

# Chronic Dementing Conditions, Genomics, and New Opportunities for Nursing Interventions

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**Purpose:** To (a) provide an overview of chronic dementing conditions; (b) discuss the etiologic and clinical characteristics of Alzheimer disease (AD) and Parkinson disease (PD) within the framework of the family systems genetic illness model; and (c) to explore opportunities to enhance outcomes through the integration of genomics information and technologies into nursing practice.

**Design:** An integrated review of the literature, including the organizing construct of the family systems genetic illness model.

**Findings:** AD and PD are both influenced by genetic and environmental factors; in a small percentage of families, gene mutations are the primary etiologic factor. Genetic testing is an option for some families experiencing early-onset, familial disease. Presymptomatic and diagnostic genetic testing have limited clinical utility for the more common late-onset AD and PD.

**Conclusions:** The current abilities of healthcare professionals to effectively intervene in people with AD and PD are limited by an incomplete understanding of the biologic basis of these diseases. Advances in genomics research and technology are providing the information and tools necessary to understand the molecular basis of these devastating disorders toward the goal of more specific and effective interventions.

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Chronic dementing conditions, such as Alzheimer disease (AD) and Parkinson disease (PD), result in significant morbidity and mortality worldwide (Wimo, Winblad, Augero-Torres, & von Strauss, 2003). The overall worldwide prevalence of dementia approaches 25 million people (Ferri et al., 2005). The prevalence rate of dementia varies by age. For example, the prevalence rate among people between the ages of 64 and 69 is approximately 1.5% to 2%; but, the prevalence of dementia in people older than age 85 is almost 25% (Ferri et al., 2005). The prevalence of dementia also varies by gender, with evidence of slightly higher rates among women, even when controlling for longevity (van den Eeden et al., 2003). Evidence also shows that overall dementia prevalence rates and rates of specific types of dementia may vary by ethnic background (Hendrie et al., 2001). For example, AD is the most prevalent dementia in Caucasians compared to vascular dementia in African American people (Hendrie et al., 2001).

Although the full scope of chronic dementing conditions worldwide is not known, the effects of chronic dementia on people including healthcare providers is clearer. Chronic dementing conditions result in a diminished quality of life for people experiencing the disorder, as well as extensive physi-

cal, psychological, and financial burdens for families across cultures (Janevic & Connell, 2001). Further, the current abilities of healthcare professionals to intervene are limited by an incomplete understanding of the biologic basis of these conditions, although genomics research and technology are making new discoveries about the molecular basis of these devastating disorders possible.

This paper includes a summary of published work regarding the etiology of AD and PD and further explores the integration of genomics into nursing research and practice for older adults with chronic dementing conditions. The

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**Table 1. Summary of the FSGI Model for AD and PD**

FSGI model	Alzheimer disease	Parkinson disease
Overall clinical severity	<ul style="list-style-type: none"> <li>• Early short-term memory loss.</li> <li>• Progressive impairment in higher-order cognitive processes.</li> <li>• Progressive impairment in managing simple and complex activities of daily living.</li> <li>• Variable presence of neuropsychologic features.</li> <li>• Classic neuropathology: extraneuronal amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex and hippocampus.</li> </ul>	<ul style="list-style-type: none"> <li>• Progressive development of 3 classic features: tremor, muscle rigidity, and bradykinesia.</li> <li>• Eventual presence of dementia in ~ 20% of people with PD.</li> <li>• Progressive impairment in managing simple and complex activities of daily living.</li> <li>• Classic neuropathology: loss of dopaminergic neurons in the substantia nigra; intracytoplasmic Lewy bodies in intact nigral neurons.</li> </ul>
Genes and disease risk	<ul style="list-style-type: none"> <li>• Causative genes in rare, early-onset disease.</li> <li>• Increased susceptibility, according to genotype, in common late-onset disease.</li> <li>• Largely unknown relationships between genotype and phenotype over time.</li> </ul>	<ul style="list-style-type: none"> <li>• Causative genes in rare, juvenile and early onset forms.</li> <li>• Increased susceptibility, according to genotype, in common late-onset disease.</li> <li>• Largely unknown relationships between genotype and phenotype over time.</li> </ul>
Onset during life cycle	<ul style="list-style-type: none"> <li>• Very small percentage of cases with onset before age 60.</li> <li>• Onset usually after age 60.</li> <li>• Prevalence increases with age.</li> </ul>	<ul style="list-style-type: none"> <li>• Juvenile-onset (&lt;age 20).</li> <li>• Early-onset (21 to 50).</li> <li>• Late-onset (&gt; age 51).</li> <li>• Prevalence increases with age.</li> </ul>
Prevention and treatment	<ul style="list-style-type: none"> <li>• Symptom-based pharmacologic management, especially for behavioral features.</li> <li>• Broad range of non-pharmacologic and biobehavioral interventions to manage clinical sequela.</li> </ul>	<ul style="list-style-type: none"> <li>• Symptom-based pharmacologic management, especially for behavioral features.</li> <li>• Broad range of non-pharmacologic and biobehavioral interventions to manage clinical sequela.</li> </ul>

