Field synopsis and systematic meta-analyses of genetic association studies in isolated dystonia

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Abstract

Background and objectives: Dystonia is a genetically complex disease with both monogenic and polygenic causes. For the latter, numerous genetic associations studies have been performed with largely inconsistent results. The aim of this study was to perform a field synopsis including systematic meta-analyses of genetic association studies in isolated dystonia

Methods: For the field synopsis we systematically screened and scrutinized the published literature using NCBI's PubMed database. For genetic variants with sufficient information in at least two independent datasets, random-effects meta-analyses were performed, including meta-analyses stratified by ethnic descent and dystonia subtypes.

Results: A total of 3,575 articles were identified and scrutinized resulting in the inclusion of 42 independent publications allowing 134 meta-analyses on 45 variants across 17 genes. While our meta-analyses pinpointed several significant association signals with variants in *TOR1A*, *DRD1*, and *ARSG*, no single variant displayed compelling association with dystonia in the available data.

Conclusions: Our study provides an up-to-date summary of the status of dystonia genetic association studies. Additional large-scale studies are needed to better understand the genetic causes of isolated dystonia.

Introduction

Genetically, dystonia is a complex disease with the parallel occurrence of forms with and without causative genetic factors. Over the past decades more than two dozen loci have been proposed as monogenic causes of dystonia[1–3] and 32 confirmed genes (28 with “DYT” labels)[4,5] have been included in the new list of isolated, combined, and complex hereditary dystonia proposed by the International Parkinson and Movement Disorder Society’s (MDS) Task Force on Genetic Nomenclature in Movement Disorders[5]. Substantially less is known about the genetic underpinnings of sporadic (i.e. non-monogenic) dystonia. Along these lines, only two GWAS on dystonia subtypes, i.e. musician’s dystonia[6] and cervical dystonia[7], have been published to date. The remainder of the existing genetics literature on sporadic dystonia is comprised of candidate gene association studies. These typically focused on genes known to cause familial dystonia as well as functionally founded candidates, such as genes involved in dopamine metabolism or the brain-derived neurotrophic factor (*BDNF*)[8]. To date, no systematic review covering all genetic polymorphisms investigated in dystonia has been published and only very few meta-analyses utilizing genetic association data exist[9–12]. As a result, it is becoming increasingly difficult to evaluate and interpret the genetics literature pertaining to sporadic dystonia. The aim of this work was to overcome this limitation and perform the first systematic synopsis - including meta-analyses of all available genetic association data - in the dystonia field. To this end, we carefully screened more than 3,500 articles and performed a total of 134 meta-analyses across 52 case-control datasets from 42 independent publications, thereby vastly increasing the number of meta-analyses currently available for dystonia[9–12]. The accrued literature database and meta-analysis results are made available in the supplement of this manuscript.

Methods

1. Literature searches

1.1. Systematic literature searches

Overall, our study followed the approach developed earlier by our group for systematic field synopses in Alzheimer's disease[13] and Parkinson's disease[14]. At the outset, this entailed a systematic literature search using NCBI's "PubMed" database for papers published until January 23, 2018. In a first stage, we searched for keywords "(dystoni* OR (writer* AND cramp) OR graphospasm OR blepharospasm OR torticollis OR meige OR spasmodic OR dysphonia OR retrocollis OR antecollis OR laterocollis OR (musician* AND cramp) OR (occupation* AND cramp) OR (golf* AND cramp) OR yips) AND associat* AND gene*". In the second stage, we separately searched for each gene identified in stage 1 and for 28 loci with a "DYT" label (Figure1; DYT designations taken from refs. 5 and 15; see Supplementary Tables S1 and S2 for more details). Of note, prior to the revision of the dystonia classification and nomenclature in 2013, isolated dystonia (i.e. pure dystonia with or without dystonic tremor) was referred to as "primary" dystonia, a term mixing phenomenological and etiological features, whose use is no longer recommended[16]. As the clinical part of the definition of "primary" dystonia was identical to that of "isolated" dystonia, we exclusively use the new and unambiguous term "isolated" dystonia for all studies referred to in this article.

1.2. Inclusion / exclusion criteria

We only considered publications representing association studies between biallelic genetic polymorphisms (minor allele frequency in included data sets or in the general population ≥ 0.01 based on ref. 17) and isolated dystonia phenotypes. Additional eligibility criteria were: publication in a peer-reviewed journal, publication in English, and analysis in at least 10 dystonia cases and 10 control subjects. We excluded studies assessing dystonia with a known etiology (previously known as "secondary" dystonia), studies using family-based designs, and

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studies on mitochondrial DNA. Furthermore, we excluded studies that contrasted their case groups against “database controls” and those with cases carrying a known dystonia mutation.

