

An Overview of the Genetic Causes of Frontotemporal Degeneration

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Abstract: Many neurodegenerative diseases (NDDs) have been thought to be caused mainly by conditions that were not controlled by genetic inheritance. Extensive research into these diseases has recently discovered that perhaps a majority of them have genetic inheritance components. Once thought to be a rare form of NDD, frontotemporal degeneration (FTD) is now considered to be the main cause of early onset NDD, and the information on genetic causes and inheritance has increased dramatically over the last 10 years. The main genes that have been found to be involved in frontotemporal degeneration, *MAPT*, *TARDBP*, *GRN C9orf72*, *VCP*, *FUS*, and *CHMP2B*, have also been found in related diseases such as Alzheimer's disease, Amyotrophic Lateral Sclerosis, and Parkinson's disease. This paper is intended as an updated review of the genetic causes of FTD. This information should aid physicians and scientists in understanding the current concepts, and encourage even more genetic testing so that a full knowledge of genetic inheritance in FTD will be soon be forthcoming.

Keywords: C9ORF72, CHMP2B, Frontotemporal degeneration, FUS, GRN, MAPT, Neurodegeneration, TARDBP, VCP.

INTRODUCTION

Frontotemporal Degeneration (FTD – also known as frontotemporal dementia; and frontotemporal lobar degeneration - FTLN) has, until recently, been considered to be a relatively uncommon disease, so little was known about the cause. In fact, there is no one single cause, either genetic or not, but many possibilities exist. Because there can be so many causes, the symptoms of the disease vary greatly among those affected. This leads to difficulties in diagnosis and potential treatment options. In order to effectively treat a disease, the medical community needs to know as much as possible about the causes.

FTD is a disease that is commonly caused by a mutation (or mutations), in one or more genes. The best way to develop treatment options is to do as many genetic studies as possible on FTD patients and their families. About 40-50% of FTD patients have a family history of related disorders [1, 2]. Unfortunately, funding for these genetic studies has not been readily available; in part because much of the funding comes from drug companies that are most interested in producing treatment options, and in part because these types of studies are time consuming and difficult. Therefore, the current data that is available on these diseases may still not accurately reflect how many people are affected as a result of inheritance (gene passed down from parents) vs. sporadic disease

(mutation has no known family inheritance). It has been estimated that having a family history of at least one first-degree relative with dementia is the reality for 25% of people 55 years of age and older [3]. Unfortunately, the accuracy in determining a family history of disease is complicated by the variation in disease presentation found in these disorders. This article gives an overview of the potential genetic causes (from what is currently known), and will discuss in a little more detail some of the leading genetic causes.

When we think about the dementia related diseases we tend to think in discrete diagnoses (Alzheimer's, FTD, etc.). In reality, all of these dementias overlap in symptoms and causes, etc., depending on the protein (and other processes) involved. In general, FTD and the diseases most closely linked to FTD (ALS, PD), have an age of onset of disease before 65; while AD patients generally have a later onset [4, 5]. There are some common genes that are associated with many types of dementias and related disorders, such as Parkinson's (PD) and ALS (amyotrophic lateral sclerosis – Lou Gehrig's disease). For example, there is a region on chromosome 17 that is a hot spot for diseases such as Alzheimer's disease (AD), FTD, and Parkinson's disease [1]. There are also multiple genes that may possibly be involved in one or more of these diseases. This is what makes understanding the causes, and developing effective therapies so difficult.

FRONTAL AND TEMPORAL LOBE FUNCTIONS

The name FTD is descriptive of the parts of the brain that are affected, the frontal and temporal lobes.

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The main functions of the frontal lobe include decision making, complex problem solving, social skills, impulse control, empathy, conscience, and working memory and recall. The primary motor cortex area of the frontal lobe, which is anterior to the central sulcus, is involved in management of speech production, and in voluntary movement. The temporal lobe functions include the regulation of memory, and recognition and understanding of spoken words [6]. Depending on which areas of these lobes are affected by the specific genetic mutations, there will be a variety of symptoms observed.

