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## RESEARCH PAPER

## Establishing diagnostic criteria for Perry syndrome

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Received 12 July 2017

Revised 19 September 2017

Accepted 18 October 2017

Published Online First

31 October 2017



Check for updates

**To cite:** Mishima T, Fujioka S, Tomiyama H, et al. *J Neurol Neurosurg Psychiatry* 2018;**89**:482–487.

## ABSTRACT

**Objective** To establish international diagnostic criteria for Perry syndrome, a disorder characterised by clinical signs of parkinsonism, depression/apathy, weight loss, respiratory symptoms, mutations in the *DCTN1* gene and TAR DNA-binding protein 43 (TDP-43) pathology.

**Methods** Data from the published literature and newly identified patients were gathered and analysed during and after the International Symposium on Perry syndrome in Tokyo to identify diagnostic criteria for Perry syndrome.

**Results** Eighty-seven patients with Perry syndrome carrying *DCTN1* mutations from 20 families were included in this study, and common signs of the disorder were identified, including parkinsonism (95.2% of patients), depression/apathy (71.4%), respiratory symptoms (66.7%) and weight loss (49.2%).

**Conclusions** Based on our findings, we propose the following definitive diagnostic criteria for Perry syndrome: the presence of four cardinal signs of Perry syndrome, accompanied by a mutation in *DCTN1*; or a family history of the disease, parkinsonism and a mutation in *DCTN1*; or the presence of four cardinal signs and pathological findings that include nigral neuronal loss and TDP-43 pathology. As patients with Perry syndrome present with uniform clinical, genetic and pathological features, we further propose the disorder be termed 'Perry disease.'

## INTRODUCTION

Perry syndrome was first reported by Perry *et al* in 1975 after study of a single affected Canadian family.<sup>1</sup> Perry syndrome is characterised by rapidly progressive parkinsonism often accompanied by depression/apathy, weight loss and central hypoventilation.<sup>1–10</sup> It is a rare hereditary disorder with an autosomal-dominant mode of inheritance.<sup>1–10</sup> In 2009, mutations in the *DCTN1* gene (OMIM: 601143) were identified as the cause of Perry syndrome.<sup>11</sup> Prior to this discovery, *DCTN1* mutations were identified as the cause of a form of distal spinal and bulbar muscular atrophy, known as distal hereditary motor neuropathy 7B (HMN7B).<sup>12</sup> To date, all *DCTN1* mutations reported in patients with Perry syndrome have been confined to exon 2, suggesting this area is a mutational hot spot for the syndrome as well as an important site mediating function of the protein encoded by *DCTN1*.<sup>11</sup> Perry syndrome has been classified as a TAR DNA-binding protein 43 (TDP-43) proteinopathy based on pathological findings of TDP-43 inclusions, as seen in amyotrophic lateral sclerosis (ALS)

and frontotemporal lobar degeneration (FTLD) with TDP-43 inclusions (FTLD-TDP).<sup>13 14</sup>

Some patients with Perry syndrome show levodopa-responsive parkinsonism characterised by resting tremor, cogwheel rigidity, bradykinesia and postural instability reminiscent of Parkinson's disease (PD) as well as autonomic dysfunction. Cardiac [123I]-metaiodobenzylguanidine (MIBG) scintigraphy reveals reduced uptake of ligand, as is typically observed in sporadic PD. Therefore, Perry syndrome may be misdiagnosed as PD, especially during early-stage disease.<sup>15–18</sup> In addition, phenotypes similar to those observed in progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) have been reported in patients with Perry syndrome.<sup>16 19</sup> Due to its rarity, a comprehensive and integrated understanding of clinical, genetic and pathological features of Perry syndrome remains elusive. In addition, diverse clinical phenotypes and the lack of internationally accepted diagnostic criteria make diagnosis difficult. Therefore, development of consensus diagnostic criteria for Perry syndrome is essential to advance both clinical care and understanding of disease mechanisms.

