

Filamin-A

Hans Vilu / 8 slides / Target 7:00 / Limit 10:00

01 Filamin-A

0:00-0:45

Filamin-A connects the structure of a cell with the forces acting on it. I will explain how its molecular structure makes that possible, and why this matters in medicine.

It is a polypeptide protein, about 280 kDa per chain.

- **Organises actin microfilaments into networks.**
- **2,647 amino acids per chain.** This is the canonical human sequence.
- **An N-terminal actin-binding domain plus 24 immunoglobulin-like repeats.** These occur in each chain.
- **Normally functions as a homodimer.** Two identical Filamin-A chains join together.

02 A flexible link inside cells

0:45-1:55

- **Identity.** Intracellular actin-binding protein; cross-links filaments into a flexible network.
- **Architecture.** Two identical chains, approximately 280 kDa each; actin-binding region and 24 repeats per chain.
- **Structure enables function.** Two actin-binding ends connect two filaments. Repeat 24 forms the dimer interface.
- **Why the hinges matter.** Flexible arms support a branching network that can deform, rather than only parallel bundles.
- **Distinction.** Binding and organisation, not an ATP-driven motor.

03 What the folded protein looks like

1:55-2:55

- **Identify the images.** Experimental fragments: the actin-binding region and repeats 19-21.
- **Recognise the folds.** Alpha helices on the left; beta-rich domains on the right.
- **Why folding matters.** Side-chain arrangement gives a binding surface its shape and chemical properties.
- **Connect to the course.** Complementary partners bind through noncovalent interactions; binding is selective and reversible.
- **Avoid confusion.** Immunoglobulin-like fold does not mean antibody.

04 Support that can sense force

2:55-4:00

First, Filamin-A links the cell membrane to the actin cytoskeleton. Integrins sit in the membrane, and Filamin-A can connect them to actin. This creates a path for mechanical force to travel through the cell.

1. **Then force changes Filamin-A's shape.** In one well-studied region, repeat 20 partly covers a binding site on repeat 21.
2. **When Filamin-A is pulled, this site becomes more exposed.** The amino-acid sequence stays the same, but the protein changes conformation.
3. **Now another protein can bind to that exposed site.** So a mechanical input — force — causes a biochemical change — new protein binding.

This is called mechanotransduction. Filamin-A is therefore not only a structural cross-linker, but also a force-sensitive scaffold.

05 A working example: platelets

4:00-5:10

- **Production first.** In experimental mice, Filamin-A-deficient megakaryocytes release oversized, fragile platelets prematurely.
- **Physiological context.** Platelets attach, spread and coordinate cytoskeletal forces during clot formation.
- **Filamin-A's contribution.** Connects receptor-associated complexes with actin.
- **Read the structure.** Teal = domain 21 of 24. Violet = integrin-tail fragment. The pointer marks the binding interface.
- **Course connection.** Selective protein-protein binding links a receptor to the cell interior.

06 When Filamin-A changes

5:10-6:10

- **Clinical example.** FLNA loss-of-function variants can cause periventricular nodular heterotopia and seizures.
- **Principle.** A protein defect can disrupt tissue development and organisation.
- **Structure-function contrast.** Some skeletal-disorder variants increase actin binding without destroying the overall fold. Stronger is not necessarily better.
- **Methods.** Western blot: approximately 280-kDa chain. Clinical context: MRI and genetic testing.

07 Sensing an abnormal neighbour

6:10-6:55

- **Experimental finding.** Filamin-A-dependent force sensing helped normal cells respond to transformed neighbours.
- **Importance.** Connects mechanics with tissue-level defence.
- **Limit.** Cell-culture research, not an established treatment.
- **Closing idea.** Two-ended architecture, folded binding surfaces and force-sensitive domain arrangement explain its functions.

Study reference / Not spoken

Wen J, Sai K, Masutani S, et al. Filamin–ETV4/5 acts as mechanosensor–mechanotransducer axis that drives cell competition-mediated elimination of transformed cells. *Nature Communications*. 2026;17:6701. Published 21 May 2026. DOI: 10.1038/s41467-026-73504-3.

08 Thank you

6:55-7:00

- **Close.** Thank you.

