



Mechanism of Disease

Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

The function of transthyretin (TTR) and the consequences of destabilisation

— 1 —



TTR Endurance
and Essential Role



Biological
Functions of TTR



TTR Stability and
Core Functions



Misfolding of
TTR Protein

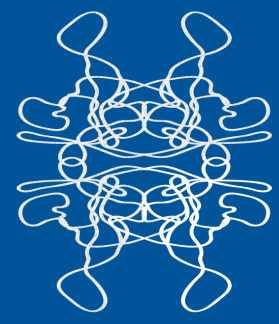


Consequences of
Untreated ATTR-CM



References

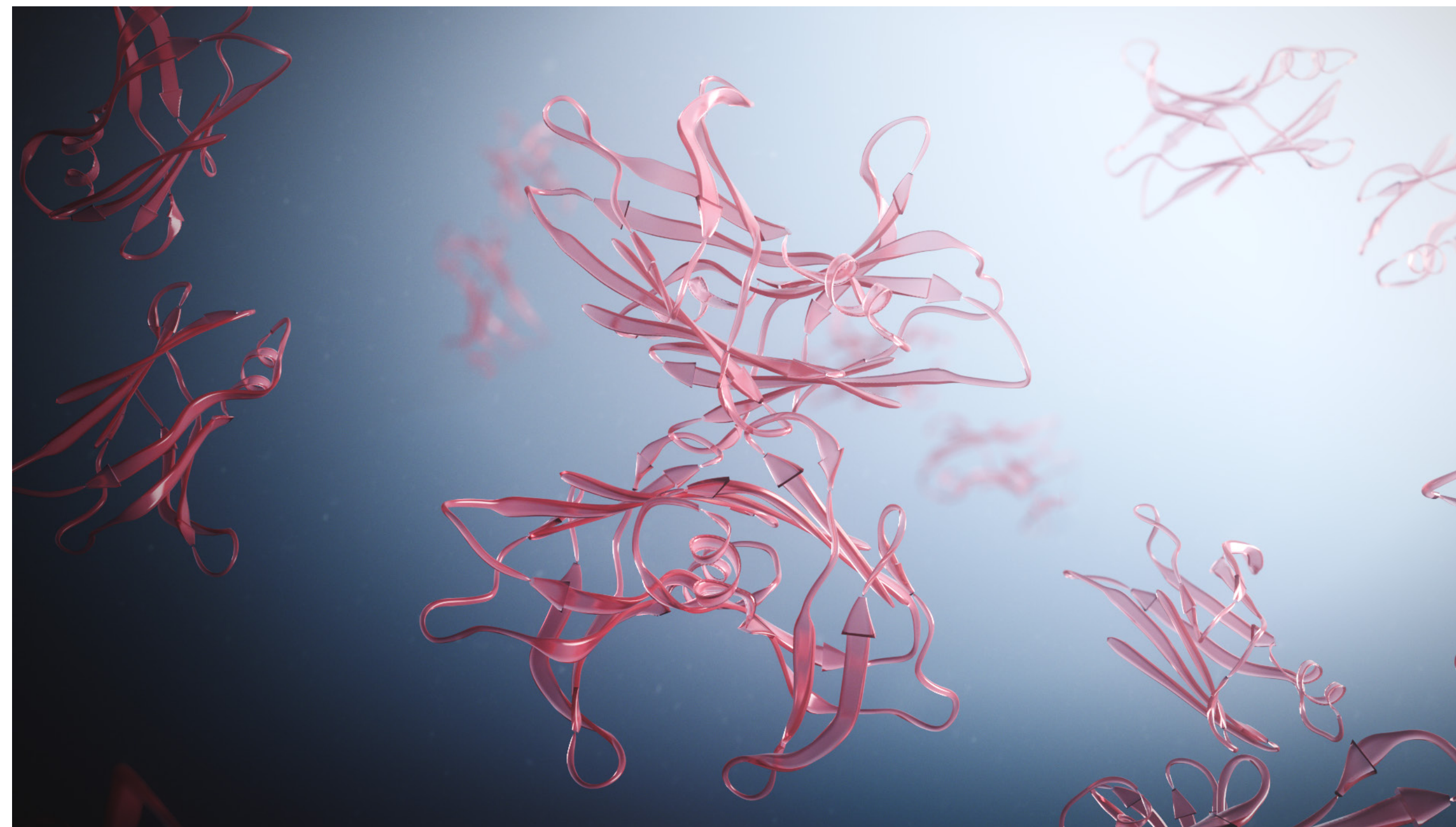




TTR Endurance and Essential Role

TTR is a tetrameric transport protein¹

TTR is a transport protein for a thyroid hormone (thyroxine [T4]) and is a retinol-binding protein.¹



TTR protein plays an important role in the body.¹ **The long-term impact of TTR reduction in humans is unknown.³**

TTR is produced mainly in the liver, but there is also some production in the choroid plexus (brain) and retinal epithelium (eye).^{1,2}

