parkinson plus syndrome. Autonomic dysfunction is one of the cardinal signs of MSA with orthostatic hypotension, impotence, and urinary incontinence or retention occurring in most patients. Motor symptoms can be either predominantly cerebellar ataxia or parkinsonism (Quinn 1989; Wenning et al. 2003). A recent report suggest that familial MSA may exist (Wullner et al. 2004), but histologic confirmation was not available in that family and no locus has been mapped. The olivo-ponto-cerebellar atrophy and degeneration of the substantia nigra and putamen in CMSD (deLahunta and Averill 1976; Montgomery and Storts 1983) is similar to the brain degenerations that occur in people with MSA, but the synuclein-positive, glial cytoplasmic inclusions that characterize MSA (Papp et al. 1989; Jellinger 2003) have not been reported in dogs with CMSD. Intraneuronal inclusions have been described in CMSD (Montgomery and Storts 1983), but the content of the inclusions has not been characterized. Affected dogs also show neither the autonomic dysfunctions nor the degeneration of the intermediolateral cell columns of the spinal cord that occur in people with MSA.

In the later stages of CMSD, the caudate nucleus undergoes dramatic degeneration. Such caudate degeneration does not occur in Parkinson's disease or MSA in humans, but is similar to the degeneration that occurs in Huntington's disease (Jellinger 1995). The neurotoxin 3-nitropropionic acid produces similar degeneration of the striatum in mice. The toxin is used alone to produce a mouse model of Huntington's disease (Beal et al. 1993) or in combination with a selective dopamine toxin such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to produce a mouse model of MSA (Wenning et al. 2003).

Our results indicate that *CMSD* maps to a 15-Mb region of CFA1. The orthologous region of HSA6 contains 76 characterized or putative genes. The function of many of these genes is unknown; however, a gene of interest in the target region is *PARK2*, which codes for the protein parkin, a ubiquitin ligase. Mutations in human *PARK2* cause autosomal recessive juvenile parkinsonism (ARJP) (Kitada et al. 1998), the most commonly occurring familial Parkinson's disease (West and Maidment 2004). Typically, ARJP patients experience early onset dystonia and parkinsonism that progresses slowly over decades (Ishikawa and Tsuji 1996). There is a marked loss of the pigmented neurons in the substantia nigra and in the locus ceruleus. Neuronal loss in the Purkinje cell layer and cerebellar ataxia are noted in some patients (van de Warrenburg et al. 2001). Patients with ARJP may also show other symptoms, such as autonomic

dysfunction (Kuroda et al. 2001; Lohmann et al. 2003; Periquet et al. 2003), prompting some authors to describe ARJP as a multiple system degeneration (Horstink et al. 2002; Kuroda et al. 2001). Degeneration of the caudate nucleus has not been reported in ARJP. Mouse models that are nullizygous for *Park2* show evidence of mild nigrostriatal defects but fail to develop the histopathological changes or motor deficits typical of human ARJP patients (Goldberg et al. 2003; Itier et al. 2003; Von Coelln et al. 2004; Perez and Palmiter 2005). It remains to be seen whether CMSD is caused by a *PARK2* mutation or whether a mutation in a nearby gene also causes a movement disorder.

Ectodermal dysplasia is defined as abnormalities in two or more ectodermal appendages, such as hair follicles, teeth, nails, and sweat glands. Chinese Crested dogs with CED have marked abnormalities of their teeth and hair coat. Their nails, however, appear normal. In dogs, sweat glands occur only on the foot pads. To our knowledge, sweat glands have not been evaluated in dogs with CED. CED is reported to be a dominant trait with homozygous lethality (Letard 1930). As expected, both "hairless" and "powderpuff" phenotypes were represented among surviving puppies from the Chinese Crested/Kerry Blue Terrier cross. The "hairless" crosses also have abnormal dentition. *CED* controls the distribution of hair on the body but not the characteristics of the hair shaft. In both the "hairless" and "powderpuff" crossbreeds, the hair was straight like Chinese Crested hair but colored like the Kerry Blue Terrier, in that puppies were black at birth but took on a bluish-gray tinge as they aged. Members of the Xoloitzcuintli dog breeds including Mexican Hairless can either be "hairless" or "coated." They have shorter, stiffer hair than Chinese Crested; however, among "hairless" individuals the hair distribution and dental abnormalities closely resemble those of "hairless" Chinese Crested dogs. Thus, mutations in *CED* may be segregating in both the Chinese Crested and Xoloitzcuintli dog breeds.

CED maps to a region of CFA17 with orthologous genes on HSA2. Human ectodermal dysplasia has been described in over 170 different clinical conditions, mostly as part of more complex syndromes (Priolo and Lagana 2001). At least 17 different causative genes have been identified (Lamartine, 2003); however, only *EDAR*, the gene for the ectodysplasin A1 receptor, occurs on HSA2. Various mutations in human *EDAR* cause dominant or recessive forms of hypohidrotic ectodermal dysplasia (Monreal et al. 1999). Furthermore, mutations in *Edar*, the murine *EDAR* ortholog, are responsible for the ectodermal dysplasia in dominant and recessive strains of "downless" mice (Headon and Overbeek 1999). However, the first build of the canine genome placed *EDAR* on CFA10. Our results confirm the localization of *EDAR* to CFA10, thereby eliminating it as a candidate for *CED*.

When Monreal et al. (1999) reported that mutations in *EDAR* caused human ectodermal dysplasia, they used three HSA2 markers, *D2S1893*, *D2S1890*, and *D2S1892*, that map near *EDAR* to establish the association between ectodermal dysplasia and *EDAR*. *D2S1893* and *D2S1890* are located near genes with orthologs on CFA10; however, *D2S1892* is

near genes with orthologs that are on CFA17 and that are within the CED target region. Using these three markers, Motreuil et al. (1999) showed that ectodermal dysplasia mapped near *EDAR* in 9 of 14 human families segregating the disease; however, mutations within *EDAR* were reported in only five of these nine families. Thus, it is possible that some cases of human ectodermal dysplasia that have been attributed to *EDAR* are caused by the human ortholog of the yet to be identified *CED* gene.

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