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HSAN-VI

A spectrum disorder based on dystonin isoform expression

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Abstract

Hereditary sensory and autonomic neuropathy (HSAN-VI) is a recessive genetic disorder that arises because of mutations in the human dystonin gene (*DST*, previously known as *bullous pemphigoid antigen 1*). Although initial characterization of HSAN-VI reported it as a sensory neuropathy that was lethal in infancy, we now know of a number of heterozygous mutations in *DST* that result in milder forms of the disease. Akin to what we observe in the mouse model *dystonia musculorum* (Dst^{dt}), we believe that the heterogeneity of HSAN-VI can be attributed to a number of dystonin isoforms that the mutation affects. Lack of neuronal isoform dystonin-a2 is likely the universal determinant of HSAN-VI because all reported human cases are null for this isoform, as are all Dst^{dt} mouse alleles. Compensatory mechanisms by intact dystonin-a isoforms also likely play a role in regulating disease severity, although we have yet to determine what specific effect dystonin-a1 and dystonin-a3 have on the pathogenesis of HSAN-VI.

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Glossary

BPAG1 = bullous pemphigoid antigen 1; **HSAN** = hereditary sensory and autonomic neuropathy.

The human dystonin gene (*DST*, also known as bullous pemphigoid antigen 1 [*BPAG1*]) consists of 496 kb located on the short arm of chromosome 6. The *DST* gene is fairly complex in that various tissue-specific promoters yield epithelial- (dystonin-e/BPAG1e), neuronal- (dystonin-a/BPAG1a), and muscle-specific (dystonin-b/BPAG1b) isoforms, whereas alternative splicing of the neuronal and muscle isoforms further produce 3 unique proteins termed dystonin-a1/b1, dystonin-a2/b2, and dystonin-a3/b3 (figure).[1] Since the dystonin proteins belong to the spectraplakin family of proteins,[2,3] they function as cytoskeletal linkers responsible for maintaining structural integrity and mediating processes such as intracellular trafficking.[4–6] Considering the large size of the human *DST* gene, it should be susceptible to mutations over time, which would eventually manifest to some observable phenotype. However, the complete lack of any reported human cases had suggested that any *DST* mutation was likely embryonic lethal.

In 2004, the first instance of a *DST* gene disruption associated with a disease phenotype was described in a female child with a 6; 15 chromosomal translocation.[7] The breakage point occurred toward the 3′ end of *DST* and was predicted to affect only dystonin-a and dystonin-b isoforms. The patient presented with esophageal atresia, and through development she would exhibit severe motor and intellectual disability, nonprogressive encephalopathy, and delayed visual maturation. Her second chromosome 6, however, was unaffected by the translocation and would still express full-length dystonin-a and dystonin-b transcripts. In an attempt to explain her clinical presentation, it was suggested that either haploinsufficiency of *DST* was enough to cause pathology or that truncated dystonin-a/b interrupted function of the full-length protein leading to manifestation of symptoms.[8]

