Structural snapshot of amyloidogenic light chain in an open dimeric conformation

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Light chain amyloidosis (AL) represents a systemic and life-threatening condition characterized by the accumulation of misfolded immunoglobulin light chains (LCs) in multiple tissues and organs throughout the body [1]. The deposited amyloid fibrils of misfolded LCs disrupt normal tissue structure and function and hence cause organ associated pathologies. The process by which an amyloidogenic protein aggregates and how proteolysis either before or after formation of amyloid fibril contribute to overall aggregation remain unclear [2]. Besides fibril deposits, pre-fibrillar amyloidogenic LCs contribute to tissue damage [3], particularly notable in patients with cardiac involvement [4]. Structurally, free LCs form homo-dimers joining two variable domains (V_L) via hydrophobic interactions and two constant domains (C_L) via disulphide bond [5-6]. However, dimeric interface between V_L-V_L domain show significant dynamics between different amyloidogenic LCs. Therefore, it is important to obtain structural information from many LCs to understand overall structural organization, their contribution to proteolysis, stability and hence potential target sites for therapeutic intervention. To gain detailed structural insights, we employed X-ray crystallography on a patient derived λ6-LC, named AL55, which shows multiorgan fibril deposit in AL patient who died with cardiac arrest. The structure, solved at a 2.7 Å resolution, revealed significant differences compared to the previously reported LCs dimer. In our crystallographic structure, which exhibits an asymmetric unit of three monomers with an unreported open LC dimer (Fig. 1), V_L-V_L intradimer interactions are lacking. When compared to the AL55 AlphaFold model (Fig. 1), which resembles the canonical LCs dimer, this AL55 open dimer differs in the relative orientation of V_L and for the presence of an extra antiparallel V_L-V_L interface occurring between the dimer and the V_L belonging to the third monomer in the asymmetric unit. The open conformation of AL55 is unique among other known toxic LCs. This non-native open dimer, may represent a conformation specific to amyloidogenic LCs, serving as an intermediate step towards the formation of pre-fibrillar amyloidogenic or fibrils and consequently being a potential target for the development of novel therapeutics.

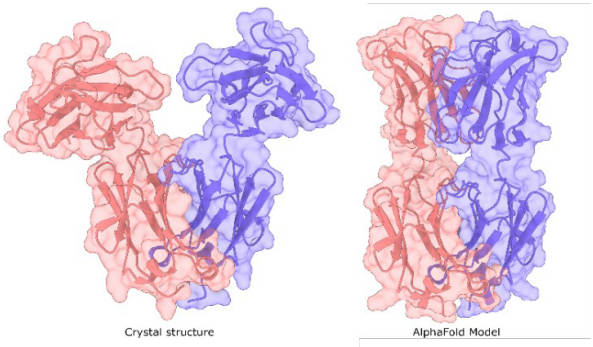

Figure 1. AL55 crystallographic structure. AL55 crystal structure (*left*) reveal a non-native open dimer that differs from the closed LCs dimer, as represented in Alphafold model (*right*), by the lack of V_L-V_L interactions.

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