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Deep Brain Stimulation for Dystonia: A Novel Perspective on the Value of Genetic Testing

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Abstract

The dystonias are a group of disorders characterized by excessive muscle contractions leading to abnormal movements and postures. There are many different clinical manifestations and underlying causes. Deep brain stimulation (DBS) provides an effect treatment, but outcomes can vary considerably among the different subtypes of dystonia. Several variables are thought to contribute to this variation including age of onset and duration of dystonia, specific characteristics of the dystonic movements, location of stimulation and stimulator settings, and others. The potential contributions of genetic factors have received little attention. In this review, we summarize evidence that some of the variation in DBS outcomes for dystonia is due to genetic factors. The evidence suggests that more methodical genetic testing may provide useful information in the assessment of potential surgical candidates, and in advancing our understanding of the biological mechanisms that influence DBS outcomes.

Keywords

Deep brain stimulation; neuromodulation; dystonia; genetics

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Introduction

The dystonias include a large group of disorders characterized by excessive muscle contractions leading to abnormal movements and postures. There are many different clinical manifestations and underlying causes. The dystonias may emerge at any age, they may affect virtually any region of the body, they may be chronically progressive or relatively static, and they sometimes are combined with other movement disorders, and often with other neurological or systemic problems. Etiologically, the dystonias also are quite heterogeneous. They may be associated with no apparent brain pathology, or obvious defects in different areas of the nervous system. Some are inherited, while others are acquired.

An international consensus committee recently provided recommendations for how the many different subtypes should be classified (Albanese et al. 2013; Jinnah and Albanese 2014). This classification system has two main axes (Table 1), the first of which addresses the clinical manifestations. The clinical axis has four dimensions that include the age at onset, body region affected, temporal features and triggering factors, and associated clinical problems. The second axis addresses etiology with two dimensions relating to histopathological abnormalities or genetic contributions. All of the dimensions in both the clinical and etiological axes are relevant when considering DBS.

Of particular relevance to DBS is the elimination of prior classification systems that variably used the terms *primary dystonia*, *secondary dystonia*, *dystonia-plus*, and *heredogenerative dystonia*. The term *isolated dystonia* replaces the older term, *primary dystonia*. The term *combined dystonia* includes syndromes where dystonia is combined with other movement disorders and sometimes with other neurological problems. These differences in nomenclature are relevant, because regulatory approvals for DBS still refer to older terminology of *primary* and *secondary* dystonia. In the United States, FDA Humanitarian Device Exemption (HDE) approval is for *primary* generalized dystonia, segmental dystonia, hemidystonia and cervical dystonia. Approval is for one of two regions, the globus pallidus interna (GPi) or the subthalamic nucleus (STN). In the European Union, CE mark approval is for both *primary* and *secondary* dystonias.

Although the correspondence between the traditional and revised nomenclature systems is not exact, the new term *isolated dystonia* is roughly equivalent to the old term, *primary dystonia*, because both refer predominantly to disorders where dystonia is relatively pure. However, the term *secondary dystonia* can refer to a number of disorders including acquired dystonias (whether or not there is clinically pure dystonia) or those that are combined with other movement disorders or systemic problems (whether or not the cause is known). These ambiguities were among the major reasons that traditional terms such as *secondary dystonia* were replaced with the more precise terminology (Jinnah and Albanese 2014).

Success in treating dystonia with DBS varies considerably among different patients, and many studies have addressed factors that influence outcomes. This evidence has been summarized in several comprehensive reviews (Speelman et al. 2010; Bronte-Stewart et al. 2011; Andrews et al. 2010; Mills et al. 2014; Vidailhet et al. 2012; Thobois et al. 2011; Holloway et al. 2006; Isaias et al. 2011; Isaias et al. 2008; Fox and Alterman 2015).

Although there are some differences of opinion, the most important factors include a clear diagnosis of dystonia, age at onset, duration of symptoms, lack of serious comorbidities, and whether abnormal movements are fixed, mobile or phasic. Some investigators also conclude that outcomes are better for isolated dystonias than other types of dystonia.

Based on these many factors, recommendations regarding patient selection criteria have been proposed (Speelman et al. 2010; Bronte-Stewart et al. 2011; Andrews et al. 2010; Mills et al. 2014; Vidailhet et al. 2012; Thobois et al. 2011; Holloway et al. 2006; Isaias et al. 2011; Isaias et al. 2008; Fox and Alterman 2015). However, these recommendations are not universally followed, because much of the data comes from uncontrolled studies, and there are some differences of opinion. One uncertain area is whether genetic testing is useful. The current article presents a summary of the evidence that DBS outcomes are influenced by genetic factors, describes how more methodical genetic testing might improve outcomes, and concludes with suggestions regarding the most useful genetic testing strategies.

