Frontotemporal dementia and parkinsonism associated with the IVS1+1G→A mutation in progranulin: a clinicopathologic study

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We previously reported a kindred with three cases of dementia, in which the proband exhibited features typical of frontotemporal dementia and parkinsonism (FTDP). An arginine insertion at codon 352 (insR352) in the presenilin-1 (PSEN1) gene was identified in the proband, but analyses in plasma and CSF suggested a mechanism of neurodegeneration not directly related to amyloid pathophysiology. The proband was followed with yearly evaluations of functional, clinical, neuropsychologic, neuropsychiatric and radiologic status, which showed relatively linear change over the initial 4 years of assessment. Upon the proband’s death at age 63, neuropathologic examination revealed frontotemporal lobar degeneration (FTLD) with ubiquitin-positive inclusions (FTLD-U). We recently identified several kindreds with familial FTDP associated with mutations in the progranulin (PGRN) gene, particularly in those cases with neuronal intranuclear inclusions. Our proband was indeed found to have such inclusions, and PGRN analysis in this proband revealed the G to A mutation in the exon 1 splice donor site (IVS1+1G→A) which is predicted to destroy the 5'-splice site of exon 1 and remove the start methionine codon and hence completely block any PGRN protein from being generated. These findings suggest that the insR352 PSEN1 is not pathogenic, and the IVS1+1G→A mutation in PGRN causes FTDP associated with FTLD-U pathology and represents a new class of neurodegenerative disease—the ‘hypoprogranulinopathies’.

Keywords: frontotemporal dementia; progranulin; presenilin; neurodegenerative disease; neurogenetics

Abbreviations: Aβ = beta-amyloid; FTD = frontotemporal dementia; NFT = neurofibrillary tangles; SP = senile plaques; VV = ventricular volume; WBV = whole-brain volume

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Introduction

Over 60 mutations in the presenilin-1 gene (PSEN1) located on chromosome 14q24.3 have been identified in autosomal dominant Alzheimer’s disease. Although the clinical phenotype associated with most mutations has been progressive memory impairment followed by progressive impairment in other cognitive domains, atypical features have been present in many, including spastic paraparesis (Crook et al., 1998), seizures, prominent ‘psychiatric’ symptoms (Tedde et al., 2000), and frontotemporal dementia (FTD) (Raux et al., 2000a, b). Almost all cases have had elevations in plasma and/or cerebrospinal fluid beta-amyloid (Aβ) levels (Borchelt et al., 1996), particularly of the Aβ40 and Aβ42 fractions, as well as characteristic ‘cotton wool’ amyloid plaques on neuropathologic...
examination (Crook et al., 1998; Dermaut et al., 2001), strongly implicating the direct causal role of abnormal amyloid protein processing in the pathogenesis of PSEN1-associated mutations regardless of clinical phenotype.

Understanding the aetiologic mechanisms underlying some of the more recently described cases with PSEN1 mutations has been perplexing. The initially described cases with the phenotype of FTD had novel mutations identified—Leu113Pro (Raux et al., 2000a, b; Rogaeva et al., 2001) and insArg352 (henceforth abbreviated ‘insR352’) (Rogaeva et al., 2001; Amtul et al., 2002; Tang-Wai et al., 2002), but no neuropathological findings have been reported on affected individuals to date. Two more recently described kindreds showing some clinical features suggesting FTD, but with different PSEN1 mutations—G183V (Dermaut et al., 2004) and M146L (Halliday et al., 2005)—have interestingly had Pick bodies, with Alzheimer-type pathology coexisting in one kindred (Halliday et al., 2005). Biochemical studies in the G183V kindred failed to show any increase in the presumed neurotoxic Aβ species, suggesting that this specific mutation did not cause the disease via amyloidogenic mechanisms. Additional data on such PSEN1 mutation/non-amyloid pathology kindreds are clearly desired to better understand the role of PSEN1 mutations in neurodegeneration.

