MFSH

Morbus Fabry Selbsthilfegruppe e.V.

D313Y

– An Example of a Controversial Fabry Variant

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Patient stories – how we got involved

- 1st annual meeting in March 2019
- met female patient, diagnosed at same time as me
- one year in therapy like me
- „Some doctor say I don´t have really Fabry Disease“

Patient stories – how we got involved

- met female patient in Nov 2019, who could walk only small distances
- was wheelchair bound for a long time
- pain started at the age of 4 years
- pacemaker at 19, disability at 29, diagnosis at 30
- stopped using wheelchair after 4 years of therapy
- she is a mother of a son, whose symptoms started when he was 3 years old!

Her story touched me deeply

Patient stories – how we got involved

- Next annual meeting in March 2020
- met both women again
- both heard from their doctors that their variant was not true Fabry disease
- is it possible!?!
- I wanted to know:
  - Are there more patients?
  - How do the doctors explain that?

We started a survey …

Most common arguments of doctors

- high residual activity of the enzyme
- no or almost no Gb3 or lyso Gb3 desposits
- high allele frequency in the population
- no sick men
- another disease must be the trigger

We wanted to check that …

Research on publications

- established a literature research team
- wanted to see, where it says D313Y doesn´t make Fabry disease
- started reading publications
- did extensive research

Search for connections …

More patients

- female, 20 years, pain started at age 10
- wandering pains, mainly in the joints
- at the age of 17 she could hardly write any more because of the pain
- fingers sometimes turned deep blue or translucent white
- started to collapse often
- diagnosis: fibromyalgia

Search for connections …

A concerned men?

- at the same time, her father had a heart biopsy
- heart pain since the age of 20
- a thick heart despite 10 years of therapy
- in addition, 3 monogenetic heart variants were identified, which alone could not cause any problems
- because there was no therapy for the cardiac variants the only option left was to try the Fabry therapy
- after several years of therapy, he is working full time again

An important patient …

The same disease?

- yes, Fabry Disease D313Y
- she was treated, too
- she was also getting better and better
- she studies and lives on the 2nd floor
- today she can jump up the stairs

These patients should motivate you to take a closer look

- female, early 40s – one of the sickest patients I met
- pain since early childhood
- strong headache, cardiac arrythmias
- she has lost many of her abilities, difficulties in reading and finding words
- she had to lie in bed most of the time and needed a nurse
- after 4 years of therapy, she has already regained many abilities and her quality of life is improving

Miracle or placebo effect …

Never late onset

- male, 10 years – diarrhea from birth
- severe burning pain in the feet from the age of 3
- start of ERT at the age of 4
- rapid improvement in all symptoms
- after 3 years of ERT, sudden recurrence of all symptoms – morning vomiting, diarrhea, burning pain in the feet
- change of home therapy nurse after 4 month, no more symptoms, what happened?

Miracle or placebo effect …

Final thoughts from me

- I cannot believe that a therapy specific to Fabry disease can cure a causally different underlying disease
- It´s not malpractice to treat a patient with Fabry therapy who has a mutation in the GLA, the Fabry gene
- Berthold now shows you what we see in our survey as well as publications and which hypotheses should be pursued further

