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Predictors of progression in patients with Friedreich ataxia

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Abstract

Friedreich ataxia is an inherited, progressive, neurodegenerative disorder that is clinically heterogeneous. It is caused by a trinucleotide (GAA) repeat expansion resulting in frataxin loss and oxidative stress. We assessed clinical features including the development of cardiomyopathy and scoliosis and disease progression including loss of ambulation and interference with activities of daily living relative to the length of the GAA repeat, age of onset, and age of diagnosis in a retrospective cohort study of 61 genetically confirmed patients. The use of antioxidants such as vitamins, dietary supplements, and idebenone was also examined. Linear regression and Cox proportional hazard models assessed predictors to disease milestones. The shorter GAA allele accounted for part of the variability in the age of diagnosis (46%) and less in the age of onset (27%). Multivariate analysis demonstrated that age at diagnosis, which may incorporate other genetic and environmental factors, is more important than GAA length in predicting cardiomyopathy, scoliosis, and disease progression.

Keywords

Friedreich ataxia; genotype; phenotype; GAA expansion; medication

INTRODUCTION

Friedreich ataxia (FRDA) is the most common form of autosomal recessive ataxia 1. Clinical features include progressive ataxia, weakness, decreased sensation, absent reflexes in the lower extremities, dysarthria, usual onset before 25 years of age, and a family history consistent with autosomal recessive inheritance^{2 3}. Other frequent findings include hypertrophic cardiomyopathy, scoliosis, and glucose intolerance or diabetes³. There is marked clinical variability both within and between families. Some of this variability can be accounted for by the nature of the causative genetic mutation.

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CONFLICT OF INTEREST

There are no competing interests involved.

FRDA is caused by an unstable GAA trinucleotide repeat expansion in intron 1 of the X25 gene located at chromosome 9q13 that encodes the protein frataxin. The expansion is homozygous in approximately 96% of patients^{4 5}; the remaining patients carry a GAA expansion on one allele and an inactivating mutation in the coding region of the other allele. The longer the GAA expansion, the lower the levels of the corresponding mRNA transcript and protein^{4 6}. Loss of frataxin results in decreased iron-sulfur cluster synthesis, increased mitochondrial iron accumulation, and susceptibility to oxidative damage^{7 8}. Based on these observations, antioxidants have been explored as a potential therapy⁹.

The size of the GAA repeat expansion correlates with the onset and severity of disease^{10–12}. In particular, the length of the smaller allele (GAA1) is more predictive of these features than the length of the larger allele (GAA2)^{10 11 13}. However, while this correlation between GAA1 and clinical features has been previously established, the onset and progression of gait difficulty and the impact on activities of daily living have not been fully explored. The purpose of this retrospective cohort study was to assess factors that may be predictive for the clinical progression of the disease. Of particular interest is the progression to different clinical milestones, such as the use of assistive devices, and the probability of developing other associated medical conditions, such as cardiomyopathy and scoliosis, as a function of genetic status and disease onset. In addition, since the use of antioxidants has been suggested as a potential therapy, the use of vitamins, supplements, and idebenone was also examined.

METHODS

Subjects

Data were collected during subject participation in safety studies of the drug idebenone conducted at the NIH Clinical Center (Bethesda, MD) with the approval of the National Institute of Neurological Disorders and Stroke Institutional Review Board under IND 62,926. These trials were registered with ClinicalTrials.gov, numbers NCT00015808 and NCT00078481 and written consent was obtained before study participation. Subjects were enrolled from the United States and Canada and stratified into three age categories: adults, adolescents, and children. Sixty-one genetically confirmed (CLIA-approved laboratories) FRDA subjects (including three sib pairs) or their parents were interviewed. Exact trinucleotide repeat expansion data were not available for three patients, and another three patients had a genetically confirmed point mutation in the coding region of the FRDA gene. Only demographic and clinical features were analyzed for those without expansion data. In those subjects with a point mutation, the allele with the expansion was categorized as GAA1, since point mutations have generally been found to be null, and clinical severity related to the length of the expanded allele¹⁴.

Interview

Participants were asked a series of telephone-based questions covering demographic information, medical history, genetic information, use of assistive devices, and use of medications, vitamins, or herbal supplements. The standard questionnaire included multiple choice, Likert-scaled, and open-ended questions. Minors were given the option of having a parent complete the interview on their behalf, and responses from minors were also reviewed with a parent or guardian for accuracy.

