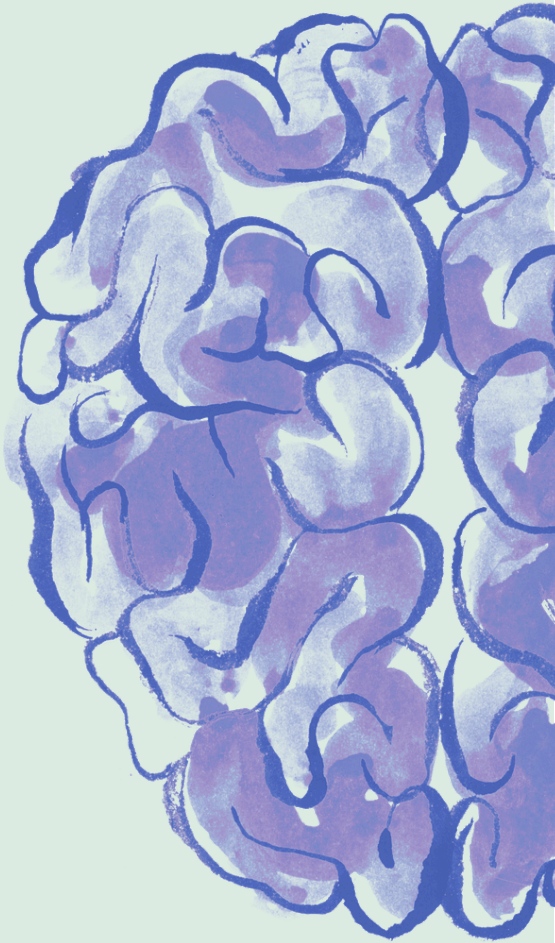
Tau Biology 101

For MAPT Families



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Educating MAPT Families to have a better understanding of the protein Tau and MAPT mutation biology leaving us empowered to have a deeper understanding of the biology of the disease that affect our families.

Introduction

Our bodies contain many different types of living cells. Although cells are microscopic, they are highly organized and active systems. Each cell must maintain its shape, produce energy, communicate, and move materials internally in a coordinated manner. In many ways, a cell resembles a small, self-contained system with structure, transport, and constant activity.

Inside a cell, molecules and materials do not simply drift randomly. Proteins, nutrients, energy sources, and signals must travel to specific locations at specific times. This movement within the cell is known as intracellular transport. For efficient transport, the cell relies on an internal structural framework composed of specialized proteins. These structures help the cell maintain its shape and serve as tracks for intracellular transport.

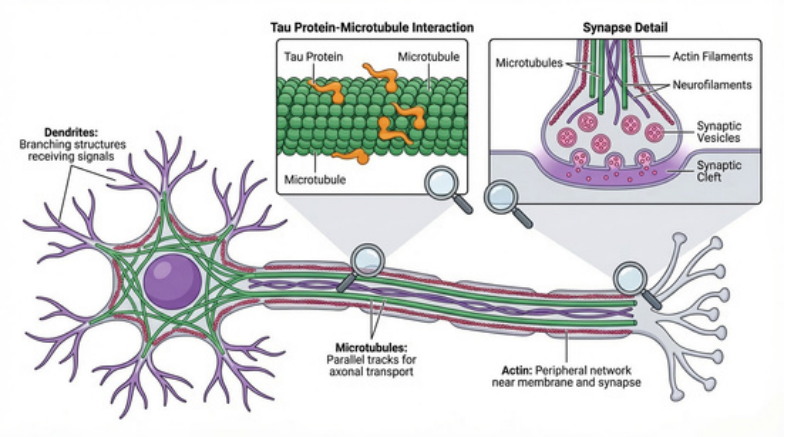


Figure 1 – Cytoskeleton of a neuron contains Microtubules, Actin filaments, and Neurofilaments.

Two major components of this framework are microtubules and actin filaments. Microtubules are long, tube-shaped structures that form stable tracks throughout the cell, while actin filaments are thinner fibers that provide flexibility, strength, and fine control of cell shape and movement (Figure 1). Actin plays an important role in helping cells change shape, maintain tension, and support processes such as cell movement, cell division, and communication between neighboring cells. Together they form the cytoskeleton — a dynamic internal scaffold that supports the cell and organizes its internal activity. The cytoskeleton is present in all cells, but it is especially important in the brain, where cells must maintain complex shapes and support constant communication over long distances. Without this structural system, cells would lose their shape, and the precise movement of materials within them would be impossible.

The brain is composed of many different types of cells working together as a tightly coordinated system. Neurons are the primary signaling cells responsible for transmitting information. Alongside them are several kinds of support cells, collectively called glial cells, which protect neurons, regulate the chemical environment, provide nutrients, and maintain overall stability in the brain (Figure 2). Microglia serve as immune defenders, while astrocytes and oligodendrocytes help maintain neuronal health and ensure efficient signal transmission. The proper function of the brain depends on the health of all these cell types (Figure 2).

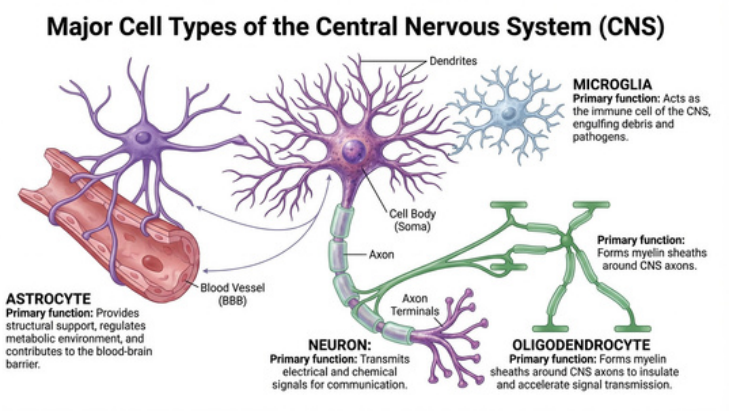


Figure 2 – Cell types in the brain showing Neurons and Glial cells (Microglia, Astrocytes and Oligodendrocytes)

Among these, neurons are particularly specialized and uniquely vulnerable. Many neurons have extremely long extensions, allowing them to transmit signals across large distances within the brain and spinal cord. Because of this length, neurons depend heavily on efficient internal transport. Materials produced in one part of the

neuron must be delivered to distant regions of the same cell, sometimes over remarkably long distances. This transport occurs primarily along microtubules, which act as stable tracks running throughout the neuron. Compared to glial cells, neurons rely heavily on long-distance transport and have limited ability to regenerate after damage, making the integrity of their intracellular transport system especially important.

When microtubules become unstable or fail to function properly, the consequences for neurons can be gradual but serious. Transport inside the cell slows or becomes disrupted. Essential materials may no longer reach critical areas, and cellular stress begins to accumulate. Over time, this can impair the neuron's ability to function and eventually lead to cell death. Because neurons are responsible for cognition, behavior, communication, and movement, their loss directly affects how the brain functions.

For this reason, a change affecting even a single important protein involved in maintaining neuronal structure can, over time, influence the brain's overall health. In the following section, we will introduce one such protein — Tau — and the gene that produces it, called MAPT, and begin to explore why changes in this system can lead to disease.

Tau: From Discovery to Function

In the early studies of brain biology, scientists sought to understand how neurons maintain their long shape and internal organization. During this work, researchers identified a molecule that bound strongly to microtubules, helping them remain stable. Microtubules themselves are built from repeating units of a structural protein called tubulin, which assemble into long tracks inside neurons (Figure 3). Scientists later discovered a protein that attaches along these tubulin tracks and helps regulate their stability and organization. This protein was named Tau, short for tubulin- associated unit, reflecting its close interaction with the microtubule system inside neurons (Figure 3).

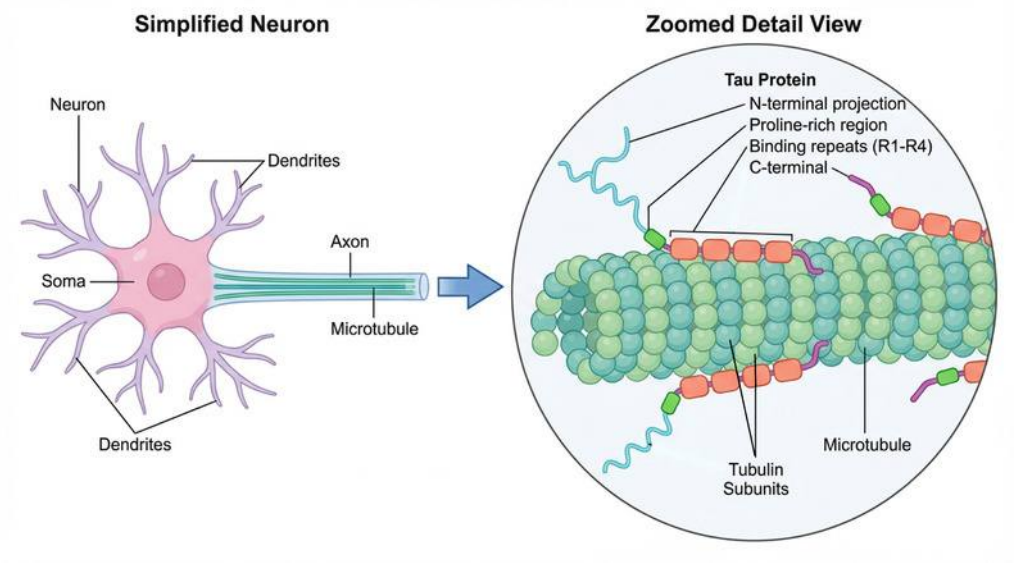


Figure 3 – Tau protein bound to microtubules via their microtubule binding domain

Tau is produced from a gene called MAPT (Microtubule-Associated Protein Tau). To understand Tau, it is helpful to distinguish between a gene and a protein. A gene is a segment of DNA that contains instructions. A protein is the functional molecule built using those instructions. The MAPT gene provides the blueprint, and the Tau protein is the working structure that carries out its role inside the cell. Even a very small change in the gene — such as a change in a single DNA letter — can alter the structure of the protein that is produced. This change can lead to disruption in the function of the protein.