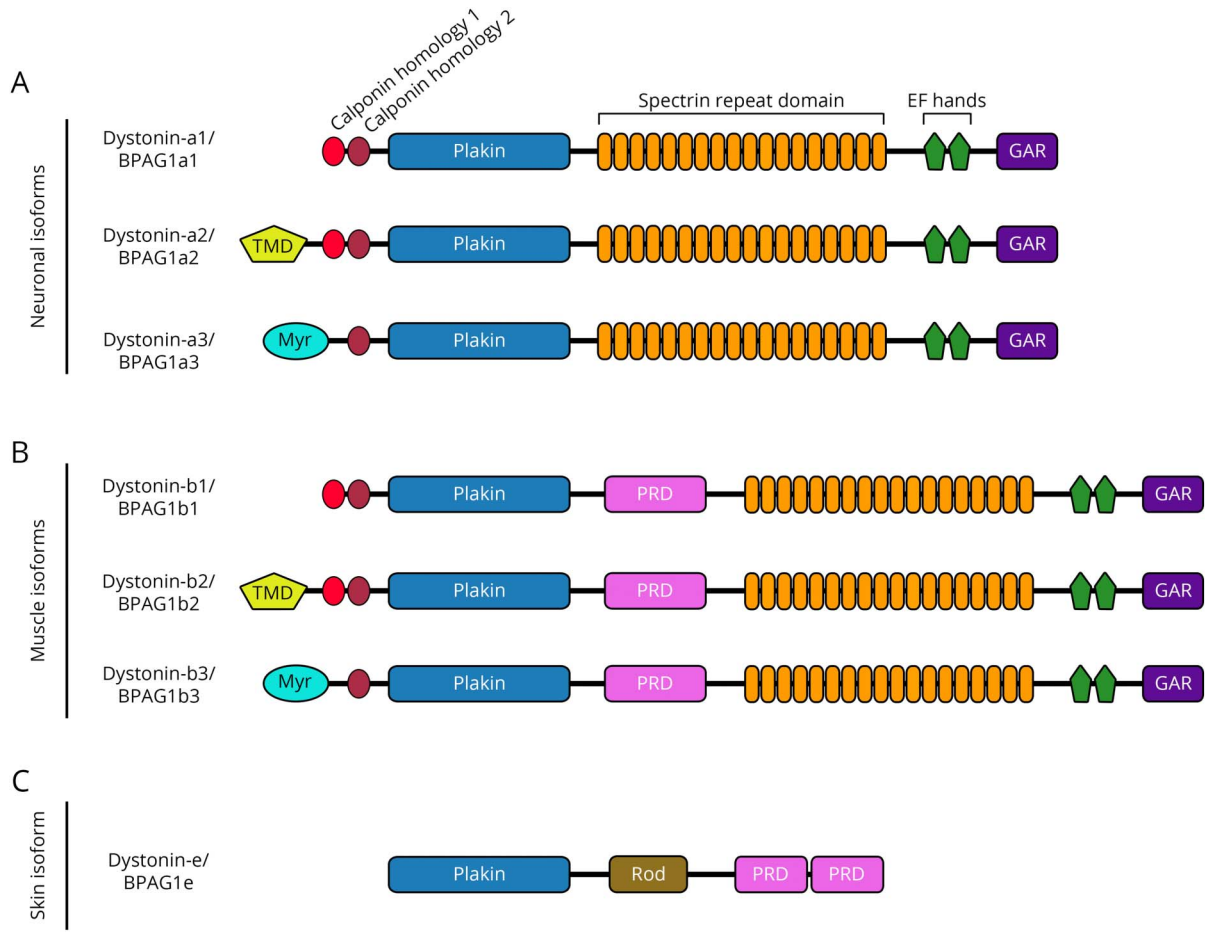
A few years later, a case of epidermolysis bullosa simplex was discovered to be caused by homozygous mutations affecting *BPAG1*/*DST*.[9] The mutation resulted in a disruption of the coiled-coil rod domain of the protein, which is specific to only the skin dystonin-e isoform. This individual was reported to have spontaneous skin blistering and erosion, as well as mild neurologic features (weakness, numbness, and headaches). Subsequent reports of individuals with the same *DST* mutations would show that only skin defects were common between these patients.[10] The neurologic features described in the initial case were instead proposed to be caused by heterozygous *NOTCH3* mutations.

In 2012, homozygous mutations in the human *DST* gene were discovered to be associated with a severe phenotype that shared many features with a subset of genetic disorders termed hereditary sensory and autonomic neuropathies (HSANs).[11,12] Three infants from 2 consanguineous families from Ashkenazi Jewish background presented with dysautonomic symptoms, distal contractures, motionless open-mouthed facies, and severe psychomotor retardation (tables 1 and 2).[13] Ultimately, all 3 patients would die around the age of 2 years from cardiopulmonary events, likely related to poor autonomic control. Also of note was that a second pregnancy for 1 of the families was aborted at 21 weeks because of signs of the same disease as its sibling. The underlying mutation in these patients was determined to be a frameshift occurring at Glu4955, which leads to the loss of 502 amino acids at the C-termini microtubule-binding domain. Because this domain is common to all dystonin-a and dystonin-b splice variants, it effectively ablates expression of the predominant neural and muscle isoforms. Considering that the disease presentation shared many clinical features such as HSAN-III (also named familial dysautonomia), although more severe, this newly identified disorder was termed HSAN-VI.