Statistical Analysis

Descriptive statistics were computed to evaluate the distribution of the following variables: age, gender, race, ethnicity, diagnosis, medication usage, allele length, age at symptom onset, age at which difficulty with walking was noticed, age at which interference with

activities of daily living (ADLs) was noticed, and age at which assistive devices were first used. Interference with ADLs was defined as having to modify a standard daily activity (bathing, dressing, eating, transferring, toileting/continence) because of level of disability. Difficulty walking was defined as having to modify daily ambulation, such as using walls for support, avoiding specific activities, or use of any assistive device. Correlations between allele length and age for each milestone were computed.

Cox univariate and multivariate survival models for time to event data were implemented using the survival package of the R program (version 2.0.1)¹⁵. Results for time to scoliosis and time to cardiomyopathy required the use of interval censored data techniques, as the actual dates for these diagnoses were unknown. Cardiomyopathy was diagnosed based upon echocardiographic evidence of cardiac wall thickness as determined by the subject's local cardiologist. The presence of scoliosis was determined based upon clinical examination by the subject's local neurologist or primary care physician. Standard multivariate linear regression analysis for uncensored outcomes, i.e., outcomes not requiring survival models, was used to model the log-transformed age of diagnosis as a function of log-transformed short and long allele lengths using the linear models package of the R program. Log transformations were more consistent with the assumptions of a constant variance and a linear relationship that are associated with linear regression models.

RESULTS

Clinical milestones and correlation to GAA length

Demographics, GAA lengths, and clinical features of the study population are listed in Table 1. The mean age of symptom onset was 11.1 years and the mean age at diagnosis was 13.4 years. While the mean age for wheelchair use was 20.3 years, subjects reported difficulty with ambulation as early as 12.1 years and interference with ADLs requiring adaptive behavior and assistance by 15.4 years. The length of GAA1 had a significant inverse correlation ($p < 0.001$) with patients' age at diagnosis, age at symptom onset, age at difficulty walking, age at which difficulty walking interfered with ADLs, and age at which the patients began using an assistive ambulation device, whereas GAA2 length had no correlation (Table 2). Analysis using the sum of the two allele lengths did not increase the strength of the correlation beyond that of GAA1 alone. Additionally, a multivariate linear regression analysis using both GAA1 and GAA2 as variables revealed a significant effect of GAA1 (regression coefficient = -0.98 , $p < 0.001$) in predicting the age at diagnosis, whereas GAA2 length had no predictive value (regression coefficient = -0.10 , $p = 0.71$). Additional analysis show that GAA1 accounts for 46% of the variability in the age at diagnosis and 27% of the variability in the age of onset.

GAA1 and age of diagnosis as predictors of associated medical conditions and functional disability

Since GAA1 alone does not fully explain the variability in the age of onset or diagnosis, it is likely that other environmental and/or genetic factors may have an effect on the clinical phenotype. If age at onset or diagnosis includes the effects of these other factors, then it may more accurately predict the clinical course than GAA1. For each of four clinical outcomes (time to wheelchair use, time to interference with ADLs, time to scoliosis, and time to cardiomyopathy) three possible predictive variables were considered in univariate and multivariate models: age at diagnosis, age at first symptom onset, and GAA1 length. Univariate analysis shows whether a predictive variable has a significant effect on the outcome, while multivariate analysis assesses which variables have the strongest predictive power that is independent of the other explanatory variables' effects. Univariate results (Table 3) were significant for both age at diagnosis and age of onset for all four clinical

outcomes ($p < 0.05$); however, age at diagnosis was a better predictor than age of onset in each case, based on their respective contributions in a multivariate model. Age at diagnosis is also a more definitive clinical milestone since it is not subject to recall bias. For example, patients may not attribute early, subtle symptoms to disease, or associate onset with seeking medical attention which may have been delayed, and consequently may not be able to accurately define when onset occurred. Also, the high correlation between age at diagnosis and age of onset (Pearson correlation of 0.96, $p < 0.001$) made the inclusion of both variables inadvisable due to high multicollinearity. We therefore chose GAA1 length and age at diagnosis as covariates in our final Cox multivariate survival model for each outcome (Table 3). The multivariate survival model p-values for GAA1 length were not significant at the 0.05 level, but the variable was retained, as its p-values were suggestive of true differences ($p \leq 0.11$ for two of the four outcomes) and the variable had strong univariate results ($p < 0.001$ for all four outcomes).