Tau's primary role is to interact with microtubules, the long structural tracks that support intracellular transport. Microtubules must remain stable and properly organized for neurons to function over long distances and long periods of time. Tau binds along microtubules and helps maintain their stability, spacing, and organization. By doing so, Tau supports the structural integrity of the neuron and helps ensure efficient

transport along microtubules. Because neurons do not readily replace themselves and must function for a lifetime, maintaining stable microtubules is especially important for their long-term survival.

To better understand how Tau performs these roles, it helps to look at how the MAPT gene is organized (Figure 4). The beginning portion of the protein, called the N-terminus, together with the short proline-rich region, helps regulate how Tau interacts with other proteins and structures within the cell. The central portion, known as the microtubule- binding domain (MBD), enables Tau to bind microtubules and directly influence their stability and organization. The ending portion, called the C-terminus, contributes to maintaining the overall structure and behavior of the protein (Figure 4). Together, these regions allow Tau to support microtubule stability, preserve neuronal structure, and help coordinate intracellular transport. Variations within these regions give rise to different forms of Tau, known as Tau isoforms, through a process called splicing.

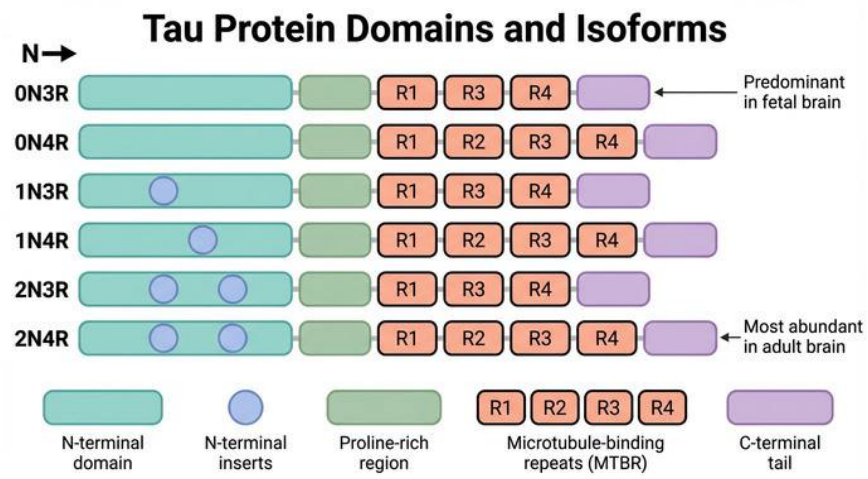


Figure 4 – Tau protein domains and isoforms

In the human brain, six main Tau isoforms are produced in healthy cells: 0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R Tau. These names reflect structural differences within the protein (Figure 4). The number before "N" refers to inserts near the beginning of the protein: 0N means no insert, 1N means one insert, and 2N means two inserts. The "R" refers to repeating segments within the microtubule-binding domain — repeated units of the region that bind microtubules. 3R contains three such repeats, and 4R contains four repeats, which influence how Tau interacts with microtubules. Variation in both the N-terminal inserts and the number of binding repeats contributes to differences in how Tau functions within neurons. Studies suggest that 4R Tau may bind microtubules more strongly and support greater stability, while 3R Tau may allow more flexibility, but the full functional differences between these forms are not yet completely understood.

The forms of Tau present in the brain change across development and aging. Before birth and during early brain development, neurons primarily produce Tau containing three microtubule-binding repeats. As the brain matures, neurons begin producing Tau containing four microtubule-binding repeats. In the healthy adult brain, both forms are present in a balanced state, which supports normal microtubule function (Figure 4).

Because Tau directly influences the stability and organization of microtubules, its structure is closely tied to its function. Changes that affect specific regions of the Tau protein can alter how it interacts with microtubules, how stable the cytoskeleton remains, and how well neurons maintain their structure over time. Understanding the normal structure and function of Tau provides the foundation for understanding how changes in MAPT can influence neuronal health.

In the next section, we will explore how different types of changes in the MAPT gene can alter Tau and how these changes can affect its function within neurons.

From Gene to Protein: Understanding MAPT Mutations

Before we examine how specific mutations in the MAPT gene may alter Tau's function, it helps to first understand how genetic information flows from genes to proteins, and how scientists annotate and interpret changes in this process. This background sets the stage for understanding how mutations in the MAPT gene are identified, described, and mapped onto Tau.

To begin, let's review how proteins are built from DNA instructions. In cells, the information stored in DNA is first copied into a temporary molecule called messenger RNA (mRNA). This mRNA is then read by the cell to build the protein. This flow of information from DNA to RNA to protein is often referred to as the central dogma of biology (Figure 5).

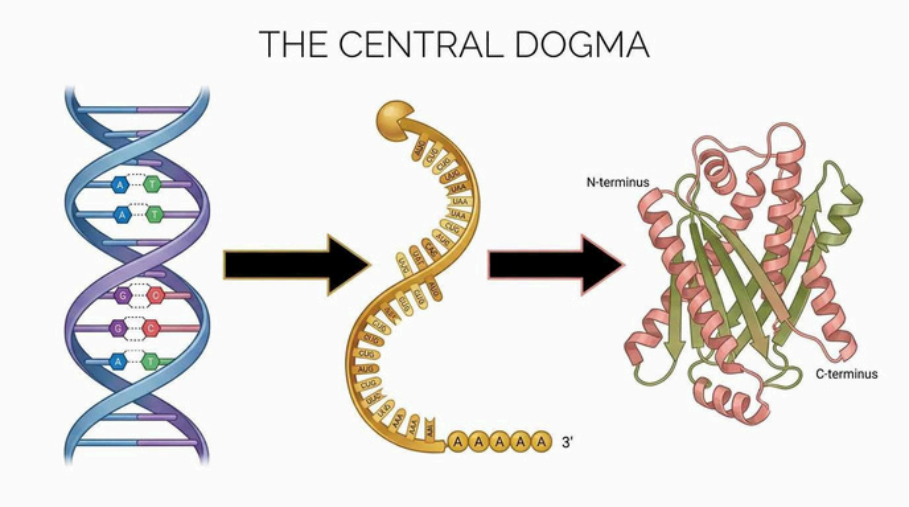


Figure 5 – The central dogma: DNA –> RNA –> Protein

All proteins in the body are built from small building blocks called amino acids. In DNA, each amino acid is specified by a triplet of DNA letters (Figure 6). Therefore, the sequence of DNA letters ultimately determines the order of amino acids that will be used to build the protein. There are 20 different amino acids used by cells to build proteins. Proteins are formed by linking these amino acids together in a specific order, creating a long chain that folds into a functional structure (Figure 6). In this sense, every protein in the body can be thought of as a sequence made from a set of 20 chemical letters.

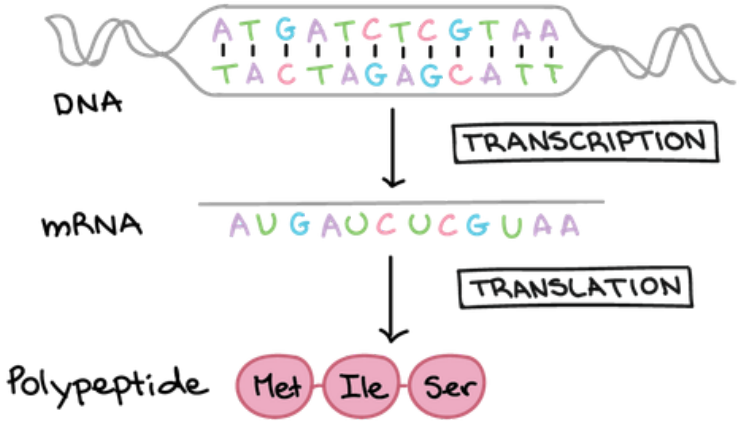


Figure 6 – 3 letters code DNA and RNA code for one amino acid, adapted from Khan Academy

In some genes, including MAPT, an additional layer of complexity exists. As described in the previous chapter, the MAPT gene undergoes splicing, producing different messenger RNA (mRNA) variants. Each mRNA produced from a gene is called a transcript (Figure 7). Genes are organized into segments called exons, which contain the instructions for building the protein, and introns, which lie between them and are removed during splicing (Figure 7). The MAPT gene has 14 exons separated by introns (Figure 7). Although introns are not part of the final protein, changes in these regions can still influence how the gene is spliced and, therefore, how the protein is produced.

