

## Dementia Test

**Disorder also known as:** Alzheimer disease, frontotemporal dementia

**Test Gene List:** APP, DCTN1, GRN, MAPT, PRNP, PSEN1, PSEN2, SQSTM1, TARDBP, TREM2, TYROBP

### **Clinical Features:**

Dementia is a term that describes a group of symptoms associated with cognitive and/or behavioral changes that interfere with the ability to perform everyday activities.<sup>1</sup> The core mental functions that may be affected include memory, communication, personality, behavior, reasoning, judgement, and visual perception.<sup>1</sup> Dementia from all causes, occurs in 5-7% of adults over 60 years of age.<sup>2</sup> Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the two most common types of dementia.<sup>3</sup> AD accounts for 60-80% of dementia, and is the most common cause of dementia in North America and Europe.<sup>4</sup> Most AD patients first develop symptoms after 65 years of age, while <10% of patients present with early-onset AD.<sup>3</sup> FTD is more commonly observed in patients younger than 65 years, with symptoms including progressive behavioral and language changes.<sup>3</sup> Other genetic conditions such as Parkinson's disease and amyotrophic lateral sclerosis can also present with symptoms of dementia.

### **Inheritance Pattern/Genetics:**

Some forms of dementia are thought to be multifactorial, resulting from the interactions of environmental and genetic factors.<sup>5</sup> However, distinct, inherited forms of dementia have been documented.<sup>5</sup> Individuals with a family history of dementia and a young age of onset are more likely to have an inherited form of dementia.<sup>6</sup> The Dementia panel at GeneDx includes analysis of 11 genes associated with inherited forms of dementia. The complete list of genes and associated disorders is included in the table below. Dementia is most often inherited in an autosomal dominant manner, however autosomal recessive inheritance also occurs.

Symptoms and age of onset can vary between and within families, and reduced penetrance has been described.<sup>6</sup> A clinical diagnosis of dementia is based on medical and family history, neurological and neuropsychological evaluations, neuropathological studies, and exclusion of other disorders with similar clinical presentations.<sup>1</sup> However, clinical evaluation alone may not be sufficient to distinguish the various genetic causes of dementia given their phenotypic and genetic heterogeneity. The Dementia gene panel at GeneDx can assist in confirming a clinical diagnosis, defining a specific type of dementia, or aiding in the development of a comprehensive medical plan including symptom management and recurrence risk assessment. Dementia is an adult onset disorder for which there is currently no specific medical intervention that, if initiated in childhood, would alter the clinical course. Therefore, in accordance with policy and position statements from the American College of Medical

Genetics (ACMG)<sup>7,8</sup>, American Society of Human Genetics (ASHG)<sup>9</sup>, and the American Academy of Pediatrics<sup>8</sup>, samples from individuals younger than 18 years of age will not be accepted for this testing.

## Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing. The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants. Alternative sequencing methods are used to analyze regions with inadequate sequence data. Reportable variants include pathogenic variants, likely pathogenic variants, and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported, but are available upon request.

## Test Sensitivity:

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. For the genes on this panel, sequencing but not deletion/duplication analysis, is performed. The hexanucleotide repeat expansion in the *C9orf72* gene is not performed as part of the Dementia Panel.

## References:

1. McKhann et al. (2011) *Alzheimers Dement* 7 (3):263-9 (PMID: 21514250)
2. Prince et al. (2013) *Alzheimers Dement* 9 (1):63-75.e2 (PMID: 23305823)
3. Pasanen et al. (2018) *Eur. J. Hum. Genet.* : (PMID: 29476165)
4. Bird TD. Alzheimer Disease Overview. 1998 Oct 23 [Updated 2015 Sep 24]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1161/>
5. Fenoglio et al. (2018) *J. Alzheimers Dis.* 62 (3):913-932 (PMID: 29562532)
6. Loy et al. (2014) *Lancet* 383 (9919):828-40 (PMID: 23927914)
7. Goldman et al. (2011) *Genet. Med.* 13 (6):597-605 (PMID: 21577118).
8. Ross et al. (2013) *Genet. Med.* 15 (3):234-45 (PMID: 23429433)
9. Botkin et al. (2015) *Am. J. Hum. Genet.* 97 (1):6-21 (PMID: 26140447).

## Dementia Panel Sequencing Analysis of 11 Genes

Gene	Disease Name	Inheritance	Disease Associations
APP	Alzheimer Disease 1	AD	15% of early onset Alzheimer Disease <sup>1</sup>
DCTN1	Perry Syndrome, distal hereditary motor neuropathy VIIB	AD	Rare overall; 100% of Perry syndrome <sup>2</sup>
GRN	Frontotemporal lobar degeneration (FTLD) with ubiquitin-positive inclusions	AD, AR	5% of all FTLD; 20% of familial FTLD <sup>3</sup> ; Rare cause of AR adult-onset NCL <sup>9</sup>
MAPT	MAPT-related FTLD with or without Parkinsonism, Progressive Supranuclear palsy (PSP)	AD	13-30% of familial FTLD; 1-4% of sporadic FTLD <sup>4</sup>
PRNP	Gerstmann-Straussler-Scheinker syndrome (GSS), familial Creutzfeldt-Jakob disease (fCJD), and fatal familial insomnia (FFI)	AD	Rare overall; 100% genetic prion disease <sup>5</sup>
PSEN1	Alzheimer Disease 3	AD	60% of early onset Alzheimer Disease <sup>1</sup>
PSEN2	Alzheimer Disease 4	AD	<5% early onset Alzheimer Disease <sup>6</sup>
SQSTM1	ALS, IBMPD, FTLD	AD	2-3% of FTLD/ALS some with Paget disease of bone <sup>7</sup>
TARDBP	ALS 10, FTLD	AD	1.5-3% of ALS with or without FTLD <sup>8</sup>
TREM2	polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS), or Nasu-Hakola disease	AR	Rare <sup>5</sup>
TYROBP	Nasu-Hakola disease	AR	Rare <sup>5</sup>

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