Gene variants of unknown significance in Fabry disease: Clinical characteristics of c.376A>G (p.Ser126Gly)

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Abstract

Background: Anderson–Fabry disease (FD) is an X-linked lysosomal storage disorder with varying organ involvement and symptoms, depending on the underlying mutation in the alpha-galactosidase A gene (HGNC: GLA). With genetic testing becoming more readily available, it is crucial to precisely evaluate pathogenicity of each genetic variant, in order to determine whether there is or might be a need for FD-specific therapy in affected patients and relatives at the time point of presentation or in the future.

Methods: This case series investigates the clinical impact of the specific GLA gene variant c.376A>G (p.Ser126Gly) in five (one heterozygous and one homozygous female, three males) individuals from different families, who visited our center between 2009 and 2021. Comprehensive neurological, nephrological and cardiac examinations were performed in all cases. One patient received a follow-up examination after 12 years.

Results: Index events leading to suspicion of FD were mainly unspecific neurological symptoms. However, FD-specific biomarkers, imaging examinations (i.e., brain MRI, heart MRI), and tissue-specific diagnostics, including kidney and skin biopsies, did not reveal evidence for FD-specific symptoms or organ involvement but showed normal results in all cases. This includes findings from 12-year follow-up in one patient with renal biopsy.

Conclusion: These findings suggest that p.Ser126Gly represents a benign GLA gene variant which per se does not cause FD. Precise clinical evaluation in individuals diagnosed with genetic variations of unknown significance should be performed to distinguish common symptoms broadly prevalent in the general population from those secondary to FD.

Keywords
diagnosis in Fabry disease, Fabry disease, gene variant, genotype/phenotype correlation, lysosomal storage disease
1 | BACKGROUND

Anderson–Fabry disease (FD) (OMIM: #301500) is an X-linked lysosomal storage disorder (Germain, 2010). The incidence of FD varies in literature from 1:40,000 to 1:117,000 (Mehta et al., 2004; Meikle et al., 1999; van der Tol, Cassimian, et al., 2014). Due to the broad range of symptoms and organ manifestations, FD is a genetic disorder with particularly complex clinical presentation. Classic symptoms, which decrease life expectancy, include renal failure and hypertrophic cardiomyopathy (Cairns et al., 2018). Additionally, FD can affect the central and peripheral nervous systems, the gastrointestinal tract, ears, eyes, and skin (Zarate & Hopkin, 2008). Because of the X-linked inheritance, men are affected more frequently and more seriously. More than 1000 distinct mutations in the alpha-galactosidase A gene (HGNC: GLA) (OMIM: #30064; HGNC: 4296) have been described so far (McCafferty & Scott, 2019). Besides “classical” mutations, known to usually cause the full clinical picture of FD, many variants of unknown or attenuated clinical significance are known to date. Some mutations can lead to a “late-onset” or “organ-specific” form of FD with mild symptoms and/or later onset of apparent disease (Oder et al., 2017). In addition, due to increasing disease awareness and better availability of genetic testing, there is increasing evidence of genetic variants with no relevant degree of disease (Oder et al., 2018). One key aspect in the management of patients with a genetic variant in the GLA is to evaluate if there is a need for FD-specific therapy (Ortiz et al., 2018). This decision can be difficult, especially in women, who show particularly high variance in disease penetration, in young male patients without manifest disease, where a “preventive” initiation of treatment is considered and in patients of both genders carrying genetic variations of unknown clinical significance (Wanner et al., 2019). Early and unnecessary treatment of benign genetic variants should clearly be avoided to prevent stigma and/or potential side effects of related individuals and their relatives, but also for health-economic reasons (Wanner et al., 2018).

This case series highlights clinical characteristics of patients carrying the c.376A>G (p.Ser126Gly) (NCBI reference sequence: NM_000169.3:c.376A>G) mutation. Until now, scientific evidence of clinical presentation linked with this mutation has been controversial. Branton et al. described p.Ser126Gly in 2002 as a pathogenic variant of FD (Branton et al., 2002). A Belgian prevalence study from 2010 linked the mutation to appearance of late-onset FD (Brouns et al., 2010). In contrast, literature research at “International Fabry Disease Genotype-Phenotype Database (dBFGP)” describes p.Ser126Gly as a likely benign variant of FD causing mutations. However, due to inconclusive clinical data available, dBFGP also recommends further assessments to confirm that this mutation is a benign variant (dBFGP.org, 2021, April 7).

