

ESC WORKING GROUP  
ON MYOCARDIAL AND  
PERICARDIAL DISEASES

## **KEY MESSAGES**

# Diagnosis and Management of Cardiac Manifestations in Anderson Fabry Disease and Glycogen Storage Diseases

● [www.escardio.org/workinggroups](http://www.escardio.org/workinggroups)



**ESC**

Working Group  
Myocardial &  
Pericardial Diseases

Special thanks to

Shire

The full article and its related educational material were produced by and under the sole responsibility of the Working Group on Myocardial and Pericardial Diseases.



# ESC WORKING GROUP ON MYOCARDIAL AND PERICARDIAL DISEASES: KEY MESSAGES on Diagnosis and management of cardiac manifestations in Anderson Fabry disease and glycogen storage diseases

## Table of contents

### Part I: Anderson Fabry Disease

1. Introduction and scope of the document.....	Page 3
2. Anderson Fabry disease overview.....	Page 4
3. Anderson Fabry disease incidence and prevalence.....	Page 4
4. Anderson Fabry disease extracardiac clinical manifestations.....	Page 6
5. Anderson Fabry disease cardiac manifestations.....	Page 12
6. Anderson Fabry disease diagnostic methods.....	Page 18
7. The role of biomarkers and biopsy.....	Page 19
8. Enzyme replacement therapy.....	Page 20
9. Chaperone therapy.....	Page 21
10. Summary.....	Page 22
11. References.....	Page 23

## Part II: Glycogen Storage Diseases

1. Introduction and scope of the document.....	Page 25
2. 2. Glycogen storage disease - Pathophysiology.....	Page 26
3. 3. Glycogen storage diseases in cardiomyopathy clinic .....	Page 28
4. Pompe's disease.....	Page 29
5. PRKAG2 cardiomyopathy .....	Page 30
6. Danon's disease.....	Page 33
7. 7. Diagnosis.....	Page 38
8. Therapy.....	Page 39
9. Summary.....	Page 41
10. References and additional reading.....	Page 43

# Part I: Anderson Fabry Disease

## 1. Introduction and scope of the document

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the  $\alpha$ -galactosidase A gene (GLA) that lead to reduced or undetectable  $\alpha$ -galactosidase A (AGAL) enzyme levels and progressive accumulation of glycolipids - primarily globotriaosylceramide (Gb<sub>3</sub>) and its deacylated form, lysoGb<sub>3</sub>, in cells throughout the body including vascular endothelial and smooth muscle cells and cardiomyocytes (Figure 1).

Besides a complex multisystemic involvement including neuropathic pain, angiokeratomas, premature stroke and renal involvement, most patients develop left ventricular hypertrophy mimicking hypertrophic cardiomyopathy (HCM). A relatively large group of patients may suffer from isolated cardiac involvement.

As many patients with AFD have multi-organ involvement, a multidisciplinary approach is essential in their management. Specific enzyme replacement therapy (ERT) administered by biweekly intravenous infusions has been shown to clear Gb<sub>3</sub> from vascular endothelium. ERT has proven beneficial effects on kidney disease progression, reduction of neuropathic pain and stabilization of cardiac mass growth. Novel therapy based on molecular chaperone was recently approved for AFD patients carrying amenable mutations. In addition, several treatments including modified enzymes, substrate reduction therapy and genetic treatments are in development.

Although the knowledge about AFD increases, about 1% of HCM patients suffer from previously unrecognized AFD. For most patients it seems essential to establish a correct and timely diagnosis since several studies indicate that the early initiation of ERT leads to favourable outcomes as compared to delayed one.

The aim of this document is to describe general and cardiac manifestations of AFD and increase the awareness about the disease among cardiologists.

## 2. Anderson Fabry disease overview

Anderson Fabry disease is a lysosomal storage disorder caused by mutations in the  $\alpha$ -galactosidase A gene (GLA) located on X chromosome (Xq22). As of today, more than 900 mutations were detected. Most of them lead to reduced or undetectable  $\alpha$ -galactosidase A (AGAL) enzyme levels. This leads to a progressive accumulation of GLA substrates - glycolipids-primarily globotriaosylceramide (Gb<sub>3</sub>) and its deacylated form, lyso-Gb<sub>3</sub>, in cells throughout the body. The storage affects multiple cells within the heart including vascular endothelial and smooth muscle cells, cardiomyocytes, conduction system cells, valvular fibroblasts, and cells within the nervous system, kidney, lungs and skin.

## 3. Anderson Fabry disease incidence and prevalence

AFD affects all ethnicities. The estimated prevalence of classical multisystemic AFD is around 1:30 000 - 40 000 adult males. Neonatal screening programmes have found an unexpectedly high incidence of genetic variants (ranging from 1:1 250 to 1:7 800). However, the large majority of detected genetic variants represent mutations causing late onset disease (mostly isolated cardiac involvement) or variants of unknown significance.

Several screening studies were seeking the prevalence of AFD in patients with unexplained left ventricular hypertrophy. The prevalence ranges from 0-12% but most studies suggest a value around 0.5-1% in adult cohorts. Recent analysis of data published between 1995 and 2017 concluded that the prevalence of GLA mutations among 4 054 screened males and 1 437 females was 1.2% and 1.53%, respectively. However, based on available data reporting detected mutations, only 0.93 % males and 0.90% females with HCM or unexplained LVH carried a definite pathogenic mutation.

Due to the X-linked character of transmission most females are heterozygous while males are by definition hemizygous. This leads to an earlier manifestation and more severe course of the disease in male patients. In females, the random chromosome inactivation may lead in some cases to a skewed inactivation of the X chromosome carrying the wild type allele thus leading to disease severity comparable to male patients.

**Table 1 Anderson Fabry disease main features**

X-linked lysosomal storage disease - glycosphingolipidosis (Xq22 locus, deficiency of  $\alpha$ -galactosidase A)

**Stored substance**

- Mainly globotriaosylceramide - Gb<sub>3</sub>
- Deacylated form - lyso-Gb<sub>3</sub> or globotriaosylsphingosine - potentially toxic, causing secondary damage and representing one of the biomarkers of the disease severity

**Clinical phenotypical presentations**

- Classical multisystemic disease - early onset of symptoms within first two decades of life
- Late-onset variants - predominantly cardiac, manifesting after the 3<sup>rd</sup> decade of life

**Prevalence and incidence**

- Classical forms 1:30-40 000 in males (raw estimate from the rate between classical and late-onset variants detected by neonatal screenings)
- Late-onset forms (based on neonatal screenings) 1:1 250 - 1:7 800 males

Prevalence among patients with unexplained LVH or diagnosed as hypertrophic cardiomyopathy ~ 1%

**Factors influencing disease severity**

- Mutation type (classical forms associated with truncating mutations and absent residual enzyme activity, late-onset forms usually due to missense mutations and preserved residual enzyme activity)
- Gender - hemizygous males are affected earlier and having more severe disease than heterozygous females
- Random vs. skewed X-chromosome inactivation in females
- Age - the disease is progressive with severe organ damage manifesting in adult patients, life expectancy is reduced particularly in untreated males

## 4. Anderson Fabry disease extracardiac clinical manifestations

The classical AFD (**Figure 2**) is a multisystemic disease with manifestations starting in childhood, mostly by gastrointestinal symptoms (diarrhea, abdominal pain, early satiety), and peripheral neuropathy with paroxysmal or permanent burning and tingling pain in hands and feet, sometimes accompanied by increased body temperature (febrile crises).

Skin manifestations - angiokeratomas - appear mainly in male patients early in life and may progress over the second decade. These reddish prominent spots have a typical distribution within the “bathing trunk”, on genitalia, limb extensor surface, and sometimes on hands, lips and oral mucosa (**Figure 3**). Most patients have limited ability to sweat (hypohidrosis or anhidrosis), in contrast, some of them may complain of hyperhidrosis. Peripheral oedemas (in some patients quite prominent) are frequently observed, male patients have frequently coarse facial features and periorbital oedemas.

