

The Genetics of Very Early Onset Alzheimer's Disease

Christopher M. Filley, M.D.,* ¶ ‡ Yvonne D. Rollins, M.D., Ph.D.,* C. Alan Anderson, M.D.,* ¶ ‡ David B. Arciniegas, M.D.,* ¶ ‡ Katherine L. Howard, M.S.,* Jill R. Murrell, Ph.D.,▪ Philip J. Boyer, M.D., Ph.D.,† Bette K. Kleinschmidt-DeMasters, MD,*† Bernardino Ghetti, M.D.▪

Departments of Neurology,* Pathology,† and Psychiatry,¶ University of Colorado School of Medicine, Denver, Colorado, Denver Veterans Affairs Medical Center,‡ and Department of Pathology, Indiana University School of Medicine▪

Objective: This study was undertaken to clarify the genetics of very early onset Alzheimer's disease (VEOAD), defined as AD beginning before age 35.

Background: AD is a leading cause of cognitive disability, affecting about 5 million Americans and 20 million people worldwide. Although considered a disease of aging, AD can present in middle-aged or even young adults, many of whom carry an autosomal dominant gene mutation. Early onset AD (EOAD) is defined by onset of symptoms before age 65, and affected individuals may harbor a mutation in presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP). VEOAD is exceedingly rare, and PSEN1 mutations have been implicated.

Methods: We encountered a man with phenotypic frontotemporal dementia beginning at age 32 and a strong family history of autosomal dementia who was found at autopsy to have AD. Histologic and genetic analyses of the patient's brain were undertaken, and a review of all published VEOAD cases was performed.

Results: Histologic findings were diagnostic of advanced stage AD. Genetic evaluation of brain tissue identified an intronic PSEN1 polymorphism; no known pathogenic mutation was found. Literature review (1934 to 2007) disclosed 101 cases of VEOAD; the youngest age of dementia onset was 24 years. In all cases in which definitive genetic analysis was available, either a PSEN1 mutation or linkage to chromosome 14 was found.

Conclusions: VEOAD can present with atypical clinical features, including findings suggestive of frontotemporal dementia. All reported cases of VEOAD with conclusive genetic analysis seem to be associated with PSEN1 mutations. Genetic testing in adults younger than 35 with dementia can identify the genetic defect and assist in diagnosis and family counseling. As knowledge of the genetics of AD and other dementias accumulates, opportunities will also expand for addressing a major worldwide source of cognitive disability.