I. Dementia from a Medical Point of View

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Frontotemporal Degeneration

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Frontotemporal degeneration (FTD) is a clinically, genetically and neuropathologically heterogeneous syndrome. The clinical syndromes of FTD are typically characterized by progressive aphasia, decline in executive functions and behavioural problems. Recently, several other phenotypes have been described, such as progressive supranuclear palsy (PSP) and the corticobasal syndrome (CBS), frequently in combinations. Furthermore, the inclusion body myopathy may be a rare feature of FTD. FTD is the most frequent early-onset (<65 years) dementia, according to different studies comprising 3–26% of all dementias. Although FTD is commonly addressed as young-onset dementia, the highest number of patients is diagnosed in the age range from 70 to 84, and the highest incidence at the age of 71, confirming the need to consider FTD in characteristic phenotypes in different age groups. Positive family history is present in 25–50% of FTD, mostly in autosomal dominant pattern, and therefore genetic studies are indicated, if FTD phenotype is present.

Keywords: frontotemporal degeneration, dementia, aphasia, behavioural changes

Epidemiology

Frontotemporal degeneration (FTD) is a clinically, genetically and neuropathologically heterogeneous syndrome [1]. The clinical syndromes of FTD are typically characterized by progressive aphasia, decline in executive functions and behavioural problems [2, 3]. Recently, several other phenotypes have been described, such as progressive supranuclear palsy (PSP) and the corticobasal

syndrome (CBS), frequently in combinations [3–5]. Furthermore, the inclusion body myopathy may be a rare feature of FTD [4].

The first patient with aphasia and presenile dementia was described by Arnold Pick in 1892. The patient had progressive aphasia, lobar atrophy and presenile dementia. Alois Alzheimer identified that Pick bodies were the underlying pathology of the disease, and for a long time FTD was diagnosed as Pick's disease [3]. Interestingly, by 1986 Pick's disease was considered to have little relevance and most dementias were attributed to Alzheimer's and vascular diseases. Since 1986, there have been significant advances in scientific research for FTD [6].

FTD is the most frequent early-onset (<65 years) dementia, according to different studies [2] comprising 3–26% of all dementias. The incidence of FTD is the lowest in the Netherlands with 0.44 [7], 1.61 in the UK [8], and the highest, 8.14 in Finland (all data presented for 100 000 person years) [7]. The prevalence of FTD is 10.8/100.000 in the UK and Europe [5]. Although FTD is commonly addressed as young-onset dementia, the highest number of patients is diagnosed in the age range from 70 to 84, and the highest incidence at the age of 71 [5, 7].

The prognosis of FTD is serious. The overall life expectancy is 4.7 years. The life expectancy depends on the dominant syndrome. The shortest life expectancy of 2.9 years is demonstrated with predominantly PSP syndrome, and the longest of 5 to 9 years with progressive aphasias [5].

1. Clinical features of FTD

Classically, FTD is characterized by two phenotypes: behavioural variant FDT and aphasia variant of FTD.

The behavioural variant of FTD (bvFTD) is the most frequent and present in 40% [7]. BvFTD is characterized by early personality changes, disinhibition or apathy, and early loss of empathy. According to diagnostic criteria, progressive deterioration of behaviour and/or cognition has to be present. Furthermore, at least three clinical features of the following must be present for the diagnosis of bvFTD: early (within the first three years) behavioural disinhibition, apathy or inertia, loss of sympathy or empathy, perseverative, stereotyped or compulsive/ritualistic behaviours, hyperorality and dietary changes, and executive deficits with relative sparing of memory and visuospatial function. FTD can be diagnosed, if three of the five behavioural criteria/cognitive criteria are fulfilled [9]. The revised criteria [9] for bvFTD have good sensitivity 95% for possible bvFTD [9, 10] and specificity 82% [10].

Behavioural disinhibition means inappropriate conduct in different social situations, also impulsive spending and lending money to strangers that may cause significant financial problems [3]. Clinical features of apathy are decreased

interest in social interactions and in everyday life, also neglect of personal hygiene. As the clinical features resemble depression, the early differential diagnosis is complicated. The loss of empathy and sympathy means that the insight to emotions and feelings of other people (closest to the person) is lost [3]. In practice, there are many situations where the patient shows complete indifference to serious problems of their family members. Likewise, stereotyped and ritualistic behaviours are typical. Sometimes binge drinking and eating develop [3]. For instance, one of our patients started to drink alcohol excessively at the age 60 years and at first the family thought that changes in her behaviour were related to her newly developed alcohol abuse. Also, some patients exhibit reduced sensation of pain, leading to burns. Interestingly, at the same time, abnormally brisk response to light touch or increased response to changes in temperature may occur [6].