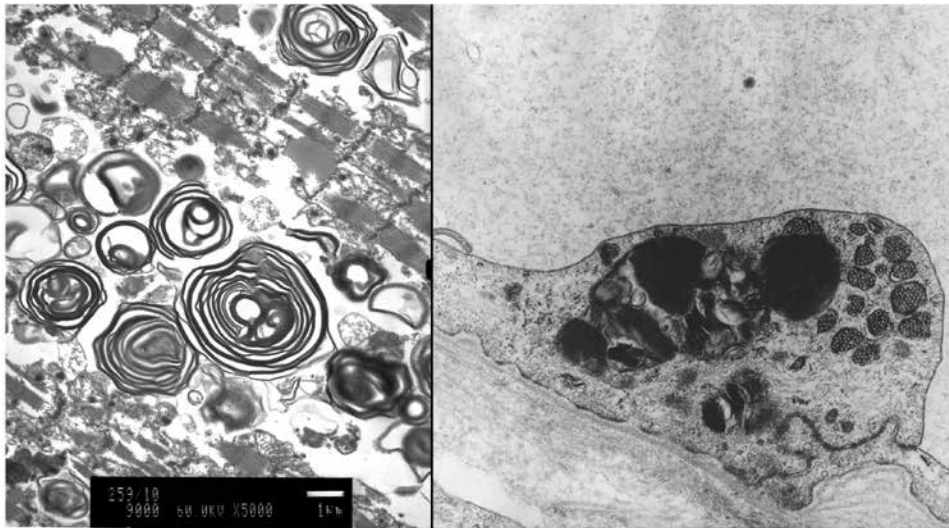
A benign yet typical ophthalmological manifestation is represented by cornea verticillata, a spoke-like corneal clouding not impacting the vision, resembling to the similar phenomenon induced by chronic amiodarone or chloroquine administration (**Figure 4**). Less specific ocular findings include vessel tortuosities.

Life threatening complications include premature stroke, development of chronic kidney disease and cardiomyopathy. Classical neurological manifestations include peripheral neuropathy and premature stroke, mostly ischemic. However, intracranial bleeding seems also more frequent than in general population. A proportion of stroke may be of cardioembolic source since atrial fibrillation seems frequent in advanced stages of cardiomyopathy.

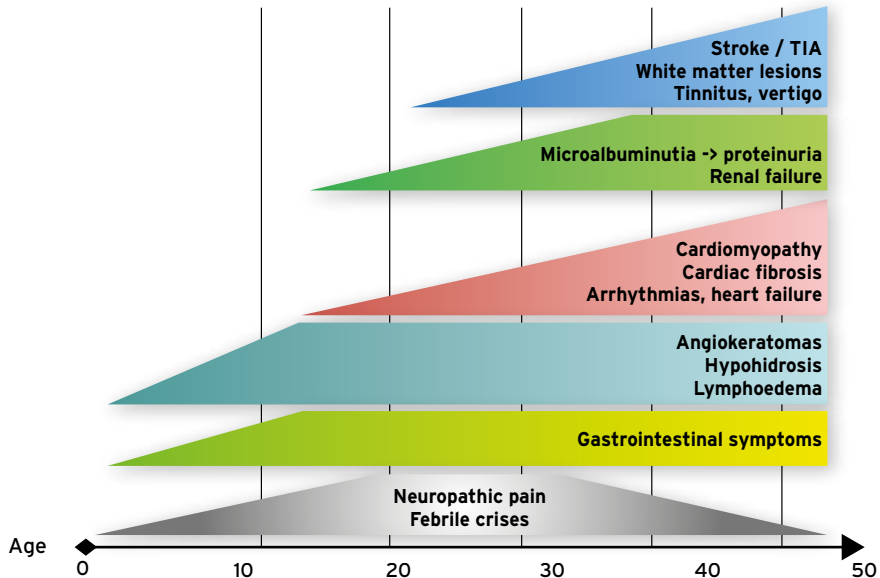
AFD-related nephropathy starts with albuminuria and progresses to overt proteinuria and progressive decline in glomerular filtration rate. End-stage renal disease may develop from the third decade predominantly in male patients.



**Figure 1** Electron microscopy showing typical intracellular storage of Gb<sub>3</sub> forming “zebra bodies” within the myocardial cells (left) and endothelial cells (right).  
Courtesy First Faculty of Medicine, Prague, CZ.



**Figure 2** Time course of classical multisystemic Anderson Fabry Disease.  
Adapted from Linhart and Elliott. Heart. 2007;93(4):528-35.



**Figure 3** Angiokeratomas in a patient with classical multisystemic Anderson Fabry disease. Courtesy First Faculty of Medicine and General University Hospital, Prague, CZ.



**Figure 4** Typical ocular manifestation of Fabry disease including cornea verticillata and posterior subcapsular 'spoke-like' cataract.

Courtesy First Faculty of Medicine and General University Hospital, Prague, CZ.



**Table 1 Extracardiac manifestations of Anderson Fabry disease**

**Neurological**

- Peripheral neuropathy - pain within extremities, painful (febrile crises)
- Autonomous nervous dysfunction
- Premature stroke (mostly ischemic, intracerebral bleeding risk is also increased)
- White matter lesions, pulvinar sign, tortuous vertebral and basilar arteries
- Tinnitus, hearing loss, vertigo

**Gastrointestinal**

- Diarrhea / constipation, abdominal pain, irritable-bowel syndrome-like manifestations
- Normal endoscopy findings, w/o bleeding risk

**Skin**

- Angiokeratomas
- Hypo / anhidrosis (in some cases hyperhidrosis)
- Lymphoedema, periorbital oedema, coarse facial features

**Kidney**

- Albuminuria - proteinuria
- Glomerular filtration decline, end-stage kidney disease

**Eye**

- Cornea verticillata
- Fabry cataract
- Tortuous conjunctival and retinal vessels

**Other non-specific findings**

- Mild anemia
- Osteoporosis
- General fatigue, weakness, reduced exercise capacity
- Depression

## 5. Anderson Fabry disease cardiac manifestations

Children and adolescents can have subtle ECG changes and a left ventricular mass at the upper limits of normal range reported for the general population but cardiovascular symptoms at this age are very rare.

In adults, the earliest clinical manifestations of Fabry related cardiac disease are ECG abnormalities (signs of left ventricular hypertrophy, short PR interval or AV conduction abnormalities, deep T inversions in precordial leads) (**Figure 5**). Echocardiographic and MRI findings reveal a slowly progressive left ventricular hypertrophy (LVH) (usually concentric and diffuse, with prominent papillary muscles) that is clinically manifest in the 3<sup>rd</sup> decade in males and 4<sup>th</sup> decade in females (**Figure 6**). LVH is associated with heart failure symptoms caused by diastolic LV dysfunction, microvascular angina and, in some patients, provokable LV outflow tract obstruction similar to that seen in patients with other forms of hypertrophic cardiomyopathy. Right ventricular hypertrophy is also frequent but does not usually result in clinical symptoms.

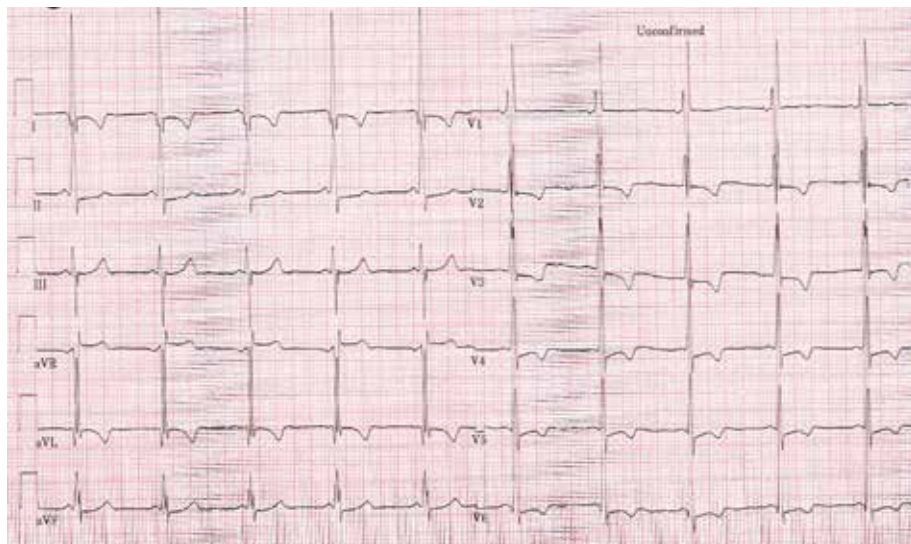
As patients get older, progressive interstitial and replacement myocardial fibrosis develops, usually starting in the mid-myocardial layer of the basal posterolateral LV wall. In advanced disease, this is accompanied by a reduction in LV contractile performance and in some cases left ventricular thinning and aneurysm formation (**Figure 7**).

