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Review

A novel diagnostic approach for patients with adult-onset dystonia

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BMJ

ABSTRACT
Adult-onset dystonia can be acquired, inherited or idiopathic. The dystonia is usually focal or segmental and for a limited number of cases causal treatment is available. In recent years, rapid developments in neuroimmunology have led to increased knowledge on autoantibody-related dystonias. At the same time, genetic diagnostics in sequencing technology have evolved and revealed several new genes associated with adult-onset dystonia. Furthermore, new phenotype–genotype correlations have been elucidated. Consequently, clinicians face the dilemma of which additional investigations should be performed and whether to perform genetic testing or not. To ensure early diagnosis and to prevent unnecessary investigations, integration of new diagnostic strategies is needed.
We designed a new five-step diagnostic approach for adult-onset dystonia. The first four steps are based on a broad literature search and expert opinion, the fifth step, on when to perform genetic testing, is based on a detailed systematic literature review up to 1 December 2021.
The basic principle of the algorithm is that genetic testing is unlikely to lead to changes in management in three groups: (1) patients with an acquired form of adult-onset dystonia; (2) patients with neurodegenerative disorders, presenting with a combined movement disorder including dystonic symptoms and (3) patients with adult-onset isolated focal or segmental dystonia. Throughout the approach, focus lies on early identification of treatable forms of dystonia, either acquired or genetic. This novel diagnostic approach for adult-onset dystonia can help clinicians to decide when to perform additional tests, including genetic testing and facilitates early aetiological diagnosis, to enable timely treatment.

INTRODUCTION
Dystonia is a hyperkinetic movement disorder characterised by involuntary sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures or both.[1] Dystonic syndromes are among the most common hyperkinetic movement disorders in adults with prevalence numbers ranging from 30 to 7320 per million across studies.[2]

Dystonia may be acquired, inherited or idiopathic. Acquired dystonias result from external factors that cause damage or degeneration of the brain, such as medication or toxic agents, structural lesions or immune-mediated disorders. In recent years, rapid developments in neuroimmunology have led to increased knowledge on autoantibody-related dystonias.[3] Inherited dystonias are forms of dystonia of proven genetic origin, typically presenting in childhood, but onset in adulthood can also occur. Moreover, dystonia in adults may be the initial manifestation of a neurodegenerative disorder, such as Parkinson's disease (PD). However, the vast majority of adult-onset cases are sporadic, without an identifiable cause.

These sporadic dystonia syndromes are focal or segmental in nature and usually involve the face, neck or arm.[4] In the consensus classification paper, Albanese *et al*[1] describe this common syndromic pattern as Focal or Segmental Isolated Dystonia with Onset in Adulthood, stating that this entity can be used to assist in the aetiological diagnosis of dystonia in clinical practice.[1] In subsequent articles, the term adult-onset isolated focal dystonia (AOIFD) is used to refer to this group of patients.[5] To keep in line with current nomenclature, in this review we will also use the term AOIFD.

In table 1, we summarised the clinical characteristics of AOIFD. Of note, the disease course of AOIFD is static, although dystonia extending to contiguous body regions can occur, usually in the 3–5 years after onset.[1 6]

Historically, AOIFD is considered to be idiopathic and usually no additional investigations are performed.[1] However, in recent years, striking progress has been made in the field of genetic diagnostics, revealing new genes that were recognised as causative for several forms of adult-onset dystonia and elucidating new phenotype–genotype correlations.[7] Examples of new dystonia-associated genes include mutations in *GNAL* and *ANO3*, typically presenting in adults in their fourth or fifth decade.[8] Occasionally, underlying genetic conditions of adult-onset dystonia are treatable, for example, dopa-responsive dystonia or Wilson disease, so particularly in these cases, early aetiological diagnosis is key.[9] Nevertheless, it is not recommended to perform genetic testing in every patient with adult-onset dystonia, because of possible disadvantages such as unexplained variants, unsolicited findings and the costs of unnecessary testing.[10–12] So, in clinical practice an essential question is: when to investigate further?

The objective of this study was to design a diagnostic algorithm for adult-onset dystonia with focus on underlying treatable (acquired or genetic) conditions. Therefore, we completed a narrative review on phenomenology and aetiology of adult-onset

Table 1 Axis I* clinical characteristics of adult-onset isolated focal dystonia (AOIFD)

Age at onset	Adulthood (>21 years)
Body distribution	Typically focal, but can extend to contiguous body regions (segmental) ▶ Cervical dystonia ▶ Blepharospasm ▶ Oromandibular dystonia ▶ Laryngeal dystonia ▶ Task-specific dystonia (eg, writer's cramp) ▶ Meige syndrome ▶ Cervical dystonia plus oromandibular dystonia
Temporal pattern	Disease course ▶ Static† Variability ▶ Persistent ▶ Action-specific (eg, writer's cramp)
Associated features	Isolated ▶ Dystonia is the only motor feature, except for tremor Absence of other neurologic or systemic features

*Axis I refers to the latest dystonia consensus classification of Albanese et al.[1]
† Static: The disease course of AOIFD is static, but most cases tend to worsen for 3–5 years, before symptoms stabilise. In less than 10% of patients, spontaneous remissions occur.

dystonia, incorporating all possible causes of dystonia. In addition, we performed a detailed systematic review of the literature specifically focused on patients with a confirmed diagnosis of genetic adult-onset dystonia, to investigate how many of them had an initial presentation compatible with AOIFD. Based on the results of both literature searches and our own clinical experience, we propose a novel algorithm to facilitate diagnostic work-up and early aetiological diagnosis in adult-onset dystonia, integrating both acquired and genetic causes.

METHODS

Two literature searches were performed:

Search 1: A narrative review on phenomenology, classification and aetiology of adult-onset dystonia (>21 years of age,[1] which served as the basis of steps 1–4 of the diagnostic algorithm.

Search 2: A systematic review to investigate how often patients with genetically proven dystonia had an initial clinical presentation with AOIFD (table 1). The results of this search are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] Step 5 of the algorithm is based on the results of this systematic review.

Search methods

Search 1: A review of the PubMed database was conducted on March 2021 for the following key terms "dystonia" combined with (synonyms of) "adults", "adulthood", "late onset", as well as (synonyms of) terms indicating possible aetiologies including "idiopathic", "sporadic", "primary", "secondary", "acquired", "genetic", "inherited" and "neurodegenerative".

Search 2: We systematically reviewed all papers regarding genetic causes of adult-onset dystonia presenting as focal or segmental dystonia. References for this review were identified by PubMed, OMIM and textbook searches up to 1 December 2021, as well as searching for the references cited in the relevant articles. Key terms we used were (synonyms of) "adult-onset dystonia", "focal dystonia" and "idiopathic dystonia" combined with all genes associated with dystonia (DYT) and dystonia-parkinsonism according to the MDS Gene Database, all genes associated with isolated dystonia and combined dystonia

according to the recommended nomenclature of genetic movement disorders from the International Movement Disorder and Society Task Force,[14] plus, a selection of genes from the current genetic dystonia panel from the UMC Groningen based on expert-opinion. Further details of both the broad literature search and the detailed systematic review are summarised in online supplemental file 1.

Eligibility criteria

Search 1: We included reviews, observational studies, and case reports with full-text display in English. Inclusion criteria for reviewing an article were: dystonia and its definition; diagnostic criteria; clinical features; aetiologies; causes; diagnostics; treatment or differential diagnosis. Reference lists of included papers were also checked for relevant papers to the topic under review. Exclusion criteria were represented by studies written in other languages than English, letters to the editor, editorial comments, animal studies and contents not related to the topic.

Search 2: Reviewed papers and abstracts were published in English. All types of studies were used, including case reports, cohort or case–control studies and poster abstracts. We included all patients with genetically proven adult-onset dystonia to investigate how many of them presented with AOIFD (table 1). All types of genetic testing (single gene testing to whole genome sequencing (WES)) were included, to capture as many potential cases of genetic dystonia presenting as AOIFD as possible. Cases were not considered as a genetic dystonia if the patient's age at onset was under 21 or uncertain, or when genetic variants were of unknown significance.

Quality assessment and data extraction

Search 1: To define the different steps of our diagnostic algorithm, multiple discussions took place in our expert group until mutual consensus was reached. For every step, we searched the literature for possible aetiologies of adult-onset dystonia and diagnostic tests. Finally, every step was compared with current recommendations from key articles on the topic.