2 | METHODS

We extensively examined five individuals from different families carrying the p.Ser126Gly variant of the GLA gene. All five patients visited the Fabry Center for Interdisciplinary Therapy (FAZiT) Würzburg, Germany. Every patient at FAZiT obtains a standardized full clinical, laboratory, and imaging examination, focusing on all possible aspects of FD. This clinical work-up involved a complete cardiac examination with echocardiographic and cardiac magnetic resonance tomography imaging (MRI), paying particular attention to cardiac hypertrophy and signs of fibrosis of the left ventricle. A Holter- and exercise-ECG for detection of cardiac arrhythmias is also implemented. Renal function assessment includes glomerular filtration rate (GFR) calculated with creatinine as well as Cystatin C, proteinuria, and renal biopsy if indicated. Patients also underwent complete neurological examination, nerve conduction studies, quantitative sensory testing (QST), and skin punch biopsy at the lower leg and back to determine the intraepidermal nerve fiber density (IENFD). Additionally, cerebral and spinal MRI scans were performed. In one case, a 12-year follow-up was possible to conduct.

This multidisciplinary approach at FAZiT ensures a complete evaluation of patient’s clinical condition. If indicated, experts from other disciplines for example, ophthalmology, otorhinolaryngology, or dermatology are consulted on site.

3 | CASE PRESENTATIONS

All patients carried the p.Ser126Gly variant and were evaluated for clinical signs or symptoms of potential FD. After evaluation, the patients were assessed for FD-specific therapy indication. Clinical characteristics of these patients are shown in Table 1.

Patient 1 was a man in his late 40’s, who presented at FAZiT with symptoms of acral pain, hypohidrosis, and heat intolerance. Past medical history includes hyperthyroidism from a multinodular goiter treated by thyroidec-tomy with postoperative hypothyroidism. Other history includes depression and Scheuermann’s disease.

Patient 2 was a man in his early 60’s, who presented with unspecific cognitive impairment, namely loss of short-term memory. Besides that, he had arterial hypertension.
## TABLE 1  Baseline characteristics of each patient

| Parameters | Patient 1, m, age: Late 40’s | Patient 2, m, age: Early 60’s | Patient 3, m, age: Early 50’s | Patient 4, f, age: Early 40’s | Patient 5, f, age: Early 30’s |
|------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Patient history | • Acral pain  
• Hypohidrosis  
• Heat intolerance  
• Vertigo (2–3 times a week) | • Short-term memory disturbance | • Lacunar cerebral stroke (age of 51 years) | • Positive tested family member for FD  
• Diarrhea | • Positive tested family member for FD |
| Medical history | • Thyroidectomy (nodular goiter)  
• Hypoparathyroidism  
• Depression  
• Small-fiber neuropathy  
• Tinnitus and loss of hearing (blast injury) | • Arterial hypertension  
• Lumbar spinal stenosis  
• Tinnitus | • Hyperlipidemia  
• Tension neck syndrome  
• Smoking history | • Depression  
• Migraine (since childhood)  
• Tinnitus (in stress situations)  
• WPW syndrome | 
| Fabry specific biomarkers | A-Gal-activity: 0.39 (0.4–1.0 nmol/min/mg protein)  
Lyso-GB3: 0.6 (&lt;0.9 ng/ml) | A-Gal-activity: 0.42 (0.4–1.0 nmol/min/mg protein)  
Lyso-GB3: 0.8 (&lt;0.9 ng/ml) | A-Gal-activity: 0.6 (0.4–1.0 nmol/min/mg protein)  
Lyso-GB3: 0.6 (&lt;0.9 ng/ml) | A-Gal-activity: 0.5 (0.4–1.0 nmol/min/mg protein)  
Lyso-GB3: 0.6 (&lt;0.9 ng/ml) | A-Gal-activity: 0.27 (0.4–1.0 nmol/min/mg protein)  
Lyso-GB3: 0.5 (&lt;0.9 ng/ml) |
| Heart | ECG: normal  
TTE: normala  
24 h tape: HR: 57–114/min  
Ergometry: max. 200 W  
Cardiac-MRI: normala  
NTproBNP & hs-Troponin: normala | ECG: T-neg. V1-V2  
TTE: normala  
24 h tape: HR: 52–94/min  
Ergometry: n.p.  
Cardiac-MRI: normala  
NTproBNP & hs-Troponin: normala | ECG: normal  
TTE: normala  
24 h tape: HR: 47–120/min  
Ergometry: max. 200 W  
Cardiac-MRI: normala  
NTproBNP & hs-Troponin: normala | ECG: normal  
TTE: normala  
24 h tape: n.p.  
Ergometry: max. 100 W  
Cardiac-MRI: normala  
NT-proBNP & hs-Troponin: normala | ECG: normal  
TTE: normala  
24 h tape: HR: 47–120/min  
Ergometry: max. 200 W  
Cardiac-MRI: normala  
NT-proBNP & hs-Troponin: normala |
| Neurological examination | Small fiber neuropathy with no other FD-specific findings | No clear signs of a severe cognitive disorder | Old lacunar infarction  
No clear correlation between infarction & FD | Normal finding | Normal finding |
| Skin biopsy | Reduction of distal and proximal intraepidermal nerve fibers  
IENFD:  
Leg: 4.1 fibers/mm  
Back: 13.9 fibers/mm | Normal  
IENFD:  
Leg: 6.4 fibers/mm  
Back: 19.5 fibers/mm | Reduction of distal and proximal intraepidermal nerve fibers  
IENFD:  
Leg: 2.1 fibers/mm  
Back: 16.6 fibers/mm | Normal  
IENFD: Leg: 5.5 fibers/mm | n. p. |

