Clinicopathologic Significance of Predominant Lambda Light Chain Deposition in IgA Nephropathy

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Introduction: IgA nephropathy (IgAN) differs from other glomerular diseases by the frequently predominant lambda over kappa light chain deposition. Using the Cure Glomerulonephropathy (CureGN) IgAN cohort, we aimed to determine whether predominant lambda chain deposition is associated with worse clinical outcomes or histopathologic markers of more active disease.

Methods: Patients were categorized based on the intensity of light chain staining. The lambda dominant (LD) group was defined by a difference in intensity score of lambda minus kappa ≥ 1+ and the kappa-lambda codominant (KL) group by a difference < 1+. We compared the clinical courses of patients in each category from the time of kidney biopsy and time of enrollment into CureGN to the time of remission (proteinuria < 0.3 g/g), 50% reduction in estimated glomerular filtration rate (eGFR), or progression to end-stage kidney disease (ESKD). We also analyzed differences in histopathologic characteristics between the 2 groups.

Results: Among 440 patients, we found no significant differences between groups in baseline clinical characteristics nor in rates of remission, 50% reduction in eGFR, or progression to ESKD. Patients in the LD group had a modestly greater frequency of IgG staining 1+. The biopsy results of 234 patients reviewed by CureGN pathologists revealed a greater frequency of endocapillary hypercellularity (51.1% vs. 36.3%, P = 0.04) in the LD group, but no other significant difference in histopathologic features.

Conclusion: In IgAN, we found an association between lambda predominance and increased endocapillary hypercellularity, but no association with clinical outcomes.

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IgAN is characterized by abnormal glomerular deposition of IgA antibodies and C3. Given the wide spectrum of disease severity in IgAN, identifying those patients who are at risk for progression to ESKD is of great interest and importance. The publication of the Oxford Classification MEST scoring system in 2009,2 and its subsequent validation and refinement studies,3,4 added histopathologic criteria to clinical
factors to improve the identification of patients at high risk for progression to ESKD.\(^5\)

Beyond light microscopy, previous studies have evaluated the association of immunostaining of IgG and C3 on the prognosis of IgAN and its correlation with light microscopy findings.\(^6,7\) However, the pattern of immunoglobulin light chain staining in IgAN and its association—if any—with disease severity or prognosis are not well understood. Previous biopsy data have revealed a predominance of lambda light chain deposition over kappa, a finding that is unique to IgAN compared with other glomerular diseases.\(^8,9\) Previous studies addressing the clinicopathologic and pathogenic impact of the lambda chain predominance have generally been limited by the rather small size of the study cohorts,\(^9,10\) thus affecting the ability to detect differences in disease severity or outcomes.

Using the IgAN cohort of the CureGN study,\(^11,12\) the goal of this study is to determine whether predominant lambda light chain deposition is associated with more severe disease at presentation or a worse prognosis. In addition, we aim to describe whether lambda predominance is associated with histopathologic markers of more severe inflammation or scarring on kidney biopsy.

### METHODS

We conducted a retrospective review of adults and children enrolled in the CureGN IgAN cohort. CureGN (https://curegn.org/) is a multicentric, National Institute of Diabetes and Digestive and Kidney Diseases–funded, longitudinal, prospective, observational study which enrolled children (<18 years old at the time of biopsy) and adults with a diagnostic biopsy within the past 5 years with either IgAN or IgA vasculitis (IgAV).\(^11\) Institutional review board approval was obtained for all participants at their respective enrolling site. The diagnostic criteria for IgAN and IgAV used by the CureGN study were as previously reported.\(^12\) Patients without lambda or kappa light chain staining by immunofluorescence microscopy (IF) were excluded from the analysis. The cohort was initially categorized into 3 groups based on the relative intensities of lambda and kappa light chain staining by IF as reported by the local pathologist. Patients with lambda staining \(\geq 2+\) and kappa staining of 0 to trace were categorized as lambda monotypic (LM). The LD group was defined by a difference in intensity score of staining of lambda minus kappa \(\geq 1+\). The KL group was defined by a difference in staining intensity lambda minus kappa of \(<1+\). This criterion for categorization between LD and KL was based on (i) the greater confidence of the study pathologists in discerning between an equal or greater \(1+\) difference in staining intensity (as opposed to a smaller difference of 0.5), (ii) review of the distributions of intensity staining which revealed that pathologists used “half-steps” infrequently, and (iii) the overall distribution of the lambda minus kappa staining intensity across the entire cohort. Using a difference of lambda minus kappa \(\geq 2+\) would be associated with markedly disproportionately distributed groups, affecting the robustness of the statistical analysis. Because the number of patients in the LM group was very small (Figure 1), this group was included in the LD group for all statistical analyses.

