Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry

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The goal of this study was to investigate the frequency of use of light-chain variable region (IGVL) genes among patients with systemic (ALS) and localized (ALL) amyloidosis and to assess for associations between IGVL gene usage and organ tropism. We evaluated clinic charts from 821 AL patients seen at the Mayo Clinic who had bone marrow, fat pad, and solid organ tissue samples typed by liquid chromatography tandem mass spectrometry (LC-MS). We identified 701 patients with ALs and 120 with ALs. Overall, we were able to identify an IGVL gene in 87 (72%) patients with ALs and 573 (82%) patients with ALs. When compared with ALs, LV6-57 was more common, whereas KV3-20 and heavy-chain codeposition were less common in ALs. In this large series of ALs, characteristics specific to specific genotypes became apparent. LV6-57 patients were more likely to have renal involvement and to harbor a translocation 11;14. LV3-01 patients were less likely to have advanced cardiac disease and renal involvement. LV2-14 patients were more likely to have peripheral nerve involvement, an intact circulating immunoglobulin, and lower circulating dFLC. LV1-44 patients were more likely to have cardiac involvement. KV1-33 patients had more liver involvement and higher circulating dFLC. Finally, KV1-05 was associated with inferior overall survival but not independently of cardiac stage. IGVL gene usage appears to provide clues about disease pathophysiology and tissue tropism. LC-MS is a high-throughput and low-resource technique that can be used to identify IGVL gene from clinical tissue specimens. (Blood. 2017;129(3):299-306)

Introduction

Systemic immunoglobulin light-chain amyloidosis (ALS) is the most common form of systemic amyloidosis, and despite significant advances in the field, it remains a fatal disease with a worse prognosis compared with that of multiple myeloma.1,2 ALs is caused by the progressive deposition of structurally unstable, clonal immunoglobulin light chains that form systemic amyloid deposits. Outcomes of patients with AL amyloidosis are primarily dictated by the type and extent of organ involvement, especially cardiac involvement.2 Little is known about what regulates organ tropism in this disease.

Sometimes, amyloid deposition may be localized to the site of amyloid precursor protein production by a neoplastic plasma cell clone. These patients are labeled as having localized AL amyloidosis (ALs) and have a much better prognosis because vital organs like heart, liver, and kidney are not compromised. These patients do not require systemic treatment of their AL amyloidosis. For these reasons, accurate distinction between the two is very important.

In an effort to elucidate mechanisms of organ tropism in ALs, prior authors hypothesized that organ tropism may be a function of light-chain variable region (IGVL) gene and gene family of the clone.4,9 These contributions have been seminal because they helped establish important trends in IGVL gene rearrangements that confer a higher risk for specific organ involvement. These studies involved a small number of patients because they relied on the use of time-consuming, polymerase chain reaction–based sequencing of bone marrow plasma cells to identify IGVL genes and have not been translated to the clinical practice because of complexity of the analytical process.

We have established a proteomics-based clinical assay for identifying amyloid types using clinical tissue sample proteomic analysis by liquid chromatography/tandem mass spectrometry (LC-MS).10-12 This method has been in routine use in a CAP/CLIA-compliant clinical laboratory in our institution since 2008. This method was expanded to identify clonotypic peptides from AL deposits and identify the IGVL gene and gene family with 100% specificity.13 Here we apply this methodology in the largest cohort of patients with ALs and ALs in an effort to definitively characterize the relationship between the IGVL gene repertoire and organ tropism in this disease. We propose that the ability to identify the amyloidogenic clone directly from clinical tissue specimens using a proteomics-based methodology is a novel and potentially powerful clinical and research tool.