In middle-aged patients, atrial fibrillation is frequent, potentially contributing to the increased stroke risk and in advanced cases malignant ventricular arrhythmias may occur, increasing the risk for sudden cardiac death. Many older patients develop sinus node dysfunction with chronotropic incompetence, and/or atrioventricular conduction abnormalities frequently requiring pacemaker implantation.

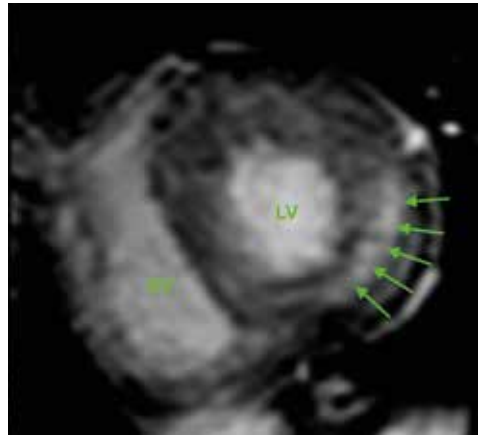
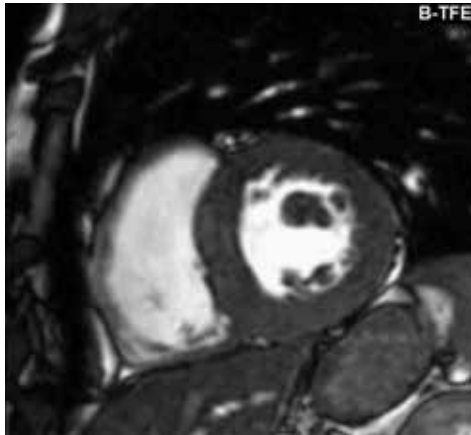
Involvement of all left heart cardiac valves is common but rarely results in valve dysfunction that requires intervention. Valvular changes are characterized mostly by valvular thickening, although some patients may present with significant mitral valve prolapse. Secondary functional mitral regurgitation may develop in patients with extensive posterolateral fibrosis. Aortic remodeling is frequent but rarely results in more than mild aortic dilatation. The coronary microcirculation is often affected leading to angina. Arterial hypertension may result from renal insufficiency, but most studies suggest that Fabry disease per se is not a cause of severe systemic hypertension.

**Figure 5** Electrocardiogram from an adult Anderson Fabry male patient showing PR interval shortening, signs of left ventricular hypertrophy and conduction abnormalities (right bundle branch block pattern) and diffuse repolarization changes.

Courtesy First Faculty of Medicine and General University Hospital, Prague, CZ.



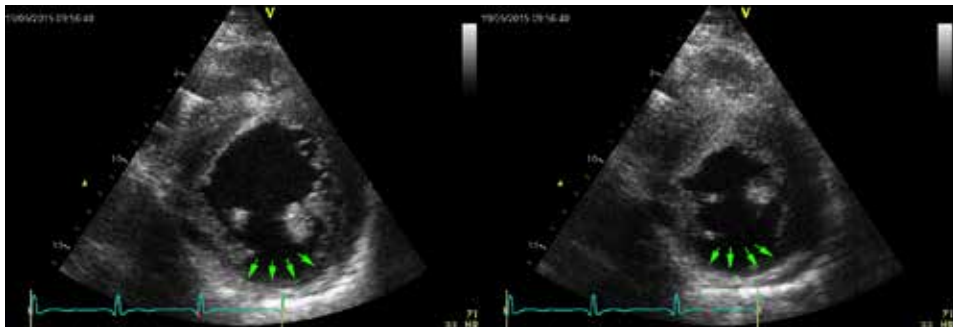
**Figures 6 and 7** Cardiac MRI showing homogenous distribution of left ventricular hypertrophy and extensive late gadolinium enhancement within the posterolateral wall (arrows).  
Courtesy First Faculty of Medicine and General University Hospital, Prague, CZ.





**Figure 8** Extensive thinning and aneurysmal bulging of the posterior LV wall in a patient with advanced cardiac phenotype of Anderson Fabry disease.

Courtesy First Faculty of Medicine and General University Hospital, Prague, CZ.



**Table 3 Main cardiac manifestations**

<b>Cardiac hypertrophy</b>	
<ul style="list-style-type: none"><li>• Mostly diffuse, in some cases may be asymmetrical mimicking obstructive hypertrophic cardiomyopathy</li><li>• LVOT obstruction may be present both at rest and provoked by exercise (less frequent than in sarcomeric HCM)</li></ul>	<ul style="list-style-type: none"><li>• Papillary muscle hypertrophy</li><li>• Right ventricular hypertrophy</li><li>• Posterolateral mid-myocardial fibrosis development, wall thinning and akinesia</li></ul>
<b>Cardiac function</b>	
<ul style="list-style-type: none"><li>• EF preserved, scar and hypo/akinesia may develop within posterolateral basal segment</li><li>• Global longitudinal strain is reduced, postsystolic shortening detectable in cases with basal fibrosis</li></ul>	<ul style="list-style-type: none"><li>• Mild-to-moderate diastolic dysfunction, restrictive filling only in very advanced stages, diastolic dysfunction is the main cause of heart failure symptoms</li><li>• Right ventricular function usually preserved</li></ul>
<b>Arrhythmias</b>	
<ul style="list-style-type: none"><li>• Short PR interval without preexcitation</li><li>• Conduction abnormalities, AV block, bundle branch blocks</li><li>• Bradycardia, chronotropic incompetence</li></ul>	<ul style="list-style-type: none"><li>• Atrial fibrillation</li><li>• Ventricular arrhythmias with an increased risk of sudden cardiac death</li></ul>
<b>Valvular changes</b>	
<ul style="list-style-type: none"><li>• Mitral and aortic valve thickening, mild-to moderate regurgitations (does not predispose to development of any valvular stenotic lesions)</li></ul>	<ul style="list-style-type: none"><li>• Mitral valve prolapse / mitral valve systolic restriction in cases with extensive posterolateral fibrosis</li><li>• Mild-to-moderate aortic dilatation, aortic dissection risk not reported</li></ul>
<b>Vascular changes</b>	
<ul style="list-style-type: none"><li>• Carotid and radial intima-media thickening, coronary wall thickening</li></ul>	<ul style="list-style-type: none"><li>• Microvascular dysfunction, reduction of coronary flow reserve</li></ul>

**Table 4 Main cardiac findings in Anderson Fabry disease**

ECG	<ul style="list-style-type: none"><li>• Short PR interval</li><li>• Bradycardia</li><li>• AV blocks of various degree, bundle branch blocks</li><li>• Signs of left ventricular hypertrophy</li><li>• Repolarization changes (deep T wave inversion in precordial leads)</li><li>• Atrial fibrillation</li><li>• Ventricular ectopy, NSVTs on Holter / loop recorder monitoring</li></ul>
Echocardiography	<ul style="list-style-type: none"><li>• Left ventricular hypertrophy - usually diffuse, may be asymmetric</li><li>• Posterior basal wall hyperdensity, thinning and akinesia</li><li>• Depressed global longitudinal strain, postsystolic contractions in posterolateral segments affected by fibrosis</li><li>• Preserved systolic function</li><li>• Mild-to-moderate diastolic dysfunction, may be severe in advanced cases</li><li>• Right ventricular hypertrophy with preserved function</li><li>• Aortic and mitral valvular thickening, mitral valve prolapse, aortic dilatation</li></ul>
Cardiac MRI	<ul style="list-style-type: none"><li>• Findings as on echocardiography</li><li>• Late gadolinium enhancement indicating replacement fibrosis within mid-myocardial layer of posterolateral segments</li><li>• T1 mapping showing a decrease in T1 in segments not affected by fibrosis</li></ul>
Perfusion imaging	<ul style="list-style-type: none"><li>• Decreased coronary flow reserve</li></ul>
Coronary angiography	<ul style="list-style-type: none"><li>• Frequently normal, IVUS may show a thickening / diffuse infiltration of arterial walls</li></ul>
Biomarkers	<ul style="list-style-type: none"><li>• BNP or NT-proBNP elevation in patients with cardiac hypertrophy, diastolic dysfunction and heart failure symptoms</li><li>• Persistent high sensitivity troponin elevation particularly in patients with myocardial fibrosis</li></ul>

## 6. Anderson Fabry disease diagnostic methods

Male patients with the classical form of the disease have very low or absent  $\alpha$ -galactosidase A activity and can be diagnosed reliably by an enzymatic test in blood leukocytes. Dry blood spot analysis with enzyme activity assessment is widely available for screening diagnostic purposes.

