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Fibrillary Glomerulonephritis, DNAJB9, and the Unfolded Protein Response

Nicole K. Andeen[a] Vanderlene L. Kung[a] Josh Robertson[b] Susan B. Gurley[b] Rupali S. Avasare[b] Sneha Sitaraman[c]

[a]Department of Pathology and Laboratory Medicine, Oregon Health & Science University, Portland, OR, USA; [b]Division of Nephrology and Hypertension, Department of Medicine, Oregon Health & Science University, Portland, OR, USA; [c]Spirovant Sciences, Inc., Philadelphia, PA, USA

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Abstract
Background: Fibrillary glomerulonephritis (FGN) is found in approximately 1% of native kidney biopsies and was traditionally defined by glomerular deposition of fibrils larger than amyloid (12–24 nm diameter) composed of polyclonal IgG. Recent identification of DNAJB9 as a sensitive and specific marker of FGN has revolutionized FGN diagnosis and opened new avenues to studying FGN pathogenesis. In this review, we synthesize recent literature to provide an updated appraisal of the clinical and pathologic features of FGN, discuss diagnostic challenges and pitfalls, and propose molecular models of disease in light of DNAJB9. ***Summary:*** DNAJB9 tissue assays, paraffin immunofluorescence studies, and IgG subclass testing demonstrate that FGN is distinct from other glomerular diseases with organized deposits and highlight FGN morphologic variants. Additionally, these newer techniques show that FGN is only rarely monoclonal, and patients with monoclonal FGN usually do not have a monoclonal gammopathy. *DNAJB9* mutation does not appear to affect the genetic architecture of FGN; however, the accumulation of DNAJB9 in FGN deposits suggests that disease is driven, at least in part, by proteins involved in the unfolded protein response. Treatments for FGN remain empiric, with some encouraging data suggesting that rituximab-based therapy is effective and that transplantation is a good option for patients progressing to ESKD. ***Key Messages:*** DNAJB9 aids in distinguishing FGN from other glomerular diseases with organized deposits. Further investigations into the role of DNAJB9 in FGN pathogenesis are necessary to better understand disease initiation and progression and to ultimately develop targeted therapies.

Introduction

Fibrillary glomerulonephritis (FGN) is seen in 0.5–1.5% [1–8] of native kidney biopsies and has historically been characterized by glomerular deposition of infiltrative fibrils larger than amyloid composed of polyclonal IgG lacking Congo red (CR) reactivity [1–8]. In 2017,

Karger@karger.com
www.karger.com/gdz

Correspondence to:
Nicole K. Andeen, andeen@ohsu.edu

DnaJ homolog subfamily B member 9 (DNAJB9) also known as endoplasmic reticulum-localized DnaJ 4 was discovered to be a highly sensitive and specific biomarker for FGN [9–11]. Since that time, investigators have worked to elucidate the role of this heat-shock protein integral to the unfolded protein response (UPR) in the development of FGN. This review will summarize the clinical and genetic associations of FGN and data regarding the association of paraproteinemia with FGN as well as lessons learned from employing newer techniques – paraffin immunofluorescence (IF), IgG subclass studies, DNAJB9 immunohistochemistry (IHC) and heavy-light-chain IF. Morphologic features, differential diagnosis, and pathologic variants of FGN will be described. Outcomes, therapies including rituximab and transplant, and the proposed pathogenic mechanisms of FGN will be discussed. Finally, lessons learned from *Dnajb9* knockout mice and other basic science approaches which have elucidated the cellular role of DNAJB9 in the kidney and other organs will be presented. The reader is also directed to recent excellent reviews on FGN [12–14].

Clinical Associations of FGN

Patients with FGN classically present in middle age (average 49–61 years) with decreased kidney function (average serum creatinine 2.1–3.7 mg/dL), microscopic hematuria (in 39–95%), and proteinuria (average 4.1–7.3 g/day) and occasionally frank nephrotic syndrome (in 15–52%) [3–8, 11, 12, 15, 16]. Approximately 41–74% of FGN patients are female, with a female predominance in US-based cohorts (female-to-male ratio 1.2–2.8:1) [12] and a male predominance reported in studies from France, Switzerland, and Greece [15–17]. FGN is rarely found in young adults [18, 19]. Hypertension (in 44–77%) is common, and coexistent diabetes (in 6–28%), hepatitis C viral infection (HCV) (in 3–27%), or autoimmune disease (in 8–30%) have been reported [3–8, 11, 12, 15, 16]. Serologic evaluation is often negative, although antinuclear antibodies (in 7–14%), antineutrophil cytoplasmic antibodies (in 2%), or hypocomplementemia (in 0–9%) have been described [3–8, 11, 12, 15, 16].

