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New Genes, New Dilemmas: FTLD Genetics and Its Implications for Families

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After Alzheimer's disease, frontotemporal lobar degeneration (FTLD) is the second leading cause of dementia in persons less than 65 years of age. Up to 40% of FTLD cases have a positive family history. Research on these families has led to the discovery of four disease-causing genes: microtubule-associated protein tau (*MAPT*), progranulin (*PGRN*), valosin-containing protein (*VCP*), and charged multivesicular body protein 2B (*CHMP2B*). *MAPT* and *PGRN* are responsible for the largest number of familial cases. Each of these genes differs by disease mechanism. Moreover mutations in both genes are associated with significant interfamilial and intrafamilial phenotypic variation. Genetic counseling needs to address the differences between the *PGRN* and *MAPT* mutations as well as the variation in clinical symptoms. The aims of this article are to describe the genetics of the FTLD spectrum and aid in the genetic counseling of individuals who may carry genetic mutations.

Keywords: genetics; frontotemporal lobar degeneration; progranulin; tau; genetic counseling

Frontotemporal lobar degeneration (FTLD) is a clinical syndrome that usually presents with behavioral/personality changes or a language disorder while initially leaving memory relatively intact.[1] Frontotemporal lobar degeneration is nearly as common as Alzheimer's disease (AD)[2-4] in patients less than the age of 65 years with the mean age of onset approximately 52 to 58 years.[2,3,5] Although mostly thought of as an early-onset form of dementia, up to one-fourth of cases have onset after the age of 65 years. Furthermore, recent work suggests that we may have underestimated the prevalence of FTLD in patients more than the age of 65 years as up to 20% of patients with AD also show neuropathological markers for FTLD.[3,6]

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Frontotemporal lobar degeneration can be divided into three major clinical subtypes: behavioral variant form of frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA).[7] Early symptoms of bvFTD are predominantly behavior and personality changes including apathy, emotional blunting, loss of insight, disinhibition, hyperorality, and aberrant motor and perseverative behavior. Semantic dementia results in the loss of language comprehension; and PNFA causes the loss of expressive language.[1,8] Patients with FTLD can develop parkinsonism and/or amyotrophic lateral sclerosis (ALS).[9,10] Additionally, FTLD is closely related both clinically and pathologically to cortical basal degeneration (CBD) and progressive supranuclear palsy (PSP).[11-13] The aims of this review are to describe the genetics of FTLD spectrum diseases and aid in the genetic counseling for individuals who may carry genetic mutations for these diseases. This article is intended for patients and their families, general practitioners, and neurologists.

Advances in neuropathology and genetics have led to a growing understanding of the molecular

basis of FTLD. A series of autopsy studies have demonstrated three distinct pathological subtypes of FTLD. Approximately one-third of FTLD cases are positive for tau in the form of neurofibrillary tangles or Pick bodies whereas the majority of cases are tau negative and have ubiquitin positive neuronal cytoplasmic inclusions (FTLD-U).[14] One-third or more of these FTLD-U cases also have rare to occasional neuronal intranuclear inclusions (FTLD-U NII).[15] A rare subtype, whose existence has recently been called into question by the advent of more sensitive ubiquitin immunostaining procedures, has been reported to have no distinctive histology (dementia lacking distinctive histology: DLDH).[14,15]

Up to 40% of FTLD is familial, although only around 10% of cases suggest an autosomal dominant pattern of inheritance.[3,5,16] This percentage differs from study to study and depends on the population and method of ascertainment. Also, family history assessments are often complicated by a lack of information or misdiagnosis of AD. Additionally, family members diagnosed with Parkinson's disease or ALS may be underascertained.[3,17,18]

The unraveling of FTLD genetics began in 1994 with the linkage of familial FTD with parkinsonism to chromosome 17q21. This new hereditary syndrome was first named disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC),[19] and then FTDP-17 after the identification of additional families linked to the same chromosomal region.[20] In 1998, the microtubule-associated protein tau (*MAPT*) was identified as the causal gene in FTDP-17 patients with tau histopathology.[21-23] The frequency of *MAPT* mutations in FTLD varies markedly depending on the patient population sampled (0% to 18%).[16,24-27] The frequency in unselected US-based studies is ~5%.[16,18,28] These estimates increase to 9% to 43% in the presence of a positive family history.