Importantly, not all exons are included in every transcript, either, which is why different transcripts can produce Tau proteins of different lengths (Figure 7). These different transcripts can therefore give rise to slightly different versions of the Tau protein, known as Tau isoforms. These transcripts are not created simply by extending the sequence at one end, as some illustrations may suggest. Instead, splicing can include or skip different segments of the gene, meaning that additional regions may appear near the beginning, middle, or end of the resulting Tau protein.

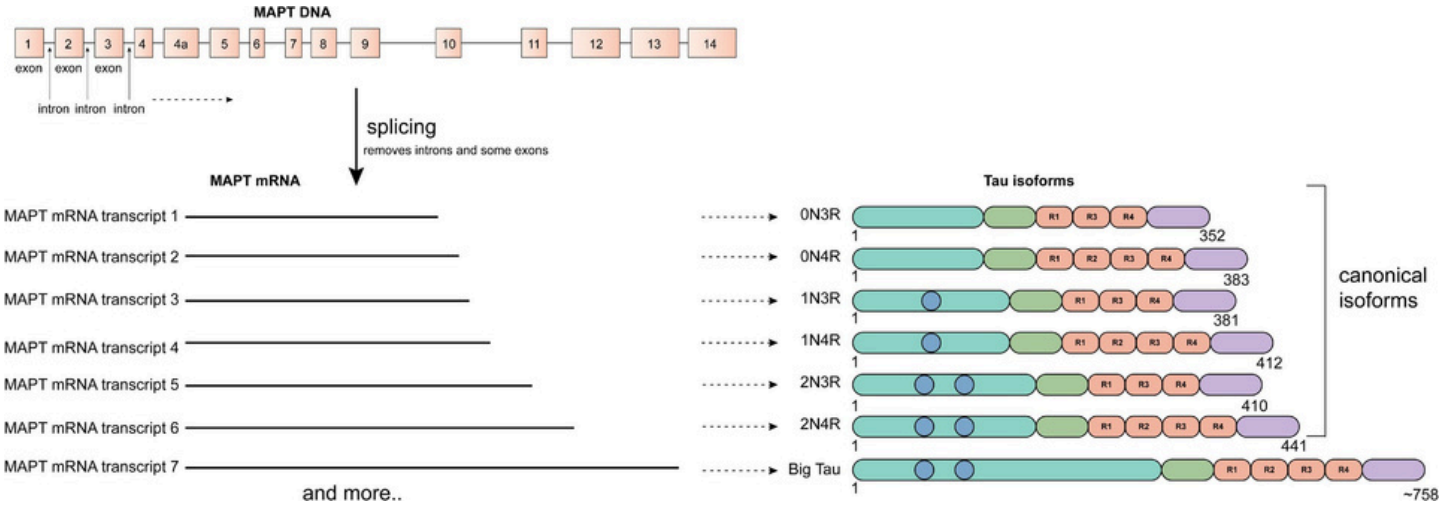


Figure 7 – Splicing leads to multiple mRNA transcripts which make different Tau isoforms

Given this complexity, when genetic sequencing identifies DNA mutations, researchers must map these changes onto the mRNA transcript and ultimately the Tau protein's amino-acid sequence. When multiple transcripts exist, amino acid numbering may differ depending on the transcript used for annotation.

Having established the importance of annotation, we can now examine how scientists describe protein mutations. Researchers use a standard system to indicate which amino acid has changed and where that change occurs in the protein.

In scientific writing, mutations are often written in a short format such as P301L or V337M. This notation describes how a single amino acid in a protein has changed. Each amino acid is represented by a single-letter abbreviation, and the number indicates its position along the protein chain. For example, V337M means that the amino acid valine (V) at position 337 has been replaced by methionine (M). Some abbreviations are not the first letter of the amino acid's name—for instance, R represents arginine, and W represents tryptophan. A mutation written as R406W, therefore, means that the amino acid arginine (R) at position 406 has been replaced by tryptophan (W).

In research, most Tau mutation numbering refers to the 2N4R isoform (Figure 8), the standard reference protein. The 2N4R Tau is the longest canonical isoform with 441 amino acids (Figure 7 and Figure 8). The mutation number indicates the amino acid's position in this sequence. For example, P301L means the proline (P) at position 301 is replaced by leucine (L) in 2N4R Tau.

Some mutations reported in CureMAPT families are annotated using a longer MAPT transcript rather than the commonly illustrated 2N4R Tau protein. The mutation P494L indicates that the amino acid proline (P) has changed to leucine (L) at position 494 of the Tau protein. However, the 2N4R Tau isoform contains just 441 amino acids, so position 494 does not exist in this reference protein. This indicates the mutation was annotated using a longer MAPT transcript. Longer Tau forms exist, such as Big Tau, which contains about 758 amino acids compared with 441 in the 2N4R Tau isoform (Figure 7).

In most cases, researchers can reconcile these different annotations by mapping them back to the commonly used 2N4R Tau reference protein. For example, a mutation annotated as R741W in a longer Tau transcript corresponds to R406W when mapped onto the 2N4R Tau sequence. Mutation databases, such as the GENFI MAPT mutation database, often present mutations using this reconciled numbering, making it easier to compare findings across studies. At present, R613W and P494L reported in Cure MAPT FTD families do not

yet appear in this database under the reconciled 2N4R numbering.

With these annotation concepts in mind, we can examine how Tau mutations are distributed along the protein. To date, researchers have identified at least 98 mutations in the MAPT gene (Figure 8). When these mutations are mapped onto the Tau protein, several clusters become visible (Figure 8). Identifying where these mutations occur highlights which parts of Tau are affected in different carriers.

One prominent cluster of MAPT mutations occurs within the microtubule-binding domain (MBD). In total, 48 known MAPT mutations fall within this region of the protein, making it the largest mutation cluster identified so far. Several mutations found in MAPT families occur in this region, including Q336H and V337M (Figure 8).

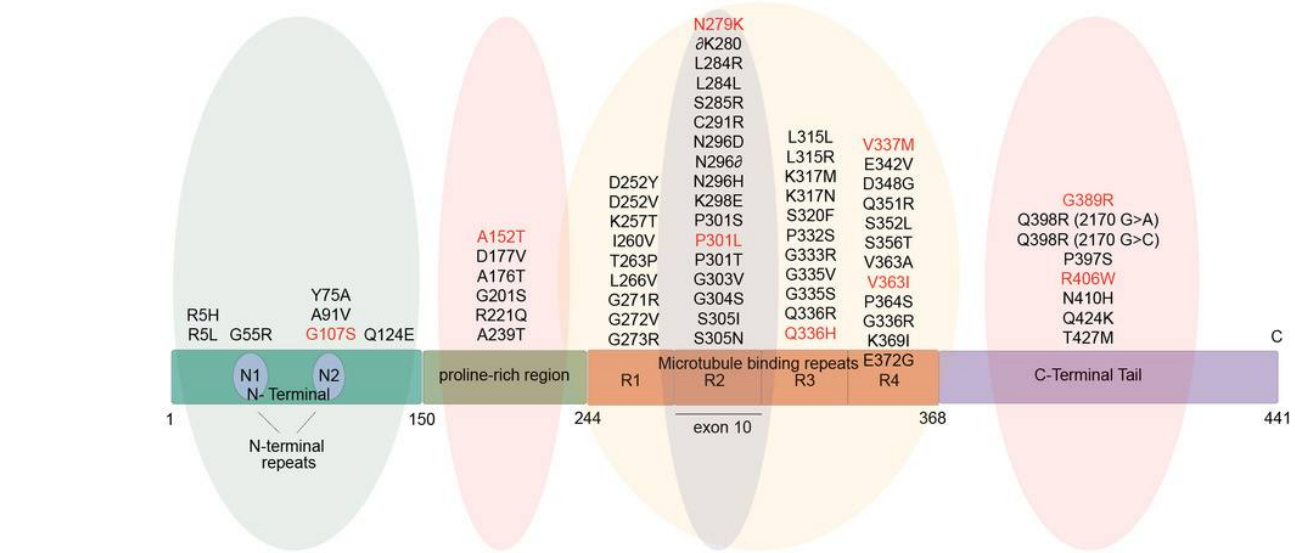


Figure 8 – MAPT mutations are found in clusters in different regions of Tau protein. Therefore, the changes to the proteins function may vary depending on the location of the mutation. CureMAPT family mutations are annotated in red.

Another group of mutations occurs in or near exon 10 of the MAPT gene. Exon 10 encodes repeat R2, one of the microtubule-binding segments of Tau. Sixteen MAPT mutations are known in this region, including N279K and P301L from the Cure MAPT network.

Fewer MAPT mutations occur in the proline-rich region of Tau, located between the N-terminal portion and the microtubule-binding domain. Six MAPT mutations have been identified in this region. For example, the A152T mutation appears in families within the CureMAPT network.

In contrast, mutations have also been identified near the C-terminal end of the Tau protein. Eight known MAPT mutations occur in this region. One example is R406W, a mutation located near the end of the Tau sequence that has also been identified in MAPT families.

Conversely, the N-terminal region of Tau has few known MAPT mutations. Six occur in this region, which marks the beginning of the Tau sequence.