The majority of FGN patients (>85%) are Caucasian [6, 20], although an association between FGN and HCV in Black patients was reported in North Carolina and Pacific Coast cohorts. In the University of North Carolina cohort, 26% of FGN patients were Black, and 26% had HCV, compared with no White patients with HCV ($p < 0.001$) [8]. In a Pacific Coast cohort of FGN patients, only 7% were Black, but 78% had HCV (vs. 16% in the total cohort, $p < 0.001$) [6], suggesting an association between chronic HCV and FGN, perhaps related to genetic background.

Both nonhematologic malignancy (in 4–23%) and paraproteinemia (in 7–16%) have been linked to FGN [3–8, 11, 12, 15, 16], though newer studies seem to refute this possibility [21, 22]. Rare cases have been described as paraneoplastic, with remission following cancer treatment [23], recurrence with lymphoma relapse [24], or with a malignancy apparently triggering recurrent crescentic FGN in an allograft [25]. FGN has also been described in the setting of graft vs. host disease [26].

For most of these comorbid conditions, the strength of association with FGN varies by cohort, and the number of conditions included in each subcategory is large enough that a mechanistic connection to FGN has not been established. Regardless, current expert recommendation is to screen FGN patients for autoimmune, neoplastic, and infectious diseases.

Genetic Associations of FGN

Human leukocyte antigens (HLAs) are inheritable modulators of disease. HLA-DR7 was identified in 50% of FGN patients (compared with a prevalence of ~20–25% in deceased donor controls and the US population) who had progressed to end-stage kidney disease (ESKD) and was significantly associated with FGN on multivariable analyses, in two separate cohorts [27, 28]. HLA-DR7 has also been described as a risk factor for steroid-sensitive nephrotic syndrome [29]. In one but not both cohorts, HLA-B35 was also significantly associated with FGN on multivariable analysis. HLA-B35 provides a potential immunologic connection between HCV and FGN as it is involved in ER stress and UPR [21, 30] and is also associated with poorer response to HCV infection [31].

Familial FGN is rare (<1% of cases), reported in 6 families [32–35]. Gene sequencing in 4 patients (including whole-exome sequencing in one familial FGN) [32] has not revealed pathogenic mutations in *DNAJB9* [10]. These familial studies – although small – and the presence of full-length DNAJB9 protein in deposits suggest that pathogenesis is not driven by *DNAJB9* mutations. To better characterize genetic determinants of FGN, genome-wide association studies with larger cohorts including diverse populations are needed.

Paraproteinemia in FGN

Approximately 6–9% of FGN cases appear light-chain-restricted by routine IF [4–6, 8, 15, 22], which historically led to the consideration that these represented a monoclonal gammopathy of renal significance-associated glomerulonephritis (MGRS) [36]. Reported rates of monoclonal gammopathy of unknown significance (MGUS) in patients with an FGN range from approximately 7–16%, which is higher than the prevalence of MGUS in 60- to 69-year-olds in the general US population (3% for Whites, 6.6% for Blacks) [37]. However, in a series of 266 patients with FGN, 95% of those with MGUS had polyclonal rather than monoclonal FGN [6]. Even prior to the routine use of newer techniques (described below), examination of 5 large FGN cohorts in which information on the correlation between an individual patient's serum paraprotein and light-chain restriction on kidney biopsy deposits is provided [4–6, 8, 15] revealed that only 5/543 (1%, all 5 from Nasr et al. [5]) of apparent light-chain-restricted FGN had a confirmed, matching serum paraprotein. Although the reason for apparent light-chain restriction in some cases of FGN was (and remains) unclear, these clinicopathologic cohort studies provide evidence against a direct mechanistic role for paraproteins in most patients with FGN.

More recent studies have revealed that many cases of apparently light-chain-restricted FGN are not composed of monoclonal proteins. Said et al. [22] (n = 35) and Kudose et al. [38] (n = 28) independently demonstrated that IF-P and IgG subclass evaluation could reveal polyclonal IgG deposits in 43–48% of DNAJB9-positive FGN cases which were light-chain-restricted by routine frozen IF. The Mayo cohort was enriched for λ light-chain-restricted cases and found IF-P was particularly useful for "unmasking" polyclonal immune deposits which initially appeared monotypic by routine frozen IF [22]. The Columbia cohort was enriched for κ light-chain-restricted cases and found analysis of IgG heavy-chain restriction in addition to light-chain restriction particularly helpful for demonstrating polyclonal FGN deposits in that setting [38]. Similarly, using immunofluorescent probes with epitopes targeting the junction of the heavy-chain and light-chain constant regions to functionally test for the presence of an intact IgG-kappa or IgG-lambda immunoglobulin in FGN, Nasr et al. [39] found that 3 of 6 cases of apparent light-chain-restricted FGN were actually polyclonal.

