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Research Article

Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset *GLA* mutation c.936+919G>A (IVS4+919G>A)†

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† Communicated by David Rosenblatt

Abstract

Fabry disease (α-galactosidase A (α-Gal A, GLA) deficiency) is a panethnic inborn error of glycosphingolipid metabolism. Because optimal therapeutic outcomes depend on early intervention, a pilot program was designed to assess newborn screening for this disease in 171,977 consecutive Taiwanese newborns by measuring their dry blood spot (DBS) α-Gal A activities and β-galactosidase/α-Gal A ratios. Of the 90,288 male screenees, 638 (0.7%) had DBS α-Gal A activity <30% of normal mean and/or activity ratios >10. A second DBS assay reduced these to 91 (0.1%). Of these, 11 (including twins) had <5% (Group-A), 64 had 5–30% (Group-B), and 11 had >30% (Group-C) of mean normal leukocyte α-Gal A activity. All 11 Group-A, 61 Group-B, and 1 Group-C males had *GLA* gene mutations. Surprisingly, 86% had the later-onset cryptic splice mutation c.936+919G>A (also called IVS4+919G>A). In contrast, screening 81,689 females detected two heterozygotes. The novel mutations were expressed in vitro, predicting their classical or later-onset phenotypes. Newborn screening identified a surprisingly high frequency of Taiwanese males with Fabry disease (~1 in 1,250), 86% having the IVS4+919G>A mutation previously found in later-onset cardiac phenotype patients. Further studies of the IVS4 later-onset phenotype will determine its natural history and optimal timing for therapeutic intervention. Hum Mutat 30:1–9, 2009. © 2009 Wiley-Liss, Inc.