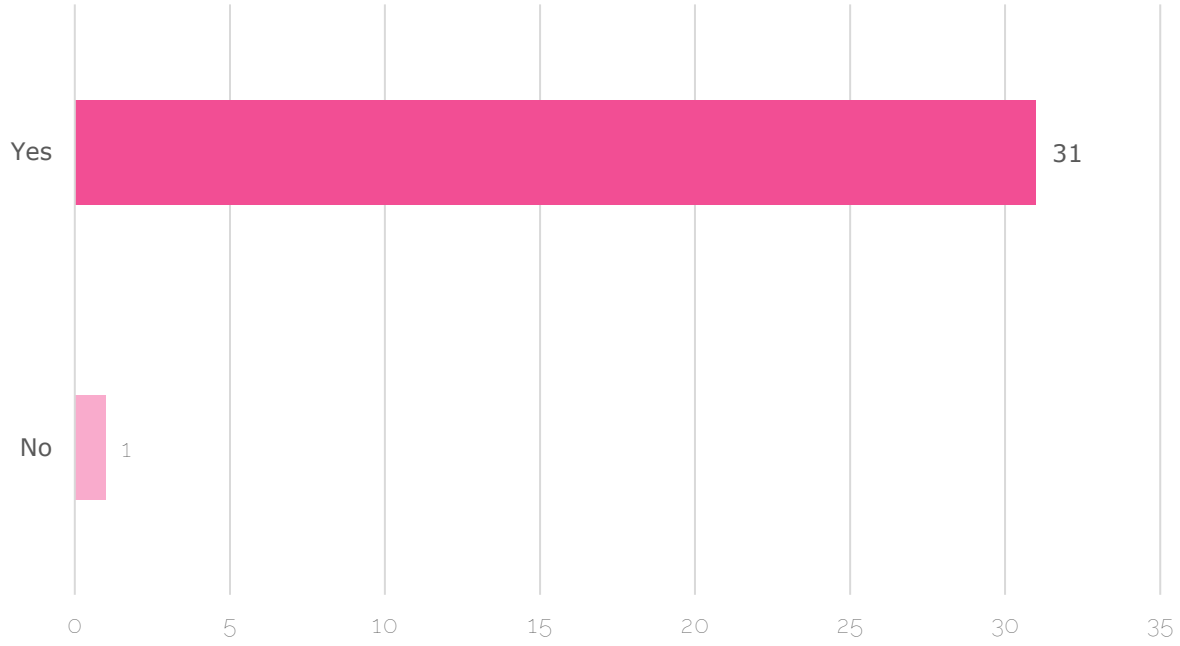
Please scan the QR code!

Results of our Survey

- online survey starting in June 2021
- link to survey on social media
- no demographics
- 32 participants with D313Y
  10 participants with A143T
- results presented for D313Y variant

Results of our Survey

- Do you have neurological symptoms?



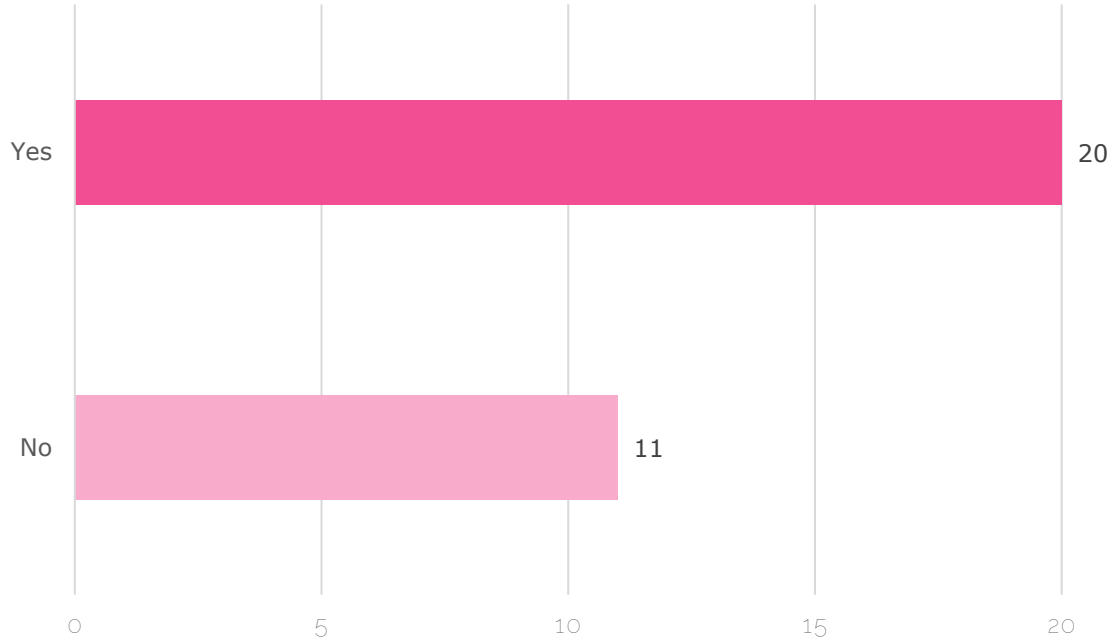
Results of our Survey

- Do you have neurological symptoms?

pain	19
fatigue	17
GI Problems	9
stroke/TIA	7
dizziness	5
heat/cold Intolerance	5

Results of our Survey

- Do you have cardiac symptoms?



