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Complementary DNA sequence of human amyloidogenic immunoglobulin light-chain precursors

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The primary structure of three amyloid precursor light chains was deduced from the sequence of complementary DNA (cDNA) from bone marrow cells from patients affected with classical λ (patient Air) or κ (patient Arn) amyloidosis and from a patient (Aub) in whom λ amyloid deposits were unusual by their perimembranous location in the kidney glomerulus. All three RNAs were of normal size, as estimated by Northern blotting, and encoded normal-sized light chains. The deduced light-chain sequence from patient Arn was related to the $V_{\kappa 1}$ subgroup, and included ten residues that had not been previously reported at these positions, only one of which (Leu-21) was located in a β -sheet (4-2). The unusual presence of Asn-70 determined a potential *N*-glycosylation site. The sequence of the light chain from patient Air belonged to the $V_{\lambda 1}$ subgroup, and included three unusually located amino acid residues, one of which had already been reported in an amyloidogenic λ -chain. The sequence of the light chain from patient Aub was related to the $V_{\lambda 3}$ subgroup, and contained five amino acid residues that had not previously been described at the corresponding positions; two of them (His-36 and Ser-77) were located in β -sheets (3-1 and 4-3 respectively). This sequence was also peculiar because of the presence of numerous acidic residues in the complementarity-determining regions. Such unusual primary structures might be responsible for the amyloidogenic properties of these light-chain precursors.

INTRODUCTION

The propensity of certain proteins to form fibrillar insoluble extracellular deposits in tissues leads to amyloidosis, a severe disease which often affects multiple organs (Glennner, 1980; Stone, 1990). A variety of amyloidogenic precursors of different origins have been identified; a common structural property is their predominant β -pleated sheet conformation, which is responsible for the general structural organization of amyloid fibrils.

Monoclonal immunoglobulin light chains are responsible for amyloid light chain (AL)-type amyloidosis. In more than 80% of cases of AL primary amyloidosis, a monoclonal light chain can be detected by sensitive methods in the patient's urine and/or serum (Gertz & Kyle, 1989), and in every case careful study of the bone marrow cells demonstrates a significant monoclonal plasma cell population (Buxbaum, 1986; Preud'homme *et al.*, 1988). Proof of the relationship between plasma cell-secreted and tissue-deposited monoclonal light chains has long been established (Glennner *et al.*, 1971). Several observations suggest that structural peculiarities of the precursor light chain may play a critical role in the pathogenesis of AL amyloidosis: the λ isotype (especially $C_{\lambda 3}$) is largely over-represented (Walker *et al.*, 1988; Gertz & Kyle, 1990), as is the rare $V_{\lambda 6}$ variability subgroup (Solomon *et al.*, 1982), and aberrant immunoglobulin biosynthesis patterns were found in bone marrow cells from patients with primary or myeloma amyloidosis (Buxbaum, 1986; Preud'homme *et al.*, 1988).

Although complete primary structures of several AL-type amyloid fibrils have been published in the last decade (Sletten *et al.*, 1981; Eulitz & Linke, 1985; Toft *et al.*, 1985; Tveteraas *et al.*, 1985; Dwulet *et al.*, 1985, 1986; Holm *et al.*, 1986;

Benson *et al.*, 1989; Liepnieks *et al.*, 1990), no specific common sequence could be identified. Unusual structural features of light chains include *N*-glycosylation (Toft *et al.*, 1985; Tveteraas *et al.*, 1985; Dwulet *et al.*, 1986; Holm *et al.*, 1986), the presence of numerous hydrophobic residues (Dwulet *et al.*, 1986) and insertion of acidic amino acids (Sletten *et al.*, 1981). However, these findings do not provide a general explanation for the mechanisms of AL amyloid fibril formation.

Since most amyloid fibrils mainly contain light-chain fragments, often with a length heterogeneity, relevant information might be better obtained from a knowledge of complete structures of amyloidogenic precursor proteins. Only a small number of circulating light-chain amyloid precursors have been studied so far at the molecular level; the three completely determined sequences belonged to the $V_{\lambda 1}$ subgroup (Takahashi *et al.*, 1980; Tonoike *et al.*, 1985; Eulitz *et al.*, 1987). Further study of a number of amyloid light chains hence would appear to be potentially useful. Large-scale studies are hardly feasible at the protein level and a cDNA cloning strategy would appear to be more suitable. We present the complete primary structures, deduced from cDNA sequences, of one κ and two λ amyloid light-chain precursors; one of the latter was associated with an unusual form of AL-type amyloidosis featuring an unusual location of kidney deposits.

