Amyloid Protein Profiles

Here we have compiled the relevant information for each protein surveyed by the accompanying review article to justify its inclusion in the review's purview. We name each protein (and its gene name) in our list, present a short description of it, name the disease or diseases its amyloid forms are associated with, describe the evidence of its amyloid nature, and describe the rationale for the amyloid mutation mechanisms assigned to it. The proteins are ordered alphabetically by protein name.

Amyloid-β precursor protein (APP)

Amyloid-β precursor protein is the protein which is cleaved by secretase complexes to produce the amyloid-β peptide. The function of amyloid-β is not entirely understood, but it has been proposed to have a variety of beneficial functions including antimicrobial activity, tumor suppression, blood-brain barrier upkeep, recovery from brain injury, and synaptic function regulation(Brothers, Gosztyla, and Robinson 2018). Aggregates of amyloid-β are a hallmark of Alzheimer's disease, cerebral amyloid angiopathy, and Down syndrome(Nilsberth et al. 2001; Masters et al. 1985; Melchor, McVoy, and Van Nostrand 2000; Van Nostrand et al. 2001). This peptide was identified as the main component of amyloid deposits in the brains of Alzheimer's patients and people with Down syndrome through mass spectrometry analysis of congophilic materials from patient brains(Masters et al. 1985; Glenner and Wong 1984; Kang et al. 1987). The pathogenic mutations in this protein can affect its cleavage by α-, β-, and γ-secretase(Selkoe 1999; Nilsberth et al. 2001; Haass et al. 1994; Watson, Selkoe, and Teplow 1999; Mullan et al. 1992; Citron et al. 1994; Hardy 1997) as well as result in a fiber structure which is more stable than the wild-type(Yang et al. 2023; Schütz et al. 2015), the mechanisms of fiber stabilization and altered processing were assigned to this protein's mutations.

Brothers, Holly M., Maya L. Gosztyla, and Stephen R. Robinson. 2018. "The Physiological Roles of Amyloid-β Peptide Hint at New Ways to Treat Alzheimer's Disease." *Frontiers in Aging Neuroscience* 10:118. https://doi.org/10.3389/fnagi.2018.00118.

Citron, M., C. Vigo-Pelfrey, D. B. Teplow, C. Miller, D. Schenk, J. Johnston, B. Winblad, N. Venizelos, L. Lannfelt, and D. J. Selkoe. 1994. "Excessive Production of Amyloid Beta-Protein by Peripheral Cells of Symptomatic and Presymptomatic Patients Carrying the Swedish Familial Alzheimer Disease Mutation." *Proceedings of the National Academy of Sciences of the United States of America* 91 (25): 11993–97. https://doi.org/10.1073/pnas.91.25.11993.

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Disease Amyloid A4 Protein Resembles a Cell-Surface Receptor." *Nature* 325 (6106): 733–36. https://doi.org/10.1038/325733a0.
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Melchor, J. P., L. McVoy, and W. E. Van Nostrand. 2000. "Charge Alterations of E22 Enhance the Pathogenic Properties of the Amyloid Beta-Protein." *Journal of Neurochemistry* 74 (5): 2209–12. https://doi.org/10.1046/j.1471-4159.2000.0742209.x.
Mullan, M., F. Crawford, K. Axelman, H. Houlden, L. Lilius, B. Winblad, and L. Lannfelt. 1992. "A Pathogenic Mutation for Probable Alzheimer's Disease in the APP Gene at the N-Terminus of Beta-Amyloid." *Nature Genetics* 1 (5): 345–47. https://doi.org/10.1038/ng0892-345.
Nilsberth, C., A. Westlind-Danielsson, C. B. Eckman, M. M. Condron, K. Axelman, C. Forsell, C. Stenh, et al. 2001. "The 'Arctic' APP Mutation (E693G) Causes Alzheimer's Disease by Enhanced Abeta Protofibril Formation." *Nature Neuroscience* 4 (9): 887–93. https://doi.org/10.1038/nn0901-887.
Schütz, Anne K., Toni Vagt, Matthias Huber, Oxana Y. Ovchinnikova, Riccardo Cadalbert, Joseph Wall, Peter Güntert, Anja Böckmann, Rudi Glockshuber, and Beat H. Meier. 2015. "Atomic-Resolution Three-Dimensional Structure of Amyloid β Fibrils Bearing the Osaka Mutation." *Angewandte Chemie (International Ed. in English)* 54 (1): 331–35. https://doi.org/10.1002/anie.201408598.
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Van Nostrand, W. E., J. P. Melchor, H. S. Cho, S. M. Greenberg, and G. W. Rebeck. 2001. "Pathogenic Effects of D23N Iowa Mutant Amyloid Beta -Protein." *The Journal of Biological Chemistry* 276 (35): 32860–66. https://doi.org/10.1074/jbc.M104135200.
Watson, D J, D J Selkoe, and D B Teplow. 1999. "Effects of the Amyloid Precursor Protein Glu693-->Gln 'Dutch' Mutation on the Production and Stability of Amyloid Beta-Protein." *Biochemical Journal* 340 (Pt 3): 703–9.
Yang, Yang, Wenjuan Zhang, Alexey G. Murzin, Manuel Schweighauser, Melissa Huang, Sofia Lövestam, Sew Y. Peak-Chew, et al. 2023. "Cryo-EM Structures of Amyloid-β Filaments with the Arctic Mutation (E22G) from Human and Mouse Brains." *Acta Neuropathologica* 145 (3): 325–33. https://doi.org/10.1007/s00401-022-02533-1.

Annexin A11 (ANXA11)

Annexin A11 is a calcium-dependent phospholipid-binding protein with functions in cell division, calcium signaling, vesicle trafficking, apoptosis, and RNA-binding(Dudas et al. 2024), and notably it is the only annexin family protein with a low-complexity domain. Annexin A11 has been shown to form amyloid fibrils in both wild-type and mutant forms *in vitro* through Congo red staining, proteinase K resistance, transmission electron microscopy, powder X-ray diffraction, and Thioflavin T fluorescence(Shihora et al. 2023). Recently, annexin A11 has been found aggregated in heteromeric fibrils composed of annexin A11 and TAR DNA-binding protein 43 which were extracted from patients with FTLD-TDP Type C(Arseni et al. 2024). This was shown through cryogenic electron microscopy of those extracted fibrils and determining the sequence of the protein directly from the well-resolved amino acid side chain densities of the cryo-EM reconstructions and comparing it against reference proteomes. The annexin A11 discovered

aggregated in these heteromeric fibrils was wild-type, but the protein is known to have mutations associated with ALS, inclusion body myopathy and FTD(Smith et al. 2017; Leoni et al. 2021; Johari et al. 2022; Kim et al. 2022). Homomeric annexin A11 fibrils have been shown to be dissolved by the protein S100A6, but when ALS-related variants are present, such as D40G and G175R, the kinetics are altered in a way that actually slows down fibril formation but makes the fibrils more resistant to dissolution by S100A6(Shihora et al. 2023). The proposed mechanism is that the mutations stabilize the fibril form, slowing the release of monomers from fibrils for S100A6 to siphon away from aggregates, which allows for the buildup of annexin A11 fibrils. Thus the amyloidogenic mechanisms of fibril stabilization and altered fibril homeostasis were assigned to the mutations of annexin A11. It should be noted, however, that the mechanism of fibril formation is likely completely different between homomeric annexin 11 fibrils and the heteromeric fibrils observed in FTLD-TDP Type C, and that tissue from cases of disease with aggregated annexin A11 exist that stain negative for the amyloid dye Thioflavin S(Robinson et al. 2024).

Arseni, Diana, Takashi Nonaka, Max H. Jacobsen, Alexey G. Murzin, Laura Cracco, Sew Y. Peak-Chew, Holly J. Garringer, et al. 2024. “Heteromeric Amyloid Filaments of ANXA11 and TDP-43 in FTLD-TDP Type C.” *bioRxiv: The Preprint Server for Biology*, June, 2024.06.25.600403. https://doi.org/10.1101/2024.06.25.600403.

Dudas, Erika F., Mark D. Tully, Tamas Foldes, Geoff Kelly, Gian Gaetano Tartaglia, and Annalisa Pastore. 2024. “The Structural Properties of Full-Length Annexin A11.” *Frontiers in Molecular Biosciences* 11:1347741. https://doi.org/10.3389/fmolb.2024.1347741.

Johari, Mridul, George Papadimas, Constantinos Papadopoulos, Sophia Xirou, Aikaterini Kanavaki, Margarita Chrysanthou-Piterou, Salla Rusanen, Marco Savarese, Peter Hackman, and Bjarne Udd. 2022. “Adult-Onset Dominant Muscular Dystrophy in Greek Families Caused by Annexin A11.” *Annals of Clinical and Translational Neurology* 9 (10): 1660–67. https://doi.org/10.1002/acn3.51665.

Kim, Eun-Joo, So Young Moon, Hee-Jin Kim, Na-Yeon Jung, Sun Min Lee, and Young Eun Kim. 2022. “Semantic Variant Primary Progressive Aphasia with a Pathogenic Variant p.Asp40Gly in the ANXA11 Gene.” *European Journal of Neurology* 29 (10): 3124–26. https://doi.org/10.1111/ene.15455.

Leoni, Tauana Bernardes, Carelis González-Salazar, Thiago Junqueira R. Rezende, Ana Luisa C. Hernández, Alexandre Hilário B. Mattos, Antônio Rodrigues Coimbra Neto, Felipe Franco da Graça, et al. 2021. “A Novel Multisystem Proteinopathy Caused by a Missense ANXA11 Variant.” *Annals of Neurology* 90 (2): 239–52. https://doi.org/10.1002/ana.26136.

Robinson, John L., EunRan Suh, Yan Xu, Howard I. Hurtig, Lauren Elman, Corey T. McMillan, David J. Irwin, Sílvia Porta, Vivianna M. Van Deerlin, and Edward B. Lee. 2024. “Annexin A11 Aggregation in FTLD-TDP Type C and Related Neurodegenerative Disease Proteinopathies.” *Acta Neuropathologica* 147 (1): 104. https://doi.org/10.1007/s00401-024-02753-7.

Shihora, Aman, Ruben D. Elias, John A. Hammond, Rodolfo Ghirlando, and Lalit Deshmukh. 2023. “ALS Variants of Annexin A11’s Proline-Rich Domain Impair Its S100A6-Mediated Fibril Dissolution.” *ACS Chemical Neuroscience* 14 (15): 2583–89. https://doi.org/10.1021/acschemneuro.3c00169.

Smith, Bradley N., Simon D. Topp, Claudia Fallini, Hideki Shibata, Han-Jou Chen, Claire Troakes, Andrew King, et al. 2017. “Mutations in the Vesicular Trafficking Protein Annexin A11 Are Associated with Amyotrophic Lateral Sclerosis.” *Science Translational Medicine* 9 (388): eaad9157. https://doi.org/10.1126/scitranslmed.aad9157.

Apolipoprotein A I (APOA1)

Apolipoprotein A I is a protein which binds cholesterol and phospholipids and is the principal component of high-density lipoproteins (HDL)(Arciello, Piccoli, and Monti 2016). This protein was first identified as a component of amyloid deposits when apolipoprotein A I with a G26R mutation was identified by amino acid sequence analysis of tryptic peptides from congophilic material from a patient's spleen with familial amyloid polyneuropathy type III(Nichols et al. 1988), and wild-type apolipoprotein A I was found to form amyloids when an N-terminal fragment was isolated from congophilic amyloid deposits in atherosclerotic plaques(Westermark et al. 1995). Mutations in this protein have various possible mechanisms associated with amyloid formation, depending on which mutation the protein has, including destabilization of the native structure, an increase in fiber-stabilizing β-sheet secondary structure, altered processing due to increased availability of the cleavage site which produces the amyloidogenic fragment, and decreased binding to its native lipid binding partners(Arciello, Piccoli, and Monti 2016; Obici et al. 2006; Lagerstedt et al. 2007; Raimondi et al. 2011).

Arciello, Angela, Renata Piccoli, and Daria Maria Monti. 2016. "Apolipoprotein A-I: The Dual Face of a Protein." *FEBS Letters* 590 (23): 4171–79. https://doi.org/10.1002/1873-3468.12468.

Lagerstedt, Jens O., Giorgio Cavigiolio, Linda M. Roberts, Hyun-Seok Hong, Lee-Way Jin, Paul G. Fitzgerald, Michael N. Oda, and John C. Voss. 2007. "Mapping the Structural Transition in an Amyloidogenic Apolipoprotein A-I." *Biochemistry* 46 (34): 9693–99. https://doi.org/10.1021/bi7005493.

Nichols, W. C., F. E. Dwulet, J. Liepnieks, and M. D. Benson. 1988. "Variant Apolipoprotein AI as a Major Constituent of a Human Hereditary Amyloid." *Biochemical and Biophysical Research Communications* 156 (2): 762–68. https://doi.org/10.1016/s0006-291x(88)80909-4.

Obici, Laura, Guido Franceschini, Laura Calabresi, Sofia Giorgetti, Monica Stoppini, Giampaolo Merlini, and Vittorio Bellotti. 2006. "Structure, Function and Amyloidogenic Propensity of Apolipoprotein A-I." *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 13 (4): 191–205. https://doi.org/10.1080/13506120600960288.

Raimondi, Sara, Fulvio Guglielmi, Sofia Giorgetti, Sonia Di Gaetano, Angela Arciello, Daria M. Monti, Annalisa Relini, et al. 2011. "Effects of the Known Pathogenic Mutations on the Aggregation Pathway of the Amyloidogenic Peptide of Apolipoprotein A-I." *Journal of Molecular Biology* 407 (3): 465–76. https://doi.org/10.1016/j.jmb.2011.01.044.

Westermark, P., G. Mucchiano, T. Marthin, K. H. Johnson, and K. Sletten. 1995. "Apolipoprotein A1-Derived Amyloid in Human Aortic Atherosclerotic Plaques." *The American Journal of Pathology* 147 (5): 1186–92.

Apolipoprotein A II (APOA2)

Apolipoprotein A II is another protein which is a component of HDL(Brewer et al. 1972). This protein was first identified as an amyloid in a case of renal amyloidosis by isolation of congophilic amyloid material from the kidneys and use of Edman degradation sequence analysis(Benson et al. 2001). When associated with HDL, this protein is aggregation-resistant, but separation from bound lipids makes it very prone to misfolding(Prokaeva et al. 2017; Gursky

2014). This protein is an ambimorph, since although only mutations cause it to be found in an amyloid state, wild-type protein (albeit with the polymorphisms constituting the so-called “C” allele) expressed in mice is able to form amyloid fibrils from which a structure was determined(Andreotti et al. 2024). All known mutations in this protein are stop codon mutations which extend the protein by 21 residues(De Gracia et al. 2006; Masahide Yazaki et al. 2003; Benson et al. 2001; M. Yazaki et al. 2001; Prokaeva et al. 2017). All amyloidogenic mutations create nearly the same aggregation-prone segment to the C-terminal of the protein, both destabilizing the native structure, stabilizing a fiber form, and detaching the protein from its native binding partners(Prokaeva et al. 2017; Gursky 2014).

Andreotti, Giada, Julian Baur, Marijana Ugrina, Peter Benedikt Pfeiffer, Max Hartmann, Sebastian Wiese, Hiroki Miyahara, et al. 2024. “Insights into the Structural Basis of Amyloid Resistance Provided by Cryo-EM Structures of AApoAII Amyloid Fibrils.” *Journal of Molecular Biology* 436 (4): 168441. https://doi.org/10.1016/j.jmb.2024.168441.

Benson, M. D., J. J. Liepnieks, M. Yazaki, T. Yamashita, K. Hamidi Asl, B. Guenther, and B. Kluve-Beckerman. 2001. “A New Human Hereditary Amyloidosis: The Result of a Stop-Codon Mutation in the Apolipoprotein AII Gene.” *Genomics* 72 (3): 272–77. https://doi.org/10.1006/geno.2000.6499.

Brewer, H. B., S. E. Lux, R. Ronan, and K. M. John. 1972. “Amino Acid Sequence of Human apoLp-Gln-II (apoA-II), an Apolipoprotein Isolated from the High-Density Lipoprotein Complex.” *Proceedings of the National Academy of Sciences of the United States of America* 69 (5): 1304–8.

De Gracia, R., E. J. Fernández, C. Riñón, R. Selgas, and J. Garcia-Bustos. 2006. “Hereditary Renal Amyloidosis Associated with a Novel Mutation in the Apolipoprotein AII Gene.” *QJM: Monthly Journal of the Association of Physicians* 99 (4): 274. https://doi.org/10.1093/qjmed/hcl032.

Gursky, Olga. 2014. “Hot Spots in Apolipoprotein A-II Misfolding and Amyloidosis in Mice and Men.” *FEBS Letters* 588 (6): 845–50. https://doi.org/10.1016/j.febslet.2014.01.066.

Prokaeva, Tatiana, Harun Akar, Brian Spencer, Andrea Havasi, Haili Cui, Carl J. O’Hara, Olga Gursky, et al. 2017. “Hereditary Renal Amyloidosis Associated With a Novel Apolipoprotein A-II Variant.” *Kidney International Reports* 2 (6): 1223–32. https://doi.org/10.1016/j.ekir.2017.07.009.