specific purposes of this paper are to: (a) provide an overview of chronic dementing conditions; (b) discuss the etiologic and clinical characteristics of two prevalent late-onset neurodegenerative disorders within the framework of the family systems genetic illness (FSGI) model (Rolland & Williams, 2005); and (c) explore current and future opportunities to enhance outcomes in these populations through the integration of genomics information and technologies into nursing practice.

## Overview of Chronic Dementing Conditions

Dementia, an acquired syndrome, consists of progressive decline in global cognitive ability of such severity that it interferes with one's usual social and occupational performance (American Psychiatric Association, 1994). The most common cause of irreversible dementia is AD, accounting for 60% of all cases (Hebert, Beckett, Scherr, & Evans, 2001) and affecting as many as 4 million Americans (National Institute on Aging, 2003). PD also is a common, age-modulated, neurodegenerative disorder (de Rijk et al., 1997). However, in contrast to AD with dementia as the defining feature, dementia occurs in approximately 20% of people with PD (Pankratz, Wojcieszek, & Foroud, 2004). The prevalence and severity of clinical features in AD and PD have led to aggressive research efforts to identify etiologic factors, including genes and environmental factors, that either cause or increase susceptibility to these disorders.

The chronic and progressive nature of these disorders, the complex role of genes and environment in their pathogenesis, and the centrality of family in the care of people with dementia, all contribute to complexity in planning and providing care.

Rolland and Williams' (2005) family systems genetic illness model is a typology for complex chronic conditions, particularly those influenced by genetics, within the context of family. The FSGI model is a useful organizing framework for discussing the clinical features and trajectory of AD and PD.

The FSGI pertains to the relationships between biologic and psychosocial aspects of common complex disease, particularly those disorders that are influenced by genomics (Rolland & Williams, 2005). This model includes categorization of disorders in four broad areas that are the most psychologically significant for families. AD and PD will be briefly discussed within these four biopsychosocial dimensions of the FSGI model: overall clinical severity, the likelihood of developing a condition because of gene mutations, timing of clinical onset in the life cycle and prevention and treatment options. **Table 1** shows a summary of this comparison.

### Overall Clinical Severity

According to the FSGI model, overall clinical severity is a function of the length and severity of a disease course that can assist clinicians and families in anticipating disease

burden (Rolland & Williams, 2005). Both AD and PD are clinically severe over time; both are slowly progressive disorders, characterized by insidious onset of symptoms, long duration, and increasing loss of functional independence. The primary clinical feature of AD is dementia, beginning with impaired short-term memory. However, other domains of cognition are compromised, including memory, language, visuospatial ability, executive function, and attention (Piccini et al., 1998). People with AD also experience increasingly impaired functional ability, for example, difficulty in managing complex self-care skills such as completing errands and driving a car. Eventually, people with AD lose the ability to manage their basic self-care activities such as toileting, bathing, dressing, and eating (Mitnitski, Graham, Mogilner, & Rockwood, 1999). Behavioral symptoms also accompany AD. For example, the prevalence of verbal and physically agitated behaviors is high, ranging from 24% to 48% (Cummings & McPherson, 2001). Depressive symptoms (Cummings & McPherson, 2001), as well as delusions and hallucinations (Lyketos et al., 2000), frequently occur, presenting challenges for both formal and informal caregivers.

