

Hypertrophic Cardiomyopathy Genetic Panels

Incidence:

Of patients with nonsyndromic HCM of an unknown etiology, 32% were identified to have a monogenetic cause for their disease.²

Fabry disease is the most common metabolic disorder in adults older than 35 with HCM with a prevalence of 0.5-1%.⁴



Overview

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy, unexplained by the loading conditions; a nondilated left ventricle; and a normal or increased ejection fraction.¹ HCM is a disorder without a distinct geographic, ethnic, or sex pattern of distribution with an estimated prevalence of 1 in 500 individuals in the United States.^{1,2}

Dominant pathogenic variants in HCM genes (*ACTC1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNI3*, *TNNT2*, and *TPM1*) encoding sarcomere proteins are the most common cause of HCM.² Other known causes of HCM include metabolic disorders such as Fabry disease and infiltrative disorders such as ATTR-amyloidosis. Selecting testing panels that include genetic causes of primary and secondary HCM can optimize management.

Fabry disease, caused by pathogenic variants in *GLA*, is a metabolic disorder which results in infiltrative cardiomyopathy. Patients with classic Fabry present with concentric LVH and progress to cardiac replacement fibrosis. Many patients develop symptoms of heart failure with preserved ejection fraction and valvular dysfunction.³ In addition to cardiac findings, patients with classic Fabry disease also typically have a history of neuropathic and gastrointestinal pain, angiokeratomas, and high-frequency hearing loss and are at increased risk of renal failure and stroke.³ Patients with non-classic Fabry disease typically present with a similar, but isolated cardiomyopathy.³

Genetic Testing Guidelines

Per practice guidelines, genetic testing should be offered to all patients with HCM.⁵

Testing should be directed to the most clearly affected family member.⁵

- If a pathogenic or likely pathogenic variant is found, then other family members are at-risk for the condition.
- With patient privacy concerns in mind, a three generation family history is a helpful tool for identifying at-risk family members.

Genetic counseling is recommended for all patients with cardiomyopathy and their family members.⁵

- Consider consulting with a genetics colleague. These individuals can be helpful with ambiguous results, incidental findings, and identification of at-risk family members.⁶
- The patient should understand the benefits and limitations of genetic testing before giving consent.⁵

Diagnosis

When a diagnosis of idiopathic HCM is present, ruling out a genetic etiology, such as Fabry, has the potential to shorten the diagnostic delay.⁷ The following evaluations may support a diagnosis of Fabry disease:⁷

History	childhood neuropathic pains, abdominal cramps and diarrhea, hypohidrosis, fatigue, depression
Family History	premature stroke, renal failure, cardiomyopathy, sudden death, absence of male-to-male transmission
Examination	angiokeratoma, cornea verticillata, proteinuria, and hearing loss

Cardiac findings that are indicative of Fabry disease:⁴

EKG and Structural Abnormalities⁴

- Short PR interval without pre-excitation
- Progressive atrioventricular conduction delay
- Chronotropic incompetence
- Increased atrioventricular valve thickness
- Increased right ventricle free wall thickness

Cardiac MRI Findings⁴

- Reduction in non-contrast T1 signal indicative of glycosphingolipid accumulation
- Presence of posterolateral LGE, indicative of replacement fibrosis

Concentric left ventricular hypertrophy

Global left ventricle hypokinesia

In a study of 90 patients with Fabry (mean age 44):⁸

Cardiac characteristics identified on imaging stratified by gender.

	Males (n=31)	Females (n=59)
LVH	48%	36%
LGE	45%	37%

1. Marian AJ, et al. *Circulation Research*. 2017;121:749-770. 2. Alfares AA, et al. *Genet Med*. 2015;17(11):880-8. 3. Yogasundaram, et al. *Can J Cardiol*. 2017;33(7):883-897. 4. Elliott PM, et al. *Eur Heart J* 2014;35:2733-2779. 5. Hershberger et al. *J Card Fail*. 2018;24(5):281-302. 6. Musunuru K, et al. *Circ Genom Precis Med*. 2020;13(4):e000067. 7. Yousef Z, et al. *Eur Heart J* 2013;34:802-808. 8. Hanneman, K et al. *Radiology*. 2020;294(1):42-49.