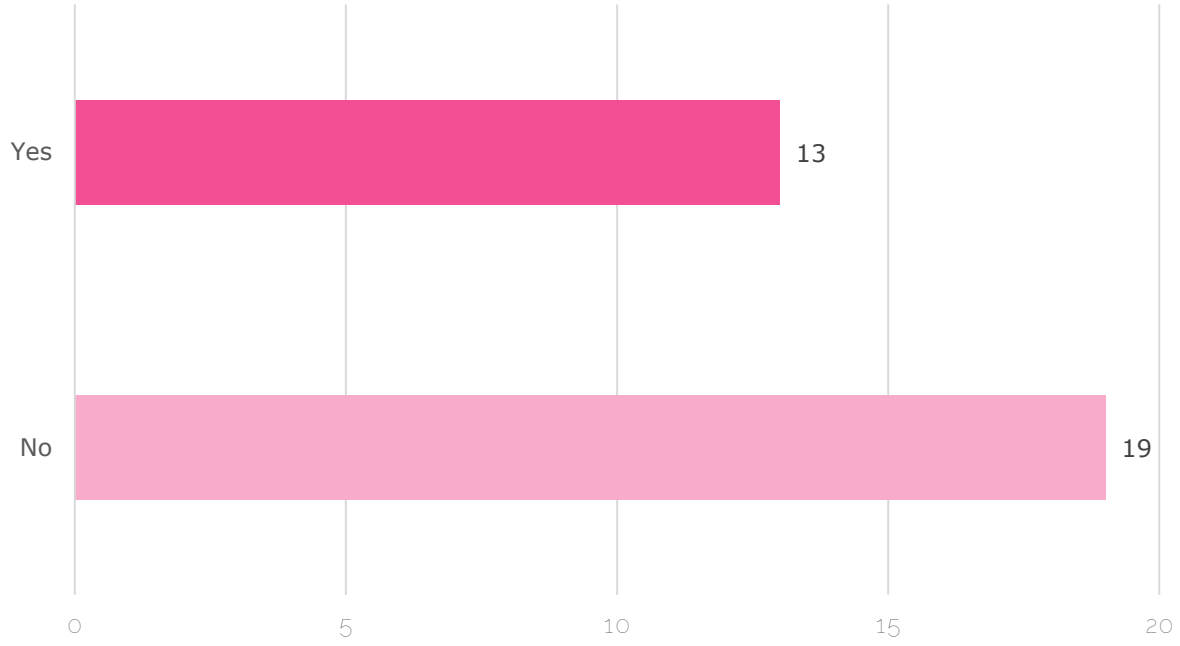
Results of our Survey

- Do you have cardiac symptoms?

arrhythmias	8
tachycardia	4
heart valve insufficiency	3
hypertrophy	1

Results of our Survey

- Do you have nephrological symptoms?