Baseline characteristics reported at the time of biopsy and at the time of enrollment in the cohort were age, sex, race, ethnicity, eGFR, degree of proteinuria, serum albumin, presence of hypertension, and a diagnosis of IgAV. Race and ethnicity were self-reported or reported by parents of children. Reporting race and ethnicity in the CureGN study was mandated by the US National Institutes of Health, consistent with the Inclusion of Women, Minorities and Children Policy. To calculate the eGFR, the Chronic Kidney Disease Epidemiology Collaboration formula was used for adults (aged \(>18\) years) and the bedside Chronic Kidney Disease in Children Study or CKiD equation for children.\(^13,14\) The clinical outcome measures of interest were the proportion of patients who achieved either a complete remission (defined as a urine protein-to-creatinine ratio [UPCR] \(<0.3\) g/g), developed a 50\% reduction in eGFR, or progressed to ESKD (defined as an eGFR \(<15\) ml/min per 1.73 m\(^2\), dialysis initiation, or kidney transplantation).

Among patients whose biopsy tissue was reviewed by the central CureGN pathologists, we compared the histopathologic changes between the LD and KL groups with respect to mesangial proliferation (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) scores, including the percent of globally sclerotic glomeruli, percent of glomeruli with fibrinoid necrosis, degree of interstitial inflammation (mild, moderate, severe), total crescents (including cellular, fibrocellular, and fibrous crescents), and the intensity and location of IgG, C1q, and C3 staining.

### Analyses

Descriptive statistical analyses were used to analyze differences between the LD and KL groups with respect to the M, E, S, T scores and other pathologic characteristics, including the aforementioned baseline clinical characteristics at time of kidney biopsy or time of enrollment into CureGN. This included mean (SD) for continuous and count (%) for categorical variables.
We retrospectively investigated the clinical course of patients in each category from the time of kidney biopsy and the time of enrollment into CureGN to the time of key clinical outcome measures of interest, which are as follows: (i) Time to remission (defined as attaining a UPCR < 0.3 g/g without a decline in eGFR of greater than 25 ml/min per 1.73 m² in the previous 12 months). The change in eGFR value was selected to exclude the possibility that a patient had a reduction of proteinuria to <0.3 g/g due to a severe reduction in GFR, as opposed to resolution of proteinuria due to disease remission or control. Two consecutive measurements of proteinuria and serum creatinine levels were required for each event determination, and the first date meeting the defining criteria was used as the time point of the event. (ii) Time to the composite of doubling of serum creatinine level from each of the baselines (biopsy or enrollment), an eGFR below 15 ml/min per 1.73 m², or initiation of renal replacement therapy.

Intergroup comparisons were conducted using t tests for continuous variables and χ² test for categorical variables.

Cumulative incidence rates of the composite renal end point and remission were calculated and plotted using Kaplan-Meier analysis. The comparison of incidence rates of both outcomes between light chain deposition categories was performed with a log-rank test. All analyses were conducted in R (R Core Team [2020]), version 4.0.2.

RESULTS

A total of 706 patients with IgAN were identified and reviewed in the CureGN data set (Figure 1). Among the 706 patients, 518 had biopsy reports that described lambda and kappa light chain stain intensity and were included in our analysis. Baseline characteristics of the patients are presented in Table 1. Among the 518 patients, 40.5% were female, 11.4% were Asian, 3.9% were Black, and 77.0% were White. A total of 110 patients (21.2%) carried a diagnosis of IgAV. A total of 155 patients (29.9%) were below the age of 18 years at the time of biopsy. At the time of biopsy, the mean age was 31.5 years ± 17.96, the mean eGFR was 73.2 ml/min per 1.73 m² ± 40.94, the mean UPCR was 2.5 g/g ± 2.7, and the mean serum albumin was 3.6 g/dl ± 0.77.