Search 2: Three authors (TJL, MS, and GL) assessed the eligibility of the articles. Disagreements and uncertainties on article selection were discussed in several consensus meetings (TJL, MS and ME). The following data were extracted: name of the first author; year of publication; total number of screened dystonia patients; results of genetic testing (genes, nucleotide change); sex; age at onset; family history and phenotype at initial presentation. Dystonia-associated genes were categorised as treatable or non-treatable dystonia syndromes (online supplemental file 1). Cases were divided into early (21–40 years) and late (>40 years) adult-onset and subsequently screened for the presence of genetic risk factors.

RESULTS

We propose a diagnostic algorithm for adult-onset dystonia (figure 1). Steps 1–4 are based on a synthesis of the narrative review (search 1) and our own clinical experience. The aim of these four steps is identification of possible underlying acquired or neurodegenerative causes. Steps 1–4 are explained in further detail below.

The fifth step of our algorithm is based on a systematic review (search 2). Three hundred and twelve publications were retrieved. One hundred and four records were excluded during the initial screening for potential relevance. Additionally, one hundred and thirty-nine references were manually screened for potential relevance. Two hundred and fifty-one articles were not eligible after
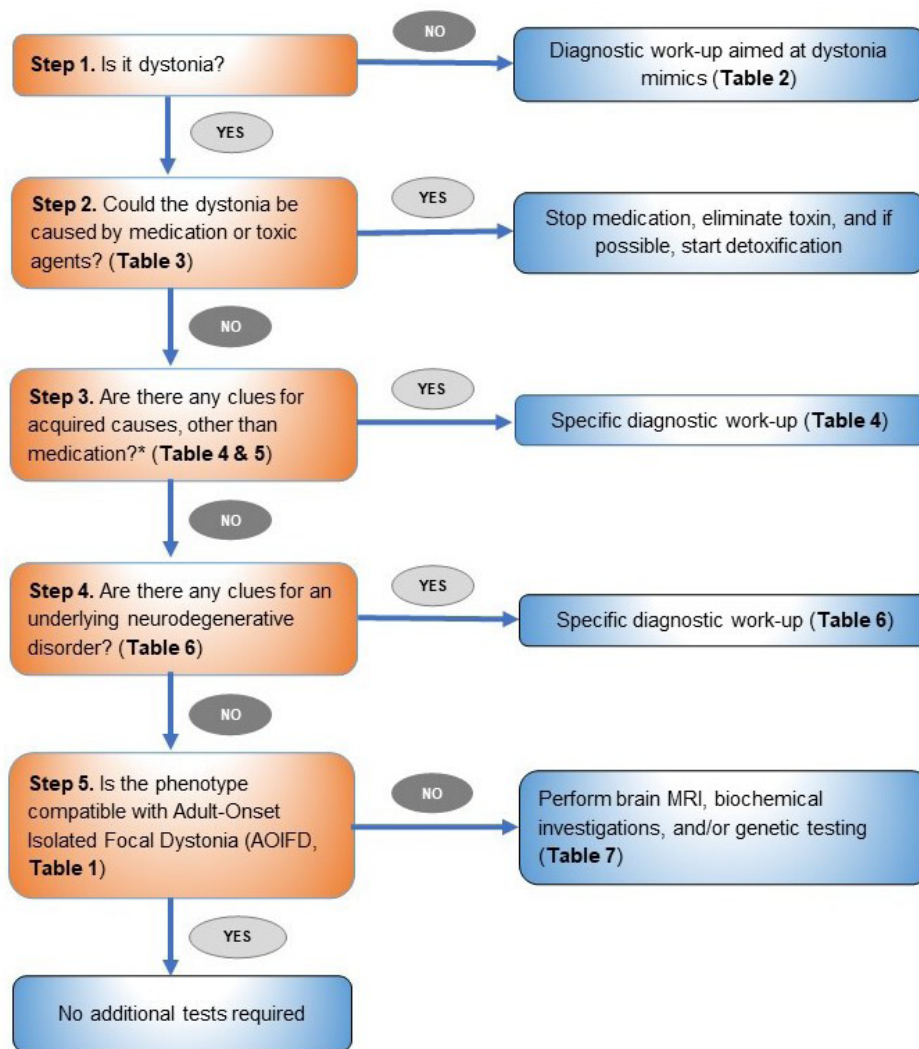
Figure 1 A novel five-step diagnostic algorithm for adult-onset dystonia. *We recommend performing TSH screening in all patients. TSH, thyroid-stimulating hormone.

full text review, as subjects did not meet the inclusion criteria. Details of the number of screened articles are visualised in a PRISMA 2009 Flow diagram (online supplemental file 2). In the remaining 96 articles, a total number of 17 127 patients with adult-onset focal or segmental dystonia with unknown cause were genetically screened. Several of the included studies were prospective cohort-studies of consecutive patients with adult-onset focal or segmental dystonia. In the vast majority of studies (>97%), the exact body localisation was described, but in a few studies, this information was lacking. Therefore, it cannot be excluded that some patients were screened with another focal dystonia than the defined subtypes described in table 1, however, presumably this number is extremely low.

In total, 179 of the screened subjects with AOIFD who were genetically tested turned out to have an underlying mutation (1.05%) (online supplemental file 3). Of these 179 patients, 111 were female (68%). A total of eighty (80) of the genetically confirmed patients (45%) had onset of their dystonia in early adulthood (21–40 years) and 99 patients (55%) developed dystonia after the age of 40. In the group with onset in early adulthood, 45 of 80 subjects reported a positive family history (56%), compared with 42 of 99 subjects (42%) in the group with onset of dystonia in late adulthood. Cervical dystonia (53%),

writer's cramp (26%) and laryngeal dystonia (14%) were the most common AOIFD-subtypes reported in cases with onset before the age of 40 years, while patients with onset in late-adulthood, initially presented with cervical dystonia (65%), blepharospasm (15%), and laryngeal dystonia (12%) as most common phenotypes.

Detected mutations were found in thirteen non-treatable dystonia-associated genes: *TOR1A* (n=15); *TAF1* (n=7); *TUBB4* (n=8); *THAP1* (n=52); *SGCE* (n=2); *PRKRA* (n=1); *CIZ1* (n=8); *ANO3* (n=33); *GNAL* (n=43); *KCTD17* (n=1); *KMT2B* (n=2); *PANK2* (n=7) and *ADCY5* (n=5). In 2 of the 17 129 screened patients (0.01%) genetic testing revealed mutations in a treatable dystonia-associated gene: *GCH1* (n=2). Mutations in *SGCE*, *PRKRA*, and *KMT2B* were only identified in patients with onset of dystonia in early-adulthood, while all cases with mutations in *KCT17* and *GCH1* presented with AOIFD in late-adulthood. An overview of all individual cases, categorised by gene, is presented in online supplemental file 4. Looking at all 17 127 patients with adult-onset dystonia who were genetically screened, it was not possible to determine if onset of their dystonia was either between 21 and 40 years or after the age of 40, as the studies on most cohorts did not disclose this information. The same applies to information on the family history of the screened patients.

Table 2 Mimics of dystonia

Type of dystonia	Mimics
Facial dystonia	Tics Hemifacial spasm (tonic component) Apraxia of eyelid opening (levator inhibition) Ptosis Trismus Hemimasticatory spasm Myotonia Tetanic spasms Hypoglossal nerve damage Functional movement disorder
Cervical dystonia (head tilt)	Klippel-Feil syndrome Atlanto-axial subluxation Congenital muscular torticollis Tics Vestibulopathy Trochlear/abducens nerve palsy ('ocular torticollis') Space-occupying lesion in posterior fossa Retropharyngeal abscess Sternocleidomastoid injuries Upper spinal cord syringomyelia Dropped head syndrome in neuromuscular disease Functional movement disorder
Truncal dystonia	Scoliosis Stiff person syndrome Functional movement disorder
Limb dystonia (posturing)	Contracture Spasticity Rigidity Abnormal posture due to paresis or atrophy Shoulder subluxation Dystonic (tonic) tics Trigger finger Myotonia or neuromyotonia Sensory ataxia and/or pseudoathetosis Stiff-person syndrome Tonic spasms (hypocalcaemia, hypomagnesaemia, alkalosis) Focal tonic seizures Functional movement disorder
Hemidystonia	Stiff-person syndrome Functional movement disorder
Generalised dystonia	Progressive encephalomyelitis with rigidity and myoclonus Carpopedal spasms Myelopathy Peripheral neuropathy Subacute combined degeneration Functional movement disorder
Paroxysmal dystonia	Focal tonic epilepsy Multiple sclerosis Tonic spasms (hypocalcaemia, hypomagnesaemia, alkalosis) Periodic paralyses Functional movement disorder

Adapted from: van Egmond ME *et al*, 2015.[51]

A NEW DIAGNOSTIC APPROACH

Based on the results of both literature reviews and clinical experience, we propose a new five-step diagnostic approach for adult-onset dystonia (figure 1). Steps 1–4 of the diagnostic algorithm are based on the broad literature search (search 1) and expert opinion. Step 5 is based on the results of the reported systematic literature search (search 2).

