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Fabry disease genotype, phenotype, and migalastat amenability: Insights from a national cohort

Albina Nowak[1,2] | Uyen Huynh-Do[3] | Pierre-Alexandre Krayenbuehl[4] | Felix Beuschlein[1] | Raphael Schiffmann[5] | Frédéric Barbey[6]

[1]Department of Endocrinology and Clinical Nutrition, University Hospital Zurich and University of Zurich, Zurich, Switzerland

[2]Department of Internal Medicine, Psychiatry University Hospital Zurich, Zurich, Switzerland

[3]Department of Nephrology and Hypertension, University Hospital Bern, Bern, Switzerland

[4]Department of Internal Medicine, Linth Hospital, Uznach, Switzerland

[5]Institute of Metabolic Disease, Baylor Scott & White Research Institute, Dallas, Texas

[6]Division of Genetic Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Correspondence
Albina Nowak, Department of Endocrinology and Clinical Nutrition, University Hospital Zurich, Rämistrasse 100, CH-8091 Zürich, Switzerland.
Email: albina.nowak@usz.ch

Abstract

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by α-galactosidase A (α-Gal A) deficiency. The progressive accumulation of globotriaosylceramide results in life-threatening complications, including renal, cardiac, and cerebrovascular diseases. The pharmacological chaperone migalastat was recently approved as an alternative to enzyme replacement therapy in patients with amenable mutations. In this article, we investigate the proportion of amenable mutations, related to phenotype, in a population of adult patients with FD in Switzerland. This study included 170 adult patients (n = 64 males) from 46 independent pedigrees with 39 different identified mutations over the last 59 years. Overall, 68% had the classic phenotype and 48% fulfilled the current amenability criteria. Migalastat was stopped in 2/11 (18%) patients: the only male classic patient, because of lack of efficacy based on lyso-Gb3 levels, and one patient with a benign variant. In males, the achieved enzyme activities in peripheral leucocytes under migalastat treatment differed from the activities in HEK-cells after incubation with migalastat (eg, 33% in PL vs 41% HEK-cells for p.F113L; 43% in leucocytes vs 36% in HEK-cells for p.N215S, 24-30% in leucocytes vs 96% in HEK-cells for S238N). In this national cohort, we found a relatively high proportion of patients with amenable *GLA* mutations, which, however, had heterogeneous extent of amenability: the higher the residual α-Gal A activity, the higher the chaperone effect. Further studies are required to investigate the long-term benefits of migalastat therapy depending on the achieved enzyme activities in different amenable mutations.

KEYWORDS

amenable mutation, Fabry disease, lyso-Gb3, migalastat, phenotype, α-Galactosidase activity

1 | INTRODUCTION

Fabry disease (FD) (OMIM#301500) is a rare X-linked inborn error of glycosphingolipid catabolism resulting from the deficient activity of the lysosomal hydrolase α-Galactosidase A (EC 3.2.1.22; α-Gal A).[1] The enzymatic defect causes progressive accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids with terminal α-linked galactosyl moieties in plasma and in cells.

There are two major phenotypes, classic and late-onset.[1-3] In males, the classic phenotype is the most severe due to very low (<3%) residual α-Gal A activity, with early symptoms including acroparesthesias, angiokeratoma, corneal opacities and hypohidrosis. The progressive deposition

of GL-3 gradually leads to cardiomyopathy, chronic nephropathy, and premature strokes.[4] In heterozygous females, α-Gal A activity can range from low to normal due to random X-chromosomal inactivation.[5] Females typically have milder symptoms, but can have very heterogeneous phenotypes.[1]

The standard treatment for FD is recombinant enzyme replacement therapy (ERT), administered intravenously every other week, with the potential disadvantage of requiring a long-term biweekly infusion.[6-8] Recently, the first oral therapy with migalastat, a pharmacological chaperone, has been approved by the EMA and FDA.[9] However, migalastat is only indicated in a subgroup of patients who have amenable pathogenic *GLA* mutations.

