Molecular Genetics and Metabolism Reports 36 (2023) 100983

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

# Clinical utility of urinary mulberry bodies/cells testing in the diagnosis of Fabry disease

Katsuya Nakamura [a,b,*], Saki Mukai [c], Yuka Takezawa [c], Yuika Natori [c], Akari Miyazaki [c], Yuichiro Ide [c], Mayu Takebuchi [c], Kana Nanato [c], Mizuki Katoh [c], Harue Suzuki [c], Akiko Sakyu [b], Tomomi Kojima [b], Emiko Kise [b], Hiroaki Hanafusa [b], Tomoki Kosho [b,d], Koichiro Kuwahara [e], Yoshiki Sekijima [a]

[a] Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan
[b] Center for Medical Genetics, Shinshu University Hospital, Matsumoto, Japan
[c] Department of Laboratory Medicine, Shinshu University Hospital, Matsumoto, Japan
[d] Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan
[e] Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan

ARTICLE INFO

*Keywords:*
Fabry disease
Mulberry body
Mulberry cell
Targeted genetic approach
*GLA*
Accuracy

ABSTRACT

*Introduction:* Variants in the galactosidase alpha (*GLA*) gene cause Fabry disease (FD), an X-linked lysosomal storage disorder caused by α-galactosidase A (α-GAL) deficiency. Recently, disease-modifying therapies have been developed, and simple diagnostic biomarkers for FD are required to initiate these therapies in the early stages of the disease. Detection of urinary mulberry bodies and cells (MBs/MCs) is beneficial for diagnosing FD. However, few studies have evaluated the diagnostic accuracy of urinary MBs/MCs in FD. Herein, we retrospectively evaluated the diagnostic ability of urinary MBs/MCs for FD.

*Methods:* We analyzed the medical records of 189 consecutive patients (125 males and 64 females) who underwent MBs/MCs testing. Out of these, two female patients had already been diagnosed with FD at the time of testing, and the remaining 187 patients were suspected of having FD and underwent both *GLA* gene sequencing and/or α-GalA enzymatic testing.

*Results:* Genetic testing did not confirm the diagnosis in 50 females (26.5%); hence, they were excluded from the evaluation. Two patients were previously diagnosed with FD, and sixteen were newly diagnosed. Among these 18 patients, 15, including two who had already developed HCM at diagnosis, remained undiagnosed until targeted genetic screening of at-risk family members of patients with FD was performed. The accuracy of urinary MBs/MCs testing exhibited a sensitivity of 0.944, specificity of 1, positive predictive value of 1, and negative predictive value of 0.992.

*Conclusions:* MBs/MCs testing is highly accurate in diagnosing FD and should be considered during the initial evaluation prior to genetic testing, particularly in female patients.

## 1. Introduction

Fabry disease (FD; MIM301500) is an X-linked lysosomal storage disorder resulting from a deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A; EC3.2.1.22). α-Gal A deficiency causes sphingolipid deposition in various cells [1]. Different *GLA* variants are associated with different levels of α-Gal A activity, resulting in a heterogeneous clinical presentation of FD. Affected males with low or undetectable α-Gal A activity exhibit the classic childhood-onset phenotype. With advancing age, renal failure, cardiac disease, and stroke contribute to a decline in daily activities and premature death. In contrast, patients with residual α-Gal A activity have late-onset and milder phenotypes of FD,

*Abbreviations:* FD, Fabry disease; α-Gal A, α-galactosidase; MBs, Mulberry bodies; MCs, Mulberry cells; HCM, hypertrophic cardiomyopathy; NBS, newborn screening.

* Corresponding author at: Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan.
*E-mail address:* katsuya@shinshu-u.ac.jp (K. Nakamura).

https://doi.org/10.1016/j.ymgmr.2023.100983
Received 24 May 2023; Accepted 30 May 2023

which are typically restricted to the main affected organs [2,3]. Despite being linked to the X chromosome, heterozygous females with pathogenic *GLA* variants can develop a more variable phenotype [1].

