Risk Factor Genes in Patients with Dystonia: A Comprehensive Review

Vasileios Siokas1, Athina-Maria Aloizou1, Zisis Tsouris1, Amalia Michalopoulou1, Alexios-Fotios A. Mentis2,3 & Efthimios Dardiotis1*

1Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Larissa, GR, 2Department of Microbiology, University of Thessaly, University Hospital of Larissa, Larissa, GR, 3Public Health Laboratories, Hellenic Pasteur Institute, Athens, GR

Abstract

Background: Dystonia is a movement disorder with high heterogeneity regarding phenotypic appearance and etiology that occurs in both sporadic and familial forms. The etiology of the disease remains unknown. However, there is increasing evidence suggesting that a small number of gene alterations may lead to dystonia. Although pathogenic variants to the familial type of dystonia have been extensively reviewed and discussed, relatively little is known about the contribution of single-nucleotide polymorphisms (SNPs) to dystonia. This review focuses on the potential role of SNPs and other variants in dystonia susceptibility.

Methods: We searched the PubMed database for peer-reviewed articles published in English, from its inception through January 2018, that concerned human studies of dystonia and genetic variants. The following search terms were included: “dystonia” in combination with the following terms: 1) “polymorphisms” and 2) “SNPs” as free words.

Results: A total of 43 published studies regarding TOR1A, BDNF, DRD5, APOE, ARSG, NALC, OR4X2, COL4A1, TH, DDC, DBH, MAO, COMT, DAT, GCH1, PRKRA, MR-1, SGCE, ATP1A3, TAFI, THAPI, GNAL, DRD2, HLA-DRB, CBS, MTHFR, and MS genes, were included in the current review.

Discussion: To date, a few variants, which are possibly involved in several molecular pathways, have been related to dystonia. Large cohort studies are needed to determine robust associations between variants and dystonia with adjustment for other potential cofounders, in order to elucidate the pathogenic mechanisms of dystonia and the net effect of the genes.

Keywords: Dystonia, genetic polymorphism, single nucleotide polymorphism, variant, cervical dystonia, blepharospasm, movement disorders

Citation: Siokas V, Aloizou AM, Tsouris Z, Michalopoulou A, Mentis AFA, Dardiotis E. Risk factor genes in patients with dystonia: a comprehensive review. Tremor Other Hyperkinet Mov. 2018; 8. doi: 10.7916/D8H439GS

Introduction

Dystonia is a movement disorder with high heterogeneity regarding phenotypic appearance and etiology.1 The prevalence of dystonia is estimated to be 16:100,000.2,3 In 2013, a new general definition and classification of dystonia were introduced by an international panel of dystonia experts.4 The two main axes of this classification are considered to be the etiology and the clinical features.5 However, the pathophysiology and cause of most dystonia cases remain largely unknown.5

A polymorphism is a variation in the DNA sequence that occurs in a population with a frequency of 1 % or higher.6,7 When a variation occurs in a single nucleotide, at a specific position in the genome, it is called an SNP (single-nucleotide polymorphism).8,9 SNPs can occur within coding sequences of genes, non-coding sequences, introns, or the regions between genes (also known as intergenic regions).10,11 An SNP across a coding sequence of a gene can be characterized as synonymous (when the protein sequence is not affected) and nonsynonymous (when the amino acid sequence of the protein is altered).10,12 The non-synonymous SNPs are divided into missense (when they result in a different amino acid) and nonsense (when they result in a premature stop codon).10,12 Recently, it has been recommended that both terms, “mutation” and “polymorphism”, be replaced by the term “variant”.13,14 An additional modifier (e.g. pathogenic, benign) to the term “variant” should be used, in order for its pathogenic or benign effect to be declared.13,14
The importance of genetic factors was unambiguously demonstrated with the identification of causative pathogenic variants in monogenic cases of familial dystonia under the autosomal dominant, autosomal recessive, or X-linked mode of inheritance. Furthermore, a few candidate gene association studies (CGASs) have suggested that the presence of specific genetic loci may confer susceptibility to dystonia. Therefore, in the present review article, discernible family history, and results from case–control studies are relatively rarely discussed. Therefore, in the present review article, we discuss the current state of knowledge regarding genetics of dystonia, by emphasizing the CGASs that have linked single nucleotide polymorphisms and variants across genes that predispose to dystonia. Owing to the lack of a widely accepted nomenclature gene classification system for dystonia, we have used gene names for loci identification. The main aim of the current comprehensive review is to shed some light on which polymorphisms predispose for dystonia, and to what extent.

**Methods: study identification and selection**

In order for any potentially relevant study to be identified, we searched through the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) for peer-reviewed articles published in English, from its inception to January 2018, that concerned human studies of dystonia and genetic polymorphisms. The following search terms were included: "dystonia" in combination with 1) "polymorphisms" and 2) "SNPs" as free words. The complete search algorithm is available in the S1 Appendix. The last literature search was performed on February 20, 2018. Additionally, reference lists of retrieved articles were examined in order to identify missing from the initial database search results. The flowchart presenting the selection procedure of the studies is presented in Figure 1. Published studies between 1996 and 2017 were included.

The following data were extracted from each study, when possible: author, year of publication, ethnicity of the studied population, numbers of cases and controls, age at disease onset, mean age and gender distribution, tested variants, family history of the participants, screening or not for the risk factors, and the tested dystonia phenotypes.

**Results and discussion**

Published studies between August 2001 and September 2017 were included. Baseline characteristics from studies regarding TOR1A, BDNF, DRD5, APOE, ARSB, NALC, OR4A2, COL4A1, TH, DDC, DBH, MAO, COMT, DA1T, GCH1, PRKRA, MR-1, SGC, ATP1A3, TAF1, THAP1, GNAL, DRD2, HLA-DRB, CBS, MTHFR, and MS are presented in Supplementary Tables 1–5. GnomAD frequencies (http://gnomad.broadinstitute.org/) and the type of individual variants are available at the S2 Appendix.

**TOR1A**

The TOR1A gene is a five-exon gene that covers an 11-kb region in chromosome 9. The TOR1A protein, called TorsinA, belongs to the family of the AAA+ ATPases. It can be found in the endoplasmic reticulum and the nuclear envelope of most cells, including those of the central nervous system. The function of TorsinA and how TOR1A gene pathogenic variants lead to dystonia remains largely unknown. TorsinA acts mainly as a molecular chaperone. The molecular and cellular processes in which TorsinA is involved include the interactions between cytoskeleton and membrane, important functions of the endoplasmic reticulum and the nuclear envelope, and the regulation of cellular lipid metabolism.