The online version of this article contains a data supplement.
Methods

Patient population and clinical data

We included patients with AL<sub>L</sub> and AL<sub>S</sub> seen at the Mayo Clinic between August of 1991 and July of 2013. The Mayo Foundation Institutional Review Board approved the study and only patients who consented to having their medical records reviewed for research purposes were included. The diagnosis of AL amyloidosis was based on the presence of a biopsy specimen that stained positive by Congo red and exhibited green birefringence under polarized light and was documented to be AL amyloidosis by typing with LC-MS. Individual patients’ records were reviewed to abstract clinical organ involvement and systemic vs localized involvement. Patients without a circulating monocalonal protein (detected by immunofixation of serum and urine and serum-free light-chain assay), a bone marrow without clonal plasma cells (detected by immunohistochemistry and/or flow cytometry), and a fat aspirate negative for Congo red–positive deposits were classified as AL<sub>L</sub>. Further tests to rule out systemic organ involvement in suspected AL<sub>S</sub> were done as clinically indicated. Organ involvement for AL<sub>S</sub> was defined using established criteria. All patients with cardiac involvement had either a positive endomyocardial biopsy or a suggestive echocardiographic picture in addition to elevation of at least one cardiac biomarker (ie, B-type natriuretic peptide [BNP], N-terminal pro B-type natriuretic peptide [NTproBNP], or troponin). No patient without biopsy-confirmed cardiac involvement had normal cardiac biomarkers. Isolated cardiac or renal involvement was defined as isolated involvement of only the heart or kidneys, respectively, without other organs being clinically involved. Accurate abstraction of absence of organ involvement was not possible for some patients based on the limited information provided in their medical records, leaving 679 (97%) patients with cardiac involvement and 664 (95%) patients with renal involvement evaluable for these analyses. Extent of cardiac involvement was graded according to the Mayo 2004 staging system, which defines stage I as troponin T <0.035 ng/mL and NT-proBNP <332 ng/mL, stage III as both biomarkers equal to or above the respective thresholds, and stage II as either biomarker equal to or above the respective thresholds. Extent of renal involvement was graded according to the recently published renal staging system.

Identification of immunoglobulin variable region gene usage and heavy-chain codeposition

The proteomics method for amyloid typing has been previously described both for solid tissue specimens and fat aspirates. Briefly, for patients with solid tissue specimens, laser microdissection (LMD) was performed on 3 to 4 Congo red–positive areas of formalin-fixed paraffin-embedded tissue blocks. The dissected tissue was digested into tryptic peptides and analyzed by LC-MS. For each fat aspirate specimen, 3 to 4 spicules were individually solubilized and digested in trypsin without undergoing LMD. Tandem MS spectra present in each sample’s raw file were identified with 3 different database search engines: Sequest, X!Tandem, and Mascot, all of which had been augmented with known protein sequences from human IGVL genes and families. The method for identifying IGVL gene was validated in an independent population (n = 30) by comparing it with mRNA sequencing performed on bone marrow samples, and it was found to be 100% specific.

All peptides identified from a patient’s sample were combined and filtered using the Scaffold software (Proteome Software, Portland, OR). Peptide identifications were accepted if they could be established with a >95% probability, at a 90% confidence interval. A spectral counting approach was used, and a count ±5 was considered to be clinically significant. For every case, we created a proteomics profile that lists all of the confident protein identifications present in each sample along with their respective spectral counts. The IGVL gene was identified based on abundance of spectral counts.

We also considered the presence or absence of heavy chains in tissue specimens. Because we do not have a robust method to identify contamination of samples by serum immunoglobulins, we excluded all IgG-class immunoglobulins for all heavy-chain analyses because these are found in high concentrations in human serum. We included all detectable IgM, IgA, and IgD types. Furthermore, because our sequence libraries are not enriched to allow identification of IGH variable genes, we only examined IGH as a dichotomous variable based on the presence or absence of IGH-constant regions in amyloid specimens.

Statistical analysis

The Fisher exact test and the Kruskal-Wallis test were used to ascertain differences between categorical and continuous variables, respectively. For gene groups that contained at least 30 patients, differences between those with and without the gene were sought for multiple characteristics including: presence or absence of organ involvement, plasma cell clone characteristics (dFLC, bone marrow plasma cells, fluorescence in situ hybridization [FISH]/cytogenetics), and differences in markers of organ damage (proteinuria, cardiac stage, renal stage). P values <.01 were considered significant to correct for multiple comparisons. P values between .01 and .05 were noted to be possible trends and worthy of future exploration with larger sample sizes of patients. Overall survival (OS) from diagnosis was calculated using the Kaplan-Meier method. All statistics were done using JMP software (SAS, Cary, NC).

Results

IGVL gene distribution and heavy-chain codeposition in AL<sub>L</sub> and AL<sub>S</sub>

The patients’ baseline characteristics for AL<sub>S</sub> and AL<sub>L</sub> are shown in Table 1. We identified 120 patients with AL<sub>S</sub> and 701 patients with...
Cardiac involvement was very prevalent and was present in 66% of patients. In spite of this, the likelihood of cardiac involvement was particularly high among patients with certain genes: 92% for patients with LV3-19 and 92% for patients with KV1-05 (Figure 2). However, these genes were identified in only 2% of ALs cases. The rate of cardiac involvement for patients with these genes and with LV1-44 (Table 2) compare to those without and were as follows: LV3-19 (92% vs 65%, \( P = .02 \)), KV1-05 (92% vs 65%, \( P = .03 \)), and LV1-44 (80% vs 65%, \( P = .03 \); Table 2). IGH deposition was not different between patients with and without renal involvement. When examining the 78 patients with and without isolated renal involvement, no significant difference in IGVL gene usage or heavy-chain codeposition was found.

