GEOGRAPHIC AND SOCIODEMOGRAPHIC FEATURES OF FRIEDREICH ATAXIA: IMPLICATIONS FOR CLINICAL RESEARCH

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ABSTRACT

Background: Friedreich ataxia (FRDA) is a rare inherited neurodegenerative disease for which there is presently no effective intervention. Natural history studies are integral to efforts to discover novel treatment approaches. How FRDA natural history cohorts compare with the general patient population and US population remains unreported. In addition, while clinical aspects of FRDA have been well described, the social and demographic features of the affected population serve a critical role in defining both the impact of the disease on patient lives and the areas in which future advances might be made.

Subjects and Methods: Subjects enrolled in a natural history study (n=608) provided geographic, demographic, and social information including educational attainment, employment, marital status, and living arrangements. Zip codes were used to identify residences as urban or rural according to a standardized classification of metropolitan and nonmetropolitan counties. Urban–rural distributions were compared between sites and between study cohort and both a general FRDA patient registry and the US population. Zip codes were used to measure distances between each subject's residence and study site. Travel distances were compared between sites.

Results: Study subjects were more urbanized compared with patients in a national registry and the overall US population. Urban–rural distributions and travel distances to care centers differed among study sites. A large majority of subjects pursued education after high school, although most were unemployed at the time of reporting and a large plurality had never been employed. Most subjects were unmarried, and a large portion of the cohort resided with parents after age 21 years.

Conclusions: The analysis suggests that FRDA carries implications beyond immediate health, affecting the individual's general social, economic, and lifestyle choices. Employment, marital status, and living arrangements are affected by the disease and provide potential indices for long-term evaluation of responses to medical intervention. Compared with the natural history study, the patient registry represents a population of patients with an urban–rural distribution more closely in line with the general US population. This discrepancy indicates the benefit of the online registry in connecting with rural-based patients. Differences in travel to each study site suggest inherent biases in clinical studies.

INTRODUCTION

Friedreich ataxia (FRDA) is an autosomal recessive disorder caused by mutations in the gene *FXN*.[1] Of people with the disorder, 98% have an expanded GAA (guanine-adenine-adenine) triplet repeat in both alleles, whereas the remaining patients carry an expanded GAA repeat on one allele and a point mutation or deletion on the other.[2] The length of the shorter GAA repeat correlates with age of onset (r=0.6–0.7).[3,4] The repeat is in the first intron, and its expansion decreases messenger RNA transcription and leads to a deficiency of the protein frataxin.[1] Similarly, point mutations in *FXN*

lead to the absence of functional frataxin.[2,5] Neurologic manifestations of FRDA are progressive and include ataxia, loss of coordination, loss of sensation, areflexia, and dysarthria. Affected individuals can also have scoliosis, cardiomyopathy, diabetes, pes cavus, bladder dysfunction, optic atrophy, and hypoacusis.[6–8] Cognitive function is traditionally believed to be minimally affected. Onset typically occurs in late childhood or early adolescence, but can be as late as the seventh decade of life.[9–11] At present, there is no approved treatment in the United States, although several clinical trials have been conducted in the past 5 years.[12–16]

Investigational drug trials in FRDA have been aided by the presence of several ongoing natural history studies that have collected broad data on the features of individuals with FRDA.[17,18] Most of the initial characterization of these patients has been directed to the neurologic aspects of FRDA. Understanding the clinical significance of neurologic change requires knowledge of the social and demographic features of disease and establishing the degree to which natural history (or clinical trial) cohorts reflect the general patient population. The present study examined questionnaire data from a US cohort of patients with FRDA enrolled in the Friedreich Ataxia Clinical Outcome Measures Study (FACOMS). Geographic features were analyzed using site-to-site comparison of the urban–rural distribution of the cohort and distance to designated care center. Urban–rural distribution of the cohort was also compared with that of the Friedreich's Ataxia Research Alliance (FARA) registry and the general US population. In addition, sociodemographic features including racial/ethnic definitions, living arrangements, marital status, education level, and employment trends of persons with FRDA were examined to define the social background upon which future advances might be made.

