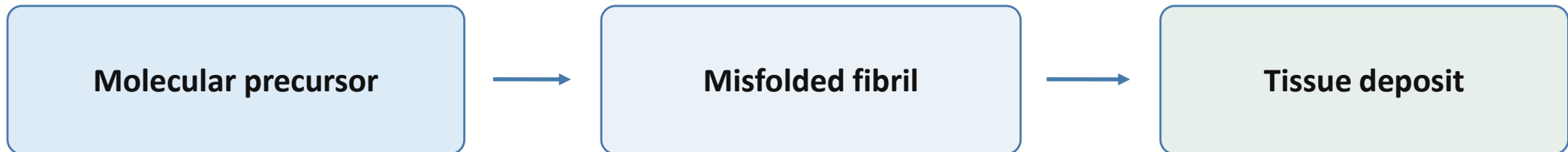


Chemical Nature of Amyloid

Proteins, fibrils, precursors and clinicopathologic interpretation



Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

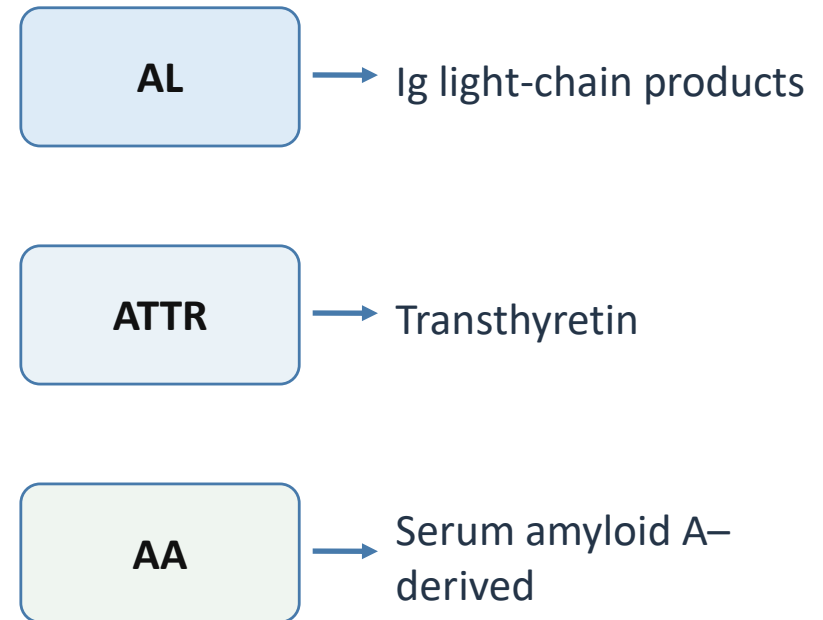
Learning objectives

- Differentiate fibril protein chemistry from common amyloid architecture.
- Identify the biochemical precursors of AL, ATTR, and AA deposits.
- Recognize A β , A β ₂-microglobulin, and prion-associated amyloid examples.
- Explain why amyloid detection and biochemical typing are separate steps.

Amyloid is a chemically heterogeneous deposit

- Amyloid is not a single biochemical substance.
- More than 40 different proteins can form amyloid.
- Histologic similarity reflects a shared fibrillar organization, not identical precursors.

Different proteins can converge on a common amyloid morphology.

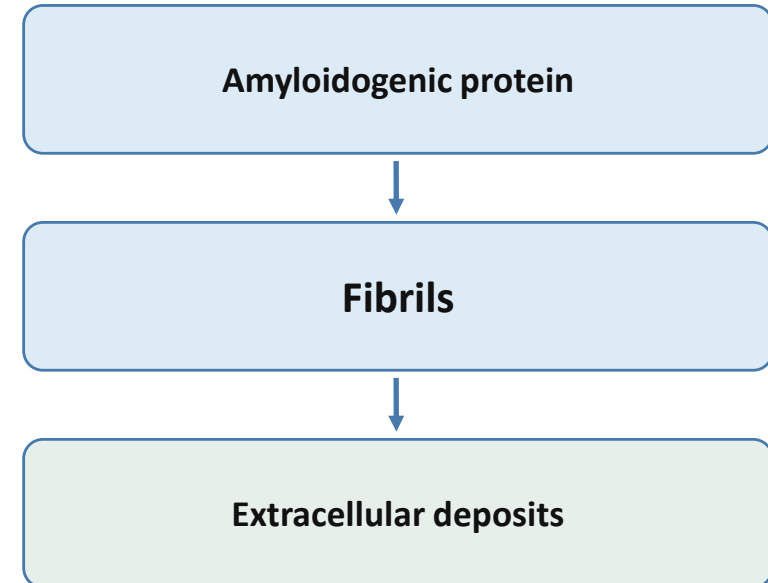


Schematic

Amyloidosis is a family of deposition disorders

- Amyloidogenic proteins form insoluble fibrils.
- Fibrils accumulate predominantly in extracellular tissues.
- Progressive deposits distort tissue architecture and impair function.

Chemical identity and affected organ together shape disease.



Shared endpoint across multiple diseases

Schematic

Microscopic similarity does not imply chemical identity

- AL, ATTR, AA, and less common proteins may look alike in routine sections.
- The precursor protein supplies the biochemical name of the fibril type.
- Typing is essential to distinguish biologically different disorders.

**Common
morphology**

Extracellular hyaline
deposits

Distinct chemistry

Different fibril
proteins and
precursors

Appearance identifies amyloid; Chemistry identifies its type.

Schematic

The deposit has a fibrillar and a nonfibrillar fraction

- Approximately 95% comprises fibril proteins.
- The remaining approximately 5% includes serum amyloid P and other glycoproteins.
- The fibril protein defines the biochemical amyloid type.

Approximate amyloid deposit composition



~95% fibril proteins

~5%

SAP and other glycoproteins

Do not confuse an associated deposit protein with the fibril precursor.

Schematic

Serum amyloid P is a deposit-associated component

- Serum amyloid P contributes to the nonfibrillar portion of deposits.
- It is present alongside different amyloid fibril types.
- It does not mean that all amyloid fibrils derive from serum amyloid P.

Amyloid fibril

Serum amyloid P

Proteoglycans

SAP is a shared component; AL, ATTR, and AA are different fibril proteins.

Schematic

Amyloid interacts with extracellular matrix molecules

- Deposits bind proteoglycans and glycosaminoglycans.
- Examples include heparan sulfate and dermatan sulfate.
- Associated molecules help explain the shared staining behavior.

An amyloid deposit contains more than the protein making its fibrils.

Amyloid fibrils

Heparan sulfate

Dermatan sulfate

Serum amyloid P

Schematic

The term amyloid does not mean starch

- The original name reflected staining features reminiscent of amylose.
- Charged sugar-containing molecules contributed to the historical impression.
- Amyloid fibrils are aggregated proteins—not starch deposits.

The name is historical; The material is predominantly protein.

Historical label

Resembled amylose
in staining

Chemical reality

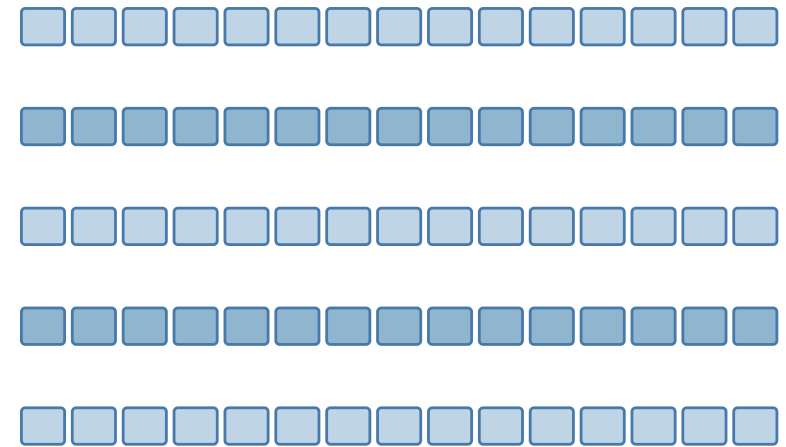
Protein-rich
extracellular fibrils

Schematic

Amyloid fibrils share a nonbranching ultrastructure

- Electron microscopy reveals continuous, nonbranching fibrils.
- The architecture is common across multiple chemical amyloid types.
- This shared geometry helps explain their common tissue appearance.

The fibril shape is a structural signature—not a protein-type label.



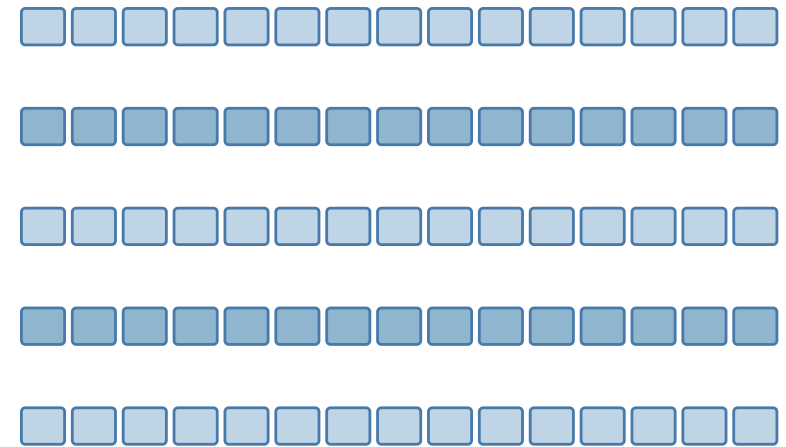
Continuous, parallel nonbranching fibrils

Schematic

The fibril diameter is approximately 8–10 nm

- Amyloid fibrils are roughly 8–10 nm in diameter.
- This is an electron-microscopic scale, not resolvable as individual fibrils by light microscopy.
- The dimension describes the fibrils, not the extent of a tissue deposit.

Never interpret a low-power H&E deposit as a single 8–10 nm fibril.