Attempts have been undertaken to estimate the proportion of mutations amenable to migalastat in a Fabry population. Testing for single mutations in patients who participated in phases I-III migalastat studies for cellular response to migalastat showed that ~45% of mutations were amenable.[10] So far, no estimates of real-life proportions of patients with amenable mutations in a given country have been published. Moreover, no study has analyzed the baseline activity and degree of amenability in relation to clinical phenotype in a patient population. We therefore explored the mutational landscape in the whole country for amenability by phenotypes and for the dynamics of new FD diagnoses by phenotype and amenability. Such analyses were possible because all patients who have ever been diagnosed with FD in Switzerland were genotyped, phenotyped, treated and followed up at three specialized Fabry centers. The Swiss experience could be extrapolated to other countries with European ancestry.

2 | METHODS

This is a retrospective analysis of a prospective, multi-center cohort in Switzerland. The study was conducted in accordance with the principles of the Helsinki Declaration. Each author has read and approved the article.

2.1 | Study participants

All patients in Switzerland who were ever diagnosed to have FD and had a confirmed pathogenic *GLA*-mutation have been included in this analysis. Consecutive FD patients were systematically registered and routinely followed-up through their lifetime, at least annually, at one of the three tertiary care hospitals—University Hospitals Zürich, Lausanne and Bern. If patients died outside of the Fabry centers, the date of death was obtained by the general practitioner, the family or the nurse administering ERT in the home care setting. For the present analyses, all demographic, clinical, biomolecular information and survival status until December 31, 2018 arise from the patients' medical records.

α-Gal A activities were originally determined at the time of diagnosis in males in the same laboratory (Universitäts-Kinderspital Zürich). In six patients on migalastat, α-Gal A activities were additionally measured after 1 to 3 months of migalastat initiation and subsequently re-measured every 3 to 6 months; in five patients α-Gal A activities were measured 1 to 2 times after migalastat initiation. The α-Gal A sampling was random and not related to migalastat administration.

These results were averaged for each patient, to determine his/her α-Gal A activity on migalastat treatment. Lyso-Gb3 levels in dried blood spots (DBS) were determined before and 6 to 18 months after therapy initiation with migalastat.

2.2 | Phenotyping and amenability categorization

The phenotype was classified based on genotype and residual α-Gal A activity in males.[2]

Nonsense, frameshift, consensus splice site and certain missense mutations encode for 0 to 3% residual α-Gal A activity and cause the classic phenotype in males. Alternative splicing mutations and certain other missense mutations encode for >3% of mean normal α-Gal A activity and cause late-onset phenotype in males. Considering novel missense mutations, the phenotype was classified based on the age of symptoms onset and the type of clinical manifestations in males and by in vitro expression assays.[10,11] The phenotype was assigned on a family basis; the assignment is shown in Table S1. These assignments are supported by previous clinical and biochemical studies reported in the Human Gene Mutation Database (HGMD)[12] and the International Fabry Disease Genotype/Phenotype Database (www.dbFGP.org).

Pathogenic mutations were assigned as amenable or non-amenable to migalastat treatment based on the amenability table http://www.galafoldamenabilitytable.com/hcp provided by Amicus Therapeutics. This database was created using results of a pharmacogenic cell-based assay in cultured HEK-293 cells to identify mutant forms of α-Gal A responsive to migalastat.[9,13] A mutation is defined as amenable to migalastat if the α-Gal A activity increases to ≥1.20-fold over baseline with an absolute increase of ≥3.0% wild-type α-Gal A activity in the presence of 10 μmoL/L migalastat.[10] The values of absolute and relative in-vitro increases of α-Gal A activities for the amenable mutations included in this study were drawn from the recent publication by Benjamin et al.[10]

2.3 | Statistical analysis

We used descriptive statistics for demographics and genotype/phenotype information. Categorical variables were

TABLE 1 Summary of demographic, survival and biochemical information of all Swiss Fabry patients according to phenotype

