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Self-Rated Health Status in Spinocerebellar Ataxia—Results from a European Multicenter Study

Tanja Schmitz-Hübsch, MD,[1] Mathieu Coudert, MSc,[2,3] Paola Giunti, MD,[4] Christoph Globas, MD,[5] Laszlo Baliko, MD,[6] Roberto Fancellu, MD,[7] Caterina Mariotti, MD,[7] Alessandro Filla, MD,[8] Maryla Rakowicz, MD, PhD,[9] Perrine Charles, MD, PhD,[10,11] Pascale Ribai, MD,[10,11] Sandra Szymanski, MD,[12] Jon Infante, MD,[13] Bart P.C. van de Warrenburg, MD,[14] Alexandra Dürr, MD, PhD,[10,11] Dagmar Timmann, MD,[15] Sylvia Boesch, MD,[16] Rafal Rola, MD, PhD,[17] Chantal Depondt, MD, PhD,[18] Ludger Schöls, MD,[5] Elszbieta Zdzienicka, MD,[19] Jun-Suk Kang, MD,[20] Susanne Ratzka, MD,[21] Berry Kremer, MD,[14] Jörg B. Schulz, MD,[22] Thomas Klopstock, MD,[23] Bela Melegh, MD,[24] Sophie Tezenas du Montcel, MD, PhD,[2,3] and Thomas Klockgether, MD,[1]

[1]*Department of Neurology, University Hospital of Bonn, Bonn, Germany*
[2]*Department of Biostatistics and Medical Informatics, Hôpital de la Pitié-Salpêtrière, Assistance Publique-Hôpitaux, Paris, France*
[3]*Modeling in Clinical Research, University Pierre et Marie Curie, Paris, France*
[4]*Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London, United Kingdom*
[5]*Department of Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany*
[6]*Department of Neurology and Stroke, County Hospital, Veszprém, Hungary*
[7]*Department of Biochemistry and Genetics, Fondazione-IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy*
[8]*Department of Neurology, University of Naples, Naples, Italy*
[9]*Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland*
[10]*INSERM, UMR_S679 Neurologie and Thérapeutique Expérimentale, F-75013, Paris, France*
[11]*AP-HP, Department of Genetics and Cytogenetics, Hôpital de la Salpêtrière F-75013, Paris, France*
[12]*Department of Neurology, St. Josef Hospital, University Hospital of Bochum, Bochum, Germany*
[13]*Department of Neurology, University Hospital "Marqués de Valldecilla," CIBERNED, Santander, Spain*
[14]*Department of Neurology, Donders Centre for Neuroscience, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*
[15]*Department of Neurology, University Hospital of Essen, Essen, Germany*
[16]*Department of Neurology, University of Innsbruck, Innsbruck, Austria*
[17]*First Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland*
[18]*Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium*
[19]*Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland*
[20]*Department of Neurology, University of Frankfurt, Frankfurt/M, Germany*
[21]*Department of Neurodegeneration and Restorative Research, Centers of Molecular Physiology of the Brain and Neurological Medicine, University Hospital of Göttingen, Göttingen, Germany*
[22]*Department of Neurology, RWTH Aachen, University Medical Hospital, Aachen, Germany*
[23]*Department of Neurology, Friedrich-Baur-Institute, University Hospital of Ludwig-Maximilians-University, München, Germany*
[24]*Department of Medical Genetics and Child Development, University of Pécs, Pécs, Hungary*

*Correspondence to: Dr. Tanja Schmitz-Hübsch, Department of Neurology, University Hospital of Bonn, Sigmund-Freud-Str 25, D-53105 Bonn, Germany E-mail: tanja.schmitz-huebsch@ukb.uni-bonn.de