2. Database

From each eligible article, we extracted a range of informative variables into a Microsoft Excel database (full database in Supplementary Table S2). The initial data entry was performed by O.O. followed by double checking of all variant IDs and genotype distributions by V.D.

3. Statistical analyses

For all eligible datasets, we calculated odds ratios (OR) and corresponding 95% confidence intervals (CIs), assuming an additive genetic model. For datasets with allele frequency information only, we calculated the corresponding genotype distributions assuming Hardy-Weinberg equilibrium. For four variants, the same or largely overlapping data sets were published in separate articles[18–21]. In these instances, we only included the genotype distributions for the larger of the two datasets, i.e. refs. 20 and 21. For variants with independent genetic data in at least two non-overlapping datasets we calculated random effects summary ORs using PLINK 1.9[22,23]. Whenever sufficient data were available, meta-analyses were stratified by ethnic descent group in addition to calculating summary ORs across all ethnic groups combined. In addition to calculating meta-analyses across all forms of isolated dystonia, we divided our analyses into focal dystonia (i.e. cervical dystonia, blepharospasm, musician’s dystonia, writer’s cramp, and spasmodic dysphonia), segmental dystonia, and generalized dystonia. Whenever possible, subgroups were further stratified into groups of differing ethnic descent. Overall, this led to 134 meta-analyses of 45 variants across 17 genes. Pairwise linkage disequilibrium estimates across SNPs within the same $\pm 1\text{Mb}$ interval in the 1000GP (phase 3) data[17] were calculated using PLINK 1.9 (Supplementary Table S3). This identified 32 independent ($r^2 < 0.3$) variants; accordingly, the study-wide significance threshold was set to $\alpha = 0.00156$ ($=0.05/32$). Heterogeneity across studies was assessed by calculating the I^2 metric ($I^2 > 75\%$ indicates excess heterogeneity[14]).

Results

1. Literature search

The systematic literature search (up-to-date until January 23rd, 2018) identified 3,575 potentially eligible articles (Figure 1). After systematic review of titles, abstracts and full text (as needed) versions of these papers we identified 42 eligible publications (describing association data in 52 independent datasets. Analyzed datasets originated from a total of 17 different countries spread across four continents. In total, 233 polymorphisms across 33 loci were investigated in these 42 publications. Most (n=40) used a candidate gene approach, while two papers were GWAS. The entire database of this field synopsis is provided in Supplementary Table 2.

2. Meta-analysis results

For the meta-analyses, we only considered variants with at least two independent non-overlapping datasets with available genotype or allele data. This included screening 557,621 SNPs from a musician's dystonia GWAS dataset[6] for an overlap with the 233 polymorphisms identified in the literature screen. Overall, this procedure resulted in sufficient data for a total of 45 variants across 17 genetic loci (median sample size per data set: 458, range 88-5,385). Of these, 42 variants could be analysed after stratification in for datasets of Caucasian descent, and 6 after stratification for Asian descent. Only five variants in *TOR1A*, *DRD1* and *ARSG* showed nominally significant evidence for association: i.e. rs4532 (OR [95 % CI]: 1.37 [1.13-1.67], P=0.00153), rs35153737 (OR [95% CI]: 1.46 [1.14-1.88], P=0.00315), rs13283584 (OR [95% CI]: 1.32 [1.08-1.61], P=0.00584), rs7342975 (OR [95 % CI]: 2.00 [1.15-3.47], P=0.00572), rs9972951 (OR [95 % CI]: 2.16 [1.06-4.40], P=0.0342), but only variant rs4532 in *DRD1* survived correction for multiple testing. Meta-analyses in subgroups stratified by ethnic descent did not reveal any additional associations (Table 1).

Meta-analyses divided by diagnostic subgroup are summarized in Table 2 and yielded five nominally significant results, two of which were not observed in the analyses without diagnostic

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stratification, i.e. rs1801968 in *TOR1A* (OR [95% C.I.]: 3.10 [1.25-7.68], $P=0.0142$), associated with writer's cramp, and rs11655081 in *ARSG* (OR [95% C.I.]: 4.42 [2.72-7.19], $P=2.11\text{e-}09$, respectively) associated with musician's dystonia (Table 2). While the latter finding surpassed the threshold of study- and genome-wide significance, we note that this meta-analysis is only based on two independent datasets, both of which originate from the same (and only) paper on the topic[6]. The same variant was also assessed in independent datasets with other focal (i.e. cervical, blepharospasm; Table 2B, D) and segmental (Table 2G) forms of dystonia but did not show any evidence for association with these dystonia subtypes[6].