To date, 41 *MAPT* mutations have been found (FTD genetic mutation database, www.molgen.ua.ac.be/ADMutations/).[18] *MAPT* mutations can be divided into two types. The first are those that partially reduce the binding of tau to the microtubule and also enhance tau aggregation into filamentous structures. Ultimately this leads to the formation of tau aggregates including Pick bodies and neurofibrillary tangles.[10] The second group of mutations disrupt the alternative splicing of *tau* exon 10 thus changing the ratio of tau protein isoforms.[29,30] Normally, six isoforms of tau are produced through alternative splicing of exons 2, 3, and 10. Because exon 10 encodes one of the microtubule binding repeat domains, the six isoforms can be grouped into those with three or four microtubule binding domains (3R and 4R tau). The average ratio of the 3R and 4R tau is approximately 1:1 in the normal adult human brain; however mutations in *MAPT* that disrupt the alternative splicing of exon 10 cause a shift in this ratio usually resulting in an increase in 4R tau. Exactly why this change in tau isoform ratio leads to neurodegeneration is currently uncertain. On autopsy, brains from patients with *MAPT* mutations inevitably have tau neurofibrillary pathology and indeed the nature of the *tau* mutation in part determines the form of tau neurofibrillary lesions that develop.[30] Both the interfamilial and intrafamilial phenotypes of *MAPT* mutation carriers are quite variable.[29,31] Age of onset, disease duration, and clinical presentation can all differ. Patients can present with classic behavioral or language changes with or without parkinsonism but can also have features of ALS,[19] corticobasal degeneration,[32,33] or progressive supranuclear palsy.[34-36] However, the mutations in *MAPT* are almost without exception highly penetrant and as a result, unless paternity is in question, sequencing *MAPT* in the absence of a positive family history is unlikely to be productive.[37] Families still wanting genetic testing to rule out the possibility of a mutation should be offered genetic counseling.

In addition to these rare highly penetrant mutations in *MAPT* that cause FTDP-17, common genetic variability in *MAPT* has also been shown to influence the risk for the sporadic tauopathies PSP and CBD. *MAPT* has 2 extended haplotypes, H1 and H2, that are defined by over 200 noncoding polymorphisms that are in complete disequilibrium with each other with no recombination between H1 and H2. This highly unusual haplotype structure was caused by an ancient genomic inversion such that H1 is inverted relative to H2 on chromosome 17. The H1/H1 genotype has been consistently associated with a higher risk of sporadic PSP and CBD.[38] In addition, interaction between a specific mutation and *MAPT* haplotype may influence the clinical phenotype in mutations carriers.[39]

Many families in which FTLD displays an autosomal dominant pattern of inheritance do not carry *MAPT* mutations. Moreover, autopsy studies demonstrate that in such families the FTLD pathology usually consists of ubiquitin-positive, tau-negative neuronal inclusions.[30] In fact, less than 40% of all FTLD cases have tau-positive inclusions.[14,40] Genetic studies of autosomal dominant families

without *MAPT* mutations have resulted in linkages to chromosomes 3, 9, and 17. A Danish family with FTD was linked to the charged multivesicular body protein 2B gene (*CHMP2B*) on chromosome 3p11 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=25978) and a mutation in the *CHMP2B* gene was subsequently identified.[41,42] *CHMP2B* is a component of the endosomal sorting complex (ESCRTIII) required for the translocation and turnover of cell surface receptor complexes. However, to date no other families have been found with a segregating *CHMP2B* mutation; thus, mutations in this gene are a rare cause of FTLD.[43,44] Three different sites on chromosome 9 have been linked to FTD. Mutations in the valosin-containing protein gene (*VCP*) at 9p13 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7415) cause inclusion body myopathy associated with Paget's disease of the bone and frontotemporal dementia (IBMPD). *VCP* is an AAA-type ATPase likely involved in endoplasmic reticulum-associated protein degradation. *VCP* mutations produce significant phenotypic variation. Although the majority of carriers develop myopathy, less than half develop Paget's disease or FTD[45] (Table 1).