A total of 212 (40.9%) patients were classified as LD and 306 (59.1%) patients were classified as KL. Given that only 26 patients had lambda monotypic deposition, the LM group was included in the LD group. Further details regarding the specific intensity of light chain staining and classification can be found in Supplementary Table S1. For comparison, we evaluated the distribution of light chain intensity staining in the CureGN cohort of 197 patients with membranous nephropathy. Using the same criteria, only 5 patients...
were treated with corticosteroids (Table 2). There were received an immunosuppressive treatment, and 31.3% with renin-angiotensin-aldosterone blockade, 72.6%.

Clinical Outcomes

Clinical Characteristics at Baseline

The LD group and the KL group were similar with respect to demographics, proportion with a diagnosis of IgAV, or any of the clinical parameters at the time of biopsy (eGFR, proteinuria, serum albumin) (Table 1). Participants in the LD group had a shorter time from biopsy to enrollment than the KL group (mean 474.5 vs. 576.0 ± 338.4 days, respectively; \( P = 0.037 \)). At the time of enrollment, the LD and KL groups were similar with respect to eGFR, diagnosis of hypertension, or IgAV (LD 19.8% vs. KL 22.5%; \( P = 0.53 \)). Patients in the LD group had modestly greater degree of proteinuria than the KL group, (UPCR 1.7 ± 2.4 vs. 1.3 ± 1.9 g/g, respectively; \( P = 0.056 \)). There were no statistically significant differences between the 2 groups with respect to any other demographic or clinical characteristics.

Association of Light Chain Dominance With Clinical Outcomes

Among the 518 patients, 90.1% received treatment with renin-angiotensin-aldosterone blockade, 72.6% received an immunosuppressive treatment, and 31.3% were treated with corticosteroids (Table 2). There were no significant differences in treatment between the LD and KL groups.

Time-to-event outcome data were available for a total of 440 of the 518 patients. Mean follow-up times from biopsy to remission or censoring were 1148 ± 878 days and 1122 ± 848 days for the LD and KL groups, respectively (median and range were 938 [12, 3969] and 914 [14, 3466], respectively). Mean follow-up times from enrollment to remission or censoring were for the LD group was 684.8 ± 688.3 days and 612 ± 666 days for the LD and KL groups, respectively (median and range were 385 [0, 2164] and 286 [0, 2176], respectively).

A total of 307 (69.8%) participants attained remission (LD 67.7% vs. KL 71.3%, \( P = 0.491 \)), 48 (9.3%) had a 50% reduction in eGFR (LD 9.9% vs. KL 8.8%, \( P = 0.792 \)), and 56 (10.8%) reached ESKD (LD 13.2% vs. KL 9.2%, \( P = 0.187 \)). A total of 32 (8.6%) participants had a UPCR of <0.3 g/g at the time of biopsy. In addition, we found no statistically significant differences between the groups in the time-to-event analyses for any of these end points from either the time of biopsy or the time of enrollment (Figures 2 and 3).

Association of Light Chain Dominance With Histopathologic Findings

The histology slides of 234 patients with IgAN/IgAV were scanned digitally and scored by CureGN pathologists (as of March 22, 2021). Of these, 96 (41%) patients were in the LD (including 7 patients with lambda monotypic staining) group and 138 (59%) in the KL group. The 2 groups were similar with respect to age, sex, and race or ethnicity (Table 3). Compared with the KL group, the LD group had a greater frequency of endocapillary hypercellularity (51.1% vs. 36.3%, \( P = 0.04 \)) and a greater frequency of IgG staining \( \geq 1 + \) (37.3% vs. 21.9%, Table 4). There were no significant

(2.5%) were classified as LD and 192 patients (97.5%) were classified as KL. The difference in distribution of light chain intensity between the 2 diseases was statistically significant \( (P < 0.001) \).