The classic clinical features of PD are tremors, bradykinesia, and muscle rigidity. Lieberman (1998) reported that tremors begin unilaterally but can affect one or both limbs and the lower face. Hand tremors occur as a unique “pill-rolling” movement (Emre, 2004). Dementia in people with PD includes impaired attention, altered executive function, and impaired memory (Emre, 2004). People with PD also experience impaired functional ability in both basic and complex activities of daily living (Lieberman, 1998). Neuropsychiatric symptoms observed in PD include depression, apathy, anxiety and hallucinations, with the prevalence of depression reported as high as 58% (Aarsland et al., 2005).

The clinical features of AD and PD progress slowly over 8 to 10 years, ranging from 2 to 20 years (National Institute on Aging, 2003). Immobility and general physical debilitation predispose people with advanced AD and PD to malnutrition, aspiration, and immunodeficiency. People with neurodegenerative disorders are also at risk to be institutionalized in long-term care facilities, usually related to functional impairments and behavioral problems (Magaziner et al., 2000; Parashos, Maraganore, O'Brien, & Rocca, 2002). These severe clinical features, resulting in functional dependence over many years, indicate complex caregiving demands for both family and caregivers.

### Likelihood of Developing a Condition Based on Genetic Mutations

The degree that genes influence disease risk is a second domain in the FSGI model typology that is particularly salient to families (Rolland & Williams, 2005). For example, as knowledge about the contribution of genes to a disorder becomes known and clinically useful, this information can enhance understanding of actual and perceived risk,

anticipation of disease onset, and characteristics of disease progression. Genetic information also might influence an individual's intervention choices. In addition, however, the information about the genetic make-up, or genotype, of an individual necessarily yields information about the genotype of biologically related family members and their subsequent risks and future health. Disease etiology, therefore, has both biologic and psychosocial implications for families. Both AD and PD are genetically heterogeneous disorders, meaning that many genes and sequence variations within these genes likely are components of their etiology. Although much is yet to be learned about the etiology of these disorders, significant progress has been made over the last 2 decades in explicating the dynamics of genetic and environmental risk factors.

**Genetic risk factors** In both AD and PD, causative genes have been identified in relatively small subsets of families who have Mendelian patterns of inheritance and symptoms at early ages. In the case of AD, the causative genes identified to date, such as the Amyloid Precursor Protein (APP), Presenilin 1 (PSEN 1), and Presenilin 2 (PSEN 2) genes, are associated with ages at onset before age 60 and autosomal dominant inheritance. A small percentage of families with PD also have autosomal dominant inheritance, but others experience onset at early ages and autosomal recessive inheritance. **Table 2** shows causative genes identified in AD and PD.

In addition to identifying causative genes for the rare familial subtypes of AD and PD, considerable effort also is underway to identify susceptibility genes for the common, late-onset disease. In contrast to rare mutations causing a disease, common sequence variants (or polymorphisms) in genes may increase risk for a disorder or modify other aspects of the disease phenotype. For example, the  $\epsilon 4$  allelic variant in the Apolipoprotein E (APOE) gene is consistently associated with increased risk for AD and earlier ages at onset (Evans et al., 2003; Pericak-Vance et al., 1991). The identification of other emerging susceptibility genes in AD is in progress (Myers & Goate, 2001), as well as research to identify genes that influence risk for developing the more common, sporadic, and later-onset PD (Foroud et al., 2003; Le et al., 2003). Susceptibility genes implicated in AD and PD are shown in **Table 2**.