Together, use of these techniques demonstrated that DNAJB9-positive, confirmed monoclonal FGN accounts for approximately 0.7–4% of FGN cases; only 4–9% of this subset have an MGUS, a rate similar to the incidence of paraproteinemia in patients with FGN with polyclonal immune deposits [22, 38]. When considering a diagnosis of monoclonal FGN, DNAJB9 IHC, IF-P, and IgG subclass studies are now recommended to establish monoclonality [12]. Thus, unlike other glomerular diseases with organized deposits, such as AL/AH amyloidosis, immunotactoid glomerulonephritis, and cryoglobulinemic glomerulonephritis, FGN does not appear to be associated with paraproteinemia and is infrequently truly monoclonal. DNAJB9 negativity accurately identifies and allows separate categorization of monoclonal FGN mimics, a substantial proportion of which are associated with B-cell lymphoproliferative disorders particularly chronic lymphocytic leukemia [38] and plasma cell neoplasms [40].

Pathology of FGN

FGN is often sclerosing or proliferative, with a membranous-like pattern observed in 0–19% [12]. A total of 17–50% of cases have cellular or fibrous crescents [12] which are usually focal; ≥25% crescents occur in approximately 6% [6]. By IF, there is smudgy mesangial and peripheral capillary wall staining for IgG and kappa and lambda light chains. When performed, IgG subclass studies usually show staining for predominantly IgG4 and IgG1 [12, 41]. Tubulointerstitial and/or vascular immune deposits are seen in 12–49% of kidney biopsies [6, 11] and also contain the characteristic fibrils by electron microscopy [11]. Electron microscopy reveals infiltration of the glomerular basement membrane (GBM) and mesangium by haphazardly arranged fibrils with an average diameter of 12–24 nm. In contrast to amyloid, FGN fibrils are often more prominent in the GBM than the mesangium. DNAJB9 IHC will usually show a similar staining pattern as IgG with regard to the degree and distribution of glomerular staining and extraglomerular deposits (Fig. 1).

The differential diagnosis of FGN after light and IF evaluation depends on the features of the particular case and may include various monoclonal gammopathy of renal significance-associated GNs (in cases with apparent light-chain restriction), anti-GBM antibody disease (anti-GBM, in cases with linear staining of GBMs and crescents), and membranous nephropathy (in the subset of cases that display a membranous pattern by light and IF) (Table 1). Other diagnostic considerations include amy-