A second chromosome 9 linkage site at 9p21.3-p13.3 is associated with familial FTD and ALS. This linkage site leads to variable expression within and between families. Additionally, reduced penetrance of about 40% by age 70 has been reported in families with disease linked to this linkage.[46,47]

Soon after the initial discovery of mutations in *MAPT* in FTDP-17, researchers started to report the linkage of *MAPT*-negative families to the same region of chromosome 17q21. All of these cases demonstrate tau-negative, ubiquitin-positive inclusion histopathology. In July 2006, this conundrum was resolved with the identification of mutations in the progranulin gene (*PGRN*) in these families.[40,48] Recent studies have indicated that the frequency of mutations in *PGRN* in a typical clinical FTD referral series is about 5% of all FTD and 13% to 20% of familial FTD.[18,28] In one of these studies the same patient series demonstrated a similar mutation frequency for *MAPT* mutations (~5%).[18] *PGRN* mutations have also been found in individuals without any family history. One study demonstrated that *PGRN* mutations were present in 3.2% of sporadic cases.[28] The extent to which this is caused by de novo mutations, reduced penetrance, variable age of onset, or simply a lack of clinical information on other family members is not yet known. However, the presence of mutations in apparently sporadic cases raises the question of whether or not to offer genetic testing even when family history is noncontributory.

In nonbrain tissues, progranulin is thought to function as a growth factor that regulates cell cycle progression and cell motility in multiple processes including development, inflammation, and wound repair.[49-51] However, the role of progranulin in the brain has received relatively little attention prior to it being linked with FTD. The fact that pathologic mutations in *PGRN* lead to a depletion of the functional protein suggests that progranulin is likely critical for neuronal survival.[40] A total of 44 different pathogenic *PGRN* mutations have been reported to date (FTD mutation database, www.molgen.ua.ac.be/FTDmutations). The majority of mutations are nonsense, frameshift, and splice-site mutations that create null alleles; additionally, several missense mutations have been reported that are predicted to result in a nonfunctional protein although the pathogenicity of these mutations remains to be confirmed.[18,28] Thus, unlike *MAPT* mutations, which result in abnormal tau aggregation and are thought to cause disease through a toxic gain of dysfunction, *PGRN* mutations result in haploinsufficiency.

The phenotype of patients with *PGRN* mutations is very similar to that of sporadic cases and *MAPT* positive cases. Like *MAPT*, *PGRN* mutations have variable intrafamilial and interfamilial phenotypic expression.[52] No phenotype/genotype correlation has been found, which is consistent with the finding that all mutations cause haploinsufficiency. The possibility therefore exists for a modifying polymorphism within the progranulin gene similar to the codon 129 of the prion gene or for a different modifying gene that affects symptom presentation.[53] Alternatively, environmental factors may influence the disease phenotype. The mean age of onset is approximately 59 years with a range of 48 to 83 years and the mean age of death is 65 years with a range of 53 to 87 years.[18] Penetrance is estimated to be 90% at age 70. Behavioral changes followed by parkinsonism late in the disease course is common.[54] Hallucinations are also more common than in sporadic or *MAPT* cases.[28] One interesting feature of *PGRN* mutation cases is the high proportion of cases presenting with primary progressive aphasia (24%).[18] Primary progressive aphaisa may be a presenting feature in some family members whereas

Table 1. Frontotemporal Lobar Degeneration (FTLD) Causative Genes

Gene name	*MAPT* (microtubule-associated protein tau)	*GRN* or *PGRN* (granulin or progranulin)	*VCP* (valosin-containing protein)	*CHMP2B* (charged multivesicular body protein 2B)
Gene location[a]	17q21.1	17q21.32	9p13.3	3p11.2
Estimated FTLD population with mutation[b]	5% (family history increases this to 9%)	5% (family history increases this to 13%)	<1%	<1%
Phenotype	FTLD	FTLD	IBMPFD (inclusion body myopathy with Paget disease and frontotemporal dementia)	FTLD
Age of onset in years: mean (range)	50 (22-78)	59 (32-83)	Myopathy/Paget onset at 42; FTD at 54	55
Number of mutations (most prevalent mutation)	41 (P301L)	44 (R493X)	9 (R155H)	3
Key references	Hutton et al (1998)[21]; Poorkaj et al (1998)[22]; Spillantini et al (1998)[23]	Baker et al (2006)[40]; Cruts et al (2006)[48]	Watts et al (2004)[45]	Skibinski et al (2005)[41]
Clinical genetic testing available	Yes: exons harboring mutations	Yes: coding region of the gene	No	No

a. Based on Gene Build 36.2.
b. Percentages based on pathogenic gene mutations in unselected patient series.

others present with behavior changes. Corticobasal syndrome is also a relatively common presentation in patients with *PGRN* mutations.[18] However, interestingly, symptoms of motor neuron disease are extremely rare in cases with *PGRN* mutations.[18]