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When considering organs other than heart and kidneys, there was a trend for patients with LV2-14 to have a higher rate of peripheral neuropathy (Table 2). KV1-33 was more likely to be associated with cardiac involvement and 664 (95%) to ascertain presence or absence of cardiac involvement and 664 (95%) to ascertain presence or absence of renal involvement.

Not surprisingly, renal involvement was more common in patients with LV6-57 compared with those without, and was less common in patients with LV3-21 compared with those without (Table 2). When considering less common genes, KV1-05 patients had a trend toward less renal involvement compared with those without: 18% vs 53%, \( P = .02 \). IGH deposition was not different between patients with and without renal involvement. When examining the 78 patients with and without isolated renal involvement, no significant difference in IGVL gene usage or heavy-chain codeposition was found.

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When considering organs other than heart and kidneys, there was a trend for patients with LV2-14 to have a higher rate of peripheral neuropathy (Table 2). KV1-33 was more likely to be associated with liver involvement and less likely to be associated with peripheral nerve involvement (Table 2).

Among the 120 patients with ALs, LV2-14 was overrepresented in those with gastrointestinal involvement (Table 3), but otherwise no
other statistically significant relationships were identified including non-IgG heavy-chain codeposition.

**IGVL association with amyloidogenicity and plasma cell clone characteristics**

Among other variables, we examined whether there were any differences in baseline dFLC levels according to IGVL gene, hypothesizing that more amyloidogenic clones could cause clinical organ involvement at lower dFLC levels compared with less amyloidogenic ones. Of 701 ALS patients, 463 (66%) had dFLC levels available at diagnosis. Finally, because bone marrow FISH has been associated with organ involvement and prognosis in ALS,18-20 we examined whether there was any differential IGVL gene usage according to bone marrow FISH.

Patients with KV1-33 were more likely to have higher and patients with LV2-14 lower baseline dFLC levels, respectively, compared with

<table>
<thead>
<tr>
<th>Gene</th>
<th>Organ involvement</th>
<th>dFLC levels/amyloidogenicity</th>
<th>Organ toxicity</th>
<th>FISH abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV6-57</td>
<td>Renal involvement</td>
<td>24-h urine protein &gt;5 g 56% vs 34%, P = .001</td>
<td>No differences</td>
<td>Trisomies 9.5% vs 22%, P &lt; .05</td>
</tr>
<tr>
<td>LV3-01</td>
<td>Renal involvement</td>
<td>Mayo stage III, 26% vs 43%, P = .023</td>
<td>No differences</td>
<td>No differences</td>
</tr>
<tr>
<td>LV2-14</td>
<td>Peripheral nerve involvement</td>
<td>dFLC 9.47 vs 24.5 mg/dL, P = .025</td>
<td>No differences</td>
<td>No differences</td>
</tr>
<tr>
<td>LV1-44</td>
<td>Liver involvement</td>
<td>dFLC 64.8 mg/dL vs 22.2 mg/dL, P &lt; .02</td>
<td>No differences</td>
<td>No differences</td>
</tr>
<tr>
<td>LV3-21</td>
<td>Renal involvement</td>
<td>Trisomies 4% vs 22%, P &lt; .05</td>
<td>No differences</td>
<td>No differences</td>
</tr>
</tbody>
</table>

**Figure 2. Cardiac and renal involvement according to immunoglobulin variable region gene usage.** Other ß2: includes rare ß genes (KV2-28, 30, 38, KV3-01, 07, 11, KV6-21, rare KV1 excluded); rare ß genes (LV1-01, 36, 52, 57, LV2-08, 11, 18, LV3-09, 10, 20, 25, LV4-60, 69, and LV10-54); cases where only family could be determined (n = 39); and cases that no gene or family could be determined (n = 77); KV1-other: includes rare KV1-genes (KV1-02, 06, 08, 09, 12, 13, 17 and 27). P = nonsignificant across groups within patients with cardiac involvement. P < .0001 across gene groups within patients with renal involvement. C, cardiac; R, renal.
patients without these IGVL genes (Table 2). Patients with a LV2-14-producing clone were also more likely to have an intact circulating immunoglobulin (Table 2). There were no differences in IGVL gene usage between patients with very low dFLC levels (<5 mg/dL) and patients with dFLC (≥5 mg/dL).

