Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data

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Summary

Background **Friedreich's ataxia is a rare autosomal recessive neurodegenerative disorder. Here we report cross-sectional baseline data to establish the biological and clinical characteristics for a prospective, international, European Friedreich's ataxia database registry.**

Methods **Within the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) framework, we assessed a cohort of patients with genetically confirmed Friedreich's ataxia. The primary outcome measure was the Scale for the Assessment and Rating of Ataxia (SARA) and secondary outcome measures were the Inventory of Non-Ataxia Signs (INAS), the performance-based coordination test Spinocerebellar Ataxia Functional Index (SCAFI), the neurocognitive phonemic verbal fluency test, and two quality-of-life measures: the activities of daily living (ADL) part of the Friedreich's Ataxia Rating Scale and EQ-5D. The Friedreich's ataxia cohort was subdivided into three groups: early disease onset (≤14 years), intermediate onset (15–24 years), and late onset (≥25 years), which were compared for clinical characteristics and outcome measures. We used linear regression analysis to estimate the annual decline of clinical outcome measures based on disease duration. This study is registered with ClinicalTrials.gov, number NCT02069509.**

Findings **We enrolled 592 patients with genetically confirmed Friedreich's ataxia between Sept 15, 2010, and April 30, 2013, at 11 sites in seven European countries. Age of disease onset was inversely correlated with the number of GAA repeats in the *frataxin* (*FXN*) gene: every 100 GAA repeats on the smaller repeat allele was associated with a 2·3 year (SE 0·2) earlier onset. Regression analyses showed significant estimated annual worsening of SARA (regression coefficient 0·86 points [SE 0·05], INAS (0·14 points [0·01]), SCAFI *Z* scores (–0·09 [0·01]), verbal fluency (–0·34 words [0·07]), and ADL (0·64 points [0·04]) during the first 25 years of disease; the regression slope for health-related quality-of-life state from EQ-5D was not significant (–0·33 points [0·18]). For SARA, the predicted annual rate of worsening was significantly higher in early-onset patients (n=354; 1·04 points [0·13]) and intermediate-onset patients (n=137; 1·17 points [0·22]) than in late-onset patients (n=100; 0·56 points [0·10]).**

Interpretation **The results of this cross-sectional baseline analysis of the EFACTS cohort suggest that earlier disease onset is associated with larger numbers of GAA repeats and more rapid disease progression. The differential estimated progression of ataxia symptoms related to age of onset have implications for the design of clinical trials in Friedreich's ataxia, for which SARA might be the most suitable measure to monitor disease progression.**

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Introduction

In 1863, Nikolaus Friedreich first described Friedreich's ataxia as a novel spinal disease.[1] Since its primary description as "degenerative atrophy of the spinal posterior columns",[1] the clinical phenotype has been continuously extended towards a multisystem disease encompassing not only characteristic neurological features, such as poor balance, impaired coordination, dysarthria, weakness, ocular fixation instability, deep sensory loss, and visual and hearing impairment,[2] but also diverse non-neurological features such as hypertrophic cardiomyopathy,[3] diabetes mellitus,[4] kyphoscoliosis, and foot deformities. Symptoms of Friedreich's ataxia occur most often around puberty,[1,2] rarely in early childhood, and in some cases later in life.

In 1996, the genetic mutation that underlies most Friedreich's ataxia cases[5] was discovered as a homozygous pathological expansion of GAA triplet repeats in the first intron of the *FXN* gene, which encodes for the mitochondrial protein frataxin. With a prevalence of about one in 50 000 in white populations, Friedreich's ataxia is a rare autosomal recessive disease.[6] A comprehensive understanding of the disease and establishment of sufficiently sensitive and robust scales for intervention trials would necessitate large, multicentre consortium studies. Therefore, in 2010, we created

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the first prospective, international European Friedreich's ataxia registry—the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS)—designed to define clinical rating scales and quality-of-life measures that can be used in clinical trials.

Here we report baseline data from the EFACTS cohort of patients with genetically confirmed Friedreich's ataxia. Our approach provides a comprehensive clinical characterisation of an international cohort of patients and a model for translational research. We build on the available knowledge of genetic mechanisms, aiming to delineate a panel of outcome measures that can be used to assess clinical trial results and identify the health problems that occur throughout the disease course.

Methods

Study design and participants

Within the EFACTS framework, patients with Friedreich's ataxia were enrolled into a prospective, longitudinal study at 11 centres in seven European countries (table 1). Baseline data for the patients were obtained between Sept 15, 2010, and April 30, 2013, and longitudinal data will be collected continuously at 1-year intervals. We aimed to create a large, prospective cohort of patients with Friedreich's ataxia by recruiting 600 patients at baseline within a 2-year timeframe. This number was calculated on the basis of regional prevalence data and the estimated monthly recruitment achievement of the participating European centres. Inclusion required a confirmed genetic diagnosis of Friedreich's ataxia. We obtained written informed consent from all patients or their authorised surrogates (eg, if the patient was aged <18 years or was unable to confirm consent owing to clinical impairment) at enrolment. The study was approved by the local ethic committees of each participating centre. Based on the association between age of onset, defined as age at first clinical symptoms, and clinical phenotype identified in previous reports,[2,7,8] we subdivided the cohort into three age-of-onset groups: early-onset (≤14 years), intermediate-onset (15–24 years), and late-onset (≥25 years).

