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# Biochemical and genetic data from the largest global Fabry cohort reported to present

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**Introduction:** Fabry disease is an X-linked inherited lysosomal storage disease characterized by a deficient alpha-galactosidase caused by mutations in GLA gene. We present here the data collected over a period of over10 years regarding in vitro Fabry diagnosis

**Material and methods:** Fabry diagnosis is performed in a high-throughput stepwise manner: (a.) males- enzymatic activity, lyso-Gb3 quantification, followed by GLA gene sequencing and, (b.) females- GLA gene sequencing followed by lyso-Gb3. Enzymatic activity was determined in dried blood spots using either MS detection or mass spectrometric detection of the enzymatic product. Lyso-Gb3 was measured using mass spectrometry (LC/MRM-MS). The biochemical diagnosis was confirmed in all cases by genetic analysis. GLA gene sequencing was performed using single gene analysis, MLPA or NGS panel sequencing.

**Summary:** We report the identification of over 390 unique GLA genetic variants in over 3,330 different individuals. From the 3,641 pathogenic alleles sequenced in this study, the most abundant were: c. 937G>T (18.3%); c. 352A>G (9.8%); c. 376C>T (6.2%); c. 427G>A (3.4%).

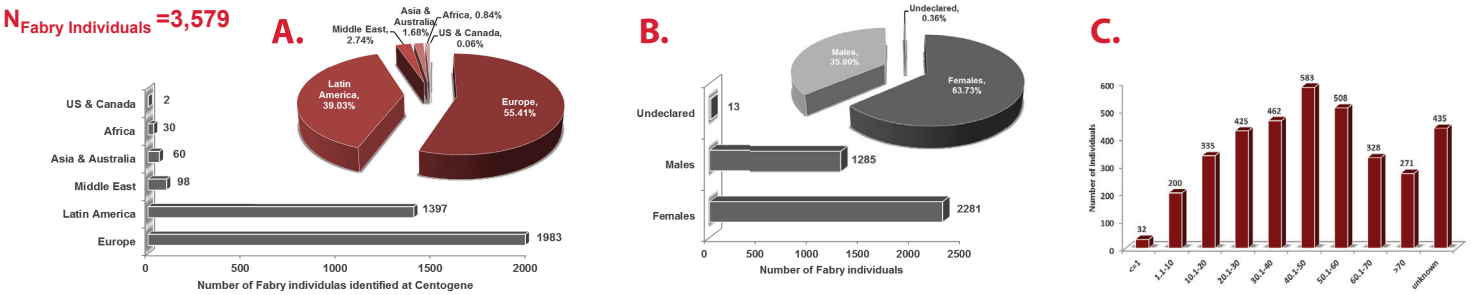



**Figure 1:** Worldwide Fabry cohort - patients diagnosed in over 10 years period ( 2006-2017): **A.** Geographical distribution ; **B.** Gender distribution; **C.** Age of diagnosis

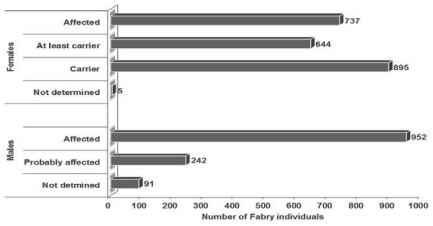



**Figure 2:** Genetic diagnosis of the Fabry cohort. NOTE: "probably affected" are Fabry male patients carrying an uncertain variant associated with pathological enzymatic levels, but biomarker levels within normal range. „at least carrier" are Fabry females carrying uncertain variants.