Furthermore, 14 distinct mutations in the MAPT gene occur in introns, the parts of the gene that do not directly encode the Tau protein. Examples of these mutations identified in the CureMAPT network include IVS10+15, IVS10+16, and IVS9-10. The numbering in these mutations refers to positions within the intron rather than within the protein itself. Although these changes do not directly alter the amino-acid sequence of Tau, they can influence how the gene is read and spliced, and therefore how different Tau isoforms are produced. In particular, mutations near exon 10 can affect the balance between the 3-repeat (3R) and 4-repeat (4R) forms of Tau discussed earlier. These are not represented in Figure 8.

In the next section, we will examine in more detail how mutations in these regions can affect Tau's function in neurons.

What Happens When Tau Is Defective?

In the previous chapters, we saw what Tau normally does and where mutations occur. The natural next question is what happens when Tau no longer works as it should. To answer it well, we first need to widen the lens and place what is known about Tau in its broader context. Let's step back and look at the larger family of diseases.

Tau dysfunction is involved in many diseases. These diseases are grouped as tauopathies, and their shared hallmark is the abnormal accumulation of Tau in the brain. More than twenty distinct tauopathies have been described. They include Alzheimer's disease, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, and the inherited frontotemporal dementia caused by MAPT mutations, which we will call MAPT-FTD.

Researchers often divide these conditions into two groups: primary tauopathies and secondary tauopathies. In a primary tauopathy, the buildup of Tau itself is the cause of the disease. Pick's disease, progressive supranuclear palsy, corticobasal degeneration, and MAPT-FTD all belong to this group. In a secondary tauopathy, Tau pathology develops alongside another process that is also driving the disease. The most familiar example is Alzheimer's Disease (AD), where Tau accumulates together with amyloid, a different protein, and both contribute to the disease.

This distinction matters for an important reason. Alzheimer's Disease has been studied far more than any other tauopathy. It is the most common cause of dementia, affecting millions of people, and therefore most of what scientists know about dysfunctional Tau comes from studying AD. But Alzheimer's is a secondary tauopathy, in which Tau is only part of the story. For families affected by MAPT-FTD, where dysfunctional Tau is the cause of the disease, this leaves a real gap. How much of the Alzheimer's data applies to MAPT-FTD has not yet been well established.

Even so, what we know about Tau in disease is well worth understanding. This knowledge lays the foundation

for making better sense of the Tau therapies under development, and much of what follows in this chapter is the vocabulary and ideas that the later discussion of therapies will rely on. With that in mind, it helps to know that the ways Tau's function can go wrong have been broadly grouped into a handful of mechanisms.

The Life of a Tau Protein, and Where It Breaks Down

Like all proteins, Tau has a life cycle. It is made, prepared for its job, put to work, and eventually cleared away and recycled. Walking through this cycle is useful in two ways: it shows how Tau normally behaves and where, in disease, each step can break down. We will take it one step at a time.

Tau is produced in the cell body, following the instructions encoded by the MAPT gene. This is the starting point: a fresh Tau protein, newly made and not yet doing anything. (Figure 9 – step 1)
Modifying Tau. Once Tau is made, the cell modifies it. Small chemical tags are added to the protein, and these tags alter Tau's behavior. Changes of this kind, made after a protein is built, are called post-translational modifications. Tau can carry several different kinds of tags, and many are important for how Tau functions. Most of what is known, however, concerns one in particular: the addition of phosphate groups, a process called phosphorylation. Because it is the best understood and most relevant to what follows, we will focus on phosphorylation here (Figure 9 - step 2).

Phosphorylation works like a dial. There are many sites along the Tau protein where a phosphate tag can be attached, and the cell adds and removes these tags to adjust how tightly Tau binds to microtubules. Adding tags at certain key positions loosens Tau's grip, allowing it to let go when needed; removing them allows Tau to bind more tightly again. The full picture of which positions do what is still being worked out. In a healthy cell, this is a normal, reversible process, and the cell uses it to control Tau during its lifecycle (Figure 9 – step 2).

What happens to Tau in disease

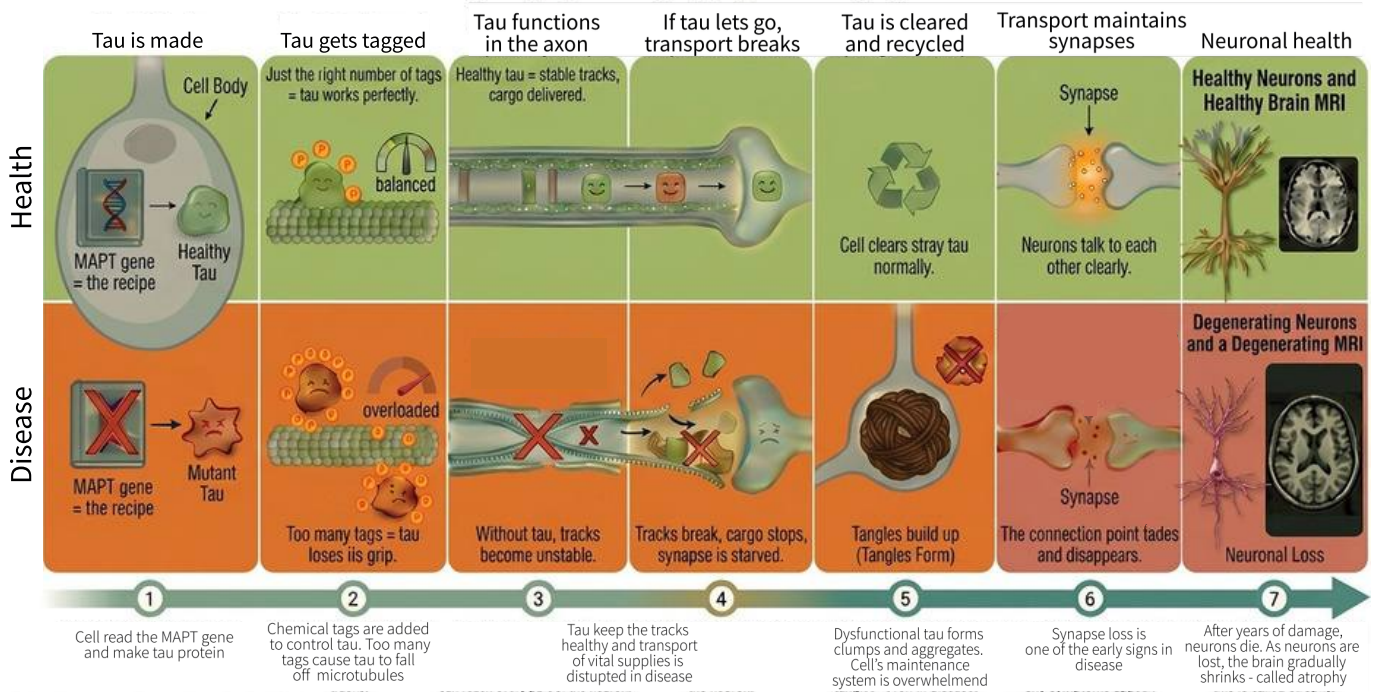


Figure 9: This figure follows Tau in a neuron, comparing a healthy cell (top row, green) with what can go wrong in disease (bottom row, orange). 1, Tau is built from the instructions encoded in the MAPT gene and then 2, modified by small chemical tags that control its behavior. With the right number of tags, Tau holds the cell's internal transport tracks steady, so that supplies travel along the axon to the points where one neuron connects to the next. These connection points are called synapses. When Tau carries too many tags, or when its shape is changed, it loses its grip. 3.4 The tracks become unstable, deliveries stall, and the synapses begin to starve. 5,Tau that the cell can no longer clear away builds into clumps, 6, the connections weaken and are lost, and 7, after years of damage the affected parts of the brain slowly shrink. This shrinkage is called atrophy, and it can be seen on an MRI scan.

In disease, this dial can be turned too far. Tau can become abnormally and persistently phosphorylated, a state called hyperphosphorylation. This can happen because the tools the cell uses to add the tags become overactive, or because the tools that remove them fail to keep up, or both at once; either way, the result is the same: an excess of tags on Tau. Heavily phosphorylated Tau tends to loosen its grip when it should be holding on, and it begins to release its grip on microtubules. Much of what is known about this comes from Alzheimer's Disease and other tauopathies, where hyperphosphorylated Tau is a consistent finding.

This is also where tests that many families may have heard of come in. Several biomarkers used in tauopathies detect Tau that carries a phosphate tag at a specific position along the protein. For example, p-tau217 refers to a phosphate modification at position 217 of the Tau protein, as explained in the previous chapter. They have become some of the most important measurements in the field, used both to study the disease and to track whether experimental treatments are working in clinical trials. Several are now in use, including p-tau181, p-tau217, and p-tau231.

It is important to be clear about what such a test measures. A phosphate tag at one of these positions is not specific to disease. Even in a healthy brain, cells constantly add and remove these tags, and the balance between the two keeps the amount of Tau tagged at a normal level. What changes in the disease is that balance. A larger share of Tau ends up carrying the tag than it should, and it is this higher level, rather than the mere presence of the tag, that
is used as a marker of disease.

What this looks like in MAPT-FTD is less clear-cut than in AD. The strength of these tests has been established mainly in AD, where levels of phosphorylated Tau in the spinal fluid and blood rise markedly over time, often to two or three times those seen in people without the disease. In people with MAPT mutations, the picture is more mixed. In carriers of the P301L and G272V mutations, no clear rise of this kind has been found. However, in carriers of the R406W mutation, phosphorylated Tau levels have been reported to be elevated compared with healthy controls. As a result, there is no reliable phosphorylated Tau biomarker specific to MAPT-FTD. Therefore, a test that is informative in Alzheimer's disease cannot be assumed to be informative for all MAPT mutations.