In 2017, we then learned that homozygous *DST* mutations do not exclusively produce a disease phenotype that is lethal in infancy since 2 separate studies described *DST* mutations in adolescent and adult patients. The first of these studies that was published identified 3 siblings from a nonconsanguineous family from southern Italy as having 2 heterozygous compound mutations in the *DST* gene, which affected the expression of dystonin-a2 and -b2 isoforms.[14] These patients exhibited impaired pain sensitivity and distal ulcerations from infancy, weakness of intrinsic foot muscles, and a number of autonomic disturbances including heat intolerance, problems with sweating, pupillary abnormalities, chronic diarrhea, and sexual dysfunction (tables 1 and 2). The other study identified a female patient with both skin and neuronal phenotype, which resulted from compound heterozygous mutations in *DST* affecting exon 7 (specific to dystonin-a1, and -a2) and exon 29 (common to dystonin-e, dystonin-a, and dystonin-b isoform).[15] She presented with chronic diarrhea, iris heterochromia, bilateral cataracts, syringomyelia from D3-D8, bilateral sensorineural hearing loss, pain insensitivity, skin blistering, and behavioral problems such as avoidant/restrictive food intake disorder, obsessive compulsive disorder, and anxiety (tables 1 and 2).

Most recently, a 2018 study identified 3 elderly siblings from an Italian family with biallelic *DST* mutations ablating dystonin-a2/b2 expression also causing dystonin-a1/b1 and dystonin-a3/b3 haploinsufficiency.[16] These patients recall experiencing dysautonomic symptoms in childhood, and between the ages of 20–40 years, they would present with painless fractures, osteomyelitis, joint deformities, and diabetes mellitus type II (tables 1 and 2).

Figure Schematic of the predominant DST isoforms



Neuronal (A) and muscle (B) dystonin isoforms possess actin binding domains at their N-termini made of calponin homology domains, and C-termini microtubule binding domains made of EF-hands and a GAR domain. Muscle isoforms however, are much larger in size (834 kD, compared with neuronal dystonin 615 kD) as they also contain a central plakin repeat domain, located between the plakin and spectrin repeat domains that the 2 tissue-specific isoforms share in common. The differences in splice variants is largely restricted to the N-termini, whereby dystonin-a/b1 contains an actin binding domain, dystonin-a/b2 has a transmembrane domain preceding the actin binding domain, and dystonin-a/b3 contains a putative myristoylation motif that precedes a single calponin homology domain (bestowing a reduced affinity for actin compared with the other isoforms). (C) The skin epithelial isoform dystonin-e is smaller in size (302 kD) and is made up of an N-terminus plakin domain, a rod domain that is unique to this isoform, followed by 2 plakin repeat domains that are involved in intermediate filament binding. TMD = transmembrane domain; myr = myristoylation domain; GAR = growth arrest-specific 2 related domain; PRD = plakin repeat domain; Rod = coiled-coil rod domain. Note that the figure is not drawn to scale.

It has only been over the past few years that we have observed the first human cases of *DST* mutation, leading to its classification as HSAN-VI, a lethal form of sensory neuropathy. Through the identification of adult patients with deleterious *DST* mutations, this definition would expand to categorize HSAN-VI as a spectrum disorder, with severity being determined by which isoforms are affected. With a growing awareness of HSAN-VI, we can expect to observe the number of reported cases to increase in the coming years.

Discovery of neuronal dystonin isoforms

Before the identification of the human disease HSAN-VI,[13] the dystonin gene and its resulting protein had long since been studied in a murine model known as the *dystonia musculorum* (Dst^{dt}) mouse.[17–21] In 1963, the Dst^{dt} mouse that arose by spontaneous mutation at The Jackson Laboratory was first described.[18,21] Severe ataxia and dystonic postures were the major phenotypic characteristics, which were also associated with significant sensory neuron degeneration. Although the underlying genetic mutation was not identified at the time, the disease was predicted to be caused by autosomal recessive mutation. In 1995, 2 separate lines of work led to the identification of the *BPAG1/Dst* gene as the causative agent for the Dst^{dt} disease.[20,22] While studying the hemidesmosomal skin protein BPAG1, generation of a BPAG1 knockout mouse unexpectedly produced the ataxic and dystonic phenotype associated with the Dst^{dt} mouse.[22] In parallel, definitive evidence came from cloning experiments identifying the gene that was disrupted by the insertion of an *hsp68-LacZ* transgene, which resulted in mice bearing the Dst^{dt} phenotype.[19,20] Ultimately, crossbreeding heterozygous mice from this line