The aim of this study was to identify epidemiological and clinical features associated with Perry syndrome based on a review of published case studies and to establish diagnostic criteria using this information. In support of this aim, we held an international meeting, the International Symposium on Perry Syndrome in Tokyo, devoted to developing consensus diagnostic criteria. We further reviewed and analysed reports of newly identified patients after the meeting.

## METHODS

The International Symposium on Perry syndrome in Tokyo was held from 22 to 23 February 2011. Before the meeting, the organising committee searched the scientific literature to identify all known families with Perry syndrome. During the meeting, consensus methodologies were used to establish criteria for diagnosis of Perry syndrome. The meeting included clinicians, geneticists and neuropathologists with expertise in neurodegenerative disorders. After the meeting, new families with a history of Perry syndrome were included in our analysis by searching on PubMed for publications through 30 November 2016. The search terms used were 'Perry syndrome', 'dynactin1' and 'DCTN1'. Inclusion criteria were (1) detailed clinical descriptions of parkinsonism in at least one family member and (2) genetically proven *DCTN1* mutations. Data

**Table 1** Clinical characteristics of patients with Perry syndrome with *DCTN1* mutations

Patients (n)	87
Age at onset (n)	61
Mean±SD (years)	49.1±6.6
Range (years)	35–70
Age at death (n)	54
Mean±SD (years)	55.0±7.4
Range (years)	39–81
Disease duration (n)	37
Mean±SD (years)	5.5±2.5
Range (years)	2–14
Four cardinal signs (n)	63
Parkinsonism (%)	95.2 (60/63)
Tremor (%)	51.7 (31/60)
Rigidity (%)	60.0 (36/60)
Bradykinesia (%)	38.3 (23/60)
Postural instability (%)	23.3 (14/60)
Response to dopaminergic treatments (%)	86.5 (32/37)
Depression/apathy (%)	71.4 (45/63)
Respiratory symptoms (%)	66.7 (42/63)
Weight loss (%)	49.2 (31/63)
Other features (n)	63
Frontal signs (%)	19.0 (12/63)
Oculomotor disorders (%)	15.9 (10/63)
Cognitive impairment (%)	15.9 (10/63)
Dysphasia (%)	14.3 (9/63)
Sleep disturbances (%)	20.6 (13/63)
Autonomic dysfunction (%)	9.5 (6/63)
Initial symptoms (n)	66
Depression/apathy (%)	56.1 (37/66)
Parkinsonism (%)	54.5 (36/66)
Weight loss (%)	9.1 (6/66)
Respiratory failure (%)	3.0 (2/66)
Cause of death (n)	33
Respiratory failure/pneumonia (%)	60.6 (20/33)
Sudden death (%)	15.2 (5/33)
Others (%)	24.2 (8/33)

evaluated included patient sex, age at onset, disease duration, initial clinical symptoms, age at death, cause of death, presence/absence of four cardinal clinical signs, other clinical features, laboratory results and treatment.

## RESULTS

### Systematic literature review

Of 65 articles identified in a systematic literature search, 24 met inclusion criteria. Clinical features were available for 87 patients (40 males, 37 females and 10 of unspecified sex) from 20 families. Nine-point mutations, all located in the *DCTN1* gene, were reported in this patient population: p.Y78C, p.Q74P, p.T72P, p.G71R, p.G71A, p.G71E, p.G67D, p.K56R and p.F52L.<sup>1 3–9 11 13–27</sup> Neuropathological features, including TDP-43 pathology, were reported in eight patients.<sup>13</sup>

### Demographic summary

Clinical characteristics of patients with Perry syndrome analysed are shown in tables 1 and 2. Age at symptom onset was 49.1±6.6 years (mean±SD; range, 35–70 years). Age at death was 55.0±7.4 years (range, 39–81 years), and mean disease

duration was 5.5±2.5 years (range, 2–14 years). A single family with a p.F52L mutation included one patient with late onset at 70 years of age and another patient with the longest disease duration (>21 years).<sup>17</sup> The most common initial feature was depression/apathy (56.1% of patients) and the most common cause of death was respiratory failure/pneumonia (60.6%). Typically, the disease began with depression/apathy, followed by weight loss and parkinsonism, followed by respiratory symptoms in late stages.<sup>1 4 23</sup> Sudden death was relatively common, occurring in 15.2% of the patients. Published papers consistently describe four cardinal signs: parkinsonism (95.2%), depression/apathy (71.4%), respiratory symptoms (66.7%) and weight loss (49.2%).

