Human Genetics (2019) 138:455–466
https://doi.org/10.1007/s00439-019-02003-x

REVIEW

Canine neuropathies: powerful spontaneous models for human hereditary sensory neuropathies

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Received: 3 January 2019 / Accepted: 18 March 2019 / Published online: 6 April 2019

Abstract
In humans, hereditary sensory neuropathies (HSN), also known as hereditary sensory and autonomic neuropathies (HSAN), constitute a clinically and genetically heterogeneous group of disorders characterized by progressive sensory loss, often accompanied by chronic skin ulcerations and nail dystrophic changes. To date, although around 20 genes have already been discovered, they do not explain the genetic causes of all patients. In dogs, similar neuropathies are also diagnosed, several breeds being predisposed to specific forms of the disease. Indeed, the breed specificity of most canine genetic diseases is due to the small numbers of founders and high levels of inbreeding. Recent knowledge and tools developed to study the canine genome efficiently allows deciphering the genetic bases of such diseases. To date, a dozen breeds are recognized to develop specific HSN. For the Border collie and hunting dog breeds, the genes involved have recently been discovered. Other affected breeds thus constitute potential genetic models, with new genes to be found in dogs that can be considered as candidate genes for human HSAN/HSN. Here, we review the different forms of human and canine HSAN/HSN and we present a novel form in Fox terrier cases, highlighting the advantages of the dog model for such rare human diseases.

Human inherited peripheral neuropathies

Inherited peripheral neuropathies (IPNs) are a large group of neurological diseases characterized by length-dependent progressive degeneration of the peripheral nervous system (PNS) and extensive phenotypic and genetic heterogeneity. These diseases are characterized clinically by distal weakness and muscle amyotrophy predominant at the lower limbs, resulting in gait difficulties. The onset usually occurs within the first 2 decades, and the disease then progresses slowly. Progression to the upper limbs and skeletal abnormalities are also present, while sensory loss is also often, but not always, described. Among IPN diseases, hereditary sensory neuropathies (HSNs) or hereditary sensory and

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autonomic neuropathies (HSANs) represent a subgroup predominantly affecting the sensory and autonomic neurons, resulting in sensory and autonomic dysfunctions such as loss of heat or pain sensitivity. Distal muscle weakness and wasting may be present and is sometimes so prominent that it becomes difficult to distinguish HSN from Charcot–Marie–Tooth syndrome (CMT). HSANs/HSNs are clinically and genetically heterogeneous, with more than 20 genes known to date, and are typically subdivided into 2 groups on the basis of their mode of inheritance. They are further categorized depending on age at onset and major clinical features; classification updates are regularly proposed, due to the continuous discovery of new disease-causing genes (Vallat et al. 2016). Here, we summarize the classification of the different HSAN forms according to the known implicated genes (Table 1).

HSAN1 is the most common form and is characterized by an autosomal dominant mode of inheritance and juvenile or adult onset. A broad description was proposed by Auer-Grumbach (2008). Several subtypes are described (HSAN1A–HSAN1F) and CMT2B, with variations in the clinical features, the electrophysiology and the genetic causes. HSAN1A main clinical features are loss of pain and temperature sensation, often resulting in ulcerations of the feet. Genetically, most HSAN1 cases are due to mutations in *SPTLC1*, encoding the *serine palmitoyltransferase long-chain base subunit 1*, a member of the class-II pyridoxal-phosphate-dependent aminotransferase family (Dawkins et al. 2001). Additional subtypes of HSAN1 and the causative genes are listed in Table 1.

The HSAN2–HSAN5 forms, characterized by congenital or infantile onset, are transmitted as an autosomal recessive

Table 1 Current classification of human HSAN/HSN

Type of HSAN	Inheritance	MIM number	Gene	Chromosome	References
HSAN1A	AD	162400	*SPTLC1*	9q22.31	Dawkins et al. (2001)
HSAN1B[a]	AD	608088	*Unknown*	3p24-p22	Kok et al. (2003)
HSAN1C	AD	613640	*SPTLC2*	14q24.3	Rotthier et al. (2010)
HSAN1D	AD	613708	*ATL1*	14q22.1	Guelly et al. (2011)
HSAN1E	AD	614116	*DNMT1*	19p13.2	Klein et al. (2011)
HSAN1F	AD	615632	*ATL3*	11q13.1	Kornak et al. (2014)
HSAN1 (CMT2B)[b]	AD	600882	*RAB7A*	3q21.3	Verhoeven et al. (2003)
HSAN2A	AR	201300	*WNK1/HSN2*	12p13.33	Lafrenière et al. (2004)
HSAN2B	AR	613115	*FAM134B/RETREG1*	5p15.1	Kurth et al. (2009)
HSAN2C	AR	614213	*KIF1A*	2q37.3	Rivière et al. (2011)
HSAN2D	AR	243000	*SCN9A*	2q24.3	Cox et al. (2006)
HSAN3 (FD)	AR	223900	*IKBKAP/ELP1*	9q31.3	Slaugenhaupt et al. (2001)
HSAN4 (CIPA)	AR	256800	*NTRK1*	1q23.1	Indo et al. (1996)
HSAN5	AR	608654	*NGF*	1p13/2	Einarsdottir et al. (2004)
HSAN6	AR	614653	*DST*	6p12.2	Edvardson et al. (2012)
HSAN7[c]	AD	615548	*SCN11A*	3p22.2	Leipold et al. (2013)
HSAN8	AR	616488	*PRDM12*	9q34.12	Chen et al. (2015)
HSAN with spastic paraplegia	AR	256840	*CCT5*	5p15.2	Bouhouche et al. (2006)
HSAN with loss of pain perception	AR	–	*FLVCR1*	1q32.3	Chiabrando et al. (2016)
HSAN with intellectual disability (FD-like)	AR	–	*TECPR2*	14q32.31	Heimer et al. (2016)
Congenital insensitivity to pain, acromutilation and spastic paraplegia	AR	–	*ARL6IP1*	16p12.3	Nizon et al. (2018)

