HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Parkinsonism Relat Disord. 2020 March ; 72: 37–43. doi:10.1016/j.parkreldis.2020.02.004.

The Impact of Ethnicity on the Clinical Presentations of Spinocerebellar Ataxia Type 3

Shi-Rui Gan, MD, PhD[1], **Karla P Figueroa, MS**[2], **Hao-Ling Xu, MD**[1], **Susan Perlman, MD**[3], **George Wilmot, MD, PhD**[4], **Christopher M Gomez, MD, PhD**[5], **Jeremy Schmahmann, MD**[6], **Henry Paulson, MD, PhD**[7], **Vikram G Shakkottai, MD, PhD**[7], **Sarah H Ying, MD**[8], **Theresa Zesiewicz, MD**[9], **Khalaf Bushara, MD**[10], **Michael D Geschwind, MD, PhD**[11], **Guangbin Xia, MD**[12], **SH Subramony, MD**[13], **Liana Rosenthal, MD, PhD**[14], **Tetsuo Ashizawa, MD**[15], **Stefan M Pulst, MD**[2], **Ning Wang, MD, PhD**[1], **Sheng-Han Kuo, MD**[16]

[1]Department of Neurology and Institute of Neurology, First Affiliated Hospital, Fujian Medical University, Fuzhou, China.

[2]Department of Neurology, University of Utah, Salt Lake City, Utah, USA.

[3]Department of Neurology, University of California, Los Angeles, California, USA.

[4]Department of Neurology, Emory University, Atlanta, Georgia, USA.

[5]Department of Neurology, University of Chicago, Chicago, Illinois, USA.

[6]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.

[7]Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA.

[8]Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA.

[9]Department of Neurology, University of South Florida, Tampa, Florida, USA.

[10]Department of Neurology, University of Minnesota, Minneapolis, Minnesota, USA.

[11]Department of Neurology, University of California, San Francisco, California, USA.

[12]Department of Neurology, School of Medicine, University of New Mexico, Albuquerque, New Mexico, USA.

Correspondence Dr. Sheng-Han Kuo, 650 West 168th Street, Room 305, New York, NY 10032, USA. Tel: (212) 342-3753, Fax: (212) 305-1304, sk3295@columbia.edu; Dr. Ning Wang, 20 Chazhong Road, Fuzhou, 350005, China. Tel: (86) 0591-8798-2772, ningwang@mail.fjmu.edu.cn.

Disclosure

Dr. Zesiewicz has served as a clinical advisor for Steminent Biotherapeutics, and she has received travel reimbursement from the department of neurology at University of Southern Florida; has received travel reimbursement for a Biohaven Pharmaceuticals meeting. Dr. Zesiewicz has served on the editorial board for Neurodegenerative Disease Management and Tremor and other Hyperkinetic Movements, and has received research support for her division for approximately 20 clinical trials for Parkinson's disease, Friedreich's ataxia, and spinocerebellar ataxias. Dr. Zesiewicz's division is a site in a multi-site trial of Parkinson's disease patients with the LRRK2 mutation and is sponsored by the National Institutes of Health but funded by Emory University. Dr. Ying is an employee of Wave Life Sciences and conducts research funded by the National Institutes of Health. The remaining authors report no conflicts of interest.

[13]Department of Neurology and McKnight Brain Institute, University of Florida, Gainesville, Florida, USA.

[14]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA.

[15]Houston Methodist Research Institute, Houston, Texas, USA.

[16]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.

Abstract

Background—For a variety of sporadic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, it is well-established that ethnicity do affect the disease phenotypes. However, how the ethnicity could contribute to the clinical symptoms and disease progressions in monogenetic disorders, such as spinocerebellar ataxia type 3 (SCA3), remains less studied.

Methods—We used multivariable linear and logistical regression models in 257 molecularly-confirmed SCA3 patients (66 Caucasians, 43 African Americans, and 148 Asians [composed of 131 Chinese and 17 Asian Americans]) to explore the influence of ethnicity on age at onset (AAO), ataxia severity, and non-ataxia symptoms (i.e. depression, tremor, and dystonia).

Results—We found that Asians had significantly later AAO, compared to Caucasians ($\beta = 4.75$, $p = 0.000$) and to African Americans ($\beta = 6.64$, $p = 0.000$) after adjusting for the pathological CAG repeat numbers in *ATXN3*. African Americans exhibited the most severe ataxia as compared to Caucasians ($\beta = 3.81$, $p = 0.004$) and Asians ($\beta = 4.39$, $p = 0.001$) after taking into consideration of the pathological CAG repeat numbers in *ATXN3* and disease duration. Caucasians had a higher prevalence of depression than African Americans ($\beta = 1.23$, $p = 0.040$). Ethnicity had no influence on tremor or dystonia.

Conclusions—Ethnicity plays an important role in clinical presentations of SCA3 patients, which could merit further clinical studies and public health consideration. These results highlight the role of ethnicity in monogenetic, neurodegenerative disorders.

Keywords

spinocerebellar ataxia type 3; neurodegeneration; ethnicity; cerebellum; depression

Introduction

In a variety of sporadic neurodegenerative diseases, it is well-established that ethnicity can affect disease phenotypes in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).[1-7] These studies provided a unique window to probe the interplay of factors of gene, environment, socioeconomic status, and access to care, in late onset, sporadic neurodegenerative disorders. While a recent study has demonstrated that ethnicity may influence disease penetrance in LRRK2-PD,[8] it remains unclear whether ethnicity also plays a key role in monogenetic, ataxic disorders.

