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Title: Non-motor symptoms and quality of life in patients with PRRT2-related paroxysmal kinesigenic dyskinesia

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ABSTRACT

Background: Monoallelic pathogenic variants of *PRRT2* often result in paroxysmal kinesigenic dyskinesia (PKD). Little is known about health-related quality of life (HrQoL), non-motor manifestations, self-esteem, and stigma in patients with PKD.

Objectives: We investigated non-motor symptoms and how they related to HrQoL in a genetically homogeneous group of *PRRT2*-PKD patients. We paid special attention to perceived stigmatisation and self-esteem.

Methods: We prospectively enrolled 21 consecutive PKD patients with a pathogenic variant of *PRRT2*, and 21 healthy controls matched for age and sex. They were evaluated with dedicated standardized tests for non-motor symptoms, HrQoL, anxiety, depression, stigma, self-esteem, sleep, fatigue, pain, and psychological well-being.

Results: Patients reported an alteration of the physical aspects of HrQoL, regardless of the presence of residual paroxysmal episodes. Non-motor manifestations were frequent, and were an important determinant of the alteration of HrQoL. In addition, patients perceived a higher level of stigmatization which positively correlated with a delay in diagnosis (ρ=0.615, $p=0.003$) and the fear of being judged (ρ=0.452, $p=0.04$), but not with the presence of paroxysmal episodes (ρ=0.203, $p=0.379$).

Conclusions: Our findings have important implications for care givers concerning patient management and medical education about paroxysmal dyskinesia. *PRRT2*-PKD patients should be screened for non-motor disorders in routine care. A long history of misdiagnosis may play a role in the high level of perceived stigmatization. Improving knowledge about diagnostic clues suggestive of PKD is mandatory.

48 Monoallelic pathogenic variants of the Proline-rich transmembrane protein 2 (*PRRT2)* gene
49 cause synaptopathy and can result in a large variety of paroxysmal neurological disorders (1–
50 3). The most frequent disorder is Paroxysmal Kinesigenic Dyskinesia (PKD) which can be the
51 sole manifestation of the disease in a large number of patients. PKD is characterized by attacks
52 of dystonia and/or chorea, typically triggered by the sudden initiation of movements or brisk
53 modification of an ongoing movement, that lasts less than a minute (4). They usually start in
54 childhood or adolescence and peak during puberty, often with a high frequency of abnormal
55 movement episodes – up to 100 per day – and complete remission between episodes. *PRRT2*-
56 PKD can be treated with low doses of anti-epileptic drugs that modulate the activity of neuronal
57 sodium channels and usually suppress the attacks (5).

58 *PRRT2* is the main culprit gene for PKD (6,7) and *PRRT2*-PKD likely reflects a primary
59 dysfunction of the cerebellum (8,9). The cerebellum has been involved in the pathogenesis of
60 several dystonic syndromes (10). It also plays a role in non-motor processes such as cognition,
61 sleep, and emotional regulation (11,12). Growing evidence indicates that non-motor
62 manifestations are part of the clinical spectrum in various dystonic disorders, including
63 idiopathic adult-onset focal dystonia and genetic forms of dystonia (13–18). Non-motor
64 manifestations can be an important determinant of health-related quality of life (HrQoL),
65 beyond the motor symptoms (15,16,19–23). Perceived stigmatization and diminished self-
66 esteem can also influence quality of life in dystonic disorders (24–26). However, HrQoL, non-
67 motor manifestations, self-esteem, and stigma have been poorly studied to date in patients with
68 paroxysmal dystonic disorders, with only a few pilot findings (27).

69 Here, we investigated non-motor symptoms and how they relate to quality of life in a genetically
70 homogeneous group of consecutive *PRRT2*-PKD patients and their age- and sex-matched
71 controls. We paid special attention to perceived stigmatization and self-esteem.