Although we have focused on phosphorylation, it is worth remembering that other tags also exist and matter for proper Tau function. Adding and removing chemical tags are among the main strategies a cell uses to control all proteins, adjusting what they do, where they go, and how long they last. Phosphorylation is simply the part of this story that is best understood for Tau, and the part for which there are established tests to measure it in the cerebrospinal fluid and blood of people with these diseases.

Tau at work in the axon

Once Tau has been made and tagged, it is found mainly where it does its job, the axon, the long cable-like extension that a neuron uses to reach other cells. As we saw in the first chapter, the axon is filled with microtubules, the long, tube-shaped tracks that the cell uses to move materials from one part of itself to another (Figure 3). Tau binds along these tracks, helping keep them stable and well-organized.

As the first chapter described, neurons can be remarkably long, and materials made in one part of the cell must often travel a great distance along microtubule tracks to reach their destination. When the tracks are stable, this transport runs smoothly. By helping to keep them stable, Tau supports the steady flow of materials that the far reaches of the neuron depend on.

When Tau is dysfunctional, this job suffers. Tau, which has loosened its grip, detaches from the microtubules (Figure 9 – step 3, 4). Once detached, it is no longer confined to the axon and can accumulate in parts of the neuron where it is not normally found, including the cell body. Meanwhile, the tracks it was meant to support become less stable. As the first chapter noted, when microtubules become unstable, transport inside the cell slows or is disrupted, and essential materials may no longer reach the areas that need them. When Tau stops doing its job properly, the neuron's internal supply lines are among the first to suffer (Figure 9 – step 3, 4).

Some of what is known about transport problems comes from studying MAPT mutations directly. Several mutations, including A152T, P301L, K369I, and R406W, have been linked to transport defects in laboratory models. The A152T variant has been examined in the most detail: it binds microtubules less tightly than normal Tau and appears to interfere with the movement of cargo back toward the cell body. However, it is important to

be careful about what such findings mean. It is not yet clear whether disrupted transport is a cause of the neuron's decline, a contributor to it, or simply one of its consequences. This question of what is cause and what is effect is one we will meet again, and it runs through much of what is known about how Tau leads to disease.

When transport falters, the cost is borne most acutely at the far end of the axon, where the neuron connects to its neighbors at structures called synapses (Figure 9 -step 3, 4, 6). Synapses are points of contact through which one neuron passes signals to the next, and they are highly active and constantly being maintained. Like the rest of the cell's distant regions, they depend on a steady delivery of new materials by axonal transport to keep them functioning and to replace the proteins that wear out. When that delivery is disrupted, synapses gradually lose the upkeep they rely on. Their function declines, and over time, some may be lost altogether Figure 9 -step 3, 4, 6).

This is not a hypothetical chain of events. Synaptic loss is, in fact, a feature of many neurodegenerative diseases, even though each disease is defined by the build-up of a different protein. It has been observed in Alzheimer's disease, Parkinson's disease, Huntington's disease, motor neuron disease, and the various forms of frontotemporal dementia, including those caused by MAPT mutations. In each case, although the protein at the heart of the disease is different, the gradual loss of synapses is among the earliest pathological changes, often beginning well before symptoms appear.

In MAPT-FTD, this has been documented in carriers of several mutations, including P301L, R406W, and IVS10+16. Studies of patient-derived neurons and brain tissue have shown changes in synaptic signaling and outright loss of synaptic connections. Spinal fluid studies in MAPT mutation carriers have also detected changes in proteins released from synapses, further indicating that synapses are being lost or are dysfunctional. In a subset of pre-symptomatic carriers, signs of this shrinkage have been detected on MRI as early as the thirties, long before symptoms appear.

Alongside this, the cell is dealing with another problem. The detached, abnormally modified Tau that is no longer

doing its job does not simply disappear. The cell has its own housekeeping systems, designed to recognize damaged or unwanted proteins and break them down so their parts can be reused. These disposal systems work continuously, and in a healthy cell, they keep abnormal Tau, like any other unwanted protein, from accumulating to harmful levels.

In MAPT-FTD, this housekeeping is overwhelmed (Figure 9 – step 5). Two things contribute to this. First, there is simply more abnormal Tau than the systems are designed to handle. Second, in several MAPT mutations, the disposal machinery itself appears to work less well. In neurons made in the laboratory from cells donated by carriers of the R406W mutation, one of the cell's main disposal pathways has been shown to be disrupted, with the result that Tau accumulates more quickly than it should. In neurons made from the carriers of the V337M mutation, another part of this machinery has also been shown to be impaired. In both cases, less of the abnormal Tau is removed than would be needed to keep up with it.

A further difficulty is that not all forms of a damaged protein are equally easy for the cell to dispose of Across neurodegenerative diseases, the proteins involved tend to clump together, and once they have clumped, they become much harder for the cell's housekeeping systems to break down. Disposal pathways that work well for individual proteins struggle with bulkier aggregates, so the more a protein clumps, the less effectively it can be cleared.

In MAPT-FTD, some mutations make this problem worse from the start. P301L and the closely related P301S are well-known examples: these changes remove a small structural feature that normally acts as a built-in brake on clumping, and as a result, the mutated Tau forms clumps more readily and more quickly than normal Tau. A newly identified MAPT mutation, P301A, was reported in a single proband and, in laboratory tests, formed clumps at a rate similar to that of P301S, suggesting that multiple changes at this position can each remove the same structural brake to varying degrees. This is one more pressure on a system that was already under strain.

Summary

The picture that emerges is not of a single defect but of a cascade of events, and it recurs across many neurodegenerative diseases, even though the protein at the center of each is different. In MAPT-FTD, abnormal modification of Tau leads to its detachment from microtubules. Detached Tau leaves the tracks less stable, disrupts transport along the axon, and contributes to the loss of synapses at the far end. At the same time, abnormal Tau is harder for the cell to clear, and some forms of mutated Tau are intrinsically more inclined to clump. As clumping accumulates, clearance is further overwhelmed, and the stress on the neuron grows.

Each step in this chain feeds the next, and over many years, this slow accumulation of pressure leads to the loss of synapses and, eventually, the death of neurons. Exactly which step in the cascade is most important, where in the chain the damage truly begins, and why some neurons are affected before others are questions still being worked out. What is clearer is that no single broken process alone explains the disease. It is the combination that builds up over time that does.

This complexity also helps explain why effective treatments have been so hard to find. Many therapies developed so far have focused on a single step downstream in the cascade, meaning they may address a disease consequence rather than its cause. Encouragingly, this is now beginning to change. A new generation of treatments aims to act much earlier in the chain by reducing the amount of Tau the cell makes in the first place, directly targeting MAPT.

MAPT Mutation Comparison

A quick side-by-side reference for MAPT mutation snapshots

Mutation	Most common early feature	Tau build-up	Gene region	Brain areas most affected on MRI	Typical age symptoms start	Typical disease duration	How often seen	Penetrance	Something to know about this mutation
R406W	Memory	3R + 4R	Exon 13	Hippocampus & temporal lobes (memory areas)	50s–60s	Often 10+ years; slow progression	Common worldwide	High	Often looks like Alzheimer's disease early on
N279K	Movement (parkinsonism , PSP-like)	4R	Exon 10 (splicing)	Frontal & temporal lobes + deep movement areas	40s–50s	5–10 years; faster than most	Common; original PPND family	High	Can look like Parkinson's disease or PSP at first
V337M	Behavior & personality	3R + 4R	Exon 12	Frontal & temporal lobes	40s–60s (sometimes 70s)	Variable, often 10+ years	Reported worldwide; less common than P301L/ R406W	High; onset varies within families	Often looks like behavioral- variant FTD
Q336H	Behavior & personality	3R	Exon 12	Frontal & temporal lobes; sometimes movement areas	50s	Limited data; roughly 8+ years reported	Rare; few families reported	Appears high (limited data)	Linked to a Pick's disease– like pattern in the brain
P301L	Behavior & personality	4R	Exon 10	Frontal & temporal lobes	40s–60s	5–10 years typical	Among the most common worldwide	High	One of the best-studied MAPT mutations
V363I	Varies (language, movement, or posterior)	4R reported (limited data)	Exon 12	Variable across reports	40s–70s (wide range)	Variable; limited data	Rare; few families reported	May be reduced; some older carriers well	Symptoms vary widely; classified as a rare MAPT variant
A152T	Varies (cognitive, behavior, or movement)	Not yet defined	Exon 7 (proline-rich region)	Variable across reports	50s–70s	Variable	Rare, but more common than most classic MAPT mutations	Low — raises risk rather than directly causing disease	Found in AD, FTD, PSP, PD, and DLB cohorts
IVS10+16 C>T	Memory (can also be behavior)	4R	Intron 10 (splicing)	Hippocampus & temporal lobes	40s–60s	5–15 years typical	Among the most common worldwide	High	Can look like Alzheimer's disease early on
IVS9-10 G>T	Behavior & movement	4R	Intron 9 (splicing)	Broad frontotemporal pattern	30s–50s	Roughly 5– 15 years	Rare; only a few families reported	Appears high (limited data)	One reported family also included motor neuron disease

Notes

- 3R and 4R tau: the two main forms of tau that build up in the brain. Mutations can change the balance between them, which affects which brain areas are most affected.