Subjects and Methods

Geographic Data

This study had the approval of each site's institutional review board, and participants provided written informed consent before enrolling. Subjects were asked for their zip code of residence at each study visit. Seven sites in the United States (8 institutions) provided zip codes for the present analysis, representing a cross-sectional cohort of individuals (n=608) with genetically confirmed FRDA: Children's Hospital of Philadelphia and University of Pennsylvania (site 1; 289 participants), University of

California Los Angeles (site 2; 183 participants), Emory University (site 3; 58 participants), University of South Florida (site 4; 34 participants), University of Chicago (site 5; 22 participants), University of Iowa (site 6; 16 participants), and Ohio State University (site 7; 6 participants).

To analyze the urban–rural distribution of the study cohort, for each zip code we generated the corresponding Federal Information Processing Standards (FIPS) county code, which uniquely identifies counties and county equivalents in the United States. Every 10 years, county codes are classified according to the Rural-Urban Continuum Code (RUCC), a scoring scheme that denotes a county's level of urbanization. Scores are determined by the US Department of Agriculture's Economic Research Service based on the population size of the county and the size of its immediate surrounding areas. Specifically, the RUCC subdivides counties into 3 metro and 6 nonmetro categories. The scores used in this study are based on the February 2013 metro–nonmetro delineations by the Office of Management and Budget (OMB).[19,20]

The categorization scheme is as follows. Metropolitan counties are defined by the OMB as either central counties with at least one densely settled urban entity of 50,000 people or more, or counties that are economically tied to core counties based on labor-force commuting. Metro counties receive scores of 1 through 3 based on the population residing in the metro area. Nonmetropolitan counties are located outside the boundaries of these metro areas, and are scored 4 through 9 based on the size of the total urban population in the county and the county's adjacency to at least one metro area.

Given the relatively small size of the natural history cohort, many sites reported fewer than 5 subjects in multiple RUCC-based categories. Consequently, the analysis classified study subjects as living in either a metropolitan county (scores 1–3) or a nonmetropolitan county (scores 4–9).[21,22] Three analyses were undertaken using these data. In the first analysis, a chi square analysis and Fisher exact test were performed to compare urban–rural distributions across 7 sites participating in the natural history study (Children's Hospital of Philadelphia and the University of Pennsylvania are combined as one study center). In the other 2 analyses, chi square testing was performed to

compare the entire study cohort to the FARA registry (n=1169) and to the general US population (n=308,745,538).[20]

Using the same zip code data, the distance between residence and care center (and study site) was approximated for each study subject. An analysis of variance (ANOVA) was performed to determine if subject access and proximity to designated care site differed among the 7 study sites.

Social and Demographic Data

Racial and ethnic background, level of education, area of employment, marital status, and living arrangements were recorded for each subject and updated at follow-up visits. For race and ethnicity, subjects could describe themselves as Hispanic/Latino, American Indian/Alaska native, Asian, black, Hawaiian/Pacific islander, or white. For education, subjects over 25 years of age were grouped into 1 of 6 categories: no high school diploma, high school diploma or GED attained, some college

completed without degree, associate degree attained, bachelor's degree attained, and graduate degree attained. Subjects over 21 years of age were grouped into 1 of 5 employment categories (labor, sales, service, management/professional occupation, or not in workforce), 1 of 3 marital status categories (never married, currently married, or previously married), and 1 of 6 living arrangement categories (independent, with parents, with spouse, with roommates, at a care facility, or other).

Results

Geographic Features of Cohort: Rural–Urban Distribution and Distance to Care Facility

From the cross-sectional cohort of 798 participants with FRDA, 608 reported US zip codes for residence. Based on the OMB metro–nonmetro demarcation, 90.1% of subjects (n=548) lived in a metropolitan county, and 9.9% (n=60) in a nonmetropolitan county (**Table 1**). By comparison, the FARA online registry contains 972