Procedures

We used structured interviews, questionnaires, performance-based coordination tests, clinical rating scales, and neuropsychological functional measures to obtain comprehensive data and demographic characteristics as well as idebenone intake. Patients' functional disability stage based on the spinocerebellar degeneration functional score (SDFS[9]) was recorded on a range from 1 (no functional handicap but signs at examination) to 7 (confined to bed). Blood and urine samples as well as genetic analysis complemented the examination. All centres applied identical study protocols of assessment and sampling of biomaterials. Use of the International Standard Classification of Education (1997 version) ensured comparability of statistics on extent of education between countries. Genetic analyses were done for all participants as described by the Laboratory of Experimental Neurology at the Université Libre de Bruxelles (Brussels, Belgium).[10]

Outcomes

The primary outcome measure was the Scale for the Assessment and Rating of Ataxia (SARA), which is validated for both spinocerebellar ataxia[11] and Friedreich's ataxia.[12] It quantifies ataxia symptoms on the basis of eight items, with a maximum score of 40 points reflecting most severe ataxia. In its original description and validation,[11] investigators noted a linear relation

	Aachen, Germany (n=25 [4%])	Bonn, Germany (n=16 [3%])	Brussels, Belgium (n=31 [5%]	Innsbruck, Austria (n=41 [7%])	London, UK (n=149 [25%])	Madrid, Spain (n=77 [13%])	Marburg, Germany (n=7 [1%])	Milan, Italy (n=137 [23%])	Munich, Germany (n=39 [7%])	Paris, France (n=48 [8%])	Tübingen, Germany (n=22 [4%])
Age (years)	30 (13–62)	41 (20–59)	26 (7–69)	29 (10–62)	31 (16–68)	32 (6–65)	42 (23–73)	33 (9–70)	31 (15–59)	36 (19–76)	40 (19–74)
Sex											
Male	10 (40%)	7 (44%)	18 (58%)	25 (61%)	62 (42%)	33 (43%)	3 (43%)	65 (47%)	19 (49%)	19 (40%)	11 (50%)
Female	15 (60%)	9 (56%)	13 (42%)	16 (39%)	87 (58%)	44 (57%)	4 (57%)	72 (53%)	20 (51%)	29 (60%)	11 (50%)
Age of onset (years)*	13 (8–21)	16 (14–28)	14 (9–20)	14 (12–23)	12 (7–17)	12 (8–18)	12 (12–25)	12 (8–17)	13 (8–20)	15 (12–24)	16 (13–30)
Disease duration (years)	14 (9–25)	18 (14–25)	9 (6–15)	13 (10–20)	19 (12–27)	16 (10–24)	25 (18–33)	18 (9–26)	17 (11–26)	18 (10–24)	19 (8–25)
Education (years)	13 (10–16)	13 (12–15)†	14 (10–17)†	12 (9–13)	15 (13–17)†	15 (11–20)†	12 (10–15)	13 (9–15)	13 (12–14)	13 (12–15)	10 (8–13)
Number of *FXN* GAA repeats											
Shorter allele	680 (390–865)	445 (262–512)	583 (380–834)	620 (367–776)	700 (450–834)	650 (420–850)	512 (112–580)	667 (384–834)	650 (385–800)	467 (250–700)	534 (284–709)
Longer allele	900 (701–1000)	850 (671–912)	934 (834–1080)	900 (744–1000)	967 (845–1100)	912 (740–1040)	712 (545–945)	980 (827–1100)	900 (767–1000)	900 (759–1034)	863 (777–985)

Data are median (IQR) or n (%). *Data for age of onset and disease duration were missing for one patient in Bonn. †Data for education were missing for one patient in Bonn, two in Brussels, one in London, three in Madrid, and one in Munich.

Table 1: **Baseline demographic characteristics, by centre**

between SARA and a global assessment of disease severity in ataxia by use of video ratings and a visual analogue scale. In a previous study to assess the sensitivity of scales to detect changes in symptoms of Friedreich's ataxia (J B Schulz, unpublished data), we compared 53 patients in the German Network of Hereditary Movement Disorders longitudinally. For a period of 12 months the standard response mean was higher for SARA (0·40) than for the International Cooperative Ataxia Rating Scale (ICARS; 0·30) or the Friedreich Ataxia Rating Scale (FARS; 0·30).

Secondary endpoints were the Inventory of Non-Ataxia Signs (INAS),[13] the Spinocerebellar Ataxia Functional Index (SCAFI), the neurocognitive phonemic verbal fluency test, and two quality-of-life measures: the activities of daily living (ADL) part of FARS and EQ-5D. INAS provides a checklist of non-ataxia symptoms such as changes in reflexes, other motor and sensory symptoms, ophthalmological findings, urinary dysfunction, and cognitive impairment. The number of items assessed determines the INAS count (maximum 16 points).

SCAFI consists of timed performance measures including an 8 m walk at maximum speed, the nine-hole peg test, and the rate of repeating the syllables "PATA" within 10 s as a measure of speech performance.[14] Total composite SCAFI *Z* scores for our study population, including those who were unable to do the tasks because of physical limitations (315 for 8 m walk, 125 for nine-hole peg test, and 36 for PATA test), were calculated as previously reported.[14] Patients who were unable to do the task for other reasons were excluded (19, 19, and 17, respectively).

Preliminary neurocognitive testing in 14 patients with Friedreich's ataxia and 16 age-matched controls showed differences in tests with an executive component—the Stroop interference test (p=0·001), revised Wechsler Adult Intelligence Scale (WAIS-R) block design (p=0·03), and phonemic word fluency (p=0·0001; J B Schulz, unpublished data)—another group has reported similar findings.[15] Of these three tests we chose phonemic verbal fluency for a measure of executive function because it is independent of motor coordination and vision, and it uses 2 min instead of 1 min to adapt for slowness due to motor impairment. Centres in Brussels (Belgium), London (UK), Madrid (Spain), Innsbruck (Austria), and all centres in Germany used the initial letters F and A, the centre in Paris (France) used V and P, and the centre in Milan (Italy) used F and P, reflecting the frequency of words beginning with these letters in the languages spoken in these areas.

