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What is This?
Consideration of Genetic Contributions to the Risk for Spasmodic Dysphonia

Nutan Sharma, MD, PhD1, and Ramon A. Franco Jr, MD2

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Abstract

Spasmodic dysphonia, a form of the neurologic condition known as dystonia, results from involuntary spams of the larynx, producing interruptions of speech and changes in voice quality. The pathogenesis of spasmodic dysphonia is not well understood. However, several genetic mutations have been identified that cause different forms of dystonia. In some individuals, these genetic mutations result in spasmodic dysphonia, either with no other signs of dystonia or as part of a broader dystonia phenotype. Thus, research in the growing field of dystonia genetics may help to inform our understanding of the pathogenesis of spasmodic dysphonia.

Keywords

spasmodic dysphonia, dystonia, genetics

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Spasmodic dysphonia (SD) is a chronic neurological disorder of central motor processing. SD may occur either as the sole manifestation of central nervous system disease or as part of a broader dystonia phenotype. Dystonia is characterized by sustained muscle contractions that typically produce twisting, repetitive movements, or abnormal postures or positions. Traditionally, dystonia has been classified according to the region(s) of the body that are affected. Focal dystonia refers to those cases in which dystonia affects only 1 body region, such as the larynx or eyelids. Segmental dystonia refers to those cases in which dystonia affects 2 contiguous body regions, such as the lower facial muscles and larynx or the neck and an arm. Multifocal dystonia refers to those cases in which dystonia affects 2 or more noncontiguous body regions, such as the larynx and right leg. Lastly, generalized dystonia refers to those cases in which both legs and at least 1 other body region are affected.

Limited information is available on the epidemiology and natural history of SD. However, the available data indicate that in most cases of SD, no other body region is affected by dystonia. More recent data indicate that in most focal SD cases, there is no known family history of dystonia. However, some cases of SD are seen as part of a broader dystonia phenotype in people carrying various genetic mutations that cause dystonia. In addition, there is emerging evidence that normal variations in the wild-type, nonmutated forms of dystonia-causing genes can affect the risk of development of focal or segmental dystonia. Thus, clues regarding the pathophysiology of the more common, nonfamilial focal form of SD may be gleaned from ongoing research on the genetic contribution toward the pathogenesis of dystonia, in general.

At least 17 different types of dystonia can be distinguished genetically and are designated DYT1-17. Some of these are considered primary dystonias, meaning that dystonia and possibly arm tremor are the only neurologic signs. Other genetic forms are considered dystonia-plus syndromes, meaning that other neurologic signs, in addition to dystonia and arm tremor, are part of the phenotype.

The most common cause of childhood-onset primary generalized dystonia is DYT1 dystonia, caused by a 3-bp deletion (ΔGAG) in the TOR1A gene that encodes the protein torsinA. Symptoms typically present before the age of 21 years with involuntary sustained muscle contractions that cause posturing of a foot, leg, or arm. The contractions frequently, but not invariably, generalize to other body regions and have been reported to include the larynx in some cases. No other neurologic abnormalities are present, except for postural arm tremor. Disease severity varies considerably within the same family, and the life span of affected individuals is not shortened.

DYT6 dystonia typically affects the cranial muscles and arms, often with voice involvement as a predominant feature. The syndrome was first described in Amish-Mennonite families, and the causative gene was recently identified as THAP1

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(thanatos-associated protein domain-containing apoptosis-associated protein 1), which encodes a DNA-binding protein. Additional DYT6 mutations have been identified in ethnically diverse patients throughout the world. DYT6 mutations underlie a broad spectrum of primary dystonia cases, ranging from childhood-onset generalized dystonia to adult-onset focal dystonia, including cases of SD.

In addition to the identification of disease-causing genetic mutations, it is also possible that normal variations, known as polymorphisms, in the wild-type versions of the same genes may play a role in increasing or decreasing the risk of developing dystonia. Thus, variability, in the form of polymorphisms, in the wild-type version of the DYT1 or DYT6 gene may contribute to the risk of developing focal dystonia. This hypothesis has been substantiated for another gene that causes neurologic illness, the alpha synuclein gene in Parkinson disease.

Recent association studies implicate polymorphisms in the DYT1 gene as being associated with adult onset, mainly focal dystonias, including cases of SD. Association studies compare the allele frequency of a polymorphic marker, or a set of markers, in unrelated patients and healthy controls to identify markers that differ significantly between the 2 groups. Our recent work on a large cohort of focal and segmental dystonia, which included SD and cervical dystonia patients, revealed a significant association between the presence of a single nucleotide polymorphism (SNP), the deletion allele at the Mtdel SNP (rs3842225), and protection from developing focal or segmental dystonia. When we analyzed the frequency of the Mtdel SNP in different dystonia subtypes, we found a significant association between the presence of the del allele and protection from developing focal cervical dystonia. However, when we analyzed those with SD alone, we found only a trend toward association between the presence of the del allele at the Mtdel SNP and protection from developing SD.

Other polymorphisms in the DYT1 gene have been shown to either increase or decrease the risk of developing dystonia. In cases of nonfamilial dystonia in the Icelandic population, a significant association was observed between having dystonia and the presence of a series of markers spanning the DYT1 gene. However, a study from Germany failed to replicate this association. Thus, data from different ethnic groups and different clinical populations with dystonia have given conflicting results regarding whether or not specific genetic polymorphisms increase or decrease the risk of developing dystonia. Although the data are inconsistent, the results as a whole support a role for genetic variability in the DYT1 genomic region as a risk factor in the development of late-onset, focal, and segmental dystonia. Further experiments examining a comprehensive battery of SNPs that account for most variation in the region in a much larger series of focal/segmental dystonia patients should clarify the associations.

The DYT6 gene was identified relatively recently. Thus, extensive data regarding polymorphisms in the wild-type DYT6 gene and whether or not they may play a role in increasing or decreasing the risk of developing focal or segmental dystonia are not yet available.

The identification of gene mutations, and variations in normal genes, that contribute to the development of dystonia may help to shed light on the pathogenesis of SD. Studies on a larger scale, involving a larger number of dystonia subjects who have undergone a comprehensive clinical evaluation, from a variety of ethnic backgrounds, are needed to help determine the way in which genetic mutations and genetic polymorphisms affect the development of dystonia.

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Nutan Sharma, drafted article; Ramon A. Franco Jr, revised article.

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