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Research Article

Functional and Clinical Consequences of Novel α-Galactosidase A Mutations in Fabry Disease

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ABSTRACT

Fabry disease (FD) is a rare metabolic disorder of glycosphingolipid storage caused by mutations in the *GLA* gene encoding lysosomal hydrolase α-galactosidase A (α-gal A). Recently, the diagnostic procedure for FD has advanced in several ways, through the development of a specific biomarker (lyso-Gb3) and the implementation of newborn screenings, which acted as a catalyst to augment general awareness of the disease. Heterologous over-expression of α-gal A variants and subsequent in vitro measurement of enzyme activity provided molecular data to elucidate the relationship between mutation, enzyme damage, lyso-Gb3 biomarker levels, and clinical phenotype. This knowledge is the foundation for improved counseling with regard to prognosis and therapeutic decisions. Herein, we resume the approach of in vitro characterization, with a further 73 mainly novel *GLA* gene mutations. Patient lyso-Gb3 data were available for most of the mutations. All mutations were tested for responsiveness to pharmacological chaperone treatment and phenotypic data for 61 hemizygous male and 116 heterozygous female patients carrying a mutation associated with ≥20% residual activity, formerly classified as “mild” variant, were collected in order to evaluate the pathogenicity. We conclude that a mild *GLA* variant is typically characterized by high residual enzyme activity and normal biomarker levels. We found evidence that these variants can still be classified as a distinctive, but milder, sub-type of FD.