To assess quality of life, we used the basic ADL part of the FARS[16] to assess impairment in the ability to perform daily activities (eg, speech, cutting food, dressing, and personal hygiene), with scores ranging from 0 to 36 points. We also used the EQ-5D self-rating of health-related quality of life on a 100-point visual analogue scale. Additionally, we report self-rated health problems based on the EQ-5D descriptive system, which includes the five dimensions of mobility, self-care, usual activities, pain and discomfort, and anxiety and depression.

Statistical analysis

Data are reported as mean (SD), median (IQR), or frequency, as appropriate. Statistical analyses were done with IBM SPSS Statistics version 22, with a p value of 0·05 set as the threshold for significance. Rating scale scores were compared between age-of-onset groups after controlling for age at examination, sex, years of education, idebenone intake, and study site by use of ANCOVA and subsequent post-hoc tests (Bonferroni corrected). Frequency distributions between age-of-onset groups were compared with χ^2 or Fisher's exact tests. We used Fisher's exact test when in one or more cells expected frequencies were less than five. We further assessed potential bias caused by missing data using Fisher's exact test and logistic regression (appendix pp 2–3).

To predict the annual rate of worsening in SARA, SCAFI, INAS, verbal fluency, ADL, and EQ-5D health-state from cross-sectional data, we did separate linear regression analyses on the basis of disease duration. In a hierarchical regression model, we first included age, sex, education, idebenone intake, and study site as regressors (stepwise inclusion criterion p<0·05) to partial out significant effects of nuisance variability (appendix p 4). In a second step, disease duration in years was set as predictor and we examined the changes in R^2 (DR^2), the corresponding effect size f^2, and regression slopes.

For ANCOVAs and linear regression analysis we used bias-corrected and accelerated bootstrap with 1000 iterations to account for non-normality and report 95% CIs. We also compared regression slopes between age-of-onset groups using the equation by Clogg and colleagues.[17,18] Since most clinical and functional measures seemed to have a linear association with disease duration for the first 20–25 years of disease, followed by a plateau, only the first 25 years were included in our regression analyses. We assessed intercorrelations between scales and disease-related variables with Pearson's coefficients or Spearman's rho, where appropriate. Interpretation of the size of correlation coefficient *r* (0·10–0·29 defined as small, 0·30–0·49 as medium, and ≥0·50 as large) and effect size f^2 (0·02 defined as small, 0·15 as medium, and 0·35 as large) followed the guidelines proposed by Cohen.[19] This study is registered with ClinicalTrials.gov, number NCT02069509.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and EFACTS policy allows all participating centres to request a complete export of study data. The corresponding author had the final responsibility for the decision to submit for publication.

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For **EFACTS** see http://www.e-facts.eu

See **Online** for appendix

Results

We obtained and assessed baseline data for 592 patients with Friedreich's ataxia (320 [54%] female), with ages ranging from 6 to 76 years (mean 33·9 [SD 13·8]), disease duration ranging from less than 1 to 55 years (mean 18·3 [10·2]), and age of onset ranging from less than 1 to 65 years (mean 15·7 [10·4]; table 1). 354 (60%) patients had early-onset, 137 (23%) intermediate-onset, and 100 (17%) late-onset disease (table 2). For one patient (male, age 25 years), age of symptom onset was unknown; we therefore excluded this patient from further subgroup analyses. 158 (27%) patients were taking idebenone at study participation (median 6·75 mg/kg [IQR 4·8–15·3]), most of whom (114 [72%]) had early-onset disease. Patients taking idebenone did not differ significantly with respect to clinical outcome measures from those not taking idebenone (SARA p=0·385; INAS p=0·113; SCAFI p=0·270; verbal fluency p=0·58; ADL p=0·665; EQ-5D health state p=0·459; all adjusted for age of onset).

577 (97%) of 592 patients were homozygous for expanded GAA repeats in the *FXN* gene, with the shorter repeat containing at least 60 GAA triplets; the remaining