Table 1: Urban–Rural Distribution of Subject Residences

Sites (N)	Metro Residents,[a] N (%)	Nonmetro Residents,[b] N (%)
Site 1 (289)	261 (90.3)	28 (9.7)
Site 2 (183)	170 (92.9)	13 (7.1)
Site 3 (58)	50 (86.2)	8 (13.8)
Site 4 (34)	31 (91.2)	3 (8.8)
Site 5 (22)	21 (95.5)	1 (4.5)
Site 6 (16)	10 (62.5)	6 (37.5)
Site 7 (6)	5 (83.3)	1 (16.7)
Total (608)	**548 (90.1)**	**60 (9.9)**
FARA patient registry (1169)	**972 (83.1)**	**197 (16.9)**
US population (308,745,538)[c]	**262,452,132 (85.0)**	**46,293,406 (14.9)**

FARA = Friedreich's Ataxia Research Alliance; Site 1 = Children's Hospital of Philadelphia/University of Pennsylvania; Site 2 = University of California Los Angeles; Site 3 = Emory University; Site 4 = University of South Florida; Site 5 = University of Chicago; Site 6 = University of Iowa; Site 7 = Ohio State University.

[a] Residents of metropolitan counties, defined by the Office of Management and Budget as central counties with at least one densely settled urban entity of 50,000 people or more, or counties that are economically tied to core counties based on labor-force commuting. Results reflect most recent county delineations (2013).

[b] Residents of nonmetropolitan counties, defined by the Office of Management and Budget as counties located outside the boundaries of metro areas.

[c] US population size represents 2010 Census Bureau data; metro-nonmetro results reflect most recent county delineations (2013).

metropolitan-based subjects (83.1%) and 197 nonmetropolitan-based subjects (16.9%). The United States consists of 262,452,132 metropolitan-based citizens (85.1%) and 46,293,406 nonmetropolitan-based citizens (14.9%). Chi square analysis showed that the study cohort was more urbanized than both the FARA registry (*P*=0.00007) and the general US population (*P* = 0.0004). Interestingly, the distributions were similar between the FARA registry and the US population, potentially showing the advantage of online registry enrollment. The registry is accessible and patient-

entered, in contrast to in-person natural history enrollment at clinics where more detailed and curated data may be entered by a physician.

By chi square analysis, significant differences were found in urban–rural distributions within the natural history study cohort across sites (*P*=0.008). The largest gaps between expected and actual urban–rural counts occurred in sites 2 and 6; site 2 was the most urbanized (92%), and site 6 was the least urbanized (62.5%). There were 4 expected counts that were less than 5: numbers
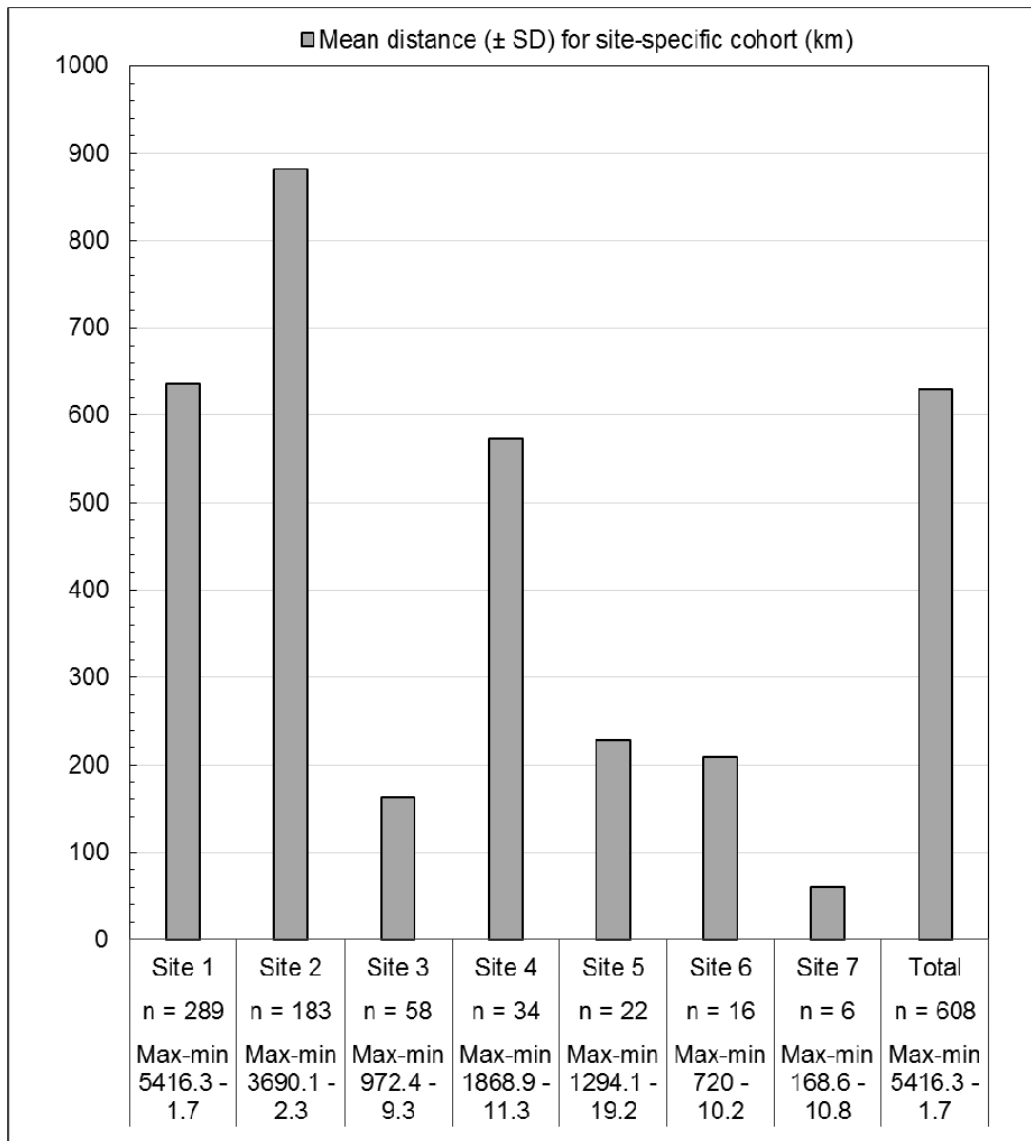
Figure 1: Distance of travel to study site from subject residences.

