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REVIEWS

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# Genetic Diversity in Frontotemporal Dementia

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**Abstract**—Frontotemporal dementia is a progressive neurodegenerative disorder with high clinical, genetic, and pathomorphological diversity It is the third most common cause of dementia in all ages and the most common cause of early onset dementia (below 65). Despite its multifactorial nature, up to 40% of patients have a family history where the autosomal dominant inheritance type is seen in a quarter of cases. In this review, we describe key genes whose mutations can result in the development of frontotemporal dementia, the possible pathogenic mechanisms of the degenerative process, and provide information on the clinical features of the disease for different genetic variants. Special emphasis is placed on the frontotemporal dementia phenotype that is associated with amyotrophic lateral sclerosis.

*Keywords:* frontotemporal dementia, amyotrophic lateral sclerosis, genetic counseling, DNA diagnostics

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## INTRODUCTION

The term frontotemporal dementia (FTD) is used to describe a group of neurodegenerative diseases, in which a steadily progressing decline of executive functions, behavior, and/or speech is observed [1]. FTD is considered the third most common cause of dementia after Alzheimer's disease (AD) and Lewy body dementia [1].

The term FTD is the designation of a clinical syndrome, associated with a certain pathomorphological process, which is called frontotemporal lobar degeneration (FTLD). FTD can be manifested through several clinical syndromes, such as behavioral variant (bvFTD), semantic variant primary progressive aphasia (svPPA), agrammatic variant primary progressive aphasia (avPPA), FTD associated with amyotrophic lateral sclerosis (FTD-ALS), and FTD with clinical manifestations of atypical parkinsonism syndromes (progressive supranuclear palsy—PSP, and corticobasal syndrome—CBS). The first three variants are diagnosed according to clinical criteria. Signs of motor neuron lesion or atypical parkinsonism may be present with any of these variants. Furthermore, a logopenic variant is included in the diagnostic criteria for svPPA, however at present this phenotype is considered AD-associated.

In FTD pathogenesis genetics plays a large role—up to 40% of patients have family history of diagnosed dementia in at least one family member, and the autosomal dominant inheritance type is present in 13.4% of all cases [2]. More than 20 genes have been identified in which mutations may be associated with FTD (Table 1). Most often, pathogenic mutations occur in three genes—*MAPT*, *C9orf72*, and *GRN*. Mutations in other genes occur at a lower frequency. However, in most cases, FTD is a sporadic disease, appearing as a result of interaction of many genetic and environmental factors [3].

The presence of abnormal aggregates of three proteins in neuronal and glial cells is typical of the histology of FTD. In most cases, pathological accumulation of tau (up to 45%) or TDP-43 (50%) proteins is found; in a small number of cases (about 5–10%), FUS protein inclusions are observed [4, 5]. The abnormal aggregation of tau is described both in patients with sporadic cases of bvFTD, CBS, avPPA and PSP, and in families where the disease is determined by the *MAPT* gene mutation [6–9]. However, as a rule, there is no aggregation of tau in svPPA. Inclusions of TDP-43 occur in most tau-negative patients. TDP-43 pathology is present in svPPA, FTD-ALS, and bvFTD, and also with mutations in the genes *C9orf72*, *GRN*, *VCP*, etc. It should be noted, that such histology rarely occurs with mutations of the *TARDBP* gene that encodes TDP-43 [7–9]. The FUS-pathology is associated with earlier FTD onset, dominant neuropsychic symptoms, and faster disease progression. FUS-pathology occurs predominantly in patients with sporadic FTD, yet it is also possible with *FUS* gene mutations [10].

Thus, at present no accurate correlations between clinical phenotypes, histology, and genetic variants of

*Abbreviations*: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; bvFTD, behavioral variant FTD; PPA, primary progressive aphasia; svPPA, semantic variant PPA; avPPA, agrammatic variant PPA; FTD-ALS, FTD associated with amyotrophic lateral sclerosis (ALS); FTLD, frontotemporal lobar degeneration.