- Gene region: which part of the MAPT gene the mutation is in. Splicing mutations change how the tau protein is made, shifting the balance of 3R and 4R tau.

- Penetrance: the chance that a person carrying the mutation will develop symptoms during their lifetime.

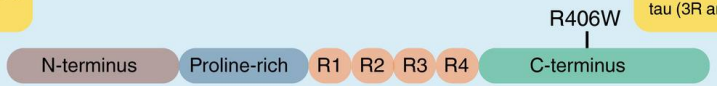
- Age of onset and duration are based on averages from published studies and may vary from family to family. For the rarer mutations, these numbers come from a small number of families and may change as more is learned.

- This table is a quick reference. Each individual snapshot has more detail about what symptoms look like, what is happening in the brain, and how well studied the mutation is.

MAPT: R406W

Most distinctive feature
This mutation often begins with memory problems, which is why it can look similar to Alzheimer's disease early on.

Type of tau build-up
This mutation leads to accumulation of both types of tau (3R and 4R) in the brain.



What's most affected?

	low	moderate	high
Memory			■
Behavior		■	
Movement	■		
Language	■		

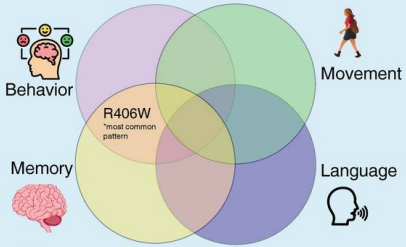
Memory: Forgetfulness and difficulty remembering recent events are often early features.

Behavior: Changes in judgment or behavior may develop over time

Movement: Movement symptoms are less common early, but may appear as the condition progresses in some people

Language: Some people may have word-finding or communication difficulties as the condition progresses.

What this usually looks like?



Symptoms usually start in the 50s–60s. Progression is often slow, with disease lasting 10+ years.

Brain scans (MRI) often show changes in the hippocampus (a key memory region) and nearby temporal areas, which can lead to early memory problems.

What happens in the brain?

- Changes in the brain often develop slowly
- Changes may start in memory areas and spread to other regions over time
- Brain cells may have a harder time sending signals to each other

Variability across families

- Variability is high
- Penetrance is high.
- Even within the same family, some may show memory-related changes while others may show behavior-related changes as different regions may be affected

How well studied?

- One of the more common MAPT mutations, reported in families worldwide.
- Studied in many research papers
- Strong clinical, pathology, and imaging data
- Tau PET has been used in research studies
- Multiple cell and animal models exist

Summary

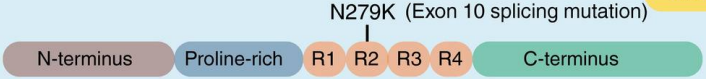
- Because memory is affected early, it is often confused with Alzheimer's
- Symptoms develop slowly, which makes changes harder to notice early
- Variability is high, so the same mutation can look different in each person, even within families
- This is a genetic form of FTD, even if it looks like Alzheimer's
- Studying this mutation has taught us a lot about how tau changes affect memory-related brain regions

MAPT: N279K

Most distinctive feature
This mutation was first identified in a large family with a condition called PPND, and it is sometimes still referred to by that name in older papers

Type of tau build-up
This mutation leads to accumulation of a form of tau called 4R tau in the brain.

cure MAPT FTD



What's most affected?

low moderate high

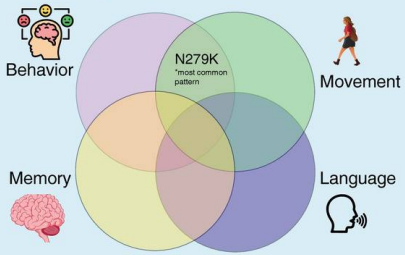
Memory
Memory can be affected, but is not usually an early feature.

Behavior
Changes in personality, judgment, or planning may develop over time.

Movement
Slower movement, stiffness, balance problems, and difficulty moving the eyes up and down are often early features. The overall pattern can resemble PSP

Language
Some people may have word-finding or communication difficulties as the condition progresses.

What this usually looks like?



Symptoms usually start in the 40s–50s. Disease often progresses faster than other MAPT mutations, typically 5–10 years.

Brain scans often show changes in the frontal and temporal lobes and in deeper movement-related brain systems, which can lead to movement problems and changes in thinking or behavior.

What happens in the brain?

- This mutation changes how tau is made, leading to more 4R tau
- Changes often affect movement and thinking regions of the brain
- Abnormal tau builds up in brain cells, especially in movement-related areas
- This may place extra stress on brain cells over time, affecting how they function and communicate

Variability across families

- Variability exsists
- Penetrance is high.
- Even within the same family, some may show movement-related symptoms early, while others show more behavioral or cognitive changes

How well studied?

- Studied in many research papers
- One of the more common MAPT mutations, first found in the large PPND family and later in families worldwide.
- Strong clinical, pathology, and imaging data
- MRI and movement-related imaging have been used in research studies
- Multiple cell and animal models exist

Summary

- Movement symptoms are often an early feature of this mutation
- This is a genetic form of FTD that can include movement-related changes, sometimes described as parkinsonism or PSP-like features
- It can sometimes be mistaken for conditions like Parkinson's disease or PSP because of similar symptoms
- Symptoms may vary across peoples and change over time
- What we've learned from this mutation has helped us understand how changes in tau affect movement and thinking

MAPT: V337M

Most distinctive feature
This mutation often begins with changes in personality, judgment, and social behavior, consistent with behavioral-variant FTD.

Type of tau build-up
This mutation leads to accumulation of both types of tau (3R and 4R) in the brain.

What's most affected?

low moderate high

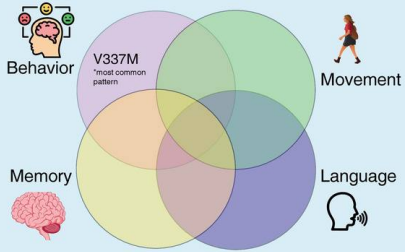
Memory
Forgetfulness and difficulty remembering recent events are often early features.

Behavior
Changes in judgment or behavior may develop over time.

Movement
Movement symptoms are less common early, but may appear as the condition progresses in some peoples.

Language
Some people may have word-finding or communication difficulties as the condition progresses.

What this usually looks like?



Symptoms usually start in the 40s–60s, though onset has been reported as late as the 70s.

Brain scans (MRI) often show changes in the frontal and temporal lobes, which can lead to changes in behavior, judgment, and social functioning.

What happens in the brain?

- This mutation affects how tau behaves inside brain cells
- Changes in frontal and temporal regions, where abnormal tau can build up
- Some brain cells in these regions may be especially vulnerable
- Brain cells may have difficulty functioning and communicating normally

Variability across families

- Behavior changes are often the first feature
- Language or memory changes may develop over time
- Penetrance is high, though age of onset can vary widely within families.
- Symptoms can vary across peoples and families

How well studied?

- Studied in many research papers
- Reported in families worldwide, though less common than P301L or R406W.
- Strong clinical, pathology, and imaging data
- Tau PET has been used in research studies
- Multiple models exist, including patient-derived cells, organoids, and animal models
- Well studied, but important questions remain

Summary

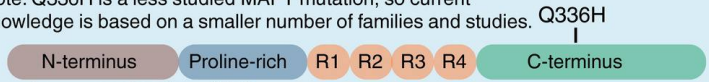
- Behavior changes are often an early feature of this mutation
- This is a genetic form of FTD that often looks like behavioral-variant FTD
- Other symptoms may develop as the condition progresses
- Researchers can track tau build-up in living people with this mutation using tau PET scans, which may help future clinical trials
- Research on this mutation has helped us understand how tau changes affect the frontal and temporal parts of the brain

MAPT: Q336H

Most distinctive feature
This mutation may increase how strongly tau binds to microtubules, which is different from many other MAPT mutations.

Type of tau build-up
This mutation leads to 3R tau build-up in the brain.

Note: Q336H is a less studied MAPT mutation, so current knowledge is based on a smaller number of families and studies.



What's most affected?

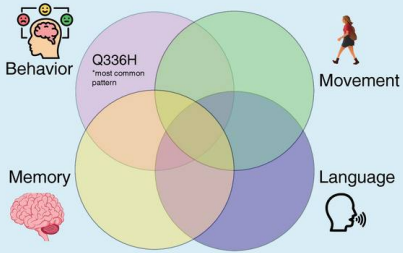
Memory — low
Memory can be affected, but is not usually an early feature.

Behavior — high
Changes in personality, judgment, and social behavior are often early features.

Movement — low
Movement symptoms are less common early, but may appear as the condition progresses in some peoples

Language — moderate
Some people may have word-finding or communication difficulties as the condition progresses.

What this usually looks like?



Symptoms usually start in the 50s. Data come from a small number of families.

Brain scans (MRI) often show changes in the frontal and temporal lobes, and may also involve deeper movement-related brain regions, which can lead to changes in behavior and movement.

What happens in the brain?