**TOR1A** remains the most extensively studied gene in both monogenic and sporadic forms of dystonia. However, results from case–control studies yielded conflicting results, with the association being affected by body distribution, ethnicity, and other phenotypic manifestations. A number of case–control studies have been conducted so far, and quite a few TOR1A variants have been investigated (rs1801968, rs2296793, rs1182, rs3842225, rs13283584, rs11787741, rs13297609, rs2287367, rs1045186, and rs35153737). Apart from case–control studies, a number of variants have been identified through mutational screening (rs766483672, rs80358233, rs75881550, rs1183, rs563498119, rs573629050, rs1045441, and rs144572721). Additionally, three meta-analyses have been conducted so far examining the effects of TOR1A gene variants on dystonia. The most recent evidence stemming from a meta-analysis, reveals a significant association of the rs1182 (allele frequency $AF = 0.1666$) and the rs1801968 (AF = 0.1236 for the G allele and AF = 0.8764 for the C allele) TOR1A variants with the development of focal dystonia (FD) and writer’s cramp (WC) respectively. Moreover, variants within 3’-UTR (untranslated region) encoded by exon 5 represent an additional functional genetic locus of TOR1A, though it may be under synergistic action with other TOR1A genetic variants. This comes in accordance with a recent case–control study, suggesting an association of the rs35153737 in the 3’-UTR of TOR1A with dystonia; a result, though, that has been attributed to functional variants that are in high linkage disequilibrium (LD).

From a functional aspect, loci containing the aforementioned variants appear to have consequences; variants across exon 4 and 3’-UTR encoded by exon 5, in particular, appear to overall influence the function of the TOR1A gene. More specifically, rs1801968 was confirmed to be associated with reduced penetrance of the ΔGAG pathogenic variant in humans. Regarding the 3’-UTR of exon 5, there is only some indication that specific variants across this region may have some functional consequences under synergistic action. Interestingly, based on the results regarding frequencies, computational analyses and function experiments, rs563498119 in the 3’-UTR of TOR1A was reported to change the expression of the TOR1A gene.
The regulation of TOR1A expression, by mutating the conserved region of the binding site of the human microRNA (hsa-miR-494), where rs563498119 is located, hints towards hsa-miR-494 being a possible therapeutic target.53

BDNF and APOE

Among the major mechanisms in dystonia, the reduced inhibition of the motor system and the increased plasticity are included.56 In greater detail, increased plasticity in the hand representation area of the motor cortex has been observed in focal hand dystonia, blepharospasm (BSP), and cervical dystonia (CD) using high-resolution transcranial stimulation.57 Consequently, abnormal plasticity within certain motor cortical circuits may represent a lineament of adult-onset dystonia forms.57,58

Synaptic plasticity is influenced by the brain-derived neurotrophic factor (BDNF). A common SNP across the BDNF gene within the prodomain region is the rs6265 (G/A) (AF=0.1896) and it results in the substitution of Val in amino acid position 66 with Met (Val→Met), which may influence synaptic plasticity59–61 and is possibly involved in dystonia development. Healthy carriers of the val66met appear to have differences in brain structure and abnormal motor cortex plasticity as well.62,63 Rs6265 has been found to be associated with quite a few diseases such as Parkinson’s disease, Alzheimer disease (AD), schizophrenia, bipolar disease, depressive disorder, and panic disorders, although strong evidence has yet to be presented.64–69

The studies that have been conducted so far regarding the role of the rs6265 on dystonia have yielded conflicting results. More precisely, rs6265 has been reported to be associated with CD and BSP in...
multiethnic and Chinese cohorts respectively.\textsuperscript{70,71} Additionally, higher frequency of bilateral postural arm tremor in CD patients with the BDNF Met66Met variant than in Val66Met and Val66Val carriers has also been observed.\textsuperscript{72} However, these results have not been replicated in Serbian, Chinese, Italian, or Caucasian dystonia cohorts.\textsuperscript{58,73–77} To date, two meta-analyses have evaluated the effects of rs6265 variant on dystonia.\textsuperscript{75,76} The most recent reports a statistically significant overall effect of the AA genotype on the development of idiopathic dystonia.\textsuperscript{76}

The THAP domain, a proline-rich region, and a carboxy-terminal nuclear factor THAP1, a zinc finger protein with an amino-terminal coupling of dopamine type 1 receptors and the adenosine A2A receptor, convey both the direct and indirect pathway to the activation of adenylyl cyclase, by coupling dopamine type 1 receptors and the adenosine A2A receptors in medium spiny neurons, respectively.\textsuperscript{89} In fact, the involvement in the indirect pathway of the activation leads to the activation of adenyl cyclase type 5 (AC5). AC5 is encoded by the adenyl cyclase 5 (ADCY5) gene, which was recently reported to be a co-founder of dystonia.\textsuperscript{101} It is possible that epistasis phenomenon with ADCY5 influences the causative effect of GNL variants. Newman at al.\textsuperscript{40} in 2012, apart from TOR1A and THAP1, which are described in the above sections, genotyped several variants of other genes as well (TAI1, GCH1, MR-1 (PNKD), SGCE, ATPIA3, PRKRA, HLA-DRB, CBS, MTHFR, and MS).

GNAL (guanine nucleotide-binding protein subunit alpha L) has been identified as responsible for adult-onset dystonia, which is primarily cervical or cranial.\textsuperscript{99} A few GNL variants (rs9303742, rs9675415, rs1895689, rs8095592, rs72865259, rs1647556, rs200508915, rs138151459, rs2071140, rs2071141, rs199571902) have been examined for association with generalized, multifocal, segmental, and focal dystonia.\textsuperscript{100} Despite the fact that no strong evidence for association with dystonia was found, novel variants are constantly reported in single dystonia patients with various phenotypes,\textsuperscript{100} leading to approximately 30 different GNL variants in dystonia patients.\textsuperscript{5} GNL encodes guanine nucleotide-binding protein G subunit alpha [Gz(ol)]. Gz(ol) is involved in both the direct and indirect pathway to the activation of adenylyl cyclase, by coupling dopamine type 1 receptors and the adenosine A2A receptors in medium spiny neurons, respectively.\textsuperscript{99} In fact, the involvement in the indirect pathway of the activation leads to the activation of adenyl cyclase type 5 (AC5). AC5 is encoded by the adenyl cyclase 5 (ADCY5) gene, which was recently reported to be a co-founder of dystonia.\textsuperscript{101} It is possible that epistasis phenomenon with ADCY5 influences the causative effect of GNL variants.

