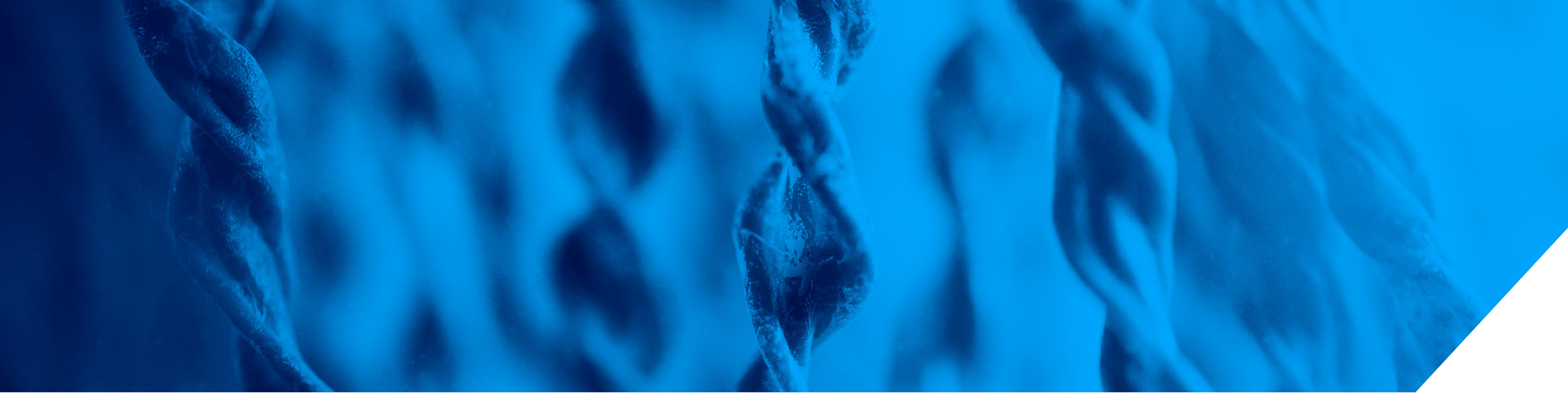


# Mechanism of Disease

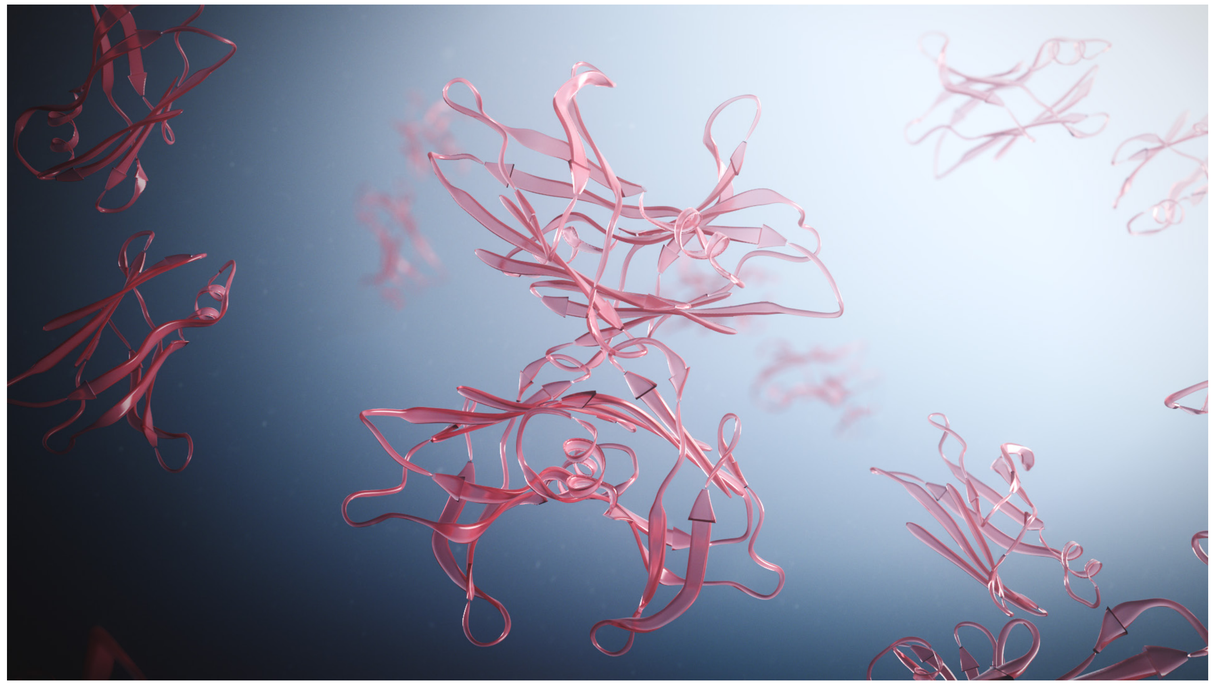
## Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