Some male patients with late-onset, predominantly cardiac forms of the disease, have significant residual  $\alpha$ -galactosidase A activity, although still far below the normal values. Diagnosis must be confirmed in all male cases by enzyme assay in blood leukocytes or dried blood spots and mutation analysis.

The activity of  $\alpha$ -galactosidase A may be normal in heterozygous females. Therefore, a diagnosis of Fabry disease in females can only be made by genotyping. However, some screening strategies use lyso-Gb<sub>3</sub> assessment for identifying AFD females before performing the gene sequencing.

Before ERT or chaperone therapy is initiated, the diagnosis should be verified by detection of the disease-causing mutation. Chaperone therapy is suitable only for patients with residual enzyme activity and "amenable" mutations. The amenability list is provided on <http://www.galafoldamenabilitytable.com>.

Biopsy may be necessary in patients with signs and symptoms suggestive of AFD in whom a genetic variant of unknown significance is identified. Specific treatment initiation in patients without proven pathogenic mutations should be avoided.

## 7. The role of biomarkers and biopsy

In many patients Gb<sub>3</sub> is elevated in plasma or urine, but may be normal in patients with isolated cardiac involvement (particularly in the urine). Recently, assessment of lyso-Gb<sub>3</sub> was proposed as a useful tool for prediction of pathogenicity of detected variants of unknown significance. It has been conclusively demonstrated that mutations leading to classical AFD are associated with higher lyso-Gb<sub>3</sub> levels as compared to later onset variants. Benign variants are usually associated with normal lyso-Gb<sub>3</sub> levels.

Biopsy of an affected organ provides definitive evidence of AFD by showing vacuolization and typical lysosomal inclusions or “zebra” bodies on electron microscopy. However, the evidence of lysosomal deposits does not necessarily correlate with disease severity and organ damage.

**Table 5 Diagnostic methods in Anderson Fabry disease**

Diagnostic method	Interpretation
$\alpha$ -galactosidase A activity • Dry blood spot (DBS) • Plasma, leukocytes	Very low or absent in males Residual activity detectable in late onset variants Low to borderline or even normal values in heterozygous women
Gb <sub>3</sub> - plasma, urine	High levels in classically affected patients Urinary Gb <sub>3</sub> nondiagnostic in cardiac variant patients
Lyso-Gb <sub>3</sub> - plasma, urine	Biomarker of disease severity High levels in classically affected patients Intermediate or low levels in cardiac variant patients Normal or borderline in non-pathogenic variants or polymorphisms
Lyso-Gb <sub>3</sub> analogues	May have better diagnostic value, availability limited
Gene sequencing	Confirmation of AFD, pathogenicity of the mutation should be verified since multiple polymorphisms and non-pathogenic mutations exist.

## 8. Enzyme replacement therapy

Enzyme replacement therapy (ERT) targets the underlying process of AFD. Studies have shown that ERT can reduce endothelial myocardial Gb<sub>3</sub> inclusions but evidence for clearance of Gb<sub>3</sub> from cardiomyocytes is less convincing. Most evidence suggests that the heart responds less well to therapy when disease is advanced.

ERT is indicated in all symptomatic patients with classical disease and at the earliest signs of organ involvement including neuropathy, nephropathy and cardiomyopathy. Two preparations of recombinant ERT are currently available on the European market: agalsidase alfa (Replagal<sup>®</sup>, Shire/Takeda), agalsidase beta (Fabrazyme<sup>®</sup>, Sanofi Genzyme). Agalsidase alfa is produced from the cell line of human fibroblasts while agalsidase beta from chinese hamster ovary cells. The amino-acid sequence of both enzymes differs only to a minimal extent. However, substantial differences in glycosylation exist. The major difference between the formulations is the prescribed dose, which is 0.2 mg/kg every 2 weeks for agalsidase alfa and 1.0 mg/kg every 2 weeks for agalsidase beta, respectively.

There is evidence from long-term follow-up studies and registries data that ERT when started early in the course of the disease may halt or slow disease progression and reduce the burden of clinical events. In particular it has been shown that ERT slows the progression rate of renal function decline, alleviates pain and improves gastrointestinal symptoms. Published data indicate that the heart responds less well to therapy when disease is advanced and minimal evidence exists about a beneficial effect of ERT in late onset cardiac variants. The evidence about reduction of stroke risk is also limited.

Mild LVH may partially regress both in classical and cardiac variant patients and one study has suggested that LV hypertrophy may be prevented by early therapy. However, there are no data showing that ERT prevents development of myocardial fibrosis and patients with extensive myocardial fibrosis probably respond less well in terms of functional improvement.

## 9. Chaperone therapy

Binding of the pharmacological chaperone (a small molecule - iminosugar 1-deoxygalactonojirimycin - migalastat, Galafold™, Amicus Therapeutics), to the active site of  $\alpha$ -galactosidase A stabilizes certain mutant enzymes, thus facilitating proper trafficking to lysosomes, where dissociation of migalastat allows  $\alpha$ -galactosidase A to catabolize accumulated substrates.

In patients who received orally migalastat for up to 24 months, a statistically significant decrease in left-ventricular mass index was observed with a trend toward a larger reduction in patients with baseline LVH.

Migalastat is approved for the use in AFD patients carrying an amenable mutation as indicated in the Summary of product characteristics of Galafold™.

<b>Table 6 Treatments for Anderson Fabry disease approved in Europe</b>	
<b>Enzyme replacement therapy</b>	<b>Posology</b>
Agalsidase alfa (Shire / Takeda) - Replagal®	0.2 mg / kg body weight administered once every 2 weeks by intravenous infusion over 40 minutes using an intravenous line with an integral filter. The safety and efficacy of Replagal in children aged 0-6 years has not yet been established.
Agalsidase beta (Sanofi Genzyme) - Fabrazyme®	1 mg/kg body weight administered once every 2 weeks by intravenous infusion. The initial infusion rate should be no more than 0.25 mg/min (15 mg/hour). The safety and efficacy of Fabrazyme in children aged 0-7 years has not yet been established.
<b>Chaperones</b>	<b>Posology</b>
Migalastat (Amicus Therapeutics) Galafold™	Adult patients with amenable mutations as indicated on SMPC of Galafold™ (see also <a href="http://www.galafoldamenabilitytable.com">http://www.galafoldamenabilitytable.com</a> ). Capsules - 123 mg orally once every other day at the same time of day. Food not to be consumed at least 2 hours prior and after the intake. The safety and efficacy of Galafold has not yet been established in pediatric patients.

## 10. Summary

In this booklet we briefly review main clinical features of AFD in classically affected patients and in those with late onset variants. The multisystemic manifestations of the disease includes angiokreatomas, cornea verticillata, peripheral neuropathy, premature stroke, renal impairment and cardiomyopathy.

We discuss diagnostic possibilities including assessment of enzyme activity from DBS kits, plasma or leukocytes, assessments of biomarkers including Gb<sub>3</sub> and lyso-Gb<sub>3</sub>, and genetic testing.

Finally, we summarize currently available treatment options including ERT and small molecular chaperone migalastat and review indications and potential benefits.