72 **METHODS**

73 ***Study Population***

74 In this exploratory study, we enrolled 21 consecutive PKD patients with a pathogenic variant
75 of *PRRT2* manifesting exclusively as PKD, and healthy controls (HC) matched for age and sex.
76 HCs were recruited from the database of the Pitié-Salpêtrière Clinical Investigation Center
77 (Paris, France). Prior to data collection, the full protocol was approved by the Ethics Committee
78 "Comité de Protection des Personnes Sud-Méditerranée" (reference: 17.060), and was
79 registered on clinicaltrial.gov (NCT03481491). In accordance with the Declaration of Helsinki,
80 all participants provided written informed consent.

81 ***Study Instruments***

82 We collected the patients' history, demographic, genetic, and clinical information including
83 initial misdiagnoses. Disease duration was calculated as the time in years between symptom
84 onset and the day of the inclusion visit. Age at disease onset was taken as the age at which
85 symptoms first occurred. Delay to diagnosis was calculated as the time in years between the
86 patient's first medical visit for their symptoms and their PKD diagnosis. The residual presence
87 of paroxysmal events was defined as having at least one episode during the month prior to
88 inclusion in the study. Patients were considered treated or non-treated depending on whether
89 they were receiving a treatment for PKD. Non-motor aspects were investigated using
90 standardized questionnaires: i) the Dystonia Non-motor Symptoms (DNMS) questionnaire,
91 which can detect non-motor problems comprising sleep disorders, autonomic dysfunction,
92 fatigue, psychiatric manifestations, stigma, and sensory symptoms (20); ii) the Stigma Scale for
93 Chronic Illness which measures perceived stigmatization (SSCI-8)(28); iii) the Hospital
94 Anxiety and Depression Scale (HADS) to investigate anxiety and depression with two specific
95 sub-scales (29); iv) the Brief Fear of Negative Evaluation Scale (BFNE)(30), the Rosenberg

96 Self Esteem Scale (RSES)(31), and the Warwick-Edinburgh Mental Wellbeing Scales
97 (WEMWBS)(32) which respectively quantify perceived stigmatization, fear of being judged by
98 others, self-esteem, and mental well-being; v) the Medical Outcomes Study 36-Item Short-
99 Form Health Survey (SF-36)(33) to evaluate HrQoL; vi) the Visual Analogue Scale of Pain
100 (34), the Fatigue Severity Scale (FSS-9)(35) and the Pittsburgh Sleep Quality Index (PSQI)(36)
101 to measure pain, fatigue and sleep disturbances, respectively.

102 Component analyses showed that SF-36 measures two distinct concepts, namely a physical
103 dimension, represented by the Physical Component Summary (PCS), and a mental dimension,
104 represented by the Mental Component Summary (MCS). PCS is composed of four primary
105 domains (physical functioning, physical role limitations, bodily pain, and general health). MCS
106 is also composed of four primary domains (social functioning, emotional role limitations,
107 mental health, and vitality). The steps for calculating the PCS and MCS have been previously
108 described (37). The SF-36 scales are standardized using a linear z-score transformation. Z-
109 scores are calculated by subtracting subscale means for a general US population sample from
110 each individual's subscale scores and dividing the difference by the standard deviation of the
111 US sample. Each of the eight z-scores is then multiplied by the corresponding factor scoring
112 coefficient for the scale. There are two different sets of factor scoring coefficients, one for the
113 PCS and another for the MCS. The products of the z-scores and factor scoring coefficients for
114 the PCS are then summed together, and a similar calculation is performed for the MCS. Each
115 resulting sum is multiplied by 10 and added to 50 to linearly transform the PCS or MCS to the
116 T-score metric, which has a mean of 50 and a standard deviation of 10 for the US general
117 population.

118 ***Statistical analysis***

119 Statistical analysis was conducted with the R software (4.0.2) system. Normality in the variable
120 distributions was assessed by the Shapiro-Wilk test. Furthermore, the Levene test was
121 performed to probe homogeneity of variances across groups.

122 We performed group analyses comparing patients to controls. Variables that failed the Shapiro-
123 Wilk or the Levene test were analyzed with nonparametric statistics. Categorical variables were
124 compared using Pearson's $\chi 2$ test or Fisher's exact test. Quantitative variables were analyzed
125 using the Student's t-test or the Mann-Whitney's test.

