Narrative review

Genetic Alterations Associated with Parkinson's and Alzheimer's Disease: Evolution and Response to Treatment

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Abstract
Parkinson's and Alzheimer's are the most frequent neurodegenerative diseases worldwide. They have a multifactorial etiology, including genetics, and are of interest in current scientific research. A narrative review was carried out with the aim of determining the genetic alterations associated with these pathologies, as well as their influence on their evolution and response to treatment. Original articles, literature reviews, systematic reviews, meta-analyses in English and Spanish, with publication date between January 1, 2018 and May 20, 2023, were consulted in databases such as PubMed and Medline. MeSH terms "Alzheimer Disease", "Parkinson Disease", "Drug Therapy" and "Mutation" were used. Hereditary risk for Parkinson's disease is usually polygenetic, however, there are genes related to monogenic mutations. Alterations in α-synuclein, glucocerebrosidase and leucine-rich kinase 2 genes have been identified that are related to an increased risk of developing Parkinson's disease, in addition to variations in the clinical picture and age of symptom onset. As for Alzheimer's disease, alterations in the genes of the amyloid precursor protein, presenilin 1 and 2 are related to the familial form of the disease; on the other hand, those of apolipoprotein E4 have been identified in the sporadic form, and are therefore considered to be the most important genetic risk factor for its development.

Keywords
Alzheimer Disease, Parkinson Disease, Drug Therapy, Mutation.

Resumen
La enfermedad de Parkinson y Alzheimer son las enfermedades neurodegenerativas más frecuentes a nivel mundial. Tienen etiología multifactorial, entre ellas, la genética; y son motivo de interés en la investigación científica actual. Se realizó una revisión narrativa con el objetivo de determinar las alteraciones genéticas asociadas a estas patologías, además su influencia en la evolución y respuesta al tratamiento de ellas. Se consultaron artículos originales, revisiones bibliográficas, sistemáticas, metaanálisis en inglés y español, con fecha de publicación entre el 1 enero de 2018 y el 20 de mayo de 2023, en bases como PubMed y Medline. Se utilizaron los términos MeSH «*Alzheimer Disease*», «*Parkinson Disease*», «*Drug Therapy*» y «*Mutations*». El riesgo hereditario para la enfermedad de Parkinson suele ser poligenético, sin embargo, existen genes relacionados con mutaciones monogénicas. Se identifican alteraciones en genes de α-sinucleína, glucocerebrosidasa y quinasa 2 rica en leucina que se relacionan con mayor riesgo de desarrollar Parkinson, además de variaciones en el cuadro clínico y edad de inicio de síntomas. En cuanto a la enfermedad de Alzheimer, las alteraciones en los genes de la proteína precursora amiloide, presenilina 1 y 2 se relacionan con la forma familiar de la enfermedad; por otra parte, las de apolipoproteína E4 se han identificado en la forma esporádica, por lo que se consideran como el factor de riesgo genético más importante para su desarrollo.

Palabras clave
Enfermedad de Alzheimer, Enfermedad de Parkinson, Tratamiento Farmacológico, Mutación.

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Alteraciones genéticas asociadas a la enfermedad de Parkinson y Alzheimer: evolución y respuesta al tratamiento

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Introduction

Among the most frequent neurodegenerative diseases, Alzheimer's disease (AD) and Parkinson's disease (PD) stand out. AD is the most common cause of dementia, accounting for 60-80 % of cases worldwide. The World Health Organization reported a prevalence of 8.5 million cases of PD by 2019, doubling its prevalence in the last 25 years.[i,ii]

Neurogenetics is the field of science that studies the role of genes in the development and function of the nervous system.[iii] Interventions in neurogenetics are aimed at identifying the primary pathophysiological processes that begin years before symptoms appear.[iv]

Multiple variants have been described in the presentation of neurodegenerative diseases, depending on the age of onset, with early or late onset. The importance of characterizing these genotypic variants lies in the possibility of identifying the genetic predisposition of some patients, who may debut with atypical and aggressive symptoms, with a worse prognosis, in a more timely manner. This provides the opportunity to identify new biomarkers, therapeutic targets, and the development of risk scales for these pathologies.[v]

In this review, a literature search of original articles and literature reviews, systematic, meta-analysis in English and Spanish, in PubMed, Medline and SciELO databases, using the MeSH terms "Alzheimer disease", "Parkinson disease", "drug therapy", "Genetic mutations", published mainly between January 1, 2018 and May 20, 2023, while also including some articles from previous years that were considered relevant to the basis of this review, was performed. Therefore, this literature review aims to determine the genetic alterations associated with Parkinson's and Alzheimer's diseases; and their influence on the evolution and response to treatment of these pathologies.