All *PGRN*-positive cases develop a characteristic neuropathology that includes cortical atrophy along with both ubiquitin-positive neuronal cytoplasmic inclusions and ubiquitin-positive NIIs. The latter are usually not found in sporadic non-*PGRN* FTLD-U cases.[15] The finding that the TAR DNA-binding protein (TDP-43) is a major component of the ubiquitin-positive inclusions in *PGRN* mutation cases as well as in other forms of FTLD-U and sporadic ALS lends credence to the belief that these diseases may share a common pathogenic pathway.[55]

Therapeutic research for the prevention and treatment of FTLD is primarily focused on the knowledge that has been gained from the discovery of the *MAPT* and *PGRN* genes. Because the mechanism of disease caused by these genes is entirely different, therapies will also presumably have to be specific for the pathogenic mechanism in each case. The generous involvement of families in genetic research has been fundamental to the identification of these genes and will be important in the future as we seek to understand how these genes interact with other genetic and environmental factors in the development of FTLD.

What Does This Mean for Families?

The ever-changing world of FTLD genetics creates many possibilities for the families dealing with hereditary forms of this disease. At the same time, significant limitations to genetic testing exist. At the present time Clinical Laboratory Improvement Amendments (CLIA) genetic testing is available for *MAPT* on a limited basis and no CLIA labs are

performing testing on *PGRN* or other possible FTLD-associated genes (http://www.genetests.com). However, CLIA testing for *PGRN* will be available in the near future. Research testing is available in certain cases; however, genetic results may be unavailable to patients and their families. Before ordering genetic testing, a very careful 3 generational pedigree must be taken that includes the presence of FTLD, Parkinson's disease, ALS, other types of dementia, and psychiatric conditions. Without a documented family history, the likelihood of finding a gene mutation is very small. However, because the age of onset of *PGRN* mutation carriers is highly variable, even families with sporadic FTLD should be offered genetic counseling. If families are hesitant to proceed with genetic testing, commercial DNA banking of blood from an affected person can be offered as an alternative (see http://www.genetests.com for DNA banks).

Regardless of whether or not families want clinical or research genetic testing, they should be offered genetic counseling from specialists knowledgeable about FTLD. Families must consider not only the benefits of genetic testing but also the effects of testing on family members and family dynamics. They must also consider the limitations of genetic testing. If a family chooses to have clinical testing, they must understand FTLD's genetic heterogeneity. Additionally, a negative test result for a specific gene does not automatically reduce familial recurrence risk because they may carry a different gene. Likewise, they must understand that any positive result will predict the probability of disease but not the age of onset or symptom expression. In fact, some mutations may have reduced penetrance and never be expressed during a person's lifetime. Additionally the interpretation of genetic results can be difficult. Whereas often-reported mutations with definitive pathogenic effects to the translated protein lead to a relatively clear interpretation, the significance of newly reported mutations or those having a questionable effect on the protein produced may be uncertain. These could be benign polymorphisms or causal mutations. Difficulty in interpreting genetic information is demonstrated by the cases reported with *PSEN1* or *MAPT* mutations, which were later found to have *PRGN* mutations, implying that the originally reported variants in *PSEN1* or *MAPT* were rare benign polymorphisms.[56,57] Great caution must also be taken with the screening protocol employed and results should not be released that have not been confirmed in a CLIA lab or repeated on a second independent sample from the patient.

Presymptomatic genetic testing should only be performed when a mutation has been identified in the person's family. Without a known mutation, a negative test result will have unknown significance. Additionally, as with any presymptomatic testing for an adult-onset neurodegenerative disease, testing should be performed through a protocol similar to that used in Huntington disease.[58] The Huntington disease protocol recommends several genetic counseling sessions, baseline neurological and neuropsychological testing, a psychological evaluation, and the presence of a support person during counseling. Deciding to have presymptomatic testing is a highly personal and emotional decision. Physicians and counselors involved with this decision should move slowly through the testing process so that the at-risk person can think through this decision carefully and cautiously. Even after blood has been taken for DNA analysis, the at-risk person should be given the option of not receiving results.

Example Case Study

The following case study is designed to demonstrate the complexity of working with families carrying *PGRN* mutations. The case is based on a compilation of several families with *PGRN* mutations (Figure 1).