Recently, disease-modifying therapies such as enzyme replacement therapy [4,5] and pharmacological chaperone therapy [6] have been approved worldwide. These treatments are preferably initiated in the early stages of FD before cardiac, renal, and other organ damages occur. Diagnosis in male FD patients can be confirmed by decreased α-GalA activity in plasma, leukocytes, and dried blood spots. In contrast, some heterozygous female patients have normal or slightly reduced α-GalA activity due to random X-chromosomal inactivation, so *GLA* sequencing is required to confirm the diagnosis [1]. Moreover, the symptoms of patients with early-stage FD lack disease-specific features [7]. Thus, simple diagnostic biomarkers specific to FD are required for better diagnosis of clinically relevant FD [8].

Mulberry bodies (MBs) are the characteristic fatty components of urinary sediments that appear as whorled laminated bodies, while mulberry cells (MCs) are distal tubular epithelial cells loaded with MBs [9]. Although the detection of urinary MBs or MCs can aid in the early diagnosis of FD [10,11], few studies have evaluated the accuracy of this diagnostic method [12,13]. Moreover, whether MBs/MCs can be detected in the urine of patients at different stages of FD, heterozygous females, and asymptomatic *GLA* variant carriers remains unknown.

This study retrospectively analyzed the outcomes of MBs/MCs testing and definitive diagnosis in patients with suspected FD to determine the clinical utility of urinary MBs/MCs as a diagnostic biomarker for FD.

## 2. Materials and methods

### 2.1. Patients

We enrolled 189 consecutive patients (125 males, 64 females) who underwent MBs/MCs testing between January 2018 and December 2022 at the Departments of Neurology, Cardiology, and Center for Medical Genetics of Shinshu University Hospital. Two female patients had already been diagnosed with FD at the time of MBs/MCs testing, and the remaining 187 patients (125 males, 62 females) were suspected of having FD and underwent *GLA* gene sequencing and/or α-GalA enzymatic testing following the MBs/MCs testing. Clinical information was retrospectively extracted from the medical records. The diagnosis of FD was confirmed based on the results of genetic testing in female patients, whereas only α-Gal A activity was evaluated for diagnosis in males.

### 2.2. α-Gal A activity and GLA gene sequencing

α-Gal A activity was evaluated in leukocytes or dried blood spots on filter paper at three specialized clinical laboratories. Total genomic DNA was extracted from patient leukocytes for DNA analysis. In the index patients, all seven exons and flanking intron sequences of the *GLA* were analyzed by direct sequencing or targeted exome sequencing according to standard protocols. Among the family members of patients previously diagnosed with FD, only the variant carried by the index patient was tested using direct sequencing.

### 2.3. Evaluation of MBs/MCs in the urine

Urinary sediments were analyzed according to the standard guidelines for examining urinary sediments by the Japanese Committee for Clinical Laboratory Standards [14]. Nine clinical laboratory technicians evaluated the urinary sediment samples in a rotating shift. When assessing urinary MBs/MCs, the technicians were blinded to the patient's detailed clinical information. Fig. 1 summarizes the methods used for MBs/MCs testing. Briefly, 10 mL of the patient's urine was centrifuged at 500 ×*g* for 5 min, and the sediment volume was reduced to 0.2 mL using an aspirator (Fig. 1A, B). The urinary sediment was thoroughly mixed, and 15 μL of the sample was placed on a glass slide (Fig. 1C), mounted using a cover glass, and examined under an optical microscope (Fig. 2). The results of the MBs/MCs tests were evaluated qualitatively.

### 2.4. Targeted genetic approach

A targeted genetic approach program was conducted at the Center for Medical Genetics and the Department of Neurology of Shinshu University Hospital. In short, a certified genetic counselor contacted the patient whenever a new index patient was referred to our group, and a familial pedigree was constructed. We identified family members at genetic risk for FD at a pre-genetic counseling meeting. During genetic counseling, we provided clients with medical and genetic information and encouraged them to inform at-risk family members to visit our hospital for genetic counseling. Genetic counseling for asymptomatic family members was provided step-by-step in the patient's pedigree, first from older at-risk family members and then down.