Yazaki, M., J. J. Liepnieks, T. Yamashita, B. Guenther, M. Skinner, and M. D. Benson. 2001. “Renal Amyloidosis Caused by a Novel Stop-Codon Mutation in the Apolipoprotein A-II Gene.” *Kidney International* 60 (5): 1658–65. https://doi.org/10.1046/j.1523-1755.2001.00024.x.

Yazaki, Masahide, Juris J. Liepnieks, Mark S. Barats, Arthur H. Cohen, and Merrill D. Benson. 2003. “Hereditary Systemic Amyloidosis Associated with a New Apolipoprotein AII Stop Codon Mutation Stop78Arg.” *Kidney International* 64 (1): 11–16. https://doi.org/10.1046/j.1523-1755.2003.00047.x.

Apolipoprotein A IV (APOA4)

Apolipoprotein A IV is a lipid-binding protein involved in various physiological functions related to lipid metabolism including being protective against atherosclerosis and inhibiting lipoprotein oxidation(Qu et al. 2019)**.** This protein was first identified as amyloidogenic when an N-terminal fragment was identified as a component of amyloid deposits in the heart of a patient with senile systemic amyloidosis (SSA) associated with the aggregation of wild-type

transthyretin(Bergström et al. 2001). This protein has no associated amyloidogenic mutations, but the aggregation-prone fragment seems to be an N-terminal signal sequence that is not present in healthy controls(Canetti et al. 2021).

Bergström, J., C. Murphy, M. Eulitz, D. T. Weiss, G. T. Westermark, A. Solomon, and P. Westermark. 2001. “Codeposition of Apolipoprotein A-IV and Transthyretin in Senile Systemic (ATTR) Amyloidosis.” *Biochemical and Biophysical Research Communications* 285 (4): 903–8. https://doi.org/10.1006/bbrc.2001.5260.

Canetti, Diana, Paola Nocerino, Nigel B. Rendell, Nicola Botcher, Janet A. Gilbertson, Angel Blanco, Dorota Rowczenio, et al. 2021. “Clinical ApoA-IV Amyloid Is Associated with Fibrillogenic Signal Sequence.” *The Journal of Pathology* 255 (3): 311–18. https://doi.org/10.1002/path.5770.

Qu, Jie, Chih-Wei Ko, Patrick Tso, and Aditi Bhargava. 2019. “Apolipoprotein A-IV: A Multifunctional Protein Involved in Protection against Atherosclerosis and Diabetes.” *Cells* 8 (4): 319. https://doi.org/10.3390/cells8040319.

Apolipoprotein C II (APOC2)

Apolipoprotein C II is a component of various triglyceride-rich lipoproteins and functions in the hydrolysis of plasma triglycerides(Wolska et al. 2017). This protein was identified as an amyloid in a case of renal amyloidosis through mass spectroscopy analysis of congophilic amyloid material from the kidney of the patient(Nasr et al. 2017). The wild-type form of this protein had previously been shown to be able to form amyloid fibers *in vitro* (albeit in a lipid-unbound state)(Hatters et al. 2000) so we could not classify it as an hereditary amyloid, despite only being found in amyloid deposits in humans when it is mutated. The amyloidogenic mutations are thought to destabilize the native structure of the protein which, in turn, also interferes with its lipid-binding capabilities(Sethi et al. 2018; Nasr et al. 2017).

Hatters, D. M., C. E. MacPhee, L. J. Lawrence, W. H. Sawyer, and G. J. Howlett. 2000. “Human Apolipoprotein C-II Forms Twisted Amyloid Ribbons and Closed Loops.” *Biochemistry* 39 (28): 8276–83. https://doi.org/10.1021/bi000002w.

Nasr, Samih H., Surendra Dasari, Linda Hasadsri, Jason D. Theis, Julie A. Vrana, Morie A. Gertz, Prasuna Muppa, et al. 2017. “Novel Type of Renal Amyloidosis Derived from Apolipoprotein-CII.” *Journal of the American Society of Nephrology: JASN* 28 (2): 439–45. https://doi.org/10.1681/ASN.2015111228.

Sethi, Sanjeev, Surendra Dasari, Emmanuelle Plaisier, Pierre Ronco, Samih H. Nasr, Isabelle Brocheriou, Jason D. Theis, et al. 2018. “Apolipoprotein CII Amyloidosis Associated With p.Lys41Thr Mutation.” *Kidney International Reports* 3 (5): 1193–1201. https://doi.org/10.1016/j.ekir.2018.04.009.

Wolska, Anna, Richard L. Dunbar, Lita A. Freeman, Masako Ueda, Marcelo J. Amar, Denis O. Sviridov, and Alan T. Remaley. 2017. “Apolipoprotein C-II: New Findings Related to Genetics, Biochemistry, and Role in Triglyceride Metabolism.” *Atherosclerosis* 267 (December):49–60. https://doi.org/10.1016/j.atherosclerosis.2017.10.025.

Apolipoprotein C III (APOC3)

Apolipoprotein C III functions to raise plasma triglyceride levels by inhibiting the hydrolysis of triglycerides(Kohan 2015). This protein was identified as an amyloid in a French family with severe renal amyloidosis by immunohistochemistry on congophilic amyloid deposits in various tissues(Valleix et al. 2016). The wild-type form of this protein had previously been shown to be

able to form amyloid fibers *in vitro*, (albeit in a lipid-unbound state)(de Messieres et al. 2014) so we could not classify it as an hereditary amyloid, despite only being found in amyloid deposits in humans when it is mutated, and only mutant protein being found in *ex vivo* amyloid samples retrieved from patients(Valleix et al. 2016). The amyloidogenic mutation disrupts the native structure, inducing more fiber-stabilizing β-sheet secondary structure, and reduces its efficiency at binding lipids(Valleix et al. 2016).

Kohan, Alison B. 2015. "Apolipoprotein C-III: A Potent Modulator of Hypertriglyceridemia and Cardiovascular Disease." *Current Opinion in Endocrinology, Diabetes, and Obesity* 22 (2): 119–25. https://doi.org/10.1097/MED.0000000000000136.

Messieres, Michel de, Rick K. Huang, Yi He, and Jennifer C. Lee. 2014. "Amyloid Triangles, Squares, and Loops of Apolipoprotein C-III." *Biochemistry* 53 (20): 3261–63. https://doi.org/10.1021/bi500502d.

Valleix, Sophie, Guglielmo Verona, Noémie Jourde-Chiche, Brigitte Nédelec, P. Patrizia Mangione, Frank Bridoux, Alain Mangé, et al. 2016. "D25V Apolipoprotein C-III Variant Causes Dominant Hereditary Systemic Amyloidosis and Confers Cardiovascular Protective Lipoprotein Profile." *Nature Communications* 7 (January):10353. https://doi.org/10.1038/ncomms10353.

Atrial natriuretic factor (ANF)

Atrial natriuretic factor is a peptide hormone secreted by the heart atria in order to regulate blood volume and pressure through acting on the kidneys to increase sodium excretion(Maack 1996; Song, Wang, and Wu 2015). It is the main component of the amyloid deposits in isolated atrial amyloidosis and was first identified as an amyloid through electron microscopy-based ultrastructural analysis and immunogold staining of amyloid fibers in a piece of right atrial appendage removed in a coronary bypass surgery, although Congo red staining was negative(Kaye et al. 1986). This protein is a sporadic amyloid, but its amyloid aggregation is associated with increased expression of the peptide; this is hard to disentangle from age-related factors, though(Podduturi et al. 2013; Pucci et al. 1991).

Kaye, G C, M G Butler, A J D'Ardenne, S J Edmondson, A J Camm, and G Slavin. 1986. "Identification of Immunoreactive Atrial Natriuretic Peptide in Atrial Amyloid." *Journal of Clinical Pathology* 39 (5): 581–82.

Maack, T. 1996. "Role of Atrial Natriuretic Factor in Volume Control." *Kidney International* 49 (6): 1732–37. https://doi.org/10.1038/ki.1996.257.

Podduturi, Varsha, Danielle R. Armstrong, Michael A. Hitchcock, William C. Roberts, and Joseph M. Guileyardo. 2013. "Isolated Atrial Amyloidosis and the Importance of Molecular Classification." *Proceedings (Baylor University. Medical Center)* 26 (4): 387–89. https://doi.org/10.1080/08998280.2013.11929013.

Pucci, A., J. Wharton, E. Arbustini, M. Grasso, M. Diegoli, P. Needleman, M. Viganò, and J. M. Polak. 1991. "Atrial Amyloid Deposits in the Failing Human Heart Display Both Atrial and Brain Natriuretic Peptide-like Immunoreactivity." *The Journal of Pathology* 165 (3): 235–41. https://doi.org/10.1002/path.1711650307.

Song, Wei, Hao Wang, and Qingyu Wu. 2015. "Atrial Natriuretic Peptide in Cardiovascular Biology and Disease (NPPA)." *Gene* 569 (1): 1–6. https://doi.org/10.1016/j.gene.2015.06.029.

C9orf72 dipeptide repeat protein (C9orf72)

C9orf72 dipeptide repeat (DPR) proteins are generated from RNA transcripts from a C9orf72 gene containing an intronic hexanucleotide repeat expansion of the sequence GGGGCC. This repeat expansion mutation causes ALS/FTD(DeJesus-Hernandez et al. 2011; Renton et al. 2011). The RNA undergoes aberrant translation potentially via repeat-associated non-ATG translation(Zu et al. 2011). This process can generate five types of dipeptide repeat proteins: glycine-alanine repeats (GA), glycine-arginine repeats (GR), glycine-proline repeats (GP), proline-arginine repeats (PR), and proline-alanine repeats (PA)(Mori et al. 2013; Balendra and Isaacs 2018); only the GA protein has been shown to form amyloid fibers. The amyloid nature of GA DPR proteins has been demonstrated only in vitro through ThT fluorescence assays, Congo red staining, electron microscopy analysis, atomic force microscopy analysis, and wide angle x-ray scattering of synthetic peptides(Flores et al. 2016; Chang et al. 2016), although longer constructs expressed in bacteria formed fibers that did not bind ThT but still have cross-β secondary structure typical of amyloid as revealed by FTIR measurement(Brasseur et al. 2020). Since the GA DPR is an aberrantly translated protein from a normally noncoding DNA sequence, meaning there is no wild-type version of the protein, we have grouped this protein with the special case proteins, despite resulting from a repeat expansion genetic mutation. For this reason, we did not assign a mutation mechanism to this protein.

Balendra, Rubika, and Adrian M. Isaacs. 2018. “C9orf72-Mediated ALS and FTD: Multiple Pathways to Disease.” *Nature Reviews. Neurology* 14 (9): 544–58. https://doi.org/10.1038/s41582-018-0047-2.

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Chang, Yu-Jen, U.-Ser Jeng, Ya-Ling Chiang, Ing-Shouh Hwang, and Yun-Ru Chen. 2016. “The Glycine-Alanine Dipeptide Repeat from C9orf72 Hexanucleotide Expansions Forms Toxic Amyloids Possessing Cell-to-Cell Transmission Properties.” *The Journal of Biological Chemistry* 291 (10): 4903–11. https://doi.org/10.1074/jbc.M115.694273.

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Calcitonin (CALCA)

Calcitonin is a peptide hormone secreted by the thyroid gland which functions to prevent hypercalcemia by reducing serum calcium levels(Felsenfeld and Levine 2015). Calcitonin amyloid is found in thyroid tissue with medullary thyroid carcinoma (MTC) and can also be found deposited in the kidneys of patients with MTC(Khurana et al. 2004; Koopman et al. 2017; Tan et al. 2020). The amyloid material in MTC was first identified as possibly an alternately processed prohormone of calcitonin by Edman degradation sequence analysis of congophilic amyloid material from a patient with MTC(Sletten, Westermark, and Natvig 1976). This identification was confirmed by immunogold staining(Butler and Khan 1986) and refined by mass spectrometry to show that the amyloid consists of the normal, full-length calcitonin hormone and not an alternately processed prohormone(Khurana et al. 2004). Calcitonin is a sporadic amyloid, since no mutations are associated with its amyloid formation, but since it is associated with cancerous thyroid tissue, calcitonin's amyloid aggregation may be downstream of significant overexpression.

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Cathepsin K (CTSK)

Cathepsin K is an extremely potent protease secreted by osteoclasts which degrades collagen during bone resorption(Dai et al. 2020). It is also expressed by multinucleated giant cells and may have a role in degrading amyloid fibers, ironically(Röcken et al. 2001). This protein was identified by Edman degradation sequence analysis as the amyloid component of a congophilic angiomyolipoma, determined to be a hamartoma, in a woman's kidney, which was removed(Linke et al. 2017). This tumor and the unpublished results of an *in vitro* study of a synthetic peptide by the same group who reported the tumor are the only data points for the amyloidogenicity of this protein, and it is unclear if the patient who was the source of the tumor had any genetic variants in their CTSK gene. So, unless it is shown otherwise, cathepsin K will be characterized as a sporadic amyloid with no known amyloidogenic mutations.

Dai, Rongchen, Zeting Wu, Hang Yin Chu, Jun Lu, Aiping Lyu, Jin Liu, and Ge Zhang. 2020. "Cathepsin K: The Action in and Beyond Bone." *Frontiers in Cell and Developmental Biology* 8:433. https://doi.org/10.3389/fcell.2020.00433.

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Cellular tumor antigen p53 (TP53)

p53 is a tumor suppressor whose loss of function is associated with over 50% of human cancers(Muller and Vousden 2013). Amyloid formation of this protein has been shown to transform it into an oncoprotein(Ano Bom et al. 2012; Navalkar et al. 2021; Ghosh et al. 2017) and amyloid deposits consisting of p53 has been shown in various cancer tissues by immunostaining and staining with amyloidophilic dyes(Ghosh et al. 2017; Navalkar et al. 2020) . Both wild-type and mutant p53 is able to form amyloid fibers, and mutations encourage amyloid formation by destabilization of the native tetrameric form(Bullock et al. 1997) along with increased aggregation propensity (fiber stabilization) and increased seeding activity(Ano Bom et al. 2012; Ghosh et al. 2017; Navalkar et al. 2020; Lee et al. 2003).

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Corneodesmosin (CDSN)

Corneodesmosin is a glycoprotein found in the cornified squamous epithelia and functions in cell adhesion in skin and hair follicles(Simon et al. 1997). Its amyloid formation is associated with hypotrichosis simplex of the scalp (HSS) and it was identified as the constituent of the amyloid deposits in HSS by immunohistochemical staining of congophilic biopsies from HSS patients(Caubet et al. 2010). Corneodesmosin is an hereditary amyloid and all the amyloidogenic mutations in this protein are nonsense mutations which truncate the protein(Caubet et al. 2010; Dávalos et al. 2005; Levy-Nissenbaum et al. 2003). The full-length protein is almost entirely disordered(Caubet et al. 2010), and the production of a shorter disordered version apparently favors fiber-formation over its native function. Since both the full-length protein and the truncations are already intrinsically disordered, the only mechanism assigned to the mutations is native structure destabilization, since they do truncate the protein and remove whatever was interrupting their amyloid aggregation.

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Cystatin C (CST3)

Cystatin C is a cysteine protease inhibitor found in bodily fluids(Levy, Jaskolski, and Grubb 2006). It may be a functional amyloid, with the wild-type protein contributing to the formation of the epididymal luminal amyloid matrix in mice(Whelly et al. 2016) and the wild-type protein has been shown to form amyloid fibers *in vitro* via ThT assay and electron microscopy(Wahlbom et al. 2007). When mutated, its amyloid aggregation causes hereditary cystatin C amyloid angiopathy (HCAA), otherwise known as hereditary cerebral hemorrhage with amyloidosis (HCHWA)(Levy, Jaskolski, and Grubb 2006; Emilsson et al. 1996; Ghiso, Jensson, and Frangione 1986; March et al. 2021; Palsdottir, Snorradottir, and Thorsteinsson 2006). Cystatin C was identified as the amyloid protein responsible for this disease through amino acid sequence analysis of amyloid fibers purified from patient tissue(Ghiso, Jensson, and Frangione 1986). Cystatin C is an ambimorph amyloid for which a single mutation, L94Q, is known to cause its associated disease. This mutation introduces a polar side chain into a hydrophobic pocket of the protein and encourages its misfolding(Palsdottir, Snorradottir, and Thorsteinsson 2006). How this affects the resulting amyloid fiber is less clear, so the amyloidogenic mechanism for this mutation is native structure destabilization. Also, since cystatin C may exist as an amyloid in a functional state and its mutation leads it to form a pathological amyloid, the mechanism of altered fibril homeostasis was also assigned.

Emilsson, Valur, Leifur Thorsteinsson, Olafur Jensson, and Gunnar Gudnnundsson. 1996. "Human Cystatin C Expression and Regulation by TGF-B1: Implications for the Pathogenesis of Hereditary Cystatin C Amyloid Angiopathy Causing Brain Hemorrhage." *Amyloid* 3 (2): 110–18. https://doi.org/10.3109/13506129609014362.

Ghiso, J., O. Jensson, and B. Frangione. 1986. "Amyloid Fibrils in Hereditary Cerebral Hemorrhage with Amyloidosis of Icelandic Type Is a Variant of Gamma-Trace Basic Protein (Cystatin C)." *Proceedings of the National Academy of Sciences of the United States of America* 83 (9): 2974–78. https://doi.org/10.1073/pnas.83.9.2974.