The second classical phenotype is aphasia. The primary aphasias were described and classified in revised form in 2011 [11]. Language phenotype is present in 29% [7]. Mainly two types of aphasias have been described in FTD. Non-fluent variant primary progressive aphasia (nfPPA) is present in 12.36% [7], and semantic variant of primary progressive aphasia (svPPA) (3,12) – in 8.61% [7]. In nfPPA, speech is impaired, slow with short sentences. Agrammatism and speech apraxia may or may not be present [6, 13]. The understanding of speech is preserved [6,12]. In addition, isolated primary progressive apraxia of speech may be present in FTD. Primary speech apraxia means that patient has only motor speech disorder without language problems. The distinction of pure speech apraxia and nfPPA is difficult and the syndromes frequently overlap [12]. When the patients have svPPA, the speech is fluent but has no meaning. Understanding the meaning of words, objects, and other sensory perceptions are impaired [3, 12].

Not surprisingly, aphasias in general are difficult to spot by family members. Especially slowly progressive reduction of speech characteristic of nfPPA aphasia is difficult to detect at onset [12], and the time from onset to diagnosis is relatively long – 3.5 years [8]. Progressive incomprehensible speech problems that are characteristic to svPPA are more obvious, and this subtype is diagnosed 1.4 years after onset [5].

In clinical practice, the described variants are not always clear syndromes according to classification. There is a lot of overlap and mixed syndromes [12]. PPA is diagnosed when the aphasia is the dominating problem during the first two years of the disease [3] and early behavioural changes are not present [14] but they appear later in the course of the disease [12]. On the other hand, patients with simultaneous onset of PPA and behavioural problems have also been described [15]. Recently, predominantly amnestic dementia syndrome with increasing incidence with advancing age (LATE) has been described with pathological changes typical for FTD. However, it is still unclear if this subtype is part of FTD spectrum or not [12, 16].

2. Cognitive dysfunction

Neuropsychological evaluation is essential in diagnostic process. During testing attention, language, visuospatial function, executive function, and social cognition functions need to be assessed [12].

The principal deficits in cognitive function are related to executive functions. In daily life, it means difficulties with planning and decision making. During formal neuropsychological testing, profound deficits in various executive functions like attention, abstraction, planning and task sequencing are frequently demonstrated. Verbal fluency is typically decreased. A reduced generation of propositional speech is also common. For instance, patients do not initiate conversation. If asked a question, they respond with short phrases. Speech may contain perseverations. In addition, emotion and social recognition are impaired [6].

In bvFTD verbal fluency, inhibition, decision making and neuroeconomics-derived tasks are most sensitive. Likewise, social cognition is severely impaired, whilst episodic memory may be preserved. Typically, well preserved functions include spatial memory, drawing, spatial orientation, and praxis [12].

In clinical practice both Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are used for screening, but frequently a more thorough neuropsychological assessment is needed to confirm the diagnosis [17].

3. Motor symptoms

Parkinsonian symptoms are present in more than 26–50% of FTD patients [5, 7]. The most common syndromes are progressive supranuclear palsy (PSP) that is present in 16% and corticobasal syndrome (CBS) that is present in 10% [7]. CBS is characterized by asymmetrical parkinsonism with alien limb, dystonia, and cortical syndromes. PSP is characterized by vertical supranuclear palsy, slowing vertical saccades, early (during the first year) prominent postural instability with falls [18]. Similarly common characteristics are striking apathy, impulsivity and behavioural changes [3].

The possible link between FTD and motor neuron disease (MND) was recognized already in 1980 [19] that has been confirmed now in many studies [3, 20–22]. MND in FTD has classical features – both upper and lower motor neuron damage. In the course of the disease, dysarthria, dysphagia, and pseudobulbar affect may develop. Interestingly, MND signs and symptoms vary in severity, showing both very mild and severe phenotypes [3, 22]. Mild symptoms were present in about 30% of studied FTD patients and MND was diagnosed in 6 to 12.5% [7, 22].

Psychiatric symptoms are relatively uncommon in FTD. However, in some genotypes florid psychotic symptoms may occur. A number of patients are

initially diagnosed with delusional psychosis, somatoform psychosis or paranoid schizophrenia [23]. Also, amnestic phenotype may be dominant at onset similar to Alzheimer's disease in 3–8%, depending on specific genotype [24]. In clinical practice, syndromes overlap and change in the course of the disease [5, 15].

4. Proteins and genes

The most common proteinopathies in FTD are tau (tauopathy) and TAR DNA-binding protein 43 (TDP-43).

Tau pathology was the first to be identified in relation to FTD [19], and about 40% of all FTD cases are tauopathies [25].