### 2.5. Protocol approvals

This study was approved by the Ethics Committee of Shinshu

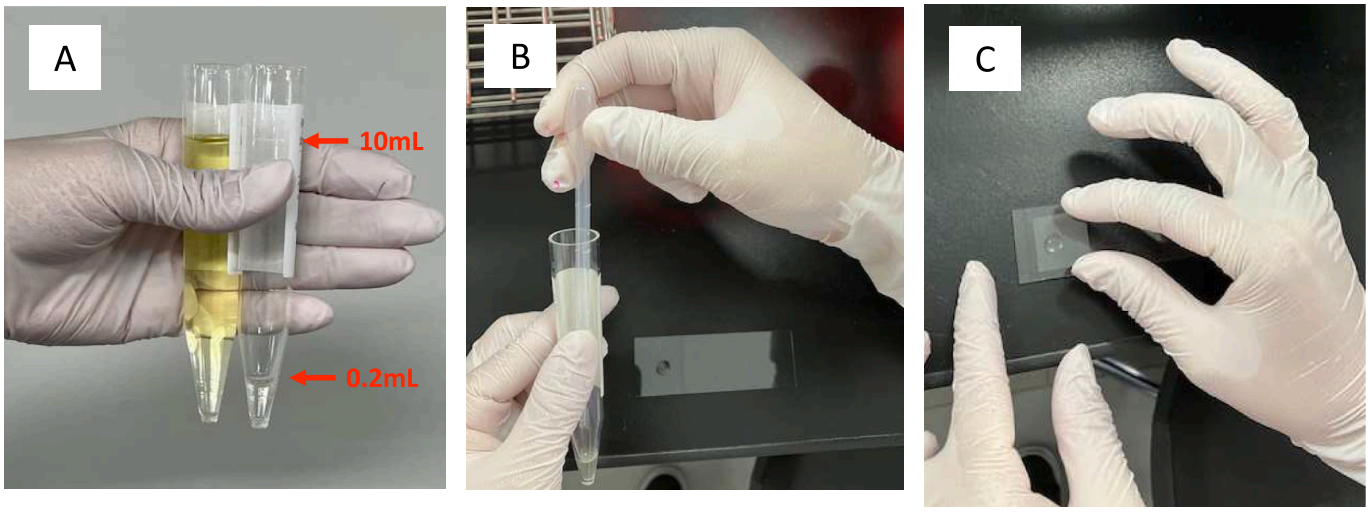


**Fig. 1.** Standard protocol for urinary Mulberry bodies/Mulberry cells testing. (A) Ten milliliters of the patient's urine was centrifuged at 500 ×*g* for 5 min, and the sediment volume was reduced to 0.2 mL using an aspirator. (B) The urine sediment was thoroughly mixed. (C) Fifteen microliters of the sediment were loaded onto a glass slide. A cover glass was placed over the sample, and the specimens were examined under an optical microscope.

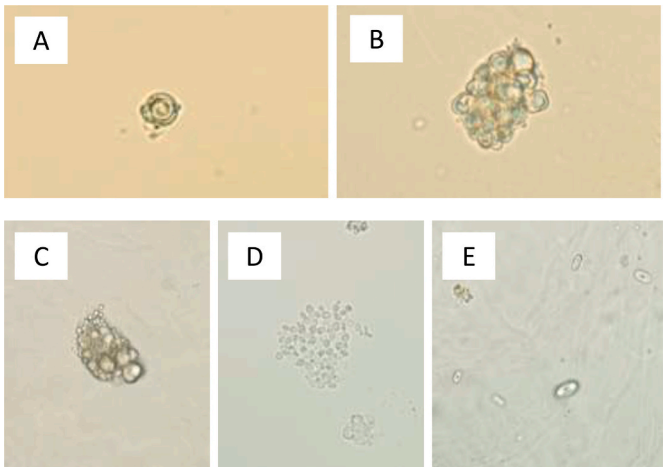


**Fig. 2.** Findings of urinary sediments. (A, B) Mulberry bodies (MBs) (A) and mulberry cells (MBc) (B) were observed. (C-E) Urine sediments which resemble MBs/MCs, (C) oval fat bodies, (D) fungus, (E) and calcium oxalate crystals.

