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LETTER TO THE EDITORS

Dystonia and mitochondrial disease: the movement disorder connection revisited in 900 genetically diagnosed patients

Elisabetta Indelicato[1,2,3] · Lea D. Schlieben[1,2] · Sarah L. Stenton[4,5] · Sylvia Boesch[3] · Matej Skorvanek[6,7] · Jan Necpal[8,9] · Robert Jech[10] · Juliane Winkelmann[1,2,11] · Holger Prokisch[1,2] · Michael Zech[1,2,12]

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Introduction

Dystonia is characterized by excessive muscle contractions leading to abnormal posturing or movements, typically worsening with voluntary action and overflow muscle activation [1]. Dystonia can arise at any age and affect virtually any muscle [1]. The disease often co-occurs in combination with other movement disorders or additional neurological signs, resulting in a wide range of clinical outcomes [2]. Due to its puzzling pathophysiology, dystonia represents one of the core topics in movement disorders research [3]. High-throughput DNA sequencing has unveiled a strong genetic background for this condition [4], and has raised a number of novel questions, such as why dystonia-linked genes are implicated in multiple seemingly unrelated pathways [3]. These comprise but are not limited to a variety of metabolic processes, cellular ion handling, DNA binding and replication, signal transduction, neurotransmitter turnover, protein folding and intracellular trafficking [3]. This heterogeneous pathophysiology is consistent with a view of dystonia as a network disorder that is not associated with changes in a single neural pathway, but may result from disturbances in multiple regions of the nervous system [3]. In contrast to Parkinson's disease [5], a pathophysiological link between monogenic dystonias and the far more frequent 'idiopathic' adult-onset isolated dystonias is missing.

Mitochondrial dysfunction has been identified as a relevant pathophysiological factor in dystonia [6] and mitochondrial DNA (mtDNA) defects have been linked to pathognomonic dystonia syndromes in an association dubbed "the movement disorder connection" [6]. This term was coined following the observation that defects in several mitochondrial pathways can all lead to the clinical outcome of dystonia, raising the hypothesis that mitochondrial defects in general may be involved in the pathogenesis of movement

Elisabetta Indelicato and Lea D. Schlieben contributed equally as first authors.

Holger Prokisch and Michael Zech contributed equally as last authors.

✉ Michael Zech
michael.zech@mri.tum.de

1 Institute of Human Genetics, Technical University of Munich, School of Medicine, Munich, Germany

2 Institute of Neurogenomics, Helmholtz Munich, Deutsches Forschungszentrum Für Gesundheit Und Umwelt (GmbH), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany

3 Center for Rare Movement Disorders Innsbruck, Department of Neurology, Medical University Innsbruck, Innsbruck, Austria

4 Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA

5 Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02115, USA

6 Department of Neurology, P. J. Safarik University, Kosice, Slovakia

7 Department of Neurology, University Hospital of L. Pasteur, Kosice, Slovakia

8 2nd Department of Neurology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

9 Department of Neurology, Zvolen Hospital, Zvolen, Slovakia

10 Department of Neurology, Charles University in Prague, 1st Faculty of Medicine and General University Hospital in Prague, Kateřinská 30, 121 08 Prague, Czech Republic