MATERIALS AND METHODS

Cell samples

Bone marrow cells were collected by aspiration from three patients with AL-type amyloidosis. After sedimentation in 0.8% gelatin for 30 min at 37 °C, a sample was analysed by immunofluorescence with specific anti-immunoglobulin heavy and light

Abbreviations used: PBS, phosphate-buffered saline; AL, amyloid light chain; FR, framework region; CDR, complementarity-determining region.

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The nucleotide sequences for *Homo sapiens* mRNA for IG V_{λ} -J λ rearranged gene (Aub), *H. sapiens* mRNA for IG V_{κ} -J κ gene (Arn) and *H. sapiens* mRNA for IG V_{λ} -J λ rearranged gene (Air) will appear in the EMBL, Genbank and DDBJ Nucleotide Sequence Databases under the accession numbers X64132, X64133 and X64134 respectively.

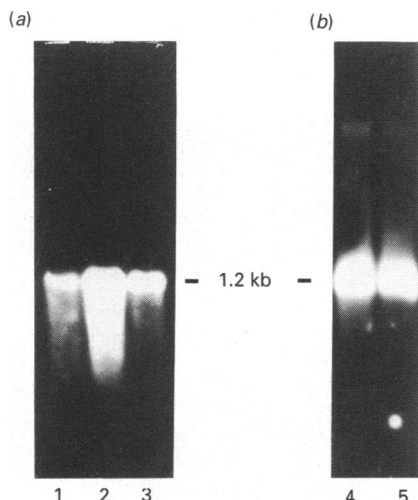


Fig. 1. Northern blot analysis of RNA (5 µg per lane) extracted from bone marrow cells of AL-amyloidosis patients

(a) Blot was hybridized with a C_{λ_2} probe; (b) blot hybridized with a C_{κ} probe. Lane 1, Burkitt's lymphoma cell line Ly67 producing a normal-sized (1.2 kb) λ -chain mRNA (control); lane 2, RNA from patient Air; lane 3, RNA from patient Aub; lane 4, Burkitt's lymphoma cell line JI producing a normal-sized κ -chain; lane 5, RNA from patient Arn.

chain antibodies; the remainder was used for RNA extraction. Bone marrow from patient Arn contained 9% monoclonal plasma cells with intracytoplasmic κ chain and no detectable heavy chain, in the absence of clinical evidence of myeloma; a κ -type Bence-Jones protein was detected in the urine. Patient Air presented with Waldenstrom's macroglobulinaemia; bone marrow smears showed a lymphoplasmacytic proliferation including 3% plasma cells containing an IgM(λ) which was present in the serum. Small amounts of urinary free λ chains were also detectable. Patient Aub had 3% bone marrow plasma cells stained by anti- α and anti- λ fluorescent antibodies; a monoclonal IgA(λ) was found in the serum and a λ -type Bence-Jones protein in the urine. In all three patients pathological, immunofluorescent and ultrastructural studies of kidney biopsy specimens showed typical fibrillar deposits stained by Congo Red, thioflavine T and anti- κ (Arn) or anti- λ (Air and Aub) antibodies. In patient Aub, glomerular deposits predominantly involved the epithelial aspect of the capillary walls.

RNA preparations

Cells from the patients' bone marrow were washed with 0.01 M-phosphate-buffered saline, pH 7.4 (PBS; 0.15 M-NaCl) and lysed in 4 M-guanidine isothiocyanate. After a 30 s homogenization with a blender, total RNA was separated by ultracentrifugation for 18 h at 170 000 g on 5.7 M-caesium chloride. Northern blot analyses were performed by electrophoresis on 1% agarose/20 mM-Mops/5 mM-sodium acetate/1 mM-EDTA/0.7 M-formaldehyde gels, transfer on to Nylon sheets and hybridization with appropriate DNA probes (Davies *et al.*, 1986): The κ probe was a 2.5 kb *EcoRI* genomic fragment including the entire constant-region exon; the λ probe was a 3.5 kb *EcoRI/HindIII* fragment containing the C_{λ_2} exon (Cogné *et al.*, 1991). Northern blots were also hybridized with heavy chain constant-region probes to evaluate the relative amount of RNA from polyclonal immunoglobulin-secreting cells: the C_{γ} probe was a 1.5 kb *PstI* fragment of the C_{γ_1} gene segment including the hinge, CH_2 and CH_3 exons (Cogné *et al.*, 1991); the



Fig. 2. cDNA sequence of the variable region of the amyloidogenic monoclonal κ -chain from patient Arn

Translation is indicated below the nucleotide sequence. Numbering is according to Kabat *et al.* (1987). The sequence of the constant segment corresponded to a normal Km(3) allele (not shown). Codons corresponding to 5' ends of segments V_{K1} , J_{K5} and C_{κ} are indicated.

