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## ORIGINAL ARTICLE

# Prevalence of Fabry disease in patients with chronic pain: Lessons from the DOUFAB and DOUFABIS studies

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## Abstract

**Background:** Fabry disease (FD) is a rare X-linked lysosomal disorder caused by alpha-galactosidase deficiency consecutive to a pathogenic variant in the *GLA* gene. Age at onset is highly variable, with a wide clinical spectrum including frequent renal, cardiac, skin and nervous system manifestations. Since pain can be an indicator of underlying FD, we wanted to estimate the prevalence of FD in a population of chronic pain patients.

**Methods:** Two studies, DOUFAB and DOUFABIS, were carried out in expert centers for chronic pain to assess the prevalence of FD by measuring alpha galactosidase A activity in men and analysing the *GLA* gene in women.

The members of the Doufabis Consortium are listed in Appendix.

Virginie Corand, Isabelle Coupry and Cyril Goizet have contributed equally.

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**Results:** Analysis of 893 patients, essentially adults, led to the diagnosis of FD in one female patient, now treated with enzyme replacement therapy.

**Conclusions:** The prevalence of FD is estimated about 1/1000 in our population of men and women suffering from various chronic pain. This is nearly the prevalence of FD observed in other previously screened high-risk populations with renal failure.

**Significance:** Although a systematic search for FD does not seem relevant in the context of unexplained chronic pain in adults, a positive family history of FD or the presence of additional FD related organ features must lead to consider this rare disease diagnosis. Therefore, pain specialists need to be aware of main features of FD, including pain characteristics.

## 1 | INTRODUCTION

Fabry disease (FD) is a rare X-linked lysosomal disorder caused by alpha-galactosidase deficiency consecutive to a pathogenic variant in the *GLA* gene with an estimated prevalence between 1/40,000 and 1/117,000 (Germain, 2010). Globotriaosylceramide (Gb3) deposits are observed in lysosomes of almost all tissues, which result in a wide clinical spectrum including frequent renal, cardiac, skin and nervous system manifestations. Over time, the accumulation of the glycosphingolipids leads to selective destruction of small sensory fibres starting with the distal extremities of the patient's limbs, and is accompanied by the development of pain (Burand & Stucky, 2021). Age at onset is highly variable, generally earlier in males than in females. It is worth noting that heterozygous females are not simply disease carriers but can also be severely affected even if the symptoms appear later than hemizygous males. Furthermore, women describe similar types of pain, which may be more intense than in men. Classic FD with paediatric onset and multi-organ involvement is due to pathogenic variants leading to no residual  $\alpha$ -galactosidase A activity while hypomorphic variants result to residual activity and late-onset FD with predominant cardiac signs (Ortiz et al., 2018). Neuropathic pain, historically described as acroparesthesias, is often the earliest and most prevalent symptom, reported in up to 80% of male and 65% of female patients with classic FD, representing a hallmark of FD (Eng et al., 2007; Hoffmann et al., 2007). However, the prevalence of pain is not known in late onset forms of FD. The availability of two enzymatic replacement therapies (ERT), as well as a chaperone molecule for certain eligible patients, now provide specific treatments for patients requiring earliest diagnosis for better prognosis (Lenders & Brand, 2021).

The prevalence of FD has been estimated in several series of 'high-risk' patients presenting a specific symptom

that could be caused by FD, such as renal failure, left ventricular hypertrophy and early onset stroke (Linthorst et al., 2010; Mallett et al., 2020; Wozniak et al., 2010). Although FD was also screened in a population of 73 patients affected by migraine with aura (Albano et al., 2010), no data are available in patients suffering from other type of chronic pain. The aim of our studies was to determine the prevalence of FD in a population of patients affected by chronic pain and followed in a secondary or tertiary expert center.

## 2 | PATIENTS AND METHODS

### 2.1 | Patients

Informed consent was obtained from each patient (including legal representatives for minor patients). All procedures were carried out with adequate understanding and written consent signed by the patient, in accordance with the declaration of Helsinki and the French law.