Just in case

Slide 2 / A flexible link inside cells

From a chain of amino acids to a cross-link

Read the diagram

1. **One arm = one polypeptide.** The V is a schematic of two long chains, not a photograph or a rigid shape. Each chain has 2,647 amino-acid residues in the canonical human sequence.
2. **Outer ends = actin-binding regions.** Each end can associate with an existing actin filament. Filamin-A does not turn into actin and does not join the filaments by making peptide bonds between them.
3. **Arms = folded repeats and flexible connections.** Each chain contains 24 compact immunoglobulin-like domains. Flexible hinges lie between repeats 15 and 16, and between repeats 23 and 24. They permit changes in the angle and arrangement of the arms.
4. **Meeting point = dimerisation.** Repeat 24 on one chain associates with repeat 24 on the other. Two approximately 280-kDa subunits give a homodimer of approximately 560 kDa.

Why this architecture is useful

1. **Two attachment points.** A cross-link needs to engage separate filaments. Dimerisation brings two actin-binding ends into the same molecule, creating that bridging arrangement.
2. **A branching network.** The arms can engage differently oriented filaments. Many such connections help form a three-dimensional network rather than simply a bundle of parallel filaments.
3. **Support with flexibility.** The hinges provide flexible connections between folded regions. A network can change its geometry under load while retaining many of its connections. Flexibility does not mean the protein provides no support.

Where in the cell?

- Filamin-A is found in the cytoplasm, including the actin-rich cortex just beneath the plasma membrane. This is a useful position for linking membrane-associated proteins to the internal actin network.

Actin versus myosin versus Filamin-A

- Actin supplies the filaments. Myosin uses ATP to generate force by interacting with actin. Filamin-A connects filaments and other proteins, helping the network transmit and respond to force. These are complementary jobs, not three names for the same protein.

Questions about identity

- **Is Filamin-A fibrous or globular?** It is an elongated cytoskeletal cross-linker built from compact folded domains. Describing it only as a compact globular protein misses its architecture; describing it as a collagen-like extracellular fibre is also misleading.

- **Is it the only filamin?**. No. Humans also have Filamin-B and Filamin-C. This presentation concerns Filamin-A, encoded by FLNA; findings about the other isoforms should not automatically be assigned to it.
- **Why two chains?**. Dimerisation produces two actin-binding ends. This enables cross-linking rather than just attachment to one filament.

Slide 3 / What the folded protein looks like

How to read a protein ribbon

What the ribbons represent

- A ribbon follows the folded protein backbone. Coiled ribbons show alpha helices, broad arrows show beta strands, and thin connections show intervening loops. Side chains and most individual atoms are omitted so the fold is readable.

Left: the actin-binding region

- This isolated fragment contains two calponin-homology domains. Their arrangement helps create the actin-binding interface. Actin itself is not present in this image. The green colour identifies the fragment; it is not the natural colour of a protein.

Right: a small part of an arm

- This fragment contains repeats 19, 20 and 21, not all 24 repeats. Blue identifies domain 19, coral domain 20 and teal domain 21. The colours separate regions of this one chain; they do not represent the two arms of the dimer. The same coral/teal distinction continues on the next slide, and domain 21 remains teal in the platelet example.

The four levels of structure

1. **Primary.** The amino-acid sequence, joined by covalent peptide bonds.
2. **Secondary.** Local alpha helices and beta sheets, stabilised largely by hydrogen bonds between backbone groups.
3. **Tertiary.** The three-dimensional arrangement of a single chain, including its domains and binding surfaces.
4. **Quaternary.** The association of the two Filamin-A chains into the functional homodimer.

Why a ligand fits

- A binding site is a surface with a suitable shape and chemical groups. Hydrogen bonds, electrostatic interactions, hydrophobic contacts and van der Waals interactions can stabilise binding. The interaction can be reversible without being weak or unimportant.

Questions about structure

- **Are these photographs?** No. They are ribbon renderings of experimentally determined atomic coordinates. The colours and viewing angle were chosen for clarity. They are not imagined molecular structures.

- **Does immunoglobulin-like mean immune function?** No. A similar domain fold can serve different purposes. Here it provides a structural unit and binding surfaces; it is not an antigen-specific antibody.
- **What if a residue changes?** A substitution can change local charge, packing, stability or binding. The whole fold need not collapse for function to change. Some substitutions have little functional effect.