Methods

This article was assembled following a comprehensive review of the available literature regarding the treatment of dystonia with DBS, the genetics of dystonia, and especially articles on the influence of genetics on DBS outcomes in dystonia. Several exhaustive reviews have been published already for the treatment of dystonia with DBS (Speelman et al. 2010; Bronte-Stewart et al. 2011; Andrews et al. 2010; Mills et al. 2014; Vidailhet et al. 2012; Thobois et al. 2011; Holloway et al. 2006; Isaias et al. 2011; Isaias et al. 2008; Fox and Alterman 2015), or the genetics of dystonia (Balint and Bhatia 2015; Lohmann and Klein 2013; Moghimi et al. 2013; LeDoux 2012). The reader is directed to these prior reviews for more details. Here, the focus is instead on the interface between these two normally independent fields of research, and specifically the evidence regarding genetic factors that may influence DBS outcomes.

Are Genetic Factors Relevant?

The genetic basis for the dystonias has been reviewed extensively (Balint and Bhatia 2015; Lohmann and Klein 2013; Moghimi et al. 2013; LeDoux 2012). There is strong evidence linking isolated dystonia with several different genes including *TOR1A*, *THAP1, GNAL,* and *ANO3.* Several other genes have also been reported to be linked with isolated dystonia (*CIZ1*, *COL6A3*, *GNAL*, and *HPCA),* although a causal relationship has been difficult to establish because the evidence is more limited. It seems likely that additional genes for isolated dystonia are yet to be found.

A much larger group of genes has been identified for the many combined dystonias. A recent review summarized more than 100 different disorders where dystonia may be combined with other clinical features, organized into 18 tables according to the typical age at onset and the most common associated clinical features (Fung et al. 2013). Since then, several additional disorders where dystonia is combined with other neurological features have been described. The majority of these disorders are genetically determined.

The question addressed here is whether the genetic basis for dystonia has any influence on DBS outcomes. Most of the genetically determined dystonias are rare, so there are no large-scale studies that specifically address this question. However, there is indirect evidence from many studies. This evidence is summarized below according to the subtypes of isolated or combined dystonia.

Heterogeneity in DBS outcomes in isolated generalized/segmental dystonia

Patients with isolated generalized dystonia often respond well to DBS. A blinded study of 22 generalized dystonia patients receiving DBS targeting the GPi comparing actual versus sham stimulation revealed overall improvement in Burke-Fahn-Marsden dystonia rating scores of 54.6% at 12 months.(Vidailhet et al. 2005) Another blinded study of GPi DBS in 40 patients with isolated generalized or segmental dystonia revealed improvements of 39.3% at 3 months (Kupsch et al. 2006). In both studies, some patients responded much better than others, and a few patients saw little or no benefit. Some of this variability is likely to be related to surgical or programming variations such as lead location and stimulation settings (Okun et al. 2005; Pauls et al. 2013). However, some variability may also be related to different underlying genetic causes.

Although some studies have found no apparent influence of *TOR1A* mutations on DBS outcomes, the weight of the evidence suggests that those with mutations respond better than those with undetermined genetic causes (Speelman et al. 2010; Bronte-Stewart et al. 2011; Andrews et al. 2010; Mills et al. 2014; Vidailhet et al. 2012; Thobois et al. 2011; Holloway et al. 2006; Isaias et al. 2011; Isaias et al. 2008; Fox and Alterman 2015). The differences in the conclusions across various studies of *TOR1A* mutations are likely to reflect relatively small numbers of mutation-positive cases evaluated, and heterogeneity among the mutation-negative cases to which they were compared. Other studies have suggested that patients with *TOR1A* mutations respond to GPi DBS more consistently than those with *THAP1* mutations (Vidailhet et al. 2012; Panov et al. 2012; Groen et al. 2010; Zittel et al. 2010; Miri et al. 2014; Mure et al. 2014). In fact, a direct comparison concluded that responses for patients with *THAP1* mutations were less predictable that those for *TOR1A* (Bruggemann et al. 2015).

Although the numbers of DBS cases reported with genetically defined dystonia are small, the results imply that genetic factors influence outcomes in DBS for isolated generalized dystonias. As a result, some authorities recommend testing for *TOR1A* because of a favorable prognosis. Others recommend testing for *THAP1*, so that patients may be informed of the lower probability of success (Bruggemann et al. 2015). However, broad consensus regarding any type of genetic testing is lacking.

Heterogeneity in DBS outcomes in isolated focal dystonia

Patients with isolated focal dystonia also show significant variations in response to DBS. For isolated cervical dystonia, a multicenter, double-blind, sham-controlled trial involving 62 patients revealed an average 26% reduction in the Toronto Western Spasmodic Torticollis Rating Scale score (Volkmann et al. 2014). Approximately one third showed no apparent benefit. Patients with isolated blepharospasm and Meige syndrome also respond to GPi

DBS, but again responses are inconsistent (Speelman et al. 2010; Bronte-Stewart et al. 2011; Andrews et al. 2010; Mills et al. 2014; Vidailhet et al. 2012; Thobois et al. 2011; Holloway et al. 2006; Isaias et al. 2011; Isaias et al. 2008; Fox and Alterman 2015). Responses among those with laryngeal dystonia are probably the least consistent.