We and others very recently identified mutations in the progranulin (PGRN) gene in several kindreds of familial FTD associated with frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) pathology (Baker et al., 2006; Cruts et al., 2006). Only scant data exists on the normal role of progranulin and on pathologic states relating to progranulin dysfunction (He and Bateman, 2003; Ong and Bateman, 2003). Progranulin is involved in epithelial cell growth and promotes tumour growth (He and Bateman, 2003; Ong and Bateman, 2003). Mutations resulting in frame shift or stop codons in PGRN likely form null alleles such that no progranulin protein is expressed (Baker et al., 2006; Cruts et al., 2006). We suspect that the lack of progranulin production leads to neurodegeneration, but the precise mechanisms underlying the neurodegenerative changes are not yet known.

We previously reported the pedigree, clinical and radiologic features (Tang-Wai et al., 2002), and biochemical findings (Amtul et al., 2002), in the small kindred noted above with FTD associated with the novel arginine insertion at codon 352 (insR352) in PSEN1 gene identified in the proband. The proband has been followed longitudinally with FTD associated with the novel arginine insertion at codon 352 (insR352) in PSEN1 (Rogaeva et al., 2001) and insArg352 (henceforth abbreviated ‘insR352’) (Rogaeva et al., 2001; Amtul et al., 2002; Tang-Wai et al., 2002), but no neuropathological findings have been reported on affected individuals to date. Two more recently described kindreds showing some clinical features suggesting FTD, but with different PSEN1 mutations—G183V (Dermaut et al., 2004) and M146L (Halliday et al., 2005)—have interestingly had Pick bodies, with Alzheimer-type pathology coexisting in one kindred (Halliday et al., 2005). Biochemical studies in the G183V kindred failed to show any increase in the presumed neurotoxic Aβ species, suggesting that this specific mutation did not cause the disease via amyloidogenic mechanisms. Additional data on such PSEN1 mutation/non-amyloid pathology kindreds are clearly desired to better understand the role of PSEN1 mutations in neurodegeneration.

Material and methods

Subjects

All available clinical records and neuroimaging studies on the proband since our original report were reviewed and analysed, and no additional members of this kindred have since become symptomatic. The proband was enrolled in the Mayo Alzheimer’s Disease Research Center, which is a Mayo Foundation Institutional Review Board-approved protocol, and was followed longitudinally with a standardized battery of functional, neuropsychologic, neuropsychiatric, clinical, laboratory and radiologic studies at ~12-month intervals until death. The neurologists who performed the neurologic evaluations and completed several functional measures (B.F.B. and D.T.W.) were blinded to scores and ratings from prior evaluations. Genetic analyses, serial MRI scans and eventual autopsy were performed after the family provided written consent.

Functional assessments

All data on the Clinical Dementia Rating (CDR) scale (Morris, 1993), Global Deterioration Scale (GDS) (Reisberg et al., 1988), and Record of Independent Living—part A (ROIL-A) (Weintraub, 1986) were tabulated and analysed.

Neuropsychological assessments

Testing included assessments of screening and global cognitive functioning [Mini-Mental State Examination (MMSE; Folstein et al., 1975)], Short Test of Mental Status (STMS; Kokmen et al., 1991; Tang-Wai et al., 2003), Mattis Dementia Rating Scale (DRS; Mattis, 1988), learning and memory [logical memory (WMS-LM) and visual reproductions (WMS-VR) of the Wechsler Memory Scale—Revised (WMS-R) (Wechsler, 1987), Auditory Verbal Learning Test (AVLT; Rey, 1964)], language functioning [Boston Naming Test (BNT; Kaplan et al., 1983), Controlled Oral Word Association Test (COWAT; Benton and Hamsher, 1978), Multilingual Aphasia Examination Token Test (TOKEN; Benton and Hamsher, 1978), and Category/Semantic Fluency (animals, fruit, vegetables) (CAT FLU)], attention/executive functioning [Trail-Making Test (TMT; Reitan, 1958), digit span (WAIS-DS) of the revised Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981), and Wisconsin Card Sorting Test (WCST; Heaton, 1981)], and visuospatial skills [block design (WAIS-BD) and picture completion (WAIS-PC) subtests of the WAIS-R (Wechsler, 1981), and Rey–Osterrieth complex figure (REY-O; Rey, 1941; Osterrieth, 1944)]. Mayo Older American Normative Studies (MOANS) norms were used to determine scaled scores for these tests, in which 10 represents the mean and the SD is 3 (Ivnik et al., 1992, 1996, 1997; Lucas et al., 1998a, b).

