Published in final edited form as:
Int Rev Psychiatry. 2013 April ; 25(2): 130–137. doi:10.3109/09540261.2013.776523.

The Epidemiology of Frontotemporal Dementia

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Abstract

Frontotemporal dementia, a heterogeneous neurodegenerative disorder, is a common cause of young-onset dementia (i.e., dementia developing in midlife or earlier). The estimated point prevalence is 15–22/100,000, and incidence 2.7–4.1/100,000. Some 25% are late-life onset cases. Population studies show nearly equal distribution by gender, which contrasts with myriad clinical and neuropathology reports. FTD is frequently familial and hereditary; five genetic loci for causal mutations have been identified, all showing 100% penetrance. Non-genetic risk factors for are yet to be identified. FTD shows poor life expectancy but with survival comparable to that of Alzheimer disease. Recent progress includes the formulation of up-to-date diagnostic criteria for the behavioral and language variants, and the development of new and urgently needed instruments for monitoring and staging the illness. There is still need for descriptive populations studies, to fill gaps in our knowledge about minority groups and developing regions. More pressing, however, is the need for reliable physiologic markers for disease. There is a present imperative to develop a translational science to form the conduit for transferring neurobiological discoveries and insights from bench to bedside.

INTRODUCTION

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous familial and sporadic neurodegenerative disorder usually manifesting, at its onset, as focal disintegration of temperament, judgment, conduct, and speech. It is, along with Alzheimer disease (AD), a leading cause of dementia developing in midlife or earlier. It typically develops in the sixth decade of life (Neary, Snowden, & Mann, 2005), but some cases arise in youth — where it may mimic psychiatric disorders such as schizophrenia, bipolar affective disorder and major depression (Velakoulis, Walterfang, Mocellin, Pantelis, & McLean, 2009) — and others in later-life (Baborie et al., 2012). The typical presentation consists of gross decline in conduct (i.e., the behavioral variant) or speech/language (the language variant). Thus results a behavioral phenotype beginning with combinations of indifference, impatience, carelessness, jocularity, insensitivity, distractibility, impulsiveness, stereotyped behaviors, compulsions and rigid routines, or language phenotypes featuring either effortful, dysfluent, agrammatical speech, and impaired comprehension of sentences, or fluent, vacuous speech, with anomia and word (and object) agnosia. Non-typical

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Declaration of interest: Dr. Onyike has received support from the Samuel I. Newhouse Foundation; the Robert Hall family; and the Jane Tanger Black Fund for Young-Onset Dementia Research. Dr. Diehl-Schmid reports no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

presentations feature prominently speech and limb apraxia, parkinsonism or motor neuron disease (MND) (Boeve, 2007). The behavioral variant seems to account for nearly 60% of cases of FTLD; the language variants are less common. The largest clinical study analyzed data from two centers in the United States and one in Germany (N=353) found that 57% were behavior variant cases, whereas 43% were language variant (Johnson et al., 2005). Eventually FTD, whatever the initial phenotype, evolves a global dementia (Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005).

This paper presents the population and clinical epidemiology of FTD, with a focus on its distribution and demographics, its risk factors (principally are genetic), its formal definitions and diagnostic criteria, its measurement and staging, and its morbidity and mortality. Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are often considered members of the FTD family, but here we focus on the forms, behavioral FTD and primary progressive aphasia, which are the commonest and also the most likely to be encountered by psychiatrists.

METHOD

The search strategy focused on studies of prevalence, incidence and survival in FTD and primary progressive aphasia (PPA). We collated familiar papers and also implemented a search strategy in PubMed and Google Scholar. The search terms are: “frontotemporal dementia” or “frontotemporal lobar degeneration” or “FTD” or “FTLD” or “semantic dementia” or “primary progressive aphasia” or “progressive aphasia” in combination with “prevalence” or “incidence” or “mortality” or “survival” or “natural history” or “life expectancy.” We reviewed the papers we found, and topical reviews, for additional pertinent papers. This review relies on full-text papers written in the English-language.