AD autosomal dominant; *AR* autosomal recessive; *ARL6IP1* ADP-ribosylation-like factor 6-interacting protein-1; *ATL* atlastin GTPase; *CIPA* congenital insensitivity to pain with anhydrosis; *CMT2B* Charcot–Marie–Tooth disease type 2B; *CCT5* chaperonin containing T-complex polypeptide-1, subunit-5; *DNMT1* DNA methyltransferase-1; *DST* dystonin; *FAM134B/RETREG1* family with sequence similarity 134, member B; *FLVCR1* feline leukemia virus subgroup C receptor-1; *FD* familial dysautonomia; *HSAN* hereditary sensory and autonomic neuropathy; *IKBKAP/ELP1* inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein/elongator acetyltransferase complex, subunit-1; *KIF1A* kinesin family member 1A; *MIM* mendelian inheritance in man; *NGF* nerve growth factor; *NTRK1* tyrosine kinase-1 receptor; *PRDM12* positive regulatory domain-containing protein 12; *RAB7* RAS-associated protein RAB7; *SCN* sodium channel, voltage-gated; *SPTLC* serine palmitoyltransferase, long-chain base subunit; *TECPR2* tectonin beta-propeller repeat-containing protein-2; *WNK1/HSN2* protein kinase, lysine-deficient 1

[a]With cough and gastroesophageal reflux

[b]This form of autosomal dominant ulcero-mutilating neuropathy is classified as a CMT, could also belong to HSAN1

[c]HSAN7 could also be classified in HSAN1 due to its transmission mode

trait. They are fully described in the review of Axelrod and Gold-von Simson (2007).

HSAN2 patients are characterized by distal numbness and progressive loss of pain, temperature and touch sensation in the extremities. Like HSAN1, several forms are described with different genes implicated. HSAN2A is caused by mutations in the *HSN2/WNK1* gene (*WNK lysine-deficient protein kinase 1*) encoding a *Serine/threonine kinase* (Lafrenière et al. 2004). HSAN2B is caused by mutations in the *FAM134B/RETREG1* gene (*reticulophagy regulator 1*) encoding an endoplasmic reticulum (ER)-anchored autophagy receptor essential for long-term survival of ganglion neurons, by facilitating ER degradation by autophagy (Kurth et al. 2009). HSAN2C is caused by homozygous or compound heterozygous mutations in the *KIF1A* gene (*kinesin family member 1A*), encoding a motor protein responsible for anterograde axonal transport of synaptic vesicle precursors (Rivière et al. 2011). HSAN2D is caused by mutations in *SCN9A*, the sodium voltage-gated channel alpha subunit 9 (Cox et al. 2006).

HSAN3, also called familial dysautonomia (FD) is found almost exclusively in Ashkenazi Jews and is characterized by strong autonomic dysfunction including repeated episodes of vomiting, tachycardia, insomnia, and/or hypertension. It is explained by mutations in the *IKBKAP* gene which regulates the migration of projection neurons during development (Anderson et al. 2001; Slaugenhaupt et al. 2001).

HSAN4, also called congenital insensitivity to pain with anhidrosis (CIPA), is a complex disorder including the absence of pain sensation, anhidrosis, fever and mild intellectual disability. The *NTRK1* gene (*neurotrophic receptor tyrosine kinase 1*) is implicated. It encodes a receptor tyrosine kinase involved in the development and the maturation of the central and peripheral nervous systems through regulation of proliferation, differentiation and survival of sympathetic and nervous neurons (Indo et al. 1996).

HSAN5 is a rare subtype characterized by congenital insensitivity to pain, leading to ulcerations and self-mutilations of the distal extremities. Mutations in the *NGF* gene (*nerve growth factor*) have been identified (Einarsdottir et al. 2004). The NGF protein is important for the development and maintenance of the sympathetic and sensory nervous systems (Smeyne et al. 1994). It is the extracellular ligand of NTRK1 receptor, implicated in HSAN4.