Discussion

This work represents the first systematic field synopsis of genetic association studies in dystonia. Overall, we present the results of 134 meta-analyses on 45 variants across 17 genes. While nominal associations with several loci were observed, only variants in *DRD1* and *ARSG* survived multiple testing correction. However, even these two most significant results should be interpreted with caution owing to comparatively small sample size.

Prior to this study meta-analyses on genetic association data in dystonia were only available for two genes, i.e. *TOR1A*[9,10] and *BDNF*[11,12], both with conflicting results, i.e. one study interpreted their results in favor of a role in dystonia susceptibility, while the other study reached an opposite conclusion. Although our results provide some degree of support for an involvement of *TOR1A* SNP rs35153737 in Asians and rs13283584 in Caucasians (Table 1), no association evidence was observed with the only available (but widely tested) SNP (rs6265) in *BDNF*.

One notable observation and important limitation of our study is that most meta-analyses are based on relatively small sample sizes (median combined sample size of across all meta-analyses was only 2,882 individuals, compared to ~4,500 for Alzheimer's[13] and ~7,500 for Parkinson's disease[14]). Provided that the genetic liability of dystonia is mostly governed by

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small effect variants with ORs <1.2, our power to detect such associations was small, and only efforts with substantially increased sample sizes for both patients and controls will have sufficient power to detect such effect sizes[14]. Other limitations of our study relate to the search strategy, which might not have identified some eligible papers, and an erroneous data extraction and representation procedure. However, while such errors are unavoidable, our ample experience in the collection, annotation and curation of genetic association data in the context of systematic field synopses[13,14,24–27] suggest that these errors will likely be infrequent and will not affect the major conclusion(s) of our paper.

Notwithstanding these and possibly other unrecognized limitations, our study represents the first systematic synopsis of genetic association studies in dystonia and the largest collection of meta-analyses in the field. Despite its comprehensiveness, and in contrast to genetic studies on monogenic forms of the disease, it currently provides only little support for an existence of strong genetic risk factors acting in sporadic dystonia. This situation will likely change upon completion of additional large-scale GWAS of sufficient size, which will hopefully provide new insights into the pathogenetic forces underlying the onset and progression of this debilitating disease.

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Legends to Tables and Figures

Main Text:

Table 1. Results of random-effects meta-analyses based on an additive model in all types of isolated dystonia. ‡C = Of Caucasian descent (i.e. more than 90% of individuals in a data set belongs to this descent group); A = Asian descent; All = All ethnic groups combined (see Table S2 for study-specific details).

Table 2. Results of random-effects meta-analyses based on an additive model in diagnostic subgroups of isolated dystonia: a) all types of focal dystonia, b) musician's dystonia, c) blepharospasm, d) cervical dystonia, e) spasmodic dystonia, f) writer's dystonia, g) segmental dystonia, h) generalized dystonia. ‡C = Of Caucasian descent (i.e. more than 90% of individuals in a data set belongs to this descent group); A = Asian descent; All = All ethnic groups combined (see Table S2 for study-specific details).

Figure 1. Flowchart of literature search, data extraction, and analysis strategies applied for the dystonia field synopsis. † Search for query terms “(dystoni* OR (writer* AND cramp) OR graphospasm OR blepharospasm OR torticollis OR meige OR spasmodic OR dysphonia OR retrocollis OR antecollis OR laterocollis OR (musician* AND cramp) OR (occupation* AND cramp) OR (golf* AND cramp) OR yips) AND associat* AND gene*”. ‡ Search for query terms outlined above and “AND ([gene name] OR [gene alias(es)])” using HGNC (HUGO Gene Nomenclature Committee at the European Bioinformatics Institute) nomenclature²⁷. ¶ Only 45 out of 233 polymorphisms were investigated in at least two independent data sets. Furthermore, two studies were excluded due to sample overlap: 1. Djarmati et al, 2009 (ref. 19) fully excluded due to overlap with Lohman et al, 2012 (ref. 21), 2. Newman et al, 2012 (ref. 18) exclusion of data for polymorphisms overlapping with Newman et al, 2014 (ref. 20; see Table S2 for more details).

Supplementary Material (available from the authors upon request):

Table S1. Overview of search algorithms on NCBI's "PubMed" database. In a first stage we searched for general keywords "(dystoni* OR (writer* AND cramp) OR graphospasm OR blepharospasm OR torticollis OR meige OR spasmodic OR dysphonia OR retrocollis OR antecollis OR laterocollis OR (musician* AND cramp) OR (occupation* AND cramp) OR (golf* AND cramp) OR yips) AND associat* AND gene*". This resulted in 896 publications. In the second stage, we separately searched for each of the genes identified in stage 1 (n=10) as well as all for 28 loci with a "DYT" label (supplement table 2; DYT designations taken from refs. 5 and 15). Each of these genes was searched for the different forms of isolated dystonia "(dystoni* OR (writer* AND cramp) OR graphospasm OR blepharospasm OR torticollis OR meige OR spasmodic OR dysphonia OR retrocollis OR antecollis OR laterocollis OR (musician* AND cramp) OR (occupation* AND cramp) OR (golf* AND cramp) OR yips)" in combination with their current official HGNC (HUGO Gene Nomenclature Committee at the European Bioinformatics Institute [28] (URL: <https://www.genenames.org/>) gene symbol as well as all previous symbols. [†]Some authors assign (COL6A3) as DYT2; here, this gene is listed under DYT27.