CAG-repeat disorders, including spinocerebellar ataxias (SCAs) and Huntington's disease (HD), are a group of neurodegenerative disorders with a strong genetic influence. Often, the length of pathological CAG repeats inversely correlates with AAO. Thus, CAG repeat diseases are often considered as prototypical disorders of neurodegeneration with a robust genetic predisposition.[9] Our overarching aim is to investigate the contribution of ethnicity in monogenetic, neurodegenerative disorders. We choose SCA3 as a disease model because SCA3 is the most common of the CAG-repeat ataxias, and occurs across different ethnicities.[10] SCA3 is caused by an expanded CAG repeat in exon 10 of *ATXN3*.[11] We recruited a multi-ethnicity cohort that consisted of Caucasians, African Americans and Asians in multi-center settings in order to compare clinical presentations in SCA3 patients of different ethnicities. This will inform the contribution of ethnicity in monogenetic, neurodegenerative disorders.

Patients and Methods

Patients

257 molecularly-confirmed SCA3 patients were included in the present study with two large cohorts: 1) the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) natural history study in the North America [12] with 66 Caucasians, 43 African Americans, and 17 Asian Americans and 2) the SCA3 study in China with 131 native Han Chinese. The clinical data of Caucasians, African Americans and Asian Americans were from the CRC-SCA cohort constitutes patients from 12 medical centers across North America, who were longitudinally followed every 6 months for 2 years during July 2009 to May 2012. The Chinese patients were recruited from the First Affiliated Hospital of Fujian Medical University, Fuzhou, China, during October 2014 to April 2017 and there were total 74 families among 131 Chinese patients. All participants exhibited clinical symptoms of cerebellar ataxia at the baseline visit and we excluded asymptomatic carriers. All study subjects had a blood draw at baseline for the genetic analyses. The uniform study protocol was approved by the local institutional review boards and informed consent was obtained from each participant.

Clinical Assessment

Each patient received face-to-face interviews and neurological examinations by ataxia specialists, either by CRC-SCA ataxia specialists in the United States or by Dr. Shi-Rui Gan, an ataxia specialist, in China. Ethnicity was identified by self-report or family informants. AAO was defined as the age for which gait ataxia occurred. Whenever possible, the AAO was corroborated by close relatives or care providers. The severity of ataxia was measured using the Scale for Assessment and Rating of Ataxia (SARA), a continuous variable (0-40) with a higher number indicating more severe ataxia.[13]

Three non-ataxia symptoms of SCAs was assessed, specifically depression, a common non-motor symptom of SCAs[14], as well as dystonia and postural tremor, two common associated motor symptoms in SCAs.[15, 16] Depressive symptoms were assessed by the 9-item Patient Health Questionnaire (PHQ-9), which has been extensively studied as a tool to measure the severity of depression.[17] Clinically relevant depression was defined as PHQ-9

≥ 10.[18] Postural tremor and dystonia were assessed by ataxia specialists at the baseline clinical visit as previously described.[19], [20] Peripheral neuropathy, defined by the loss of vibration sensation in the feet, and restless leg syndrome[21] were also investigated as non-ataxia symptoms. We did not have measurement of these non-ataxia symptoms in the Chinese SCA3 patients (n=131), therefore, the analyses of non-ataxia symptoms were only conducted in SCA3 patients from the CRC-SCA.

Genetic Analyses

The length of CAG repeats (CAG repeat numbers) for both alleles in *ATXN3* for the 126 SCA3 patients from the CRC-SCA was determined via multiplex polymerase chain reaction combined with capillary electrophoresis with internal standards in Dr. Stefan Pulst's laboratory, using the standardized procedure described previously.[22] For verification of CAG repeat length, 10% of all samples were re-genotyped using DNA Sanger sequencing. For participants whose blood samples were not available in the research lab, the data for CAG repeat numbers by commercial labs was used. Furthermore, the length of CAG repeats of both alleles in *ATXN2* and *HTT* was also investigated to adjust for the effects of these genetic modifiers on AAO of SCA3, as it has been suggested that the CAG repeats in *ATXN2* and *HTT* (responsible genes for SCA2 and HD, respectively) might influence the AAO of SCA3; The length of the CAG repeats of both alleles in *ATXN3, ATXN2,* and *HTT* in the Chinese cohort was determined by DNA Sanger sequencing at Dr. Ning Wang's laboratory, as previously described.[23]

Statistical Analyses

For analyses of basic demographics between the three ethnicities (Caucasians, African Americans, Asians), two-way analysis of variance followed by Tukey's post hoc analyses and independent samples Kruskal-Wallis tests were used, for normally and non-normally distributed variables, respectively. The normal distribution of the data was determined by Kolmogorov-Smirnov tests. For analyses of basic demographics between two ethnicities (Caucasians vs. African Americans, Caucasians vs. Asians, and African Americans vs. Asians), Student's independent samples t-test and Mann-Whitney U tests were used for normally and non-normally distributed variables, respectively. Chi-squared tests were used to compare the gender distribution between ethnicities.

To determine the influence of ethnicity on AAO, a multivariable linear regression model was constructed, for which AAO was the dependent variable, and ethnicity, gender (binary), the length of expanded CAG repeats in *ATXN3* were independent variables. Studies have shown that "normal" CAG repeat allele of *ATXN3* can also influence AAO;[24] therefore, we additionally include this variable as another independent variable in the linear regression model. We additionally constructed a multivariable linear regression model to investigate whether the influence of ethnicity on AAO in SCA3 is related to CAG repeats in *ATXN2* and *HTT*. In this model, AAO served as the dependent variable, and ethnicity, the length of CAG repeats in both alleles of *ATXN2* and *HTT,* along with gender (binary), the length of normal and expanded CAG repeats in *ATXN3* were independent variables.

To analyze the influence of ethnicity on the severity of ataxia, we established another multivariable linear regression model, for which SARA score was the dependent variable, and ethnicity, gender (binary), age at the first visit, disease duration, and the length of normal and expanded CAG repeats in *ATXN3* were independent variables.

