Background: The significance of the presenilin 1 (PSEN1) Glu318Gly polymorphism has been described as either a causal mutation with reduced penetrance or a benign polymorphism. When this polymorphism is found in a symptomatic person with a family history of dementia, counseling on recurrence risk becomes very problematic.

Objective: To demonstrate that the PSEN1 Glu318Gly polymorphism should be interpreted cautiously.

Design: Case histories of 2 patients with presenile dementia and family histories of dementia are described. The PSEN1 gene was sequenced in the patients and in 11 family members of patient 1.

Results: Two patients with presenile dementia and personality change were found to carry the PSEN1 Glu318Gly polymorphism. The presence of the polymorphism was confirmed in several family members of patient 1 but was absent in 1 symptomatic relative.

Conclusions: The Glu318Gly polymorphism may be associated with risk for neurodegenerative disease; however, in the cases described here, it did not appear to be a risk factor. Until there is consensus on whether it is associated with disease, families should be informed that the clinical significance of the polymorphism is uncertain.

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Although the majority of Alzheimer disease (AD) cases appear to be sporadic, about 5% of patients with AD meet criteria for autosomal dominant disease.1 Three autosomal dominant genes are associated with early-onset familial AD: presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the amyloid precursor protein (APP) genes. The PSEN1 gene accounts for 18% to 50% of early-onset familial AD.1 The age of disease onset and phenotype in these families are variable.2 The PSEN1 gene is highly penetrant.3 In addition to more than 130 mutations, several polymorphisms within the PSEN1 gene have been identified.

There has been considerable debate over the significance of 1 particular polymorphism, Glu318Gly. It is unclear whether this polymorphism is benign or a disease-associated mutation with incomplete penetrance.4-7 The Glu318Gly polymorphism has been described in patients with early- and late-onset AD with and without family histories of AD.3 This polymorphism occurs in a weakly conserved area of the gene where no other causative mutations have been identified.8 Dermaut et al9 concluded that since this polymorphism does not increase production of β-amyloid 42 from amyloid precursor protein, it does not cause AD. However, Helisalmi et al7 found that Finnish patients with familial AD were 7.6 times more likely and patients with sporadic AD were 3 times more likely than controls to have the polymorphism. They concluded that this polymorphism might be in linkage disequilibrium with a causal mutation in PSEN1. Other studies in different populations show that the frequency of the polymorphism is similar in patients with AD and in normal controls.10

We describe 2 cases in which a Glu318Gly PSEN1 polymorphism was identified to demonstrate how the uncertainty about the clinical significance of this mutation can cause dilemmas for the clinician reporting PSEN1 genetic test results to patients and their families.

METHODS

Two case histories are described with a review of medical records, autopsy records, and
genetic testing results. Analysis of PSEN1 and apolipoprotein E (APOE) genotypes was performed on each proband by Athena Diagnostics, Worcester, Mass. Confirmation of the Glu318Gly polymorphism in patient 1 and genotyping of 11 family members of this patient were performed after the autopsy of patient 1. The presence of the Glu318Gly polymorphism was detected by restriction site–generating fragment length polymorphism analysis as described by Helisalmi et al.7

### RESULTS

#### PATIENT 1

A 57-year-old woman came to the clinic with a 6-year history of functional and personality changes. She was fired from several jobs because of inappropriate behavior and disorganization. Three years later, she could no longer maintain her checkbook or do mechanical jobs around the house. Simultaneously, she began to exhibit disinhibition such as making loud remarks about people’s weights. Over the next year, she began craving sweets, gained 27 kg, and became apathetic. When she came to our clinic, she was having problems with activities of daily living. On examination, the patient acted overly familiar but otherwise cooperative. The neurological examination was unremarkable. A brain magnetic resonance image revealed bifrontal lobe atrophy. A neuropsychological battery demonstrated severe impairments on all of the tests of verbal memory, executive function, language, and visuospatial skills. The patient scored 10 of 30 on the Mini-Mental State Examination.9

![Figure 1. Pedigree of case 1.](image)

**Table. Correlation of Disease Symptoms With Glu318Gly Polymorphism in Case 1 Family**

<table>
<thead>
<tr>
<th>Family Members†</th>
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<tr>
<td>Glu318Gly polymorphism</td>
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Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; ET, essential tremor; FTD, frontotemporal dementia; MND, motor neuron disease.

*See pedigree, Figure 1.

shows a significant family history of autopsy-proven frontotemporal dementia (FTD), amyotrophic lateral sclerosis, and parkinsonism.