**Table 1.** Main genes pathologically associated with frontotemporal dementia

| Gene | Protein function |
|---|---|
| *MAPT* | Microtubule assembly and stabilization, cytoskeleton organization |
| ***GRN*** | Growth factor (regulation of early embryogenesis, tissue repair, and inflammation processes in adults) |
| ***C9orf72*** | Nucleocytoplasmic transport, autophagy, intercellular transport |
| *CHMP2B* | Autophagy, participation in protein transport and degradation |
| *CP-1* | Autophagy, participation in protein transport and degradation |
| *SQSTM1* | Autophagy, protein degradation |
| *CHCHD10* | Mitochondrial protein |
| *TBK1* | Autophagy, participation in protein transport and degradation |
| *TARDBP* | Transcription factor |
| *FUS* | Transcription factor |
| *UBQLN2* | Autophagy, participation in protein transport and degradation |
| *TUBA4A* | Cytoskeleton organization |

The most significant genes are indicated in bold.

FTD are known, which significantly complicates diagnostics even in familial cases of the disease. Moreover the absence of correlations complicates the analysis of the pathogenic course in family and sporadic FTD cases, which hinders the development of disease modifying therapy. In this review, we considered the main genes, whose mutations may be important genetic factors in FTD development.

## THE *MAPT* GENE

In 1994, it was shown for the first time that autosomal dominant cases of FTD with parkinsonism can be associated with the 17q21.2 locus [11, 12], these cases were subsequently called FTDP-17. The gene localized in this area was found several years later and called *MAPT* (*Microtubule Associated Protein Tau; OMIM *157140*) [13]. The *MAPT* gene consists of 16 exons and encodes the tau protein, which participates in the assembly and stabilization of microtubules and the organization of neuronal cytoskeleton [13]. The MAPT mRNA is subjected to alternative splicing, resulting in six isoforms of the protein, each of which is involved in maintaining microtubule structure. An excess of tau results in the formation of protein aggregates, which fill up the cell and cause toxicity. At the C-terminus of tau, four repeating domains, which mediate the interaction with microtubules, are localized. These domains are encoded by exons 9–12, in which most of the pathogenic mutations are detected. In addition, as a result of alternative splicing of exon 10, isoforms, containing three (3R) or four (4R) repeats from a 31 aminoacidic residue, appear [13] (Fig. 1).

The pathology in all mutations of the *MAPT* gene is characterized by deposits of insoluble hyperphosphorylated tau protein aggregates in neurons and glial cells in the brain cortex and other areas [14]. More than 40 pathogenic mutations in *MAPT* have been described, each of which is classified according to its position, influence on transcription, and tauopathy type. The mutation frequency in the *MAPT* gene in FTD is 6–11%. FTD with mutations in this gene, which are characterized by high penetrance, has autosomal dominant inheritance and develops faster than FTD with mutations in other genes [15, 16].

The pathological effect of each mutation depends on the type and localization of the genetic defect and is manifested by disruption of the normal functioning of tau protein, for example, destabilization of microtubule and tubulin binding. Some mutations result in an increase in cytoplasmic free protein that maintains tau aggregation, while other mutations change tau phosphorylation, which disrupts microtubule stabilization [17]. It has been shown that mutations in the donor splicing site, localized after exon 10, increase the probability of the inclusion of exon 10 of the *MAPT* gene into mRNA via the destabilization of the hairpin structure, which camouflages the splicing site. This results in an increase in the production of the 4R tau protein isoform. Mutation in the acceptor splicing site, following exon 10, also increases inclusion of this exon into the mRNA [18]. Other mutations, affecting the alternative splicing process, lead to a shift in the tau isoform ratio (3R/4R). Most missense variants, like p.P301L, worsen the ability of tau protein to bind microtubules and maintain the structure [19]. In addition, it has been shown in vitro that some mutations localized in protein-encoding gene areas, accelerate tau protein aggregation [20]. In 2009, a 17.3 kbp heterozygous deletion responsible for the exclusion of exons 6–9 from the *MAPT* mRNA gene, was found in an FTD patient [21]. This deletion resulted in loss of the first domain, responsible for connection with microtubules, and decreased the ability of tau to bind with microtubules. Duplication of a site including *CRHR1*, *MAPT*, and *STH* genes has also been also