Given that the cohort of Asians in this study is consisted of Asian Americans and native Han Chinese, we further conducted a subgroup analysis using two multivariable linear regression models, for which the dependent and independent variables were the same as those aforementioned analyses to study the influence of ethnicity on AAO and on the severity of ataxia, except that ethnicity was replaced by population (binary, Asian Americans vs. Chinese) as an independent variable.

To further analyze the influence of ethnicity on ataxia progression, repeated-measures linear regression (an exchangeable working within-subject correlation model by a generalized estimating equation [GEE]) was constructed with time-varying SARA as an dependent variable, and independent variables were ethnicity, gender (binary), the age at the first visit, the length of expanded CAG repeats in *ATXN3*, and interaction terms ([African-Americans vs. Caucasians] x time, [Asian Americans vs. Caucasians] x time, and [Asian Americans vs. African-Americans] x time) to assess the longitudinal patterns of progression in three pairs of two ethnicities during the 2-year observation. Coefficients of the interaction terms reflected how the rate of progression differed in different ethnicities. As the Chinese SCA3 patients only had the baseline visit, this GEE model only included CRC-SCA patients.

For the non-ataxia symptoms, we compared the prevalence of depression, dystonia, postural tremor, restless leg syndrome, and peripheral neuropathy between different ethnicities using chi-square tests. Given that depression, dystonia, and postural tremor in SCA3 can be influenced by multiple factors,[18-20] a multivariate logistic regression model was used to explore inter-ethnicity effects on these three symptoms. The presence or absence of 3 types of non-ataxia symptoms (binary) were the dependent variables, respectively, and ethnicity, along with gender (binary), age at the first visit, SARA scores, disease duration, and the length of normal and expanded CAG repeats in *ATXN3* were independent variables. We included SARA scores in these models because the degree of ataxia might confound symptoms of depression[18] and tremor[25].

Ethnicity was considered as a categorical variable: Caucasians and African Americans comparing to Asians, respectively, were set as dummy variables successively in all analyses. All statistical analyses were performed using R (version 3.2.2, 2015, The R Foundation for Statistical Computing). The results were considered statistically significant at $p < 0.05$.

Results

The demographic features of SCA3 patients

The basic demographics of the SCA3 participants were shown in Table 1. There were no significant differences in SCA3 patients of different ethnicities with respect to gender, AAO, and depression symptoms. Compared to Caucasians and African Americans, Asians had the youngest age at the baseline enrollment and the shortest disease duration. Asians also had

significantly lower SARA scores than Caucasians or African Americans. Interestingly, in contrast to their low SARA scores, Asians had the longest expanded CAG repeat length with a similar AAO.

The influence of ethnicity on ataxia severity

To examine the influence of ethnicity on AAO, we performed multivariable linear regression models controlling for age at first visit, gender, the length of normal and expanded CAG repeats in *ATXN3*. We found that Asians had, on average, 4.75 years and 6.64 years later AAO than Caucasians and African Americans, respectively (Asians vs. Caucasians: β = 4.75, $p = 0.000$; Asians vs. African Americans: β = 6.64, $p = 0.000$, Table 2). Caucasians and African Americans were not different in AAO (Caucasians vs. African Americans: β = 1.88, $p = 0.226$, Table 2). To further adjust the effects of CAG repeats in *ATXN2* and *HTT* on AAO in SCA3, we conducted a multivariable linear regression model. In this model, the length of longer CAG repeats of *ATXN2* was inversely related to AAO of SCA3 (Supplemental Table 1), which was consistent with previous studies.[22] After adjusting the genetic effects of *ATXN2* and *HTT,* we still found significant differences in AAO between ethnicities (Asians vs. Caucasians: β = 4.46, $p = 0.004$; Asians vs. African Americans: β = 6.40, $p = 0.000$, Supplemental Table 1).

We next examined the influence of ethnicity on ataxia severity (SARA score), and we applied multivariable linear regression models controlling for age of the first visit, gender, the length of normal and expanded CAG repeats in *ATXN3,* and disease duration. Whereas there was no significant difference in ataxia severity between Asians and Caucasians (Asian vs. Caucasian: β = −0.59, $p = 0.597$, Table 2), African Americans had significantly more severe ataxia than either Asians or Caucasians (Caucasians vs. African Americans: β = −3.81, $p = 0.004$; Asians vs. African Americans: β = −4.39, $p = 0.001$, Table 2).

To test whether the Asian group is a relatively homogeneous group, we investigate the differences of AAO and ataxic severity between Chinese and Asian Americans, we thus established multivariable linear regression models between the subgroups. Neither of these models demonstrated significant differences between Asian Americans and Chinese for AAO (Chinese vs. Asian Americans: β = 2.93, p = 0.123, Supplemental Table 2) or ataxic severity (Chinese vs. Asian Americans: β = −1.25, p = 0.463, Supplemental Table 2), suggesting that it was reasonable to pool these two cohorts together to analyze AAO and ataxic severity and to compare with the other two ethnicities.

To further investigate the influence of ethnicity on the progression of ataxia, GEE models were performed between Caucasians, African Americans, and Asian Americans. However, we did not find any significant differences in the progression of ataxia between these groups (Supplemental Table 3).

The influence of ethnicity on non-ataxia symptoms

For five non-ataxia symptoms, the occurrence of each symptom was assessed. Compared to the other two ethnicities, Asian Americans had significantly lower prevalence of dystonia (Asian Americans: 5.88%, Caucasians: 24.24%, African Americans: 34.88%, $p = 0.046$, Table 3). Except for the restless syndrome, the prevalence of the other four non-ataxia

symptoms were trending lower in Asian Americans, though the differences were not consistently significant (Table 3).