Discussion

Genetic alterations related to Parkinson's disease

It is estimated that between 3 and 5 % of PD cases are linked to alterations in known genes with monogenic inherited risk, and between 16 and 6 % to non-monogenic inherited risk, with more than 90 variants described as being involved;[vi] Nalls *et al.* conducted a genome-wide association study, in which they compared 37 688 PD cases with 1.4 million controls, identifying 78 loci affecting PD risk. Their findings suggest that the most frequently identified variants present lower pathogenic risk, but when interacting with genetic and environmental factors contribute to the degree of PD risk. However, monogenic mutations in the α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), parkin (PRKN), PTEN-induced kinase 1 (PINK1), and glucocerebrosidase (GBA) genes generate elevated risk.[vii]

For the SNCA gene, on chromosome 4q, which encodes the α-synuclein protein, variants with undetermined significance in autosomal dominant PD have been identified by sequencing studies; Day *et al.* suggest that these mutations produce protein misfolding, subsequent accelerated aggregation and intracellular accumulation, increasing oxidative stress by interrupting proteasome function.[viii]

The LRRK2 gene, located on chromosome 12q, encodes the enzyme kinase, where its mutations are associated with autosomal dominant PD, being identified in approximately 1 to 2 % of all PD patients and in 5 % of the familial form.[ix] Jankovic *et al.* describe that the mutation hotspots are mainly located in the functional domains of the enzyme, generating dysregulation of the kinase and GTPase activities, with a toxic gain of function that could be the underlying mechanism.[x]

Mutations in the PRKN and PINK1 genes, located on chromosomes 6q and 1p respectively, have been identified in up to 77 % of juvenile PD cases and between 10 to 20 % of early-onset cases. They have autosomal recessive inheritance; generating dysfunctional mitochondria lysosomes by macroautophagy, which produces altered mitophagy. Simon *et al.* describe that PARKIN indirectly regulates PGC-1α levels, an important transcriptional regulator, involved in gene expression necessary for mitochondrial biogenesis and multiple antioxidant defenses.[vi,ix]

The GBA gene, located on chromosome 1q, encodes the lysosomal enzyme glucocerebrosidase, which breaks down glucocerebroside into glucose and ceramide, important in the degradation of sphingolipids. Variants of this occur in approximately 8.5 % of patients with PD and autosomal dominant inheritance pattern; carriers have an approximately four times higher risk of PD than the general population, associated with accumulation and aggregation of α-synuclein.[x]

Alzheimer's disease

For early-onset AD (before 65 years of age), more than 400 mutations have been identified in three genes: amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2), which represent 5 % of cases of AD with an autosomal dominant inheritance pattern. Late-onset AD (after 65 years of age) is associated with polymorphisms of the apolipoprotein E (Apo E) gene, present in up to 65 % of cases, being the main susceptibility gene.[ii]

The APP gene, located on chromosome 21q, encodes a transmembrane protein from which amyloid β (Aβ) is derived by the action of gamma-secretases; Kamboh *et al.* describe that its mutation represents 10 % to 15 % of cases of autosomal dominant familial AD, affecting the function of gamma-secretase and increasing the production of Aβ.[xi]

The PSEN1 and PSEN2 genes, located on chromosomes 14q and 1q, respectively, encode the PSEN1 and PSEN2 proteins, part of the gamma-secretase complex that regulate the proteolytic activity of gamma-secretase on APP. Breijyeh *et al.* describe that their mutations are mostly of undetermined significance with an autosomal dominant inheritance pattern.[xii]

Qin *et al.* postulate that PSEN1 mutation is frequent in up to 75 % of cases of familial AD, with more than 200 variations in it; on the other hand, mutations in PSEN2 occur in about 12 % with more than 40 variations; with altered gamma-secretase function, producing Aβ; PSEN1 mutations alter neuronal function affecting GSK-3β activity and kinesin-I based motility, leading to neurodegeneration.[xiii]

On chromosome 19 is located the gene for Apo E, a glycoprotein expressed in astrocytes and microglia, in three isoforms: Apo E2, Apo E3 and Apo E4; this protein acts as a receptor-mediated endocytosis ligand for lipoproteins, including cholesterol, important for myelin production and normal brain function; on the other hand, carriers of the Apo E4 allele have a higher risk of developing AD, increasing three times for heterozygous carriers and 15 times in homozygotes; while the homozygosity of the Apo E2 allele has been identified as a protective factor for AD.[xiv]

