NATION-WIDE SCREENING OF FABRY DISEASE IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY IN CZECH REPUBLIC (BY DRY BLOOD SPOT METHOD)

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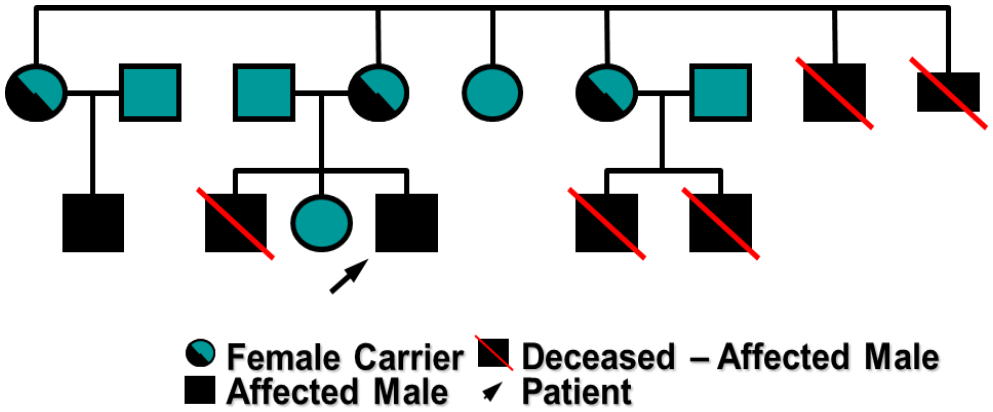
Fabry disease

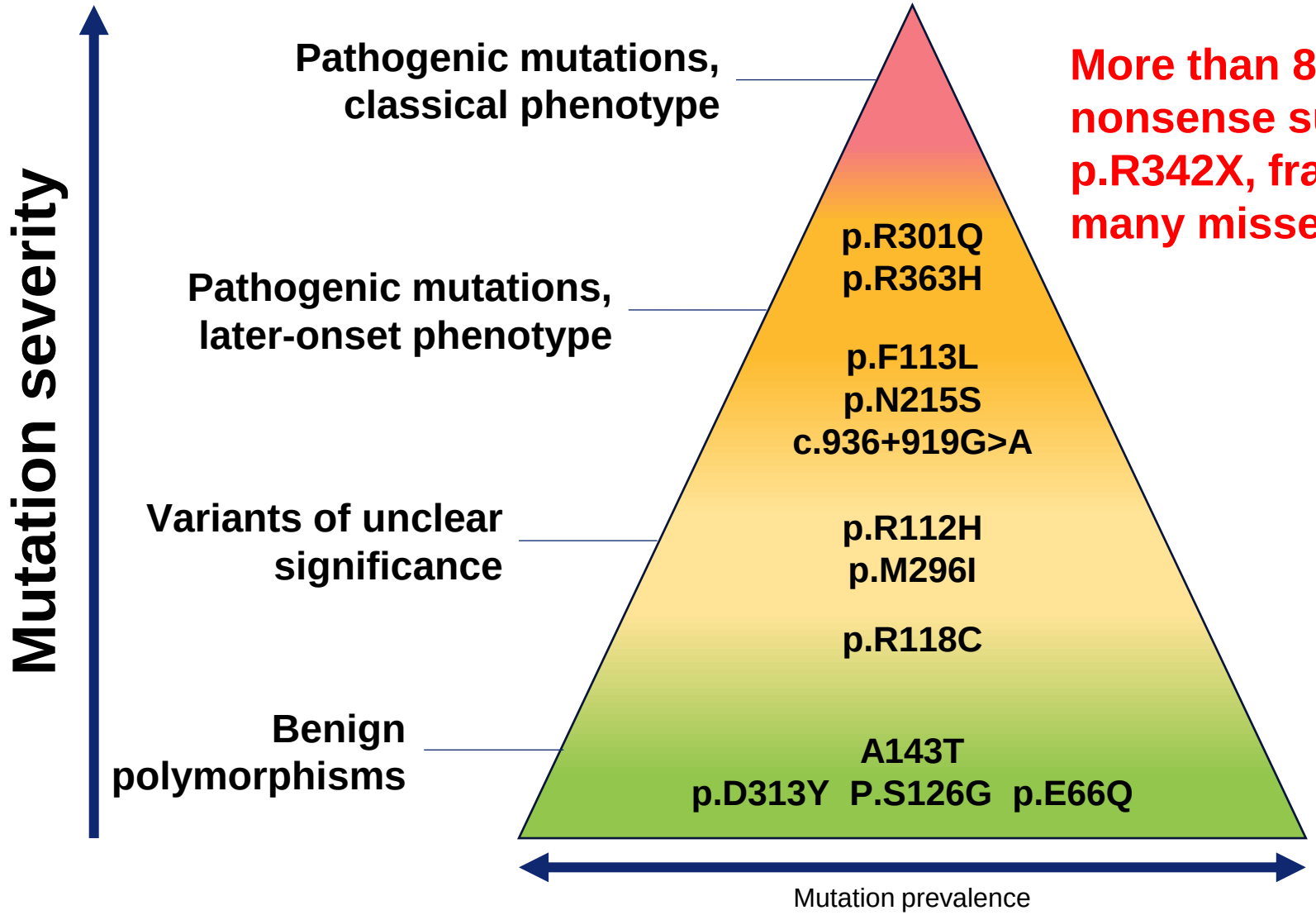
- Human lysosomal storage disorder (LSD)
- X-linked disorder of glycosphingolipid metabolism
- α-Galactosidase A deficiency (α-gal A)
- the gene on Xq22 >841 mutations identified (pathogenicity?)
- Frequency
  - > classical variant 1:30-40.000 male births
  - > 1:2.500-3.000 based on neonatal screening (enzymatic…)



Spada et al. Am. J. Hum. Genet. 2006;79:31–40.
Mechtler et al. Lancet 2012;379:335-41

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004059/WC500208435.pdf

Pathogenicity of mutations in Fabry disease



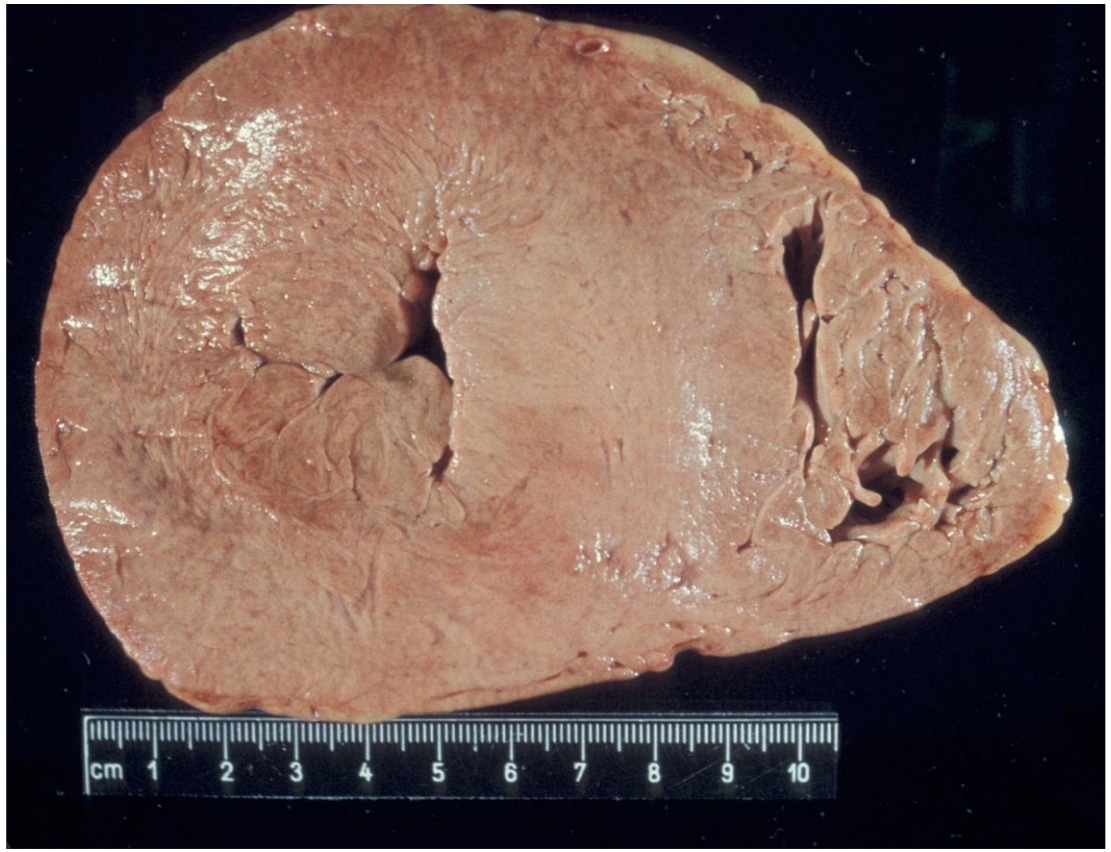
More than 840 mutations, e.g. nonsense such as p.R227X, p.R220X, p.R342X, frameshift, deletions and many missense mutations

Ortiz A. et al. Molecular Genetics and Metabolism 123 (2018) 416–427

Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease

Report on a case simulating hypertrophic non-obstructive cardiomyopathy

M. Elleder [1], V. Bradová [1], F. Šmíd [1], M. Buděšínský [5], K. Harzer [4], B. Kustermann-Kuhn [4], J. Ledvinová [2], Bělohlávek [3], V. Král [6], and V. Dorazilová [1]



LV hypertrophy in a 63-year-old male with Fabry disease:
LV mass 1100 g

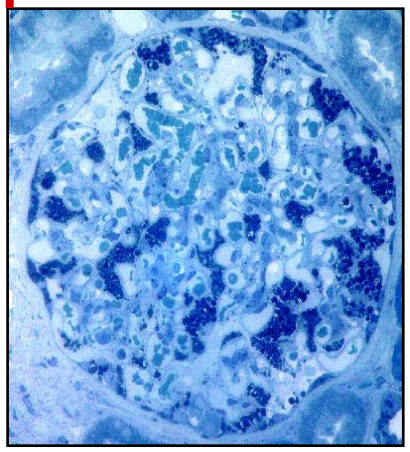
Gb3 content: 1%

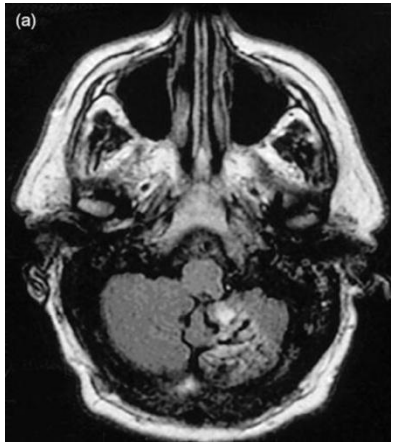
Based on offspring genetic analysis:
N215S mutation