126 To further explore HrQoL alteration in the patient group, we first used Spearman correlation
127 (continuous variables) and rank-biserial correlation (binary variables: sex and treatment)
128 coefficients to examine the associations between variables which were different between the
129 patients and controls, and between those variables and important characteristics (age, sex, age
130 at onset, disease duration, delay to diagnosis, treatment, or the persistence of PKD attacks) that
131 could influence HrQoL.

132 Second, we performed a multivariable linear regression model. Five variables were selected to
133 be included in the model: three variables were selected based on the statistical significance on
134 between-group comparisons and three variables were selected because we thought they might
135 be important to explain HrQoL (age at onset, treatment - being treated or not - and persistence
136 of paroxysmal events). We only considered the PCS score as the dependent variable (the MCS
137 was not different between the patient and control groups), and the above-mentioned variables
138 as independent variables. The multivariable regression model was based on the stepwise
139 method. Assumptions of using the linear regression method included normal distribution of
140 PCS and lack of outlier data.

141 The data are expressed as mean+/-SD, and $p < 0.05$ was assumed to be statistically significant.

142 **RESULTS**

143 We analyzed data from 21 (mean age 33.7y) consecutive PKD patients with a pathogenic
144 variant of *PRRT2*, and 21 matched healthy controls (HC). The patients' characteristics and
145 group comparisons are summarized in **Table 1**.

146 ***Quality of life evaluation***

147 Compared to the HC, the patients had an altered HrQoL in four domains of the SF-36, namely
148 physical functioning, bodily pain, energy/fatigue, and general health perceptions (**Figure**
149 **1**). Accordingly, the PCS score was lower showing a poorer physical component of HrQoL for
150 the patients ($p<0.001$). There was no difference between the groups for MCS.

151 ***Global non-motor evaluation***

152 There was a group difference for non-motor symptoms (**Table 2**): 100% of the patients and
153 29% of the HCs ($p<0.001$) reported non-motor symptoms causing impairment of activities of
154 daily living on the DNMS questionnaire. 52% of patients and 9.5% of HCs reported at least
155 four non-motor symptoms. In the patient group, the most prevalent non-motor symptoms were
156 loss of self-confidence due to stigma (100%), sleep disorders (71%) (particularly difficulty to
157 fall asleep), anxiety (48%), fatigue (43%), and depression (29%). The non-motor symptoms
158 burden (i.e., total DNMS score) was higher in the patients (3.76 ± 3.33) than in the HCs (0.57
159 ± 1.52; $p<0.001$).

160 ***Psychological evaluation***

161 HADS scores evaluating anxiety and depression related symptoms were similar between the
162 groups ($p=0.91$), and no subject exceeded cut-off scores. The patients had lower self-esteem
163 (RSES score) ($p=0.01$) and their fear of being judged by others (BNFE score) tended to be

164 higher *(p=0.067)*. Global well-being (WEMWBS) was similar in the patients and HCs
165 (*p=0.152*). The patients had a higher perceived stigmatization with a mean SSCI-8 score of
166 18.8 (*p<0.001*).

167 ***Sleep, fatigue, and pain***

168 The patients reported a poorer quality of sleep (PSQI-total score) although not significant
169 (*p=0.116*). They needed more time to fall asleep (30 minutes for patients and 14 minutes for
170 HCs, *p=0.032*). The patients also reported more fatigue (FSS) although the difference was not
171 significant (*p=0.133*). They did not report more pain (VAS) (*p=1*) compared to the HCs.

172 ***Misdiagnosis***

173 62 % of the patients were initially misdiagnosed. Wrong diagnoses included functional disorder
174 (6 patients), epilepsy (4 patients), panic attack (2 patients), Tourette syndrome (2 patients), and
175 dystonia (1 patient). Two of them sequentially received two wrong diagnoses (epilepsy and
176 functional disorder for one; Tourette syndrome and functional disorder for the other).

