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Original Investigation

Unrecognized Fibrinogen A α-Chain Amyloidosis: Results From Targeted Genetic Testing

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Background: Fibrinogen A α-chain (AFib) amyloidosis results from autosomal-dominant mutations in the gene encoding AFib (*FGA*). Patients with this disorder typically present with proteinuria. Isolated cases of AFib amyloidosis, carrying the *FGA* p.Glu545Val variant, were identified in the district of Braga, in northwest Portugal. This observation led us to hypothesize that this disorder might be an unrecognized cause of kidney disease in that region and prompted us to carry out targeted genetic testing for the p.Glu545Val variant in the local hemodialysis population and family members of identified cases.

Study Design: Case series.

Setting & Participants: 3 groups of participants: (1) kidney biopsy registry, n = 4; (2) hemodialysis facility, n = 122 of 267 patients; and (3) genetically at-risk individuals; n = 69 of 167 family members.

Outcomes: Kidney disease, kidney disease progression, and survival.

Results: The p.Glu545Val variant was identified in all 4 patients of the biopsy registry, 12 of 122 (9.8%) hemodialysis patients tested, and 34 of 69 (49%) relatives tested. These 50 cases belonged to 13 unrelated families with kidney disease or amyloidosis identified in 61% of probands. 35 individuals presented with hypertension at a mean of 51.0 ± 10.4 years. Of these, 30 developed kidney disease at a mean of 56.7 ± 12.0 years, and 21 initiated dialysis therapy at a mean of 61.4 ± 11.3 years. Heart, liver, spleen, colon, and ileum were involved along the progression of the disease. Kidney disease was formerly attributed to hypertension in 25% of patients with AFib amyloidosis undergoing hemodialysis.

Limitations: Retrospective data collection for patients with amyloidosis previously diagnosed.

Conclusions: AFib amyloidosis appears to be an under-recognized disorder in Braga, Portugal, where we found a high frequency of the *FGA* p.Glu545Val variant. Due to the nonspecific nature of its major clinical features, the diagnosis of AFib amyloidosis should have a high index of suspicion, particularly in populations in which hypertension is prevalent.

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INDEX WORDS: Amyloidosis; chronic kidney disease (CKD); fibrinogen A alpha-chain; genetic screening; hemodialysis; mutation; proteinuria; hypertension; *FGA* p.Glu545Val; Portugal; end-stage renal disease (ESRD).

Fibrinogen A α-chain (AFib) amyloidosis is a systemic disease caused by extracellular deposition of insoluble amyloid fibrils composed of abnormal fibrinogen, arising from autosomal-dominant mutations in the gene encoding AFib (*FGA*).[1-5] Patients with AFib amyloidosis invariably develop chronic kidney disease (CKD), typically progressing to end-stage renal disease (ESRD) within 5 years of recognition of renal involvement.[3] Diagnosis is based on the occurrence of proteinuric nephropathy, positive family history, identification of amyloid deposits in affected tissues by immunohistochemistry or mass spectrometry, and detection of an *FGA* amyloidogenic genetic variant.[1-6] Incomplete penetrance may complicate the diagnosis of AFib amyloidosis and should be taken into account in genetic counseling.

To date, 13 amyloidogenic *FGA* variants have been described,[7] accounting for 8% of hereditary amyloidoses.[8] Although AFib amyloidosis was originally described in 1993 in a Peruvian kindred, segregating with a mutation in *FGA* identified as p.Arg554Leu (ie, indicating a substitution of arginine by leucine at amino

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acid 554),[1] the most common *FGA* amyloidogenic variant reported worldwide is one described as p.Glu526Val (substitution of glutamate by valine at amino acid 526), having been identified in a Canadian kindred of Polish origin[9] and in families from the United Kingdom,[3,10] France,[11] Germany,[12] Brazil,[13] United States,[14] and China.[15] According to recommendations of the Human Genome Variation Society,[16] the p.Arg554Leu and p.Glu526Val variants should be described, respectively, as p.Arg573Leu and p.Glu545Val (ie, considering the translation initiation site as amino acid 1, instead of basing the numbering on the cleaved protein). In line with this, the Nomenclature Committee of the International Society of Amyloidosis[17] recommends that hereditary amyloidosis associated with the *FGA* p.Glu545Val variant should be designated AFibE526V (p.Glu545Val) amyloidosis, and this nomenclature will be followed hereinafter.

In Portugal, the first patient with AFib amyloidosis was reported in 2004,[2] and the p.Glu545Val variant was found to be the causative mutation. Subsequently, 4 other apparently unrelated patients,[18] including a woman with a homozygous mutation,[19] were given a diagnosis of AFib amyloidosis by retrospective immunohistochemical characterization of 102 kidney biopsies showing amyloid nephropathy, retrieved from the archive of Centro Hospitalar de São João, a major university hospital in Porto, in the northwest of Portugal. Because all 4 patients carried the p.Glu545Val variant and were from the same confined geographic area, we hypothesized that AFibE526V (p.Glu545Val) amyloidosis may be an underdiagnosed cause of ESRD in that region and carried out targeted genetic screening among the local outpatient hemodialysis population, offering cascade genetic screening to at-risk relatives of all identified cases.