The 53-year-old proband (III:4) presented in clinic with tremors and rigidity in one limb, as well as mild gait and speech apraxia. The patient was given an initial diagnosis of atypical Parkinson disease. An examination 1 year later revealed apraxic eye movements worse in the horizontal plane, postural instability, and alien limb phenomenon. Cognitive impairment was seen upon neuropsychometric evaluation. Magnetic resonance imaging (MRI) revealed right frontal, parietal, and temporal cortical atrophy. A diagnosis of corticobasal degeneration was assigned to the patient. Over the next year the patient's symptoms progressively worsened including falls and changes in behavior. The patient became mute 1 year before death approximately 6 years after the onset of symptoms. A brain autopsy was performed and the pathological diagnosis of "nonspecific degenerative changes" was given. The autopsy was reviewed again later using new techniques and was found to be FTLD-U NII.

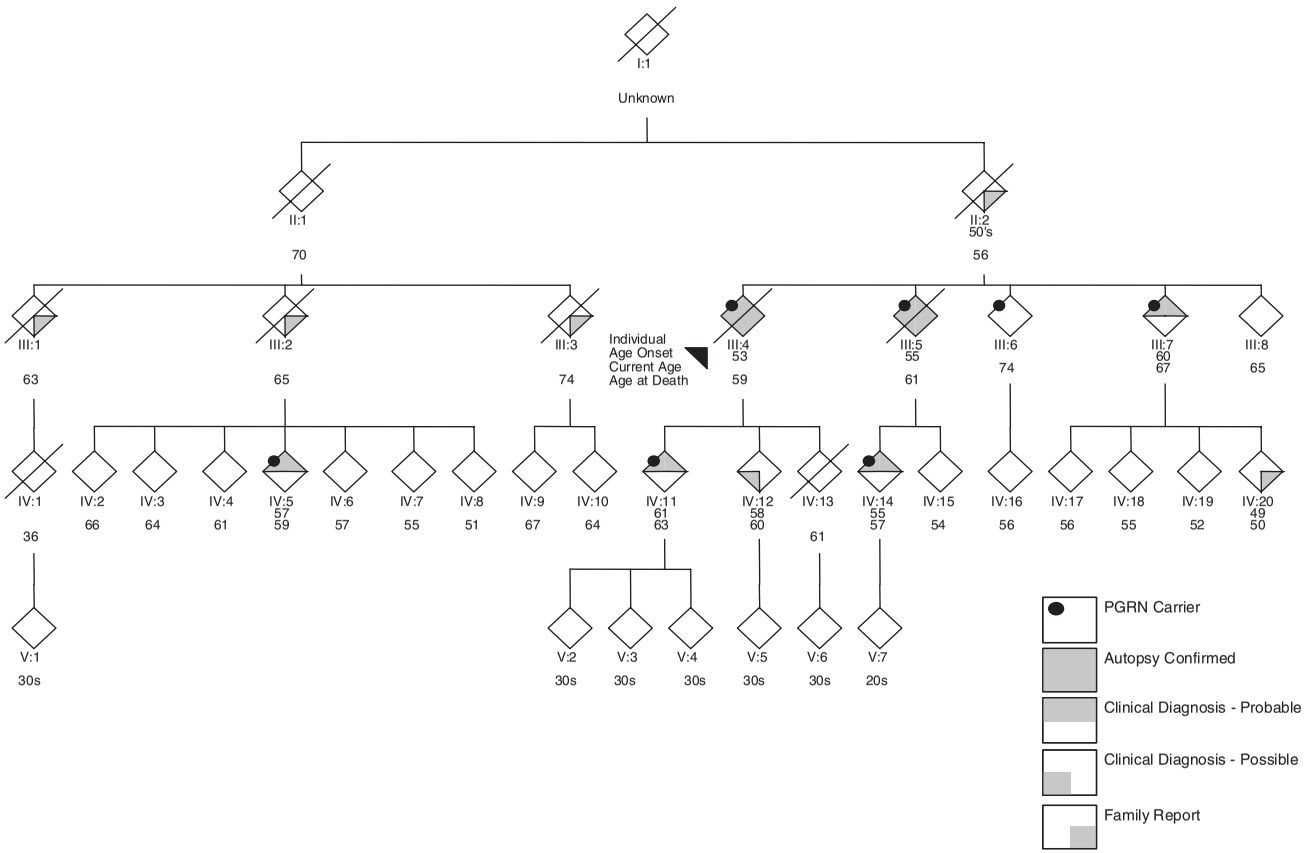

Figure 1. Case study pedigree.