Abbreviations: A-Gal-activity, Alpha-galactosidase enzyme activity; ECG, electrocardiography; FD, Fabry disease; GFR, glomerular filtration rate; HR, heart rate; IENFD, intraepidermal nerve fiber density; MRI, magnetic resonance imaging; n. p., not performed; NTproBNP, pro B-type natriuretic peptide; TTE, transthoracic echocardiogram; WPW syndrome, Wolff–Parkinson–White syndrome.  
aExact results are shown in Table 2.
Patient 3 was a man in his early 50’s, who suffered from lacunar cerebral stroke at the age of 51. His medical record showed hyperlipidemia, tension neck syndrome, and smoking history.

Patient 4 was a woman in her early 40’s, who was referred to our center because of FD-specific positive genetic testing in a family member. The patient suffered from episodes of migraine since childhood and depression.

Patient 5 was a woman in her early 30’s, who was also referred to our center because of FD-specific positive genetic testing in a family member. No FD-specific signs or symptoms could be found. Medical history showed Wolff–Parkinson–White Syndrome and Tinnitus. Genetic testing revealed a homozygous gene variant which indicates, that both, mother and father have the specific FD-variant. p.Ser126Gly has an assumed heterozygous allele frequency of 0.0007 (prevalence: 7: 10,000), which results in an assumed allele frequency of 0.00000049 for the homozygous variant. Therefore, the prevalence for homozygous p.Ser126Gly variant is 4.9:10,000,000 (Phan et al., 2020; “Reference SNP (rs) Report: rs149391489,” 2021). In a country like Germany with approximately 80,000,000 citizens homozygous allele frequency should be present in about 40 people. According to Patient 5 only the mother received a genetic test (positive for p.Ser126Gly), but both parents—at the time point of investigation in their early 60’s—are reported to be healthy and show no symptoms related to FD.

In four patients, alpha-galactosidase A enzyme activity was normal. The homozygous female (Patient 5) showed an intermediate level of enzyme activity (mean: 0.436 nmol/min/mg protein; range 0.27–0.6). Lyso-GB3-levels were normal in all five patients (mean: 0.62 ng/ml; range: 0.5–0.8). There were no other laboratory signs for FD. Kidney function at baseline was also normal (eGFR range: 0.5–0.8). There were no other laboratory signs for FD.

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Over the whole follow-up period, the patient never suffered from FD-associated pain or showed signs of autonomic dysregulation like hyper- or hypohidrosis. There were no clinical signs of small fiber neuropathy although skin biopsies taken from the lower leg and back showed progressive reduction of intraepidermal nerve fibers density (intraepidermal nerve fiber density: lower leg: 3.9 fibers/mm; back: 15.8 fibers/mm).

Because of an initial external report, which diagnosed Cornea verticillata in the patient’s right eye, the patient received a repeat full ophthalmological assessment, which concluded that the patient has a mild corneal opacity but no signs of FD typical Cornea verticillata.
frequency in genetic testing, more patients with mutations of unclear significance such as p.Ser126Gly are found (Ortiz et al., 2018; van der Tol, Cassiman, et al., 2014). Ortiz et al. described, that pathogenic “classical” mutations are rarer and “non-classical” mutations are more common but difficult to evaluate. In these cases, symptoms can imitate FD but not arise from it (Ortiz et al., 2018). One of the main obstacles for physicians evaluating FD patients is to determine the individual need and ideal time point for specific therapy. Our current clinical report discusses findings from five individuals with p.Ser126Gly. Based on clinical evaluation, p.Ser126Gly represents a benign variant not causing FD.