BASICS OF NEURODEGENERATIVE DISEASE

The basis of neurodegenerative diseases is that brain cells (neurons) are dying. This loss of neurons leads to loss of a potential multitude of abilities (from loss of executive decision making to loss of mobility, etc.), depending on where in the brain the cells are dying. The main reason that the cells die is that they commit suicide (apoptosis). Cells in our bodies are programmed to go through apoptosis when processes in the cell become faulty (this is a protective mechanism, usually for our benefit). In the case of FTDs, there is an accumulation (many times an aggregation) of proteins in the cell (quite often this is due to gene mutations that produce faulty proteins), and eventually the cell dies. In a normally functioning cell, any abnormal or misfunctional proteins are usually bound by ubiquitin. These abnormal proteins are then ushered to a proteasome where they are degraded. In FTDs, the abnormal proteins are not able to be degraded, and so accumulate in the cell. When this occurs the cell will signal itself to go through apoptosis [7]. Sometimes the aggregates contain what should be normally functioning proteins [8, 9]. Mutations in other proteins (or yet unknown processes) may be the cause of these aggregates, but the result is the same – cell death. There are also several other proteins (or potential proteins – functions yet unknown) that are involved in neurodegenerative dementias. The most common of these known proteins, their genes, and gene mutations will be discussed in this work.

INHERITANCE IN NEURODEGENERATIVE DISEASE

Within the last 10 years or so, the main ideas about inheritance in the FTD related diseases have changed dramatically, primarily due to the massive amount of new information that researchers have been able to discover during that time. While it was initially believed that these diseases were primarily caused by sporadic

mutations [10, 11], it is now believed that the majority of cases may actually be transmitted via familial inheritance [12]. For the disorders and genes that will be covered here, the type of inheritance is autosomal dominant. While the issue of penetrance is being researched [3, 13], it is currently almost impossible to determine penetrance with any accuracy due to the basic genetics involved. Not only are these diseases caused via autosomal dominant transmission, there are also almost no known cases of patients who are homozygous for a mutation. The fact that patients are heterozygous for mutations, plus other factors (most yet unknown), makes disease presentation, age of onset, etc. extremely variable. Therefore, the concept of penetrance in these diseases seems to be moot. Hopefully, in a few years we will know enough about the genetics of these diseases to have pertinent information on penetrance.

PATHOLOGY OF NEURODEGENERATIVE DISEASE

The histopathology of the neurons in these diseases is mainly based on detection of the accumulated normal or abnormal proteins, known generally as cellular inclusions. There are a number of different categories that define these diseases, but no one category is specific to any individual disease. There are two major categories of pathology described; those cells with tau protein inclusions (around 40%), and those without tau (around 50%) [14, 15]. Those cells without tau protein inclusions most commonly contain TAR DNA-binding protein 43 (TDP-43) protein inclusions; less commonly, FUS proteins, and a small minority apparently contain ubiquitin inclusions with no other proteins included, or no inclusions [16]. Table 1 summarizes the genetic pathology of genes associated with FTD.

MAPT

The tau protein is produced by the *MAPT* (microtubule-associated protein tau) gene, which is located on chromosome 17 (17q21.1) in that hot spot region that was mentioned earlier. It is expressed primarily in neurons, and the tau protein functions by binding to microtubules to facilitate their polymerization, thus helping in stabilization [17]. Mutations which allow the protein to be hyperphosphorylated are known to be a major cause of disease [18, 19]. Mutations that cause the loss of the ability of tau to bind to microtubules or promote the assembly of tau filaments are known to be responsible for about 5% of FTDs [16]. There are at least 50 known mutations; most of which are located in

or near exon 10 [8, 20]. Mutations in *MAPT* are responsible for 3-5% of FTD related diseases, and up to 10% of familial FTD (fFTD) [20, 21]. Tau protein aggregates are seen in FTDs and also commonly seen in AD. Cells with tau positive pathology are rarely associated with any of the other known proteins involved in frontotemporal neurodegenerative diseases [4, 22]. The inclusions in cells with certain tau proteins were originally designated as 'Pick's bodies', so this type of FTD is also known as Pick, or Pick's disease [23]. Tau pathology is often present when there are no mutations in the *MAPT* gene [24]. Mutations in *MAPT* occur more commonly in AD patients [25]. Mutations in *MAPT* alone may not necessarily cause disease [13].

