

### Most distinctive feature

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

# MAPT: R406W

### Type of tau build-up

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



N-terminus

Proline-rich

R1

R2

R3

R4

C-terminus

R406W

## What's most affected?



### Memory

low moderate high

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



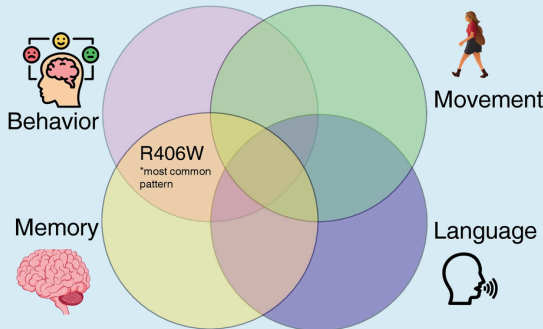
### Language

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

- 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

## Variability across families

## What this usually looks like?



Behavior

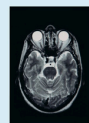
Movement

Memory

Language

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

## What happens in the brain?



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

- 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

- 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

## How well studied?



## 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

### 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

# MAPT: N279K

### Type of tau build-up

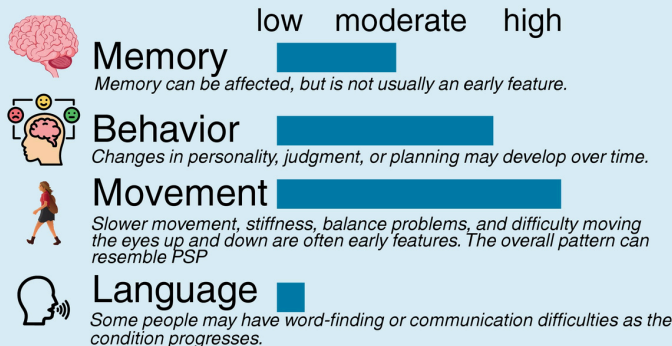
This mutation leads to accumulation of a form of tau called 4R tau in the brain.



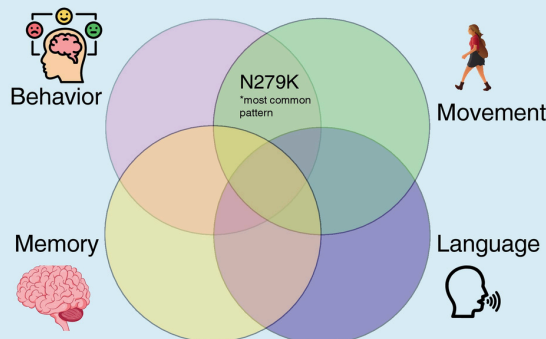
N279K (Exon 10 splicing mutation)



## What's most affected?



## What this usually looks like?



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

## What happens in the brain?

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.

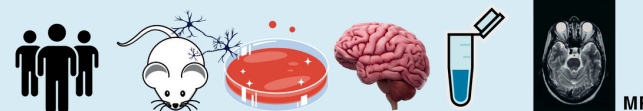
- This mutation changes how tau is made, leading to more 4R tau
- Changes often affect movement and thinking regions of the brain
- Abnormal tau builds up in brain cells, especially in movement-related areas
- This may place extra stress on brain cells over time, affecting how they function and communicate

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

## Variability across families

- 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

## How well studied?



## 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

### Most distinctive feature

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

# MAPT: V337M

### Type of tau build-up

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



N-terminus

Proline-rich

R1

R2

R3

R4

C-terminus

V337M

## What's most affected?



### 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.



Behavior

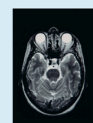
V337M

\*most common pattern

Movement

Memory

Language



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

- 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

## Variability across families

## What this usually looks like?

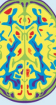
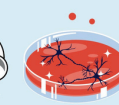
Symptoms usually start in the 40s–60s, though onset has been reported as late as the 70s.

## 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

- 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

## How well studied?



Tau PET

## 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

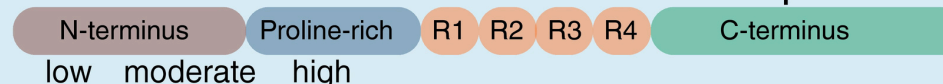
## Most distinctive feature

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

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



### Behavior

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



### Movement

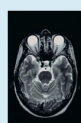
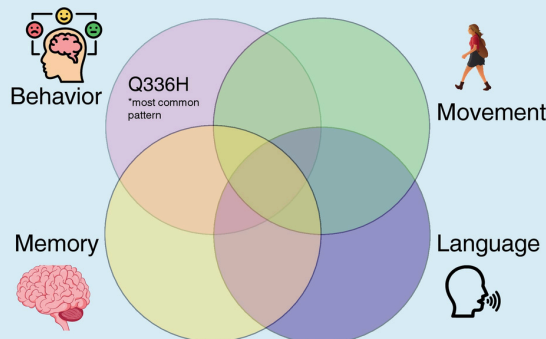
Movement symptoms are less common early, but may appear as the condition progresses in some people.



