Phenomenology, Genetics, and CNS Network Abnormalities in Laryngeal Dystonia: A 30-Year Experience

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Objective: Laryngeal dystonia (LD) is a functionally specific disorder of the afferent–efferent motor coordination system producing action-induced muscle contraction with a varied phenomenology. This report of long-term studies aims to review and better define the phenomenology and central nervous system abnormalities of this disorder and improve diagnosis and treatment.

Methods: Our studies categorized over 1,400 patients diagnosed with LD over the past 33 years, including demographic and medical history records and their phenomenological presentations. Patients were grouped on clinical phenotype (adductor or abductor) and genotype (sporadic and familial) and with DNA analysis and functional magnetic resonance imaging (fMRI) to investigate brain organization differences and characterize neural markers for genotype/phenotype categorization. A number of patients with alcohol-sensitive dystonia were also studied.

Results: A spectrum of LD phenomena evolved: adductor, abductor, mixed, singer’s, dystonic tremor, and adductor respiratory dystonia. Patients were genetically screened for DYT (dystonia) 1, DYT4, DYT6, and DYT25 (GNAL)—and several were positive. The functional MRI studies showed distinct alterations within the sensorimotor network, and the LD patients with a family history had distinct cortical and cerebellar abnormalities. A linear discriminant analysis of fMRI findings showed a 71% accuracy in characterizing LD from normal and in characterizing adductor from abductor forms.

Conclusion: Continuous studies of LD patients over 30 years has led to an improved understanding of the phenomenological characteristics of this neurological disorder. Genetic and fMRI studies have better characterized the disorder and raise the possibility of making objective rather than subjective diagnoses, potentially leading to new therapeutic approaches.

Key Words: Laryngeal dystonia, botulinum toxin, dysphonia.

INTRODUCTION

The purpose of this article is to review many of our 30+ years of experience and concurrent studies of patients with laryngeal dystonia (LD). It will review the evolution of the understanding of the phenomenology, including altering the symptoms with botulinum toxin. We also will review the genetic studies and brain evaluations, which ultimately will lead to a more objective diagnosis of this syndrome and provide targeted treatments of the functional brain abnormalities.

Historical Background

Laryngeal dystonia (known as spasmodic dysphonia) is a functionally specific movement disorder. The disorder has been long recognized but was not categorized as a focal dystonia until the late 1980s. The nomenclature of the disorder has undergone many iterations over time. Historically, dystonic voice alterations were first described as “spastic dysphonia” by Traube in 1871 when describing a patient with nervous hoarseness. Schnitzler2 used the term “spastic aphonia” (now called abductor LD) and “phonie laryngeal spasms” (now called adductor LD). Nothnagel later called the condition “coordinated laryngeal spasms,” whereas Fraenkel3,4 used the term “mogiphonia” for a slowly developing disorder of the voice characterized by increasing vocal fatigue, spasmodic constriction of the muscles of the throat, and pain around the larynx. Fraenkel...
Dystonia is a disorder of the afferent sensory-efferent motor coordination system, producing action-induced sustained muscle contraction causing abnormal postures or repetitive movements that may be intermittent, affecting any voluntary group of muscles. Some forms of focal dystonia, such as LD and writer’s cramp, are action-induced and task-specific movement disorders. In the case of LD, the task, or action, is phonation, or active functional use of the vocal musculature. Isolated dystonia may occur at any age, but generalized dystonia tends to onset in childhood, whereas focal dystonias tend to occur in the third to fourth decade. There are a number of suspected etiologies in secondary or acquired dystonia, including hereditary forms and environmental (trauma, infections, vascular, tumors, toxins, and drugs). Greater than 60% are termed idiopathic,15,16 (see Table I).

Our group, studying SD (spasmodic dysphonia) patients clinically and with electromyography (EMG), confirmed that SD was a focal LD, paralleling the work of Marsden et al.11 In later reports, Schaefer17 and Ludlow18 also showed with EMG evidence that this disorder, like other dystonias, is a disorder of motor control. Recently, structural alterations in brain organization were demonstrated in patients with LD, including focal reduction of axonal density and myelin along the corticobulbar/corticospinal tract that sends motocortical output to the brainstem phonatory motoneurons.19 We therefore believe that the more appropriate nomenclature for these disorders should be laryngeal dystonia (LD), with multiple phenomenological presentations. We will use this nomenclature in the remainder of this article.