Apo E4 binds competitively to Aβ receptors on the surface of astrocytes, preventing Aβ uptake, promotes the seeding and aggregation of Aβ into oligomers and fibrils, reducing its elimination from the interstitial fluid. These depositions of Aβ in the form of amyloid plaques cause cerebral amyloid angiopathy and cerebral vascular damage, important in the pathogenesis of AD.[xv]

Relationship of genetic alterations to the clinical course and prognosis of patients

Parkinson's disease

The clinical presentation of PD is characterized by motor and non-motor symptoms; classic symptoms being resting tremor, rigidity, bradykinesia and postural disturbances. The non-motor symptoms described are cognitive impairment, orthostatic autonomic dysfunction, hyperhidrosis, depression, anxiety, dementia, sleep disorders and sensory abnormalities such as anosmia, paresthesia and pain.[xvi]

Post *et al.* define early-onset PD as the onset of symptoms between 21 and 40 years of age, and describe that there are usually genetic alterations associated with differences to the clinical course of classic PD, with a higher frequency of dystonia and dyskinesias associated with the use of levodopa. The classic subtype of late-onset PD is characterized by onset of symptoms after the age of 60 years.[xvii]

As part of the UK Tracking Parkinson's Study, Malek *et al.* studied 1893 patients with PD and found that the L444P mutation was the most frequent pathogenic mutation of the GBA gene. Patients with this mutation were on average five years younger at the onset of PD than non-carriers, more likely to have gait difficulty, postural instability with no significant differences in cognitive function in early stages of the disease compared to non-carriers.[xviii]

A meta-analysis by Creese *et al.* found that PD patients carrying GBA mutations have a 2.4-fold increased risk of developing cognitive impairment, as well as a 1.8-fold and 2.2-fold increased risk of developing psychosis and depression, respectively, compared to patients with sporadic PD (non-mutation carriers).[xix]

Variants in LRRK2 have also been associated with changes in the clinical phenotype of PD patients. The presence of the G2019S mutation is associated with slower motor deterioration compared with PD patients not carrying the mutation. Yahalom *et al.* evaluated 225 Ashkenazi Jewish patients with PD and found that the G2019S mutation was associated with younger age of symptom onset compared to patients with N370S mutation or patients without mutations.[xx]

Omer *et al.* studied 10 090 PD patients and compared patients with mutations in LRRK2, GBA and LRRK2+GBA, identifying that carriers of LRRK2 alone or LRRK2+GBA have a milder clinical phenotype with better scores on the unified PD rating scale compared to those with mutations in GBA alone.[xxi]

Pang *et al.* describe that mutations in LRRK2 modify the effect of GBA mutations, resulting in PD with milder symptoms compared to patients with mutations in GBA alone. However, carriers of both mutations have much higher risk for developing PD and lower age of symptom onset than patients carrying only one mutation.[xxii]

Alterations in the SNCA gene also confer changes in the clinical phenotype of

PD patients. Magistrelli *et al.* found that mutations in SNCA have a lower age of symptom onset, more severe non-motor symptoms and earlier onset.[xxiii] A meta-analysis conducted by Shu *et al.* found that some variants in SNCA of the variants of the 271-bp allele confer a higher risk of presenting symptoms at a younger age, while variants of the 267-bp allele have the opposite effect.[xxiv]

PD with PRKN mutations is characterized by disease onset at younger ages, lower limb dystonia at presentation, absence of cognitive impairment, frequent motor fluctuations and dyskinesias[xxv]. On the other hand, the PD phenotype with PINK1 mutations is characterized by slower progression with typical symptoms of tremor, bradykinesia, rigidity, younger age of symptom onset. Cognitive impairment and psychiatric disturbances such as psychosis are rare in these patients.[xxvi]

Alzheimer's disease

AD is clinically characterized by progressive cognitive impairment with insidious onset and progressive alterations in episodic memory, visual/spatial and executive functions; the most frequent presentation is at advanced age (over 60 years). Subsequently, topographical disorientation and difficulties with multitasking emerge, in addition to behavioral changes, mobility problems, hallucinations and seizures.[xxvii]

The Apo E4 gene is considered the most important genetic risk factor for sporadic AD. Tellechea *et al.* found that the presence of Apo E4 is associated with younger age of onset of AD symptoms, more often of the amnesic type compared to the pattern of preservation in the hippocampus.[xxviii]

Baril *et al.* found an association between Apo E4 and greater severity of insomnia, which worsens cognitive function and memory in AD.[xxix] Frey *et al.* studied 144 patients with AD and found that those who do not carry the E4 allele of the Apo E gene have a non-amnestic AD phenotype, showing cognitive impairment in domains unrelated to memory (language, behavior, attention, executive and visuospatial functions).[xxx]