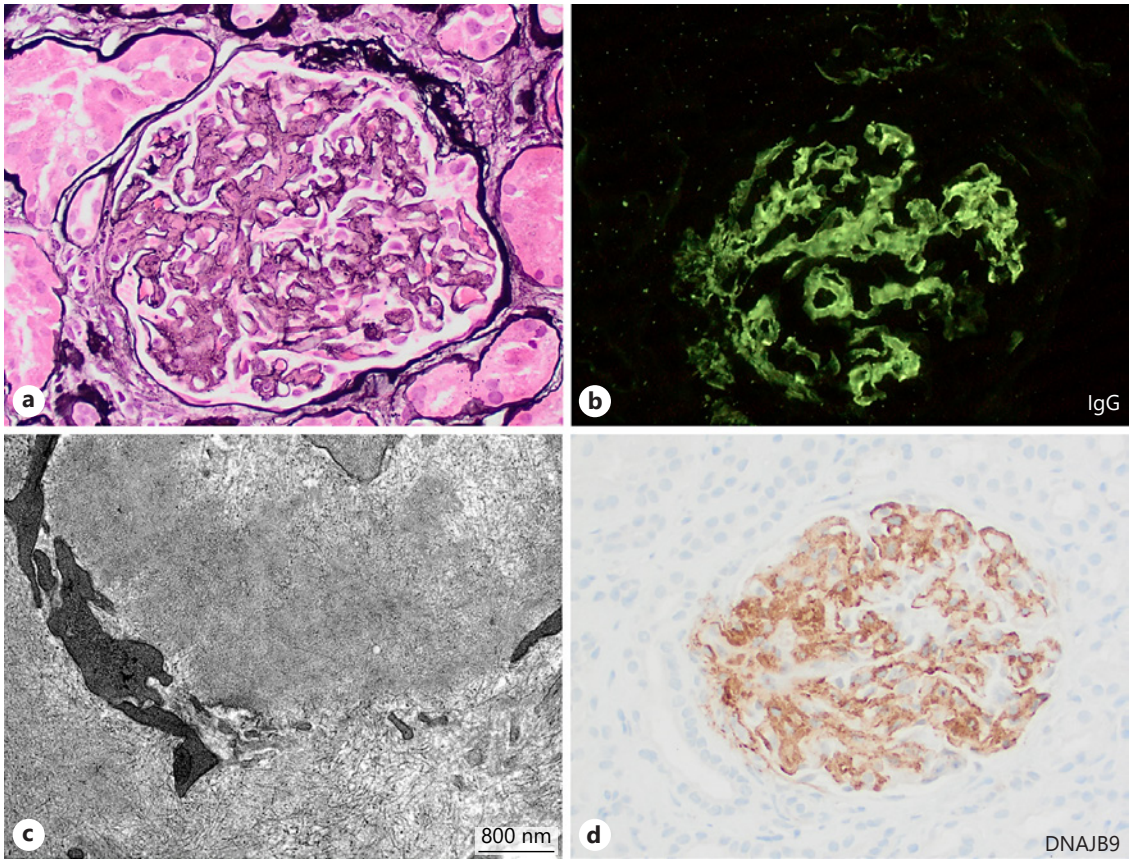

Fig. 1. Fibrillary glomerulonephritis, with mesangial and segmental capillary wall expansion due to accumulation of eosinophilic material (**a,** Jones methenamine silver stain, ×400), smudgy mesangial and peripheral capillary wall staining for IgG (**b**), infiltration of the mesangium by haphazardly arranged fibrils (**c**, transmission electron microscopy, direct magnification, ×6,800), staining for DNAJB9 by IHC (**d**, ×400).

loidosis (especially in cases of CR-positive FGN), diabetic nephropathy (in which dull linear staining of basement membranes for polyclonal IgG and glomerular collagen fibrils may be observed), and cryoglobulinemic GN. Ultrastructural evaluation, DNAJB9 IHC, and additional studies as needed can discriminate among these possibilities.

Histologic Variants of FGN

Approximately 4–5% of FGN cases are CR positive [6, 42] and may have small fibril diameter (≤10 nm) which can lead to misdiagnosis as amyloid. DNAJB9 IHC and/or mass spectrometry can help discriminate between amyloid and FGN, even when both coexist [6, 42, 43]. Proteomic analysis of DNAJB9-positive congophilic FGN [42] demonstrated that these cases lack the abundance of amyloid signature proteins – including serum amyloid P and apolipoprotein L4 – but have a modest increase in one of them, apolipoprotein E, a protein with the β-pleated sheet structure characteristic of amyloid. The structural basis for the congophilia may be related to shared fibrillogenesis properties.

Immunoglobulin-negative FGN was described in a multi-institutional cohort of 9 cases of a fibrillar GN with DNAJB9 expression which appear to lack IgG by frozen and paraffin IF and mass spectrometry [44]; the presence of IgG heavy and light chains had previously been considered a defining feature of FGN [7, 44–46]. Scant IgG staining with prominent C3 deposits and crescents has also been described [47]. The presence of DNAJB9 and lack of substantial IgG in these rare cases suggest that DNAJB9, not IgG, could be the major player in initial fi-

Table 1. Fibrillary glomerulonephritis (FGN), differential diagnosis, and summary of shared and distinguishing features to aid in making the diagnosis

	LM	IF	EM	CR	DNAJB9 IHC
AL/AH amyloidosis	Amyloid deposits involve glomeruli, arterioles, arteries	FGN may initially appear monoclonal but is infrequently monoclonal after additional testing*	FGN fibrils (12–24 nm) are generally thicker in diameter than amyloid fibrils (7–12 nm)	Amyloid is CR+. FGN is uncommonly CR+	Antibody to DNAJB9 does not stain AL/AH amyloid
AA amyloidosis	Amyloid deposits involve glomeruli, arterioles, tubulointerstitium	AA amyloid is consistently IgG negative. FGN is rarely IgG negative	FGN fibrils (12–24 nm) are generally thicker in diameter than amyloid fibrils (7–12 nm)	Amyloid is CR+. FGN is uncommonly CR+	Antibody to DNAJB9 may nonspecifically bind to Amyloid A
Immunotactoid GN	May appear indistinguishable	Approximately 2/3rds of immunotactoid GN cases are monoclonal, but FGN is infrequently monoclonal after additional testing*	Immunotactoid deposits have microtubular substructure with fibrils typically >30 nm in diameter	Negative	DNAJB9 does not stain immunotactoid GN
Cryo GN	Glomerular capillary "pseudothrombi" when seen are unique to cryo GN	FGN usually has limited to no staining for IgM or C1q unlike cryo GN. FGN is infrequently monoclonal after additional testing*	Cryo GN deposits are variable in appearance (conventional, microtubular) and often mesangial and subendothelial rather than infiltrative into the GBM	Negative	DNAJB9 does not stain glomeruli of cryo GN
anti-GBM nephritis	FGN can be focally crescentic but is rarely diffusely crescentic, unlike anti-GBM nephritis	FGN can show linear GBM and focal TBM staining for IgG, similar to anti-GBM	FGN has fibrils (12–24 nm). Anti-GBM nephritis is without ultrastructural deposits	Negative	DNAJB9 does not stain glomeruli of typical or atypical anti-GBM nephritis
MN	FGN can display a predominantly membranous pattern	FGN usually has pseudolinear to granular capillary wall staining for polyclonal IgG	FGN has fibrils (12–24 nm) infiltrating the GBM and mesangium. MN usually has subepithelial immune deposits with a conventional electron-dense appearance	Negative	DNAJB9 does not stain MN. MN deposits can be highlighted by specific antibodies (PLA2R, NELL1, etc.)
Diabetic glomerulosclerosis	Diabetic mesangial sclerosis is silver and PAS positive, whereas mesangial expansion in FGN is often paler on silver and PAS stains	Dull linear staining for IgG is seen not just along GBMs but along Bowman's capsule and all basement membranes in diabetic kidney disease	Diabetic fibrillosis may resemble FGN fibrils, but mesangial fibrils in diabetes are generally more organized, curved, segmental, and noninfiltrative	Negative	DNAJB9 does not stain diabetic mesangial matrix