University School of Medicine and the Ethics Committees of all participating clinical neurology centers. Written informed consent was obtained from all patients who underwent genetic evaluation.

## 3. Results

### 3.1. Results of the MBs/MCs testing and clinical diagnosis

Fig. 3 summarizes the demographic characteristics of the enrolled patients. Of the 189 patients, two (1.1%) had previously been diagnosed with FD, whereas 187 (98.9) had clinically suspected FD. In addition, 16 (9.5%) of the 187 patients had a confirmed diagnosis of FD, whereas 121 (64.0%) did not. Furthermore, 50 females (26.5%) were considered clinically negative for FD; however, this was not confirmed by genetic testing. Therefore, we excluded them from further evaluation. The MBs/MCs testing results were positive in 17 of the 18 patients with FD and negative in all 121 patients without FD. The MBs/MCs testing sensitivity, specificity, positive predictive value, and negative predictive value were 0.944, 1, 1, and 0.992, respectively (Table 1). For specificity, we confirmed that MBs/MCs were negative in two patients with other lysosomal diseases, including Gaucher disease and mucopolysaccharidosis type II.

### 3.2. Clinical data of patients with FD

The clinical, biochemical, and molecular characteristics of patients with FD are summarized in Table 2. Altogether, 18 patients (6 males and 12 females) from five families were diagnosed with FD. Among them, five patients developed hypertrophic cardiomyopathy (HCM), and one patient developed sudden hearing loss. Five patients experienced limb pain. Furthermore, among the 18 patients, 15, including two who already developed HCM at diagnosis, remained undiagnosed until targeted genetic screening of at-risk family members of patients with FD was performed. All patients showed preserved eGFR, and three patients exhibited albuminuria. Except for one patient (Patient 6), all patients were positive for MBs and/or MCs, including asymptomatic male and female variant carriers. Patient 6 was interviewed and suspected of being unable to collect sufficient urine for MBs/MCs testing.

## 4. Discussion

To date, only two studies have reported the accuracy of MBs/MCs testing in diagnosing FD. Selvarajah et al. reported that the sensitivity and specificity of these tests were 97.1% and 100%, respectively, in 35 patients with FD and 21 controls with other renal diseases [12]. In contrast, Yonishi et al. reported a relatively lower positivity ratio and showed that 32 of the 51 (62.7%) patients with FD were positive for MBs/MCs [13]. Here, we evaluated the accuracy of MBs/MCs testing in FD patients and found that these tests have high sensitivity and specificity. Interestingly, urinary MBs/MCs were detected in most patients with FD, including an asymptomatic 6-year-old boy and an 80-year-old male with normal renal function at the time of testing. Moreover, all asymptomatic female carriers tested positive for MBs/MCs. These findings suggest that MBs/MCs testing should not only be considered an initial screening option before genetic testing, particularly in female patients, but could also be useful in areas where diagnostic facilities and resources are limited.

In patients with FD, accurate diagnosis and subsequent initiation of disease-modifying therapies at an early stage are critical for preserving organ function and improving prognosis. However, epidemiological studies suggest that most patients are diagnosed ten or more years after the onset of FD symptoms [7]. It is also estimated that a significant number of patients remain undiagnosed [15]. To improve FD diagnosis,