— 2 —



TTR Endurance
and Essential Role



Biological
Functions of TTR



TTR Stability and
Core Functions



Misfolding of
TTR Protein



Consequences of
Untreated ATTR-CM



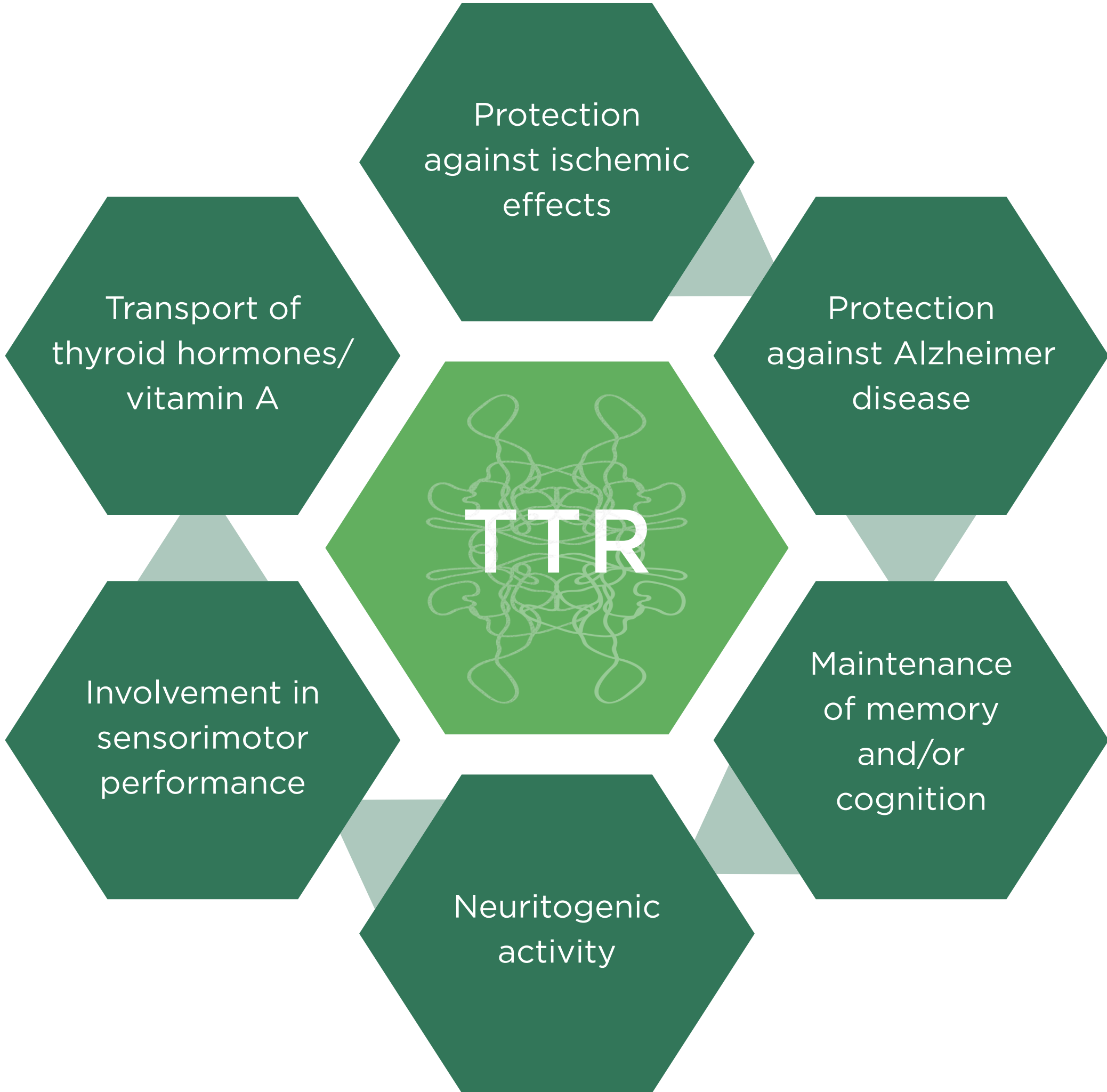
References





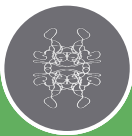
Biological Functions of TTR

Known functions of TTR from mouse and human studies^{1*}



The complete absence of TTR in humans has not been reported.¹

¹Human and mouse TTR share >80% similarity at the amino acid level, so it may be expected that insights into the physiological function of human TTR could be gained through the generation of *TTR* knockout mice.¹

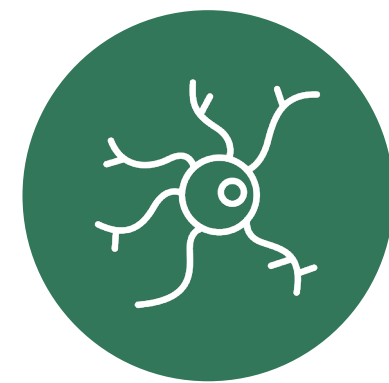




TTR Stability and Core Functions

Functions of TTR independent of protein transport

The physiologic role of TTR is not fully defined, but the growing body of evidence suggests TTR has additional important functions.¹



1. Neuroprotection in the PNS and CNS

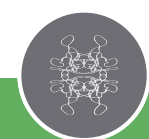
- Neuroprotective effects have been shown in both the peripheral nervous system (PNS) and central nervous system (CNS)¹
- These effects were demonstrated in both animal and clinical studies¹
 - In response to ischaemic injury and nerve regeneration¹
 - In the promotion of neurite outgrowth¹



2. Protection against neurodegeneration and Alzheimer disease¹

- In a mouse model, TTR expression was selectively increased in the hippocampus, a brain region with high levels of amyloid beta (A β), suggesting its upregulation may be a protective response to increased A β levels¹
- The impact of TTR as a neuroprotective agent has been proposed to be related to its tetrameric stability¹
 - Drug-induced stabilisation of TTR increased A β protein uptake in cell-based assays¹