Slide 4 / Support that can sense force

Follow the force, then the binding change

Outside to inside

1. **Attachment.** An integrin spans the plasma membrane. Its extracellular region binds material outside the cell; its cytoplasmic tail can interact with intracellular proteins.
2. **Mechanical connection.** Filamin-A can connect receptor-associated complexes to actin. Pulling on the attachment, or myosin-generated tension inside the cell, can load this connection.
3. **Structural response.** In the repeat 20-21 pair, part of repeat 20 can mask a ligand-binding surface on repeat 21. Force can favour a more open, accessible arrangement.
4. **Biochemical consequence.** A partner that can reach the exposed site may bind more readily. A physical input has changed a molecular interaction.

What actually moves?

- Protein segments shift relative to each other; some local unfolding may occur under force. A ligand also moves through the cytoplasm and can associate with an accessible site. Filamin-A is not sending a tiny object along its arm to carry a message.

Not all stretching is the same

- The gate is an analogy for accessibility, not an all-or-nothing switch. Force can shift how often a site is accessible. The diagram simplifies a particular domain arrangement; it does not mean that every Filamin-A site is normally hidden, that every ligand binds more strongly under tension, or that unlimited force is beneficial.

Scaffold versus enzyme

- A scaffold organises binding partners in space. An enzyme catalyses a chemical reaction. Filamin-A's central role here is scaffolding and mechanical regulation, rather than catalysis or ATP hydrolysis.

Questions about the mechanism

- **Does Filamin-A use ATP to pull?** Not as a motor in this mechanism. Myosin can supply force; Filamin-A binds, transmits force and changes the accessibility of some binding sites.
- **Is force-induced opening denaturation?** It may involve local rearrangement or partial unfolding rather than complete loss of the entire protein's structure. Reversible regulation is different from indiscriminate damaging denaturation.

- **Does Filamin-A go to DNA to relay this force?** That is not what the slide shows. A changed binding interaction can influence downstream signalling. Filamin-A is not presented here as a transcription factor.

Slide 5 / A working example: platelets

From a vessel injury to a molecular contact

Before the mature platelet: production

- Megakaryocytes are large bone-marrow cells that produce platelets. In Begonja and colleagues' experimental mouse model, loss of Filamin-A in this cell lineage led to premature release of oversized, mechanically unstable platelets. They fragmented and were removed rapidly by macrophages. This supports a role in platelet formation and survival, as well as mature platelet function; it is not a claim that every human FLNA variant has the same effect.

The physiological sequence

1. **Injury exposes an adhesive surface.** Platelets attach through several receptor systems. Adhesion and activation change their shape and promote further platelet recruitment.
2. **The internal network reorganises.** Actin assembly and myosin activity help platelets spread and generate contractile force. Filamin-A contributes connections and organisation; it does not perform every step alone.
3. **Receptors communicate with the interior.** Integrin alpha-IIb/beta-3 participates in platelet aggregation. Connections involving its cytoplasmic tails help coordinate receptor attachment with the cytoskeleton.

Exactly what is in the image?

- Teal is domain 21 of Filamin-A's 24 repeat domains. Violet is an alpha-IIb integrin cytoplasmic-tail fragment bound to it. The pointer marks their contact region, located from the experimental coordinates. This is a local interface, not the entire receptor, an actin filament or a whole platelet. One representative structure from the NMR ensemble is shown.

What it demonstrates, and what it does not

- The image demonstrates a binding arrangement. By itself it cannot show a platelet moving, prove how much force it generates, or establish the timing of every signalling step. Integrin regulation also involves other proteins, including talin; Filamin-A is not a universal on-switch.

Two uses of the word protein

- Both binding partners are proteins or protein fragments. A ligand does not have to be a small molecule such as oxygen: one protein can be a ligand for another protein's binding surface.

Questions about the physiological example

- **Does Filamin-A have another role in platelets?** Yes. It contributes to platelet production from megakaryocytes and to platelet stability. In an experimental mouse study, its absence caused premature release of large, fragile platelets that were cleared rapidly from the circulation. This is separate from its role linking receptors to actin in mature platelets.