Table 1 Genetic comparison of the various patients with HSAN-VI

			DST Isoforms predicted to be present			
	Family Background	**Variant type**	**DST-e**	**DST-a/b1**	**DST-a/b2**	**DST-a/b3**
Edvardson et al.[13]	Consanguineous Ashkenazi Jewish	Frameshift deletion c.14865delA (exon 86) leading to loss of microtubule-binding domain	+	−	−	−
Manganelli et al.[14]	Nonconsanguineous southern Italian	Compound heterozygote—allele 1 c.687+1 G > A and allele 2 c.616C>T (exons 4 and 5); both disrupt the N-terminal transmembrane domain of DST-a/b2	+	+	−	+
Cappuccio et al.[15]	Nonconsanguineous	Compound heterozygote—allele 1 c.806A>G and allele 2 c.3886A>G (exons 7 and 29). Allele 1 disrupts N-terminal of DST-a/b1 and -2 isoforms, whereas allele 2 likely disrupts the plakin domain of all DST isoforms	+/−	−	−	+/−
Fortugno et al.[16]	Nonconsanguineous Italian	Compound heterozygote - allele 1 c.608C>A and allele 2 c.12988A>T (exons 4 and 70). Allele 1 disrupts DST-a/b2 N-terminal region, Allele 2 truncates DST-a/b within spectrin repeat domain	+	+/−	−	+/−

+/− = haploinsufficient; HSAN = hereditary sensory and autonomic neuropathy.

and the BPAG1 knockout line onto The Jackson Laboratory Dst^{dt} line revealed that these mice were allelic, and thus, their mutations mapped to the same genetic locus. This indicated that the gene responsible for producing the BPAG1 skin protein was also responsible for producing the neuronal dystonin protein underlying Dst^{dt} pathology.[19,23]

Subsequent studies would later propose splice variants of neuronal dystonin that were predicted to interact with intermediate filaments (termed BPAG1n), much like how the epithelial isoform dystonin-e interacts with keratin filaments in skin. It was hypothesized that loss of these BPAG1n isoforms was responsible for the neurologic phenotype of the Dst^{dt} mice.[24] However, in 2001, a study evaluating BPAG1 isoform expression in mice found that BPAG1n messenger RNA went completely undetected in neural tissue.[1] This led to the discovery of the larger, more prominently expressed neuronal and muscle isoforms: dystonin-a and dystonin-b, respectively.

In the years to come, these neuronal- and muscle-specific splice variants would also be identified (figure). Elucidating the roles of the neuronal-specific splice variants would become the focus, considering that sensory neurons are the major cell type affected in the Dst^{dt} mice. However, the major challenge of studying dystonin and its various isoforms lies in the fact that the protein is remarkably large (dystonin-a = 615 kDa, dystonin-b = 834 kDa) and shares high amino acid sequence similarity between the isoforms.[1,25,26] This has made the development of Dst antibodies an incredibly arduous task, and as such, there are currently no reliable isoform-specific antibodies available. Much of what we have learned about the functions of the individual isoforms has come from in vitro experiments using small interfering RNA knockdowns and fusion protein constructs, as well as in vivo examination of the Dst^{dt} alleles that differ in the nature of their mutations and thus in the isoforms affected.