Case–control studies regarding THAP1 variants are limited\textsuperscript{35,40} because of the variety and the rarity of THAP1 variants. Therefore, most findings derive from mutation screening and the comparison between dystonia cases and healthy individuals.\textsuperscript{86,87,90–96} However, there is an indication that the frequency of the G allele of the c.71+126T>G pathogenic variant was elevated in British dystonia patients.\textsuperscript{90} –237_236GA>TG was also over-represented in dystonia when compared with controls in a European cohort\textsuperscript{84} but these results could not be replicated.\textsuperscript{90,91,97} Furthermore, the IVS2-87 A>G (rs11989331, AF=0.003428) was over-represented in dystonia in an Indian study.\textsuperscript{95} The MAF of rs20029986 was also found to be significantly higher in dystonic patients (MAF=0.359%) than in the controls (MAF=0.0318%, p<0.05) in the Vemula et al.\textsuperscript{40} study and the 1000 Genomes project (MAF=0.0916%, p<0.05), but not when compared with the EVS database (MAF=0.199%, p=0.13).

The large amount of THAP1 pathogenic variants linked to dystonia may suggest an interplay between environmental and genetic factors.\textsuperscript{50} Further, the type of work or the exposure to environmental factors, such as pesticides, may possibly predispose to dystonia development in pathogenic variant carriers.\textsuperscript{71,86,87}
leading to a deficiency in dopamine and serotonin.\textsuperscript{104} Therefore, a possible role of \textit{GCH1} in non-monogenic forms of dystonia should not be dismissed, as scientific reasoning could not be substituted by statistical analysis.\textsuperscript{105}

Finally there is no strong evidence for the association between \textit{HLA-DRB} variants or variants in the homocysteine pathway (cystathionine \(\beta\)-synthase [CBS], methionine tetrahydrofolate reductase [MTHFR], methionine synthase [MS] genes) with dystonia.\textsuperscript{50}

**Dopamine pathway genes (DAT1, DRD1, DRD2, DRD3, DRD4, DRD5, COMT, DAT, TH, MAO-A and -B, DDC, and DBH)**

Dystonic movements are considered the result of impaired function and abnormalities of dopaminergic neurotransmission and signaling in the basal ganglia.\textsuperscript{106} The involvement of the dopaminergic system in the pathophysiology of dystonia has also been enhanced via the mutated genes of the dopamine pathway in monogenic forms of dystonia (\textit{GCH1}).\textsuperscript{**107**} Allele 2 of the \textit{DRD5} has been associated with increased risk of CD and BSP in British cohorts.\textsuperscript{108,109} Allele 6 and allele 4 of the \textit{DRD5} have been associated with CD in British and Italian cohorts respectively.\textsuperscript{109,110} thus strongly supporting the involvement of the \textit{DRD5} gene in dystonia.\textsuperscript{111} However, \textit{DRD5} has not been associated with dystonia in Italian, US, and German studies.\textsuperscript{109,50} Dopamine receptor genes regulate neurotransmission in response to dopamine.\textsuperscript{112} Dopamine receptors are divided into two families, based on either the activation (D1-like receptors: \textit{DRD1} and \textit{DRD3}) or the inhibition (D2-like receptors: \textit{DRD2}, \textit{DRD3}, and \textit{DRD4}) of adenylate cyclase.\textsuperscript{113} Although the negative results in genes of dopamine signaling pathway (dopamine receptors) are few,\textsuperscript{49,114,115} Groen et al.\textsuperscript{115} suggested that changes in dopamine levels may be secondary during the dystonia course and that rare single nucleotide variants of dopamine genes are possibly associated with dystonia.\textsuperscript{116}

**ARSG, NALC, OR4X2, COL4A1**

To date, only two genome-wide association studies (GWASs) have been performed in order to identify variants that may predispose to dystonia.\textsuperscript{117,118} According to their results, there is a preliminary indication that alylsulfatase G (\textit{ARSG}) and sodium leak channel (\textit{NALCN}) variants play that role.\textsuperscript{117,118}

In a GWAS executed by Lohmann et al.,\textsuperscript{117} it was suggested that the intronic rs11655081 (\(AF=0.181\)) of the \textit{ARSG} gene was associated with musician’s dystonia and writer’s cramp. The missense rs61999318 (\(AF=0.002619\)) was significantly higher in the group of writer’s cramp patients than in European Americans in the EVS database (\(p=0.0013\)).\textsuperscript{119} Functional analysis suggested that rs61999318 may represent a functional variant, as the underlying amino acid substitution of isoleucine at position 493 with threonine (p.I493T) appears to be disease causing.\textsuperscript{119} \textit{ARSG} is the protein encoded by \textit{ARSG}; it hydrolyzes sulfates esters and is therefore implicated in cell signaling, synthesis of hormones, and protein degradation.\textsuperscript{120} Moreover, it may be involved in neuronal ceroid lipofuscinosis,\textsuperscript{121} which can present itself as dystonia.\textsuperscript{117} In view of the former considerations, \textit{ARSG} could be targeted as a gene for further study mainly in task-specific dystonias.

According to the GWAS from Mok et al.,\textsuperscript{118} the cluster of variants near exon 1 of \textit{NALCN} was found nearest to the significance threshold in a British population with CD. The most statistically significant variants were \textit{rs61973742, rs1338051, rs9518385, rs9518384, rs1338041} rs3916908, \textit{COLA1} (rs619152), \textit{RGL1} (rs12132318), \textit{OR4X2} 3 (rs67963238), intergenic (rs1249277, rs1249281, rs9146795), \textit{KIAA1715} (rs10930717), \textit{ORHBI} (rs35872350).\textsuperscript{118} However, a replication of this GWAS case-control study did not report any association of \textit{NALCN}, \textit{OR4X2}, \textit{COLA1}, and intergenic variants,\textsuperscript{122} and the results for \textit{NALC} (rs1338041), \textit{rs61973742} were also not reproduced in a Chinese population.\textsuperscript{123} \textit{NALCN} is a voltage-independent and cation-non-selective channel. Its main function is the leaky sodium transport across neuronal membranes and the regulation of neuronal excitability.\textsuperscript{124} In general, variants in genes, whose protein also acts like an ion channel, are crucial components and may be additional factors for dystonia development.\textsuperscript{117} \textit{AN03} is among the confirmed genes that cause a monogenic form of late-onset cranioencephal dystonia, with a possible effect on the calcium-activated chloride channel.\textsuperscript{5,125}