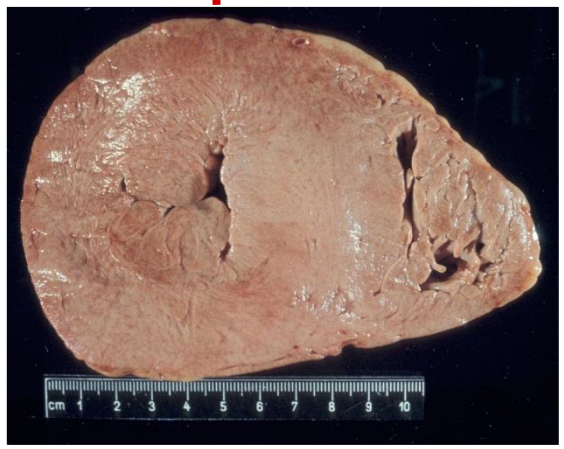
Figure from Elleder M, *et al*.
Gb3, globotriaosylceramide; LV, left ventricular
Elleder M, *et al*. *Virchows Arch A Pathol Anat Histopathol.* 1990;417:449–455

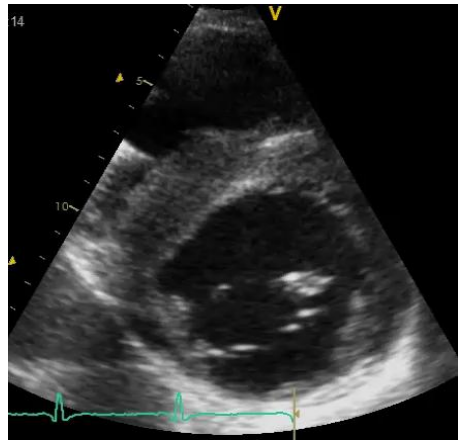
Fabry Phenotypes

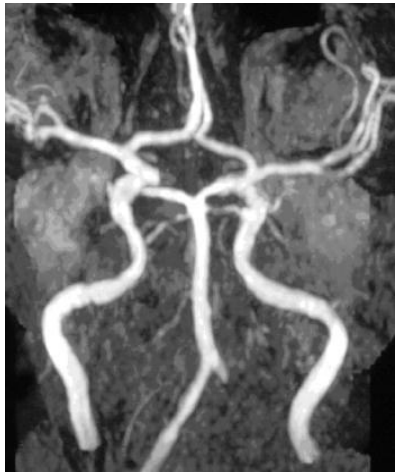
- **Classical / multiorgan**
- **Late onset / variant**

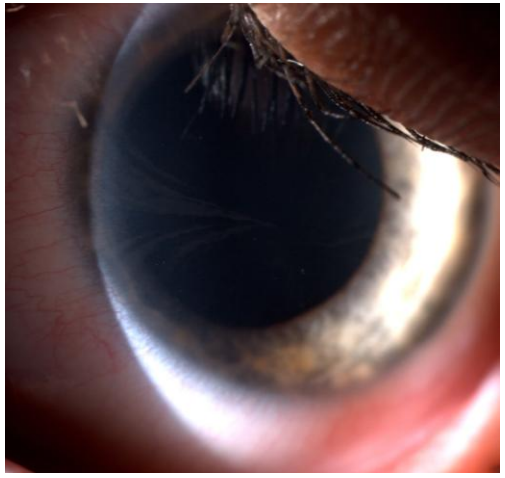












Adapted from: Mehta et al. Eur J Clin Invest (2004)34: 236–242; Hegemann, S. Eur J Clin Invest. 2006 Sep;36(9):654-62.; Burlina *et al. J Neurol* 2008;255:738–744; Elleder et al. Virchows Arch A Pathol Anat Histopathol. 1990;417(5):449-55.

Hypertrophic cardiomyopathy?

Presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions.

In an adult ≥15 mm in one or more LV myocardial segments—by any imaging technique

- **In relatives ≥13 mm**
- **Genetic & nongenetic disorders 13–14 mm**

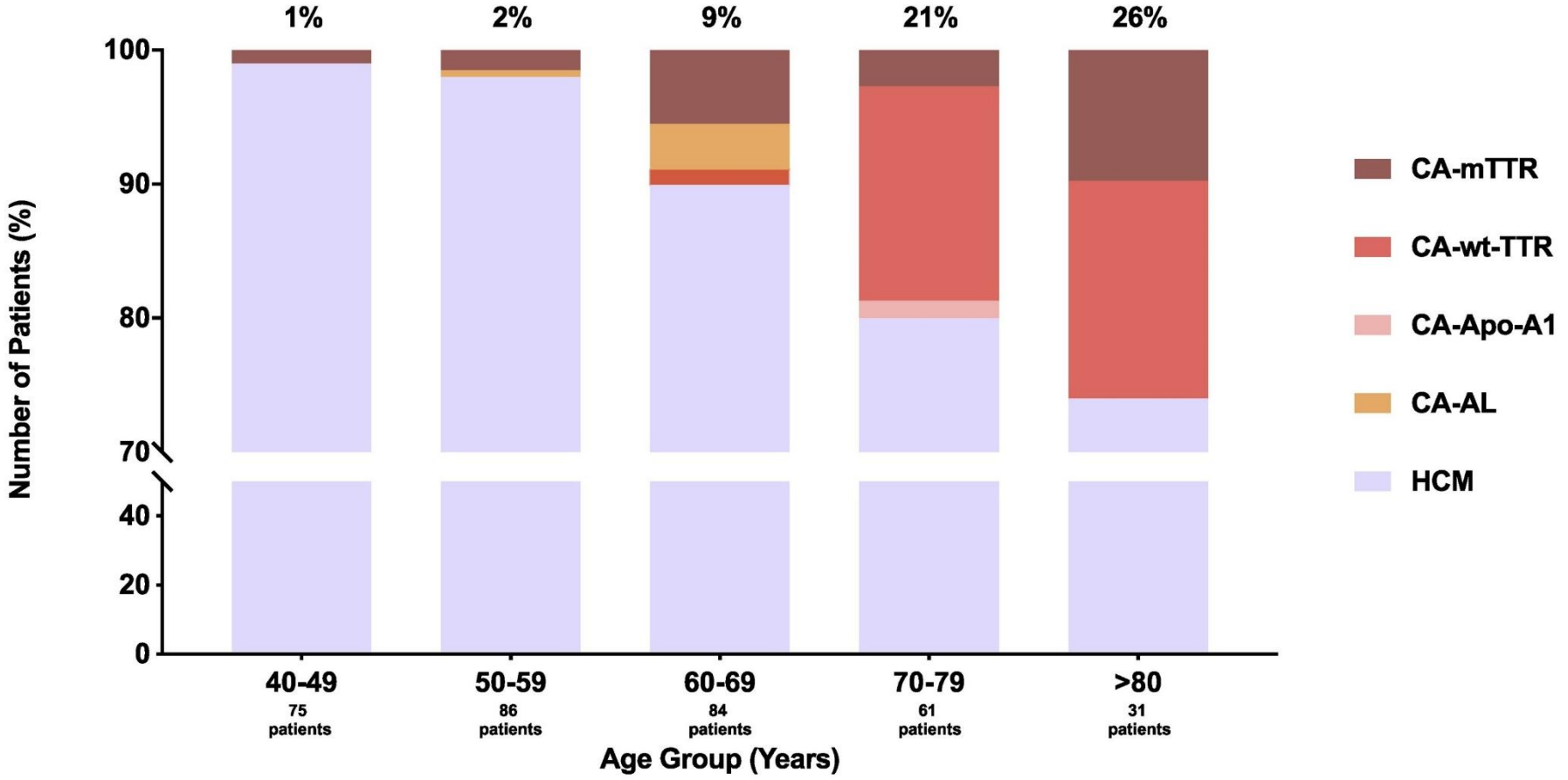
In children > 2 SD of the predicted mean **(z-score >2)**

Elliott et al. Eur Heart J. 2014 Oct 14;35(39):2733-79.

Misdiagnosis in patients with tentative dg. of HCM

343 consecutive patients aged ≥40 years referred with a tentative HCM diagnosis in the period 2014–201

32(9%) patients were diagnosed with CA + 6 (2%) variants in GLA gene



Maurizi et al. Int J Cardiol 300 (2020) 191-195

Revisited prevalence of FD among high risk populations

- **haemodialysis n= 36 820 (23 954 M and 12 866 F)**
  - **0.21% males**
  - **0.15% females**
- **renal transplant n = 3 074 (2 031M and 1 043F)**
  - **0.25% males**
  - **no females**
- **LVH / HCM n = 5491 (4054M and 1437F)**
  - **0.94% males**
  - **0.90% females**
- **stroke n = 5978 (3 904 M and 2 074 F)**
  - **0.13% males**
  - **0.14% females**

Doheny D, et al. J Med Genet 2018;0:1–8.

J Inherit Metab Dis
DOI 10.1007/s10545-013-9659-2

ORIGINAL ARTICLE

Prevalence of Fabry disease in male patients with unexplained left ventricular hypertrophy in primary cardiology practice: prospective Fabry cardiomyopathy screening study (FACSS)

Tomas Palecek · Jitka Honzikova · Helena Poupetova · Hana Vlaskova · Petr Kuchynka · Lubor Golan · Sudheera Magage · Ales Linhart

Patient number	Age (years)	Maximal LV wall thickness (mm)	Conduction disease	NYHA class	Renal function	AGAL activity in leukocytes (nmol/hour/mg protein)*	Mutation in the *GLA* gene
1	56	21	Incomplete RBBB	2	Normal	3.31	c.[801+48 T>G];[0], r.[801_802ins801+1_801+66;801+48U>G]
2	48	14	Incomplete RBBB	1	Normal	1.50	c.[454 T>C];[0]
3	49	17	–	2	Normal	3.52	c.[801+48 T>G];[0], r.[801_802ins801+1_801+66;801+48U>G]
4	53	19	Short PR interval with delta wave and incomplete RBBB	2	Decreased	4.82	c.[644A>G];[0]

AGAL, α-galactosidase A; LV, left ventricular; RBBB, right bundle branch block

*normal range 25–76 nmol/h/mg protein; mean ± SD 47.1 ± 10.2 nmol/h/mg protein

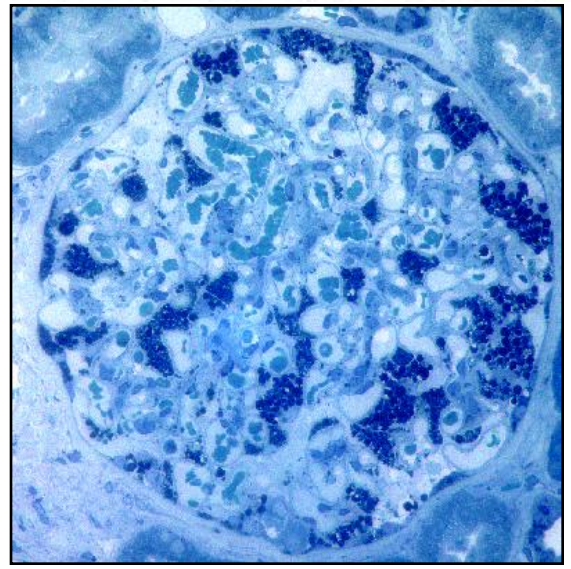
How were the patients diagnosed in the Czech Republic?