	Classic phenotype, (129 patients)	Late-onset phenotype, (41 patients)	*P*-value
Number of different mutations	32	7	
Number of families	34	12	
Number of alive males, n (%)	33 (26)	15 (37)	
Number of alive females, n (%)	71 (55)	22 (54)	
Number of deceased males, n (%)	14 (11)	0 (0)	
Number of deceased females, n (%)	10 (7.8)	1 (2.4)	
Age in years, median (range)			
Alive males	39 (19-71)	51 (24-72)	.02
Alive females	40 (17-79)	39 (17-77)	.37
Deceased males	57 (40-76)	n.a.	n.a.
Deceased females	66 (36-84)	51 (51-51)	.30
Year of diagnosis, median (range)	2004 (1960-2019)	2012 (1995-2019)	<.001
Number of patients with amenable mutations, n (%)	43 (33)	41 (100)	
Type of mutations			
Missense, n (%)	71 (55)	37 (100)	
Deletions, n (%)	26 (20)	0 (0)	
Duplications, n (%)	17 (13)	0 (0)	
Nonsense, n (%)	10 (7.8)	0 (0)	
Consensus Splice Site, n (%)	8 (6.2)	0 (0)	

expressed as proportions, continuous variables as medians with ranges. Comparisons between the study groups were performed using Mann-Whitney *U* test and the Chi-square test as appropriate. A multiple line of α-Gal A activity by months of measurement was constructed for each migalastat patient. A bivariate correlation between the relative increase of the α-Gal A activities and the residual α-Gal A activities was calculated in the peripheral leucocytes of patients and in HEK-cells, the latter as previously published.[10] A bivariate correlation between the change of lyso-Gb3 levels, determined in DBS, and the relative increase of α-Gal A activities on migalastat in leucocytes was calculated.

The statistical analyses were performed using the SPSS/PC (version 25.0; SPSS Inc., Chicago, IL) software package. All statistical tests were two-sided, and *P* values <.05 were considered significant.

3 | RESULTS

Overall, 170 patients from 46 families (n = 64 males and 106 females) with 39 different mutations were diagnosed during the last 59 years in Switzerland. The demographic, survival and biochemical information of the patients, according to phenotype, is summarized in Table 1. Detailed information on genotype, phenotype, demographics and ongoing specific treatment for each Fabry family is displayed in Supplementary Table 1.The α-Gal A activity of all males with late-onset phenotype is shown in Table S2.

There were considerably more classic than late-onset phenotype patients (129 vs 41; 68%) diagnosed in Switzerland. Classic phenotype patients included 82 females (47% of the cohort) and 47 males (29%) (Figure S1A). Classic phenotype males were significantly younger than late-onset males (mean age: 39 vs 51 years, $P = .02$). Females of both groups had a similar age (40 vs 39 years, $P = .37$, based on last examination).

In the whole cohort, 84 patients (48%) had amenable mutations, including 43 (25%) patients with classic phenotype (Figure S1B). One third of the classic Fabry patients had an amenable mutation (Table 1).

All 41 patients with late-onset phenotype had amenable missense mutations.

Overall, 11 different mutations were amenable, four encoding for the classic, and seven for the late-onset phenotype (Figure 1). Published data showed that after incubation with migalastat, in vitro α-Gal A activity of the Swiss amenable mutations was 3.7% to 114.8% of mean wild type (control), corresponding to an absolute increase of enzyme activity level between 3.7% and 59.3%.[10]