### Parkinsonism

Parkinsonism was present in almost all patients (95.2%) and included features of bradykinesia (38.3%), rigidity (60.0%), tremor (51.7%) and postural instability (23.3%). According to previous reports, asymmetry in parkinsonism is not prominent both in early and advanced stages in patients with Perry syndrome, but rather varied on a case-by-case basis. Postural tremor alone or in combination with resting tremor was reported in several patients.<sup>6 8 13 19</sup> Responsivity to levodopa was present in most patients (86.5%), but responses ranged from no response<sup>1 4</sup> to excellent response.<sup>8</sup> Patients generally demonstrated transient, mild to moderate improvement with high doses of levodopa therapy, not infrequently accompanied by rapid development of motor fluctuation and levodopa-induced dyskinesias.<sup>8 16 18 21 24 27</sup> Punding and impulse control disorders related to dopaminergic dysfunction such as pathological gambling, pathological shopping and compulsive eating were observed in two Japanese patients.<sup>28</sup> Inconclusive benefits were derived from antiparkinsonian agents, including apomorphine, pergolide, pramipexole, selegiline, trihexyphenidyl and amantadine.<sup>1 5 6 8 27</sup>

### Depression/apathy

Depression was more severe than that occurring in sporadic PD, and three patients committed suicide or entertained suicidal thoughts.<sup>6 8 16</sup> Apathy, characterised by loss of interest and withdrawal from society, and depression were present in a number of patients (71.4%).<sup>1 3 5 7 9 13 16 20 26</sup> Depression with concurrent apathy was present in five patients.<sup>1 3 16</sup> Depression symptoms were poorly responsive to antidepressant therapy.<sup>10</sup> Electroconvulsive therapy without benefit was also reported.<sup>1</sup>

### Respiratory symptoms

Respiratory symptoms, typically including dyspnoea and tachypnoea, are critical signs since they precede respiratory failure and death.<sup>1 3–11 13–17 20–26</sup> Respiratory symptoms were seen in many patients (66.7%), but central hypoventilation was present in a minority of patients (19.0%). This may have been due to limited use of polysomnography (PSG) used to reveal irregular breathing, central hypoventilation and central apnoea. Central hypoventilation was predominantly nocturnal and this may have contributed to sudden nocturnal death.<sup>10</sup> Apnoea was also an important symptom that occurred (14.3%).<sup>1 3 13 15 16 20 24 26</sup> Non-invasive intermittent positive pressure ventilation prolonged life expectancy, but invasive ventilation support was ultimately needed.<sup>13–15 21 24–26</sup> One patient was fitted with a bilateral diaphragmatic pacemaker, possibly alleviating respiratory insufficiency.<sup>25 26</sup>