Cryo, cryoglobulinemic; GN, glomerulonephritis; MN, membranous nephropathy; GBM, glomerular basement membrane; CR, Congo red; +, positive; PLA2R, phospholipase A2 receptor; NELL1, neural epidermal growth factor-like 1; EM, electron microscopy. * Additional testing includes IgG subclass studies, paraffin IF, heavy-light-chain IF.

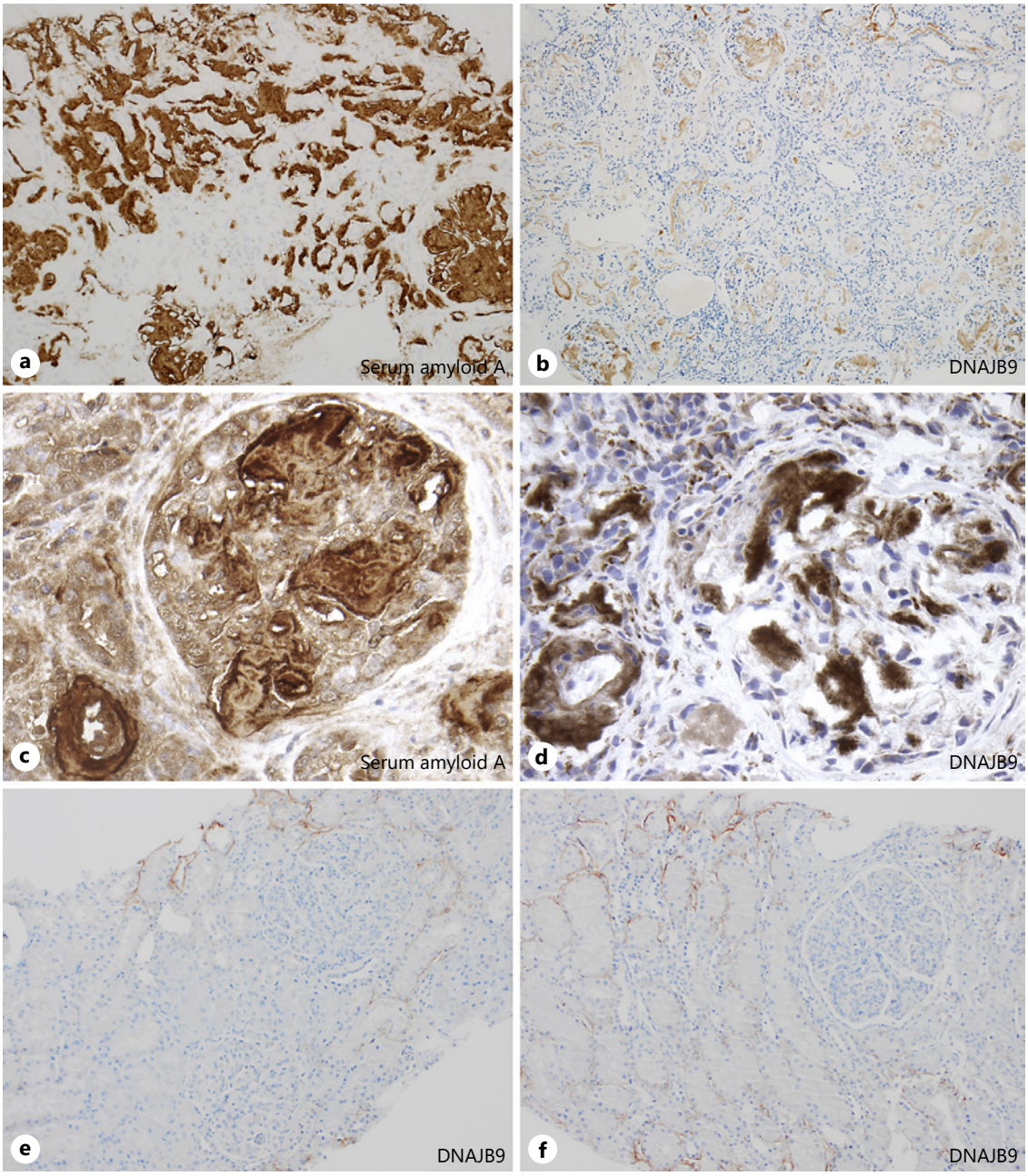

Fig. 2. DNAJB9 staining in nonfibrillary GN cases. **a**, **b** Secondary (serum amyloid A) amyloidosis with glomerular and extraglomerular staining for serum amyloid A protein (**a**, ×100) and DNAJB9 by IHC (**b**, ×100) (images courtesy of Dr. Megan Troxell). **c**, **d** Secondary amyloidosis with staining for serum amyloid A protein (**c**, ×400) and DNAJB9 (**d**, ×400) (images courtesy of Dr. Cynthia Nast). **e**, **f** Hepatitis C-associated cryoglobulinemic glomerulonephritis with tubular basement membrane and peritubular capillary staining for DNAJB9 but no glomerular staining (×200).

bril formation, a mechanistic distinction with potential therapeutic implications [44].

FGN with concurrent IgAN is rare and has demographics and disease course more similar to FGN than IgAN [48]. There are also rare examples of extrarenal FGN with splenic deposits [11, 49], suggesting a systemic disease and/or circulating source.

Interpretation of DNAJB9 Immunohistochemical Staining

Glomerular DNAJB9 expression has >98% sensitivity and specificity for FGN [11], raising questions as to whether DNAJB9-negative FGN exists and if DNAJB9 reactivity is both necessary and sufficient for a diagnosis of FGN. Cross-reactivity of DNAJB9 in cases of secondary (serum amyloid A, AA) amyloidosis has also been observed (Dr. Megan Troxell and Dr. Cynthia Nast, personal communication) (Fig. 2), which represents a potential diagnostic pitfall with Ig-negative and/or CR-positive FGN, in the setting of limited clinical history. Cases of DNAJB9-positive AA amyloidosis are Ig negative, CR positive and have been observed in patients with a history of heroin use and chronic bacterial infections (with or without HCV infection), behaviors and conditions which are associated with AA amyloidosis [50]. One case of AA amyloid which was weakly DNAJB9-positive occurred in a patient with a history of Crohn's disease and carcinoma of the small intestine (Dr. Megan Troxell, personal communication). Mass spectrometry may be utilized to demonstrate the presence of true DNAJB9 abundance in challenging circumstances. We have also observed rare cases of extraglomerular (but not glomerular) DNAJB9 staining in HCV-associated cryoglobulinemic GN (Fig. 2). Thus, although DNAJB9 is a highly sensitive and specific biomarker and may be disease-defining for FGN, it is also a protein expressed in most tissues, especially those with abundant ER such as the kidney, liver, and placenta [51]; as with all such tools, some caution must be exercised in interpretation.