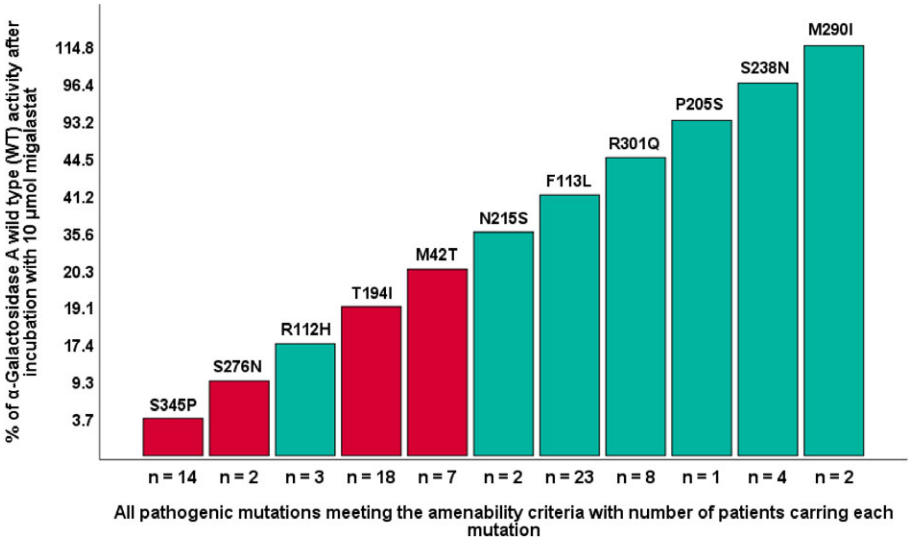

FIGURE 1 Effect of migalastat on the α-Gal A activities Measured in HEK-293 cell lysates with classic (red) and late-onset (green) mutations which meet the amenability criteria

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At present, nine (5 males and 4 females) of the 76 follow-up patients (12%; 3 with classic and 6 with late-onset phenotype) with amenable mutations are treated with migalastat (Table 2). The development of the α-gal A activity in leucocytes of each patient under migalastat treatment is shown in Figure 2.

Migalastat was stopped in 2/11 (18%) patients. A classic male carrying mutation p.S276N had been switched back from migalastat to ERT because of the lyso-Gb3 increase. In another male carrying the benign variant p.R118C, migalastat was initiated because of vertigo and hearing loss which, at this time, were assumed to be Fabry-related, while no other Fabry-related manifestations were present in the patient. However, migalastat was stopped after 1.5 years of treatment due to lack of improvement.

In the leucocytes of our patients, the medians of the achieved α-Gal A activities under migalastat treatment correlated with their residual α-Gal A activities: 0.68, 0.04 (Figure S2). When analyzing previously published data,[10] we remarked that the proportional increase of α-Gal A activities in HEK-Cells after incubation with migalastat in all amenable mutations of this cohort correlated with the residual α-Gal A activities: $R = .94$, $P < .001$ (Figure S3). Overall, 41 determinations of α-Gal A activities in leucocytes were available in the 11 patients, with 1 to 7 determinations in each patient.

Lyso-Gb3 level changes, measured in DBS 6 to 18 months after migalastat treatment initiation, did not correlate with the increase in enzyme activities in the leucocytes in patients on migalastat ($R = .05$, $P = .91$). In patients switched from ERT to migalastat, lyso-Gb3 levels rather increased, particularly in the classic male with mutation p.S276N (Table 2). In contrast, in the late-onset male with mutation p.S238N who was naïve to treatment, lyso-Gb3 level greatly decreased (Table 2).

During the last 59 years in Switzerland, classic families were identified significantly earlier compared to the late-onset families, ($P < .001$, Table 1, Figure 2).

In the last 10 years, 33 of 40 Fabry patients (83%) diagnosed in Switzerland had a late-onset phenotype, suspected in the index cases on the basis of an unexplained cardiac hypertrophy (Figure 3). Subsequently, a cascade screening of their family members was performed.

4 | DISCUSSION

This study investigated the phenotypic, genetic and enzyme amenability spectrum of 39 different *GLA* pathogenic mutations identified in 170 patients from 46 independent pedigrees diagnosed during the last 59 years in Switzerland. All patients were diagnosed based on clinical events or FD-related symptoms and/or after a family screening; all have been confirmed as having a pathogenic *GLA* mutation, as shown in Supplementary Table 1. Almost half the patients (n = 84; 48%) in the Swiss cohort had amenable mutations. Among those, 33% of the classic and 100% of the late-onset phenotype patients had missense mutations fulfilling the current amenability criteria for therapy with migalastat. Interestingly, the amenability degree varied: the higher the residual α-Gal A activity in the leucocytes, the higher the degree of amenability in the treated patients. Along the same lines, the published data using HEK-cells in vitro assay showed that α-Gal A activity before incubation with migalastat correlated with α-Gal A activity achieved with migalastat incubation.[10]

Our study also shows that most late-onset phenotype patients were diagnosed during the last 10 years. This result is most likely due to increasing disease awareness among cardiologists.