## Movement disorders

**Table 2** Cardinal signs of patients with Perry syndrome with *DCTN1* mutations

Authors	Year	Country	Mutations	Four cardinal signs				Other features
				Parkinsonism	Depression/ apathy	Weight loss	Respiratory symptoms	
Perry <i>et al</i> <sup>1,4</sup>	1975	Canada	p.G71R	+	+	+	+	Cognitive impairment, autonomic dysfunction, sleep disturbances
Wider <i>et al</i> <sup>13</sup>	1990							
Felicio <i>et al</i> <sup>24</sup>	2009							
Roy <i>et al</i> <sup>3</sup>	2014							
Wider <i>et al</i> <sup>13</sup>	1988	USA	p.T72P	+	+	+	+	Frontal signs, cognitive impairment, sleep disturbances
Lechevalier <i>et al</i> <sup>5,9</sup>	2009							
	1992	France	p.G71E	+	+	+	+	–
	2005							
Bhatia <i>et al</i> <sup>6</sup>	1993	England	p.G71A	+	+	–	–	Oculomotor disorders, cognitive impairment
Elilbol <i>et al</i> <sup>7</sup>	2002	Turkey	p.G71R	+	+	+	+	Frontal signs, oculomotor disorders, cognitive impairment, sleep disturbances
Saka <i>et al</i> <sup>21</sup>	2010							
Tsuboi <i>et al</i> <sup>8,38</sup>	2002	Japan	p.G71A	+	+	+	+	Punding, impulse control disorders
	2008							
Mishima <i>et al</i> <sup>28</sup>	2015							
Wider <i>et al</i> <sup>14</sup>	2010	Hawaii	p.G71A	+	–	–	+	–
Ohshima <i>et al</i> <sup>15</sup>	2010	Japan	p.Q74P	+	+	+	+	Cognitive impairment, autonomic dysfunction, sleep disturbances
Wider <i>et al</i> <sup>14</sup>	2010							
Newsday <i>et al</i> <sup>22</sup>	2010	England	p.G71R	+	+	+	+	Frontal signs, oculomotor disorders, autonomic dysfunction, sleep disturbances
Aji <i>et al</i> <sup>23</sup>	2013	England	p.G67D	+	+	+	+	Frontal signs, oculomotor disorders, sleep disturbances
Araki <i>et al</i> <sup>17</sup>	2014	Japan	p.F52L	+	+	+	+	Frontal signs, cognitive impairment, autonomic dysfunction
Mishima <i>et al</i> <sup>18</sup>	2016							
Caroppo <i>et al</i> <sup>16</sup>	2014	France	p.G71E	+	+	+	+	Frontal signs, oculomotor disorders, cognitive impairment
Chung <i>et al</i> <sup>25</sup>	2014	Korea	p.G67D	+	+	+	+	–
Chung <i>et al</i> <sup>25</sup>	2014	Korea	p.G71R	+	+	+	+	Oculomotor disorders, sleep disturbances
Chung <i>et al</i> <sup>25</sup>	2014	Korea	p.Y78C	+	–	–	–	Frontal signs, oculomotor disorders
Tacik <i>et al</i> <sup>27</sup>	2014	New Zealand	p.Y78C	+	+	+	+	Cognitive impairment
Tacik <i>et al</i> <sup>27</sup>	2014	USA	p.G71R	+	+	+	+	–
Pretelt <i>et al</i> <sup>26</sup>	2014	Columbia	p.G71R	+	+	+	+	–
Tacik <i>et al</i> <sup>27</sup>	2014							
Gustavsson <i>et al</i> <sup>19</sup>	2016	Canada	p.K56R	+	–	–	–	Oculomotor disorders, cognitive impairment
Gustavsson <i>et al</i> <sup>19</sup>	2016	Taiwan	p.K56R	+	–	–	–	Cognitive impairment

### Weight loss

Weight loss occurred in approximately half of all patients and progressed at a rate of  $1.2 \pm 1.3$  kg/month (range, 0.5–5.0 kg/month). Paradoxically, weight gain occurred in four patients.<sup>3,4,21,27</sup> After treatment with amitriptyline, one patient's appetite improved, resulting in 6 kg gained over 7 months.<sup>4</sup> Another patient showed weight gain due to compulsive eating.<sup>27</sup> Two other patients regained weight after introduction of ventilatory support<sup>3,21</sup> and nasogastric feeding.<sup>3</sup>