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Abstract: Patient-based measures of subjective health status are increasingly used as outcome measures in interventional trials. We aimed to determine the variability and predictors of subjective health ratings in a possible target group for future interventions: the spinocerebellar ataxias (SCAs). A consecutive sample of 526 patients with otherwise unexplained progressive ataxia and genetic diagnoses of SCA1 (117), SCA2 (163), SCA3 (139), and SCA6 (107) were enrolled at 18 European referral centers. Subjective health status was assessed with a generic measure of health related quality of life, the EQ-5D (Euroqol) questionnaire. In addition, we performed a neurological examination and a screening questionnaire for affective disorders (patient health questionnaire). Patient-reported health status was compromised in patients of all genotypes (EQ-5D visual analogue scale (EQ-VAS) mean 61.45 ± 20.8). Specifically, problems were reported in the dimensions of mobility (86.9% of patients), usual activities (68%), pain/discomfort (49.4%), depression/anxiety (46.4%), and self care (38.2%). Multivariate analysis revealed three independent predictors of subjective health status: ataxia severity, extent of noncerebellar involvement, and the presence of depressive syndrome. This model explained 30.5% of EQ-VAS variance in the whole sample and might be extrapolated to other SCA genotypes. © 2010 Movement Disorder Society

Key words: spinocerebellar ataxia; subjective health rating; quality of life; EQ-5D; depression

The spinocerebellar ataxias (SCAs) are a clinical and genetically heterogeneous group of autosomal dominantly inherited progressive cerebellar disorders. Up to now, >25 different gene loci have been found. In >15 SCAs, the affected genes and causative mutations have been identified. The most common SCAs, which together account for more than half of all affected families, are SCA1, SCA2, SCA3, and SCA6. Each of these disorders is caused by a translated CAG repeat expansion mutation.

Recently, there has been major progress in the development of rater-based clinical assessment instruments for SCAs[1] and the identification of factors that determine disease severity measured by these instruments.[2] However, studies in various neurodegenerative disorders have shown that subjective health status is only partly related to disease-related factors that are assessed by clinical instruments. Other factors, such as emotional well-being, coping strategies, and comorbidity may play a role for health perception.[3] Therefore, patient-based measures are increasingly considered to be important for the outcome assessment in interventional trials. There are two types of instruments to assess subjective health status. Disease-specific instruments like the Parkinson's disease questionnaire-39 for Parkinson's disease[4] have been developed to assess the impact of one specific disease on health perception. They have the advantage of a high-discriminant ability in that disease. In contrast, generic instruments like the medical outcome study, 36-item short form[5] or measure of health related quality of life, part one: five dimensions (EQ-5D)[6] can be used in patients suffering from various diseases. They are less specific, but allow comparisons between diseases or of patient groups with the general population.

To study subjective health perception in patients with SCA1, SCA2, SCA3, and SCA6 we used the generic instrument EQ-5D, which is easy to administer, can be obtained from the public domain, and is available in validated translations in various languages. EQ-5D has been formally tested for practicality, reliability, and validity (see www.euroqol.org), and population norms are available for different populations.[7–10]

To evaluate a possible impact of emotional disturbance on subjective health status, we assessed symptoms of depression or anxiety with parts of the patient health questionnaire (PHQ). The PHQ was developed and validated to screen for psychiatric comorbidity in general medical practice in accordance with criteria of the American Psychiatric Association[11,12] and has been translated into various languages. The data reported here were collected during the ongoing EUROSCA natural history study (www.eurosca.org).

PATIENTS AND METHODS

Patients

The study was performed at 17 European centers which together form the EUROSCA clinical group. Inclusion criteria were progressive, otherwise unexplained ataxia and a positive molecular genetic testing for either SCA1, SCA2, SCA3, or SCA6. Cases were ascertained with the help of an electronic patient registry that contains data of all SCA patients that have been in contact with one of the study centers. Patients were consecutively recruited within a predetermined period between July 2005 and August 2006. The study population consisted of 526 patients (SCA1: 117 patients from 90 families, SCA2: 163 patients from 103 families, SCA3: 139 patients from 107 families, SCA6: 107 patients from 81 families). The study was approved by the ethics committees of the contrib-

uting centers. Written informed consent was obtained from each participant.

Measure of Health Related Quality of Life, Part One: Five Dimensions

Paper copies of the EQ-5D p.1–3 and selected PHQ items (question 1a–1i: depressive symptoms; question 2a–2e: anxiety symptoms, question 3: impairment by reported symptoms) were distributed and filled in on-site. If single questions were found unanswered on return, probands were prompted to try and answer this question. If they felt unable to answer a question, that item was reported as missing.