177 ***Correlation analysis***

178 When investigating the possible determinants of PCS alteration in the patients, we found that
179 PCS was not related to the presence of residual PKD attacks but negatively correlated with the
180 stigma score SSCI8 (ρ=-0.480, *p=0.028*) and time needed to fall asleep (ρ=-0.544, *p=0.011*).
181 Higher stigma scores correlated with a higher NMS burden (ρ=0.554, *p=0.009*), a greater delay
182 to PKD diagnosis (ρ=0.615, *p=0.003*), and lower physical components of HrQoL (ρ=-0.480,
183 *p=0.028*).
184 HrQoL was not correlated with the demographical and clinical variables of age, sex, age at
185 onset, disease duration, treatment, or persistence of PKD attacks. Detailed information can be
186 found in **Figure 2** and **Supplementary Material**.

187

188 ***Regression analysis***

189 The independence of PCS predictors in the patients was assessed by stepwise linear regression,
190 with PCS as a response variable and age at onset, DNMS, SSCI, RSES scores and treatment
191 (being treated or not for PKD), and persistence of paroxysmal events as predictive variables
192 (Table 2). From this model (Adjusted R^2= 0.245), only the total DNMS was found to predict
193 PCS in the patients (β = -2.06, 95% CI -3.628 - -0.487, *p = 0.013*). Finally, the global non-
194 motor burden was inversely related to the PCS.

195

196 **DISCUSSION**

197 Patients with PKD caused by pathogenic variants of *PRRT2* reported an alteration of the
198 physical aspects of HrQoL, regardless of the presence of residual paroxysmal episodes or use
199 of treatments. Non-motor manifestations observed in these patients were an important
200 determinant of the alteration of HrQoL. In addition, patients perceived a high level of
201 stigmatization positively correlated with delay in diagnosis but not with the presence of
202 paroxysmal episodes. As observed in other dystonic syndromes, non-motor symptoms may be
203 an entire part of the phenotype of patients with paroxysmal dystonic manifestations and should
204 be investigated and recognized in clinical practice. Our findings have important implications
205 for the management of these patients and for medical education about PKD.

206 The main strengths of our work are the clinical (typical PKD) and genetic (*PRRT2* pathogenic
207 variant) homogeneity of the patient group, the presence of a matched comparison group, and
208 the prospective and standardized data collection. Our study was innovative in that we focused
209 on non-motor aspects which represents an emerging concern in the field of dystonic disorders.
210 A few limitations deserve to be mentioned. First, some patients were on chronic treatment,

211 mainly comprising low dose carbamazepine. Although we observed no relevant difference
212 between medicated and non-medicated patients, chronic treatments might have influenced our
213 results. In addition, carbamazepine is commonly used in *PRRT2*-related PKD and thus our
214 results remain overall relevant for the *PRRT2* population. Of note, patients with a milder form
215 of the disease are less likely to receive medication and this should be taken into account when
216 interpreting the lack of difference between medicated and non-medicated patients. Secondly,
217 we binarized the presence or absence of residual PKD attacks in the past month instead of
218 considering their exact reported frequency. The main reason for this was that frequency values
219 are unstable and fluctuant in this disorder, being highly dependent on exposure to triggering
220 factors in activities of daily living. Thirdly, our study only involved a small sample of patients
221 and is thus exploratory, warranting confirmation from larger studies.

222

223 HrQoL is altered in patients with dystonia, including various idiopathic adult-onset focal
224 dystonia (38) and genetic dystonia (14,39,40). A seminal study found an alteration of HrQoL
225 in a large but genetically heterogeneous sample of patients with PKD (27). In this study, the
226 patients' data were compared with normative data in the absence of a control group. In keeping
227 with the genetic heterogeneity of the population, the majority of these heterogeneous PKD
228 patients had an incomplete response to treatment, which is unusual in *PRRT2*-PKD.

229 We also found an alteration of HrQoL in our group of *PRRT2-PKD* patients, as compared with
230 controls. Interestingly, this altered HrQoL was not linked to the presence of residual paroxysmal
231 events or to treatment, suggesting a contribution of non-motor manifestations. Indeed, the
232 global non-motor burden was the only determinant of altered physical components of HrQoL
233 retained by the stepwise regression analysis in our patients.