23.5 % of cases were identified by high-risk populations screening

Data of The General University Hospital, Prague,

Fabry disease diagnosis

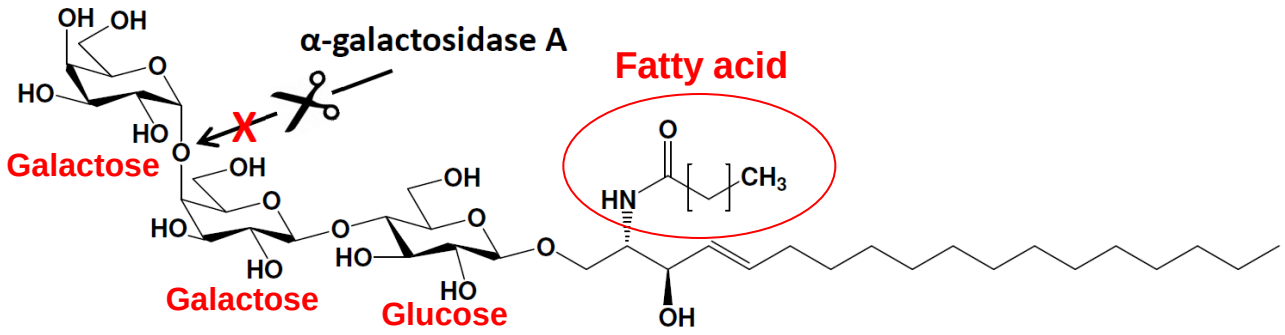
- **Typical symptoms**
  - pain, proteinuria, renal failure, skin and ocular manifestations, cardiomyopathy, early stroke
- **α-Galactosidase A activity**
  - leukocytes, fibroblasts, plasma
  - dry blood spot
- **Lyso Gb_3 concentrations**
  - plasma, DBS
  - low in late onset variants and females
- **Biopsy (renal, cardiac, GIT???)**
- **Gene sequencing (females!!!)**



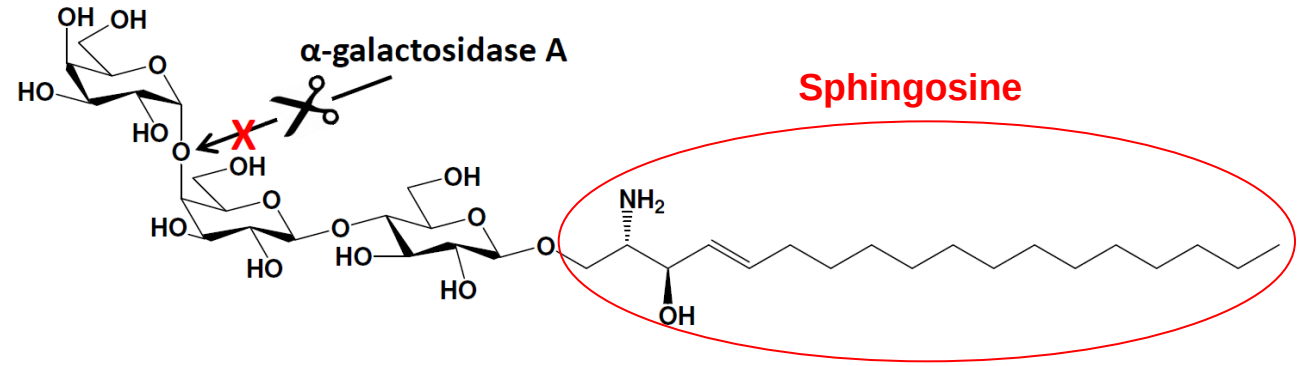
Author´s own opinion

Gb_3 and Lyso-Gb_3

Globotriaosylceramide (Gb_3)

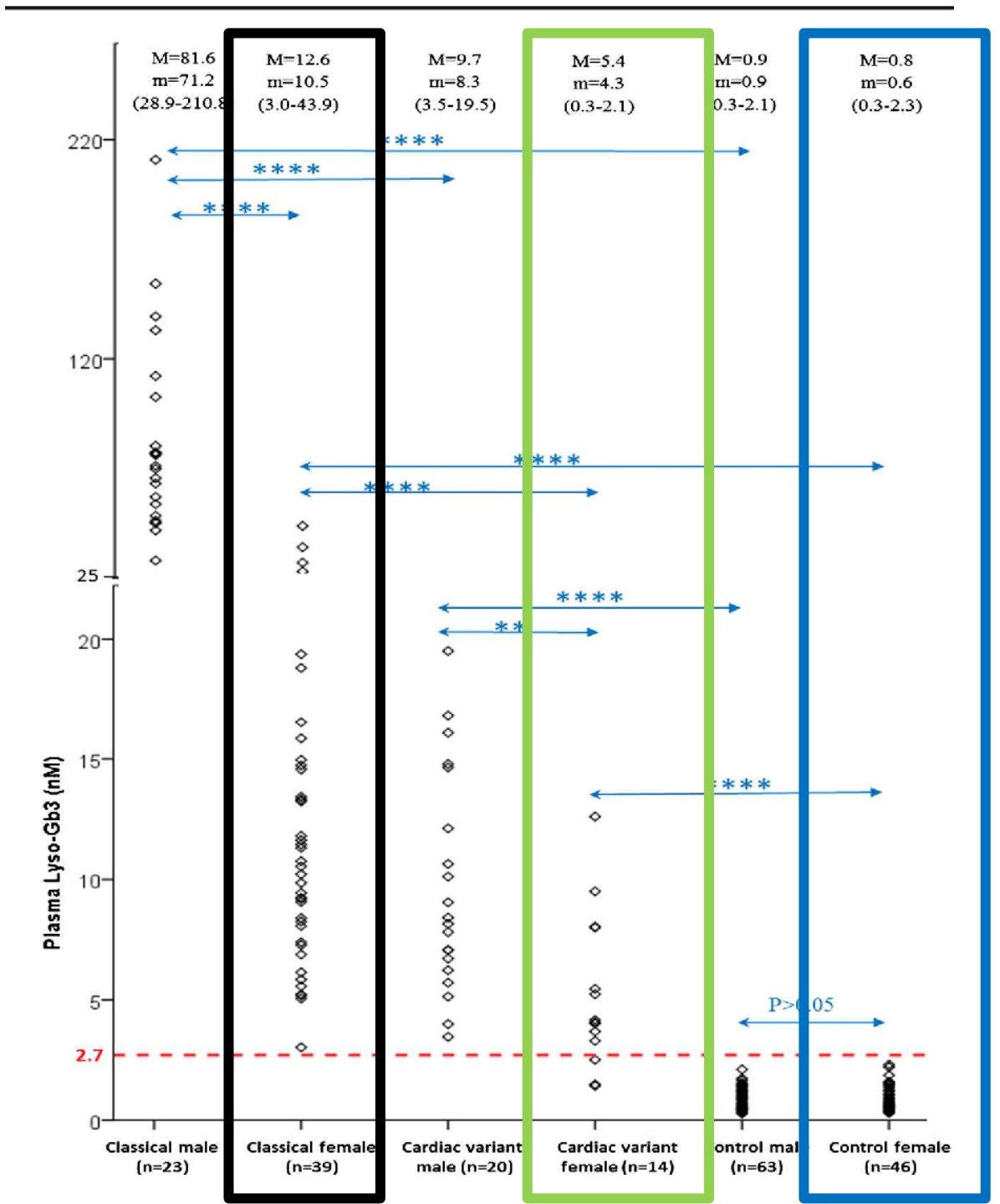


Globotriaosylsphingosine (Lyso-Gb_3)



Aerts JM, et al. *PNAS*. 2008;105(8):2812–2817

Biomarkers Depend on Gender and Mutation Type



Alharbi et al. J Inherit Metab Dis. 2018 Mar;41(2):239-247

ESC HEART FAILURE
ESC Heart Failure (2022)
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ORIGINAL ARTICLE

Nationwide screening of Fabry disease in patients with hypertrophic cardiomyopathy in Czech Republic

David Zemánek[1], Jaroslav Januška[2], Tomáš Honěk[3], Karol Čurila[4], Miloš Kubánek[5], Štěpánka Šindelářová[6], Lucie Zahálková[7], Petr Kloféč[8], Eliška Laštůvková[9], Eva Lichnerová[10], Renata Aiglová[11], Jan Lhotský[12], Jiří Vondrák[13], Gabriela Dostálová[1], Miloš Táborský[11], David Kasper[14] and Aleš Linhart[1]*

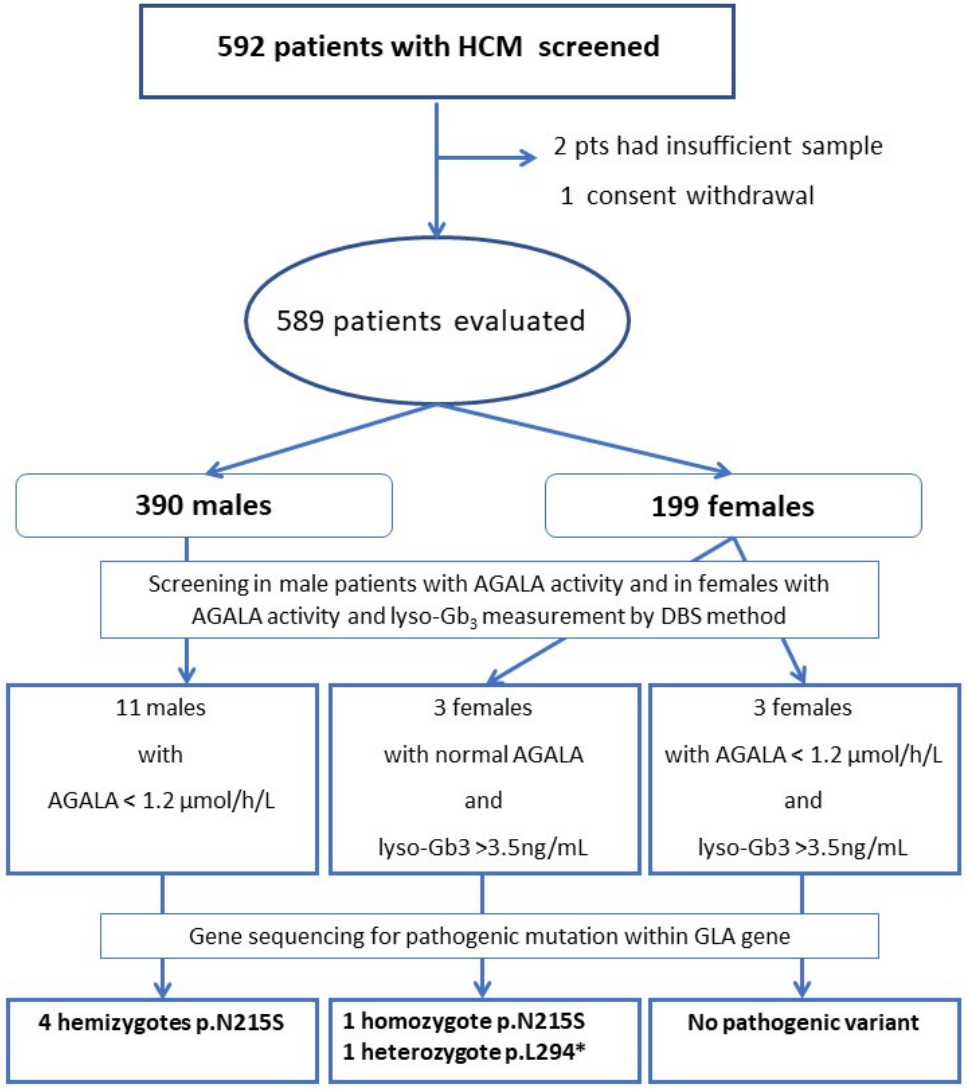
[1]*2nd Department of Internal Medicine Cardiology and Angiology, General University Hospital and 1st Faculty of Medicine of Charles University, Prague, Czech Republic;* [2]*Cardiocentre Podlesí, Třinec, Czech Republic;* [3]*1st Department of Internal Medicine - Cardioangiology, St Anne's University Hospital and Masaryk University, Brno, Czech Republic;* [4]*Department of Cardiology, 3rd Faculty of Medicine, Charles University and University Hospital Kralovské Vinohrady, Prague, Czech Republic;* [5]*Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic;* [6]*Department of Cardiology, Hospital České Budějovice, České Budějovice, Czech Republic;* [7]*1st Department of Medicine - Cardioangiology, Charles University Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic;* [8]*Department of Cardiology, Regional Hospital Liberec, Liberec, Czech Republic;* [9]*Department of Cardiology, Hospital Jihlava, Jihlava, Czech Republic;* [10]*Department of Cardiovascular Disease, University Hospital in Ostrava, Ostrava, Czech Republic;* [11]*Department of Internal Medicine I - Cardiology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic;* [12]*Department of Cardiology, University Hospital and Faculty of Medicine Pilsen, Charles University, Prague, Czech Republic;* [13]*Department of Cardiology, Regional Hospital Pardubice and Faculty of Health Studies, University of Pardubice, Pardubice, Czech Republic; and* [14]*ARCHIMED Life Science GmbH, Vienna, Austria*