DISTRIBUTION OF FTD IN THE POPULATION

Surveillance of FTD in the population is difficult and expensive because disease frequency is low, the at-risk population is very large, and diagnosis relies on expert proficiency (Knopman & Roberts, 2011). Nevertheless, within the last decade prevalence and incidence data have accumulated from population studies conducted in Canada (Feldman et al., 2003), Japan (Ikejima et al., 2009), Italy (Bernardi et al., 2012; Borroni et al., 2010; Gilberti et al., 2012) the Netherlands (Rosso, Kaat, Baks, & Joosse, 2003a), Spain (Garre-Olmo et al., 2010), the United Kingdom (Harvey, Skelton-Robinson, & Rossor, 2003; Mercy, Hodges, Dawson, Barker, & Brayne, 2008; Ratnavalli, Brayne, Dawson, & Hodges, 2002) and the United States (Knopman, Petersen, Edland, Cha, & Rocca, 2004). These data are summarized in Tables 1 and 2. Notice that all but one were conducted in Europe or North America — these studies featuring samples that >95% Caucasian (except for the one study) and thus underrepresentation of non-Caucasian populations. That exception is similarly homogenous in its Japanese enrollment (Ikejima et al., 2009). There are recent preliminary studies of FTD prevalence from India (Alladi et al., 2011) and China (Ren et al., 2012).

Population studies of FTD generally are conducted within a regional catchment area. Most relied on medical record linkage and coding, a few utilized passive surveillance and disease registries (Borroni et al., 2010; Garre-Olmo et al., 2010; Gilberti et al., 2012), and fewer still recruited and examined subjects (Bernardi et al., 2012; Feldman et al., 2003). This has spawned non-trivial variation in sampling frames and methodologies, as well as in case ascertainment strategies. Nevertheless these data are valuable sources on the frequency and distribution of FTD.

Table 1 shows that prevalence estimates of FTD have varied widely, ranging from 2.0/100,000 in Zuid-Holland (Rosso et al., 2003a) to 31/100,000 in Vallemonica (Gilberti et

al., 2012). This wide variation can be explained: many report point-prevalence and some cumulative prevalence; there are differences in the age distribution of FTD; there are also differences in sampling frames and ascertainment methods (thus differences in proportions of missed cases and misclassifications); and there are regional variations in the risk factors for FTD. The Italian studies, which reported the three highest prevalence estimates, illustrate many of the issues. The Brescia study (Borroni et al., 2010) analyzed data from eight years of surveillance in six centers in their network, thus reporting an 8-year cumulative prevalence in the 45-64 age group and higher rates in older subjects. The Vallemonica study also reports a 10-year cumulative prevalence and, like the Reggio Calabria study (Bernardi et al., 2012), sampled a relatively isolated community hosting hereditary FTD. In contrast, the comparative rarity of hereditary cases in Japan (Ikeda, Ishikawa, & Tanabe, 2004) probably contributed to the much lower point prevalence reported in the Ibaraki study (Ikejima et al., 2009).

Knopman and Roberts (Knopman & Roberts, 2011) have attributed low point prevalence estimates reported in the Zuid-Holland and Ibaraki studies, 4.0/100,000 and 2.0/100,000 respectively, to the relative insensitivity of the Lund-Manchester diagnostic criteria (The Lund and Manchester Groups, 1994) and, in Ibaraki, also to relative unfamiliarity of local practitioners with FTD syndromes. We note, however, these criteria were applied in the London study (Harvey et al., 2003) that reported four- and seven-fold higher prevalence than Zuid-Holland and Ibaraki, respectively. Knopman and Roberts (Knopman & Roberts, 2011) have also estimated that the true point prevalence of FTD is 15-22/100,000; their analyses used ratios derived from large neuropathological (Rascovsky et al., 2011) and clinical (Johnson et al., 2005) series to adjust for age differences in the frequency of FTD reported in Zuid-Holland. We accept this finding, but with the proviso that neuropathological and clinical series may undercount older cases of FTD that show amnesic features mimicking Alzheimer disease.

There is much less data on the incidence of FTD (see Table 2). Two of the three studies were conducted in Europe, the other in the United States. Estimates. The Rochester (Knopman et al., 2004) and Cambridgeshire (Mercy et al., 2008) studies relied on medical record linkage and review, whereas the Girona study (Garre-Olmo et al., 2010) did three years of passive surveillance. Nevertheless the estimates of FTD incidence show little variability (2.7–4.1/100,000 in individuals <70 years) in comparison to the prevalence data.