The chronic pain patients came from geographical areas close to the expert centre in chronic pain (ECCPs) in which the two studies were conducted. The DOUFAB study was realized via the expert center at Bordeaux University Hospital. For the DOUFABIS study, the 12 centers involved were spread throughout France, including one in an overseas territory. Pain assessment and treatment centers are considered to be referral centers, with a high level of expertise, which is monitored by French government agencies. Under French law, the collection of data relating to race and ethnicity is prohibited. Only information concerning a patient's place of residence may be collected. The first study, DOUFAB (NCT01178164), was exploratory and conducted from September 2010 to September 2012, in a single tertiary ECCP at Bordeaux University Hospital. The following one, DOUFABIS

(NCT02450604), was multicentric, and carried out in 12 French ECCPs, between 5 March 2015 and 5 May 2020. Both were interventional studies with a single open arm for diagnostic purposes. Patients underwent clinical examination and completed a questionnaire covering the study's inclusion criteria. The primary outcome measures were the diagnosis of FD in at least one patient suffering from chronic pain.

In DOUFAB, the inclusion criteria were patients with an age between 6 and 65 years, who came for a clinical visit in the centre, with the presence of chronic pain of unknown cause. Pain typology was characterized by acroparesthesia, pain crises, continued neuropathic pain, multiple pains and/or recurrent abdominal crises of pain (Figure 1). Exclusion criteria were chronic pain of known cause or FD already known in the family. Two hundred inclusions were expected.

The subsequent DOUFABIS study had slightly different inclusion criteria, less restrictive on pain characteristics to improve recruitment feasibility. The investigators planned to evaluate the prevalence of FD in a series of 1000 consecutive patients suffering from variable chronic pain of undetermined cause. The pain typology was characterized by acroparesthesia, pain in the upper or lower limbs, predominantly distal, and/or continuous diffuse pain or pain evolving in crises (Figure 1).