In many cases the frequency of genetic variants and associated disease risks varies across ethnic groups and populations with important implications for scientists and clinicians internationally. For example, the risk associated with the APOE- $\epsilon 4$  allele in Caucasians is consistent, but it is equivocal in African Americans. Some studies have shown a potent  $\epsilon 4$  effect upon AD risk among African Americans (Graff-Radford et al., 2002), but other studies have shown no  $\epsilon 4$  effect on disease risk (Evans, et al., 2003). As causative and susceptibility genes are discovered in one population, therefore, replications of these studies are needed across ethnic groups to design accurate education and counseling interventions for individuals, families, and communities.

**Table 2. Summary of Genetic Basis of Alzheimer Disease and Parkinson Disease**

	Alzheimer disease		Parkinson disease	
	Gene name (acronym) locus source	Phenotype	Gene name (acronym) locus source	Phenotype
Causative genes	Amyloid Precursor Protein (APP) 21q21 (Goate et al., 1991)	<ul style="list-style-type: none"> <li>• Autosomal dominant</li> <li>• Early onset</li> </ul>	Alpha Synuclein (SNCA) 4q21 (Polymeropoulos et al., 1997)	<ul style="list-style-type: none"> <li>• Autosomal dominant</li> </ul>
	Presenilin 1 (PSEN1) 14q24.3 (St. George-Hyslop et al., 1992)	<ul style="list-style-type: none"> <li>• Autosomal dominant</li> <li>• Early onset</li> </ul>	Ubiquitin-Carboxy-Terminal Esterase L1 (UCHL1) 4p14 (Leroy et al., 1998)	<ul style="list-style-type: none"> <li>• Autosomal dominant</li> </ul>
	Presenilin 2 (PSEN2) 1q31-q42 (Levy-Lahad et al., 1995)	<ul style="list-style-type: none"> <li>• Autosomal dominant</li> <li>• Early onset</li> </ul>	Parkin 6q25.2-q27 (Kitada et al., 1998) PTEN-induced Putative Kinase 1 (PINK1) 1p36 (Valente et al., 2002)	<ul style="list-style-type: none"> <li>• Autosomal recessive</li> <li>• Juvenile onset</li> <li>• Autosomal recessive</li> <li>• Early onset</li> </ul>
Susceptibility genes	Apolipoprotein E (APOE) 19q13.2 (Pericak-Vance et al., 1991)	<ul style="list-style-type: none"> <li>• APOE-ε4 allele</li> <li>• Increased disease risk</li> <li>• Earlier ages at onset</li> </ul>	DJ-1 1p36 (Van Duijn et al., 2001) Nuclear Receptor 4, Subfamily 4, Group A, Member 2 (NR4A2) 2q22-q23 (Le et al., 2003)	<ul style="list-style-type: none"> <li>• Autosomal recessive</li> <li>• Early onset</li> </ul>
			Parkin 6q25.2-q27 (Foroud et al., 2003)	
			Synuclein Alpha Interacting Protein (SNCAIP) 5q23.1-q23.3 (Marx et al., 2003)	

**Environmental risk factors.** Although AD and PD are genetically heterogeneous, genetic variants alone do not fully explain their etiology. Environmental variables were initially believed to be the primary etiologic agents in PD, and the drug, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), produced symptoms of PD in people who abused that drug (Langston, Ballard, Tetrud, & Irwin, 1983). Subsequent research also showed an increased risk of PD with overexposure to manganese and copper (Gorell et al., 1999; Racette et al., 2001), pesticide exposure (Priyadarshi, Khuder, Schaub, & Shrivastava, 2000), and certain agricultural occupations (Kirkey et al., 2001). In AD, evidence links head injury accompanied by loss of consciousness with an increased disease risk, with increasing risk associated with increasing age at injury (Ikonovic et al., 2004). The mechanism behind this association is still under investigation.