The EQ-5D dimensions mobility, self-care, usual activities, pain/bodily discomfort (named "EQ-5D pain" in Results section), anxiety/depression (named "EQ-5D mood" in Results section) are answered as 1 (no problem), 2 (some problem), or 3 (severe problem). The visual analogue scale (EQ-VAS) yields a number of 0 to 100 between the anchors "worst imaginable health state" (0) and "best imaginable health state" (100).

Patient Health Questionnaire

Answers in PHQ items were used for algorithmic classifications as "no depressive syndrome—any depressive syndrome" and "no anxiety syndrome—any anxiety syndrome" as described previously[11] and given as relative frequencies. For the anxiety classifications, because some patients deviated from the conditioned answers in question 2b to 2e (answer only if 2a has been answered yes), we performed a sensitivity analysis with exclusion and after inclusion of such cases which did not change the results in terms of significance.

Clinical Assessment

Severity of ataxia was assessed clinically with the scale for the assessment and rating of ataxia (SARA)[1] scoring from 0 (no ataxia) to 40 (most severe ataxia). Additional extracerebellar signs or symptoms were assessed as present or absent with the inventory of nonataxia symptoms (INAS). A sum score from 0 to 16 was formed from the number of signs or symptoms present in each patient (INAS count). The details of SARA scores and INAS count in this patient sample have been reported elsewhere.[2]

Statistical Analysis

The results of EQ-5D dimensions are reported as frequency distributions. Differences between genotypes were tested with Chi-square test or Fisher's exact test when appropriate.

Individual domains of EQ-5D were treated as nominal variables and the relation between EQ-5D dimensions and the ordinal variables age, age at onset, disease duration, SARA, and INAS count tested using univariate ANOVA. *P*-values were Bonferroni corrected since there are five EQ-5D dimensions.

Results of the EQ-VAS were treated as quantitative variables. Correlations between EQ-VAS and ordinal variables were studied with Pearson's correlation coefficients and the relation between EQ-VAS and nominal variables was analyzed using univariate ANOVA.

The relation of EQ-VAS with PHQ classifications and single INAS count components was tested using simple logistic regressions. The generalized estimating equations approach was used to adjust on family effect.

For the whole sample, a mixed linear model of EQ-VAS as dependent variable was performed with gender, age, disease duration, SARA, INAS count, and PHQ depression/anxiety categories included as independent variables. The model was obtained with stepwise selection. Genotype, family, and country were regarded as random effects for adjustment.

All tests were two-sided and considered significant when $P < 0.05$. Statistics were computed using SAS 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics are given in Table 1. SCA6 patients were of older age and showed less extracerebellar signs (lower INAS count), whereas sex ratio, disease duration, and disease severity as measured by SARA did not differ between genotypes. The EQ-5D was not applied in five cases due to reading or language difficulties. Of the 521 patients who completed, data were missing in <2% of all items (EQ-VAS: 9 patients, EQ-5D pain/discomfort and anxiety/depression items: 2). Assignment to the PHQ categories of depressive or anxiety syndrome was possible in 515 and 503 cases.

The EQ-5D and PHQ results are given in Table 2. Among the five EQ-5D dimensions, patients reported most frequently problems with mobility and usual activities (86.9% and 68%). Approximately half of the patients considered pain or depression/anxiety as a problem and only 38% of the patients reported problems with self care. The median EQ-VAS was 61.5. According to the PHQ ratings, 17% of the patients were categorized as "any depressive syndrome" and