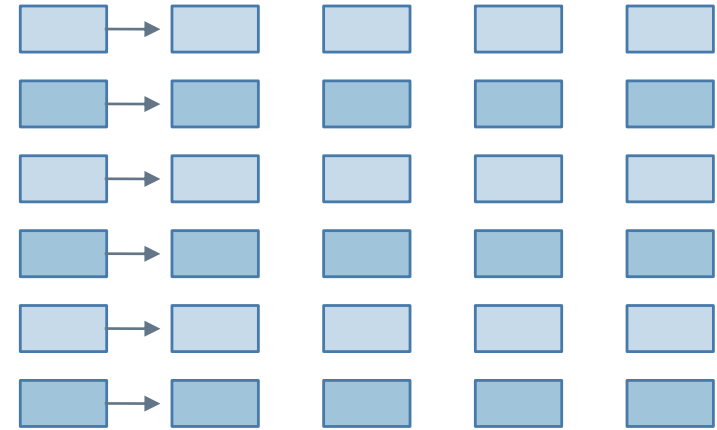
Continuous, parallel nonbranching fibrils

Schematic

β -pleated structure is the organizing motif

- Amyloid fibrils contain β -pleated structural elements.
- Protofilaments are arranged into stacked molecular assemblies.
- Side-chain interactions help bind these arrangements together.

The common molecular packing underlies shared staining properties.



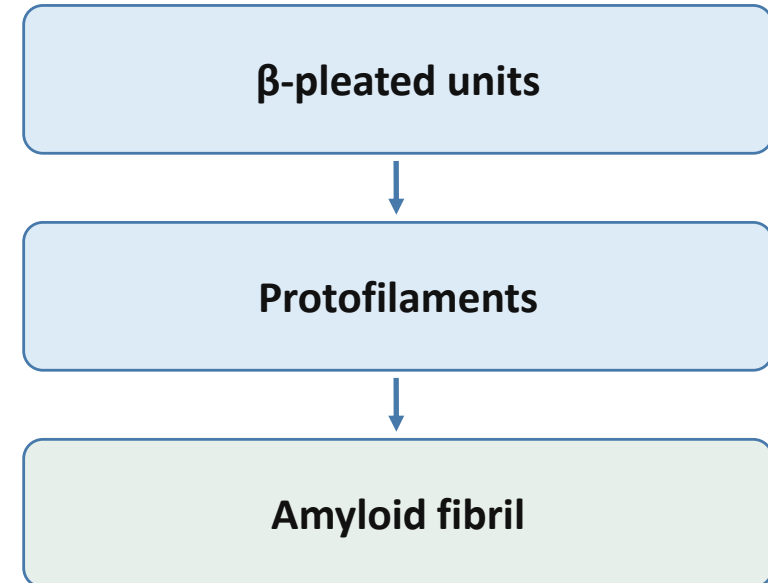
β -pleated sheets $\rightarrow$ aligned protofilaments

Schematic

Protofilaments organize into mature fibrils

- A protofilament is part of a higher-order fibrillar structure.
- Repeated β -pleated molecular units assemble into organized fibers.
- The resulting amyloid fibril is insoluble and tends to persist in tissues.

Protein source differs; Hierarchical fibril assembly is shared.

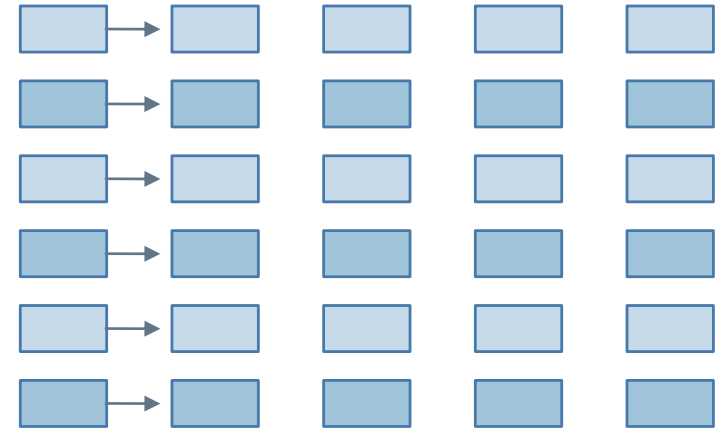


Schematic

Side-chain interactions stabilize fibrillar packing

- Protofilament associations involving side chains.
- Different amino-acid sequences can adopt the same overall fibrillar architecture.
- Common conformation should not be mistaken for a common sequence.

Architecture is conserved even when the precursor protein changes.



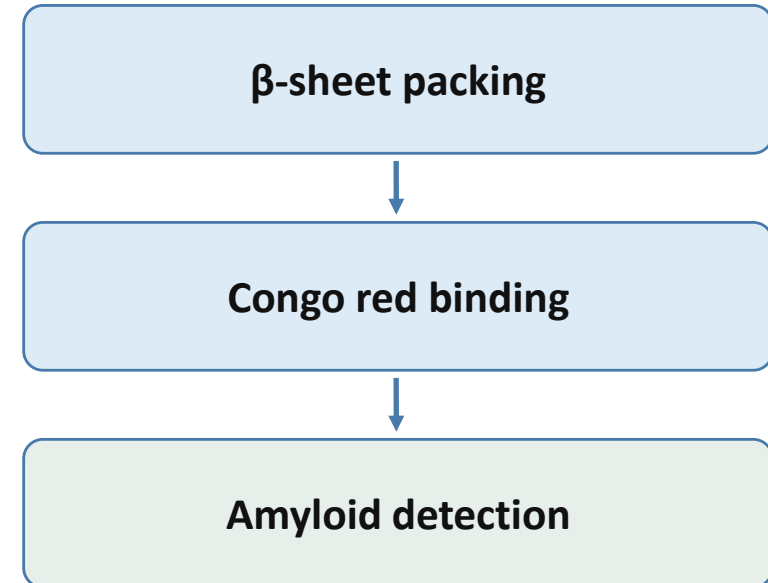
β -pleated sheets $\rightarrow$ aligned protofilaments

Schematic

Conformation connects chemistry to Congo red

- Congo red staining is characteristic of the amyloid fibril arrangement.
- The structural feature is shared across chemically distinct amyloid types.
- Therefore Congo red indicates amyloid but does not define AL, ATTR, or AA.

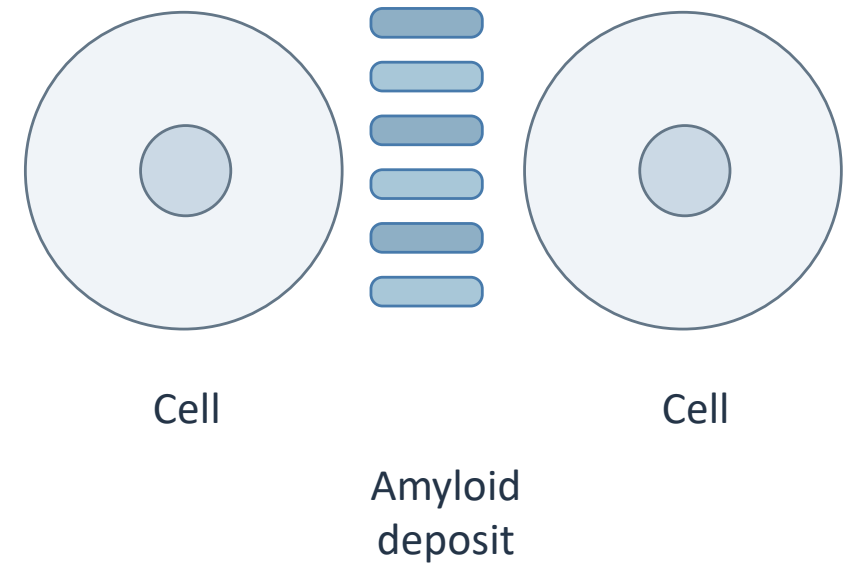
A structural stain is not a protein-typing assay.



Schematic

Routine H&E shows amorphous extracellular material

- Amyloid appears as an amorphous, eosinophilic, hyaline extracellular substance.
- Collagen and fibrin can create superficially similar appearances.
- A specific histochemical assessment is therefore useful.



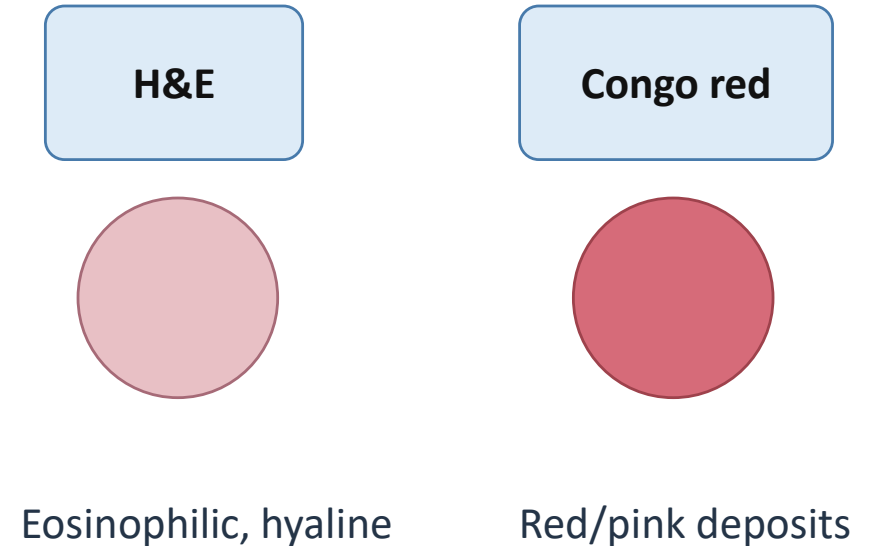
Schematic

H&E raises suspicion; Morphology alone is not chemically specific.

Congo red gives deposits a pink–red appearance

- In ordinary illumination, Congo red stains amyloid deposits pink or red.
- The stain is used after morphologic recognition of an extracellular deposit.
- Interpretation also requires appropriate examination under polarized light.

Color under ordinary light is not the whole diagnostic signature.



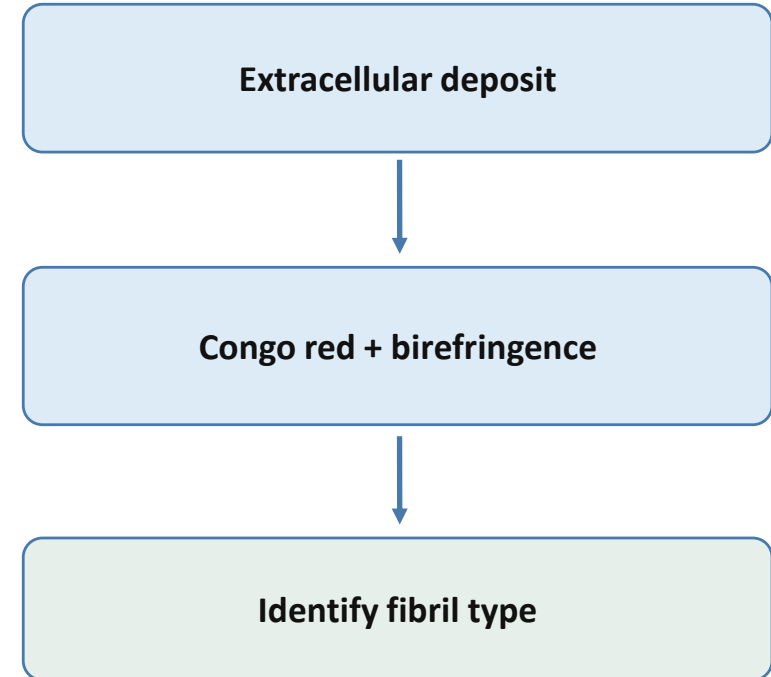
Polarizing microscopy assesses birefringence

Schematic

Polarized light adds the characteristic birefringence

- Congo red–stained amyloid shows characteristic birefringence with polarization.
- This feature is more distinctive than pink-red staining alone.
- The result establishes amyloid deposits without specifying fibril composition.