### Other clinical features

Frontal signs including disinhibition, hyperorality, primitive reflexes and dysexecutive syndrome occurred in 19.0% of patients. Oculomotor disorders, such as vertical saccades and supranuclear gaze palsy, were also present in some patients (15.9%). Dysphasia was identified in 14.3% of patients. This sign may predict respiratory failure, as respiratory symptoms often followed dysphasia.<sup>1</sup> Cognitive impairment was present in 15.9% of patients, consistent with a finding of dementia in the original description of Perry syndrome.<sup>4</sup> Sleep disorders

including insomnia and sleep apnoea syndrome were reported in 20.6% of patients. Autonomic dysfunction presenting as erectile dysfunction, anhidrosis, pollakiuria (increased frequency of micturition), orthostatic hypotension and constipation was present in five patients.<sup>15,18,21</sup> Hallucination in patients with Perry syndrome has been reported. However, such patients are uncommon and detailed symptoms were reported in only two patients.<sup>1,3</sup>

### Biochemical studies

Routine laboratory tests of blood sample were normal. Cerebrospinal fluid (CSF) analysis was normal with the exception of one report of elevated protein levels.<sup>3</sup> Taurine deficiency was found in plasma, CSF and brain tissue reported by Perry *et al*,<sup>1</sup> a finding replicated in one patient included in the present analysis.<sup>8</sup> However, other studies reported normal taurine levels.<sup>3,4</sup> Reductions in CSF homovanillic acid, 5-hydroxyindoleacetic acid and  $\gamma$ -aminobutyric acid were reported in two patients.<sup>4,8</sup>

## Neuroimaging

Though recently published papers have described brain atrophy associated with frontal signs, oculomotor disorders and cognitive impairment, brain CT and MRI were typically normal in patients with Perry syndrome in this study.<sup>16–19 21 24</sup> The pattern of brain atrophy seen in patients with Perry syndrome was the frontotemporal and frontal cortical areas, and the midbrain.<sup>16–19 21 24</sup>

Functional imaging including fluorodeoxyglucose positron emission tomography (PET) and single photon emission CT (SPECT) images showed reduced glucose metabolism or blood perfusion in the frontal, temporal, frontotemporal, parietal and occipital lobes.<sup>9 16 24 27</sup> These findings are suggestive of diffuse cortical lobe involvement, which is clinically correlated with psychiatric symptoms, frontal signs and dementia. Striatal dopaminergic functions were evaluated using [18F]-6-fluoro-L-dopa PET, (+)-11C-dihydrotetrabenazine PET, [18F]-fluorinated N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-iodophenyl) nortropane PET and [123I]-FP-CIT-SPECT.<sup>4 18 23 24</sup> These imaging studies showed reduced striatal tracer uptake in all patients. Reduced striatal tracer uptake was also observed in an asymptomatic carrier of a p.T72P mutation in the *DCTN1* gene,<sup>23</sup> suggesting neurodegeneration may precede symptomatic disease onset. Serotonin transporter imaging using [11C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile PET exhibited reduced tracer uptake in cortical and subcortical regions.<sup>23</sup> A single patient had normal SPECT imaging (the tracer was not reported).<sup>7</sup> Two patients showed hyperechogenicity in the substantia nigra, comparable to that observed in PD by transcranial sonography.<sup>20</sup> In two Japanese families, decreased cardiac uptake with MIBG scintigraphy was reported.<sup>15 17 18</sup>

## Genetic testing

Nine mutations in the *DCTN1* are associated with parkinsonism, the most common being p.G71R. No clear genotype–phenotype correlation has been identified, with the exception of a p.F52L mutation associated with delayed disease onset and progression.<sup>17</sup> Anticipation has not been reported in Perry syndrome.

Several variants of *DCTN1* have been reported in familial FTD and ALS.<sup>28–33</sup> In the Chamorro people of Guam, ALS/parkinsonism-dementia complex (PDC) was traced to a p.T54I variant in *DCTN1*. One patients with PDC and one patient with ALS carried the p.T54I variant, in addition to a heterozygous *PINK1* mutation in this family.<sup>32</sup> Therefore, it remains unclear whether the p.T54I variant is really pathogenic. Moreover, *DCTN1* variants have been reported in primary lateral sclerosis,<sup>34</sup> neuropathy<sup>35</sup> and complex neurological disease with a slowly progressive, chronic axonal-distal motor neuropathy and extrapyramidal syndrome.<sup>36</sup> The case of extrapyramidal syndrome presented with ataxia, and also had *NEFH* and *KIF5A* variants.<sup>36</sup> Contrary to our expectations, these variants did not completely segregate in these families.