- This mutation affects how tau behaves inside brain cells
- Changes often affect frontal and temporal regions of the brain
- Unhealthy tau (mainly the 3R form) builds up inside brain cells
- Brain cells may have difficulty functioning and communicating normally
- A related mutation at the same spot, called Q336R, works in a similar way and causes a similar Pick's disease–like pattern

Variability across families

- Penetrance appears high based on the few reported families.
- Behavior changes are often the first major feature
- Other symptoms may also develop as the condition progresses
- Current understanding is based on a smaller number of families and studies

How well studied?

- Studied in a smaller number of papers
- Strong pathology and lab-based tau studies
- Includes test-tube tau studies and cell-based assays
- Less clinical and imaging data than for some other MAPT mutations

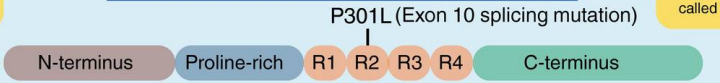
Summary

- Behavior changes are often an early feature of this mutation
- This is a genetic form of FTD that can be linked to a Pick's disease–like pattern of tau build-up
- Language or memory changes may also develop as the condition progresses
- Studying this mutation has helped us understand a Pick's disease–like pattern of tau build-up

MAPT: P301L

Most distinctive feature
This mutation is one of the best-studied MAPT mutations and is strongly linked to behavior-led FTD with meaningful movement overlap.

Type of tau build-up
This mutation leads to accumulation of a form of tau called 4R tau in the brain.



What's most affected?

low moderate high

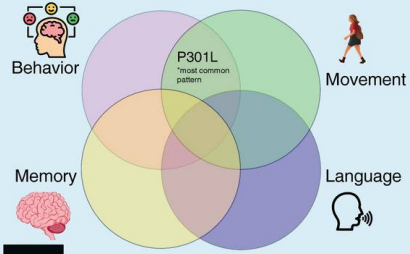
Memory
Memory can be affected, but it is not usually the main early feature. The literature emphasizes behavior and parkinsonism more strongly.

Behavior
Changes in personality, judgment, and social behavior are often early features. This mutation is most often linked to behavioral-variant FTD.

Movement
Movement symptoms can also be important, and parkinsonian features may occur. This mutation can include parkinsonism.

Language
Some people may have word-finding or communication difficulties as the condition progresses. Clinical presentation can vary across families.

What this usually looks like?



Symptoms usually start in the 40s–60s. Disease duration typically runs 5–10 years.

Brain scans (MRI) may show changes in the frontal and temporal lobes, which can affect behavior and judgment.

What happens in the brain?

- This mutation makes tau more likely to clump together.
- It is linked to build-up of 4R tau in the brain.
- These tau changes can disrupt the cell's internal transport system.
- Over time, this can damage frontal, temporal, and movement-related brain regions.

Variability across families

- Penetrance is high.
- Behavior changes are often the first major feature
- Even within the same family, symptoms and diagnoses can differ
- Reported diagnoses have included bvFTD, svPPA, CBD, and Alzheimer's disease–like presentations

How well studied?

- Studied in many research papers
- One of the most common MAPT mutations worldwide.
- Strong clinical, pathology, and imaging data
- Tau PET has been used in research studies
- Many models exist, including lab-based tau studies, cell models, inertebrate and animal models
- This is one of the best-studied MAPT mutations

Summary

- Behavior changes are often an early feature of this mutation.
- This is a genetic form of FTD that often looks like behavioral-variant FTD, but movement symptoms can also be important.
- Different people in the same family may still be given different diagnoses.
- We've learned a great deal from this mutation about how tau builds up and affects the brain

MAPT: V363I

Most distinctive feature
Marked clinical variability, with reduced microtubule binding and abnormal tau aggregation suggesting a mixed tau dysfunction phenotype.

Type of tau build-up
Reported 4R tau pathology, but more pathology data are needed across cases

cure MAPT FTD

What's most affected?

low moderate high

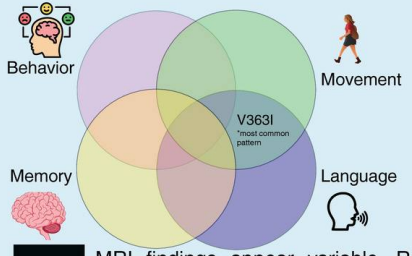
Memory
Memory symptoms can occur, but this mutation is not most clearly defined by a memory-led pattern.

Behavior
Behavioral change may be part of the picture, but it appears less central than language or movement.

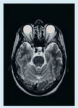
Movement
Movement features are also prominent, especially corticobasal and PSP-like patterns.

Language
Language symptoms are a major theme, including nonfluent and semantic presentations.

What this usually looks like?



Age of onset has varied widely (40s–70s) across the small number of reported cases.



MRI findings appear variable. Reported cases include posterior/parietal atrophy in some movement-led presentations, while other reports place V363I in a more temporal-language pattern.

What happens in the brain?

- Tau may not bind microtubules normally, which can affect cell structure and transport.
- Tau may also be more likely to misfold and build up abnormally over time.
- Which brain regions are most affected may vary, which may help explain the mix of language, movement, and posterior cortical features reported in V363I.

Variability across families

- Symptoms can vary considerably in families
- Reported cases include language-led, movement-led, and posterior cortical presentations.
- Penetrance may be reduced — some older carriers have remained well.

How well studied?

- A rare MAPT mutation reported in a small number of families.
- Moderately studied for a rare MAPT mutation
- Some clinical and pathology data are available
- Some tau biology and aggregation studies have been done
- Models include lab-based tau studies and a C. elegans model
- Still less established than the best-known MAPT mutations

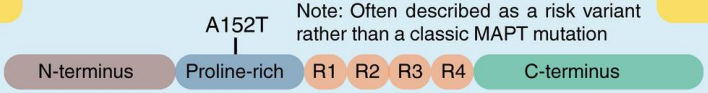
Summary

- Rare MAPT mutation in the R4 microtubule-binding region of tau
- Marked clinical variability across reported cases
- Language-led, movement-led, and posterior cortical presentations have all been described
- Studies suggest reduced microtubule binding and abnormal tau aggregation
- Reported 4R tau pathology in at least one confirmed case
- Moderately studied, but still less established than the best-known MAPT mutations

MAPT: A152T

Most distinctive feature
Acts more like a broad tau risk variant than a classic single-syndrome MAPT mutation.

Type of tau build-up
Not enough evidence yet to define one consistent tau build-up pattern.



Note: Often described as a risk variant rather than a classic MAPT mutation

What's most affected?

low moderate high

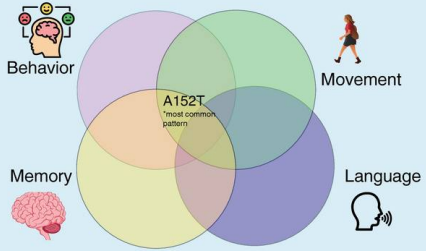
Memory
Early signs may include cognitive or memory changes, including AD-like presentations.

Behavior
Behavioral change may also appear as part of the FTD-spectrum picture.

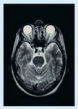
Movement
Movement changes may be part of the picture, including PSP- or parkinsonism-like features.

Language
Language symptoms can occur, but they are less often the main early feature.

What this usually looks like?



Age of onset has varied widely (50s–70s) across reported cases.



MRI findings appear variable rather than mutation-specific.Reported cases include parietal or posterior cortical atrophy in some patients, especially in AD-like presentations.

What happens in the brain?

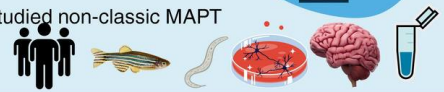
- Tau may not support microtubules as well as usual, which can affect cell structure and transport.
- A152T has been linked to increased formation of small toxic tau clusters, called oligomers.
- Nerve cells may become more easily worn down over time

Variability across families

- Symptoms may look quite different from person to person.
- Reported presentations include AD-like, FTD-spectrum, and PSP/parkinsonism-like disease.
- Penetrance is low — A152T raises risk rather than causing disease directly. Also reported in people with Parkinson's disease and dementia with Lewy bodies.

How well studied?

- Well studied for a MAPT risk variant
- A rare MAPT variant, but found more often than most classic MAPT mutations.
- Strong clinical, pathology, and lab-based tau biology data
- Human neuron and cell models have been used
- Animal models include mouse, zebrafish, and C. elegans
- This is one of the better-studied non-classic MAPT variants



Summary

- Rare MAPT variant in the proline-rich region of tau
- Often described as a risk variant rather than a classic MAPT mutation
- Linked to overlapping AD-like, FTD-spectrum, and PSP/parkinsonism-like presentations
- Studies suggest weaker microtubule binding, increased tau oligomers, and greater neuronal stress
- Well studied for a MAPT risk variant, with human, cell, and animal models available

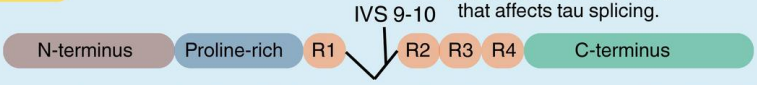
MAPT: IVS9-10G>T

Most distinctive feature
Intronic splice-site mutation that shifts tau toward excess 4R tau.

Type of tau build-up
Predominantly 4R tau build-up, consistent with a 4R tauopathy.

cure MAPT FTD

This is an intronic mutation that affects tau splicing.