**Concluding remarks**

Genetic factors confer susceptibility to dystonia development. More precisely, based on our review, exon 4 and the 3’-UTR of exon 5 represent loci that appear to have a strong influence on the function of the \textit{TOR1A} gene, and their pathogenic variants may be associated with sporadic forms of dystonia, specifically with focal distribution. Moreover, rs6265 of \textit{BDNF} appears to be strongly associated with dystonia as well. As the function of the \textit{BDNF} gene may be influenced by other variants, additional loci across it may be worth examining. Further analysis of the \textit{ARSG} gene, notably the rs61999318 in focal task-specific dystonia cohorts and the \textit{DRD5} gene in focal dystonia, is warranted. Additional studies of \textit{GCH1} may be required. Owing to their rarity, \textit{THAP1} gene variants are insecure targets for future case–control studies. The continuing identification of pathogenic variants that cause monogenic forms of dystonia will lead us to new possible targets for case–control studies.\textsuperscript{1,3}

Next-generation sequencing has led to the identification of new dystonia genes on a monthly basis.\textsuperscript{5,123,126} Therefore, a large amount of common and rare genetic variants that may predispose to dystonia have been identified. Also, a few identified variants may affect penetrance, age at onset, spread to adjacent body, or the phenotype of dystonia.\textsuperscript{127} However, it is not prudent to assume that all these genes truly lead to dystonia, and therefore results need to be interpreted with caution. Therefore, applying the CGASs approach to next-generation data could possibly shed some light on the mechanisms of the complex traits.\textsuperscript{127}

The understanding of the genetic basis of monogenic and sporadic forms of dystonia will permit the identification and deeper knowledge of dystonia’s pathogenesis. This will provide physicians with more personalized tools to manage dystonia in the future, even from the time of diagnosis, and they may also be used for assessing the biological progression of the disease and guide the treatment decisions.\textsuperscript{128}
considered as new possible targeted therapeutic approaches.\textsuperscript{53,59} The stronger grasp on dystonia’s genetic susceptibility will also improve genetic testing and counseling.

The lack of validation reproducibility of the positive results could be attributed to several factors; firstly, the culture of null hypothesis significance testing.\textsuperscript{77} Moreover, low power CGASs because of relatively small sample sizes is a common phenomenon, as the effective population should ideally be very large (~10,000 individuals) in order for a modest genetic effect to be identified.\textsuperscript{129} The interplay between environmental (e.g. pesticides)\textsuperscript{98,99} and genetic factors, as well as among genetic factors,\textsuperscript{5} may variably determine the penetrance of pathogenic variants and the phenotype.\textsuperscript{10,20,26,98,130,131} Furthermore, the phenotypic divergence of dystonia and the possible classification bias should be considered, as the majority of the studies were performed before the new dystonia classification.\textsuperscript{4,15} Finally, epigenetic mechanisms may represent an additional explanation for the lack of result validation.\textsuperscript{26}

Therefore, it is of great necessity that more collaborative studies\textsuperscript{132,133} with adjustment for other potential cofounders (e.g. gene-environment interactions with adjustment for pesticide exposure,\textsuperscript{96} air pollution,\textsuperscript{141} diseases of the anterior segment of the eye, preceded injury, trauma, surgical intervention or sore throat,\textsuperscript{130} time spent handwriting per day and the writing time before dystonia onset,\textsuperscript{135} genome methylation status) and a supportive functional analysis be conducted in the future. In this way, the pathogenic mechanisms of dystonia and the net effect of the genes could be elucidated and, consequently, the inherent limitations of association studies will be avoided.\textsuperscript{136}

Certain limitations of the present review need to be acknowledged. Firstly, supportive data regarding functional analysis of variants would give more robustness to our conclusions. Moreover, we included relevant studies regardless of the sample power and without any prior quality assessment. Therefore, a possible confounding by population stratification or technical factors cannot totally be excluded. Finally, based on our search strategy procedure, it is possible that some eligible studies might not have been identified. However, this is an inherent limitation of such studies, and the inclusion of a large number of studies does not affect the major conclusions of our results.

We should bear in mind that positive results from genetic association studies require biological and functional evidence that the risk variant is actually involved in the pathophysiology and the pathogenesis of the relevant disease. Pathway-based analysis could facilitate more robust analysis even of GWAS and provide additional biological insights on the mechanisms of disease complex traits.\textsuperscript{137,138} Therefore, the scientific reasoning could not be replaced by any single statistical value, index, or test.\textsuperscript{105,139} As a consequence, by the correct interpretation of statistical values, the misinterpretation of results could be avoided.\textsuperscript{140}

\textbf{References}

1. Balint B, Valente EM. KMT2B: a new twist in dystonia genetics. Mov Disord 2017;32:529. doi: 10.1002/mds.26957

2. Steeves TD, Day L, Dykenman J, Jette N, Pringsheim T. The prevalence of primary dystonia: a systematic review and meta-analysis. Mov Disord 2012;27:1789–1796. doi: 10.1002/mds.25244

3. Lehmann K, Klein C. Update on the genetics of dystonia. Curr Neurol Neurosci Rep 2017;17:26. doi: 10.1007/s11910-017-0735-0

4. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28:663–673. doi: 10.1002/mds.25475

5. Standaert DG. Update on the pathology of dystonia. Neurobiol Dis 2011;42:148–151. doi: 10.1016/j.nbd.2011.01.012

6. Brooks AJ. The essence of SNPs. Gene 1999;234:177–186. doi: 10.1016/S0378-1119(99)00219-X

7. Kara E, Xiromerisiou G, Spanaki G, Bozi M, Koutsi G, Pana M, et al. Assessment of Parkinson’s disease risk loci in Greece. Neurobiol Aging 2014;35:442.e9–e16. doi: 10.1016/j.neurobiolaging.2013.07.011

8. Dardiotis E, Fountas KN, Dardioti M, Xiromerisiou G, Kapsaliaki E, Tasiou A, et al. Genetic association studies in patients with traumatic brain injury. Neurosurg Focus 2010;28:E9. doi: 10.3171/2009.10.FOCUS09215

9. Moraitou M, Hadjiyorgiou G, Monopolis I, Dardiotis E, Bozi M, Vassilatis D, et al. β-Glucocerebrosidase gene mutations in two cohorts of Greek patients with sporadic Parkinson’s disease. Mov Disord 2011;104:149–152. doi: 10.1002/mds.23015

