Neurology Multi-Gene Panel Testing

Overview[1]

- Fabry disease, an X-linked lysosomal storage disorder, is characterized by **multisystemic involvement** including the **central and peripheral nervous systems. Neurological involvement** in FD includes **small fiber neuropathy (SFN), frequent and severe neuropathic pain, abdominal pain, early transient ischemic attacks (TIAs) and strokes**
- Recognizing and **managing FD-related neurological complications** is crucial for improving **long-term prognosis** and **quality of life**
- Fabry disease should be considered in patients with **neurological pain or stroke of unknown etiology. Multi-gene panels which include *GLA* can aid in making the diagnosis of FD**

Fabry Pain Facts

Neuropathic pain is the most frequent symptom reported in patients with classic Fabry disease;[2] this pain begins during childhood and adolescence.[3,4] Neuropathic pain is:

- reported as presenting symptom in **60% male** and **40% female pediatric** patients[2]
- reported by **59% of boys** (median age: 7 years) and **41% of girls** (median age: 9 years) with Fabry disease[2]
- experienced by **60–70% adult males** and **40–77% adult females** with **Fabry disease**[5,6]
- most frequently reported in **hands** (females 60%; males 76%) and **feet** (females 52%; males 73%)[7]

Fabry Pain Characteristics[5]

Most patients report constant pain coupled with recurrent episodes of pain crises, which they describe as **"like lightning"**, **"excruciating"**, **"agonizing"** and **"stabbing"**[8]

- Often **begin** in the **distal extremities** and **radiate proximally** over the entire body
- Can occur daily, **may last for hours or days**, and confine the patient to bed
- Are usually **resistant to analgesic** treatment

Pain Triggers[8]

- Rapid changes in core body temperature#
- Rapid changes in humidity; fatigue

Fabry Stroke Facts

Initial strokes occur in Fabry patients significantly younger than strokes in the general population[9]

	Males		Females	
Characteristics	Classic	Later-onset	Classic	Later-onset
Number of patients	102	25	145	12
Median age at 1st stroke	37.9	47.3	45.4	44.8

- **64.7% of classic males** and **42.1% of classic females** who experience a Fabry-related stroke, do so **prior to their diagnosis of Fabry disease**[9]
- **Ischemic strokes** are the **most common stroke** in patients with Fabry disease[10]

Fabry in Cryptogenic Stroke

- In a study of **721 patients (432 males; 289 females)** with cryptogenic stroke <55 years old and negative for typical risk factors, **4.9% of males and 2.4% of females** were found to have a pathologic variant in GLA consistent with diagnosis of Fabry disease. This estimates a **prevalence of FD in patients with acute cryptogenic stroke of 3.8%**[11]
- The prevalence of cryptogenic stroke in FD is **highly variable** among studies. However, compared to single strokes, FD was seen more commonly in patients with **recurrent strokes** and in patients with **cryptogenic stroke ≤ 55 years of age**[12]
- Red flags suggesting FD in patients with cryptogenic stroke: **Proteinuria (with or without diabetes)**; **childhood history of acroparesthesia and/or neuropathic pain**[11]

Progression of Fabry Disease Neurological Manifestations over Time[11-18]

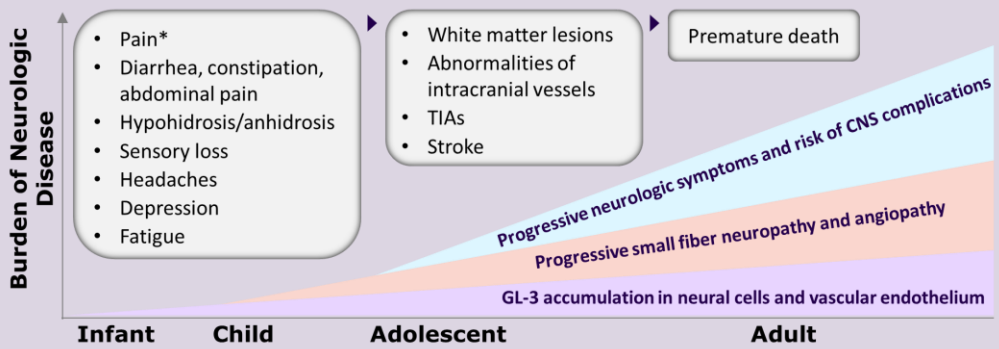
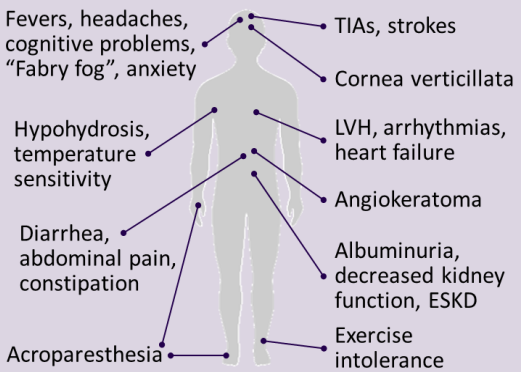


Figure adapted from Eng CM, et al. J Inherit Metab Dis 2007;30:184–192

Organ involvement Beyond Stroke Provides Insight into Diagnosis:[3,18,19]

Current or past history of:



#Due to sudden exposure to cold, fever, stress or physical activity; may be exacerbated by patients' decreased ability to sweat; *Chronic, attack.