- **Does this alone make a blood clot?** No. Platelet receptors, actin, myosin, adhesive proteins and the coagulation system all contribute. Filamin-A is one part of the organisation and mechanical coupling.
- **Which partner is the ligand?** When discussing Filamin-A's site, the integrin-tail peptide is the ligand. The term describes the binding relationship, not a special class of small molecules.

Slide 6 / When Filamin-A changes

Connect a molecular defect to a clinical finding

A teaching example, not a reported patient

- Imagine a person assessed for seizures whose MRI shows nodules of grey matter along the lateral ventricles. One possible explanation is FLNA-related periventricular nodular heterotopia. MRI appearance and symptoms alone do not prove which gene is responsible.

Periventricular nodular heterotopia (PVNH): word by word

1. **Peri- = around or surrounding.** This prefix tells you where something is located.
2. **Ventricular = relating to the ventricles.** The brain's ventricles are fluid-filled spaces. Together, peri- and ventricular mean around or beside these spaces.
3. **Nodular = forming nodules.** Nodules are small rounded lumps or clusters. Here, they are clusters of neurons.
4. **Hetero- = different or other.** This is the first part of heterotopia.
5. **-topia = place or location.** Heterotopia means tissue in an abnormal location, not necessarily abnormal-looking cells.

Put together

- Periventricular nodular heterotopia means small clusters of brain tissue in an abnormal position beside the brain's ventricles.

What happens during brain development?

1. **Normally.** During fetal development, many neurons are produced near the ventricles and migrate outward to their places in the cerebral cortex.
2. **In PVNH.** Some neurons do not reach their usual cortical position. Instead, they remain as nodules along the walls of the ventricles. This describes the outcome; the underlying developmental mechanisms are more complex.

Memory cue

- Peri = around; ventricular = ventricles; nodular = little clusters; heterotopia = wrong place.

Why does a structural protein affect the brain?

- Neural development depends on coordinated cell shape, adhesion, tissue integrity and migration. Defective Filamin-A can disrupt these processes. It is too simple to describe it as one broken motor preventing every neuron from walking to its destination.

Different variants, different effects

- A loss-of-function variant reduces an important normal activity or the amount of functional protein. Other variants can alter binding or regulation differently, including gain-of-function mechanisms in some skeletal disorders. Not every FLNA variant causes the same disease or is pathogenic.

A concrete sequence-to-function example

- In experiments on the isolated actin-binding region, the skeletal-disorder variant E254K increased actin binding even though the overall fold remained similar. E254K means glutamate at residue 254 is replaced by lysine: a negatively charged side chain is replaced by a positively charged one. A local stabilising interaction is lost, illustrating how local chemistry can alter function without a complete structural collapse. The molecular image on slide 3 shows the wild-type fragment, not this variant.

What would the laboratory methods tell us?

1. **SDS-PAGE.** Denatured proteins are separated mainly by size. Filamin-A's identical chains run at approximately 280 kDa, not as an intact approximately 560-kDa dimer.
2. **Western blot.** Proteins are transferred to a membrane and probed with an antibody. A band helps identify Filamin-A; abundance alone does not prove normal function.
3. **Immunofluorescence.** A fluorescent antibody can show where Filamin-A is in cells. Co-localisation with actin suggests proximity, not proof of direct binding.
4. **Clinical assessment.** MRI examines the brain's structure; genetic testing examines the FLNA sequence. Neither is the same question as measuring the amount of protein in an experimental cell lysate.

Questions linking the case to the laboratory

- **Why one 280-kDa band, not two?.** The two chains are identical in size and migrate together after dissociation. A single band can contain many molecules of the same chain; it does not mean the intact protein was a monomer.
- **Can a normal blot exclude a functional defect?.** No. A variant may leave the protein amount and approximate mass normal while altering binding or regulation. Functional assays and genetic context answer different questions.
- **Does every patient have seizures?.** No. Clinical manifestations vary. FLNA-associated disease can involve several organs; this talk uses one recognised example rather than a universal presentation.

Slide 7 / Sensing an abnormal neighbour

Separate the finding from the possible application

What was studied?

- Researchers used cultured mouse epithelial cells alongside Ras-transformed cells. Filamin-A depletion impaired the elimination response. The work connected mechanical sensing to ETV4/5-dependent gene regulation and PRKG2, while leaving parts of the intervening mechanism unresolved.