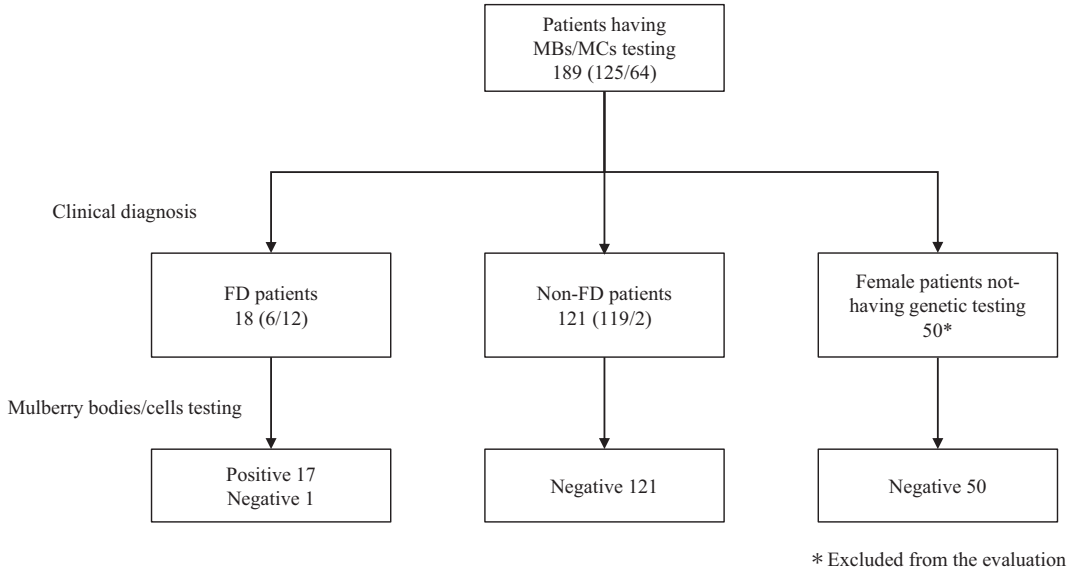


**Fig. 3.** Flowchart depicting the study design.

**Table 1**
Diagnostic accuracy of mulberry bodies/cells testing used for the diagnosis of Fabry diseases.

| Results of MBs/Mcs testing | FD patients ($n = 18$) | Non-FD patients ($n = 121$) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| Positive | 17 | 0 | 94.40% | 100% | 100% | 99.20% |
| Negative | 1 | 121 | | | | |

FD: Fabry disease; PPV: positive predictive value; NPV: negative predictive value.

**Table 2**
Clinical features of patients with *GLA* gene mutation.

| Patient | Age | Sex | Disease duration* (years) | αGalA activity (%) | *GLA* variant | Results of MBs/MCs testing | CKD stages | proteinuria (mg/dl) | albuminuria (mg/l) | Other clinical manifestations |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 69 | F | 25 | normal | c.1235_1236del | positive | G3a | 100 | >150 | HCM |
| 2 | 41 | F | 0 | 80% | c.2 T > C (p.M1T) | positive | G2 | 15 | 80 | HCM |
| 3 | 9 | M | 0 | 8% | c.2 T > C, (p.M1T) | positive | G1 | nd | 10 | pain |
| 4 | 80 | M | 6 | 10.60% | c.547 + 4A > G | positive | G3b | nd | 10 | HCM |
| 5 | 50 | F | 0 | normal | c.547 + 4A > G | positive | G2 | nd | 30 | – |
| 6 | 21 | M | 0 | 12.10% | c.547 + 4A > G | negative | G1 | nd | 10 | – |
| 7 | 80 | F | 0 | normal | c.950C > T (p.I317T) | positive | G2 | nd | 10 | – |
| 8 | 61 | M | 34 | nd | c.950C > T (p.I317T) | positive | G2 | nd | 30 | HCM |
| 9 | 58 | F | 0 | normal | c.950C > T (p.I317T) | positive | G1 | nd | 10 | – |
| 10 | 50 | F | 0 | normal | c.950C > T (p.I317T) | positive | G1 | 15 | 80 | – |
| 11 | 34 | F | 0 | 47.60% | c.950C > T (p.I317T) | positive | G2 | nd | 30 | pain |
| 12 | 32 | F | 3 | ne | c.950C > T (p.I317T) | positive | G1 | nd | 30 | sudden hearing loss |
| 13 | 26 | M | 0 | 0.20% | c.950C > T (p.I317T) | positive | G1 | nd | 10 | pain |
| 14 | 25 | F | 0 | normal | c.950C > T (p.I317T) | positive | G1 | nd | 10 | – |
| 15 | 24 | F | 0 | normal | c.950C > T (p.I317T) | positive | G1 | nd | 10 | – |
| 16 | 5 | M | 0 | ne | c.950C > T (p.I317T) | positive | ne | ne | ne | – |
| 17 | 45 | F | 1 | normal | c.658C > T (p.R220X) | positive | G2 | nd | 10 | pain, HCM |
| 18 | 20 | F | 0 | 74% | c.658C > T (p.R220X) | positive | G2A | 15 | 30 | pain |