CNS, central nervous system; ESKD, end stage kidney disease; FD, Fabry disease; GL-3, globotriaosylceramide; TIA, transient ischemic attack; LVH, left ventricular hypertrophy.

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Testing Options

Sanofi does not review or control the content of non-Sanofi websites. These listings do not constitute an endorsement by Sanofi of information provided by any other organizations. The following is a selection of laboratories offering cerebrovascular and neuropathy panels. This is not an exhaustive list of labs or an endorsement of any one lab. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. To test individuals with a family history of Fabry for a known familial mutation, please contact your lab of choice to discuss. Content is current at time of printing and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics.

Laboratory	Cerebrovascular Panels		Neuropathy Panels	
	Panel Name	Genes	Panel Name	Genes
Fulgent	Hemiplegia/Stroke	15	Hereditary Neuropathies Panel	41
GeneDx			Hereditary Neuropathy Panel	89
HNL Genomics	Cerebral Small Vessel Disease Panel	6		
Mayo Medical Laboratories	Comprehensive Cerebrovascular Gene Panel	30	Comprehensive Peripheral Neuropathy Gene Panel	190
			Inherited Motor and Sensory Neuropathy Gene Panel	87
			Inherited Sensory Neuropathy Gene Panel	23
Labcorp (MNG Laboratories)	Stroke Panel	84	Comprehensive Neuropathies Panel	866
			Hereditary Sensory & Autonomic Neuropathy Panel	153
Prevention Genetics	Stroke, Cerebral Hemorrhage, Hemiplegia, and Migraine Panel	160		
The Lantern Project	Pain and Cerebrovascular Panel	73	Pain and Cerebrovascular Panel	73

Laboratory	Sample Requirements	Kits	Avg TAT	Genetic Counselor Available to Patients	Billing	Contact
Fulgent Genetics	WB: two 4 mL EDTA (lavender) tubes; Saliva; Buccal swab	Blood; Saliva; Buccal	3-5 w	No	Inst, Self-Pay, Ins	P: 626-350-0537 E: info@fulgentgenetics.com W: www.fulgentgenetics.com
GeneDx	WB: 2-5 mL EDTA (lavender) tube (preferred); Buccal swab	Blood; Buccal	4 w	Yes	Inst, Self-Pay, Ins	P: 301-519-2100 E: zebras@genedx.com W: www.genedx.com
HNL Genomics	WB: 3 mL EDTA (lavender) tube; Saliva	No	2-4 w	No	Inst, Self-Pay, Ins	P: 877-402-4221 W: www.hnl.com
Mayo Medical Laboratories	WB: 3 ml EDTA (lavender) or ACD (yellow) tube	No	21-28 d	No	Inst (ins can be billed in some cases, Inst account required)	P: 800-533-1710 E: mcl@mayo.edu W: www.mayocliniclabs.com
Labcorp (MNG Laboratories)	WB: 7 ml EDTA (lavender) tube or ACD (yellow) tube	Blood; Saliva		No	Inst, Ins, Self-pay	P: 800-345-4363 W: www.labcorp.com
Prevention Genetics	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube (preferred); DBS: 5 spots; Saliva	Blood; Saliva	18 d	No	Inst, Self-Pay, Ins	P: 715-387-0484 E: support@preventiongenetics.com W: www.preventiongenetics.com
The Lantern Project (Revvity Omics)	WB: 2-10 ml EDTA (lavender) DBS card: 3 circles; Saliva – Oragene kit	Blood; DBS; Saliva	3 weeks	No	*No charge	P: 866-354-2910 E: genomics@revvity.com W: www.LanternProjectDx.com

***testing is performed at no charge; local charges may apply for sample collection, processing, or shipping**

Abbreviations: Avg TAT = average turnaround time; d = days; ins = insurance; inst = institution; WB = whole blood; w = weeks

References:

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16. Moore DF et al. Brain Res Bull 2003;62:231-40; 17. Cole AL et al. J Inherit Metab Dis 2007;30:943-51; 18. Schiffmann R, et al. Kidney Int. 2017;91:284–293; 19. Korver, S. J Inherit Metab Dis. 2020 Sep;43(5):1070-1081.

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