HSAN6 has been first described by Edvardson et al. (2012), in one family of Ashkenazi Jewish descent with autosomal recessive HSAN. All patients had neonatal hypotonia with poor feeding and poor respiratory effort with apneic spells necessitating artificial ventilation. Features consistent with HSAN included alacrima and absent corneal reflexes with subsequent corneal scarring, decreased fungiform papillae, absent deep tendon reflexes, absence of an axon flare with intradermal histamine, recurrent hyperpyrexia, and episodic bradycardia or tachycardia with labile blood pressure. A homozygous truncating mutation in the *DST* gene (*dystonin*) was implicated and since then, several other families have been described with mutations in *DST*. The protein coded by *DST* is required for anchoring either intermediate filaments to the actin cytoskeleton in neural and muscle cells, or keratin-containing intermediate filaments to hemi-desmosomes in epithelial cells (Edvardson et al. 2012).

HSAN7 is an autosomal dominant subtype due to mutations in *SCN11A* (*sodium voltage-gated channel alpha subunit 11*), encoding the *Na(v)1.9* voltage-gated sodium channel (Leipold et al. 2013). *Na(v)1.9* is highly expressed in nociceptive neurons of dorsal root ganglia and trigeminal ganglia and is a major effector of peripheral inflammatory pain hypersensitivity. The clinical features in HSAN7 involve a congenital inability to experience pain since birth resulting in self-mutilations, slow-healing wounds, and multiple painless fractures. Patients might also have mild muscle weakness and delayed motor development. Insufficient activation of calcium ion channels would result in impaired neurotransmitter release at presynaptic nerve terminals to transmit pain signals to the spinal cord.

HSAN8 was first reported in 11 families with autosomal recessive congenital insensitivity to pain resulting in ulceration to the fingers, tongue, lips, and other distal appendages. Affected individuals may also have decreased sweating and tear production and ten different homozygous mutations were identified in the *PRDM12* gene (*PR/SET domain 12*) encoding a transcriptional regulator of the PRDM family. Prdm proteins are a family of epigenetic regulators that control neural specification and neurogenesis. It has been shown that *Prdm12* is expressed in nociceptors and their progenitors and participates in the development of sensory neurons in Xenopus embryos (Chen et al. 2015).

Recently, the involvement of several new genes has been described in rare autosomal recessive forms of HSANs: (1) *FLVCR1* (*feline leukemia virus subgroup C receptor 1*) gene, which encodes a broadly expressed heme exporter, in autosomal recessive sensory neurodegeneration with loss of pain perception (Chiabrando et al. 2016); (2) *TECPR2*, a positive regulator of autophagy, which functions as a molecular scaffold linking early secretion pathway and autophagy, in a new subtype of familial dysautonomia such as (FD-like) HSAN with intellectual disability (Heimer et al. 2016); (3) *ARL6IP1*, an ER-shaping protein required for neural crest development during embryogenesis, causes congenital insensitivity to pain, acromutilation and spastic paraplegia (Nizon et al. 2018); (4) *CCT5*, whose mutations cause autosomal recessive HSAN with spastic paraplegia (Bouhouche et al. 2006), encodes a subunit of the 950-kD chaperonin containing TCP1 complex (CCT), which is involved in the proper folding of cytoskeletal proteins.

In conclusion, around 20 genes are known to date to be implicated in this complex group of HSAN/HSN diseases (Table 1). They play different roles in the nervous system explaining the differences in the clinical features and disease characteristics. Several studies have screened the known candidate genes in additional patients, through dedicated sequencing panels, but did not identify any new causative mutation, suggesting that there are additional genetic causes of HSANs/HSN (Rotthier et al. 2009; Davidson et al. 2012). With the availability of next generation sequencing (NGS) techniques, more and more patients can benefit from whole-exome or even whole-genome sequencing, and variant databases are generated, such as the Genesis 2.0 database (Gonzalez et al. 2015). In addition, the availability of models close to human physiopathology and spontaneously developing HSAN can be of great help to unravel new genes and pathways in the physiopathology of these diseases.