	Early-onset group (age ≤14 years; n=354 [60%])	Intermediate-onset group (age 15–24 years; n=137 [23%])	Late-onset group (age ≥25 years; n=100 [17%])	Total cohort (n=592)
Age (years)	26 (20–35); p<0·0001	35 (28–43); p<0·0001	50 (43–58); p<0·0001	32 (23–43)
Sex (male *vs* female)	168 (48%) *vs* 186 (52%); p=0·774	62 (45%) *vs* 75 (55%); p=1·0	41 (41%) *vs* 59 (59%); p=1·0	272 (46%) *vs* 320 (54%)
Education (years)*	13 (11–16); p=1·0	14 (12–17); p=0·003	13 (10–15); p=0·015	13 (11–16)
Family history of Friedreich's ataxia	95/351 (27%); p<0·0001	47/137 (34%); p=0·363	48/99 (49%); p=0·096	190/588 (32%)
Age of onset (years)†	10 (7–12); p<0·0001	17 (16–20); p<0·0001	32 (29–40); p<0·0001	13 (9–19)
Disease duration (years)†	17 (10–25); p=0·135	17 (10–25); p=1·0	14 (11–22); p=0·340	17 (10–25)
Intake of idebenone	114 (32%); p=0·012	27 (20%); p=0·021	17 (17%); p=1·0	158 (27%)
First symptoms				
Scoliosis	105 (30%); p<0·0001	36 (26%); p=1·0	4 (4%); p<0·0001	146 (25%)
Cardiomyopathy	25 (7%); p=0·012	2 (2%); p=0·075	0	27 (5%)
Gait instability	269 (76%); p=0·036	104 (76%); p=1·0	88 (88%); p=0·084	462 (78%)
Falls	85 (24%); p=0·171	16 (12%); p=0·009	15 (15%); p=1·0	116 (20%)
Diabetes mellitus	1 (<1%); p=0·372	1 (1%); p=1·0	2 (2%); p=1·0	4 (1%)
Disability stage‡	6 (1–7); p=0·001	5 (2–6); p =0·001	4 (1–6); p=0·001	5 (1–7)
Number of *FXN* GAA repeats				
Shorter allele	745 (600–850); p<0·0001	500 (367–667); p<0·0001	234 (150–367); p<0·0001	648 (384–800)
Longer allele	974 (849–1100); p<0·0001	900 (759–1000); p<0·0001	810 (534–995) p<0·0001	912 (789–1050)
Clinical and functional measures				
SARA‡§	28 (19–32); p=0·001	20 (12–28); p=0·001	13 (10–20); p=0·001	23 (13–31)
INAS‡	6 (4–7); p=0·001	4 (3–6); p=0·001	4 (3–5); p=0·001	5 (3–6)
SCAFI‡¶	−1·1 (−1·7 to −0·3); p=0·001	−0·6 (−1·0 to 0·4); p=0·001	0·1 (−0·3 to 0·8); p=0·001	−0·8 (−1·4 to 0·2)
Verbal fluency‡‖	11 (9–15); p=0·001	13 (10–19); p=0·003	17 (13–22); p=0·001	13 (9–18)
Quality-of-life measures				
ADL‡**	17 (11–23); p=0·001	12 (6–17); p=0·001	9 (6–13); p=0·001	14 (8–20)
EQ-5D health state‡††	60 (50–80); p=0·104	65 (50–79); p=0·500	65 (50–75); p=0·280	62 (50–80)
Mobility	246/252 (98%); p=0·147	110/118 (93%); p=0·138	86/93 (92%); p=1·0	443/464 (95%)
Self-care	208/269 (77%); p<0·0001	60/120 (50%); p<0·0001	33/93 (35%); p=0·114	301/483 (62%)
Usual activities	210/268 (78%); p=0·207	88/120 (73%); p=0·897	64/93 (69%); p=1·0	362/482 (75%)
Pain or discomfort	143/269 (53%); p=1·0	48/120 (40%); p=0·063	50/93 (54%); p=0·159	241/483 (50%)
Anxiety or depression	111/270 (41%); p=1·0	57/120 (48%); p=0·804	40/92 (43%); p=1·0	208/483 (43%)

Data are median (IQR), n (%), or n/N (%), unless otherwise indicated. p values are from Bonferroni-corrected post-hoc tests after significant χ^2, Fisher's exact test, ANOVA or ANCOVA (controlled for age, sex, education, idebenone intake, and study site); p values in the early-onset column are versus the late-onset group, those in the intermediate-onset column are versus the early-onset group, and those in the late-onset column are versus the intermediate-onset group. SARA=Scale for the Assessment and Rating of Ataxia. INAS=Inventory of Non-Ataxia Symptoms. SCAFI=Spinocerebellar Ataxia Functional Index. ADL=activities of daily living. *Data for education were missing for four patients in the early-onset group, two in the intermediate-onset group, and two in the late-onset group. †For one patient (male, age 25 years of age), age of symptom onset and disease duration were unknown. ‡ANCOVA used for statistical analysis. §Data for SARA were missing for three patients in the early-onset group and two in the intermediate-onset group. ¶Data for SCAFI were missing for ten patients in the early-onset group, seven in the intermediate-onset group, and six in the late-onset group. ‖Data for verbal fluency were missing for 151 patients in the early-onset group, 54 in the intermediate-onset group, and 29 in the late-onset group. **Data for ADL were missing for five patients in the early-onset group, two in the intermediate-onset group, and one in the late-onset group. ††Data for EQ-5D health state were missing for 96 patients in the early-onset group, 23 in the intermediate-onset group, and eight in the late-onset group.

Table 2: **Baseline characteristics, by age-of-onset group**

15 (3%) patients were compound heterozygotes with an expanded GAA repeat on one allele and an *FXN* point mutation on the other. Five missense mutations that had been previously identified in patients with Friedreich's ataxia and are known to affect the functional properties of frataxin were detected in seven individuals: Val125Gly (n=1), Gly130Val (n=3), Arg165Pro (n=1), and Trp173Gly (n=2). One patient had a mutation (3G→T) affecting the N-terminal methionine codon, which could result in the use of a downstream methionine as translation start site, generating a shorter protein lacking part of the mitochondrial targeting sequence. Two patients had single nucleotide deletions in the coding sequence (157delC and 187delA), causing a frameshift and a premature stop codon. Three patients had splice-site mutations expected to cause aberrant splicing leading to a frameshift and a premature stop codon. In two individuals we could not detect any clearly pathogenic mutation in heterozygosity with the expanded GAA repeat. Similar to previously reported cases,[20] 190 (32%) of 588 patients reported a family history of Friedreich's ataxia.

Age of onset was inversely correlated with the number of GAA repeats, particularly in the shorter allele (r=–0·60 for the shorter allele and –0·34 for the longer allele; both p<0·0001; figure 1). Regression analysis for the prediction of age of onset based on GAA repeats on both alleles showed a 2·3 years [SE 0·2] earlier disease onset with every 100 GAA repeats added to the shorter allele, but no significant predictive value of GAA repeats on the longer allele. When only homozygous individuals for expanded GAA repeats were included, the slope of earlier onset increased to 2·7 years per 100 GAA repeats (r=–0·66, p<0·0001). Patients with compound heterozygous frataxin point mutations had a mean age of onset of 13·9 years (SD 7·7; figure 1).