TARDBP

The non-tau pathology type most commonly includes cells with TDP-43 positive inclusions. The TDP-43 protein is produced by the *TARDBP* (trans-activation response DNA-binding protein) gene located on chromosome 1 (1p36.22). The TDP-43 protein is known to be involved in DNA and RNA binding and in alternative splicing of mRNA. Normal, but hyperphosphorylated TDP-43 aggregates are what are seen in most FTD related diseases, being present in up to 60% of FTD patients, and up to 90% of ALS patients [9, 26]. The normal proteins are relocated from the nucleus to the cytoplasm and phosphorylation causes them to be sequestered in inclusions [27]. Mutations may also cause proteins to aggregate, making it difficult for the cell to degrade them. These mutations are most commonly found in the C-terminal of the protein [28, 29]. The normal protein has an intrinsic tendency to aggregate via the C-terminal [30]. Mutations in *TARDBP* are most commonly seen in ALS patients [1, 2]. Rarely, mutations have been found in FTD or FTD with ALS-like symptoms [31], and also have been seen in AD, PD and Huntington's disease (HD) [32, 33]. In most diseases involving TDP-43 pathology there are other abnormal proteins associated with the disease process, and there may not be an actual mutation in the *TARDBP* gene. The most common of these other proteins include the progranulin (produced by the *GRN* gene) or C9orf72 (produced by the *C9orf72* gene) proteins, with a rare association with the valosin-containing protein (VCP) [34, 35]. For a minority of TDP-43 pathology-associated cases there are no other proteins yet known to be involved.

GRN

One of the proteins associated with FTD related diseases that have TDP-43 pathology is progranulin.

The *GRN* gene is located in the hot spot region of chromosome 17 (17q21.32). Progranulin is a neurotrophic factor that is known to enhance neuronal survival [36]. Expression of this protein is regulated by proinflammatory Th1 (negative regulation) and Th2 (positive regulation) [37]. The progranulin protein can be cleaved by elastase and other proteases to form granulins. Full-length progranulin appears to suppress inflammation, while cleaved granulins promote inflammation [38]. Mutations have been found in all exons (except 13), and most commonly result in a progranulin loss of function [5, 39, 40]. Decreased amounts of functional progranulin leads to pathological processing of TDP-43 by caspase-3, which may explain the TDP-43 inclusions [41]. In addition, *GRN* mutations affect the expression of multiple genes in the frontal cortex [4]. When the cause is loss of function mutations, it's not enough to try to increase levels of functional protein, as this hasn't been shown to halt cell destruction [42]. Over 70 mutations have been found in *GRN*, and account for up to 25% of FTD cases [16, 43]. A couple of cases have been noted where there were *MAPT* mutations and *GRN* mutations, but the cells did not have tau pathology [24]. Some rare *GRN* mutations have been found in cases where cells had neither tau nor TDP-43 inclusions [44].

C9ORF72

The other major protein associated with FTD related diseases that have TDP-43 pathology is C9orf72. The name comes from the gene name (*C9orf72*) as the function of this protein has not yet been elucidated, and refers to its location on chromosome 9 (9p12.1). Even though the existence of this protein's involvement in FTD related diseases has only been known for a few years, it is now believed that mutations in this gene are responsible for a majority of these diseases [12]. The disease causing mutation in this gene is similar to that seen in HD; an expanded hexanucleotide (GGGGCC) repeat at one end of the gene. The expansion is thought to involve the loss of an alternatively spliced *C9orf72* transcript and result in formation of nuclear RNA foci [12, 45]. Other research has shown that the hexanucleotide repeats are translated into dipeptide-repeat proteins that co-aggregate [46]. A normal number of repeats is considered to be 20 or fewer, and abnormal is 30 repeats or more [47]. The majority of non-affected individuals possess 8 repeats or fewer, with 2 repeats being by far the most common [2, 48, 49]. Mutations in *C9orf72* have been found in FTD, ALS, FTD/ALS or other motor neuron diseases