TDP-34 protein pathology was discovered in 2006 as cause of FTD [26, 27]. Currently, more than 50% of all FTD are TDP-34 positive, both in familial and sporadic forms [1]. Importantly, TDP-34 was present both in FTD and MND phenotypes, confirming that two seemingly different diseases are both TDP34 proteinopathies [27]. These findings confirmed earlier clinical observations of the link between the two diseases [19]. At present, four different subtypes of TDP-34 have been identified associated with different genotypes, but in some patients, different subtypes are present simultaneously [6, 28, 29].

More recently, aggregation of all members of the FET protein family pathology was discovered that accounts for 5–10% of all FTD cases. In conclusion, it is suggested that vast majority of proteinopathies present in FTD have been discovered [1].

Although the phenotypes of different proteinopathies are somewhat different there is still overlap and coexistence of different proteinopathies in patients. Therefore, predicting the specific proteinopathy based on clinical features is unreliable and unnecessary [12].

5. Genetic factors

Positive family history is present in 25–50% of FTD, mostly in autosomal dominant pattern [1].

The first gene linked to FTD was microtubule-associated protein tau (MAPT) gene on chromosome 17 that codes tau protein and was discovered in 1998 (30). Incidence of the MAPT gene associated with FTD is very variable across different populations. Generally, it is present in 1.5% of sporadic and 6.3% of familial cases [4]. Interestingly, in Sweden [31] and in Finland [32] the frequency of the MAPT gene is very low but in the Netherlands 43% of familial cases were carrying mutations to MAPT gene [33].

MAPT gene mutations are usually fully penetrant. [34]

MAPT gene explained only about 5–20% of familial FTD cases [1]. Taking into account the high incidence of familial cases, it was obvious that other genes play an important role.

Mutations of the progranulin (GRN) gene on chromosome 17 were identified in 2006, and the results were published in two separate papers in July [35] and in August [36]. GRN gene is associated with TDP-34 pathology [1]. GRN gene is very close to MAPT gene region that made it difficult to discover [4, 36]. GRN gene mutations cause 5–10% of all FTD cases [4]. FTD with GRN mutations has autosomal dominant mode of inheritance and 95% of patients have at least one affected family member [4,37]. GRN mutations have age-related penetrance with a number of patients demonstrating first symptoms in their 80s and 90s [34, 38].

The expansions of the hexanucleotide repeats of the *C9orf72* gene on chromosome 9 in relation to FTD was discovered in 2011 and published simultaneously by two groups [21, 39]. The number of repeats in affected individuals is often >1000 but already more than 30 repeats cause FTD. [39–42]

C9orf72 is responsible for 4–29% of all FTD cases and in 24–29% if family history is present [39, 42, 43].

These expansions are associated with variable TDP-34 pathology [1]. It has also been confirmed that *C9orf72* mutations cause TDP-34 pathology both in FTD and MND phenotypes [20].

Mutations in the gene encoding Valosin-Containing Protein (VCP) on chromosome 9 were discovered in 2004 [44]. VCP gene is associated with 1.6% of FTD, and causes TDP-34 proteinopathy [37, 45].

Some other genes causing TDP-34 pathology (including TARDB) have been described, but the incidence of these genes is rare and available data are still limited [1].

Mutations in the fused in sarcoma (FUS) gene are on occasion described in FET proteinopathies [28].

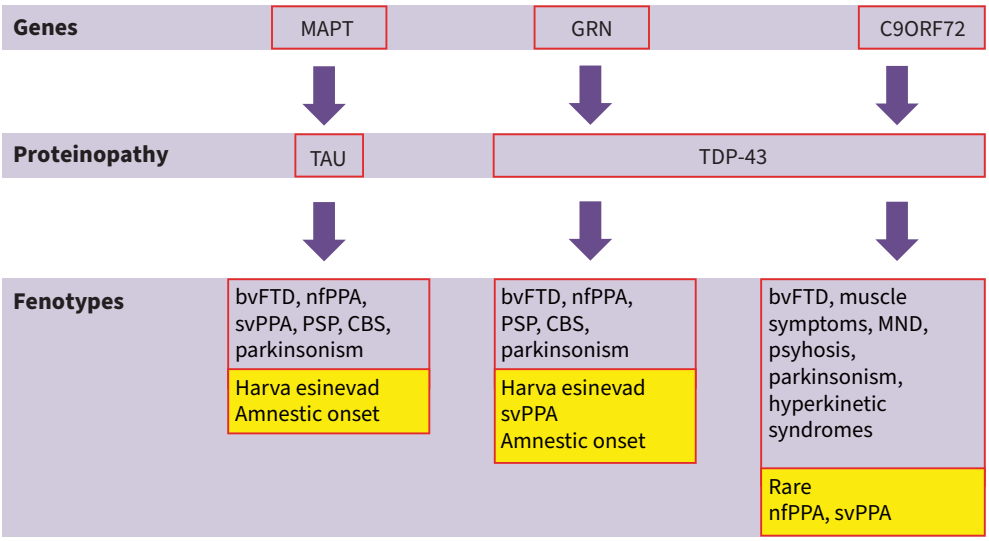
6. Genotype-phenotype correlations with the most frequent genotypes

6.1 MAPT gene phenotypes (figure 1)

MAPT gene mutations have large variety of phenotypes. However, by far the most common is bvFTD [4, 46]. Rare mutations of the MAPT gene cause CBS [46–48], PSP [46, 48], nfPPA [49, 50] and svPPA phenotypes [51].