11 Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

12 Institute for Advanced Study, Technical University of Munich, Lichtenbergstrasse 2 a, 85748 Garching, Germany

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disorders [6]. Beyond the 37 proteins and RNAs encoded by the mtDNA, more than 1500 nuclear encoded proteins are involved in mitochondrial structure and function [7]. It is nowadays established that defects in all these factors may result in mitochondrial dysfunction, leading to a new concept of mitochondrial disease genes [7]. Movement disorders, including dystonia, are a frequent manifestation of nuclear-encoded mitochondrial defects as shown by numerous case reports and corroborated by a few smaller case series [8–11]. However, the implication of nuclear mitochondrial disease genes in dystonia has not yet been assessed systematically at a cohort-wide level [3]. This unresolved issue along with scarce experimental evidence hinders firm conclusions to be drawn on the contribution of mitochondrial dysfunction to dystonia pathophysiology. Understanding the role of mitochondrial impairment in larger numbers of dystonia-affected individuals may also have relevance for the more common isolated dystonias presenting to the adult neurology clinic. Early studies hint toward mitochondrial dysfunction in 'idiopathic' dystonia [12, 13], however, these have not been followed by in-depth replication. Recent reports describing isolated dystonia phenotypes in the setting of complex V defects prompted us to reexamine the contribution of mitochondrial defects in the wider spectrum of dystonic diseases [14] and vice versa the frequency of dystonia in pediatric mitochondrial disease cases [15].

Herein, we explored the contribution of nuclear-encoded mitochondrial disease gene defects to dystonia from a cohort-level perspective. The study analyzed two large collections of individuals who underwent whole exome sequencing (WES) for the indications of (i) dystonia and (ii) clinically suspected mitochondrial disease. The aim of this study was to define (1) the frequency of mitochondrial disease gene defects in cases ascertained for dystonia, (2) the prevalence of dystonia as a clinical feature in patients with genetically diagnosed mitochondrial disease, and (3) whether specific molecular pathways related to mitochondrial dysfunction are more often perturbed in each of these settings.

Methods

Study population

Within a multicenter study on the monogenic background of dystonia a total of 1,100 index cases with dystonic disorders were assessed for mitochondrial disease gene defects using WES (patients previously published in [2]). Both adults (≥21 years, 67%) and children/adolescents (<21 years, 33%) were included [2]. A molecular diagnosis was identified in 220 cases within the dystonia cohort [2]. Patients with clinically suspected mitochondrial disease were extracted from the GENOMIT consortium, as previously described [16]. Within GENOMIT, 2023 pediatric patients with at least a "possible" diagnosis of mitochondrial disease according to the Nijmegen Mitochondrial Disease Criteria [17] were recruited and genetically tested using WES. Details on the study protocol are provided in Stenton et al. [15]. Within the cohort, 1,109 patients (55%) received a molecular diagnosis, of whom 683 cases were solved by the detection of variants in nuclear-encoded mitochondrial genes. The here-evaluated patients have been reported in our previous cohort studies on genetic dystonias and mitochondrial disorders [2, 15, 16].

Definition of nuclear mitochondrial disease genes

Mitochondrial disease genes were grouped into seven previously published functional subcategories [7, 15]: (1) oxidative phosphorylation (OXPHOS) subunits, assembly factors, and electron carriers, (2) mtDNA replication and expression, (3) mitochondrial dynamics, homeostasis, and quality control, (4) metabolism of substrates, (5) metabolism of cofactors, (6) metabolism of toxic compounds and (7) others/unknown function. For this study, we focused solely on nuclear-encoded mitochondrial disease genes due to the applied testing design of the study cohorts: all patients underwent WES with targeted analysis of the nuclear genome. The mitochondrial genome was not analyzed in the dystonia samples (mtDNA calling pipeline not available for all cases). We therefore gave priority to analysis of nuclear gene defects in this study.

Results

Among 220 genetically resolved dystonia exomes [2], 29 patients had disease-causing variants in nuclear-encoded mitochondrial disease genes (13%), spanning 19 different genes (Table 1). The most frequent mitochondrial disease gene hits were *PANK2* (6/29 cases, 21%), *WARS2*, and *COQ8A* (each with 3/29 cases, 10%). The majority of diagnosed gene etiologies (15/19 genes) were reported in single cases only. The largest gene cluster was related to "mitochondrial dynamics, homeostasis and quality control" (8/19 genes, including: *AFG3L2, DNM1L, OPA1, PINK1, PRKN, SERAC1, SPG7, VPS13D*), followed by genes directly related to OXPHOS composition, cofactors, or assembly. The majority of genetic defects were inherited in an autosomal recessive manner (79%), while in six out of 29 patients (21%) the mode of inheritance was autosomal dominant. Five patients (one each with variants in *COQ8A, OPA1, PINK1, SPG7, WFS1)* had adult-onset dystonia, while the other 24 patients had an onset of dystonia before the age of 21. With regard to clinical presentation, most of the patients (20/29 cases, 69%) fell into the category of "complex"