Of the 58 patients with short allele length data available, 33 (57%) had a history of cardiomyopathy and 44 (76%) had scoliosis. In the multivariate survival model, the age at diagnosis was significantly associated with development of cardiomyopathy ($p < 0.001$, effect on hazard rate = 0.78) and scoliosis ($p < 0.001$, effect on hazard rate = 0.83), whereas GAA1 was not (Table 3). Hazard rate is approximately the probability of developing a condition in a one-year period, given that the individual did not have that condition at the beginning of the year. Thus, increasing age at diagnosis is associated with decreased risk of cardiomyopathy and scoliosis.

Similarly, a total of 48 subjects (83%) reported interference with ADLs and 34 subjects (59%) reported using a wheelchair with some frequency, although not all participants categorized themselves as wheelchair-bound. Multivariate survival analysis of risk factors for ADLs and wheelchair use showed that age of diagnosis had strongest impact on impairment of ADLs ($p = 0.0045$, effect on hazard rate = 0.89) and wheelchair use ($p = 0.0051$, effect on hazard rate = 0.84), while GAA1 length showed a univariate relationship but lost its statistical significance in this model with two explanatory variables. Thus, the age of diagnosis is a more predictive variable than GAA1 when considering both variables relative to these clinical features.

Using this model, the probability of remaining ambulatory for an individual can be estimated taking into account GAA1 and age of diagnosis (Figure 1). The solid line based on the sample median short allele length (752) and median age of diagnosis (10 years) shows the estimated probability of remaining free of wheelchair use as age changes, e.g., at age 13 there is a 78% chance, at age 20 a 25% chance and at age 30 only a negligible chance. Two other curves are shown for allele length of 752 and age of diagnosis of 7, and allele length of 752 and age of diagnosis of 14. Such curves can be drawn for various combinations of short allele length and age of diagnosis. Table 4 shows estimated ages associated with 50% likelihood of wheelchair use according to different allele lengths and ages. The chosen lengths and ages correspond to the 20th percentile, median, and 80th percentile length and age of diagnosis in our sample. In addition to the estimated age corresponding to 50% chance of wheelchair use, 95% confidence intervals for the actual likelihood of wheelchair use at that age are given. While the table shows that age to wheelchair use declines as allele length increases and age to diagnosis decreases, the age of diagnosis has a greater impact than GAA1.

Use of Vitamins, Dietary Supplements, and Medication

Ninety percent of subjects report taking antioxidants; the majority had taken either coenzyme Q10 (84%, mean duration 33.75 months) and/or vitamin E (84%, mean duration 41.13 months), while the percentage of patients that had used other vitamins and dietary

supplements such as creatine, vitamin C, N-acetyl cysteine, and alpha lipoic acid was smaller (<21% for all). Twenty-two participants (36%), ranging in age from 9 to 68 years (mean = 20.1 years) had independently taken idebenone for more than one month (mean duration 19.5 months), while 14 participants (23%) were taking idebenone at the time of the survey (age range 9 to 19 years, mean age 13.3 years, mean duration 22.6 months).

DISCUSSION

In this study, we retrospectively examined the ages at which FRDA patients first had difficulty with ambulation, used assistance devices, and had interference with ADLs as related to GAA1 repeat length, age of onset, and age of diagnosis. We also determined the incidence of two common medical conditions in FRDA, cardiomyopathy and scoliosis, in relation to these same factors. Our results indicate that while GAA1 length is significantly correlated to several clinical milestones in a univariate model, age at disease diagnosis is more predictive of disease progression to events such as loss of ambulation and interference with ADLs. Additionally, the majority of patients reported previous or current use of antioxidants.

While our participants' different experiences with clinical trials, medications, antioxidants, and other treatments may make their progression different from those in other studies, the average age of onset and allele lengths reported in this study are within range of what has been previously reported in other studies^{10 11 13 16-18}. The average age of first wheelchair use (20.3 years) is slightly lower in our study than in previous studies although "use" in our study was not defined as wheelchair dependence. Thus, many subjects in our study population may have opted for wheelchair use for convenience and safety over the risks associated with independent ambulation. Our results are thus consistent with the studies that report the age at being wheelchair-bound to range in the early to mid 20's^{10 11 19}.