Alterations in PSEN1 are associated with a lower average age at symptom onset compared to alterations in the APP and PSEN genes2.[xxxi] Huang *et al.* found that the Asp678His mutation in the APP gene was associated with faster progression to severe dementia within 5 to 10 years of the age of symptom onset.[xxxii] Wang *et al.* found that patients with the Ile716Thr mutation in APP had marked impairment *in situ*ational memory, with an age of symptom onset between 35 and 40 years.[xiii]

In studying the V717I mutation of APP in five Chinese families, Zhang *et al.* found that the mean age of symptom onset was 54.7 years, the initial symptoms were executive dysfunction, disorientation and subtle memory loss; neurological symptoms were of late onset and were characterized by marked spastic paraparesis and cerebellar ataxia.[xxxiii]

Qiu *et al.* found a new genetic alteration (Gly111Val) in the PSEN1 gene; they found no differences in the clinical phenotype of carriers, with short-term memory loss being the most frequent symptom.[xxxiv] In contrast, Li *et al.* studied the Glu116Lys variant, and found that carriers presented disorientation and memory impairment from the age of 35 years and progressed rapidly with psychiatric symptoms; some patients died at the age of 40 years.[xxxv]

Another study conducted by Qiu *et al.* found the M139L alteration in PSEN1 and reports that the mean age of symptom onset was 45 years, the main symptoms experienced by carriers were progressive memory impairment, visuospatial disturbances and irritability.[xxxvi] Li *et al.* also found the Ile202Phe variant, whose carriers showed memory impairment from the age of 36 years and subsequently developed language difficulties and personality changes.[xxxvii]

Mutations in PSEN2 tend to be rarer. Qin *et al.* found that patients with these mutations have an older age of symptom onset than patients with mutations in APP or PSEN1, have a slower progression and symptoms similar to sporadic or idiopathic AD.[xiii]

Relationship of genetic alterations to response to treatment

Parkinson's disease

In PD, levodopa remains the gold standard in initial management, with greater benefit in control of motor manifestations compared to dopaminergic agonists. Two important pathways are involved in dopamine synthesis: the catechol o-methyltransferase pathway and amino oxidase B pathway.[xxxviii]

Initial descriptions of LRRK2 emphasized the clinical similarities between this condition and idiopathic PD, specifically that both are progressive forms of parkinsonism that respond well to levodopa (L-DOPA) therapy.[xxxix]

Lantin *et al.* conducted a study to explore the association between polymorphisms in dopaminergic pathway genes, finding that the rs921451 polymorphism in the dopa-decarboxylase gene had an effect on

response to L-DOPA treatment in Chinese PD patients. However, this could vary due to ethnic differences.[xl]

Likewise, mutations associated with dopaminergic pathways have an important effect on the adverse effects of drugs. Yin *et al.* evidenced in their meta-analysis that the AA genotype of the rs4680 polymorphism of catechol-O-methyltransferase potentially increases the risk of levodopa-induced dyskinesia in a recessive genetic model for PD patients.[xli]

Alzheimer's disease

The Food and Drug Administration has approved two pharmacological groups for the treatment of AD, acetylcholinesterase inhibitors (ACE inhibitors), including donepezil, rivastigmine and galantamine. Another group are the N-methyl-D-aspartate receptor modulators, in which only memantine has been approved.[xlii] It is important to note that they do not act at the level of the pathological processes involved in the development of the disease, and the different genetic variants are responsible for approximately 75 to 85 % of the variability in response to treatment.[xliii]

Cheng *et al.*, in a meta-analysis that included 30 studies, did not identify any significant influence on the response to treatment with ICS in patients carrying the Apo E4 allele compared to non-carriers.[xliv] Jia *et al.* carried out a prospective multicenter study with 241 patients in which they identified a better response to treatment by non-carriers, with an increase in the Mini-Mental State Examination score.[xlv]

Similarly, a better response to treatment with donepezil or rivastigmine has been identified in patients carrying the Apo E3 variant compared to Apo E4.[xlvi] In patients who also present the BCH K genotype, there is less response to rivastigmine and memantine, due to the synergy between the Apo E4 allele and this variant.[xlvii]

Wallin *et al.*, in a prospective multicenter study, identified a better response to treatment with galantamine in older patients with low cognitive and functional capacities at the start of the study, a faster rate of progression prior to treatment, and a lower incidence of the Apo E4 allele.[xlviii]

Drugs for AD patients with PSEN1-mutated AD are limited to symptomatic therapies and no specific treatments are available. Drug repurposing based on induced pluripotent stem cells identified bromocriptine as a therapeutic candidate for AD with PSEN1 mutation.[xlix] Table 1 summarizes the main genetic alterations studied in this review and some less frequent ones, but also of interest to the scientific community.