What the Dst^{dt} alleles can tell us about HSAN-VI heterogeneity

By comparing the *DST* mutations identified in the individuals with HSAN-VI, the commonality among the cases is that dystonin-a2 is absent. From what we know through studies on Dst^{dt} mice and through knockdown experiments on immortalized cells, dystonin-a2 is the most crucial isoform for neuronal functioning since its loss is associated with the most profound and lasting defects to intracellular pathways.[4,25,27,28] We have also observed a moderate rescuing effect when dystonin-a2 is partially restored to neurons in $Dst^{dt\text{-}Tg4}$ mice, which lack both dystonin-a/b1 and -a/b2.[25] These mice have significantly longer lifespans and show improvements in many pathways that are normally defective in the $Dst^{dt\text{-}Tg4}$ mice.[29] The results provided by the Dst^{dt} mouse experiments strongly suggest that dystonin-a2 is the major determinant for disease. Supportive evidence for this comes from the patients described in the earlier 2017 HSAN-VI study.[14] The affected siblings have a milder form of HSAN-VI that continues into adulthood and is associated with mutations affecting only the neuronal dystonin-a2 isoform (dystonin-b2 is also likely affected, although muscle defects are not primary disease features). It therefore seems highly likely that disrupted expression of dystonin-a2 is both necessary and sufficient to produce HSAN-VI. However, mutations affecting only

Table 2 Symptom comparison of the various HSAN-VI patients

	Gender	Skin defects	Bone/joint defects	Neurologic symptoms	Dysautonomic symptoms	Other	Cause of death	Age at onset
Edvardson et al.[13]								
Patient 1	F	Blotching	Distal contractures	Severe psychomotor retardation, absent deep tendon reflex	Absent tearing, feeding and breathing difficulties	Motionless, open mouth facies; early death (<2 y/o)	Cardiopulmonary arrest	Birth
Patient 2	M						Severe apneic episode	
Patient 3	F						Cardiopulmonary arrest	
Fetus 1	N/A	N/A	Bilateral club feet and hand clenching	N/A	N/A	Aborted	N/A	N/A
Manganelli et al.[14]								
Patient 4	M	Distal ulcers	Joint deformities, distal amputations	Pain insensitivity, impaired touch and vibration sensitivity, altered deep tendon reflex	Hypohidrosis and heat intolerance, chronic diarrhea	Weakness in intrinsic foot muscles	N/A	Infancy
Patient 5	M		Joint deformities, distal amputations		Hypohidrosis and heat intolerance, chronic diarrhea, pupillary abnormalities, erectile dysfunction			
Patient 6	M		Distal amputations		Hypohidrosis and heat intolerance, chronic diarrhea, pupillary abnormalities			
Cappuccio et al.[15]								
Patient 7	F	Recurrent blistering, peeling, ulcers, atrophic scars	Osteoporosis	Bilateral sensorineural hearing loss, pain insensitivity, headaches, behavioural disorders	Chronic diarrhea, abdominal pain	Iris heterochromia, cataract, syringomelia	N/A	4 mo
Fortugno et al.[16]								
Patient 8	M	Ulcers	Painless fractures, recurrent septic osteoarthritis, joint deformities, toe amputations	Severe pain insensitivity, symmetric sensorineural hearing loss, altered deep tendon reflex	Hyperhidrosis and heat intolerance, pupillary abnormalities, urinary incontinence	Type II diabetes, general muscle weakness	N/A	37 y/o
Patient 9	M		Painless fractures, recurrent septic osteoarthritis, joint deformities, toe amputations	Altered deep tendon reflex, reduced pain sensation	N/R			N/R

Continued

Table 2 Symptom comparison of the various HSAN-VI patients *(continued)*

	Gender	Skin defects	Bone/joint defects	Neurologic symptoms	Dysautonomic symptoms	Other	Cause of death	Age at onset
Patient 10	F	Ulcers	Painless bone fractures, osteomyelitis, toe amputations	Severe pain insensitivity, altered deep tendon reflex	Hypohidrosis and heat intolerance, xerophthalmia, xerostomia, vaginal dryness	Type II diabetes, general muscle weakness	N/A	Childhood

HSAN = hereditary sensory and autonomic neuropathy; N/R = not reported.