TABLE 1. *Patient characteristics*

	SCA1 (n = 117)	SCA2 (n = 163)	SCA3 (n = 139)	SCA6 (n = 107)	Comparison between genotypes	Whole sample (n = 526)
Gender (M/F)	71/46	75/88	73/66	58/49	NS	277/249
Age (yr)	46.33 ± 12.25	46.34 ± 13.27	48.76 ± 11.80	64.88 ± 11.05	<0.001	50.72 ± 14.17
Age at onset (yr)	36.96 ± 10.64	34.89 ± 12.74	37.07 ± 11.38	54.46 ± 10.25	<0.001	39.91 ± 13.62
Disease duration (yr)	9.53 ± 5.47	11.34 ± 6.52	11.62 ± 5.93	10.42 ± 6.44	NS	10.82 ± 6.16
Nb of repeat longer allele	47.39 ± 5.23	39.33 ± 3.24	68.84 ± 4.63	22.36 ± 0.94	–	–
Nb of repeat shorter allele	29.89 ± 1.69	22.19 ± 1.41	21.72 ± 5.03	12.59 ± 1.15	–	–
SARA sum score	15.58 ± 9.08	15.78 ± 8.00	15.15 ± 8.57	15.00 ± 6.56	NS	15.41 ±- 8.13
INAS count	4.98 ± 2.28	4.63 ± 2.16	5.22 ± 2.55	2.04 ± 1.75	<0.001	4.34 ± 2.51

Data are expressed as numbers or mean ± standard deviation.

14% as "any anxiety syndrome." There were no differences between the genotypes except in the EQ-5D dimension of pain/bodily discomfort, where problems were reported more frequently by SCA3 patients than by patients with one of the other genotypes ($P = 0.015$). Therefore, subsequent analyses of EQ-VAS were only performed for the whole group.

To screen for factors that might determine subjective health status, we tested for relations between EQ-VAS and demographic and disease-related factors. EQ-VAS decreased with disease duration (Pearson $r = -0.21$, $P < 0.001$), while it was not correlated with age or age at disease onset. EQ-VAS did not differ between men and women. Patients with higher SARA ratings scored themselves lower on EQ-VAS ($r = -0.37$, $P < 0.001$). In addition, higher SARA ratings were observed in patients who reported problems in any of the EQ-5D dimensions ($P < 0.001$ except pain $P = 0.003$; Fig. 1). Similarly, there were higher INAS count, that is more extracerebellar symptoms, among the patients who had lower EQ-VAS ratings (Spearman Tau $= -0.32$, $P < 0.001$) or reported more problems in the dimensions mobility, self care, usual activities (all $P < 0.001$) and mood ($P = 0.002$). Among the 16 nonataxia symptoms recorded by INAS, only paresis, urinary dysfunction, cognitive impairment (all $P < 0.0001$), dystonia ($P = 0.0012$), areflexia ($P = 0.0018$), and muscle atrophy ($P = 0.0024$) were

TABLE 2. *Patient ratings on EQ-5D and PHQ assignment to depression or anxiety syndrome*

Item	Answer options	SCA1	SCA2	SCA3	SCA6	Comparison between genotypes*	Whole sample
EQ-5D mobility	No problem	11/115 (9.6)	25/162 (15.4)	19/137 (13.9)	13/107 (12.2)	NS	68/521 (13.1)
	Some problem	99/115 (86.1)	129/162 (79.6)	110/137 (80.3)	93/107 (86.9)		431/521 (82.7)
	Severe problem	5/115 (4.4)	8/162 (4.9)	8/137 (5.8)	1/107 (0.9)		22/521 (4.2)
EQ-5D self care	No problem	65/115 (56.5)	104/162 (64.2)	88/137 (64.2)	65/107 (60.8)	NS	322/521 (61.8)
	Some problem	40/115 (34.8)	47/162 (29)	39/137 (28.5)	38/107 (35.5)		164/521 (31.5)
	Severe problem	10/115 (8.7)	11/162 (6.8)	10/137 (7.3)	4/107 (3.7)		35/521 (6.7)
EQ-5D usual activities	No problem	32/115 (27.8)	68/162 (42)	44/137 (32.1)	23/107 (21.5)	NS	167/521 (32.1)
	Some problem	63/115 (54.8)	75/162 (46.3)	73/137 (53.3)	68/107 (63.6)		279/521 (53.6)
	Severe problem	20/115 (17.4)	19/162 (11.7)	20/137 (14.6)	16/107 (15)		75/521 (14.4)
EQ-5D pain/discomfort	No problem	53/114 (46.5)	90/162 (55.6)	54/136 (39.7)	66/107 (61.7)	0.015*	263/519 (50.7)
	Some problem	57/114 (50)	66/162 (40.7)	73/136 (53.7)	41/107 (38.3)		237/519 (45.7)
	Severe problem	4/114 (3.5)	6/162 (3.7)	9/136 (6.6)	0/107 (0)		19/519 (3.7)
EQ-5D anxiety/ depression	No problem	56/114 (49.1)	90/162 (55.6)	70/136 (51.5)	62/107 (58)	NS	278/519 (53.6)
	Some problem	52/114 (45.6)	60/162 (37)	54/136 (39.7)	39/107 (36.5)		205/519 (39.5)
	Severe problem	6/114 (5.3)	12/162 (7.4)	12/136 (8.8)	6/107 (5.6)		36/519 (6.9)
EQ-VAS		59.6 ± 21.9 60 (0–100)	63.3 ± 20.5 65 (0–100)	59.1 ± 21.6 60 (0–99)	63.7 ± 19 70 (20–100)	NS	61.45 ± 20.8 61.5 (0–100)
PHQ[a] depression		25/114 (21.9)	25/157 (15.9)	25/137 (18.3)	12/107 (11.2)	NS	87/515 (16.9)
PHQ[a] anxiety		20/110 (18.2)	22/156 (14.1)	14/131 (10.7)	15/106 (14.2)	NS	71/503 (14.1)