## 10. References

1. Germain DP. Fabry disease. *Orphanet J Rare Dis*. 2010 Nov 22;5:30.
2. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick RJ; Fabry Disease Clinical Trial Study Group. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med*. 2007 Jan 16;146(2):77-86.
3. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA*. 2001 Jun 6;285(21):2743-9.
4. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. *N Engl J Med* 2016; 375: 545-55.
5. Weidemann F, Niemann M, Störk S, Breunig F, Beer M, Sommer C, Herrmann S, Ertl G, Wanner C. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. *J Intern Med*. 2013 Oct;274(4):331-41.
6. Weidemann F, Breunig F, Beer M, Sandstede J, Störk S, Voelker W, Ertl G, Knoll A, Wanner C, Strotmann JM: The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. *Eur Heart J* 2005, 26:1221-1227.
7. Patel MR, Cecchi F, Cizmarik M, Kantola I, Linhart A, Nicholls K, Strotmann J, Tallaj J, Tran TC, West ML, Beitner-Johnson D, Abiose A. Cardiovascular events in patients with fabry disease natural history data from the fabry registry. *J Am Coll Cardiol*. 2011 Mar 1;57(9):1093-9.
8. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ. Fabry Disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995-2017. *J Med Genet*. 2018 Jan 12. pii: jmedgenet-2017-105080.
9. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, Jabbour F, Beldjord C, De Mazancourt P, Germain DP. X-chromosome inactivation in female patients with Fabry disease. *Clin Genet*. 2016 Jan;89(1):44-54.
10. Yousef Z, Elliott PM, Cecchi F, Escoubet B, Linhart A, Monserrat L, Namdar M, Weidemann F. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. *Eur Heart J*. 2013 Mar;34(11):802-8.
11. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart*. 2007 Apr;93(4):528-35.

12. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudová J, Karetová D, Zeman J, Ledvinová J, Poupetová H, Elleder M, Aschermann M. New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J.* 2000 Jun;139(6):1101-8.
13. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, Elliott PM; European FOS Investigators. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J.* 2007 May;28(10):1228-35.
14. Nowak A, Mechtler T, Kasper DC, Desnick RJ. Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and Later-Onset Fabry disease. *Mol Genet Metab.* 2017 Aug;121(4):320-324.
15. Namdar M, Steffel J, Vidovic M, Brunckhorst CB, Holzmeister J, Lüscher TF, Jenni R, Duru F. Electrocardiographic changes in early recognition of Fabry disease. *Heart.* 2011 Mar;97(6):485-90.
16. Patel V, O'Mahony C, Hughes D, Rahman MS, Coats C, Murphy E, Lachmann R, Mehta A, Elliott PM. Clinical and genetic predictors of major cardiac events in patients with Anderson-Fabry Disease. *Heart.* 2015 Jun;101(12):961-6.
17. Calcagnino M, O'Mahony C, Coats C, Cardona M, Garcia A, Janagarajan K, Mehta A, Hughes D, Murphy E, Lachmann R, Elliott PM. Exercise-induced left ventricular outflow tract obstruction in symptomatic patients with Anderson-Fabry disease. *J Am Coll Cardiol.* 2011 Jun 28;58(1):88-9.
18. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G, Weidemann F. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. *Eur Heart J.* 2013 Jun;34(21):1587-96.
19. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G, Weidemann F. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. *Eur Heart J.* 2013 Jun;34(21):1587-96.
20. Auray-Blais C, Lavoie P, Boutin M, Ntwari A, Hsu TR, Huang CK, Niu DM. Biomarkers associated with clinical manifestations in Fabry disease patients with a late-onset cardiac variant mutation. *Clin Chim Acta.* 2017 Mar; 466:185-193.
21. Nordin S, Kozor R, Medina-Menacho K, Abdel-Gadir A, Baig S, Sado DM, Lobascio I, Murphy E, Lachmann RH, Mehta A, Edwards NC, Ramaswami U, Steeds RP, Hughes D, Moon JC. Proposed Stages of Myocardial Phenotype Development in Fabry Disease. *JACC Cardiovasc Imaging.* 2018 May 11. pii: S1936-878X(18)30307-3.

## Part II: Glycogen Storage Diseases

### 1. Introduction and scope of the document

The aim of this document is to describe general and cardiac manifestations of glycogen storage diseases and increase the awareness about the disease among cardiologists.

Glycogen is a branched glucose polymer formed around a core protein called glycogenin. It serves as a rapidly available energy reservoir in muscle. Glycogen storage diseases (GSDs), are characterized by abnormal tissue accumulation of glycogen, and are caused by defects along the synthesis or the degradation pathways. There are currently 15 distinct GSDs known, only some of them have a prominent cardiac involvement.

GSDs are rare diseases caused by gene mutations affecting different steps in glycogen metabolism. Most are transmitted as an autosomal recessive trait. There are also examples of autosomal dominant or X-linked inheritance, which have a specific relevance to cardiomyopathy clinic. The age of presentation spans from early pediatrics to adulthood and even maturity. Cardiac involvement may be part of severe multisystem disease or predominate the clinical picture, presenting as hypertrophic or dilated cardiomyopathy.

This document will describe the principal manifestations of main GSDs involving the heart to increase the awareness about the disease among cardiologists.

## 2. Glycogen storage disease - Pathophysiology

Glycogen is a branched glucose polymer formed around a core protein called glycogenin. It serves as a rapidly available energy reservoir in muscle. Aged glycogen is degraded in the lysosome.

Glycogen storage diseases may be caused by:

- defects along the degradation pathways
- defects in the synthesis pathway giving rise to abnormal (nonsoluble) product
- metabolic dysregulation causing excess glycogen synthesis
- lysosomal glycogen accumulation occurs due to defects in lysosomal degradation

Disease manifestations are caused either by energetic deficiency or by toxic effects of the accumulated glycogen. Inability to mobilize glucose during fasting or exercise may lead to hypoglycemia and/or muscle injury. Deposits induce organomegaly, distort the cellular architecture, affect cellular biophysical properties and impair organelle (lysosome, mitochondria) function. Cardiac injury evokes a non-specific hypertrophic response. Contractile dysfunction may be an early sign or develop later in an already hypertrophied heart. Conduction disturbances are common including enhanced conduction at the early stage followed by arrhythmia and conduction block.

The principal features of GSDs causing a prominent cardiac involvement are presented in **Table 1**.

The aim of this document is to describe general and cardiac manifestations of AFD and increase the awareness about the disease among cardiologists.

**Table 1 Principal features of glycogen storage disorders involving the heart**

	Inheritance	Deposits	Age	Cardiac involvement	Myopathy	Other
GSD II (Pompe, acid maltase deficiency)	Autosomal recessive	Lysosomal glycogen	Infantile Teenage Adult	Severe HCM Minor Rare	Severe Severe Moderate	Hepatomegaly
GSD III (Cori, Debrancher enzyme def.)	Autosomal recessive	Cytosolic glycogen	Variable	HCM	Severe	Hepatomegaly Hypoglycemia
PRKAG2 (AMPK dysfunction)	Autosomal dominant	Cytosolic glycogen and polyglucosan	Teenage and Adult	HCM	None/ minor	No
Danon's (LAMP 2 deficiency)	X-linked	Lysosomal glycogen and autophagosomes	Teenage and Adult	HCM, DCM, hypokinetic HCM	Mild	Impaired liver enzymes Encephalopathy
PHK deficiency	Autosomal recessive	Cytosolic glycogen		DCM	Yes	Hepatomegaly
GSD IV (Brancher enzyme def.)	Autosomal recessive	Polyglucosan	Variable	DCM	Yes	Cirrhosis Encephalopathy
Glycogenin-1 deficiency	Autosomal recessive	Polyglucosan	Teenage and Adult	DCM or hypokinetic HCM	Yes	??

GSD = glycogen storage disease; AMPK = AMP activated protein kinase; PHK = phosphorylase kinase; Polyglucosan = a non-soluble glucose polymer; HCM = hypertrophic cardiomyopathy; DCM = dilated cardiomyopathy.

### 3. Glycogen storage diseases in cardiomyopathy clinic

Among patients with glycogen storage disease and cardiac involvement, some will be referred from other disciplines because of coexisting problems with or without an established etiological diagnosis. Others will be primarily seen by a cardiologist. Some of these will have extracardiac manifestations, but those may be subtle and easily overlooked. Extracardiac and pathognomonic cardiac manifestations may be initially absent but may show up on follow up or on family investigation.