Early-onset, intermediate-onset, and late-onset groups differed significantly in number of GAA repeats (table 2). The number of patients with more than 600 GAA repeats on the shorter allele was 265 (75%) in the early-onset group, 45 (33%) in the intermediate-onset group, and five (5%) in the late-onset patients.

The most frequently reported first symptom at disease onset for the overall cohort was gait instability, followed by scoliosis, falls, and, less frequently, cardiomyopathy and diabetes mellitus (table 2). The order of frequency was the same for early-onset and intermediate-onset patients; the late-onset subgroup reported scoliosis as first symptom less frequently than the other groups, and cardiomyopathy less frequently than early-onset patients.

For our primary outcome measure of SARA, scores were available for 587 (99%) of 592 patients; data for INAS were available for 592 (100%) patients, composite SCAFI *Z* scores were available for 569 (96%) patients, and data for ADL for 584 (99%) patients (appendix pp 2–3). However, more patients were unable to do at least one of the SCAFI timed measures because of physical limitations in the early-onset group (n=240) than in the intermediate-onset group (n=60) and the late-onset group (n=16). Data were missing for verbal fluency (data available for 358 [60%] patients) and EQ-5D health state (available for 465 [79%]), and missing data seemed to be associated with age of onset, age, and study site (appendix pp 2–3).

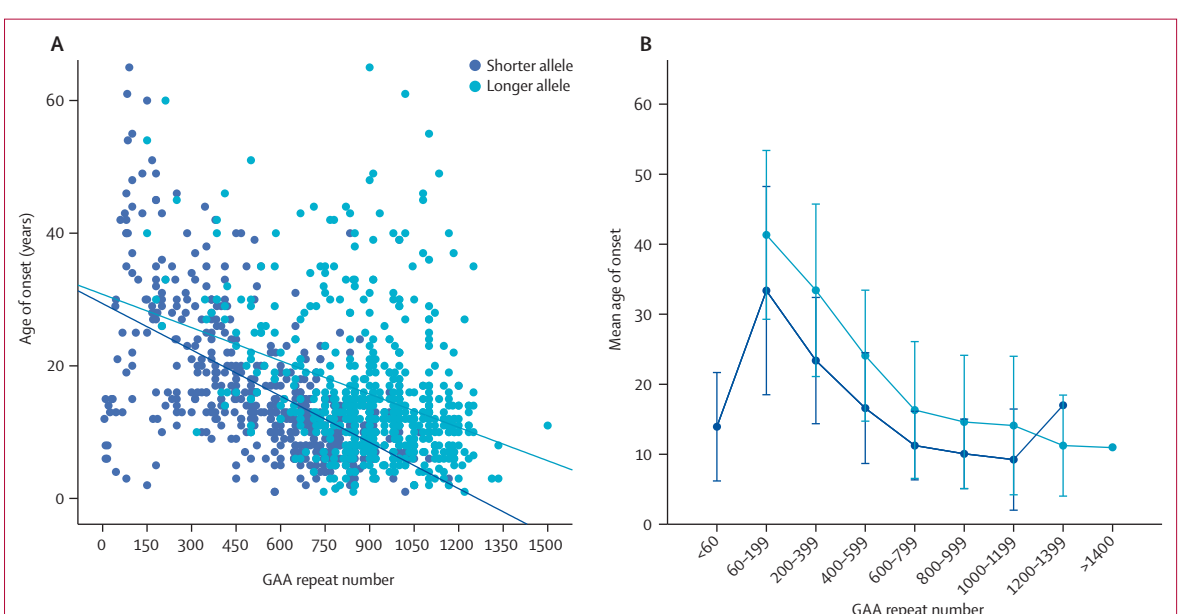

Figure 1: **Genetic background and age of onset**
(A) Age of onset plotted against *FXN* GAA repeat number, subdivided into the shorter allele and the longer allele. (B) Mean age of onset plotted against *FXN* GAA repeat number, subdivided into the shorter allele and the longer allele. Error bars show SDs.