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 HCM gene 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	Comprehensive Cardiology Panel		Comprehensive Cardiomyopathy Panel		Hypertrophic Cardiomyopathy Panel	
	Panel Name (Test Code)	# of Genes	Panel Name (Test Code)	# of Genes	Panel Name (Test Code)	# of Genes
Ambry	CardioNext (8911)	92	CMNext (8887)	56	HCMNext (8936)	30
ARUP	Cardiomyopathy and Arrhythmia Panel (2010183)	78			Hypertrophic Cardiomyopathy Panel (3001579)	34
Blueprint	Comprehensive Cardiology Panel (CA1301)	260	Cardiomyopathy Panel (CA1201)	217	Hypertrophic Cardiomyopathy (HCM) Panel (CA1901)	92
Fulgent	Comprehensive Cardiovascular	264	Comprehensive Cardiomyopathy	129	Hypertrophic Cardiomyopathy	86
GeneDx	Combined Cardiac Panel (936)	138	Cardiomyopathy Panel (694)	102	Hypertrophic Cardiomyopathy (HCM) Panel (J553)	42
Invitae	Unlock Cardiomyopathy and Arrhythmia Program*	122	Cardiomyopathy Comprehensive Panel (02251)	121	Hypertrophic Cardiomyopathy Panel (02261)	44
Revvity			Comprehensive Cardiomyopathy Panel (D4101)	122	Hypertrophic Cardiomyopathy Panel (D4103)	39
Prevention	Comprehensive Cardiology Panel (2663)	196	Pan Cardiomyopathy Panel (5263)	106	Hypertrophic Cardiomyopathy Panel (1313)	56

Laboratory (formal name)	Sample Requirements	Kits	Avg TAT	Mobile Blood Draw	Genetic Counselor Available to Patients	Billing	Contact
Ambry Genetics	WB: 6-10 mL EDTA (lavender) tube; Saliva	Blood; Saliva	14-21 d	Yes	Yes	Inst, Self-Pay, Ins	P: 919-900-5500 E: info@ambrygen.com W: https://www.ambrygen.com
ARUP Laboratories	WB: 3 mL EDTA (lavender) or ACD (yellow) tube	No	3-6 w	No	No	Self-Pay, Ins	P: 1-800-522-2787 E: clientservices@aruplab.com W: https://www.aruplab.com
Blueprint Genetics	WB:: 1 mL EDTA (lavender) tube; Saliva	Blood	4 w	No	No	Inst, Self-Pay, Ins	P: 650-452-9340 Ext. 0 E: support.us@blueprintgenetics.com W: https://blueprintgenetics.com
Fulgent Genetics	WB: two 4 mL EDTA (lavender) tubes; Saliva; Buccal swab	Blood; Saliva; Buccal	3-5 w	No	No	Inst, Self-Pay, Ins	P: 626-350-0537 E: info@fulgentgenetics.com W: https://www.fulgentgenetics.com
GeneDx	WB: 2-5 mL EDTA (lavender) tube (preferred); Buccal swab	Blood; Buccal	4 w	No	Yes	Inst, Self-Pay, Ins	P: 301-519-2100 E: zebras@genedx.com W: https://www.genedx.com
Invitae	WB: 3 mL EDTA (lavender) tube (preferred); Saliva; Buccal swab	Blood; Saliva; Buccal	10-21 d	No	No	Inst, Self-Pay, Ins	P: 800-436-3037 E: clinconsult@invitae.com W: https://www.invitae.com
Revvity Omics (fka PerkinElmer Genomics)	WB: 5-10 mL EDTA (lavender) tube (preferred); DBS: 1 card; Saliva	Blood; DBS; Saliva	3-5 w	No	No	Inst; Self-Pay	P: 866-354-2910 E: genomics@revvity.com W: https://www.perkinelmergenomics.com
Prevention Genetics	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube (preferred); DBS: 5 spots; Saliva	Blood; Saliva	18 d	No	No	Inst, Self-Pay, Ins	P: 715-387-0484 E: support@preventiongenetics.com W: https://www.preventiongenetics.com

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

Avg TAT = average turnaround time; d = days; DBS = dried blood spot; ins = insurance; inst = institution; WB = whole blood; w = weeks