

BRIEF REPORT

Characterization of Lifestyle in Spinocerebellar Ataxia Type 3 and Association with Disease Severity

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Relevant conflicts of interest/financial disclosures: H.H., P.M., J.F., N.S., P.G., K.R., L.P.A., M.M.S., C.J., P.S., A.T., J.I., J.d.V., K.B., H.J., C.O., J.D.S., J.H.-S., and M.S. have nothing to report. H.G.-M. reports the EU Joint Programme–Neurodegenerative Disease Research (JPND) project, supported through the following funding organization under the aegis of JPND: Medical Research Council. Grant from CureSCA3. T.K. reports JPND project, supported through the following funding organization under the aegis of JPND: Federal Ministry of Education and Research (funding codes 01ED1602A/B). B.v.W. reports research support from ZonMW (Grant 733051066). M.L. and A.F.F. report the JPND project, supported through the following funding organization under the aegis of JPND: FCT (JPCOFUND/0002/2015). L.S. reports the JPND project, supported through the following funding organization under the aegis of JPND: Federal Ministry of Education and Research (funding codes 01ED1602A/B).

Funding agencies: This publication is an outcome of the European Spinocerebellar ataxia type 3/Machado-Joseph disease initiative (ESMI), an EU Joint Programme–Neurodegenerative Disease Research (JPND) project (see www.jpnd.eu). The project is supported through the following funding organizations under the aegis of JPND: Germany, Federal Ministry of Education and

Research (funding codes 01ED1602A/B); The Netherlands, The Netherlands Organisation for Health Research and Development; Portugal, Foundation for Science and Technology (FCT); United Kingdom, Medical Research Council. This project has received funding from the European Union's Horizon 2020 research and innovation program under Grant 643417. At the US sites, this work was in part supported by the National Ataxia Foundation and the National Institute of Neurological Disorders and Stroke Grant R01 NS080816. P.G. is supported by the National Institute for Health Research University College London Hospitals (UCLH) Biomedical Research Centre. P.G. receives also support from the North Thames Clinical Research Network (CRN). P.G. and H.G.M. work at University College London Hospitals/University College London, which receives a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. P.G. received funding from CureSCA3 in support of H.G.M.'s work. This work was moreover supported, in part, by the Deutsche Forschungsgemeinschaft (German Research Foundation) No. 441409627, as part of the Progression chart of Spastic ataxias (PROSPAX) consortium under the frame of the European Joint Programme on Rare Diseases (EJP RD), under the EJP RD COFUND-EJP N° 825575 (to M.S., B.v.W.) and Grant 779257 "Solve-RD" from the Horizon 2020 research and innovation program to M.S.

Received: 16 June 2021; **Revised:** 3 September 2021; **Accepted:** 2 October 2021

Published online in Wiley Online Library
(wileyonlinelibrary.com). DOI: 10.1002/mds.28844

ABSTRACT: Background: Lifestyle could influence the course of hereditary ataxias, but representative data are missing.

Objective: The objective of this study was to characterize lifestyle in spinocerebellar ataxia type 3 (SCA3) and investigate possible associations with disease parameters.

Methods: In a prospective cohort study, data on smoking, alcohol consumption, physical activity, physiotherapy, and body mass index (BMI) were collected from 243 patients with SCA3 and 119 controls and tested for associations with age of onset, disease severity, and progression.

Results: Compared with controls, patients with SCA3 were less active and consumed less alcohol. Less physical activity and alcohol abstinence were associated with more severe disease, but not with progression rates or age of onset. Smoking, BMI, or physiotherapy did not correlate with disease parameters.

Conclusion: Differences in lifestyle factors of patients with SCA3 and controls as well as associations of lifestyle factors with disease severity are likely driven by the influence of symptoms on behavior. No association between lifestyle and disease progression was detected. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: lifestyle; SCA3; alcohol; physical activity; body mass index