The dog, a spontaneous model for human sensory neuropathies

Dogs as genetic models for human neuropathies

Similar to humans, hereditary sensory neuropathies are also diagnosed in dogs, usually reported by veterinarians as "acral mutilation syndromes" (AMS). The disease results in progressive mutilation of the distal extremities of the limbs; it can lead to toe loss and phalangeal fractures, similarly to HSANs. AMS is a rare condition in the dog general population, but few breeds are known to be at risk, due to the particular population structure of the canine species. Indeed, as a consequence of breeding practices (inbreeding and "popular sire effect"), many dog breeds are affected by specific genetic diseases, most often transmitted as autosomal recessive traits. To date, nearly 400 dog breeds are recognized by the international canine societies, such as FCI ("Fédération Cynologique Internationale") and AKC (American Kennel Club). High heterogeneity exists between breeds, while homogeneity is present within breeds, each representing a genetic isolate. Indeed, humans created breeds according to their needs and desires using a few studs carrying desirable traits. Unfortunately, mutations responsible for diseases were co-selected in this artificial selection process. Therefore, many breeds are severely affected by particular diseases and, as a breed descends from a few dogs, it is assumed that, generally, in a given breed, all affected dogs carry the same genetic defect. Moreover, due to the breeding practices and the consanguinity, the inheritance pattern is mostly monogenic recessive, comparable to disease affecting consanguineous human families (Galibert and André 2008; Ostrander et al. 2017). In recent years, many genetic diseases have been well characterized in dogs and, for some of them, the genetic causes have been identified and the implicated genes are identical in dogs and humans. Thus, the dog is now well recognized as a relevant spontaneous model of human diseases and its whole-genome sequence was published in 2005 (Lindblad-Toh et al. 2005) with successive annotations (Hoeppner et al. 2014; Wucher et al. 2017). In the past few years, several genetic analyses of dog diseases led to the identification of the same gene involved in the corresponding human disease. The discovery of a novel gene implicated in ichthyosis is a good example of the power of this natural model in genetics to identify genes involved in rare human diseases. Ichthyosis is characterized by abnormal desquamation over the whole body, described both in dogs and humans (Grall et al. 2012). Taking the Golden retriever breed as a spontaneous model, a mutation in the *PNPLA1* gene was first discovered in this breed, and then mutations were discovered in humans by screening the same gene in human families affected by the same type of ichthyosis. This gene was previously not known to be implicated in human ichthyoses, and both its function in the skin and its role in a human form of ichthyosis were discovered through the study in the affected Golden retrievers. Another example is the discovery of mutations in *CCDC39*, a novel gene involved in primary ciliary dyskinesia in old English sheepdog, which led to the identification of mutations in the same gene in human patients (Merveille et al. 2011). Many examples can be cited, strengthening the importance of genetic studies in dog for the discovery of new culprit genes in human rare genetic diseases. These studies also benefit dogs, by allowing the development of diagnosis and prediction genetic tests to improve dog's health. Thus, the dog appears to be a better spontaneous model for rare genetic diseases than classically used induced animal models, as it is closer to the clinical, physiological and genetic features of human diseases. In addition, performing genetic analyses in dogs, in the course of their health care, is fully in respect with the "3R rules" (replace, reduce and refine) for animal model management.

In this context, the Canine Genetics team has developed in the year 2000 the Cani-DNA biological resource centre (BRC) (http://dog-genetics.genouest.org). This BRC owns a national collection of canine biological samples, collected through a dedicated network (French practitioners, the four National Veterinary Schools, the animal genetic testing company Antagene, as well as specialized veterinary clinics and hospitals and veterinary histopathology and biology laboratories). Thanks to National and European fundings, Cani-DNA contains DNA samples from 20,000 canine blood samples and over 3000 tissue samples, as well as their clinical and pedigree data. To date, Cani-DNA contains the DNA samples of 50 dogs affected by sensory neuropathies (AMS), from 5 hunting dog breeds, Border collies, Doberman pinschers, Fox terriers and American Staffordshire terriers.

Classification of canine neuropathies

In dogs, sensory dysfunctions are difficult to detect, but owners can report abnormal gait and self-mutilation of the paws. Supplementary clinical examinations are necessary to exclude other causes for these symptoms. In the past, several dog breeds with few affected dogs have been reported to be affected by different types of neuropathies, with a suspected hereditary transmission (Coates and O'Brien 2004). A classification of such diseases was proposed by Granger in 2011. In this review, inherited motor and sensory neuropathies are differentiated from inherited sensory and autonomic neuropathies, which include automutilation syndromes cases (Granger 2011).

Compared to the human classification, canine-inherited motor and sensory neuropathies are close to Charcot-Marie-Tooth diseases, also termed hereditary motor and sensory neuropathies (HMSN), which are, as HSANs, a subgroup of human inherited peripheral neuropathies. Cases of both sensory or sensorimotor polyneuropathies have been reported in specific dog breeds with a higher frequency than in the general dog population, which led to the hypothesis of founder effects and unique genetic origins of each disease in each at-risk breed. Inherited sensory and autonomic neuropathies are less frequent than inherited motor and sensory neuropathies, as it is the case for humans HSANs. To date, reported canine cases are mainly polyneuropathies with sensory components. Advances were recently made in the genetics of canine neuropathies and their relevance for human genetics is presented here.

Potential new models of canine sensory neuropathies

The breeds predisposed to specific neuropathies, for which the genetic causes are still unknown, constitute interesting models for human neuropathies, with potentially new genes to discover (Table 2).

For the Doberman breed, the "dancing doberman disease" was described by Coates and O'Brien (2004). While a pedigree analysis with 19 related dogs indicated likely an autosomal recessive inheritance, the causal mutation has yet to be identified. Electron microscopy examination of a sensory nerve detected an almost complete absence of unmyelinated axons, which may explain the allodynia of these dogs (JMV personal communication). Similarly, for Long-Haired Dachshund cases, a sensory neuropathy was diagnosed (Duncan et al. 1982), but to our knowledge, no more cases were reported and no genetic cause has been identified yet.