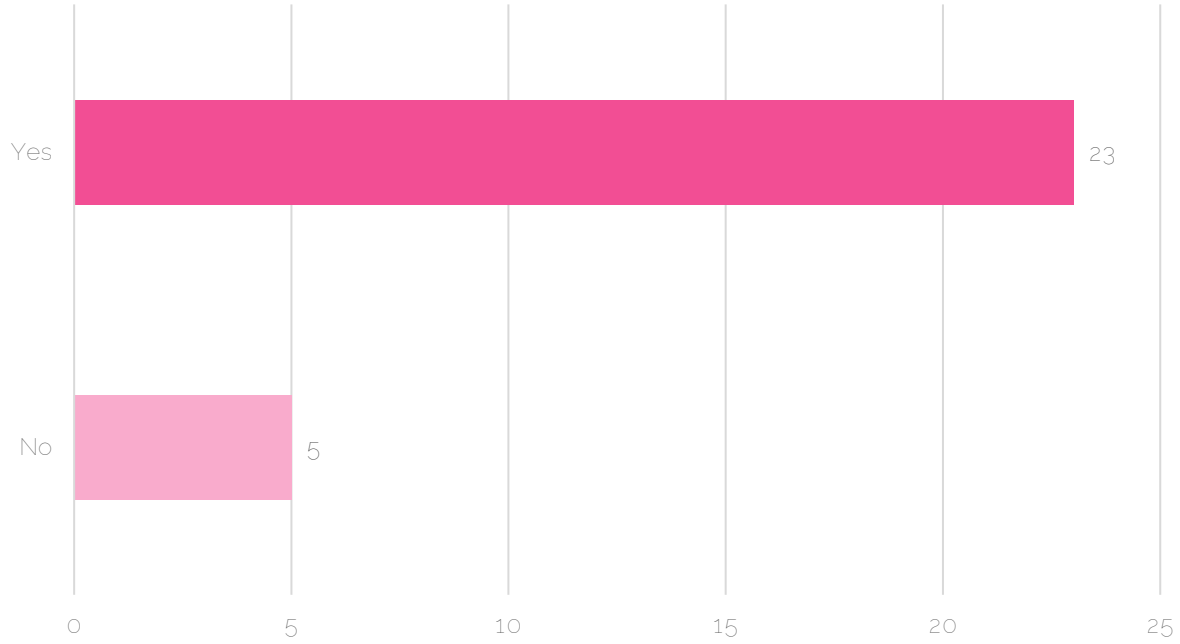
Results of our Survey

- Do you have nephrological symptoms?

proteinuria	7
renal insufficiency	3
elevated nitrite levels	2

Results of our Survey

- Do you have other symptoms?



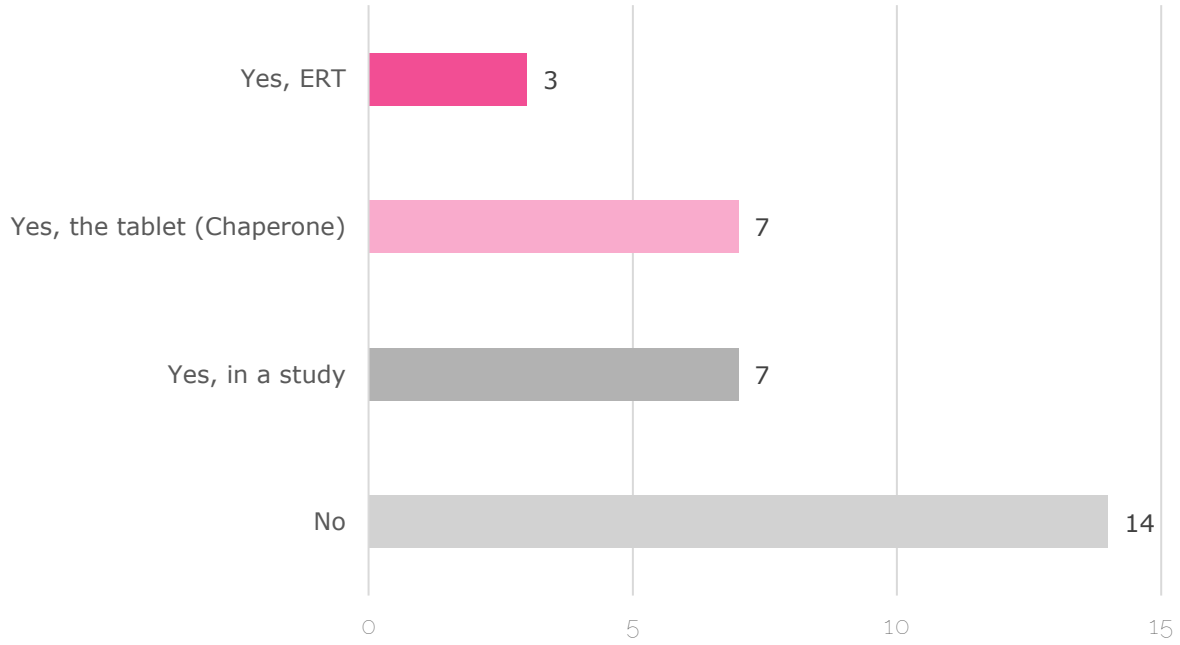
Results of our Survey

- Do you have other symptoms?

adhesions/bone growths/ joint changes (no rheumatism)	3
dental problems	2
cognitive problems	2
angiokeratomas, edema, sleep disturbances, ...	