Table S2. Detailed summary of genetic association studies identified for this field synopsis and meta-analyses. Tabs correspond to diagnostic subgroups of dystonia; these were also utilized for the meta-analyses.

Table S3. Estimates of pairwise linkage disequilibrium between meta-analyzed SNPs within the same 1Mb interval, this only related to variants in *PRKRA*, *DRD1*, *THAP1*, *TOR1A*, *DBH*, *DRD2*, *NACL*, *GCH1*, *ARSG* and *COMT* based on genotype data from the 1000 genomes project, LD was calculated using PLINK v1.9. SNP pairs with $r^2 > 0.3$ were considered not independent. Bold font indicates $r^2 > 0.3$.

Table 1. Results of random-effects meta-analyses based on an additive model in all types of isolated (a.k.a. “primary”) dystonia.

Chr-position	Gene	SNP	Allele	Ethnicity ‡	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
1:236885200	MRT	rs1805087	G vs A	C	227 vs 1072 (2/2)	0.93 (0.66-1.29)	0.5852	0.00
2:178433097	PRKRA	rs6739142	G vs A	C	357 vs 1200 (2/2)	0.99 (0.73-1.36)	0.9910	39.77
2:178449632	PRKRA	rs1967327	C vs G	C	357 vs 1200 (2/2)	1.10 (0.86-1.42)	0.4392	0.00
2: 218326846	PNKD	rs10932774	A vs G	C	357 vs 1200 (2/2)	1.02 (0.84-1.24)	0.8736	0.00
3:114171968	DRD3	rs6280	C vs T	C	188 vs 200 (2/2)	0.82 (0.61-1.11)	0.1979	0.00
5:175441837	DRD1	rs155417	T vs C	C	188 vs 200 (2/2)	0.73 (0.31-1.74)	0.4792	0.00
5:175443147	DRD1	rs4532	C vs T	C	315 vs 1172 (3/3)	1.37 (1.13-1.67)	0.0015	0.00
7:94635805	SGCE	rs10235385	C vs A	C	357 vs 1200 (2/2)	0.90 (0.69-1.16)	0.4028	0.00
8:42838423	THAP1	rs111989331	C vs T	All	499 vs 360 (2/2)	0.69 (0.31-1.54)	0.3686	74.48
8:42842898	THAP1	rs71521601	G vs A	C	864 vs 510 (3/3)	1.20 (0.66-2.21)	0.5484	73.02
8:42843330-1	THAP1	rs370983900 & rs184497763	AA vs CT	C	3679 vs 2315 (7/7)	1.07 (0.73-1.56)	0.7431	40.61
9:129812583	TOR1A	rs13283584	T vs C	C	473 vs 749 (2/2)	1.32 (1.08-1.61)	0.0058	0.00
9:129813148	TOR1A	rs3842225	- vs C	All	2287 vs 2503 (11/10)	1.05 (0.91-1.21)	0.4862	43.18
9:129813148	TOR1A	rs3842225	- vs C	C	1835 vs 2083 (9/8)	1.01 (0.86-1.18)	0.9450	44.67
9:129813148	TOR1A	rs3842225	- vs C	A	452 vs 420 (2/2)	1.28 (0.99-0.65)	0.0505	0.00
9:129813558	TOR1A	rs35153737	- vs C	A	452 vs 420 (2/2)	1.46 (1.14-1.88)	0.0031	0.00
9:129813781	TOR1A	rs1182	A vs C	All	2213 vs 2526 (11/10)	1.05 (0.85-1.30)	0.6742	72.36
9:129813781	TOR1A	rs1182	A vs C	C	1572 vs 2010 (8/7)	1.01 (0.77-1.32)	0.9607	79.00
9:129813781	TOR1A	rs1182	A vs C	A	641 vs 516 (3/3)	1.15 (0.90-1.45)	0.2647	0.00
9:129816005	TOR1A	rs11787741	G vs A	C	473 vs 749 (2/2)	0.95 (0.77-1.17)	0.6260	0.00
9:129818407	TOR1A	rs13297609	C vs G	All	351 vs 428 (2/2)	1.16 (0.89-1.52)	0.2742	0.00
9:129818622	TOR1A	rs1801968	G vs C	All	2075 vs 2699 (11/11)	0.95 (0.78-1.16)	0.6332	43.00
9:129818622	TOR1A	rs1801968	G vs C	C	1428 vs 1925 (6/6)	1.02 (0.87-1.20)	0.7870	5.33
9:129818622	TOR1A	rs1801968	G vs C	A	626 vs 494 (4/4)	0.74 (0.44-1.26)	0.2641	62.34
9:129822779	TOR1A	rs2296793	A vs G	All	1692 vs 2277 (10/9)	1.02 (0.87-1.18)	0.8381	42.61
9:129822779	TOR1A	rs2296793	A vs G	C	1454 vs 1946 (8/7)	1.02 (0.86-1.21)	0.8221	45.59
9:129822779	TOR1A	rs2296793	A vs G	A	238 vs 331 (2/2)	0.99 (0.60-1.64)	0.9738	64.39
9:133636819	DBH	rs2797849	C vs G	C	490 vs 3054 (2/2)	1.09 (0.89-1.32)	0.4079	38.64
9:133639458	DBH	rs2797851	A vs G	C	490 vs 3054 (2/2)	1.07 (0.87-1.34)	0.5395	42.38
9:133657065	DBH	rs1611131	G vs A	C	490 vs 3054 (2/2)	1.12 (0.83-1.51)	0.4528	69.85
9:133657152	DBH	rs6271	T vs C	C	490 vs 3054 (2/2)	2.97 (0.37-24.02)	0.3002	96.73
9:133663599	DBH	rs129886	T vs C	C	490 vs 3054 (2/2)	1.01 (0.86-1.20)	0.8704	0.00
10:28431147	intergenic	rs1249277	G vs C	C	464 vs 5515 (2/2)	0.77 (0.41-1.45)	0.4215	89.34
11:27658369	BDNF	rs6265	T vs C	All	1591 vs 2780 (7/7)	1.09 (0.98-1.21)	0.1165	0.00
11:27658369	BDNF	rs6265	T vs C	C	1146 vs 2350 (5/5)	1.05 (0.91-1.21)	0.4936	7.52
11:27658369	BDNF	rs6265	T vs C	A	445 vs 430 (2/2)	1.19 (0.98-1.43)	0.0759	0.00
11:48246304	OR4X2	rs67863238	C vs G	C	464 vs 5515 (2/2)	2.17 (0.40-11.70)	0.3482	96.50