SD=standard deviation. Site 1=Children's Hospital of Philadelphia/University of Pennsylvania; Site 2=University of California Los Angeles; Site 3= mory University; Site 4=University of South Florida; Site 5=University of Chicago; Site 6=University of Iowa; Site 7= hio State University.

of nonmetro subjects from sites 4, 5, 6, and 7. Because chi square analysis is unreliable when expected values are less than 5, a Fisher exact test was also performed. Consistent with the chi square result, the exact test highlighted a difference between sites (P=0.023).

Overall, subjects traveled approximately 630 km from home residence to study site and care center. The maximum distance traveled was over 5416 km and the minimum distance was less than 2 km (**Figure 1**). To address the absence of a normal distribution in the sample, a one-way ANOVA was performed using the log transformations of the distances to care center. A between-groups difference was found for distance to care center (F[6,601] = 7.50; P< 0.0001). Most of the site-specific cohorts traveled a distance less than the study-wide mean to their respective care centers, with site 7 subjects presenting the shortest mean distance (60 km) followed by site 3 (163 km). Site 2 subjects displayed the largest mean distance to care center (882 km). Homogeneity of variance was not met, however, as Bartlett's chi square analysis revealed a significant difference in variance of results for each site (X^2[6] = 16.2; P<0.013). Because homogeneity is an assumption for an ANOVA, a Kruskal-Wallis one-way ANOVA was conducted using the log transformations of the distances. A significant difference across sites was detected (X^2[6]=51.264; P=0.0001), supporting the validity of the previous result.

Demographic Features of Cohort: Race/Ethnicity, Education, Employment, Marital Status, and Living Arrangements

The vast majority of subjects (93.2%) described themselves as white (**Table 2**). This finding is not surprising, as FRDA generally affects people of European and Middle Eastern descent.[23] Most of the remaining subjects were either Hispanic/Latino or Asian.