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Whelly, Sandra, Archana Muthusubramanian, Jonathan Powell, Seethal Johnson, Mary Catherine Hastert, and Gail A. Cornwall. 2016. "Cystatin-Related Epididymal Spermatogenic Subgroup Members Are Part of an Amyloid Matrix and Associated with

Extracellular Vesicles in the Mouse Epididymal Lumen." *Molecular Human Reproduction* 22 (11): 729–44. https://doi.org/10.1093/molehr/gaw049.

Cytotoxic granule associated RNA binding protein TIA1 (TIA1)

Cytotoxic granule associated RNA binding protein TIA1, or just RNA-binding protein TIA1, is a functional amyloid protein with roles in stress granule function and RNA metabolism(Rayman and Kandel 2017). Mutations in this protein cause ALS/FTD and Welander distal myopathy (WDM). RNA-binding protein TIA1 is known to form stress granules via its prion-like domain (PLD) which is responsible for reversible, homotypic aggregation(Gilks et al. 2004), and the protein has been demonstrated by thioflavin T fluorescence, Congo red binding, and electron microscopy to form fibrous aggregates *in vitro*(Furukawa et al. 2009; Li et al. 2014). The molecular structure of the amyloid fibril has also been determined for the wild-type protein and also a mutant version with an ALS-associated mutation(Inaoka et al. 2023). Mutations in RNA-binding protein TIA1 have been shown to increase fibril-forming propensity and create more solid phase-separations(Ding et al. 2021; Mackenzie et al. 2017), so the mechanism of fibril stabilization was assigned. Since these mutations are in an intrinsically disordered low-complexity domain, the mechanism of native structure destabilization was not assigned. At least one other mutation has also been shown to reduce, but not eliminate, fibril-forming propensity and lead to the formation of fibrils with an altered structure compared to the wild-type protein(Inaoka et al. 2023), so altered fibril homeostasis has also been assigned as a mechanism.

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Desmin (DES)

Desmin is an intermediate filament protein present in muscle fibers which forms an extra-sarcomeric cytoskeleton connecting myofibers to each other and other structures(Clemen et al. 2013). Conversion of desmin into amyloid fibers is hypothesized to be associated with myofibrillar myopathy, cases of which have been shown to develop congophilic lesions which desmin colocalizes with(De Bleecker, Engel, and Ertl 1996; Selcen, Ohno, and Engel 2004). Wild-type and mutant desmin has been shown to form amyloid fibers *in vitro* and mutant desmin has accelerated fiber formation(Kedia et al. 2019). Desmin amyloid was also shown to be toxic to mouse myoblast cells(Kedia et al. 2019). Mutations in desmin destabilize the native protein, as demonstrated by its reduced solubility and critical concentration for amyloid formation(Kedia et al. 2019) and seem to stabilize the amyloid form since not all destabilizing mutations in this protein cause it to form amyloids. The mutations also have been shown to exhibit increased seeding(Kedia et al. 2019) as well as induce mislocalization of the protein(Brodehl et al. 2013; Schröder et al. 2003), although it is unclear if the mislocalization precedes amyloid formation.

Brodehl, Andreas, Mareike Dieding, Bärbel Klauke, Eric Dec, Shrestha Madaan, Taosheng Huang, John Gargus, et al. 2013. “The Novel Desmin Mutant p.A120D Impairs Filament Formation, Prevents Intercalated Disk Localization, and Causes Sudden Cardiac Death.” *Circulation. Cardiovascular Genetics* 6 (6): 615–23. https://doi.org/10.1161/CIRCGENETICS.113.000103.

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EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1)

EGF-containing fibulin-like extracellular matrix protein 1, also known as fibulin-3, is a protein which competes with epidermal growth factor for binding to the EGF receptor and promotes tumor growth in adenocarcinoma(Camaj et al. 2009). While it has a role in the progression of cancer, this protein also forms amyloids mainly in the venous walls of the bowels of mainly elderly females, but also in other tissues(Dao et al. 2021), and was first identified to do so by mass spectrometry and immunohistochemical analysis of congophilic intestinal venous walls obtained at autopsy from a patient(Tasaki et al. 2019). This protein is a sporadic amyloid, so has no mutations associated with its amyloid formation, and, in fact, a patient with Doyne honeycomb retinal dystrophy caused by an autosomal dominant mutation in fibulin-3 did not have amyloid deposits of the protein(Tasaki et al. 2019). However, higher expression of the protein seems to accompany aging and the amyloid deposits consist of a C-terminal fragment of the protein(Tasaki et al. 2019), although it is unclear why this cleavage product is generated.

Camaj, Peter, Hendrik Seeliger, Ivan Ischenko, Stefan Krebs, Helmut Blum, Enrico N. De Toni, Dagmar Faktorova, Karl-Walter Jauch, and Christiane J. Bruns. 2009. “EFEMP1 Binds the EGF Receptor and Activates MAPK and Akt Pathways in Pancreatic Carcinoma Cells.” *Biological Chemistry* 390 (12): 1293–1302. https://doi.org/10.1515/BC.2009.140.

Dao, Linda N., Paul J. Kurtin, Thomas C. Smyrk, Jason D. Theis, Surendra Dasari, Julie A. Vrana, Angela Dispenzieri, Samih H. Nasr, and Ellen D. McPhail. 2021. “The Novel Form of Amyloidosis Derived from EGF-Containing Fibulin-like Extracellular Matrix Protein 1 (EFEMP1) Preferentially Affects the Lower Gastrointestinal Tract of Elderly Femalesa.” *Histopathology* 78 (3): 459–63. https://doi.org/10.1111/his.14276.

Tasaki, Masayoshi, Mitsuharu Ueda, Yoshinobu Hoshii, Mayumi Mizukami, Sayaka Matsumoto, Makoto Nakamura, Taro Yamashita, et al. 2019. “A Novel Age-Related Venous Amyloidosis Derived from EGF-Containing Fibulin-like Extracellular Matrix Protein 1.” *The Journal of Pathology* 247 (4): 444–55. https://doi.org/10.1002/path.5203.

Fibrinogen α chain (FGA)

Fibrinogen α chain is a glycoprotein which is essential for blood coagulation(Chapman and Dogan 2019). Its amyloid formation is associated with hereditary renal amyloidosis and it was first identified as the amyloid component by amino acid sequence analysis of amyloid material harvested from the renal transplant of a patient (harvested postmortem), and all sequences corresponded to the C-terminal portion of the protein(Benson et al. 1993). Fibrinogen α chain is an hereditary amyloid and there are 15 known amyloidogenic mutations in it, all in the C-terminal region, which consist of substitution mutations, indels, and frame-shifts(Chapman and Dogan 2019). Some of these mutations (namely the frame-shifts) seem to interfere with the normal function of the protein, evidenced by lower circulating plasma levels of it(Uemichi et al. 1996) so the mechanism of native structure destabilization was assigned to this protein. However, many other mutations (namely the substitution mutations) do not seem to interfere with the function(Serpell et al. 2007), and so likely do not significantly affect the native structure, so we can infer that these mutations stabilize a fiber form. Also, since the amyloid seems to consist exclusively of a C-terminal fragment, and wild-type C-terminal fragments are not found in the amyloid deposits, we can infer that the normal processing of the protein has been disrupted by the mutations.

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Uemichi, T., J. J. Liepnieks, T. Yamada, M. A. Gertz, N. Bang, and M. D. Benson. 1996. “A Frame Shift Mutation in the Fibrinogen A Alpha Chain Gene in a Kindred with Renal Amyloidosis.” *Blood* 87 (10): 4197–4203.

Galectin-7 (LGALS7)

Galectin-7 is an epidermal protein with various functions including controlling apoptosis, cell migration, and cell adhesion(Sewgobind, Albers, and Pieters 2021). Its amyloid formation was associated with localized cutaneous amyloidosis by identification of galectin-7 and actin as components of amyloid deposits in skin lesions of patients through mass spectrometry and immunohistochemistry analyses(Miura et al. 2013). However, this result was contested by a more refined analysis using mass spectrometry and immunohistochemistry analysis of laser microdissected of skin biopsies which detected only keratin proteins (mainly keratin-5) in the congophilic material and galectin-7 only in the surrounding non-congophilic epidermis, while actin was found in both(Chapman et al. 2021). Still, galectin-7 and peptide fragments of the protein were shown to be capable of forming amyloid fibers *in vitro*, though only at very low pH (pH 2.0 and 4.0)(Ono et al. 2014). The amyloid nature of galectin-7 is somewhat unclear, but if it can form amyloids it would be a sporadic amyloid, as no amyloidogenic mutations have been found in it.

Chapman, Jessica R., Anna Liu, San S. Yi, Enmily Hernandez, Maria Stella Ritorto, Achim A. Jungbluth, Melissa Pulitzer, and Ahmet Dogan. 2021. “Proteomic Analysis Shows That the Main Constituent of Subepidermal Localised Cutaneous Amyloidosis Is Not Galectin-7.” *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 28 (1): 35–41. https://doi.org/10.1080/13506129.2020.1811962.

Miura, Yoshinori, Satoru Harumiya, Koji Ono, Eita Fujimoto, Minoru Akiyama, Noriko Fujii, Hiroo Kawano, Hiroshi Wachi, and Shingo Tajima. 2013. “Galectin-7 and Actin Are Components of Amyloid Deposit of Localized Cutaneous Amyloidosis.” *Experimental Dermatology* 22 (1): 36–40. https://doi.org/10.1111/exd.12065.

Ono, Koji, Eita Fujimoto, Norihiro Fujimoto, Minoru Akiyama, Takahiro Satoh, Hiroki Maeda, Noriko Fujii, and Shingo Tajima. 2014. “In Vitro Amyloidogenic Peptides of Galectin-7: Possible Mechanism of Amyloidogenesis of Primary Localized Cutaneous Amyloidosis.” *The Journal of Biological Chemistry* 289 (42): 29195–207. https://doi.org/10.1074/jbc.M114.592998.

Sewgobind, Nishant V., Sanne Albers, and Roland J. Pieters. 2021. “Functions and Inhibition of Galectin-7, an Emerging Target in Cellular Pathophysiology.” *Biomolecules* 11 (11): 1720. https://doi.org/10.3390/biom11111720.

Gelsolin (GSN)

Gelsolin is a calcium-binding protein which modulates the growth of actin filaments(Solomon et al. 2012). Its amyloid formation is associated with hereditary gelsolin amyloidosis, also known as familial amyloidosis of the Finnish type, which presents as lattice corneal dystrophy(Solomon et al. 2012; de la Chapelle et al. 1992; Schmidt et al. 2020; Kiuru-Enari and Haltia 2013; Maury, Alli, and Baumann 1990; Haltia et al. 1990; Maury 1991). Its amyloid nature was first identified through Edman degradation sequence analysis of congophilic amyloid material from a patient's kidney obtained at autopsy(Maury, Alli, and Baumann 1990) and confirmed by another group very shortly after(Haltia et al. 1990). The amyloid deposits consisted of a central fragment of the protein and the group which identified gelsolin as the amyloid protein first also confirmed that the amyloidogenic protein fragment had a D to N substitution(Maury 1991). This protein is an hereditary amyloid, so only familial mutations have been found to enable its amyloid formation, namely two mutations at a single residue: D214N and D214Y (also numbered D187 for the mature protein). These mutations interrupts gelsolin's calcium binding activity, which also causes it to spend a longer time in an intermediate state between its active and inactive state(Solomon et al. 2012). This intermediate state is more susceptible to furin-mediated cleavage, which produces a fragment which is further cleaved to eventually produce the amyloidogenic fragment(Solomon et al. 2012). For these reasons, we assigned the mutation mechanisms of native structure destabilization, altered proceeding, and decreased binding to native partners. Also, it has been shown the fragments corresponding to the amyloidogenic fragment but with the wild-type sequence do not form amyloid fibers *in vitro* while the mutant fragment does(Solomon et al. 2012; de la Chapelle et al. 1992; Maury and Nurmiaho-Lassila 1992; Maury, Nurmiaho-Lassila, and Rossi 1994), so the mechanism of fiber stabilization was also assigned.

Chapelle, A. de la, R. Tolvanen, G. Boysen, J. Santavy, L. Bleeker-Wagemakers, C. P. Maury, and J. Kere. 1992. "Gelsolin-Derived Familial Amyloidosis Caused by Asparagine or Tyrosine Substitution for Aspartic Acid at Residue 187." *Nature Genetics* 2 (2): 157–60. https://doi.org/10.1038/ng1092-157.

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Maury, C. P., K. Alli, and M. Baumann. 1990. "Finnish Hereditary Amyloidosis. Amino Acid Sequence Homology between the Amyloid Fibril Protein and Human Plasma Gelsoline." *FEBS Letters* 260 (1): 85–87. https://doi.org/10.1016/0014-5793(90)80072-q.

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Maury, C. P., E. L. Nurmiaho-Lassila, and H. Rossi. 1994. "Amyloid Fibril Formation in Gelsolin-Derived Amyloidosis. Definition of the Amyloidogenic Region and Evidence of

Accelerated Amyloid Formation of Mutant Asn-187 and Tyr-187 Gelsolin Peptides." *Laboratory Investigation; a Journal of Technical Methods and Pathology* 70 (4): 558–64.
Schmidt, Eeva-Kaisa, Tuuli Mustonen, Sari Kiuru-Enari, Tero T. Kivelä, and Sari Atula. 2020. "Finnish Gelsolin Amyloidosis Causes Significant Disease Burden but Does Not Affect Survival: FIN-GAR Phase II Study." *Orphanet Journal of Rare Diseases* 15 (1): 19. https://doi.org/10.1186/s13023-020-1300-5.
Solomon, James P., Lesley J. Page, William E. Balch, and Jeffery W. Kelly. 2012. "Gelsolin Amyloidosis: Genetics, Biochemistry, Pathology and Possible Strategies for Therapeutic Intervention." *Critical Reviews in Biochemistry and Molecular Biology* 47 (3): 282–96. https://doi.org/10.3109/10409238.2012.661401.

Glucagon (GCG)

Glucagon is a peptide hormone secreted by alpha cells of the pancreas which regulates blood glucose levels by encouraging production of glucose through the breakdown of energy storage molecules like glycogen and triglycerides(Jiang and Zhang 2003). It was found in an amyloid form in a patient with pancreatic neuroendocrine tumors which were positive for Congo red staining(Ichimata et al. 2021). The amyloid was confirmed to consist of glucagon through mass spectrometry analysis with laser microdissection along with immunohistochemistry. The peptide was also shown to form fibers rapidly at the acidic pH required to solubilize it and an atomic structure of the fibers was solved using solid-state NMR(Gelenter et al. 2019). This protein is ostensibly a sporadic amyloid, as no mutations have been associated with its fiber formation, but in the case of the pancreatic tumor glucagon was being produced in high quantities but was not being secreted by the pancreas, and the tumor may have needed to reach a non-physiological critical concentration of nonfunctional glucagon before amyloid deposits began to form.

Gelenter, Martin D., Katelyn J. Smith, Shu-Yu Liao, Venkata S. Mandala, Aurelio J. Dregni, Matthew S. Lamm, Yu Tian, et al. 2019. "The Peptide Hormone Glucagon Forms Amyloid Fibrils with Two Coexisting β-Strand Conformations." *Nature Structural & Molecular Biology* 26 (7): 592–98. https://doi.org/10.1038/s41594-019-0238-6.
Ichimata, Shojiro, Nagaaki Katoh, Ryuta Abe, Tsuneaki Yoshinaga, Fuyuki Kametani, Masahide Yazaki, Takeshi Uehara, and Yoshiki Sekijima. 2021. "A Case of Novel Amyloidosis: Glucagon-Derived Amyloid Deposition Associated with Pancreatic Neuroendocrine Tumour." *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 28 (1): 72–73. https://doi.org/10.1080/13506129.2020.1785417.
Jiang, Guoqiang, and Bei B. Zhang. 2003. "Glucagon and Regulation of Glucose Metabolism." *American Journal of Physiology. Endocrinology and Metabolism* 284 (4): E671-678. https://doi.org/10.1152/ajpendo.00492.2002.

Glucagon-like peptide 1 (Liraglutide)

Liraglutide is a peptide drug which is a mimic of glucagon-like peptide 1 which is administered through subcutaneous injections for the management of diabetes and acts through stimulating glycogenesis(Martins et al. 2018). It was found in amyloid deposits of abdominal skin biopsies of an elderly man taking the drug to manage diabetes and was confirmed as the main constituent of the amyloid through mass spectrometry analysis of the samples(Martins et al. 2018). The

dangers of this amyloid buildup were noted to be possible drug resistance due to poor absorption as well as misdiagnosis of AL amyloidosis(Martins et al. 2018). This is included in our list of amyloid proteins since, although it is a drug, it is a peptide with over 90% sequence homology to the peptide hormone glucagon-like peptide 1. It is also worth noting that Liraglutide has some important differences from the hormone it is based on including being a shorter version of the peptide and having a substitution corresponding to K125R using the numbering of the glucagon prohormone. Because of this, it is not entirely clear if the actual glucagon-like peptide 1 can form amyloids in the same way.