Review of Our Studies
Over the last 33 years, we have clinically diagnosed over 1,400 patients with LD. These patients had all their demographic and medical history recorded, as well as clinical and endoscopic evaluation of their phenomenological presentations assessed. In the review that follows, subsets of this broader cohort are discussed in the context of the individual studies.

Phenomenology
Among the 1,400 patients, 63% were female; 82% had adductor symptoms; and 17% had abductor symptoms. Typically, abductor patients are reported to make up about 10% of LD cases; however, our higher numbers are most likely due to referral bias.20

Our review of these patients also revealed other variants, including mixed adductor and abductor types during speech (n = 6), singer’s dystonia (n = 7), adductor respiratory dystonia (n = 14), and patients with dystonic tremor (25%). In general, dystonic tremors can be rapid and irregular and repetitive, with a directional
Adductor Laryngeal Dystonia

When the adductor group was evaluated, a cross-sectional sample of 60 consecutive subjects with adductor laryngeal dystonia (ADLD) was assessed with voice-related questionnaires, vocal tasks, and blinded clinician evaluation. Voice samples were recorded as the subjects read the Rainbow Passage aloud, described the Cookie Theft picture, sang “Happy Birthday,” and counted from 80 to 89. Two laryngologists and two speech-language pathologists reviewed the recordings to identify and rate the severity of the voice symptoms on the Unified Spasmodic Dysphonia Rating Scale (USDRS). During the review of the reading Rainbow Passage, all clinicians identified and timed the duration of voice arrests as momentary (<1 second), short (1–2 seconds), or long (>2 seconds in duration). The average age in this series was 61.3 years, with a mean duration of the disorder of 16.1 years. The average age of onset was 48 years. The mean Voice Handicap Index-10 (VHI-10) score was 21.3, and the mean USDRS overall symptom severity score was 4.0 (±1.0). The VHI-10 ratings were recent scores. The most frequent and severe symptoms identified by both subjects and clinicians were roughness (82%), strain/strangle (80%), and increased expiratory effort (64%). Abrupt voice initiation (5%), voice arrest (4%), and aphonification (0%) were rare. Patients rated vocal symptoms as significantly more severe at initial diagnosis than at the time of the evaluation due to their treatment with botulinum toxin (P < 0.0001). Of the patients who had voice arrests (N = 21–38.2%), 71.4% had two or fewer arrests, and five (23.8%) had three or more arrests. There was uniform agreement among all four clinicians regarding the presence or absence of voice arrests for only 10 subjects (18.2%). Therefore, we concluded, in contrast to other groups, that counting only the number of breaks in LD patients was a poor tool for diagnosis.

All 1,400 patients had flexible laryngoscopic examination with video recording so that the results could later be evaluated. The adductor variety was categorized on a 4-point scale of hyperadduction: type 1 with vocal fold hyperadduction on connected speech segments at the glottal level, type 2 with the same findings at the glottal level and also hyperadduction of the false vocal folds, type 3 with additional anterior pull of arytenoids toward the epiglottis, and type 4 with sphincteric closure of the glottis. The adductor patients had clear abduction while attempting to phonate during connected speech segments, such as on counting from 60 to 70 or sentences such as “Harry’s Happy Hat” or “The Pretty Puppy Bit the Tape.” All other laryngeal functions were normal.

In another study, we reviewed 350 patient charts, which revealed that 169 charts showed patient who recalled the circumstances surrounding the onset of their symptoms. Forty-five percent were described as sudden onset. The most common factors associated with the sudden onset were stress (42%), upper respiratory infection (33%), and pregnancy and parturition (10%).

Abductor Laryngeal Dystonia

Abductor LD is characterized by breathy breaks or aphonification during speech. This is due to intermittent abduction of the vocal folds during phononation, resulting in reduction of loudness or aphonification of speech segments. The vocal folds during unvoiced segments become fixed in opening or they delay in closure for voiced segments of speech. Fiberoptic laryngoscopy in these patients reveal synchronous and untimely abduction of the true vocal folds, allowing air escape and minimizing sound production. These spasms are triggered by consonant sounds, particularly when they are in the initial position in words. These patients are usually worse under stress or on the telephone and may have a normal laugh, normal yawn, normal humming, and occasionally normal singing. In our center, there are about 230 patients or 17% of the total series who present with abductor phenomena. This is higher than the roughly 10% in most series due to a referral bias.