Thus there are considerable variations in response to DBS among the isolated focal dystonias. Some of this variability may be related to lead location and/or stimulation settings. Some variability also may be confounded by side effects that do not occur among patients with generalized dystonia, such as bradykinesia or gait impairment (Berman et al. 2009). However, some variability also is likely related to varying underlying causes.

Evidence regarding the contribution of genetic factors among isolated focal/segmental dystonias is scarce because genetic testing is rarely conducted. As a result, there is only a small amount of indirect evidence. *THAP1* mutations have been associated with relatively prominent laryngeal or orobulbar dystonia (LeDoux et al. 2012). As noted above, patients with *THAP1* mutations respond less predictably to DBS than other types of dystonias. If genetic factors influence the distribution of dystonia in the body, then they are relevant to DBS outcomes. Similarly, *ANO3* mutations have been linked with tremor-dominant cervical dystonia (Stamelou et al. 2014; Charlesworth et al. 2012). Although there is insufficient evidence regarding responses to GPi DBS in cases with proven *ANO3* mutations, some investigators have argued that tremor-dominant dystonia responds better to thalamic DBS (Fasano et al. 2014; Hedera et al. 2013; Morishita et al. 2010; Buhmann et al. 2013; Pauls et al. 2014). If genetic factors influence tonic or phasic features of different dystonias, then they may be relevant for the surgical target.

Heterogeneity in DBS outcomes in combined dystonias

DBS originally was approved in the United States and Europe only for *primary* dystonias. It was not originally approved for *secondary* dystonias, because early experience led some investigators to conclude that patients with these other types of dystonia respond well to DBS. However, this statement is now recognized to be oversimplified, because some non-primary dystonias do respond to DBS (Saleh et al. 2013), and DBS has been approved for *secondary* dystonia in Europe.

Among the inherited combined dystonias, consistently good responses to GPi DBS have been reported for the myoclonus-dystonia syndrome and X-linked dystonia-parkinsonism (Lubag). However, other combined dystonias respond poorly, such as rapid-onset dystonia parkinsonism. Outcomes are variable for others such as Lesch-Nyhan disease, Wilson's disease, Huntington's disease, and paroxysmal dyskinesias. The list of these disorders and their responsiveness to DBS been reviewed several times (Speelman et al. 2010; Bronte-Stewart et al. 2011; Andrews et al. 2010; Mills et al. 2014; Vidailhet et al. 2012; Thobois et al. 2011; Holloway et al. 2006; Isaias et al. 2011; Isaias et al. 2008; Fox and Alterman 2015), with some focusing specifically on secondary forms (Saleh et al. 2013). Although definitive conclusions for many of the combined dystonias are impossible because of the small numbers of cases, these observations provide strong evidence that genetic factors influence outcomes.

Varying responses to DBS also occur among disorders traditionally viewed as acquired. For example, most investigators agree that drug-induced tardive dystonia responds consistently to GPi DBS. Recent studies also show good responses in cerebral palsy, where dystonia is uncomplicated by significant spasticity. It is important to acknowledge that both of these "acquired" disorders may be genetically determined. Several genes have been linked with tardive syndromes (Aquino and Lang 2014), and a large proportion of cases with cerebral palsy have a genetic cause (McMichael et al. 2015; MacLennan et al. 2015). Thus genetic factors may be under-appreciated in presumably acquired dystonias.

Summary of genetic influences on DBS outcomes

Overall, the available literature suggests that DBS outcomes in dystonia are influenced by the distribution of dystonia in the body, the predominance of tonic or phasic movements or tremor, and whether or not dystonia is combined with other neurological features. All of these factors are influenced by genetic factors. However, definitive conclusions regarding the role of genetic factors in DBS outcomes are not feasible for several reasons. The main reason is that the rarity of individual dystonia syndromes makes it challenging to methodically evaluate large numbers of genetically homogeneous cases. As a result, current conclusions are based on non-blinded evaluations and/or small numbers of cases.

Second, most available information is limited to *TOR1A* mutations, because it was the first dystonia gene cloned and clinical diagnostic testing has been available for many years. Other genes were identified more recently, but the available information is less robust. Because genetic testing is not routinely conducted prior to DBS, obtaining conclusive information regarding other relevant genes is likely to take many years.

Third, there is a widely recognized problem of selective reporting of positive outcomes. Poor outcomes are rarely reported, so even meta-analyses of the published literature do not provide an accurate depiction of what actually happens in the community. The extent of the problem with biased reporting is impossible to determine.

Can Genetic Testing Improve DBS Outcomes?

As outlined below, the application of DBS in dystonia may benefit from more methodical genetic testing. In the short term, genetic testing may improve diagnostic certainty, enabling more accurate counseling regarding expected outcomes. In the long run, it may provide guidance regarding surgical targets, and new insights into novel genes that may influence DBS outcomes.

