Novel Genes and Novel Pathogenetic Mechanisms in Adult-Onset Primary Dystonia

Charlesworth G, Plagnol V, Holmström KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. *Am J Hum Genet.* 2012;91:1041–1050.

Fuchs T, Saunders-Pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet. 2012;45:88–92.

Adult-onset primary dystonia (AOPD) is the most prevalent form of primary torsion dystonia. It often involves the cranial and cervical areas and tends to remain focal or segmental in distribution. Most AOPD cases are sporadic, yet some families display autosomal dominant inheritance with variably reduced penetrance. Although 2 genes (*DYT1-TOR1A* and *DYT6-THAP1*) are known to cause autosomal dominant early-onset dystonia, the genetic basis of AOPD has remained elusive. In 2012, thanks to the advent of revolutionary whole-exome sequencing (WES) technology, the identification of 3 novel dystonia genes has begun to shed light on the genetic defects and pathogenetic mechanisms underlying AOPD.

Xiao et al first reported heterozygous mutations in the *CIZ1* gene in a large family and in 2 of 308 subjects with adult-onset cervical dystonia. *CIZ1* encodes for a zinc-finger nuclear protein involved in DNA synthesis and cell-cycle control.[1] Very recently, 2 more genes were identified. Charlesworth et al performed WES in a British family with cranial-cervical dystonia and onset mostly late in the fourth decade and then tested candidate variants in a cohort of 188 cervical AOPD cases. Six pathogenic mutations were detected in the *ANO3* gene, encoding a predicted calcium-gated chloride channel highly expressed in the striatum.[2] Finally, in 2 families with cervical dystonia and mean onset in the fourth decade, Fuchs et al identified mutations in *GNAL*; this gene was also found to be mutated in 6 of 39 families with focal-segmental dystonia and predominant neck involvement. GNAL encodes the stimulatory G-protein α-subunit $G\alpha_{olf}$, which couples dopamine and adenosine receptors to the activation of the adenylate cyclase type 5 pathway in the striatum.[3]

Although the actual frequency of these genes still requires further screening in large patient cohorts, their identification provides novel and exciting insights in understanding the mechanisms of AOPD. For instance, evidence that ANO3 and GNAL proteins are highly expressed in the striatum points to a key role for striatal neurons in the pathophysiology of dystonia, either through abnormalities of dopamine and/or adenosine signal transduction pathways or through abnormal neuronal excitability related to the malfunctioning of chloride channels. These findings also open promising new lines of research in the search for therapeutic strategies for primary dystonia.

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