We report demographic and clinical features of individuals carrying the *FGA* p.Glu545Val variant identified in this study, irrespective of their medical condition, and characterize the natural history and major outcomes of AFibE526V (p.Glu545Val) amyloidosis.

METHODS

Study Design, Participant Ascertainment, and Data Collection

Participants enrolled in this study were ascertained by 3 distinct sequential case-finding protocols (Fig 1), starting with the 4 patients who were retrospectively given diagnoses of AFibE526V (p.Glu545Val) amyloidosis, by review and immunohistochemical classification of archived kidney biopsies showing amyloid nephropathy (phase I).[18]

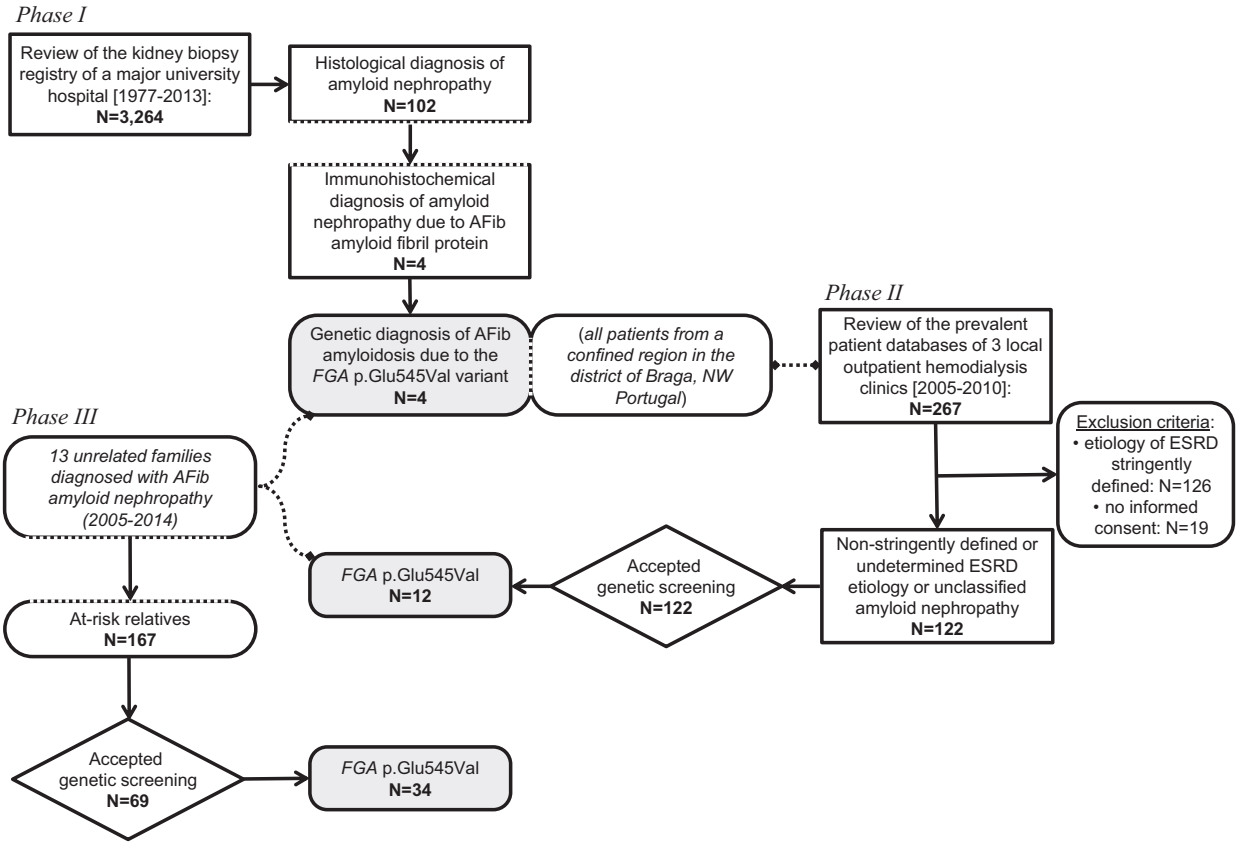

Figure 1. Study design shows setting, eligibility, and results of included cases. Targeted genetic testing led to the identification of 50 individuals with the *FGA* p.Glu545Val variant in the same geographical region. Abbreviations: AFib, fibrinogen A α-chain; ESRD, end-stage renal disease; *FGA*, fibrinogen A α-chain gene; NW, northwest.