Singer’s Laryngeal Dystonia. We also found a small number (seven) of patients who had symptoms only during singing. These were all professional singers, and four of the five were of the adductor type. In two of these patients, the symptoms ultimately progressed to also include their speaking activity.

Adductor Breathing Laryngeal Dystonia. We identified and described another task-specific LD, which involved adductor spasms during inspiration. This caused stridor but never hypoxia. It did not involve speaking, and often disappeared if the breath was preceded with humming or laughing. It never occurred while the patient was asleep.

Mixed Adductor/Abductor Laryngeal Dystonia. Seven of our 1,400 patient group switched over time from adductor to abductor or vice versa, and six who were truly mixed adductor/abductor. This observation may be consistent with Cannito’s 1981 notion that all...
patients are mixed with an adductor or abductor predominance.

The abnormal phenomena in functionally specific dystonic processes seem not only to be related to muscular response to an abnormal efferent signal but also to abnormal processing of afferent or sensory signals. The muscle spindle fibers are most commonly seen in the interarytenoid muscle but are sparse in the other laryngeal muscle. Most of the sensory feedback seems, from recent studies, to be from mucosal deflection mechanoreceptors. Phonation causes repeated mechanical perturbation to the vocal folds, and central suppression likely plays a role in facilitating fluidity of sound production during vocalization and speech by controlling the adductor reflex responses.

Modification of Phenomena With Local Injections of Botulinum Toxin

To manage the symptoms of LD, in April 1984 we treated the first LD patient with botulinum toxin injection of laryngeal muscles with success. The start and establishment of this treatment in LD was a natural progression in the field, utilizing techniques and botulinum toxin type A (Oculinum; Oculinum Inc., Berkeley, California, U.S.A.), developed by Dr. Allen Scott for the management of strabismus and blepharospasm (a dystonia affecting eyelid closure). Since that first injection, we have treated over 1,400 patients (near 25,000 injections) and have developed dosing patterns that in our clinic maximize the therapeutic benefit for symptom control.

Biological Effect of Botulinum Toxin

After injection, the toxin is internalized into nerve endings. The neurotoxin light chain is translocated across the vesicular membrane into the cytosol via a process involving the heavy chain. The light chain functions as a zinc-dependent endopeptidase that cleaves one or more proteins necessary for vesicular neurotransmitter release. Each botulinum toxin serotype cleaves at least one peptide bond on a SNARE protein (soluble N-ethylmaleimide-sensitive factor attachment protein receptor), which make up the vesicle docking and fusion apparatus required for neurotransmitter exocytosis. Botulinum toxin types A, C1, and E cleave SNAP-25 (synaptosomal membrane-associated protein 25 kD), whereas types B, D, F, and G cleave the vesicle associated membrane proteins (VAMPs; synaptobrevins). Serotype C1 also cleaves syntaxin.

Clinical Effect of Botulinum Toxin

The clinical effects of botulinum neurotoxins last approximately 3 to 4 months on average, and re-injection is typically required to maintain clinical benefits. Botulinum neurotoxins not only inhibit acetylcholine release from alpha motor neuron terminals but also from gamma motor neurons. This action has been found to reduce the muscle spindle inflow to alpha motorneurons, which may alter reflex muscular tone. The well-known action-induced, task-specific nature of LD suggests that, indeed, afferent feedback may play a role in its pathophysiology. Further, the phenomenon of the sensory trick suggests that the alteration of afferent signals may be therapeutically useful. Over time, the sensory trick generally loses its effectiveness. The reason for this is not known, but it appears that the central nervous system (CNS) eventually overrides this change in input by returning to the uncompensated state of sending inappropriate signals to involved muscles. This may explain why interventions have been largely unable to control symptoms permanently in various dystonias. In the case of LD, although recurrent nerve section, anterior commissure release, and other surgical measures have all produced encouraging short-term results, long-term benefit has proved difficult to achieve in many patients because the abnormal central programming seems to defeat the surgical treatment.