Improving diagnostic certainty among isolated dystonias

Most articles addressing patient selection criteria for DBS agree that a clear diagnosis of dystonia is critical. A clear diagnosis is important for counseling regarding expected outcomes, and for exclusion of dystonia mimics that do not respond to DBS. A clear diagnosis also is essential for establishing well-defined patient populations for clinical trials.

However, obtaining a "clear" diagnosis is not as straightforward as many believe. Many studies have documented that making a diagnosis of dystonia takes a surprisingly long time

(Table 2). Even among experts, two studies addressing inter-observer reliability for diagnosis revealed surprisingly low levels of agreement (Beghi et al. 2014; Logroscino et al. 2003). One of the main reasons for poor diagnostic recognition is that the dystonias are relatively uncommon, and they are frequently mistaken for more common disorders such as Parkinson's disease (Cardoso 2012; Jog et al. 2011; Lalli and Albanese 2010; Albanese and Lalli 2009; McKeon et al. 2008; Schneider et al. 2007; Schneider et al. 2006) or essential tremor (Fasano et al. 2014; Pita Lobo et al. 2013; Elble 2013; Cardoso 2012; Schiebler et al. 2011; Lalli and Albanese 2010). Children with generalized dystonia are frequently confused with cerebral palsy (Jan 2004; Friedman et al. 2012). Perhaps the most difficult area of misdiagnosis involves patients with psychogenic dystonia (Bramstedt and Ford 2006; Ramos et al. 2015; Lalli and Albanese 2010). The community of providers for DBS frequently discuss cases who had DBS for presumed isolated dystonia, but were later discovered to have another disorder. These errors are rarely reported in the literature.

These observations emphasize that establishing a clear diagnosis of dystonia is not straightforward, and that current recommendations for "a clear diagnosis of dystonia" prior to DBS are difficult to operationalize. Genetic testing has the potential to provide more objective diagnostic evidence for diagnosis, at least for some subtypes of dystonia.

Improving diagnostic certainty among combined dystonia syndromes

The combined dystonia syndromes present an even greater challenge for accurate diagnosis. Among more than 100 different combined dystonias, ~80 have known genes. Although definitive conclusions are limited by the very small numbers of cases for each subtypes treated with DBS, there are several common themes. The first is that some combined dystonia syndromes respond well to DBS while others do not, as outlined above.

A second common theme is that for virtually all combined dystonias, patients may sometimes present with atypical syndromes. Complex neurometabolic disorders that typically present in childhood may sometimes present in older adults, or complex degenerative syndromes may initially mimic an isolated dystonia before other features become apparent. These cases are readily misdiagnosed as isolated dystonia, and may be offered DBS with unrealistic expectations. An obvious example is Wilson's disease, which may first present as isolated dystonia in adults, but DBS is not the most appropriate initial therapy (Hedera 2014; Machado et al. 2006; Svetel et al. 2001; Walshe and Yealland 1992). Another example is ataxia telangiectasia, which may first present in adults with isolated dystonia rather than ataxia (Meneret et al. 2014; Charlesworth et al. 2013; Saunders-Pullman et al. 2012; Verhagen et al. 2009). Similarly, dystonia may be the dominating clinical feature of several spinocerebellar ataxias (Neychev et al. 2011; Rossi et al. 2014). There is little information regarding DBS in these populations. Genetic testing can identify these atypical cases. It is particularly valuable for the identification of the more than 20 neurological disorders with dystonia where there are more appropriate therapies (Jinnah and Factor 2015; van Egmond et al. 2014).

Different surgical targets for different dystonias

The utility of any treatment is dependent on the pathogenesis of the disorder. Parkinson disease can be caused by many different genetic or acquired insults, but the vast majority of cases ultimately share a similar pathogenesis that involves degeneration of substantia nigra dopamine neurons and abnormal signaling in downstream nodes of the basal ganglia motor circuit. These nodes include the GPi and STN, both of which are approved DBS targets for advanced Parkinson disease. DBS targeting of these nodes provides a logical treatment strategy regardless of the original genetic or acquired insult, so genetic testing seems to have little impact. However, genetic testing in Parkinson disease can reveal additional factors that influence DBS outcomes, such subsequent risk of developing cognitive impairments (Angeli et al. 2013).

Dystonia is not one disorder, but a collection of different disorders. In fact, there is growing evidence that different subtypes of dystonia may results from disruption of different anatomical circuits involving the basal ganglia, cerebellum, or some interaction between the basal ganglia and cerebellum (Prudente et al. 2014; Neychev et al. 2011). The majority of studies have targeted the GPi for dystonia, but some have targeted the thalamus (Buhmann et al. 2013; Fukaya et al. 2007; Mills et al. 2014; Morishita et al. 2010; Pauls et al. 2014) or cerebellum (Sokal et al. 2015). It is possible that different subtypes of dystonia may respond more optimally to stimulation at different targets.