The patient met Neary criteria10 for FTD. However, because of the possibility of early-onset familial AD, the family consented to diagnostic testing for APOE and PSEN1 and research testing for MAPT, the tau gene. Athena Diagnostics reported an APOE E3/E3 genotype and identified the Glu318Gly polymorphism on 1 allele of the PSEN1 gene. The PSEN1 report stated that this allele represented a benign polymorphism previously described in the literature. No MAPT mutations were found.

The patient died at age 60 years. A standard brain autopsy was performed for diagnostic purposes at the University of Pennsylvania Center for Neurodegenerative Disease Research. The patient had a moderate to high density of senile plaques and neurofibrillary tangles in multiple neocortical areas and limbic regions. There were no Lewy bodies, Pick bodies, motor neuron–type disease inclusions, infarcts, or other lesions. The neuropathological abnormalities were sufficient to meet neuropathological criteria for AD11 and were classified as Braak and Braak stage VI.12 Owing to the unexpected autopsy finding of AD, the patient’s files were reviewed.

The University of Pennsylvania Center for Neurodegenerative Disease Research confirmed the PSEN1 Glu318Gly polymorphism from banked DNA and tested for the polymorphism in relatives. Results of this genotyping are shown in the Table.
A 61-year-old man had a 9-year history of speech difficulty and disinhibited behavior, including extramarital affairs and a preoccupation with pornography. Within the preceding 3 years, he developed problems with short- and long-term memory and activities of daily living. He also began craving sweets and gained a significant amount of weight.

At the time he came to our clinic, the patient’s neurological evaluation was unremarkable. A brain magnetic resonance image revealed moderate frontal lobe atrophy and thinning of the corpus callosum. The temporal lobes including the hippocampi were normal. Patient 2 exhibited severe impairments in all of the domains of cognition, and he scored 9 of 30 on the Mini-Mental State Examination.

Family history was significant for psychiatric problems and dementia (Figure 2).

Patient 2 met Neary criteria for the progressive nonfluent aphasia subtype of frontotemporal lobar degeneration as well as possible AD by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Associations’ criteria. Because of age and possible family history of AD, PSEN1 and APOE testing were performed. The PSEN1 testing revealed the presence of a benign polymorphism, Glu318Gly, on 1 allele. The APOE genotype was E3/E4.

On follow-up evaluation 1 year later, his speech output, praxis, activities of daily living, and nighttime agitation were worse. However, his disinhibited behavior and sweet cravings had lessened. Repeated magnetic resonance imaging demonstrated increased frontal and left insular atrophy as well as significant bilateral hippocampal atrophy. As a result of the experience with patient 1, the Glu318Gly polymorphism and the APOE genotype were reconsidered as possible contributing factors to the disease of patient 2.

The 2 cases described here illustrate several points. First, the presence of the Glu318Gly polymorphism in patient 1, her affected cousin, her father, and patient 2 raises the possibility that this polymorphism may be associated with neurodegeneration with incomplete penetrance or may interact or be in linkage disequilibrium with other modifier genes. However, the absence of the polymorphism in individual 4 of case 1 (Figure 1) reduces this possibility. Second, our experience as well as the significant literature supporting the possible causal nature of the Glu318Gly polymorphism suggest that genetic testing laboratories should include available information about the clinical significance of polymorphisms with relevant references in the reports, particularly when the significance is controversial.

Lastly, these cases illustrate how overlapping symptoms can make a family history of dementia misleading. Both FTD and AD can exhibit changes in language or personality. Descriptions of familial presentations of FTD associated with PSEN1 mutations further complicate diagnosis.

These cases also demonstrate how family history contributes to, and sometimes complicates, the clinical diagnosis. In case 1, autopsy-proven FTD/amyotrophic lateral sclerosis in 2 relatives in combination with initial symptoms that were frontal executive in nature led to an incorrect clinical diagnosis of FTD in patient 1. In case 2, early disinhibition and progressive aphasia with a family history of psychiatric symptoms and dementia also led to a diagnosis of FTD.

Genetic testing is appropriate when a young age of onset of dementia is present in conjunction with a family history of a similar dementia. In both cases described here, mutation analysis of PSEN1, APOE genotyping, and research genetic testing for MAPT were performed. Pretesting and posttesting genetic counseling were held for education and counseling about these tests and the implications of the results for family members. We suggest that in cases like these, families should be informed that although all of the first-degree relatives are at an increased lifetime risk for dementia, the absolute risk and probable age of onset cannot be given because the role of the Glu318Gly PSEN1 polymorphism is unclear. Likewise, without a full understanding of the etiology of the disease, presymptomatic testing is not possible.

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