PPA is usually combined with behavioural symptoms, but rare mutations can cause isolated PPA [4]. Parkinsonian symptoms may be present at onset with bvFTD or develop during the course of the disease [48].

Figure 1. **MAPT gene phenotypes. Genes, proteinopathies and clinical feature of the most common frontotemporal degeneration types**



MAPT = microtubule-associated protein tau, GRN = progranulin, TDP-43 = TAR DNA-binding protein 43, bvFTD = behavioral variant of FTD, nfPPA = Non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, PSP = progressive supranuclear palsy, CBS = corticobasal syndrome, MND = motor neuron disease

Few cases have been described with predominantly amnestic syndrome at onset that may lead to clinically misdiagnosed Alzheimer's disease [4].

Importantly, heterogeneity of phenotypes and incomplete penetration may be present also within one family with the same mutations, further complicating the clinical evaluation of patients [52].

6.2 GRN gene phenotypes

The phenotypes of GRN gene mutations are similar to MAPT gene phenotypes with the most common syndrome bvFTD [4, 53]. PPA is relatively common, and present in 20–25%, nfPPA is the most frequent subtype [4, 14, 53, 54].

Amnestic onset is atypical for FTD and this subtype is difficult to differentiate from Alzheimer's disease at onset. Parkinsonian syndrome or behavioural problems develop during the course of the disease. The absence of amyloid pathology typical for Alzheimer's disease is helpful for differential diagnosis [12].

Importantly, phenotypes with the same GRN mutations may vary within one family, for instance, bvFTD and nfPPA have been described within the same family with the same mutations [54]. Parkinsonian syndromes, like CBS and PSP, are less frequent [4, 53].

6.3 *C9orf72* expansion phenotypes

The most typical phenotypes of *C9orf72* expansions are FTD with or without MND [55]. Patients may present with combinations of clinically definite FTD and MND. However, about 30–40% of FTD patients may have either MND or mild symptoms like muscle wasting, rare fasciculations or muscle weakness that may indicate underlying pathology [22].

The most typical variant of FTD is bvFTD [9, 54].

Importantly, 38% of patients presented with florid psychosis and 28% had paranoid delusion and irrational thinking that was present in patients with or without MND [23].

Parkinsonian features may present in the form symmetrical rigidity, with or without tremor and autonomic dysfunction [56]. PPA is rarely seen in *C9orf72* expansions [4].

Importantly, *C9orf72* expansions may also present as Huntington's disease-like hyperkinetic disorder [57].

The penetrance, and therefore the development of clinical phenotypes depend on repeat size of *C9orf72* expansion. When the repeat size is high the symptoms develop earlier (mean age 53) compared to lower repeat size when symptoms develop later (mean age 62) [58]. Also, anticipation (earlier onset in younger generations) may occur [58–60].

6.4 VCP gene phenotypes

VCP gene phenotypes are different as the clinical picture includes inclusion body myositis, Paget disease with or without FTD [37, 44, 45, 60]. In fact, 90% of VCP gene carriers have inclusion body myositis and 30% FTD.

The FTD phenotype is bvFTD but psychiatric disorders, language problems and very rarely parkinsonian syndrome have been described [4]. The most common syndrome is inclusion body myositis [60] making the link to FTD difficult sometimes.

Clinical features of FTD are very heterogenous and change in time. Therefore, categorical delineation of the leading syndrome like bvTFD, PPA or specific parkinsonian syndromes may not be always possible as syndromes overlap [5, 15]. Typically, behavioural symptoms develop in 95% of patients with svPPA [5]. Also, taking into account that the same mutation/expansion may result in different phenotypes the distinction may not be so important in clinical practice.

Conclusions

FTD is the most common form of dementia with the onset before the age of 65, but it is most commonly diagnosed in the age frame from 70 to 84 [5]. It is important to recognize early onset of behavioural changes in patients with dementia, indicating the possibility of bvFDT. Unfortunately, many FTD patients manifest with associated symptoms that are not always considered characteristic of FTD. Although PPA is frequently sporadic [49], many FTD patients manifest with more or less isolated PPA. Also, the differential diagnosis of atypical parkinsonian syndromes, especially in patients with PSP or CBS phenotypes or without frank dementia point to the possibility of FTD. MND is a relatively common manifestation of FTD. Likewise, mild muscle symptoms: mild wasting, weakness, rare fasciculations may indicate the underlying FTD.