Data are expressed as frequency/sample size (%) or mean ± standard deviation, median (range).
*For EQ-5D dimensions: *P*-value adjusted for multiple comparisons.
[a]Classification as any depressive syndrome or any anxiety syndrome respectively as described in Patients and Methods section.

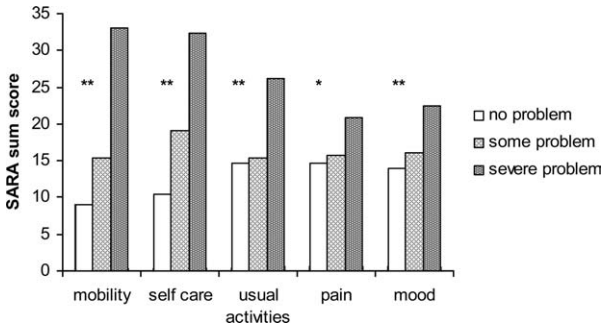

FIG. 1. Relation of the five EQ-5D dimensions to ataxia severity (SARA sum score). $^{**}P < 0.001$, $^{*}P = 0.003$.

associated with lower EQ-VAS ratings, but not hyperreflexia, extensor plantar response, spasticity, fasciculations, myoclonus, rigidity, chorea/dyskinesia, resting tremor, sensory symptoms, or brainstem oculomotor signs (Bonferroni corrected significance level set at 0.0031).

Patients classified as having any depressive syndrome or any anxiety syndrome according to PHQ were all more likely to give worse EQ-VAS ratings (depressive: 47.7 ± 21.2 vs. 64.5 ± 19.4, $P < 0.001$; anxiety: 56.3 ± 21.0 vs. 62.6 ± 20.6, $P = 0.015$). Patients classified as having any depressive syndrome were more likely to report more severe problems in all EQ-5D dimensions. In contrast, patients classified as having any anxiety syndrome were more likely to report problems in usual activities, pain and mood, but not in mobility and self care.

To understand which factors independently determine subjective health status, we performed a multivariate analysis using a mixed linear model with EQ-VAS as dependent variable and gender, age, disease duration, SARA, INAS count, and PHQ categories of depression and anxiety syndrome as independent variables (family, center, and genotype included as random effects). Ataxia severity, the number of extracerebellar symptoms and the presence of PHQ-depression all independently affected EQ-VAS (Table 3). This yielded a model that explained 30.5% of EQ-VAS variability in our sample.