We noted that patients with LV6-57 were more likely to have more advanced renal disease (24-hour urine protein >5 gr) independently of baseline dFLC levels (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.2-5.4; P = .02). Patients with LV3-08 had a trend toward lower (OR 2.6, 95% CI 1.1-6.6; P = .03) and patients with KV1-05 had a trend toward higher (OR 4.4, 95% CI 1.03-30; P = .045) rates of stage III cardiac disease, respectively, an effect independent of baseline dFLC levels.

There was a trend for patients with LV6 to be more likely to harbor the t(11;14) translocation and less likely to harbor trisomies. When considering patients with LV1-44, trisomies appeared to be less common (Table 2). Finally, LV3-21 patients had a trend of higher bone marrow plasmacytosis and higher frequency of monosomy 13 (Table 2).

**IGVL and overall survival**

We performed limited exploratory analyses evaluating IGVL usage and OS mostly because we felt we there were a lot of missing data to draw safe conclusions in regards to OS, which is influenced by several factors we were not able to accurately capture in this study (hematologic response, organ response, host factors, delayed diagnosis). Of 701 patients with ALs, first-line treatment data were available for 385 (55%) patients, hematologic response to first-line treatment was available for 361 (51%) patients, and only 103 (23%) patients with cardiac involvement and 143 (40%) patients with renal involvement had at least 12 months of follow-up for organ response.

Only KV1-05 appeared to be associated with a decreased OS compared with patients harboring other IGVL genes; median survival 12 months vs 59 months, P = .003 (supplemental Figure 1, available on the Blood Web site). This effect, however, was not independent of cardiac stage on a multivariate model including KV1-05, IGVL type and cardiac stage.

**Discussion**

This is the largest study to date reporting on IGVL gene and family usage in patients with systemic and localized AL amyloidosis. For the first time, we demonstrate that IGVL gene usage is different between ALs and AL4, and that non-IgG heavy-chain deposition is more common in AL4 compared with ALs. We identify new potential predilections for IGVL gene usage in ALs patients with cardiac, renal, and hepatic involvement, and AL4 patients with gastrointestinal involvement. Finally, we identify new clones that are more likely to be associated with different levels of organ damage in ALs.

Figure 3 provides a comparison between our results and those that have been published in the literature, and those that can be found in AL Base. Of the 29 to 33 functional IGV λ genes and the 31 to 36 functional IGV κ genes in the human genomic repertoire, consistent with previous publications, LV6-57 is the most common IGVL gene identified among patients with ALs. Approximately one half of the light-chain variable gene repertoire in ALs is comprised of LV6-57, LV3-01, and LV2-14 genes and the KV1 family (particular KV1-33). Not only are these genes the most commonly observed in ALs, but they and their gene families are also conspicuously more common in ALs than in the normal B-repertoire. In contrast, the distribution of IGVL genes and families for patients with AL4, was very similar to that seen in the normal B-cell repertoire, with LV6 found less commonly and the KV3 family (and the KV3-20 gene in particular) more commonly. The potential mechanisms underlying the differences between IGVL gene usage in ALs and AL4, nonamyloidogenic plasma cell dyscrasias, and normal controls are not clear. In the case of AL4, the bias of IgV gene usage might be explained by different antigenic stimuli. AL4 is often associated with autoimmune diseases and lymphoproliferative disorders that may be autoimmune driven (ie, MALT lymphomas).

When considering patients with cardiac involvement, some of our results are consistent with those of Perfetti and colleagues. We also found a greater than twofold higher rate of cardiac involvement among patients with LV1-44. In their study of 99 patients with ALs, Perfetti and colleagues observed trends for a lower risk for patients with LV3-01 and LV6-57 to have “dominant” cardiac involvement. In our study, rates of cardiac involvement for these two genotypes were no different from those found in other genotypes, but patients with LV3-01 were more likely to have less severe cardiac involvement by Mayo stage. Our study also revealed provocative trends among cardiac patients that will need to be reproduced in larger cohorts. For example, >90% of patients with KV1-05 and LV3-19 had cardiac involvement; the significance of this finding is tempered by the fact that there were only 16 and 13 patients with these variable genes in our systemic
cohort. KV1-05 was also the only IGVL associated with worse overall survival, although this effect appeared to be dependent on cardiac stage.