Table 1 Nuclear-encoded mitochondrial disease gene diagnoses identified in solved dystonia cases

Functional Category	Gene	Mode of inheritance	Dystonia category	n. of cases
OXPHOS subunits, assembly factors, and electron carriers	*ATP5F1A*	AD	*Complex* (ID, ataxia, spasticity)	1
	ATP5MC3	AD	*Combined* (spasticity)	1
	COQ8A	AR	*isolated/combined* (ataxia)	3
	SCO2	AR	*Complex* (ID)	1
Mitochondrial DNA replication and expression	*NARS2*	AR	*Complex* (epilepsy)	1
	WARS2	AR	*Complex* (ID, parkinsonism)	3
Mitochondrial dynamics, homeostasis, and quality control	*AFG3L2*	AD	*Complex* (ID, ataxia)	1
	DNM1L	AD	*Complex* (ID, epilepsy)	1
	OPA1	AD	*Complex* (optic atrophy)	1
	PINK1	AR	*Combined* (parkinsonism)	1
	PRKN	AR	*Combined* (parkinsonism)	1
	SERAC1	AR	*Complex* (ID)	1
	SPG7	AR	*Combined* (ataxia)	1
	VPS13D	AR	*Complex* (ID, ataxia)	1
Metabolism of substrates	***FA2H***	AR	*Complex* (ID, spasticity)	1
Metabolism of cofactors	*MECR*	AR	*Complex* (optic atrophy)	1
	PANK2	AR	*Complex* (ataxia, spasticity, cognitive decline)	6
	PLA2G6	AR	*Combined/complex* (ataxia, ID)	2
	WFS1	AD	*Complex* (optic atrophy, deafness, migraine)	1

Genes associated with NBIAs are shown in bold. While some genes may be associated with both autosomal recessive (AR) and autosomal dominant inheritance (AD), we herein reported only the mode of inheritance specific to the variants detected in the present study. ID: intellectual disability

dystonia, presenting with additional non-movement disorder features such as intellectual disability or epilepsy [2]. Seven patients displayed dystonia combined with another movement disorder (ataxia, parkinsonism, spasticity) [2]. Only one patient carrying compound heterozygous *COQ8A* variants presented with isolated dystonia. Of the 19 mutated genes, five are not formally linked to a dystonia phenotype in OMIM (*SPG7, DNM1L, NARS2, OPA1, WFS1*). There are however cumulative reports in the literature supporting an association with dystonia for at least 4 of these genes [18–21].

Out of 683 solved exomes of pediatric patients with nuclear-encoded mitochondrial gene-related disease, 83 cases presented clinically with dystonia (12%). The molecular diagnoses spanned 45 different mitochondrial disease genes, of which more than half (n = 27) were detected in single cases only (Table 2). The most frequent genetic etiologies were *ECHS1*-related disorder (16/83 cases, 19%), as well as *NDUFAF6*- (4 cases), *COQ4*-, *PANK2*- and *SERAC1*-related diseases (each with 3 cases). Considering the different functional pathways, the largest gene category in this cohort was the OXPHOS subunits or assembly factors (n = 12), followed by genes involved in the metabolism of cofactors (n = 10). All patients with mitochondrial gene-related disease displayed an autosomal recessive mode of inheritance, with the exception of one X-linked case. Regarding the clinical presentation, all 83 patients fell in the category of "complex dystonia".

The only gene category showing a tendency towards more frequent implication in the dystonia cohort, as compared to the mitochondrial disease cohort, was that related to "mitochondrial dynamics, homeostasis, and quality control" (category 3). Six gene etiologies (*FA2H, PANK2, PLA2G6, SERAC1, SPG7*, and *WARS2*) were identified both in the dystonia and in the mitochondrial disease cohort. Three of these genes (*FA2H, PANK2, PLA2G6)* are associated with a group of disorders known as NBIAs (neurodegeneration with brain iron accumulation).