DISCUSSION

We evaluated the self-reported health status in a large multinational group of patients with SCA1, SCA2, SCA3, and SCA6 and aimed to explore predictive factors. There were no differences between genotypes in EQ-VAS ratings and EQ-5D dimensions (except pain dimension) in unweighted comparison. This finding is interesting, as SCA6 patients differed clinically from the other genotypes in our group with respect to age and extent of extracerebellar involvement. The more frequent reporting of problems with pain/bodily discomfort in SCA3 could be associated with the more frequent occurrence of dystonia in this genotype (24% in SCA3 vs. 5–14% in other genotypes, Ref. 2). However, such link could not be proven in our sample ($P = 0.098$, Fisher exact test). Numerous studies reported decreased subjective health status in probands with neurological or other chronic diseases in comparison with population means. In our study, such comparison is hampered by the fact that subjective health ratings are thought to differ between countries due to differences in health care and general value settings.[13] Population surveys are currently not available for all countries who contributed to our study. In comparison with the most recent German data set[8] with an EQ-VAS mean of 77.4 ± 19 or the first UK sample[9] with 83.4 ± 22, the SCA patients of all genotypes had lower average scores. Taking this difference as a surrogate for "burden of disease"—with all theoretical limitations to that concept—the impact of disease on health perception in our group is comparable with previous reports in patients with Friedreich's ataxia (EQ-VAS 64.9 ± 19.1),[14] epilepsy (61.6 ± 20.3),[15] or Parkinson's disease (64.0 ± 22.8).[16] Accordingly, the proportions of our SCA patients who reported problems in the EQ-5D dimensions of mobility (86.9%), self care (38.2%), and usual activities (68%) exceed the respective mean frequencies from the available population

TABLE 3. *Analysis of the predictors of self-rated health status (EQ-VAS)*

	Multivariate analysis		Univariate analysis	
	Beta coefficient	*P* (multivariate analysis)	Pearson coeff, OR (univariate analysis)	*P* (univariate analysis)
Intercept	77.09		–	–
SARA score	−0.67	<0001	−0.37[a]	<0.001
INAS count	−0.98	0.0456	−0.32[a,b]	<0.001
PHQ—depression	−11.79	<0001	0.959[c]	<0.0001
PHQ—anxiety	–	NS	0.986[c]	0.0145
Disease duration	–	NS	−0.21[a]	<0.001
Age	–	NS	–	NS
Gender	–	NS	–	NS

Genotype, family, and country as random effects. R^2, 0.308; −2 logL, 3458.8.
[a]Pearson coefficient.
[b]Analysis corrected by genotype.
[c]OR.

surveys (<30% mobility, <10% self care, and <20% usual activities[7]). For the dimensions of pain and mood, the distinction from population norms is less clear. Problems were reported by over 45% of our patients in both dimensions, and the frequencies reported from different population surveys show a wide range from 19 to 64% (pain) and from 11 to 52% (mood).[7] This implies that these two dimensions are possibly less determined by the SCA disease process. Nevertheless, pain and emotional disturbance are relevant for subjective health perception—as shown by fair relation of all EQ-5D dimensions to EQ-VAS ratings—and should be considered in patient care. Of note, problems in these dimensions are usually not captured by clinical assessments of disease severity.

In accordance with several studies in other diseases,[14,17–20] the determinants of health status in our sample differ from those reported for the general population. For example, the decrease of health status with age reported in the general population or worse health perception in women[7] was not confirmed in our sample. This is not surprising as factors that influence health perception in nondiseased populations (like age or gender) are likely overwhelmed by the impact of a chronic disease.