Cases of peripheral neuropathies were described in other breeds, such as a case reported in a Great Dane presenting gastric dilatation, intestinal dysmotility, and one episode of gastric rupture: this was actually a case of autonomic neuropathy with severe loss of myelinated fibers (Spoo and Shelton 2014). A case of suspected inherited polyneuropathy was also described in a Chihuahua (Tsuboi et al. 2013). To our knowledge, no other cases were reported.

Concerning the Miniature Pinscher, a first case of AMS was described in 2011 in Spain (Bardagí et al. 2011). This case, a 18-month-old female, presented severe mutilations of the hind feet at 6 months of age. The neurological examination showed a diminished sensitivity to painful stimuli on the distal hind limbs. Following euthanasia of the dog, sampling of nervous tissues was performed. The authors concluded that the changes observed by microscopy were consistent with a sensory neuropathy. In the absence of other cases with a comparable clinical description in the breed, the authors did not conclude on possible breed predisposition for AMS. Through the Cani-DNA BRC, seven additional cases of Miniature Pinscher with AMS were collected from Spain, Italy and France. The main clinical symptoms reported are the same as those described in Bardagí et al. (2011), with age of disease onset varying between 5 months and 1 year, intense licking and biting of the limb leading to severe amputation. Therefore, the Miniature Pinscher breed appears as a relevant spontaneous model for human HSAN and additional DNA samples are being collected.

Concerning the Terrier group, a recently recognized motor and sensitive polyneuropathy has been characterized in American Staffordshire Terriers: 14 cases were examined and showed locomotor weakness with or without respiratory

Table 2 List of breeds presenting inherited sensory and autonomic neuropathies, for which no genetic mutation was yet identified

Breed	Age of onset	References
Doberman	6 months to 7 years	Coates and O'Brien (2004)
Long-Haired Dachshund	8–12 weeks	Duncan et al. (1982)
Great Dane	1–5 years	Spoo and Shelton (2014)
Chihuahua	21 months	Tsuboi et al. (2013)
Miniature Pinscher	5 months to 1 year	Bardagí et al. (2011)
American Staffordshire Terriers	Juvenile onset	Vandenberghe et al. (2018)
Jack Russell Terrier	Birth	Franklin et al. (1992)
Fox Terrier	Less than 1 year	This review

signs and juvenile onset. The clinical features are consistent with a degenerative polyneuropathy of genetic origin (Vandenberghe et al. 2018). Most recently, two cases of Fox terrier presenting similar clinical features including an automutilation syndrome were referred to the CaniDNA BRC. Both cases were diagnosed in their 1st year of age, the fingers and the pads being affected, with numerous ulcerations and loss of claws (Fig. 1). For the first case (Fig. 1a), the right front paw was first affected and strongly ulcerated. Even with a good follow-up the progression of the disease to other paws led to euthanasia at the age of 2. For the second case (Fig. 1b), the left rear paw was first affected and was finally amputated. Six months later, the other back leg became affected, leading to the euthanasia of the dog. An electroneuromyogram and motor and sensory nerve conduction velocities (EMG) along with sciatic nerve biopsies were performed. EMG was unremarkable; amplitudes of compound muscle action potentials and motor nerve conduction velocities were within usual limits, similar to sensory conduction velocities. We observed a mild decrease of sensory potential amplitudes, which is usually difficult to obtain in dogs. Electron microscopy of the sciatic nerve showed quantitative and qualitative alterations of small fibers leading to the diagnosis of peripheral neuropathy, involving selectively small myelinated fibers and unmyelinated fibers (Fig. 2). The number of unmyelinated fibers was half the count of the control dog: a mean of 53,624/mm^2 in the control dog and a mean of 20,887/mm^2 in the affected dog ($p = 0.0007$) (Table 3). Samples from other Fox terriers of the same family, as well as unrelated, affected and unaffected, are being collected to conduct further genetic analyses. It is worth noting that over 25 years ago, a case of sensitive polyneuropathy was described in a Jack Russell terrier (Franklin et al. 1992), and it might be the same disease in these two close breeds.

Thus, such at-risk dog breeds (Table 2) constitute interesting models that could lead to the identification of new genes in dogs, as relevant candidates for human HSAN/HSN.