Step 1: Is it dystonia?

The first step in the diagnostic approach includes careful phenotyping, as it can be difficult to recognise dystonia. Diagnosis is based on an accurate history, a detailed neurological examination and close observation of movements, including the onset, spread, duration, rhythmicity, topography and predictability.[15] Movement disorders that may be misdiagnosed as dystonia are listed in table 2.

Table 3 Drugs and toxins that may cause dystonia

Drugs	
Dopamine receptor blocking drugs	(antipsychotics, antiemetics)
Dopamine depleting drugs	
Dopamine receptor stimulants	(levodopa, dopamine receptor agonists)
Tricyclic antidepressants	
Selective serotonin reuptake inhibitors	
Antiepileptic drugs	(eg, phenytoin, carbamazepine)
Antihistaminic drugs	(eg, promethazine)
Cholinergic agonists	
Antimalarials	(eg, chloroquine, amodiaquine)
Calcium channel blockers	(eg, flunarizine, cinnarizine)
Disulfiram	
Lithium	
Stimulants	(eg, methylphenidate)
Illicit drugs	
Amphetamine	
Methamphetamine	
3,4-methylenedioxymethamphetamine (Ecstasy)	
Methcathinone (Ephedrone)	
Cocaine	
Toxins	
3-nitropropionic acid Carbon monoxide Cobalt Cyanide Manganese Mercury Methanol Organophosphate	

Dystonia is classified according to a system based on consensus criteria published in 2013.[1] This classification involves two axes: the first axis focuses on clinical characteristics, the second axis on aetiology.

The clinical characteristics include age at onset, body distribution, temporal pattern, coexistence of other movement disorders and the occurrence of other neurological or systemic conditions. Adult-onset dystonia is defined as dystonia manifesting from the age of 21 years, with onset either in early adulthood (21–40 years) or late adulthood (>40 years). In contrast to children, in whom limb (usually leg) onset of dystonia typically spreads into a generalised dystonia, dystonic symptoms in adults are more likely to remain focal and the chance of progression to widespread dystonia is very low.[16] In most cases, dystonia severity gradually increases in the first few years and then remains stable, although occasionally dystonia becomes segmental as spreading of dystonic symptoms to adjacent muscle groups occurs. In adulthood, dystonic syndromes usually remain isolated, meaning that dystonia remains the only movement disorder, apart from dystonic tremor. In general adult-onset dystonia is not associated with co-occurrence of other neurological or systemic conditions, except for so-called 'non-motor features' such as alterations of mood, sleep and fatigue.[17]

Step 2. Could the dystonia be acquired and caused by medication or toxic agents?

The main acquired cause of adult-onset dystonia is medication-induced dystonia. Therefore, an important step is to consider if any medication, psychostimulant or toxic agent can be the cause of the dystonia (table 3).[18]

Many therapeutic and illicit drugs can cause neurological adverse effects, including dystonia. In most cases patients develop an acute dystonic reaction resulting after first exposure. Features are usually focal and can affect any muscle group, but most commonly involves the head, neck, jaw and mouth.[19] Symptoms can be painful and distressing. In acute medication-induced or toxin-induced dystonia, the provoking agent must be discontinued if possible. Furthermore, an antidote (if available) or symptomatic treatment may be considered.[20]

Another type of drug-induced dystonia is called tardive dystonia. The term tardive means 'late' to indicate that the condition occurs some period after drug exposure. The most common causes are dopamine receptor blocking drugs including neuroleptics and antiemetics.[21] Tardive dystonic symptoms typically involve (but are not necessarily limited to) the muscles of the face. Symptoms may also include muscle spasms of the neck, trunk and/or arms. Treatment of tardive dystonia can be challenging. Treatment options range from low dose propranolol and botulinum toxin to deep brain stimulation for medication-refractory cases.[22]

> **Step 3: Are there any clues for acquired causes other than medication of toxic agents?**
>
> If dystonia is not caused by external chemical substances, the next step is to consider other acquired causes of dystonia, such as structural lesions, infections, and immune-mediated disorders. To facilitate recognition of these acquired aetiologies of adult-onset dystonia, clinical red flags and recommendations for additional investigations are listed below and summarised in table 4. If at this point in the diagnostic framework thyroid function was not yet determined, we recommend performing TSH screening in all patients.

Table 4 Clinical clues suggesting an acquired cause of dystonia

Red flags	Differential diagnosis	Tests
Focal (non-task specific) limb dystonia or hemidystonia	Structural lesion	Neuroimaging
	External insult*	Neuroimaging
	Autoantibody-associated movement disorder	Autoantibodies in serum and CSF
	Demyelinating disease†	Neuroimaging, CSF
	Antiphospholipid syndrome	Neuroimaging, serum, CSF
Acute onset dystonia or rapidly progressive course	Structural lesion	Neuroimaging
	External insult*	Neuroimaging
	Autoantibody-associated movement disorder	Autoantibodies in serum and CSF
	Demyelinating diseases†	Neuroimaging, CSF
	Infection	Neuroimaging, serum, CSF
Psychiatric symptoms (de novo)	Autoantibody-associated movement disorder	Autoantibodies in serum and CSF
	Infection	Neuroimaging, serum, CSF
Seizures (de novo)	Structural lesion	Neuroimaging
	Autoantibody-associated movement disorder	Autoantibodies in serum and CSF
	Infection	Neuroimaging, serum, CSF
Signs of meningo-encephalitis or encephalitis	Infection	Neuroimaging, serum, CSF
	Autoantibody-associated movement disorder	Autoantibodies in serum and CSF
Local signs of autonomic disturbances and pain	Complex regional pain syndrome type I	Clinical diagnosis

Adapted from: van Egmond ME *et al*, 2015.[51] Adjustments based on the results of 'search 1' (see the Methods section) and expert opinion.
*External insults include head trauma and hypoxic insults caused by near-drowning, cardiac arrest or status epilepticus.
†Demyelinating diseases including ADEM, multiple sclerosis and neuromyelitis optica.
ADEM, acute disseminated encephalomyelitis; CSF, cerebral spinal fluid.

At this stage of the diagnostic approach, additional testing is only recommended in case of the presence of one or more of the red flags mentioned in the first column of table 4.

Structural lesions
Acquired brain lesions may produce either hemidystonia or focal (non-task specific) limb dystonia and are prevalently located in the basal ganglia, thalamus, corticospinal tract or cerebellum. The most common lesions resulting in dystonia are ischaemic lesions, haemorrhages and arteriovenous malformation, but also brain tumours, head trauma, radiotherapy, electrical injury and postanoxic.[23] Demyelinating lesions will be discussed in the next section.

Immune-mediated disorders
Dystonia, just like any other movement disorder, can present as a manifestation of autoantibody-mediated neurological syndromes, such as autoimmune encephalitis or a paraneoplastic neurological syndrome. Disease onset is typically subacute, where dystonia may either be the main neurological feature or part of a broader neurological syndrome, including epileptic seizures and cognitive deterioration. Early diagnosis is important because this group of disorders is potentially treatable. Furthermore, these conditions can be a red flag for neoplasia, as the autoantibody specificity may predict an underlying tumour association. With early adequate treatment (immunosuppression or immunomodulation, tumour treatment as appropriate), many patients show good recovery, although in some cases neurological deficits may persist.[24 25]

Autoantibody-mediated neurological syndromes are divided into broad categories according to the mechanism underlying the immune response involved: (1) autoantibodies targeting cell-surface antigens (GABA$_A$R, LGI1, NMDAR) and (2) autoantibodies targeting intracellular antigens (Ma2, CV2/CRMP5, Ri/ANNA-2).[26 27] The clinical characteristics of autoantibody-mediated neurological syndromes that can present with dystonia are summarised in table 5 .