The data summarized in the two tables pertain, with a few exceptions, to the prevalence and incidence of FTD in the age group 45–64 years. The studies also yielded prevalence data in cases younger than 45 years and older than 65. Data from the Zuid-Holland study show 12.7% were <50 years of age and 22% were >65; prevalence was highest in the age group 60–69. In the London study, which focused on young-onset dementias (i.e., dementia in individuals <65 years), 12% of FTD cases were <50 years. In contrast, 66.2% of FTD cases in Brescia were >65 years — a finding inconsistent with clinical experience and numerous clinical and neuropathological samples. We suspect, as have others (Knopman & Roberts, 2011), that diagnostic misclassification skews the data from the Brescia study. The Rochester (Knopman et al., 2004) and Girona (Garre-Olmo et al., 2010) studies report age-stratified incidence rates: For the age groups 40–49, 50–59 and 60–69 years, respectively, these were 2.2, 3.3, and 8.9/100,000 person-years in Rochester and 1.2, 2.4, and 7.7/100,000 person-years in Girona. With respect to sex distribution of FTD, the Cambridgeshire study observed a 4.7-fold higher prevalence among men, whereas the Zuid-Holland study reported a 1:1 sex distribution. The Brescia and Ibaraki studies showed sex distribution close to that reported in the Zuid-Holland study. The Reggio Calabria and Vallemonica studies reported a 3:1 female predominance in the cases, observations that cannot be generalized beyond these isolated populations that harbor genetic mutations that cause FTD.

GENETIC RISK FACTORS

The convergent data from family, clinical and population studies showing that FTD is familial in 30–50% of cases, and up to 40% an autosomal-dominant pedigree (Bird et al., 2003; Goldman et al., 2005), stimulated a vigorous search for the causal genes in North America and Europe. Within the last 15 years the search has led to the identification of five genetic loci for causal mutations:

- Chromosome 9 open reading frame 72 (C9ORF72), chromosomal location 9p21.2, found by association studies of familial FTD-MND, followed by mutation analysis of positional candidate genes (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Some sporadic cases of FTD-MND have this mutation. Psychosis at presentation is not uncommon in carriers (Snowden et al., 2012).
- Progranulin (GRN), location 17q21.32, by linkage analysis followed by mutation analysis of positional candidate genes (Baker et al., 2006; Cruts et al., 2006).
- Microtubule-associated protein tau (MAPT), location 17q21.32, identified by linkage analysis of familial FTD with parkinsonism and gene-phenotype correlation (Hutton et al., 1998).
- Valosin-containing protein (VCP), location 9p13.3, by linkage analysis of a familial disorder characterized by inclusion body myopathy with osteolytic bone disease and FTD (Watts et al., 2004).
- Chromatin-modifying protein 2B (CHMP2B), location 3p11.2, by linkage analysis (Skibinski et al., 2005).

Cases with C9ORF72, GRN and VCP mutations have intraneuronal inclusions that stain for TAR DNA-binding protein 43 (TDP-43), cases with MAPT mutations have tau-positive inclusions, and cases with the CHMP2B mutation are tau and TDP-43 negative. Mutations in the C9ORF72, GRN and MAPT genes show complete penetrance, although age-dependence has been described for GRN (Gass et al., 2006; Rademakers et al., 2007). Most hereditary FTD, >80%, appears attributable to mutations of C9ORF72, GRN and MAPT; C9ORF72 and GRN mutations are the primary causes of hereditary tau-negative FTD (Rademakers, Neumann, & Mackenzie, 2012), whereas MAPT mutations account for virtually all hereditary tau-positive FTD. The C9ORF72 mutation also appears to the most common cause of hereditary MND (van der Zee et al., 2013). Mutations at CHMP2B and VCP are rare causes of hereditary FTD, accounting for <1% of cases. Mutations in the TDP-43 (Sreedharan et al., 2008), Fused-in-Sarcoma (FUS) (Vance et al., 2009) and Ubiquilin-2 genes (Deng et al., 2011) have been linked to MND but do not appear to cause FTD.

Knowledge of FTD susceptibility genes is in its infancy because the most research efforts focused on finding the causal genes, but lately two susceptibility loci have now been identified (Rademakers et al., 2008; van der Zee et al., 2011). The interested reader is referred to two recent and excellent reviews of the molecular genetics of FTD (Rademakers et al., 2012; Sieben et al., 2012).