Neuropsychiatric assessments

Neuropsychiatric Inventory (NPI; Cummings et al., 1994) data were provided by the proband’s husband. The total score (sum of the products of frequency and severity for the 12 neuropsychiatric features, maximum value of 12 for each item) was used to quantify the neuropsychiatric burden, with increasing values reflecting increasing burden. The product of (frequency × severity) for each item over all evaluations was also presented graphically and analysed.
Clinical evaluations

All comprehensive neurobehavioural clinical data (Members of the Department of Neurology, 1998) were reviewed and summarized. The modified motor subtest of the United Parkinson’s Disease Rating Scale (UPDRS) was used to assess the degree of parkinsonism (range 0–44); increasing values reflect greater degrees of parkinsonism (Fahn et al., 1987).

Laboratory analyses

Sequence analysis of PSEN1, amyloid precursor protein (APP), microtubule-associated tau protein (MAPT), and PGRN from patient genomic DNA was performed as described previously (Hutton et al., 1996, 1998; Tang-Wai et al., 2002; Baker et al., 2006).

Neuroimaging examinations

MRI was performed using a GE scanner at 1.5 T, and images of the brain were obtained in the sagittal (T1-weighted), axial (proton-density, T2-weighted, and fluid attenuation inversion recovery (FLAIR)), and coronal (T1-weighted) planes. Changes in whole-brain volume (WBV) and ventricular volume (VV) were measured from serial MRI studies using the boundary shift integral (BSI) method as described (Gunter et al., 2003; Boeve et al., 2005).

1H magnetic resonance spectroscopy (1H MRS) studies were performed with the automated single voxel MRS package: Proton Brain Examination/Single Voxel (PROBE/SV). Point resolved spectroscopy (PRESS) pulse sequence with TR = 2000 ms, TE = 30 ms, 2048 data points and 128 excitations were used for the examinations. An 8 cm³ (2 × 2 × 2 cm³) voxel, prescribed on a mid-sagittal T1-weighted image, included right and left posterior cingulate gyri and inferior precunei. The anterior border of splenium, the superior border of corpus callosum and the cingulate sulcus were the anatomical landmarks to define the anterior inferior and the anterior superior border of the 8 cm³ voxel as described previously (Kantarci et al., 2004). We analysed the metabolite intensity ratios, using creatine (Cr) as an internal reference metabolite to control for acquisition and scanner related variability.

Neuropathologic examination

Sections of neocortex, hippocampus, amygdala, basal ganglia, thalamus, midbrain, pons, medulla and cerebellum were stained with haematoxylin and eosin. Sections of cortex, hippocampus and amygdala are studied with Bielschowsky and thioflavin-S fluorescent microscopy. Sections of cortex and hippocampus were immunostained for Aβ (6F/3D, 1:10; DAKO, Carpinteria, CA), phospho-tau (AT8, 1:1000; Endogen, Woburn, MA, USA), ubiquitin (Ubi-1, 1:40 000; Chemicon, Temecula, CA, USA), and alpha-synuclein (LB509, 1:100; Zymed, South San Francisco, CA, USA), HLA-DR (LN3; 1:100) and ubiquitin. For immunohistochemistry 5-μm thick paraffin sections were deparaffinized and rehydrated and stained with a DAKO Autostainer (DAKO, Carpinteria, CA) using 3,3’-diaminobenzidine (DAB) as the chromogen. For Aβ and α-synuclein, the sections were pretreated with 95% formic acid for 30 min and then steamed in distilled water for 30 min. After immunostaining, the sections were counterstained with haematoxylin.