C_{α} probe was a 1.2 kb *PstI* genomic fragment containing the 3' end of CH_1 , the CH_2 and 5' part of CH_3 exons (Cogné & Preud'homme, 1990).

Poly(A) mRNA was isolated from total RNA preparations by affinity chromatography on oligo(dT)-cellulose (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions.

cDNA cloning and sequencing

cDNA libraries were constructed using standard procedures (Davis *et al.*, 1986). Briefly, single-stranded cDNAs were synthesized with reverse transcriptase by extending oligo(dT) primers on poly(A) mRNA from each patient (Amersham International, Amersham, Bucks., U.K.). Double-stranded cDNA was obtained by adding RNAase H and DNA polymerase I and cloned in the λ gt10 vector using *EcoRI* adaptors (Amersham); recombinant phages were screened with the appropriate light-chain probes. All cDNA clones were sequenced on both strands by cloning full-length cDNA and their restriction fragments in mp18 and mp19 M13 vectors. Sites used for subcloning were a *SacI* restriction site in the constant region of the light chain from patient Arn, two *EcoRI* sites in the V-J segment of the light chain from patient Air and two *BamHI* sites in the variable and 3' flanking regions of the light chain from patient Aub. In addition, synthetic primers complementary to the 5' end of the C_{κ} and C_{λ} exons allowed us to obtain sequences overlapping variable-region restriction sites. Sequencing was performed by the dideoxy termination method (Sanger *et al.*, 1977) with T7 polymerase using an automated laser fluorescence DNA sequencer (ALF; Pharmacia).

```

                Leader
                -19
TGAGCGCAGAAGGCAGGACTCGGGACAATCTTCATC  ATG ACC TGC TCC CCT CTC CTC
                Met Thr Cys Ser Pro Leu Leu

                Vλ1 region
                +1
CTC ACC CTT CTC ATT CAC TGC ACA GGG TCC TCG GCC CAG TCT GTG TTG
Leu Thr Leu Leu Ile His Cys Thr Gly Ser Ser Ala Gln Ser Val Leu

                +11
ACG CAG CCG CCC TCA GTG TCT GCG GCC CCA GGA CAG AAA GTC ACC ATC
Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile

                +27 D E
TCC TGC TCT GGA AGC AGC TCC AAC ATT GCG AAT AAT TAT GTA TCC TGG
Ser Cys Ser Gly Ser Ser Asn Ile Ala Asn Asn Tyr Val Ser Trp

                +41
TAC CAG CAA CTC CCA GGA GCA GCC CCC AAA CTC CTC ATC TAT GAA AAT
Tyr Gln Gln Leu Pro Gly Ala Ala Pro Lys Leu Leu Ile Tyr Glu Asn

                +51
GTT AAG CGA CCC TCA GGA ATT CCT GAC CGA TTC TCT GGC TCC AAG TCT
Val Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser

                +61
GGC ACG TCA GCC ACC CTG GGC ATC ACC GGA CTC CAG ACT GGT GAC GAG
Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu

                +71
GCC GAG TAT TAC TGC GGA ACA TGG GAT AGC AGC CTG AGT GGT GTG GAA
Ala Glu Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Ser Gly Val Glu

                Jλ2
                +91
TTC GGC GGA GGG ACC AAG CTG ACC GTC CTA GGT CAG...
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln...

                Cλ2 region

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Fig. 3. cDNA sequence of the variable region of the amyloidogenic monoclonal λ -chain from patient Air

RESULTS

Analyses of total RNA extracted from the patients' bone marrow samples by Northern blotting with light-chain constant-region probes showed essentially normal-sized transcripts of the respective light chain type (Fig. 1). In every case, a study of the cDNA library showed more than 1% of the λ gt10 cDNA clones hybridizing with the corresponding light-chain probe. Identification of the predominant monoclonal light chain was achieved by sequencing different cDNA clones; in two cases (patients Air and Arn) three out of three clones studied were identical. In patient Aub, one cDNA clone out of four appeared to originate from the polyclonal B-cell population. These sequences confirmed the normal size of the three amyloid precursors, and revealed overall normal structures but original substitutions in all cases.

The sequence from patient Arn included a variable segment related to the $V_{\kappa 1}$ subgroup, rearranged with $J_{\kappa 5}$ and a normal C_{κ} segment of the Km(3) allotype (Fig. 2). Comparisons of the deduced peptide sequence with complete $V_{\kappa 1}$ sequences (Kabat *et al.*, 1987) showed ten previously unreported amino acid residues: two in framework region (FR)1 (Gly-18, Leu-21), three in FR2 (Val-40, Glu-42, Met-48), one in complementarity-determining region (CDR)2 (Tyr-53), two in FR3 (Leu-60, Asn-70) and two in CDR3 (Ser-92, Phe-96); the sequence Asn-Tyr-Ser determined a potential *N*-glycosylation site at position +70. Among these residues, only Leu-21 was located in a β -sheet (β -sheet 4-2, Edmundson *et al.*, 1975).

The sequence from patient Air included a $V_{\lambda 1}$ segment rearranged with $J_{\lambda 2}$ and a normal $C_{\lambda 2}$ exon (Fig. 3). Three amino-acids, Val-52 (CDR2), Glu-85 (FR3) and Glu-97 (CDR3), had never been found at the corresponding locations in previously described $V_{\lambda 1}$ sequences; all were located in loops between β -sheets.

The sequence from patient Aub was made up of a $V_{\lambda 3}$, a $J_{\lambda 2}$ and a $C_{\lambda 2}$ segment (Fig. 4). It included five amino acid residues