11:113400106	DRD2	rs1800497	A vs G	C	222 vs 267 (3/3)	0.89 (0.65-1.22)	0.4758	0.00
11:113425564	DRD2	rs1079597	T vs C	C	188 vs 200 (2/2)	1.00 (0.69-1.46)	0.9913	0.00
11:113475529	DRD2	rs1799732	- vs G	C	188 vs 200 (2/2)	0.74 (0.46-1.19)	0.2064	0.00
13:101406511	NALCN	rs1338041	C vs A	All	565 vs 5804 (3/3)	0.90 (0.59-1.36)	0.6014	89.79
13:101406511	NALCN	rs1338041	C vs A	C	464 vs 5515 (2/2)	0.75 (0.51-1.10)	0.1445	83.78
13:101407929	NALCN	rs9518385	C vs A	C	339 vs 6145 (2/2)	0.73 (0.51-1.05)	0.0901	76.89
13:101430922	NALCN	rs61973742	G vs A	All	665 vs 5804 (3/3)	1.38 (0.41-4.64)	0.6001	96.35
13:101430922	NALCN	rs61973742	G vs A	C	464 vs 5515 (2/2)	1.85 (0.26-13.37)	0.5245	97.41
14:54837362	GCH1	rs2145945	A vs G	C	357 vs 1200 (2/2)	0.92 (0.66-1.27)	0.6038	64.12
14:54839739	GCH1	rs10483639	C vs G	C	360 vs 2062 (2/2)	1.09 (0.72-1.64)	0.6990	76.69
14:54841286	GCH1	rs17739146	G vs A	C	357 vs 1200 (2/2)	0.91 (0.66-1.27)	0.5921	22.85
14:54888313	GCH1	rs998259	T vs C	C	357 vs 1200 (2/2)	0.97 (0.74-1.27)	0.7973	36.39
17:68368608	ARSG	rs1558877	T vs C	C	357 vs 5272 (2/2)	0.96 (0.78-1.18)	0.6883	39.26
17:68368663	ARSG	rs1558878	C vs T	C	357 vs 5272 (2/2)	0.88 (0.75-1.02)	0.0846	0.00
17:68386068	ARSG	rs11655081	C vs T	All	2420 vs 3608 (9/1)	1.33 (0.95-1.86)	0.0989	77.20
17:68386068	ARSG	rs11655081	C vs T	C	2243 vs 3409 (8/1)	1.38 (0.92-2.08)	0.1224	79.97
17:68395091	ARSG	rs7342975	G vs A	C	357 vs 5272 (2/2)	2.00 (1.15-3.47)	0.0057	0.00
17:68395135	ARSG	rs9972951	A vs G	C	357 vs 5272 (2/2)	2.16 (1.06-4.40)	0.0342	68.35
22:19950115	COMT	rs5993883	T vs G	C	490 vs 3056 (2/2)	0.90 (0.61-1.31)	0.5671	83.57
22:19964609	COMT	rs4646316	T vs C	C	490 vs 3056 (2/2)	1.08 (0.92-1.27)	0.3332	0.00
22:19968169	COMT	rs9332377	T vs C	C	490 vs 3056 (2/2)	1.11 (0.92-1.34)	0.2678	0.00