Table 1: Genetic Pathology of Genes Associated with FTD

Ubiquitinated Inclusions	Main Inclusion Protein	Other Gene Mutations Involved
Yes	Tau (<i>MAPT</i>) – with or without mutation	Usually none
Yes	TDP-43 (<i>TARDBP</i>) – with or without mutation	<i>GRN</i> <i>C9orf72</i> <i>VCP</i>
Yes	FUS (<i>FUS</i>) – with or without mutation	None
No	None detectable	<i>CHMP2B</i>

(MNDs), and PD. One study has shown that a repeat number of between 20-30 may be a risk factor for Parkinson's [50]. There is also evidence to suggest that the number of repeats directly correlates with cellular toxicity [51]. One case has been noted that involved a patient who was homozygous for expanded repeats, but no difference in symptoms was seen compared with those who were heterozygous [52].

Interestingly, there have been instances where the mutation in *C9orf72* has been seen without TDP-43 pathology in FTD and ALS/MND [53, 54]; or without TDP-43 pathology, but with tau pathology [55]. There are also instances where *C9orf72* mutation is seen with mutations in some of the other FTD genes: mutation in *TARDBP* in FTD/ALS [56]; mutation in *TARDBP* and *FUS* in ALS [57, 58]; mutation in *GRN* in FTD [59-61]; and mutation in *MAPT* in FTD [60].

VCP

The *VCP* gene is located on Chromosome 9p13.3. The *VCP* protein is a member of the ATPase associated with diverse cellular activities (AAA) superfamily, and phosphorylation is required for its activation [62]. The *VCP* protein has a variety of functions, as it is widely expressed. It is well known for roles in transporting misfolded proteins from the endoplasmic reticulum (ER) to be degraded by the proteasome [4, 63]. Loss of *VCP* leads to a decrease in the production of cellular ATP [17]. Rare mutations (<1%) in *VCP* are known to cause FTD and familial ALS, and other diseases such as Charcot-Marie-Tooth type 2 disease, hereditary spastic paraplegia, inclusion body myopathy, and Paget's disease of the bone [64]. At least 24 different mutations have been identified so far [63]. In FTD, mutations in *VCP* are seen with TDP-43 proteinopathy. It is thought that mutations in *VCP* lead to an alteration in protein function, a decrease in proteasome activity, and relocation of TDP-43, which lead to the TDP-43 proteinopathy [62].

FUS

A small number of cases involve cells that have tau negative, TDP-43 negative, and ubiquitin positive pathology, and have been found to contain aggregates of the fused in sarcoma (*FUS*) protein. The *FUS* protein has DNA- and RNA-binding functions and shares functional homology with TDP-43 [65]. The RNAs that are bound by TDP-43 versus those bound by *FUS* are largely distinct [66]. As part of its function, *FUS* is shuttled in and out of the nucleus, and it is involved in regulating alternative splicing of proteins related to axonal biology [67]. It has been found that overexpression of normal *FUS* protein can cause neurodegeneration in mice [68], and cytoplasmic inclusions of normal *FUS* may occur in up to 9% of FTD patients [66]; so *FUS*opathy may be observed with or without mutations in *FUS* [69]. *FUS* protein pathology is usually seen in ALS, PD, and Huntington's disease, and may be seen in a small number of FTDs related to ALS and PD [70-72]. The *FUS*opathies that are seen associated with ALS versus FTD differ in protein composition [73]. Mutations in *FUS* are rarely seen in FTD (<5%) [43], and are more commonly found in ALS [74].

CHMP2B

A very small number of FTD related cases show only ubiquitin-based inclusions (tau negative and TDP-43 negative). These have been found to be associated with the charged multivesicular body protein 2B (*CHMP2B*). *CHMP2B* is a component of the endosomal complex [4, 43]. Mutations in *CHMP2B* have been found in a splice site which result in a decreased ability of the cell to degrade these proteins [75]. Some mutations may result in truncation of the protein at the C-terminal [76]. Mutations in this protein may result in disassembly of cell structure, increased calcium in the endoplasmic reticulum lumen, and a decrease in available ATP [77]. Rarely, mutations are associated with fFTD and fALS [77-80]. Some very rare cases do

not seem to have cellular inclusions, and there is little information yet on what other genes may be involved [43].