234 When screened with the DNMS, our *PRRT2*-PKD patients more frequently reported non-motor
235 symptoms as compared to the controls, especially loss of self-confidence due to stigma and
236 sleep problems. Investigation with semi-quantitative dedicated scales similarly identified loss
237 of self-esteem and stigma in the patients, as well as a non-significant trend toward more fatigue
238 and poorer sleep quality compared to the controls. The single questions related to depression
239 and anxiety of the DNMS yielded different responses for patients and controls, which was not
240 confirmed by the between-groups comparison on the HADS subscores. This discrepancy is not
241 surprising as the accuracy of the specific anxiety and depression DNMS questions has not been
242 validated against the anxiety/depression severity scales. Overall, non-motor symptoms have
243 been identified as part of the phenotype in various dystonic disorders and they are an important
244 determinant of quality of life (13,19). In particular, the prevalence of psychiatric disorders, pain,
245 sleep problems and fatigue is often greater in patients with idiopathic adult-onset focal dystonia
246 (20,21,38,41–43). For example, a controlled study using the same evaluation tool (DNMS) in
247 patients with idiopathic adult-onset cervical dystonia revealed that pain, insomnia, and stigma
248 were highly prevalent and that non-motor symptoms were major determinants of their
249 HrQoL(21). A higher prevalence of psychiatric disorders, sleep problems, and fatigue was also
250 found in a mixed group of patients with dystonia – mostly genetic dystonia (dopa-responsive
251 dystonia, myoclonus-dystonia, and idiopathic adult-onset cervical dystonia) – as compared with
252 controls (22). Likewise, non-motor symptoms were also linked to HrQoL in this study.

253 Stigmatization was perceived as important in our *PRRT2*-PKD patients. For example, perceived
254 stigmatization evaluated with the same measurement tool was higher in our patients than in
255 patients with multiple sclerosis or epilepsy, which can be considered to be more visible and
256 debilitating disorders (28,44,45). The young age of our patients may have influenced this result
257 since young patients with neurological disorders seem to be more prone to feelings of
258 stigmatization, as demonstrated in the context of cervical dystonia and other neurological

disorders (21,28). As the perceived stigmatization was tightly linked to delay to diagnosis, we suggest that a long history of misdiagnosis – often involving a wrong diagnosis of functional disorders (29% of patients) – may play a role in the high level of perceived stigmatization (44–47). This emphasizes the need to increase knowledge about the diagnostic clues suggestive of PKD.

Interestingly, the global non-motor burden did not correlate with the presence of residual paroxysmal episodes. It is therefore possible that the additional non-motor phenotype is not a consequence of motor problems but rather reflects *PRRT2*-related brain dysfunction. If so, then non-motor manifestations could be related to the well-known *PRRT2*-related cerebellar dysfunction (8,48,49). For example, sleep disorders, especially insomnia, have been linked to structural and functional abnormalities of the cerebellum (49,50,51). Consistently, the cerebellum has sleep-related activity patterns, and its output neurons, which express clock genes, are connected with the wake-sleep brain network (49, 51). Alternatively, non-motor manifestations could be the consequence of other brain dysfunctions considering the wide expression of *PRRT2* in the brain (52).

Paroxysmal disorders, such as PKD, are often seen as more “benign” compared with continuous movement disorder. Our findings indicate that early diagnosis is also critical in PKD, and suggest that more attention should be paid to the hidden non-motor part of the disease. For this reason, some patients, at least, would benefit from long-term follow-up by a neurologist even after optimal control of the paroxysmal episodes.

280 **AUTHOR ROLES**

281 (1) Research project: A. Conception, B. Organization, C. Execution;