Detection and chemical identification answer separate questions.



Schematic

A positive amyloid stain cannot distinguish its precursor

- AL, ATTR, and AA share key structural staining features.
- A tissue deposit therefore requires contextual or specific protein typing.
- Never infer the amyloid class merely from its Congo red pattern.

Conformation is common; Precursor identity is not.

Detection

Amyloid architecture

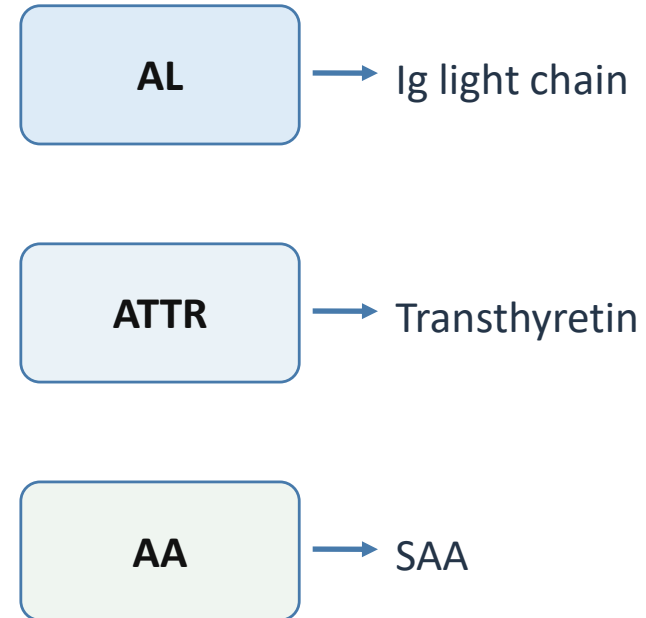
Classification

Fibril protein origin

Schematic

The biochemical name points to the fibril protein

- AL denotes an immunoglobulin light-chain–derived fibril.
- ATTR denotes transthyretin-derived amyloid.
- AA denotes a product derived from serum amyloid A.



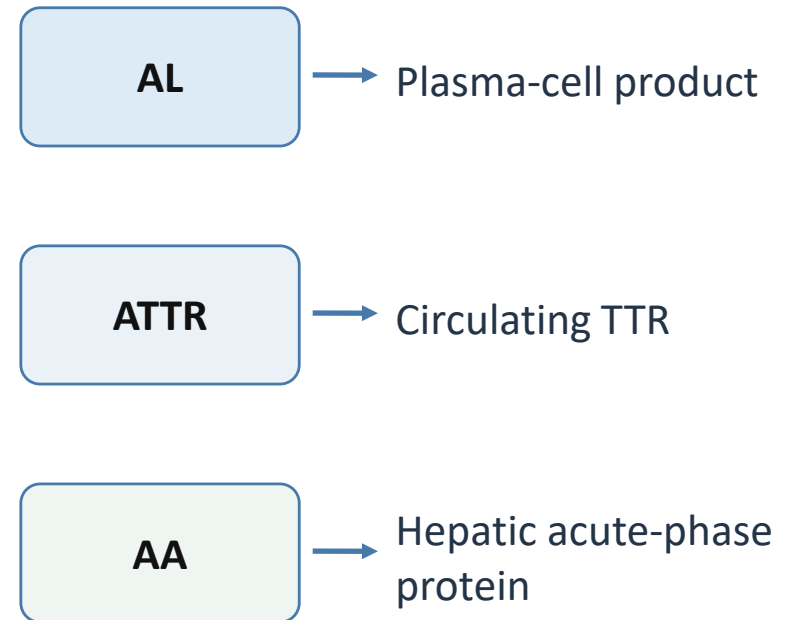
Start each amyloid mechanism by identifying its precursor.

Schematic

Three common amyloid types have different origins

- AL originates from monoclonal plasma-cell light chains.
- ATTR originates from transthyretin, in wild-type or variant forms.
- AA originates from liver-produced serum amyloid A after proteolysis.

The dominant fibril protein is also a clue to pathogenesis.



Schematic

Fibril type and precursor are not interchangeable

- A circulating precursor may be processed before becoming a fibril.
- AL can contain intact light chains or amino-terminal fragments.
- AA is proteolytically generated from a larger SAA molecule.

Name the final fibril protein and the source precursor precisely.

AL

Intact chains and/or fragments

AA

Derived by SAA cleavage

ATTR

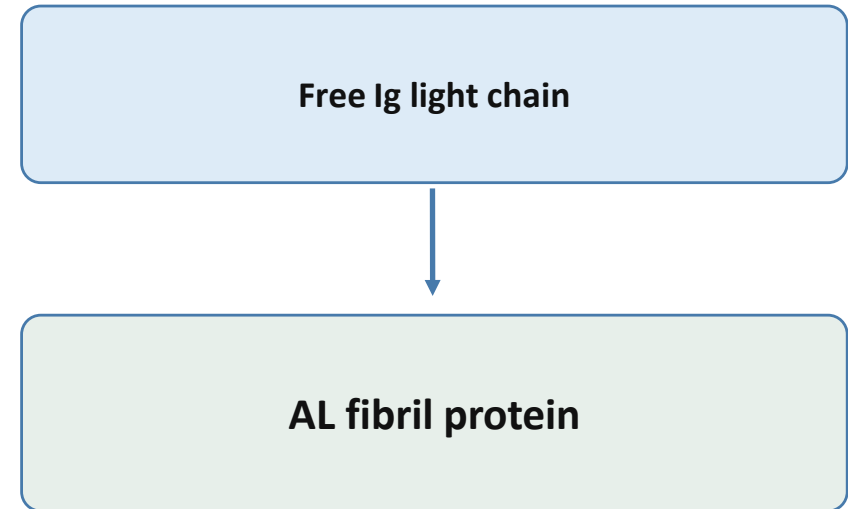
Composed of TTR

Schematic

AL means amyloid light chain

- The precursor is an immunoglobulin light chain secreted by a clonal plasma-cell population.
- AL fibrils can contain entire light chains, fragments, or both.
- The designation concerns the fibril protein, not the site of deposition.

AL chemistry connects tissue amyloid to monoclonal immunoglobulin production.



Schematic

Complete immunoglobulin light chains can form AL

- Not every AL fibril consists exclusively of a small peptide fragment.
- Robbins explicitly includes complete light chains in AL deposits.
- The common category is origin from the Ig light-chain polypeptide.

AL is a biochemical family rather than a single fixed fragment.

Complete chain

Full light-chain
polypeptide

Fragment

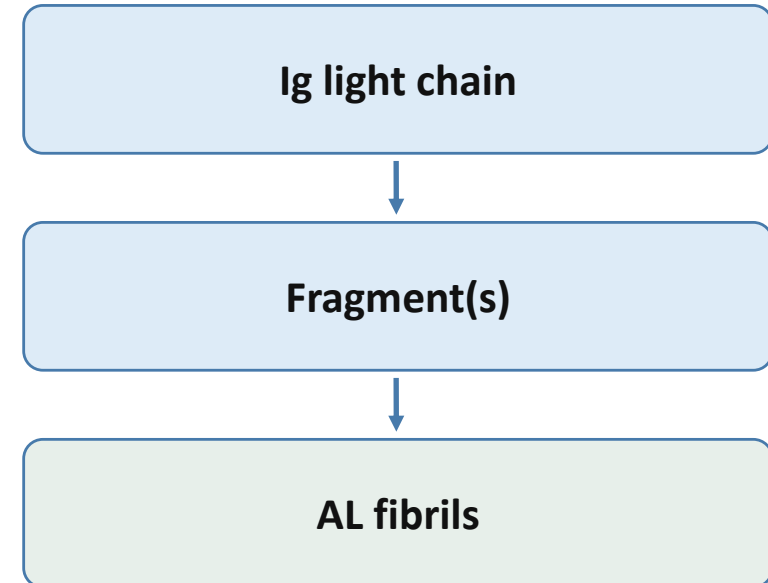
Amino-terminal-
derived segment

Schematic

Amino-terminal fragments also contribute to AL

- AL amyloid may contain amino-terminal portions of light chains.
- A deposit can contain both whole-chain and fragmented light-chain material.
- Proteolytic history is therefore relevant to deposit composition.

Do not define AL as exclusively intact light chains.



Schematic

Lambda light chains predominate among analyzed AL

- Most characterized AL proteins are λ light-chain–derived.
- κ light chains or their fragments can also form amyloid.
- Light-chain class alone does not establish fibril formation in an individual.

Both λ and κ can be amyloidogenic; λ predominance is not exclusivity.

λ light chain

More frequent in
reported AL samples

κ light chain

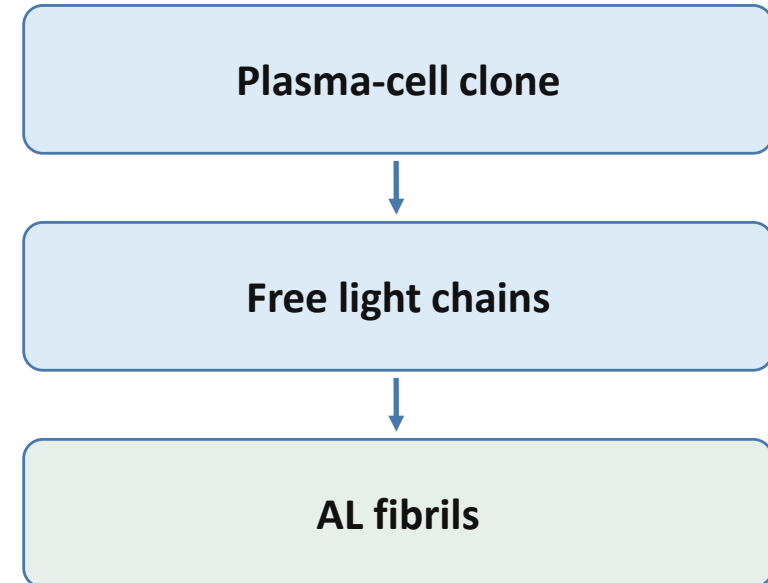
Also capable of
forming AL

Schematic

The AL precursor comes from a monoclonal clone

- A monoclonal plasma-cell population secretes free Ig light chains.
- A subset of the secreted molecules has amyloid-forming potential.
- Deposits may be associated with plasma-cell neoplasms.