‡C = Of Caucasian descent (i.e. more than 90% of individuals in a data set belongs to this descent group); A = Asian descent; All = All ethnic

groups combined (see Table S2 for study-specific details).

Table 2. Results of random-effects meta-analyses based on an additive model in diagnostic subgroups of isolated dystonia: a) all types of focal dystonia, b) musician's dystonia, c) blepharospasm, d) cervical dystonia, e) spasmodic dystonia, f) writer's dystonia, g) segmental dystonia, h) generalized dystonia.

A. All types of focal dystonia.

Chr-position	Gene	SNP	Allele	Ethnicity [†]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
1:236885200	MRT	rs1805087	G vs A	C	227 vs 1072 (2/2)	0.93 (0.66-1.29)	0.5852	0.00
3:114171968	DRD3	rs6280	C vs T	C	188 vs 200 (2/2)	0.82 (0.61-1.11)	0.1979	0.00
5:175441837	DRD1	rs155417	T vs C	C	188 vs 200 (2/2)	0.73 (0.31-1.74)	0.4792	0.00
5:175443147	DRD1	rs4532	C vs T	C	315 vs 1172 (3/3)	1.37 (1.13-1.67)	0.0015	0.00
8:42843330-1	THAP1	rs370983900 & rs184497763	AA vs CT	C	1838 vs 1885 (2/2)	1.13 (0.82-1.56)	0.4483	0.00
9:129813148	TOR1A	rs3842225	- vs C	C	747 vs 906 (4/3)	1.09 (0.92-1.29)	0.3423	0.00
9:129813781	TOR1A	rs1182	A vs C	All	895 vs 1200 (5/4)	1.07 (0.93-1.27)	0.3105	0.00
9:129813781	TOR1A	rs1182	A vs C	C	747 vs 906 (4/3)	1.07 (0.90-1.27)	0.4348	0.00
9:129818622	TOR1A	rs1801968	G vs C	All	1116 vs 1905 (6/6)	1.06 (0.89-1.27)	0.5114	5.33
9:129818622	TOR1A	rs1801968	G vs C	C	889 vs 1674 (4/4)	1.07 (0.87-1.31)	0.5170	13.98
9:129818622	TOR1A	rs1801968	G vs C	A	227 vs 231 (2/2)	0.99 (0.55-1.80)	0.9872	41.70
9:129822779	TOR1A	rs2296793	A vs G	All	729 vs 973 (5/4)	0.97 (0.81-1.16)	0.7446	14.35
9:129822779	TOR1A	rs2296793	A vs G	C	612 vs 842 (4/3)	1.01 (0.83-1.23)	0.9066	9.29
9:133636819	DBH	rs2797849	C vs G	C	490 vs 3054 (2/2)	1.09 (0.89-1.32)	0.4079	38.64
9:133639458	DBH	rs2797851	A vs G	C	490 vs 3054 (2/2)	1.07 (0.87-1.34)	0.5395	42.38
9:133657065	DBH	rs1611131	G vs A	C	490 vs 3054 (2/2)	1.12 (0.83-1.51)	0.4528	69.85
9:133657152	DBH	rs6271	T vs C	C	490 vs 3054 (2/2)	2.97 (0.37-24.02)	0.3002	96.73
9:133663599	DBH	rs129886	T vs C	C	490 vs 3054 (2/2)	1.01 (0.86-1.20)	0.8704	0.00
10:28431147	intergenic	rs1249277	G vs C	C	464 vs 5515 (2/2)	0.77 (0.41-1.45)	0.4215	89.34
11:27658369	BDNF	rs6265	T vs C	All	739 vs 2030 (4/4)	1.13 (0.91-1.41)	0.2678	43.72
11:27658369	BDNF	rs6265	T vs C	C	589 vs 1813 (3/3)	1.07 (0.81-1.41)	0.1689	43.77
11:48246304	OR4X2	rs67863238	C vs G	C	464 vs 5515 (2/2)	2.17 (0.40-11.70)	0.3482	96.50
11:113400106	DRD2	rs1800497	A vs G	C	222 vs 267 (3/3)	0.89 (0.65-1.22)	0.4758	0.00
11:113425564	DRD2	rs1079597	T vs C	C	188 vs 200 (2/2)	1.00 (0.69-1.46)	0.9913	0.00
11:113475529	DRD2	rs1799732	- vs G	C	188 vs 200 (2/2)	0.74 (0.46-1.19)	0.2064	0.00
13:101406511	NALCN	rs1338041	C vs A	All	665 vs 5804 (3/3)	0.90 (0.59-1.36)	0.6014	89.79
13:101406511	NALCN	rs1338041	C vs A	C	464 vs 5515 (2/2)	0.75 (0.50-1.11)	0.1445	83.78
13:101407929	NALCN	rs9518385	C vs A	C	339 vs 6145 (2/2)	0.73 (0.51-1.05)	0.0901	76.89
13:101430922	NALCN	rs61973742	G vs A	All	665 vs 5804 (3/3)	1.38 (0.41-4.64)	0.6001	96.35
13:101430922	NALCN	rs61973742	G vs A	C	464 vs 5515 (2/2)	1.85 (0.26-13.37)	0.5245	97.41
17:68368608	ARSG	rs1558877	T vs C	C	357 vs 5272 (2/2)	0.96 (0.78-1.18)	0.6883	39.26
17:68368663	ARSG	rs1558878	C vs T	C	357 vs 5272 (2/2)	0.88 (0.75-1.02)	0.0846	0.00
17:68386068	ARSG	rs11655081	C vs T	All	2007 vs 3608 (9/1)	1.34 (0.93-1.94)	0.1108	78.22
17:68386068	ARSG	rs11655081	C vs T	C	1877 vs 3409 (8/1)	1.41 (0.91-2.20)	0.1226	80.61
17:68395091	ARSG	rs7342975	G vs A	C	357 vs 5272 (2/2)	2.00 (1.15-3.47)	0.0057	0.00