Nearly 75% of study subjects 25 years of age and older pursued education beyond high school (**Figure 2**). By comparison, 58.6% of US citizens in this age range pursued education after high school. Study subjects and US citizens showed similar trends in educational attainment with the exception of 2 benchmarks: completion of high school and completion of undergraduate college. The percentage of study subjects who earned only a high school diploma or GED was less than half of the percentage for US citizens, with a 15-point margin (14.4% vs 29.7%). For the percentages of those earning a bachelor's degree, study subjects surpassed US citizens by a 17-point margin (37.9% vs. 20.2%). The comparison between subjects and white non-Hispanic US citizens followed a similar trend, with 63.4%

Table 2: Racial/Ethnic Background of Study Cohort

Race/Ethnicity	N	Percent of Cohort
White	717	93.2
Hispanic/Latino	25	3.3
Asian	19	2.5
Black	8	1.0
American Indian/Alaska native	8	1.0
Hawaiian or other Pacific islander	4	0.5

Table 3. Occupational Features of Subjects Over Age 21 Years

Occupation	Most of Career		Current	
	N	Percent of cohort	N	Percent of cohort
Management/ Professional	162	35.9	89	19.4
Service	42	9.3	16	3.5
Sales	43	9.5	18	3.9
Labor	25	5.5	12	2.6
Not in workforce	179	39.7	324	70.6
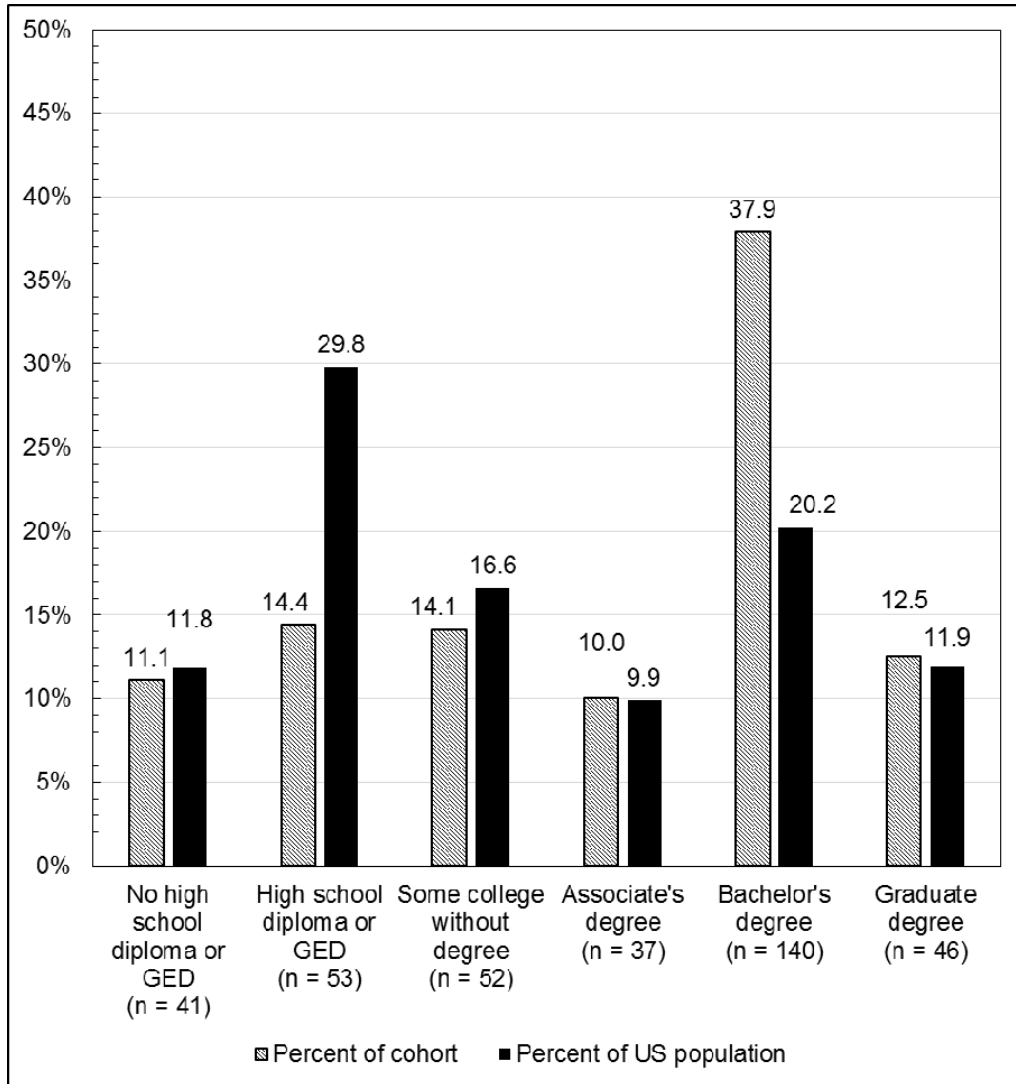
Figure 2. Level of education attainment in subjects over age 25 years: study cohort vs US population.