Smoking is perhaps the most controversial environmental risk factor for both AD and PD. In a meta-analysis of 19 case-control studies of smoking and risk for AD, Lee (1994) found a protective effect of smoking, even when studies with methodologic flaws were excluded from the analysis. Almeida, Hulse, Lawrence, and Flicker (2002) also found conflicting results between studies of smoking and risk for AD. Evidence also has indicated that smoking is protective for PD (Gorell, Rybicki, Johnson, & Peterson, 1999). The mechanism for these protective effects is unclear. In addition, differences in study design likely contribute to these results (Kukull, 2001) and indicate the need for additional research.

Further research is needed to explore the contribution of environmental and genetic risk factors in the etiology of these disorders. Likewise, research to examine the interaction between genetic and environmental risk factors is

needed to fully understand disease pathogenesis and thus provide a foundation for improved, more specific interventions.

### Timing of Clinical Onset in the Life Cycle

The timing of clinical onset in the life cycle is a third domain in the FSGI typology that influences family well-being and the ability to move between developmental tasks. A novel aspect of the FSGI model is that it includes the time before clinical diagnosis as relevant to the family system. Typically AD and PD are late-adult-onset disorders, although variability in age at onset occurs. For example, the clinical symptoms of AD usually begin after age 60. In a small percentage of families in which mutations in a single gene are etiologic, onset occurs before age 60. Although PD also typically occurs in late adulthood (after age 50), onset is also observed before age 20 (juvenile onset), and between ages 20 and 50 (early onset). Clinical symptoms in AD and PD can occur in and span many different developmental stages of a family, requiring different types and amounts of caregiving support as a result. In addition, people may know they are at increased risk to develop AD or PD before symptom onset as a result of genetic testing in a small percentage of families (Bird, 2005). The effect of this information on family well-being and function is an important area of research.

### Prevention and Treatment

The final domain of the FSGI model is the degree to which disease onset or progression can be altered through intervention. Although the first gene discoveries in AD and PD occurred 15 years ago, genomics-based interventions are not imminent, largely because gene discovery is only the first step in understanding the biologic defect in a disorder (Collins, Green, Guttmacher, & Guyer, 2003). Consequently, evidence-based strategies are not yet available to prevent AD and PD. Current medical and nursing interventions remain primarily symptom-based (National Institute on Aging, 2003). Pharmacologic therapies are generally unable to slow the underlying neuronal loss and are often targeted toward clinical features, such as depression, agitated behaviors, delusions, or hallucinations. Nonpharmacologic interventions are also available to manage or prevent selected clinical features, such as agitated behaviors (McGonigal-Kenny & Schutte, 2006). As researchers continue to examine the mechanisms underlying disease etiology, the opportunity for more precise medical therapies such as microelectrode-guided pallidotomy (i.e., a neurosurgical procedure to destroy targeted, overactive brain cells), fetal tissue transplantation, and gene therapy are anticipated (National Institute of Neurological Disorders and Stroke, 2004).

The FSGI model is a helpful typology for organizing the characteristics of chronic dementing conditions that are particularly relevant to both individuals and their families. This typology allows for comparison between chronic dementing

conditions, thus providing a heuristic model for setting research priorities, synthesizing research findings, anticipating client needs, or selecting intervention strategies. Given that genes and environment are involved in the etiology of AD and PD, a salient challenge for professional nurses now is to consider whether and how emerging genomics information and technologies, in particular, can be used to improve care for these individuals and families.

## Integration of Genomics of AD and PD Into Nursing Practice

The identification of genes involved in the etiology of AD and PD, even without understanding the underlying biologic mechanisms, opens the door for the clinical integration of genomics information into nursing practice. Initially, this integration will likely be driven by the availability of genetic testing. However, other opportunities exist to integrate genomics into the nursing care of people with AD and PD.

