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An Ethical Context For Presymptomatic Testing in Alzheimer’s Disease

Kenneth S. Kosik, Stephen G. Post, and Kimberly A. Quaid

Shall it be male or female? say the fingers
That chalk the walls with green girls and their men.
I would not fear the muscling-in of love
If I were tickled by the urchin hungers
Rehearsing heat upon a raw-edged nerve.
I would not fear the devil in the loin
Nor the outspoken grave.

—Dylan Thomas

Introduction

Myths—from Adam eating the forbidden fruit to Faust exchanging his soul to the Devil—teach us that profound knowledge can be a dangerous thing. The danger lies in knowing the future. Among the modern temptations toward a knowledge that may hold dangers as well as rewards is the genetic code. Although increasingly detailed probing of our own genomes seems inevitable, the appropriate uses of this information are much debated. The Faustian myth teaches us that a quest for knowledge, despite its price, is part of human nature. What is the price of knowing our genes?

If we learn that lying quietly within our genome is a mutation that will cause a disease when we reach our third, fourth, or fifth decade, then this knowledge can be the source of overriding despair. In a relatively small, but heuristically vital group of patients, Alzheimer’s disease (AD) is caused by any of several mutations. Current estimates suggest that 1–3% of all cases of AD are caused by known genetic mutations. These scientific advances have forcefully put the issue of genetic testing before us. The ease with which genetic testing is done

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leads to pressure on patients from many directions, including the physician who is enthusiastic about the new technology, but has not considered the profound personal and psychosocial implications of genetic testing, particularly the potential consequences for education, employment, and insurance. Ideally, an individual should have the right to know his or her genetic profile without the burden this knowledge creates in the hands of others. In a recent editorial President Clinton stated: “... none of our discoveries should be used to label or discriminate against any group or individual. With stunning speed, scientists are now moving to unlock the secrets of our genetic code. Genetic testing has the potential to identify hidden inherited tendencies toward disease and to spur early treatment. But that information could also be used, for example, by insurance companies and others to discriminate and stigmatize people” (1).

Genetic Markers for the Presymptomatic Diagnosis of Alzheimer’s Disease

There are three known genetic loci where mutations cause a fully penetrant form of AD most distinctly characterized by an early age of onset. These loci are the presenilin 1 (PS-1) gene on chromosome 14 (2), the presenilin 2 (PS-2) gene on chromosome 1 (3), and the amyloid precursor protein (APP) gene on chromosome 21 (4). Five mutations have been described in APP, which lead to AD and a sixth mutation (A692G) that can lead to AD or cerebral hemorrhages (5). At this time approximately 45 different mutations in PS-1 have been described, and all but one of these are missense mutations. The single exception is an in-frame deletion of exon 9 (6). Among the families that harbor mutations in PS-1 is the extended Colombian family, which represents the largest kindred in the world with familial AD (7). In PS-2, two different mutations have been described, one of which is found in another very large kindred known as the Volga Germans. All of these mutations cause an inherited form of AD that is clinically and pathologically indistinguishable from sporadic disease except for the early age of onset. Although specific cases vary greatly, the disease onset with APP and PS-2 is about a decade later than PS-1 mutations, which often have an onset in the 40s. However, even within families that carry the same mutation there may be more than a 20-year span in age at onset, and therefore it is not possible to predict when the individual carrying a mutation will develop the disease. All of these mutations are fully penetrant autosomal dominant, and therefore, if the individual lives long enough, the disease will inexorably develop. (There are exceedingly rare anecdotal reports of individuals with an Alzheimer-type mutation who escape the disease and therefore a more conservative estimation of disease occurrence with a mutation is probably higher than 99%, but less than 100%).