During the late stages of the proband's disease, a 55-year-old sibling, III:5, became socially withdrawn, developed poor decision-making ability and a significant weight gain. The patient was diagnosed as having depression. On proband's autopsy, III:5 underwent a full neurological evaluation. Poor concentration and disinhibition were noted by the neurologist. An MRI revealed right temporal, frontal, and parietal atrophy. The patient was diagnosed with FTD. *MAPT* mutation testing was negative. The disease duration was approximately 7 years. Unlike the proband, this individual did not develop parkinsonism until late in the disease course. Autopsy revealed a pathological diagnosis of FTLD-U NII.

Several years later, a third sibling, III:7, began having personality and language changes and at age 60, was given a diagnosis of FTD. A review of family history indicated that the father of these individuals developed memory problems and began to wander in his early 50s. The father also developed rigidity in one arm. His disease duration was 5 years, and there was no formal diagnosis ever made. Although the paternal uncle died of coronary artery disease at age 70 and was not demented, his children all died with dementia at ages 63, 65, and 74 years of age. III:7 was found to have a mutation in *PGRN* that accounts for the disease in this family.

Other family members that participated in research studies have since been screened for *PGRN* mutations under research protocols approved by the institutional review board. One family member carries the *PGRN* mutation and is asymptomatic despite being 20 years over the average age of disease onset within the family. Yet, another individual (IV:12) who has been clinically diagnosed with mild memory impairment does not carry the mutation. Other family members are interested in presymptomatic testing when CLIA laboratory testing becomes available.

Prior to any presymptomatic testing that would reveal gene status, it is vital that this family understand the limitations of *PGRN* testing. Although a known mutation in the family allows for easy testing of other family members, the family history demonstrates the phenotypic variation both in symptoms and age of onset. The mean age of onset in this family appears to be in the mid to late 50s. However, one uncle died before showing any FTD symptoms and it is unknown whether he would have developed symptoms had he lived longer. Although there is no reason to believe that *PGRN* has genetic anticipation, the earlier age of onset in the proband's cousins might be because of modifier genes or environmental factors. This family also demonstrates the potential for individual's conflicting interests. The proband's unaffected sibling chose not to participate in the testing, believing that she does not carry the mutation because of her age. However, her children wish to be tested. If they are tested and carry the mutation, then their mother is an obligate carrier and may develop symptoms. Although these results could be kept from her, family secrets create their own problems.

Every family member considering presymptomatic testing should have a clear understanding of the presymptomatic testing protocol, which should include several genetic counseling sessions prior to testing, a baseline neurological examination, a psychiatric evaluation as deemed necessary, and genetic results session. Counseling sessions should include discussion about the personal reasons for testing, the anticipated effect of positive and negative test results on themselves and their families, and coping skills. Additionally, the discussion should cover the resulting ambiguity both of not testing and testing without knowing when or even if they will develop symptoms. Those individuals wishing to go forward with testing also should decide if and how they will share results with other family members.

Conclusions

With the discovery of the *PGRN* gene and TDP-43, the study of FTLD has taken a giant step forward. However, much about FTLD genetics remains unknown. Modifier genes/environmental factors that contribute to the intrafamilial and interfamilial variations in phenotypic expression of all known FTLD genes have yet to be found. The possibility of finding additional *PGRN* mutations in sporadic cases also exists because of the highly variable age of onset and apparent reduced penetrance of the mutations in this gene. Determining the frequency of PGRN mutations in FTLD is further complicated by the difficulty in consistently detecting whole gene deletions, which would also be expected to cause disease. Additional studies will therefore be needed over the coming years to determine the full impact of this already major FTLD locus.

Families at risk for FTLD are often eager to receive information concerning their recurrence risks. Each case will present different problems and dilemmas resulting from family history, family

dynamics, individual personalities, and the actual genetic analyses. Supportive counseling and information should be provided to these families, but caution must be used when offering genetic testing. However, the need for additional CLIA-approved sites that offer rapid, accurate screening of known FTLD genes is clearly growing.