For genetically determined disorders, it is likely that the pathophysiology and exact neuronal pathways most affected are determined by regional expression of the gene product. Neuroimaging studies (Carbon and Eidelberg 2009) and physiological studies (Sadnicka et al. 2013; Carbon and Eidelberg 2009) both have shown that mutations in *TOR1A* and *THAP1* are associated with abnormalities in different circuits. These differences may contribute to why GPi DBS is more consistently effective for *TOR1A* mutations compared to *THAP1* mutations (Bruggemann et al. 2015). In fact, some reports have suggested that GPi may not be the ideal target for patients with *THAP1* mutations (Zittel et al. 2010; Miri et al. 2014; Mure et al. 2014; Bruggemann et al. 2015) Others have similarly argued for the need to target regions other than the GPi in myoclonus-dystonia syndrome (Vidailhet et al. 2012) or Wilson's disease (Hedera 2014).

Additionally, there are multiple reports suggesting that dystonic tremor may respond better to DBS of the thalamus rather than the GPi (Hedera et al. 2013; Morishita et al. 2010; Pauls et al. 2014). The association of specific genes such as *ANO3* with a tremor-dominant phenotype suggests that more careful delineation of genetic substrates may be useful for investigating additional DBS targets.

Scientific value of genetic testing

As outlined above, there is immediate practical value for genetic testing in making a precise diagnosis for counseling regarding prognosis, and possibly for selecting surgical targets. There also are important scientific reasons for genetic testing. Regardless of the genetic subtype of dystonia or the surgical target selected, DBS outcomes may be influenced by

mechanisms unrelated to the disorder itself, such neural plasticity or neuronal excitability, both of which are genetically determined (Quartarone and Hallett 2013).

For example, the outcome of DBS in dystonia may depend on neuroplastic changes. A comprehensive genetic screen related to plasticity has the potential to identify such mechanisms, which could ultimately lead to a better understanding of the biological mechanisms underlying DBS. Such a study would require a large number of cases with varied responses to DBS, and a comprehensive evaluation of known genetic influences on neuroplasticity, or an agnostic screen to identify potentially new influences.

Why is genetic testing conducted so infrequently?

For the isolated dystonias, several genes have been known for many years. However, testing for these genes is only rarely conducted for several reasons. The main reason is that several large screening studies have indicated that all of the currently known genes collectively account for ~2% of all cases of isolated dystonia (LeDoux et al. 2016). Thus globally testing for these genes is unattractive because of a high risk for a negative result. Further, each of the genetically distinct subtypes shows considerable phenotypic overlap. Therefore using the phenotype to guide more selective testing is unattractive. Finally, some of the genes reported to cause dystonia have recently been questioned because they have not been replicated (Domingo et al. 2016). Thus it is not entirely clear which genes should be tested.

For the combined dystonia syndromes, diagnostic testing traditionally involves delineating the clinical syndrome, and testing for a few specific genes that seem most relevant (Jinnah and Factor 2015; Balint and Bhatia 2015; van Egmond et al. 2014; Fung et al. 2013). This approach requires a high level of expertise on neurogenetics, which is not widely available in the community. Even among experts, the syndromic approach is subject to error, because there is phenotypic overlap among genetically distinct subgroups, and atypical phenotypes may occur.

Several other factors have diminished enthusiasm for genetic testing in dystonia. One has been a widely held view that delineating genes does not alter treatment strategies. As outlined above, this opinion is no longer tenable in light of evidence that genes re important for DBS outcomes. Another has been limited availability of genetic tests, especially for those genes recently discovered. The final factor has been cost, especially when multiple genes are tested. Because modern genetic testing is available only through a small number of specialized facilities and insurance plans often do not reimburse costs incurred outside a limited geographical area, patients and their families often bear the burden of paying for genetic testing. Fortunately, solutions for most of these limitations have emerged in recent years.

What Genetic Tests Are Most Appropriate?

Three traditional strategies have been used to delineate genetic contributions to specific disorders or clinical traits, such as response to DBS (Manolio et al. 2013; Rehm 2013; Biesecker and Green 2014; Olgiati et al. 2016). The first strategy involves evaluating a candidate gene, with a method known as “Sanger sequencing”. The second is an extension

of the candidate gene approach with targeted Sanger sequencing of a limited panel of genes. The third is a more global search for genetic risk involving a genome-wide association study (GWAS). Two additional relatively newer methods, both based on “next generation sequencing” (NGS) technology include large-scale sequencing of all exons (whole exome sequencing, WES) or the entire genome (whole genome sequencing, WGS). A related strategy involves starting with WES and adding more focused coverage of specific genes associated with a disorder. Each of these methods has specific advantages and disadvantages that are summarized in Table 3 (Olgiati et al. 2016).