Discussion

Herein, we systematically re-evaluated two large WES cohorts to delineate the contribution of nuclear-encoded mitochondrial disease genes to the clinical expression of dystonia. We found that variants in nuclear-encoded mitochondrial disease genes accounted for 13% of diagnoses in 220 WES-solved dystonia cases, whereas 12% of 683 pediatric cases with monogenic mitochondrial disease due to variants in nuclear-encoded mitochondrial disease genes had

Table 2 Nuclear genes implicated in genetically solved mitochondrial disease cases presenting with dystonia

Functional category	Gene	Mode of inheritance	Neurological features other than dystonia	Extraneurological features	n. of cases
OXPHOS subunits, assembly factors, and electron carriers	*ATP5F1E*	AR	ID, ataxia, neuropathy		2
	ATP5PO	AR	DD, hypotonia, epilepsy, microcephaly		1
	BCS1L	AR	DD, hypotonia, ID, epilepsy, myoclonus, spasticity	Hypoglycemia, gastrointestinal dysmotility, lactic acidosis,	1
	COQ4	AR	DD, hypotonia, ID, epilepsy, microcephaly	Facial dysmorphism	3
	COX10	AR	DD, hypotonia, ataxia	Failure to thrive, lactic acidosis	1
	DNAJC30	AR	DD, ataxia		1
	FOXRED1	AR	DD, epilepsy, myoclonus, visual impairment	Lactic acidosis	1
	LYRM7	AR	DD/ DR, ID, hypotonia, microcephaly, deafness, visual impairment, tremor	Failure to thrive, hypoglycemia, facial dysmorphism, lactic acidosis, exercise intolerance	1
	NDUFA12	AR	DD/DR, ID, hypotonia, spasticity, visual impairment, microcephaly, tremor, neuropathy	Lactic acidosis, scoliosis	2
	NDUFA4	AR	DD/DR, ataxia	Failure to thrive, lactic acidosis, hypertrophic cardiomyopathy, myopathy, exercise intolerance	1
	NDUFAF5	AR	DD/DR, ataxia	Lactic acidosis	2
	NDUFAF6	AR	DD/DR, spasticity, ataxia, visual impairment	Gastrointestinal dysmotility, lactic acidosis, scoliosis	4
Mitochondrial DNA replication and expression	*GFM1*	AR	DD, epilepsy, spasticity, neuropathy, visual impairment	Muscular dystrophy, lactic acidosis	1
	GFM2	AR	DD/DR, hypotonia, ID, epilepsy, microcephaly, spasticity, neuropathy	Failure to thrive, gastrointestinal dysmotility, lactic acidosis, muscular dystrophy, exercise intolerance	1
	MRPS34	AR	DD, ID, microcephaly		1
	MTFMT	AR	DD, ID, hypotonia, ataxia, attention deficit-hyperactivity disorder	Failure to thrive, lactic acidosis, anemia, strabismus, hypertrophic cardiomyopathy	2
	PNPT1	AR	DR, ID		2
	SARS2	AR	DD/DR, hypotonia, spasticity	Lactic acidosis, cataract	1
	WARS2	AR	DD, ID, athetosis, hemiballismus,		1
Mitochondrial dynamics, homeostasis, and quality control	*CLPB*	AR	hypotonia, epilepsy	Neutropenia, anemia, apneas	1
	SERAC1	AR	DD, hypotonia, ID, spasticity, microcephaly, deafness, epilepsy, ataxia, optic atrophy	Failure to thrive, facial dysmorphism, lactic acidosis, hypoglycemia, kidney dysfunction, liver failure	3
	SPG7	AR	DD, ID, ataxia		1
	TIMM50	AR	DD, epilepsy, spasticity, optic atrophy	Failure to thrive, neutropenia, cardiomyopathy, lactic acidosis, scoliosis	1
	YME1L1	AR	DR, ataxia	Lactic acidosis, cardiomyopathy, exercise intolerance	1