References

1. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.* 1998;51:1546-1554.
2. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology.* 2002;58: 1615-1621.
3. Rosso SM, Donker Kaat L, Baks T, et al. Frontotemporal dementia in the Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain.* 2003;126(Pt 9):2016-2022.
4. Bird T, Knopman D, VanSwieten J, et al. Epidemiology and genetics of frontotemporal dementia/Pick's disease. *Ann Neurol.* 2003;54(suppl 5):S29-S31.
5. Chow TW, Miller BL, Hayashi VN, Geschwind DH. Inheritance of frontotemporal dementia. *Arch Neurol.* 1999;56:817-822.
6. Amador-Ortiz C, Lin WL, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann Neurol.* 2007;61:435-445.
7. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol.* 2001;58:1803-1809.
8. Boxer AL, Miller BL. Clinical features of frontotemporal dementia. *Alzheimer Dis Assoc Disord.* 2005;19(suppl 1): S3-S6.
9. Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology.* 2003;60:1094-1097.
10. Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurol.* 2005;4:771-780.
11. Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol.* 2003;54 (suppl 5):S15-S19.
12. Graff-Radford NR, Woodruff BK. Frontotemporal dementia. *Semin Neurol.* 2007;27:48-57.
13. Tuite PJ, Clark HB, Bergeron C, et al. Clinical and pathologic evidence of corticobasal degeneration and progressive supranuclear palsy in familial tauopathy. *Arch Neurol.* 2005;62:1453-1457.
14. Shi J, Shaw CL, Du Plessis D, et al. Histopathological changes underlying frontotemporal lobar degeneration with clinicopathological correlation. *Acta Neuropathol (Berl).* 2005;110:501-512.
15. Mackenzie IR, Baker M, Pickering-Brown S, et al. The neuropathology of frontotemporal lobar degeneration caused by mutations in the progranulin gene. *Brain.* 2006;129(Pt 11):3081-3090.
16. Poorkaj P, Grossman M, Steinbart E, et al. Frequency of tau gene mutations in familial and sporadic cases of non-Alzheimer dementia. *Arch Neurol.* 2001;58: 383-387.
17. Goldman JS, Farmer JM, Van Deerlin VM, Wilhelmsen KC, Miller BL, Grossman M. Frontotemporal dementia: genetics and genetic counseling dilemmas. *Neurologist.* 2004;10:227-234.
18. Gass J, Cannon A, Mackenzie IR, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. *Hum Mol Genet.* 2006;15:2988-3001.
19. Wilhelmsen KC, Lynch T, Pavlou E, Higgins M, Nygaard TG. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. *Am J Hum Genet.* 1994;55:1159-1165.
20. Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. *Ann Neurol.* 1997;41:706-715.
21. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature.* 1998;393:702-705.
22. Poorkaj P, Bird TD, Wijsman E, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol.* 1998;43:815-825.
23. Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci USA.* 1998;95:7737-7741.
24. Fabre SF, Forsell C, Viitanen M, et al. Clinic-based cases with frontotemporal dementia show increased cerebrospinal fluid tau and high apolipoprotein E epsilon4 frequency, but no tau gene mutations. *Exp Neurol.* 2001;168:413-418.
25. Houlden H, Baker M, Adamson J, et al. Frequency of tau mutations in three series of non-Alzheimer's degenerative dementia. *Ann Neurol.* 1999;46:243-248.
26. Rizzu P, Van Swieten JC, Joosse M, et al. High prevalence of mutations in the microtubule-associated protein tau in a population study of frontotemporal dementia in the Netherlands. *Am J Hum Genet.* 1999;64:414-421.
27. Binetti G, Nicosia F, Benussi L, et al. Prevalence of TAU mutations in an Italian clinical series of familial frontotemporal patients. *Neurosci Lett.* 2003;338:85-87.
28. Le Ber I, van der Zee J, Hannequin D, et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia [published online ahead of print April 13, 2007]. *Hum Mutat.*