What can we conclude?

- The study supports a role for Filamin-A in this experimental form of cell competition. It does not demonstrate a safe drug, a benefit in patients, or a reason to increase Filamin-A everywhere in the body.

How to describe the diagram

- It is a conceptual diagram of neighbouring cells and extrusion, not microscopy from the study. An upward arrow means removal from the epithelial layer, not necessarily that the cell immediately dies.

Terms for questions

Protein structure

- **Filamin-A.** An intracellular protein that cross-links actin filaments and binds other proteins, linking the cytoskeleton to adhesion and force-sensitive regulation.
- **Protein.** A molecule made of one or more folded amino-acid chains. Different structures allow proteins to bind, support, transport or catalyse reactions.
- **Amino acid.** A building block of proteins. Each has an amino group, a carboxyl group and a side chain that helps determine its chemical properties.
- **Residue.** An amino-acid unit within a polypeptide after it has been incorporated into the chain.
- **E254K.** A substitution in which glutamate (E) at position 254 is replaced by lysine (K). In Filamin-A's actin-binding region, this studied variant alters binding without destroying the overall fold.
- **Glutamate.** An amino acid whose side chain is usually negatively charged at physiological pH. Its one-letter code is E.
- **Lysine.** An amino acid whose side chain is usually positively charged at physiological pH. Its one-letter code is K.
- **Polypeptide.** A chain of amino-acid residues joined by peptide bonds. A protein may contain one or several such chains.
- **Peptide bond.** The covalent amide bond joining the carboxyl group of one amino acid to the amino group of another.
- **Peptide.** A relatively short amino-acid chain. A small peptide segment can still form an important binding interface.
- **Canonical.** The standard reference sequence used for a protein. Alternative forms can differ from it.
- **Kilodalton.** A unit of molecular mass: one kilodalton is 1,000 daltons. Filamin-A is approximately 280 kDa per full-length chain.
- **Subunit.** One component chain of a multi-chain protein complex.
- **Homodimer.** A complex of two identical protein subunits. Homo means same; dimer means two units.
- **Dimer.** A two-subunit complex, or the process by which its two subunits associate.
- **Domain.** A region of a protein that forms a recognisable three-dimensional fold, often with a particular function.
- **N-terminal.** The end of a polypeptide chain with a free amino group. Filamin-A's actin-binding domain is near this end.
- **Microfilament.** Another name for actin filaments: thin protein fibres that help support the cell and enable movement.
- **Repeat.** A recurring sequence or structural unit within one protein. Filamin-A has 24 immunoglobulin-like repeats per chain.
- **Immunoglobulin-like.** A beta-rich fold resembling a domain found in antibodies. Many non-antibody proteins use this fold too.

- **Immunoglobulin.** An immune protein with specific antigen-binding sites. Filamin-A is not an antibody despite having immunoglobulin-like domains.
- **Calponin-homology domains.** A family of compact, alpha-helix-rich protein domains. Two occur together in Filamin-A's actin-binding region.
- **Hinge.** Flexible regions that permit adjacent parts of a protein to change their relative orientation.
- **Primary structure.** The order of amino-acid residues in a protein chain.
- **Secondary structure.** Local backbone arrangements such as alpha helices and beta sheets.
- **Alpha helix.** A coiled secondary structure held by a repeating pattern of backbone hydrogen bonds.
- **Beta sheet.** A beta strand is an extended stretch of backbone; neighbouring strands form a sheet through hydrogen bonds.
- **Tertiary structure.** The overall three-dimensional arrangement of a single protein chain.
- **Quaternary structure.** The arrangement of separate protein subunits in a complex, such as Filamin-A's two chains.
- **Protein backbone.** The repeating main chain of a polypeptide, excluding the amino-acid side chains.
- **Side chain.** The variable group on each amino acid, determining properties such as charge and hydrophobicity.
- **Fold.** The three-dimensional arrangement a protein chain adopts. Folding places distant sequence regions next to one another.
- **Conformation.** The spatial arrangement of a molecule. It can change without changing its amino-acid sequence.
- **Denaturation.** Loss of some or all of a protein's normal folded structure. Ordinary denaturation does not cut the chain's peptide bonds.