Candidate gene approach

The simplest and most commonly suggested strategy is to look for mutations in specific genes known or suspected to contribute to dystonia, such as *TOR1A* or *THAP1.* A related strategy is to search for genes linked with neural plasticity, because they may influence DBS outcomes, as described above. This approach is attractive because it is hypothesis-driven, feasible, and effective.

However, the candidate gene approach has many limitations that make it non-viable. The cost of Sanger sequencing depends on the number of genes selected, their lengths, and the specific types of mutations anticipated (Neveling et al. 2013). Costs range from a few hundred to a few thousand US dollars per gene. The long list of genes and associated costs mean that comprehensive Sanger sequencing is financially unattractive. Also, because the currently known genes account for ~2% of all isolated dystonias (Lohmann and Klein 2013), the candidate gene approach is likely to be informative for only a small proportion of cases. This strategy also focuses on known genes, and cannot identify other genes beyond the ones chosen. The final limitation of the candidate gene approach is that the list of genes grows every year. The growing list means that results obtained at one point in time become obsolete as new genes are reported.

GWAS approach

This approach is based on the assumption that patients with common diseases or genetic traits share contiguous stretches of DNA (Manolio 2013, 2010; Manolio et al. 2009). By searching for specific single nucleotide polymorphisms across the genome, it is possible to link specific genetic variants with a disorder or trait. This approach is attractive because the development of high-throughput strategies has made it very inexpensive, with a cost of only $100 per sample. In addition, *a priori* hypotheses regarding potential candidate genes are not required, so novel genetic associations can be discovered.

Unfortunately, This approach is not a viable solution. GWAS is aimed at common disorders that presumably share common genetic variants. Dystonia is a rare disorder, and the ideal sample sizes of 1000–10,000 cases needed for a meaningful result are not realistically obtainable. The mutations for many dystonia genes also are not shared but rather heterogeneous; and many arise de novo. Very heterogeneous and de novo mutations are not suitable for GWAS. Finally, the GWAS design is not capable of linking a specific gene with a disorder or trait. The vast majority of polymorphisms selected for the GWAS design have no known functional consequence. Thus even a “positive hit” must be validated through

additional work involving identification of the responsible gene and functional tests of its significance.

Whole genome sequencing

Recent advances now make it feasible to read an individual's entire genetic code (Guerreiro et al. 2014; Biesecker and Green 2014; Manolio et al. 2013; Manolio 2013; Olgiati et al. 2016). WGS is capable of simultaneously detecting sequence variants in ~20,000 genes. It also can define sequence variants in non-coding regions of the genome, which make up the vast majority of human DNA. WGS is attractive because a priori hypotheses regarding candidate genes are not required, it is comprehensive, and the data for individual cases can be re-examined whenever new dystonia genes are discovered. Further, data from WGS are relatively standardized and durable, with good measures to assess quality. This latter aspect means that WGS data can be combined across labs, or at different times, for meta-analyses.

In addition to being forward compatible with new gene discovery, WGS can contribute to new gene discovery. In brief, WGS generates large amounts of data on sequence variants associated with pathogenic genes. WGS generates an even larger amount of data regarding sequence variants that have unknown significance because they have never previously been associated with any disease. Because the pathogenicity of any sequence variant is determined in part by how many times a specific disorder is associated with a specific gene, regularly re-examining WGS data from cohorts of patients with dystonia increases the power to detect relevant genes as WGS data accumulate over time.

WGS also has some drawbacks. First, it does not provide equally good coverage for all genes. It is not well suited for genes with a high content of guanine and cytosine bases (GC-rich areas). It also is not well suited for genes with pseudosequences, because they cannot be discriminated from the real gene. It is not well suited for detection of certain types of mutations, such as triplet nucleotide repeats or large deletions or duplications. However, technological advances are likely to address these limitations in the near future. For example, novel analytical algorithms have now been established to identify some deletions and duplications. A more troublesome limitation of WGS is that it provides an enormous amount of incidental data regarding genetic variants of unknown significance. The clinical significance of most of these variants is difficult to determine, and an average of ~6 million sequence variants per individual presents an overwhelming bioinformatics problem. Once again, the impact of this limitation is likely to lessen as bioinformatics tools improve. The final limitation of WGS is cost, which currently is about $2,500 per sample.

Whole exome sequencing

Whole exome sequencing (WES) is similar to WGS, except that it focuses on the portions of the genome that encode proteins. Exomes constitute only 1% of the total genome, but harbor ~85% of all disease-causing genes. WES has all of the same advantages of WGS; it covers ~20,000 genes, a priori hypotheses regarding candidate genes are not required, and data can be re-queried or combined at a future date. WES is increasingly used in clinical diagnostic laboratories, and methods for data analysis are more mature than for WGS. Most importantly, strategies for designating a genetic variant as pathological or benign are better

developed (Jurgens et al. 2015; Amendola et al. 2015; Green et al. 2013; Dorschner et al. 2013). Finally, WES is about half the cost of WGS (Fogel et al. 2016).

