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 over 10 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/MS/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.

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

**Figure 6:** Over 76000 sequenced alleles

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

**Figure 7:** Summary of mutations.

**References**

1. www.centomd.com

**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.