Link the fibril protein to its producing cell population.

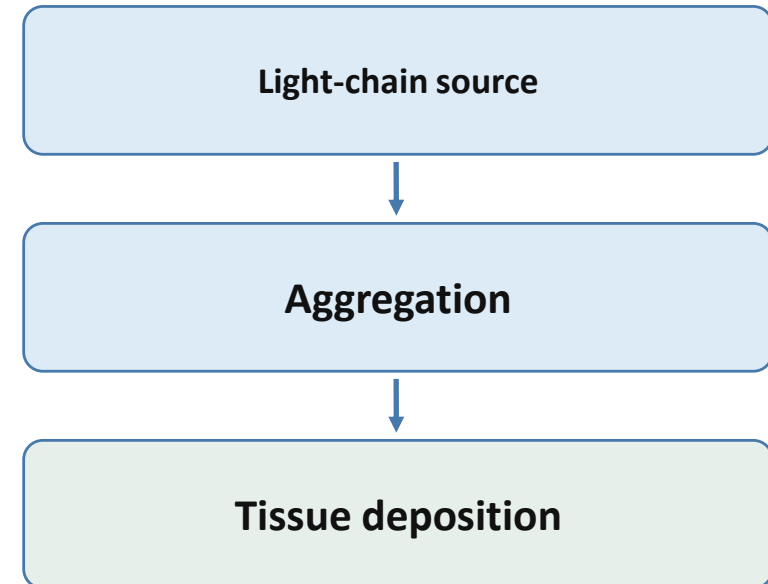


Schematic

AL deposition links protein production to tissue damage

- A precursor is generated by abnormal plasma-cell production.
- Amyloidogenic light chains aggregate and deposit extracellularly.
- The tissue deposit is the mechanism of organ injury in amyloidosis.

The source clone and the affected tissue may be anatomically separate.



Schematic

AL is not synonymous with multiple myeloma

- Robbins relates AL to certain plasma-cell tumors and monoclonal populations.
- The molecular definition is light-chain composition of the fibril.
- An AL diagnosis requires attention to the protein source, not a tumor label alone.

Distinguish amyloid type from its associated hematologic disorder.

Amyloid protein

AL light-chain fibril

Associated disorder

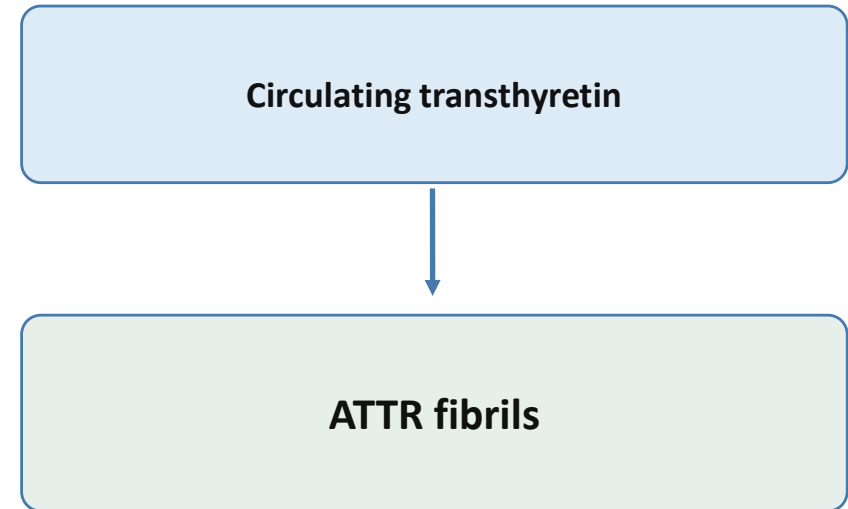
Monoclonal plasma-cell disease

Schematic

Transthyretin is the precursor of ATTR

- ATTR fibrils are composed of transthyretin (TTR).
- TTR is a circulating plasma protein.
- Its transport roles for thyroxine and retinol.

A normal physiologic transport protein can become amyloidogenic.

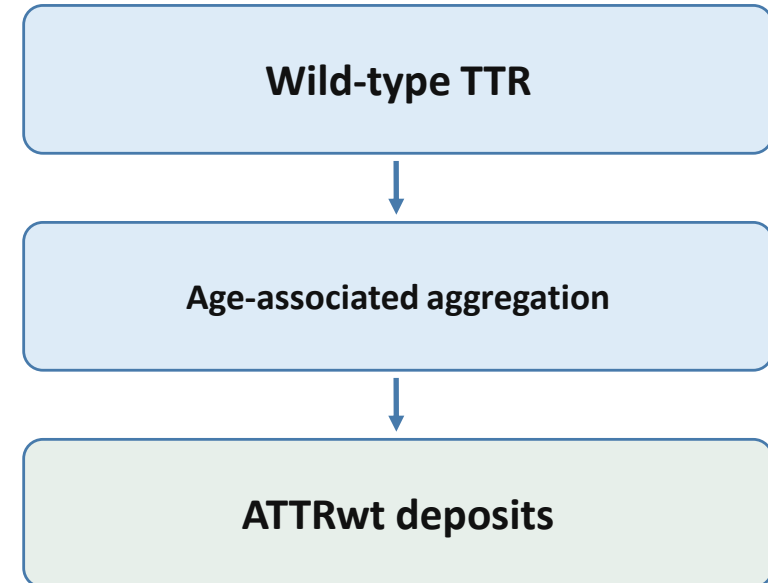


Schematic

Wild-type transthyretin can aggregate

- ATTRwt denotes deposits produced from unmutated or wild-type TTR.
- Aging favors the amyloidogenic behavior.
- This form commonly involves the heart.

A genetic TTR variant is not required for all ATTR amyloid.



Schematic

ATTRwt has a characteristic cardiac association

- The heart as the usual site of ATTRwt deposition.
- It particularly describes older men, commonly above age 70.
- Organ distribution provides a clinical clue, not a substitute for amyloid typing.

Consider precursor and organ together; Neither alone confirms the type.

Wild-type TTR

Cardiac deposition

Older adults

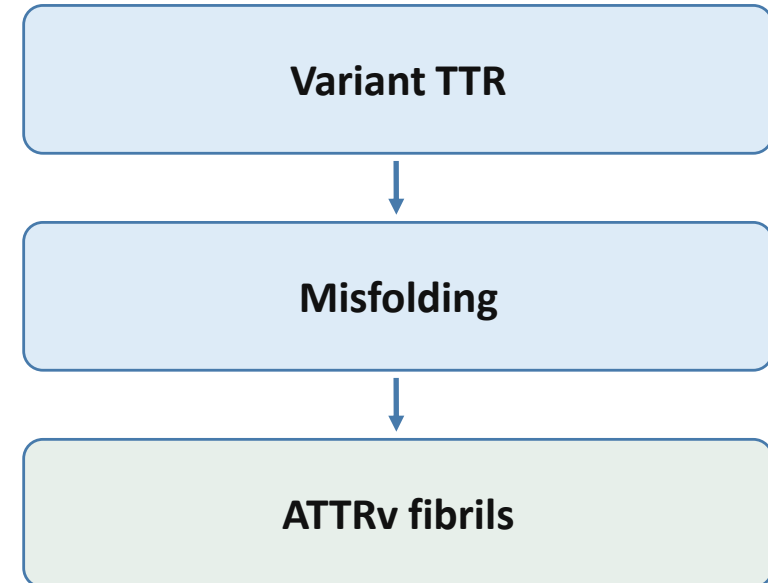
Systemic amyloid

Schematic

Variant transthyretin forms ATTRv

- ATTRv arises from variant forms of transthyretin.
- Variant TTR can misfold and form extracellular fibrils.
- This is chemically distinct from AL and AA despite shared morphology.

The altered molecule remains transthyretin-derived amyloid.

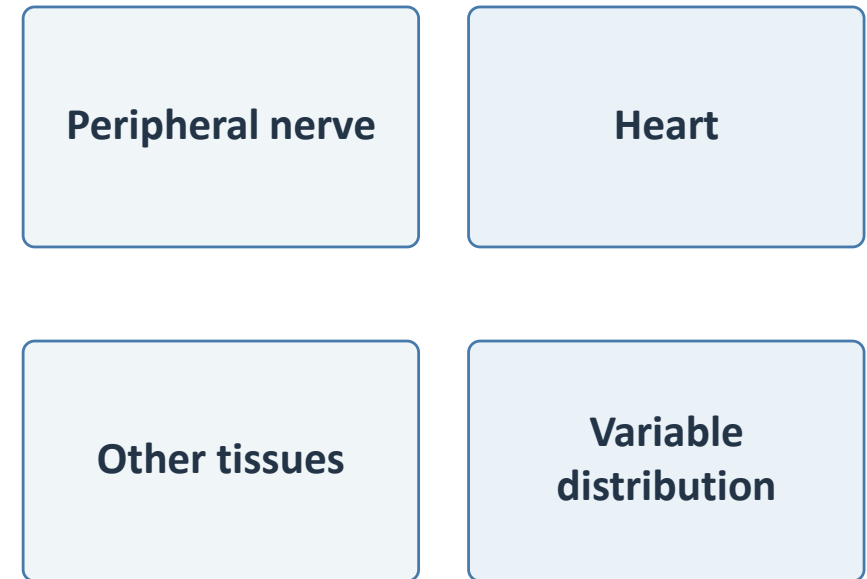


Schematic

ATTRv may involve nerves as well as heart

- Heart, peripheral nerves, and additional tissues as sites.
- Different variant TTR proteins can show different organ distributions.
- Distribution cannot by itself specify the exact variant.

Variant protein identity and tissue tropism are related but not identical.



Schematic

Wild-type and variant ATTR share the same protein family

- Both classes deposit transthyretin-derived fibrils.
- ATTRwt refers to aggregation of wild-type protein.
- ATTRv refers to amyloid associated with altered TTR sequence.