dystonin-a1 or dystonin-a3 have not been described in humans or in the Dst^{dt} mouse models, and we therefore do not know to what extent these isoforms contribute to disease etiology. It may be that mutations in either of these isoforms do not result in any major clinical pathology, which could explain the absence in reported cases. In addition, isoform compensation may be a mechanism that could be involved in masking these mutations, as we recently observed this phenomenon in the $Dst^{dt\text{-}Tg4}$ mice.[30] Because these mice retain dystonin-a3, we saw a significant upregulation of this isoform in neural tissues most affected by dystonin loss of function. This upregulation was associated with maintenance of microtubule stability in sensory neurons (a function previously unknown to this isoform), which was reversed on loss of transcript overexpression.[30] This pattern of upregulation is consistent with dystonin-a3 compensating for the loss of dystonin-a1 and -a2. Thus, it is reasonable to believe that each of the dystonin-a isoforms possesses the ability to modify its normal function and substitute for an absent or nonfunctional isoform. Nevertheless, future work involving isoform specific knockouts is still needed to conclusively determine the role of each isoform in HSAN-VI pathogenesis.

Seeing as *DST* mutations can result in a milder form of HSAN-VI expanding into adulthood, HSAN-VI should be recognized as a spectrum disorder whereby severity of the disease may be predicted based on the isoforms affected. Of interest, the Dst^{dt-27J} mice, which are completely null for all neuronal isoforms of dystonin, present with the most severe phenotype (ataxic affecting all limbs and dystonic postures) and have the shortest lifespan.[26,30] This Dst^{dt-27J} allele would most closely resemble the first group of very severe patients with HSAN-VI.[13] The adolescent girl described in the later 2017 HSAN-VI study may be the most severe one among the adult patients with HSAN-VI.[15] Her genotype would mostly resemble $Dst^{dt\text{-}Tg4}$ or $Dst^{Gt(E182H05)Wrst}$ alleles because she lacks both dystonin-a1 and -a2[26,31] but is haploinsufficient for dystonin-a3. Although her symptoms are not identical to the other adult patients with HSAN-VI, her younger age may indicate that these symptoms are yet to develop. She does, however, have a number of unique symptoms including iris heterochromia, cataracts, syringomyelia from D3-D8, osteoporosis, headaches, and behavioral problems (anxiety, obsessive compulsive disorder, and avoidant/restrictive food intake disorder), suggesting potential roles for dystonin-a1 and -a2 in these systems. Retention of the dystonin-a/b3 isoforms might also contribute to her longer lifespan compared with the dystonin-a/b null infants. She also experienced skin blistering, which was hypothesized to be because of dystonin-e haploinsufficiency. However, considering the presence of skin ulceration and a lack of dystonin-e isoform involvement in the other adult patients with HSAN-VI, it is likely that her skin blisters are due to peripheral neuropathy leading to skin damage going unnoticed. Furthermore, heterozygous Dst^{tm1EFu} mice (dystonin knockouts) do not display skin symptoms and have intact hemidesmosomes at the dermoepidermal junction.[22] Thus far, the 3 siblings described in the earlier 2017 study likely represent the mildest form of HSAN-VI because they only have dystonin-a2/b2 isoforms affected. With coming age, patients with HSAN-VI may develop new symptoms indicating novel roles of dystonin isoforms that would never have been characterized in the Dst^{dt} mice due to limitations such as short lifespan and objective measures. As more individuals with *DST* mutations are identified and as we continue our investigation of affected tissues and mechanisms in the Dst^{dt} mice, we hope to gain a better understanding of how each isoform contributes to disease.

Moving forward

With the recent identification of adult patients with deleterious *DST* mutations, it has become clear that HSAN-VI can present on a spectrum based on which neuronal dystonin isoforms are affected. Current evidence indicates that dystonin-a2 is the most important factor dictating development of HSAN-VI. Although to further advance our knowledge of what roles the other neuronal dystonin isoforms play in the development of HSAN-VI, if any, dystonin-a1 and -a3 should be independently assessed. As isoform compensation is a mechanism that potentially modulates disease presentation, expression levels of remaining isoforms should also be evaluated. Although many HSAN-VI symptoms have been accurately predicted by the Dst^{dt} mice, the short lifespan of these mice is a major limitation for addressing how dystonin loss of function affects adult patients with HSAN-VI. In addition, considering the diverse expression pattern of dystonin-a across tissues, this suggests there are many more

roles for the dystonin isoforms that have yet to be characterized. Further evaluation of these patients with HSAN-VI and identification of novel *DST* mutations will be pivotal in our understanding of the biological roles of the dystonin isoforms and how they relate to pathogenesis.

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