Metabolic disease mimicking HCM or DCM in a cardiomyopathy clinic belongs to what a category of conditions called phenocopies. In pediatric cardiology metabolic disorders account to about 20% of all cardiomyopathies. Pompe disease is one of the most common metabolic causes of infantile HCM. Other GSDs (see **Table 1**) are substantially less common. In grown-up and adult cardiology, the prevalence of phenocopies is lower and amounts to 5-10% in referral centers. This estimate comprises infiltrative disease, syndromic HCM and metabolic cardiomyopathies. The most common glycogen storage conditions to cause cardiomyopathy in adults are PRKAG2 cardiomyopathy and Danon's disease. They were reported to account for up to 1-3% of HCM in specialized clinics. The prevalence appears to be lower than that in a large series of genetically tested unselected cardiomyopathy patients (Dr. Lorenzo Monserrat, Health in Code, personal communication).

Cori disease patients do develop HCM but they usually have a preexisting diagnosis. The diagnosis of debrancher enzyme deficiency is usually established in childhood following hypoglycemia, hepatomegaly and elevated liver enzymes. Skeletal myopathy is already profound when HCM develops in grown-ups.

Several clues "Red Flags" should draw attention to a possibility of glycogen storage disease in a patient with cardiomyopathy:

1. Early conduction disease such as WPW, short PR interval, unexplained sinus bradycardia or atrio-ventricular block.
2. Familial conduction disease in the presence of cardiomyopathy.
3. Extreme ECG voltage.

4. Extracardiac manifestations such as clinical or enzymatic. evidence of myopathy, hepatic dysfunction, mental problems, etc.
5. Rapidly progressive hypertrophy or heart failure development.
6. Family history suggestive of autosomal recessive or X-linked inheritance.

## 4. Pompe's disease

Pompe's disease is a lysosomal glycogen storage disease caused by homozygous (or compound heterozygous) mutations in acid alpha-glucosidase (GAA, acid maltase) gene. Secondary defects in lysosomal function and autophagy ensue. The incidence is estimated at 1:100 000 in newborns but higher in populations with high level of consanguinity.

The infantile form is characterized by severe myopathy ("floppy baby"), hepatomegaly and rapidly progressive/massive cardiac hypertrophy. Associated findings are extreme voltage and short PR interval on the ECG suggestive of delta waves. The disease is easily diagnosed by enzyme activity test which may be performed in a blood test.

Enzyme replacement therapy (ERT) is available and may lead to a dramatic improvement of the cardiac condition. However, the long-term prognosis is grim due to inadequate response of skeletal muscle to enzyme replacement. The penetration of recombinant enzyme into striated muscle appears to inferior compared to the heart. The cardiac condition may worsen during long-term ERT therapy because of emergence of resistance due to neutralizing antibodies.

Juvenile and adult onset Pompe manifest mostly by myopathy. Patients get immobilized and may require respiratory support. Left ventricular hypertrophy is rare and mild if present. ECG abnormalities such as short PR, delta waves, atrioventricular block and atrial arrhythmia may be present. Interestingly, 13% develop aortic dilatation.

## 5. PRKAG2 cardiomyopathy

Autosomal dominantly transmitted mutations in PRKAG2, the gene encoding the gamma-2 regulatory subunit of AMP-activated protein kinase (AMPK), cause a unique cardiomyopathy characterized by left ventricular hypertrophy and Wolf Parkinson White syndrome.

Atrial arrhythmia including pre-excited atrial fibrillation, atrio-ventricular reentry tachycardia as well as sinus bradycardia and conduction block are common (**Figure 1**). On electrophysiological studies single or multiple accessory pathways have been demonstrated. The combination of HCM with such a conduction disease in several family members is highly suggestive of the diagnosis.

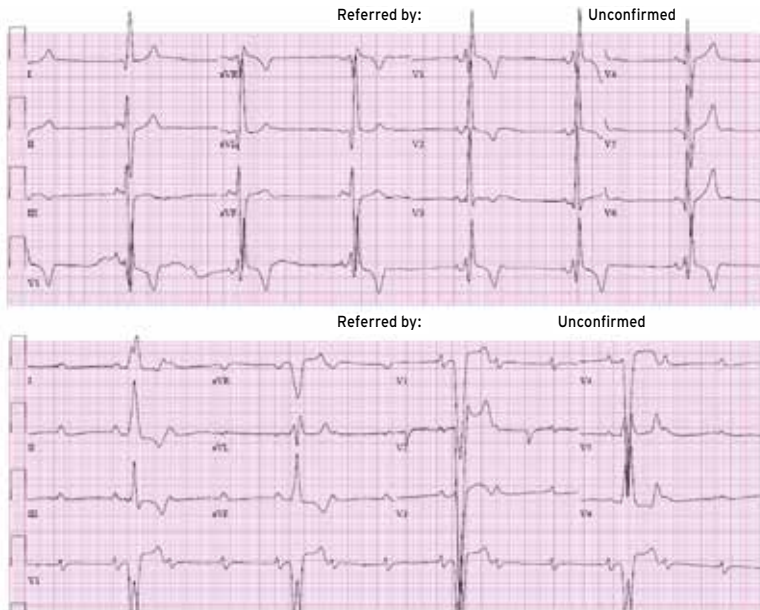
Left ventricular hypertrophy is not much different from common forms of HCM and compatible with long-term survival (**Figure 2**) but many of the patients will eventually require a pacemaker. Hypokinetic HCM may develop as a consequence of glycogen deposition and/or the detrimental effect of long-term right ventricular pacing. Ventricular arrhythmia and sudden death may occur as in other HCM patients. The clinical features of PRKAG2 cardiomyopathy are summarized in **Table 2**.

The role of glycogen in pathogenesis became clear when glycogen deposits and vacuoles were found in myocardial biopsies from patients (**Figure 2**). The mechanism of PRKAG2 cardiomyopathy involves dysregulation and abnormal activation of AMPK by mutations in its regulatory subunit. Cardiomyocytes experience increased fatty acid oxidation concomitant with increased glucose uptake and synthesis of glycogen. Other effects of AMPK activation also contribute to myocyte hypertrophy.

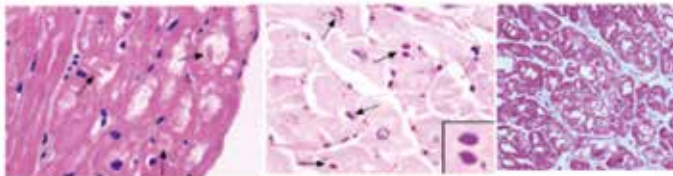
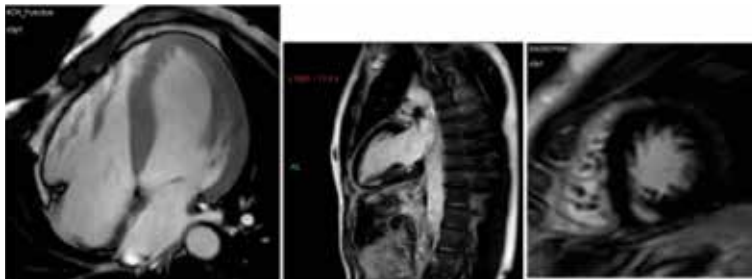
The age of presentation is teens to adulthood but other extremes have been described. The disease was initially considered to be confined to the heart but minor muscle discomfort with or without CK elevation were later reported. An overt disease involving the liver and nervous system was reported as a "malignant" neonatal form.



**Figure 1** ECG traces from 2 unrelated patients with a R302Q PRKAG2 mutation aged 52 (upper) and 41 (lower) years.



**Figure 2** CMR images from a 41 years old patient with R302Q PRKAG2 mutation demonstrating mild concentric hypertrophy 13-14 mm and minor fibrosis (upper). Endomyocardial biopsies from patients PRKAG2 mutations demonstrating vacuoles and residual glycogen (lower, adopted from Arad et al, J Clin Invest 2002).



Arad & Seidman , JCI 2020

**Table 2 Main clinical features of the most common and the largest series of PRKAG2 mutations adopted from Porto et al, Circ Arrhyth. Electr. 2016**

Mutation	Number age at Dg.	LVH	Short PR WPW	CSD (PM)	Heart failure	SCD
R302Q	110 36 yr.	42%	79%	55%	4%	10%
N488I	40 19 yr.	70%	58%	30%	NA	2.5%
All	190 30 yr.	53%	68%	43%	12.5%	9%

Dg. = diagnosis; LVH = left ventricular hypertrophy; CSD (PM) = conduction system disease requiring pacing; SCD = sudden cardiac death.