### Language

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

## What this usually looks like?



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.

- 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

## What happens in the brain?

- 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

- 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



## Variability across families

## How well studied?



## 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

### 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.

# MAPT: P301L

### Type of tau build-up

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



P301L (Exon 10 splicing mutation)

N-terminus

Proline-rich

R1

R2

R3

R4

C-terminus

## What's most affected?



### 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.



Behavior

Memory

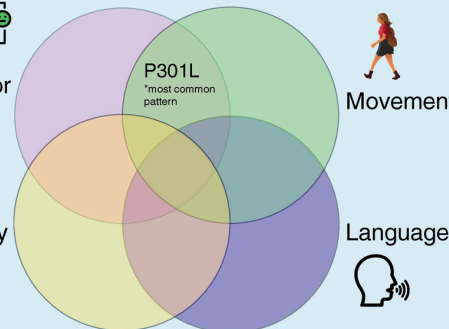


Movement

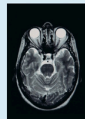
Language



low moderate high



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



- 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.

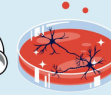
## What happens in the brain?

- 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

## Variability across families

- 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, invertebrate and animal models
- This is one of the best-studied MAPT mutations

## How well studied?



Tau PET

## 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

### Most distinctive feature

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

# MAPT: V363I

### Type of tau build-up

Reported 4R tau pathology, but more pathology data are needed across cases



N-terminus

Proline-rich

R1

R2

R3

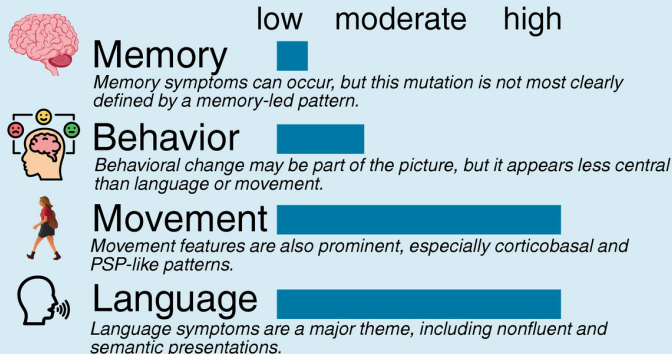
R4

C-terminus

V363I



## What's most affected?

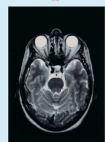


## What this usually looks like?

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

## 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.



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.

- 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.

## Variability across families

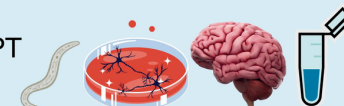
- A rare MAPT mutation reported in a small number of families.
- Moderately studied for a rare MAPT mutation
- Some clinical and pathology data are available
- Some tau biology and aggregation studies have been done
- Models include lab-based tau studies and a C. elegans model
- Still less established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

## How well studied?



## 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



### Most distinctive feature

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

# MAPT: A152T

### Type of tau build-up

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



A152T

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

N-terminus

Proline-rich

R1

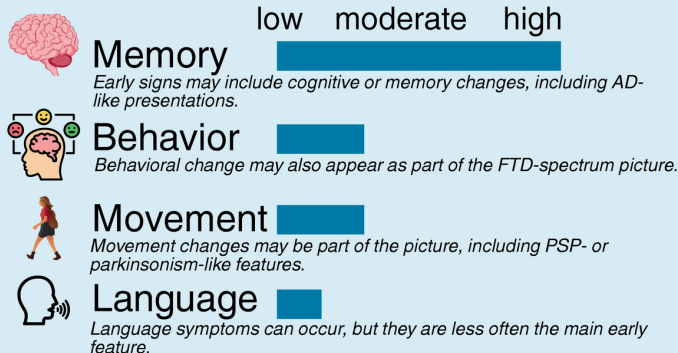
R2

R3

R4

C-terminus

## What's most affected?

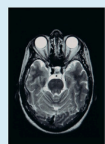


## What this usually looks like?

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

## 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



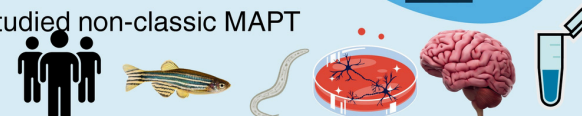
MRI findings appear variable rather than mutation-specific. Reported cases include parietal or posterior cortical atrophy in some patients, especially in AD-like presentations.