Table 1. Baseline characteristics by light chain deposition type

| Characteristic                        | Overall | Lambda dominant | Kappa-lambda codominant | \( P \) value |
|--------------------------------------|---------|-----------------|-------------------------|--------------|
| Overall, N                           | 518     | 212             | 306                     |              |
| Age at biopsy, (yr), mean (SD)       | 31.5 (17.96) | 31.9 (16.8)   | 31.2 (18.8)             | 0.668        |
| Age at enrollment, (yr), mean (SD)   | 33.0 (18.03) | 33.2 (16.8)   | 32.8 (18.8)             | 0.805        |
| Gender: female, N (%)                | 210 (40.5) | 84 (39.6)      | 126 (41.2)              | 0.792        |
| Race, N (%)                          | 40 (7.7)  | 14 (6.6)       | 26 (8.5)                |              |
| Ethnicity: Hispanic/Latinx, N (%)    | 91 (17.6) | 37 (17.5)      | 54 (17.6)               | 1            |
| Hypertension at enrollment, N (%)    | 72 (14.2) | 26 (12.3)      | 46 (15.1)               | 0.531        |
| Serum albumin biopsy, (g/dL), mean (SD) [missing] | 3.6 (0.7) | 3.5 (0.8) | 3.6 (0.7) | 0.067 |
| eGFR at biopsy, (ml/min/1.73 m²), mean (SD) [missing] | 73.2 (40.94) | 72.3 (36.6) | 73.8 (43.9) | 0.969 |
| UPCR at biopsy, (g/g), mean (SD) [missing] | 2.5 (2.70) | 2.4 (2.5) | 2.6 (2.9) | 0.604 |
| Race, N (%)                          | 399 (77.0) | 162 (76.4) | 237 (77.5)              |              |

eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.

\( P \) values from \( \chi^2 \) test (categorical variables) or t tests (continuous variables), testing for differences between lambda dominant and lambda kappa codominant groups.
differences between groups in M, S, or T scores, total crescents, percent of globally sclerotic glomeruli, percent of glomeruli with fibrinoid necrosis, degree of interstitial inflammation, the intensity or location of C3 staining, C1q staining, IgA staining, or the glomerular localization of kappa staining or lambda staining (Table 4 and Supplementary Table S2).

We also compared the intensity of IgG and C3 staining between the LD and KL groups based on the larger cohort (N = 518) because these data were extractable from the biopsy reports (Supplementary Table S3). The difference in frequency of IgG staining ≥ 1+ between the LD group compared with the KL group was small (32.9% vs. 29.3%, respectively). The intensity of C3 staining was likewise confirmed to be similar between the 2 groups (C3 staining ≥ 1+ in 85.2% vs. 79.6% in the LD vs. KL groups, respectively).

**DISCUSSION**

In this study of patients with IgAN and IgAV, we evaluated the association between predominant lambda light chain deposition and clinical outcomes and measures of histopathologic disease activity.

With respect to clinical characteristics at baseline and the outcome measures of interest, we did not find significant differences between patients with predominant lambda light chain deposition versus those with KL codominant deposition. However, our data do suggest that lambda predominant deposition may be of histopathologic significance as patients were more...
likely to have increased endocapillary hypercellularity and IgG deposition.

Lambda predominant light chain deposition in IgAN was initially described by Lai et al., and subsequent studies have confirmed this finding. Importantly, lambda predominance is unique to IgAN when compared with other glomerular diseases. This was demonstrated by Dr. J. Charles Jennette’s review of immunohistochemistry among patients with various glomerulonephritides. On the basis of large multicenter and multiethnic CureGN cohort, our data confirm the relative predominance of lambda chain deposition in patients with IgAN. We also confirm that the relative predominance of lambda chain seems to be “specific” of IgAN, at least when compared with another disease with glomerular immunoglobulin deposition from the CureGN study, namely membranous nephropathy (the other 2 disease categories included in CureGN, focal segmental glomerulosclerosis and minimal change disease, have no or scant glomerular immunoglobulin deposits). Although the findings of lambda monotypic IgAN has been recognized and reported, its frequency seems quite low in this large cohort of patients.