ATTRwt

Wild-type TTR; Often
cardiac

ATTRv

Variant TTR; Heart
and/or nerves

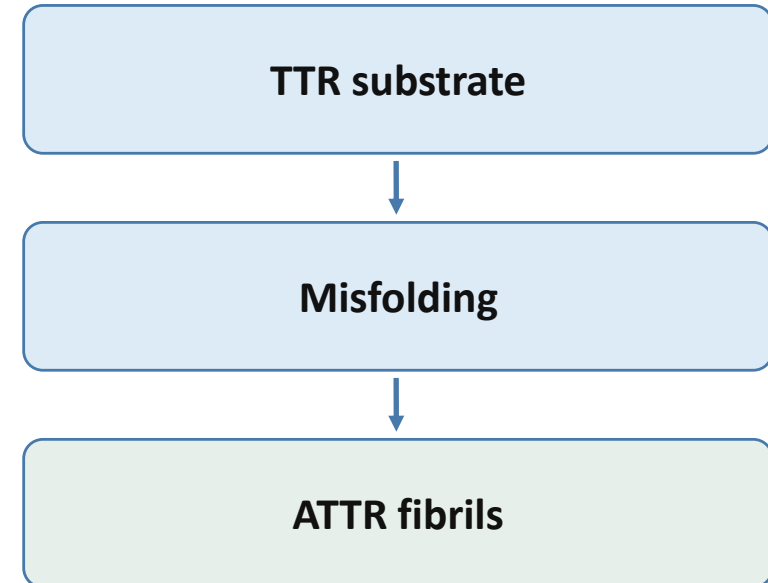
The wt/v distinction describes precursor status within ATTR.

Schematic

Aging and molecular variation are distinct routes

- Normal proteins may become amyloidogenic in an age-associated setting.
- Variant proteins can have enhanced tendency toward abnormal folding.
- Both routes converge on extracellular fibrils.

Multiple upstream causes can produce the same structural endpoint.

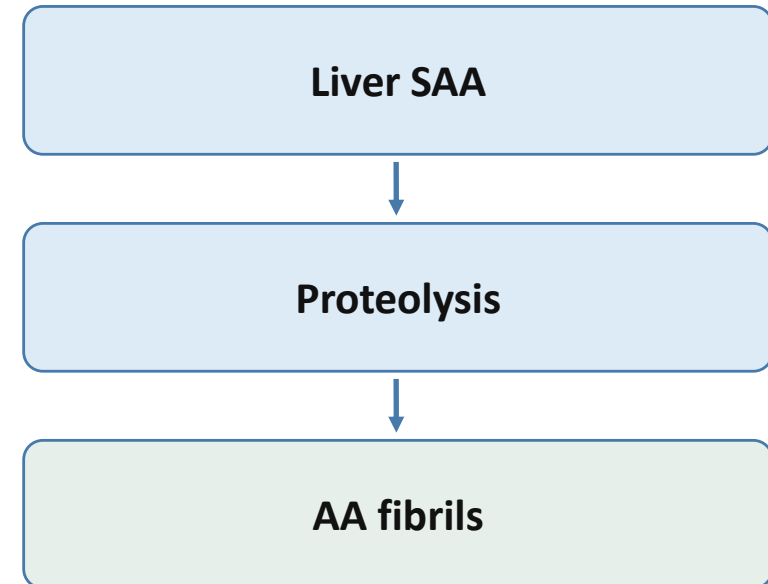


Schematic

AA is a processed product of serum amyloid A

- AA fibril protein is generated from a larger precursor, SAA.
- SAA is synthesized by hepatocytes and released into blood.
- Proteolysis links the circulating precursor to the deposited fibril component.

The deposited AA protein is not equivalent to the intact SAA precursor.

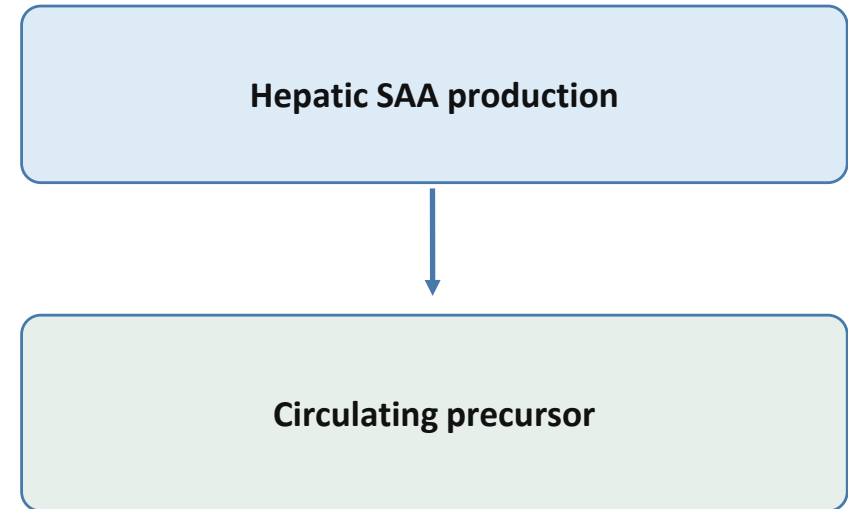


Schematic

SAA is produced in the liver

- The precursor protein enters the circulation after hepatic synthesis.
- This explains how a protein made at one site can deposit in distant organs.
- A systemic precursor should not be confused with localized tissue production.

Hepatic origin is a defining biochemical feature of AA.

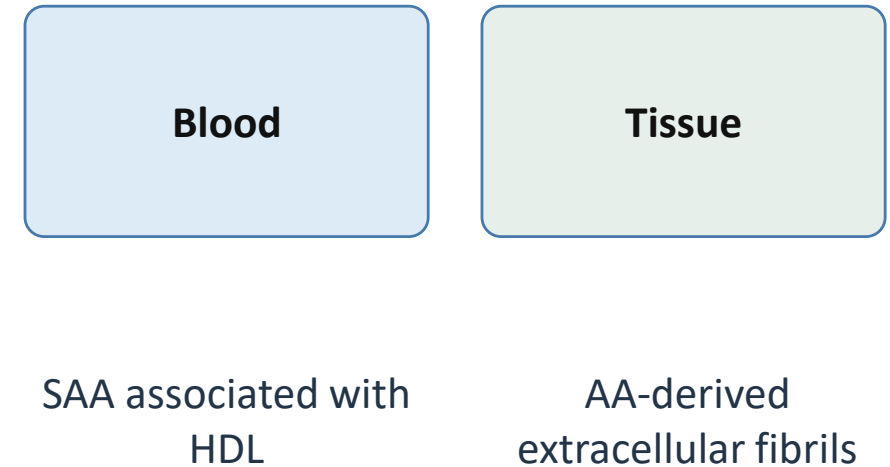


Schematic

Circulating SAA associates with HDL

- The source states that SAA circulates bound to high-density lipoproteins.
- The lipoprotein association concerns precursor transport in plasma.
- AA deposits ultimately contain fibrils derived from this precursor.

Separate the circulating molecular complex from insoluble tissue fibrils.

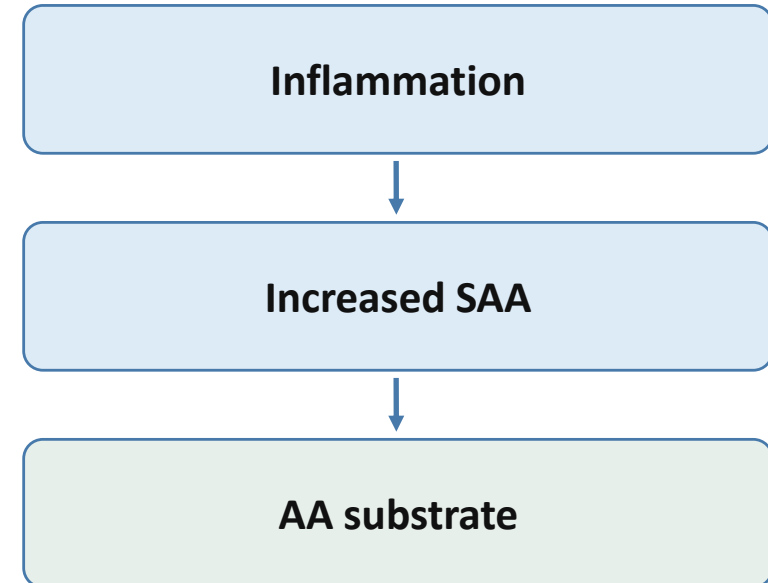


Schematic

SAA is an acute-phase reactant

- Inflammatory states increase SAA production.
- Raised SAA reflects the hepatic acute-phase response.
- Sustained precursor exposure is associated with AA amyloidosis.

The inflammatory context explains the source of abundant substrate.

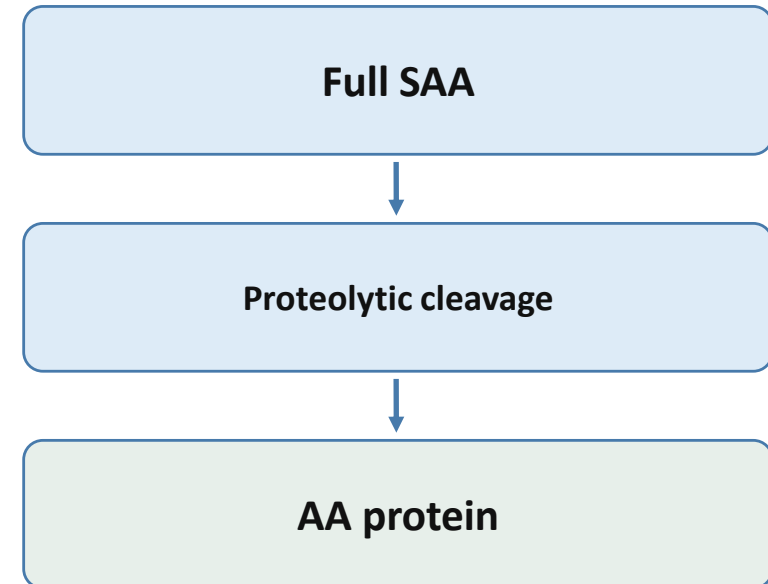


Schematic

Proteolysis converts SAA into AA components

- The final AA fibril protein is derived from a larger SAA polypeptide.
- Proteolytic processing generates the smaller amyloid-associated product.
- Thus precursor processing is integral to AA nomenclature.

AA names the deposited amyloidogenic product; SAA names its precursor.