Martins, Carlo O., Cecilia Lezcano, San S. Yi, Heather J. Landau, Jessica R. Chapman, and Ahmet Dogan. 2018. “Novel Iatrogenic Amyloidosis Caused by Peptide Drug Liraglutide: A Clinical Mimic of AL Amyloidosis.” *Haematologica* 103 (12): e610–12. https://doi.org/10.3324/haematol.2018.203000.

Heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1)

Heterogeneous nuclear ribonucleoprotein A1 is potentially a functional amyloid, as there is evidence that is able to form reversible amyloid fibers and this reversible form of aggregation is necessary for its function(Gui et al. 2019). This protein is an RNA-binding protein mainly localizing to the nucleus with various functions in RNA processing including transcription, splicing, translation, nuclear export, and others(Clarke et al. 2021). Its reversible aggregation is related to its ability to form stress granules in the cytoplasm during cell stress(Gui et al. 2019). Amyloidogenic mutations in this protein are associated with ALS and MSP(Kim et al. 2013). Although amyloid fibers of this protein have not been isolated from human tissue thus far, there is ample *in vitro* evidence (ThT assays and electron microscopy including a cryo-EM structure of the wild-type amyloid) that the protein is able to form amyloid fibers, and that this activity is enhanced by disease-relevant mutations(Kim et al. 2013; Sun et al. 2020). The amyloidogenic mutations in this protein fall in its low-complexity domain, or prion-like domain, which is intrinsically disordered and already able to form a reversible fiber, so the mechanism is stabilization of the fiber form. Also, since this protein may be a functional amyloid and mutations cause the protein to form pathological amyloids, the mechanism of altered fibril homeostasis was assigned. The PY-nuclear localization signal of the protein also appears to be a key driver of its self-association (being the main component of the wild-type amyloid fiber(Sun et al. 2020)) and is within the low-complexity domain, however it is unclear if the mutations affect the normal activity of the PY-nuclear localization signal, so mislocalization was not assigned as a mutation mechanism.

Clarke, Joseph P., Patricia A. Thibault, Hannah E. Salapa, and Michael C. Levin. 2021. “A Comprehensive Analysis of the Role of hnRNP A1 Function and Dysfunction in the Pathogenesis of Neurodegenerative Disease.” *Frontiers in Molecular Biosciences* 8:659610. https://doi.org/10.3389/fmolb.2021.659610.

Gui, Xinrui, Feng Luo, Yichen Li, Heng Zhou, Zhenheng Qin, Zhenying Liu, Jinge Gu, et al. 2019. “Structural Basis for Reversible Amyloids of hnRNPA1 Elucidates Their Role in Stress Granule Assembly.” *Nature Communications* 10 (1): 2006. https://doi.org/10.1038/s41467-019-09902-7.

Kim, Hong Joo, Nam Chul Kim, Yong-Dong Wang, Emily A. Scarborough, Jennifer Moore, Zamia Diaz, Kyle S. MacLea, et al. 2013. “Mutations in Prion-like Domains in

hnRNPA2B1 and hnRNPA1 Cause Multisystem Proteinopathy and ALS." *Nature* 495 (7442): 467–73. https://doi.org/10.1038/nature11922.
Sun, Yunpeng, Kun Zhao, Wencheng Xia, Guoqin Feng, Jinge Gu, Yeyang Ma, Xinrui Gui, et al. 2020. "The Nuclear Localization Sequence Mediates hnRNPA1 Amyloid Fibril Formation Revealed by cryoEM Structure." *Nature Communications* 11 (1): 6349. https://doi.org/10.1038/s41467-020-20227-8.

Heterogeneous nuclear ribonucleoprotein A2 (HNRNPA2B1)

Heterogeneous nuclear ribonucleoprotein A2 is the main isoform of the two spliceoforms of the HNRNPA2B1 gene. This RNA-binding protein which mainly localizes to the nucleus is potentially a functional amyloid and has similar functions related to RNA metabolism as the previous entry and also forms cytoplasmic stress granules under cell stress(Kapeli, Martinez, and Yeo 2017). A mutation in this protein, D290V (also numbered D302V for the longer isoform), is associated with MSP(Kim et al. 2013). Although amyloids of this protein have not been extracted from human tissue, there is ample *in vitro* evidence (ThT assays and electron microscopy including both wild-type and mutant cryo-EM structures) that both wild-type and mutant protein can form amyloid fibers, and that the disease mutation enhances fiber formation(Kim et al. 2013; Lu et al. 2020; 2024). Since the region of the protein which drives fiber formation is a low-complexity domain which is intrinsically disordered and already able to form a reversible fiber, the mutation mechanism was assigned to be fiber stabilization. Also, the cryo-EM structure of the mutant fiber reveals that the mutation causes the PY-nuclear localization signal of this protein to become buried in the fiber core(Lu et al. 2024) while in the wild-type structure it is exposed, so the mutation may be encouraging an aggregated form which precludes relocalization to the nucleus after the formation of cytoplasmic stress granules, so subcellular mislocalization was also assigned as a mutation mechanism. Also, since this protein may be a functional amyloid and mutations cause the protein to form pathological amyloids, the mechanism of altered fibril homeostasis was assigned.

It is worth noting here that another RNA-binding protein, heterogeneous nuclear ribonucleoprotein D-like (HNRNPDL) is a functional amyloid with a cryo-EM structure of its reversible amyloid form which also has a disease-causing mutation in an aspartic acid residue in its low-complexity domain. However, the mutant forms of this protein are actually less prone to aggregate than the wild-type and cytoplasmic inclusions are absent in those with these mutations(Garcia-Pardo et al. 2023), so while it is an amyloid protein, its pathogenic mechanism is not likely to be amyloid formation.

Garcia-Pardo, Javier, Andrea Bartolomé-Nafría, Antonio Chaves-Sanjuan, Marcos Gil-Garcia, Cristina Visentin, Martino Bolognesi, Stefano Ricagno, and Salvador Ventura. 2023. "Cryo-EM Structure of hnRNPDL-2 Fibrils, a Functional Amyloid Associated with Limb-Girdle Muscular Dystrophy D3." *Nature Communications* 14 (1): 239. https://doi.org/10.1038/s41467-023-35854-0.
Kapeli, Katannya, Fernando J. Martinez, and Gene W. Yeo. 2017. "Genetic Mutations in RNA-Binding Proteins and Their Roles in ALS." *Human Genetics* 136 (9): 1193–1214. https://doi.org/10.1007/s00439-017-1830-7.
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hnRNPA2B1 and hnRNPA1 Cause Multisystem Proteinopathy and ALS." *Nature* 495 (7442): 467–73. https://doi.org/10.1038/nature11922.
Lu, Jiahui, Qin Cao, Michael P. Hughes, Michael R. Sawaya, David R. Boyer, Duilio Cascio, and David S. Eisenberg. 2020. "CryoEM Structure of the Low-Complexity Domain of hnRNPA2 and Its Conversion to Pathogenic Amyloid." *Nature Communications* 11 (1): 4090. https://doi.org/10.1038/s41467-020-17905-y.
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Huntingtin (HTT)

Huntingtin is a protein whose function is not explicitly known, but it potentially has various roles including mediating trafficking of vesicles and organelles, regulating transcription, and acting as an antiapoptotic agent(Schulte and Littleton 2011). Regardless, this protein is essential, as double-knockouts in mice are embryonic lethal(Nasir et al. 1995), and haploinsufficient. Huntingtin is found in an aggregated state in the brains of individuals with Huntington's disease (HD)(Huang et al. 1998; DiFiglia et al. 1997; Zhou et al. 2003). Brain samples from HD patients display positive Congo red staining and cellulose acetate filter assays, which capture insoluble protein aggregates, show that insoluble material from patient brains contains huntingtin protein in a conformation distinct from its soluble form(Huang et al. 1998). Also, *in vitro* studies have shown that huntingtin exon 1 recombinant protein aggregates into congophilic aggregates with ultrastructural features typical of amyloid(Scherzinger et al. 1997; Hoop et al. 2016; Scherzinger et al. 1999). HD is caused by a polyglutamine expansion in exon 1 of the HTT gene which codes for huntingtin(Scherzinger et al. 1997), and aggregation of huntingtin exon 1 recombinant protein into amyloid fibers is dependent on having a pathological number of glutamine repeats, making huntingtin an hereditary amyloid. Aggregates in patients' brains are mainly composed of N-terminal fragments of huntingtin(DiFiglia et al. 1997; Zhou et al. 2003), so *in vitro* experiments on N-terminal constructs of huntingtin have disease relevance. Polyglutamine tracts tend to be intrinsically disordered(Wear et al. 2015), but at a critical length of repeats, ~40 minimum for huntingtin, the formation of β-sheets with polar zippers becomes energetically favorable(Perutz 1995; 1996), so only fiber stabilization was assigned as the amyloidogenic mechanism of the mutation. The evidence of amyloid formation by other proteins containing pathogenic polyglutamine expansions is not as strong as for huntingtin.

DiFiglia, M., E. Sapp, K. O. Chase, S. W. Davies, G. P. Bates, J. P. Vonsattel, and N. Aronin. 1997. "Aggregation of Huntingtin in Neuronal Intranuclear Inclusions and Dystrophic Neurites in Brain." *Science (New York, N.Y.)* 277 (5334): 1990–93. https://doi.org/10.1126/science.277.5334.1990.
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Huang, C. C., P. W. Faber, F. Persichetti, V. Mittal, J. P. Vonsattel, M. E. MacDonald, and J. F. Gusella. 1998. “Amyloid Formation by Mutant Huntingtin: Threshold, Progressivity and Recruitment of Normal Polyglutamine Proteins.” *Somatic Cell and Molecular Genetics* 24 (4): 217–33. https://doi.org/10.1023/b:scam.0000007124.19463.e5.

Nasir, J., S. B. Floresco, J. R. O’Kusky, V. M. Diewert, J. M. Richman, J. Zeisler, A. Borowski, J. D. Marth, A. G. Phillips, and M. R. Hayden. 1995. “Targeted Disruption of the Huntington’s Disease Gene Results in Embryonic Lethality and Behavioral and Morphological Changes in Heterozygotes.” *Cell* 81 (5): 811–23. https://doi.org/10.1016/0092-8674(95)90542-1.

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Immunoglobulin heavy chain (IGH)

The immunoglobulin heavy chain is the large subunit of an antibody, or immunoglobulin, and is linked to another heavy chain and a light chain by disulfide bonds. The heavy chain consists of a “variable” region, which are different between individual antibodies, and multiple “constant” regions, which are conserved between individual antibodies. The amyloid aggregation of this protein is associated with what is called “primary amyloidosis” or multiple myeloma-associated amyloidosis(Eulitz, Weiss, and Solomon 1990; Solomon, Weiss, and Murphy 1994; Tan et al. 1994; Mai et al. 2003), the same disease caused by amyloid aggregation of the antibody light chain. When caused by the heavy chain, it is referred to as AH amyloidosis. This protein was first found to form amyloids in this disease through immunoblotting and amino acid sequence analysis of congophilic amyloid material extracted from a patient’s spleen(Eulitz, Weiss, and Solomon 1990). Heavy chain amyloidosis has been reported several times since the initial

report(Solomon, Weiss, and Murphy 1994; Tan et al. 1994; Mai et al. 2003) and in all but one case(Tan et al. 1994) the amyloid fibers were composed of a heavy chain fragment which included the variable domain. Interestingly, in the first reported case the amyloid protein was the heavy chain variable region connected directly to the third constant region, constituting a large internal deletion(Eulitz, Weiss, and Solomon 1990). This is the reason this protein is one of the "special cases": the fragments forming amyloids in people all ostensibly have distinct amino acid sequences from each other and even from other antibodies within the same patient. This makes it difficult to connect the protein's amino acid sequence to its amyloidogenicity.

Eulitz, M., D. T. Weiss, and A. Solomon. 1990. "Immunoglobulin Heavy-Chain-Associated Amyloidosis." *Proceedings of the National Academy of Sciences of the United States of America* 87 (17): 6542–46. https://doi.org/10.1073/pnas.87.17.6542.

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Immunoglobulin light chain (IGL or IGK)

The immunoglobulin light chain is the small subunit of an antibody, or immunoglobulin, and is linked to a heavy chain by a disulfide bond. The light chain consists of a "variable" region, which are different between individual antibodies, and a "constant" region, which are conserved between individual antibodies. The amyloid aggregation of this protein is associated with what is called "primary amyloidosis" or multiple myeloma-associated amyloidosis(V. Perfetti et al. 2001; Glenner et al. 1971; 1970; Vittorio Perfetti et al. 2012; Kourelis et al. 2017), the same disease caused by amyloid aggregation of the antibody heavy chain. When caused by the light chain, it is referred to as AL amyloidosis. This kind of amyloidosis has long been associated with conditions like myeloma, and so a connection to immunoglobulin proteins had been hypothesized long before it was confirmed. Gamma globulin was shown to be a main component of the congophilic amyloid material in human patients as early as 1956(Dixon and Vazquez 1956). The sequence of the protein component of this amyloid material was later confirmed to be the sequence of the antibody light chain(Glenner et al. 1971; 1970). The amyloid component always contains the variable region of the protein which is the reason this protein was grouped into "special cases": the fragments forming amyloids in people all ostensibly have distinct amino acid sequences from each other and even from other antibodies within the same patient. However, certain amino acid compositions have been associated with higher incidence of amyloidosis(Brumshtein et al. 2018; Vittorio Perfetti et al. 2012; Kourelis et al. 2017; Radamaker et al. 2019) and λ light chains form amyloids more often than κ light chains(Abraham et al. 2003).

Abraham, Roshini S., Susan M. Geyer, Tammy L. Price-Troska, Cristine Allmer, Robert A. Kyle, Morie A. Gertz, and Rafael Fonseca. 2003. “Immunoglobulin Light Chain Variable (V) Region Genes Influence Clinical Presentation and Outcome in Light Chain-Associated Amyloidosis (AL).” *Blood* 101 (10): 3801–8. https://doi.org/10.1182/blood-2002-09-2707.

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Insulin (INS)

Insulin is a hormone secreted by the beta cells of the pancreas which functions to regulate blood glucose levels by decreasing blood glucose through signaling cells to uptake blood glucose and store it(Rahman et al. 2021). Insulin is an iatrogenic amyloid, so its amyloidosis is associated with drug forms of the protein, not the native protein. These drugs include porcine insulin, glargine, lispro, and others(Dische et al. 1988; Nagase et al. 2009; Iwaya et al. 2019; Nagase et al. 2014). Insulin forms subcutaneous amyloid deposits at sites of injection. This amyloidosis has been referred to as “insulin ball”, but is more commonly referred to as insulin-derived amyloidosis(Nagase et al. 2009; Iwaya et al. 2019; Nagase et al. 2014; Shiba

and Kitazawa 2016). There is some evidence to suggest these amyloid deposits are toxic to surrounding tissue(Iwaya et al. 2019) and there is at least one case of insulin amyloid deposits increasing in size even after decreasing insulin dosage and cessation of injections into existing amyloid deposits(Shiba and Kitazawa 2016). Otherwise, adverse effects are mainly interference with insulin absorption leading to reduced efficacy of insulin drugs(Nagase et al. 2009; 2014). Insulin was first shown to be amyloidogenic for the case of porcine insulin through immunohistochemistry and amino acid sequence analysis of congophilic material from a patient's thigh biopsy(Dische et al. 1988).

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Integral membrane protein 2B (ITM2B or BRI or BRI2)

Integral membrane protein 2B is a protein whose function is not entirely clear, but there is evidence to suggest it has roles in triggering apoptosis as well as inhibition of the buildup and aggregation of amyloid-β peptide(Fotinopoulou et al. 2005; J. Kim et al. 2008; Fleischer, Ayllon, and Rebollo 2002; Fleischer and Rebollo 2004). It has a furin cleavage site near the C-terminal of the protein, and the normal protein is cleaved here during its processing(S. H. Kim et al. 1999). The C-terminal cleavage product forms amyloid deposits in familial British dementia (FBD) and familial Danish dementia (FDD), as identified by mass spectrometry analysis of isolated congophilic amyloid material from patients and immunohistochemistry(Vidal et al. 2000; 1999). These two diseases are caused by two different, but related mutations. FBD is caused by a stop codon mutation which changes the normal stop codon (codon 267) to a codon for arginine, extending the protein from 267 to 277 amino acids(Vidal et al. 1999). FDD is caused by a frame-shift mutation caused by a decamer duplication in the DNA sequence between

codons 265 and 266 also extending the protein to 277 amino acids(Vidal et al. 2000). Since only mutation results in this protein forming amyloids, it is an hereditary amyloid. Though each mutation results in a different C-terminal amino acid sequence, both cause the resulting extended C-terminal cleavage product (both the same length) to become amyloidogenic. Since the cleavage product is a 34-amino acid peptide, which likely lacks significant secondary structure, and production of this peptide is enhanced when a mutation is present, the amyloidogenic mechanisms of fiber stabilization and altered processing were assigned to this protein's mutations.