Organization and inclusion criteria

- The screening 1 June 2 017 - 31 December 2018 (at least 12 months in each centre).
- HCM was defined by the presence of increased LV wall thickness (≥15 mm) in one or more myocardial segments on echocardiography, MRI, or cardiac CT.
- Patients with known FD and HCM phenocopies including infiltrative diseases (e.g. amyloidosis) were excluded.
- All patients had to be older than 18 years
- Informed consent

Zemánek et al. ESC Heart Failure(2022)

Nationwide screening of Fabry disease in HCM patients – The Czech Republic experience



In males AGALA activity <1.2 µmol/h/L

in females with either low AGALA activity or lyso-Gb3 > 3.5 ng/mL

Zemánek et al. ESC Heart Failure(2022)

Fabry Screening Programme in hypertrophic cardiomyopathy in the Czech Republic

Lead investigators: David Zemánek and Aleš Linhart

589 patients (390 males, 66%)

DBS (Archimed)

17 patients (11 males, 65%) – screened positive

6 patients (4 males, 67%) confirmed by gene sequencing

DBS, dry blood spot

Zemánek et al. ESC Heart Failure(2022)

Characteristics of Czech patients with HCM

Age (years)	58.4 ± 14.7
Males (n; %)	390; 66%
Maximal LV wall thickness (mm)	19.1 ± 4.3
Family history of hypertrophic cardiomyopathy (n; %)	102; 17%
Presence of LVOT obstruction (n; %)	259; 44%
ICD implantation (n; %)	94; 16%
Fabry non-cardiac manifestation (n; %)	124; 21%
- Proteinuria or renal insufficiency	61; 10%
- Acroparesthesia	39; 7%
- Stroke/TIA	38; 6%
- Angiokeratoma, cornea verticillata	5; 1%

ICD = implantable cardioverter-defibrillator, LV = left ventricle, LVOT = left ventricular outflow tract, TIA = transitory ischemic attack

Zemánek et al. ESC Heart Failure(2022)

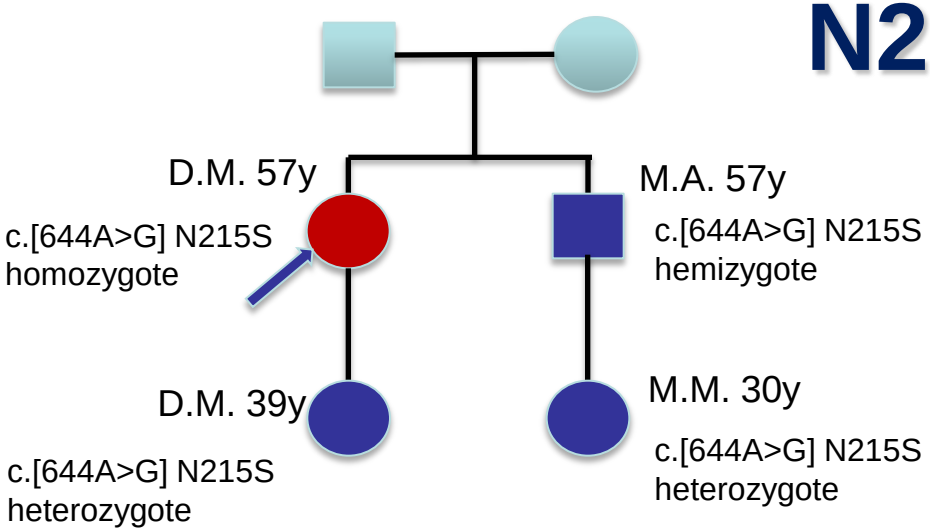
Fabry Screening Programme in the Czech Republic

Sex	Age	Gene mutation	AGAL activity (μmol/l/h)	Lyso-Gb3 (ng/mL)	Max. wall thickness (mm)	LVOTO	ICD	Positive family history	Non-cardiac FD manifestation
M	56	N215S	0.4	-	30	yes	no	no	no
M	57	N215S	0.7	-	23	no	no	no	no
F	56	N215S	0.3	10.0	24	yes	yes	yes	Proteinuria Acroparesthaesia
M	66	N215S	0.3	-	24	no	no	yes	Proteinuria
F	53	L294*	0.6	16.0	18	no	no	no	no
M	55	N215S	0.3	-	20	no	no	no	no

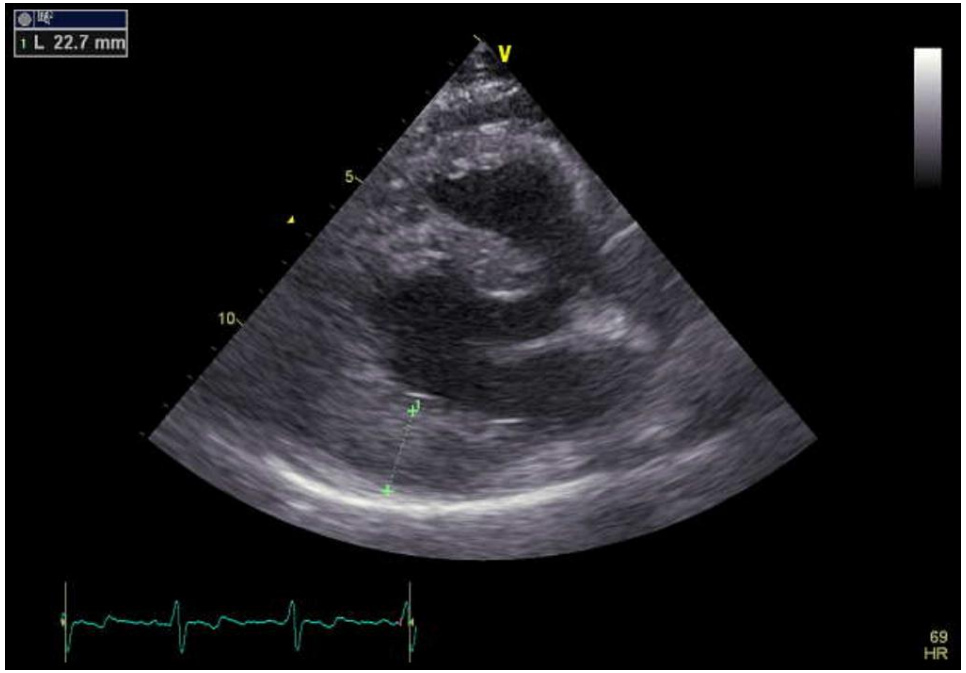
AGAL, α-galactosidase A; FD, Fabry disease; ICD, implantable cardioverter defibrillator; LVOTO, left ventricular outflow tract obstruction
Zemánek and Linhart, submitted

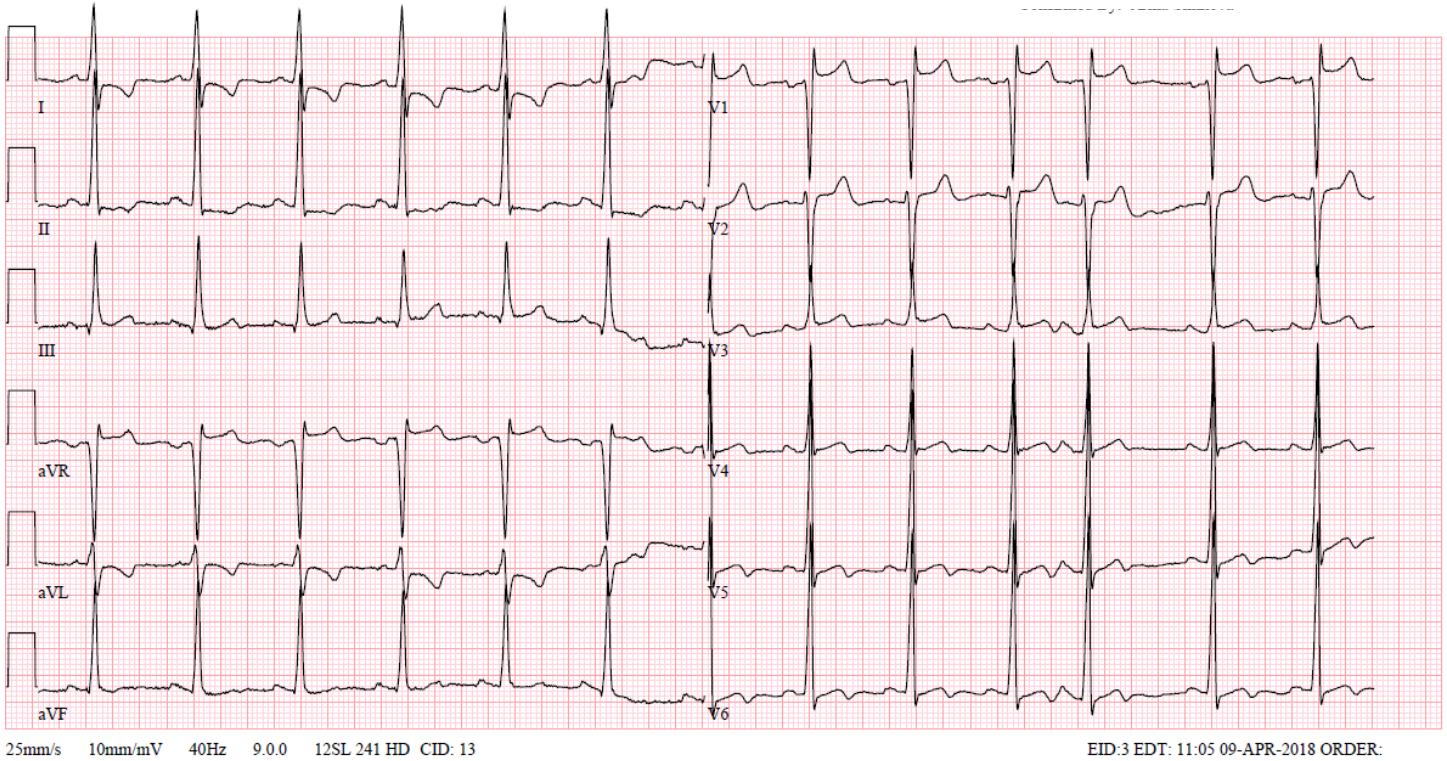
Zemánek et al. ESC Heart Failure(2022)