In neurological practice, we may see psychiatric symptoms less commonly, but it is well recognized that florid psychosis is relatively frequently present in FTD, sometimes erroneously leading to the misdiagnosis of a psychiatric disorder. The predominantly amnestic onset does not rule FTD out completely as several cases have been described with clinical features at onset that resemble Alzheimer's disease.

Comprehensive family history is crucial. Several aspects should be kept in mind. First, even in one family the phenotype and penetrance may be very different. So, it is important to analyse in detail all neurological, psychiatric and muscle (and bone) diseases in relatives. It has been shown that many patients are diagnosed with Alzheimer's disease, Parkinson's disease, psychiatric disorders including schizophrenia, muscle disease, but all these may be FTD mimics. Likewise, anticipation has been described in some families, therefore detailed history of the offspring is equally important.

Unfortunately, even the most detailed clinical picture does not reliably predict the underlying broad genetic pathology. Therefore, next generation whole exome or genome sequencing studies are appropriate. It is also important to remember, that c9orf is a repeat expansion pathology and cannot be detected during whole exome sequencing.

How rare are these conditions in everyday clinical practice?

Since 2016, at West-Tallinn Central Hospital have been identified 4 patients with c9orf, 4 patients with GRN mutations, 2 patients with TARDB and also 2 patients with mutations of MAPT and VCP.

Low threshold for ordering genetic testing in neurological diseases including FTD is important and enables to reach accurate diagnosis that is important for patients and their families.

REFERENCES

1. Neumann M., Mackenzie I. R. A. Review: Neuropathology of non-tau frontotemporal lobar degeneration. Neuropathology and Applied Neurobiology. 2019; Feb; 45 (1): 19–40. DOI: 10.1111/nan.12526
2. Vieira R. T., Caixeta L., Machado S., Cardoso Silva A., Nardi A. E., Arias-Carrión O., et al. Epidemiology of early-onset dementia: a review of the literature. Clinical Practice & Epidemiology in Mental Health. 2013; Jun; 45 (1): 88–95. DOI: 10.2174/1745017901309010088
3. Bang J., Spina S., Miller B. L. Frontotemporal Dementia. The Lancet. 2015; Oct 24; 386 (10004): 1672–1682. DOI: 10.1016/S0140-6736(15)00461-4
4. Zecca C., Tortelli R., Carrera P., Dell'Abate M. T., Logroscino G., Ferrari M. Genotype-phenotype correlation in the spectrum of frontotemporal dementia-parkinsonian syndromes and advanced diagnostic approaches. Critical Reviews in Clinical Laboratory Sciences. 2023; 60 (3): 171–188. DOI: 10.1080/10408363.2022.2150833
5. Coyle-Gilchrist I. T. S., Dick K. M., Patterson K., Rodríquez P. V., Wehmann E., Wilcox A., et al. Prevalence, Characteristics, and Survival of Frontotemporal Lobar Degeneration SyndromeS. Neurology. 2016; May 3; 86 (18): 1736–1743. DOI: 10.1212/WNL.0000000000002638
6. Snowden J. S. Changing perspectives on frontotemporal dementia: A review. Journal of Neuropsychology. 2023; Jun; 17 (2): 211–234. DOI: 10.1111/jnp.12297
7. Logroscino G., Piccininni M., Graff C., Hardiman O., Ludolph A. C., Moreno F., et al. Incidence of Syndromes Associated with Frontotemporal Lobar Degeneration in 9 European Countries. JAMA Neurology. 2023; Mar 13; 80 (3): 279–286.
8. Coyle-Gilchrist I. T. S., Dick K. M., Patterson K., Vázquez Rodríquez P., Wehmann E., Wilcox A., Lansdall C. J., Dawson K. E., Wiggins J., Mead S., Brayne C., Rowe J. B. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016; 86 (18): 1736–1743. DOI: 10.1212/WNL.0000000000002638
9. Rascovsky K., Hodges J. R., Knopman D., Mendez M. F., Kramer J. H., Neuhaus J., et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011; 134 (9): 2456–2477.
10. Harris J. M., Gall C., Thompson J. C., Richardson A. M., David Neary C., Du Plessis D., et al. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. Neurology. 2013; May 14; 80(20): 1881–1887. DOI: 10.1212/WNL.0b013e318292a342.
11. Gorno-Tempini M. L., Hillis A. E., Weintraub S., Kertesz A., Mendez M., Cappa S. F., et al. Classification of primary progressive aphasia and its variants. Neurology. 2011; Mar 15; 76 (11): 1006–1014. DOI: 10.1212/WNL.0b013e31821103e6
12. Rohrer J. D., Boeve B. F., Boxer A. L., Kumfor F., Pijnenburg Y., Rohrer J. D. Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations. Lancet Neurology. 2022; Mar; 21 (3): 258–272. DOI: 10.1016/S1474-4422(21)00341-0