Small fiber neuropathy as described in Patient 1 can be a FD-related symptom, however with low specificity (Üçeyler & Sommer, 2012). In this case it is more likely, that small fiber neuropathy emerged because of a different reason like hypothyroidism (van der Tol, Smid, et al., 2014). Patient 3 had a lacunar cerebral stroke. Similar to small fiber neuropathy in Patient 1, stroke or transient ischemic attack are among the typical spectrum of FD-related symptoms (Liu et al., 2018), but there are also many other potential underlying reasons, often questioning causality. In this case, no specific reason could be evaluated. Hyperlipidemia and smoking history are risk factors, which can lead to stroke. However, previous screening studies showed low prevalence of FD in young patients with cryptogenic stroke or transient ischemic attack (Dubuc et al., 2013; Reisin et al., 2018; Sarikaya et al., 2012).

After precise examination, it was not possible to confirm FD as cause of any of the patients’ symptoms. Additionally, alpha-galactosidase A enzyme activity was only mildly reduced in one patient and lyso-GB3 Were in all cases normal. Slightly reduced enzyme activity in Patient 5 was accompanied by homozygosity for p.Ser126Gly, representing a rarity. Despite slightly abnormal enzyme activity, no accumulation of Lyso-GB3 or FD-specific results were detected.

The follow-up of Patient 4 demonstrates the importance of diagnosing FD patients with high accuracy. Because of its unspecific and wide-ranging symptoms,
FD might be suggested in many different clinical findings. Patient 4 was diagnosed for several potential FD symptoms such as corneal opacity and renal impairment, which in combination can be interpreted as FD-specific symptoms. Coupled with “positive” genetic testing, a diagnosis of FD can be assumed wrongly. In our case, we had to figure out if renal impairment arises from FD and if there is a need for therapy. After extensive investigations, including histology by renal biopsy, FD was not confirmed and FD-specific therapy was therefore not initiated.

Van der Tol et al. created an algorithm for patients with uncertain symptoms and a questionable FD (van der Tol, Smid, et al., 2014). All our examined patients with p.Ser126Gly showed insufficient evidence for FD when using this diagnostic tool.

With many new possibilities in genetic testing and rising awareness of FD, it is getting increasingly important to critically evaluate, if specific gene variants have a clinical impact, which might be seen as one key task for specialized FD centers. As shown in previous studies, especially some of the most prevalent genetic variants such as D313Y or A143T have comparable clinical presentations (Lenders et al., 2016; Oder et al., 2018). These mutations also demonstrate the importance of accurate diagnostics of GLA variants of unknown significance. In related cases, it is important to clearly identify and name “healthy” individuals and to release these patients from the stigma of being “chronically and/or severely ill”. This approach is not only important for the patients’, but also needed to protect health care systems from unnecessary therapy costs, which, especially in FD, are particularly substantial for each affected individual.

5 | CONCLUSION

Based on findings from extensive clinical characterization, p.Ser126Gly appears to be a benign GLA gene variant not related to development of FD. This prevents clinical necessity for FD-specific therapy or repetitive short-interval follow-up examinations. Especially in gene variants with unclear clinical significance, precise clinical evaluation and characterization of pathogenicity with highest possible accuracy should be aimed at.
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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Peter Nordbeck, Christoph Wanner, and Kolja Lau created the study conception and research design. Tereza Cairns, Lora Lorenz, Nurcan Üçeyler, Claudia Sommer, Magnus Schindehütte, and Kerstin Amann performed data collection and patients’ examination. All authors performed analysis and interpretation of results. Kolja Lau and Peter Nordbeck wrote the manuscript. All authors reviewed the manuscript and approved the final version of the paper.