of the latter pursuing education after high school, 22.3% earning bachelor's degrees, and 13.3% earning graduate degrees (data not shown).[24]

Approximately 71% of study subjects over the age of 21 years described themselves as not currently in the workforce (**Table 3**). At the time of reporting, 19.4% held a management or professional position at their most recent study visit; the remaining subjects were in sales, service, and labor. When subjects were asked in which area of the workforce they had spent the majority of their career, nearly 40% reported never entering the workforce while 35.9% reported management and professional positions.

Of those subjects over the age of 21 years, 60.4% were unmarried (had never married), 30.1% were married, and 9.5% were previously but no longer married, divorce being the most common reason for the terminated marriage (**Table 4**). On average, unmarried subjects were approximately 15 years younger than their married and previously married counterparts, while married and previously married subjects were close to the same age. Among subjects over 21 years of age, 32.3% reported living with parents, 30.6% with a spouse, and 22.6% independently (**Table 4**). On average, subjects living with

parents or roommates were approximately 10 years younger than those living independently and over 15 years younger than those living with a spouse. These trends show that while patients and nonpatients follow a similar progression of life (ie, changing residence and marital status over time), the disease may have the effect of slowing this progression, although disease severity may play a part as well.

Discussion

The natural history data on FRDA subjects collected here characterize not the medical features of FRDA, but rather where patients live and their social situation. The FRDA population from the FACOMS natural history study is urbanized in a manner that resembles both the FARA registry and the US population. Although our patient cohort is slightly more localized in metro counties than are persons in either the registry or the general US population, all 3 groups are predominantly urban-based at rates above 80%. The FARA registry and the US population are approximately equal in their levels of urbanization, so the difference between the natural history cohort and the general population suggests a modest recruitment bias in the study likely based on the locations of the sites. Recruitment into the natural

Table 4. Marital Status and Living Arrangements of Subjects Over Age 21 Years

Marital Status	N	Percent of Cohort	Mean Age, years
Unmarried	281	60.4	31
Married	140	30.1	47
Previously married	44	9.5	45
Living Arrangement	N	Percent of Cohort	Mean Age, years
With parents	150	32.3	28
With spouse	142	30.6	46
Independently	105	22.6	38
With roommates	26	5.6	29
Care facility/caregiver	10	2.2	48
Other	41	8.8	36

history study (which requires annual visits to 1 of 7 study locations, all of which are in urban centers) may be more difficult in rural areas, whereas patient-directed online registration in the FARA database can expand more readily beyond metro communities. Patient-directed and -entered data can be useful for locating and identifying a broader base of individuals when dealing with a rare disease like FRDA. The FARA database may include rural residents with less access to the major care centers participating in the natural history study. To reach such subjects in clinical trials, which may be important due to the rare nature of FRDA, it may be necessary to adopt protocols that allow components of the study to be performed locally and provide support to reduce the burden of traveling to more centrally located sites.

Populations also vary across natural history sites in both urbanization and distance of travel to study sites. This variation reflects the geographic distribution of sites and population. The sites with the most urban-based cohorts (sites 1, 2, and 5) are all located in 3 of the most populous metropolitan areas in the country. Average distance of travel is highest for study subjects at sites 1 and 2, which also account for the 2 largest groups of subjects in the overall study cohort. While such differences are sustainable for natural history studies that require annual visits to clinic, they burden the subjects and could create inherent biases in clinical trials that involve more frequent in-clinic follow-up. The overt differences could reflect varying levels of exhaustion from travel; different levels of financial support needed for study participation; different exposures and environmental factors in subjects from urban and non-urban areas; and different demographic and genetic backgrounds.