CKD:chronic kidney disease stages; HCM: hypertrophic cardiomyopathy; FH: family history of Fabry disease; ne: not examined; nd: not detected. *The disease duration is defined as the period from the statement of first cardiac, renal, or central nervous symptoms to diagnosis.

newborn screening (NBS) programs have become widespread in some countries [16,17]. These screenings have significant potential to identify more FD patients than estimated in cross-sectional studies. However, since these NBS programs are based on the measurement of α-Gal A activity, FD might be underdiagnosed in heterozygous women. MBs/MCs testing is simple and cost-effective; hence, it can be used as the first-step screening of FD, particularly in the female population. Knowledge about MBs/MCs testing should be promoted to increase the number of skilled clinical laboratory technicians. In the future, the development of new technologies, including automated urinary sediment testing with artificial intelligence-based decision support system, may improve FD diagnosis [18].

Although this was a single-center study, it included 16 patients with newly diagnosed FD. Among them, 13 (81.3%) were at-risk family members of the patients previously diagnosed with FD. The patients visited our hospital for targeted genetic testing. Genetic testing of at-risk family members may improve the early diagnosis of FD; however, potential barriers have been identified, including screening and treatment costs, local regulations, and cultural issues [19]. Similar to our targeted genetic approach, several studies have reported the benefits of clinical genetic approaches using genetic counseling and family screening [20,21]. These programs included predictive genetic testing, which could have adverse psychological effects on clients [22,23]. For psychosocial support of at-risk family members, teams experienced in predictive testing should optimize the targeted genetic approach for these individuals [24].

Our study included only a limited number of females for whom FD could be excluded based on genetic testing. All 50 female patients with no clinical suspicion of FD were negative for MBs/MCs, although FD could have been underdiagnosed in these cases. Therefore, our results might have overestimated the sensitivity of heterozygous females. This study qualitatively assessed urinary MBs/MCs; however, a recent semi-quantitative measurement study showed that the excretion of urinary MBs resulted from podocyte injury, and ERT significantly reduced urinary MBs excretion. Further studies are needed to clarify the potential of MBs/MCs testing as a surrogate marker for FD.

## 5. Conclusion

MBs/MCs testing is highly reliable in diagnosing patients with clinically suspected FD, having sensitivity, specificity, positive predictive value, and negative predictive value of 0.944, 1, 1, and 0.992,

respectively. Because MBs/MCs are urinary sediments that can be easily underdiagnosed, clinical information about a patient with suspected FD should be provided to the laboratory technician when the physician orders the MBs/MCs testing. Promoting the acquisition of MBs/MCs testing skills by clinical technologists is necessary to improve the diagnosis of FD, particularly in female patients.

## Human participants

This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was not required for this study because it did not include any individually identifiable human subject data or protected health information.

## Animal rights

This article does not contain any studies on animals performed by any of the authors.

## Details of the contributions of individual authors

KN has contributed to pertinent aspects of the planning, execution, and reporting of the work described in the article. Study concept and design: KN, TK, KK, and YS. Data collection and analysis: SM, YT, YN, AM, YI, MT, KN, MK, HS, AS, TK, EK, and HH. Original draft preparation: KN. The author(s) read and approved the final manuscript.

## Data sharing statement

The data that support the findings of this study are available from the corresponding author on request.

## Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare no use of generative AI or AI-assisted technologies during the writing process.

## Declaration of Competing Interest

KN reports receiving speakers' bureau fees from Amicus Therapeutics, Sanofi, Sumitomo, and Takeda; and grants/research funding from Amicus Takeda. Other authors declare no competing interests.

## Data availability

Data will be made available on request.

## Acknowledgments

The authors thank Dr. T. Sakashita and Dr. S. Nagai for their insightful discussions. This study was partially supported by a Grant-in-Aid from the Takeda Japan Medical Office Funded Research Grant.

## References

[1] A. Mehta, D.A. Hughes, Fabry Disease. Gene Review®, Available from: https://www.ncbi.nlm.nih.gov/books/NBK1292/ (Accessed on April 10, 2023).
[2] S. Nakao, T. Takenaka, M. Maeda, C. Kodama, A. Tanaka, M. Tahara, et al., An atypical variant of Fabry's disease in men with left ventricular hypertrophy, N. Engl. J. Med. 333 (5) (1995) 288–293, https://doi.org/10.1056/NEJM199508033330504.
[3] S. Nakao, C. Kodama, T. Takenaka, A. Tanaka, Y. Yasumoto, A. Yoshida, et al., Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype, Kidney Int. 64 (3) (2003) 801–807, https://doi.org/10.1046/j.1523-1755.2003.00160.x.
[4] C.M. Eng, N. Guffon, W.R. Wilcox, D.P. Germain, P. Lee, S. Waldek, et al., Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease, N. Engl. J. Med. 345 (1) (2001) 9–16, https://doi.org/10.1056/NEJM200107053450102.
[5] R. Schiffmann, J.B. Kopp, H.A. Austin Iii, S. Sabnis, D.F. Moore, T. Weibel, et al., Enzyme replacement therapy in Fabry disease, JAMA. 285 (21) (2001) 2743–2749, https://doi.org/10.1001/jama.285.21.2743.
[6] M. Lenders, E. Brand, Fabry disease: the current treatment landscape, Drugs. 81 (6) (2021) 635–645, https://doi.org/10.1007/s40265-021-01486-1.
[7] M. Beck, U. Ramaswami, E. Hernberg-Ståhl, D.A. Hughes, C. Kampmann, A. B. Mehta, et al., Twenty years of the Fabry outcome survey (FOS): insights, achievements, and lessons learned from a global patient registry, Orphan. J. Rare Diseas. 17 (1) (2022) 238, https://doi.org/10.1186/s13023-022-02392-9.
[8] A. Nowak, T.P. Mechtler, R.J. Desnick, D.C. Kasper, Plasma LysoGb3: a useful biomarker for the diagnosis and treatment of Fabry disease heterozygotes, Mol. Genet. Metab. 120 (1–2) (2017) 57–61, https://doi.org/10.1016/j.ymgme.2016.10.006.
[9] H. Shimohata, H. Maruyama, Y. Miyamoto, M. Takayasu, K. Hirayama, M. Kobayashi, Urinary mulberry cells and mulberry bodies are useful tool to detect late-onset Fabry disease, CEN Case Rep. 6 (2) (2017) 148–151, https://doi.org/10.1007/s13730-017-0262-5.
[10] T. Nakamichi, M. Miyazaki, K. Nakayama, M. Sato, N. Akiu, T. Sato, et al., Fabry's disease discovered with chance urinary mulberry cells: a case report, CEN Case Rep. 2 (1) (2013) 49–52, https://doi.org/10.1007/s13730-012-0038-x.
[11] R.C. Pabico, B.C. Atancio, B.A. McKenna, T. Pamukcoglu, R. Yodaiken, Renal pathologic lesions and functional alterations in a man with Fabry's disease, Am. J. Med. 55 (3) (1973) 415–425, https://doi.org/10.1016/0002-9343(73)90140-x.