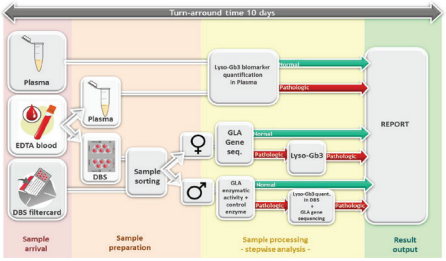
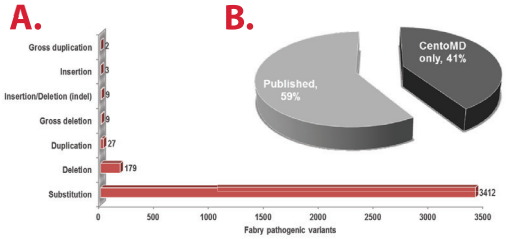


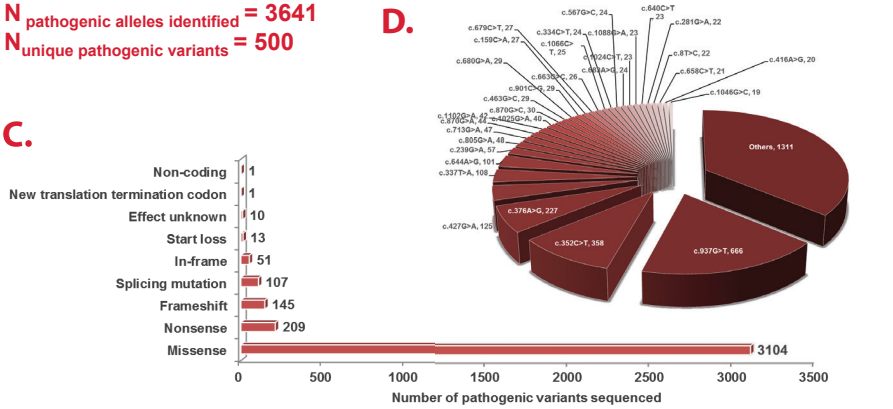

**Figure 3:** Fabry diagnosis workflow

**Figure 4:** GLA mutations found in the analyzed Fabry cohort: A. Type of GLA mutation; B. newly detected unique variants; C. Effect of the GLA mutations; D. Most abundant GLA pathogenic variants. Note: from a total of 3641 sequenced GLA alleles, we identified 500 unique GLA variants

**Over 76000 sequenced alleles**

**N pathogenic alleles identified = 3641**
**N unique pathogenic variants = 500**



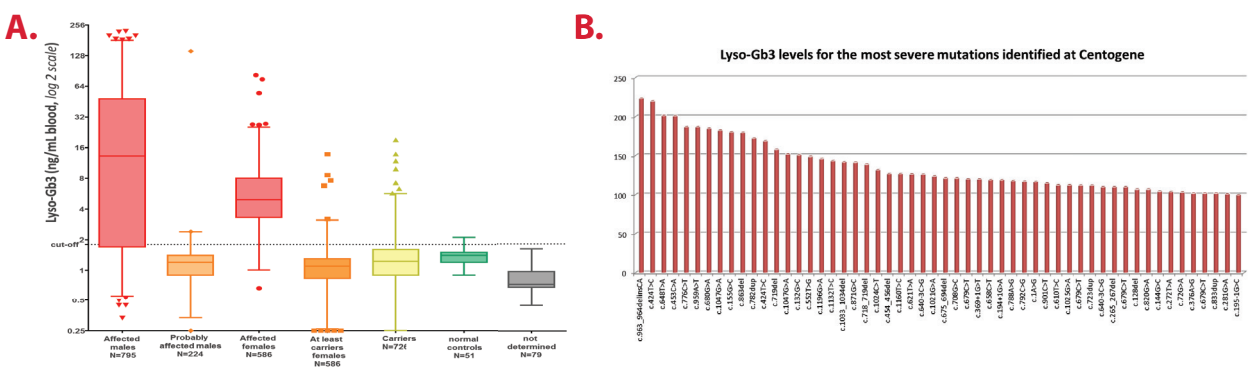




**Figure 5:** Lyso-Gb3 levels in Fabry individuals: **A.** Overal Lyso-Gb3 values for Fabry groups; **B.** Fabry mutations with the highest lyso-Gb3 values (cut-off: 1.8 ng/mL blood)

## References

1. www.centomd.com
2. Lukas J. et al,2016

## Disclosure of conflict of interest:

This study was sustained in part by Centogene AG, Rostock, Author of the presentation, Claudia Cozma, and 5 co-authors are employees of Centogene AG, Rostock, Germany

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