282 (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

283 (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

284 A.E.: 1A, 1B, 1C, 2A, 2B, 2C, 3A

285 M.D.: 2A, 2B, 2C, 3A

286 P.J.: 1B, 1C

287 A.H.: 1B, 1C

288 A.M., P.D., J.P., A.R., E.M., C.T., Q.W., M.V: 1C, 3B

289 C.G., Y.W, 1A, 3B

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322 This study was approved by the Regional Ethics Committee "Comité de Protection des
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472 **FIGURE LEGENDS**
473
474 ***Figure 1:*** Radar chart with the eight domains of the Quality of life (Short Form-36) for PRRT2
475 patients and Healthy Controls (red line: *PRRT2* patients, blue line: Healthy Controls). Each
476 spoke on the radar chart represents an SF-36 domain on a scale of 0-100, with higher scores
477 representing better health-related quality of life. The four green domains (Physical functioning,
478 Role physical, Bodily pain and General health) contribute to the scoring of PCS measure. The
479 four orange domains (Vitality, Social functioning, Role emotional and Mental Health)
480 contribute to the scoring of MCS measure. *** $p<0.001$, ** $p<0.01$, * <0.05, using *Student's t-*
481 *test or the Mann-Whitney's test* as appropriate.
482 ***Figure 2:*** Correlation matrix across Age, Sex, Age at onset, Disease duration, Diagnostic delay,
483 PCS, DNMS, SSCI8, RSES, Paroxysmal events and Treatment. Color of each box indicates the
484 significance of the correlation (Spearman's ρ or rank-biserial correlation coefficient), while size
485 of the circles indicates its magnitude.

486
487
488 **TABLES**

Table 1: Characteristics of subjects and results of the non-motor evaluation

Characteristics	***PRRT2* Patients** (n = 21)	**Healthy Controls** (n = 21)	**P value**
Age; Age range (years)	33.66 (± 12.37); 17 – 51	31.7 (± 12.1); 21 – 56	0.55‡
Sex (female/male)	7/14	7/14	1†
Age at onset (years)	9.3 (± 3.0)	–	
Disease duration (years)	22.4 (± 12.5)	–	
Diagnostic delay (years)	9.33 (± 10.78)	–	
Treated patients n=11) CBZ/LTG/LEV)	9/1/1	–	
Residual Paroxysmal events (yes/no)	6/15		
PCS	52.53 (± 6.34)	58.52 (± 4.02)	**0.001**¶
MCS	41.57 (± 10.80)	42.59 (± 9.36)	0.743¶
DNMS	3.76 (± 1.64)	0.57 (± 1.21)	**0.000**‡
PSQI	6.19 (± 3.71)	4.43 (± 3.38)	0.116¶
HA HD	2.05 (± 2.06) 4.10 (± 2.59)	2.38 (± 2.80) 4.19 (± 3.87)	0.612 0.969‡
SSCI-8	18.38 (± 4.86)	10.00 (± 2.06)	**0.000**‡
RSES	21.05 (± 5.71)	25.52 (± 3.59)	**0.003**‡
BFNE	39.04 (± 9.74)	34.76 (± 8.32)	0.067¶
WEMWBS	50.57 (± 9.58)	53.71 (± 9.97)	0.152¶
VAS	5%	0%	1ϒ
FSS	25.19 (± 17.32)	17.71 (± 10.32)	0.133‡

Legend: **CBZ** = carbamazepine; **LTG** = lamotrigine; **LEV** = levetiracetam; **PCS** = Physical Component Summary; **MCS** = Mental Component Summary; **DNMS** = Dystonia Non-Motor Symptoms questionnaire; **PSQI** = Pittsburgh Sleep Quality Index; **HA** = Hospital Anxiety scale; **HD** = Hospital Depression scale; **SSCI-8** = Stigma Scale for Chronic Illnesses 8-item; **RSES** = Rosenberg Self-Esteem Scale; **BFNE** = Brief Fear of Negative Evaluation Scale; **WEMWBS** = Warwick-Edinburgh Mental Wellbeing Scale; **VAS** = Visual Analogue Scale for pain; **FSS** = Fatigue Severity Scale.

Quantitative data are expressed as mean (±SD).

¶ Student's t-test; † Pearson's χ^2 test; ‡ Mann-Whitney test; ϒ Fisher exact test; Significant results indicated in bold: $p<0.05$.

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Table 2: Non-motor symptoms

Symptoms	**Patients♦**	**Controls♦**	**p-value**
Sleep disorders	61.90%	9.52%	**< 0.001**†
Difficulties to fall asleep	61.90%	9.52%	**< 0.001**†
Dizziness	0%	0%	–
Fatigue	42.86%	14.29%	**0.040***†
Anxiety	47.62%	19.05%	0.050*†
Depression	28.57%	0%	**0.008***§
Loss of self-confidence due to stigma	100%	0%	**< 0.001**†
Flat moods	28.57%	4.76%	**0.038***§
Chewing/swallowing	0%	0%	–
Unpleasant sensations	0%	0%	–
Speech	0%	0%	–
Vision	0%	0%	–
Pain	4.76%	0%	0.311§
Balance/walking	0%	0%	–

Legend: ♦ Percentage of positive response of the subjects to the 14 items of the dystonia non motor symptoms questionnaire † Pearson's χ^2 test; § Fisher exact. Significant results indicated in bold: $p<0.05$.