## 2.2 | Genetics and biochemical analyses

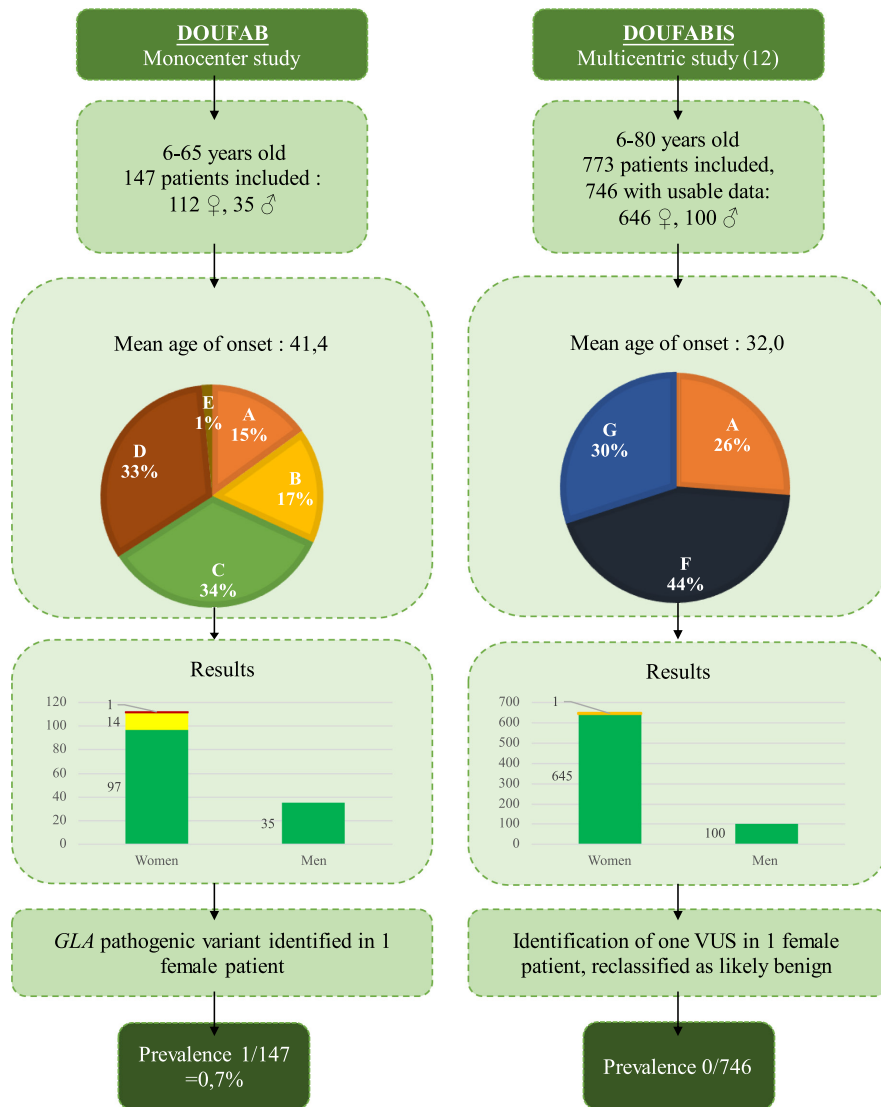
In both studies, FD diagnosis has been performed by gold standard procedures following international recommendations (Germain, 2010; Lidove et al., 2007). These require the search for a deficient alpha-galactosidase A activity in males and direct analysis of the *GLA* gene in females (Caudron et al., 2015). For the DOUFAB study, genomic DNA was extracted from total blood by Wizard genomic DNA Kit (Promega, Lyon, France) and molecular analyses of *GLA* were performed by Sanger sequencing of coding regions and intron-exon junctions amplified by PCR (primer sequences and PCR conditions are available from the authors upon request). In DOUFABIS, genetic analyses were carried out using genomic DNA extracted from an Oragene saliva kit (DNAGenotek, Ontario, Canada) and processed by next-generation sequencing (NGS) on the MiSeq system (Illumina, Evry, France). The *GLA*-specific region (30 kb) was analysed by SureSelect QXT capture (Agilent Technologies, Les Ulis, France). Data generated were analysed using MiSeq reporter and IGV software. If copy number variation was suspected based on NGS coverage depth (normalized number of reads by exon) or the identification of potentially hemizygous SNPs

on all the *GLA* region, search for gene dosage anomaly was performed using dedicated microarray comparative genomic hybridization (aCGH, Agilent Technologies) and CytoGenomics software analysis (v2 to v4, Agilent Technologies), according to previously published conditions (Moutton et al., 2016). Biochemical analyses of enzymatic activity were carried out either on blood sample (DOUFAB) or on blotting paper (DOUFABIS) at the French national reference centre for Fabry disease (<http://centre-geneo.com>). When a diagnosis of FD was suspected, the patient was contacted for an additional visit in the investigating centre in order to confirm the biochemical or molecular result through diagnosis procedures and, when confirmed, to propose specialized assessment and management.

## 3 | RESULTS

The DOUFAB study included 147 consecutive patients, 112 females and 35 males with a mean age at pain onset of 41.4 years. Pain typology is described in Figure 1. No male patients displayed enzymatic deficiency and two likely benign variants (Class 2, according to ACMG classification (Richards et al., 2015)) were present in female patients: p.(Asp315Asp) in one patient and p.(Asp313Tyr) in two patients. The DOUFAB study led to the diagnosis of FD in one patient, a 63-year-old-woman. This patient presented paresthesiae in hands and feet and crises of burning pain in upper limbs, as well as asthenia for 2 years. She also had a history of crises of abdominal pain associated with constipation from 15 to 35 years. There was no family history of FD or pain. At clinical examination, she had numerous skin lesions suggestive of angiokeratomas on the abdomen. Direct sequencing of *GLA* revealed a previously described missense heterozygous pathogenic variant in exon 7: NM\_000169.3: c.1087C>T, p.(Arg363Cys) (Shabbeer et al., 2005) which was confirmed through diagnosis procedures. She then had FD baseline assessment including alpha-galactosidase A activity, which was decreased (4 nmol/h/mg vs. 36 for control), and urine Gb3, which was increased (27.1 nmol/mmol creatinine). Renal assessment showed significant proteinuria (0.35 g/L), with the measured glomerular filtration rate of 91.1 mL/min/1.73 m<sup>2</sup>. Other investigations (ophthalmological, echocardiography, ECG and brain MRI) were normal. Electroneuromyogram revealed a severe sensory asymmetric neuropathy in upper limbs unexpected in the context of FD. A large secondary paraclinical assessment including thoracic-abdominal CT scan led to the diagnosis of paraneoplastic neuropathy related to an ileus carcinoma, in addition with FD neuropathy. The carcinoma was cured by surgery and chemotherapy before ERT with intravenous infusions of agalsidase beta every two weeks was initiated.