Besides these autoantibody-associated syndromes, dystonia has been described in patients with multiple sclerosis and other autoimmune inflammatory demyelinating diseases like neuromyelitis optica spectrum disorder, acute disseminated encephalomyelitis and central pontine myelinolysis.[28] Although the causal relationship between the demyelinating disorder and dystonia has often been disputed, in some reported cases the dystonic symptoms were temporally and anatomically related to plaques in the central nervous system and both dystonia and MRI-abnormalities improved after treatment.[29] However, dystonia as a clinical manifestation of demyelinating disease remains uncommon, and dystonia as a first and isolated symptom is extremely rare. Important clues to diagnosis of dystonia related to demyelinating disease are co-occurrent clinical signs of central nervous system involvement, the characteristic MRI lesions and, in neuromyelitis optica spectrum disorder, the presence of aquaporin-4 or myelin-oligodendrocytic glycoprotein antibodies.[30]

Infections
Infectious encephalitis rarely causes brain lesions resulting in dystonia, but during the acute phase dystonia may develop, often combined with chorea. It is usually transient.[23] Possible infectious causes of dystonia include viral encephalitis, subacute sclerosing panencephalitis, HIV and encephalitis lethargica. Infection should be suspected particularly in adult-onset dystonia patients with pre-existing immunodeficiency or signs

Table 5 Clinical characteristics of autoantibody-mediated neurological syndromes that can present with dystonia

Antigen	Movement disorders	Other clinical features	Tumour association
Cell-surface antigens			
GABA$_A$R	Chorea, dystonia, ataxia, opsoclonus myoclonus syndrome. Possible association with SPSD	Encephalopathy, epilepsy, behavioural or cognitive problems, reduced consciousness	Thymoma, lung carcinoma, rectal cancer, myeloma
LGI1	Faciobrachial dystonic seizures, chorea, parkinsonism	Limbic encephalitis hyponatraemia, bradycardia, amnesic syndrome	Thymoma, SCLC, breast, prostate
NMDAR	Chorea, stereotypies, dystonia, catatonia, opisthotonos, OMS, myoclonus, tremor, myorhythmia, orofacial dyskinesia	Psychosis, seizures, autonomic dysfunction, language disintegration, impaired consciousness with paradoxical reactivity, limbic encephalitis	Ovarian, testicular teratoma
Intracellular antigens			
Ma2/Ta	Parkinsonism, ataxia, dystonia	Limbic, diencephalic or brainstem encephalitis, myelopathy or radiculoplexopathy, with encephalopathy, hypothalamic-pituitary endocrine dysfunction, weight gain, prominent sleep disorders, eye movement abnormalities (opsoclonus, supranuclear gaze palsy), dysphagia, muscular atrophy, fasciculations	Testicular, breast, lung, colon cancer
CV2/CRMP5	Chorea, ataxia, dystonia	Optic neuritis, myelitis (can mimic neuromyelitis optica), cognitive decline, neuropathy	SCLC, thymoma
Ri/ANNA-2	Dystonia (jaw closing dystonia, laryngospasms), opsoclonus myoclonus ataxia syndrome, oculopalatal myoclonus, cerebellar ataxia, SPSD	Brainstem encephalitis with cranial nerve palsies, nystagmus, dysarthria, ataxia, rigidity, trismus, pyramidal signs	SCLC, breast cancer

ANNA-2, anti-neuronal nuclear autoantibody 2; CRMP5, collapsin response mediator protein 5; GABA$_A$R, gamma aminobutyric acid A type receptor; LGI1, leucine-rich glioma inactivated 1; NMDAR, N-methyl-D-aspartic acid receptor; OMS, opsoclonus-myoclonus syndrome; SCLC, small cell lung cancer; SPSD, stiff person spectrum disorders.

of meningoencephalitis or encephalitis. In these cases, patients should be treated empirically with antibiotic, antiviral and/or antifungal therapies.[31]

Endocrine and metabolic abnormalities

There have been just a few case reports describing presentations of AOIFD associated with thyroid dysfunction.[32 33] Although rare, it is recommended to check serum thyroid-stimulating hormone concentration in patients with dystonic symptoms with unknown cause.[34] Serum biochemistry can identify early liver or renal disease or abnormalities in iron, manganese, calcium or parathyroid hormone levels, which is particularly relevant in cases of basal ganglia abnormalities on brain MRI.[35]

Step 4: Are there any clues for an underlying neurodegenerative disorder?

Isolated or combined dystonia in adults may be the initial manifestation of PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and -less commonly- dementia with Lewy bodies (DLB) and Creutzfeldt-Jakob disease (CJD).[36] Diagnosis of these disorders is based on clinical criteria combined with neuroimaging and in rare cases, DNA analysis.[37–41] To facilitate recognition of these conditions, an overview of key clinical features is provided in table 6.

Table 6 Neurodegenerative disorders with dystonia as a possible clinical feature

Neurodegenerative disorders	Key clinical features	Imaging and biochemical diagnostic markers
Idiopathic Parkinson's disease	Bradykinesia, muscular rigidity, rest tremor, postural instability	Dopamine transporter SPECT scans show decreased putaminal tracer uptake.
Multiple system atrophy	Autonomic failure, poorly levodopa-response, parkinsonism, cerebellar syndrome, stridor, Babinski sign with hyperreflexia	Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum 'Hot-cross bun sign' with cruciform hyperintensity in mid pons in T2-weighted images, and 'slit-like void sign' with hypointensity in association with hyperintense rim in the external putamen in T2-weighted images
Progressive supranuclear palsy	Vertical supranuclear palsy, slowing of vertical saccades, postural instability with early falls, symmetric akinesia or rigidity, urinary incontinence, behavioural changes.	'Hummingbird' or 'penguin' sign with volume loss in the midbrain and relative preservation of the pons in sagittal T1-weighted images, and 'Mickey mouse' or 'morning glory' sign with concavity of the lateral margin of midbrain tegmentum on T2-weighted axial images
Corticobasal degeneration	Limb rigidity or akinesia, limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit, alien limb phenomena.	Structural MRI reveals asymmetric atrophy predominantly involving the posterior frontal and superior parietal lobes.
Dementia with Lewy bodies	Dementia, visual hallucinations, parkinsonism, REM sleep behaviour disorder, severe neuroleptic sensitivity, deficits of attention, executive function, and visuospatial ability.	Low dopamine transporter uptake in the basal ganglia shown by SPECT or PET imaging.
Creutzfeldt-Jacob disease	Rapidly progressive dementia, myoclonus, visual changes leading to cortical blindness, ataxia, akinetic mutism.	Periodic sharp wave complexes on EEG, positive 14-3-3 CSF assay. MRI high-intensity signal abnormalities in caudate nucleus and/or putamen on DWI or FLAIR imaging

CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalography; FLAIR, fluid attenuation inversion recovery; PET, positron emission tomography; REM, rapid eye movement; SPECT, single photon emission CT.

Dystonia in PD

In approximately 30% of patients suffering from PD, dystonic features can be found. In most of these cases, dystonia presents with a focal or segmental distribution. Frequently dystonia is a result of chronic therapy, for example, 'off-dose dystonia' and 'peak dose dystonia' in patients on dopaminergic treatment or stimulation-induced dystonia after deep brain surgery. However, dystonia as a presenting sign is described in ten percent of PD patients and is more prevalent in young-onset PD.[42]

Of note, according to the current criteria for PD, dystonia in patients with parkinsonism should raise the suspicion of an atypical parkinsonian syndrome.[43]

Dystonia in atypical parkinsonian disorders

Dystonia has been described in atypical parkinsonian disorders such as MSA, PSP and CBD. The dystonia phenomenology may vary within and between atypical parkinsonian disorders, including body distribution, timing of appearance, severity and relationship to the intake of medication. The main examples are axial dystonia and blepharospasm causing the starring expression associated with PSP, facial dystonia and antecollis-like postures seen in patients with MSA, and the often fixed-arm dystonic posture seen in CBD.[36]

Dystonia in dementia with Lewy bodies

The most common reported form of dystonia in DLB is Meige syndrome, occurring in up to 25% of pathology-confirmed cases.[36] Rarely anterocollis and tongue dystonia may manifest in DLB as side effects of dopaminergic, cholinergic or neuroleptic medications, which after discontinuation usually reverse.[44 45]

Dystonia in CJD

In rare cases, dystonia has been observed as an early symptom of sporadic or familial CJD. Dystonia in CJD is usually unilateral and with distal distribution, but can be segmental, and at the late stages generalised dystonia has been more commonly reported.[46]

Step 5: Is the phenotype compatible with adult-onset isolated focal dystonia (AOIFD)?