Our analysis also reveals that FRDA does not impair primary education and the pursuit of learning after high school. Individuals with FRDA are more likely than the general US population to pursue education after attaining a high school diploma or GED, and they attain bachelor's degrees at almost twice the rate that US citizens do. On the other hand, the disease does affect employment outcomes, likelihood of marriage, and housing status for patients. Most study subjects described themselves as currently jobless and unmarried. The majority of employed subjects reported holding professional and management positions. The minority of subjects holding jobs in sales, service, and labor may reflect levels of mobility, travel, and physical exertion that those jobs

demand, compared with management positions. Future studies can use these findings to determine the extent that these social indices correspond with disease severity and progression, or whether specific disability services might be better utilized by individuals with FRDA.

The large portions of the cohort who were jobless, unmarried, and living with parents identify an influence of the disease on social aspects of living, which may be useful as potential long-term outcome measures for clinical interventions. Their feasibility would depend on the rate at which these measures can change over time in response to medical intervention. Changes to employment, marriage, and living arrangements may demonstrate clinically meaningful improvements, but they also represent personal decisions that are subjective according to lifestyle and are heavily confounded by nonmedical factors. In a study with a sufficiently long follow-up period, marital status, living habits, and employment could provide possible indices to examine the degree to which medical intervention impacts patient lives.

The current analysis is limited in several ways. The analysis of distance to care center between study sites is limited by the lack of homogeneity of variance, reflecting the substantial differences in variance across the study locations. When comparing geographic features between the cohort and the US population, other demographic differences such as race and ethnicity (though FRDA is restricted to individuals of European decent), patient or family socioeconomic status, home circumstances, and family size were not included. Additionally, analysis of the demographic features of the cohort does not account for degree of disability. Assessment of a well-defined psychosocial element or prevalence of depression and mental illness, though these are not primary features of FRDA, could help to clarify whether social limitations due to disease are largely physical, emotional, or both. Age is also an important factor, because it is a correlate of disease severity, and needs to be more thoroughly described in the analysis. For the assessment of education, marriage, and living status, the analysis focused only on subjects over the age of 25 years. The analysis of employment data focused on subjects over the age of 21 years to account for early entry into the workforce. These constraints create biases in the data; for example, some of those individuals reporting to have never entered the workforce may still be attending school, and those under the age of 25 years and holding a

bachelor's degree were not included in the evaluation of educational attainment. Analyzing educational attainment in subjects 21 years and older reveals only minor variation in rates compared with the older subset of the cohort (data not shown). Comparing groups of subjects based on age, we found that those living with parents were younger than those living independently, and unmarried subjects were younger than their married and previously married counterparts. These match the natural evolution of events in most people's lives, but the differences in marriage and living status demonstrate the effect the disease has on these characteristics of life. The larger number of married and independently living subjects could also reflect genetic status and age of onset, as later-onset subjects generally have less disability. These issues notwithstanding, the present study offers novel insight into various elements of the disorder, which could prove useful for clinical research design and postmarketing studies.

CONCLUSIONS

Our analysis suggests that individuals with FRDA are highly urbanized but still traveling significant distances to participate in research studies. Because the study population was more urban-based than the FARA patient registry, large interventional studies may benefit by expanding recruitment strategies beyond in-person clinical visits and reducing the travel burden on prospective study subjects. The data also indicate that adult patients with FRDA are not substantially limited from pursuing higher education, but they are more likely to be unemployed and unmarried. If follow-up studies demonstrate that these trends are the effects of disease and not of personal choice, they may represent long-term parameters for evaluating the impact of future medical interventions. Meanwhile, further analysis of living conditions should focus on how educational attainment, employment, marriage, and living arrangements vary with age of onset, disease severity, ambulatory status, patient-reported health status, and presence or absence of clinical comorbidities including heart disease and diabetes. In addition, the geographic differences between site-specific cohorts shows that location and distance to care and study centers need to be accounted for when assessing clinical outcomes, including responses to medical interventions.

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References

1. Campuzano V, Montermini L, Molto MD, et al. Friedreich's ataxia: Autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science.* 1996;271(5254):1423-1427.