Spinocerebellar ataxia type 3 (SCA3) is the most common dominantly inherited ataxia, leading to severe disability and premature death.¹ Although a curative treatment is not currently available, several approaches to reduce the mutant protein have been developed, and pilot trials appear to be within reach.^{2,3} Nevertheless, symptomatic treatment and patient counseling will remain as the cornerstones of care for patients with SCA3. Although significant progress has been made in understanding the natural history of SCA3,^{4,5} the observed high variability in disease severity, progression, and age of onset can only be partly explained by the repeat length of expanded alleles.^{6,7} This suggests that other genetic or environmental factors, including lifestyle factors, could contribute to such variability. To date, the role of lifestyle factors has remained unclear, primarily due to the lack of studies in representative cohorts. In addition to understanding the natural history of SCA3, the results might have implications for stratification in upcoming interventional trials and patient counseling. This multicentric prospective

observational study assessed lifestyle factors including alcohol consumption, smoking, body mass index (BMI), physical activity, and ataxia-specific physiotherapy in 243 patients with SCA3 and explored possible associations with age of onset, disease severity, and progression.

Methods

Study Cohort and Data Collection

The study cohort was based on the European Spinocerebellar ataxia type 3/Machado-Joseph disease initiative (ESMI), a large multicenter prospective observational study of patients with SCA3. Patients with genetically confirmed SCA3 were recruited at ataxia clinics in London (United Kingdom), Bonn (Germany), Aachen (Germany), Nijmegen (The Netherlands), Coimbra (Portugal), Essen (Germany), Santander (Spain), Groningen (The Netherlands), Azores (Portugal), Tübingen (Germany), Heidelberg (Germany), and from additional sites in the United States (Minneapolis, Minnesota; Baltimore, Maryland; and Boston, Massachusetts). Control individuals without a history of neurological or psychiatric disease were recruited at the same centers from relatives accompanying the patients and hospital staff. A total of 243 patients with SCA3 with manifest ataxia and 119 healthy controls were included in the study.

Ataxia severity was quantified using the Scale for the Assessment and Rating of Ataxia (SARA) as described previously.^{8,9} The observed age of onset of ataxia was self-reported. The residual age of onset (rAOO) was defined as the difference between observed age of onset and predicted age of onset based on the pathogenic CAG repeat length.¹⁰ The predicted age of onset was calculated using the model described previously.¹¹

Annual SARA progression rates were calculated for each proband using the differences in scores between baseline and the last available visit. Functional status was evaluated by the self-reported Activities of Daily Living (ADL) score of the Friedreich's Ataxia Rating Scale.¹² Lifestyle data were collected at each visit by a questionnaire including items on the lifestyle categories physical activity, smoking, alcohol consumption, and ataxia-specific physiotherapy (Supplemental Material S1). In detail, physical activity was evaluated using the short form of the International Physical Activity Questionnaire (IPAQ), and data were processed as recommended.¹³ Patients who were wheelchair-bound were excluded from further analysis regarding physical activity, as the walking domain was not applicable. Based on the IPAQ, multiples of the resting metabolic rate (MET) minutes/week were estimated, and probands were categorized into three levels of physical activity (high, moderate, and low) following the IPAQ

guidelines. A moderate level of physical activity on the IPAQ approximately reflects the minimum recommendation of physical activity of the World Health Organization (WHO).¹⁴ Alcohol consumption was assessed in a standardized interview asking about consumption on the previous workday and during the past weekend, allowing for a rough estimation of daily alcohol consumption.¹⁵ Weight and height were measured or reported by patients if measures were not obtained due to logistic difficulties. BMI was calculated using the following formula: weight/(height)². BMI was then categorized as underweight (<18.5), normal (18.5–25), overweight (25–30), and obese (>30).

The study was approved by the local institutional review boards of all participating centers. Written informed consent was obtained from all study participants before enrollment.

Statistics

Data were analyzed using RStudio Version 1.2.5033 (RStudio, Boston, Massachusetts). As none of the outcome parameters were normally distributed, the nonparametric Kruskal-Wallis test followed by the Mann-Whitney U test was used for group comparisons. Bonferroni correction was applied with number of hypotheses (m) = 19 to correct for multiple testing in the primary analysis of the association between lifestyle factors (alcohol, smoking, BMI, physical activity, physiotherapy) and measures of disease severity (SARA score, ADL score, progression rate, age of onset). Thus, P values <0.0026 were considered significant. Other secondary comparisons were regarded as exploratory analyses, and for these, no Bonferroni correction was applied. Correlations were calculated using the Spearman rank correlation.