As explained above, the term AOIFD is used to describe those adult-onset focal or segmental isolated dystonias that are usually sporadic without an identifiable cause (table 1). The last step of the diagnostic algorithm is to verify if the patient's phenotype is compatible with AOIFD. In that case, we recommend to refrain from further testing. If the phenotype does not fit AOIFD, we recommend performing additional investigations to identify genetic disorders, with focus on possible treatable inherited conditions (table 7).

For patients with adult-onset dystonia without any clues for an acquired or neurodegenerative dystonia (step 1–4) and with a phenotype compatible with AOIFD (table 1), we recommend to refrain from further investigations. This recommendation is based on the results of our systematic literature search (search 2). In clinical practice, it is important to accurately verify if the phenotype is in line with the characteristics described in table 1, so careful phenotyping is key. For example, if the temporal pattern shows a progressive course, diurnal variability or paroxysmal dystonia, this would not fit AIOFD.[1] If the phenotype is indeed compatible, further testing is not recommended and the next step is to consider symptomatic treatment, such as botulinum toxin injections or other treatment options.[8]

Yet, if the phenotype does not fit AOIFD, a broader diagnostic work-up is indicated. Neuroimaging is now recommended, as the results may provide specific diagnostic clues for an aetiological diagnosis. For most patients brain MRI will be the investigation of choice.[47] Besides neuroimaging, we advise to consider genetic testing for all patients with a non-AOIFD phenotype. Currently, the most used genetic technique for neurological disorders is WES.[48] In selected cases, we propose biochemical investigations parallel to genetic testing, aimed at early identification of treatable forms of genetic dystonia.[9 35] In table 7, we provide an overview of clinical clues to facilitate recognition of these ultrarare disorders and list relevant tests to consider. Depending on local facilities, we suggest prioritising the fastest diagnostic way to get to the diagnosis (genetic testing, biochemical testing or both).

DISCUSSION

In this paper, we propose a novel diagnostic approach for adult-onset dystonia (figure 1) based on the current literature and a systematic review of more than 17 000 cases. This approach guides clinicians through the diagnostic process, facilitates early aetiological diagnosis, and, importantly, helps to refrain from unnecessary diagnostics.

Recent developments in neuroimmunology and neurogenetics, with new dystonia-related autoantibodies and wider availability of genetic testing, provided inspiration for this study.[3 7 11] Due to this increased knowledge, the dilemma for clinicians of 'who to test' can be challenging, especially for patients with AOIFD (Table 1), which is by far the most common manifestation of adult-onset dystonia.

Our new algorithm is based on the principle that genetic testing is unlikely to provide diagnostic information in three groups of patients: (1) patients with an acquired form of adult-onset dystonia; (2) patients with neurodegenerative disorders, such as PD, presenting with a combined movement disorder including dystonic symptoms, and (3) patients with AIOFD. Steps 1–4 of the algorithm are based on the results of a broad literature search (search 1) and expert opinion, and aimed at identification of possible acquired or neurodegenerative causes of adult-onset dystonia. If clues for an acquired or neurodegenerative cause are lacking, a key question is if genetic testing is indicated (step 5). For this diagnostic step, we focused on AOIFD and performed a systematic search to investigate how often adults with a confirmed diagnosis of genetic adult-onset dystonia initially presented with AOIFD.

The results of this systematic literature review showed that of 17 127 genetically screened patients with an initial presentation of adult-onset focal or segmental dystonia, only 179 patients (1.05%) had an underlying mutation. Importantly, only 2 of 17 127 patients (0.01%) turned out to have a treatable genetic disorder (both *GCH1*-associated dystonia). This extremely low percentage is an important finding, and therefore we recommend to refrain from genetic testing in patients with AOIFD at step 5 of the algorithm (figure 1).

Looking into more detail at the results of the systematic literature search, we tried to extract possible clinical clues for a genetic disorder. First, a positive family history was reported by 87 of 179 patients (48,6%) with genetic dystonia and an initial presentation with AOIFD. This high percentage may indicate that a positive family history could be a clinical clue for a genetic dystonia, however it is unknown how many of the 17 127

Table 7 Clinical features and tests to consider in treatable adult-onset inherited dystonias

Disorder	Gene	Typical clinical features	Tests to consider	Treatment
Abetalipoproteinaemia (Bassen-Kornzweig syndrome)	MTTP	Progressive ataxia, chorea, dystonia (often oromandibular), seizures, acanthocytosis, retinitis pigmentosa, fat malabsorption syndrome	Fasting lipid panel, vitamin A, E and K in serum, blood smear	Early treatment with vitamin E and reduced-fat diet can prevent or reduce symptoms
Ataxia with vitamin E deficiency	TTPA	Ataxia, visual loss, neuropathy; occasionally patients present instead with dystonia	Vitamin E in serum	Early treatment with vitamin E can prevent or reduce symptoms
Cerebrotendinous xanthomatosis	CYP27A1	Ataxia, spasticity, dementia, dystonia, myoclonus, and tendon xanthomas	Cholestanol in plasma or serum	Chenodeoxycholic acid may prevent progression or reverse some symptoms
Coenzyme-Q10 deficiency	Multiple	Varied phenotypes of progressive ataxia or encephalopathy, sometimes with dystonia	Creatine kinase and lactate in serum	Coenzyme Q10 can prevent or reduce symptoms
Dopa-responsive dystonia, classic	GCH1	Dystonia often combined with parkinsonism	Pterins and biogenic amines in CSF	Levodopa can reverse symptoms
Dopa-responsive dystonia, complex	TH PTPS SPR	Dystonia often combined with parkinsonism, oculogyric crises, and autonomic disturbances	HVA, 5-HIAA, sepiapterin in CSF	Levodopa, 5-hydroxytryptophan or tetrahydrobiopterin or a combination of them can completely or partly reverse symptoms
Dystonia with brain manganese deposition	SLC30A10 SLC39A14	Progressive dystonia with parkinsonism, liver disease and polycythaemia	Manganese and iron in serum, blood smear	Chelation therapy can prevent or at least partly reverse symptoms
Galactosaemia	GALT GALK1 GALE	Ataxia and tremor, lactose intolerance, sometimes with mild dystonia	GALT-activity in red blood cells	Lactose restriction can prevent or mitigate symptoms
Glucose transporter type one deficiency	SLC2A1	Developmental delay, seizures; sometimes paroxysmal exertional dystonia	Glucose in CSF or serum	Ketogenic diet or triheptanoin can prevent or reduce symptoms
Glutaric aciduria type 1	GCDH	Developmental delay with encephalopathic crisis leading to generalised dystonia	Organic acids in urine, acylcarnitines in serum	Avoiding or treating intercurrent illness with lysine restriction can prevent encephalopathic crises
Niemann-Pick disease type C	NPC1 NPC2	Dementia, ataxia, spasticity, seizures, supranuclear gaze palsy; sometimes with progressive generalised dystonia	Oxysterol, lysosphingolipids, bile acid metabolites in plasma skin biopsy	N-butyldeoxynojirimycin can prevent or mitigate some symptoms
Rapid-onset dystonia-parkinsonism	ATP1A3	Psychomotor delay with bulbar or generalised dystonia after encephalopathic crisis	HVA in CSF	Avoiding or treating intercurrent illness can prevent encephalopathic crises
Wilson disease	ATP7B	Liver disease, Kayser-Fleischer rings, progressive dystonia, cognitive and neuropsychiatric abnormalities	Slit lamp examination, copper and ceruloplasmin in plasma, copper in 24 hours urine	Zinc or tetrathiomolybdate can prevent or reduce symptoms

CSF, cerebrospinal fluid; GALT, Galactose-1-phosphate uridyltransferase; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid.

screened adult-onset dystonia patients without a genetic cause reported a positive family history, which hampers this conclusion. A second clinical factor pointing towards a genetic cause might be onset in early-adulthood (21–40 years), which was described in 80 of the 179 (44.7%) patients with genetic dystonia and an initial presentation with AOIFD. As epidemiological data show that the prevalence of early-adulthood onset dystonia is much lower than late-adulthood onset dystonia,[2 5] this might indicate that the percentage of 44.7% is relatively high, although detailed information is lacking here as well. Taken together, both a positive family history and onset in early adulthood might be, but currently not convincing, positive factors to suggest a genetic basis in a patient with an AOIFD. Further research to support this hypothesis is needed, but for now, considering the very low numbers of patients with a genetic background with AOIFD, we recommend to refrain from further testing in all patients

with AOIFD at step 5 of the algorithm. Obviously, if during the course of the disease new symptoms arise, re-evaluation with careful phenotyping is warranted.