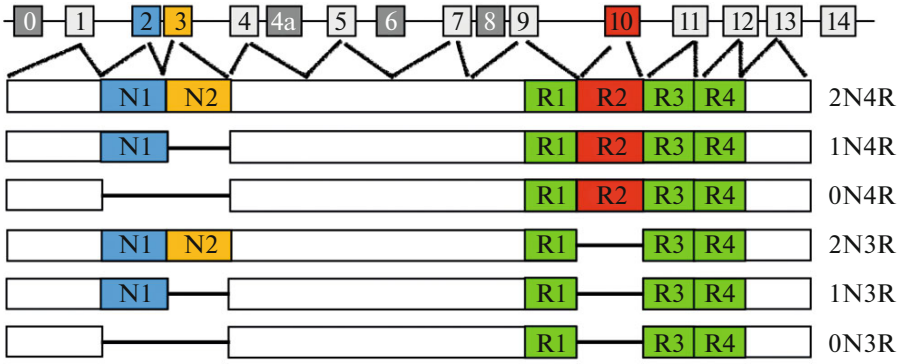


**Fig. 1.** The *MAPT* gene and tau protein isoforms, formed as a result of alternative splicing in the human brain. The *MAPT* gene consists of 16 exons (the top of the figure). Exons E1, E4, E5, E7, E9, E11, E12, and E13 are constitutive (light-grey squares), others are subjected to the alternative splicing. Exons E0 and E1 encode the 5'-untranslated region of MAPT mRNA, and the E14 exon encodes the part of the 3'-untranslated region. The E0 exon is part of the promoter region, it is transcribed but not translated. The initiation ATG codon is localized in the E1 exon. The exons E4a, E6, and E8 are transcribed only in peripheral tissues. Six isoforms of human brain tau protein are formed as a result of the alternative splicing of exons E2 (N1, blue), E3 (N2, yellow), and E10 (R2, red). These isoforms differ from each other by the presence of 0, 1, or 2 near-N-terminal insertions (0N, 1N, and 2N correspondingly), and also the R2 repeat (red), which result in the appearance of three of four C-terminal repeating domains (3R or 4R, correspondingly) in different tau subtypes.

described in a patient with clinical presentation of behavioral and amnestic (memory) disorders [22].

Atrophy of the frontotemporal lobes and basal nuclei, and the presence of tau-positive inclusions are detected in autopsy in cases of *MAPT* gene mutation [23]. The clinical presentation in carriers of mutations in the *MAPT* gene most often consists of a combination of FTD with the parkinsonism syndrome with an average age of onset of about 50. Behavioral disorders in *MAPT* gene mutation carriers most often include disinhibition, stereotypies, and obsessive disorders. It is noteworthy, that apathy is less common in these patients, than in carriers of mutations in the *GRN* and *C9orf72* genes. The semantic disorders develop at later stages of the disease. Despite the variable clinical presentation, atrophy of the temporal lobes is observed in practically all *MAPT* gene mutation carriers, mostly on the right.

## THE *GRN* GENE

The detection of mutation in the *MAPT* gene did not explain all familial cases of FTD with autosomal dominant inheritance (in combination with parkinsonism or without); in addition, in some patients without mutations in the *MAPT* gene, a genetic association with the same chr17q21 chromosomal region is revealed [24, 25]. The pathomorphological picture in these cases was completely different, as shown by tau-negative and ubiquitin-positive staining. As a result, in 2006, the *GRN* (*Granulin precursor*; *OMIM *138945*) gene localized at 6.2 Mb from the *MAPT* locus, was identified. The insertion of 4 bp of CTGC between nucleotides 90 and 71, resulting in a frameshift and premature termination of the translation of progranulin (C31LfsX34) became the first mutation found in the *GRN* gene [23]. A mutation in the area of the intron following the first noncoding exon of *GRN* (IVS1+5G>C) was found in a parallel study. This mutation results in the excision of intron 0 during splicing, retention of mRNA in the nucleus, and its subsequent degradation [25].

Later, mutations in *GRN* gene were found in 5–20% of familial cases with autosomal dominant inheritance and in 15% of sporadic cases of FTD [3]. *GRN* encodes progranulin—a glycoprotein 88 kDa in size, which is expressed in neurons and microglial cells [26]. In early life, *GRN* is expressed at a low level, and expression increases during maturation. Progranulin is a secreted growth factor of 593 aminoacidic residues, consisting of 7.5 cysteine enriched domains, in the following order: P–G–F–B–A–C–D–E, where A–G are full repeats, and P is a half-repeat, known as paragranulin [27]. Some proteases are thought to be able to split progranulin into subunits 6 kDa in size, the so-called granulins. Granulins belong to a family of proteins, which have many biological functions (development, wound repair, inflammation), which are realized via activation of the cell cycle and cell motility controlling signal cascade [28].