Results

Characteristics of the study population are given in Table 1. Compared with controls, patients with SCA3 were less active, achieving a lower number of MET minutes per week (median SCA3, 1440 minutes; median controls, 2826 minutes; $P < 0.001$). More SCA3 probands were classified in the low physical activity group (SCA3, 39%; control cohort, 19%; $P < 0.05$), not reaching the WHO-recommended minimal physical activity.¹⁴ Alcohol was consumed by 58% of the patients with SCA3, less frequent than in the control group (87%; $P < 0.001$). Of the patients with SCA3, 26% had previously consumed alcohol, and 16% had never consumed alcohol. Among the probands who drank alcohol, the estimated amount of daily alcohol consumption was comparable between patients with SCA3 and controls (median SCA3, 21.0 g/d; median controls, 19.0 g/d). Current smokers were more frequent in the SCA3 cohort (18% of patients; median number of pack-

TABLE 1 Study population characteristics

Demographic information	Patients with SCA3	Healthy controls
N, BL/FUP1/FUP2	243/167/84	119
Period between baseline and last follow-up, months	22.5 (13.5–28.1)	NA
Age, years	51 (42.0–59.0)	46 (38.0–59.0)
Sex, female/male	124 (51)/119	60 (50)/59
Age of onset, years	39.0 (33.0–46.0)	NA
CAG repeat length, longer allele	70.0 (67.0–73.0)	NA
SARA	12 (8.0–19.5)	0 (0–0.5)
ΔSARA per year, BL to last FUP	1.27 (0.16–2.54)	NA
ADL	9.0 (5.0–16.25)	0 (0–0)
Smoking, yes/previously/no	43 (18)/69 (28)/131 (54)	9 (8)/44 (37)/64 (55)
Alcohol, yes/previously/no	140 (58)/63 (26)/40 (16)	102 (87)/6 (5)/9 (8)
Physical activity, high/moderate/low	55 (29)/60 (32)/74 (39)	39 (40)/35 (41)/16 (19)
Ataxia specific physiotherapy, yes/no	149 (61)/94	NA
Body mass index	23.7 (21.2–26.6)	24.8 (22.3–27.0)
MET minutes per week	1440 (420–3144)	2826 (1309–4488)

Data are presented as n (%) or median (interquartile range).

Abbreviations: SCA3, spinocerebellar ataxia type 3; BL, baseline visit; FUP1, follow-up 1; FUP2, follow-up 2; SARA, Scale for the Assessment and Rating of Ataxia; ΔSARA, annual SARA progression rate; FU, follow-up; ADL, Activities of Daily Living; MET, multiples of the resting metabolic rate; NA, not available.

years, 15.0 [interquartile range, 7.8–23.1]) than in the control group (8%; median number of pack-years, 7.6 [interquartile range, 4.5–12.1]). Exsmokers were more frequent in the control group (37%) than in the SCA3 cohort (28%).

The BMI was slightly lower in patients with SCA3 than in controls (medians 23.7 in SCA3 and 24.8 in controls; $P = 0.047$); 12 of the patients with SCA3 but none of the control individuals were underweight (BMI <18.5).

Next, we analyzed if these lifestyle factors were associated with disease severity as assessed by the SARA score, rAOO, annual SARA progression rate, and ADL score (Fig. 1, Supplemental Table S1). Significant differences affecting SARA and ADL scores were found for alcohol consumption and physical activity. Alcohol abstinence was significantly associated with higher