Given potential confounding factors that can contribute to depression, dystonia, and postural tremor in different ethnicities, we conducted multivariable logistic regression to analyze the effect of ethnicity on the occurrence of each three non-ataxia symptom, controlling for gender, age at the first visit, SARA score, disease duration, and the length of normal and expanded CAG repeats in *ATXN3*. In these models, we did not observe any ethnic differences in terms of postural tremor or dystonia (Table 4). Interestingly, Caucasian SCA3 patients were more likely to have depression than African American patients (Caucasians vs. African Americans: $\beta = 1.23$, $p = 0.040$, Table 4).

Discussion

We found that Asians have the latest AAO, compared to African Americans and Caucasians, whereas African Americans have the most severe ataxia, compared to Asians and Caucasians, suggesting that Asians appear to have the mildest ataxia phenotypes while African Americans have the most severe phenotypes in SCA3. On the other hand, Caucasian SCA3 patients more commonly have depression. We also found that Asians have the shortest disease duration at the enrollment, which might suggest the ethnic differences for seeking medical attention. These data suggest that ethnicity could have distinct impact on motor and non-motor symptoms associated with cerebellar dysfunction. Moreover, these influence of ethnicity is independent of known genetic modifiers for SCA3, including the normal allele of *ATXN3,* and also repeat length of *ATXN2* and *HTT*. Our current study highlights the role of ethnicity in SCA3, a monogenetic, neurodegenerative disorder.

The contribution of ethnicity just begins to be understood in monogenetic disorders. A study of a moderate sized HD cohort (84 cases) concluded no genetic and phenotypic differences within different Jewish populations within Israel.[26] Other studies showed that SCA3 patients of African descent exhibited parkinsonism more often than their European counterparts,[27] and SCA3 patients from Southern Brazil and Taiwan have a later AAO than those from Europe.[28] Another study reported that the progression of ataxia in SCA3 is similar between Chinese and Caucasians based on the retrospective analysis of literature data.[29] Along with our current study, which constitutes a large multi-center cohort of SCA3 patients from multiple countries and multiple ethnic origins, these studies collectively advance our understanding of the role of ethnicity in monogenic neurodegenerative diseases.

Our study does highlight clear ethnic differences among multiple SCA3 phenotypes, with clinical implications. For example, our findings might be relevant to the design of future clinical studies. Moreover, in countries like the United States and Europe which have multi-ethnic populations, our findings of particularly early AAO and more severe ataxia in SCA3 patients of African descent are likely to improve the accuracy of SCA3 diagnosis and the impact of genetic counselling if this ethnic-specific disease expression has been taken into consideration. In addition, attention should be paid to depressive symptoms in SCA3 patients, especially among Caucasians who more commonly have depression. This approach of studying the impact of ethnicity on clinical phenotypes could be further applied to other

monogenetic disorders, which will likely to have a broad impact in clinical care and research.

The mechanism underlying ethnic differences in SCA3 patients is not known. The important consideration for ethnic differences in SCA3 patients is the disparity of socioeconomic status in different ethnicities. Others have noted that in PD, African Americans are less likely to be diagnosed and more likely to under-report PD related-disability.[30] Poor access to health care could lead to low incidence and prevalence of ALS in non-European/North American regions.[31] In addition, in PD as well as other medical conditions there are numerous examples for disparities in advanced care and mortality between African Americans and Caucasians.[32, 33] These disparities in access to medical care, report of clinical features, and mortality due to differences in the socioeconomic status could play an important role for ethnic differences in monogenetic disorders such as SCA3.

The current study has some limitations. First, the self-reported ethnicity has accuracy limitations. However, the determination of ethnicity by self-report was widely used in studies on the role of ethnicity in late onset, sporadic neurodegenerative diseases,[1, 2, 6, 7] and thus could serve as a starting point for future, more defined study design. Second, we only had a small number of Asians in the CRC-SCA cohort, which might make some analyses under-powered to detect differences between Asians and other ethnic groups, for instance, the longitudinal analysis for ataxia progression. Moreover, the lack of longitudinal data and some non-ataxia phenotypes for 131 Chinese SCA3 patients clearly limited the scope of several of our comparisons. While the Chinese participants are all of the Han ethnicity, the lack of more specific ethnicity information for the Asian American patients in CRC-SCA cohort can complicate data interpretations. We also did not assess parkinsonism features and pyramidal symptoms, which can be prominent in some SCA patients, and we do not know whether some participants are from the same family for separate familial analyses, which will be an important future direction. Finally, we were unable to take into account the impact of socioeconomic status and racial disparities on AAO and disease severity. The etiology of these disparities in care is likely multifactorial and with the current investigation we are unable to take into account these differences.

In conclusion, we have demonstrated ethnicity-dependent SCA3 phenotypic variations, which merit future clinical research and also public health consideration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors sincerely thank the participants for their help and willingness to participate in this study. We also thank the reviewers for their helpful comments.

Study funding

The CRC-SCA natural history study was supported by the Rare Disease Clinical Research Network (RDCRN) (RC1NS068897), and the National Ataxia Foundation. Dr. Kuo is supported by the NINDS K08 NS083738, Louis V. Gerstner Jr. Scholarship, American Brain Research Training Fellowship, Parkinson Disease Foundation,

American Parkinson's Disease Association, Rare Disease Clinical Research Network (RDCRN) (RC1NS068897), International Essential Tremor Foundation, and NIEHS pilot grant ES009089, the Smart Foundation. Dr. Wang is supported by the National Natural Science Foundation of China (U1505222). Dr. Gan is supported by the Natural Science Foundation of Fujian Province (2018J01156).