What's most affected?

low moderate high

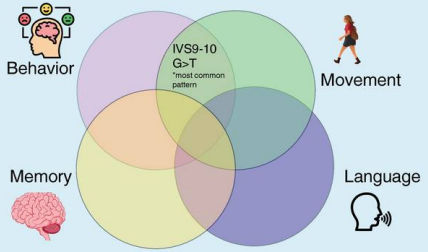
Memory
Memory change can occur, but it does not seem to be the main early feature.

Behavior
Behavioral change is a major recurring theme, including disinhibition and bvFTD-like presentations.

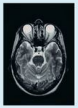
Movement
Early signs may include parkinsonism and other movement-related symptoms.

Language
Language difficulties may be part of the picture, including dysphasic features.

What this usually looks like?



Symptoms have started in the 30s–50s in reported families. Disease duration has ranged from about 5–15 years.



MRI findings are not yet well defined for this mutation, but available reports suggest a broad frontotemporal pattern.

What happens in the brain?

- This intronic mutation changes tau splicing, increasing inclusion of exon 10.
- This shifts the normal balance of tau toward the 4-repeat (4R) form.
- Over time, excess 4R tau may build up abnormally and interfere with nerve cell function.

Variability across families

- Symptoms can vary considerably within the same family.
- Penetrance appears high based on the few reported families.
- Behavioral change and parkinsonism have both been reported across affected relatives, and one family study also noted motor neuron disease.
- This mutation may therefore show more than one clinical pattern.

How well studied?

- Moderately studied for a rare MAPT splicing mutation
- A rare splice-site mutation reported in only a handful of families.
- Best supported by human clinical, pathology, and imaging data
- The splicing mechanism is fairly well understood
- Dedicated experimental model systems are still limited
- Less developed than major MAPT mutations such as P301L, R406W, and N279K

Summary

- Rare intronic MAPT splice-site mutation near exon 10
- Changes tau splicing and shifts tau toward excess 4R tau
- Behavioral and movement symptoms are the strongest recurring clinical themes
- Symptoms may vary even within the same family
- Moderately studied, with human clinical, pathology, imaging, and splicing data available

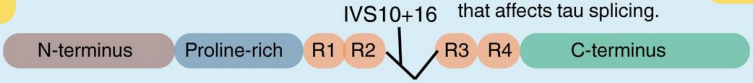
MAPT: IVS10+16 C>T

Most distinctive feature
Intronic splice-site mutation near exon 10 that shifts tau toward excess 4R tau. Often starts with memory changes, which can make it look like Alzheimer's disease early on.

Type of tau build-up
This mutation leads to accumulation of a form of tau called 4R tau in the brain.

cure MAPT FTD

This is an intronic mutation that affects tau splicing.



What's most affected?

low moderate high

Memory
Memory problems are often an early feature, similar to what is seen in Alzheimer's disease.

Behavior
Changes in personality, judgment, or behavior often develop over time.

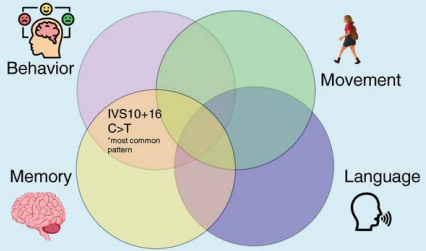
Movement
Movement symptoms are less common early, but parkinsonism or balance problems can develop later.

Language
Some people may have word-finding or communication difficulties as the condition progresses.

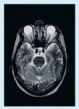
Variability across families

- Variability exists between and within families
- Most people show memory-led symptoms, but some develop behavior-led or mixed patterns
- Penetrance is high

What this usually looks like?



Symptoms usually start in the 40s–60s. Disease duration typically runs 5–15 years.



Brain scans (MRI) often show changes in the hippocampus and temporal lobes, similar to R406W. This pattern is linked to early memory problems.

How well studied?

- One of the most common MAPT mutations worldwide
- Studied in many research papers
- Strong clinical, pathology, and imaging data
- Tau PET has been used in research studies
- Multiple cell and animal models exist

What happens in the brain?

- This intronic mutation changes tau splicing, increasing inclusion of exon 10
- This shifts the normal balance of tau toward the 4-repeat (4R) form
- Over time, excess 4R tau builds up abnormally in brain cells
- Changes often start in memory areas and spread to other regions over time

Summary

- Because memory is affected early, it is often confused with Alzheimer's disease
- One of the most common MAPT mutations and well-studied
- This is a genetic form of FTD, even if it looks like Alzheimer's
- Symptoms can vary across people and families
- Studying this mutation has taught us a lot about how changes in tau splicing affect memory-related brain regions

Rare & Understudied MAPT Variants

An educational summary of three rare or uncertain MAPT variants

About this page

Most MAPT mutation snapshots describe mutations that have been studied in multiple families and followed for many years. Some MAPT variants, however, have been reported in only one or a few people — either because they are still classified as variants of uncertain significance (VUS), or because they are confirmed as pathogenic but have only been described in a small number of families. This page summarizes what is currently known in the published literature about three such variants: R613W, P494L, and IVS10+15 A>C. It is an educational resource only and is not intended as medical or genetic advice.

VUS and rare-but-pathogenic variants

When genetic testing identifies a change in the MAPT gene, clinical geneticists classify it using a standard set of rules. If the available evidence is not sufficient to determine whether the change causes disease, it is labelled a variant of uncertain significance (VUS). If the evidence is strong — for example, clear segregation with disease across a multi- generational family, or functional data showing that the change disrupts tau protein function — the variant may be classified as pathogenic or likely pathogenic.

A VUS is not the same as “no variant found.” It means the change is real, but the research community does not yet have enough data to classify it with confidence. Over time, as additional carriers are identified and functional studies are performed, a VUS may be reclassified as pathogenic, likely pathogenic, likely benign, or benign.

A variant can also be classified as pathogenic while remaining rare — meaning there is sufficient evidence to conclude that it causes disease, but only a small number of affected families have been described. In such cases, the full clinical picture is still being characterized.

MAPT R613W

Also written as c.1837C>T (p.Arg613Trp), NM_001377265.1

R613W is a very rare MAPT variant.

What is currently known

- Classified as a variant ofuncertain significance (VUS) in ClinVar (RCV002668422).
- Reported in very few individuals; family segregation data are limited.
- Because only a small number of carriers have been described, typical clinical features, age of onset, and disease course are not established for this variant.
- No functional studies, neuropathology, or brain imaging data specific to R613W have been published.

MAPT P494L

Also written as c.1481C>T (p.Pro494Leu), NM_016835.4

P494L has been reported in a single published case: a 54-year-old Italian woman with idiopathic Parkinson's disease who later developed ALS — an unusual combination sometimes called Brait–Fahn–Schwarz syndrome (Ferrari et al., 2024).

What is currently known

- Classified as a variant of uncertain significance (VUS).
- The variant is very rare in population databases
- No specific study published yet and several questions remain.

MAPT IVS10+15 A>C

Also written as c.915+15A>C (NM_005910)

IVS10+15 A>C is a rare intronic mutation in the splice-site region just after exon 10 — the same region of the

gene where the better-known IVS10+16 C>T mutation sits. It is classified as pathogenic, but has been described in a limited number of families.

What is currently known

- Originally described in a large Irish family with 21 affected individuals across four generations, with inheritance consistent with an autosomal-dominant pattern (McCarthy et al., 2015).
- Affected carriers in the published family generally presented with behavioural-variant frontotemporal dementia; MRI and FDG-PET typically showed bilateral anterior temporal lobe atrophy and hypometabolism.
- The mutation fall in a region that regulates exon 10 splicing leading to an increased proportion of 4R tau isoforms — similar in mechanism to IVS10+16 C>T.
- Classified as pathogenic on Alzforum. Because relatively few families have been described, data on age-of-onset range, disease duration, and full clinical variability remain limited.

Key References

MAPT R613W

ClinVar.(accessed 2026). NM_001377265.1(MAPT):c.1837C>T (p.Arg613Trp) AND Inborn genetic diseases. ClinVar accession RCV002668422. https://www.ncbi.nlm.nih.gov/clinvar/RCV002668422/

The ClinVar entry for R613W, classified as a variant of uncertain significance. The numbering uses the longer "Big Tau" reference transcript (NM_001377265.1).

MAPT P494L

FerrariC,Ingannato A, Matà S, et al. (2024). Parkinson-ALS with a novel MAPT variant. Neurological Sciences. 45(3):1051–1055. PMID: 37730935.

Single published case of P494L: a 54-year-old Italian woman with idiopathic Parkinson's disease followed by ALS ("Brait–Fahn–Schwarz" phenotype). Classified as a variant of uncertain significance (ACMG); computational tools give mixed predictions of damaging vs. tolerated.

MAPT IVS10+15 A>C

McCarthy A, Lonergan R, Olszewska DA, et al. (2015). Closing the tau loop: the missing tau mutation. Brain. 138(Pt 10):3100–3109. PMID: 26297558.

The primary description of IVS10+15 A>C in a large Irish family with 21 affected individuals over four generations. Establishes pathogenicity and describes the clinical and imaging features.

Alzforum. (ongoing). MAPT IVS10+15 A>C — mutation database entry. https://www.alzforum.org/mutations/mapt-ivs1015-ac

Continuously updated summary of IVS10+15 A>C pathogenicity, clinical features, and reported families.

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