Vilariño-Güell *et al* reported that *DCTN1* mutations were not a common, if at all, cause of ALS, FTD or PD.<sup>37</sup> Therefore, the pathogenicity of *DCTN1* mutations in non-Perry syndrome phenotypes remains to be determined except the p.G59S mutation of HMN7B.

## Pathology

Neuropathological studies have shown substantial neuronal loss and gliosis in the substantia nigra of patients with Perry syndrome. However, neurofibrillary tangles and Lewy bodies were typically absent from patients with Perry syndrome analysed in the present study.<sup>1 3 4 6 8 11 13</sup> Some neuronal loss was found in the

locus coeruleus, dorsal raphe nucleus, lentiform nucleus, hypothalamus, periaqueductal grey matter and the brainstem reticular formation.<sup>13</sup> Selective loss of putative respiratory neurons in the medulla has also been found in one patient.<sup>38</sup>

Neuropathological features were available from eight patients with Perry syndrome, and all showed TDP-43 positive lesions. Lesions were notably distributed in the extrapyramidal system and brainstem.<sup>13</sup>

Dynactin subunit p50 neuronal cytoplasmic inclusions (NCIs) were reported,<sup>11</sup> as seen in the patient with HMN7B.<sup>39</sup> In one patient with HMN7B, neuronal loss was observed in the ventral horn of the spinal cord and the hypoglossal nucleus. p50-positive NCIs were found in the hypoglossal nucleus.<sup>39</sup>

## Differential diagnosis

In some patients, Perry syndrome was misdiagnosed as PD, especially during early-stage disease.<sup>15–18</sup> In one Japanese carrier of a *MAPT* mutation, four cardinal signs of Perry syndrome were present. The autopsy of the patient revealed the presence of tau-positive inclusions and the absence of TDP-43 positive inclusions.<sup>40</sup> PSP-like phenotypes such as vertical saccades and supranuclear gaze palsy were also present in patients with Perry syndrome.<sup>16 19</sup>

## PROPOSED INTERNATIONAL DIAGNOSTIC CRITERIA

Clinical diagnostic criteria for Perry syndrome consisting of clinical and laboratory features are shown in table 3. In addition, features supporting (and contravening) diagnosis of Perry syndrome are shown in table 4. Only 34.9% of patients in the current study displayed all four cardinal signs at the time of diagnosis though looking across the entire time course of the progression of Perry syndrome, the four cardinal signs are seen in a majority of patients. Therefore, diagnosis of Perry syndrome does not require the presence of all of the four cardinal signs. Parkinsonism must include two or more of the clinical features of rigidity, tremor (with postural tremor acceptable), bradykinesia or postural instability. Systemic diseases including cardiac and pulmonary diseases must be excluded. Since weight loss and depression/apathy are non-specific symptoms, these are not included as symptoms for the family history. If other mutations or neurodegenerative disease pathology are present, both cardinal laboratory features must be present (a mutation in the *DCTN1* gene, accompanied by nigral neuronal loss and TDP-43 pathology in the brainstem and basal ganglia) for a diagnosis of Perry syndrome.

In 65 published reports, 18 families met criteria for definitive diagnosis of Perry syndrome,<sup>1 3–9 11 13–18 20–27 38</sup> and 1 family member met criteria for probable diagnosis of Perry syndrome.<sup>40</sup> Two patients with p.K56R mutations<sup>19</sup> showed late disease onset, slow progression and no family history, and thus did not meet criteria for diagnosis of Perry syndrome.