ETHICAL COMPLIANCE
Informed consent was obtained by the study participants. Permission to use patient-specific pictures in Figure 1 was obtained. All patients obtained consent to be part in HEAL-FABRY observational study (ClinicalTrials.gov Identifier: NCT03362164).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES
Branton, M. H., Schiffmann, R., Sabnis, S. G., Murray, G. J., Quirk, J. M., Alтаrescu, G., Goldfarb, L., Brady, R. O., Balow, J. E., Austin Iii, H. A., & Kopp, J. B. (2002). Natural history of Fabry renal disease: Influence of alpha-galactosidase a activity and genetic mutations on clinical course. Medicine (Baltimore), 81(2), 122–138. https://doi.org/10.1097/00005792-200203000-00003
Brouns, R., Thijs, V., Eyskens, F., van den Broeck, M., Belachew, S., van Broeckhoven, C., Redondo, P., Hemelsoet, D., Fumal, A., Jeangette, S., Verslegers, W., Baker, R., Hughes, D., de Deyn, P. P., & BeFaS Investigators. (2010). Belgian Fabry study: Prevalence of Fabry disease in a cohort of 1000 young patients with cerebrovascular disease. Stroke, 41(5), 863–868. https://doi.org/10.1161/strokeaha.110.579409
Cairns, T., Müntze, J., Gernert, J., Spingler, L., Nordbeck, P., & Wanner, C. (2018). Hot topics in Fabry disease. Postgraduate Medical Journal, 94(1118), 709–713. https://doi.org/10.1136/postgradmedj-2018-136056
Dubuc, V., Moore, D. F., Gioia, L. C., Saposnik, G., Selchen, D., & Lanthier, S. (2013). Prevalence of Fabry disease in young patients with cryptogenic ischemic stroke. Journal of Stroke and Cerebrovascular Diseases, 22(8), 1288–1292. https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.10.005
Germain, D. P. (2010). Fabry disease. Orphanet Journal of Rare Diseases, 5, 30. https://doi.org/10.1186/1750-1172-5-30
International Fabry Disease Genotype-Phenotype Database (dbFGP). (2021, April 7). International Fabry disease genotype-phenotype database (dbFGP)—SI26G. http://www.dbfgp/dbfgp/fabry/Mutation.html#
Lenders, M., Weidemann, F., Kurschat, C., Canaan-Kühl, S., Duning, T., Spytmann, J., Schmitz, B., Reiermann, S., Krämer, J., Blaschke, D., Wanner, C., Brand, S. M., & Brand, E. (2016). Alpha-galactosidase a p.A143T, a non-Fabry disease-causing variant. Orphanet Journal of Rare Diseases, 11(1), 54. https://doi.org/10.1186/s13023-016-0441-z
Liu, D., Hu, K., Schmidt, M., Müntze, J., Manicu, O., Gensler, D., Oder, D., Salinger, T., Weidemann, F., Ertl, G., Frantz, S., Wanner, C., & Nordbeck, P. (2018). Value of the CHA2DS2-VASc score and Fabry-specific score for predicting new-onset or recurrent stroke/TIA in Fabry disease patients without atrial fibrillation. Clinical Research in Cardiology, 107(12), 1111–1121. https://doi.org/10.1007/s00392-018-1285-4
McCafferty, E. H., & Scott, L. J. (2019). Migalastat: A review in Fabry disease. Drugs, 79(5), 543–554. https://doi.org/10.1007/s40265-019-01090-4
Mehta, A., Ricci, R., Widmer, U., Dehout, F., Garcia de Lorenzo, A., Kampmann, C., Linhart, A., Sunder-Plassmann, G., Ries, M., & Beck, M. (2004). Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry outcome survey. European Journal of Clinical Investigation, 34(3), 236–242. https://doi.org/10.1111/j.1365-2362.2004.01309.x
Meikle, P. J., Hopwood, J. J., Clague, A. E., & Carey, W. F. (1999). Prevalence of lysosomal storage disorders. JAMA, 281(3), 249–254. https://doi.org/10.1001/jama.281.3.249
Oder, D., Liu, D., Hu, K., Üçeyler, N., Salinger, T., Müntze, J., Lorenz, K., Randolf, R., Gröne, H. J., Sommer, C., Ertl, G., Wanner, C., & Nordbeck, P. (2017). α-Galactosidase a genotype N215S induces a specific cardiac variant of Fabry disease. Circulation. Cardiovascular Genetics, 10(5), e001691. https://doi.org/10.1161/circgenetics.116.001691
Oder, D., Wanner, C., & Nordbeck, P. (2018). The D313Y genotype—Pathogenic mutation or polymorphism? Clinical Genetics, 93(6), 1257. https://doi.org/10.1111/cge.13237
Ortiz, A., Germain, D. P., Desnica, R. C., Politei, J., Mauer, M., Burlina, A., Eng, C., Hopkin, R. J., Laney, D., Linhart, A., Waldek, S., Wallace, E., Weidemann, F., & Wilcox, W. R. (2018). Fabry disease revisited: Management and treatment recommendations for adult patients. Molecular Genetics and Metabolism, 123(4), 416–427. https://doi.org/10.1016/j.ymgme.2018.02.014
Phan, L., Zhang, Y. J. H., Qiang, W., Shekhtman, E., Shao, D., Revoe, D., Villamarín, R., Ivanchenko, E., Kimura, M., Wang,
Z. Y., Hao, L., Sharopova, N., Bihan, M., Sturcke, A., Lee, M., Popova, N., Wu, W., Bastiani, C., Ward, M., ... Kattman, B. L. (2020). ALFA: Allele frequency aggregator. National Center for Biotechnology Information, U.S. National Library of Medicine. www.ncbi.nlm.nih.gov/snp/docs/gsr/alfa/