To date, more than 70 mutations in the *GRN* gene in FTD have been described. The most well known pathogenic mutations (splicing mutations, nonsense mutations) result in premature stop sign formation. As a result, mRNA with impaired structure is subjected to degradation via the nonsense-mediated mechanism, resulting in haploinsufficiency [28]. Rarer partial and complete deletions of the whole gene have been described [29]. The penetrance of the *GRN* mutation is age-dependent: by 60, only half of the mutation carriers develop symptoms of the disease; by 70, this index increases to up to 90%. The manifestation age of

the disease significantly varies even between members of same family (from 47 to 79) [30].

In a pathomorphological study of FTD associated with mutation in the *GRN* gene, ubiquitin-positive tau-negative inclusions that are different from the tau-positive inclusions associated with mutations in the *MAPT* gene, were detected. The truncated and hyperphosphorylated isoforms of TDP-43 (transactive response (TAR), a DNA-binding protein of 43 kDa) are the main component of ubiquitin-containing inclusions. These isoforms are present in familial FTD cases associated with mutation in the *GRN* gene, in sporadic FTD cases, and in some ALS cases [31]. It is of note that mutations in *GRN* in the homozygous state are associated with another disease—the adult form of neuronal ceroid lipofuscinosis [32, 33], while heterozygous mutations result in the occurrence of FTD-typical neuronal and glial inclusions that are immune-positive for TDP-43 [32].

Mutations in the *GRN* gene are clinically associated with various phenotypes, yet PPA occurs most often [34]. About 40% of patients have parkinsonism in the clinical presentation, and difficulties with episodic memory are often observed, which in some cases result in misdiagnosis of AD [35]. In rare cases there is an association of genetic FTD variants with mental disorders. For example, two cases of FTD with the Thr272fs mutation in the *GRN* gene with premorbid bipolar disorder in the patient's medical history have been described [36].

Evaluation of the blood plasma progranulin level, which decreases in *GRN* mutation carriers even without symptoms of the diseases, makes its own contribution to correct diagnostics [37, 38].

## THE *C9orf72* GENE

About 10 years ago, in families, compromised by both FTD and ALS, an association of these diseases with the 9q21-22 locus was detected. The first data on the gene localization of in this locus were obtained in a study of FTD-ALS-associated families with autosomal dominant inheritance [39]. In 2011, the *C9orf72* (*Chromosome 9 open reading frame 72; OMIM *614260*) gene was identified in the 9q21-22 locus by two international research groups [40, 41]. The mutation is an expansion of hexanucleotide repeats (GGGGCC) in the first intron, localized between the 1a and 1b exons of *C9orf72*. In addition, the expansion of the repeat may be situated either in the intron, or in the promoter area, depending on which of transcription start site is used [40]. Normally, the number of repeats varies from 2 to 20. In FTD and ALS patients, the expansion size usually consists of from 100 to several thousand copies of the repeat. The minimal size of the expansion considered risk factor for the development of the disease is not yet established, perhaps because of somatic mosaicism. It is known that the expansion size varies in different tissues even within one human, which complicates the precise detection of gene-phenotype correlations [42].

The repeat expansion in the *C9orf72* gene is considered the most frequent cause of FTD (regardless of the association with ALS) in the world. It is especially high in the population of Finland, which is perhaps determined by the founder effect, while in the Asian cohort of patients, occurrence of the expansion is lower [43]. The clinical phenotype of this form of molecular neurodegeneration is very diverse, as well as the manifestation age and the duration of the disease. According to various data, the manifestation age varies between 27 and 83, and the disease duration—between 1 and 22 years. The most frequent clinical phenotypes of the disease are FTD, ALS, or the combination of these syndromes. As was already mentioned, in families with the FTD-ALS clinical phenotype, the expansion in the *C9orf72* gene occurs very often, in more than 50% of cases [44]. Clinical FTD is represented mainly in behavioral disorders, while speech disorders occur more rarely. Besides classical behavioral disorders including apathy, disinhibition, asocial behavior, and empathy loss, in carriers of the repeat expansion in the *C9orf72* gene, a high frequency of hallucinations, psychoses, and illusions is typical [45], which can lead to an initial diagnosis of schizophrenia and bipolar disorder [46, 47]. In some cases, episodic memory difficulties in the beginning of the disease are present, which can result in an initial diagnosis of AD [44, 48]. In carriers of the hexanucleotide expansion repeat in the *C9orf72* gene early parkinsonism syndrome development, which is very rare in carriers of mutations in the *MAPT* and *GRN* genes, is observed [45].