FTD SYMPTOM GROUPS

The diagnosis of FTD does not indicate a single specific disease. Instead, FTD is a widely varied group of disorders that share similar symptoms, and some genetic causes as well. These disorders can be loosely grouped by early presentation of symptoms (eventually, if a patient has FTD long enough, they are more likely to exhibit any or all of the symptoms) [12]. There have been several excellent attempts to classify these symptoms into discrete diagnostic groups [5, 43, 81, 82]. Because there is so much variation in symptoms, even among patients with the same genetic mutation, these designated groups are still far from completely descriptive. As we learn more about these diseases it may become easier (or more difficult) to establish symptom groups. For the sake of simplicity, this paper will use some very basic group designations. These symptom groups are:

- 1) Behavioral variant (bvFTD) – loss of inhibition or restraint;
- 2) Primary progressive aphasia (PPA), which can be broken down into two subgroups:
 - a) Semantic dementia (svFTD or svPPA) – words spoken by the patient indicate a loss of word meaning,
 - b) Progressive nonfluent aphasia (nfvFTD or nfvPPA) – patient loses the ability to speak fluently;
- 3) Movement disorders (often referred to as motor neuron disease – MND) – these exhibit symptoms closely related to Parkinson's and/or ALS; presenting with symptoms such as shakiness, muscle dysfunction, and walking and balance problems.

These generalized symptoms groups, and the fact that until very recently there was no definitive noninvasive testing available for diagnosis, has made the diagnosis of FTDs very difficult. Physicians have had to rely heavily on descriptions by family and friends of the behavior, speech, and movement changes in the patient. The use of MRI testing is less helpful early in the disease as small changes in the brain may be

difficult to spot (but should be performed to use as a baseline for comparison with later MRIs).

The bvFTD type is currently considered to be the most common early presentation (perhaps because behavioral issues may be easier to detect). The changes seen may include a variety of socially inappropriate behaviors (loss of etiquette and tact, restlessness, etc.) that eventually will be very discernable when loss of inhibition and restraint lead to obsessions such as with sexual issues and, quite often, overeating (the patient loses the ability to judge what is appropriate in food consumption, and often has an oral fixation – wants to put everything in their mouth) [6, 40].

In the PPA disorders the emphasis is on changes in language. For svFTD, the patient is initially able to speak without difficulty, but demonstrates a loss of understanding of meaning and comprehension in the choice of words, and in interpreting what other people say. In nfvFTD, the patient has actual speaking difficulties. They may exhibit slow speech or stuttering, and may have difficulty finding the correct word to say. These patients may also have difficulties in writing and reading comprehension [6, 40].

The movement disorders related to FTDs are most commonly initially mistaken for (although may actually be connected with) diseases such as Parkinson's and ALS, as well as other related movement disorders [53, 78]. Until the disease has progressed (perhaps for many years) and symptoms of dementia are seen, an accurate diagnosis is difficult. Sometimes these patients may be diagnosed as having a movement disorder and a separate dementia when what they actually have is a form of FTD. Since much more research needs to be performed relating to these specific movement disorders, this paper will not be going into detail on these, except as to how they relate directly to FTDs in general.

These descriptions of the FTDs are not all inclusive, and actually the symptom presentation and progression of the diseases may involve very complex genetic manifestations. This paper will be discussing how some of the commonly known genes that may be involved in these diseases relate to symptomology, but keep in mind that any one patient may actually have mutations in more than one of these genes. This can make the interpretation of symptom presentation and eventual diagnosis a very tricky process.