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Interleukin-1 receptor antagonist protein (Anakinra)

Anakinra is a recombinant protein drug which acts as an IL-1 blocker for the treatment of rheumatoid arthritis and neonatal onset multisytem inflammatory disease (NOMID). This is an iatrogenic amyloid: anakinra-associated amyloidosis is caused by subcutaneous injection of the drug. Anakinra was confirmed as the amyloidogenic agent by mass spectrometry of laser dissected congophilic material from biopsies from two patients with NOMID(Alehashemi et al. 2022). As an iatrogenic amyloid, its aggregation is probably a result of increased local concentration of protein at the injection site.

Alehashemi, Sara, Surendra Dasari, Adriana A. de Jesus, Edward W. Cowen, Chia-Chia Richard Lee, Raphaela Goldbach-Mansky, and Ellen D. McPhail. 2022. “Anakinra-Associated Amyloidosis.” *JAMA Dermatology* 158 (12): 1454–57. https://doi.org/10.1001/jamadermatol.2022.2124.

Islet amyloid polypeptide (IAPP)

Islet amyloid polypeptide, or amylin, is a peptide hormone secreted by the beta cells of the pancreas. Its function is not entirely understood, but its main function seems to be regulation of insulin activity(Per Westermark, Andersson, and Westermark 2011). The amyloid aggregation of this protein is associated with type 2 diabetes. The formation of amyloid in type 2 diabetes had been noticed as early as 1900(Opie 1901) and later confirmed(Ahronheim 1943), but only much later was the protein responsible for the amyloid deposits identified as a novel amyloid protein(P. Westermark et al. 1986; 1987; Cooper et al. 1987) through amino acid sequence analysis of congophilic material extracted from insulin-producing tumors and pancreas samples from patients with type 2 diabetes and also immunohistochemical analysis. The fiber structures of wild-type and mutant islet amyloid polypeptide reveal that the mutant fibers are not necessarily more stable than the wild-type(Gallardo et al. 2020) (although this conclusion is not universal(Cao et al. 2020)), so the amyloidogenic mutation (S20G) is hypothesized to act mainly through rearrangement of the monomer, so native structure destabilization was assigned as a mutation mechanism. Also, gene promoter mutations have been reported for IAPP which are associated with type 2 diabetes(Poa, Cooper, and Edgar 2003), so altered processing was also assigned as a mechanism.

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Keratin-5 (KRT5)

Keratin-5, like other cytokeratin proteins, is a protein which forms heteropolymer intermediate filaments in epithelial tissue, and keratin-5 is found in the epidermis(Irvine and McLean 1999). This protein is associated with localized cutaneous amyloidosis, which is a type of amyloidosis with two types of presentations: primary (sometimes called lichen or macular amyloidosis) or secondary which is associated with skin neoplasms(Kobayashi and Hashimoto 1983; Huilgol et al. 1998; Chang et al. 2004). Evidence of its amyloid nature mainly comes in the form of immunohistological studies of the keratin profiles in congophilic amyloid deposits of patients, the results of which always show positive staining for keratin-5, but variable staining for other keratins(Kobayashi and Hashimoto 1983; Huilgol et al. 1998; Chang et al. 2004). It should be noted that keratin-5 normally interacts with keratin-14 and keratin-14 was detected immunohistochemically in some amyloid deposits, but was not as ubiquitous as keratin-5**.** Interestingly, mutations in keratin-5 lead to non-amyloid conditions, namely epidermolysis bullosa simplex (EBS) and Dowling-Degos disease(Irvine and McLean 1999; Betz et al. 2006). However, one mutation (V324A) was associated with a case of Weber-Cockayne type EBS presenting with cutaneous amyloidosis and the congophilic amyloid deposits stained positive for an anti-keratin antibody which reacts with keratin-1, -5, -10, and -14(Chiang et al. 2008). There is not enough biochemical data on the amyloid nature of this protein in the wild-type or mutant state to determine an amyloidogenic mechanism for the V324A mutation.

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Keratin-8 (KRT8)

Keratin-8, like other cytokeratin proteins, is a protein which forms heteropolymer intermediate filaments in hepatocytes(Lim and Ku 2021). This protein is thought to form amyloids in the form of aggregates called Mallory-Denk bodies in the liver of patients with alcoholic steatohepatitis(Murray et al. 2022). Also, amyloidogenic mutations in keratin-8 are associated with cryptogenic liver disease(Ku et al. 2001). Keratin-8 was identified as an amyloid protein through a computational screen intending to identify mutations which modify a segment capable of reversible aggregation into a segment prone to irreversible aggregation(Murray et al. 2022). The amyloid nature of keratin-8 was confirmed through ThT fluorescence, x-ray fiber diffraction, and electron microscopy-based ultrastructural analysis of the head domain of wild-type and mutant keratin-8 as well as peptide crystal structures of wild-type and mutant segments of the protein. The head domain, where the amyloidogenic mutations are, is intrinsically disordered and the mutations significantly increase amyloidogenicity, based on the kinetics observed in ThT assays, and crystal structures of the mutants reveal stronger side chain interactions and more stable secondary structure. For these reasons, the amyloidogenic mechanism of fiber stabilization was the only one assigned to mutations in keratin-8.

Ku, N. O., R. Gish, T. L. Wright, and M. B. Omary. 2001. “Keratin 8 Mutations in Patients with Cryptogenic Liver Disease.” *The New England Journal of Medicine* 344 (21): 1580–87. https://doi.org/10.1056/NEJM200105243442103.
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Lactadherin (MFGE8)

Lactadherin is a glycoprotein which is secreted into milk and binds to milk-fat-globule membranes. It has a variety of functions, many related to immune response, such as playing a role in phagocytosis, and other cellular functions like cell adhesion(Kamińska, Enguita, and Stępień 2018). A fragment of this protein spanning residues 245-294, called medin, is the main constituent of aortic medial amyloid. This was elucidated through amino acid sequence analysis of congophilic material from patient aortic tissue and immunohistochemistry(Häggqvist et al.

1999). A synthetic octapeptide consisting of part of the medin sequence was also shown to form amyloid fibers *in vitro*(Häggqvist et al. 1999). No familial mutations have been associated with amyloidosis lactadherin, and, in fact, aortic medial amyloid is found in the vast majority of individuals over 60 years old(Häggqvist et al. 1999; Mucchiano, Cornwell, and Westermark 1992). The health impact of these amyloid deposits is not fully understood.

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Lactotransferrin (LTF)

Lactotransferrin, also called lactoferrin, is a glycoprotein found in secretory fluids, such as milk and saliva, and also in granulocytes. It has various immune functions, mainly as an antimicrobial agent, particularly by binding to free iron which is required for bacterial growth(Giansanti et al. 2016). Lactoferrin has been found in amyloid deposits in familial subepithelial corneal amyloidosis, also called gelatinous drop-like corneal dystrophy, (an hereditary corneal dystrophy similar to lattice corneal dystrophy which is caused by amyloidosis of gelsolin)(Klintworth et al. 1997), secondary corneal amyloidosis associated with trichiasis(Ando et al. 2002; Araki-Sasaki et al. 2005), along with localized amyloidosis in various other organs (pancreas, bronchus, seminal vesicle)(Baugh et al. 2021; Ichimata et al. 2019; Tsutsumi, Serizawa, and Hori 1996). It was first proposed to be an amyloid protein when congophilic material from localized amyloidosis of the seminal vesicle was positively immunostained with antibodies against lactotransferrin, and demonstration through electron microscopy that the amyloid fibrils themselves were being decorated by the antibodies(Tsutsumi, Serizawa, and Hori 1996). Soon after, it was shown to be present in amyloid deposits in gelatinous drop-like corneal dystrophy through Edman degradation amino acid sequence analysis of proteins extracted from congophilic corneal tissue and immunohistochemistry(Klintworth et al. 1997). The result for gelatinous drop-like corneal dystrophy was somewhat doubted, however, since mutations in proteins besides lactoferrin cause this hereditary disease(Ando et al. 2002; Tsujikawa et al. 1999), and the protein identified in that study was ostensibly wild-type. Although, mutations in one protein causing a disease in which a different protein forms amyloids is not uncommon, so this skepticism may be unwarranted. Variant lactoferrin (E579D) was found in amyloid deposits of patients with trichiasis-associated secondary corneal amyloidosis(Ando et al. 2002; Araki-Sasaki et al. 2005), and wild-type lactotransferrin can only form amyloids *in vitro* under conditions which are far from physiological(Ando et al. 2002; Nilsson and Dobson 2003), but the genetics of the patients with other forms of localized lactoferrin amyloidosis are unknown(Klintworth et al. 1997; Baugh et al. 2021; Ichimata et al. 2019; Tsutsumi, Serizawa,

and Hori 1996). Although, the variant found in individuals with secondary corneal amyloidosis associated with trichiasis is also present in healthy individuals, although at lower frequencies(Araki-Sasaki et al. 2005), making this variant allele a polymorphism rather than a mutation. For this reason, this protein was classified as a sporadic amyloid. It should be noted, however, that all individuals studied with secondary corneal amyloidosis associated with trichiasis harbored this polymorphism. And although a polymorphism is not considered a mutation, an amyloidogenic mechanism for this variant allele has been proposed: the variant residue is hypothesized to disrupt a stabilizing hydrogen bond interaction and increase flexibility enough to expose a hydrophobic patch(Araki-Sasaki et al. 2005).

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Leukocyte cell-derived chemotaxin-2 (LECT2)

Leukocyte cell-derived chemotaxin-2 is a protein with a wide variety of functions including chemotaxis, liver regeneration, immune modulation, bone growth, neuronal development, glucose metabolism, and more(Slowik and Apte 2017). This protein forms amyloid deposits in cases of renal amyloidosis and hepatic amyloidosis(Benson et al. 2008; Mann et al. 2022;

Larsen et al. 2014; Murphy et al. 2010). It was first identified as an amyloid protein through Edman degradation sequence analysis of congophilic material from kidney tissue and immunohistochemistry(Benson et al. 2008). All patients with amyloidosis of this protein who have been genetically sequenced are homozygous, or very rarely heterozygous, for the same polymorphism coding for a valine at position 58 (40 in the mature protein) rather than an isoleucine(Benson et al. 2008; Mann et al. 2022; Larsen et al. 2014; Murphy et al. 2010; Mereuta et al. 2014; Rezk et al. 2018; Ortega Junco et al. 2018). Since this is a polymorphism and not a mutation, and thus the variant residue is seen in healthy individuals in the population, this protein was classified as a sporadic amyloid. However, it should be noted that the valine residue may destabilize the native structure relative to an isoleucine residue(Murphy et al. 2010; Ha et al. 2021), but the polymorphic valine residue was not resolved in a recombinant protein structure of the fibril core(Richards et al. 2023).

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Lysozyme (LYZ)

Lysozyme is a bacteriolytic enzyme found in mucosal secretions(Ferraboschi, Ciceri, and Grisenti 2021). It forms amyloids in hereditary non-neuropathic systemic amyloidosis Ostertag type, now known as hereditary lysozyme amyloidosis(Pepys et al. 1993). Lysozyme was first found to be the amyloid component in this disease through amino acid sequence analysis of protein extracted from congophilic amyloid deposits from a patient's kidney, and also immunohistochemistry(Pepys et al. 1993). Lysozyme is only found to form amyloid deposits if it harbors one of the documented dominant hereditary mutations, and, in fact, wild-type lysozyme is not detectable in the amyloid deposits(Moura et al. 2020), making lysozyme an hereditary amyloid. Although, at least one study has shown that in unphysiologically low pH conditions (even for lysosomes) wild-type lysozyme is destabilized and is able to form amyloid fibers(Morozova-Roche et al. 2000). The initial report of lysozyme being the amyloid protein hypothesized that the mutation was destabilizing the native structure of the protein and later molecular dynamics simulations lead to the same conclusion for many of the known lysozyme mutations(Nasr et al. 2017), so native structure destabilization was assigned as the mutation mechanism for this protein.

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Major prion protein (PRNP)

The major prion protein is a glycosylphosphatidylinositol anchored membrane protein whose total suite of functions is not entirely clear, although this highly conserved protein in mammals is known to have functions in cell signaling, neuritogenesis, and neuronal homeostasis among others(Legname 2017). This protein forms amyloids in humans in Creutzfeldt-Jakob disease (CJD) (familial, sporadic, and iatrogenic), fatal familial insomnia (FFI) (and sporadic fatal insomnia), Gertsmann–Sträussler–Scheinker (GSS), and Kuru(M.-O. Kim et al. 2018; Prusiner 1998). The prion protein was first proposed to be the infectious agent of the animal disease scrapie by Prusiner in 1982(Prusiner 1982).It was later found to be the major component of amyloid deposits in scrapie evidenced by Congo red staining and electron microscopy-based ultrastructural characterization of purified scrapie prion protein(Prusiner et al. 1983) as well as immunoelectron microscopy and immunohistochemistry on scrapie-infected brains(DeArmond et al. 1985). Prion protein was first shown to exist as an amyloid in humans through immunostaining of congophilic plaques in human brains with CJD and GSS(Kitamoto et al. 1986). There are over 60 known pathogenic mutations in major prion protein(M.-O. Kim et al. 2018; Minikel et al. 2016). Wild-type prion protein is able to undergo a transition from α-helical secondary structure to β-sheet secondary structure and form very stable fibers. Some mutant fibers have even been shown to be less stable than wild-type fibers(L.-Q. Wang et al. 2021). The amyloidogenic mechanism of mutations in this protein seem to mainly be destabilization of the native fold. This can occur through disruption of important intramolecular interactions like salt bridges(Prusiner 1998; L.-Q. Wang et al. 2021; Hadži et al. 2015) or protein truncation. Likewise, altered processing through destabilization of the native structure makes the protein vulnerable to aberrant proteolytic processing, leading to production of amyloidogenic fragments of the protein(Hallinan et al. 2022; Tagliavini et al. 1991; Ghetti, Piccardo, and Zanusso 2018; Roeber et al. 2005).

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Melanocyte protein PMEL (PMEL)

Melanocyte protein PMEL is a protein which, after extensive post-translational modification, forms functional amyloid fibers inside melanosomes. These amyloid fibers form a structural foundation for the organelle to store melanin pigments(Raposo and Marks 2007). Mutations in this protein in humans cause pigmentary dispersion syndrome (PDS), characterized by shedding of pigmented material from the iris, which can lead to pigmentary glaucoma (PG), which can lead to blindness(Lahola-Chomiak et al. 2019). Many of the PMEL variants linked to this disease have been shown to lead to formation of abnormal fibers, rather than abolishing fiber formation altogether, ostensibly forming a pathological amyloid rather than a functional amyloid(Lahola-Chomiak et al. 2019; Watt et al. 2011). This abnormal fiber formation is seen by electron microscopy of pseudomelanosomes formed in HeLa cells expressing PMEL variants. Since mutations cause the conversion of a functional amyloid to a nonfunctional amyloid which becomes pathological, the mechanism of altered fibril homeostasis was assigned. Also, western blot analysis of the lysate of the HeLa cells mentioned above reveals defects in proteolytic processing and post-translational modification of the variant forms of the

protein(Lahola-Chomiak et al. 2019), so altered processing was assigned as the amyloidogenic mutation mechanism.

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Microtubule-associated protein tau (MAPT)

Microtubule-associated protein tau is a neuronal protein which binds to and stabilizes microtubules(Michel Goedert 2005), but it may have other biological roles as well such as RNA-binding(Zhang et al. 2017). Tau protein is found in amyloid deposits in over 20 human diseases, collectively called tauopathies(Michel Goedert, Eisenberg, and Crowther 2017), and mutant forms of tau cause diseases with a wide variety of presentations collectively referred to by the umbrella term “frontotemporal dementia and parkinsonism linked to chromosome 17” (FTDP-17)(Michel Goedert 2005; Wolfe 2009; Buée et al. 2000), but at least one has been specifically identified as Pick’s disease (PiD) mutations(Tacik et al. 2015) and some polymorphisms are risk factors for other tauopathies. Microtubule-associated protein tau was shown to be an amyloid protein when it was identified as the constituent protein of Alzheimer’s disease paired helical filaments (PHFs) through immunoblotting of tau with anti-microtubule antibodies cross-reactive for PHFs, and also immunostaining of Alzheimer’s tangles and plaque neurites with affinity-purified tau antibodies(Grundke-Iqbal et al. 1986). Mutations in Microtubule-associated protein tau can have different amyloidogenic mechanisms from each other. Some mutations operate by altered processing through affecting the alternative splicing of MAPT, specifically exon 10 which contains the fourth tandem repeat of the four microtubule binding domain imperfect repeats(Spina et al. 2008; Spillantini et al. 1998; Varani et al. 1999; Hasegawa et al. 1999; Hutton et al. 1998; Michel Goedert 2005; Buée et al. 2000). Mutations can either increase or decrease the inclusion of this exon in transcripts, but the ratio of tau protein with four repeats to tau protein with three repeats seems to be tightly regulated and disruption of this ratio leads to amyloid aggregation. The mechanism is potentially related to limited binding availability of microtubules to certain isoforms of tau protein(Spillantini et al. 1998; Michel Goedert 2005). Other mutations disrupt binding to microtubules directly, releasing free tau protein to aggregate(Michel Goedert 2005; Michel Goedert, Eisenberg, and Crowther 2017; Wolfe 2009; Buée et al. 2000; Ando et al. 2020). However, there are examples of mutations which actually increase binding to microtubules, but this may encourage pathological hyperphosphorylation leading to aggregation(Pickering-Brown et al. 2004). In either case, dysregulation of binding to the native binding partner leads to amyloid aggregation. There are also many mutations which have been shown to accelerate aggregation *in vitro* where the

protein is ostensibly disordered(Jeganathan et al. 2008), meaning these mutations must stabilize the fiber form in some way(Michel Goedert 2005; Pickering-Brown et al. 2004; Barghorn et al. 2000; Nacharaju et al. 1999; M. Goedert, Jakes, and Crowther 1999; Gamblin et al. 2000; von Bergen et al. 2001). Since the protein is intrinsically disordered when not bound to microtubules(Jeganathan et al. 2008), native structure destabilization could not be assigned as a mutation mechanism. It should be noted that post-translational modifications like phosphorylation and acetylation seem to be important for the amyloid aggregation of tau protein(A. Alonso et al. 2001; Buée et al. 2000; A. C. Alonso, Grundke-Iqbal, and Iqbal 1996; Cohen et al. 2011; Li et al. 2023), however the relationship between mutations and these features is not clear.

