Letters to the Editor

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Genetic Testing Should Not Be Advocated as a Diagnostic Tool in Familial Forms of Dementia

To the Editor:

In their article in the January 2000 issue of the *Journal,* Finckh et al. advocate the use of a molecular diagnostic program in patients with early-onset dementia (EOD) and a family history of dementia (Finckh et al. 2000). In 36 patients with EOD, Finckh et al. screened for mutations in the presenilin (PSEN)–1 and -2 genes (MIM 104311 and MIM 600759, respectively), the amyloid-precursor protein (APP) gene (MIM 104760), and the prion protein (PRNP) gene (MIM 176640); in 12 patients, they found mutations that were considered to be disease causing. Finckh et al. argue that, in the absence of specific antemortem diagnostic markers for familial Alzheimer disease (AD) or hereditary prion disease, molecular testing is important to ensure that treatable dementias are not missed. Although the findings by Finckh et al. are of interest, we think that the implications of these findings for clinical practice are seriously limited. We offer several arguments against the use of genetic testing as a diagnostic tool for the differential diagnosis of dementia in general practice.

One significant limit on the usefulness of genetic testing arises from the distribution and prevalence of APP, PSEN, and PRNP mutations in EOD. The usefulness of a clinical diagnostic test is determined, in large part, by the composition of the patient population. Among the disease-causing mutations found by Finckh et al., two-thirds were associated with AD, and one-third occurred in the PRNP gene. This distribution is surprising and does not reflect the typical clinical experience. The prevalence of early-onset AD is estimated to be 18.2–41.2 persons per 100,000 at risk, and that of autosomal-dominant early-onset AD is estimated to be 5.3 persons per 100,000 at risk, whereas the familial forms of the prion diseases, which include familial Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinkers syndrome, and fatal familial insomnia, have an estimated incidence of only 1/10 million/year (Haywood 1997; Campion et al. 1999). Even in highly specialized neurological or geriatric centers, a clinician will not encounter a demented population in which 33% of patients have prion disease. The rarity of patients with prion disease underscores the very atypical composition of the population studied by Finckh et al. and the limited relevance that their study has for ordinary diagnostic practice. Furthermore, we and others have found that, in a population-based sample, only ~20% of patients with early-onset familial AD have a causative mutation (Cruts et al. 1998; Kamimura et al. 1998), whereas Finckh et al. observed a mutation in 45% of such patients. We argue that, for clinical practice, the findings in a population-based study are more relevant than those in a highly selected population.

Our second concern is related to the application of molecular screening of dementia genes in clinical practice. In contrast to the mutations in the APP gene, which are clustered around exons 16 and 17, a large number of rare mutations in the PSEN genes are known to be distributed throughout the gene. More than 50% of these PSEN mutations are genetically "private"; that is, they are found only in a particular patient or family (Blacker and Tanzi 1998; Cruts et al. 1998). As shown by Finckh et al., novel mutations are still found. Also, previously unknown mutations are detected in the PRNP gene (Laplanche et al. 1999). The causative effects of these are difficult to interpret. A notorious example of misjudging the pathogenicity of a presumed missense mutation is the Glu318Gly substitution in the PSEN-1 gene. For example, an 86-year-old woman fulfilling the National Institute of Neurological Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria for probable AD was referred to the Memory Clinic of Erasmus University Medical School. Her family history revealed early- and late-onset AD in several first-degree relatives. We therefore screened for the known AD-associated genes, and we detected an E318G mutation in the PSEN-1 gene. This substitution was earlier reported as a causative mutation in patients with familial early-onset AD (Cruts and Van Broeckhoven 1998). In 1999, however, Dermaut et al. demonstrated that an elderly group of 256 control subjects included 9 carriers of this substitution who were not demented, results indicating that the frequency in control sub-