— 4 —



TTR Endurance
and Essential Role



Biological
Functions of TTR



TTR Stability and
Core Functions



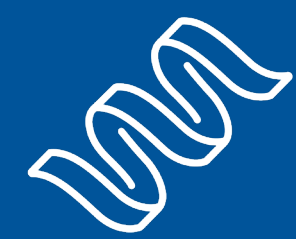
Misfolding of
TTR Protein



Consequences of
Untreated ATTR-CM

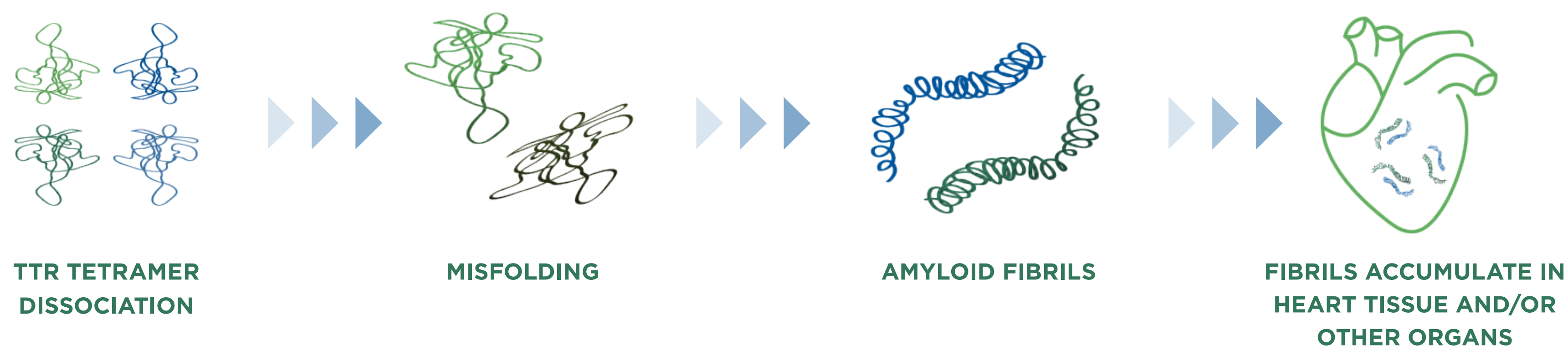


References



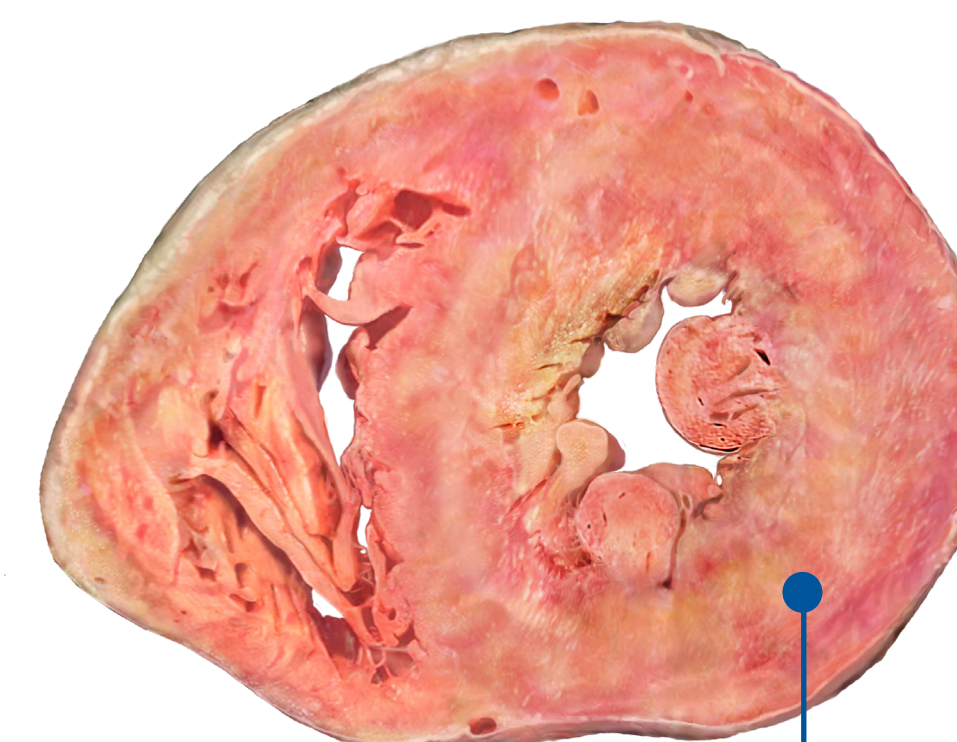
ATTR Amyloidosis Is Due to the Misfolding of TTR Protein⁴