Appendix

Appendix 1:

Authors

Name	Location	Role	Contribution
Shi-Rui Gan, MD, PhD	Fujian Medical University, Fuzhou, China	Author	study concept and design, statistical analysis and interpretation, writing of the manuscript, critical revision of the manuscript for important intellectual content
Karla P Figueroa, MS	University of Utah, Utah	Author	study concept and design, statistical analysis and interpretation
Hao-Ling Xu, MD	Fujian Medical University, Fuzhou, China	Author	study concept and design, statistical analysis and interpretation
Susan Perlman, MD	University of California, California	Author	acquisition of data
George Wilmot, MD, PhD	Emory University, Georgia	Author	acquisition of data
Christopher M Gomez, MD, PhD	University of Chicago, Illinois	Author	acquisition of data
Jeremy Schmahmann, MD	Harvard Medical School, Massachusetts	Author	acquisition of data
Henry Paulson, MD, PhD	University of Michigan, Michigan	Author	acquisition of data
Vikram G Shakkottai, MD, PhD	University of Michigan, Michigan	Author	acquisition of data
Sarah H Ying, MD	Johns Hopkins University, Maryland	Author	acquisition of data
Theresa Zesiewicz, MD	University of South Florida, Florida	Author	acquisition of data
Khalaf Bushara, MD	University of Minnesota, Minnesota	Author	acquisition of data
Michael D Geschwind, MD, PhD	University of California, California	Author	acquisition of data
Guangbin Xia, MD	University of New Mexico, New Mexico	Author	acquisition of data
SH Subramony, MD	University of Florida, Florida	Author	study concept and design, acquisition of data, study supervision
Liana Rosenthal, MD, PhD	Johns Hopkins School of Medicine, Baltimore	Author	study concept and design, acquisition of data, study supervision
Tetsuo Ashizawa, MD	Houston Methodist Research Institute, Texas	Author	study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision
Stefan M Pulst, MD	University of Utah, Utah	Author	study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision
Ning Wang, MD, PhD	Fujian Medical University, Fuzhou, China	Author	study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision

Name	Location	Role	Contribution
Sheng-Han	Columbia	Author	study concept and design, acquisition of data,
Kuo, MD	University, New York		analysis and interpretation, critical revision of the manuscript for important intellectual content

References

[1]. Chen HY, Panegyres PK, The Role of Ethnicity in Alzheimer's Disease: Findings From The C-PATH Online Data Repository, Journal of Alzheimer's disease : JAD. 51 (2016) 515–23. doi: 10.3233/JAD-151089. [PubMed: 26890783]

[2]. Mehta KM, Yaffe K, Perez-Stable EJ, Stewart A, Barnes D, Kurland BF, Miller BL, Race/ethnic differences in AD survival in US Alzheimer's Disease Centers, Neurology. 70 (2008) 1163–70. doi: 10.1212/01.wnl.0000285287.99923.3c. [PubMed: 18003939]

[3]. Bassiony MM, Warren A, Rosenblatt A, Baker A, Steinberg M, Steele CD, Lyketsos CG, Isolated hallucinosis in Alzheimer's disease is associated with African-American race, International journal of geriatric psychiatry. 17 (2002) 205–10. doi: 10.1007/s00415-012-6531-5. [PubMed: 11921146]

[4]. Fernandes GC, Socal MP, Schuh AF, Rieder CR, Clinical and Epidemiological Factors Associated with Mortality in Parkinson's Disease in a Brazilian Cohort, Parkinsons Dis. 2015 (2015) 959304. doi: 10.1155/2015/959304. [PubMed: 26819798]

[5]. Orlev Y, Yahalom G, Cohen OS, Elincx-Benizri S, Kozlova E, Inzelberg R, Goldbourt U, Hassin-Baer S, Exploring determinants of progression in Parkinson's disease. Is there a difference among Jewish ethnic groups?, Parkinsonism Relat Disord. 21 (2015) 184–8. doi: 10.1016/j.parkreldis.2014.10.009. [PubMed: 25550275]

[6]. Rana AQ, Athar A, Owlia A, Siddiqui I, Awan N, Fattah A, Rana MA, Impact of ethnicity on non-motor symptoms of Parkinson's disease, Journal of Parkinson's disease. 2 (2012) 281–5. doi: 10.3233/JPD-129002.

[7]. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG, Race/ethnicity, socioeconomic status, and ALS mortality in the United States, Neurology. 87 (2016) 2300–2308. doi: 10.1212/WNL.0000000000003298. [PubMed: 27742817]

[8]. Hentati F, Trinh J, Thompson C, Nosova E, Farrer MJ, Aasly JO, LRRK2 parkinsonism in Tunisia and Norway: a comparative analysis of disease penetrance, Neurology. 83 (2014) 568–9. doi: 10.1212/WNL.0000000000000675. [PubMed: 25008396]

[9]. Stoyas CA, La Spada AR, The CAG-polyglutamine repeat diseases: a clinical, molecular, genetic, and pathophysiologic nosology, Handb Clin Neurol. 147 (2018) 143–170. doi: 10.1016/B978-0-444-63233-3.00011-7. [PubMed: 29325609]

[10]. Schols L, Bauer P, Schmidt T, Schulte T, Riess O, Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis, Lancet neurology. 3 (2004) 291–304. doi: 10.1016/s1474-4422(04)00737-9. [PubMed: 15099544]

[11]. Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, Nakamura S, Nishimura M, Akiguchi I, et al., CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1, Nature genetics. 8 (1994) 221–8. doi: 10.1038/ng1194-221 [PubMed: 7874163]

[12]. Ashizawa T, Figueroa KP, Perlman SL, Gomez CM, Wilmot GR, Schmahmann JD, Ying SH, Zesiewicz TA, Paulson HL, Shakkottai VG, Bushara KO, Kuo SH, Geschwind MD, Xia G, Mazzoni P, Krischer JP, Cuthbertson D, Holbert AR, Ferguson JH, Pulst SM, Subramony SH, Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study, Orphanet J Rare Dis. 8 (2013) 177. doi: 10.1186/1750-1172-8-177. [PubMed: 24225362]