The etiology for the lambda light chain predominance in IgAN is not well understood, but it is maybe related to charge distribution of lambda light chains bound to IgA and increased affinity for mesangial deposition. Another possible etiology for this predominance may be related to the pathogenetic role of

![Figure 3. Cumulative hazard plots of time to complete remission at any time from (a) biopsy and (b) enrollment.](image)

**Table 3.** Baseline characteristics of patients with detailed biopsy review by CureGN pathologists categorized by light chain deposition type

| Characteristic                        | Total cohort | Lambda dominant | Kappa-lambda codominant | P value |
|--------------------------------------|--------------|-----------------|-------------------------|---------|
| N                                    | 234          | 96              | 138                     |         |
| Age at biopsy (yr), mean (SD)        | 36.7 (17.5)  | 36.0 (15.4)     | 37.1 (18.9)             | 0.606   |
| Age at enrollment (yr), mean (SD)    | 37.9 (17.4)  | 37.1 (15.3)     | 38.4 (18.7)             | 0.668   |
| Sex: female, N (%)                   | 90 (38.5)    | 34 (35.4)       | 56 (40.6)               | 0.508   |
| Race, N (%)                          |              |                 |                         | 0.322   |
| Asian                                | 26 (11.1)    | 15 (15.6)       | 11 (8.0)                |         |
| Black/African American               | 12 (5.1)     | 5 (5.2)         | 7 (5.1)                 |         |
| Other                                | 17 (7.3)     | 6 (6.2)         | 11 (8.0)                |         |
| White                                | 179 (76.5)   | 70 (72.9)       | 109 (79.0)              |         |
| Ethnicity: Hispanic/Latinx, N (%)    | 36 (15.4)    | 15 (15.6)       | 21 (15.2)               | 1       |
| eGFR at biopsy, (ml/min/1.73 m²) mean (SD) | 66.5 (35.2) | 67.3 (33.3)     | 64.4 (36.5)             | 0.566   |
| UPCR at biopsy, (g/g), mean (SD)     | 2.8 (4.8)    | 3.1 (6.4)       | 2.6 (3.2)               | 0.523   |
| Serum albumin at biopsy, (g/dL), mean (SD) | 3.6 (0.8)   | 3.6 (0.7)       | 3.6 (0.8)               | 0.723   |
| Days from biopsy to enrollment, mean (SD) | 462.8 (537.6) | 431.3 (578.5) | 484.7 (508.2) | 0.466 |
| eGFR at enrollment, (ml/min/1.73 m²), mean (SD) | 67.3 (32.7) | 67.1 (30.8)     | 67.4 (34.0)             | 0.952   |
| UPCR at enrollment, (g/g), mean (SD) | 1.9 (4.2)    | 2.5 (8.1)       | 1.6 (1.9)               | 0.134   |
| Serum albumin at enrollment, (g/dL), mean (SD) | 3.8 (0.6)   | 3.8 (0.6)       | 3.9 (0.7)               | 0.721   |

*P* values from *χ²* test (categorical variables) or *t* tests (continuous variables), testing for differences between lambda dominant and lambda kappa codominant groups.
mucosa-associated lymphoid tissue and gut-associated lymphoid tissue in IgAN. A study from France revealed that lymphoid tissues derived from the human tonsils and the gastrointestinal tract have predominantly lambda light chain-secreting plasma cells. This was contrary to the plasma cells derived from the bone marrow, which secreted predominantly kappa light chains.17 An additional study by Su et al.18 revealed that human intestinal plasma cells that express IgA favor lambda light chain production. Previous studies have revealed that in the serum, when looking at IgG and IgM, kappa light chains are more frequently expressed than lambda light chains, generally at a ratio of 2:1. However, the ratio is significantly lower for IgA, closer to 1.1 to 1.2:1.19,20 These findings suggest that mucosa-associated lymphoid tissue and gut-associated lymphoid tissue may be unique in their composition and function compared with other lymphoid tissues and are composed of a greater number of plasma cells that secrete lambda light chains.18 A recent study has likewise revealed that, compared with healthy controls, the peripheral blood B cells with membrane-bound, galactose-deficient IgA1 of patients with IgAN expressed predominantly lambda light chains and cellular receptors involved in their homing to the respiratory and digestive tract mucosa.21 The link between greater lambda light chain expression by mucosa-associated lymphoid tissue and gut-associated lymphoid tissue and the light chain predominance in IgAN is intriguing and may suggest a more significant role in the pathogenesis of IgAN. It would also be consistent with the proposed role of mucosal immunity in the pathogenesis of IgAN.22 The growing recognition of this mucosa-kidney axis has been the basis of therapeutic trials using tonsillectomy23 or the targeting of gut-associated lymphoid tissue with a formulation of budesonide directed for release in the distal ileum.24