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494 **SUPPLEMENTARY LEGENDS**
495
496 ***Supplementary Table 1:*** Data of the eight domains of the Short Form (36) health survey for
497 PRRT2 patients and Healthy Controls (HC). PCS= Physical Component Summary,
498 MCS=Mental Component Summary, PF=Physical functioning, RP=Role physical, RE=Role
499 emotional, VT=Vitality, MH=Mental Health, SF=Social functioning, BP=Bodily pain and
500 GH=General health, ¶ Student's t-test; ‡ Mann-Whitney test.
501
502 ***Supplementary Table 2:*** Correlations across Age, Sex, Age at onset, Disease
503 duration, Diagnostic delay, Physical Component Summary (PCS) of the Short Form (36)
504 health survey, Dystonia non-motor symptoms scale (DNMS), Stigma Scale for Chronic
505 Illness (SSCI8), Rosenberg Self Esteem Scale (RSES), Paroxysmal Events and Treatment.
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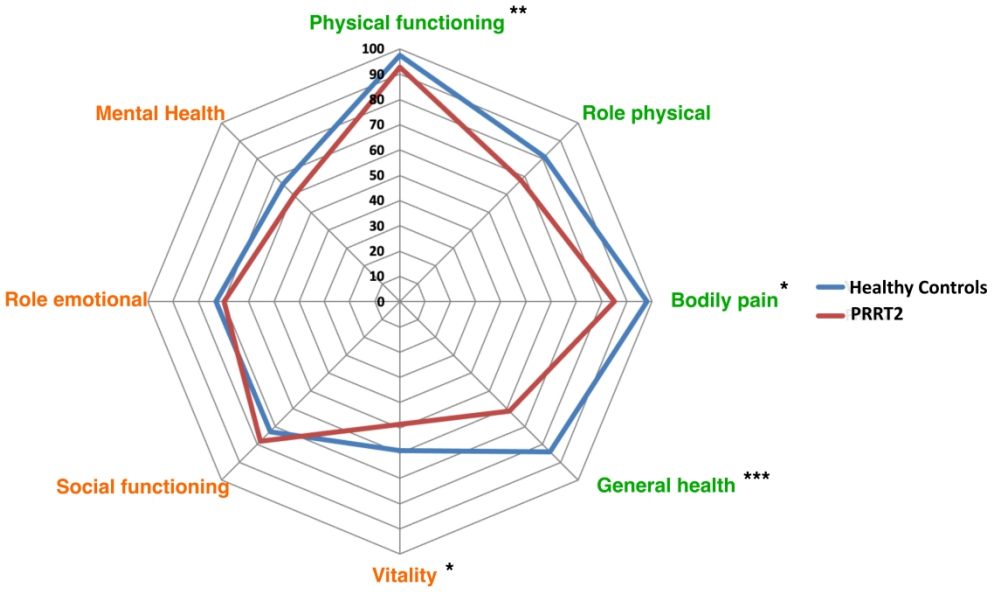

Figure 1. Radar chart with the eight domains of the Quality of life (Short Form-36) for PRRT2 patients and Healthy Controls (red line: PRRT2 patients, blue line: Healthy Controls). Each spoke on the radar chart represents an SF-36 domain on a scale of 0-100, with higher scores representing better health-related quality of life. The four green domains (Physical functioning, Role physical, Bodily pain and General health) contribute to the scoring of PCS measure. The four orange domains (Vitality, Social functioning, Role emotional and Mental Health) contribute to the scoring of MCS measure. *** $p<0.001$, ** $p<0.01$, * <0.05, using Student's t-test or the Mann-Whitney's test as appropriate.