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Odontogenic ameloblast-associated protein (ODAM)

Odontogenic ameloblast-associated protein is a protein secreted by ameloblasts which plays a role in odontogenesis and is incorporated into the enamel matrix of mature enamel layers(Zhu et al. 2022). This protein is found in the amyloid deposits associated with Calcifying epithelial odontogenic tumors (CEOTs), also known as Pindborg tumors(Murphy et al. 2008; Solomon et al. 2003). The protein was first identified to be the constituent of the amyloid deposits by Edman degradation amino acid sequence analysis of amyloid material extracted from congophilic tumors, reverse transcription-PCR analysis of mRNA from tumor samples, and immunohistochemistry(Murphy et al. 2008; Solomon et al. 2003). This protein does not have any associated amyloidogenic mutations, making it a sporadic amyloid.

Murphy, Charles L., Daniel P. Kestler, James S. Foster, Shuching Wang, Sallie D. Macy, Stephen J. Kennel, Eric R. Carlson, John Hudson, Deborah T. Weiss, and Alan Solomon. 2008. “Odontogenic Ameloblast-Associated Protein Nature of the Amyloid Found in Calcifying Epithelial Odontogenic Tumors and Unerupted Tooth Follicles.” *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 15 (2): 89–95. https://doi.org/10.1080/13506120802005965.
Solomon, Alan, Charles L. Murphy, Kristal Weaver, Deborah T. Weiss, Rudi Hrncic, Manfred Eulitz, Robert L. Donnell, Knut Sletten, Gunilla Westermark, and Per Westermark. 2003. “Calcifying Epithelial Odontogenic (Pindborg) Tumor-Associated Amyloid Consists of a Novel Human Protein.” *The Journal of Laboratory and Clinical Medicine* 142 (5): 348–55. https://doi.org/10.1016/S0022-2143(03)00149-5.
Zhu, Sipin, Chuan Xiang, Oscar Charlesworth, Samuel Bennett, Sijuan Zhang, Maio Zhou, Omar Kujan, and Jiake Xu. 2022. “The Versatile Roles of Odontogenic Ameloblast-Associated Protein in Odontogenesis, Junctional Epithelium Regeneration and Periodontal Disease.” *Frontiers in Physiology* 13 (September):1003931. https://doi.org/10.3389/fphys.2022.1003931.

Parathyroid hormone (PTH)

Parathyroid hormone is a hormone secreted by the parathyroid glands which regulates blood calcium levels(Khan, Jose, and Sharma 2023). This protein makes up the amyloid deposits associated with parathyroid adenoma and parathyroid hyperplasia(Colombat et al. 2021). Parathyroid hormone had been shown to be able to form amyloid fibers *in vitro*(Kedar, Ravid, and Sohar 1976; Gopalswamy et al. 2015) before its identification as the component of parathyroid tumors, but it was confirmed *in vivo* through mass spectrometry proteomic analysis of microdissected congophilic parathyroid adenoma samples and immunohistochemistry(Colombat et al. 2021). Parathyroid hormone does not have any associated amyloidogenic mutations, making it a sporadic amyloid, but it should be noted that

parathyroid adenomas are associated with elevated parathyroid hormone levels, and this increase in production of the amyloidogenic protein may be necessary for amyloidogenesis.

Colombat, Magali, Béatrice Barres, Claire Renaud, David Ribes, Sarah Pericard, Mylène Camus, Rodica Anesia, et al. 2021. “Mass Spectrometry-Based Proteomic Analysis of Parathyroid Adenomas Reveals PTH as a New Human Hormone-Derived Amyloid Fibril Protein.” *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 28 (3): 153–57. https://doi.org/10.1080/13506129.2021.1885023.

Gopalswamy, Mohanraj, Amit Kumar, Juliane Adler, Monika Baumann, Mathias Henze, Senthil T. Kumar, Marcus Fändrich, Holger A. Scheidt, Daniel Huster, and Jochen Balbach. 2015. “Structural Characterization of Amyloid Fibrils from the Human Parathyroid Hormone.” *Biochimica Et Biophysica Acta* 1854 (4): 249–57. https://doi.org/10.1016/j.bbapap.2014.12.020.

Kedar, I., M. Ravid, and E. Sohar. 1976. “In Vitro Synthesis of ‘Amyloid’Fibrils from Insulin, Calcitonin and Parathormone.” *Israel Journal of Medical Sciences* 12 (10): 1137–40.

Khan, Maqsood, Alvin Jose, and Sandeep Sharma. 2023. “Physiology, Parathyroid Hormone.” In *StatPearls*. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK499940/.

Polyadenylate-binding protein 2 (PABPN1)

Polyadenylate-binding protein 2 is a nuclear protein which stimulates the addition of poly(A) tails on mRNA(Wahle 1991). This protein forms fibrous nuclear aggregates in oculopharyngeal muscular dystrophy, confirmed by immunofluorescent labeling and immunoelectron microscopy(Calado et al. 2000), although these aggregates were not characterized as amyloids. This protein was later shown to be able to form fibers with amyloid characteristics *in vitro*, as evidenced by affinity to ThT and ultrastructural characterization by electron microscopy(Scheuermann et al. 2003). This protein causes disease due to a trinucleotide expansion which extends a polyalanine region near the N-terminal of the protein(Calado et al. 2000; Scheuermann et al. 2003). It has been shown that the wild-type protein can form ThT-positive aggregates, but the polyalanine expansion greatly accelerates their formation(Scheuermann et al. 2003), so this protein is classified as an ambimorph amyloid. Also, this protein can cause disease through a mutation which mimics the polyalanine expansion by substituting a glycine, which interrupts the polyalanine region of the protein, for an alanine(Robinson et al. 2006), and this presumably induces the disease through the same mechanism as the polyalanine expansion, which is formation of fibrillar nuclear aggregates. In N-terminal fragments, the polyalanine expansion seems to induce α-helical secondary structure in an otherwise unstructured region of the protein(Scheuermann et al. 2003), but how this influences fiber formation is unclear, and since this region in the native protein is unstructured we did not consider this to fall under the mechanism of native structure destabilization. However, since this mutation accelerates the *in vitro* fiber formation of an otherwise unstructured protein, the mutation must be stabilizing the fiber form in some way, possibly through a capacity to transition from the induced α-helical secondary structure to β-sheet secondary structure, so fiber stabilization was assigned as the mutation mechanism.

Calado, A., F. M. Tomé, B. Brais, G. A. Rouleau, U. Kühn, E. Wahle, and M. Carmo-Fonseca. 2000. “Nuclear Inclusions in Oculopharyngeal Muscular Dystrophy Consist of Poly(A) Binding Protein 2 Aggregates Which Sequester Poly(A) RNA.” *Human Molecular Genetics* 9 (15): 2321–28. https://doi.org/10.1093/oxfordjournals.hmg.a018924.

Robinson, D. O., A. J. Wills, S. R. Hammans, S. P. Read, and J. Sillibourne. 2006. “Oculopharyngeal Muscular Dystrophy: A Point Mutation Which Mimics the Effect of the PABPN1 Gene Triplet Repeat Expansion Mutation.” *Journal of Medical Genetics* 43 (5): e23. https://doi.org/10.1136/jmg.2005.037598.

Scheuermann, Till, Barbe Schulz, Alfred Blume, Elmar Wahle, Rainer Rudolph, and Elisabeth Schwarz. 2003. “Trinucleotide Expansions Leading to an Extended Poly-L-Alanine Segment in the Poly (A) Binding Protein PABPN1 Cause Fibril Formation.” *Protein Science: A Publication of the Protein Society* 12 (12): 2685–92. https://doi.org/10.1110/ps.03214703.

Wahle, E. 1991. “A Novel Poly(A)-Binding Protein Acts as a Specificity Factor in the Second Phase of Messenger RNA Polyadenylation.” *Cell* 66 (4): 759–68. https://doi.org/10.1016/0092-8674(91)90119-j.

Prolactin (PRL)

Prolactin is a hormone secreted by the pituitary gland with various physiological functions, but mainly promotion of milk production and development of mammary glands in breast tissue(Al-Chalabi, Bass, and Alsalman 2023). Prolactin forms amyloid deposits in prolactin-producing pituitary adenomas and also tumor-free pituitary glands of individuals of advanced age(Westermark et al. 1997; Hinton et al. 1997). Prolactin was identified to be the component of the amyloid fibers in both cases through amino acid sequence analysis of amyloid material extracted from congophilic deposits in pituitary gland samples. Interestingly, in both studies, commercial anti-prolactin antibodies were not reactive with the amyloid material. This is either due to aberrant proteolytic cleavage of prolactin (so the amyloid is composed of a fragment of the protein lacking the epitope recognized by the antibody) or the conformational change accompanying amyloid formation buries or alters the epitope recognized by the antibody. Prolactin amyloidogenesis is not associated with any mutations, so it is classified as a sporadic amyloid.

Al-Chalabi, Mustafa, Autumn N. Bass, and Ihsan Alsalman. 2023. “Physiology, Prolactin.” In *StatPearls*. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK507829/.

Hinton, D. R., R. K. Polk, K. D. Linse, M. H. Weiss, K. Kovacs, and J. A. Garner. 1997. “Characterization of Spherical Amyloid Protein from a Prolactin-Producing Pituitary Adenoma.” *Acta Neuropathologica* 93 (1): 43–49. https://doi.org/10.1007/s004010050581.

Westermark, P., L. Eriksson, U. Engström, S. Eneström, and K. Sletten. 1997. “Prolactin-Derived Amyloid in the Aging Pituitary Gland.” *The American Journal of Pathology* 150 (1): 67–73.

Protein TFG (TFG)

Protein TFG functions in the trafficking of secretory vesicles between the endoplasmic reticulum (ER) and ER-Golgi intermediate compartments(Johnson et al. 2015). Mutations in protein TFG

are associated with Charcot-Marie-Tooth disease type 2 and hereditary motor and sensory neuropathy with proximal dominant involvement(Tsai et al. 2014; Ishiura et al. 2012). The mutations associated with both these diseases have been shown to induce amyloid aggregation of the protein *in vitro* as evidenced by ThT fluorescence, x-ray fiber diffraction, and electron microscopy-based ultrastructural analysis(Rosenberg et al. 2022). Wild-type recombinant protein was also able to form amyloid fibers *in vitro*, although at a slower rate, so this protein is classified as an ambimorph amyloid. The mutations occurring in the disordered low-complexity domain of the protein and cryo-EM structures reveal that the mutant residues form key stabilizing interactions in the fiber core(Rosenberg et al. 2023), so fiber stabilization is the only mutation mechanism assigned.

Ishiura, Hiroyuki, Wataru Sako, Mari Yoshida, Toshitaka Kawarai, Osamu Tanabe, Jun Goto, Yuji Takahashi, et al. 2012. “The TRK-Fused Gene Is Mutated in Hereditary Motor and Sensory Neuropathy with Proximal Dominant Involvement.” *American Journal of Human Genetics* 91 (2): 320–29. https://doi.org/10.1016/j.ajhg.2012.07.014.

Johnson, Adam, Nilakshee Bhattacharya, Michael Hanna, Janice G. Pennington, Amber L. Schuh, Lei Wang, Marisa S. Otegui, Scott M. Stagg, and Anjon Audhya. 2015. “TFG Clusters COPII-Coated Transport Carriers and Promotes Early Secretory Pathway Organization.” *The EMBO Journal* 34 (6): 811–27. https://doi.org/10.15252/embj.201489032.

Rosenberg, Gregory M., Romany Abskharon, David R. Boyer, Peng Ge, Michael R. Sawaya, and David S. Eisenberg. 2023. “Fibril Structures of TFG Protein Mutants Validate the Identification of TFG as a Disease-Related Amyloid Protein by the IMPAcT Method.” *PNAS Nexus* 2 (12): pgad402. https://doi.org/10.1093/pnasnexus/pgad402.

Rosenberg, Gregory M., Kevin A. Murray, Lukasz Salwinski, Michael P. Hughes, Romany Abskharon, and David S. Eisenberg. 2022. “Bioinformatic Identification of Previously Unrecognized Amyloidogenic Proteins.” *The Journal of Biological Chemistry* 298 (5): 101920. https://doi.org/10.1016/j.jbc.2022.101920.

Tsai, Pei-Chien, Yen-Hua Huang, Yuh-Cherng Guo, Hung-Ta Wu, Kon-Ping Lin, Yu-Shuen Tsai, Yi-Chu Liao, et al. 2014. “A Novel TFG Mutation Causes Charcot-Marie-Tooth Disease Type 2 and Impairs TFG Function.” *Neurology* 83 (10): 903–12. https://doi.org/10.1212/WNL.0000000000000758.

Pulmonary surfactant-associated protein C (SFTPC)

Pulmonary surfactant-associated protein C, also called lung surfactant protein C, is a transmembrane lipopeptide which functions to lower alveolar surface tension at the air-liquid interface(Sehlmeyer et al. 2020). This protein forms amyloids in pulmonary alveolar proteinosis (PAP), confirmed by Edman degradation amino acid sequence analysis of congophilic amyloid material extracted from bronchoalveolar lavage (BAL) fluid from a PAP patient(Gustafsson et al. 1999). No mutations are associated with the amyloid formation of this protein, making it a sporadic amyloid. Interestingly, this protein, despite being a 35-residue peptide, exists as a stable α-helix in lipid membranes, but transitions to β-sheet aggregates in solution(Gustafsson et al. 1999; Szyperski et al. 1998). This transition is dependent on removal of palmitoyl groups from the protein’s cysteine residues, and this modification along with increased levels of the protein seem to strongly contribute to its amyloid conversion, although the cause of the protein’s depalmitoylation is unknown.

Gustafsson, M., J. Thyberg, J. Näslund, E. Eliasson, and J. Johansson. 1999. “Amyloid Fibril Formation by Pulmonary Surfactant Protein C.” *FEBS Letters* 464 (3): 138–42. https://doi.org/10.1016/s0014-5793(99)01692-0.

Sehlmeyer, Kirsten, Jannik Ruwisch, Nuria Roldan, and Elena Lopez-Rodriguez. 2020. “Alveolar Dynamics and Beyond - The Importance of Surfactant Protein C and Cholesterol in Lung Homeostasis and Fibrosis.” *Frontiers in Physiology* 11:386. https://doi.org/10.3389/fphys.2020.00386.

Szyperski, T., G. Vandenbussche, T. Curstedt, J. M. Ruysschaert, K. Wüthrich, and J. Johansson. 1998. “Pulmonary Surfactant-Associated Polypeptide C in a Mixed Organic Solvent Transforms from a Monomeric Alpha-Helical State into Insoluble Beta-Sheet Aggregates.” *Protein Science: A Publication of the Protein Society* 7 (12): 2533–40. https://doi.org/10.1002/pro.5560071206.

RNA-binding protein FUS (FUS)

RNA-binding protein FUS is a nuclear protein involved in transcription and DNA repair, but also forms cytosolic stress granules through liquid-liquid phase separation(Lagier-Tourenne, Polymenidou, and Cleveland 2010; Zinszner et al. 1997). In stress granules, this protein forms reversible aggregates consisting of fibers with amyloid qualities, demonstrated *in vitro* through electron microscopy-based ultrastructural analysis and x-ray fiber diffraction(Murray et al. 2017; Kato et al. 2012). This protein is also found in cytoplasmic inclusions in diseases including frontotemporal lobar degeneration (FTLD-FUS) and amyotrophic lateral sclerosis (ALS)(Lagier-Tourenne, Polymenidou, and Cleveland 2010; Kwiatkowski et al. 2009; Z. Sun et al. 2011; Patel et al. 2015). The low-complexity domain of RNA-binding protein FUS has been shown to form reversible, liquid-like aggregates *in vitro* which transition to solid, irreversible, cytotoxic amyloid fibers over time(Y. Sun et al. 2022), and disease mutations have been shown to accelerate this transition(Nomura et al. 2014). Since these mutations promote aggregation of an otherwise disordered region of the protein, fiber stabilization was assigned as the mechanism. Other mutations seem to not directly increase aggregation propensity(Z. Sun et al. 2011), but rather contribute to cytoplasmic mislocalization of the protein, which contributes to its pathological aggregation, so subcellular mislocalization was also assigned as a mechanism. Also, since this protein may be a functional amyloid (due to its role in stress granule formation) and mutations cause the protein to form pathological amyloids, the mechanism of altered fibril homeostasis was assigned.