10. Aerts J, Wetzels Y, Cohen N, Aarsen J. Data mining of public SNP databases for the selection of intragenic SNPs. Hum Mutat 2002;20:162–173. doi: 10.1002/humu.10107

11. Xiromerisiou G, Kyratzi E, Dardiotis E, Bozi M, Tsimourtou V, Stamoulis E, et al. Lack of association of the UCH-L1 gene with Parkinson’s disease in a Greek cohort: a haplotype-tagging approach. Mov Disord 2011;26:1955–1957. doi: 10.1002/mds.23694

12. Lee EK, Gorospe M. Coding region: the neglected post-transcriptional code. RNA Biol 2011;8:44–48. doi: 10.4161/rrna.8.1.13863

13. Hoskinson DC, Dubac AM, Mason-Suares H. The current state of clinical interpretation of sequence variants. Curr Opin Genet Dev 2017;42:33–39. doi: 10.1016/j.gde.2017.01.001

14. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424. doi: 10.1038/gim.2015.30

15. Siokas V, Dardiotis E, Tsironi EE, Tsivgoulis G, Rikos D, Sokratous M, et al. The role of TOR1A polymorphisms in dystonia: a systematic review and meta-analysis. Phs one 2017;12:e0169934. doi: 10.1371/journal.pone.0169934

16. Balint B, Bhatia KP. Isolated and combined dystonia syndromes – an update on new genes and their phenotypes. Eur J Neurol 2015;22:610–617. doi: 10.1111/ene.12650

17. Camargo CH, Camargo ST, Cardoso FE, Teive HA. The genetics of the dystonias—a review based on the new classification of the dystonias. Arq Neuropsiquiatr 2015;73:350–358.

18. Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain 2013;136(Pt 7):2017–2037. doi: 10.1093/brain/awt138
28. Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, et al. Candidate gene studies in focal dystonia. *J Neurol Sci* 2003;61:189–193. doi: 10.1016/j.jns.2002.07.005

29. Clarrigois M, Ayot E, Armond J, et al. Genetic markers of DYT1 dystonia in a French community sample. *Mov Disord* 2011;26:1939–1943. doi: 10.1002/mds.23800

30. Clarimon J, Asgeirsson H, Singleton A, Jakobsson F, Hjaltason H, Hardy K, et al. Strong genetic evidence for association of the D10A locus with idiopathic primary dystonia in the Chinese Han population. *Parkinsonism Relat Disord* 2012;19:399–401. doi: 10.1016/j.parkreldis.2012.08.013

31. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

32. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

33. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

34. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

35. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

36. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

37. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

38. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

39. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

40. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

41. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

42. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

43. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

44. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

45. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126

46. Foroud T, Risch N, Nusbaum C, et al. Genetic analysis of DYT1 dystonia in a population sample. *Nat Genet* 2002;32:184–188. doi: 10.1038/ng1002-126
51. Hague S, Klaffke S, Clarimon J, Hemmer B, Singleton A, Kopsch A, et al. Lack of association with TorsinA haplotype in German patients with sporadic dystonia. *Neurology* 2006;66:951–952. doi: 10.1223/01.wnl.0000203344.43324.18

52. Li J, Long Y, Huang X, Chen Y, Chen W, Liu S, et al. Deletion variant rs5135377 in *TOR1A* is associated with isolated dystonia in a southwestern Chinese population. *Neurosci Lett* 2017;657:1–4. doi: 10.1016/j.neulet.2017.07.042

53. Long Y, Chen Y, Qian Y, Wang J, Luò L, Huang X, et al. A rare variant in *TOR1A* exon 5 associated with isolated dystonia in southwestern Chinese. *Mov Disord* 2017;32:1083–1087. doi: 10.1002/mds.27016

54. Kamm C, Fischer H, Garavaglia B, Kullmann S, Sharma M, Schrader C, et al. Susceptibility to DYT1 dystonia in European patients is modified by the D216H polymorphism. *Neurology* 2008;70:2261–2262. doi: 10.1212/01.wnl.0000313838.05734.8a

55. Risch NJ, Bressman SB, Senthil G, Ozelius LJ. Intragenic cis and trans modification of genetic susceptibility in DYT1 torsion dystonia. *Am J Hum Genet* 2000;67:560–566. doi: 10.1086/303045

56. Kojevic M, Parees I, Kassavetis P, Palomar J, Mir P, Teo JT, et al. Secondary and primary dystonia: pathophysiological differences. *Brain* 2013;136( Pt 7):2038–2049. doi: 10.1093/brain/awt150

57. Quaratine A, Morgante F, Sant’angelo A, Rizzo V, Bagnato S, Terranova G, et al. Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia. *Brain* 2015;126:9–19.

58.atsapp://www.tremorjournal.org

59. Hemptstead BL. Brain-derived neurotrophic factor: three ligands, many actions. *Trans Am Clin Climatol Assoc* 2015;126:9–19.

60. Notaras M, Hill R, van den Buuse M. The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy. *Mov Disord* 2015;30:916–930. doi: 10.1002/mds.25938

61. Anastasia A, Hemptstead BL, BDNF function in health and disease (Poster). *Nat Rev Neurosci* 2014;15: doi: https://www.nature.com/nrn/posts/bdnf/index.html

62. Cheeckan B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to tTMS. *J Physiol* 2008;586:5717–5725. doi: 10.1113/jphysiol.2008.159905

63. Kırım JA, Chan S, Pringle E, Schallert K, Procaccio V, Jimenez R, et al. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. *Nat Neurosci* 2006;9:735–737. doi: 10.1038/nrn1699

64. Chen J, Liang X, Li B, Jiang X, Xu Z. Gender-related association of brain-derived neurotrophic factor gene 196A/G polymorphism with Alzheimer’s disease—a meta-analysis including 6854 cases and 6868 controls. *Int J Neurosci* 2014;124:724–733. doi: 10.3109/00207454.2013.869594

65. Chen K, Wang N, Zhang J, Hong X, Xu H, Zhao X, et al. Is the Val66Met polymorphism of the brain-derived neurotrophic factor gene associated with panic disorder? A meta-analysis. *Asia-Pacifc Psychiatry* 2017;9. doi: 10.1111/appy.12228

66. Zintzaras E. Brain-derived neurotrophic factor gene polymorphisms and schizophrenia: a meta-analysis. *Psychiatr Genet* 2007;17:69–75. doi: 10.1097/YPG.0b013e3280119da