## 6. Danon's disease

Danon disease was originally described as an X-linked glycogen storage disease comprising myopathy, cardiomyopathy and mental retardation, and even designated as "GSD IIb -Pompe's with normal acid maltase». In 2000, Nishino and Co. identified LAMP2 mutations causing lysosomal membrane protein deficiency, and implicated lysosomal dysfunction as a cause of Danon's disease. LAMP2 deficiency leads to failure to complete the final step of the autophagic process, where digestion of aged cellular contents and organelles takes place. Importantly, failure to remove aged mitochondria (mitophagy) leads to mitochondrial dysfunction, energetic deficiency and oxidative stress.

Because of a high glycogen turnover in muscle, vacuoles with undigested glycogen may predominate in biopsy specimens but this is neither necessarily present, nor diagnostic. In advanced myocardial disease fibrosis of either interstitial or replacement type is the most prominent feature.

Nowadays, Danon's diagnosis is usually made by genetic testing demonstrating a radical LAMP2 in a patient presenting with compatible clinical features. The clinical presentation however, is highly variable. Some patients are diagnosed and treated by neurologists and geneticists while their cardiac phenotype is recognized at a later stage. Others present with cardiac disease and their extra-cardiac features may be minor (or absent) and therefore overlooked. It was initially a surprise to identify LAMP2 mutations as a disease cause in HCM patients studied in referral centers, as well as women presenting with postpartum cardiomyopathy.

The cardiac disease is characterized by rapid progression: teenage males typically manifest with rapidly progressive left ventricular hypertrophy that may involve the papillary muscles and the right ventricle (Figure 3). Hypokinetic HCM develops in a few years and is associated with decrease in wall thickness and severe heart failure due to combined systolic and diastolic dysfunction. Serial CMR studies and pathological specimens demonstrate rapidly progressive fibrosis. The clinical profile in women is more heterogeneous. Some present with HCM like males in their teens or twenties. Others manifest in their forties or later, as hypokinetic cardiomyopathy with or without some degree of left ventricular hypertrophy and/or dilatation, compatible with the current definition of dilated cardiomyopathy (DCM). Since some families have been followed for more than 10 years it is clear that, the presenting cardiac phenotype was DCM rather than "burned-out" HCM.

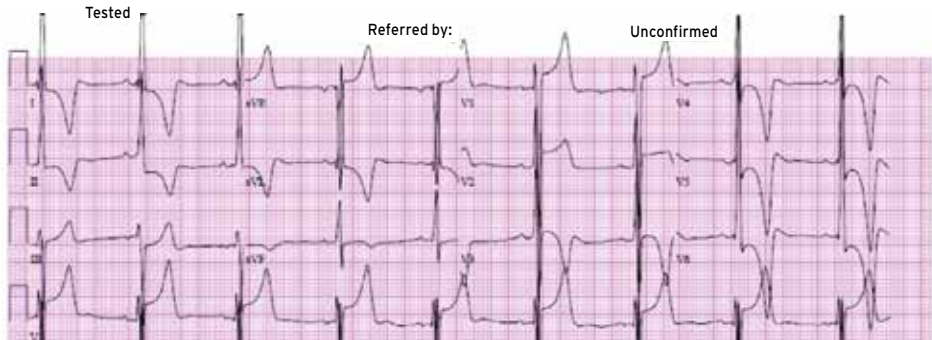
Electrical abnormalities such as extreme ECG voltage, WPW and early atrio-ventricular block are rather nonspecific features suggesting a possibility of metabolic disease being the cause of cardiomyopathy (Table 3). Ventricular arrhythmia and sudden cardiac death are common in both genders.

Even in the absence of muscle weakness, subtle myopathy is nearly always present in males manifesting by persistently elevated creatine kinase. Male patients often undergo repeat investigations in gastroenterology clinics due to transaminase elevation with no other indication of liver disease. Neuropsychiatric manifestations range from overt mental retardation or psychosis to minor behavioral abnormalities, attention deficit disorder, anxiety disorder or may be very absent. Pigmentary retinopathy may be quite common when sought for in specialized clinics, but rarely leads to clinically manifest visual disturbances.

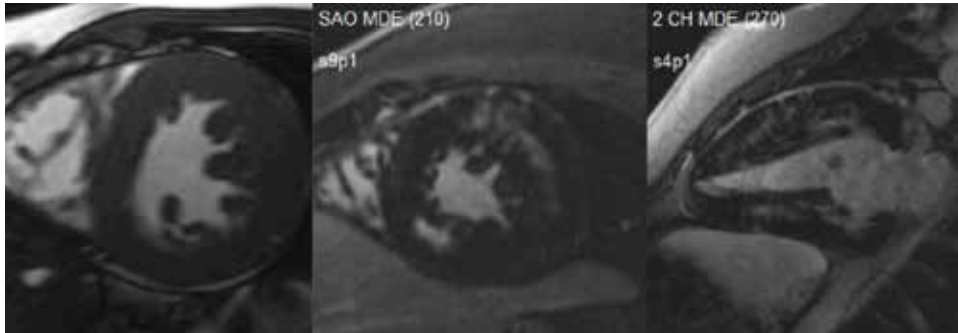
**Table 3 Main clinical features in males and females with Danon's disease according to gender adopted from Boucek & Taylor, Genetics in Medicine 2011**

Feature	Males (n=26)	Females (n=18)	Feature	Males (n=26)	Females (n=18)
Age Onset (y)	12 ± 6	27 ± 14	HCM	88%	33%
Age of death (y)	20 ± 5	40 ± 13	DCM & mixed	12%	28%
Myopathy	80%	50%	Conduction abnormality	86%	80%
Mental problems	100%	47%	WPW	68%	27%
CPK ALT/AST elevation	100% x2-10	Rare <x2	Visual	69%	64%

**Figure 3** Cardiac findings in a 16 years old boy with Danon's disease diagnosed at age 13 on athletes screening. The ECG shows extreme voltage with profound repolarization changes.



**Figure 3 (continued)** CMR shows concentric hypertrophy (15 mm) with prominent papillary muscles and extensive fibrosis by gadolinium enhancement.



## 7. Diagnosis

Historically GSDs were diagnosed by histopathology and enzyme activity assays. Tissue samples are usually obtained by liver or skeletal muscle biopsy. Fresh frozen samples are needed for enzyme activity studies.

Hematoxylin and eosin staining of paraffin-embedded tissue sections may demonstrate vacuoles to suggest storage. Hypertrophic changes and fibrosis may or may not be present. Periodic Acid-Schiff (PAS) stains polysaccharides such as glycogen. Confirmation of glycogen deposits is obtained by a combined incubation with diastase to digest the polymer into smaller sugar units, to be washed out of the section. Polyglucosan, a non-digestible glucose polymer, may be found in Brancher enzyme deficiency (GSD IV), glycogenin-1 defects and PRKAG2 cardiomyopathy.

Glycogen may “disappear” or be dissolved following long sample incubation in formaldehyde. Fresh tissue processing, electron microscopy and Toluidine Blue staining are useful when there is a high suspicion of GSD.

Tissue diagnosis of Danon's disease is typically confirmed by absence of LAMP2 on immunohistochemistry. However, that may not be necessarily true with certain mutations allowing for production of residual protein and in heterozygous women. Nowadays biopsy is rarely needed. The tissue to be samples should not be necessarily the heart, unless the heart is the only organ involved.

We advocate vigilance and attention to clinical, laboratory and family Red Flags, to arise a suspicion of storage disease. An appropriate work up will than be initiated in coordination with an expert metabolic consultant. One such hint may be vacuolated leukocytes on a blood smear. Measurement of acid maltase activity in leukocytes facilitated the diagnosis of Pompe's disease and dry blood spot (DBS) testing is readily available similar to Fabry's and other metabolic diseases.

The genes of common cardiac glycogenoses, PRKAG2, LAMP2 and usually GAA (for Pompe), AGL (for Cori) are included in contemporary cardiomyopathy gene panels.



Extensive Glycogen Storage Disease gene panels are also available. Since these are extremely rare and because of potential problems with interpreting genetic results, tissue diagnosis is advisable prior to using these panels. The organ to be biopsied and tissue processing should be discussed in advance to get the maximal yield from the procedure at a minimal risk.

Exome sequencing gained popularity and may diagnose rare and novel genetic causes of disease. This technique may be considered once common conditions have been ruled out. It is especially applicable in kindreds with recessive conditions with more than one affected individual.