Table 2 (continued)

Functional category	Gene	Mode of inheritance	Neurological features other than dystonia	Extraneurological features	n. of cases
Metabolism of substrates	*ALDH18A1*	AR	DD, hypotonia, ID, epilepsy, microcephaly, spasticity	Failure to thrive, cataract	1
	FA2H	AR	DD, ID, ataxia		2
	MDH2	AR	DD, epilepsy, hypotonia	Failure to thrive, lactic acidosis	1
	PDHA1	X-linked	DD, spasticity, visual impairment	Lactic acidosis	2
Metabolism of cofactors	***COASY***	AR	DD, ID, ataxia, spasticity		1
	FDXR	AR	hypotonia, ID, epilepsy, ataxia, spasticity, optic atrophy, visual impairment, deafness, ophthalmoplegia, neuropathy	Myopathy, diabetes mellitus	1
	ISCA2	AR	DD/DR, epilepsy, spasticity	Anemia, lactic acidosis	1
	LIPT2	AR	DD/DR, hypotonia, ID, microcephaly, epilepsy, spasticity	Lactic acidosis	2
	MECR	AR	DD		1
	PANK2	AR	DD, ID, ataxia, spasticity, tremor		3
	SEPSECS	AR	DD, ID		1
	SLC19A3	AR	DD, ataxia		2
	SLC25A42	AR	DD, hypotonia, ID, macrocephaly, choreoathetosis	Rhabdomyolysis, failure to thrive, gastrointestinal dysmotility, facial dysmorphism, lactic acidosis	2
	TPK1	AR	DD	Feeding difficulties, muscular dystrophy	1
Metabolism of toxic compounds	*ECHS1*	AR	DD/DR, ID, hypotonia, microcephaly, epilepsy, spasticity, ataxia, deafness, neuropathy, optic atrophy, stroke-like episodes,	Failure to thrive, gastrointestinal dysmotility, lactic acidosis, diabetes insipidus, abnormality of temperature regulation, hypertrophic cardiomyopathy, kidney dysfunction, exercise intolerance, hepatomegaly, apneas	16
	ETHE1	AR	DD/DR, myoclonus, ataxia, spasticity	Lactic acidosis	1
	HIBCH	AR	DD/DR	Failure to thrive	1
Others/Unknown function	***C19orf12***	AR	DD, ID, ataxia		2
	FBXL4	AR	DD, ID, hypotonia, spasticity		1
	PLA2G6	AR	DD, ID, ataxia		3
	SPATA5	AR	DD, epilepsy, microcephaly, myoclonus, spasticity, deafness, visual impairment	Failure to thrive, lactic acidosis	2

Genes associated with NBIAs are shown in bold. While some genes may be associated with both autosomal recessive (AR) and autosomal dominant inheritance (AD), we herein reported only the mode of inheritance specific to the variants detected in the present study. DD: developmental delay; DR: developmental regression; ID: intellectual disability

dystonia. Overall, variants in 57 nuclear-encoded mitochondrial disease genes were involved in a dystonia phenotype in the two explored large patient collections.