[13]. Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, Giunti P, Globas C, Infante J, Kang JS, Kremer B, Mariotti C, Melegh B, Pandolfo M, Rakowicz M, Ribai P, Rola

R, Schols L, Szymanski S, van de Warrenburg BP, Durr A, Klockgether T, Fancellu R, Scale for the assessment and rating of ataxia: development of a new clinical scale, Neurology. 66 (2006) 1717–20. doi: 10.1212/01.wnl.0000219042.60538.92 [PubMed: 16769946]

[14]. Schmitz-Hubsch T, Coudert M, Tezenas du Montcel S, Giunti P, Labrum R, Durr A, Ribai P, Charles P, Linnemann C, Schols L, Rakowicz M, Rola R, Zdzienicka E, Fancellu R, Mariotti C, Baliko L, Melegh B, Filla A, Salvatore E, van de Warrenburg BP, Szymanski S, Infante J, Timmann D, Boesch S, Depondt C, Kang JS, Schulz JB, Klopstock T, Lossnitzer N, Lowe B, Frick C, Rottlander D, Schlaepfer TE, Klockgether T, Depression comorbidity in spinocerebellar ataxia, Mov Disord. 26 (2011) 870–6. doi: 10.1002/mds.23698. [PubMed: 21437988]

[15]. Bonnet C, Apartis E, Anheim M, Legrand AP, Baizabal-Carvallo JF, Bonnet AM, Durr A, Vidailhet M, Tremor-spectrum in spinocerebellar ataxia type 3, J Neurol. 259 (2012) 2460–70. doi: 10.1007/s00415-012-6531-5. [PubMed: 22592286]

[16]. Nunes MB, Martinez AR, Rezende TJ, Friedman JH, Lopes-Cendes I, D'Abreu A, Franca MC Jr., Dystonia in Machado-Joseph disease: Clinical profile, therapy and anatomical basis, Parkinsonism Relat Disord. 21 (2015) 1441–7. doi: 10.1007/s00415-012-6531-5. [PubMed: 26552869]

[17]. Spitzer RL, Kroenke K, Williams JB, Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire, JAMA. 282 (1999) 1737–44. doi: 10.1001/jama.282.18.1737. [PubMed: 10568646]

[18]. Lo RY, Figueroa KP, Pulst SM, Perlman S, Wilmot G, Gomez C, Schmahmann J, Paulson H, Shakkottai VG, Ying S, Zesiewicz T, Bushara K, Geschwind M, Xia G, Yu JT, Lee LE, Ashizawa T, Subramony SH, Kuo SH, Depression and clinical progression in spinocerebellar ataxias, Parkinsonism & related disorders. 22 (2016) 87–92. doi: 10.1016/j.parkreldis.2015.11.021. [PubMed: 26644294]

[19]. Kuo PH, Gan SR, Wang J, Lo RY, Figueroa KP, Tomishon D, Pulst SM, Perlman S, Wilmot G, Gomez CM, Schmahmann JD, Paulson H, Shakkottai VG, Ying SH, Zesiewicz T, Bushara K, Geschwind MD, Xia G, Subramony SH, Ashizawa T, Kuo SH, Dystonia and ataxia progression in spinocerebellar ataxias, Parkinsonism Relat Disord. 45 (2017) 75–80. doi: 10.1016/j.parkreldis.2017.10.007. [PubMed: 29089256]

[20]. Gan SR, Wang J, Figueroa KP, Pulst SM, Tomishon D, Lee D, Perlman S, Wilmot G, Gomez CM, Schmahmann J, Paulson H, Shakkottai VG, Ying SH, Zesiewicz T, Bushara K, Geschwind MD, Xia G, Subramony SH, Ashizawa T, Kuo SH, Postural Tremor and Ataxia Progression in Spinocerebellar Ataxias, Tremor Other Hyperkinet Mov (N Y). 7 (2017) 492. doi: 10.7916/d8gm8krh. [PubMed: 29057148]

[21]. Leschziner G, Gringras P, Restless legs syndrome, BMJ. 344 (2012) e3056. doi: 10.1136/bmj.e3056. [PubMed: 22623643]

[22]. du Montcel S. Tezenas, Durr A, Bauer P, Figueroa KP, Ichikawa Y, Brussino A, Forlani S, Rakowicz M, Schols L, Mariotti C, van de Warrenburg BP, Orsi L, Giunti P, Filla A, Szymanski S, Klockgether T, Berciano J, Pandolfo M, Boesch S, Melegh B, Timmann D, Mandich P, Camuzat A, A. Clinical Research Consortium for Spinocerebellar, E. network, Goto J, Ashizawa T, Cazeneuve C, Tsuji S, Pulst SM, Brusco A, Riess O, Brice A, Stevanin G, Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes, Brain : a journal of neurology. 137 (2014) 2444–55. doi: 10.1093/brain/awu174. [PubMed: 24972706]

[23]. Gan SR, Ni W, Dong Y, Wang N, Wu ZY, Population genetics and new insight into range of CAG repeats of spinocerebellar ataxia type 3 in the Han Chinese population, PloS one. 10 (2015) e0134405. doi: 10.1371/journal.pone.0134405. [PubMed: 26266536]

[24]. Durr A, Stevanin G, Cancel G, Duyckaerts C, Abbas N, Didierjean O, Chneiweiss H, Benomar A, Lyon-Caen O, Julien J, Serdaru M, Penet C, Agid Y, Brice A, Spinocerebellar ataxia 3 and Machado-Joseph disease: clinical, molecular, and neuropathological features, Annals of neurology. 39 (1996) 490–9. doi: 10.1002/ana.410390411. [PubMed: 8619527]

[25]. Lai RY, Tomishon D, Figueroa KP, Pulst SM, Perlman S, Wilmot G, Gomez CM, Schmahmann JD, Paulson H, Shakkottai VG, Ying SH, Zesiewicz T, Bushara K, Geschwind M, Xia G, Subramony SH, Ashizawa T, Kuo SH, Tremor in the Degenerative Cerebellum: Towards the

Understanding of Brain Circuitry for Tremor, Cerebellum. (2019). doi: 10.1007/s12311-019-01016-6.