**FIGURE 1** Schematic representation of the process and main results of the DOUFAB and DOUFABIS projects.



**Legend :**

Chronic pain of unknown origin :

A : Acroparesthesia

B : Pain crises

C : Continued neuropathic pain

D : Multiple pains

E : Recurrent abdominal crises of pain

F : Pain in the upper or lower limbs, predominantly distal

G : Continuous diffuse pain or pain evolving in crises

■ : no variant

■ : benign variant (class 1) or likely benign variant (class 2)

■ : VUS, class 3

■ : pathogenic variant

DOUFABIS involved 12 pain centres and recruited 773 patients from 6 to 80 years old. Of these 773 patients, the data were usable for 746, including 100 males and 646 females. The mean age at pain onset was 32 years; the median age of onset was 33 years (first interquartile range 17, third interquartile range 44 years). Only 15% of patients had isolated acroparaesthesia as initial pain, and 7% as current pain (Figure 1).

The DOUFABIS study did not reveal any enzymatic deficiency in the male patients and identified six

different benign or likely benign variants (Class 1 and 2) in 14 female patients (3 missense and 3 synonymous) (Table 1) and one variant of uncertain significance (VUS, Class 3) NM\_000169.3: c.311G > A, p.(Gly104Asp) at heterozygous state, in one female patient. At the time of the study, this variant was absent from the GnomAD database (v2.1.1). It has now been reported once (GnomAD v4.0.0), with an allele frequency of  $9.114e^{-7}$ . Screening of 15 female patients for gene dosage anomalies following the identification of homozygous SNPs

**TABLE 1** Classification of variants identified in the *GLA* gene of patients included in the DOUFABIS project.

Variants nomenclature and ACMG classification			Carrier patient number
c.376A>G	p.(Ser126Gly)	Class 2	3
c.478C>T	p.(Tyr152Tyr)	Class 2	1
c.525C>G	p.(Asp175Glu)	Class 3	1
c.560T>C	p.(Leu180Leu)	Class 1	2
c.702T>C	p.(Asp234Asp)	Class 2	1
c.937G>T	p.(Asp313Tyr)	Class 2	6

failed to reveal any *GLA* deletion. The patient carrying the p.(Gly104Asp) variant is a 58-year-old woman with a 10-year history of chronic pain, initially presenting as acroparesthesia, suggestive of neuropathic pain. This VUS in *GLA* was confirmed through diagnosis procedures. The biochemical assessment revealed neither enzymatic deficiency nor plasma lysoGb3 accumulation in this female patient. A family segregation study showed that her two sons were carriers of the VUS at hemizygous state. They had normal alpha-galactosidase A activity leading to consider the VUS as a likely benign variant (Class 2) and to rule out the diagnosis of FD in their family.