Results

Genetic analyses

A PSEN1 mutation analysis in the proband revealed that there was one normal allele, while the other had a 3 bp insertion (a repeat of the previous 3 bp) after nt 1055 at codon 352 in exon 10 (Tang-Wai et al., 2002). No mutation was identified in APP or MAPT. Genomic sequence analysis of all PGRN exons revealed a G to A mutation of the first intronic base following the end of exon 1 [IVS1+1G→A; exon numbering corresponds to that previously published by Baker et al. (2006) and Cruts et al. (2006)]. The predicted effect of this change is to destroy the 5’-splice site of exon 1 (leading to the splicing out of exon 1 from the mRNA) and removal of the start methionine codon, thereby completely blocking any PGRN protein from being generated.

Analyses of longitudinal clinical and functional data

The proband, proband’s father, and proband’s paternal grandfather exhibited dementia and prominent neuropsychiatric features, with the onset of symptoms developing in the early to middle 60s in the proband’s father and grandfather and at age 56 in the proband (Tang-Wai et al., 2002). The proband’s initial symptoms included repeated questioning, forgetting appointments, forgetting financial matters, taking medication erroneously and excessive daytime sleepiness. She later developed features consistent with the Kluver–Bucy syndrome (Lilly et al., 1983) with prominent hyperphagia and hypersexuality, as well as illusions, delusions and visual hallucinations. Additional details of her clinical course through age 59 have been reported (Tang-Wai et al., 2002), and subsequently her cognitive impairment progressed such that she was fully dependent on her husband for activities of daily living. At age 61, subtle left hemiparkinsonism had evolved, which was modestly levodopa-responsive; there was no convincing apraxia. By age 62 she was mute and tended to hold her left upper extremity in a flexed posture at the elbow and wrist. She had mild dystonia involving the posterior cervical muscle group, but no true alien limb phenomenon, myoclonus or fasciculations. She expired at age 63 from bronchopneumonia.

Changes in her clinical and functional status are shown in Figs 1 and 2, with the interpretation of the data described in the figure legend.

Analyses of longitudinal neuropsychological data

Changes in her neuropsychological performance are shown in Figs 3 and 4, with the interpretation of the data described in the figure legend.
Analyses of longitudinal neuropsychiatric data

Changes in her neuropsychiatric status are shown in Fig. 5, with the interpretation of the data described in the figure legend.

Analyses of longitudinal radiologic data

Representative MRI are shown in Fig. 6, and the longitudinal WBV and VV calculations are graphically shown in Fig. 7. The calculated annualized changes in WBV and VV, respectively, were $-43.1$ ($-3.34\%$/year) and $+37.4$ ml/year ($+27.78\%$). The change in MR spectroscopy from Evaluations 1–2 compared with control is shown in Fig. 8, with the interpretation of the data described in the figure legend.

Post-mortem data

The fixed right hemibrain weighed 512 g and the calculated whole-brain weight was 1024 g. The sulci and gyri revealed marked cortical atrophy over the frontal lobe, with less marked atrophy affecting the temporal pole. The orbital frontal had moderate atrophy. The parietal and temporal convexities and medial temporal lobe had minimal atrophy. There was sparing of the occipital pole. The corpus callosum was thin.

Sequential coronal sections through the supratentorial tissues (Fig. 9) revealed marked enlargement of the lateral ventricles, especially the frontal and temporal horns of the lateral ventricle. The cortical grey mantle was slightly thinner than usual in the frontal lobe. The subjacent white matter showed marked atrophy, especially in the frontal and temporal lobes, with relative sparing of central parts of the centrum semiovale in the parietal and occipital lobes. The hippocampal formation and amygdala had minimal atrophy. Basal ganglia showed marked atrophy of the caudate nucleus with thinning of the anterior limb of the internal capsule. The dorsal and medial regions of the thalamus were...
atrophic. The aqueduct of Sylvius was patent. Horizontal sections of the midbrain, pons and medulla at right angles to the neuraxis showed marked loss of pigment in the substantia nigra and mild atrophy and discolouration of the medial third of the cerebral peduncle. The locus ceruleus had normal pigmentation. The cerebellar sections showed no unusual features.