Kato, Masato, Tina W. Han, Shanhai Xie, Kevin Shi, Xinlin Du, Leeju C. Wu, Hamid Mirzaei, et al. 2012. “Cell-Free Formation of RNA Granules: Low Complexity Sequence Domains Form Dynamic Fibers within Hydrogels.” *Cell* 149 (4): 753–67. https://doi.org/10.1016/j.cell.2012.04.017.

Kwiatkowski, T. J., D. A. Bosco, A. L. Leclerc, E. Tamrazian, C. R. Vanderburg, C. Russ, A. Davis, et al. 2009. “Mutations in the FUS/TLS Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis.” *Science (New York, N.Y.)* 323 (5918): 1205–8. https://doi.org/10.1126/science.1166066.

Lagier-Tourenne, Clotilde, Magdalini Polymenidou, and Don W. Cleveland. 2010. “TDP-43 and FUS/TLS: Emerging Roles in RNA Processing and Neurodegeneration.” *Human Molecular Genetics* 19 (R1): R46-64. https://doi.org/10.1093/hmg/ddq137.

Murray, Dylan T., Masato Kato, Yi Lin, Kent R. Thurber, Ivan Hung, Steven L. McKnight, and Robert Tycko. 2017. “Structure of FUS Protein Fibrils and Its Relevance to Self-Assembly and Phase Separation of Low-Complexity Domains.” *Cell* 171 (3): 615-627.e16. https://doi.org/10.1016/j.cell.2017.08.048.

Nomura, Takao, Shoji Watanabe, Kumi Kaneko, Koji Yamanaka, Nobuyuki Nukina, and Yoshiaki Furukawa. 2014. “Intranuclear Aggregation of Mutant FUS/TLS as a Molecular Pathomechanism of Amyotrophic Lateral Sclerosis.” *The Journal of Biological Chemistry* 289 (2): 1192–1202. https://doi.org/10.1074/jbc.M113.516492.

Patel, Avinash, Hyun O. Lee, Louise Jawerth, Shovamayee Maharana, Marcus Jahnel, Marco Y. Hein, Stoyno Stoynov, et al. 2015. “A Liquid-to-Solid Phase Transition of the ALS Protein FUS Accelerated by Disease Mutation.” *Cell* 162 (5): 1066–77. https://doi.org/10.1016/j.cell.2015.07.047.

Sun, Yunpeng, Shenqing Zhang, Jiaojiao Hu, Youqi Tao, Wencheng Xia, Jinge Gu, Yichen Li, Qin Cao, Dan Li, and Cong Liu. 2022. “Molecular Structure of an Amyloid Fibril Formed by FUS Low-Complexity Domain.” *iScience* 25 (1): 103701. https://doi.org/10.1016/j.isci.2021.103701.

Sun, Zhihui, Zamia Diaz, Xiaodong Fang, Michael P. Hart, Alessandra Chesi, James Shorter, and Aaron D. Gitler. 2011. “Molecular Determinants and Genetic Modifiers of Aggregation and Toxicity for the ALS Disease Protein FUS/TLS.” *PLoS Biology* 9 (4): e1000614. https://doi.org/10.1371/journal.pbio.1000614.

Zinszner, H., J. Sok, D. Immanuel, Y. Yin, and D. Ron. 1997. “TLS (FUS) Binds RNA in Vivo and Engages in Nucleo-Cytoplasmic Shuttling.” *Journal of Cell Science* 110 (Pt 15) (August):1741–50. https://doi.org/10.1242/jcs.110.15.1741.

S100-A8/A9 (S100A8/A9)

S100-A8 and S100-A9, also known as calgranulin-A and calgranulin-B, respectively, are calcium and zinc binding proteins which have various biological roles including pro-inflammatory roles and acting as an antifungal agent(Vogl, Gharibyan, and Morozova-Roche 2012). These proteins can form homodimers and heterodimers, but also a heterotetrameric form called calprotectin. These proteins were found in congophilic corpora amylacea, a type of extracellular inclusion found in various tissues, from prostate tissue extracted from patients with prostate cancer(Yanamandra et al. 2009), although corpora amylacea can exist in noncancerous aged prostate as well. S100-A8 and S100-A9 were identified as the amyloid component by mass spectrometry analysis and immunostaining, along with atomic force microscopy analysis of the amyloid material. We will note, however, that the *ex vivo* fibers and those generated *in vitro* in this work do not, in our view, necessarily look like typical amyloid fibers which are explicitly unbranched. The histology and mass spectrometry analysis, however, provide evidence consistent with other established amyloid proteins. It is also unclear which form the proteins take in these aggregates: homopolymers, polymers of the heterodimers, or polymers of calprotectin (a heterotetramer). Both proteins are evidently present in the amyloid aggregates, but the segments of the proteins which are predicted to be most aggregation-prone also seem to be involved in their native oligomerization, so it may be the case that disruption of the oligomeric states of these proteins leads to their amyloid aggregation. If this is the case, it is unlikely that the amyloid fibers are heteropolymers, but whether or not this is the case is not clear from the evidence. These proteins have no mutations associated with their amyloid

aggregation, making them a sporadic amyloid, but their aggregation may be linked to increased local concentration due to chronic inflammation.

Vogl, Thomas, Anna L. Gharibyan, and Ludmilla A. Morozova-Roche. 2012. “Pro-Inflammatory S100A8 and S100A9 Proteins: Self-Assembly into Multifunctional Native and Amyloid Complexes.” *International Journal of Molecular Sciences* 13 (3): 2893–2917. https://doi.org/10.3390/ijms13032893.

Yanamandra, Kiran, Oleg Alexeyev, Vladimir Zamotin, Vaibhav Srivastava, Andrei Shchukarev, Ann-Christin Brorsson, Gian Gaetano Tartaglia, et al. 2009. “Amyloid Formation by the Pro-Inflammatory S100A8/A9 Proteins in the Ageing Prostate.” *PloS One* 4 (5): e5562. https://doi.org/10.1371/journal.pone.0005562.

Semenogelin 1 (SEMG1)

Semenogelin 1 is the main protein component of human semen and promotes sperm survival, motility, and fertility(Sakaguchi et al. 2020). This protein forms amyloid deposits in senile seminal vesicle amyloid, a localized amyloidosis associated with male aging. Semenogelin 1 was confirmed as the amyloidogenic protein through mass spectrometry analysis of congophilic material from seminal vesicle samples with amyloid and immunohistochemistry(Linke et al. 2005). No mutations are associated with the amyloid formation of this protein, so it is a sporadic amyloid. Of note, the amyloid component of this protein seems to be an N-terminal fragment of semenogelin 1.

Linke, Reinhold P., Reinhild Joswig, Charles L. Murphy, Shuching Wang, Hui Zhou, Ulrich Gross, Christoph Rocken, Per Westermark, Deborah T. Weiss, and Alan Solomon. 2005. “Senile Seminal Vesicle Amyloid Is Derived from Semenogelin I.” *The Journal of Laboratory and Clinical Medicine* 145 (4): 187–93. https://doi.org/10.1016/j.lab.2005.02.002.

Sakaguchi, Daiki, Kenji Miyado, Teruaki Iwamoto, Hiroshi Okada, Kaoru Yoshida, Woojin Kang, Miki Suzuki, Manabu Yoshida, and Natsuko Kawano. 2020. “Human Semenogelin 1 Promotes Sperm Survival in the Mouse Female Reproductive Tract.” *International Journal of Molecular Sciences* 21 (11): 3961. https://doi.org/10.3390/ijms21113961.

Serum amyloid A (SAA1)

Serum amyloid A is an acute-phase response protein which is secreted by the liver into the blood in response to inflammatory conditions(Eklund, Niemi, and Kovanen 2012). This protein is found in amyloid deposits in individuals with amyloid A amyloidosis, a systemic secondary amyloidosis resulting from chronic inflammation(Liberta et al. 2019). This disease can also manifest as a primary amyloidosis due to a mutation in the SAA1 promoter region inducing overexpression(Sikora et al. 2022), making this protein an ambimorph amyloid. This protein was first identified as a unique amyloid protein through amino acid sequence analysis of congophilic amyloid material from livers and spleens of patients with secondary amyloidosis associated with familial Mediterranean fever, tuberculosis, Hodgkin’s lymphoma, and bronchiectasis(Levin et al. 1972), and this result was corroborated by other groups later(Linke et al. 1975; Rosenthal et al. 1976). Since the mutation associated with primary amyloid A amyloidosis is a promoter mutation which causes overexpression, altered processing was assigned as the mutation mechanism.

Eklund, Kari K., K. Niemi, and P. T. Kovanen. 2012. “Immune Functions of Serum Amyloid A.” *Critical Reviews in Immunology* 32 (4): 335–48. https://doi.org/10.1615/critrevimmunol.v32.i4.40.

Levin, M., E. C. Franklin, B. Frangione, and M. Pras. 1972. “The Amino Acid Sequence of a Major Nonimmunoglobulin Component of Some Amyloid Fibrils.” *The Journal of Clinical Investigation* 51 (10): 2773–76. https://doi.org/10.1172/JCI107098.

Liberta, Falk, Matthies Rennegarbe, Reinhild Rösler, Johan Bijzet, Sebastian Wiese, Bouke P. C. Hazenberg, and Marcus Fändrich. 2019. “Morphological and Primary Structural Consistency of Fibrils from Different AA Patients (Common Variant).” *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 26 (3): 164–70. https://doi.org/10.1080/13506129.2019.1628015.

Linke, R. P., J. D. Sipe, P. S. Pollock, T. F. Ignaczak, and G. G. Glenner. 1975. “Isolation of a Low-Molecular-Weight Serum Component Antigenically Related to an Amyloid Fibril Protein of Unknown Origin.” *Proceedings of the National Academy of Sciences of the United States of America* 72 (4): 1473–76. https://doi.org/10.1073/pnas.72.4.1473.

Rosenthal, C. J., E. C. Franklin, B. Frangione, and J. Greenspan. 1976. “Isolation and Partial Characterization of SAA-an Amyloid-Related Protein from Human Serum.” *Journal of Immunology (Baltimore, Md.: 1950)* 116 (5): 1415–18.

Sikora, Jakub, Tereza Kmochová, Dita Mušálková, Michal Pohludka, Petr Přikryl, Hana Hartmannová, Kateřina Hodaňová, et al. 2022. “A Mutation in the SAA1 Promoter Causes Hereditary Amyloid A Amyloidosis.” *Kidney International* 101 (2): 349–59. https://doi.org/10.1016/j.kint.2021.09.007.

Somatostatin (SST)

Somatostatin is a pancreatic prohormone which is cleaved into two small peptide hormones, somatostatin-14 and somatostatin-28, which regulate the production of pituitary hormones(O’Toole and Sharma 2023). One of these peptide hormones, somatostatin-14, was shown to form amyloid fibers *in vitro* as evidenced by Congo red staining, electron microscopy-based ultrastructural analysis, and x-ray fiber diffraction(van Grondelle et al. 2007). Somatostatin was found in amyloid deposits in somatostatin-producing neuroendocrine tumors (somatostatinomas)(Ichimata et al. 2022; Van Treeck et al. 2022). Somatostatin was confirmed as the amyloid protein through mass spectrometry analysis of microdissected congophilic tissue and immunohistochemistry. Interestingly, somatostatin-28 was the major species present in the *in vivo* amyloid deposits, not somatostatin-14, based on immunostaining results. Amyloidosis of somatostatin is not associated with any mutations, making it a sporadic amyloid. However, it should be noted that the amyloid formation in the case of neuroendocrine tumors may be reliant on the increased production of the protein by the tumor.

Grondelle, Wilmar van, Carmen López Iglesias, Elisenda Coll, Franck Artzner, Maïté Paternostre, Frédéric Lacombe, Merce Cardus, et al. 2007. “Spontaneous Fibrillation of the Native Neuropeptide Hormone Somatostatin-14.” *Journal of Structural Biology* 160 (2): 211–23. https://doi.org/10.1016/j.jsb.2007.08.006.

Ichimata, Shojiro, Nagaaki Katoh, Ryuta Abe, Tsuneaki Yoshinaga, Fuyuki Kametani, Masahide Yazaki, Yukiko Kusama, Kenji Sano, Takeshi Uehara, and Yoshiki Sekijima. 2022. “Somatostatin-Derived Amyloid Deposition Associated with Duodenal Neuroendocrine Tumour (NET): A Report of Novel Localised Amyloidosis Associated with NET.” *Amyloid:*

The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis 29 (1): 64–65. https://doi.org/10.1080/13506129.2021.1979513.
O'Toole, Timothy J., and Sandeep Sharma. 2023. "Physiology, Somatostatin." In *StatPearls*. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK538327/.
Van Treeck, Benjamin J., Surendra Dasari, Paul J. Kurtin, Jason D. Theis, Samih H. Nasr, Lizhi Zhang, Saba Yasir, Rondell P. Graham, Ellen D. McPhail, and Samar Said. 2022. "Somatostatin-Derived Amyloidosis: A Novel Type of Amyloidosis Associated with Well-Differentiated Somatostatin-Producing Neuroendocrine Tumours." *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis* 29 (1): 58–63. https://doi.org/10.1080/13506129.2021.1979512.

Superoxide dismutase (SOD1)

Superoxide dismutase is a metalloenzyme which catalyzes a dismutation reaction of superoxide radicals into O_2 and H_2O_2(Y. Wang et al. 2018). Superoxide dismutase is found in pathological inclusions in both familial and sporadic ALS(Chattopadhyay and Valentine 2009; Gruzman et al. 2007). Mutant superoxide dismutase has been shown to form fibers in transgenic mice with amyloid characteristics as evidenced by immunoelectron microscopy and thioflavin S staining(Basso et al. 2006; J. Wang et al. 2003). Wild type and mutant recombinant protein can be induced to form thioflavin T-positive, fibrillar aggregates (amyloids) under reducing conditions *in vitro*, mimicking the reducing environment of the cell(L.-Q. Wang et al. 2022; Chattopadhyay et al. 2008). There are over 200 documented mutations in superoxide dismutase which are linked to familial ALS (https://alsod.ac.uk/output/gene.php/SOD1), although not all of them are necessarily amyloidogenic. These mutations likely induce aggregation by interrupting its ability to bind metal ions, since the mature, metal-bound protein is very resistant to aggregation and inclusions in transgenic mice and cell lines expressing mutant superoxide dismutase contain metal-deficient, disulfide reduced protein(Tiwari, Xu, and Hayward 2005; Chattopadhyay and Valentine 2009; J. Wang et al. 2003; Chattopadhyay et al. 2008). Since mutations in this protein likely disrupt an important binding site, the mutation mechanisms assigned are native structure destabilization and decreased binding to native partners.

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TAR DNA-binding protein 43 (TARDBP)

TAR DNA-binding protein 43 is a nuclear DNA- and RNA-binding protein with roles in regulating transcription of RNA(Lagier-Tourenne, Polymenidou, and Cleveland 2010). It can also be found in the cytoplasm as a constituent of pathological inclusions in FTLD-TDP and ALS(Lagier-Tourenne, Polymenidou, and Cleveland 2010; Johnson et al. 2009; Jiang et al. 2016; Neumann et al. 2006; Kwong et al. 2008; Jiang et al. 2013). Inclusions in the brains of individuals with FTLD-TDP have been shown to bind thioflavin S and also be immunoreactive to antibodies against TAR DNA-binding protein 43(Bigio et al. 2013). Immunoelectron microscopy studies also reveal this protein exists in the form of filamentous inclusions in tissue samples from a variety of neurodegenerative diseases(Lin and Dickson 2008). It has also been shown that fibrillar aggregates of TAR DNA-binding protein 43 from patient brains can act as seeds which induce aggregation in cultured cell lines(Nonaka et al. 2013). The structure of the amyloid fiber has also been solved from material extracted from the brain of a patient with ALS with FTLD(Arseni et al. 2022). Disease mutations in this protein concentrate in the low-complexity C-terminal region, which is disordered(Lagier-Tourenne, Polymenidou, and Cleveland 2010), and many of these mutations have been shown to accelerate aggregation(Johnson et al. 2009; Guo et al. 2011), so the mutation mechanism of fiber stabilization was assigned. Since aggregates are mislocalized to the cytoplasm and this mislocalization can be enhanced by mutations(Barmada et al. 2010), subcellular mislocalization was also assigned as a mechanism. Also, since this protein may be a functional amyloid(Vogler et al. 2018) and mutations cause the protein to form pathological amyloids, the mechanism of altered fibril homeostasis was assigned. There are also noncoding variants for this protein associated with ALS(Luquin et al. 2009), but many of them are polymorphisms, not mutations, and their effects on protein

production are not entirely clear, so altered processing was not included as a mutation mechanism for this protein.