67. Zintzaras E, Hadjigeorgiou GM. The role of G196A polymorphism in the brain-derived neurotrophic factor gene in the cause of Parkinson’s disease: a meta-analysis. *J Hum Genet* 2005;50:560–566. doi: 10.1007/s10038-005-0295-z

68. Li M, Chang H, Xiao X. BDNF Val66Met polymorphism and bipolar disorder in European populations: a risk association in case-control, family-based and GWAS studies. *Neurosci Biobehav Rev* 2016;68:218–233. doi: 10.1016/j.neubiorev.2016.05.031

69. Xiromerisiou G, Dardiotis E, Tsimourtou V, Kountra PM, Paterkakis KN, Kapsalaki EZ, et al. Genetic basis of Parkinson disease. *Neuropsych Focus* 2010;28:E7. doi: 10.3171/2010.9.FOCUS09220

70. Chen Y, Song W, Yang J, Chen K, Huang R, Zhao B, et al. Association of the Val66Met polymorphism of the BDNF gene with primary cranial-cervical dystonia patients from South-west China. *Parkinsonism Relat Disord* 2013;19:1043–1045. doi: 10.1016/j.parkreldis.2013.06.004

71. Cramer SC, Sampat A, Hase-Palominino M, Nguyen S, Procaccio V, Hermannowicz N. Increased prevalence of val66met BDNF genotype among subjects with cervical dystonia. *Neurosci Lett* 2010;468:42–45. doi: 10.1016/j.neulet.2009.10.059

72. Groen JJ, Ritz K, Veleboer DC, Aramiadich M, van Hilten JJ, Boon AJ, et al. Association of BDNF Met66Met polymorphism with arm tremor in cervical dystonia. *Mov Disord* 2012;27:796–797. doi: 10.1002/mds.24922

73. Ma L, Chen Y, Wang L, Yang Y, Cheng F, Tian Y, et al. Brain-derived neurotrophic factor Val66Met polymorphism is not associated with primary dystonia in a Chinese population. *Neurosci Lett* 2013;533:100–103. doi: 10.1016/j.neulet.2012.11.037

74. Svetel MV, Djuric G, Novakovkovic I, Dobricic V, Stefanova E, Kresojevic N, et al. A common polymorphism in the brain-derived neurotrophic factor gene in patients with adult-onset primary focal and segmental dystonia. *Acta Neurolog Belg* 2013;113:243–245. doi: 10.1007/s13760-013-0183-9

75. Gomez-Garre J, Huertas-Fernandez I, Caceres-Redondo MT, Alonso-Canovas A, Bernal-Bernal I, Blanco-Ollo A, et al. BDNF Val66Met polymorphism in primary adult-onset dystonia: a case-control study and meta-analysis. *Mov Disord* 2014;29:1083–1086. doi: 10.1002/mds.25938

76. Sako W, Murakami N, Izumi Y, Kaji R. Val66Met polymorphism of brain-derived neurotrophic factor is associated with idiopathic dystonia. *J Clin Neurosci* 2015;22:575–577. doi: 10.1016/j.jocn.2014.08.014

77. Lash TL. The harm done to reproducibility by the culture of null hypothesis significance testing. *Am J Epidemiol* 2017;186:627–635. doi: 10.1093/aje/kws261

78. Beggane T, Bundo M, Murata Y, Kawai K, Kato T, Isamoto K. DNA methylation of the BDNF gene and its relevance to psychiatric disorders. *J Hum Genet* 2013;58:434–438. doi: 10.1038/jhg.2013.65

79. Terracciano A, Piras MG, Lobina M, Mulas A, Meirelles O, Sutin AR, et al. Genetics of serum BDNF: meta-analysis of the Val66Met and genome-wide association study. *World J Biol Psychiatry* 2013;14:583–589. doi: 10.3109/15629275.2011.616533
80. Nagahara AH, Tuszyński MH. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nat Rev Drug Discov* 2011;10:209–219. doi: 10.1038/nrd3366

81. Longo FM, Massa SM. Small-molecule modulation of neurotrophin receptors: a strategy for the treatment of neurological disease. *Nat Rev Drug Discov* 2013;12:507–325. doi: 10.1038/nrd4024

82. Deng P, Anderson JD, Yu AS, Annett G, Fink KD, Nolta JA. Engineered BDNF producing cells as a potential treatment for neurologic disease. *Expert Opin Biol Ther* 2016;16:1025–1033. doi: 10.1080/14712598.2016.1183641

83. Mahley RW, Rall SC, Jr. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 2000;1:507–537. doi: 10.1146/annurev.genom.1.1.507

84. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* 2013;9:106–118. doi: 10.1038/nrneurol.2012.263

85. Matsumoto S, Nishimura M, Sakamoto T, Asanuma K, Izumi Y, Shihasaki H, et al. Modulation of the onset age in primary dystonia by APOE genotype. *Neurology* 2003;60:2003–2005. doi: 10.1212/01.WNL.0000068161.38412.1F

86. Xiromerisiou G, Daridiotis E, Tsironi EE, Hadjigeorgiou G, Ralli S, Kara E, et al. THAP1 mutations in a Greek primary blepharospasm series. *Parkinsonism Relat Disord* 2013;19:404–405. doi: 10.1016/j.parkreldis.2012.08.015

87. Xiromerisiou G, Houlden H, Scarlmes N, Stamou M, Kara E, Hardy J, et al. THAP1 mutations and dystonia phenotypes: genotype phenotype correlations. *Mov Disord* 2012;27:1290–1294. doi: 10.1002/mds.25146

88. Blanchard A, Ea V, Roubertie A, Martin M, Coquart C, Clanstres M, et al. DYT6 dystonia: review of the literature and creation of the UMD Locus-Specific Database (LSDB) for mutations in the THAP1 gene. *Hum Mutat* 2011;32:1213–1224. doi: 10.1002/humu.21564

89. Gavarrini S, Cayrol C, Fuchs T, Lyons N, Ehrlich ME, Girard JP, et al. Direct interaction between causative genes of DYT1 and DYT6 primary dystonia. *Am J Hum Genet* 2010;68:549–553. doi: 10.1016/ana2.21238

90. Houlden H, Schneider SA, Paudel R, Melchers A, Schwingenschuh P, Edwards M, et al. THAP1 mutations (DYT6) are an additional cause of early-onset dystonia. *Neurology* 2010;74:486–490. doi: 10.1212/01.wnl.0b013e318141f276d