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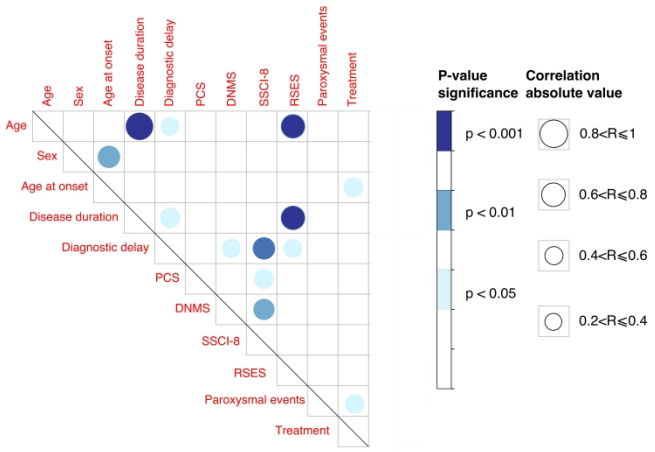

Figure 2. Correlation matrix across Age, Sex, Age at onset, Disease duration, Diagnostic delay, PCS, DNMS, SSCI8, RSES, Paroxysmal events and Treatment. Color of each box indicates the significance of the correlation (Spearman's ρ), while size of the circles indicates its magnitude.

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1 **Supplementary Results**

2 **Quality of life**

3 Supplementary Table 1: Quality of life (Short Form-36).

4 PCS= Physical Component Summary, MCS=Mental Component Summary, PF=Physical
5 functioning, RP=Role physical, RE=Role emotional, VT=Vitality, MH=Mental Health,
6 SF=Social functioning, BP=Bodily pain and GH=General health, ¶ Student's t-test; ‡ Mann-
7 Whitney test;

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	Healthy controls (mean±sd)	**PRRT2 patients (mean**±sd)	**Mean difference (95% Confidence Interval)**	p-value
PF	97.62±6.82	92.86±7.68	4.76 (0.23-9.29)	0.006‡
RP	80.95±30.52	67.86±35.48	13.1 (-7.56-33.75)	0.189‡
RE	73±41.69	69.86±43.35	3.14 (-23.38-29.67)	0.768‡
VT	59.05±12.81	48.57±16.89	10.48 (1.11-19.85)	0.029¶
MH	65.71±14.56	59.24±13.42	6.48 (-2.26-15.21)	0.142¶
SF	72.76±21.83	78.14±21.91	-5.38 (-19.02-8.26)	0.417‡
BP	97.9±4.45	85±21.49	12.9 (2.96-22.85)	0.023‡

GH	84.29±10.28	61.43±22.92	22.86 (11.62-34.09)	< 0.001¶
PCS	58.52±4.02	52.53±6.34	6 (2.67-9.32)	0.001¶
MCS	42.59±9.36	41.57±10.8	1.03 (-5.28-7.33)	0.96‡

10

11 Supplementary Table 2: Correlations across Age, Sex, Age at onset, Disease

12 duration, Diagnostic delay, PCS, DNMS, SSCI8, RSES, Paroxysmal Events and Treatment.

	Age	Sex	Age at onset	Disease duration	Diagnostic delay	PCS	DNMS	SSCI-8	RSES	Paroxysmal events	Treatment
Age	1	-0.008	0.122	0.944**	0.435*	0.02	0.405	0.282	0.734**	-0.044	-0.075
Sex		1	0.623**	-0.167	-0.176	0.1	0.246	-0.295	-0.336	-0.224	-0.143
Age at onset			1	-0.155	-0.169	-0.182	0.217	-0.199	-0.133	0.105	-0.488*
Disease duration				1	0.504*	0.048	0.355	0.378	0.739**	-0.061	0.05
Diagnostic delay					1	-0.016	0.442*	0.615**	0.439*	-0.009	0.328
PCS						1	-0.405	-0.480*	0.068	0.035	0.15
DNMS							1	0.554**	-0.044	-0.292	0.323
SSCI-8								1	0.174	0.203	0.211
RSES									1	0.053	-0.076
Paroxysmal events										1	-0.447*
Treatment											1

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