

Psychosis in Genetic Frontotemporal Dementia

Mariana Lima Magalhães, Mariana Andrade, Teresa Gouveia
ULS São José | Júlio de Matos Hospital | Lisbon, Portugal

1. Introduction

Frontotemporal Dementia (FTD) is a neurodegenerative disorder characterised by **behavioural, language and motor** symptoms. (1)

Is the **second** most common form of **early-onset dementia** after Alzheimer’s disease. (3)

FTD can occur in both **familial and sporadic forms**. **Familial FTD (fFTD)** has been associated with several genes, particularly **MAPT, GRN, and C9orf72**, witch account for **60–70% of all fFTD cases** and **10–20% of sporadic cases**. (3)

Neuropsychiatric manifestations, including psychosis, **may precede cognitive decline** and frequently **lead to an initial diagnosis of a primary psychiatric disorder**, thereby **delaying recognition** of the underlying **neurodegenerative process**. (1)

Earlier studies estimated the **prevalence of psychosis in FTD** to be approximately **6–7%**, whereas more recent reviews suggest higher rates, ranging from **10% to 15%**.(5)

Notably, **psychosis** appears to be more prevalent in **genetically determined forms of FTD - C9orf72, MAPT and GRN** - with a reported prevalence of **21-56%**, and **may precede disease onset by decades**. (3)

However, the **prevalence of neuropsychiatric profiles** and their **correlation with genetic and pathogenic FTD forms** has been difficult to ascertain.

2. Aim

This review aims characterize the **association between psychosis** and the most common **genetic mutations predisposing to FTD** – MAPT, C9orf72 and GRN - as well as they **distribution across clinical phenotypes** and **pathological subtypes**.

3. Methodology

A **non-systematic narrative review** of the literature was conducted using the **PubMed database**.
The search strategy included the following terms: “psychosis”, “frontotemporal dementia”, “C9orf72”, “MAPT”, “GRN”, “TDP-43” and “TAU”.

4. Results

1.Prevalence of Psychosis:

- According to the literature, psychosis is mort frequent in **C9orf72 (~32%)**, followed by **GRN (15%)** and **MAPT (~9%)** mutation carriers. (1)
- Psychosis in **MAPT** mutation carriers tends to occur at a **younger age** (mean onset **~36.5 years**) compared with other genetic groups - **C9orf72 (~60 years)** and **GNR (~56 years)**. (1)

2. Clinical Phenotypes:

Overall, **psychotic features appear to be less frequent** in **MAPT mutation carriers** when compared with **GRN and C9orf72**. (1)

- A recent systematic review reports that **delusions** were the **most frequently reported** psychotic symptom among **C9orf72** carriers. (3)
- In contrast, **hallucinations - particularly visual hallucinations** – **were more common in GRN** mutation carriers than delusions.(1)
- In **MAPT** mutation carriers, **delusions** were the **predominant psychotic feature**, whereas hallucinations were rare.(1)

Finally, one study reported that the **presence of right thalamic atrophy** was associated with psychotic symptoms in FTD. (4)

3. Pathological Phenotypes:

- From a pathological perspective, **C9orf72** and **GRN** are associated with **TDP-43 pathology**, and **MAPT** mutation is associated with **Tau pathology**. (1)
- Patients with **FTLD (Frontotemporal Lobar Disorder)-TDP** are **more likely to develop psychosis** compared with patients with **FTLD-tau**. Most of the **FTLD-TDP** cases with psychosis were associated with **TDP-43 pathological subtype B**. (1)
- The reason for the difference in prevalence of **psychosis** across different pathological groups **remains unclear**. Genetic overlap between different disorders may contribute to this variability. (1)

Mutation	Psychosis Prevalence	Age of onset	Psychotic Phenotype	Pathology
C9orf72	(~32%),	~60	Delusions are more prevalent than hallucinations (more auditory and visual types);	TDP-43
GRN	(15%)	~56	Visual hallucinations prevalence versus auditory; Delusions less present;	TDP-43
MAPT	(~9%)	~37	Delusions it's the more prevalent presentation; Hallucinations are rare.	Tau

Table N°1: Genetic Phenotypes Characterization. Adapted from Chatterjee, A. (2024)

5. Conclusion

Psychosis is a frequent manifestation in FTD, particularly in **genetically determined forms**, and is **more prevalent in C9orf72**.