SYMPTOMS ASSOCIATED WITH GENE MUTATIONS

This paper will attempt to provide the most common initial symptoms associated with each of the genes that have been discussed. There is significant variation in symptoms even in those individuals who share the same mutation. Studies utilizing identical twins (with identical mutations) have shown that one twin may get the disease and the other not (this is a very rare occurrence); more commonly, there are differences in age of disease onset (by possibly several years), presentation of symptoms, and length of disease duration (again, by many years). Interestingly there is no significant differences associated with gender [83, 84]. The diversity of symptoms, age at onset, and length of disease are even more varied among family members who share the same mutation(s). An example of this from one family with two brothers who had FTD shows typical diversity. These brothers had a paternal grandmother who died with Parkinson's disease. The brothers were two years apart in age. The younger brother developed symptoms first at around age 54. This brother presented with typical bvFTD which progressed slowly until before his death, this brother was no longer able to speak or walk. He had the disease for 18 years before he died. The older brother did not present with detectable symptoms until around age 60. His initial symptoms were more like mild epilepsy, but within two years he began to exhibit memory loss. He then developed more typical bvFTD symptoms, but these were followed fairly soon by gait issues suggestive of Parkinson's disease. Very soon after that he developed symptoms suggestive of ALS. He rapidly became completely nonmobile and died at age 72 [data unpublished].

Because of these variations the information contained here is only a general guideline. One of the purposes of this paper is to help scientists and clinicians understand the genetic complexities of these diseases, and to encourage more genetic testing and analysis to further our knowledge on this subject. Information on age at onset of disease and disease duration/age at death will also be included here. Table 2 summarizes the genetic and clinical profiles of these genes associated with FTD.

MAPT

Cellular inclusions of tau are most often associated in FTD with bvFTD symptoms, with a small number being associated with nvPPA symptoms [21, 40, 85,

86]. *MAPT* has also been associated with FTDs related to Parkinson's and Alzheimer's, but has not been associated with ALS, or MND-type symptoms. Mutations in *MAPT* are more commonly found in AD and PD; approximately 19% of PD individuals have a mutation in *MAPT* [87]. The average age of onset of tau associated disease is 45 with a range of between 25-65; and the average years of survival after onset is 7 with a range of between 2-25 years [84].

TARDBP

Cellular inclusions of TDP-43 are associated with a variety of symptoms, depending on whether the *TARDBP* gene contains a mutation, and what other abnormal proteins may be present (progranulin, C9orf72, VCP, etc.). Mutations in the *TARDBP* gene are associated with AD, ALS, FTD and PD. In ALS and PD initial symptoms will usually be MND-related. Age at disease onset with mutations in *TARDBP* is an average of 54-56 with a range of 35-74. Average disease duration is 6-9 years with a range of 1-21 years [16, 88]. In FTD the most common initial symptom type is bvFTD because that is the most common initial symptom for C9orf72 and *GRN* mutations [89], and average age at onset and length of disease is related to which other genes and mutations are present (see those mutations below).

GRN

Mutations in the *GRN* gene which cause disease are almost always associated with TDP-43 pathology (the TDP-43 protein in these cases is usually normal). There are over 70 different known disease causing mutations. These mutations are associated with AD, FTD, and PD. In FTD the most common initial symptom is bvFTD, with some instances of nvFTD and svFTD as well. Patients who have mutations in both *GRN* and *TARDBP* usually exhibit bvFTD. The average age at disease onset is 56-59 with a range of between 35-83; and average length of disease duration is 6-7 years with a range of between 1-15 years [16, 84, 90]. Recently, testing has been made available for measuring progranulin levels in blood serum. The blood level of protein in individuals with mutations in *GRN* is much lower than in those without mutations [91].