The neocortex had marked thinning of the cortical ribbon with neuronal loss, gliosis and neuropil vacuolation in all layers consistent with status spongiosis. The severe cortical degeneration was most marked in frontal lobe, especially the orbital frontal lobe and frontal pole, but also affecting convexity mid- and superior frontal gyri. The insular cortex was also severely affected. There was less marked cortical neuronal loss and gliosis with spongiosis in the parietal and temporal lobes. The occipital lobe, including the visual cortex, was spared. There were many neuritic processes and neuronal cytoplasmic inclusions with ubiquitin immunostaining (Fig. 10). A few neuronal intranuclear inclusions are also present. With silver stains as well as tau and Aβ immunostains no senile plaques (SP) or neurofibrillary tangles (NFTs) were detected and there was no evidence of amyloid angiopathy.

The subcortical white matter had extensive rarefaction with fibre loss and astrocytic gliosis throughout the frontal centrum semiovale and to a lesser extent in the temporal white matter. There were no lipid laden macrophages. Blood vessels had no significant arteriosclerotic changes. The hippocampus had no NFT with silver stains as well as tau immunohistochemistry, but the ubiquitin immunostain showed round, crescent shaped and granular cytoplasmic inclusions in the dentate fascia. Both anterior and posterior hippocampal sections showed extensive neuronal loss and gliosis in subiculum and CA1 (Fig. 11). No SP were present in either the pyramidal layer or the molecular layer of the dentate fascia. The entorhinal and perirhinal cortices showed mild neuronal loss and gliosis with no SP or NFT and preservation of neurons in layer II. The Braak NFT stage was consistent with Stage 0.

The basal nucleus of Meynert had a normal neuronal population and no NFT. The hypothalamus was free of SP and NFT. No SP or NFT were present in the amygdala, but there was mild focal gliosis in the basolateral region. There was extensive and severe atrophy of the basal ganglia and diffuse neuronal loss and gliosis in caudate and nucleus accumbens. The dorsal caudate was more affected than the ventral. The ubiquitin immunostain showed a few dystrophic neurites and neuronal inclusions. The anterior limb of the internal capsule was atrophic and gliotic with marked loss of myelinated fibres. There was less neuronal loss and gliosis in the putamen, while the globus pallidus was least affected. There were a few axonal spheroids in the globus pallidus and the pars reticularis of the substantia nigra. The thalamus had marked atrophy and gliosis in the anterior and dorsomedial regions, with minimal involvement of the ventral and lateral regions. The mammillary body was markedly atrophic and had many pyknotic neurons and diffuse gliosis consistent with transneuronal degeneration. The subthalamic nucleus was unremarkable.

The substantia nigra had patchy neuronal loss with extraneuronal neuromelanin and gliosis, but no Lewy bodies or NFT. The neuronal loss was scattered in all areas with no clear predilection for medial or lateral cell groups. The cerebral peduncle had atrophy with fibrillary gliosis of the medial third (i.e. frontobulbar fibres). There was also lesser fibre loss and gliosis in the lateral peduncle (i.e. temporoparietobulbar fibres). The raphe nucleus, locus coeruleus and reticular formation were well populated and free of Lewy bodies and NFT. The lower brainstem and brainstem fibre tracts were remarkable for myelin and
axon degeneration in the longitudinal fibres in the pontine base. The pontine nuclei neurons had cytoplasmic swelling. The medullary pyramids were preserved. There was no neuronal loss or gliosis in the hypoglossal nucleus. The cerebellum was unremarkable, except for mild autolysis of the internal granular layer.