```

                Leader
                -19
GGAAGCAGCACTGGTGGTGCCTCAGCC  ATG GCC TGG ACC GTT CTC CTC
                Met Ala Trp Thr Val Leu Leu

                Vλ3 region
                +1
CTC GGC CTC CTC TCT CAC TGC ACA GGC TCT GTG ACC TCC TAT GTG GTG
Leu Gly Leu Leu Ser His Cys Thr Gly Ser Val Thr Ser Tyr Val Val

                +11
ACT CAG CCA CCC TCG GTG TCA GTG GCC CCA GGA CAG ACG GCC AGG ATT
Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile

                +21
ACC TGT GGC GGA AAC AAC ATT GGA AGT GAC AGT GTG CAT TGG CAC CAG
Thr Cys Gly Gly Asn Asn Ile Gly Ser Asp Ser Val His Trp His Gln

                +31
CAG AAG TCA GGC CAG GCC CCT GTG CTG GTC ATC TAT GAT GAT AGC GAC
Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr Asp Asp Ser Asp

                +41
CGG CCC TCA GGG ATC CCT GAG CGA TTC TCT GGC TCC ACC TCT GGC AAC
Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Thr Ser Gly Asn

                +51
ACG GCC ACC CTG ACC ATC AGC AGT GTC GAA GCC GGA GAT GAG GCC GAC
Thr Ala Thr Leu Thr Ile Ser Ser Val Glu Ala Gly Asp Glu Ala Asp

                +61
TAT TAC TGT CAG GTG TGG GAG AGT AGT GTA ATA TTC GGC GGA GGG
Tyr Tyr Cys Gln Val Trp Glu Ser Ser Val Ile Phe Gly Gly Gly

                Jλ2
                +91
ACC AAG CTG ACC GTC CTG GGT CAG CCC...
Thr Lys Leu Thr Val Leu Gly Gln Pro...