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TATA-binding protein-associated factor 2N (TAF15)

TATA-binding protein-associated factor 2N is a nucleic-acid binding protein coded by the gene TAF15 which is in the same family as FUS and EWS. The protein functions in RNA splicing, transcription, mRNA transport, signaling, modification, translation and maintenance of genome integrity(Tang et al. 2023). This protein is found in amyloid deposits in FTLD and ALS. The protein was first identified as amyloid-forming after its structure was determined by cryoEM after extraction from the brains of FTD-FUS (also called FTD-FET) patients and amyloid deposits in the brain were shown to be immunoreactive for TATA-binding protein-associated factor 2N(Tetter et al. 2024). This protein harbors a mutation that causes ALS, A31T, making it an ambimorph. Since the protein's low-complexity domain is the amyloid-forming segment, and the A31T mutation may increase intralayer hydrogen-bonding to Q48(Tetter et al. 2024) the mutation mechanism of fibril stabilization was assigned. Although, it should be noted that intralayer hydrogen bonding of Q48 would be a tradeoff for an interlayer glutamine ladder formed by Q48 and it is not clear which hydrogen-bonding pattern would drive amyloid formation more readily.

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Transcription elongation regulator 1 (TCERG1 or CA150)

Transcription elongation regulator 1, or CA150, is a transcription factor which codeposits with huntingtin aggregates in Huntington's disease and seems to be a modifier of the age of onset(Holbert et al. 2001). CA150 rapidly forms amyloid fibers *in vitro* as evidenced by thioflavin T fluorescence, light scattering, electron microscopy-based ultrastructural analysis, optical diffraction of fibers, and solid state NMR structure determination(Ferguson et al. 2006; 2003). There are no pathogenic mutations associated with CA150, making it a sporadic amyloid.

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Transforming growth factor-beta-induced protein ig-h3 (TGFBI)

Transforming growth factor-beta-induced protein ig-h3, also called kerato-epithelin, is an extracellular matrix protein which is abundant in the corneal stroma(Dyrlund et al. 2012). It is found in amyloid deposits in lattice corneal dystrophy, but also non-amyloid aggregates in other corneal dystrophies(Klintworth 2009; Venkatraman et al. 2017; Munier et al. 1997; Korvatska et al. 2000; 1999). The contribution of kerato-epithelin to amyloid deposits was confirmed by immunohistochemical staining of congophilic deposits in patient corneal tissue(Korvatska et al. 1999). Peptide fragments of the protein were also shown to be able to form amyloid fibers *in vitro* evidenced by circular dichroism spectra, thioflavin T fluorescence, and electron microscopy-based ultrastructural analysis(Venkatraman et al. 2017; Sørensen et al. 2015). Mutations in this protein which result in amyloid deposition seem to lead to deposition of unique proteolytic fragments of the protein not found in wild-type corneas, specifically from the fourth fasciclin-1 domain (FAS1-4)(Karring et al. 2012; 2013; Poulsen et al. 2014), and for this reason the mutation mechanism assigned to this protein is altered processing. The wild-type form of this protein does not seem to develop into amyloid fibers, so kerato-epithelin is classified as an hereditary amyloid.

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Transmembrane protein 106B (TMEM106B)

Transmembrane protein 106B is a transmembrane glycoprotein which localizes to the membranes of lysosomes and interacts with progranulin(Nicholson et al. 2013). This protein is found as an amyloid fiber in a wide variety of neurodegenerative diseases including FTLD-TDP, progressive supranuclear palsy (PSP), dementia with lewy bodies (DLB), Alzheimer's disease, corticobasal degeneration, FTDP-17, argyrophilic grain disease, Parkinson's disease, limbic-predominant neuronal inclusion body four-repeat tauopathy, aging-related tau astrogliopathy, MSA, and ALS(Chang et al. 2022; Schweighauser et al. 2022). Although, the connection of the protein's amyloidogenesis to disease is unclear because it can also be found in fibrillar form in healthy, aged brains(Fan et al. 2022). It was independently shown to be an amyloid protein by three separate groups at the same time by the same method: cryo-EM structure determination of brain-extracted amyloid fibers(Chang et al. 2022; Schweighauser et al. 2022; Jiang et al. 2022).There are no familial mutations associated with transmembrane protein 106B, making it a sporadic amyloid, but there is a polymorphism at residue 185 (threonine or serine)(Van Deerlin et al. 2010). This polymorphism may influence expression of the protein(Nicholson et al. 2013) and having a serine at this position is hypothesized to be protective against disease due to more rapid degradation of the protein with the serine polymorph(Nicholson et al. 2013; Cruchaga et al. 2011).

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Transthyretin (TTR)

Transthyretin, also called prealbumin, is a thyroid hormone distributor protein which is secreted into the blood by the liver and into the cerebro-spinal fluid (CSF) by the epithelial cells of the choroid plexus(Richardson 2007). Transthyretin functions as a tetramer and binds to thyroid hormones and retinol-binding protein, as well as certain drugs and pollutants(Richardson 2007). This protein forms amyloid deposits in systemic transthyretin amyloidosis, which is characterized by amyloid deposition in multiple organs and commonly manifests as cardiomyopathy and/or polyneuropathy(Adams et al. 2019; Ruberg et al. 2019). Transthyretin was first identified as an amyloid protein by matching the immunoreactivity of antisera raised against prealbumin to an antisera raised against amyloid fiber protein extracted from the kidneys of patients with familial amyloidotic polyneuropathy(Costa, Figueira, and Bravo 1978). This result was later repeated in other cases of familial amyloidosis as well as sporadic amyloidosis(Westermark et al. 1990). There are over 120 amyloidogenic mutations in transthyretin, but the most common one is V50M (V30M with the numbering of the mature protein)(Adams et al. 2019; Planté-Bordeneuve and Said 2011). Comparison of wild-type and mutant structures of transthyretin amyloid fibers(Schmidt et al. 2019; Steinebrei et al. 2022)

reveals that they have nearly identical structures, meaning the mutation mechanism is solely disruption of the native tetramer, so native structure destabilization is the only assigned mutation mechanism.

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Ubiquilin-2 (UBQLN2)

Ubiquilin-2 is a protein which interacts with ubiquitinated proteins and delivers them to the proteasome for degradation(Ko et al. 2004). Intracellular aggregates of this protein are found in various neurodegenerative diseases including ALS, synucleinopathies, and polyglutamine diseases(Sharkey et al. 2018; Mori et al. 2012; Rutherford et al. 2013; Zeng et al. 2015; Deng et al. 2011), and mutations in its proline-rich repeat (PXX) domain cause dominant X-linked ALS and FTD. Ubiquilin-2 was shown to form amyloids in vitro through ThT fluorescence and electron microscopy-based ultrastructural analysis(Sharkey et al. 2018). In regard to the full-length protein, only the construct with the P506T mutation was able to form amyloid fibers and the wild-type could not. For this reason, we have classified this protein as an hereditary amyloid. However, it has not escaped our attention that the wild-type protein with its N-terminal ubiquitin-like (UBL) domain (residues 1-106) deleted was able to form amyloid fibers. Also, the protein’s C-terminal ubiquitin-associated (UBA) domain alone (residues 575-624) was able to

form amyloid fibers and the P506T ubiquilin-2 had reduced fiber formation with this region deleted. The UBA domain is responsible for binding to ubiquitinated substrates, and disruption of this binding capability has been shown to lead to aggregation in a cell model(Sharkey et al. 2018). The P506T mutation has also been shown to increase cellular aggregation, so it likely disrupts the UBA domain's binding activity, so the mutation mechanism of decreased binding to native partner was assigned. However, differences between the aggregation behavior of wild-type and mutant protein in vitro (in the absence of binding partners) cannot be explained by this mechanism. The PXX domain is intrinsically disordered(Dao et al. 2018), and proline residues discourage β-strand formation because of the geometry of their peptide bonds and discourage amyloid fiber formation by reducing the capacity for interstrand backbone hydrogen bonding. Point mutations away from proline may be sufficient to permit the PXX domain to be incorporated into the core of an amyloid fiber, although this is only speculation. Nevertheless, for this reason we also assigned fiber stabilization as a mutation mechanism.

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von Hippel-Landau disease tumor suppressor (VHL)

von Hippel-Landau disease tumor suppressor is a tumor suppressor which functions mainly through regulation of proteolytic degradation of hypoxia-induced factor (HIF)(Haase 2009). Amyloid formation of this protein is linked to von Hippel-Landau disease, which is a predisposition to the development of both cancerous and noncancerous tumors. It was first shown that the full length protein could form amyloid *in vitro* and when expressed in bacteria through ThT-binding, electron microscopy, and Congo Red staining(Kumar et al. 2024). Before this, peptide fragments were already known to form amyloid in vitro by ThT-binding, electron microscopy, and Congo Red staining(Kumar et al. 2021). This protein is an ambimorph amyloid, and although the protein has disordered segments, disease mutations such as N78S, F119L, and F136L have been shown to make the protein even less stable and interfere with binding to HIF(Shmueli et al. 2013), so native structure destabilization and decreased binding to native partner are the assigned mutation mechanisms.

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α-crystallin (CRYAA, CRYAB)

α-crystallin is a structural protein in the eye lens as well as a chaperone which helps to keep other crystallin proteins soluble(Bloemendal et al. 2004). Notably, it has been shown to retain its chaperone function even when it has formed amyloid fibrils itself(Garvey et al. 2017). It functions as a hetero-oligomer composed of two subunits: α-crystallin A chain and α-crystallin B chain, although α-crystallin B chain is found alone in other tissues besides the eye. α-crystallin forms amyloid deposits in cataracts and desmin-related myopathy (DRM). It was first explicitly identified as amyloid in murine lens tissue through binding to amyloidophilic dyes ThT and Congo Red(Frederikse 2000). Evidence of crystallin amyloid in the human eye has been shown through 2D IR spectroscopy(Alperstein et al. 2019). *In vitro* demonstration of the individual crystallins ability to form amyloid was demonstrated in purified bovine crystallins through electron microscopy, ThT-binding, Congo Red staining, and X-ray diffraction(Meehan et al. 2004). α-crystallin harbors many disease-causing mutations(Graw 2009), making it an ambimorph, and one α-crystallin B chain mutation has been more thoroughly studied: R120G(Alperstein et al. 2021; Meehan et al. 2007). Although, the amyloidogenic mechanism is not clear since the mutant protein is still able to form amyloid fibrils, but seems less prone to

than the wild-type. Indeed, this may be more of a toxic oligomer-inducing mutation than an amyloidogenic mutation, or simply a loss of function which encourages amyloid formation of other crystallin proteins without promoting amyloidogenesis of α-crystallin explicitly.

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α-synuclein (SNCA)

α-synuclein is a protein whose function is not entirely clear, but localizes to presynaptic terminals and interacts with lipid membranes, i.e. vesicles, and is able to adopt an α-helical secondary structure when associated with membranes despite being disordered in solution(Burré 2015). This protein is the main component of Lewy bodies and Lewy neurites which are the hallmarks of Parkinson’s disease (PD) and dementia with Lewy bodies (DLB)(Spillantini et al. 1997) and also aggregates in multiple system atrophy (MSA) as well as other “synucleinopathies”. Both wild-type and mutant α-synuclein has been observed to form amyloid fibers *in vitro*, making it an ambimorph amyloid, as evidenced by circular dichroism spectrometry, thioflavin T fluorescence, electron microscopy and atomic force microscopy ultrastructural analysis, immunoelectron microscopy, x-ray and electron fiber diffraction, and cryo-EM structure determinations(Sun et al. 2020; Zhao et al. 2020; Ghosh et al. 2014; Boyer et

al. 2019; Sun et al. 2021; Boyer et al. 2020; Narhi et al. 1999; Conway, Harper, and Lansbury 1998; Ruggeri et al. 2020; Serpell et al. 2000). α-synuclein was confirmed to exist as an amyloid fiber *in vivo* in Lewy bodies through microbeam X-ray diffraction of thin sections of Parkinson's disease brain samples(Araki et al. 2019). Many mutations in this protein have been shown to accelerate fiber formation *in vitro* and form more stable fibers than the wild-type protein(Porcari et al. 2015; Narhi et al. 1999; Conway, Harper, and Lansbury 1998), and since the protein is disordered in solution(Weinreb et al. 1996; Uversky 2003), only the mutation mechanism of fiber stabilization could be assigned for these. α-synuclein has also been shown to have increased seeding capacity when it has certain mutations, so increased seeding was also assigned(Rutherford et al. 2017; Sun et al. 2020; Zhao et al. 2020). There are also duplications and triplications of the SNCA gene which increases expression leading to disease(Chartier-Harlin et al. 2004; Singleton et al. 2003), so altered processing was also assigned as a mechanism. Lastly, some mutations have been shown to reduce binding to lipid membranes(Ghosh et al. 2014; Robotta et al. 2017) so reduced binding to native partners was also assigned as a mechanism.

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β-crystallin (CRYBA1, CRYBA2, CRYBA4, CRYBB1, CRYBB2, CRYBB3)

β-crystallin is one of the main structural components of the eye lens and is found as multiple different types of oligomers(Graw 2009). Subunits are either acidic (A subunits) or basic (B subunits) and there are seven subunits: β-crystallin A1-4 and β-crystallin B1-3. β-crystallin forms amyloid deposits in cataracts. It was first explicitly identified as amyloid in murine lens tissue through binding to amyloidophilic dyes ThT and Congo Red(Frederikse 2000). Evidence of crystallin amyloid in the human eye has been shown through 2D IR spectroscopy(Alperstein et al. 2019). *In vitro* demonstration of the individual crystallins ability to form amyloid was demonstrated in purified bovine crystallins through electron microscopy, ThT-binding, Congo Red staining, and X-ray diffraction(Meehan et al. 2004). β-crystallin harbors many disease-causing mutations(Graw 2009), making it an ambimorph, although no biochemical studies on specific mutations have been performed so the amyloidogenic mechanism of the mutations are unclear.

Alperstein, Ariel M., Joshua S. Ostrander, Tianqi O. Zhang, and Martin T. Zanni. 2019. “Amyloid Found in Human Cataracts with Two-Dimensional Infrared Spectroscopy.” *Proceedings of the National Academy of Sciences of the United States of America* 116 (14): 6602–7. https://doi.org/10.1073/pnas.1821534116.

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β2-microglobulin (B2M)

β2-microglobulin is a component of the class 1 major histocompatibility complex and, when it dissociates from the complex, is cleared from the body by the kidneys(Bernier 1980). Patients with renal failure requiring dialysis can build up β2-microglobulin in their blood because dialysis machines are not able to clear it efficiently(Gejyo et al. 1986; Dember and Jaber 2006), although this problem has been mitigated significantly (but not entirely) by modern machinery(Dember and Jaber 2006; Hoshino et al. 2016). This can lead to the formation of amyloid fibers by β2-microglobulin in a condition known as dialysis-related amyloidosis (DRA) which manifests as painful bone and joint-related ailments like carpal tunnel syndrome and arthritis(Gejyo et al. 1985; 1986). Mutations like V47M can also influence the clinical presentation of DRA(Mizuno et al. 2021). β2-microglobulin was first identified as an amyloidogenic protein through amino acid sequence analysis of congophilic amyloid material extracted during a carpal tunnel release operation on a patient who had been on dialysis for 13 years(Gejyo et al. 1985). There are also documented mutations in this protein associated with hereditary systemic amyloidosis: D96N (D76N with the numbering of the mature protein)(Valleix et al. 2012) and P52L (P32L with the numbering of the mature protein)(Prokaeva et al. 2022). The D96N mutation alters the surface charge landscape of the protein, as revealed by the crystal structure of the mutant protein, and reduces its denaturation resistance in guanidine hydrochloride(Valleix et al. 2012), and the P52L mutation is also experimentally validated to reduce stability in the protein(Prokaeva et al. 2022),

so native structure destabilization was assigned as a mechanism. The mutations also greatly increased the aggregation propensity of the protein compared to the wild-type under physiological conditions, as revealed by cryo-EM structures, so fiber stabilization was also assigned as a mechanism. Lastly, both the D96N and P52L mutations were shown to increase susceptibility of the protein to proteolysis and contribute to the generation of amyloidogenic truncations of the protein such as ΔN6(Prokaeva et al. 2022; Esposito et al. 2000), so altered processing was also assigned as a mechanism.

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γ-crystallin (CRYGA, CRYGB, CRYGC, CRYGD, CRYGS)

γ-crystallin is one of the main structural components of the eye lens and its subunits function as monomers(Graw 2009). There are five subunits in humans which are functional: CRYGA-D and CRYGS. γ-crystallin forms amyloid deposits in cataracts. It was first explicitly identified as amyloid in murine lens tissue through binding to amyloidophilic dyes ThT and Congo Red(Frederikse 2000). Evidence of crystallin amyloid in the human eye has been shown through 2D IR spectroscopy(Alperstein et al. 2019). *In vitro* demonstration of the individual crystallins ability to form amyloid was demonstrated in purified bovine crystallins through electron microscopy, ThT-binding, Congo Red staining, and X-ray diffraction(Meehan et al. 2004). γ-crystallin harbors many disease-causing mutations(Graw 2009), making it an ambimorph, and some mutations have been more explicitly studied, such as CRYGD G61C(Zhang et al. 2011), CRYGS G18V(Roskamp et al. 2017), and CRYGS G57W(Khan, Chandani, and Balasubramanian 2016). The main amyloidogenic mechanism of these mutations seems to be native structure destabilization, and mutations such as CRYGD G61C also seem to stabilize the fibril form.

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