Participants in this study were diagnosed at a mean age of 13.4 years, while they had onset of symptoms at a mean age of 11.1 years and had difficulty walking at a mean age of 12.1 years. This represents an average lag of 1-2 years from symptom onset to diagnosis. Not surprisingly, the five of our participants with an affected sibling were all diagnosed when they first developed symptoms. While initial symptoms may be subtle, timely genetic diagnosis is important not only to alleviate uncertainty in the face of physical decline, but also to facilitate participation in clinical therapeutic studies to potentially delay the progression or mitigate disease manifestations, particularly where earlier treatment(s) may be more likely to be effective.

The negative correlation between GAA1 length and age at diagnosis (-0.671 , $p < 0.001$) indicates that patients with shorter GAA1 lengths are diagnosed later than patients with longer repeats. Additionally, the multivariate analysis performed for age at diagnosis in relation to GAA1 (regression coefficient = -0.98 , $p < 0.001$) and GAA2 length (regression coefficient = -0.10 , $p = 0.71$) indicates that the length of the short allele is of primary influence in determining age of diagnosis and the longer allele does not have an additional contribution, in agreement with previous studies^{13 18 19}. We found that a 10% increase in GAA1 length is associated with a 10% decrease in the age of diagnosis on a logarithmically transformed scale. For example, an individual with a GAA1 length of 700 has an average age of diagnosis of 13.0 years, while an individual with a GAA1 length of 770 has an average age of diagnosis of 11.7 years. Two previous studies noted that GAA1 length accounted for 61% and 50% of the variability in age of onset^{13 20} whereas in our study GAA1 accounts for only 27% of the variability in age at onset and 46% of the variability in age at diagnosis. Thus, other genetic and/or environmental factors likely have an effect on age of disease diagnosis, which in turn is more predictive of disability according to our

findings. Although, age at disease diagnosis does not directly influence the manifestations of the disease, it is a variable that is a useful predictor of phenotypic severity.

We also considered the effect of allele length and age at diagnosis on other systemic manifestations and clinical milestones of FRDA. Multivariate survival analysis showed a significant association of age at diagnosis with cardiomyopathy, scoliosis, interference with ADLs, and wheelchair use (Table 3). Our results indicate that a one-year increase in the age at diagnosis decreases the hazard rate for cardiomyopathy by 22%. Similarly, a one-year increase in diagnosis age is associated with a 17% decrease in the hazard rate for scoliosis and an 11% decrease in the hazard rate for ADLs. Although additional factors acting on the clinical variability remain unexplained, our data suggest that age at diagnosis may included some of these other factors as well as the effect of GAA1 length on these outcomes.

In addition to interference with ADLs, loss of ambulation is an important clinical milestone in the disease progression of FRDA. This study showed that both GAA1 length and age at diagnosis are statistically significant factors predictive of wheelchair use, though when taken together in a multivariate model, age at diagnosis proved to be the only significant variable predicting loss of ambulation. However, the p-value for GAA1 in the multivariate model showed a trend toward effect, suggesting that GAA1 does influence disease milestones. Based on these data, we have been able to develop predictive curves for loss of ambulation, taking into consideration both age of diagnosis and GAA1 (Figure 1 and Table 4). The confidence intervals for individual curves are relatively wide, indicating these predictive patterns have substantial uncertainty, but do provide insight into the predictive value of these variables and the probable time course to loss of ambulation.

There has been increasing interest in antioxidants as an approach to treatment for FRDA since oxidative stress and respiratory chain defects and have been implicated in the clinical manifestations of the disease^{9 21-23}. We found that the majority of our study patients have taken antioxidants for varying durations. While 36% (mean age 20) of all participants had taken idebenone independent of trial participation, only 23% (mean age 13) were taking idebenone at the time of the interview, consistent with a previous study²⁴. Idebenone treatment has been shown to reduce cardiac wall thickness and since younger patients are more likely to have cardiomyopathy, they may continue to take the medication in hopes of benefiting the cardiomyopathy in the absence of outward benefit. Cost and availability likely play roles in the decision to use antioxidants. Sixty-seven percent (CoQ10) and 77% (vitamin E) of participants were using these two more cost-efficient, readily available antioxidants at the time of the interview, higher than in another study²⁴. Our study was unable to determine if antioxidant therapy between users and nonusers affected clinical outcome or progression, as the general use and length of use for several supplements was ascertained in the absence of concurrent follow-up.

Defining the factors that play a role in disease development and progression in FRDA is essential to understanding this condition. In this study, we have shown that, when factoring in additional explanatory variables, age at diagnosis is the more predictive variable for disease progression, possibly for its ability to account for other genetic and environmental factors that could influence symptom progression. Additionally, the large majority of patients in this study have used vitamins, dietary supplements, or antioxidants. Understanding patient use may prove important for future clinical studies, and ultimately treatments for Friedreich ataxia. The impact of these supplements on disease progression is unknown, and could potentially affect what we have come to know about the natural history of the condition.