The characterization of specific clinical and pathological profiles may help identify the disease at earlier stages, when the cognitive decline is not yet evident.

The **precise mechanisms** underlying psychosis in FTD **remain unclear**;

Further studies are required to elucidate the structural and biological substrates of psychosis in FTD and to improve early diagnostic recognition.

6. Acknowledgements

Thank you to my colleagues for help me with this work.



BIBLIOGRAPHY

Psychosis in Genetic Frontotemporal Dementia

Mariana Lima Magalhães, Mariana Andrade, Teresa Gouveia
ULS São José | Júlio de Matos Hospital | Lisbon, Portugal

1. Introduction

I. Frontotemporal Dementia (FTD):

- Is a neurodegenerative disorder characterised by **behavioural, language** and **motor** symptoms.
- **Neuropsychiatric manifestations** are present in FTD and **may precede cognitive decline**, leading to **misdiagnosis as primary psychiatric disorders**;
- **Prevalence of psychosis in FTD** is **10-15%**, and is more prevalent in **genetic forms**, with a prevalence of **21-56%**;
- The characterization of **neuropsychiatric** profiles and its **correlation** with **genetic and pathogenic FTD forms** is not well defined in literature.

2. Aim

Characterize the **association between psychosis** and the most common **FTD genetic mutations** – **MAPT, C9orf72 and GRN**.

3. Methodology

- A **non-systematic narrative review** of the literature using **PubMed database**.

Psychosis in Genetic Frontotemporal Dementia

Mariana Lima Magalhães, Mariana Andrade, Teresa Gouveia
ULS São José | Júlio de Matos Hospital | Lisbon, Portugal

3. Results

1.Prevalence of Psychosis (1):

- C9orf72 has the highest frequency (~32%) followed by GRN (15%) and MAPT (~9%);
- Psychosis in MAPT mutation occur at a younger age (~36.5 years) compared to C9orf72 (~60 years) and GNR (~56 years);

2. Clinical Phenotypes (1):

- We have a lower frequency of psychotic symptoms in MAPT mutation when compared with GRN and C9orf72;
- C9orf72 □ delusions are more prevalent than hallucinations;
- GRN □ we have a visual hallucinations prevalence; Delusions are less present;
- MAPT □ Delusions are the more prevalent presentation; Hallucinations are rare;

3. Pathological Phenotypes (1):

- Psychosis in patients with FTLD-TDP is more frequent than in patients with FTLD-tau;
- TDP- 43 pathological subtype B is more associated with psychosis.

Mutation	Psychosis Prevalence	Age of onset	Psychotic Phenotype	Pathology
C9orf72	(~32%),	~60	Delusions are more prevalent than hallucinations (more auditory and visual types);	TDP-43
GRN	(15%)	~56	Visual hallucinations prevalence versus auditory; Delusions less present;	TDP-43
MAPT	(~9%)	~37	Delusions it's the more prevalent presentation; Hallucinations are rare.	Tau

Table N°1: Genetic Phenotypes Characterization. Adapted from Chatterjee, A (2024).

4. Conclusion

- Psychosis is a frequent manifestation in genetic FTD forms, and is more prevalent in C9orf72.
- The characterization of specific clinical and pathological profiles may help identify the disease at earlier stages;
- The precise mechanisms underlying psychosis in FTD remain unclear;
- Further studies are required to better characterize psychosis in FTD and to improve early diagnostic recognition.