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Review

Genetic analysis of genes associated with Mendelian dementia

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Abstract. *Background and aim:* Dementia is a disease associated with cognitive and/or behavioral changes that interfere with the ability to perform daily activities. Alzheimer's disease is the most common type of dementia. The aim of this mini-review is to summarize all the syndromes characterized by dementia and for which the associated gene is known. *Methods:* We searched those syndromes in PubMed and OMIM database. *Results:* Two forms of dementia exist: the multifactorial dementia results from the interaction of different genetic and environmental factors, the hereditary dementia associated with a single gene. Individuals with a family history of dementia and early onset of the disease are more likely to have a hereditary form of dementia. Dementias are mainly autosomal dominant, but they can also be autosomal recessive or X-linked. *Conclusions:* Since dementia has high clinical and genetic heterogeneity, the use in diagnostics of a large panel of genes may greatly help to speed up the determination of the molecular diagnosis and/or establish a risk of recurrence in family members for the purpose of planning appropriate preventive and/or therapeutic measures. (www.actabiomedica.it)

Key words: Mendelian dementia, Alzheimer disease, Parkinson disease

Dementia is a disease associated with cognitive and/or behavioral changes that interfere with the ability to perform daily activities (1). Dementia occurs in 5-7% of individuals over 60 years of age (2). Alzheimer's disease (AD) is the most common type of dementia (about 60-80% of cases), of which <10% have early onset. It is familial in 25% cases (3) and is a degenerative dementia characterized by cortical disorders such as agnosia, aphasia and apraxia. Other degenerative dementias are frontotemporal dementia (Pick's disease, primary progressive aphasia, semantic dementia), progressive supranuclear paralysis, Lewy's body dementia, Parkinson's dementia, Huntington's disease, prion disease and cortical-basal degeneration. There are also reversible dementias and vascular dementias (4,5). Pharmacological treatment is supportive. Diagnosis of dementias involves neurological examination, including mental status examination, neuropsychological evaluation, laboratory tests and neuroimaging. The differential diagnosis of Alzheimer's disease includes other causes of dementia, particularly treatable forms of cognitive decline that include depression, chronic drug intoxication, chronic central nervous system infection, thyroid disease, vitamin deficiencies, inflammatory central nervous system angioitis and normal pressure hydrocephalus. A distinction must also be made between different forms of dementia (3). Multifactorial forms of dementia, resulting from the interaction of different genetic and environmental factors, and hereditary forms of dementia are known (6). Individuals with a family history of dementia and early onset of the disease are more likely to have a hereditary form of dementia (1). Dementias are mainly autosomal dominant, but they can also be inherited in an autosomal recessive or X-linked manner (Table 1). Reference guidelines for genetic testing are contained

Table 1. Syndromes characterized by dementia for which the genetic basis is known