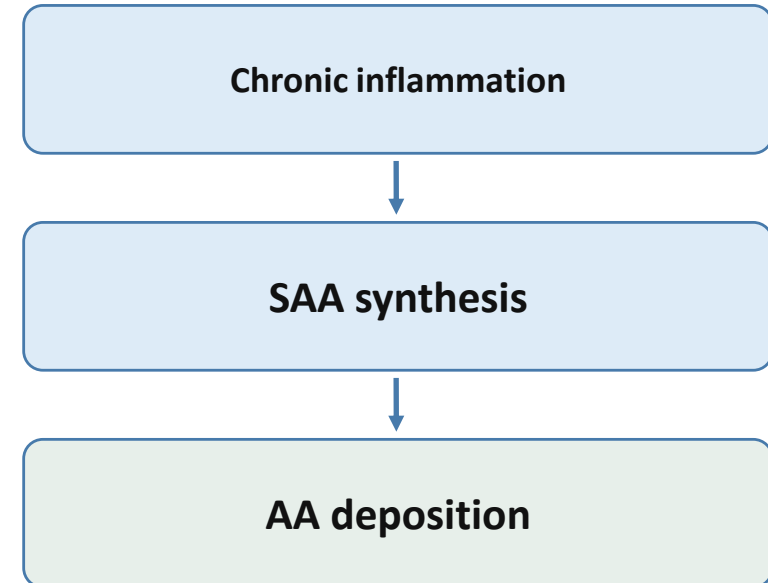


Schematic

Chronic inflammation explains AA association

- Inflammation increases liver synthesis of SAA.
- Long-standing inflammatory conditions can maintain precursor abundance.
- This supplies a biochemical connection to AA fibril accumulation.

In AA amyloidosis the clinical setting and chemical precursor are linked.

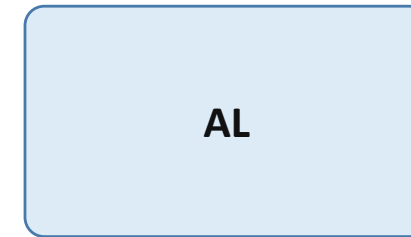


Schematic

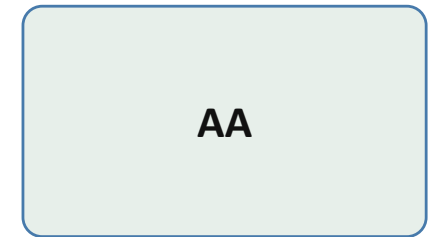
AL and AA differ in the source of their precursor

- AL involves an Ig light chain produced by monoclonal plasma cells.
- AA involves hepatic SAA increased by an inflammatory response.
- Both precursors can ultimately yield extracellular amyloid fibrils.

Different upstream biology; Convergent fibrillar phenotype.



Plasma-cell Ig light
chains

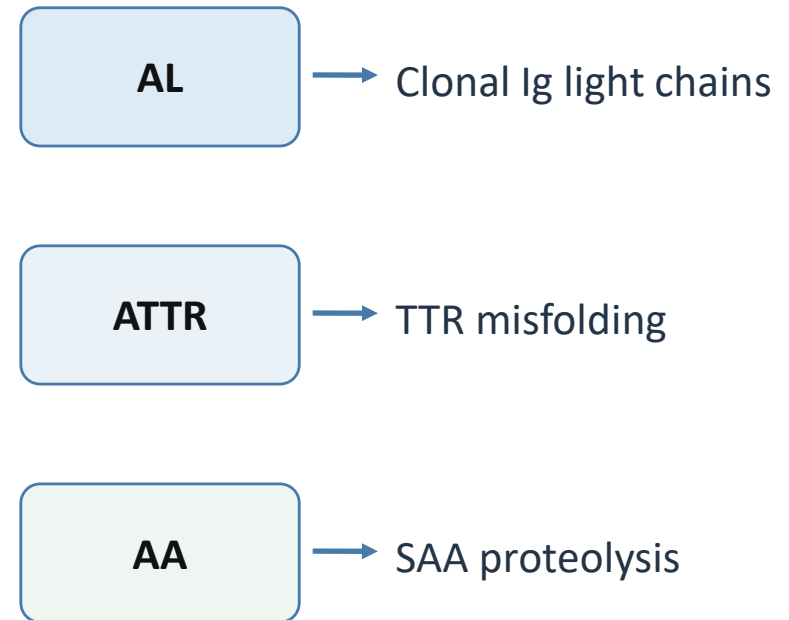


Hepatic acute-phase
SAA

Schematic

Three major precursors follow distinct pathways

- AL: Monoclonal free light-chain production.
- ATTR: Wild-type or variant transthyretin aggregation.
- AA: Increased SAA and generation of AA fragments.



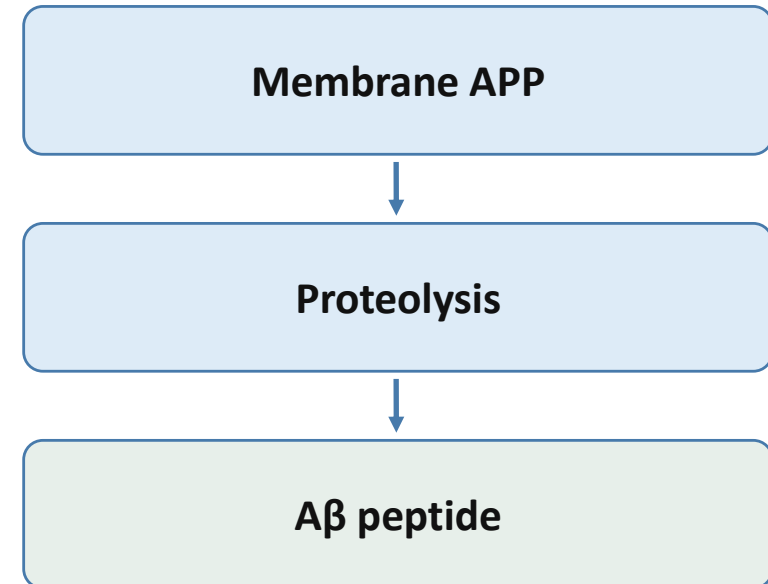
Precursor identification is the organizing principle of amyloid chemistry.

Schematic

A β is derived from amyloid precursor protein

- Amyloid- β is formed by proteolysis of amyloid precursor protein (APP).
- APP is a larger transmembrane glycoprotein.
- A β represents a distinct biochemical amyloid species.

A β is not another name for AL, ATTR, or AA.

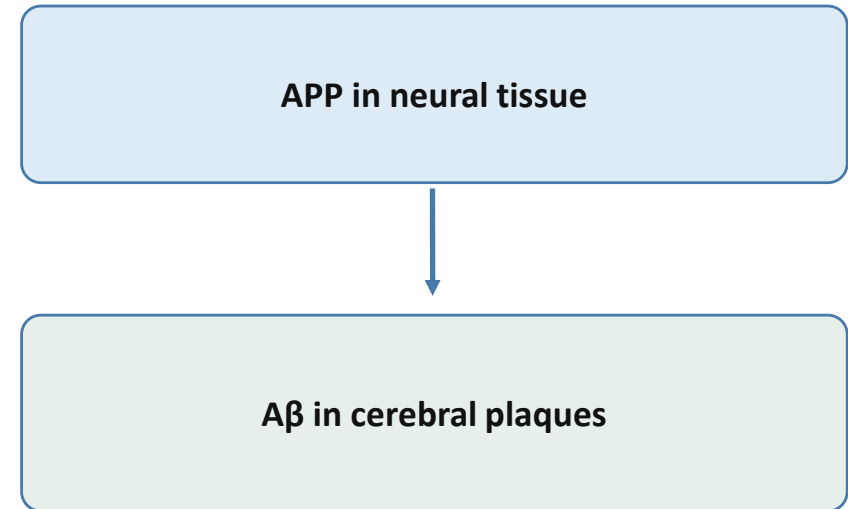


Schematic

A β forms the core of Alzheimer plaques

- The A β protein forms a central component of cerebral plaques in Alzheimer disease.
- This is a tissue-specific association given by the source.
- The biochemical identity differs from circulating light chains or TTR.

Brain amyloid can arise from local processing of a membrane precursor.

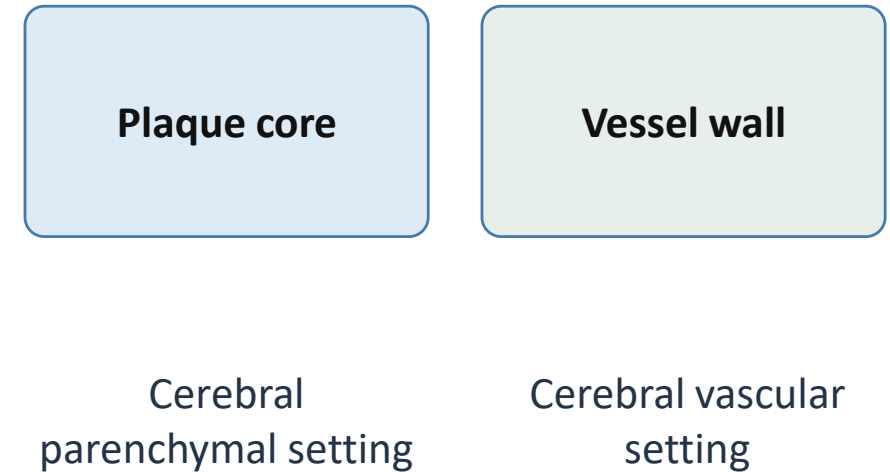


Schematic

A β also deposits in cerebral blood vessel walls

- A β deposits in walls of cerebral vessels.
- Plaque and vessel-wall deposition are distinct anatomical patterns.
- Both can involve the same biochemical A β protein species.

One fibril protein may occur in more than one cerebral compartment.