In pathomorphological study in various areas of brain tissue, inclusions, containing TDP-43 protein, are detected. Furthermore, ubiquitin- and p62-positive neuronal inclusions are described in the cerebellar granular layer, hippocampal pyramidal neurons, and other anatomical areas. These inclusions are formed by DPR dipeptides (dipeptide repeat protein), which are translated form GGGGCC-copy areas via repeat-associated non-ATG translation (RAN). Five types of DPR dipeptides are distinguished , three translated from the sense RNA—poly-Gly-Pro (GP), poly-Gly-Ala (GA), and poly-Glu-Arg (GR), and three from the antisense RNA—poly-Pro-Ala (PA), poly-Pro-Arg (PR), and poly-GP from different reading frames (Fig. 2) [49, 50].

A high toxicity of arginine-containing dipeptides (poly-GR and poly-PR), which may also cause the formation of nuclear and cytoplasmic inclusions in neurons, has been shown in transgenic *Drosophila* [51, 52]. On a cell and primary neuron culture, it has been shown that poly-GA overexpression results in the formation of p62-positive inclusions and neurotoxicity, typical of ubiquitin-proteasome system disorders [53]. However, the clinical significance of dipeptides and

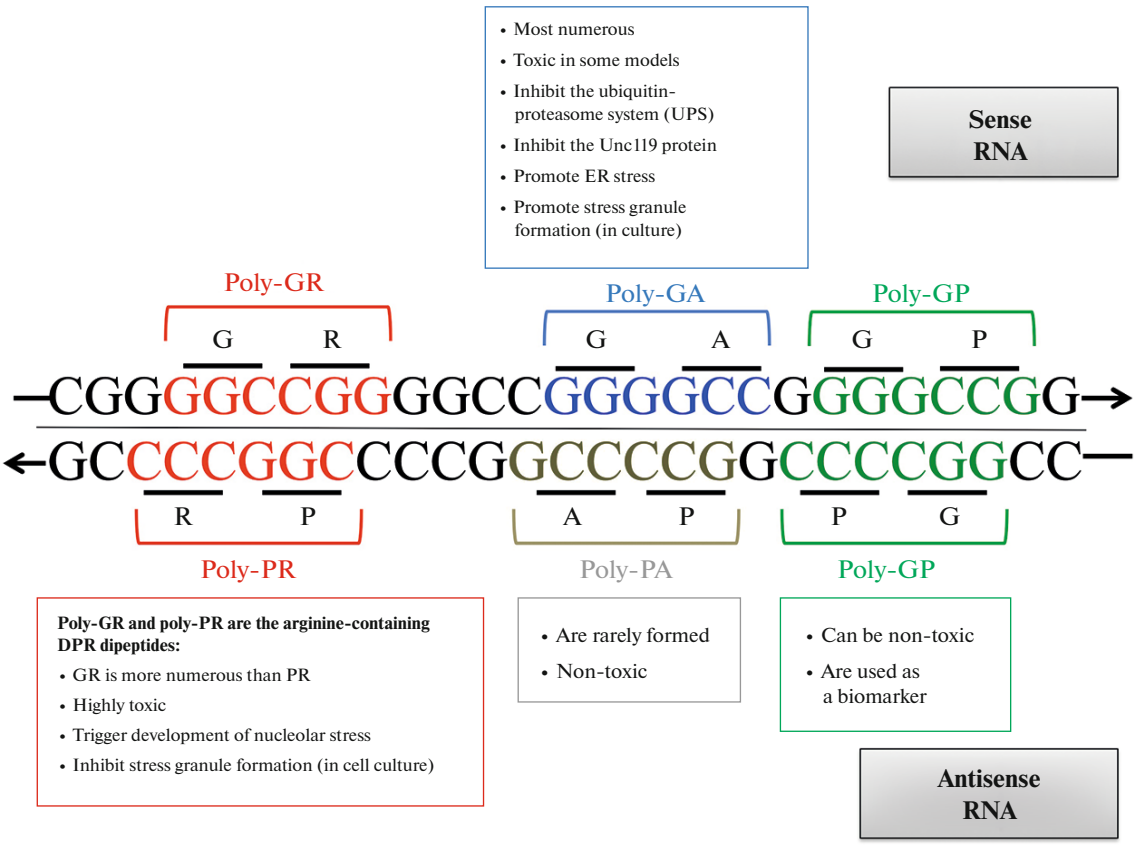


**Fig. 2.** Types of DPR dipeptides. The non-ATG translation of RNA repeats results in the formation of five different DPR dipeptides depending on the reading frame, three of which are synthesized from the sense chain: poly-GR, poly-GA, and poly-GP. Three others are formed from the antisense chain: poly-PR, poly-PA, and again poly-GP. Differences in the effects of the listed dipeptides are shown in diverse model systems.

their changes during the course of disease progression is not yet understood. In 2017 Lehmer et al. developed an immunological method for poly-GP dipeptide detection in cerebrospinal fluid in order to find patients with hexanucleotide expansion in the *C9orf72* gene [54]. The poly-GP dipeptide level found in the cerebrospinal fluid of asymptomatic expansion carriers (compared to healthy donors), is similar to the level in symptomatic carriers, and is potentially applicable as a diagnostic biomarker in addition to genetic screening [54].

Normally, the functions of *C9orf72* are related to nucleocytoplasmic transport, autophagy, intercellular transport, and protein aggregation. In 2013, it was shown that RNA, consisting of repeating hexanucleotides (GGGGCC)n, form extremely stable G-quadruplex structures, which can theoretically influence promoter activity, genetic stability, splicing, translation, and RNA localization in the axon [56]. In several studies carried out on cells and tissues obtained from patients, it was shown that these structures are able to sequester RNA-binding proteins, disrupting the nuclear transport system [51]. However, the mechanism linking the formation of focuses of RNA and sequestered proteins with the neurodegenerative process is not well studied. Besides the formation of RNA focuses and DPR dipeptides, another pathological mechanism of *C9orf72* gene expression suppression via methylation has been suggested [57].