## DISCUSSION

In this study, we propose diagnostic criteria for Perry syndrome based on analysis of 87 patients with Perry syndrome carrying *DCTN1* mutations from 20 families. Genetic mutations causing Perry syndrome are clustered in the CAP-Gly domain of *DCTN1*, suggesting the functional importance of this domain.<sup>11 37</sup> The *DCTN1* encodes the large subunit of the dynactin complex, p150<sup>glued</sup>, which is essential in both intracellular transport and non-motile processes. *DCTN1* mutations in the CAP-Gly domain have been reported to disrupt axonal transport and diminish microtubule binding, leading to intracytoplasmic inclusions.<sup>11</sup>



## Movement disorders

**Table 3** Diagnostic criteria for Perry syndrome

Clinical features		Laboratory features
Cardinal	Supportive	Cardinal
(A) Parkinsonism	(a) Rapid disease progression within 5 years of onset	(1) Genetic test: mutation in the <i>DCTN1</i> gene
(B) Apathy or depression	(b) Onset younger than 50 years	(2) Pathology: nigral neuronal loss and TDP-43 pathology in the brainstem and basal ganglia
(C) Respiratory symptoms		
(D) Unexpected weight loss		
(E) Positive family history of parkinsonism or respiratory symptoms		

Definite: presence of (A) and (E) plus cardinal laboratory features of positive genetic test (1) or presence of (A), (B), (C) and (D) plus cardinal laboratory features of positive genetic test (1) or presence of (A)–(D) plus cardinal laboratory features of TDP-43 pathology (2). If an evidence of other mutations or neurodegenerative disease pathology is present, there must also be both cardinal laboratory features.

Probable: presence of (A)–(E).

Possible: presence of (A) and (E) plus supportive clinical features of (a) or (b).

(A) Parkinsonism requires two or more among rigidity, tremor (with postural tremor acceptable), bradykinesia and postural instability. (C) Respiratory symptoms require exclusion of cardiac and pulmonary diseases.

TDP-43, TAR DNA-binding protein 43.

Given the causal role of *DCTN1* mutations in the disorder, screening for mutations in *DCTN1* is a reasonable strategy for initiating investigation when a diagnosis of Perry syndrome is suspected. Before the discovery of *DCTN1* mutations in patients with Perry syndrome, the incidence of new cases of Perry syndrome is estimated to have been 0.21 new cases per year. This increased sharply to 1.75 per year after identification of pathogenic mutations. Thus, while discovery of causal genetic mutations advanced diagnosis of patients with Perry syndrome, early diagnosis of Perry syndrome remains challenging as it may not be considered until respiratory symptoms appears. Since patients with early-stage disease do not show all the cardinal features, we recommend performing genetic testing in patients with ‘possible’ in the criteria as early diagnosis can inform patient care. For example, providing respiratory care may prevent sudden patient death,<sup>17</sup> and ventilatory support can increase patient independence.<sup>25 26</sup> In addition, high caloric intake and ventilation support may be helpful in maintaining body weight. Early diagnosis of Perry syndrome can thus significantly increase patients’ quality of life.

The present study represents the results of an international collaboration to review case studies with Perry syndrome. This builds on previously proposed diagnostic criteria,<sup>10</sup> which preceded discovery of the *DCTN1* mutations and TDP-43 pathology as hallmarks of the disease.<sup>11 13</sup> Given the rarity of the disorder, our analysis offers the best presently available platform for establishing international diagnostic criteria. As for other movement disorders, combinations of major clinical features are included in the diagnostic criteria.

In conducting genetic counselling and genetic testing, how to inform patients about penetrance, disease severity and prognosis are challenging problems. Careful attention must be paid to the presence of depression and suicidal thoughts.<sup>10</sup> Psychiatric follow-up may help to reduce risk of suicide. Despite high penetrance, genetic counselling and open communication with patients are critical. Care must be provided for motor impairment and respiratory symptoms in patients with Perry syndrome. In particular, PSG and arterial blood gas analysis should be conducted for evaluating central hypoventilation or central apnoea and for preventing sudden death frequently occurred in this disease. Clinicians should raise Perry syndrome as a differential diagnosis for patients with familial parkinsonism without known genetic background and consider genetic testing after genetic counselling.