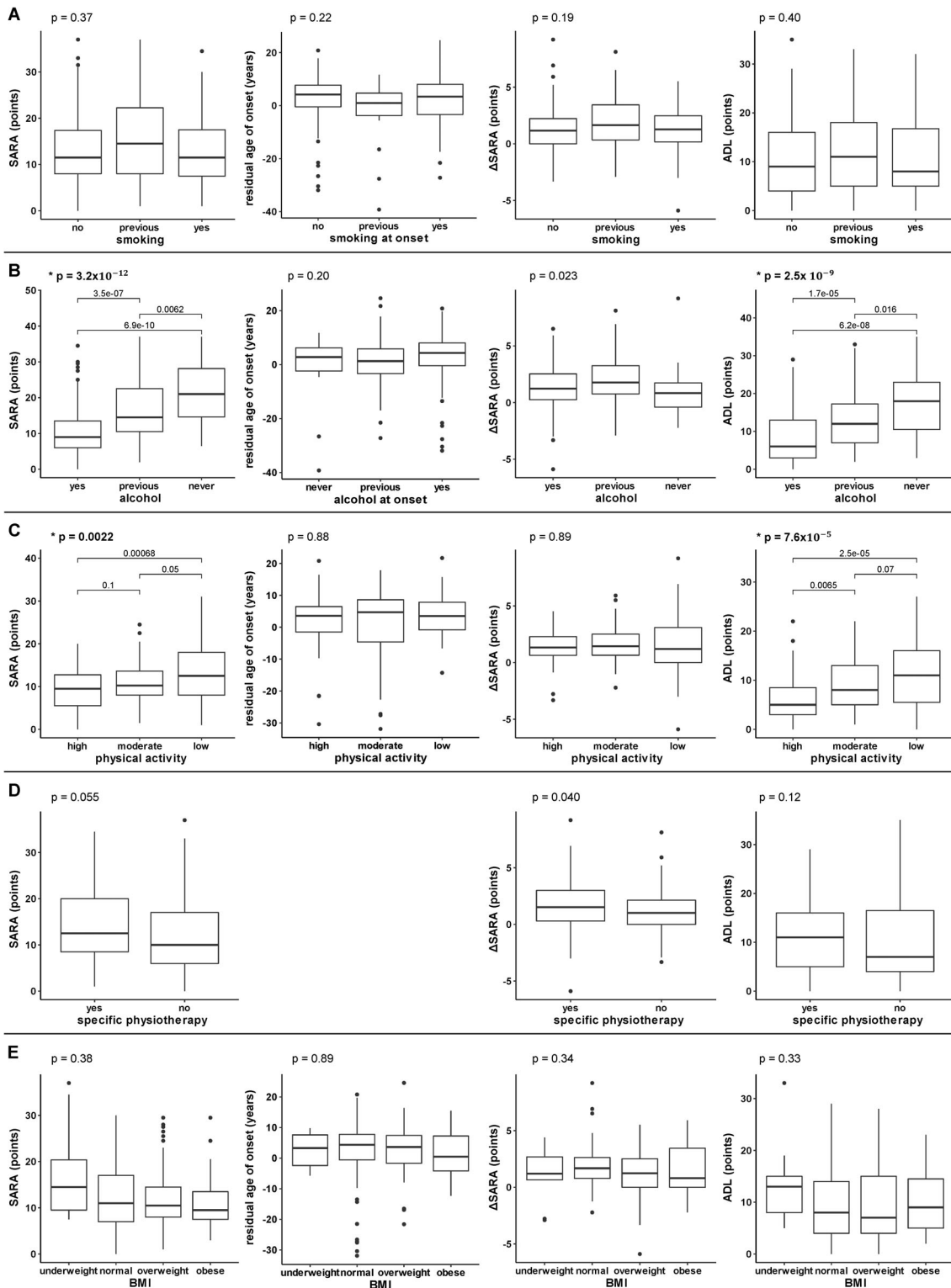


FIG. 1. Primary analysis of the association between lifestyle factors and the predefined measures of disease severity (SARA score, residual age of onset, annual SARA progression rate [Δ SARA], and ADL score). After Bonferroni correction for multiple testing (number of hypotheses (m) = 19), the results were considered to be significant at $P < 0.0026$. Group comparisons regarding the residual age of onset were calculated with the respective values at the time point of disease onset for smoking and alcohol, for physical activity and BMI, the values at baseline visit had to be used. **(A)** Smoking was not significantly associated with any outcome parameter. **(B)** Alcohol consumption was significantly associated with lower SARA and ADL scores, whereas residual age of onset and SARA progression rates did not significantly differ. **(C)** SARA and ADL scores were significantly lower in patients with moderate and high levels of physical activity, whereas residual age of onset and SARA progression rates were not significantly different. **(D)** Patients receiving physiotherapy showed a tendency toward higher SARA and ADL scores and higher progression rates. **(E)** BMI analysis showed a trend toward more severe disease with higher ADL and SARA scores in underweight patients. ADL, Activities of Daily Living; BMI, body mass index; SARA, Scale for the Assessment and Rating of Ataxia.