NON-GENETIC RISK FACTORS

A small retrospective case-control study from the Netherlands (Rosso et al., 2003b) investigated the influence of environmental risk factors in 80 patients with sporadic FTD and 124 cognitively healthy controls. The study found that head trauma was associated with a 3.3-fold higher risk for FTD, and thyroid disease with a 2.5-fold higher risk. No other risk

factors were identified. The retrospective case-control-design limits the scope of interpretation of these data, along with the fact that the observations still await replication.

DIAGNOSTIC RULES

For nearly 20 years, the diagnosis of FTD, particularly in research settings, has been codified and operationalized in formal criteria (Gorno-Tempini et al., 2011; McKhann et al., 2001; Anonymous:1994vy; Neary et al., 1998; Rascovsky et al., 2011). The latest diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011), formulated by the International Behavior-variant FTD Criteria Consortium — consisting of international experts in the field — were developed to incorporate new knowledge into the diagnostic process and address the problems of the preceding criteria (Rascovsky et al., 2007). The new diagnostic criteria for behavior-variant FTD, bvFTD (Rascovsky et al., 2011) have introduced flexibility in the application (necessary given the heterogeneity of presentations) and a hierarchy of diagnostic confidence (i.e., 'possible', 'probable' or 'definite' bvFTD), and achieved the incorporation of brain imaging, genetic testing and neuropathological data into the diagnostic decision-making. A diagnosis of 'possible' bvFTD requires sustained functional decline and three of six items that codify impairments of conduct and executive dysfunction. The diagnosis ranks as 'probable' when there is evidence of focal frontal and/or temporal atrophy or physiologic dysfunction (based on CT, MRI or FDG-PET scans). Assigning 'definite' bvFTD requires pathophysiologic evidence, i.e., a causal genetic mutation or neuropathological characterization (the usual context being post-mortem brain examination). The new bvFTD criteria showed sensitivity superior the Neary Criteria (Neary et al., 1998), the previous standard, (0.75, 95% CI:0.68–0.82 versus 0.52, 95% CI: 0.44–0.60) when both were applied retrospectively to FTD cases from research center brain banks (i.e., cases with neuropathological diagnosis) (Rascovsky et al., 2011). The specificity of these criteria has not yet been reported as this would require large and expensive prospective study.

Another set of diagnostic criteria codifies the diagnosis of PPA (Gorno-Tempini et al., 2011). These criteria define three subtypes of PPA: non-fluent aphasia, semantic dementia and logopenic aphasia. These criteria illustrated the differences between the subtypes; non-fluent aphasia cases show agrammatism, effortful and halting speech with sound distortions and errors, and impaired comprehension of syntactically complex sentences. Semantic dementia cases show impairments in naming, word comprehension and object knowledge, and surface dyslexia and/or dysgraphia (i.e., regularization errors in reading or spelling when presented with irregular words). The logopenic aphasia cases show impaired word retrieval, halting speech without agrammatism, disproportionate impairment of sentence repetition, and phonological errors in spontaneous speech. The sensitivity and specificity of these criteria await formal, prospective estimation.

MEASUREMENT

Defining severity and stage of illness in FTD is difficult due to heterogeneity of syndromes and presentations; variation in the frequency, timing, persistence and intensity of signal behavioral features; limited information on the rate of progression in FTD; and relative preservation of memory, orientation and other cognitive faculties impaired early in DAT. Clinical estimations rely on synthesis of data from different sources – interview, examination, brain images, and psychometric instruments. For research the picture is more complicated, because research aims. Most research has depended on the Mini-Mental State Examination (MMSE) (M. Folstein, Folstein, & McHugh, 1975) and the Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982), both developed for measurement of AD. Recent data indicate FTD and AD differ in the profile and tempo of

decay in MMSE scores (Tan, Libon, Rascovsky, Grossman, & Xie, 2013). This may result from the MMSE not measuring the asocial or behavioral aspects of the FTD phenotype, or to focal decline in language (Chow, Hynan, & Lipton, 2006). Nevertheless, the MMSE is useful for estimating impairment, tracking decline, describing interval change and comparing populations, albeit in relative rather than absolute terms. The scoring algorithm of the CDR (Morris, 1997) does not take into account language and behavioral dysfunction, and is weighted to represent memory impairment more than other cognitive and disability factors. Since amnesia is usually not a prominent feature, it is not surprising the CDR underestimates disability in early FTD (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010). A modified version, the Frontotemporal Lobar Dementia CDR (FTLD-CDR), is gradually supplanting the CDR in FTD research because the two added domains for behavioral and language impairments have improved its sensitivity for impairment and interval change in FTD (Knopman, Weintraub, & Pankratz, 2011).