91. Groen JL, Yildirim E, Ritz K, Baas F, van Hilten JJ, van der Meulen HM, et al. THAP1 mutations are infrequent in spasmodic dysphonia. *Mov Disord* 2011;26:1952–1954. doi: 10.1002/mds.23682

92. Golanska E, Gajos A, Sieruta M, Szybka M, Rudzinska M, Ochudlo S, et al. Screening for THAP1 mutations in Polish patients with dystonia shows known and novel substitutions. *Pho seen* 2015;10:o129656. doi: 10.1371/journal. pone.0129656

93. Xiao J, Zhao Y, Bastian RW, Perlmutter JS, Racette BA, Tabbl SD, et al. Novel THAP1 sequence variants in primary dystonia. *Neurology* 2010;74:229–238. doi: 10.1212/WNL.0b013e3181e00ca

94. Djarmati A, Schneider SA, Lohmann K, Winkler S, Pawlack H, Hagenah J, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. *Lancet Neurol* 2009;8:447–452. doi: 10.1016/S1474-4422(09)70083-3

95. Giri S, Naya T, Equbal Z, Sankhla CS, Das SK, Ray K, et al. Genetic screening of THAP1 in primary dystonia patients of India. *Neurosci Lett* 2017;637:31–37. doi: 10.1016/j.neulet.2016.11.060

96. Vemula SR, Xiao J, Zhao Y, Bastian RW, Perlmutter JS, Racette BA, et al. A rare sequence variant in intron 1 of THAP1 is associated with primary dystonia. *Mol genet genomics* 2014;2:261–272. doi: 10.1007/rmgg3.67

97. Xiao J, Zhao Y, Bastian RW, Perlmutter JS, Racette BA, Tabbl SD, et al. The c.-237_236GA>T THAP1 sequence variant does not increase risk for primary dystonia. *Mov Disord* 2011;26:549–552. doi: 10.1002/mds.23551

98. Daridiotis E, Xiromerisiou G, Hadjichristodoulou C, Tsatsakis AM, Wilks MF, Hadjigeorgiou GM. The interplay between environmental and genetic factors in Parkinson's disease susceptibility: the evidence for pesticides. *Toxicology* 2013;307:17–23. doi: 10.1016/j.tox.2012.12.016

99. Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, et al. Mutations in GNAL cause primary torsion dystonia. *Nat Genet* 2013;45:88–92. doi: 10.1038/nrg12496

100. Miao J, Wan XH, Sun Y, Feng JC, Cheng FB. Mutation screening of GNAL gene in patients with primary dystonia from Northeast China. *Parkinsonism Relat Disord* 2013;19:910–912. doi: 10.1016/j.parkreldis.2013.05.011

101. Carapito R, Paul N, Untrau M, Le Gentil M, Ott L, Alsahel G, et al. A de novo ADCY5 mutation causes early-onset autosomal dominant chorea and dystonia. *Mov Disord* 2015;30:423–427. doi: 10.1002/mds.26115

102. Newman JR, Todorovic M, Silburn PA, Sutherland GT, Mellick GD. Lack of reproducibility in re-evaluating associations between GCH1 polymorphisms and Parkinson’s disease and isolated dystonia in an Australian case–control group. *Parkinsonism Relat Disord* 2014;20(6):668–70. doi: 10.1016/j.parkreldis.2014.02.014

103. Opladen T, Hoffmann G, Horster F, Hinz AB, Neidhardt K, Klein C, et al. Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. *Mov Disord* 2011;26:157–161. doi: 10.1002/mds.23329

104. Hsu WL, Chiu YW, Lai SY, Lee YM. Dopa-responsive dystonia is induced by a dominant-negative mechanism. *Am J Hum Genet* 2009;8:609–613. doi: 10.1002/humg.20138

105. Rothman KJ. Disengaging from statistical significance. *Eur J Epidemiol* 2013;31:443–444. doi: 10.1007/s10654-016-0582-0

106. Tanabe LM, Kim CE, Alagem N, Dauer WT. Primary dystonia: molecules and mechanisms. *Nat Rev Neurosci* 2009;5:589–609. doi: 10.1038/nrn2009.160

107. Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Neurology* 1994;8:236–242. doi: 10.1002/nnu.1194-236

108. Misbahuddin A, Placek MR, Chaudhuri KR, Wood NW, Bhatia KP, Warner TT. A polymorphism in the dopamine receptor DRD5 is associated with blepharospasm. *Neurology* 2002;58:124–126. doi: 10.1212/WNL.38.1.124

109. Placek MR, Misbahuddin A, Chaudhuri KR, Wood NW, Bhatia KP, Warner TT. Cervical dystonia is associated with a polymorphism in the dopamine (D5) receptor gene. *J Neurol Neurosurg Psychiatry* 2001;71:262–264. doi: 10.1136/jnp.71.2.262
110. Brancati F, Valente EM, Castori M, Vanacore N, Sessa M, Galardi G, et al. Role of the dopamine D5 receptor (DRD5) as a susceptibility gene for cervical dystonia. *J Neurol Neurosurg Psychiatry* 2003;74:665–666. doi: 10.1136/jnnp.74.5.665

111. Mishbahuddin A, Placek MR, Warner TT. Focal dystonia is associated with a polymorphism of the dopamine D5 receptor gene. *Adv Neurol* 2004;94:143–146.

112. Houley DJ, Nikolaus M, Venta PJ, Jernigan KA, Waldman ID, Nigg JT, et al. SNP discovery and haplotype analysis in the segmentally duplicated DRD5 coding region. *Ann Hum Genet* 2009;73(Pt 3):274–282. doi: 10.1111/j.1469-1809.2009.00513.x

113. Gingrich JA, Caron MG. Recent advances in the molecular biology of dopamine receptors. *Annu Rev Neurosci* 1993;16:299–321. doi: 10.1146/annurev.ne.16.030195.001503

114. Zeuner KE, Acevich A, Knutzen A, Dresler D, Lohmann K, Witt K. Dopamine DRD2 polymorphism (DRD2/ANNK1-Taq1A) is not a significant risk factor in writer’s cramp. *J Neurol* 2004;251 Suppl 2:1340–1343. doi: 10.1002/ajmg.b.30980

115. Groen JJ, Simon-Sanchez J, Ritz K, Bochdanovits Z, Fang Y, van Hilten JJ, et al. Cervical dystonia and genetic common variation in the dopamine pathway. *Parkinsonism Relat Disord* 2013;19:346–349. doi: 10.1016/j.parkreldis.2012.08.016