17:68395135	ARSG	rs9972951	A vs G	C	357 vs 5272 (2/2)	2.16 (1.06-4.40)	0.0342	68.35
22:19950115	COMT	rs5993883	T vs G	C	490 vs 3056 (2/2)	0.90 (0.61-1.31)	0.5671	83.57
22:19964609	COMT	rs4646316	T vs C	C	490 vs 3056 (2/2)	1.08 (0.92-1.27)	0.3332	0.00
22:19968169	COMT	rs9332377	T vs C	C	490 vs 3056 (2/2)	1.11 (0.92-1.34)	0.2678	0.00

B. Musician's dystonia.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
9:129818622	TOR1A	rs1801968	G vs C	C	239 vs 1213 (2/2)	0.79 (0.58-1.08)	0.1522	0.00
17: 68368608	ARSG	rs1558877	T vs C	C	258 vs 5272 (2/2)	0.93 (0.69-1.25)	0.6176	67.05
17: 68368663	ARSG	rs1558878	C vs T	C	258 vs 5272 (2/2)	0.87 (0.73-1.05)	0.1464	12.22
17:68386068	ARSG	rs11655081	C vs T	C	243 vs 1097 (2/1)	4.42 (2.72-7.19)	2.11e-09	0.00
17:68395091	ARSG	rs7342975	G vs A	C	258 vs 5272 (2/2)	2.00 (1.15-3.47)	0.0141	0.00
17:68395135	ARSG	rs9972951	A vs G	C	258 vs 5272 (2/2)	2.16 (1.02-4.55)	0.0425	66.99

C. Blepharospasm.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
8:42843331	THAP1	rs370983900 & rs184497763	AA vs CT	C	228 vs 1885 (2/2)	0.80 (0.39-1.65)	0.5470	3.80
9:129813148	TOR1A	rs3842225	- vs C	C	205 vs 381 (2/1)	1.10 (0.70-1.72)	0.6807	52.83
9:129813781	TOR1A	rs1182	A vs C	All	227 vs 675 (3/2)	1.12 (0.84-1.49)	0.4261	0.00
9:129813781	TOR1A	rs1182	A vs C	C	205 vs 381 (2/1)	1.08 (0.73-1.59)	0.7185	38.15
9:129818622	TOR1A	rs1801968	G vs C	All	125 vs 472 (3/2)	1.21 (0.60-2.44)	0.5994	53.92
9:129818622	TOR1A	rs1801968	G vs C	A	94 vs 231 (2/2)	0.91 (0.38-2.19)	0.8377	44.02
9:129822779	TOR1A	rs2296793	A vs G	All	281 vs 512 (3/2)	0.85 (0.66-1.09)	0.2000	0.00
9:129822779	TOR1A	rs2296793	A vs G	C	205 vs 381 (2/1)	0.87 (0.65-1.16)	0.3309	0.00
11:27658369	BDNF	rs6265	T vs C	All	289 vs 1004 (2/2)	1.44 (0.76-2.71)	0.2634	80.88
17:68386068	ARSG	rs11655081	C vs T	C	303 vs 1020 (3/1)	0.91 (0.63-1.33)	0.6372	0.00

