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Dystonia; a roadmap is needed for future genetic studies

Dystonia is a condition featuring continuous or intermittent muscle contractions leading to abnormal involuntary posture or movements. Dystonia can be a feature of complex multi-systemic neurological disorders or an isolated clinical entity in which these muscle contractions are the main or only clinical feature. In the case of the latter, dystonia can be classified as isolated or combined, depending on the presentation of additional symptoms (i.e. myoclonus or parkinsonism), and as genetic or idiopathic, depending on whether a genetic cause can be identified. In addition, dystonia as a sign can be a feature of numerous disorders, including focal brain lesions, different forms of parkinsonism, metabolic disorders, mitochondrial disorders and others, adding to the complexity of studying dystonia. Lastly, dystonia can also be clinically classified based on the affected regions of the body such as focal, segmental or generalized [1,2]. Therefore, it is clear that the etiology of dystonia is complex, and thus dystonia should be viewed as a group of disorders which are clinically characterized by dystonia as a main feature but with various underlying causes, rather than a single disease. As such, and due to its rarity with an estimated prevalence of about 16/100,000 [3], understanding the genetic basis underlying dystonia can be challenging.

Thus far, our knowledge of the genetic basis of isolated dystonia has been mainly driven by studies of familial or early-onset cases, or small cohorts of specific types of dystonia. Mutations in genes such as *TOR1A* [4], *THAP1* [5], *ANO3* [6] and *GNAL* [7] have been identified in families with autosomal dominant isolated dystonia, of which *TOR1A* mutations are the most common. Autosomal recessive isolated dystonia is rarer, and while mutations in several genes were suggested to be causative, thus far only *HPCA* has been conclusively determined as causal [1]. As for combined dystonia, mutations in many other genes were identified, including *GCH1*, *TH*, *PRKRA*, *TAF1*, *ATP1A3, SGCE* and *KCTD17* [1,8]. Finally, mutations in *KMT2B* have been recently recognized as a frequent cause of childhood onset dystonia, frequently associated with other minor and often overlooked clinical features, such as short stature, mild facial dysmorphisms or intellectual disability [9].

However, mutations in these genes are exceedingly rare in cases with late onset focal dystonia, which represent the commonest form of disease [10,11]. Hence, our understanding of the genetic basis of "idiopathic" dystonia is still very limited, and most of these cases remain genetically undiagnosed. Importantly, a relevant contribution of genetic factors to disease pathogenesis is highly likely also in this category, as clearly indicated by the frequent report of a positive family history in patients with focal dystonia (~15–20%, increasing up to ~50% in cases with tremulous cervical dystonia) [12,13]. As a rare group of diseases, collecting large enough sample sizes to perform meaningful genetic studies is challenging. This can be further complicated by the possibility that some (or even many) of these dystonia cases are caused or influenced by neurotoxins or other environmental, infectious, immunological or other factors [1]. Thus far, only two genome-wide association studies (GWAS) have been performed on case-control cohorts with dystonia. One study was focused on musician's dystonia [14] and the second on cervical dystonia [15], both with less than 500 patients each, making them highly underpowered to detect GWAS hits that are typically with odds ratios ranging between 1.1 and 1.5.