Our findings are similar to those of a recent retrospective Japanese study by Katafuchi et al.25 Evaluating the significance of light chain deposition in 526

| Table 4. Selected histopathologic findings by light chain deposition type |
|------------------|------------------|------------------|------------------|------------------|------------------|
| Histopathologic score | Total cohort | Lambda dominant | Kappa-lambda codominant | P value |
|------------------|------------------|------------------|------------------|------------------|
| Overall | 234 | 96 (41.0) | 138 (59.0) | 0.161 |
| M, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| M0 | 115 (50.2) | 41 (44.1) | 74 (54.4) |
| M1 | 114 (49.8) | 52 (55.9) | 62 (45.6) |
| Missing | 5 | 3 | 2 |
| E, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| E0 | 132 (57.6) | 46 (48.9) | 86 (63.7) |
| E1 | 97 (42.4) | 48 (51.1) | 49 (36.3) |
| Missing | 5 | 2 | 3 |
| S, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| S0 | 75 (32.5) | 26 (27.7) | 49 (35.8) |
| S1 | 156 (67.5) | 68 (72.3) | 88 (64.2) |
| Missing | 3 | 2 | 1 |
| T, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| T0 | 143 (62.2) | 60 (63.8) | 83 (61.0) |
| T1 | 60 (26.1) | 22 (23.4) | 38 (27.9) |
| T2 | 27 (11.7) | 12 (12.8) | 15 (11.0) |
| Missing | 4 | 2 | 2 |
| C0, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| C0 | 125 (54.6) | 48 (52.2) | 77 (56.2) |
| C1 | 67 (38.0) | 38 (41.3) | 49 (35.8) |
| C2 | 17 (7.4) | 6 (6.5) | 11 (8.0) |
| Missing | 5 | 4 | 1 |
| IgG intensity, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| 0–0.5 | 166 (71.9) | 59 (62.8) | 107 (78.1) |
| 1–1.5 | 43 (18.6) | 26 (27.7) | 17 (12.4) |
| 2+ | 22 (9.5) | 9 (9.6) | 13 (9.5) |
| Missing | 3 | 2 | 1 |
| C3 intensity, N (%) | 0.161 | 0.037 | 0.25 | 0.722 | 0.878 | 0.012 |
| 0–0.5 | 48 (20.6) | 16 (16.7) | 32 (23.4) |
| 1–1.5 | 57 (24.5) | 26 (27.1) | 31 (22.6) |
| 2+ | 128 (54.9) | 54 (56.2) | 74 (54.0) |
| Missing | 1 | 0 | 1 |

*C* score represents total crescents (cellular, fibrous, and fibrocellular). 
*P* values from *χ*² test.
patients with IgAN, Katafuchi et al.\textsuperscript{25} did not find any difference in renal survival among patients with monotypic, lambda dominant, or polytypic light chain deposition. Contrary to our findings, they did not detect any significant differences in histologic disease activity among the different groups with respect to M, E, S, and T scores. Regarding baseline patient characteristics, the LD group in their study had the highest median UPCR at 1 g/g and had a significantly greater degree of proteinuria in comparison to the kappa monotypic group. However, the study of Katafuchi et al.\textsuperscript{25} and ours differ in several respects. The study by Katafuchi et al.\textsuperscript{25} was a single-center cohort from Japan, as opposed to the multicenter, international, multiethnic (but predominantly White) CureGN cohort. Ethnic differences in IgAN severity and prognosis have previously been reported.\textsuperscript{26} The 2 studies differ also in the categorization of patients based on the light chain predominance with 5 groups in the Japanese study versus initially 3 groups in our study. Katafuchi et al.\textsuperscript{25} defined lambda dominance for patients with at least a 2+ difference in IF intensity between lambda and kappa, as opposed to the difference of 1+ in our study. Nevertheless, our 2 study findings overall suggest a trend toward more proteinuria in patients with lambda predominant light chain deposition, but no significant difference in other measures of disease severity or outcomes.