These findings can therefore be characterized as fronto-temporal lobar degeneration with ubiquitin-positive cytoplasmic and intranuclear neuronal inclusions, marked striatal degeneration, wallerian degeneration of the corticobulbar fibres, transneuronal degeneration of the mammillary bodies, and hippocampal sclerosis (HS).

**Discussion**

**Clinical characterization**

While the proband had a history of forgetfulness, neuro-psychometric evidence of definite memory impairment and visuospatial dysfunction, and parietal hypoperfusion on SPECT (all more suggestive of underlying Alzheimer’s disease than FTD), the bulk of her clinical, neuropsychological, neuropsychiatric, and neuroimaging findings were more consistent with FTD than Alzheimer’s disease (Neary et al., 1998; McKhann et al., 2001). Later in her course, the asymmetric motor features were thought during life to represent asymmetric paraparesis due to the known association of PSEN1 mutations and spastic paraparesis. There was no apraxia, cortical sensory loss, myoclonus, dystonia, etc. that is more characteristic of the corticobasal syndrome (Boeve et al., 2003). The most parsimonious characterization of her clinical features was FTD with some atypical features initially, followed by asymmetric pyramidal tract findings compatible with evolving motor neuron disease restricted clinically to the central nervous system; there were no clinical findings of lower motor neuron dysfunction during the 5 years of in-person clinical follow-up.

**Longitudinal characterization**

Remarkably little longitudinal data has been collected in a standardized manner and published in FTD, and such characterization will be critical in the current ‘natural history’ state of affairs with no known drug that significantly alters the course of the diseases that present as FTD. We recently presented longitudinal data on two siblings with the S305N mutation in MAPT (Boeve et al., 2005), in which the functional and radiologic parameters appeared to reflect the most consistent degree of change over time (i.e. slopes were most linear when data were presented graphically). In our proband, the neuropsychiatric burden was high in the early and middle portions of her clinical course, particularly when the Kluver–Bucy symptomatology was prominent, and these features proved challenging to manage, similar to
many other patients with FTD. Several measures changed in a relatively linear fashion over time, at least over the initial 3–4 evaluations, suggesting these measures may be worthy of including in future drug trials in ‘hypoprogranulinopathies’. A multi-centre protocol currently being conducted in the United States (NIA RO1 AG23195), which is specifically focused on measuring longitudinal change in FTD-spectrum patients, will likely provide further insights into which parameters will be most appropriate for assessing change in future FTD treatment trials.

**Fig. 5** Graphical representation of longitudinal scores (product of frequency times severity) on the proband on the 12 items of the Neuropsychiatric Inventory, with scores on Evaluations 1–3 best seen in the top figure and scores on Evaluations 4–6 best seen in the bottom figure. Note that apathy, disinhibition, irritability, aberrant motor behaviour, and appetite/eating change were most frequent and severe in Evaluations 2–4, and with disease progression (Evaluations 5–6) aberrant motor behavior and appetite/eating change remained most frequent and severe. Abbreviations: Del-F × S = delusions-frequency × severity; Hal-F × S = hallucinations-frequency × severity; Ag-F × S = agitation-frequency × severity; Dep-F × S = depression-frequency × severity; Anx-F × S = anxiety-frequency × severity; Eu-F × S = euphoria-frequency × severity; Apa-F × S = apathy-frequency × severity; Dis-F × S = disinhibition-frequency × severity; Ir-F × S = irritability-frequency × severity; Ab-F × S = aberrant motor behaviour-frequency × severity; Nt-F × S = night-time disturbance-frequency × severity; App-F × S = appetite/eating change-frequency × severity.
Neuropathologic characterization

The absence of amyloid pathology in this case makes the diagnosis of Alzheimer’s disease untenable, and Pick’s disease and other tauopathies are excluded with no tau-positive inclusions being present. Furthermore, the findings were highly typical of FTLD-U, which in hindsight would have been higher on the differential diagnosis list of possibilities had the PSEN1 genetic data not ‘clouded’ the suspicion of the underlying disorder. This case exemplifies the critical need to obtain autopsy in patients with unique and perplexing ante-mortem and/or genetic findings.