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Figure 1. The estimated probability of a patient being ambulatory with a GAA1 length of 752 given three different ages of diagnosis.

Table 1

Demographic and Clinical Features

Males, No. (%)	33 (54)
Age in years, mean (SD)	20.8 (12.8)
GAA length-allele 1, mean (SD)	703 (201)
GAA length-allele 2, mean (SD)	940 (177)
Ambulatory, No. (%)	27 (44)
Cardiomyopathy, No. (%)	33 (54)
Scoliosis, No. (%)	44 (72)

Table 2

Correlations between allele lengths and clinical milestones

Clinical Milestones	N	Mean, y (SEM)	Range	GAA1 Correlation (p-value)	GAA2 Correlation (p-value)
Age of Initial Symptom	61	11.1 (1.1)	2-50	-0.61 (<0.001)	-0.18 (n.s.)
Age of Diagnosis	61	13.4 (1.4)	4-65	-0.67 (<0.001)	-0.10 (n.s.)
Age of Difficulty with Walking	56	12.1 (1.3)	2-60	-0.68 (<0.001)	-0.08 (n.s.)
Age of Interfering ADLs	48	15.4 (1.3)	5-56	-0.62 (<0.001)	-0.22 (n.s.)
Age of Using Any Device	41	18.7 (2.0)	6-64	-0.74 (<0.001)	-0.17 (n.s.)
Age of Using Cane	10	24.3 (3.4)	9-36	-0.68 (0.062)	-0.28 (n.s.)
Age of Using Walker	22	20.0 (2.9)	7-64	-0.54 (0.015)	-0.15 (n.s.)
Age of Using Wheelchair	34	20.3 (2.2)	7-67	-0.69 (<0.001)	-0.15 (n.s.)
Age of Other Devices or Assistance	17	20.2 (3.3)	6-56	-0.75 (<0.001)	-0.54 (n.s.)
Presence of Cardiomyopathy *	35	NA	NA	0.56 (<0.001)	0.12 (n.s.)
Presence of Scoliosis *	46	NA	NA	0.04 (n.s.)	-0.21 (n.s.)

* The p-values for cardiomyopathy and scoliosis correlations were computed using exact statistical methods with values of 1 for presence of illness and 0 otherwise.

Multivariate analysis of risk factors for developing associated clinical conditions of Friedreich's ataxia

Table 3

Condition	N	Variable	Univariate P-value	Multivariate P-value	Multivariate Effect on Hazard Rate [*]	Multivariate 95% Confidence Limits
Wheelchair Use	34	GAA1 length/100	2.7×10 ⁻⁵	0.11	1.28	0.95
		Age of diagnosis	1.1×10 ⁻⁴	0.0051	0.84	0.75
Interference with ADLs	48	GAA1 length/100	4.4×10 ⁻⁵	0.074	1.23	0.98
		Age of diagnosis	7.4×10 ⁻⁵	0.0045	0.89	0.83
Cardiomyopathy	33	GAA1 length/100	1.9×10 ⁻⁴	0.66	1.06	0.82
		Age of diagnosis	2.5×10 ⁻⁷	<0.0001	0.78	0.69
Scoliosis	44	GAA1 length/100	4.1×10 ⁻⁴	0.54	0.93	0.72
		Age of diagnosis	3.9×10 ⁻⁶	<0.0001	0.83	0.75

^{*} If a variable has an effect on hazard rate > 1.0, increases in that variable are associated with increased probability of outcome, e.g., longer GAA1 lengths are associated with increased risk of wheelchair use. Increases in variables with effects on hazard rate < 1.0 are associated with decreased risk.

Table 4

Estimated age corresponding to 50% chance of wheelchair use and associated 95% confidence interval (CI) for probability of wheelchair use at that age

	Diagnosis age = 7 (95% CI)	Diagnosis age = 10 (95% CI)	Diagnosis age = 14 (95% CI)
Allele length = 577	17.3 (22%,78%)	19.1 (21%,79%)	23.3 (20%,80%)
Allele length = 752	16.2 (27%,73%)	17.8 (26%,74%)	20.5 (19%,81%)
Allele length = 874	12.8 (28%,72%)	17.1 (25%,75%)	19.7 (15%,85%)