13. Graham N. L., Leonard C., Tang-Wai D. F., Black S., Chow T. W., Scott C. J. M., et al. Lack of Frank Agrammatism in the Nonfluent Agrammatic Variant of Primary Progressive Aphasia. Dementia and Geriatric Cognitive Disorders Extra. 2016; Sep 9; 6 (3): 407–423. DOI: 10.1159/000448944
14. Mesulam M. M., Coventry C. A., Bigio E. H., Sridhar J., Gill N., Fought A. J., et al. Neuropathological fingerprints of survival, atrophy and language in primary progressive aphasia. Brain. 2022; Jun 1; 145 (6): 2133–2148. DOI: 10.1093/brain/awab410
15. Murley A. G., Coyle-Gilchrist I., Rouse M. A., Jones P. S., Li W., Wiggins J., et al. Redefining the multidimensional clinical phenotypes of frontotemporal lobar degeneration syndromes. Brain. 2020; May; 143 (5): 1555–1571. DOI: 10.1093/brain/awaa097
16. Nelson P. T., Dickson D. W., Trojanowski J. Q., Jack C. R., Boyle P. A., Arfanakis K., et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain. 2019; Jun 1; 142 (6): 1503–1527. DOI: 10.1093/brain/awz099
17. Maito M. A., Santamaría-García H., Moguilner S., Possin K. L., Godoy M. E., Avila-Funes J. A., et al. Classification of Alzheimer's disease and frontotemporal dementia using routine clinical and cognitive measures across multicentric underrepresented samples: A cross sectional observational study. Lancet Regional Health – Americas. 2023; Jan 1; 17 (2). DOI: 10.1016/j.lana.2022.100387
18. Litvan I., Agid Y., Calne D., Campbell G., Dubois B., Duvoisin R. C., et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP international workshop. Neurology. 1996; 47 (1): 1–9. DOI: 10.1212/wnl.47.1.1
19. Mckhann G. M., Albert M. S., Grossman M., Miller B., Dickson D., Trojanowski J. Q. Clinical and Pathological Diagnosis of Frontotemporal Dementia Report of the Work Group on Frontotemporal Dementia and Pick's Disease. Archives of Neurology. 2001; Nov; 58 (11): 1803–1809. DOI: 10.1001/archneur.58.11.1803.
20. Hsiung G. Y. R., Dejesus-Hernandez M., Feldman H. H., Sengdy P., Bouchard-Kerr P., Dwosh E., et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Brain. 2012; 135 (3): 709–722. DOI: 10.1093/brain/awr354
21. DeJesus-Hernandez M., Mackenzie I. R., Boeve B. F., Boxer A. L., Baker M., Rutherford N. J., et al. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. Neuron. 2011; Oct 20; 72 (2): 245–256. DOI: 10.1016/j.neuron.2011.09.011
22. Burrell J. R., Kiernan M. C., Vucic S., Hodges J. R. Motor Neuron dysfunction in frontotemporal dementia. Brain. 2011; Sept; 34 (9): 2582–2594. DOI:10.1093/brain/awr195
23. Snowden J. S., Rollinson S., Thompson J. C., Harris J. M., Stopford C. L., Richardson A. M. T., et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012; Mar; 135 (3): 693–708. DOI: 10.1093/brain/awr355

24. Moore K. M., Nicholas J., Grossman M., McMillan C. T., Irwin D. J., Massimo L., et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurology. 2020; Feb 1; 19 (2): 145–156. DOI: 10.1016/S1474-4422(19)30394-1

25. Mackenzie I. R. A., Rademakers R. The molecular genetics and neuropathology of frontotemporal lobar degeneration: Recent developments. Neurogenetics. 2007; Nov; 8 (4): 237–48. DOI: 10.1007/s10048-007-0102-4

26. Arai T., Hasegawa M., Akiyama H., Ikeda K., Nonaka T., Mori H., et al. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochemical and Biophysical Research Communications. 2006; Dec 22; 351 (3): 602–611.

27. Neumann M., Sampathu D. M., Kwong L. K., Truax A. C., Micsenyi M. C., Chou T. T., et al. Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis. Science. 2006; 314 (5796): 130–133. DOI: 10.1126/science.1134108

28. Mackenzie I. R., Neumann M. Reappraisal of TDP-43 pathology in FTLD-U subtypes. Acta Neuropathologica. 2017; Jul 1; 134 (1): 79–96.