The most commonly used measure for capturing the intensity of behavioral disorder in FTD is the Frontal Behavior Inventory (FBI) (Kertesz, Nadkarni, Davidson, & Thomas, 2000). It is based on proxy interview, and has been shown to discriminate FTD from other dementias and capture interval change (Marczinski, Davidson, & Kertesz, 2004). Its limitation is that it does not measure many domains of cognition, such as memory and orientation, which will inevitably decline. The items focus on asocial behaviors, apathy, impulsions and compulsions, all subject to attenuation or disappearance as the illness advances – one might observe ‘improvement’ in the scores after long intervals.

The Frontotemporal dementia Rating Scale (FRS) (Mioshi et al., 2010) measures illness progression. It was constructed by item analysis of 30 probe questions culled from two older instruments designed to measure dementia-related behavior and disability. Statistically defined thresholds were computed to define levels of severity. The Dementia Disability Rating (DDR) (Onyike et al., 2011), developed to measure disability in heterogeneous dementia phenotypes, takes a different approach. It has been designed to quantification capacities that are immediately pertinent to everyday living, thus it is informed by a disablement perspective (Barberger-Gateau et al., 2004; Barberger-Gateau, Fabrigoule, Amieva, Helmer, & Dartigues, 2002) in an “etiologically neutral” approach to dementia related functional decline. Preliminary data show inter-rater reliability of ratings of FTD severity to be better than reliability achieved using the CDR, with both systems showing comparable reliability for rating AD (Onyike et al., 2011).

LIFE EXPECTANCY AND SURVIVAL

FTD causes dramatic reduction in life expectancy (Brodaty, Seeher, & Gibson, 2012), taking into account its midlife onset. The condition advances inexorably until death from pneumonia, failure to thrive, or cardiopulmonary failure. Population studies of FTD survival are difficult to conduct, because FTD is relatively uncommon and phenotypically heterogeneous. Thus most studies of survival in FTD derive from specialist clinic cohorts, using outcomes that describe the evolution of morbidity and disability, or measure milestones, illness duration and survival.

Survival varies widely from 3-14 years; the tempo of decline depends on the phenotype. Early survival analyses showed median survival from diagnosis of FTD to be 7-13 years in clinic cohorts and 6-8 years in neuropathology series (Onyike, 2011). The clinical studies find that SD has the longest median survival (12 years), and PNFA and bvFTD show comparable survival (9 years) (Nunnemann et al., 2011; Roberson et al., 2005). FTD-MND has the poorest prognosis with death occurring within 2-3 years of symptom onset (Hodges, Davies, Xuereb, Kril, & Halliday, 2003), although survival for up to 5 years has been

reported (Hu et al., 2009). Some data have shown that tau-positive FTD has higher median survival (9.0 years) than tau-negative pathology (Hodges et al., 2003; Rascovsky et al., 2005; Xie et al., 2007), but this may reflect inclusion of FTD-MND cases (which are tau-negative) in some analyses.

Survival has not been shown to be associated with the demographic characteristics of FTD subjects, their age at illness onset, or the severity of their dementia at the time of diagnosis (Hodges et al., 2010; Nunnemann et al., 2011; Roberson et al., 2005). There are, to our knowledge, no data showing whether illness features such as mutism, oral-buccal apraxia, dysphagia, choking, parkinsonism and falls affect survival. It is not known whether comorbid conditions, such as obesity, diabetes mellitus, recurrent urinary tract infections, and others, affects survival in FTD.