Gene	**OMIM# Gene**	**Inheritance**	**Phenotype**	**OMIM# Phenotype/ Reference**	**Gene function** (https://www.genecards.org/)
APOE	107741	ADo	AD2	104310	Essential for catabolism of triglyceride-rich lipoproteins
APP	104760	ADo	AD	104300	Neurite growth, neuronal adhesion, axonogenesis, synaptogenesis
C9orf72	614260	ADo	FTDALS1	105550	Regulation of endosomal trafficking, autophagy
CHMP2B	609512	ADo	FTD3	600795	Involved in recycling/degradation of growth factor receptors, lysosomal enzymes, lipids
CSF1R	164770	ADo	HDLS	221820	Cytokine controlling macrophages production, differentiation, function
DCTN1	601143	ADo	Perry syndrome	168605	Endoplasmic reticulum-to-Golgi transport, movement of lysosomes/endosomes, spindle formation, chromosome movement, nuclear positioning, axonogenesis
FUS	137070	ADo, AR	ALS6	608030	Crucial for dendritic spine formation/ stability, RNA transport/stability, synaptic homeostasis
GRN	138945	ADo	Frontotemporal lobar degeneration with TDP43 inclusions	607485	Inflammation modulation in neurons by preserving neuron survival, axonal outgrowth, neuronal integrity
MAPT	157140	ADo	FTD, Pick disease of brain	600274, 172700	Neuronal polarity establishment/maintenance
PRNP	176640	ADo	HDL1, spongiform encephalopathy with neuropsychiatric features	603218, 606688	Neuronal development, synaptic plasticity. Required for neuronal myelin sheath maintenance
PSEN1	104311	ADo	AD, FTD	607822, 600274	Regulation of neurite outgrowth, presynaptic facilitation, spike transmission, synaptic vesicles replenishment
PSEN2	600759	ADo	Alzheimer disease-4	606889	Modulation of Ca^{2+} ion shuttling between endoplasmic reticulum and mitochondria
SIGMAR1	601978	ADo	Frontotemporal lobar degeneration-motor neuron disease	(7)	Necessary for axonal retrograde movement of mitochondria in motor neurons
SORL1	602005	ADo	Late-onset AD	/	Positive regulation of BDNF signaling
SQSTM1	601530	ADo	FTDALS3	616437	Formation/degradation of ubiquitin-containing inclusions, involved in cell differentiation, apoptosis, immune response, regulation of K^+ channels
TARDBP	605078	ADo	ALS10	612069	Splicing regulation of mRNAs encoding proteins involved in neuronal survival
TREM2	605086	AD	PLOSL2	618193	Regulation of microglial proliferation, chemotaxis, outgrowth, activation and phagocytosis of apoptotic neurons and myelin debris, neuronal synapses during brain development

(continued on next page)

Table 1 *(continued)***.** Syndromes characterized by dementia for which the genetic basis is known

Gene	**OMIM# Gene**	**Inheritance**	**Phenotype**	**OMIM# Phenotype/ Reference**	**Gene function** (https://www.genecards.org/)
TYROBP	604142	AR	PLOSL1	221770	Promotion of neuronal apoptosis during brain development and proinflammatory responses in microglia after nerve injury
UBQLN2	300264	XLD	ALS15	300857	Regulation of ubiquitin-proteasome system, autophagy, endoplasmic reticulum-associated protein degradation pathways
VCP	601023	ADo	IBMPFD1	167320	Ubiquitin-dependent sorting of membrane proteins to lysosomes

AD = Alzheimer's dis ease; Ado = autosomal dominant; FTDALS = frontotemporal dementia and/or amyotrophic lateral sclerosis; FTD = frontotemporal dementia; HDLS = hereditary diffuse leukoencephalopathy with spheroids; ALS = amyotrophic lateral sclerosis with/without frontotemporal dementia; HDL = Huntington disease-like; PLOSL = polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy; IBMPFD = inclusion body myopathy with early-onset Paget disease with/without frontotemporal dementia.

in "Genetics Home Reference" (ghr.nlm.nih.gov) and Gene Reviews (3). Detection of variations in the genes in Table 1 is based on analysis of a multi-gene panel by next generation sequencing of the coding regions and their intron-exon junctions. Testing aims to identify variants in genes known to be associated with dementia in subjects suspected to have Mendelian dementia.

Our NGS test has an analytical sensitivity and specificity ≥99%. On the other hand, diagnostic sensitivity in individuals with early-onset familial Alzheimer's disease with a pathogenic variant in *APP*, *PSEN1* or *PSEN2* can be identified in 40-80% of cases (8). A pathogenic variant can be identified in about 65% of cases of frontotemporal dementia (9). A genetic cause can be identified in about 10-15% of cases of prion disease (10). The diagnostic specificity of Alzheimer's disease is about 70% (11).

Although dementia has high clinical and genetic heterogeneity, our test makes it possible to determine the molecular diagnosis of new subjects and/or establish a risk of recurrence in family members for the purpose of planning appropriate preventive and/or therapeutic measures.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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