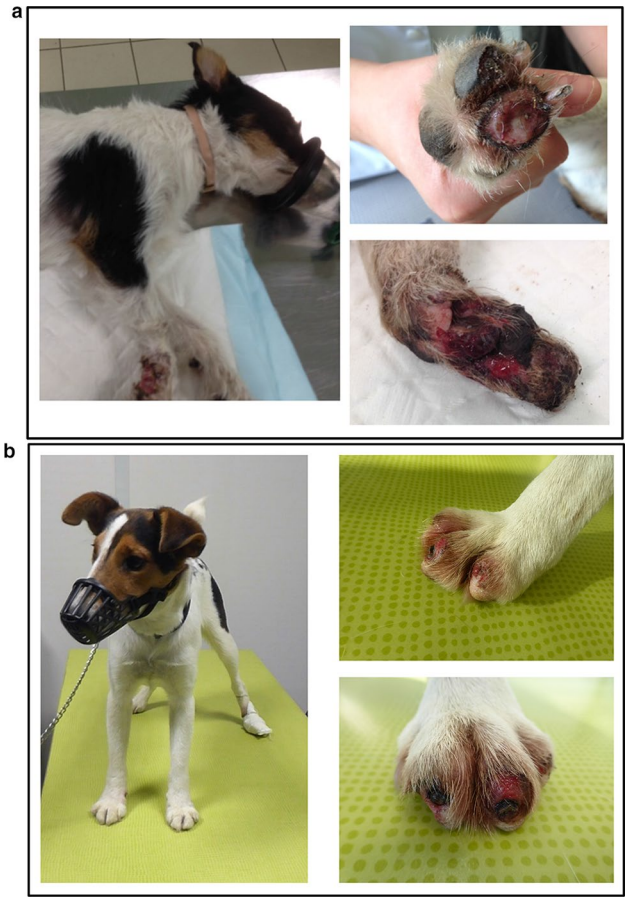

Fig. 1 Pictures of the two Fox terrier cases affected by AMS. **a** Case 1: at diagnosis at 7 months, the right front paw was severely affected with ulcerated pads, as shown on the upper right picture. The disease progressed to a dramatic self-mutilation with loss of phalangia, claws and pads as shown on the lower right picture. **b** Case 2: at diagnosis in its 1st year of age, the left rear paw was affected with loss of claws, as shown on the right pictures. To prevent the dog from self-mutilation, he had to wear a muzzle. However, the disease quickly progressed and the dog was amputated 5 months later. Pictures of case 1 from Dr. E. Orain; pictures of case 2 from Dr. C. Mège

Models of canine neuropathies with a known genetic cause

Advances were recently made in canine genetics of peripheral neuropathies and their relevance for human genetics is presented here.

Breed-specific polyneuropathies

Similar symptoms of peripheral polyneuropathy were described in Alaskan malamutes and Greyhounds, showing comparable symptoms. Alaskan malamute presented voice changes and/or noisy breathing. Symptoms evolved to gait abnormalities, exercise intolerance, and noise during respiration, suggesting the presence of laryngeal paresis or paralysis (Bruun et al. 2013). Greyhounds presented also exercise intolerance, walking difficulties and later severe muscle atrophy, ataxia and dysphonia (Drögemüller et al. 2010). Ages of disease onset were comparable (from the age of 3 to 19 months for the Alaskan malamute; between 3 and 9 months for the Greyhound). In both dog breeds, mutations were identified in the *NDRG1* gene (*N-myc downstream regulated 1*): a G–T point mutation for Alaskan malamutes and a 10 bp deletion for the Greyhounds. In humans, *NDRG1* is the causative gene for an autosomal recessive demyelinating form of Charcot-Marie-Tooth disease, called 'CMT4D' (OMIM 601455) (Kalaydjieva et al. 2000), or 'AR-CMTde-*NDRG1*' (Nomenclature from Mathis

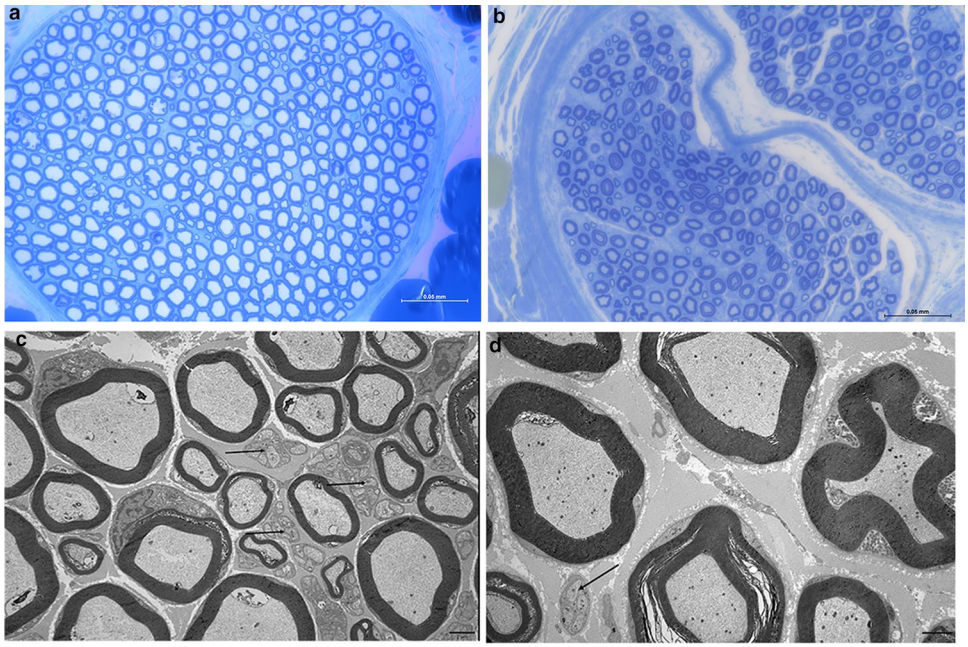

Fig. 2 Transversal sections of sciatic nerve from one control dog and one dog affected by AMS. Semi-thin sections from a control dog (age matched) (**a**) and from a Fox terrier affected by AMS (**b**). Electron microscopy from a control dog (**c**) and from a Fox terrier affected by AMS (**d**). Arrows indicate unmyelinated fibers which are almost completely absent in **d**

