Is the glass half empty or half full?
Genetically determined disease in frontotemporal dementia

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Genetic studies are a critical source of knowledge about neurodegenerative diseases. The identification of families with an autosomal dominant pattern of inheritance has proven crucial in improving our care of patients with conditions such as Alzheimer disease (AD) and Parkinson disease. This work has led to improvements in diagnostic accuracy, a better understanding of the biologic mechanisms underlying disease, and most importantly, the identification of targets for therapeutic intervention. Recently, genetic studies of patients with frontotemporal dementia (FTD) have proven to be very fruitful. Two distinct, genetically determined causes have been defined in the last decade. These include the locus of the gene coding for the microtubule-associated protein tau (MAPT) on chromosome 17,1 and within the last 2 years, the gene coding for progranulin (GRN), also on chromosome 17.2,3

In this issue of Neurology®, Seelaar et al. report their comprehensive assessment of the frequency and cause of a strong family history of disease in a very large cohort of patients with FTD.4 The patients were also studied clinically, and when possible, pathologically. The survey confirmed the presence of an autosomal dominant family history in 27% of their cohort. This is very large in comparison to other neurodegenerative diseases. The investigators were able to define a specific genetic mutation in over half of these patients, including MAPT (11%) and GRN (6%). Pathologic examination in these patients was concordant with their genetic diagnosis. Individuals with a MAPT mutation demonstrated neuronal inclusions of tau, while patients with a GRN mutation showed ubiquitin- and TDP-43-immunoreactive inclusions. Both groups showed neuronal loss and gliosis. From this perspective, the glass is half full: In a remarkable scientific achievement for the field, we now know the specific cause of FTD in 17% of these patients. Etiologically based treatments are being developed for patients with these conditions, and we should be able to change the natural history of this neurodegenerative disease in a large number of patients in the near future.

Seelaar et al. also made important advances in helping us define the cause of FTD in some of the remaining patients. These researchers identified some of the critical parameters that should be pursued in defining the genetic cause of disease in the remaining 10% of individuals with an autosomal dominant family history of FTD. One subgroup with memory difficulty severe enough to warrant a clinical diagnosis of AD showed the presence at autopsy of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and hippocampal sclerosis. While prominent enough to cause a significant memory deficit, the contribution of hippocampal sclerosis should be interpreted cautiously because of the widespread presence of this pathologic feature. A second subgroup with a clinical history of FTD and motor neuron disease (FTD+MND) showed motor neuron loss in the brainstem and spinal cord as well as ubiquitin/TDP-43 pathology. Indeed, these observations anticipated the identification of a mutation in the gene coding for TDP-43 on chromosome 1 in familial MND that was reported soon after this article was accepted for publication.5-7 The precise locus of a possible genetic defect associated with FTD+MND on chromosome 9 remains to be identified.

Despite these remarkable advances, the glass remains half empty. Why? There is substantial reason to be optimistic about our ability to identify the cause of FTD in up to 27% of patients with an autosomal dominant family history. However, the cause of disease remains a mystery in 73% of patients with FTD. Many pieces of the puzzle remain to be found. Very few studies have pursued interacting genetic factors, for example, and even fewer studies have examined environmental risk factors for FTD and more complex interactions between genetics and the environment. Much biomarker work is needed to identify the histopathologic abnormalities during life of patients with sporadic FTD who show accumulations of the same aberrant proteins at autopsy. This
would allow treatments developed for familial FTD to be administered safely and confidently to patients with similar sporadic diseases.

The report of Seelaar et al. provides us with an important yardstick indicating our remarkable success in identifying the cause of FTD in an impressively large percentage of these patients. They also point us in informative directions for future work that can identify the cause of disease in some additional familial patients with FTD. Before breaking out the champagne, however, we should consider the large amount of work that remains before we can improve the care of all patients with FTD.

REFERENCES