## 8. Therapy

Enzyme therapy with a recombinant  $\alpha$ -glucosidase is available for Pompe's disease and may lead to a dramatic improvement of the cardiac condition. The enzyme preparation is administered IV on a 2-weekly basis. However, the long-term prognosis in infantile Pompe is still grim due to inadequate response of skeletal muscle to enzyme replacement. The penetration of recombinant enzyme into striated muscle appears to be inferior compared to the heart. The cardiac condition may worsen again on the follow up despite ERT, because of emergence of resistance due to neutralizing antibodies. The effect of immunomodulation is being studied. There is no consensus how long to continue and if discontinue ERT in respirator dependent terminal patients.

The clinical course of juvenile and adult Pompe is less malignant. Patients primarily suffer from progressive skeletal myopathy but mild or no cardiomyopathy. They may benefit from a combination of ERT with respiratory support and assisted ambulation.

No specific therapy is available in Cori disease, PRKAG2 cardiomyopathy and Danon's disease.

Dietary modification is helpful in children with Cori disease (frequent feeding, uncooked cornstarch, high protein), reducing the risk of hazardous hypoglycemia and liver failure. HCM in adults behaves and is attended quite similar to sarcomeric HCM.

PRKAG2 cardiomyopathy runs a similar course to sarcomeric HCM and is compatible with a nearly normal survival. Specific issues are arrhythmia due to preexcitation, high prevalence of atrial fibrillation and conduction abnormalities. Development of heart block needs to be expected and followed. Once paced, these hearts may have a higher risk of developing systolic dysfunction.

Danon's is a lethal orphan disease with no specific therapy. Early diagnosis is of huge importance to foresee the course of Danon's disease, to diagnose family members instituting appropriate medical follow up, and to prevent transmission to next generations. Another obvious benefit of timely diagnosis is preventing unnecessary invasive diagnostic procedures.

Current medical therapies seem to help control symptoms but do little to prevent disease progression. Intense physical activity, should probably be strictly forbidden. Drugs to attenuate fibrosis and preserve myocardial energy may be considered. Experts advocate low threshold for ICD implantation, what is reasonable given the reported prevalence of malignant ventricular arrhythmia either on presentation or at follow up. The exact timing during the disease course and the role of standard risk indicators are not known, warranting a close follow up. There is also a recommendation for early listing for heart transplantation. Since heart transplantation may be complicated in male patients because of post-transplant myopathy and aggravation of psychiatric issues, referral to highly specialized centers may be considered.

The disease course may be more modest, late onset and protracted in females with Danon. Yet, they may suffer from the same cardiac complications but have less extracardiac issues. Therefore the approach to female patients should be individualized according to age and mode of presentation. Reproductive counselling is of utmost importance.

## 9. Summary

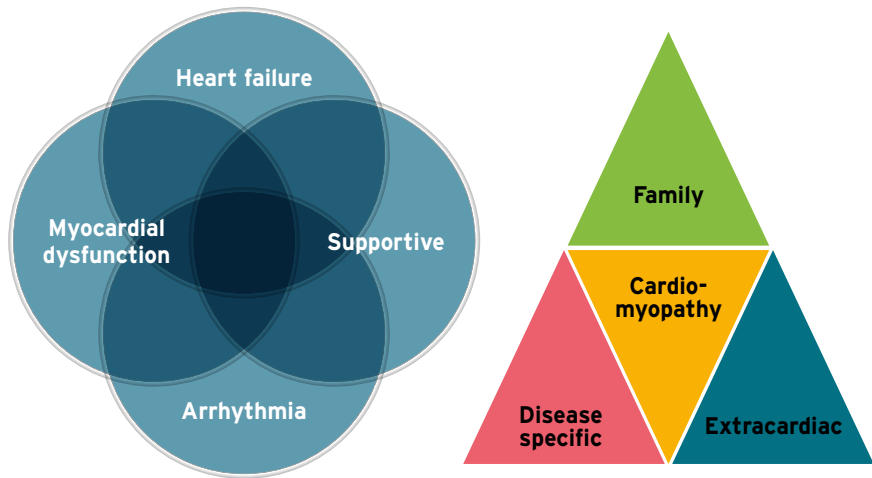
According to the World Health Organization, a disease is considered rare when it affects ~ 1 in 2000 persons. There are approximately 7,000 known rare diseases (RDs), 80% of which are genetic in origin. Many of these diseases have no specific therapy. Why then it is important to diagnose?..... There are several good reasons.

- 1) Reaching the diagnosis is soul of medicine. Diagnosing and managing rare conditions is where a skill becomes an art.
- 2) Diagnosis defines the prognosis and therapy. Even when no specific therapy is available we provide a better care when we know the natural history and expect the complications.
- 3) Knowing the diagnosis helps to avoid hazardous medications and spares further unnecessary and potentially harmful diagnostic procedures.
- 4) Precise etiological classification, structured follow up and international collaboration are a cornerstone of progress in rare diseases. This is the way to study potential therapies, apply exciting knowledge and develop disease-specific solutions.

With rare diseases there is always a place for additional learning. Multidisciplinary collaboration is the key to provide better solutions for patients and families (**Figure 4**).

**Figure 4** Cardiological management of a patient with metabolic cardiomyopathy necessarily involves several subspecialties within the field of cardiovascular medicine. Multidisciplinary approach for diagnosis and comprehensive therapy.

## Metabolic cardiomyopathy management



## 10. References and additional reading

1. Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Heliö T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013May;34(19):1448-58
2. Elliott PM, Anastakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014 Oct 14;35(39):2733-79
3. Arbustini E, Di Toro A, Giuliani L, Favalli V, Narula N, Grasso M. Cardiac Phenotypes in Hereditary Muscle Disorders: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018 Nov 13;72(20):2485-2506
4. Tarnopolsky M, Katzberg H, Petrof BJ, Sirrs S, Sarnat HB, Myers K, Dupré N, Dodig D, Genge A, Venance SL, Korngut L, Raiman J, Khan A. Pompe Disease: Diagnosis and Management. Evidence-Based Guidelines from a Canadian Expert Panel. *Can J Neurol Sci*. 2016 Jul;43(4):472-85.
5. Arad M, Seidman CE, Seidman JG. AMP-activated protein kinase in the heart: role during health and disease. *Circ Res*. 2007 Mar 2;100(4):474-88.
6. Kim M, Hunter RW, Garcia-Menendez L, Gong G, Yang YY, Kolwicz SC Jr, Xu J, Sakamoto K, Wang W, Tian R. Mutation in the  $\gamma$ 2-subunit of AMP-activated protein kinase stimulates cardiomyocyte proliferation and hypertrophy independent of glycogen storage. *Circ Res*. 2014 Mar 14;114(6):966-75.
7. Porto AG, Brun F, Severini GM, Losurdo P, Fabris E, Taylor MRG, Mestroni L, Sinagra G. Clinical Spectrum of PRKAG2 Syndrome. *Circ Arrhythm Electrophysiol*. 2016 Jan;9(1):e003121. doi: 10.1161/CIRCEP.115.003121 e003121.
8. Nishino I, Fu J, Tanji K, Yamada T, Shimojo S, Koori T, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature*. 2000;406(6798):906-10.

9. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med*. 2005;352:362-72.
10. Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. *Genet Med*. 2011 Jun;13(6):563-8.
11. D'souza RS, Levandowski C, Slavov D, Graw SL, Allen LA, Adler E, et al. Danon disease: clinical features, evaluation, and management. *Circ Heart Fail*. 2014;7:843-9.

### **Contributing authors :**

Ales Linhart, Michael Arad, Perry M. Elliott, Alida L.P. Caforio, Antonis Pantazis and Yehuda Adler.



# ESC

Working Group  
Myocardial &  
Pericardial Diseases

European Society of Cardiology ●

Working Groups Department  
Les Templiers - 2035 route des colles  
CS 80179 BIOT  
06903 Sophia Antipolis Cedex, France

Tel.: +33 (0)4 92 94 76 00  
Fax: +33 (0)4 92 94 76 01  
Email: [workinggroups@escardio.org](mailto:workinggroups@escardio.org)

● [www.escardio.org/workinggroups](http://www.escardio.org/workinggroups)