[26]. Zitser J, Thaler A, Inbar N, Gad A, Faust-Socher A, Paleacu D, Anca-Herschkovitch M, Balash Y, Shabtai H, Ash EL, Merkin L, Manor Y, Kestenbaum M, Bar David A, Peretz C, Naiman T, Bar-Shira A, Orr-Urtreger A, Dangoor N, Giladi N, Gurevich T, Two Ethnic Clusters with Huntington Disease in Israel: The Case of Mountain Jews and Karaites, Neurodegener Dis. 17 (2017) 281–285. doi: 10.1159/000479375. [PubMed: 28848105]

[27]. Subramony SH, Hernandez D, Adam A, Smith-Jefferson S, Hussey J, Gwinn-Hardy K, Lynch T, McDaniel O, Hardy J, Farrer M, Singleton A, Ethnic differences in the expression of neurodegenerative disease: Machado-Joseph disease in Africans and Caucasians, Mov Disord. 17 (2002) 1068–71. doi: 10.1002/mds.10241. [PubMed: 12360561]

[28]. de Mattos EP, Leotti VB, Soong BW, Raposo M, Lima M, Vasconcelos J, Fussiger H, Souza GN, Kersting N, Furtado GV, Saute JAM, Camey SA, Saraiva-Pereira ML, Jardim LB, Age at onset prediction in spinocerebellar ataxia type 3 changes according to population of origin, European Journal of Neurology. 26 (2019) 113–120. doi: 10.1111/ene.13779. [PubMed: 30125433]

[29]. Lin YC, Lee YC, Hsu TY, Liao YC, Soong BW, Comparable progression of spinocerebellar ataxias between Caucasians and Chinese, Parkinsonism Relat Disord. (2018). doi: 10.1016/j.parkreldis.2018.12.023.

[30]. Dahodwala N, Karlawish J, Siderowf A, Duda JE, Mandell DS, Delayed Parkinson's disease diagnosis among African-Americans: the role of reporting of disability, Neuroepidemiology. 36 (2011) 150–4. doi: 10.1159/000324935. [PubMed: 21508648]

[31]. Zaldivar T, Gutierrez J, Lara G, Carbonara M, Logroscino G, Hardiman O, Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study, Neurology. 72 (2009) 1640–5. doi: 10.1212/WNL.0b013e3181a55f7b. [PubMed: 19433736]

[32]. Riley WJ, Health disparities: gaps in access, quality and affordability of medical care, Transactions of the American Clinical and Climatological Association. 123 (2012) 167–72; discussion 172-4. [PubMed: 23303983]

[33]. Wright Willis A, Evanoff BA, Lian M, Criswell SR, Racette BA, Geographic and ethnic variation in Parkinson disease: a population-based study of US Medicare beneficiaries, Neuroepidemiology. 34 (2010) 143–51. doi: 10.1159/000275491. [PubMed: 20090375]

1. Ethnicity plays a role in clinical presentations of SCA3.
2. Asian SCA3 patients have significantly older age of disease onset.
3. African American SCA3 patients have more severe ataxia.
4. Caucasian SCA3 patients more commonly have depression.
5. Ethnicity has distinct impact on motor and non-motor symptoms of SCA3.

Table 1.

The demographic features of SCA3 participants in different ethnicities

	Caucasian	African American	Asian [#]	*p*-value for three ethnicities	*p*-value for two ethnicities		
					Caucasians vs. African Americans	Caucasians vs. Asians	African Americans vs. Asians
Sample size, N (%)	66 (25.68%)	43 (16.73%)	148 (57.59%)	/			
Gender, M : F	32 : 34	27 : 16	77 : 71	0.325[a]	0.143[a]	0.632[a]	0.212[a]
Age at first visit, Yr	52.42 ± 12.79 Median = 52.5	49.70 ± 11.34 Median = 50.0	45.05 ± 12. 54 Median = 44.5	**0.000**[b]	0.216[c]	**0.000**[d]	**0.016**[c]
Length of expanded CAG repeats in *ATXN3*, N	70.83 ± 4.62 Median = 71.0	71.09 ± 3.81 Median = 71.0	74.28 ± 3.87 Median = 74.0	**0.000**[b]	0.842[c]	**0.000**[c]	**0.000**[c]
Length of normal CAG repeats in *ATXN3*, N	22.35 ± 5.63 Median = 23.0	23.88 ± 6.73 Median = 23.0	19.81 ± 6.74 Median = 23.0	**0.001**[b]	0.188[c]	**0.014**[c]	**0.001**[c]
Disease duration, Yr	12.95 ± 7.38 Median = 12.0	12.98 ± 7.67 Median = 11.50	8.75 ± 5.64 Median = 8.0	**0.000**[b]	0.940[c]	**0.000**[c]	**0.000**[c]
Age at onset, Yr	39.47 ± 12.35	36.38 ± 11.25	36.32 ± 11.28	0.166[e]	0.531[f]	0.200[f]	1.000[f]
SARA score	14.27 ± 7.94 Median = 12.5	17.14 ± 9.25 Median = 17.0	12.85 ± 8.76 Median = 8.0	**0.016**[b]	0.114[c]	0.142[c]	**0.004**[c]
PHQ-9 score	7.88 ± 5.95 Median = 7.0	6.91 ± 5.72 Median = 6.0	6.65 ± 4.69 Median = 6.0	0.596[b]	0.353[c]	0.512[c]	0.928[c]

Abbreviations: F = Female, M = Male, N = Number, PHQ-9 = The 9-item Patient Health Questionnaire, SARA = Scale for Assessment and Rating of Ataxia, SCA = Spinocerebellar Ataxia, Yr = Year.