N215S homozygote



- 2017 – septal reduction – alcohol ablation
- 2017 – ICD implantation
- FD diagnosed by a screening study in HCM
- Acroparesthesias
- Borderline eGFR, microalbuminuria
- Cornea verticillata

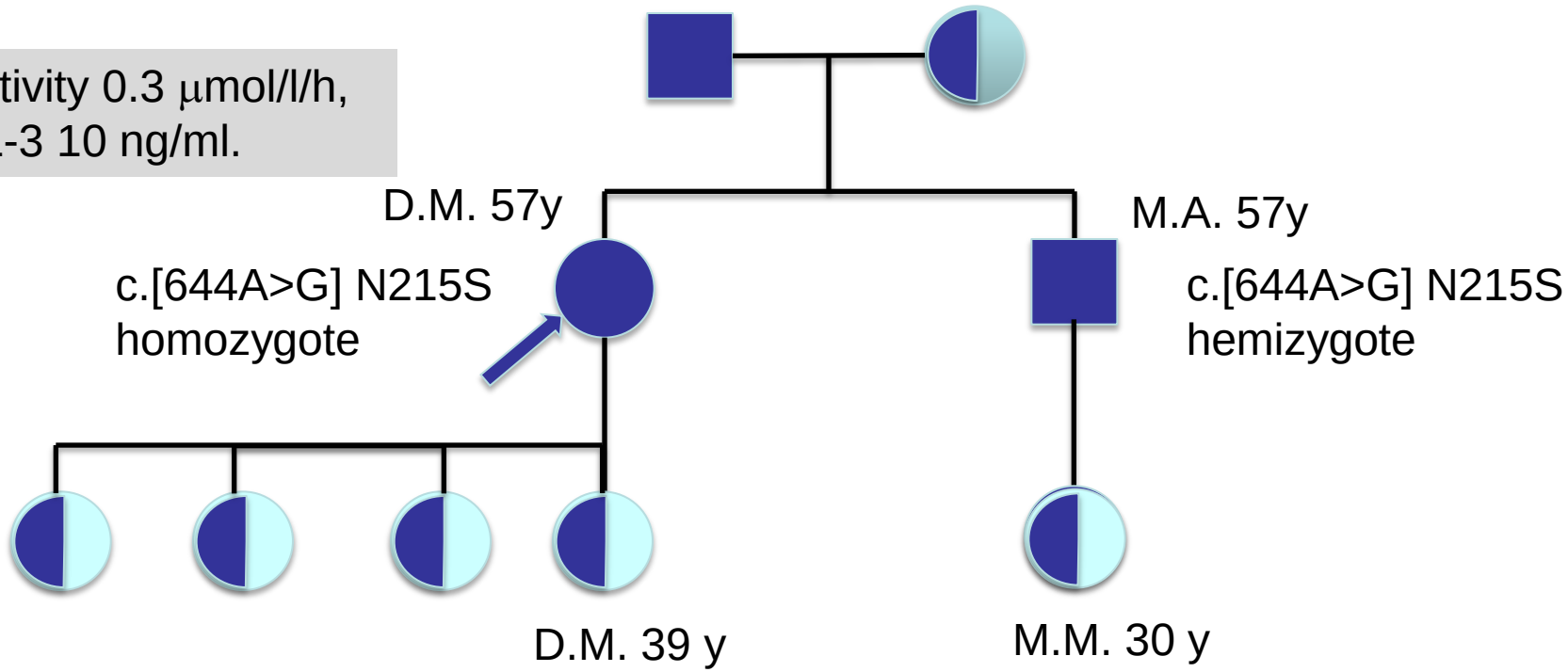




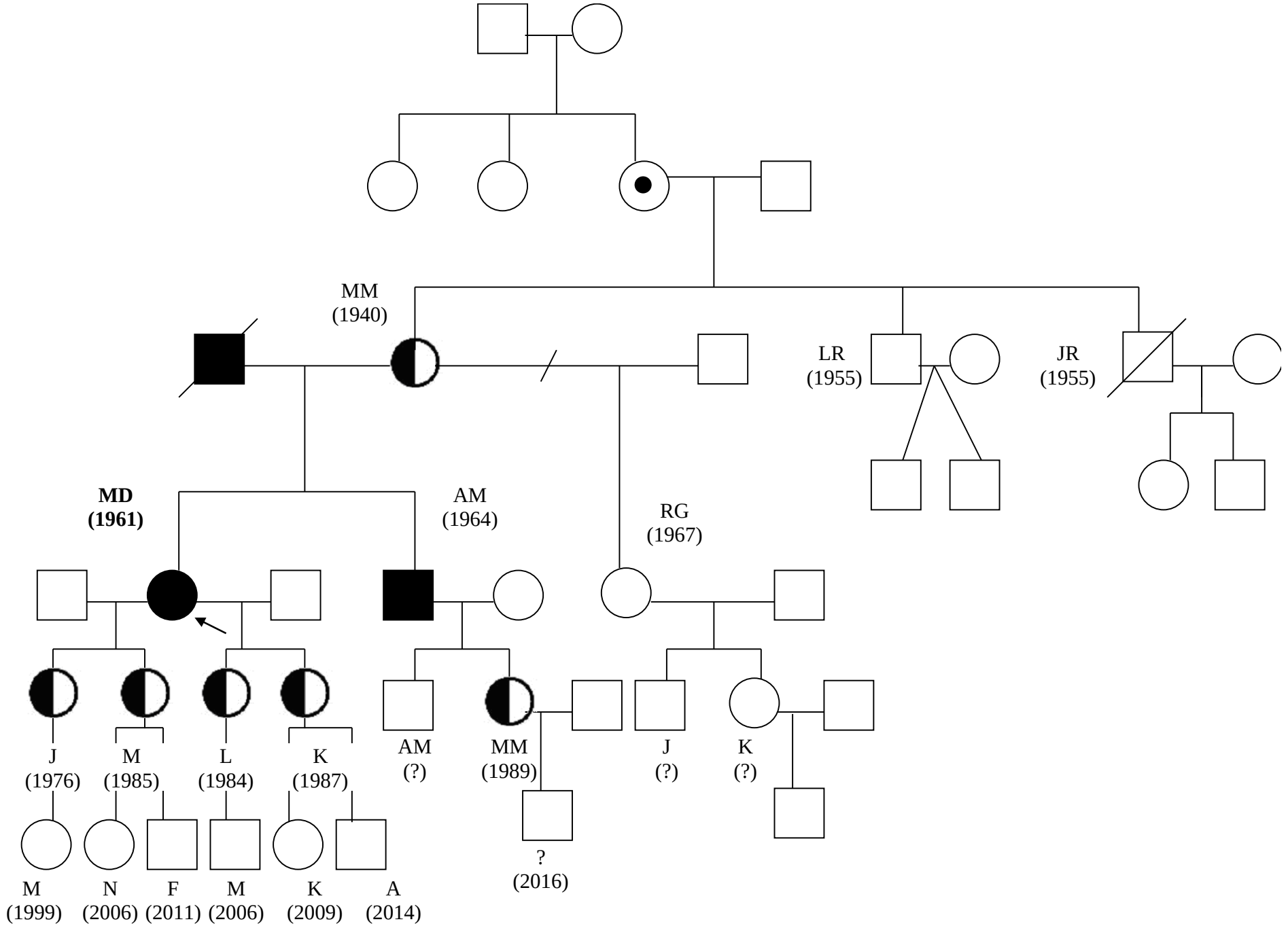
eGFR, estimated glomerular filtration rate; FD, Fabry disease; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator
Cases and imaging source: General University Hospital, Prague, CZ

Index patient D.M. – female

Enz. activity 0.3 μmol/l/h,
lyso-GL-3 10 ng/ml.