DISCUSSION

It has been 30 years since the rekindling of interest in FTD that began with pivotal descriptions of its phenotypic and pathologic heterogeneity (Constantinidis, Richard, & Tissot, 1974). In the interval since, there has been an explosion of knowledge and activity relating to FTD. This includes a growing understanding of the frequency and distribution of FTD, the advances in case definition and classification, the introduction of brain imaging technologies into clinical practice and research, the description of diverse pathologic states, and the identification of causal genes. Genetic discoveries, in particular, have resulted in extraordinary insights into neurobiology of these conditions and accelerated the pace and expanded the scope of inquiry. These discoveries are also providing new and sometimes, unexpected, information about phenotypes and pathologic states that test our conceptualization of FTD and its phenotypic boundaries.

Thus epidemiological inquiry and investigation still has an important role to play. At the basic level, we are still missing accurate estimates of the population distribution of FTD, particularly in developing countries and among minority groups in developed countries. Large, prospective, collaborative studies can plug these gaps, provide the setting and data for examining new phenotypic data, validating and calibrating new diagnostic criteria and psychometric instruments, and identifying the susceptibility genes and non-genetic risk factors that shape illness expression. Thus far the clinical epidemiology of FTD has focused on the description and measurement of phenotypes, characterization of morbidity and development of treatments. In the future, as disease pathophysiology becomes known, a translation science will be required to bring bioassays and other physiologic measures of disease status into the clinic.

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Table 1

Prevalence of frontotemporal dementia (FTD)

Location/Study	Sampling frame and method	Sample	Age group	Age at onset	Sex ratio (M:F)	N	Prev.*	95% CI
Cambridgeshire, UK (Ratnavalli et al., 2002)	Regional network; coded records and recruitment	FTD+PPA	45–64	52.8	14:3	11	15.1	8.4–27.0
Canada (Feldman et al., 2003)	National cohort; cross-section of subjects	FTD	<70	NR	NR	36	12.1	NR 9.1–24.3
London, UK (Harvey et al., 2003)	Regional network; coded records	FTD	45–64	57	NR	18	15.4	
Zuid-Holland, Netherlands (Rosso et al., 2003)	Regional network; coded records	FTD	45–64	58	1:1	55	4.0	2.8–5.7
Ibaraki, Japan (Ikejima et al., 2009)	Regional network; coded records	FTD	45–64	60	1.5:1	17	2.0	1.3–3.2
Brescia, Italy (Borroni et al., 2010)	Regional network; surveillance registry	FTD+PPA	45–64	65.6	1:1.2	213	22**	17.0–27.0
Reggio Calabria, Italy (Bernardi et al., 2012)	Regional network; active ascertainment	FTD	50+	75.9	1:3	18	18	NR
Vallecamonica, Italy (Gilberti et al., 2012)	Regional center; surveillance registry	FTD+PPA	45–65	66.1	1:3	10	31**	20.0–42.0

Mean age at onset for the Cambridgeshire, Brescia, Reggio Calabria and Vallemonica studies, and median age at onset for the London, Zuid-Holland and Ibaraki studies. Median age of onset for London and Ibaraki studies was calculated from data in the published report.

NR = not reported.

FTD = frontotemporal dementia; PPA = primary progressive aphasia. Three studies report prevalence for subtypes of FTD.

* Prevalence per 100,000 population, except in the case of Canada where prevalence is defined as a percentage of ascertained cases.

** Cumulative prevalence over 8 and 10 years in Brescia and Vallemonica, respectively.

Table 2

Incidence of frontotemporal dementia (FTD)

Location/Study	Sampling Frame and method	Interval (Years)	Sample	Age group	Age at onset	Sex ratio (M:F)	N	Incidence	95% CI
Rochester, USA (Knopman et al., 2004)	City/suburban network; linked and coded records	4	FTD+PPA	40–69	57.5	0:4	4	4.1	1.1–10.4
Cambridgeshire, UK (Mercy et al., 2008)	Regional network; coded records	6	FTD	45–64	57	1.3:1	16	3.5	2.0–5.7
Girona, Spain (Garre-Olmo et al., 2010)	Regional network; surveillance registry	3	FTD+PPA	30–64	NR	NR	14	1.3	0.7–2.2
				65+		NR	56	16.7	12.6–21.7
				45–64		NR	14	2.7	1.5–4.6*

Median age at onset calculated from data provided in the published reports.

NR = not reported.

FTD=frontotemporal dementia; PPA = primary progressive aphasia. Three studies report prevalence for subtypes of FTD.

*As computed and reported by Knopman and Roberts, 2011 (Knopman & Roberts, 2011).