Values represent mean ± standard deviation or number, and for variables with non-normal distribution, the median is reported as well.

[#]Composed with 131 SCA3 patients from Chinese cohort and 17 Asian American SCA3 patients from the CRC-SCA cohort. Since the Chinese patients had no PHQ-9 data, the value for the PHQ-9 score was only calculated from Asian Americans.

[a]Chi-square test

[b]independent samples Kruskal-Wallis tests

[c]Mann-Whitney U tests

[d]Student's independent samples t-test

[e]analysis of variance

[f]Tukey's post hoc analyses

Table 2.

The influence of ethnicity on age at onset and severity of ataxia in SCA3 via multivariate linear regression

Age at onset			
	Coefficient (β)	**Standard error**	***p*-value**
Gender (M vs. F)	−1.37	0.98	0.163
Length of expanded CAG repeats in *ATXN3*, N	−2.16	0.12	**0.000**
Length of normal CAG repeats in *ATXN3*, N	0.05	0.08	0.509
Ethnicity (Caucasians vs. African Americans)	1.88	1.55	0.226
Ethnicity (Asians vs. Caucasians)	4.75	1.25	**0.000**
Ethnicity (Asians vs. African Americans)	6.64	1.45	**0.000**
Severity of ataxia			
	Coefficient (β)	**Standard error**	***p*-value**
Gender (M vs. F)	0.03	0.84	0.973
Age at first visit, Yr	0.40	0.06	**0.000**
Disease duration, Yr	0.47	0.08	**0.000**
Length of expanded CAG repeats, N	1.09	0.16	**0.000**
Length of normal CAG repeats, N	−0.02	0.07	0.783
Ethnicity (Caucasians vs. African Americans)	−3.81	1.31	**0.004**
Ethnicity (Asians vs. Caucasians)	−0.59	1.11	0.597
Ethnicity (Asians vs. African Americans)	−4.39	1.30	**0.001**

Abbreviations: F = Female, M = Male, N = Number, SCA = Spinocerebellar Ataxia, Yr = Year.

Parkinsonism Relat Disord. Author manuscript; available in PMC 2021 March 01.

Table 3.

The rate (%) of non-ataxia manifestations in SCA3 participants

	Caucasian N = 66	**African American N = 43**	**Asian American[#] N = 17**	***p*-value [a]**
Dystonia				**0.046**
Yes	16 (24.24)	15 (34.88)	1 (5.88)	
No	50 (75.76)	28 (65.12)	16 (94.12)	
Postural tremor				0.175
Yes	9 (13.64)	5 (11.63)	0 (0.00)	
No	57 (86.36)	38 (88.37)	17 (100.00)	
Depression (PHQ9 > = 10)				0.357
Yes	23 (34.85)	12 (27.91)	3 (17.65)	
No	43 (65.15)	31 (88.37)	14 (82.35)	
Peripheral neuropathy				0.953
Yes	37 (56.06)	23 (53.49)	9 (52.94)	
No	29 (43.94)	20 (46.51)	8 (47.06)	
Restless legs syndrome				0.366
Yes	6 (9.09)	1 (2.33)	1 (5.88)	
No	60 (90.91)	42 (97.67)	16 (94.12)	

Abbreviations: SCA = Spinocerebellar Ataxia.

[#]All 17 SCA3 patients are from the CRC-SCA cohort.

[a]Chi-square test

Parkinsonism Relat Disord. Author manuscript; available in PMC 2021 March 01.

Table 4.

The influence of ethnicity on the non-ataxia manifestations in SCA3 via multivariate logistic regression

	Depression			Dystonia			Postural tremor		
	Coefficient (β)	**Standard error**	***p*-value**	**Coefficient (β)**	**Standard error**	***p*-value**	**Coefficient (β)**	**Standard error**	***p*-value**
Age at first visit, Yr	−0.11	0.04	**0.005**	−0.12	0.04	**0.004**	0.02	0.05	0.784
Disease duration, Yr	0.08	0.04	**0.047**	0.00	0.05	0.997	0.0	0.05	0.117
Gender (M vs. F)	0.92	0.52	0.078	0.05	0.61	0.929	0.584	0.64	0.363
Length of expanded CAG repeats in *ATXN3*, N	−0.30	0.11	**0.004**	−0.01	0.11	0.903	0.25	0.16	0.118
Length of normal CAG repeats in *ATXN3*, N	0.03	0.04	0.403	−0.09	0.05	0.098	−0.06	0.06	0.348
SARA score	0.16	0.04	**0.000**	0.20	0.05	**0.000**	−0.20	0.05	0.682
Ethnicity (Caucasians vs. African Americans)	1.23	0.60	**0.040**	0.00	0.62	0.999	−0.19	0.75	0.800
Ethnicity (Asian Americans vs. Caucasians)	−1.05	0.84	0.212	−2.20	1.23	0.074	−16.53	1482.78	0.991
Ethnicity (Asian Americans vs. African Americans)	0.175	0.92	0.850	−2.20	1.25	0.080	−16.72	182.78	0.991

Abbreviations: F = Female, M = Male, N = Number, SARA = Scale for Assessment and Rating of Ataxia, SCA = Spinocerebellar Ataxia, Yr = Year.

Since Chinese patients had no data in non-ataxia symptoms, the analyses of non-ataxia symptoms only conducted between Caucasians, African Americans and Asian Americans.