To our knowledge, our diagnostic approach is the first algorithm that covers all forms of adult-onset dystonia, including acquired, neurodegenerative and genetic causes. The recommendation to refrain from further investigations in patients with AOIFD at step 5 of our algorithm, is in line with a recently introduced scoring algorithm for dystonia, predicting the diagnostic utility of genetic testing by using WES.[49] According to this prediction tool, which was based on a large exome-wide study,[50] an AOIFD-phenotype will lead to a sum score of 0 or 1 points, indicating that genetic testing is not recommended. Both in the prediction tool[49] as in our algorithm the clinical characteristics 'age at onset', 'body distribution' and 'associated features' are incorporated. However, in the criteria of the prediction tool

'temporal pattern' is not included and no distinction is made between typical (Table 1) and atypical dystonias, such as focal leg dystonia which can be an important clue for an underlying inherited condition, or lead to a diagnosis of an acquired or neurodegenerative disorder earlier in the diagnostic process.

Our study needs to be interpreted in the context of its potential limitations. First, to support the last step (step 5) of our diagnostic algorithm, we performed a detailed systematic review of the literature with the aim to investigate which AOIFD patients may benefit from genetic testing. In an ideal situation, this search would comprise multiple large prospective studies in which unselected adult-onset dystonia patients are screened for all known dystonia-associated genes. However, these studies do not exist. Therefore, we systematically reviewed all published cases of genetically proven adult-onset dystonias and investigated how many of these patients initially presented as AOIFD. Second, there is the issue of selection bias. The exact prevalence of AOIFD in the general population is unknown and not all genetically tested cases of adult-onset dystonia have been published, so inevitably, the results of our systematic literature search comprise only a sample of the total population. However, we assume that this sample is representative, particularly because several included studies were prospective cohort-studies of unselected consecutive patients. Moreover, one might argue that in the other types of studies particularly genetically confirmed cases will have been published, which might in our study even lead to an overestimation of genetically confirmed cases with respect to the prevalence in the general population. Third, in the investigated studies, different genetic tests were used, varying from single gene analysis to whole genome screening. However, recently in a large WES study with 764 subjects similar results to our study have been reported.[50] Future studies are needed to systematically evaluate the diagnostic value of our stepwise approach.

In conclusion, we present a comprehensive overview of adult-onset dystonia and propose a novel five-step approach to facilitate early aetiological diagnosis. A key step of the presented algorithm is the recommendation to refrain from further investigations in patients with AOIFD, if there are no clinical clues for an acquired or neurodegenerative condition. To define AOIFD, good clinical phenotyping is essential. We believe that this new diagnostic approach is a useful framework for all practising clinicians who encounter patients with adult-onset dystonia.

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Supplement 1

Search criteria broad literature search and detailed systematic review

For the first steps of our algorithm (**Step 1-4**), we performed a broad literature
search on phenomenology, classification, and aetiology of adult-onset dystonia. We
reviewed papers regarding adult-onset dystonia, which is from 21 years of age. The key
terms we used were "dystonia" combined with (synonyms of) "adults", "adulthood",
"late onset", as well as (synonyms of) terms indicating possible aetiologies including
"idiopathic", "sporadic", "primary", "secondary", "acquired", "genetic", "inherited", and
"neurodegenerative". All reviewed papers and abstract were presented in English.

Secondly, to support the last step (**Step 5**) of our diagnostic algorithm, we performed a
detailed systematic review of the literature with the aim to investigate
which AOIFD patients may benefit from genetic testing. Ideally, this search consists
of multiple prospective studies of adult-onset dystonia patients screened for all
genes known to be associated with dystonia. However, these studies do not exist.
Therefore, we looked at all published cases of genetically proven adult-onset
dystonias who presented as one of our defined AOIFD-subtypes, with
focus on underlying treatable inherited causes. References for this review were
identified by PubMed, OMIM and Textbook search up to December 2021, as well as
searching for the references cited in the relevant articles.

The key terms we used were (synonyms of) "adult-onset dystonia", "focal dystonia" and
"idiopathic dystonia" combined with all genes associated with Dystonia (DYT) and
Dystonia-Parkinsonism (DYT/PARK) according to the MDS Gene Database, all genes
associated with Isolated Dystonia and Combined Dystonia according to the
recommended Nomenclature of Genetic Movement Disorders from the International
Movement Disorder and Society Task Force, plus, a selection of genes from the current
genetic dystonia panel from the UMC Groningen based on expert-opinion.

Key electronic search strategy for PubMed:

"Blepharospasm" [Mesh] OR "Meige Syndrome" [Mesh] OR "Torticollis"[Mesh] OR "focal-dystonia" [tiab] OR blepharospasm*[tiab] OR torticollis [tiab] OR cervical-dystonia[tiab] OR oromandibular-dystonia[tiab] OR meige-syndrome[tiab] OR task-specific-dystonia[tiab] OR idiopathic-dystonia*[tiab] OR (Adult-Onset[tiab] AND Dystonia*[tiab]) AND (TOR1A[tiab] OR DYT1[tiab] OR TAF1[tiab] OR DYT3[tiab] OR TUBB4[tiab] OR DYT4[tiab] OR GCH1[tiab] OR DYT5a[tiab] OR TH[tiab] OR DYT5b[tiab] OR THAP1[tiab] OR DYT6[tiab] OR SGCE[tiab] OR DYT11[tiab] OR PRKRA[tiab] OR DYT16[tiab] OR CIZ1[tiab] OR DYT23[tiab] OR ANO3[tiab] OR DYT24[tiab] OR GNAL[tiab] OR DYT25[tiab] OR ADCY5[tiab] OR SLC30A10[tiab] OR NPC1[tiab] OR NPC2[tiab] OR ATP7B[tiab] OR MTTP[tiab] OR TTPA[tiab] OR CYP27A1 [tiab] OR GALT[tiab] OR CABC1[tiab] OR ADCK3[tiab] OR ATP1A3[tiab] OR SPR[tiab] OR GLB1[tiab] OR TIMM8A[tiab] OR ATXN3[tiab] OR FTL[tiab] OR PANK2[tiab] OR C19ORF12[tiab] OR KMT2B[tiab] OR KCTD17[tiab] OR HPCA[tiab] OR SLC6A3[tiab] OR PTS[tiab] OR PLA2G6[tiab] OR CP[tiab])

Filter activated: Humans, English

Dystonia-associated genes were categorized as treatable or non-treatable dystonia syndromes.