SARA and ADL scores ($P = 3.2 \times 10^{-13}$ and $P = 2.5 \times 10^{-9}$, respectively). Concerning physical activity, the highly active patients had significantly lower SARA and ADL scores than those with moderate or low physical activity levels ($P = 0.0022$ and $P = 7.6 \times 10^{-5}$, respectively). However, rAOO and SARA progression rate did not differ significantly for any lifestyle factor. Furthermore, smoking tobacco, receiving ataxia-specific physiotherapy, and BMI categories did not show significant differences in any tested outcome variables. Subgroup analyses did not detect associations between the frequency or the estimated amount of alcohol consumption per day with changes in SARA progression rates (Supplementary Fig. S1A,B). For physical activity, there was no correlation between the estimated MET minutes per week for each patient and SARA progression rates (Supplementary Fig. S1C). Likewise for ataxia-specific physiotherapy, there was no correlation between hours of training per week and the progression rate (Supplementary Fig. S1D).

BMI and repeat length were inversely correlated (Supplementary Fig. S1E; Spearman's $\rho = -0.26$, $P = 0.00092$). SARA scores and self-reported ADL scores showed a high positive correlation (Supplementary Fig. S1F; Spearman's $\rho = 0.83$, $P = 2.2 \times 10^{-16}$), confirming this finding as previously reported in Friedreich's ataxia.¹⁶

Discussion

This observational study characterized the lifestyle factors alcohol consumption, smoking, BMI, physical activity, and physiotherapy in patients with SCA3 and explored the associations between these variables and disease progression.

We found that higher alcohol consumption was significantly associated with less severe disease (lower SARA and ADL scores), which does not mean that alcohol consumption prevents severe stages of SCA3 but may be interpreted as a hint that patients with more severe ataxia refrain from alcohol, as the ethyltoxic aggravation of the movement disorder is no longer tolerable. Consistent with this hypothesis, many patients (47 of 61 SCA3 probands) named health reasons for giving up alcohol consumption. The significant association between higher levels of physical activity and less severe disease can be interpreted in a similar way, which is that patients with more severe ataxia may not be able to engage in much physical activity. However, in terms of SARA progression rate, we did not find associations for either the IPAQ categories or estimated total MET minutes per week.

The number of patients receiving physiotherapy to ameliorate ataxia was 61%, which was about the same as in a previous Dutch study.¹⁷ Unexpectedly, patients receiving ataxia-specific physiotherapy tended to have

higher SARA and ADL scores. We hypothesize that this association could be attributed to differences in prescribing and that more severely affected patients are more likely to receive ataxia-specific physiotherapy.

Another interesting finding was the tendency that patients with a higher BMI had less severe ataxia. As severe disease promotes inactivity and, therefore, the risk of gaining weight, this correlation may reflect the consumptive nature of SCA3. Indeed, a negative association between disease severity and weight has been previously described in SCA,^{18,19} and an inverse correlation was found between repeat length and BMI.²⁰ Similar effects have also been observed with Huntington's disease, another trinucleotide repeat expansion disorder.^{21,22}

Although we present an overview of lifestyle factors in SCA3, conclusions on potentially protective or deleterious lifestyle effects are limited. The observational nature of this study allows only to delineate associations, whereas it is not possible to distinguish whether lifestyle factors are disease modifiers or whether symptoms influence patients' behavior. To establish causal relations between lifestyle and the course of disease, a prospective, long-term study with randomized assignments to groups of alcohol consumption, smoking, physical activity, and BMI would be required. Not least because of different attitudes and mind-sets, this is not realistic.

Although this study included one of the largest SCA3 cohorts worldwide, our study was underpowered concerning longitudinal progression data. It has been previously estimated that in a 1-year trial, two groups of 202 patients with SCA3 need to be observed to detect a 50% change in SARA progression rates.⁴ However, our data do not suggest strong effects of lifestyle factors on the course of SCA3. As stated previously, the association of less alcohol use and physical activity with more severe disease likely reflects secondary effects of symptoms on behavior. Our data do not provide evidence that stratification for lifestyle factors is required in upcoming interventional trials. ■