Table 3 Count of myelinated and unmyelinated fibers in a normal dog and a Fox terrier dog affected with acral mutilation syndrome (AMS), showing a 50% significant decrease of unmyelinated fibers (p value < 0.005)

	Control dog	Affected dog	t test
Myelinated fibers			
Total myelinated fibers	9949/mm^2	6871/mm^2	$p=0.02$
Small myelinated fibers	4436/mm^2	2481/mm^2	$p=0.04$
Unmyelinated fibers	53,624/mm^2	20,887/mm^2	$p=0.0007$

Counts were obtained on serial slides of nerve biopsies on semi-thin sections and by electron microscopy (nerve fibers were manually counted by using the ImageJ 1.50i software)

et al. 2015). Patients with CMT4D develop a sensorimotor polyneuropathy usually characterized by distal motor deficit leading to gait impairment in the first decade, followed by a proximal deficit in the 2nd decade; nerve biopsies show typical signs of demyelination, axonal loss and pleiomorphic deposits in the adaxonal space (Ricard et al. 2013).

Another breed, the Leonberger, presents at least two different forms of polyneuropathies with comparable clinical symptoms but different ages of onset. The main clinical symptoms are generalized weakness, decreased tendon reflexes and laryngeal paralysis. The severe form with a early-onset disease was associated with an homozygous *ARHGEF10* deletion (*Rho guanine nucleotide exchange factor 10*) (Ekenstedt et al. 2014). *ARHGEF10* had not yet been implicated in human neuropathies, but is nonetheless included in some gene panels for diagnosis (Høyer et al. 2014). An other form observed in Leonberger, with a later age of onset, was associated with a frameshift variant in the *GJA9* gene (*gap junction protein alpha 9*) (Becker et al. 2017). *GJA9* encodes connexin 59 and mutations in *GJB1*, encoding connexin 32, are causing CMT1B, a frequent cause of CMT in human. To our knowledge, *GJA9* is not yet implicated in human neuropathies (Abrams and Scherer 2012) and thus constitutes a good candidate gene for human neuropathies.

A juvenile-onset polyneuropathy was reported by Granger (2011) in two Black Russian terriers. The main clinical symptoms are laryngeal paralysis, microphthalmia and proprioceptive ataxia. Genetic analyses led to the identification of the causal mutation: a 1 bp deletion in the *RAB3GAP1* gene (*Rab3 GTPase-activating protein catalytic subunit*) (Mhlanga-Mutangadura et al. 2016). This gene is implicated in Warburg microsyndrome in humans (OMIM 600118), which include eye abnormalities and other neurological symptoms (brain malformations, progressive axonal peripheral neuropathy, muscular dystrophy, etc.) (Handley et al. 2013).

Breed-specific sensory autonomic neuropathies

The Border Collie breed is affected with a progressive proprioceptive ataxia with self-mutilation with an age of onset between 2 and 7 months (Harkin et al. 2005; Vermeersch et al. 2005) (Table 4). A case with suspected hereditary polyneuropathy was also described by Tsuboi et al. (2013). The neuropathy in this breed was afterwards classified as a sensory and autonomic neuropathy and an inversion disrupting the *FAM134B* gene has been identified through whole genome sequencing of one case (Forman et al. 2016). As presented previously, *FAM134B* was already implicated

Table 4 List of breeds presenting inherited sensory neuropathies, for which the implicated genes are known

Breed	Age of onset	Implicated gene	References
Border collie	2–7 months	*FAM134B*	Vermeersch et al. (2005) Tsuboi et al. (2013) Forman et al. (2016)
French spaniel German short-haired pointer English pointer English springer spaniel English cocker spaniel	4 months	*GDNF*	Paradis et al. (2005) Plassais et al. (2016) Correard et al. (2017)

in human HSAN2B. In fact, in humans, *FAM134B*-related disorder (OMIM 613115) combines a mutilating hereditary sensory neuropathy (early childhood onset of distal sensory impairment and variable autonomic features) and spastic paraplegia (Aydinlar et al. 2014).