WES has some of the same limitations as WGS; it has unequal coverage of different genes and it is insensitive to certain types of mutations. Additionally, WES is expected to miss ~15% of potentially relevant genes that fall in non-coding DNA. WES also generates a large amount of data that may not be interpretable, with ~30,000 sequence variants of uncertain significance per individual. However, the proportion of un-interpretable data is expected to steadily decrease as WES becomes more widely used and large international databases such as the Human Gene Mutation Database and ClinVar accumulate data to define variants as benign or pathological (Riggs et al. 2013; Stenson et al. 2014; Bean et al. 2013).

Disease-specific NGS panels

The concept of disease-specific gene panels has evolved dramatically over recent years. Early panels were based on Sanger sequencing of a few genes related with a specific phenotype, and are still offered by many diagnostic laboratories. In recent years, many test labs have begun to offer larger disease-specific gene panels (DGP) that are based on the newer NGS methods and include much larger panels of genes. Several clinical testing laboratories now offer dystonia gene panels that include up to 100 or more genes. By focusing on a smaller list of relevant genes, the analytical burden is greatly reduced. In addition, the quality of the data being obtained for each target gene in the DGP can be assessed, and complementary methods can be added to correct any deficiencies in the coverage of GC-rich regions, triplet repeats, copy number variants, or pseudogenes. These features make a DGP better than WES for known genes.

DGPs also have some limitations. Although known genes are covered, some additional effort is needed to accommodate newly discovered genes. However, because these panels are often based on WES of all genes, the DGP is partly forward-compatible with new gene discovery, by reexamining the original data for any new gene found. If a new gene was adequately covered by the original sequencing run, then the original results can be used to assess the contributions of the new gene. The new gene can also be added to the DGP. Some additional effort also is needed to use the data to discover new genes. Here, the WES data for genes not covered by the DGP must be interrogated. Another limitation is that most DPGs are based on WES, which means that mutations falling in many non-coding regions cannot be detected. For most human disorders, this means that ~15% of mutations will be missed. The final limitation is that DGPs have developed very recently, and their performance is not yet established. Several diagnostic laboratories now offer panels for more common disorders such as mental retardation or ataxia, but few offer a dystonia panel. Because these panels are still under development, different laboratories may include different genes, with varying levels of complementary methods to address specific deficiencies.

Summary of genetic test strategies

The advantages and disadvantages of various strategies are summarized in Table 3. The candidate gene approach and GWAS are relatively straightforward methods, but provide limited value. WGS and WES provide more powerful and flexible solutions, but have some

known limitations and generate large amounts of data that can be difficult to handle. DGPs may provide a compromise, and currently may be the preferred option for DBS. Although DGPs are very new, they are superior to WES when considering their greater specificity and sensitivity for known genes. Although WGS may be more comprehensive because it has the potential to capture ~15% of additional non-coding mutations, DGPs are more cost-effective. As new bioinformatics strategies are being developed, WGS is likely to become the preferred approach in the future.

How Many Subjects Need to Have Genetic Testing to Demonstrate Value for DBS?

The number of subjects needed to demonstrate the potential value of genetic testing depends on the goal of this testing. If the goal is to refine knowledge of the diagnostic subtype to aid in counseling regarding expected outcomes, then testing of individual patients has value. The identification of even a single case with a subtype that is more appropriately treated with alternatives to DBS may avoid a surgical procedure that is not indicated would be of high value.

If the goal is to determine if a particular genetically defined subtype of dystonia responds to DBS, then a statistical power analysis is required. The results of this analysis will depend on the tools used to measure outcomes, the average response with the tool, and measurement variance across the population. Some rough estimates can be made for *TOR1A*-associated dystonia from several published reports (Table 4). Assuming that DBS causes a conservative average reduction in the Fahn-Marsden Dystonia Rating Scale of ~50%, 7–31 patients would be needed to demonstrate a significant effect in a double-blind, placebo-controlled trial. If a blinded cross-over design is used, even fewer patients would be needed, because statistical variance between cases can be mitigated by using each case as his or her own control. These estimates mean that studies with genetically defined subtypes are feasible.

On the other hand, if the goal is to determine if one particular genetic subtype responds better than another genetic subtype (e.g. *TOR1A* versus *THAP1*), a power analysis addressing measurement outcomes and variance for both populations is needed. This goal is of academic interest, but has less practical value than demonstrating efficacy in the *THAP1* population independent from the *TOR1A* population.

Conclusions

Many different genes cause many different types of dystonia. Although current data are limited because genetic testing is not routinely conducted prior to DBS, the available evidence indicates that genetic factors play an important role in outcomes. More methodical genetic testing can address some of the known challenges associated with the diagnosis of dystonia, and could potentially provide valuable information for patient selection and perhaps even target selection. More methodical genetic testing also has the potential to aid the scientific effort in discovering novel genes that may cause dystonia, and other unrecognized genes that may predict DBS outcomes. For rare disorders such as dystonia, systematic and multicenter efforts may be needed to definitively address genetic influences

on DBS outcomes. Among the many genetic testing strategies available, NGS-based dystonia gene panels may provide the best option. However, as new bioinformatics strategies are developed, WGS approaches may become the preferred option in the future.