Cells and mechanical function

- **Cell.** The basic living unit of an organism, bounded by a membrane and containing molecular machinery for its functions.
- **Tissue.** An organised group of cells and surrounding material working together, such as an epithelial layer.
- **Signalling.** Communication that changes a cell's behaviour through molecular interactions. It may involve a relay of binding and chemical reactions.
- **Nucleus.** The membrane-enclosed compartment containing most of a human cell's DNA. Platelets have no nucleus.
- **Cytosol.** The fluid component of the cytoplasm, in which many soluble molecules and reactions are found.
- **Organelle.** Specialised structures inside a cell, such as mitochondria, that carry out particular functions.
- **Coagulation.** Coagulation generates fibrin, a protein network that stabilises a blood clot. This complements the platelet response.
- **Antigen.** An antigen is a molecular structure recognised by immune receptors or antibodies. Antigen-specific means recognising a particular antigen.

- **Actin.** Actin subunits assemble into long filaments. These support cell shape and participate in movement, adhesion and contraction.
- **Filament.** A long, thin assembly of repeating protein subunits, such as an actin filament.
- **Cytoskeleton.** The internal network of protein filaments that organises a cell and helps it withstand force, move and change shape.
- **Cross-link.** A connection between separate structures. Filamin-A binds two actin filaments; it does not make a new peptide bond joining them.
- **Intracellular.** Inside a cell, rather than outside it.
- **Extracellular.** Outside a cell. A membrane receptor may have both extracellular and intracellular portions.
- **Cytoplasm.** The cell's contents outside the nucleus, including cytosol, organelles and cytoskeletal structures.
- **Cell cortex.** The layer of actin-rich cytoskeleton just beneath the plasma membrane; it helps control surface shape and tension.
- **Plasma membrane.** The lipid bilayer surrounding a cell, containing proteins for transport, attachment and signalling.
- **Integrin.** A two-subunit membrane receptor that links extracellular binding to cell adhesion and intracellular responses.
- **Alpha-IIb/beta-3.** Alpha-IIb and beta-3 are the two subunits of a major platelet integrin. Its extracellular binding supports aggregation; intracellular tails connect to regulatory proteins.
- **Receptor.** A protein that recognises a binding partner and connects that interaction with a cellular response.
- **Cytoplasmic tail.** The short part of a membrane protein that projects into the cell and can bind intracellular partners.
- **Adhesion.** The association of a cell with another cell or its surroundings through molecular interactions.
- **Ligand.** A molecule that binds a particular site on another molecule. It can be a small molecule, peptide or whole protein.
- **Binding site.** A molecular region whose shape and chemical groups allow a particular partner to associate with it.
- **Interface.** The contacting surfaces where two molecular partners meet.
- **Protein-protein recognition.** Selective association between protein surfaces with compatible shapes and chemical properties.
- **Hydrogen bond.** A directional noncovalent interaction involving a hydrogen atom and electronegative atoms. Many together stabilise protein structures.
- **Electrostatic interactions.** Attraction or repulsion involving electrical charges, such as oppositely charged amino-acid side chains.
- **Hydrophobic contacts.** Nonpolar groups tend to associate away from water. This helps stabilise protein interiors and some binding interfaces.
- **Van der Waals interactions.** Short-range interactions between closely packed atoms, contributing to molecular fit and stability.