                Cλ2 region

```

Fig. 4. cDNA sequence of the variable region of the amyloidogenic monoclonal λ -chain from patient Aub

which had not been reported at these positions: Ser-30 and Asp-31 in CDR1, His-36 in FR2, Ser-77 in FR3 and Glu-92 in CDR3; His-36 and Ser-77 were located in β -sheets 3-1 and 4-3 respectively.

DISCUSSION

AL-type amyloidosis is a structurally heterogeneous entity. Indeed, a feature of each case is visceral deposits of a homogeneous monoclonal light chain and/or its fragments with a unique variable region. This makes the study of structure-pathogenicity relationships complex, since large series of experiments are required to be able to draw conclusions. The present results show that cDNA sequencing of the precursor light chain at the secreting clone level is a possible approach, having the following advantages over protein studies: (1) circulating light chains are not always detectable in biological fluids; (2) obtaining fresh tissues containing amyloid proteins is restricted by a number of practical factors; (3) purification of amyloid substances in sufficient amount without proteolysis is tedious and sometimes difficult.

Several structural features of the amyloidogenic light chains reported here are worth noting. Previously unreported or infrequent amino acid residues were found at certain locations. As already suggested by others (Dwulet *et al.*, 1985), it is probable that these residues present in the framework regions, especially in portions corresponding to β -sheets, are more likely to influence the conformation of the domain than amino acids located in the CDRs.

Amyloidogenic light chain from patient Arn was related to the $V_{\kappa 1}$ subgroup, which is the most frequent subgroup among monoclonal κ -chains and is slightly over-represented in amyloidosis (Solomon & Weiss, 1988). Only Leu-21 appeared to be an unusual residue inside a β -sheet (most sequenced $V_{\kappa 1}$ regions bear an isoleucine at this position) and it is unlikely that

it could markedly modify the folding of the light chain. None of the other rare amino acid residues of the sequence from patient Arn was found in the two known $V_{\kappa 1}$ amyloid proteins (Dwulet *et al.*, 1986; Liepnieks *et al.*, 1990). The potential glycosylation site at position +70 has not previously been described in $V_{\kappa 1}$ light chain. In a patient with light chain deposition disease and a deposited κ -light chain of the $V_{\kappa 4}$ subgroup, we have demonstrated that Asn-70 was actually glycosylated (Cogné *et al.*, 1991); *N*-glycosylation could play some role in tissue deposition in both light chain deposition disease and amyloidosis. Indeed, an important proportion of sequenced amyloid light chains, including one of the $V_{\kappa 1}$ subgroup (Dwulet *et al.*, 1986), proved to be *N*-glycosylated (Toft *et al.*, 1985; Tveteraas *et al.*, 1985; Holm *et al.*, 1986; Dwulet *et al.*, 1986).

The sequence from patient Air belonged to the $V_{\lambda 1}$ subgroup. Three $V_{\lambda 1}$ subgroup amyloidogenic Bence-Jones proteins [NIG51 (Takahashi *et al.*, 1980), NIG77 (Tonoike *et al.*, 1985) and ZIM (Eulitz *et al.*, 1987)] and one amyloid substance [EPS, (Toft *et al.*, 1985)] have already been sequenced. Several rare amino acids (Ala-13, Gly-74 and Gly-89 in β -sheets 4-1, 4-3 and 3-2 respectively and Thr-80 and Gly-81 in peptide loops) were also present in the amyloid protein EPS. Such similarity between the variable regions of the light chain of patient Air and the protein EPS, especially in the β -sheets, might possibly lead to delineation of an 'amyloidogenic family' inside the $V_{\lambda 1}$ subgroup. However, strong similarities were also found to proteins NIG64 (Tonoike *et al.*, 1985), New (Langer *et al.*, 1968) and BL2'CL (Tsujimoto & Croce, 1984), which are not known to be associated with amyloidosis. Finally, it is noticeable that the presence of alanine at position +42 has been reported in the amyloidogenic Bence-Jones protein NIG51 only (instead of a threonine in 12 out of 13 other $V_{\lambda 1}$ light chains and lysine in the other one) (Takahashi *et al.*, 1980).

The sequence from patient Aub belonged to the $V_{\lambda 3}$ subgroup. Only one such AL-type amyloid variable region had been completely analysed so far (protein Mol; Holm *et al.*, 1986). None of the infrequent amino acids found in the light chain of patient Aub was present in protein Mol. A striking difference was the absence of an *N*-glycosylation site in the light chain of patient Aub, whereas protein Mol was glycosylated on Asn-90. The sequence from patient Aub demonstrated a high density of acidic residues (Asp-31, -50, -51 and -53, Glu-92) in the CDRs. Insertion of two aspartic acid residues between positions 66 and 67 was noted in the $V_{\lambda 8}$ amyloid protein AR (Sletten *et al.*, 1981), and a possible role for interactions between charged amino acids in amyloid fibril formation has been suggested (Solomon & Weiss, 1988). This is in accordance with the finding of a low mean isoelectric point for urinary Bence-Jones proteins in amyloidosis (Bellotti *et al.*, 1990). Patient Aub presented with an unusual type of AL-amyloidosis with predominant perimembranous deposits, as already described in a few cases for which molecular studies had not been carried out (Shiiki *et al.*, 1989). The study of further patients might allow us to delineate special structural features of perimembranous-type amyloidosis.

In conclusion, our results confirm that the structural abnormalities of immunoglobulin light chains that could play a role in amyloidosis are multiple. cDNA sequencing seems to be a powerful strategy for accumulating molecular data and defining

more precisely the complex relationship between light-chain structure and pathogenicity.

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