D. Cervical dystonia.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
8:42843331	THAP1	rs370983900 & rs184497763	AA vs CT	C	712 vs 1885 (2/2)	1.12 (0.69-1.82)	0.6472	22.08
9:129813781	TOR1A	rs1182	A vs C	All	448 vs 655 (2/2)	1.03 (0.82-1.29)	0.787	0.00
9:129818622	TOR1A	rs1801968	G vs C	All	570 vs 833 (4/4)	1.19 (0.95-1.49)	0.1276	0.00
9:129818622	TOR1A	rs1801968	G vs C	C	478 vs 602 (2/2)	1.27 (0.92-1.75)	0.1502	38.78
9:129818622	TOR1A	rs1801968	G vs C	A	92 vs 231 (2/2)	0.93 (0.51-1.71)	0.8158	0.00
9:129822779	TOR1A	rs2296793	A vs G	All	399 vs 492 (2/2)	1.00 (0.79-1.26)	0.9953	0.00
10:28431147	intergenic	rs1249277	G vs C	C	464 vs 5515 (2/2)	0.77 (0.41-1.45)	0.4215	89.34
11:27658369	BDNF	rs6265	T vs C	All	289 vs 1004 (2/2)	1.04 (0.84-1.29)	0.7138	0.00
11:48246304	OR4X2	rs67863238	C vs G	C	464 vs 5515 (2/2)	2.17 (0.40-11.70)	0.3482	96.50
13:101406511	NALCN	rs1338041	C vs A	All	665 vs 5804 (3/3)	0.90 (0.59-1.36)	0.6014	89.79
13:101406511	NALCN	rs1338041	C vs A	C	464 vs 5515 (2/2)	0.75 (0.51-1.10)	0.1445	83.78
13:101430922	NALCN	rs61973742	G vs A	All	665 vs 5804 (3/3)	1.38 (0.41-4.64)	0.6001	96.35
13:101430922	NALCN	rs61973742	G vs A	C	464 vs 5515 (2/2)	1.85 (0.26-13.37)	0.5245	97.41
17:68386068	ARSG	rs11655081	C vs T	All	1051 vs 2233 (6/1)	1.01 (0.82-1.23)	0.9456	0.00
17:68386068	ARSG	rs11655081	C vs T	C	961 vs 2034 (5/1)	0.97 (0.76-1.24)	0.8145	0.00

E. Spasmodic dystonia.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
8:4284333	THAP1	rs370983900 & rs184497763	AA vs TC	C	482 vs 1885 (2/2)	1.47 (0.92-2.35)	0.1040	0.00

F. Writer's cramp.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
9:129818622	TOR1A	rs1801968	G vs C	C	55 vs 341 (2/1)	3.10 (1.25-7.68)	0.01421	65.44

G. Segmental dystonia.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
8:42843331	THAP1	rs370983900 & rs184497763	AA vs TC	C	267 vs 1885 (2/2)	1.09 (0.59-2.03)	0.7765	0.00
17:68386068	ARSG	rs11655081	C vs T	All	344 vs 1219 (4/1)	1.06 (0.80-1.40)	0.6835	0.00
17:68386068	ARSG	rs11655081	C vs T	C	297 vs 1020 (3/1)	1.10 (0.76-1.59)	0.6078	6.72

H. Generalized dystonia in all populations.

Chr-position	Gene	SNP	Allele	Ethnicity [‡]	Cases vs Controls (# data sets/ # publications)	OR (95%CI)	P-Value	I ²
9:129818622	THAP1	rs370983900 & rs184497763	AA vs CT	C	99 vs 1885 (2/2)	0.85 (0.30-2.43)	0.7672	0.00

[‡]C = Of Caucasian descent (i.e. more than 90% of individuals in a data set belongs to this descent group); A = Asian descent; All = All ethnic groups combined (see Table S2 for study-specific details).

Figure 1. Flowchart of literature search, data extraction, and analysis strategies applied for the dystonia field synopsis.