List of genes considered to be treatable:
GCH1, TH, SLC30A10, NPC1, NPC2, ATP7B, MTTP, TTPA, CYP27A1, GALT, CABC1, ADCK3, ATP1A3, SPR, PTS, CP

List of genes considered to be non-treatable:
TOR1A, TAF1, TUBB4A, THAP1, SGCE, PRKRA, CIZ1, ANO3, GNAL, ADCY5, GLB1, TIMM8A, ATXN3, FTL, PANK2, C19ORF12, KMT2B, KCTD17, HPCA, SLC6A3, PLA2G6

Supplement 2

PRISMA 2009 Flow Diagram
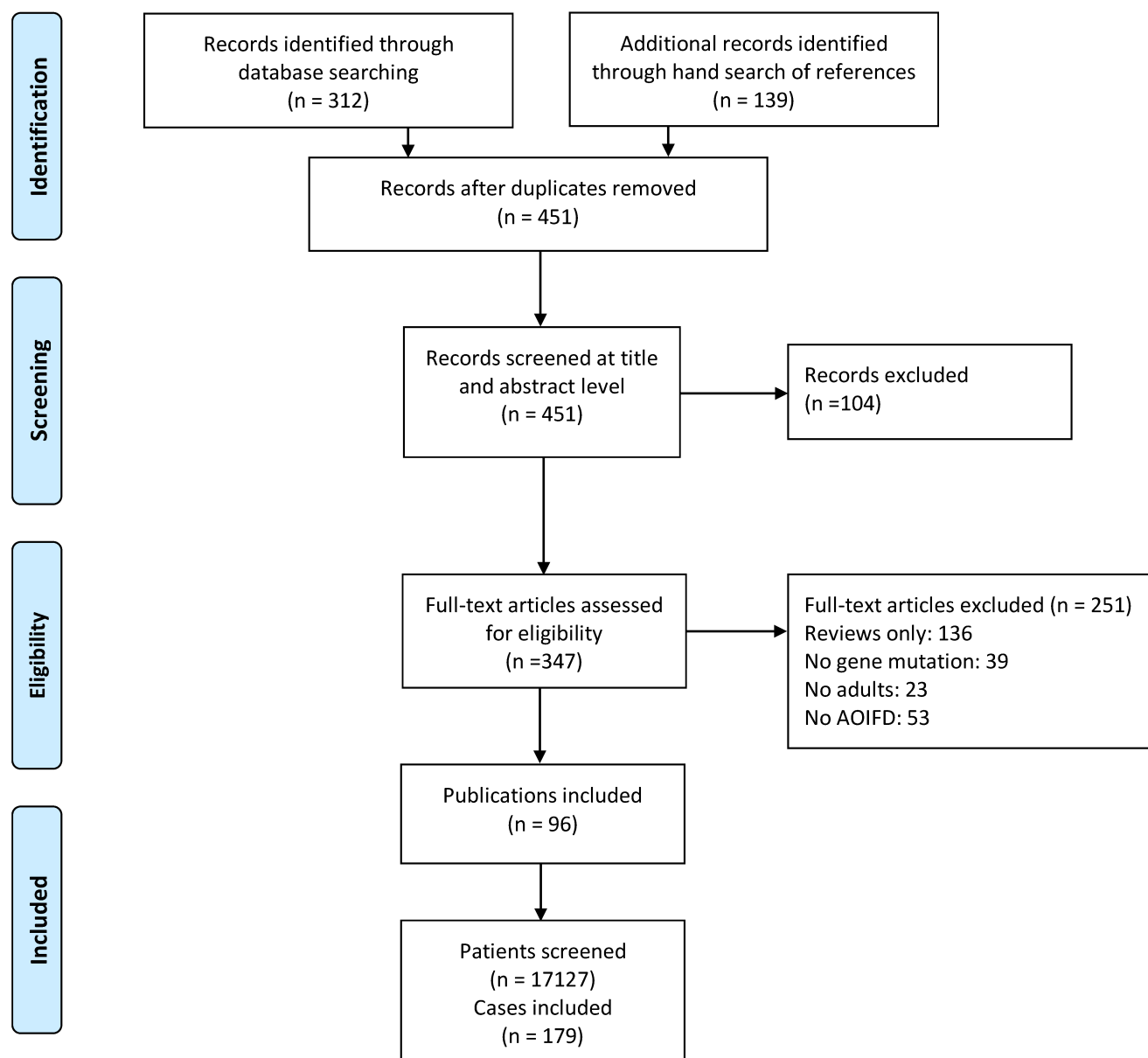
Supplement 3. Results of the systematic literature review: genetic dystonias that presented with Adult-Onset Idiopathic Focal Dystonia (AOIFD)

Gene	Typical Age at Onset	AOIFD Subtype	Number of Cases			
			21-40 years	>40 years	FH +	Total
Inherited isolated adult-onset dystonia syndromes						
TOR1A	Childhood	Cervical dystonia	5 (2) *	5 (3)	5	16
		Writer's cramp	4 (4)	1 (1)	5	
		Oromandibular dystonia	0	1 (0)	0	
TUBB4A	Early Adulthood	Laryngeal dystonia	5 (0)	1 (0)	0	8
		Cervical dystonia	2 (1)	0	1	
THAP1	Early Adulthood	Cervical dystonia	7 (0)	14 (6)	6	48
		Laryngeal dystonia	2 (0)	9 (3)	3	
		Blepharospasm	0	8 (0)	0	
		Writer's cramp	5 (5)	0	5	
		Musician's dystonia	1 (0)	0	0	
		Oromandibular dystonia	0	1 (0)	0	
		Meige syndrome	1 (0)	0	0	
SGCE	Childhood	Cervical dystonia	1 (1)	0	1	2
		Writer's cramp	1 (1)	0	1	
PRKRA	Adolescents	Writer's cramp	1 (0)	0	0	1
CIZ1	Late Adulthood	Cervical dystonia	3 (3)	5 (2)	5	8
ANO3	Early Adulthood	Cervical dystonia	4 (3)	11 (5)	8	28
		Blepharospasm	0	5 (2)	2	
		Laryngeal dystonia	2 (2)	0	1	
		Writer's cramp	2 (0)	1 (0)	0	
		Meige syndrome	0	2 (1)	1	
		Oromandibular dystonia	0	1 (0)	0	
GNAL	Early Adulthood	Cervical dystonia	17 (14)	22 (13)	27	44
		Laryngeal dystonia	2 (1)	0	1	
		Blepharospasm	0	1 (0)	0	
		Oromandibular dystonia	1 (1)	0	1	
		Cervical dystonia + Oromandibular dystonia	1 (0)	0	0	
KCTD17	Childhood	Laryngeal dystonia	0	1 (1)	1	1
KMT2B	Childhood	Writer's Cramp	2 (2)	0	2	2
Inherited combined adult-onset dystonia syndromes						
TAF1	Late Adulthood	Cervical dystonia	1 (1)	3 (3)	4	7
		Blepharospasm	1 (1)	1 (1)	2	
		Writer's cramp	1 (1)	0	1	
PANK2	Childhood	Writer's Cramp	5 (1)	0	1	7
		Laryngeal dystonia	0	1 (0)	0	
		Oromandibular dystonia	1 (0)	0	0	
ADCY5	Childhood	Cervical dystonia	2 (1)	3 (0)	1	5
Treatable inherited combined adult-onset dystonia syndromes						

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GCH1	Childhood	Cervical dystonia	0	1 (0)	0	2
		Oromandibular dystonia	0	1 (1)	1	
		Total number of cases	**80 (45)**	**99 (42)**	**87**	**179**

(Childhood 0-12 years, Adolescents 13-20 years, Early-Adulthood 21-40 years, Late-Adulthood > 40 years); FH: Family history)

* In brackets number of cases with a positive family history

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Supplement 4.
The profile and classification of genetically confirmed cases who presented with an AOIFD subtype

TOR1A					
Reference	**Nucleotide change**	**Sex**	**Age at onset**	**Family history**	**AOIFD subtype**
Zech, 2016	c.-39G > T	F	42	-	CD
	c.445-8T > C	F	58	-	CD
	c.488C > T	M	26	+	WC
	c.692T > A	F	32	-	CD
	c.962C > T	M	33	-	CD
Calakos, 2010	c.613T >A	M	>40	-	OMD
LeDoux, 2016	c.962C > T	F	40	+	CD
Dobričić, 2015	c.385G > A	F	38	-	CD
Vulinovic, 2014	c.40_45del	F	31	+	CD
Dhaenens, 2005	CAG-del	M	20-40	+	WC
Kostic, 2006	CAG-del	M	45	+	CD
Opal, 2002	CAG-del	F	64	+	WC
Kramer, 1990	N/A	F	21	+	CD
Valente, 1998	CAG_del	F	21	+	WC
	CAG_del	F	50	+	CD
Gómez-Garre, 2021	c.904_906delGAG	M	27	+	WC
TAF1					
Lee, 2011	N/A	F	47	+	BS
		F	49	+	CD
		F	48	+	CD
Evidente, 2004	N/A	F	42	+	CD
Evidente, 2002	N/A	M	37	+	CD
		M	37	+	BS
		M	31	+	WC
TUBB4A					
Wilcox, 2011	N/A	M	42	+	LD
Bally, 2020	c.G137T	M	21	+	LD
	c.G1272C	M	21	+	LD
Lohmann, 2013	c.4C > G	F	30	+	LD
Hersheson, 2013	c.4C > G	F	21	+	LD
	c.4C > G	F	23	+	LD
	c.4C > G	M	28	+	CD
Vulinovic, 2017	c.1015_1017del	M	21	-	CD
GCH1					
Grantham, 2015	GCH1_del	F	40	+/-	CD
Steinberger, 1999	c.582G >T	M	46	+	OMD
THAP1					
De Gusmão, 2016	c.11C >T	M	24	-	LD