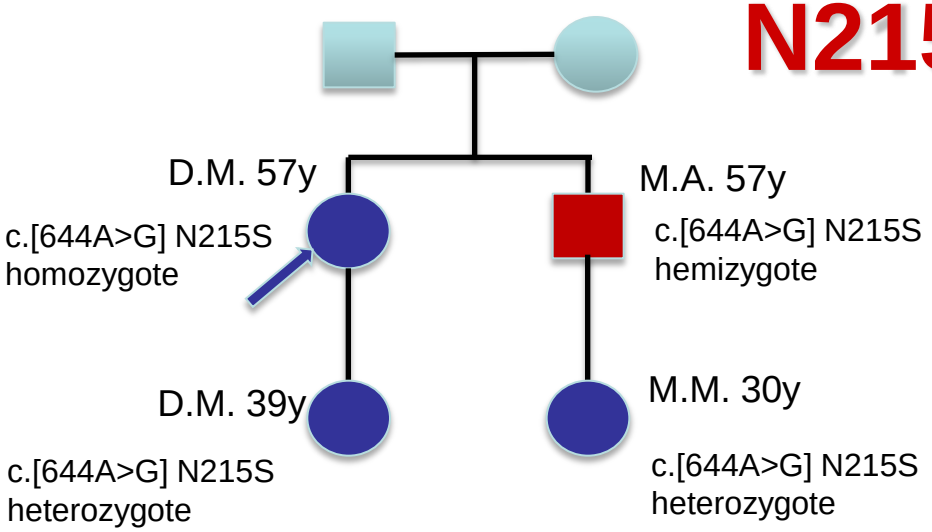


Cases and imaging source: General University Hospital, Prague, CZ

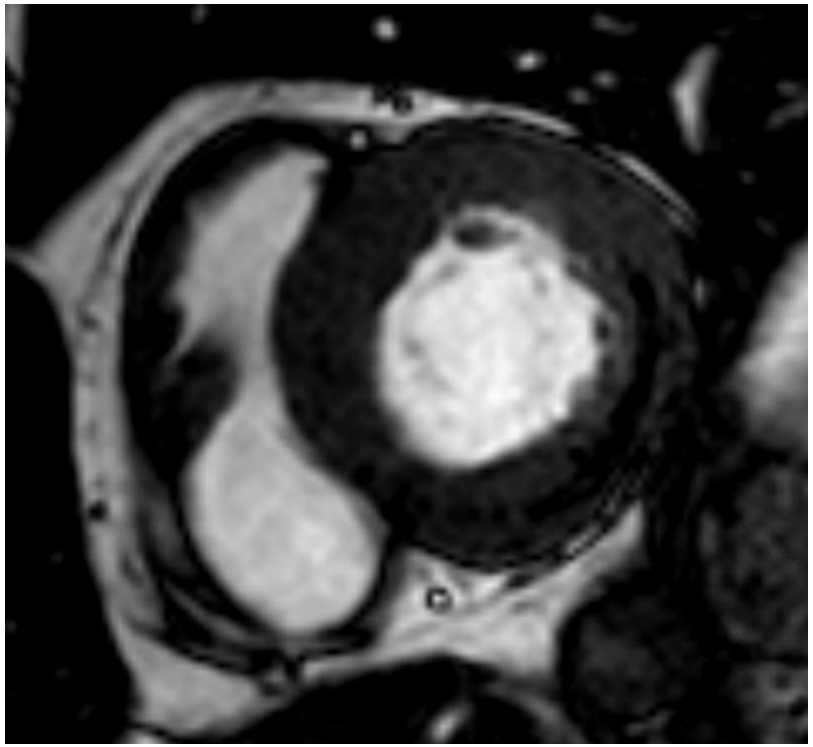


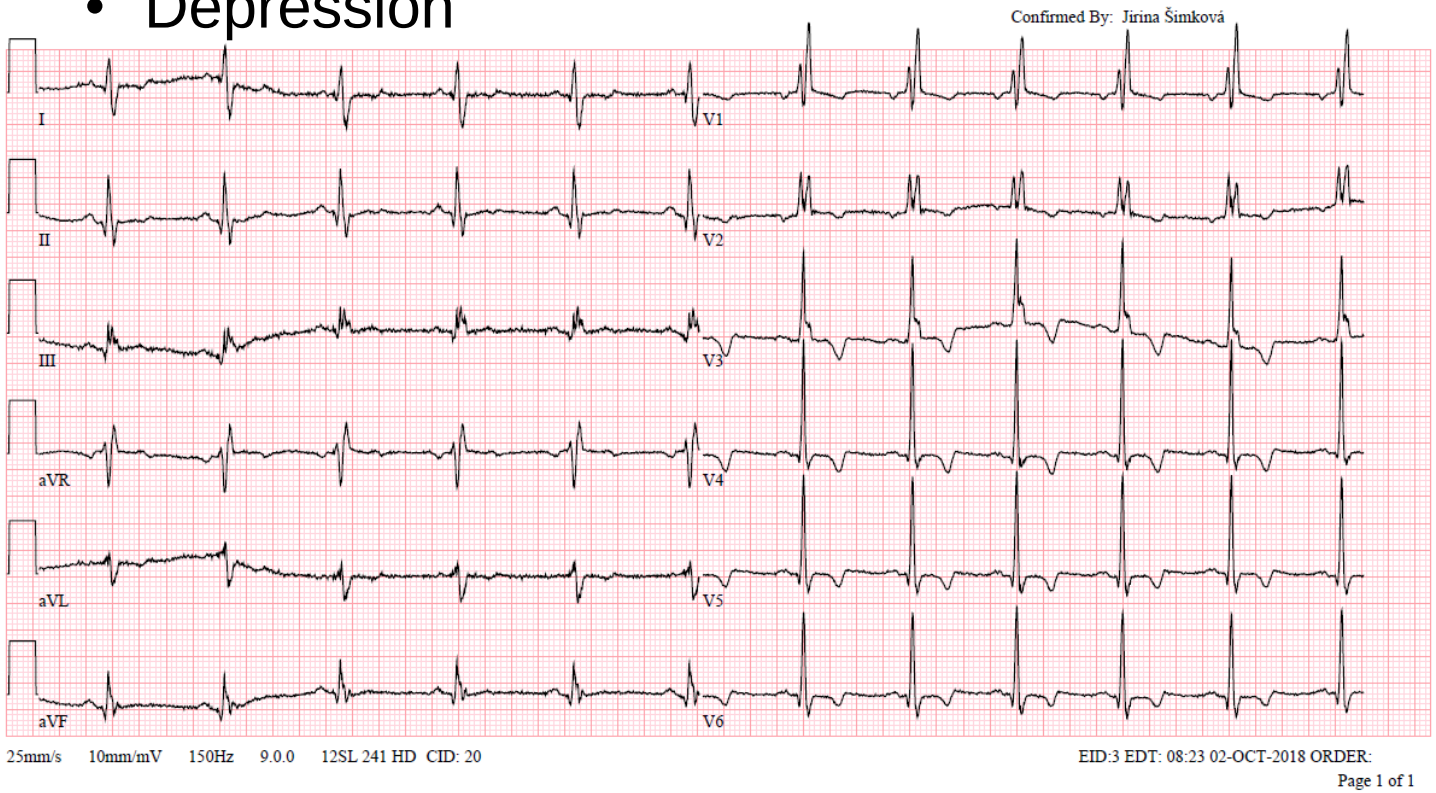
Cases and imaging source: General University Hospital, Prague, CZ

N215S hemizygote, male, 57 years old



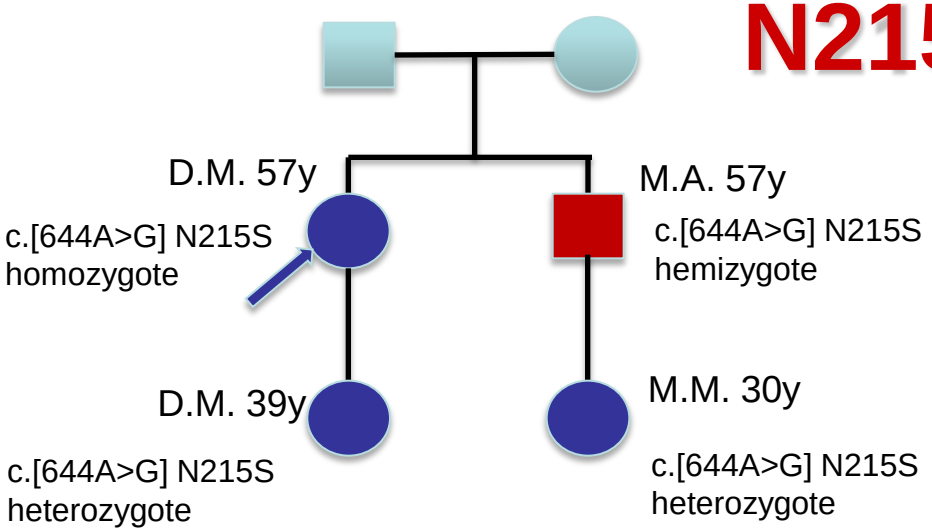
- NYHA III (max. exercise tolerance 100 W)
- Peripheral neuropathy
- Hypacusis
- Vessel tortuosities
- Microalbuminuria
- Depression





NYHA, New York Heart Association
Cases and imaging source: General University Hospital, Prague, CZ

N215S hemizygote, male, 57 years old



- NYHA III (max. exercise tolerance 100 W)
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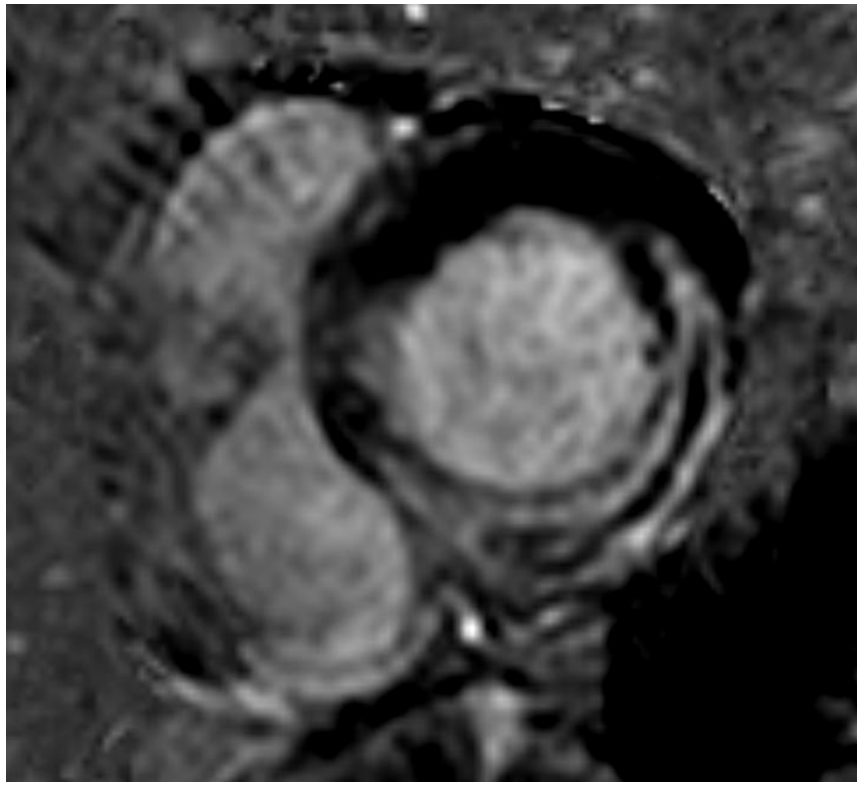
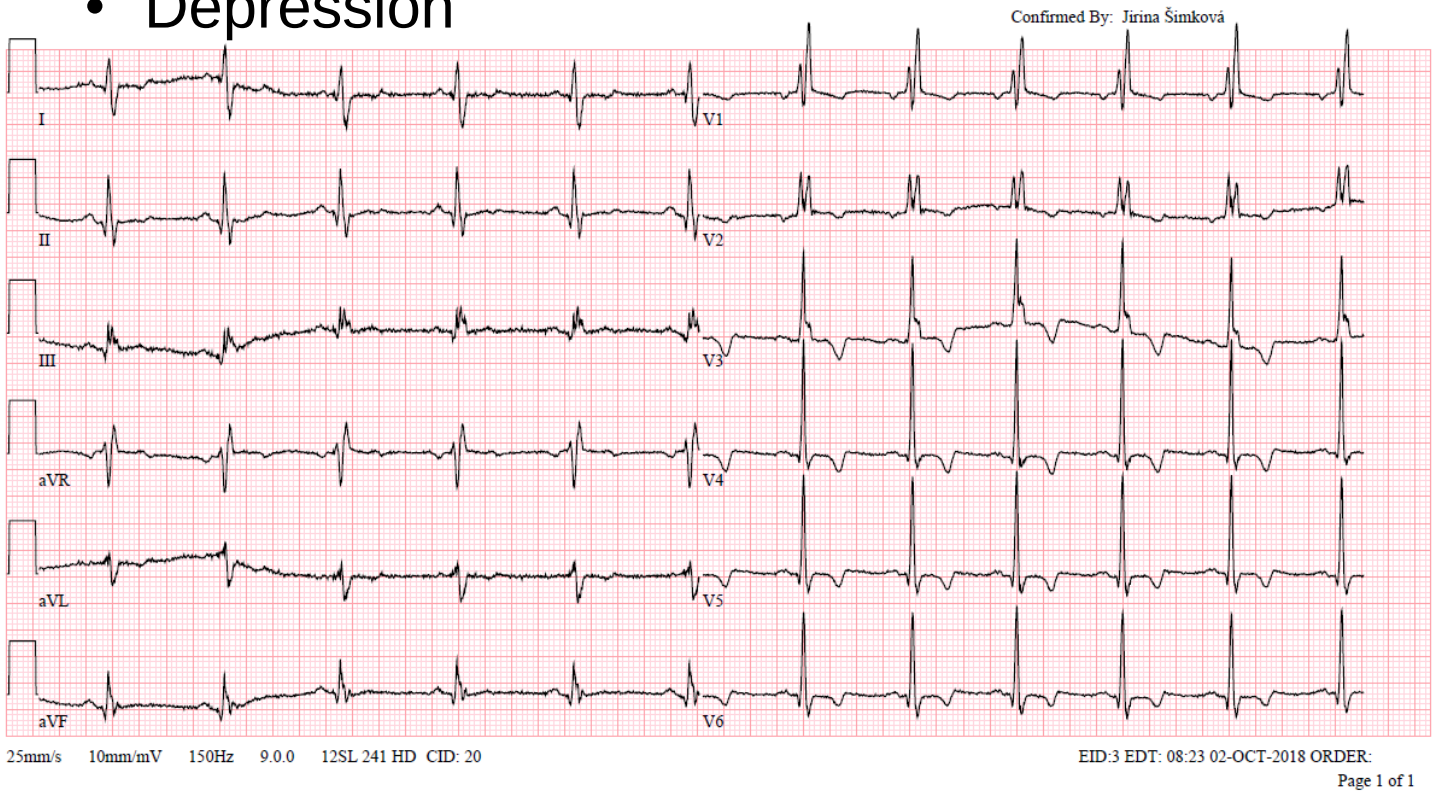
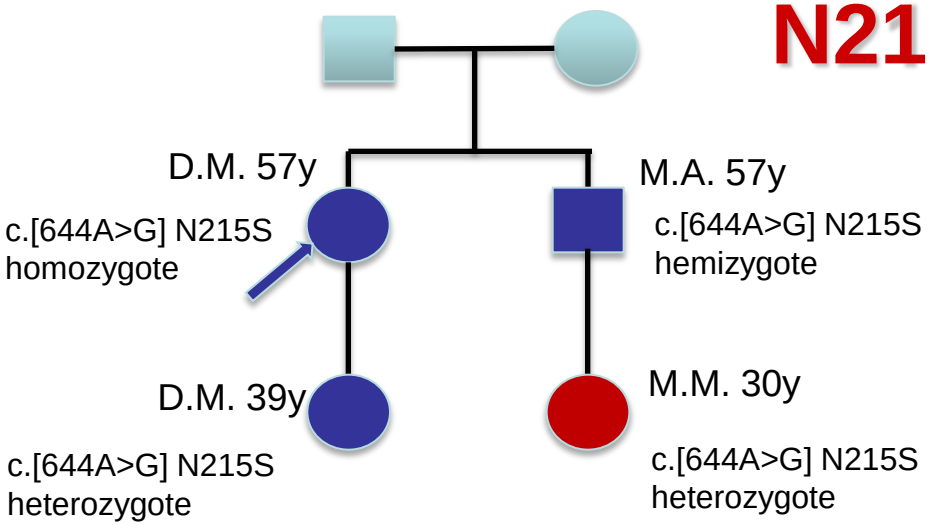


