Mutations in the GLA Gene and LysoGb3: Is It Really Anderson-Fabry Disease?

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Abstract

Anderson-Fabry disease (FD) is a rare, progressive, multisystem storage disorder caused by the partial or total deficit of the lysosomal enzyme α-galactosidase A (α-Gal A). It is an X-linked, lysosomal enzymopathy due to mutations in the galactosidase alpha gene (GLA), encoding the α-Gal A. To date, more than 900 mutations in this gene have been described. In our laboratories, the study of genetic and enzymatic alterations related to FD was performed in about 17,000 subjects with a symptomatology referable to this disorder. The accumulation of globotriaosylsphingosine (LysoGb3) was determined in blood of positives. Exonic mutations in the GLA gene were detected in 471 patients (207 Probands and 264 relatives): 71.6% of mutations were associated with the classic phenotype, 19.8% were associated with the late-onset phenotype, and 8.6% of genetic variants were of unknown significance (GVUS). The accumulation of LysoGb3 was found in all male patients with a mutation responsible for classic or late-onset FD. LysoGb3 levels were consistent with the type of mutations and the symptomatology of patients. α-Gal A activity in these patients is absent or dramatically reduced. In recent years, confusion about the pathogenicity of some mutations led to an

association between non-causative mutations and FD. Our study shows that the identification of FD patients is possible by associating clinical history, GLA gene analysis, α-Gal A assay, and blood accumulation of LysoGB3. In our experience, LysoGB3 can be considered a reliable marker, which is very useful to confirm the diagnosis of Fabry disease.

Keywords: Fabry disease; GLA gene; LysoGb3.

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