## THE *CHMP2B* GENE

In several families with FTD-compromised family history, mutations are described in the *CHMP2B* (*charged multivesicular body protein 2B, OMIM *609512*) gene, which encodes one of the components of the ESCRT III (Endosomal Sorting Complexes Required for Transport) heterodimer complex, that is involved in endosome transport [58]. The protein product of the *CHMP2B* gene participates in sorting and transport of surface receptors or proteins into intraluminal vesicles for degradation in lysosomes, and also binds the Vps4 (Vacuolar protein sorting) protein, responsible for the dissociation of ESCRT components [59].

The first mutation in the *CHMP2B* gene was identified in a big family from Denmark [60]. All the mutations described (missense mutations and truncation

mutations) have a common mechanism of action: deletion of the C-terminal protein area with loss of the Vsp4 binding domain [59]. This results in the accumulation of mutant CHMP2B on endosome membranes and prevents the involvement of other proteins required for the fusion of endosome and lysosome. This phenomenon results in the disruption of late endosome transport and promotes the development of neurodegenerative process in FTD [60]. Extended abnormal endosome structures are observed in the brain tissues of such patients [61]. Histological study revealed ubiquitin- and p62-positive and TDP-43-negative neuronal cytoplasmic inclusions in patients with a mutation in the *CHMP2B* gene [62]. Behavioral and cognitive disorders, associated with extrapyramidal and pyramidal symptoms, are the main features of clinical presentation in such patients.

## THE *VCP-1* AND *SQSTM1* GENES

Mutations in the *VCP (valosin containing protein; OMIM *601023)* gene were described for the first time in patients with autosomal dominant type inheritance and a clinical triad, including IBMPFD—inclusion body myopathy with Paget's disease of the bone and frontotemporal dementia [63]. Myopathy is the most frequent clinical symptom, typical for 90% of patients, while FTD is observed in about 33% and usually develops many years after the manifestation of the muscle impairment symptoms. Considering the peculiarity of the clinical picture, *VCP-1* involvement in FTD is not indisputable, however, the pathomorphological confirmation suggests a possible connection of this gene with FTD [64, 65]. In carriers of the mutation in the *VCP-1* gene, TDP-43 and p62-positive inclusions are found in brain neuronal nuclei [66].

*VCP-1* encodes a protein of 806 aminoacidic residues. VCP-1 regulates many processes such as ubiquitin-dependent protein quality control and the creation of labels for degradation, and the coordination of protein aggregate removal via multivesicular body formation [67].