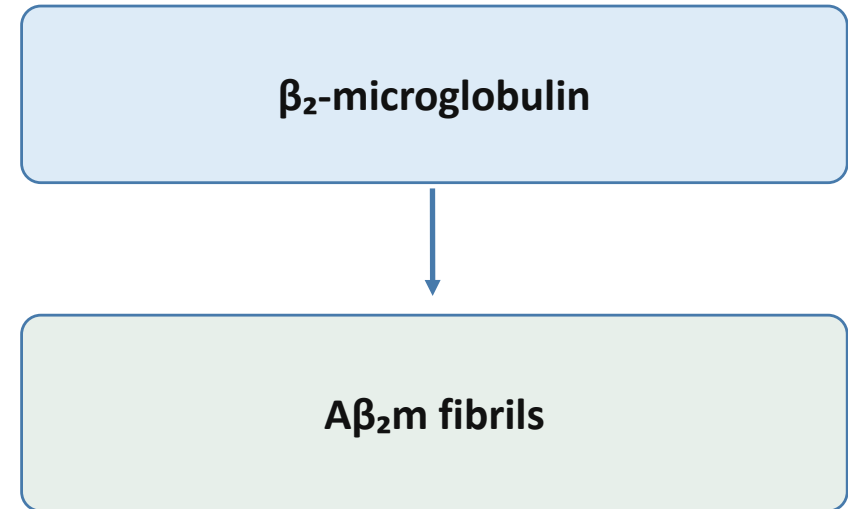


Schematic

β_2 -microglobulin is an MHC class I component

- β_2 -microglobulin normally associates with MHC class I molecules.
- It is also a normal circulating plasma protein.
- Under particular clinical conditions it can become the amyloid fibril protein.

A physiologic host protein can become an amyloid precursor.

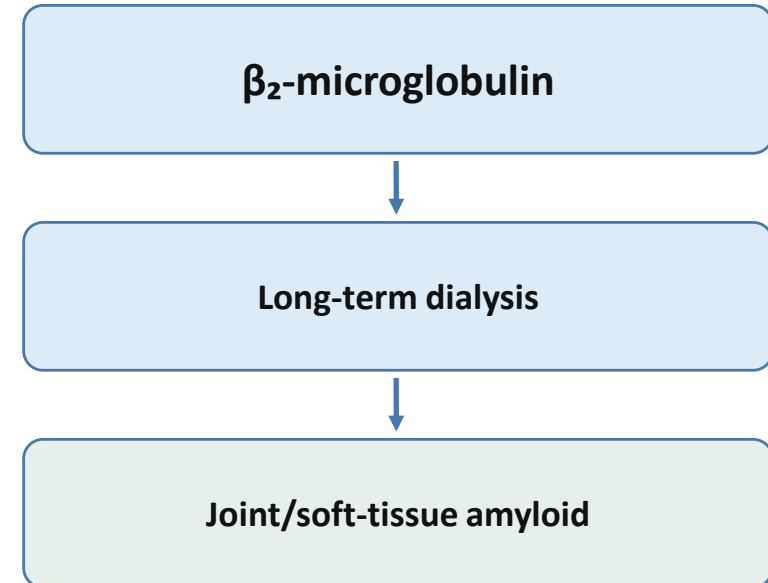


Schematic

Long-term dialysis is associated with $A\beta_{2m}$

- β_2 -microglobulin amyloid with long-term hemodialysis.
- Deposits appear in or around joints and soft tissues.
- This is a distinct precursor from $A\beta$ in the central nervous system.

Similar abbreviations must not obscure unrelated proteins.

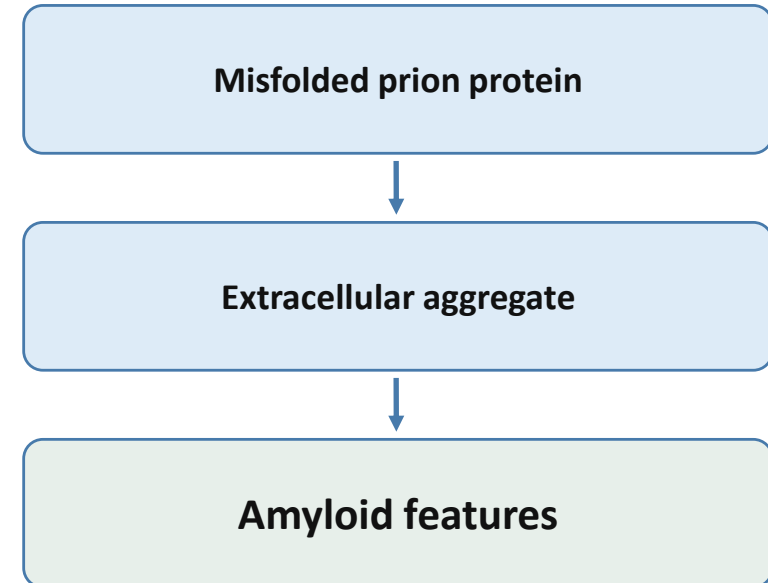


Schematic

Prion proteins can rarely form amyloid deposits

- In a minority of CNS prion-disease cases, misfolded prion proteins aggregate extracellularly.
- The aggregates can acquire amyloid-like structural and staining properties.
- This is a special, less common amyloid example.

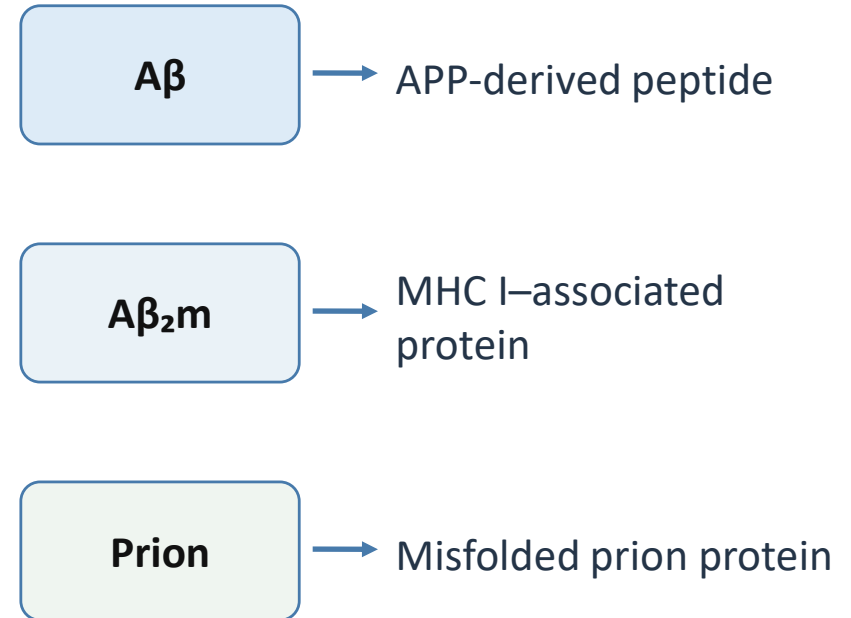
Amyloid conformation can arise from another structurally distinct protein.



Schematic

Less common proteins broaden amyloid chemistry

- A β is associated with Alzheimer plaques and cerebrovascular deposits.
- β_2 -microglobulin is associated with long-term hemodialysis.
- Some misfolded prion proteins can acquire amyloid characteristics.



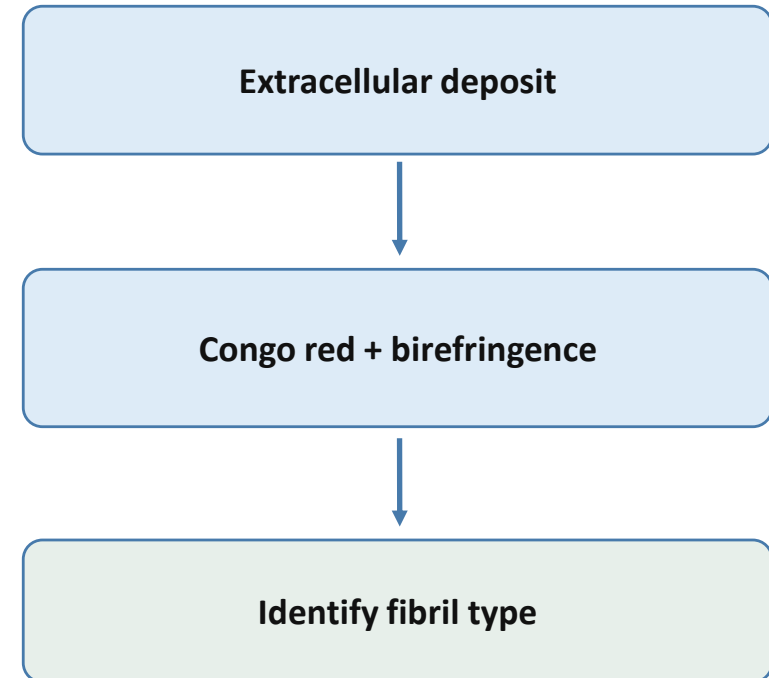
Amyloid represents a material class formed by multiple proteins.

Schematic

Identical staining may conceal different diseases

- Congo red detects shared fibril architecture.
- Amyloid chemistry separates plasma-cell, TTR, inflammatory, cerebral, and dialysis-related pathways.
- Clinicopathologic interpretation therefore needs both morphology and protein identity.

Avoid a one-to-one mapping from staining phenotype to disease category.

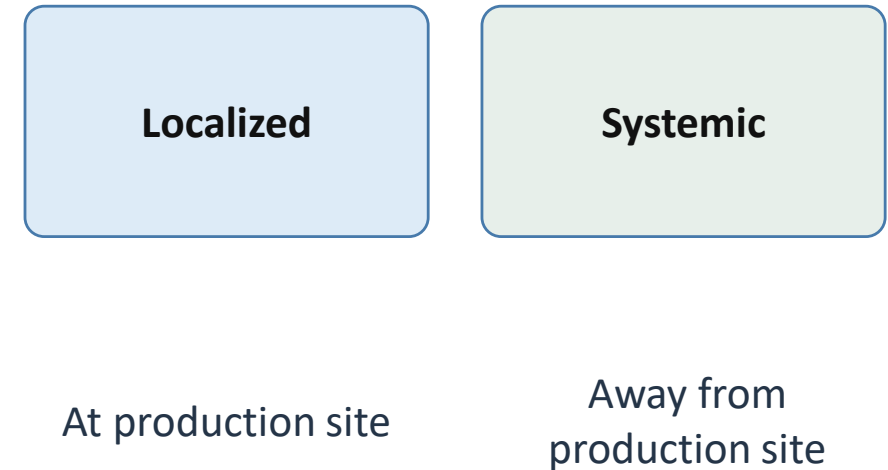


Schematic

Localized and systemic deposits reflect precursor context

- Local deposition from deposits occurring away from protein production.
- Circulating precursors can support systemic involvement.
- Local precursors can be associated with restricted deposition patterns.

Chemical source and distribution are linked concepts, not identical labels.