- **Noncovalent.** Interactions that do not create a shared-electron covalent bond. Together they can still produce stable, selective binding.
- **Covalent.** A chemical bond involving shared electrons, such as a peptide bond.
- **Affinity.** How strongly two partners associate at equilibrium. It is not the same as how much protein is present.
- **Reversible.** Able to proceed in both directions, such as a ligand binding and later dissociating.
- **Myosin.** An actin-associated motor protein that uses ATP to generate mechanical force.
- **ATP.** ATP is a nucleotide that transfers chemical energy. Hydrolysis of ATP can power processes such as myosin movement.
- **Enzyme.** An enzyme accelerates a chemical reaction without being consumed; this activity is catalysis.
- **Scaffold.** A protein that organises other molecules through binding. Regulating site access can change which partners assemble.
- **Mechanotransduction.** Mechanosensing detects force or deformation. Mechanotransduction converts that mechanical input into a biochemical or cellular response.
- **Tension.** Tension is a pulling force. Mechanical inputs can deform protein structures and change molecular interactions.
- **Autoinhibition.** A molecule's own structure restrains an activity or blocks access to a binding site.
- **Talin.** An intracellular protein that binds integrin tails and actin and plays an important role in integrin activation and adhesion.
- **Platelet.** Small anucleate blood-cell fragments that adhere and aggregate at vessel injury and contribute to haemostasis.
- **Megakaryocyte.** A large bone-marrow cell that produces platelets by releasing portions of its cytoplasm.
- **Macrophage.** An immune cell that engulfs microbes, damaged material and cells or cell fragments being cleared from tissues or blood.
- **Aggregation.** Platelets joining together, supported by adhesive molecules that bridge activated receptors.
- **Clot.** Haemostasis stops bleeding through platelet responses and coagulation. A clot contains a platelet/fibrin structure.
- **Contractile.** Related to pulling or shortening generated by cellular machinery such as actin and myosin.
- **Cell migration.** Directed cell movement or the ability to move, requiring coordination of shape, adhesion and force.

Disease and laboratory methods

- **FLNA.** The X-chromosomal gene encoding Filamin-A. The gene and the protein it encodes are not the same physical molecule.
- **Gene.** A DNA sequence containing information used to produce a functional RNA or protein product.
- **DNA.** The nucleic acid that stores genetic information in its base sequence.
- **Variant.** A change in a DNA sequence. Its effect depends on the change; not every variant causes disease.

- **Loss-of-function.** A change that reduces or removes an important normal activity or the amount of functional protein.
- **Gain-of-function.** A change producing increased, altered or new molecular activity, rather than simply loss of protein.
- **Pathogenic.** Capable of causing disease in the relevant context; not a label for every sequence difference.
- **Periventricular nodular heterotopia.** Clusters of neurons beside the brain's ventricles rather than in their usual cortical location; certain FLNA variants are one cause.
- **Periventricular.** Located around or beside the brain's ventricles.
- **Ventricular.** Relating to a ventricle. Here it refers to the brain's fluid-filled spaces, not the heart's pumping chambers.
- **Fetal.** Relating to the developing baby before birth, after the early embryonic stage.
- **Nodular.** Arranged in small rounded clusters or lumps.
- **Heterotopia.** A normally recognisable tissue present in an abnormal anatomical location.
- **Neuron.** A neuron is a nerve cell specialised for receiving and transmitting information. Neural means relating to the nervous system.
- **Ventricle.** In this presentation: fluid-filled spaces in the brain, not the pumping chambers of the heart.
- **Cortical.** The cerebral cortex is an outer brain region rich in neuronal cell bodies. Grey matter refers to tissue rich in those cell bodies and their connections.
- **Seizure.** An episode caused by abnormal excessive or synchronised brain electrical activity; manifestations vary.
- **MRI.** Magnetic resonance imaging uses magnetic fields and radiofrequency signals to form detailed images of internal structures.
- **Genetic testing.** Examining DNA for changes that may explain an inherited or genetic condition.
- **SDS-PAGE.** SDS-PAGE separates detergent-denatured proteins through a gel mainly by molecular size; smaller proteins generally travel farther.
- **Western blot.** A method that transfers gel-separated proteins to a membrane and uses antibodies to detect a selected protein.
- **Band.** A visible region of a gel or blot where molecules of a similar apparent size accumulate.
- **Immunofluorescence.** Using fluorescently labelled antibodies, directly or indirectly, to show where an antigen such as Filamin-A is located.
- **Co-localisation.** Signals appearing in the same region of an image. This alone does not demonstrate direct molecular binding.
- **Cell lysate.** The mixture released when cells are broken open for laboratory analysis.
- **Biomarker.** A measurable biological feature used to inform health or disease assessment. Not every clinically important protein is a routine blood biomarker.
- **X-ray crystallography.** A method that uses diffraction from a crystal to infer molecular structure.
- **NMR.** Nuclear magnetic resonance provides structural information from atomic nuclei in magnetic fields. An ensemble contains multiple models consistent with the experimental restraints.