116. Groen JJ, Ritz K, Warner TT, Baas F, Tijsen MA. DRD1 rare variants associated with tardive-like dystonia: a pilot pathway sequencing study in dystonia. *Parkinsonism Relat Disord* 2014;20:782–785. doi: 10.1016/j.parkreldis.2014.04.002

117. Lohmann K, Schmidt A, Schillert A, Winkler S, Albanese A, Baas F, et al. Genome-wide association study in musician’s dystonia: a risk variant at the arylsulfatase G locus? *Mov Disord* 2014;29:921–927. doi: 10.1002/mds.25791

118. Mok KY, Schneider SA, Trabzuni D, Stamelou M, Edwards M, Kasparovicute D, et al. Genomewide association study in cervical dystonia demonstrates possible association with sodium leak channel. *Mov Disord* 2014;29:245–251. doi: 10.1002/mds.25732

119. Nibbeling E, Schaake S, Tijsen MA, Weishach A, Groen JL, Altenmuller E, et al. Accumulation of rare variants in the arylsulfatase G (ARSG) gene in task-specific dystonia. *J Neurovirol* 2015;21:1340–1343. doi: 10.1007/p01415-015-7718-3

120. Sardiello M, Annunziata I, Roma G, Ballabio A. Sulfonylases and sulfatase modifying factors: an exclusive and promiscuous relationship. *Hum Mol Genet* 2005;14:3203–3217. doi: 10.1093/hmg/ddi351

121. Abitbol M, Thibault JL, Olby NJ, Hitte C, Puech JP, Maurer M, et al. A canine Arylsulfatase G (ARSG) mutation leading to a sulfatase deficiency is associated with neuronal ceroid lipofuscinosis. *Proc Natl Acad Sci USA* 2010;107:14775–14780. doi: 10.1073/pnas.0914206107

122. Gomez-Garre P, Huertas-Fernandez I, Caceres-Redondo MT, Alonso-Canovas A, Bernal-Bernal I, Blanco-Olloa E, et al. Lack of validation of variants associated with cervical dystonia risk: a GWAS replication study. *Mov Disord* 2014;29:1823–1828. doi: 10.1002/mds.26044

123. Zhou Q, Yang J, Cao R, Chen Y, Wei Q, Ou R, et al. Association analysis of NALCN polymorphisms rs1338041 and rs61973742 in a Chinese population with isolated cervical dystonia. *Parkinsons Dis* 2016;2016:9281790. doi: 10.1155/2016/9281790

124. Topalidou I, Cooper K, Pereira L, Alion M. Dopamine negatively modulates the NCA ion channels in C. elegans. *PLoS Genet* 2017;13:e1007032. doi: 10.1371/journal.pgen.1007032

125. Domingo A, Erro R, Lohmann K. Novel dystonia genes: clues on disease mechanisms and the complexities of high-throughput sequencing. *Mov Disord* 2016;31:471–477. doi: 10.1002/mds.26600

126. Coughlin DG, Bardakjian TM, Spindler M, Deik A. Hereditary myoclonus dystonia: a novel sgce variant and phenotype including intellectual disability. *Tremor Other Hyperkinet Mov* 2018;8. doi: 10.7916/D8J11FRZ

127. Pattnaik R, Clements J, Batra J. Candidate gene association studies: a comprehensive guide to useful in silico tools. *BMC Genet* 2013;14:39. doi: 10.1186/1471-2156-14-39

128. Overdoorn DLM, van Egmond ME, Ascencio LC, van Dijk JMC, Saryeva A, Beudel M, et al. Reversal of status dystonicus after relocation of pallidal electrodes in DYT6 generalized dystonia. *Tremor Other Hyperkinet Mov* 2018;8.

129. Zintzaras E, Lau J. Trends in meta-analysis of genetic association studies. *J Hum Genet* 2006;51:1–9. doi: 10.1007/s10038-006-0223-5

130. Defazio G, Berardelli A, Halliet M. Do primary adult-onset focal dystonias share aetiological factors? *Brain* 2007;130( Pt 5):1183–1193. doi: 10.1093/brain/awl355

131. Defazio G, Matarin M, Peckham EL, Martino D, Valente EM, Singleton A, et al. The TOR1A polymorphism rs1182 and the risk of spread in primary blepharospasm. *Mov Disord* 2009;24:613–616. doi: 10.1002/mds.22471

132. Evangelou E, Maragaronne DM, Annesi G, Brighina L, Brice A, Elbaz A, et al. Non-replication of association for six polymorphisms from meta-analysis of genome-wide association studies of Parkinson’s disease: large-scale collaborative study. *Am J Med Genet B Neuropsychiatr Genet* 2010;153b:220–8. doi: 10.1002/ajmg.b.30980

133. Theuns J, Verstraeten A, Sleegers K, Wauters E, Gijselinck I, Smolders S, et al. Global investigation and meta-analysis of the C9orf72 (G4C2)n repeat in Parkinson disease. *Neurology* 2014;83:1906–1913. doi: 10.1212/WMN.00000000000001012

134. The Lancet. Air pollution and brain health: an emerging issue. *Lancet Neurol* 2018;17:103. doi: 10.1016/S1474-4422(17)30462-3

135. Vidaillhet M, Grahl D, Roze E. Pathophysiology of dystonia. *Curr Opin Neurol* 2009;22:406–413. doi: 10.1097/WCO.0b013e32832fd8e3

136. Cardon LR, Bell JL. Association study designs for complex diseases. *Nat Rev Genet* 2001;2:91–99. doi: 10.1038/35052543

137. Wang K, Li M, Hakonarson H. Analysing biological pathways in genome-wide association studies. *Nat Rev Genet* 2010;11:834–854. doi: 10.1038/nrg2884

138. Li Y, Rowland G, Xiromerisiou G, Lagier RJ, Schrodi SJ, Dradiotis E, et al. Neither replication nor simulation supports a role for the axon guidance pathway in the genetics of Parkinson’s disease. *PLoS One* 2008;3:e2707. doi: 10.1371/journal.pone.0002707

139. Wasserstein RL, Lazar NA. The ASA’s statement on p-values: context, process, and purpose. *Am Stat* 2016;70:129–33. doi: 10.1080/00031305.2016.1154108

140. Greenland S. Invited commentary: the need for cognitive science in methodology. *Am J Epidemiol* 2017;186:639–645. doi: 10.1093/aje/kwx259