C9ORF72

Mutations in the *C9orf72* gene cause the widest variation in initial symptoms and disease progression

Table 2: Genetic and Clinical Profiles of the Most Common Genes Associated with FTD

Gene	No. of Known Mutations	Mutation Frequency in FTD	Most Common Initial Symptom	Mean Age at Onset of Symptoms (Range)	Mean Duration of Disease (Range)
<i>MAPT</i>	>50	5-10%	bvFTD	45 (22-65)	7 (2-25)
<i>TARDBP</i>	>50	1-3%	bvFTD	depends on associated genes	depends on associated genes
<i>GRN</i>	>70	10-20%	bvFTD>PPA	57.5 (35-83)	6-7 (1-15)
<i>C9orf72</i>	expanded repeat >20	25-30% FTD >80% FTD/MND	bvFTD	57 (33-85)	5 (1-26)
<i>VCP</i>	>20	<1%	bvFTD, MND	55 (37-79)	6 (1-21)
<i>FUS</i>	>50	<1%	bvFTD	43 (30-60)	3 (3-7)
<i>CHMP2B</i>	5	<1%	bvFTD	58 (46-71)	10 (5-21)

[92]. Disease is almost always associated with TDP-43 pathology, and the TDP-43 protein is usually normal. Mutations in this gene are now thought to be the most common cause of familial cases of FTD and ALS, and cause up to 29% of FTD, up to 50% of ALS, and up to 88% of FTD/ALS [2, 93]. The most common symptom at onset is bvFTD [94]. Repeat expansion numbers of over 4000 have been found, and one large study found a correlation between size of repeat expansion and age at onset of disease [95]. The average age at onset of disease is 57 with a range of between 33-85; and the average length of disease duration is 5 years, with a range of between 1-26 years [48, 84]. These wide ranges reflect the fact that patients with ALS symptoms usually have a much shorter time of disease duration.

VCP

Mutations in the *VCP* gene are very rarely seen in FTD disease, and are associated with TDP-43 pathology. There are at least 24 mutations known to be associated with ALS and FTD/ALS [63, 96]. The most common initial symptom is bvFTD (around 35%), and MND, with other initial symptoms being highly variable. Average age of onset of disease is 55 with a range of between 37-79; and average length of disease duration is 6 years with a range of between 1-21 years [16].

FUS

FUS pathology in cells is not usually associated with TDP-43 or tau pathology. The FUS pathology may occur with or without mutations in the *FUS* gene, and over 50 mutations have been found that can cause disease [74]. FUS pathology has been found in ALS and PD, and very rarely in FTD cases [15, 31, 43]. The initial symptoms of FTD associated with FUS are nearly

always bvFTD, with early onset and severe and rapidly progressing behavioral issues [1, 16, 97]. The average age of onset of disease is 43 with a range of between 30-60, and the average duration of disease is 3 years with a range of between 3-7 years [16].

CHMP2B

Disease associated with *CHMP2B* mutations are also not associated with TDP-43 or tau pathology. Mutations are a rare cause of FTD and only a small number of mutations have been identified, most commonly in familial FTD [16, 78]. The most common initial symptom is bvFTD. The average age of onset of disease is 58 with a range of between 46-71, and the average length of disease duration is 10 years with a range of between 5-21 years [16].

DISCUSSION

Unfortunately for medical science, gene inheritance is not always a straightforward event. There are many factors that affect whether a person receives a mutated gene, and especially how that gene is expressed in any individual. Often, gene expression is regulated or affected by other genes (sometimes many other genes), and environmental conditions, for example, may also play a role in disease. The symptoms and onset of the FTDs and other dementias may vary greatly even among people who have the same gene mutation. There are differences in age of disease onset (by possibly several years), presentation of symptoms, and length of disease before death (again, by many years). These differences may appear among family members who carry the same mutation. These observations make it clear that determining if an FTD is inherited within a family may be extremely difficult.

There are many genes that are known to be, or suspected to be involved in causing FTDs. These diseases are not necessarily (and perhaps not very often) caused by a mutation in a single gene. Most probably there are two or more genes involved (scientists have already found this to be so). This makes it even more difficult for medical scientists to discover which genes may be involved. In addition, how these genes are regulated by direct and indirect factors adds to the puzzle. This is probably why so many of these diseases overlap in symptom presentation, etc.

Will finding the genetic cause of these diseases mean that a cure is imminent? Unfortunately, no; but, the more that we can find out about the genetic causes, the better the chances are that physicians will be able to develop targeting therapies. With increased knowledge of the mutations and the functions of the proteins involved, drug companies should then be able to develop treatments that will at least lessen the symptoms and delay death, and eventually a cure may be found.

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