	c.580T >C	F	50	+	LD
Jurek, 2014	c.15 C > G	F	50	+	CD
Song, 2011	c.214_215InsA	M	26	-	CD
	c.489C > G	F	65	-	BS
	c.489C > G	M	67	-	BS
	c.489C > G	F	67	-	BS
Prudente, 2013	c.268-31A > G	F	53	+/-	CD
	c.71+9C > A	F	40	-	CD
Da Silva-Junior, 2014	c.C289T	F	46	+	CD
Söhn, 2010	c.388_389delTC	F	35	-	CD
	c.427A > G	F	46	-	CD
	c.247T > C	F	34	-	CD
Lohmann, 2012	c.570delA	F	49	+	CD
	c.-32C4T	M	33	-	Mus
	c.238A>G	M	41	-	CD
Xiao, 2010 and Vemula, 2013	c.446T > C	F	49	+	CD
	c.559C > A	F	53	+	CD
	c.50A > G	F	43	-	CD
	c.395T > C	F	51	-	LD
	c.496G > A	F	62	-	LD
	c.42 C > T	F	69	-	BS
	c.42 C > T	F	62	-	LD
	c.57 C > T	F	33	-	Mei
	c.71 + 9C > A	F	50	-	BS
	c.71 + 9C > A	F	69	-	BS
	c.71 + 9C > A	M	61	-	OMD
	c.71 + 9C > A	F	25	-	CD
	c.71 + 9C > A	F	58	-	CD
	c.71 + 9C > A	M	55	-	CD
	c.71 + 9C > A	F	48	-	LD
	c.71 + 9C > A	F	66	+	LD
	c.71 + 9C > A	F	58	+	LD
Xiromerisiou, 2013	c.208A > G	F	55	-	BS
	c.-40T > C	F	64	-	BS
Gómez-Garre, 2021	c.37C > G	F	21	-	CD
	c.86G > A	F	40	-	CD
	c.292G > T	F	69	-	LD
	c.605C > T	F	62	+	CD
Fuchs, 2009	ins:del	F	34	+	WC
	ins:del	M	31	+	WC
	ins:del	F	28	+	WC
	ins:del	M	38	+	WC
LeDoux, 2012	c.238A > G	M	23	+	WC
Groen, 2010	c.495C > T	F	50	-	CD
Dobričić, 2013	c.85C > T	M	36	-	LD
	c.-220C > T	M	26	-	CD
	c.-220C > T	M	41	-	LD
SGCE					
Vidailhet, 2001	N/A	M	38	+	CD
Koukouni	N/A	M	39	+	WC

PRKRA

Dos Santos	c.C665T	M	25	+/-	WC

CIZ1

Xiao, 2012	c.790A > G	M	41	+	CD
	c.790A > G	M	49	+	CD
	c.790A > G	M	35	+	CD
	c.790A > G	F	32	+	CD
	c.790A > G	F	23	+	CD
	c.2015G > T	F	70	-	CD
	c.139C > T	F	44	-	CD
	c.1180C > G	F	40	-	CD

ANO3

Zech, 2014	c.2947A > G	F	40	-	CD
	c.2917G > C	F	69	-	Mei
Miltgen, 2016	c.1969G > A	F	53	+	BS
	c.1969G > A	F	40	+	BS
	c.1969G > A	M	40	+	CD
Stamelou, 2014	c.1480A > T	F	27	+	CD
	c.1480A > T	M	40	+	CD
	c.1480A > T	M	30	+	LD
	c.1480A > T	F	30	+	CD
Jiang, 2021	c.-11G > T	F	67	+/-	CD
	c.-11G > T	F	46	-	CD
	c.1127A > G	M	57	-	CD
	c.1235T > A	F	53	-	OMD
	c.1531-3T > C	M	65	+/-	BS
Zech, 2017	c.674A > G	F	44	-	BS
	c.835T > A	F	65	+/-	CD
	c.1387G > A	F	50	-	BS
	c.1964_1966dupATA	F	51	-	CD
Charlesworth, 2012	c.2053A > G	F	25-30	+	LD
Olschewski, 2019	c.433-2A > G	F	25	-	WC
	c.982C > T	M	28	-	WC
	c.982C > T	F	36	-	CD
	c.2906G > A	M	45	-	WC
Ma, 2015	c.2540A > G	M	39	+	CD
	c.2540A > G	M	41	+	CD
	c.2540A > G	F	44	+	CD
	c.2540A > G	F	50-60	+	CD
	c.2540A > G	M	56	+	Mei

GNAL

Zech, 2014	c.436G > A	F	63	-	CD
Kumar, 2014	c.637G > A	M	40	-	CD
	c.1057G>A	F	44	+	CD
Dufke, 2014	c.733C > T	F	49	-	CD
Vemula, 2015	c.682G > T	M	45	+	CD
	c.591dupA	F	38	+	CD
	c.591dupA	F	37	+	CD
	c.733C > T	F	45	+	CD
	c.3G > A	F	40	+	CD
	c.3G > A	F	41	+	CD

LeDoux, 2016	c.1018G > A	F	68	-	CD
	c.1060C > A	M	43	+	CD
	c.139C > A	F	45	-	CD
	c.214C > G	F	42	-	CD
Dobričić, 2014	c.1061T > C	F	40	-	CD
Fuchs, 2013	c.409G > A	M	31	+	CD
	c.409G > A	F	26	+	CD
	c.409G > A	F	50	+	CD
	c.409G > A	F	22	+	CD
	c.878C > A	F	48	+	CD
	c.878C > A	M	35	+	CD
	c.878C > A	M	47	+	CD
	c.878C > A	M	32	+	CD
	c.878C > A	M	35	+	CD
	c.283_284insT	F	33	+	CD
	c.283_284insT	F	39	+	OMD
	c591_592insA	M	47	+	CD
	c591_592insA	F	38	+	CD
	c591_592insA	F	31	+	CD
	c.274-5T > C	M	54	+	CD
	c.274-5T > C	F	36	+	CD
	c.61C > T	M	25	+	CD
	c.61C > T	M	42	+	CD
	c.61C > T	F	25	+	LD
Miao, 2013	c.284C > T	F	41	-	CD
	c.932-7T > G	F	26	-	CD
Ziegan, 2014	c.166_ 167insA	F	35	-	CD
Carecchio, 2016	c.628G > A	M	36	+	CD
	c.628G > A	F	42	+	CD
Gómez-Garre, 2021	c.694G > A	M	29	-	CD
	c.828C > A	F	45	-	CD
	c.1330C > T	M	59	-	BS
Saunders-Pullman, 2015	c.514G > A	F	21	-	LD
Dos Santos, 2016	c.399C > A	F	23	-	CD + OMD

KCTD17

Todisco, 2020	c.229C > A	M	51	+	LD

KMT2B

Winslow, 2020	c.4960T > C	M	25-30	+	WC
	c.4960T > C	F	>20	+	WC

PANK2

Paraskevas, 2017	c.1424T > C	M	22	-	WC
Diaz, 2013	c.881A > T	F	48	-	LD
Lee, 2016	c.1133A > G	M	23	-	OMD
	c.1153delCinsTT	M	25	+	WC
	c.1003A > G	M	21	-	WC
	c.823_824del	M	38	-	WC
Aggarwal, 2010	c.1379C > T	M	37	-	WC

ADCY5

Zech, 2017	c.1196C > T	F	50	-	CD

	c.1400A > G	F	26	-	CD
	c.2180G > A	F	29	+	CD
	c.3177_3182del	M	58	+/-	CD
	c.3625A > G	F	53	-	CD

CD: Cervical dystonia; WC: Writer's Cramp; OMD; Oromandibular dystonia; BS: Blepharospasm;
LD: Laryngeal dystonia; Mei: Meige syndrome; Mus: Musician's dystonia

Note: a complete list of all included studies including number of screened patients per study is available upon request.