[12] M. Selvarajah, K. Nicholls, T.D. Hewitson, G.J. Becker, Targeted urine microscopy in Anderson-Fabry disease: a cheap, sensitive and specific diagnostic technique, Nephrol. Dial. Transplant. 26 (10) (2011) 3195–3202, https://doi.org/10.1093/ndt/gfr084.
[13] H. Yonishi, T. Namba-Hamano, T. Hamano, M. Hotta, J. Nakamura, S. Sakai, et al., Urinary mulberry bodies as a potential biomarker for early diagnosis and efficacy assessment of enzyme replacement therapy in Fabry nephropathy, Nephrol. Dial. Transplant. 37 (1) (2021) 53–62, https://doi.org/10.1093/ndt/gfaa298.
[14] Standard Guideline for Urinary Sediment Examination: The Japanese Committee for Clinical Laboratory Standards, Available from: https://www.jccls.org/pdf/approval/2010_GP1-P4.pdf, 2010 (Accessed on April 10, 2023).
[15] T. Inoue, K. Hattori, K. Ihara, A. Ishii, K. Nakamura, S. Hirose, Newborn screening for Fabry disease in Japan: prevalence and genotypes of Fabry disease in a pilot study, J. Hum. Genet. 58 (8) (2013) 548–552, https://doi.org/10.1038/jhg.2013.48.
[16] T. Sawada, J. Kido, S. Yoshida, K. Sugawara, K. Momosaki, T. Inoue, et al., Newborn screening for Fabry disease in the western region of Japan, Mol. Genet. Metabol. Rep. 22 (2020), 100562, https://doi.org/10.1016/j.ymgmr.2019.100562.
[17] V. Gragnaniello, A.P. Burlina, G. Polo, A. Giuliani, L. Salviati, G. Duro, et al., Newborn screening for Fabry disease in northeastern Italy: results of five years of experience, Biomolecules. 11 (7) (2021) 951, https://doi.org/10.3390/biom11070951.
[18] H. Uryu, O. Migita, M. Ozawa, C. Kamijo, S. Aoto, K. Okamura, et al., Automated urinary sediment detection for Fabry disease using deep-learning algorithms, Mol. Genet. Metabol. Rep. 33 (2022), 100921, https://doi.org/10.1016/j.ymgmr.2022.100921.
[19] D.P. Germain, S. Moiseev, F. Suárez-Obando, F. Al Ismaili, H. Al Khawaja, G. Altarescu, et al., The benefits and challenges of family genetic testing in rare genetic diseases—lessons from Fabry disease, Mol. Genet. Genom. Med. 9 (5) (2021), e1666, https://doi.org/10.1002/mgg3.1666.
[20] P.A. Rozenfeld, F.M. Masllorens, N. Roa, F. Rodriguez, M. Bonnano, C. Yvorra, et al., Fabry pedigree analysis: a successful program for targeted genetic approach, Mol. Genet. Genom. Med. 7 (7) (2019), e00794, https://doi.org/10.1002/mgg3.794.
[21] S. Moiseev, E. Tao, A. Moiseev, N. Bulanov, E. Filatova, V. Fomin, et al., The benefits of family screening in rare diseases: genetic testing reveals 165 new cases of Fabry disease among at-risk family members of 83 index patients, Genes. 13 (9) (2022) 1619, https://doi.org/10.3390/genes13091619.
[22] E. Almqvist, M. Bloch, R. Brinkman, D. Craufurd, M. Hayden, A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease, Am. J. Hum. Genet. 64 (5) (1999) 1293–1304, https://doi.org/10.1086/302374.
[23] A. Hubers, E. Duijn, R. Roos, D. Craufurd, H. Rickards, B. Landwehrmeyer, et al., Suicidal ideation in a European Huntington's disease population, J. Affect. Disord. 151 (1) (2013) 248–258, https://doi.org/10.1016/j.jad.2013.06.001.
[24] K. Nakamura, Y. Sekijima, Genetic counseling and predictive testing for hereditary neuromuscular diseases, Clin. Neurol. 61 (9) (2021) 588–593, https://doi.org/10.5692/clinicalneurol.cn-001608.