Currently, the evidence is still building. Studies are underway to evaluate the influence of genetics on the clinical and response to specific treatments in people with neurodegenerative diseases such as PD and AD.

Table 1. Summary of the main genetic alterations related to PD and AD. Own Authorship[xiii,xxvi,l]

Mutation	Inheritance pattern	Risk level	Frequency	Clinical presentation	Response to treatment	Evolution
Parkinson's Disease						
GBA	Dominant	Medium	Common	Younger age of symptom onset, greater severity of motor symptoms	There may be less response to treatment, but studies are inconclusive.	Motor phenotype similar to idiopathic PD. Non-motor symptoms are greater, with more cognitive, neuropsychiatric involvement and autonomic dysfunction.
LRRK2	Dominant	Very high	Common	More benign clinical course, symptoms similar to sporadic or idiopathic PD	There are no significant differences with respect to levodopa therapy.	Slower progression almost similar to the progression of idiopathic PD. There may be early olfactory disturbances.
SNCA	Dominant	Very high	Uncommon	Clinical course similar to sporadic or idiopathic PD. May present at an early age.	There is a good initial response to treatment.	Progression similar to idiopathic PD unless it occurs together with other alterations in GBA or LRRK2, being more accelerated. Dementia and cognitive impairment may develop.

Mutation	Inheritance pattern	Risk level	Frequency	Clinical presentation	Response to treatment	Evolution
PRKN	Recessive	Very high	Rare	Younger age of onset of symptoms, usually less cognitive impairment.	Good response to levodopa, motor fluctuations and dystonia are common.	Overall good prognosis for patients or similar to sporadic PD.
PARK1	Recessive	High	Rare	Younger age of onset of symptoms, typical PD symptoms predominate.	Good response to levodopa treatment.	Better or similar prognosis than patients with sporadic PD
DJ1	Recessive	High	Very rare	It is associated with juvenile onset.	Adequate response to levodopa treatment.	It usually progresses slowly
PINK1	Recessive	Very high	Very rare	It is associated with juvenile onset.	Adequate response to levodopa treatment.	Progresión lenta.
VPS35	Dominant	Very high	Very rare	Earlier age of onset.	Adequate response to levodopa treatment.	Earlier age of onset than idiopathic PD. Similar clinical course.
Alzheimer's disease						
APP	Dominante	High	Rare	Age of onset of symptoms similar to sporadic PD. Greater impairment in situational and visuospatial memory.	Similar response to sporadic AD.	Faster and more severe progression to dementia. Lower frequency of psychiatric alterations. In some publications it was identified in cases of early onset. May be associated with myoclonus and epileptic seizures..
PSEN1	Dominante	High	Rare	Age of onset of symptoms lower than sporadic AD and AD with alterations in APP or PSEN2. Episodic memory loss is the most frequent symptom.	Similar response to sporadic AD.	Faster progression or similar to sporadic AD. Faster and more severe progression to psychiatric disturbances and personality changes. Progression of dementia similar or faster than sporadic AD.
PSEN2	Dominante	High	Rare	Age of onset of symptoms similar to sporadic AD.	Similar or better response as sporadic AD.	Similar or slower progression to sporadic AE.
Apo E4	Dominante	Medium to high	Uncommon	Younger age of symptom onset, marked amnestic clinical phenotype similar to sporadic AD.	Lower response to treatment with AChEIs* vs. non-carriers	Progression similar to sporadic or idiopathic AD. There may be early sleep and circadian cycle disturbances. There is variability in clinical presentation.
Apo E4	Dominante	Medio a Alto	Poco común	Menor edad de aparecimiento de los síntomas, fenotipo clínico amnésico marcado similar a EA esporádica.	Menor respuesta al tratamiento con CEI contra no portadores.	Progresión similar a EA esporádica o idiopática. Puede haber alteraciones del sueño y del ciclo circadiano de manera temprana. Hay variabilidad en la presentación clínica.

Conclusion

Genetic variations have been described that influence the age of symptom presentation in neurodegenerative diseases, with ages of presentation lower than the usual evolution, in addition to more disabling neurocognitive and motor symptoms. In PD, earlier ages of symptom onset are observed in patients with mutations of the GBA, SNCA, PRKN and PARK1 genes.

In terms of response to treatment, in patients with GBA mutations, less response has been described with faster progression to cognitive deficit. In AD, dementia develops at a younger age in people with PSEN1 gene mutations. Less response to conventional treatments has been observed with APO E4 mutations. Progression is faster and more severe in APP and PSEN1 gene mutations.

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