

**TABLE 35-2 THE MOLECULAR BASIS FOR DEGENERATIVE DEMENTIA**

Dementia	Molecular Basis	Causal Genes (Chromosome)	Susceptibility Genes	Pathologic Findings
AD	A $\beta$ /tau	<i>APP</i> (21), <i>PS-1</i> (14), <i>PS-2</i> (1) (<2% carry these mutations, most often in <i>PS-1</i> )	<i>Apo E4</i> (19)	Amyloid plaques, neurofibrillary tangles, and neuropil threads
FTD	Tau	<i>MAPT</i> exon and intron mutations (17) (about 10% of familial cases)	H1 <i>MAPT</i> haplotype	Tau neuronal and glial inclusions varying in morphology and distribution
	TDP-43	<i>GRN</i> (10% of familial cases), <i>C9ORF72</i> (20–30% of familial cases), rare <i>VCP</i> , very rare <i>TARDBP</i>		TDP-43 neuronal and glial inclusions varying in morphology and distribution
	FUS	Very rare <i>FUS</i>		FUS neuronal and glial inclusions varying in morphology and distribution
DLB	$\alpha$ -Synuclein	Very rare <i>SNCA</i> (4)	Unknown	$\alpha$ -Synuclein neuronal inclusions (Lewy bodies)
CJD	PrP <sup>Sc</sup>	<i>PRNP</i> (20) (up to 15% of patients carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	PrP <sup>Sc</sup> deposition, panlaminar spongiosis

**Abbreviations:** AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

with slowly progressive memory loss over several years is likely to suffer from AD. Nearly 75% of patients with AD begin with memory symptoms, but other early symptoms include difficulty with managing money, driving, shopping, following instructions, finding words, or navigating. Personality change, disinhibition, and weight gain or compulsive eating suggest FTD, not AD. FTD is also suggested by prominent apathy, compulsivity, loss of empathy for others, or progressive loss of speech fluency or single-word comprehension and by a relative sparing of memory and visuo-spatial abilities. The diagnosis of DLB is suggested by early visual hallucinations; parkinsonism; proneness to delirium or sensitivity to psychoactive medications; rapid eye movement (REM) behavior disorder (RBD; the loss of skeletal muscle paralysis during dreaming); or Capgras syndrome, the delusion that a familiar person has been replaced by an impostor.

A history of stroke with irregular stepwise progression suggests vascular dementia. Vascular dementia is also commonly seen in the setting of hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. In patients suffering from cerebrovascular disease, it can be difficult to determine whether the dementia is due to AD, vascular disease, or a mixture of the two because many of the risk factors for vascular dementia, including diabetes, high cholesterol, elevated homocysteine, and low exercise, are also putative risk factors for AD. Moreover, many patients with a major vascular contribution to their dementia lack a history of stepwise decline. Rapid progression with motor rigidity and myoclonus suggests CJD (**Chap. 453e**). Seizures may indicate strokes or neoplasm but also occur in AD, particularly early-age-of-onset AD. Gait disturbance is common in vascular dementia, PD/DLB, or NPH. A history of high-risk sexual behaviors or intravenous drug use

**TABLE 35-3 EVALUATION OF THE PATIENT WITH DEMENTIA**

Routine Evaluation	Optional Focused Tests	Occasionally Helpful Tests
History	Psychometric testing	EEG
Physical examination	Chest x-ray	Parathyroid function
Laboratory tests	Lumbar puncture	Adrenal function
Thyroid function (TSH)	Liver function	Urine heavy metals
Vitamin B <sub>12</sub>	Renal function	RBC sedimentation rate
Complete blood count	Urine toxin screen	Angiogram
Electrolytes	HIV	Brain biopsy
CT/MRI	Apolipoprotein E	SPECT
	RPR or VDRL	PET
		Lab screen for autoantibodies
Diagnostic Categories		
Reversible Causes	Irreversible/Degenerative Dementias	Psychiatric Disorders
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B <sub>12</sub> deficiency	Huntington's	
Normal-pressure hydrocephalus	Dementia with Lewy bodies	
Subdural hematoma	Vascular	
Chronic infection	Leukoencephalopathies	
Brain tumor	Parkinson's	
Drug intoxication		
Autoimmune encephalopathy		
Associated Treatable Conditions		
	Depression	Agitation
	Seizures	Caregiver "burnout"
	Insomnia	Drug side effects

**Abbreviations:** CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).