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Table 1

Criteria for Classifying Dystonias

Axis	Dimension for classification	Subgroups
Axis I: Clinical Features	Age at onset	Infancy (birth to 2 years)
		Childhood (3–12 years)
		Adolescence (13–20 years)
		Early adulthood (21–40 years)
		Late adulthood (40 years and older)
	Body distribution	Focal (one isolated body region)
		Segmental (2 or more contiguous regions)
		Multifocal (2 or more non-contiguous regions)
		Hemidystonia (half the body)
		Generalized (trunk plus 2 other sites)
	Temporal pattern	Disease course (static vs progressive)
		Short-term variation (e.g. persistent, action-specific, diurnal, paroxysmal)
	Associated features	Isolated (with or without tremor)
		Combined (with other neurological or systemic features)
Axis II: Etiology	Nervous system pathology	Degenerative
		Structural (e.g. focal static lesions)
		No degenerative or structural pathology
	Heritability	Inherited (e.g. sex-linked or autosomal, dominant or recessive, mitochondrial)
		Acquired (e.g. brain injury, drugs/toxins, vascular, neoplastic)
	Idiopathic	Sporadic
		Familial

Table 2

Diagnostic Delays for Common Dystonias

Type of Dystonia	Source	Total Cases	Average years to diagnosis
Blepharospasm	Canada (Jog et al. 2011)	87	4.5
Blepharospasm	Italy (Macerollo et al. 2015)	100	4.8
Cervical dystonia	Canada (Jog et al. 2011)	47	6.4
Cervical dystonia	Italy (Macerollo et al. 2015)	50	7.1
Cervical dystonia	USA (Tiderington et al. 2013)	146	3.7
Hand dystonia	Italy (Macerollo et al. 2015)	21	10.1
Laryngeal dystonia	USA (Creighton et al. 2015)	107	4.4
Mixed	Australia (Bertram and Williams 2015)	133	3.8

This table shows the average length of time (in years) between symptom onset and diagnosis for different types of dystonia in different parts of the world.

Table 3

Comparison of Genetic Methods

Characteristic	GWAS	CGA	WGS	WES	DGP
Applicable to rare disorders such as dystonia	limited	yes	yes	yes	yes
Applicable to disorders with multiple genes such as dystonia	limited	limited	yes	yes	yes
Applicable to genes with heterogeneous mutations such as dystonia	no	yes	yes	yes	yes
Requires extensive clinical expertise in dystonia syndromes	no	yes	no	no	no
Requires selecting specific dystonia genes	no	yes	no	no	yes
Can simultaneously detect all currently known genes for isolated dystonias	no	no	yes	yes	yes
Can simultaneously detect all currently known genes for combined dystonias	no	no	yes	yes	yes
Forward-compatible with discovery of novel dystonia genes	no	no	yes	yes	yes
Capable of contributing to discovery of new genes genes	limited	no	yes	yes	yes
High sample throughput	yes	yes	no	no	no
Cost per subject[1]	$100	$100–10,000[2]	$3,000	$1500	$1500
Burden of data analysis	low	low	very high	high	moderate

Abbreviations: CGA, candidate gene approach; DGP, dystonia gene panel, GWAS, genome wide association study; WES, whole exome sequencing; WGS, whole genome sequencing.

[1] estimates are based on typical clinical diagnostic labs in the USA;

[2] actual amount depends on the numbers and sizes of genes selected.

Table 4

Statistical Power Analyses for DBS in Dystonia Associated with *TOR1A* Mutations

Source	Empirical observations				Expected improvement			
	Cases (N)	FM AVG	FM SD	Observed % Change	40%	50%	60%	70%
Coubes, 2004 (Coubes et al. 2004)	14	62.6	26.7	72	18	11	8	6
Vidailhet, 2005 (Vidailhet et al. 2005)	7	55.1	21.9	53	15	10	7	5
Starr, 2006 (Starr et al. 2006)	6	59.2	20.3	59	12	7	5	4
Alterman, 2007 (Alterman et al. 2007)	12	38.0	21.7	76	33	20	14	10
Bruggemann, 2015 (Bruggemann et al. 2015)	9	43.8	30.7	60	48	31	21	16

This table was based on published reports where relatively large numbers of cases with proven *TOR1A* mutations were presented with adequate information to calculate average pre-operative Fahn-Marsden Dystonia Rating Scale scores (FM AVG), standard deviations of these scores (FM SD) and average reductions in these scores following DBS (Observed % Change). The differences in the numbers of cases estimated to reach the expected degree of improvement are related to differences in the average starting severity and variance of the population reported.