Previous case series [8–11] report a variable frequency of dystonia in mitochondrial disease cohorts, ranging from 0.8% to 10%. Differences may be explained by heterogeneous recruitment criteria for genetic testing and variable representation of pediatric versus adult cases. Furthermore, the diagnosis of dystonia within early-onset severe multisystemic phenotypes (such as most mitochondriopathies) is challenging, likely resulting in unreported individuals [22]. By analyzing a large cohort referred for WES with the primary indication of dystonia, we also tackled the research question from the opposite perspective. Our estimation based on this cohort might, therefore, better reflect the "real-world" frequency of nuclear-encoded mitochondrial etiologies in monogenic dystonias. Nevertheless, our findings may still underestimate the overall burden of mitochondrial defects in the pathogenesis of dystonia, as we specifically addressed nuclear gene defects in our cohort. In the present study and in previous cohorts [8–11], dystonia mostly occurred within complex phenotypes, as expected considering the pleiotropic effect of mitochondrial dysfunction. Unbiased sequencing increasingly allows detection of mitochondrial defects in isolated dystonia cases [3]. In the dystonia cohort studied here, one index case with isolated dystonia harbored compound heterozygous disease-causing *COQ*8 variants. Indeed, isolated writer's cramp is a recurrent early feature in the multisystemic *COQ8*-related disease spectrum [23]. Recently, heterozygous variants in complex V-encoding genes, including *ATP5F1B*, have also been linked to isolated dystonia [24].

The greatest diagnostic overlap between the dystonia cohort and the mitochondrial disease cohort was in genes classically associated with NBIAs, a group of disorders sharing the hallmark of pathological iron deposition in the basal ganglia [25]. Interestingly, NBIA is usually caused by defects in proteins with no direct role in iron metabolism, but often with an established function in mitochondrial pathways. Patients with NBIA are therefore often included in mitochondrial disease cohorts [25]. The clinical presentation of NBIAs is very heterogeneous, spanning from early-onset severe neurodevelopmental phenotypes to juvenile-onset dystonia and/or parkinsonism. The characteristic basal ganglia hypointensities in iron-sensitive MRI sequences may be subtle or not present at all at the time of genetic diagnosis [25]. Thus, unbiased WES can decisively contribute to the identification of these conditions in a "genetics first" approach. This may explain the relative high frequency of these rare and ultra-rare diagnoses in our study and the different landscape of identified variants as compared to earlier case series studying genetic mitochondrial-disease contributions [8–11] In this light, it might be anticipated that newer technologies, e.g. genome-wide long-read sequencing with analysis of non-coding gene regions, would again reshape the genetic understanding of such disorders and improve the yield of genetic testing [26].

The awareness of an underlying mitochondrial defect in patients with dystonia has a number of implications in daily clinical practice, such as the avoidance of specific drugs and dedicated perioperative measures. Moreover, sparse literature suggests a relevant role of mitochondrial disease genes in children presenting with the life-threatening complication of status dystonicus [27, 28].

Dissecting the contribution of mitochondrial dysfunction to monogenic dystonias may guide investigations on the pathophysiology of more common forms of adult-onset isolated dystonia [14, 29]. On the one hand, subtle alterations in mitochondrial function may produce an endophenotype which determines a susceptibility in key networks [29]. On the other hand, declining mitochondrial quality due to impaired biogenesis and mitophagy, as seen with aging [30], may act as "second hit" in a susceptible genetic background [14]. Notably, variants in genes related to mitochondrial dynamics, homeostasis, and quality control (category 3 in our study) are a recurrent cause of monogenic movement disorders with adult onset [18, 31, 32]. Across different disorders, defects in mitochondrial pathways share common consequences at the cellular level consisting of oxidative stress, iron dysmetabolism and inflammation [30, 33, 34]. Targeting these pleiotropic downstream effects represents an attractive approach with potential application in different diseases. The pharmacological modulation of the transcription factor *NRF2* is an example of such strategy [35]. In response to various stimuli, *NRF2* binds specific "antioxidant response elements" in the promoter region of at least 250 target genes and activates a plethora of cellular processes aiming at preserving the cellular redox homeostasis and mitochondrial function. A *NRF2* activator has been recently approved for the treatment of the nuclear gene-related mitochondrial disease Friedreich's ataxia [35]. The modulation of *NRF2* has been repurposed also for the treatment of Parkinson´s disease and multiple sclerosis [33]. For dystonia, in-depth studies on the mechanistic events connecting mitochondrial dysfunction with this clinical phenotype are urgently needed to prioritize therapeutic targets for further investigation.

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Declarations

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