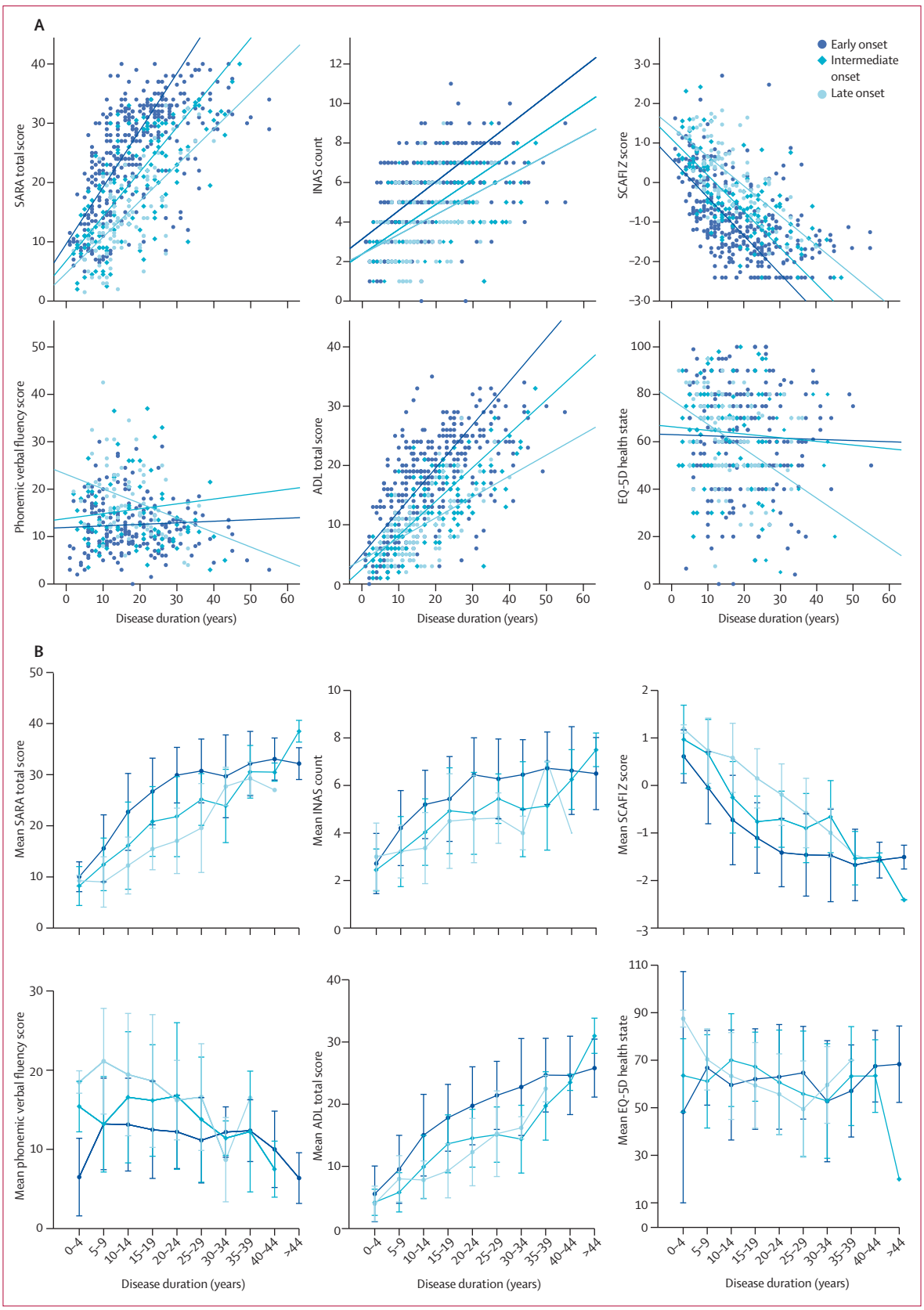

Figure 2: **Clinical, cognitive, and quality-of-life measures relative to disease duration** (A) Scale for the Assessment and Rating of Ataxia (SARA) total scores, Inventory of Non-Ataxia Symptoms (INAS) count, Spinocerebellar Ataxia Functional Index (SCAFI) *Z* scores, phonetic verbal fluency performance score, activities of daily living (ADL) assessment score, and EQ-5D health state, plotted against disease duration (regression lines are based on the first 25 years of disease duration), subdivided into early-onset, intermediate-onset, and late-onset groups. (B) Mean SARA total scores, INAS counts, SCAFI *Z* scores, phonetic verbal fluency performance scores, ADL assessment scores, and EQ-5D health states by disease duration in 5-year intervals. Error bars show SDs.

Age of onset was significantly associated with all clinical and functional measures, with the early-onset group showing the most severe impairment and the late-onset group being the least impaired (groups adjusted for demographic characteristics and study site; table 2, figure 2). However, age-of-onset groups did not differ in self-perceived overall health state.

455 patients with a disease duration up to 25 years were included in the linear regression analyses to predict the annual rate of worsening in outcome measures based on cross-sectional baseline data (appendix p 3). The predicted annual increase in SARA scores was 0·86 points (SE 0·05) for the whole cohort, 1·04 (0·13) for the early-onset group, and 1·17 (0·22) for the intermediate-onset group. Estimated progression for the early-onset and intermediate-onset groups were significantly faster (Bonferroni-adjusted p=0·008 and p=0·034, respectively) than for the late-onset group (table 3).

The INAS score increased during the first 25 years of disease by 0·14 points (SE 0·01) per year across the whole cohort, with small to medium effect sizes in the regression analyses for each group (table 3). Regression slopes did not differ between age-of-onset groups.

For SCAFI, regression analysis showed an annual decline of 0·09 points (SE 0·01) across all patients and medium to large effect sizes for all three age-of-onset groups (table 3). However, for SCAFI we noted floor effects with 35 (6%) patients reaching the minimum *Z* score of –2·41 and 50 (9%) with a *Z* score of less than –2·0. The floor effect was more substantial in the early-onset group, with 45 (13%) patients having a *Z* score of less than –2·0 (n=31 [9%] with a *Z* score of –2·41), compared with only five (4%) of patients in the intermediate-onset group (n=4 [3%] with a *Z* score of –2·41).

Verbal fluency also differed significantly between age-at-onset groups when demographic characteristics and study site were taken into account (table 2). After controlling for PATA speech performance, the late-onset group did significantly better than the early-onset and intermediate-onset groups (data not shown). Across all patients, we calculated an estimated annual decline in verbal fluency performance of 0·34 words (SE 0·07; table 3).

ADL scores differed between the age-of-onset groups, with the worst scores in the early-onset group (table 2). Regression analyses predicted an annual worsening of ADL scores by 0·64 points (SE 0·04) in the whole cohort, 0·97 points (0·11) in the early-onset group, 0·81 points (0·13) in the intermediate-onset group, and 0·31 points (0·08; table 3) in the late-onset group. Estimated progression for the early-onset and intermediate-onset groups was significantly worse than for the late-onset group (Bonferroni-adjusted p<0·0001 and p=0·004, respectively). The result of the regression analysis with EQ-5D health-state was not significant, apart from for the late-onset group (table 3). Additionally, on the EQ-5D scale, early-onset patients reported more problems in self-care than did those in the intermediate-onset and late-onset groups, although groups did not differ in self-perceived overall health state.