## 4 | DISCUSSION

Overall, the search for FD in nearly 1000 patients followed in chronic pain care and treatment expert centers led to the diagnosis of FD in one patient providing an estimated prevalence of about 1/1000 (specifically 1/147 and 0/746) for the studied population. This rate appears to be lower than in populations of patients suffering from renal failure, stroke or left ventricular hypertrophy (LVH), where the prevalence varies according to the studies, as well as the sex of the patients, but appears to be between 0.1% and 0.3% for patients with renal failure, between 0.1% and 4% for stroke and around 1% for LVH. The diagnostic methods used in the studies were mainly based on the measurement of alpha-galactosidase A activity, which fails to diagnose FD in a third of women (Linthorst et al., 2010). Moreover, several of these studies led to erroneous conclusions based on largely admitted pitfalls and difficulties of FD diagnosis (Cabrera & Perretta, 2018; Froissart et al., 2003; Smid et al., 2015; Togawa et al., 2012). Indeed, some benign variants or VUS were misinterpreted as pathogenic leading to overestimation of FD prevalence in some high-risk populations (Albano et al., 2010; Rolfs et al., 2005). In DOUFABIS, we identified such a VUS in *GLA*, c.311G>A, p.(Gly104Asp), illustrating the need for

careful interpretation of the identified variants. Indeed, the final assignment of the status 'likely benign' to this variant has required an extensive and time-consuming family segregation study. This situation, which is common in clinical genetics, illustrates the need for molecular experts to interpret results in *GLA*, and the need for close relationships with a department of medical genetic, which may carry out familial investigations when required for final interpretation (Germain et al., 2022).

Importantly, we identified a FD female patient through the pilot DOUFAB study, although the recruitment of patients was much more important in DOUFABIS. The inclusion criteria were different in terms of pain typology among both studies, allowing us to easily target the type of pain classically found in FD. The DOUFABIS study had broader inclusion criteria, first on age, but also on pain typology, enabling more patients to be included, including patients with a diagnosis of fibromyalgia. Given the frequency of chronic pain in general population of western countries (around 10% in adults (Mansfield et al., 2016)), a diagnosis of FD was expected every 19,000 patients screened. Our study may be positive only by chance and further screening studies on chronic pain population are needed.

In conclusion, a systematic search for FD in chronic pain patients enabled the diagnosis to be made in one of the 893 patients analysed in these two studies. Consequently, the estimated prevalence of FD does not appear to be higher in this type of population, and it does not seem justified to systematically search for FD in patients with chronic pain who have no other relevant personal or family symptoms that could be FD-related. Nevertheless, pain specialists should bear in mind the main features of FD, including pain characteristics associated with small fibre neuropathy (burning, tingling, prickling), (Politei et al., 2016), in order to consider this diagnosis during etiological assessment of their patients, to shorten the classic wandering time observed for FD diagnosis and to offer access to a specific treatment, which is highly effective in reducing pain, particularly in women. (Burand & Stucky, 2021; Feriozzi et al., 2024; Wilcox et al., 2008).

## AUTHOR CONTRIBUTIONS

C.A., V.C., I.C. and C.G. conceived the study, designed the experiments, analysed and interpreted data, and wrote the manuscript. I.C. and G.L., performed experiments; P.F., C.R., D.P.G. and F.J. analysed and interpreted CGH and/or biochemical data. C.A., C.G. analysed the clinical data. C.B. and M-P.B assisted with data analysis and/or experimental design. V.C., M.C., A.-S.B., S.B., A.C., L.D., N.C., S.R.-G., M.M., G.D.M., C. M.-D., E.S., E.S., R.B., J.-M.W., S.R., V.P., J-P.L., J.B. and

M.S. provided human specimens and clinical data. All authors were participants in the discussion of the results and review of the manuscript. V.C., I.C. and C.G. contributed equally to this work.

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## CONFLICTS OF INTEREST STATEMENT

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## APPENDIX A

The DOUFABIS consortium: Myriam Cadenne, Anne-Sophie Blanchet, Sylvie Berciaud, Alexandre Cauchie, Virginie Corand, Laurence David, Nathalie Cantagrel, Stéphanie Ranque-Garnier, Maud Martial, Géraldine De Montgazon, Caroline Maindet-Dominici, Eric Salvat, Elizabeth Sarrazin, Rémi Bellance, Jean-Michel Wattier, Stéphanie Roggerone, Virgine Piano, Jean-Pascal Lefaucheur, Julie Bismuth, Marc Sorel.