29. Rademakers R, Cruts M, van Broeckhoven C. The role of tau (MAPT) in frontotemporal dementia and related tauopathies. *Hum Mutat.* 2004;24:277-295.
30. Goedert M, Jakes R. Mutations causing neurodegenerative tauopathies. *Biochim Biophys Acta.* 2005;1739: 240-250.
31. van Swieten JC, Rosso SM, van Herpen E, Kamphorst W, Ravid R, Heutink P. Phenotypic variation in frontotemporal dementia and parkinsonism linked to chromosome 17. *Dement Geriatr Cogn Disord.* 2004;17:261-264.
32. Bugiani O, Murrell JR, Giaccone G, et al. Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. *J Neuropathol Exp Neurol.* 1999;58:667-677.
33. Casseron W, Azulay JP, Guedj E, Gastaut JL, Pouget J. Familial autosomal dominant cortico-basal degeneration with the P301S mutation in the tau gene: an example of phenotype variability. *J Neurol.* 2005;252:1546-1548.
34. Bird TD, Nochlin D, Poorkaj P, et al. A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). *Brain.* 1999;122(Pt 4):741-756.
35. Stanford PM, Shepherd CE, Halliday GM, et al. Mutations in the tau gene that cause an increase in three repeat tau and frontotemporal dementia. *Brain.* 2003;126(Pt 4):814-826.
36. Soliveri P, Rossi G, Monza D, et al. A case of dementia parkinsonism resembling progressive supranuclear palsy due to mutation in the tau protein gene. *Arch Neurol.* 2003;60:1454-1456.
37. Stanford PM, Brooks WS, Teber ET, et al. Frequency of tau mutations in familial and sporadic frontotemporal dementia and other tauopathies. *J Neurol.* 2004;251: 1098-1104.
38. Houlden H, Baker M, Morris HR, et al. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology.* 2001;56:1702-1706.
39. Baba Y, Baker MC, Le Ber I, et al. Clinical and genetic features of families with frontotemporal dementia and parkinsonism linked to chromosome 17 with a P301S tau mutation. *J Neural Transm.* 2007;114:947-950.
40. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature.* 2006;442:916-919.
41. Skibinski G, Parkinson NJ, Brown JM, et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat Genet.* 2005;37:806-808.
42. Brown J, Ashworth A, Gydesen S, et al. Familial nonspecific dementia maps to chromosome 3. *Hum Mol Genet.* 1995;4:1625-1628.
43. Cannon A, Baker M, Boeve B, et al. CHMP2B mutations are not a common cause of frontotemporal lobar degeneration. *Neurosci Lett.* 2006;398:83-84.
44. Momeni P, Rogaeva E, Van Deerlin V, et al. Genetic variability in CHMP2B and frontotemporal dementia. *Neurodegener Dis.* 2006;3:129-133.
45. Watts GD, Wymer J, Kovach MJ, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat Genet.* 2004;36:377-381.
46. Morita M, Al-Chalabi A, Andersen PM, et al. A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology.* 2006;66:839-844.
47. Vance C, Al-Chalabi A, Ruddy D, et al. Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3. *Brain.* 2006;129(Pt 4):868-876.
48. Cruts M, Gijselinck I, van der Zee J, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature.* 2006;442:920-924.
49. He Z, Bateman A. Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis. *J Mol Med.* 2003;81:600-612.
50. He Z, Ong CH, Halper J, Bateman A. Progranulin is a mediator of the wound response. *Nat Med.* 2003;9:225-229.
51. Daniel R, Daniels E, He Z, Bateman A. Progranulin (acrogranin/PC cell-derived growth factor/granulin-epithelin precursor) is expressed in the placenta, epidermis, microvasculature, and brain during murine development. *Dev Dyn.* 2003;227:593-599.
52. Masellis M, Momeni P, Meschino W, et al. Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. *Brain.* 2006;129(Pt 11):3115-3123.
53. Mesulam M, Johnson N, Krefft TA, et al. Progranulin mutations in primary progressive aphasia: the PPA1 and PPA3 families. *Arch Neurol.* 2007;64:43-47.
54. Snowden JS, Pickering-Brown SM, Mackenzie IR, et al. Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. *Brain.* 2006;129(Pt 11):3091-3102.
55. Davidson Y, Kelley T, Mackenzie IR, et al. Ubiquitinated pathological lesions in frontotemporal lobar degeneration contain the TAR DNA-binding protein, TDP-43. *Acta Neuropathol (Berl).* 2007;113:521-533.
56. Boeve BF, Baker M, Dickson DW, et al. Frontotemporal dementia and parkinsonism associated with the IVS1+ 1G→A mutation in progranulin: a clinicopathologic study. *Brain.* 2006;129(Pt 11):3103-3114.
57. Pickering-Brown SM, Baker M, Gass J, et al. Mutations in progranulin explain atypical phenotypes with variants in MAPT. *Brain.* 2006;129(Pt 11):3124-3126.
58. International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *J Med Genet.* 1994;31:555-559.