29. Sieben A., Van Langenhove T., Engelborghs S., Martin J. J., Boon P., Cras P., et al. The genetics and neuropathology of frontotemporal lobar degeneration. Acta Neuropathologica. 2012; 124 (3): 353–372. DOI: 10.1007/s00401-012-1029-x

30. Hutton M., Lendon C. L., Rizzu P., Baker M., Froelich S., Houlden H., et al. Association of missense and 5-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998; Jun 18; 393 (6686): 702–705. DOI: 10.1038/31508

31. Ingelson M., Fabre S. F., Lilius L., Andersen C., Viitanen M., Almkvist O., et al. Increased risk for frontotemporal dementia through interaction between tau polymorphisms and apolipoprotein E epsilon4. Neuroreport. 2001; Apr 17; 12 (5): 905–909. DOI: 10.1097/00001756-200104170-00008

32. Kaivorinne A. L., Krüger J., Kuivaniemi K., Tuominen H., Moilanen V., Majamaa K., et al. Role of MAPT mutations and haplotype in frontotemporal lobar degeneration in Northern Finland. BMC Neurology. 2008; Dec 17; 8:48. DOI: 10.1186/1471-2377-8-48

33. Rizzu P., Van Swieten J. C., Joosse M., Hasegawa M., Stevens M., Tibben A., et al. High Prevalence of Mutations in the Microtubule-Associated Protein Tau in a Population Study of Frontotemporal Dementia in the Netherlands. The American Journal of Human Genetics. 1999; Feb; 64 (2): 414–421. DOI: 10.1086/302256

34. Greaves C. V., Rohrer J. D. An update on genetic frontotemporal dementia. Journal of Neurology. 2019; Aug; 266 (8): 2075–2086. DOI: 10.1007/s00415-019-09363-4

35. Baker M., Mackenzie I. R., Pickering-Brown S. M., Gass J., Rademakers R., Lindholm C., et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006; Aug 24; 442 (7105): 916–919. DOI: 10.1038/nature05016

36. Cruts M., Gijselinck I., Van Der Zee J., Engelborghs S., Wils H., Pirici D., et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature. 2006; Aug 24; 442 (7105): 920–924. DOI: 10.1038/nature05017

37. Van Der Zee J., Pirici D., Van Langenhove T., Engelborghs S., Vandenberghe R., Hoffmann M., et al. Clinical heterogeneity in 3 unrelated families linked to VCP p.Arg159His. 2009; Aug 25; 73 (8): 626–632. DOI: 10.1212/WNL.0b013e3181b389d9

38. Gass J., Cannon A., Mackenzie I. R., Boeve B., Baker M., Adamson J., et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Human Molecular Genetics. 2006; Oct 15; 15 (20): 2988–3001. DOI: 10.1093/hmg/ddl241

39. Renton A. E., Majounie E., Waite A., Simón-Sánchez J., Rollinson S., Gibbs J. R., et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011; Oct 20; 72 (2): 257–268. DOI: 10.1016/j.neuron.2011.09.010

40. Van Mossevelde S., Engelborghs S., Van Der Zee J., Van Broeckhoven C. Genotype-phenotype links in frontotemporal lobar degeneration. Nature Reviews Neurology. 2018; Jun; 14 (6): 363–378. DOI: 10.1038/s41582-018-0009-8.

41. Van Der Ende E. L., Jackson J. L., White A., Seelaar H., Van Blitterswijk M., Van Swieten J. C. Unravelling the clinical spectrum and the role of repeat length in C9ORF72 repeat expansions. Journal of Neurology, Neurosurgery and Psychiatry. 2021; May; 92 (5): 502–509. DOI: 10.1136/jnnp-2020-325377

42. Marogianni C., Rikos D., Provatas A., Dadouli K., Ntellas P., Tsitsi P., et al. The role of C9orf72 in neurodegenerative disorders: a systematic review, an updated meta-analysis, and the creation of an online database. Neurobiology of Aging. 2019; Dec 1; 84: 238.e25-238.e34. DOI: 10.1016/j.neurobiolaging.2019.04.012.

43. Majounie E., Renton A. E., Mok K., Dopper E. G. P, Waite A., Rollinson S., et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurology. 2012; Apr; 11 (4): 323–330. DOI: 10.1016/S1474-4422(12)70043-1

44. Watts G. D. J., Wymer J., Kovach M. J., Mehta S. G., Mumm S., Darvish D., et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nature Genetics. 2004; Apr; 36 (4): 377–381. DOI: 10.1038/ng1332

45. Kimonis V. E., Fulchiero E., Vesa J., Watts G. VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: Review of a unique disorder. Biochimica et Biophysica Acta. 2008; Dec; 1782 (12): 744–748. DOI: 10.1016/j.bbadis.2008.09.003