Outcomes and Treatment for FGN

Up to 50% of FGN patients progress to ESKD within a few years of biopsy [5, 6], but the disease course remains highly variable as some patients with sub-nephrotic proteinuria and well-preserved kidney function can have more of a chronic, smoldering course over time. Risk factors for progression include estimated glomerular filtration rate (eGFR) at diagnosis, male sex, age, degree of proteinuria, crescents, and degree of glomerulosclerosis [5, 6].

There is no standard-of-care treatment for FGN. Rituximab may be the most promising treatment for progressive FGN. The first study on rituximab for FGN [52] showed reduction in proteinuria and stabilization of kidney function in patients (n = 3) with well-preserved kidney function at diagnosis (Cr 0.6–0.8 mg/dL). Subsequently, Javaugue et al. [15] reported partial response to rituximab in 5/7 FGN patients with well-preserved kidney function (median eGFR 77 mL/min/1.73 m^2). Hogan et al. [53] demonstrated nonprogression of serum creatinine (stable or <25% increase) in 4/12 patients with FGN treated with rituximab (median eGFR of 39 mL/min/1.73 m^2 at diagnosis). In the Pacific Coast cohort, 8 patients were treated with rituximab, 7 of whom had no progression to ESKD, compared with a rate of ~50% ESKD in the overall cohort [6]. In this group with a median eGFR of 38 mL/min/1.73 m^2 at diagnosis, rituximab was the only immunosuppressive agent significantly associated with a lack of progression to ESKD [6]. Each of these retrospective studies used different criteria for response, and proteinuria was often not included.

In the first prospective clinical trial of rituximab in 11 patients with FGN, investigators observed no significant change in the eGFR at 12 months [54]. At 1 year, there was an overall ~50% reduction in proteinuria (which did not meet statistical significance), and 3 patients experienced a partial response [54]. Neither treatment nor disease remission status affected DNAJB9 serum levels [54].

A prospective trial of Acthar Gel (repository corticotrophin injection) with or without tacrolimus in 15 patients with FGN found high rates of reduction in proteinuria, with 60% of patients achieving a ≥50% reduction in proteinuria at 12 months [55]. Response to repository corticotropin injection has also been described in a case report [56].