The broad success of botulinum toxin as a treatment for focal dystonias, LD among them, may be due to the specificity, repeatability, and reversibility of the chemodenervation. Nerve terminal recovery from chemodenervation is a continuous, multi-phase process, beginning shortly after acetylcholine release is blocked in preclinical models. The cycle of recovery and reinjection with botulinum toxin may make it impossible for the central nervous system to defeat the denervation, such as may occur in a permanent treatment, because it never reaches a stable plateau. The voice benefit from injection sometimes extends beyond that expected from the observed in vitro activity of botulinum toxin and suggests that its clinical effect may be due to more than simple acetylcholine blockade at the neuromuscular junction. Some authors have hypothesized that botulinum toxin may affect neurotransmission in the afferent system as well. In fact, there is evidence that, in dystonia, botulinum toxin has a transiently functional effect on the mapping of muscle representation areas in the motor cortex, with reorganization of inhibitory and excitatory intracortical pathways, probably through peripheral mechanisms. In LD, changes in muscle activation are observed in both injected and noninjected muscles; however, functional MRI provided contradictory results showing both alleviation and the lack of any effects on abnormal brain activation.

Dosing Regime

The use of botulinum toxin has been reviewed by professional societies since 1990, and we have continued to treat patients off-label in our clinics. Our injections are based on a standard dilution of 4.0 mL of preservative-free saline/100 units vial of onabotulinumtoxin A (Botox, Allergan, Parsippany, New Jersey, Irvine California, U.S.A.) for the larynx, diluting the solution further in the syringe as needed for each patient. The effective dose is not proportional to body mass or dysphonia severity and varies considerably. Because injecting a large quantity of fluid into the vocal folds may cause dyspnea, we try to limit the volume of each
Botulinum Toxin in Adductor Laryngeal Dystonia

The symptoms for this disorder tend to wax and wane, and to have modifiers such as stress. Therefore, the doses and specific treatment paradigm are often adjusted at each visit based on current symptoms. For adductor LD, our initial dose is approximately one unit per side, which represents a low average dose for our patient population. All dosing reported in this article are dosing units related to onabotulinumtoxinA (Botox, Allergan) units. In a recent publication, we did find a gender difference. In a study of 201 patients we found that females had an average dose per vocal fold of 1.3 units ± 1.1 and males 0.6 units ± 0.42.57 Some patients do not tolerate bilateral injections due to experiencing excessive breathiness or aspiration of fluids, and we empirically found that unilateral injections of an average of 1.5 units or less, and alternating sides, have more consistent voicing but usually a shorter duration of symptom control. Some patients need bilateral injection but cannot tolerate the initial weak voice, and we stagger the injection sides 2 or more weeks apart. We also have a small number of patients who receive more frequent mini-dose injections as low as 0.01 units per side. For patients who displayed severe supraglottic squeeze with connected speech segments, we reported a technique of injecting the supraglottic musculature with EMG guidance and fiberoptic visualization.58 A very few of our patients needed additional treatment of the interarytenoid muscle, especially those with significant dystonic tremor.59 Because with botulinum toxin injections we are treating symptom and not disease, we found the best results with individualized the treatment for each patient. With these patient- and visit-specific considerations in a prospective study of 100 patients, we found two response curves. One had a few days of breathy voice, followed by an increased percentage function, which maintains for 3 to 4 months. The second group had no voice loss but a consistent improvement over several days, until the peak at > 90% was reached and maintained for 3 to 4 months.60 We may add a small dose a few weeks after the initial one if the voice does not become fluent. In the great majority of patients, dysphonia is well controlled for 3 months or more with a small dose and effects of rimabotulinumtoxinA (Myobloc, Solstice Neurosciences, Louisville, Kentucky, U.S.A.) to onabotulinumtoxinA (Botox, Allergan) and found about a 53.1:1 relative dosing comparator, with a faster onset (2.09 days vs. 3.2 days) but a shorter duration with Myobloc (Solstice Neurosciences) (10.8 weeks vs. 17 weeks).67

Botulinum Toxin in Abductor Laryngeal Dystonia

For abductor spasmodic dysphonia, we initially inject one posterior cricoarytenoid (PCA) muscle with 3.75 units of botulinum toxin, and estimate the contralateral dose after evaluating vocal fold mobility 2 weeks later. A vocal fold that is completely unable to abduct requires that the other side be treated with a small dose to avoid the inability to abduct on inspiration, whereas a more mobile one permits a larger dose to be used. Asymmetric dosing is the rule in abductor LD. Fluctuations in disease severity in spasmodic dysphonia occasionally may require small adjustments in dose. These injections are given with EMG control either with rotation of the larynx and injecting behind the posterior thyroid lamina, through the pyriform sinus, and into the PCA overlying the cricoid—and with injection through the cricothyroid membrane, traversing the airway, and then going through the rostrum of the cricoid to reach the PCA. The former approach is more difficult in older patients (particularly males) due to increased calcification in the cricoid.