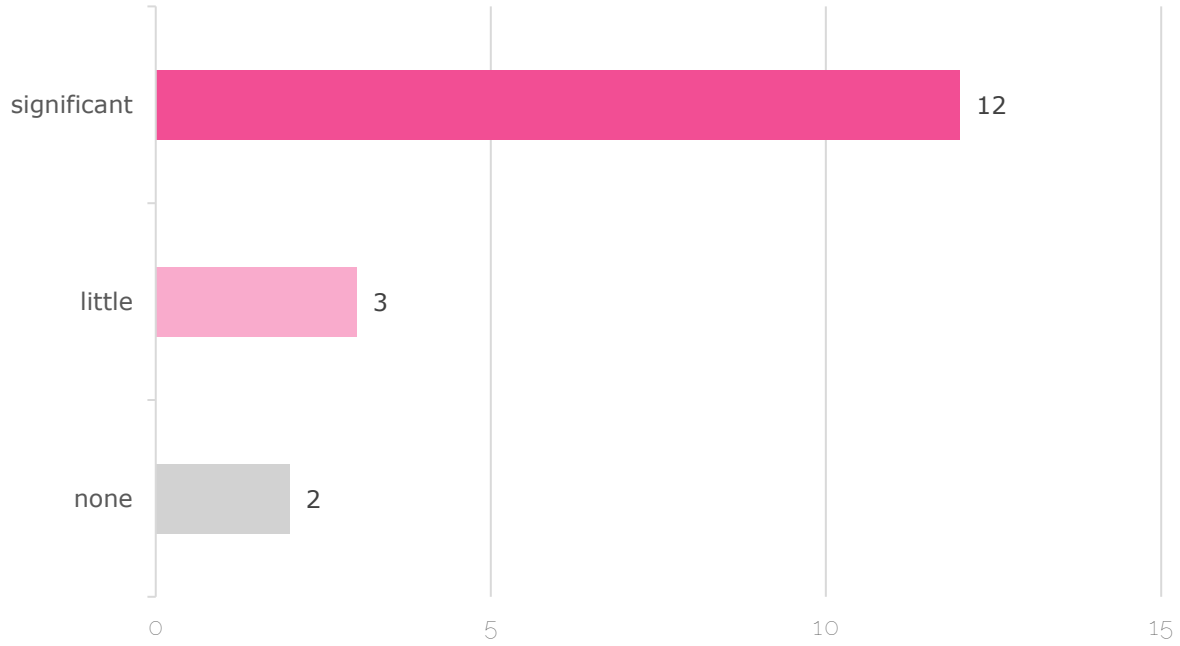
Results of our Survey

- Are you receiving therapy for Fabry disease? (multiple answer were possible)



Results of our Survey

- Do you feel any improvement as a result of the therapy?



Our Research on Publications

Lenders M et al. (2013)

- patient (58, M) with D313Y variant
- pain & paresthesia in both hands and feet
- white matter lesions (WML)
- small fiber neuropathy (SFN)
- WML also in 6 relatives (34, 41, 49, 58, 71, 76) with D313Y variant
- no WML in 2 sons

Our Research on Publications

du Moulin et al. (2017)

- retrospective analysis of charts
- 14 patients with D313Y variant in 5 families (single center)
- 7 with pain & acroparesthesia in hands, feet etc.
- 4 with stroke
- 8 with eye affection
- 2 with cardiac hypertrophy
- …

Our Research on Publications

Godel et al. (2019)

- 11 D313Y variant, 16 healthy, 10 classical FD variants
- volumes of dorsal root ganglia increased,
  but less compared to patients with classical FD variant
- no change of dorsal root ganglia vascular permeability,
  which was decreased in patients with classical FD variant
- "This suggests that the GLA gene variant p.D313Y causes a potentially treatable condition resembling an early stage of Fabry disease."

Our Research on Publications

Von Cossel et al. (2021)

- 9 females with D313Y variant examined by skin punch biopsies
- 7 had small fiber neuropathy (SFN)
- 6 hypo-/hyperhidrosis
- 4 acral paresthesias and neuropathic pain

Summary of Fabry Symptoms

- Pain
- Paresthesia
- Stroke
- White matter lesions
- Small fiber neuropathy
- Heat intolerance
- Other ...