The effect of SCA disease on subjective health status could be specified as a negative correlation of EQ-VAS with disease duration, ataxia severity (SARA), and extent of extracerebellar affection (INAS count) in univariate analyses. The correlation with the clinical assessment of ataxia severity in our sample is similar to the correlation of EQ-VAS and the disease-specific scale Unified Multiple System Atrophy Rating Scale (UMSARS) in multiple system atrophy.[19] Interestingly, such correlation was not found in Parkinson's disease using the widely accepted Unified Parkinson's Disease Rating Scale (UPDRS) motor assessment of disease severity.[21] In our sample, a higher number of noncerebellar symptoms was associated with lower EQ-VAS ratings in all genotypes. Relevant symptoms for self-rated health status like urinary dysfunction or dystonia are not assessed by our clinical scale of disease severity but are informative for patient counseling, as such symptoms might be amenable to symptomatic treatment. An effect of emotional disturbance could be confirmed by a relation with PHQ ratings: both the presence of depressive and anxiety syndrome were associated with lower EQ-VAS ratings. A role of depressive symptoms for subjective health perception has also been described in other neurological diseases.[22–24] In the multivariate model, when genotype, family, and country were included as random effects, only the extent of neurological symptoms (SARA and INAS) and depressive status independently determined subjective health ratings to a different extent. The intercept of 77.09 roughly equals the EQ-VAS means reported from general population surveys.[7] Starting from there, each SARA point increase will lead to an average 0.67 reduction in EQ-VAS and each INAS count increase to an EQ-VAS decrease of 0.98. However, depressive status will lead to a massive reduction in EQ-VAS of 11.79, an effect that would otherwise only be seen with an 18-point decrease in SARA scores. This underlines the strong effect of depressive symptoms on subjective health status in addition to disease-specific impairments and the need for adequate depression screening and treatment. In the light of known differences in EQ-5D reporting between countries, the inclusion of country as a random factor in our model might seem questionable. However, the studied SCA genotypes exhibit significant geographical clustering among the centers who contributed, which made it impossible to differentiate between effects of country and genotype. The final model had an explanatory power of 30.5%, which is comparable with other studies using EQ-VAS that yielded models with R^2 of 0.38[22,24] or 0.22[25] in stroke or R^2 of 0.45 in MSA patients.[19] The unexplained quality of life (QoL) fraction of variance is commonly attributed to other disease-related and disease-independent factors, which are not covered by the items of the QoL questionnaire. For example, it can be assumed that factors like fatigue[26] or perceived social support[20,27] that have been reported to determine variability in QoL self-ratings in different diseases, are also relevant in our sample but not included among the EQ-5D dimensions. Future studies thus might improve our model by inclusion of other known determinants of subjective health ratings. Recent criticism of the EQ-5D (and other frequently used QoL tools)[28,29] stated that such instruments do not allow valid description of health related QoL as they do not explore values, expectations, or coping. We agree that the evaluation of such truly subjective factors is warranted to improve predictive models, but are aware that they are less amenable to a quantitative approach. Nevertheless, our results show that the EQ-5D does include important aspects like pain, social interaction and mood that are not covered by clinical assessment but are relevant for subjective health ratings. The EQ-5D proved well applicable in our sample and might help to evaluate the acceptance of therapeutic interventions as well as the clinical relevance of otherwise measured treatment effects. Its suitability as an outcome measure for treatment studies in SCA

patients that aim to ameliorate ataxia or slow down disease progression remains to be determined.

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She is employed at the Department of Clinical Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland; J-SK reports no disclosures; SR was employed at Bezirkskrankenhaus Augsburg and Klinikum Augsburg, Germany; BK reports no disclosures; JBS received grants from the BMBF (German Ministry of Education and Research) for the projects NGFNplus and Competence Network Degenerative Dementias; TK was supported by grant GeneMove/01 GM 0503 from the German Ministry of Education and Research (BMBF) and received other grants from the BMBF and Deutsche Forschungsgemeinschaft (DFG). He received funding by Santhera Pharmaceuticals for clinical trials with idebenone in Friedreich ataxia and Leber hereditary optic neuropathy; BM received grants from the Hungarian Science Foundation (OTKA), T 73430 (Functional variants of the 5q31 chromosome region: connections between polygenic diseases and the carnitine system). 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execution), statistical analysis (design, review and critique), manuscript (review and critique); RF: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); CM: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); AF: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); MR: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); PC: Research project (organization, execution), statistical analysis (review and critique), manuscript (review and critique); PR: Research project (organization, execution), statistical analysis (review and critique), manuscript (review and critique); SS: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); JI: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); BVDW: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); AD: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); DT: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); SB: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); RR: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); CD: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); LS: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); EZ: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); J-SK: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); SR: Research project (organization, execution), statistical analysis (review and critique), manuscript (review and critique); BK: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); JS: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); TK: Research project (organization, execution), statistical analysis (review and critique), manuscript (review and critique); BM: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (review and critique); ST: Research project (conception), statistical analysis (design, execution), manuscript (review and critique); TK: Research project (conception, organization, execution), statistical analysis (design, review and critique), manuscript (writing of the first draft).

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