

Congress Abstract

One GLA Variant, Multiple Phenotypes: Intrafamilial Heterogeneity in Fabry Disease

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ABSTRACT

Background: Fabry disease is an X-linked lysosomal storage disorder caused by variants in the GLA gene, leading to progressive multisystem involvement of the kidneys, heart, and central nervous system. Marked phenotypic variability among female carriers is attributed to random X-chromosome inactivation, but pronounced discordance in organ predominance across multiple branches of a single family sharing an identical genotype is rarely documented. We describe such a family carrying the GLA variant c.137A>G (p.His46Arg).

Case presentation: The proband, a 47-year-old woman, presented with recurrent ischemic strokes (four episodes since 2004) and a spinal cord infarction, initially misdiagnosed as multiple sclerosis for over a decade until molecular testing in 2018 confirmed Fabry disease (α -galactosidase A activity 3.4; lyso-Gb3 5.4). She developed a fixed pyramidal tetrasymptom with neuropathic pain, started enzyme replacement therapy, and recently experienced a sixth cerebrovascular event accompanied by new-onset oliguria suggestive of emerging renal involvement. Her mother had died of renal failure at age 31 (not genetically confirmed). Her 26-year-old daughter, despite abnormal biochemistry (enzyme 0.3; lyso-Gb3 46.2), remains largely asymptomatic, while her 16-year-old son does not carry the variant. The proband's maternal aunt (73 years), a confirmed carrier, required pacemaker implantation for cardiac conduction impairment; her three sons displayed a strikingly different, predominantly renal phenotype: one died young of acute kidney injury, one has required hemodialysis since 2013 and shows lacunar cerebral infarcts on MRI with left ventricular hypertrophy on ECG, and one has nephrotic syndrome but declined further evaluation. A second maternal aunt, also genetically confirmed, remains asymptomatic; her two mutation-positive sons have refused testing and treatment. All affected relatives share the identical GLA variant.

Conclusion: This three-generation family illustrates striking intrafamilial phenotypic heterogeneity - cerebrovascular, cardiac, and renal - despite a shared GLA genotype, underscoring the limited predictive value of genotype-phenotype correlation in Fabry disease. The decade-long misdiagnosis as multiple sclerosis highlights the need to consider Fabry disease in unexplained recurrent stroke. Cascade family screening should be offered to all at-risk relatives regardless of sex, age, or symptom status, since disease severity and target-organ involvement in one member do not predict outcomes in others.

Keywords: Fabry Disease; GLA Gene Mutation; Nephropathy; Intrafamilial Phenotypic Heterogeneity; Ischemic Stroke; X-Linked Lysosomal Storage Disorder

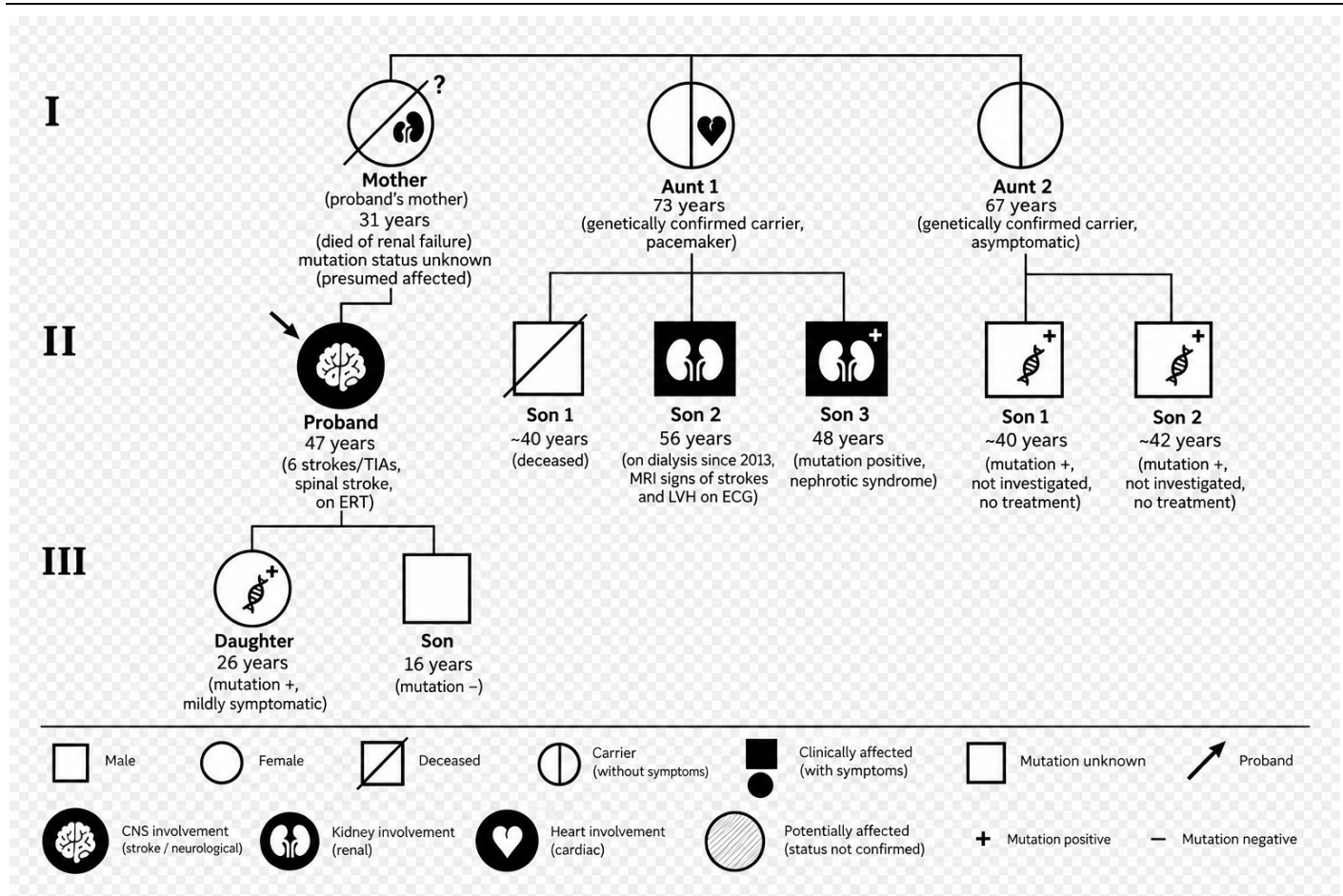


Figure 1: Pedigree of a three-generation family with Fabry disease. Pedigree of a three-generation family with Fabry disease demonstrating intrafamilial phenotypic heterogeneity.