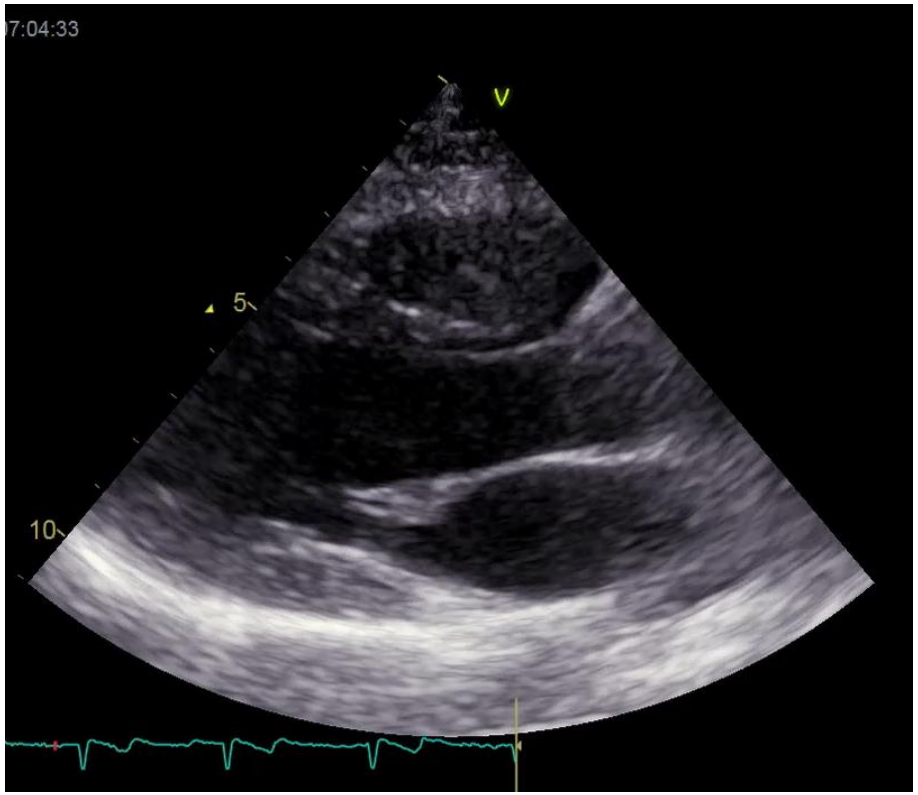


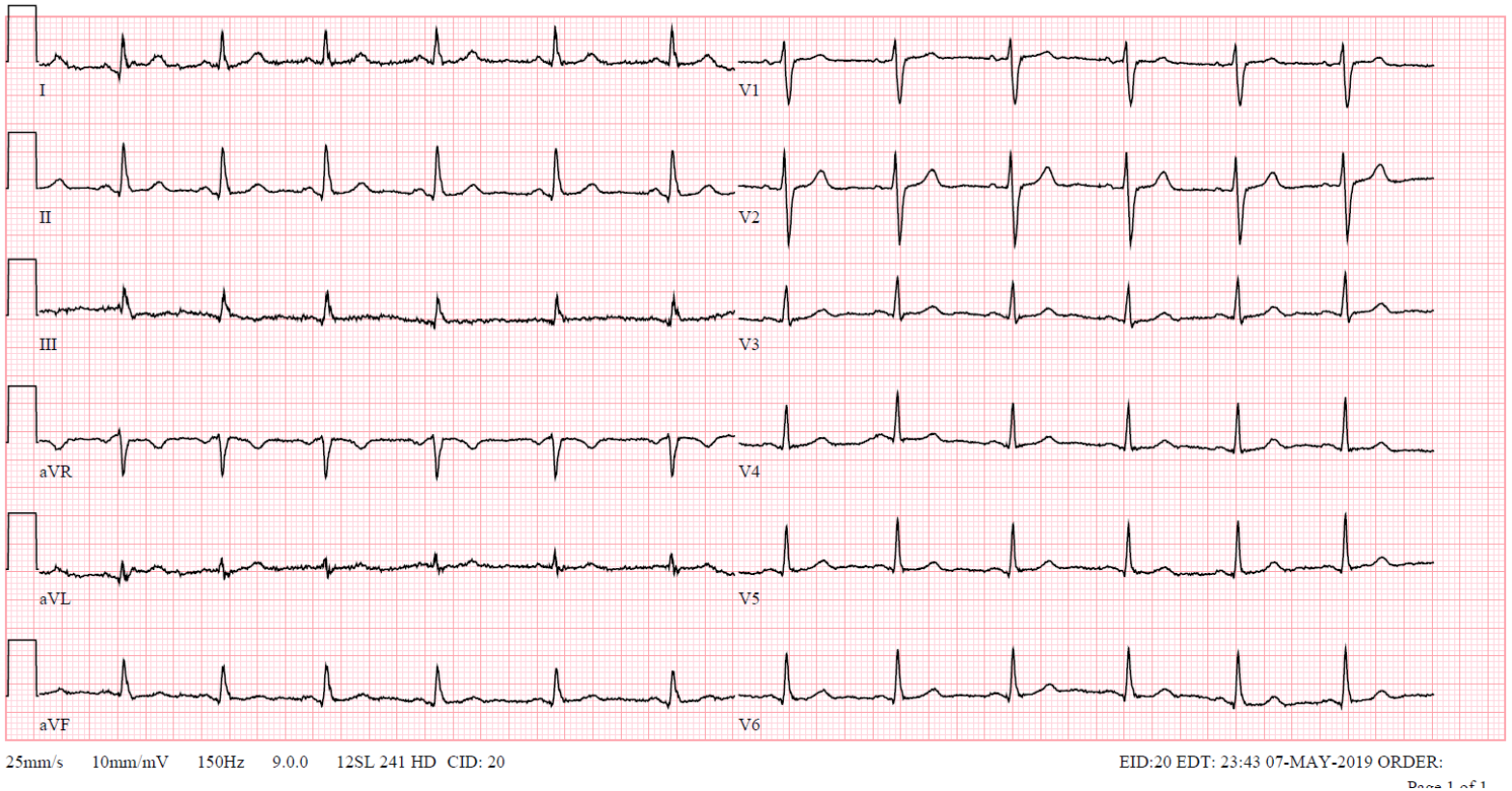
NYHA, New York Heart Association
Cases and imaging source: General University Hospital, Prague, CZ

N215S heterozygote, female, 39 years old



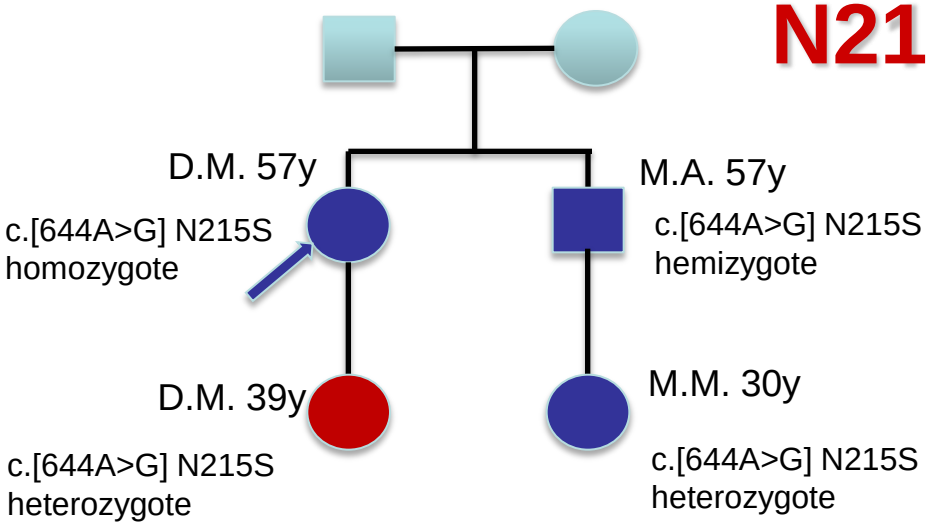
- Posterior wall – 10 mm
- LA enlargement
- Microalbuminuria