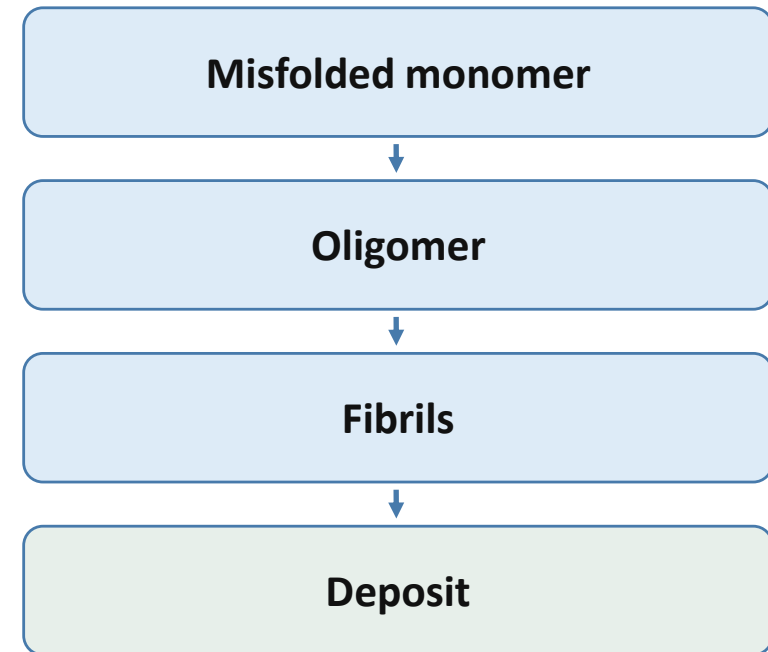


Schematic

Protein folding is the shared final route

- Amyloidogenic proteins misfold and form oligomers.
- Oligomers can progress to larger aggregates and insoluble fibrils.
- The precursor determines which amyloid protein reaches this pathway.

Shared structural pathway; Distinct initial biochemical input.

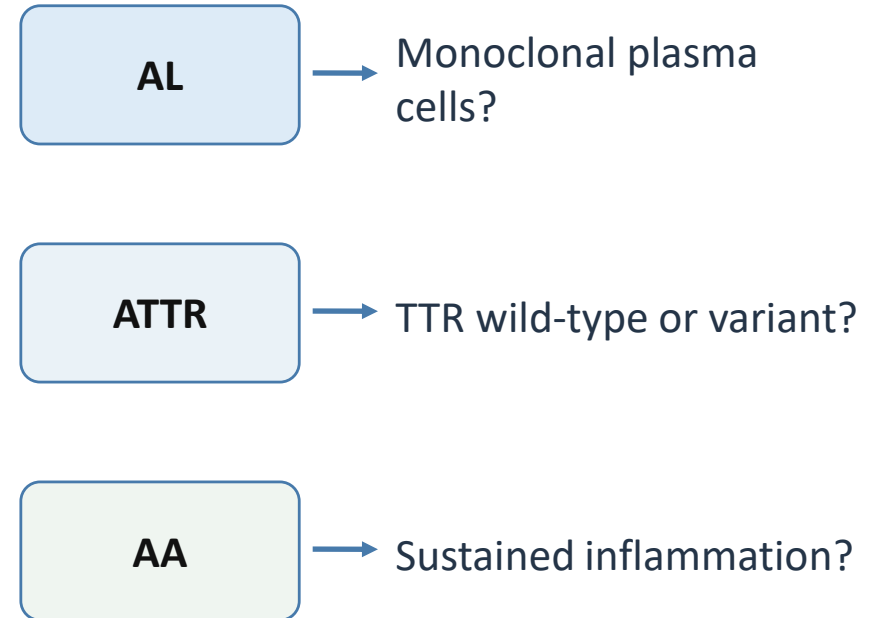


Schematic

Chemical typing changes the etiologic question

- If fibrils are AL, investigate the immunoglobulin light-chain source.
- If fibrils are ATTR, consider wild-type versus variant TTR.
- If fibrils are AA, examine the inflammatory/SAA pathway.

The type guides the next clinicopathologic question.

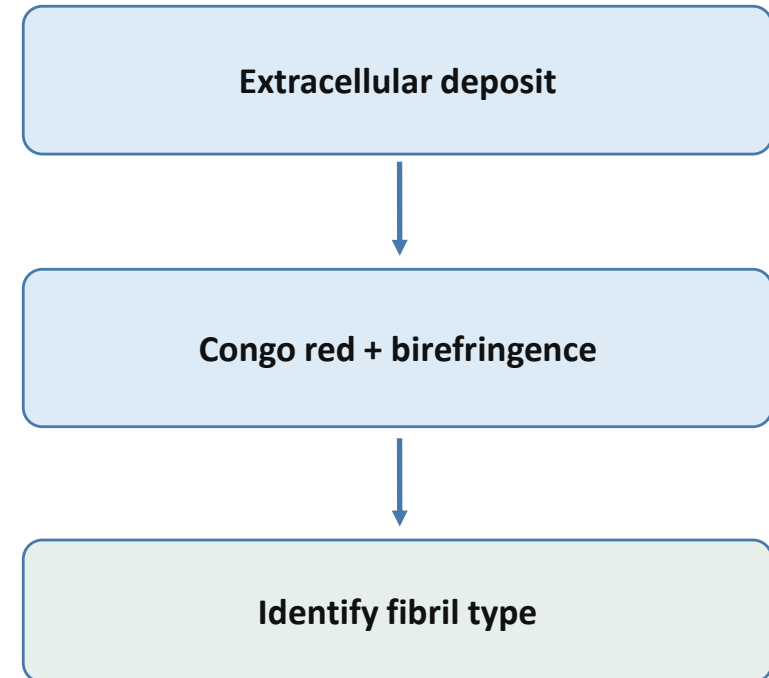


Schematic

Do not identify AL simply from birefringence

- An extracellular Congo red–positive deposit suggests amyloid.
- The structural stain does not specify the light-chain composition.
- AL requires evidence that the deposited fibril protein is light-chain derived.

Detection is necessary but insufficient for biochemical typing.



Schematic

Clinical exercise: Monoclonal light-chain production

- A patient has extracellular amyloid and a monoclonal plasma-cell population.
- Free Ig light chains are the candidate fibril precursor.
- Which biochemical amyloid type does this suggest, and why?

Identify the precursor

Ig light chain → AL

Expected reasoning: Precursor origin → AL.

Schematic

Clinical exercise: Cardiac amyloid in later life

- An older man has a cardiac amyloid deposit.
- Wild-type transthyretin is a recognized substrate in this setting.
- Which fibril type should be considered, without assuming it is proven?

Identify the precursor

Wild-type TTR → ATTRwt

Expected reasoning: Wild-type TTR → possible ATTRwt.

Schematic

Clinical exercise: Long-standing inflammation

- A patient with chronic inflammatory disease develops tissue amyloid.
- The liver produces increased SAA during the acute-phase response.
- Which proteolytic product forms the relevant fibrils?

Identify the precursor

SAA → AA

Expected reasoning: SAA processing → AA.

Schematic

Clinical exercise: Distinct cerebral deposits

- Amyloid occurs in an Alzheimer-type cerebral plaque.
- The implicated peptide is derived from a transmembrane precursor.
- Name the peptide and its larger source protein.

Identify the precursor

APP → Aβ

Expected reasoning: Aβ is produced from APP.

Schematic

Clinical exercise: Amyloid around joints

- A long-term hemodialysis patient has periarticular amyloid.
- The precursor is normally part of MHC class I complexes.
- Which fibril protein does this point toward?

Identify the precursor

β_2 -microglobulin

Expected reasoning: β_2 -microglobulin $\rightarrow$ A β_2 m.

Schematic

Chemical identity and organ site: A reasoning grid

- AL: Immunoglobulin-derived, often associated with plasma-cell proliferation.
- ATTR: TTR-derived, particularly relevant to cardiac and neural deposits.
- AA: SAA-derived, linked to inflammatory states.
- Other types: A β , A β_2 m, and occasional prion amyloid.

Map tissue findings to possible precursors—not to a single automatic diagnosis.

Source

Identify producing system

Tissue

Recognize distribution

Fibril

Determine biochemical type

Schematic

Five biochemical distinctions to retain

- Amyloid deposits have common β -pleated fibril organization but many protein origins.
- Approximately 95% of deposit mass is fibril protein.
- AL, ATTR, and AA have distinct precursor molecules.
- A β and A β_2 m are different proteins despite similar abbreviations.

Chemical type should be specified separately from the demonstration of amyloid.

Conformation

Protein fraction

AL / ATTR / AA

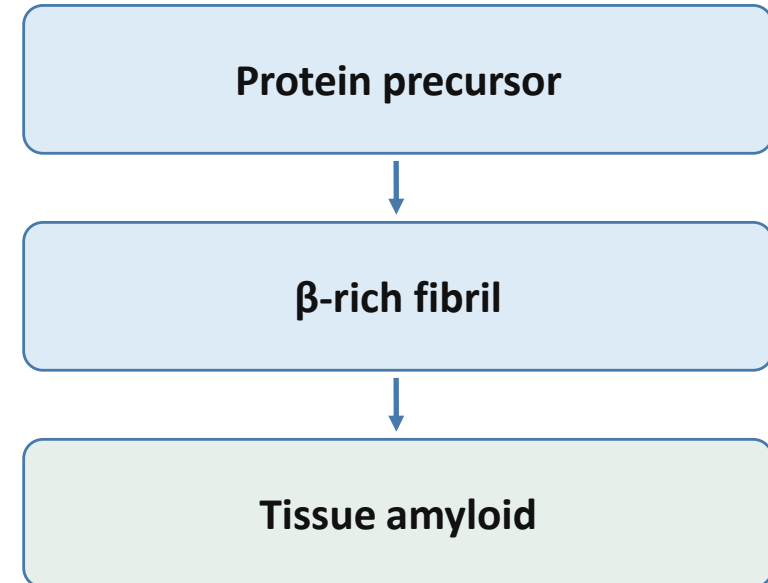
Other precursors

Schematic

Integrating structural and chemical evidence

- Electron-microscopic structure explains similar Congo red behavior.
- Chemical precursor explains differences among amyloid diseases.
- Clinical context narrows hypotheses but does not replace typing.

Best mental model: Shared fibril architecture + distinct precursor protein.



Schematic

Selected source and interpretation notes

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), section: Amyloidosis.
- Primary section: Chemical Nature of Amyloid; contextual sections: Properties and Physical Nature of Amyloid.
- Adjacent topics provide limited context on pathogenesis, AL, ATTR, and AA; no outside clinical criteria were introduced.
- All visuals are editable teaching schematics; none represents an authentic microscopic specimen.