In patients with renal involvement, LV6-57 was more commonly encountered, which is similar to prior reports. In addition, our observations that renal involvement was less common in patients with LV3-01 and LV3-21 are novel. Furthermore, LV6-57 was associated with higher levels of proteinuria independent of baseline dFLC levels, suggesting that LV6-57 might be more nephrotoxic. LV6-57 was more commonly associated with translocation 11;14, which is the most common FISH abnormality found in AL amyloidosis but also in other monoclonal gammopathies of renal significance and multiple myeloma patients presenting with renal damage.28

Other interesting novel observations included increased and decreased rates of peripheral neuropathy in patients with LV2-14 and KV1-33, respectively. Finally, patients with hepatic involvement have previously been shown to be more commonly κ restricted, although the dominance of KV1-33 is a novel finding in our study.

In general, the KV1 family appeared to be less amyloidogenic in vivo, because it required higher levels of circulating free light chains (ie, dFLC) to lead to clinically significant organ involvement. This has been supported by biophysical experiments. In contrast, some of the increased amyloidogenicity seen with LV2-14 could be attributed to the higher burden of nonconservative mutations—which have been associated with increased amyloidogenicity—within the λ family. Our results regarding extent of organ involvement and IGVL amyloidogenicity are novel and potentially hypothesis-generating but at the same time exploratory and require further validation.

In our study, heavy chains were more commonly codeposited in ALλ. Furthermore, our study probably underestimated the codeposition of IGH in ALλ, because we had to exclude all IgG-class IGH for the lack of a robust mechanism to exclude sample contamination by serum IgG. Nonetheless, IGH codeposition has been noted in both ALλ and ALκ in the past. It needs to be noted, however, that we could not identify the variable heavy-chain region in codeposited IGH, and therefore we could not differentiate between monoclonal or polyclonal IGH deposits. The fact that in most ALκ patients the heavy chain isolated in the amyloid deposits was also detected in the serum suggests that a systemic deposition mechanism exists at least for the IgM and IgA immunoglobulin subclasses in ALκ.

Our results suggest that the IGVL gene and family restriction is only part of the puzzle that constitutes clinical organ tropism and amyloid toxicity. Other, yet unidentified, factors, either intrinsic to the structure of the light-chain protein or related to the microenvironment of the amyloid plaque, as well as the composition of the codeposited proteins within the amyloid plaque itself, have also been postulated to play a role and should be the focus of future research.

Limitations of our study include the small number of patients harboring specific IGVL clones, which limits the power of some of our observations. Furthermore, there is still room for improvement in terms of the sensitivity of this assay, which will improve as our IGVL sequence template libraries and peptide identification algorithms improve. The number of cases included in this study is proven to be powerful enough to uncover significant trends, but further study will be required. Extent of organ involvement and amyloid toxicity is a function of other factors in addition to baseline dFLC, which could not always be captured with accuracy in this retrospective study (delay in diagnosis, host factors). Finally, we did not perform comprehensive OS or any organ response analyses primarily because of missing data. Furthermore, organ response and survival are influenced by several variables that we were not able to accurately capture in this retrospective study (eg, depth and especially duration of hematologic response, host factors, disease stage at presentation). Some of these exploratory analyses have been published in abstract form and no association was found.39

Strengths of the study include the size of the cohort, the inclusion of a large number of ALλ patients, as well as the methodology itself, which is a fast and inexpensive method to evaluate IGVL genes from data already generated as part of the clinical typing assay.

In conclusion, we have clarified IGVL gene and family usage in a large cohort of patients with systemic and localized AL amyloidosis, using a novel methodology that relies on MS of clinical tissue
specimens. We show for the first time that IGVL gene and family repertoire is different between ALs and ALd. Our data show that IGVL gene family usage does not entirely explain clinical organ tropism, but they can provide a platform upon which future research exploring how other aspects of the amyloid proteome relate to organ tropism and clinical outcome. Moreover, our observations about propensity of certain genes being more amyloidogenic and associated with particular presentations could have direct clinical implications, especially as the methodology for top down sequencing of circulating monoclonal proteins moves into the mainstream. For example, individuals with an apparent monoclonal gammopathy of undetermined significance with KV3 gene usage are unlikely to have or develop ALs, in contrast, patients with LV6-57 monoclonal gammopathy should be comprehensively evaluated for ALs and followed closely, because LV6-57 is more common in ALs than in the normal B-cell repertoire. In this fashion, the results presented in this study could be applied in ALs prevention, a major bottleneck in improving patient outcomes.40

Authorship

Contribution: T.V.K., S.D., P.J.K., and A.D. conceived and designed the study; T.V.K., S.D., and A.D. analyzed and interpreted data; and all authors provided study materials of patients, collected and assembled data, and wrote and gave final approval of the manuscript.
Conflict-of-interest disclosure: The authors declare no competing financial interests.
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