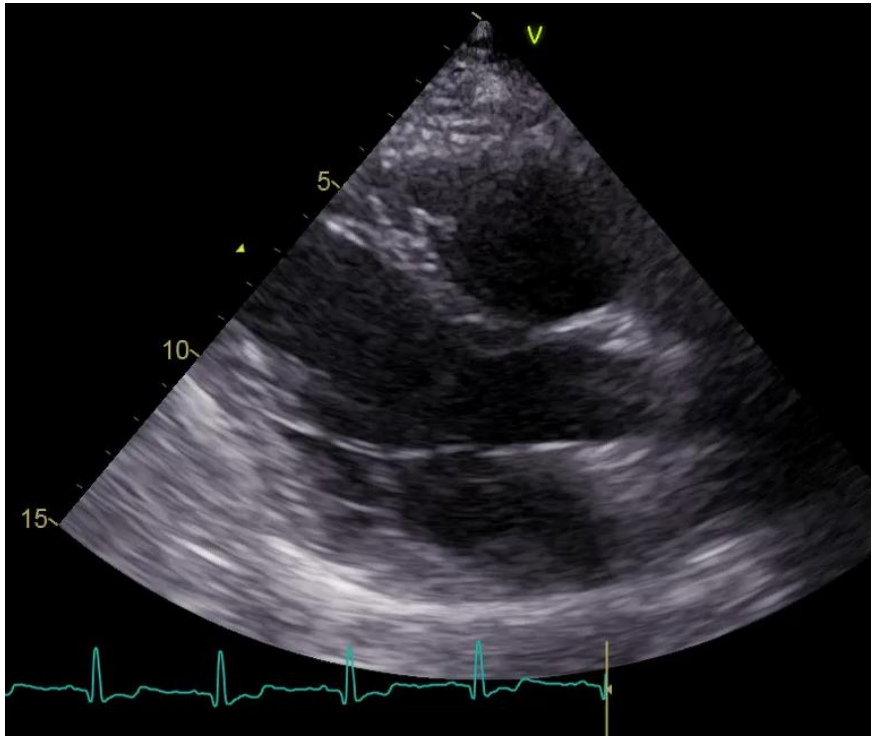


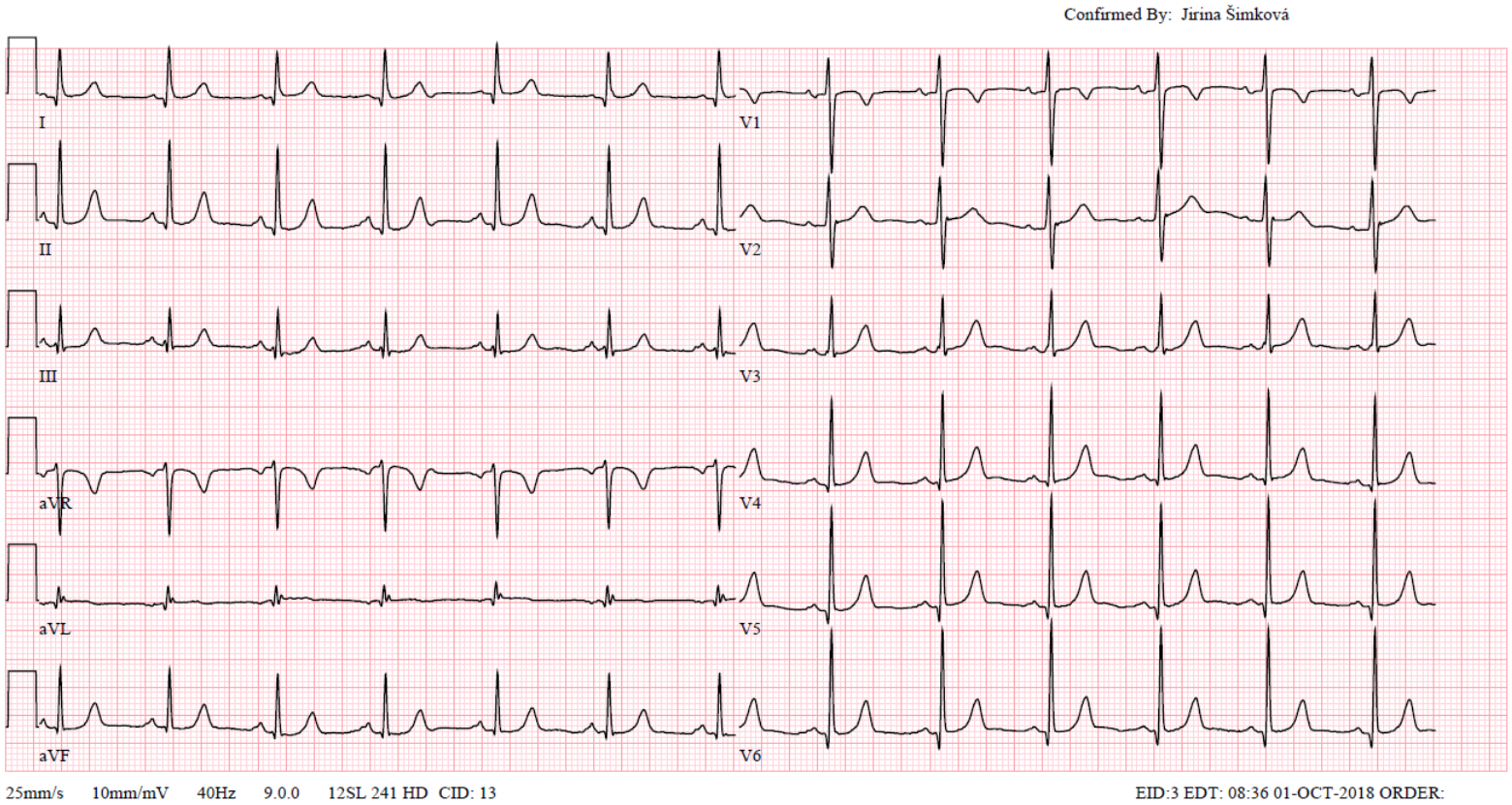
LA, left atrial
Cases and imaging source: General University Hospital, Prague, CZ

N215S heterozygote, female, 39 years old



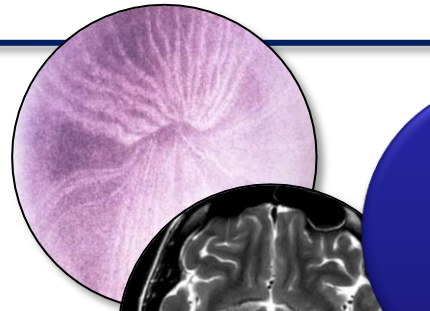
- Asymptomatic





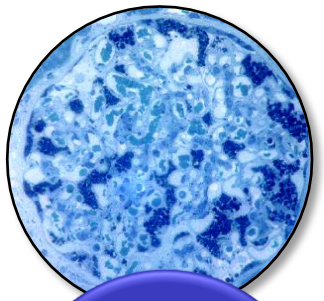
Cases and imaging source: General University Hospital, Prague, CZ

When to suspect Fabry?



Peripheral neuropathy

Stroke history



Skin lesions (angio-keratomas)

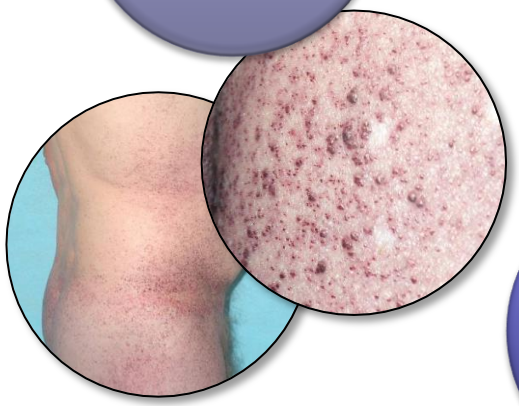
Hypohidrosis

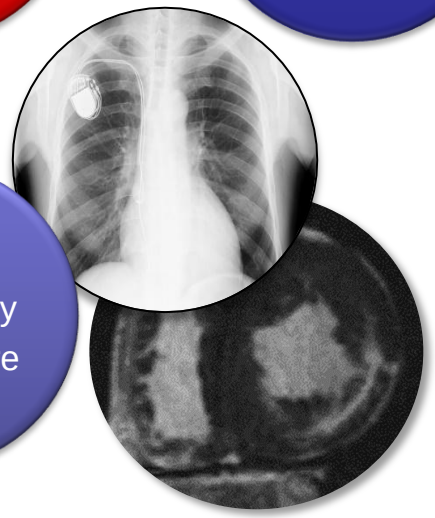
Pain

Febrile episodes

Proteinuria

Renal function impairment

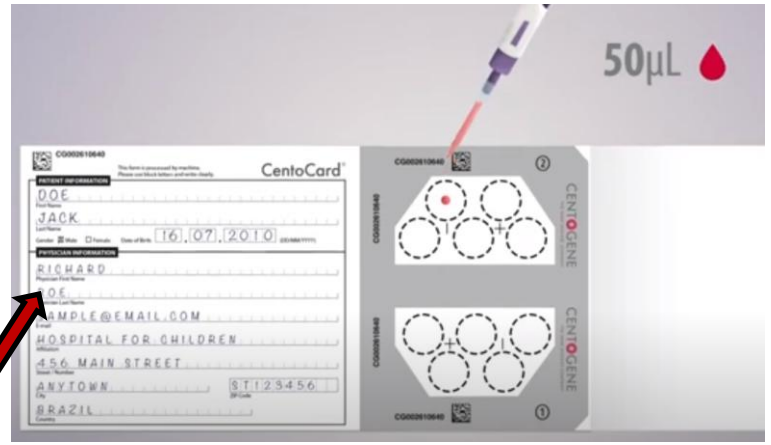




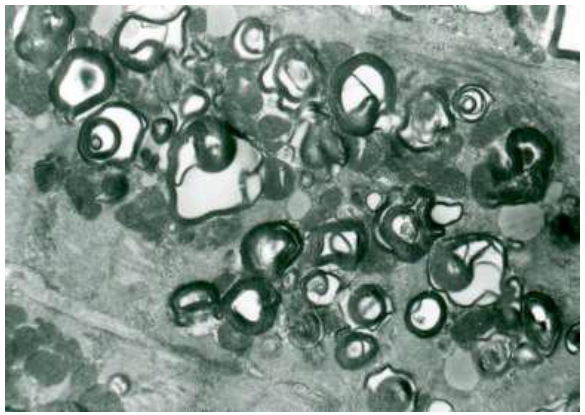
Cardiac hypertrophy

Heart failure

Dry blood spot testing



Biopsy – kidney, heart, skin



Images: General University Hospital, Prague

Author´s own opinion

Fabry disease in cardiology

- HCM is a common pathology
- Fabry Disease is one of the most frequent mimics of HCM
- Diagnosis can be made by enzyme activity and Lyso-Gb_3 measurements on Dry Blood Spots or by gene sequencing (in females or systematic)
- All diagnosed patients identified by the screening are on targeted therapy


Thanks for your attention !
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