Four hunting dog breeds (French spaniel, German short-haired pointers, English pointers and English springer spaniel) were found to be affected with insensitivity to pain often leading to self-mutilation (Cummings et al. 1981; Paradis et al. 2005) (Table 4). The age of onset varies from 2 to 12 months with an average of 4 months. Clinical signs consist of sudden intense licking, biting and severe self-mutilation of one or several feet. If affected dogs are not restrained, auto-amputation of claws, digits and footpads usually occurs. GWAS and targeted sequencing of 24 affected and 30 unaffected hunting dogs from both France and Canada led to the identification of a mutation (chr4.g.70,875,561 C>T), located ~90 kb upstream of the *Glial-cell Derived Neurotrophic Factor gene* (*GDNF*), in an intergenic region with genetic marks corresponding to a regulatory region (Plassais et al. 2016; Correard et al. 2017). This mutation was shown to be absent in 900 unaffected dogs from 130 other breeds, thus strengthening its pathogenic role. A decrease of *GDNF* expression in Dorsal Root Ganglia (DRG) of affected dogs compared to DRG of unaffected dogs was shown, thus implicating a default of *GDNF* regulation in the dogs' disease (Plassais et al. 2016). These findings led to the development of a genetic test for hunting dog breeds and the last reports indicated that, based on 250 tested hunting dogs from French spaniels and English Springer spaniels breeds, 5% and 1%, respectively, are homozygous for the mutated allele localized in *GDNF* regulatory region; 31% and 17% are heterozygous, and 64% and 82% are homozygous for the wild-type allele, indicative of a frequency of the *GDNF* mutated allele of 20% and 10% in the French spaniels and the English springer spaniels, respectively. In addition, dogs from other related hunting breeds have been tested for the *GDNF* mutation and the English cocker spaniel was found to carry the mutation and to present the disease. Out of 1300 English cocker spaniels, 2% are homozygous for the mutated allele and 16% are heterozygous, indicating a frequency of the mutation of 10% for the *GDNF* mutation in this breed (data provided by Antagene, La tour de Salvagny, France).

GDNF is a neurotrophic factor essential for the development and maintenance of sensory neurons, and its regulation was already implicated in neurological diseases implicating the autonomic system such as Parkinson's disease (Hunot et al. 1996; Bäckman et al. 2006). It was previously shown that transgenic mice, which do not express *GDNF* transcript ($gdnf^{-/-}$ mice) died 1–1.5 days after birth, whereas heterozygous mice were normal in size and indistinguishable from wild-type littermates (Moore et al. 1996). From these observations, and experiments on this gene, Ibáñez and Andressoo (2017) confirmed its relevance as a candidate gene for neurological disorders in humans.

Conclusion

The dog was previously shown to be a relevant spontaneous model for the identification of genes implicated in human diseases, especially for rare human diseases for which the related diseases are frequent in a given dog breed. Success stories have been published for several dermatological diseases, such as ichthyosis (Grall et al. 2012), keratoderma (Drögemüller et al. 2014; Plassais et al. 2015), acrodermatitis (Bauer et al. 2018) and for neurological diseases, such as epilepsy (Lohi et al. 2005; Seppälä et al. 2011; Koskinen et al. 2015) and hereditary sensory neuropathies (Table 4). Owing to strong genetic founder effects, the genetic analyses of affected dog breeds allowed the identification of new disease genes, which represented excellent candidate genes for the related human diseases. These genes were then proved to be involved in human, thereby allowing improved diagnosis and therapy for both human and veterinary medicine. In rare human diseases, the genetic causes might be really challenging to identify, due to the small number of patients and the large list of candidate variants identified after NGS experiments. Indeed, in rare diseases, the selection of genetic variants from NGS data and diagnosis panels constitute a real challenge. HSANs, as many other neurological diseases, may present complex genetic forms, involving accumulation

of unknown variants, rare variants or even common variants, acting with other genetic or epigenetic changes to induce the disease. We do hope that the clinical, physiopathology and genetic characterization of neuropathy-affected dog breeds will serve as HSAN/HSN models for human medicine and also for veterinary medicine to provide diagnosis and prediction genetic tests to diminish the disease frequency in affected breeds.

Thus, the availability of natural animal models, such as dogs, represent opportunities to unravel genetics and therapies for humans and for dogs themselves, in the frame of the one health comparative medicine and fully in respect of the 3R rule (replace, reduce, refine) for a better management of animal models.

Acknowledgements The authors are grateful to dog owners who donated samples and follow-up of their dogs and to French referring veterinarians, especially Dr. Christian Collinot, Pr. Marie-Christine Cadiergues (Université de Toulouse, ENVT) and Dr. Frédérique Degorce (Veterinary Diagnostic Laboratory LAPVSO). We particularly thank Dr. Sophie Cognard (Clinique Vétérinaire «Les grands crus» Chenôve, France), Dr. Elodie Orain (Clinique Vétérinaire "La prairie", St Amand Montrond, France) and Romain François (MICEN-Vet, Créteil France) for clinical data and sampling blood and tissue samples. We do thank Dr. Edouard Cadieu (IGDR) and the Cani-DNA CRB (http://dog-genetics.genouest.org), which is part of the CRB-Anim infrastructure, ANR-11-INBS-0003. We thank Antagene (Animal genetics laboratory, La Tour de Salvagny, France), especially Caroline Dufaure de Citres and Guillaume Queney, for sharing statistical data of the dog AMS genetic tests. We also thank Pr. Sylvie Odent (CHU Rennes) and Pr. Eric Leguern (ICM, Pitié Salétrière, Paris) for helpful discussions and advices.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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