In the December 2018 issue of *Parkinsonism and related disorders,* Ohlei and colleagues have performed a comprehensive field synopsis and meta-analyses of case-control studies of sporadic dystonia [16]. A total of 134 meta-analyses using data from 52 datasets were performed after a thorough literature review, and a total of 42 single nucleotide polymorphisms (SNPs) from 17 loci were analyzed after harmonizing the data. The meta-analyses included all types of isolated dystonia, and specific forms of dystonia including musician's dystonia, blepharospasm, cervical dystonia, spasmodic dysphonia, writer's dystonia, segmental dystonia and generalized dystonia were also separately analyzed. When analyzing all dystonia cases combined, only five variants reached a nominal $p < 0.05$, and only one variant in the dopamine receptor D1 (*DRD1*) locus was associated with dystonia after correction for multiple comparisons. In specific dystonia types, only one variant, an intronic SNP in the arylsulfatase G (*ARSG*) gene, was associated with musician's dystonia after correction for multiple comparisons, as was previously reported in the GWAS that first identified this association and from which the data was extracted [14]. Exemplifying the challenges mentioned above, these meta analyses mainly included variants in already known dystonia-related genes, and included data from a total of 323 individuals (patients and controls) in the smallest analysis up to 6484 individuals in the largest. In the vast majority of analyses, the total number of patients analyzed was below 1000. Therefore, there was not sufficient power to reach statistical significance in most analyses, considering ORs of < 1.3 that are typically seen in most GWASs. However, it is important to note that for variants in which the association did not remain statistically significant after correction for multiple comparison (and thus cannot be considered as a true association), this does not rule out a potential importance of these variants and these genes in sporadic dystonia, and larger cohorts are needed to examine their role in risk for dystonia. For example, the three *ARSG* SNPS rs11655081, rs7342975 and rs9972951 are in LD and represent a haplotype that includes an intronic variant, a synonymous variant (p.P370P) and a non-synonymous variant (p.R385H) in *ARSG*, respectively. Such haplotype (which warrants additional, independent replications), represents an opportunity for functional studies in attempt to elucidate if and how these variants affect molecular or cellular functions that may be associated with dystonia. The possibility that common variants in genes that are already known to cause mendelian forms of the disease also affect disease risk was demonstrated in other

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neurological disorders. For example, in Parkinson's disease (PD) and atypical parkinsonism, common variants in genes such as *SNCA*, *LRRK2*, *GBA, GCH1* and *VPS13C* are implicated in GWAS, and rare variants in these genes lead to mendelian forms of parkinsonism or confer high risk for PD (https://www.biorxiv.org/content/early/2018/08/09/388165). Therefore, the results presented by Ohlei et al. are encouraging as they are likely to represent true associations and may drive additional studies.

While the study by Ohlei et al. is mostly negative and adds little to our understanding of the genetic basis and pathogenic mechanisms underlying dystonia, it does provide an up-to-date synopsis of the field, provides targets for genetic validation, and specifically emphasizes the need for much larger genetic studies of dystonia. Large genetic consortia have been proven to be very useful in identifying novel genes involved in rare and common neurological disorders. For example, European and North American consortia focusing on amyotrophic lateral sclerosis (ALS) or hereditary spastic paraplegia (HSP), which are rarer than dystonia, were able to identify in recent years several new genes and potential mechanisms involved in ALS and HSP using cohorts with hundreds to tens of thousands of patients [17–20]. A consortium dedicated to the genetics on dystonia can take two main approaches to identify novel genes: a GWAS approach to identify common genetic factors associated with risk for dystonia, and a full sequencing approach to identify the cumulative effects of rare genetic variants in dystonia. For both types of approaches, a large consortium is required to reach the number of patients needed for achieving sufficient power for these genetic analyses. Of note, even based on a prevalence of 16/100,000 (it is possible that the actual prevalence of dystonia, as the third most common movement disorder, is actually higher), there should be about 50,000 dystonia patients in the US alone, more than 100,000 in Europe and more than 200,000 in China. Therefore, the numbers are there, yet many challenges are involved in creating such a consortium, most of which could be solved by proper funding and engagement of clinicians and researchers. Furthermore, to facilitate future analyses with more power, there is a need for data driven phenotyping and phenotype harmonization across dystonia subtypes. This can be also achieved by utilizing large national biobanks and healthcare systems. While a few initiatives have emerged in recent years [10,21], they are still too small to generate meaningful, large-scale genetic studies. The current paper by Ohlei et al. can be viewed as an urgent call for such an effort. This would probably be the only way to identify novel genes and genetic variants involved in dystonia, which will ultimately lead to a better understanding of the disease and identification of novel targets for therapeutic development.

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