Publications in Replies

Effraimidis et al. (2020)

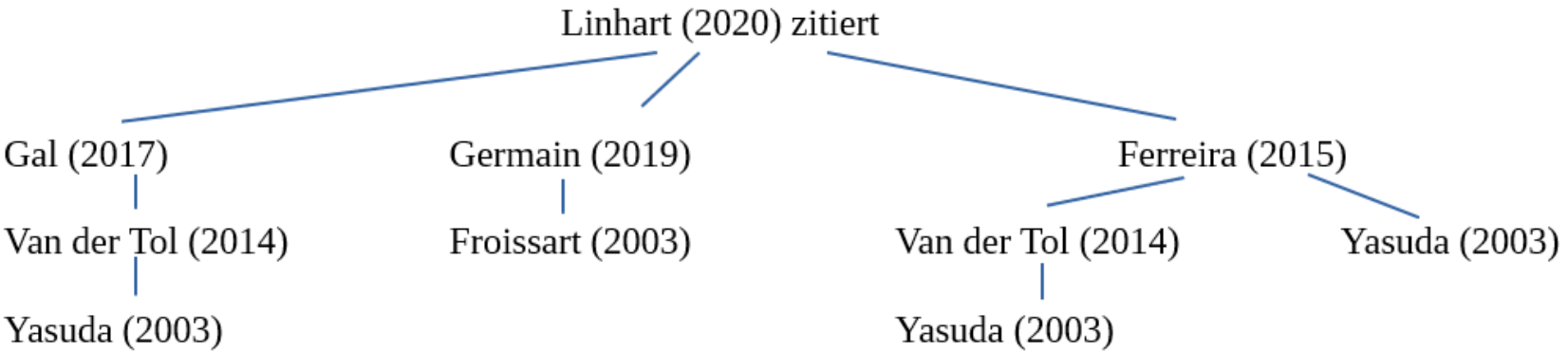
For and against the p.Asp313Tyr classification as neutral variant	
High frequency in the general population	✔
High residual enzyme activity (>50%)	✔
Non-elevated lysoGb$_3$/Gb$_3$ concentrations	✔
Lack of intracellular Gb$_3$ accumulation in biopsies	✔
Co-occurrence with additional variants with known pathogenicity in severe affected patients	✔
Possible association between the variant and the brain	?
Characterized as damaging in silico	✘

Gb3: globotriaosylceramide, lysoGb3: globotriaosylsphingosine

FIGURE 2 Main findings of the systematic review

Publications in Replies

Linhart et al. (2020)



Publications in Replies

Yasuda et al. (2003), Froissart et al. (2003)

- activity of D313 in cell lysate, 60% (Yasuda) and 76% (Froissart), respectively
- activity stable at pH 4.6, but instable pH at 7.4
- “pseusodeficiency”
- D313Y reaches lysosomes, but delayed (only Froissart et al.)
- exchange of Aspartate with Tyrosine on enzyme surface has no influence

Our Interpretation

Yasuda et al. (2003), Froissart et al. (2003)

- instability at pH 7.4 + delayed transport to lysosomes
  - ➢ D313Y acts different in ER compared to wt
- exchange of Aspartate with Tyrosine has influence on folding process

Another Pathomechanism

Braunstein et al. (2020)

- fly model
- A156V + A285D (pathogenic) are retained in ER
- led to activation of unfolded protein response (UPR) and ER-associated degradation (ERAD)
- UPR could be alleviated by Migalastat
- cell death in fly's dopaminergic cell (improvable by Migalastat)

Another Pathomechanism

Bonapace et al. (2022)

- poster presented at SSIEM Annual Symposium 2022
- ex vivo model
- S126G (classified as non-pathogenic) triggers ER retention + reduces enzyme activity in lysosome

Another Pathomechanism

Hypothesis

- certain GLA variants (e.g. D313Y, but also A143T) require effort to be folded properly in ER
- dependent on cell type specific gene expression
  - low ER stress from other protein biosynthesis
    - ➢ enzyme ends up in lysosome
  - High ER stress from other protein biosynthesis
    - ➢ enzyme transport to lysosome is reduced

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