We noted strong correlations between SARA, INAS, and SCAFI (SARA–SCAFI *r*=–0·87, SARA–INAS *r*=0·67, INAS–SCAFI *r*=–0·61; p<0·0001 for all three correlations), but all of these measures showed weak to moderate associations with verbal fluency (SARA *r*=–0·25, p<0·0001; SCAFI *r*=0·32, p<0·0001; INAS *r*=–0·11, p=0·038). ADL score was also strongly correlated with clinical measures (SARA *r*=0·89, SCAFI *r*=–0·83, INAS *r*=0·66; p<0·0001 for all three correlations), but was weakly correlated with verbal fluency (*r*=–0·21, p<0·0001). Only SARA and ADL showed a weak

	b (SE; 95% CI)	p value	ΔR^2	f^2
SARA, points				
All patients	0·86 (0·05; 0·75 to 0·97)	0·001	0·33	0·52
Early onset	1·04 (0·13; 0·80 to 1·28)	0·001	0·13	0·26
Intermediate onset	1·17 (0·22; 0·73 to 1·62)	0·001	0·13	0·23
Late onset	0·56 (0·10; 0·35 to 0·77)	0·001	0·23	0·33
INAS, points				
All patients	0·14 (0·01; 0·11 to 0·16)	0·001	0·60	0·27
Early onset	0·10 (0·03; 0·04 to 0·16)	0·003	0·03	0·04
Intermediate onset	0·15 (0·04; 0·07 to 0·25)	0·001	0·06	0·10
Late onset	0·11 (0·03; 0·05 to 0·17)	0·001	0·13	0·16
SCAFI, points				
All patients	–0·09 (0·01; –0·10 to –0·08)	0·001	0·31	0·50
Early onset	–0·11 (0·02; –0·14 to –0·08)	0·001	0·12	0·21
Intermediate onset	–0·13 (0·03; –0·82 to –0·07)	0·001	0·13	0·24
Late onset	–0·07 (0·01; –0·10 to –0·04)	0·001	0·24	0·33
Phonemic verbal fluency, words				
All patients	–0·34 (0·07; –0·47 to –0·22)	0·001	0·07	0·11
Early onset	–0·24 (0·13; –0·49 to 0·02)	0·067	0·01	0·02
Intermediate onset	0·13 (0·10; –0·06 to 0·30)	0·251	0·02	0·02
Late onset	–0·24 (0·14; –0·54 to 0·02)	0·077	0·04	0·05
ADL, points				
All patients	0·64 (0·04; 0·55 to 0·74)	0·001	0·31	0·47
Early onset	0·97 (0·11; 0·75 to 1·20)	0·001	0·16	0·28
Intermediate onset	0·81 (0·13; 0·53 to 1·07)	0·001	0·14	0·28
Late onset	0·31 (0·08; 0·15 to 0·49)	0·001	0·14	0·19
EQ-5D health state, points				
All patients	–0·33 (0·18; –0·68 to 0·02)	0·064	0·01	0·01
Early onset	–0·05 (0·29; –0·60 to 0·52)	0·860	0·00	0·0
Intermediate onset	–0·26 (0·30; –0·83 to 0·23)	0·366	0·01	0·01
Late onset	–1·03 (0·33; –1·66 to –0·40)	0·004	0·11	0·14

All regression parameters refer to disease duration up to 25 years as a regressor (after controlling for significant effects of age, sex, education, idebenone intake, and study site in the first step). b is the regression coefficient; SE, 95% CI, and p values estimated by bias-corrected and accelerated bootstrap. DR^2 is the change in R^2 after including disease duration as a regressor. f^2 is the effect size for the increase in R^2. SARA=Scale for the Assessment and Rating of Ataxia. INAS=Inventory of Non-Ataxia Symptoms. SCAFI=Spinocerebellar Ataxia Functional Index. ADL=activities of daily living.

Table 3: **Linear regression analysis for the prediction of clinical, functional, cognitive, and quality-of-life measures based on the first 25 years of disease duration**

correlation with the overall health state of EQ-5D (SARA r=–0·11, p=0·015; ADL r=–0·12, p=0·010). Disability stage was strongly correlated with clinical and functional measures (SARA r=0·88, SCAFI r=–0·82, INAS r=0·64, ADL r=0·85; p<0·0001 for all four correlations), but was weakly correlated with verbal fluency (r=–0·18, p=0·001).

Discussion

Dividing our cohort of patients with Friedreich's ataxia into subgroups by age of onset, we confirmed that age of symptom onset is inversely correlated with the GAA repeat number, particularly in the shorter allele.[7,21] The results of our analysis predict a 2·3 year earlier onset for every 100 GAA repeats added to the shorter allele. However, GAA repeats account for only 36% of the variability of age of onset, the remainder being potentially accounted for by other genetic and epigenetic modifiers yet to be assessed.

Early age of onset was associated with a higher frequency and severity of neurological and non-neurological symptoms, as evidenced by worse clinical, cognitive, and functional scores. Conversely, patients with late-onset disease had a milder phenotype and slower disease progression.[22,23] The estimated annual worsening of cross-sectional SARA scores (and thus ataxia symptoms) in the early-onset and intermediate-onset groups were almost twice as high as in the late-onset group, although progression in the intermediate-onset group showed greater variability.