jects was similar to that found in patients (Dermaut et al. 1999). Rather than being a pathogenic mutation, the E318G is a rare allele, that is not associated with either AD or dementia in general and does not influence the β-amyloid formation. In the absence of any population data, we might have incorrectly reasoned that our patient represented a genetic case with late onset. This example illustrates that, even in familial cases, studies of a large series of controls should be performed before conclusions are drawn about the pathogenicity and penetrance of a particular mutation. For any untreatable disease with a devastating course, as is the case in AD and prion diseases, the burden of an incorrect molecular diagnosis should be prevented by all possible means, since genetic testing does not have implications for the patient alone but also discloses predictive information to family members, which could influence such issues as life expectancy, insurability, and psychosocial well-being.

We are especially concerned by the emphasis given to the use of molecular screening of AD genes and the PRNP gene, in light of the importance of ascertaining the presence of treatable dementias. First, considerably easier ways to diagnose treatable dementias exist. In clinical settings it is more straightforward to test for the presence of a treatable dementia directly (e.g., by measuring levels of thyroid-stimulating hormone level to test for dementia associated with hypothyroidism). Second, the presence of a mutation does not eliminate the possibility of the coexistence of a treatable form of dementia. Conditions such as depression, drug intoxication, vascular dementia, and metabolic disorders can mimic and coincide with AD, especially in patients with a long disease course. Even when a major mutation is present in the family, tests for treatable causes of dementia should not be omitted in clinical practice.

Finckh et al. report interesting data on novel mutations. Furthermore, they raise an intriguing question regarding the use of genetic testing as a diagnostic tool. However, it is of major importance to recognize their report's limited applicability to clinical practice. We argue that the contribution of genetic testing to clinical diagnosis is small and does not counterbalance the problems associated either with interpretation of any mutation that is found or with secondary effects on family members. Nevertheless, for scientific reasons, genetic testing is very worthwhile. Testing may increase our knowledge about the different mutations, which could have clinical applications in the future. However, the limits of current knowledge are too great to justify clinical use of genetic testing in the diagnostic process.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PSEN-1 and -2 [MIM 104311 and MIM 600759, respectively], APP [MIM 104760], and PRNP [MIM 176640])

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Reply to Croes et al.

To the Editor:

Croes et al. (2000 [in this issue]) make the point that genetic testing as a diagnostic tool shows poor performance in differential diagnosis in general medical practice. We fully agree with this comment. Therefore, one of the goals of our study (Finckh et al. 2000) was to establish criteria that would increase the chance of identifying a pathogenic mutation in the setting of a specialized clinic. Indeed, among patients who had both onset at an early age and positive family history for early-onset dementia (EOD), diagnostic sequencing identified disease-relevant mutations in >50% of the patients analyzed by us. Another notable result of our study was the finding of four prion mutations among the 36 EOD patients, which suggested that atypical forms of prion disease may remain underdiagnosed. This assumption is supported by independent observations, such as those made by two coauthors of the letter by Croes et al. (2000), who found a *PRNP* insertion mutation in a patient with both prion disease and ante mortem diagnosis of familial Alzheimer disease (FAD) (Dermaut et al. 1998).

We agree with Croes et al. that assessment of the relevance of previously unknown mutations is a difficult issue. Nonetheless, in recent screening studies of FAD, 72%–83% of the sequence changes corresponded to pathogenic mutations already reported (Kamimura et al. 1998; Campion et al. 1999). In our study, 58% of the mutations had been previously described by others. Repeated identification of any given rare mutation in a rare disorder, together with the absence of the mutation in control probands, significantly increases the likelihood that it has causative effects.

We were pleased to see that Croes et al. agree with our conclusion that E318G in PS1 is a nonpathogenic polymorphism and that they reemphasize the importance of a careful and critical analysis of the literature. The importance of early and disease-specific diagnosis of EOD as a way of identifying treatable forms of dementia is an issue separate from our assertion that diagnostic sequencing of the four known EOD genes may provide important information for proper clinical and genetic counseling in the early phases of the disorder.

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