Perry syndrome may be difficult to distinguish from PD, PSP and FTD. Familial early-onset parkinsonism (EOP) caused by mutations in genes such as *PRKN*, *PINK1*, *DJ-1* and *SCA2* needs to be distinguished from Perry syndrome. Clinical features of weight loss, respiratory symptoms and rapid progression in Perry syndrome generally allow it to be distinguished from EOP; however, during the early period of the illness, some clinical features of Perry syndrome may be reminiscent of EOP, raising the possibility of misdiagnosis. Cognitive impairment and frontal signs in Perry syndrome may be reminiscent of FTD. The age of onset is similar in both diseases and associated with levodopa-resistant parkinsonism. Perry syndrome needs to be distinguished from FTD caused by mutations in the *MAPT*, *C9orf72* and *GRN* genes. The presence of oculomotor disorders, a cardinal sign

**Table 4** Features supporting and contravening diagnosis of Perry syndrome

Clinical features		Laboratory features	
Supporting features	Non-supporting features	Supporting features	Non-supporting features
(1) Frontal signs	(1) Hypoxia and hypercapnia due to cardiac and pulmonary diseases	(1) MRI/CT: normal or frontotemporal atrophy	(1) Genetic test: mutation in the <i>MAPT</i> gene
(2) Oculomotor disorders	(2) Seizures	(2) Functional imaging: reduction of striatal tracer uptake	(2) Pathology: evidence of other neurodegenerative diseases
(3) Cognitive impairment	(3) Myoclonus	(3) Cardiac MIBG scintigraphy: decreased uptake	
(4) Autonomic dysfunction	(4) Cerebellar ataxia	(4) Functional imaging: frontotemporal hypometabolism	
(5) Sleep disturbances	(5) Sensory impairment		
	(6) Amyotrophy		

MIBG, [123I]-metaiodobenzylguanidine.

in PSP, does not exclude the diagnosis of Perry syndrome since oculomotor disorders are frequent in Perry syndrome.

Perry syndrome is characterised by unique clinical, genetic and neuropathological characteristics throughout the disease course though it is sometimes difficult to differentiate PD, PSP and FTD, especially in the early stage. Thus, we propose the nomenclature of 'Perry disease' more appropriately describes the condition rather than syndrome. We believe diagnostic criteria identified in the current study will be useful for genetic testing and counselling, patient care and in elucidating the epidemiology and pathogenesis of this devastating disease. We expect that future studies encompassing a larger number of patients as well as healthy controls will further strengthen the criteria identified here.

**Contributors** TM: execution of the project; analysis and interpretation of data; writing of the first draft. SF and HT: interpretation of data; review and critique. IY, OAR, MJF, DWD, ZKW and NH: review and critique. RK, NF and RN: review and critique; data collection. YT: conception and organisation of the project; execution of the project; analysis and interpretation of data; editing the manuscript.

**Funding** This study was supported by Grants-in-Aid from the Research Committee of CNS Degenerative Diseases and Perry syndrome, the Ministry of Health, Labour and Welfare of Japan (NH, YT and HT, 22140901), Grants-in-Aid from the Research Committee of CNS Degenerative Diseases, Grants-in-Aid for Scientific Research (HT, 21591098; NH, 090052131), for Scientific Research on Priority Areas (NH, 08071510), for Young Scientists (MF, 20790625), Grant-in-Aid for Scientific Research on Innovative Areas (NH, 23111003; MF, 23129506) by the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Grants from Health and Labor Sciences Research (NH, 22140901), and JST, CREST, Grants from JSPS KAKENHI (TM, 26860678), Grants from Establishment of diagnostic criteria for Perry disease, Research on rare and intractable diseases, Health and Labour Sciences Research Grants (YT, TM, SF and NH). The Mayo Clinic is a Morris K. Udall Center of Excellence in Parkinson's disease Research (DWD, OAR, ZKW, P50 NS072187).

**Competing interests** None declared.

**Ethics approval** Fukuoka University-Medical Ethics Review Board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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