Despite the fact that the majority (68%) of all diagnosed patients in the Swiss cohort had a classic phenotype in

TABLE 2 Genetic and clinical characteristics of the Swiss Fabry patients treated with migalastat

GLA mutation, Predicted amino acid change	Phenotype	Age, years	Previous treatment	Leucocytes α-gal A activity, % of controls		α-Gal A Activity in HEK-cells, % of wild type		LysoGb3 levels in DBS, ng/mL (reference<3.5 ng/mL)	
				Residual	+Migalastat[b]	−Migalastat	+Migalastat	Before migalastat[b]	Under migalastat[c] (months since migalastat initiation)
Males									
c.827G>A, p.S276N	Classic	42	α-agalsidase	3.0	9.9 [8.9-10.6]	2.3	9.3	27	109 (18)
c.337T>C, p.F113L	Late-onset	60	-	9.2	33	18	41		
c.644A>G, p.N215S	Late-onset	67	α-agalsidase	BLD[a]	45 [30-62]	16	36	3.6	4.7 (18)
c.713G>A, S238N	Late-onset	63	-	6.8	30	37	96	13	5.6 (7)
c.713G>A,p.S238N	Late-onset	58	α-agalsidase	4.0	24	37	96		8.0 (18)
c.713G>A, p.S238N	Late-onset	56	α-agalsidase	9.0	25	37	96		7.0 (13)
Females									
c.125T>C, p.M42T	Classic	29	α-agalsidase	25	34	2.5	20	6.3	5.9 (3)
c.581C>T, p.T194I	Classic	60	α-agalsidase	7.2	8.9 [4.3-15.5]	2.3	19	7.9	8.2 (12)
c.1033T>C, p.S345P	Classic	33	-	25	71 [70-103]	BLD	3.7	5.3	6.7 (17)
c.902G>A, p.R301Q	Late-onset	71	α-agalsidase	61	127 [112-167]	5.5	45	3.6	3.6 (6)

[a]This result has been repeatedly confirmed and validated by normal enzymatic activity of β-Glucuronidase.
[b]If available; for leucocytes α-gal A activity, median and interquartile range was calculated if >2 measurements were available.
[c]Measured 6 to 18 months after migalastat initiation.
Abbreviations: BLD, below the limit of detection; DBS, dried blood spots; ERT, enzyme replacement therapy.

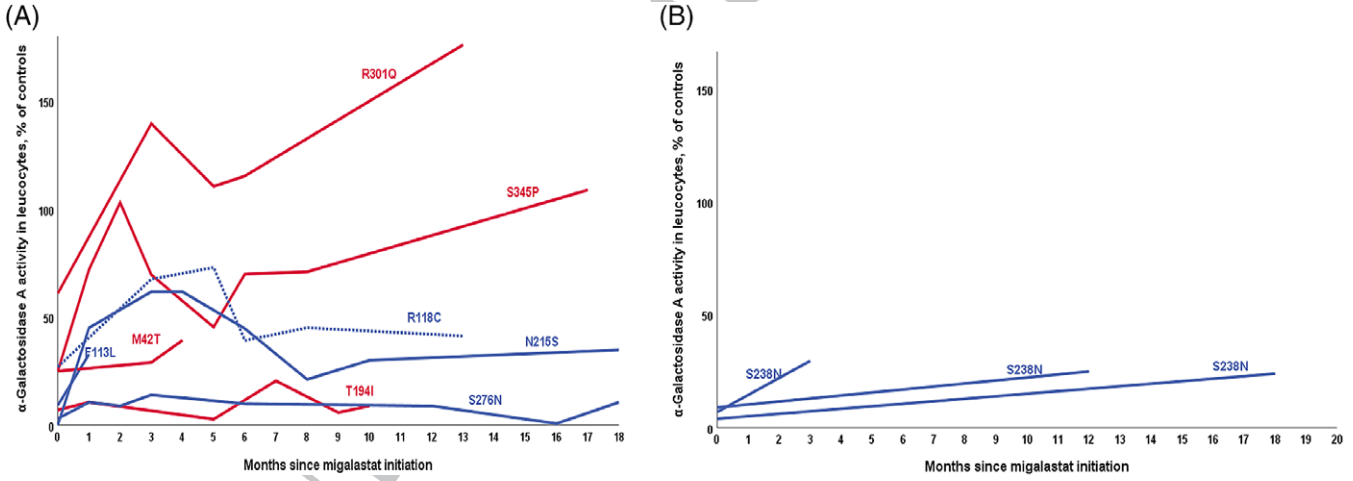

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FIGURE 2 Development of the α-Gal A activities in the peripheral leucocytes for each male and female under migalastat treatment. Dotted line represents the non disease causing variant R118C