- 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.

## Variability across families

- 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

## How well studied?



## 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

### Most distinctive feature

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

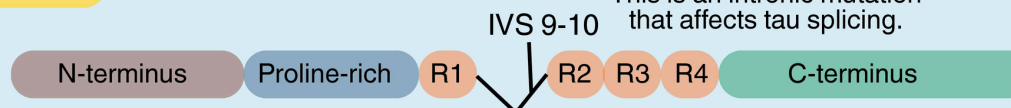
# MAPT: IVS9-10G>T

### Type of tau build-up

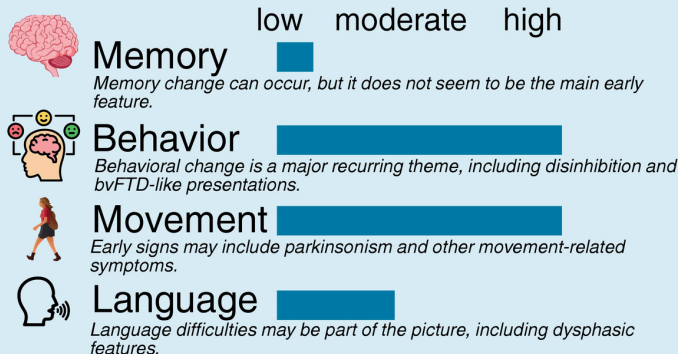
Predominantly 4R tau build-up, consistent with a 4R tauopathy.



This is an intronic mutation that affects tau splicing.



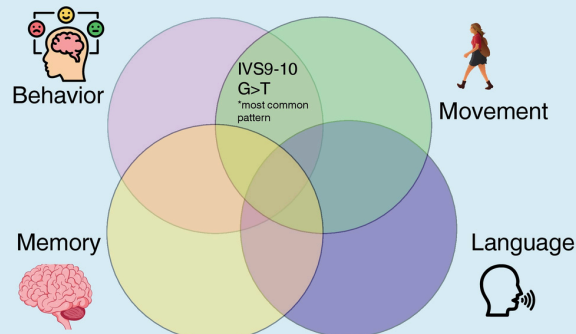
## What's most affected?



- 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.

## Variability across families

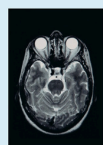
## What this usually looks like?



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

## What happens in the brain?

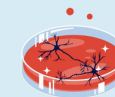
- This intronic mutation changes tau splicing, increasing inclusion of exon 10.
- This shifts the normal balance of tau toward the 4-repeat (4R) form.
- Over time, excess 4R tau may build up abnormally and interfere with nerve cell function.



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

- 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

## How well studied?



## 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

### Most distinctive feature

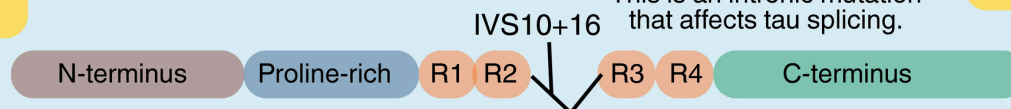
Intronic splice-site mutation near exon 10 that shifts tau toward excess 4R tau. Often starts with memory changes, which can make it look like Alzheimer's disease early on.

# MAPT: IVS10+16 C>T

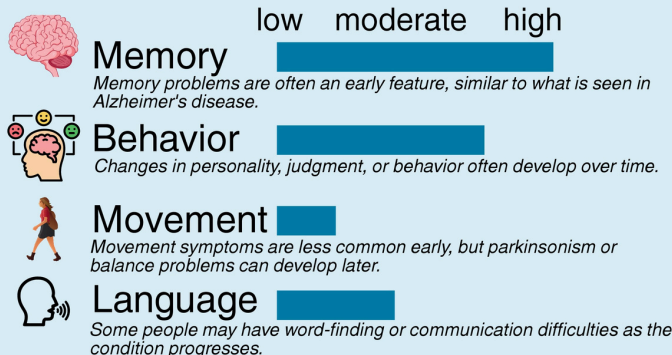
### Type of tau build-up

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

This is an intronic mutation that affects tau splicing.



## What's most affected?



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

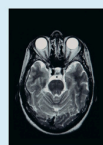
## Variability across families

## What this usually looks like?

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

## 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



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

- 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

## How well studied?



## 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