By contrast with previous studies (panel),[7] the design of our study was prospective and complemented by quantitative and objectively timed functional and quality-of-life measures, in addition to ataxia and non-ataxia rating scales. Although we noted strong associations between SARA, SCAFI, and INAS, regression analyses based on disease duration for the prediction of annual worsening in these measures showed medium to large effect sizes for SARA and SCAFI but with differential progression rates related to age of disease onset only for SARA. The predicted annual progression in SARA scores in the early-onset group is 2·6% per year within the first 25 years of disease. Thus, SARA captures disease progression in Friedreich's ataxia to a similar extent as does ICARS.[7,29] By contrast with SARA, we did not identify different predicted annual rates of worsening related to age of onset for INAS or SCAFI. However, floor effects for SCAFI occurred, particularly in the early-onset group. The high numbers of missing values, especially for the 8 m walk test and the early-onset-group, compromises interpretation of the scoring procedure for patients unable to do the task because of physical limitations. Missing scores for verbal fluency and EQ-5D health state in early-onset patients might also have reduced the power of our statistical analysis to identify differences between age-of-onset subgroups for these measures. Clinical measures were also closely associated with the ADL assessment, with patients with early-onset and intermediate-onset disease facing more severe reductions in quality of life and a faster rate of progression than patients with late-onset disease.

One limitation of the present analysis of baseline data is its cross-sectional nature, which is especially relevant to our attempt to decipher progression in clinical measures based on disease duration. This issue hampers the interpretation of these findings. Although the large cross-sectional sample allows for an estimate of annual worsening of clinical and functional measures, the continuing annual follow-up data will enable more certain and precise conclusions about the rate of progression and its variability for different clinical and functional domains, as well as for specific subgroups. Our data show the predictive value of the applied clinical and functional measures. With longitudinal findings we will, however, be able to verify their usefulness in the monitoring of disease progression and the effects of disease-modifying treatments. The longitudinal data will allow us to estimate the numbers of patients needed for investigational trials with new treatments. Furthermore, in line with previous studies investigating the natural history in Friedreich's ataxia (appendix p 1), the effect of age of symptom onset on differential patterns of disease progression has important implications for clinical trial

Panel: Research in context

Systematic review

We searched PubMed for articles on Friedreich's ataxia published in English between Jan 1, 1996, and Nov 15, 2014, using the search terms "Friedreich ataxia AND clinical", "Friedreich ataxia AND progression", and "Friedreich ataxia AND natural history" (appendix p 1). We identified two retrospective surveys that analysed disease progression by defining five disease stages[24] or by the occurrence of neurological symptoms, disease milestones, or interference with activities of daily living.[25] The investigators of one cross-sectional study[26] analysed health-related quality-of-life measures, and in one large cross-sectional study[7] the researchers combined the baseline data from three clinical interventional trials and data obtained in three clinical centres to estimate disease progression. Three studies combined a cross-sectional and a longitudinal approach, with follow-up investigations of 2 years[27,28] or more.[8] Using disease stages, clinical rating scales, or timed functional measures, the results of these studies showed that earlier disease onset predicts a more rapid disease progression,[7,8,24,25,28] disease progression is driven by *FXN* GAA repeat number on the shorter allele,[7,28] and that the International Cooperative Ataxia Rating Scale and the Friedreich Ataxia Rating Scale can show a ceiling effect in severe stages of the disease.[7,28]

Interpretation

In this baseline analysis of a large, prospective, observational registry cohort (European Friedreich's Ataxia Consortium for Translational Studies [EFACTS]), we assessed different outcome measures in search of those that would be clinically meaningful for study of the natural history of Friedreich's ataxia and for the development of future clinical trials. For all outcome measures apart from EQ-5D health state, we identified significant estimated annual disease progression in the overall study cohort. The EFACTS baseline data emphasise the advantages of the Scale for the Assessment and Rating of Ataxia, which is a fast and easy clinical scale, to assess ataxia, and of activities of daily living to detect functional deterioration in Friedreich's ataxia. Although these data are cross-sectional they have substantial implications for the design of future interventional studies and the selection of outcome markers.

designs and outcome measures. EFACTS provides baseline data for fast, clinically applicable, and disease-specific clinical rating scales as well as quality-of-life measures, which should be considered in future clinical trials of Friedreich's ataxia.[10]

In conclusion, our baseline analysis of the EFACTS cohort quantifies progression as a variable of GAA repeat number, and allows cross-correlation with a broad range of neurological and non-neurological features captured by various standard clinical measures. The combination of genetics, functional and cognitive data, and biomaterial samples in the EFACTS registry provides a broad database for future studies and reliable predictors of disease progression, moving us closer to identifying outcome measures and target points for therapeutic trials in this devastating multisystem disease.

Contributors

MD, PG, CM, AD, SB, KB, MPand, and JBS conceived the study. MD, KF, PG, MHP, CM, MPanz, LN, JA, IS-G, AD, CP, SB, WN, TK, IK, CD, JMvH, LS, IAG, TK, KB, MPand, and JBS organised the study. MD, KR, PG, MHP, CM, MPanz, LN, JA, IS-G, AD, PC, SB, WN, TK, IK CD, JMvH, LS, IAG, TK, KB, MPand, and JBS enrolled participants and did genetic testing. KF is the data monitor of the registry. KR, ID, ASC, KF, and JBS designed the statistical analysis. KR, ID, and ASC did the statistical analysis. KR, ID, ASC, MD, KF, PG, MHP, MGS, CM, MPanz, LN, JA, IS-G, AD, CP, SB, WN, TK, IK, CD, JMvH, LS, IAG, TK, KB, MPand, and JBS reviewed and interpreted the results of the analyses. KR, ID, and JBS wrote the first draft of the report, and all other authors reviewed and revised the report.

Declaration of interests

We report no competing interests.

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