### Expanded Application of Genomics Information

Genetic testing is the identification of one's genotype at a particular gene locus for clinical purposes. These clinical purposes include establishing a diagnosis or clarifying one's risk for developing disease (presymptomatic and predictive testing). To date, diagnostic and predictive genetic testing are options for some families experiencing early-onset, familial AD or PD, exhibiting Mendelian patterns of inheritance (<http://www.genetests.org>). However, presymptomatic and diagnostic genetic testing currently have limited clinical utility for common late-onset AD and PD (Holston & Schutte, 2004). Although the clinical application of genetic testing in AD and PD remains relatively limited, the availability of any genetic testing necessitates active participation by professional nurses. This participation includes identifying clients and their families that might benefit from genetic testing, referring clients to specialty genetics providers, and supporting clients and their families through decisions regarding genetic testing and its consequences, whether they choose to be tested or not (American Nurses Association, 1998).

### Expanded Opportunities for Professional Nursing

New genomics information and technologies also indicated expanded opportunities for nurses to consider how genomics might be used to improve the effectiveness of nursing interventions. Nurses in the US and other countries have major responsibility for the care of people with dementia in various settings. In most cases, nursing interventions are broadly applied to the population with modest outcomes (McGonigal-Kenny & Schutte, 2006). One explanation for the modest effectiveness of biobehavioral interventions may be a lack of specificity of intervention. Lack of data on variations in clinical phenotype among people with AD and PD,

and lack of data regarding the biologic or behavioral predictors of this variation, limits researchers' ability to identify specific clinical subgroups that might be more or less amenable to a particular intervention and to target interventions to these subgroups (Schutte, 2004). An examination of the relationship between genetic variants and clinical phenotype in AD is feasible (Schutte, Maas, & Buckwalter, 2003), and it is necessary for professional nurses in order to identify genetic predictors of phenotype and develop genotype-directed interventions. Nurse scientists are ideally positioned to lead research efforts to explicate phenotypic variability (Schutte et al., 2006). The anticipated benefit of improved specificity is increased cost-effectiveness and improved client outcomes.

Given the increasing availability of genetic testing for more adult and late-adult-onset diseases, professional nurses can also lead efforts clinically to design and evaluate genetics' services that are responsive to the needs of older adults from diverse social and cultural backgrounds. What setting and media are the most appropriate to reach older adults about genetics and health care? Are any psychosocial implications of genetic testing unique to the older adult population? What is the best format for sharing information about genetics and genetic testing with older adults? Initial efforts to explore the willingness and motivation of older adults to seek genetic testing have been reported (Hurley et al., 2005; Skirton et al., 2006). However, more clinical research and innovation are needed.

Finally, in recognition of the growing elderly population worldwide and the consequent increasing prevalence of people with dementia worldwide, the consideration of genomic information, technology, and clinical innovation in a global context is necessary. How do ethnicity, culture, and health literacy influence the utility and desirability of genetics information and technology? Do the psychosocial implications of genetic testing vary across cultures? Is the concept of genetic risk relevant across cultures? How does genetics information and technology fit into the healthcare priorities of local and global communities? Research to examine cultural competence within the context of genetics' services delivery is in process (Barlow-Stewart, Yeo, Meiser, Goldstein, & Tucker, 2006), but this focus is understudied. Additional consideration of these questions can provide a framework for professional nurses to lead policy development efforts, in both local and global venues, to assure that genomics' information and technologies are integrated into healthcare practices in ways that are beneficial and just for aging populations around the world (Abel, Horner, Tyler, & Innerarity, 2005).

## Conclusions

AD and PD are two prevalent chronic dementing conditions that will only increase in their effects on global health in the immediate and extended future. New genomics tools and information are the groundwork for improved under-

standing of the pathologic underpinnings of these disorders. New genomics tools and information also are a foundation for professional nurses to undertake more comprehensive examination of the effects of these complex genetic disorders on the well-being of individuals and families, including the psychological and social effects of genetic information and genetic and environmental predictors of disease risk and progression. The equitable and effective integration of genomics into nursing research and clinical services for individuals and families experiencing these challenging disorders requires the full engagement and collaboration of professional nurses around the world.

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