Acknowledgments: We are grateful to the patients and their relatives as well as healthy volunteers from the hospital staff for participating in this study. H.H., M.S., T.K., B.v.W., and L.S. are members of the European Reference Network for Rare Neurological Diseases–Project (project ID 739510). The Nijmegen Site would like to thank Judith van Gaalen for her help in patient assessment and data collection. The London Site would like to thank Robyn Labrum and James Polke (Neurogenetics Laboratory, National Hospital for Neurology and Neurosurgery, University College London Hospitals National Health Service Foundation Trust) for their technical support, and Cristina Gonzalez-Robles (Ataxia Centre, Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology) for her assistance with data uploading.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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P.M.: 2A, 3B

J.F.: 1C, 3B

H.G.-M.: 1C, 3B

N.S.: 1C, 3B

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Financial Disclosures

H.H. receives support by the intramural fortune program of the Medical Faculty of the University of Tübingen (Grant 2554-0-0) and the Deutsche Forschungsgemeinschaft (DFG, HE 8803/1-1). P.M., N.S., P.G., M.M.S., C.J., J.L., J.d.V., K.B., H.J., and C.O. have nothing to disclose. J.F. receives funding of the National Ataxia Foundation and as a fellow of the Hertie Academy for Clinical Neuroscience. H.G.-M. has received funding from AtaxiaUK and CureSCA3. T.K. has received research support from the Bundesministerium für Bildung und Forschung (BMBF), the Bundesministerium für Gesundheit, and the National Institutes of Health. He has received consulting fees from Roche, UCB Pharma, Uniqure, and Vico Therapeutics. K.R. has received grants from the German Federal Ministry of Education and Research (BMBF 01GQ1402, 01DN18022), the German Research Foundation (IRTG 2150), and Alzheimer Forschung Initiative e.V. (NL-18002CB) and honoraria for presentations or advisory boards from Biogen and Roche. B.v.W. receives research support from Radboudumc, ZonMW, Hersenstichting, and the Gossweiler Foundation; royalties from Bohn Stafleu van Loghum (BSL) – Springer Nature; and scientific advisory board compensation from uniQure. L.P.A. reports European Regional Development Fund (ERDF) through the Regional Operational Program Center 2020, Competitiveness Factors Operational Program (COMPETE 2020), and National Funds through Fundação para a Ciência e a Tecnologia (FCT; Foundation for Science and Technology) Project UID/NEU/04539/2020, BrainHealth2020 projects (CENTRO-01-0145-FEDER-000008), ViraVector (CENTRO-01-0145-FEDER-022095), and SpreadSilencing POCI-01-0145-FEDER-029716 and private funding from PTC Therapeutics. P.S. reports FCT through the financed fellowship (SFRH/BD/148451/2019). A.T. receives support from the

Universitätsmedizin Essen Clinician Scientist Academy (UMEA) clinician scientist programme of the Medical Faculty of the University of Duisburg-Essen and DFG (FU 356/12-1). M.L. receives support from the Fundo Regional para a Ciência e Tecnologia (support to the Azores participation in the European Spinocerebellar ataxia type 3/Machado-Joseph disease initiative (ESMI) network). A.F.F. receives PhD grant (SFRH/BD/121101/2016) support from FCT and Fundo Social Europeu. J.D.S. is site principal investigator for Biohaven NCT03701399 and NCT03952806; consultant to Biogen and IQVIA; inventor of the Brief Ataxia Rating Scale, the Cerebellar Cognitive Affective/Schmahmann Syndrome Scale, and the Patient Reported Outcome Measure for Ataxia, which are copyrighted to The General Hospital Corporation; and receives royalties from Elsevier, Oxford, Mac Keith, and Springer. J.H.-S. received support from the National Ataxia Foundation, Center of Rare Diseases Medical Faculty, and University of Tübingen and the excellence program Athene of the University of Tübingen. M.S. received consultancy honoraria from Janssen Pharmaceuticals, Ionis Pharmaceuticals, and Orphazyme Pharmaceuticals. L.S. reports the following: European Reference Network on Rare Neurological Diseases (EU-ERN-RND) (Grant 947,588); E-rare/BMBF-Treat-Ion (Grant 01GM1907A); E-rare/BMBF-TreatHSP (Grant 01GM1905A); Innovationsfond-ZSE-DUO (Grant 01NVF17031); and Innovationsfond-Translate-NAMSE (Grant 01NVF16024).