A variety of other agents have been used to treat FGN, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, steroids, cyclophosphamide, and mycophenolate mofetil. Direct-acting antiviral treatment should be considered for those with FGN in the setting of HCV.

Transplant in FGN

Kidney transplant should be considered in otherwise medically eligible FGN patients. Including data from small case series, FGN has an allograft kidney recurrence rate of 8–47% [57–60]. In the largest series of patients with ESKD due to FGN and kidney transplant (n = 14), El Ters et al. [59] observed a 21% recurrence rate at a median follow-up time of 10 years. In this series, there were no differences in the outcome or incidence of kidney allograft failure [59] in those who experienced recurrence versus those who did not. This and prior reports suggest

that FGN recurrences post-transplant usually occur late and follow a more indolent course [2, 57–61], although early recurrence [62] and repeat recurrences [60] have been reported. The slower progression of FGN in allografts may be due to earlier detection with protocol biopsies, immunosuppression, or other factors. Intriguingly, reports of nearly asymptomatic FGN in the allograft [58–60] and native [32] kidney raise the possibility that the FGN may be a slowly progressive disease that is frequently diagnosed upon the onset of clinical symptoms, late in the disease course.

There are rare reports of persistent donor-derived FGN, which suggest that unlike immune complex-mediated GN deposits, FGN fibrils do not resolve in a new immune environment. Specifically, there are two case reports of unresolved donor-derived FGN, with repeat allograft biopsies showing no definitive morphologic improvement [59, 63]. This is distinct from donor-derived immune complex disease such as membranous nephropathy [64] and IgA deposits [65], which can improve or completely resolve in a new host environment.

The Unfolded Protein Response

Mechanisms for disease development may be theorized by examining DNAJB9's role in the UPR. The UPR is a dynamic signaling pathway that adjusts protein synthesis, protein folding, and degradation of misfolded proteins in response to stress. The UPR is initiated through three protein sensors located on the ER membrane: inositol requiring kinase 1 (IRE1α), pancreatic ER eukaryotic translation initiation factor 2 (eIF2α) kinase (PERK), and activating transcription factor 6 (ATF6). The UPR sensors are inactivated by binding to the master ER chaperone immunoglobulin heavy-chain binding protein (GRP78/BiP), which prevents downstream signaling. During ER stress, GRP78/BiP engages the accumulating misfolded or unfolded protein substrates, thus releasing the UPR transducers to initiate an adaptive response. The UPR is briefly discussed in the following paragraphs. Readers are directed to the following reviews for extensive details [66–69].

In response to ER stress, IRE1α dimerizes, leading to autophosphorylation and activation of its RNase and kinase activities. Activated IRE1α splices the transcription factor X-box-binding protein 1, which subsequently transcriptionally activates genes involved with the ER-associated degradation (ERAD) machinery to enhance ER protein folding and protein degradation capacities. Additionally, IRE1α promotes degradation of ER-associated mRNAs through the regulated IRE1-dependent decay of mRNA pathway. IRE1α integrates ER stress with pro-inflammatory signaling by binding to adapter protein tumor necrosis factor alpha receptor-associated factor 2, subsequently activating the nuclear factor-kappa B and c-Jun N-terminal kinase pathways.

Activated PERK phosphorylates eIF2α, which attenuates global protein synthesis, thereby reducing the protein load in the ER. Phosphorylation of eIF2α is transient as GADD34 rapidly dephosphorylates eIF2α to restore protein synthesis. Phosphorylation of eIF2α also promotes translation of a specific subset of mRNAs including ATF4, which is a transcription factor that regulates expression of genes associated with ERAD and anti-oxidative stress response [70]; importantly, however, control of protein synthesis and not ATF4 activation promotes cell survival [70].

The ER stress sensor ATF6 traffics to the Golgi, where it undergoes sequential proteolytic processing by site 1 (S1) and site 2 (S2) proteases. Cleaved ATF6 subsequently migrates to the nucleus to activate transcription of genes involved in the ERAD machinery, similar to IRE1α signaling, thus regulating cellular and ER protein load.

Acute ER stress activates adaptive UPR allowing for cell survival, whereas cells that are chronically stressed undergo UPR-mediated apoptosis. ER stress and UPR activation determine cell fate and function, thereby contributing to the pathogenesis of several diseases.

Role of DNAJB9 in the UPR

DNAJB9 was identified as a GRP78/BiP co-chaperone, expressed highly in secretory tissues [71–73]. DNAJB9 is a 223-amino acid protein member of the DNAJ family of chaperones, which influence cellular processes by regulating heat-shock proteins. Expression of *DNAJB9* is induced during the UPR, demonstrated by *DNAJB9* mRNA upregulation in response to expression of a terminally misfolded protein [74]. *DNAJB9* expression is specifically induced in an IRE1α/X-box-binding protein 1-dependent manner during UPR.