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

# TTR Endurance and Essential Role

## TTR is a tetrameric transport protein[1]

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

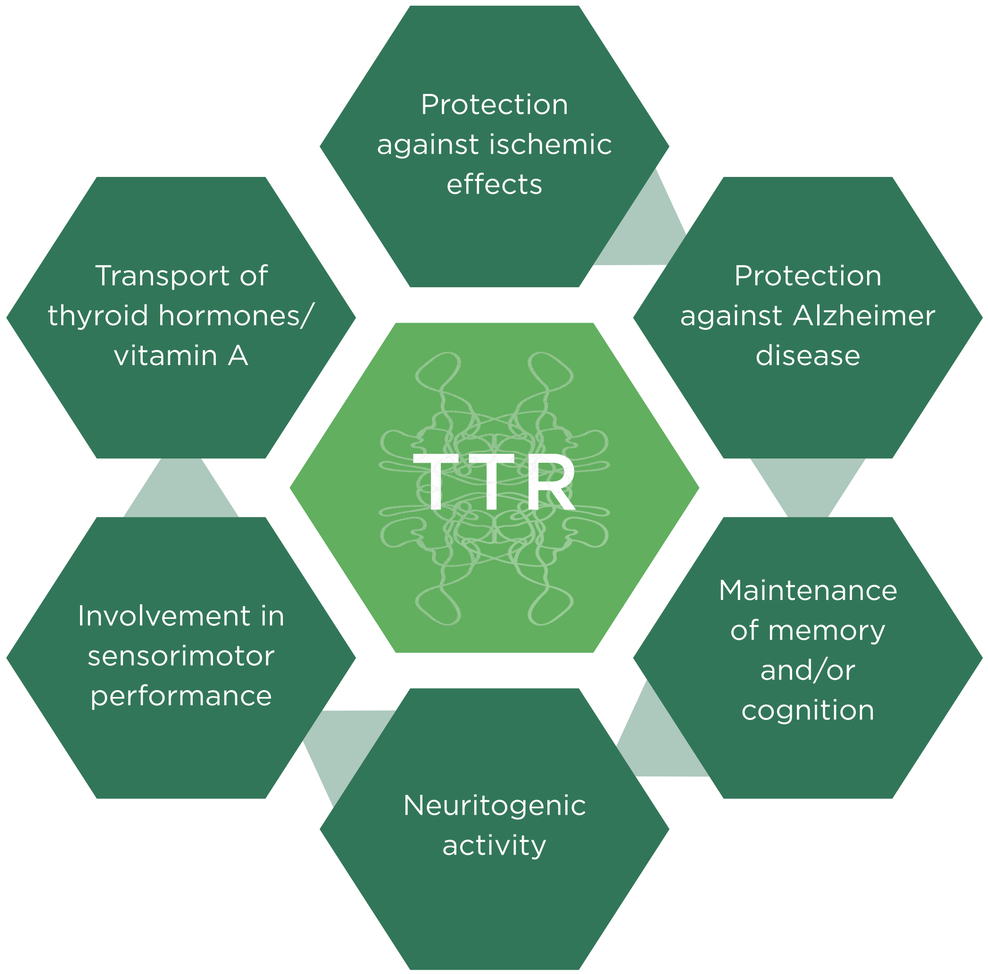


TTR is produced mainly in the liver, but there is also some production in the choroid plexus (brain) and retinal epithelium (eye).[1,2]

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

# 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]**

*Human 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 studies[1]
  - In response to ischaemic injury and nerve regeneration[1]
  - In the promotion of neurite outgrowth[1]

### 2. Protection against neurodegeneration and Alzheimer disease[1]

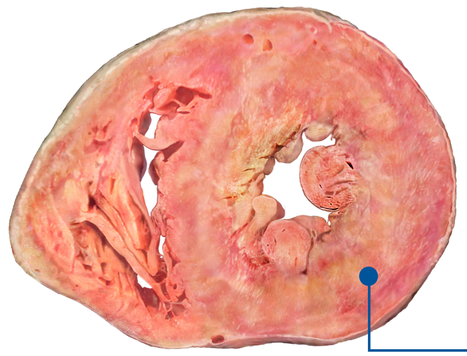
- In a mouse model, TTR expression was selectively increased in the hippocampus, a brain region with high levels of amyloid beta (Aβ), suggesting its upregulation may be a protective response to increased Aβ levels[1]
- The impact of TTR as a neuroprotective agent has been proposed to be related to its tetrameric stability[1]
  - Drug-induced stabilisation of TTR increased Aβ protein uptake in cell-based assays[1]

# ATTR Amyloidosis Is Due to the Misfolding of TTR Protein[4]

## The pathogenesis of ATTR amyloidosis is caused by the destabilisation, not production, of TTR protein tetramers[1]


### In ATTR-CM:

- *TTR* gene mutation or age-related changes destabilise the protein tetramers[5]
- Following this, they separate into monomers[5]
- These monomers misfold and aggregate into amyloid fibrils[5]
- These fibrils accumulate in the heart over time[1]



Illustrative representation of ATTR amyloidodis heart.

**TTR amyloid deposition in the heart can cause life-threatening conditions such as ventricular stiffening and heart failure[4]**

**Deposition of amyloid in the heart can cause ATTR-CM, which can lead to heart failure[5]**

# Consequences of Untreated ATTR-CM

## ATTR-CM is an underdiagnosed cause of heart failure[6]

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 outcomes**[6]

*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**

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