Reference SNP (rs) Report: rs149391489. (2021). https://www.ncbi.nlm.nih.gov/snp/rs149391489#frequency_tab

Reisin, R. C., Mazzotti, J., Cejas, L. L., Zinnerman, A., Bonardo, P., Pardal, M. F., Martinez, A., Riccio, P., Ameriso, S., Bendersky, E., Nofal, P., Cairola, P., Jure, L., Sotelo, A., Rozenfeld, P., Ceci, R., Casas-Parera, I., & Sánchez-Luceros, A. (2018). Prevalence of Fabry disease in young patients with stroke in Argentina. Journal of Stroke and Cerebrovascular Diseases, 27(3), 575–582. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.045

Sarikaya, H., Yilmaz, M., Michael, N., Miserez, A. R., Steinmann, B., & Baumgartner, R. W. (2012). Zurich Fabry study—Prevalence of Fabry disease in young patients with first cryptogenic ischaemic stroke or TIA. European Journal of Neurology, 19(11), 1421–1426. https://doi.org/10.1111/j.1468-1331.2012.03737.x

Üçeyler, N., & Sommer, C. (2012). Fabry disease: Diagnosis and treatment. Schmerz, 26(5), 609–619. https://doi.org/10.1007/s00482-012-1238-1

van der Tol, L., Cassiman, D., Hougé, G., Janssen, M. C., Lachmann, R. H., Linthorst, G. E., Ramaswami, U., Sommer, C., Tondel, C., West, M. L., Weidemann, F., Wijburg, F. A., Svarstad, E., Hollak, C. E., & Biegstraaten, M. (2014). Uncertain diagnosis of fabry disease in patients with neuropathic pain, angokeratoma or cornea verticillata: Consensus on the approach to diagnosis and follow-up. JIMD Reports, 17, 83–90. https://doi.org/10.1007/8904_2014_342

van der Tol, L., Smid, B. E., Poorthuis, B. J. H. M., Biegstraaten, M., Deprez, R. H. L., Linthorst, G. E., & Hollak, C. E. M. (2014). A systematic review on screening for Fabry disease: Prevalence of individuals with genetic variants of unknown significance. Journal of Medical Genetics, 51(1), 1–9. https://doi.org/10.1136/jmedgenet-2013-101857

Wanner, C., Arad, M., Baron, R., Burlina, A., Elliott, P. M., Feldt-Rasmussen, U., Fomin, V. V., Germain, D. P., Hughes, D. A., Jovanovic, A., Kantola, I., Linhart, A., Mignani, R., Monserrat, L., Namdar, M., Nowak, A., Oliveve, J. P., Ortiz, A., Pieroni, M., ... Hilz, M. J. (2018). European expert consensus statement on therapeutic goals in Fabry disease. Molecular Genetics and Metabolism, 124(3), 189–203. https://doi.org/10.1016/j.mgm.2018.06.004

Wanner, C., Germain, D. P., Hilz, M. J., Spada, M., Falissard, B., & Elliott, P. M. (2019). Therapeutic goals in Fabry disease: Recommendations of a European expert panel, based on current clinical evidence with enzyme replacement therapy. Molecular Genetics and Metabolism, 126(3), 210–211. https://doi.org/10.1016/j.mgm.2018.04.004

Zarate, Y. A., & Hopkin, R. J. (2008). Fabry’s disease. The Lancet, 372(9647), 1427–1435. https://doi.org/10.1016/S0140-6736(08)61589-5

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