Nearly 20% of the abductors only require unilateral injection for control of symptoms. Due to the potential airway issues, limiting the ability to administer simultaneous bilateral injections, greater than 30% of the abductors are also on low dose oral agents for dystonia. The results in a 225-patient cohort show an average onset of toxin effect at 4.1 days, a peak effect at 10 days, and an average best percent function of 70.3% of normal function. Two percent of our patients had mild wheezing and 6% had transient difficulty swallowing solids.68–72

Secondary Nonresponse

Secondary nonresponse is rare in LD treatment probably due to the small doses used and therefore a reduced antigenic challenge. We have six of 1,400 primary LD patients who have become secondary responders. They were switched to rimabotulinumtoxinB (Myobloc) for a year and then were challenged again with onabotulinumtoxinA (Botox); all but one responded. One failed but was challenged with incobotulinumtoxinA (Xeomin, Merz, Raleigh, North Carolina, U.S.A.), and that patient is still responding for greater than 1 year.73 The patient may have antibody to accessory proteins rather than the toxin itself.

Genetic Studies

During the last 20 years, several genes for various forms of dystonia have been discovered (see Table II). Although only 12% of our LD population had a positive family history of dystonia, we undertook genetic studies...
to assess the role of these genes in our patient population. Indeed, in one of our early studies, the proband presented with LD.76 Some of our patients were included in collaborative studies with Dr. Mark LeDoux (University of Tennessee). Using various subsets of our patient samples, he found no mutations in the TOR1A gene77 or the TUBB4A gene78 but did identify novel THAP1 mutations in LD patients,79 as well as an association with a rare intronic variant in THAP1 across various focal dystonias, including LD (3 cervical dystonia; 3 LD; 1 oromandibular dystonia; 2 blepharospasm; and 3 unclassified).

Our group also looked for mutations in TOR1A, TUBB4A, THAP1, and GNAL in 57 LD patients undergoing imaging studies. A single patient with adductor LD was identified with a GNAL mutation, showing for the first time that mutations in GNAL may represent a causative genetic factor in isolated LD.80 Exploratory evidence of distinct neural abnormalities in the GNAL carrier compared to sporadic and familial LD cases without known genetic mutations may suggest a divergent pathophysiological cascade underlying this disorder. Specifically, the GNAL carrier had increased activity in the frontoparietal cortex and decreased activity in the cerebellum when compared to 26 patients without the mutation.80 The GNAL mutation mapped in some patients with LD seems to be associated with dysregulation of dopamine metabolism in the striatum, producing dystonic symptoms.19

**Ultrasound and Functional Brain Imaging Studies**

In collaboration the Dr. Uwe Walter and colleagues at the University of Rostock, Germany, we studied 14 patients with adductor LD (10 female; 4 male) with age- and gender-matched controls using sonography of the brain. We found lenticular nuclear and caudate nuclear hyperrechogeneity in 12 of the patients and only one control. This hyperrechogeneity might be related to small amounts of mineral deposition.81–84

With the advent of functional brain imaging, much has been learned about normal and abnormal brain function during speaking. Over the past several years, we have studied the variations in laryngeal dystonic phenomenology, their genetic profiles, and functional brain patterns to try to better understand the abnormalities producing the poor vocal function.85

The topology, as well as global and local features of large-scale brain networks, were studied across different

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* = Isolated dystonia genes.  
+ = Genes associated with laryngeal dystonia.  
DYT = dystonia.
focal task-specific and nontask-specific dystonias, and findings were compared to healthy normal controls. The dystonic patients showed altered network architecture with abnormal expansion or shrinkage of neural communities, such as breakdown of basal ganglia-cerebellar community, loss of pivotal region of the information transfer hub in the premotor cortex, and pronounced connectivity reduction within the sensorimotor and frontoparietal regions. This suggests that isolated focal dystonias represent a disorder of large-scale functional networks. Distinct symptoms may be linked to disorder-specific network aberrations.85–88