The pathogenesis of ATTR amyloidosis is caused by the destabilisation, not production, of TTR protein tetramers¹



In ATTR-CM:

- *TTR* gene mutation or age-related changes destabilise the protein tetramers⁵
- Following this, they separate into monomers⁵
- These monomers misfold and aggregate into amyloid fibrils⁵
- These fibrils accumulate in the heart over time¹



Illustrative representation of ATTR amyloidosis heart.

TTR amyloid deposition in the heart can cause life-threatening conditions such as ventricular stiffening and heart failure⁴

Deposition of amyloid in the heart can cause ATTR-CM, which can lead to heart failure⁵



Consequences of Untreated ATTR-CM

ATTR-CM is an underdiagnosed cause of heart failure⁶



When left untreated, prognosis worsens rapidly with continued amyloid deposition, subsequent advancing organ dysfunction, and a **significant reduction in quality of life**^{6,7}

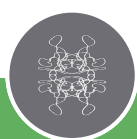


The median survival for these untreated patients is only **~2 to 3.5 years after diagnosis**⁷

In a study of 116 untreated patients with wild-type transthyretin (wtATTR) amyloidosis, **low levels of TTR were significantly associated with shorter survival and worsening cardiac disease**^{8*}

Early, accurate diagnosis of ATTR-CM may benefit patient care and lead to improved outcomes⁶

*In this longitudinal study from Boston University Amyloidosis Center, wild-type ATTR amyloidosis was confirmed with biopsy and genetic sequencing. Serum TTR concentrations were measured using an immunoturbidimetric assay for prealbumin.⁸





Learn more about ATTR-CM at **SuspectandDetect.com**

1. Liz MA, Coelho T, Bellotti V, Fernandez-Arias MI, Mallaina P, Obici L. A narrative review of the role of transthyretin in health and disease. *Neurol Ther.* 2020;9(2):395-402. doi:10.1007/s40120-020-00217-0
2. Vieira M, Saraiva MJ. Transthyretin: a multifaceted protein. *Biomol Concepts.* 2014;5(1):45-54. doi:10.1515/bmc-2013-0038
3. Adams D, Cauquil C, Labeyrie C, Beaudonnet G, Algalarrondo V, Théaudin M. TTR kinetic stabilizers and TTR gene silencing: a new era in therapy for familial amyloidotic polyneuropathies. *Expert Opin Pharmacother.* 2016;17(6):791-802. doi:10.1517/14656566.2016.1145664
4. Coelho T, Merlini G, Bulawa CE, et al. Mechanism of action and clinical application of tafamidis in hereditary transthyretin amyloidosis. *Neurol Ther.* 2016;5(1):1-25. doi:10.1007/s40120-016-0040-x
5. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation.* 2012;126(10):1286-1300. doi:10.1161/CIRCULATIONAHA.111.078915
6. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail.* 2019;7(8):709-716. doi:10.1016/j.jchf.2019.04.010
7. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation.* 2017;135(14):1357-1377. doi:10.1161/CIRCULATIONAHA.116.024438
8. Hanson JLS, Arvanitis M, Koch CM, et al. Utility of serum transthyretin as a prognostic indicator and predictor of outcome in cardiac amyloid disease associated with wild-type transthyretin. *Circ Heart Fail.* 2018;11(2):e004000. doi:10.1161/CIRCHEARTFAILURE.117.004000

For the use only of registered medical practitioner, or a hospital or a laboratory

Pfizer Products India Pvt. Ltd, The Capital – B Wing, 1802, 18th floor, Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India

© 2021 Pfizer Inc. All rights reserved