Research vocabulary

- **Isoform.** Related versions of a protein. Filamin-A, -B and -C are encoded by different genes; alternative forms can also arise from a single gene.
- **CGMP.** Cyclic guanosine monophosphate, an intracellular signalling molecule that can activate certain protein kinases.
- **Phosphate group.** A phosphorus-containing chemical group. Adding one to a protein can change its charge, shape or interactions.
- **Epithelial.** Epithelium is a layer of closely connected cells covering a surface or lining an organ. Epithelial cells form that layer.
- **Cell culture.** Cells grown under controlled laboratory conditions outside the organism.
- **Transformed cells.** In this experiment, cells with cancer-associated changes in growth regulation. An altered laboratory cell is not equivalent to a patient's tumour.
- **Ras.** Ras proteins regulate signalling pathways controlling growth and other cell behaviours. A persistently active cancer-associated form is used in some transformation models.
- **Cell competition.** Interactions in which differences between neighbouring cells influence which cells remain in a tissue.
- **Extrusion.** Removal of a cell from an epithelial layer. Extrusion describes a movement, not necessarily immediate cell death.
- **Depletion.** An experimental reduction in the amount of a gene product, used to test its contribution to a process.
- **Gene regulation.** Control of when and how much a gene is expressed; cells can respond to stimuli by changing gene expression.
- **ETV4/5.** Two related transcription factors. They help regulate gene expression by interacting with DNA regulatory regions.
- **Transcription factor.** A protein that helps control transcription by interacting with DNA regulatory sequences and other proteins.
- **Transcription.** Transcription copies DNA information into RNA. Gene expression includes using genetic information to produce functional RNA or protein.
- **RNA.** A nucleic acid with roles including carrying protein-coding messages and helping cells produce proteins.
- **PRKG2.** The gene encoding cGMP-dependent protein kinase II, an enzyme that phosphorylates target proteins.
- **Phosphorylation.** Phosphorylation adds a phosphate group to a molecule. A protein kinase catalyses this reaction and can alter a target protein's activity or interactions.
- **Clinical.** Relating to people and their health or care. Clinical relevance does not by itself establish an effective treatment.
- **Physiological.** Relating to how a living organism normally functions, rather than only to what happens in disease.

Questions & Answers

1. What is Filamin-A, and what does it do?

An intracellular actin-binding protein that organises actin microfilaments into networks and connects them to other proteins, including membrane receptors.

2. How large is one Filamin-A chain?

About 280 kDa, with 2,647 amino acids in the canonical human sequence. A homodimer contains two such chains, approximately 560 kDa in total.

3. What are the main parts of each chain?

An N-terminal actin-binding domain followed by 24 immunoglobulin-like repeats, with two flexible hinge regions. Repeat 24 contributes to joining the two chains.

4. What does homodimer mean, and why is it useful here?

Two identical protein chains associate. This gives Filamin-A two actin-binding ends, so one molecule can connect two different actin filaments.

5. Does immunoglobulin-like mean Filamin-A is an antibody?

No. It describes the shape of a folded domain, not an antibody function. These beta-sheet-rich repeats provide structural units and protein-binding surfaces.

6. Which proteins are its binding partners?

Examples include actin, integrin cytoplasmic tails and other receptor-associated or signalling proteins. Different regions of Filamin-A recognise different partners.

7. How does Filamin-A turn force into a biochemical response?

Force can change its conformation. In the repeat 20-21 region, this can expose a binding site on repeat 21 and allow a new partner to bind. The amino-acid sequence does not change.

8. Does Filamin-A use ATP to move actin?

It is not an ATP-driven motor like myosin. Its role here is binding, organising and transmitting force through the actin network.

9. What are its two roles in platelets?

It helps link receptors to actin in mature platelets and contributes to platelet production and stability. In experimental mice, its absence caused premature release of large, fragile platelets from megakaryocytes.

10. What medical condition illustrates its importance?

Certain FLNA variants cause periventricular nodular heterotopia: clusters of neurons remain beside the brain's ventricles instead of reaching their normal cortical position. Seizures can occur.

11. What did the 2026 study show, and is it a treatment?

In cultured epithelial cells, Filamin-A-dependent force sensing helped normal cells respond to transformed neighbours through ETV4/5 and PRKG2. The normal cells enlarged and helped extrude the transformed cells. This is experimental tissue-defence research, not an established cancer treatment.