2. Bidichandani SI, Ashizawa T, Patel PI. Atypical Friedreich ataxia caused by compound heterozygosity for a novel missense mutation and the GAA triplet-repeat expansion. *Am J Hum Genet*. 1997;60(5):1251-1256.

3. Durr A, Cossee M, Agid Y, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med*. 1996;335(26):1169-1175.

4. Lynch DR, Farmer AM, Tsou AY, et al. Measuring Friedreich ataxia: complementary features of examination and performance measures. *Neurology*. 2006;66(11):1711-1716.

5. Cossee M, Durr A, Schmitt M, et al. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. Ann Neurol. 1999;45(2):200-206.

6. Lynch DR, Farmer JM, Balcer LJ, et al. Friedreich ataxia: effects of genetic understanding on clinical evaluation and therapy. *Arch Neurol*. 2002;59(5):743-747.

7. Pandolfo M. Friedreich ataxia. *Arch Neurol*. 2008;65 (10):1296-1303.

8. Regner SR, Lagedrost SJ, Plappert T, et al. Analysis of echocardiograms in a large heterogeneous cohort of patients with Friedreich ataxia. *Am J Cardiol*. 2012;109 (3):401-405.

9. Friedman LS, Farmer JM, Perlman S, et al. Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design. *Mov Disord*. 2010;25(4):426-432.

10. Pandolfo M. Molecular pathogenesis of Friedreich ataxia. *Arch Neurol*. 1999;56(10):1201-1208.

11. Galimanis A, Glutz L, Spiegel R, et al. Very-late-onset Friedreich ataxia with disturbing head tremor and without spinal atrophy—case report. *Mov Disord*. 2008;23(7):1058-1059.

12. Lynch DR, Perlman SL, Meier T. A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. *Arch Neurol*. 2010;67(8):941-947.

13. Boesch S, Sturm B, Hering S, et al. Neurological effects of recombinant human erythropoietin in Friedreich's ataxia: a clinical pilot trial. *Mov Disord*. 2008;23(13):1940-1944.

14. Schols L, Zange J, Abele M, et al. L-carnitine and creatine in Friedreich's ataxia. A randomized, placebo-controlled crossover trial. *J Neural Transm (Vienna)*. 2005;112(6):789-796.

15. Velasco-Sanchez D, Aracil A, Montero R, et al. Combined therapy with idebenone and deferiprone in patients with Friedreich's ataxia. *Cerebellum*. 2011;10(1):1-8.

16. Tsou AY, Friedman LS, Wilson RB, et al. Pharmacotherapy for Friedreich ataxia. *CNS Drugs*. 2009;23(3):213-223.

17. Regner SR, Wilcox NS, Friedman LS, et al. Friedreich ataxia clinical outcome measures: natural history evaluation in 410 participants. *J Child Neurol*. 2012;27(9):1152-1158.

18. Filipovic Pierucci A, Mariotti C, Panzeri M, et al; EFACTS Study Group. Quantifiable evaluation of cerebellar signs in children. *Neurology*. 2015 Mar 24;84(12):1225-1232.

19. US Department of Agriculture, Economic Research Service. Rural-urban continuum codes. http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx#.UYJuVEpZRvY. Updated May 10, 2013. Accessed July 1, 2015.

20. US Census Bureau. Current lists of metropolitan and micropolitan statistical areas and delineations. http://www.census.gov/population/metro/data/metrodef.html. Revised May 6, 2013. Accessed July 1, 2015.

21. Weaver A, Himle JA, Taylor RJ, et al. Urban vs rural residence and the prevalence of depression and mood disorder among African American women and non-Hispanic white women. *JAMA Psychiatry*. 2015;72(6):576-583.

22. Allen JA, Perrine CG, Scanlon KS. Breastfeeding supportive hospital practices in the US differ by county urbanization level. *J Hum Lact*. 2015;31(3):440-443.

23. Labuda M, Labuda D, Miranda C, et al. Unique origin and specific ethnic distribution of the Friedreich ataxia GAA expansion. *Neurology*. 2000;54(12):2322-2324.

24. US Census Bureau. Education attainment. http://www.census.gov/hhes/socdemo/education/data/cps/2014/tables.html. Revised January 5, 2015. Accessed July 1, 2015.

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