DNAJB9 associates with unfolded and misfolded substrates, and loss of *DNAJB9* results in an accumulation of such proteins [74]. Hypomorphic expression of *Dnajb9* in mice results in altered hematopoiesis and lymphocyte function, highlighting the in vivo requirement for DNAJB9 in the UPR activated during B-cell maturation and antibody production [75]. Additionally, *Dnajb9* deficien-

cy is associated with defects in growth, development, and metabolism [72], indicating an expanded role for DNAJB9 in the adaptive UPR that is activated during development. Collectively, these data highlight the important role of DNAJB9 in maintenance of cellular homeostasis during stress response.

Proposed Pathogenic Mechanisms of FGN

One theory of FGN pathogenesis proposes that DNAJB9 – perhaps in an altered or misfolded form – is an autoantigen in FGN, which is then bound by IgG [12, 14, 76]. This fits with the autoimmune glomerular disease construct in which the autoantigen is present in glomerular immune deposits and is supported by the colocalization of DNAJB9 with IgG and fibrils [9, 10, 77, 78]. The identification of rare cases of DNAJB9-positive but immunoglobulin-negative FGN [44] however suggests that DNAJB9 is the initiator of disease, but, circulating anti-DNAJB9 antibodies have not yet been identified. The presence of full-length DNAJB9 protein in immune deposits [9, 10] and lack of *DNAJB9* mutations in a few tested patients [10, 32] provide evidence against a genetically mutant form of DNAJB9 as a driver of FGN, although posttranscriptional or epigenetic modifications are possible.

A second theory is that DNAJB9 binds to misfolded IgG. Supporting this possibility is DNAJB9's known cellular roles, particularly its propensity to bind aggregation prone peptide regions [74, 79], as discussed above. Additionally, serum levels of DNAJB9 are elevated in FGN patients, possibly due to increased protein production [80], although they do not appear to correlate with the disease state or response to therapy [54] and have an inverse correlation with the eGFR [80, 81], suggesting that some of the elevation could potentially be due to decreased filtration in the setting of chronic kidney disease. However, if DNAJB9 were present simply in response to a misfolded protein, a similar abundance may be expected in amyloidosis. Furthermore, other components of the UPR are not upregulated in the FGN proteome [9], and *DNAJB9* is not transcriptionally upregulated in FGN glomeruli by RNA in situ hybridization [82], which together suggest that the abundance of DNAJB9 in FGN is not due to local induction of DNAJB9 or the UPR.

Collectively, these data indicate a yet unidentified role for DNAJB9, perhaps indepenent of known UPR functions. DNAJB9 mRNA may be posttranscriptionally regulated, consistent with the increasing observations that mRNA abundance is a poor predictor of protein levels, particularly under conditions of stress [83]. Posttranslational modifications leading to altered stability of the DNAJB9 protein may also explain the increased abundance of the DNAJB9 protein in FGN. Other theories have suggested that FGN is due to decreased degradation of DNJAB9 or failure of a downstream interaction or effector in the ERAD pathway or decreased functionality of DNAJB9 or the UPR due to epigenetic modifications [14]. It is currently unknown if the rate of protein synthesis is altered in FGN; ER membrane-bound DNAJB9 was shown to promote mTORC2 assembly in the cytosol in the murine liver, thereby controlling protein synthesis in obese primary hepatocytes [84]. Therefore, analysis of pathways controlling mRNA translation (such as PERK-eIF2α and mTOR signaling) merits further investigation in FGN.

Conclusion

Newer laboratory techniques – DNAJB9 as a biomarker for fibrillary GN, IF-P, IgG subclasses, and heavy-light-chain IF – have enhanced recognition of the morphologic spectrum of FGN. These recent studies and reappraisal of historic data provide evidence against a direct mechanistic connection between paraproteins and FGN in the great majority of patients. Variants of DNAJB9-positive FGN include Ig-negative and congophilic FGN, which do not have known significant clinical differences, but their existence provides additional datapoints about potential pathogenesis of FGN. Small studies suggest rituximab may be a useful therapeutic agent to stabilize disease in FGN. Whether pathogenesis is driven primarily by misfolding of DNAJB9 or IgG, autoimmune phenomenon with generation of a neo-antigen, aberrations of DNAJB9-associated cellular functions in the UPR or ERAD pathways (decreased function or degradation rather than overproduction of DNAJB9), epigenetic modifications, or a variety of these are exciting avenues for future study. Targeted treatment will evolve with improved understanding of pathogenesis.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Nicole K. Andeen and Sneha Sitaraman drafted the manuscript. Vanderlene L. Kung, Josh Robertson, Susan B. Gurley, and Rupali S. Avasare edited the manuscript and approved the final version.

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