Our analyses suggested greater degree of endocapillary hypercellularity and a higher intensity of IgG staining in the LD compared with the KL groups with detailed histopathologic review. Previous studies have revealed an increased likelihood of receiving immunosuppression if endocapillary hypercellularity is present and an improved renal survival with immunosuppression.\textsuperscript{2,27} The intensity of IgG staining has also been previously linked with greater histologic disease activity and possibly worse prognosis.\textsuperscript{28,29} Previous data have revealed that IgG antibodies targeting galactose-deficient IgA1 can cause macrophage activation and glomerular injury, including complement activation and further kidney injury.\textsuperscript{30,31} More recently, studies have highlighted the role of the complement in kidney injury in patients with IgAN. Specifically, the alternative pathway and mannose-binding lectin pathway of complement activation have been implicated in the development of nephritis. Regarding the alternative pathway, dysregulation related to abnormalities with complement factor H has been described.\textsuperscript{32} It is known that IgA itself is a poor activator of the complement, but polymeric IgA bound in immune complexes can influence complement activation, although the mechanism of activation is not well understood.\textsuperscript{32} Mouse models of IgAN have found complement activation and inflammation in the presence of immune complexes that consisted of human IgG specific for galactose-deficient IgA1.\textsuperscript{33} These studies reveal the important role of IgG in the development of kidney injury and potentially its impact in sustaining ongoing inflammation; this may be the etiology of the increased endocapillary cellularity in the lambda predominant group. In our study, despite the association of lambda predominance with 2 factors previously linked with worse clinical prognosis, we did not find a difference in clinical outcomes between patients in the LD compared with the KL groups.

These findings are in contrast with a recent study by Zhang et al.\textsuperscript{34} who found that lambda restriction in mesangial deposits in patients with IgAN was associated with a worse eGFR within 6 years of follow-up. Furthermore, they found that lambda restriction was associated with increased systemic inflammation characterized by higher serum fibrinogen levels and increased histopathologic disease activity characterized by formation of crescents. Direct comparison between our study and that by Zhang et al.\textsuperscript{34} is difficult given they reported on a single-center experience among Chinese patients with lambda restriction (no kappa light chain staining) as opposed to lambda dominance (kappa staining present). However, taken in conjunction with our findings of increased endocapillary hypercellularity in patients with lambda dominance, the findings of Zhang et al.\textsuperscript{34} of increased number of crescents and worse kidney prognosis with lambda restriction support the possibility that lambda light chains may have increased pathogenicity in IgAN.

**Strengths and Limitations**

Strengths of this study include the relatively large size of the cohort from multiple health care centers, consistency in MEST score reporting as they were scored by the same group of expert CureGN pathologists, and duration of follow-up. There are limitations of this study. Using a difference of 1+ in IF staining intensity may not represent true predominance in all cases given semiquantitative nature of IF scoring. However, using the same criterion, we found a marked difference in lambda predominance between the CureGN patients with IgAN and those with membranous nephropathy, with a kappa light chain predominance in the latter group. Although CureGN is a prospective cohort study with protocolized data capture, the data derived from the period between biopsy and enrollment were acquired retrospectively. Our analyses of kidney function outcomes are limited by the relatively short duration of follow-up. The robustness of our results is diminished by multiple testing and the absence of replication in an independent cohort.
Predominant lambda light chain glomerular deposition in IgAN maybe associated with greater histologic disease activity, revealed by increased endocapillary hypercellularity. However, we did not find an association of lambda predominance with a doubling of serum creatinine or progression to ESKD. These results would need confirmation in a larger cohort and longer follow-up. Further studies are needed to elucidate whether the predominance of lambda chains represents a unique pathogenesis related to mucosal and gut-associated lymphoid tissue in a subset of patients.

APPENDIX

List of CureGN Collaborators

The CureGN Consortium members listed subsequently, from within the 4 participating clinical center networks and data coordinating center, are acknowledged by the authors as collaborators. **CureGN Principal Investigators; *CureGN Site Principal Investigators; #CureGN Lead Coordinators.

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DISCLOSURE
All authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Table S1. Light chain staining intensity score distribution in the lambda dominant and kappa-lambda codominant groups in the cohort of 518 patients with IgAN or IgAV.
Table S2. IgG and C3 staining intensity score distribution in the cohort of 518 patients with IgAN or IgAV.
Table S3. Additional histopathologic findings by light chain deposition type.

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