males, an increasing number of diagnosed patients (83% during the last 10 years) had a late-onset phenotype, outlining a paradigm change in diagnosis of the disease in recent times. This trend suggests that an even greater proportion of patients with amenable mutations currently remains undiagnosed and may become part of the Fabry community in the future. This consideration is supported by the fact that incidence of FD late-onset phenotype in Europe is 8 to 20-fold as frequent as incidence of classic phenotype, as shown in the newborn screening studies.[14,15]

Only 12% of Fabry patients with amenable mutations are actually treated with migalastat. These patients had classic or late-onset phenotype. While all males with pathogenic *GLA* mutations are treated in Switzerland, asymptomatic female patients with classic or late-onset phenotype are untreated but have an annual follow-up. Some male and

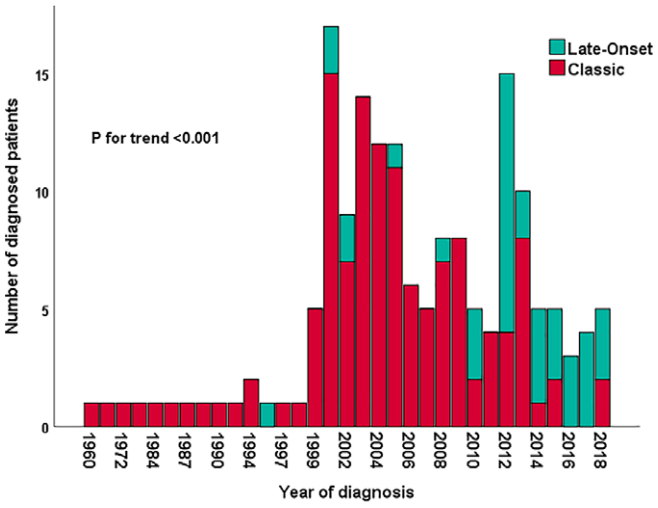

FIGURE 3 Number of patients with classic and late-onset phenotype mutations diagnosed per year

female patients with amenable mutations have been treated with ERT for several years. Due to a stable disease course under ERT, these patients or their treating physicians have chosen not to switch to migalastat.

Two previous studies estimated the proportion of amenable mutations in the databases containing different disease-causing mutations derived from FD patients who participated in phase I-III migalastat studies.[9,16,17] In one of these studies, Wu et al found significant concentration-dependent increases in α-Gal A activity in response to migalastat in 60% (49 of 81) of the mutations included in the database. Similarly, in the other study, Benjamin et al demonstrated that 45% (268 of 600) of mutations showed an increase in α-Gal A activities, fulfilling the amenability criteria.[10] However, the actual proportion of patients who can be considered for migalastat therapy is important: in contrast to a mutation database, a community of Fabry patients consists of families rather than of single mutations, and the cohort composition depends on the diagnostic approaches within a country, such as national screening programs and programs increasing physicians' awareness of the disease. In a study of the Fabry center in Würzburg (Germany), Muntze et al mentioned that 37% of their FD patients had amenable mutations,[18] which is less than in the present Swiss Fabry cohort.

However, clinical experience with migalastat is too short to predict its potential for long-term benefits in patients with amenable mutations. The amenable mutation p. S345P, identified in a family of 14 members in our cohort, results into an absolute activity with migalastat of 3.7% of wild type in the in vitro assay. Despite the fact that the enzymatic increase satisfied the definition of amenability, it is doubtful that the increase in enzyme activity is clinically beneficial.