The *SQSTM1 (sequestosome 1 gene; OMIM *601530)* is another gene involved in protein degradation and FTD pathogenesis. This gene encodes the p62 protein, which serves as a link between ubiquitinated proteins and autophagy receptor or proteasomal degradation pathways [68]. Mutations in the *SQSTM1* gene, described initially in Paget's disease, are the cause of about 30% of family cases of this disease [69].

## THE *CHCHD10* GENE

The *CHCHD10 (coiled-coil-helix-coiled-coil-helix domain containing 10; OMIM *615903)* gene encodes a mitochondrial protein that maintains the cristae structure in the intermembrane space. Massive parallel sequencing methods made it possible to identify the first pathogenic p.S59L mutation in this gene in a family with late manifestation of motor neuron disease, FTD, cerebellar ataxia, and mitochondrial myopathy [70]. In the genetic studies followed, other potentially pathogenic mutations were identified in FTD and ALS patients with a frequency of 1–3% [71]. A new nonsense mutation (p.Gln108*) was described relatively recently in a patient with atypical clinical FTD presentation and pathology confirmed Parkinson's disease, [72].

## THE *TBK1* GENE

In 2015, mutations in the *TBK1 (TANK binding kinase 1; OMIM *604834)* gene were detected in a cohort of patients with sporadic ALS in a case-control study using whole-genome sequencing [73]. Afterwards, mutations in the *TBK1* gene, resulting in loss of function, were detected in FTD-ALS-compromised families and in isolated FTD cases [73]. Most of the identified mutations result in the loss of function of the gene as a result of up to a 50% decrease in expression. Missense mutations impair the binding of TBK1 with optineurin (OPTN). Along with VCP and p62, TBK1 participates in protein degradation and autophagy. It phosphorylates p62 or OPTN, the additional participants in autophagy. In 2015, in a group of *C9orf72-* and *GRN*-negative patients with FTD and pathology confirmed TDP-43 protein aggregation (the most common pathomorphological variant among all FTD cases—up to 50%) were revealed five cases (4.8%) with nucleotide sequence variants in the *OPTN* and *TBK1* genes, which were estimated as highly pathogenic. These data confirm that both genes are involved in the pathogenesis of this FTD variant [74].

## THE *TARDBP* GENE

The *TARDBP (TAR DNA-binding protein; OMIM *605078)* gene encodes the nuclear TDP-43 protein, capable of forming heterogeneous nuclear ribonucleoprotein complexes (hnRNP), performing various functions associated with RNA regulation, such as the control of splicing, stability, and mRNA transport. The suggestion about the association between FTD and ALS development and disorders in the TDP-43 protein is based on the fact that TDP-43 regulates axon growth in in vivo and in vitro models, i.e. changes in TDP-43 functioning affects the ability of neurons to form and maintain the correct axon structure [75].

## THE *FUS* GENE

The *FUS (Fused in sarcoma; OMIM *137070)* gene encodes a highly conservative protein, expressed in various tissues. The FUS protein is one of the hnRNP components, participating in RNA transport and splicing, and in DNA/RNA metabolism [67]. Mutations in the *FUS* gene were identified in 2009 in 3% of ALS family cases. Most of the mutations are localized

in the site encoding the C-terminal region of the FUS protein, especially in the nuclear localization region, which results in the impairment of the tranportin-mediated nuclear transport of FUS [76]. Mutations in this gene are associated with the family form of ALS, which may be both associated and not associated with FTD. In carriers of mutations in the *FUS* gene, abnormal cytoplasmic FUS-positive neuronal and glial inclusions are found. However, in several cases of ALS with FUS-positive inclusions, no mutations in *FUS* were found. Some FTD cases with a mutation in this gene were characterized by the atrophy of frontal and temporal lobes, as well as atrophy of the striatum regions.

## THE *UBQLN2* GENE

The *UBQLN2 (ubiquilin 2; OMIM *300264)* gene is related to a rare X-linked family form of ALS and FTD-ALS [77]. Mutations in the UBQLN2 protein are usually located in a highly conservative domain enriched by proline residues and containing PXXP repeats, which participates in the ubiquitin-proteasomal misfolded protein degradation and autophagy.