The serial MRI scans demonstrated progressive increased signal in the subcortical white matter which was topographically associated with extensive rarefaction with fibre loss and astrocytic gliosis in the subcortical white matter, maximal in the frontal subcortical region. The histopathologic underpinnings of increased signal changes in neurodegenerative disorders are not well understood, but in this case, they may reflect rarefaction in the subcortical white matter.

The neuronal intranuclear inclusions in the setting of FTLD-U pathology have led some investigators to propose that such findings suggest the presence of a familial disorder (Mackenzie et al., 2006). Indeed recent evidence suggests that neuronal intranuclear inclusions are associated with mutations in PGRN (Baker et al., 2006) as well as VCP (Forman et al., 2006). Neuronal intranuclear inclusions have also been detected in non-familial cases of FTLD-U (Katsuse and Dickson, 2005) indicating caution in interpreting the significance of intranuclear inclusions in the setting of FTLD-U.

HS is often associated with FTLD-U pathology (Josephs et al., 2004). The aetiology of HS pathology as being of degenerative versus vascular origin continues to be debated, but this case supports the neurodegenerative perspective. How specific HS plus FTLD-U pathology is associated with PGRN mutations will also require further study.

Pathophysiologic considerations

The critical pathophysiologic issue is whether the insR352 PSEN1 is directly or indirectly pathogenic, or represents a
very rare but benign polymorphism, as we pondered in our original reports (Amtul et al., 2002; Tang-Wai et al., 2002).

Since (i) other groups of investigators had reported findings consistent with amyloid pathophysiology underlying clinical presentations consistent with FTD (Johnson et al., 1999), (ii) the insR352 mutation had not been found in numerous other FTD, Alzheimer’s disease or control subjects and (iii) the L113P mutation in PSEN1 had been linked with a clinical phenotype resembling FTD in a larger pedigree (Raux et al., 2000b), we thought it plausible that the insR352 mutation was pathogenic and may do so via chronic partial inhibition of γ-secretase activity (Amtul et al., 2002). We can now argue with much greater certainty that the insR352 does not exert any pathogenic effect via any increase in circulating amyloid nor by amyloid deposition in brain. The results from our previous and currently-presented data imply that mutations that cause complete loss of PSEN1 function do not cause Alzheimer’s disease—unless they also impact the function of the normal allele (dominant-negative mutations). Furthermore, the insR352 mutation is distinct from known familial Alzheimer’s disease (FAD)-linked PSEN1 mutations in that it occurs in a non-evolutionarily conserved region of the PSEN1 protein in an area within the large cytoplasmic loop that is devoid of most other FAD-linked mutations that typically cluster within or near the membrane spanning and hydrophobic domains. Until the
mutation in PGRN was identified, the question remained whether the insR352 is involved in neurodegeneration via its effects on γ-secretase and notch processing, or through other unknown mechanisms.

The other plausible explanation is that the insR352 mutation is a very rare but benign polymorphism and is therefore entirely unrelated to the disease in this kindred. This possibility would be strongly supported if a mutation was found in a different gene associated with the FTD syndrome and/or FTLD-U pathology. We now believe the insR352 ‘mutation’ is non-pathogenic in our kindred.

Our findings also have implications for interpreting the recent findings of Pick body pathology in other kindreds with an FTD-type phenotype, particularly the case with Pick’s disease pathology with no elevation in Aβ40 and Aβ42 and no amyloid deposition (Dermaut et al., 2004), which at least calls into question the pathogenicity of PSEN1 mutations causing a neurodegenerative disease not directly related to abnormal amyloid deposition. The findings of the Glu318Gly (Mattila et al., 1998; Goldman et al., 2005) and Thr354Ile (Lee et al., 2006) ‘mutations’ in PSEN1 failing to segregate with the disease in familial FTD suggests that indeed not all rare alterations in PSEN1 are pathogenic.

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