The minimal α-Gal A activity required to avoid FD has been considered to be 30% to 35% of mean control.[19-21] However, to define amenability for a certain mutation, we currently can only use the expression results in HEK 293 cells. It is unclear to what extent the α-Gal A activity in HEK 293 cells correlate with the in vivo activities in PL of affected Fabry males. For instance, mutation S238N in our cohort has been shown to express 37% of mean control in HEK-cells without migalastat[10]; this value exceeds the mentioned pathogenic threshold of 30% to 35%. However, all three males with this mutation clearly have FD, and their α-Gal A activity was below 10% of mean controls in the leucocytes, as shown in Table 2. Similarly, enzyme activity of the M290I variant expressed in HEK-cells is 68% of mean controls,[10] but has been shown to be clinically associated with FD.[22]

The fact that α-Gal A activity in vivo and in HEK 293 cells can differ illustrates the importance of enzyme testing in both, in vitro and in vivo, at baseline and on migalastat. Importantly, the increase of α-Gal A activities in the leucocytes of our patients correlated with the residual activity, suggesting that (a) patients with higher residual activity derive more benefit from migalastat treatment and (b) the determinations of α-Gal A activity, before and on migalastat should be introduced as standard and used as part of the clinical amenability definition and as a way to follow patients on migalastat. Interestingly, enzyme activity in the patient with the benign variant R118C also increased under migalastat. Nevertheless, migalastat therapy was stopped after 1.5 years of treatment due to the lack of improvement for symptoms initially assumed to be FD-related (vertigo, hearing loss). Consequently, patients with benign non disease-causing variants should not be treated, although their mutations fulfill the amenability criteria.

In the treatment naïve male with late-onset phenotype, lyso-Gb3 decreased along with the increasing α-Gal A activity. In contrast, in the treatment naïve female with the classic phenotype, lyso-Gb3 slightly increased despite an α-Gal A activity increase. In patients switched from ERT to migalastat, lyso-Gb3 tended to increase, particularly in a male with classic phenotype. In patients on ERT, it is not surprising that the change in endogenous enzyme activity does not correlate with change in lyso-Gb3, as they were treated with exogenous enzyme. An increasing level of lyso-Gb3 after switch to migalastat has already been observed in a recent article by Muntze et al.[18] These findings suggest that migalastat cannot stabilize important biomarkers in all patients; the clinical impact of this result needs to be further studied.

Appropriate biomarkers for migalastat therapy monitoring need to be developed.

Importantly, the classic and the late-onset phenotype represent two different entities requiring different diagnostic and therapeutic strategies. The symptomatic classic phenotype can

be clinically suspected and diagnosed early. In contrast, the late-onset phenotype usually remains asymptomatic until the 5th-6th decade, due to significant residual α-Gal A activity. Adult males present relatively early with hypertrophic cardiomyopathy or with chronic kidney disease, often at an advanced stage because of the silent disease progression.[22-25] Thus, for the initially subtle late-onset phenotype, screening programs in risk populations[26] with subsequent cascade family screening may help decrease the number of undiagnosed patients.

The strength of this study is that the phenotypic and amenability composition of the Swiss cohort resulted from the study of a real-life population over a significant 59 year period at multiple centers. Due to Swiss regulations, all adult patients ever diagnosed and treated with FD in Switzerland were registered at the three specialized centers and ERT prescriptions and patient follow-up were preserved at the Fabry centers. This study is limited by the relatively small number of families affected by this rare disease. Additionally, we cannot report long-term clinical treatment experience with migalastat and we also cannot, so far, systematically correlate the α-Gal A activities in the HEK 293 cell assay with that of leucocytes in a large number of males with amenable mutations on migalastat treatment.

In conclusion, patients with both classic and late-onset phenotypes can have amenable mutations. In a national cohort where no systematic screening program has been conducted most patients have classic phenotype, and almost half the patients in the entire cohort have amenable mutations. However, further studies are required to investigate the long-term benefits of migalastat therapy depending on the achieved enzyme activity of different amenable mutations.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Design of the study: A.N., U.H-D., P-A.K., R.S., and F.B. Statistical analysis and first draft: A.N. Wrote the article: A.N., U.H-D., P-A.K., R.S., and F.B. In addition, all authors participated in analysis and interpretation of data and provided critical revisions to the manuscript drafts. All authors read and approved the final article.

ETHICS STATEMENT

This project was approved by the Zurich Ethics Committee; reference number KEK-ZH-Nr. 2014–0534. Q4

ORCID

Albina Nowak https://orcid.org/0000-0002-4119-5516

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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