## THE *TUBA4A* GENE

The *TUBA4A (Tubulin, alpha-4a; OMIM *191110)* gene encodes one of eight human α-tubulins, which is polymerized with β-tubulin and forms neuronal cytoskeleton. Mutations in the *TUBA4A* gene are mainly associated with ALS, although cognitive disorders whose degree of expression varies from moderate to FTD are described in some patients. To date, in family or sporadic ALS cases, some of which are associated with FTD, 10 missense and one nonsense mutation, and one mutation in the splicing donor site, have been described [72].

## THE MODIFIER GENES

Beside the genes described, in which mutations mainly occur in family cases with autosomal dominant inheritance, other genes, whose mutations might be the risk factors for the development of the disease, have been found. The most important of them is the *TMEM106B (transmembrane protein 106b; *613413)* gene. In 2010, Van Deerlin at al. published results of a whole-genome association search in 515 patients with FTD and TDP-43 pathology, revealed by pathomorphological study. A possible locus in the 7p21 chromosome, containing the *TMEM106B* gene, was identified [78]. Three nucleotide polymorphisms (SNP)—rs102004, rs6966915 and rs1990622, associated with the decrease in *TMEM106B* expression, have been found. It is established, that in carriers of a mutation in the *GRN* gene, the SNP rs1990622 C-allele can act as protective towards FTD [79]. The protective effect of the *TMEM106B* gene variants in carriers of the hexanucleotide repeat expansion in the *C9orf72* gene has also been also detected [80, 81]. The *TMEM106B* gene encodes glycosylated membrane type 2 protein, localized in late endosomes and lysosomes, where it probably performs important functions. The overexpression of the TMEM106b protein in cell cultures causes disorders in vacuole formation and in processes of endolysosomal pathway [82].

The role of various SNPs in the main genes in which mutations result in FTD, the risk factors of this disease (for example, SNP rs5848 in the supposed site of microRNA binding in the 3'-untranslated region (3'UTR) of the *GRN* gene), are also studied. The role of this polymorphism still remains unclear, because its association is shown in the first cohort of patients studied with FTD-TDP-43 and was not found in the following studies [83]. At the 11th international conference on FTD in Sydney, 2018, a research group from The Mayo Clinic (US) presented data that the carriage of minor T-allele and homozygous states can result in granulin expression (to a lesser degree than in pathogenic mutations). These data may suggest that the decrease in progranulin level in FTD is possible not only in carriers of mutations in the *GRN* gene.

The conduction of a whole-genome association search made is possible to identify other loci: the HLA (human leukocyte antigen, or human tissue compatibility antigen) locus on the 6p21.3 chromosome and a locus on the 11q14 chromosome, containing the *RAB8 (RAS-associated protein; *606281)* and *CTSC (cathepsin C; *602365)* genes [84]. In the latter two genes, the connection between some SNPs of the RAB8/CTSC locus and a 50% decrease in the RAB8 level in the blood of patients was revealed. This may serve as a proof of the fact that the loss of function of RAB8, which participates in lysosome regulation and protein transport, plays a role in FTD development. The association with the HLA locus may indicate a connection between FTD pathogenesis and the immune system [84].

## CONCLUSION

Up to 40% of FTD patients have positive family history, and mutations in the three main genes (*GRN, MAPT, and C9orf72*) have been revealed in almost 60% of FTD cases. The conduction of DNA diagnostics should be discussed with all patients with compromised family history in such neurological diseases as FTD, AD, parkinsonism, ALS, myopathy with inclusions, or psychoses in adulthood with dominant inheritance. Despite the prevalence of sporadic forms, detailed research of genetic variants promotes better understanding of the molecular and cellular mechanisms of FTD. Further research of FTD pathogenesis can discover new potential therapeutic targets for the development of effective agents that can modify the course of the disease. As of today, there are no such agents, and treatment is aimed at symptomatic correction and the application of agents that had been earlier

suggested for AD. However, medicine that modifies the course of the disease, associated with mutations in the three main FTD genes, are under development and clinical testing [85]. Thus, the detection of the genetic cause of FTD is important not only for medico-genetic consulting for healthy members of compromised families, but may also be necessary for the personalized selection of agents, that modify the disease course both in manifested and preclinical stages.

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## COMPLIANCE WITH ETHICAL STANDARDS

This paper does not contain any studies involving humans or animals as subjects.

*Conflict of interests*. The authors declare no conflicts of interests.

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