46. Baba Y., Baker M. C., Le Ber I., Brice A., Maeck L., Kohlhase J., et al. Clinical and genetic features of families with frontotemporal dementia and parkinsonism linked to chromosome 17 with a P301S tau mutation. Journal of Neural Transmission. 2007; Jul; 114 (7): 947–950. DOI: 10.1007/s00702-007-0632-9

47. Kouri N., Carlomagno Y., Baker M., Liesinger A. M., Caselli R. J., Wszolek Z. K., et al. Novel mutation in MAPT exon 13 (p.N410H) causes corticobasal degeneration. Acta Neuropathologica. 2014; Feb; 127 (2): 271–282. DOI: 10.1007/s00401-013-1193-7

48. Rohrer J. D., Guerreiro M. R., Vandrovcova J., Uphill J., Reiman B. D., Beck J., et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009; Nov 3; 73 (18): 1451–1456. DOI: 10.1212/WNL.0b013e3181bf997a.

49. Munoz D. G., Ros R., Fatas M., Bermejo F., De Yebenes J. G. Progressive nonfluent aphasia associated with a new mutation V363I in tau gene. American Journal of Alzheimer's Disease and other Dementias. Weston Medical Publishing; 2007; Aug-Sep; 22 (4): 294–299. DOI: 10.1177/1533317507302320

50. Villa C., Ghezzi L., Pietroboni A. M., Fenoglio C., Cortini F., Serpente M., et al. A Novel MAPT Mutation Associated with the Clinical Phenotype of Progressive Nonfluent Aphasia. Journal of Alzheimer's Disease. 2011; Jan 1; 26 (1): 19–26. DOI: 10.3233/JAD-2011-102124

51. Bessi V., Bagnoli S., Nacmias B., Tedde A., Sorbi S., Bracco L. Semantic dementia associated with mutation V363I in the tau gene. Journal of the Neurological Sciences. 2010; Sep 15; 296 (1–2): 112–114. DOI: 10.1016/j.jns.2010.06.007

52. Van Herpen E., Rosso S. M., Serverijnen L. A., Yoshida H., Breedveld G., Van De Graaf R., et al. Variable Phenotypic Expression and Extensive Tau Pathology in Two Families with the Novel tau Mutation L315R. Annals of Neurology. 2003; Nov; 54 (5): 573–581. DOI: 10.1002/1531-8249(199910)46:4<617::aid-ana10>3.0.co;2-i

53. Rademakers R., Baker M., Gass J., Adamson J., Huey E. D., Momeni P., et al. Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C→T (Arg493X) mutation: an international initiative. Lancet Neurology. 2007; Oct; 6 (10): 857–868. DOI: 10.1016/S1474-4422(07)70221-1

54. Snowden J. S., Pickering-Brown S. M., Mackenzie I. R., Richardson A. M. T., Varma A., Neary D., et al. Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. Brain. 2006; 129 (11): 3091–3102. DOI: 10.1093/brain/awl267

55. Rohrer J. D., Isaacs A. M., Mizlienska S., Mead S., Lashley T., Wray S., et al. C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. Lancet Neurology. 2015; Mar; 14 (3): 291–301. DOI: 10.1016/S1474-4422(14)70233-9

56. Baizabal-Carvallo J. F., Jankovic J. Parkinsonism, movement disorders and genetics in frontotemporal dementia. Nature Reviews Neurology. 2016; Mar; 12 (3): 175–185. DOI: 10.1038/nrneurol.2016.14.

57. Ida C. M., Butz M. L., Lundquist P. A., Dawson D. B. C9orf72 Repeat Expansion Frequency among Patients with Huntington Disease Genetic Testing. Neurodegenerative Diseases. 2018; 18 (5–6): 239–253. DOI: 10.1159/000492499

58. Gijselinck I., Van Mossevelde S., Van Der Zee J., Sieben A., Engelborghs S., De Bleecker J., et al. The *C9orf72* repeat size correlates with onset age of disease, DNA methylation and transcriptional downregulation of the promoter. Molecular Psychiatry. 2016; Aug 1; 21 (8): 1112–1124. DOI: 10.1038/mp.2015.159

59. Van Mossevelde S., Van Der Zee J., Gijselinck I., Sleegers K., De Bleecker J., Sieben A., et al. Clinical evidence of disease anticipation in families segregating a *C9orf72* repeat expansion. JAMA Neurology. 2017; Apr 1; 74 (4): 445–452. DOI: 10.1001/jamaneurol.2016.4847

60. Van Mossevelde S., Engelborghs S., Van der Zee J., Van Broeckhoven C. Genotype–phenotype links in frontotemporal lobar degeneration. Nature Reviews Neurology. 2018; Jun; 14 (6): 363–378. DOI: 10.1038/s41582-018-0009-8