A study of patients with a clinical diagnosis of ADLD and ABLD was performed evaluating the neural correlates of abnormal sensory discrimination in these individuals. Based on the clinical phenotype, the adductor form-specific correlations were observed in the frontal cortex, whereas the abductor form-specific correlations were in the cerebellum and putamen. These studies suggest the presence of potentially divergent pathophysiological pathways underlying the different manifestations of this disorder.89

A study of LD with and without tremor was performed to define dystonic tremor pathophysiology. This was done with fMRI, voxel-based morphometry, and diffusion-weighted imaging. When compared to controls, LD patients with and without tremor showed increased activation in the sensorimotor cortex, inferior frontal and superior temporal gyri, putamen, and ventral thalamus, as well as deficient activation in the inferior parietal cortex and middle frontal gyrus (MFG). Direct patient group comparisons showed that LD with tremor had additional abnormalities in MFG and cerebellar function and white matter integrity in the posterior limb of the internal capsule. Onset in LD patients with and without tremor was associated with right putaminal volumetric change. These are heterogenous disorders with the same pathophysiological spectrum, each carrying a characteristic neural signature that may help establish differential markers80 (see Fig. 1).

From our study group, during the past several years we recruited 98 patients, who were grouped based on clinical phenotype (adductor or abductor) and underlying putative genotype (sporadic and familial). Their data on brain activity were submitted to independent component analysis and linear discriminant analysis to investigate brain organization differences and to characterize neural markers for genotype/phenotype categorization.89

We showed abnormal functional connectivity within the sensorimotor and frontoparietal networks of LD patients compared to normals, which provide a 71% accuracy in characterizing LD from normal subjects, an 81% accuracy in separating sporadic and familial LD, and 71% accuracy in discriminating adductor and abductor LD forms based on their neural abnormalities.90 This study laid the first foundation for the development of objective neural biomarkers of LD, which can potentially be translated into clinical practice for accurate and unbiased diagnosis of this disorder as well as its several subtypes.

Alcohol Responsiveness and Sodium Oxabate
A number of patients with alcohol-responsive LD have been described. A total of 406 LD patient records from the National Spasmodic Dysphonia Association patient registry were studied. Among these, 76.5% had pure LD and 23.5 had LD + voice tremor. Based on patient reports, a total of 55.9% of LD were alcohol-responsive, whereas 58.4% of the LD+ voice tremor were alcohol-responsive. This group was segregated because tremor patients alone can be alcohol-responsive.

Fig. 1. Diagram showing central nervous system and network changes associated with laryngeal dystonia. [Color figure can be viewed at www.laryngoscope.com.]
The effects of alcohol on the patient reported symptoms in both groups lasted 1 to 3 hours. It is thought that alcohol may modulate the pathophysiologic mechanisms underlying abnormal neurotransmission of GABA (γ-aminobutyric acid) in dystonia. This may open new pathways for novel therapeutic options.25,91

Based on the above study, we conducted an open-label study using sodium oxabate (Xyrem, Jazz Pharmaceuticals, Dublin, Ireland), which has the therapeutic effects on LD symptoms similar to those of ethanol. A total of 53 patients were recruited. Of those, 30 patients had LD and 23 had LD with voice tremor. In the combined group, the drug had a significant effect on the vocal symptoms observed 30 to 45 minutes after taking 1.5 grams of drug and lasted an average of 3.5 hours, gradually wearing off by 5 hours. All patients tolerated the drug without major side effects. In contrast to botulinum toxin, sodium oxabate had similar effects in the adductor and abductor groups.92 The drug is known to convert into GABA within the brain and increases the dopamine level mediated by GABA receptors.92,93

CONCLUSION
Continuous studies of LD patients over 33 years have led to an improved understanding of the phenomenological characteristics of the neurological disorder. Genetic, therapeutic, and fMRI studies have provided new insights into the disorder and new clues to a possibility of objective rather than subjective diagnoses, which may lead to new therapeutic approaches. The data acquired may also lead to future clinical trials to better understand the pathophysiologic differences in the subgroups of LD, which may be relevant to more specific diagnosis, treatment options, and information for genetic counseling.

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