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Research Article

Genes involved in the development of Parkinson

Abstract

Background: Parkinson's disease is the second most important neurodegenerative disorder, affecting 3% of individuals older than 80 years of age. Main clinical symptoms are resting tremor, postural instability, bradykinesia and rigidity, with a good response to levodopa therapy.

Purpose of the study: The main goal of this work is to make a deep analysis on the genetic factors and kind of heritage involved in the development of Parkinson.

Main findings: Over the last years, numerous studies allowed to confirm the unquestionable contribution of genetic factors to the complex pathogenesis of this disease. Highly penetrant mutations producing rare, monogenic forms of the disease have been identified in singular genes such as *SNCA*, *Parkin*, *DJ-1*, *PINK1*, *LRRK2*, and *VPS35*. Unique variants with incomplete penetrance in *LRRK2* and *GBA* genes were identified as strong risk factors for Parkinson's disease in certain populations. Additionally, over 20 common variants with small effect sizes are now recognized to modulate the risk for Parkinson's disease.

Investigating Mendelian forms of Parkinson disease has provided precious insight into the pathophysiology that underlies the more common idiopathic form of this disorder.

Conclusions: The challenge over the next decade will be to get more data that strengthens the already available knowledge concerning genetics on Parkinson's disease, through the discovery of biological consequences of risk variants. Moreover, it is also expected that the advent of genome-wide association studies and the implementation of new research technologies will help in the identification of novel risk variants for the sporadic forms of Parkinson disease.

Introduction

The first detailed clinical description of Parkinson's disease (PD) dates from 200 years ago. Since then, Parkinson was defined as a fundamental motor disorder. This idea was not substantially changed in the 150 years after [1,2]. Only in century XXI, with the increase in knowledge concerning this disorder, scientists realized the importance of non-motor symptoms in the evolution of the disease.

Parkinson is a neurodegenerative disorder belonging to a heterogeneous group of diseases characterized by progressive and selective loss of anatomic and physiological autonomy of the nervous system [3]. It has a complex etiology, involving base ganglia and gives rise to movement, muscular and postural disturbances [4], contributing to a marked decline of patients life quality with implications at family, social and finance levels.

Nowadays, this pathology is the most frequent disorder related to movement, and the second most common neurodegenerative disorder, after Alzheimer [5]. In developed countries, the prevalence of this disorder is estimated to be 0,3% in total population. In the population above 60 years this value increases to 1-2% and above 80 years to 3-4% [6].

A higher incidence of Parkinson is observed in males together with an earlier onset [7]. Women present an attenuated form of the disease with slow progression [7].

With the exponential increase of elderly population, prevalence of Parkinson is expected to increase in the next years and new social and economic challenges will come up.

Materials and Methods

Papers and other publications were searched for, in a period between August and October 2016, using the websites *PubMed*, *Science Direct* and *b-On*. Keywords used were: Parkinson's disease, Genes involved, Risk alleles that were interconnected in several ways.

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Inclusion criterion used was papers published after 2000 and written in English, Portuguese, French or Spanish. Papers previous to 2000 were also selected according with the pertinence of the theme. Another criterion used was that selected papers were new literature about the chosen theme.

Symptoms

Parkinson is a progressive and chronic disorder. Symptoms become more intense with time due to degeneration and cell death of dopaminergic neurons in nigra substance and consequent decrease of brain capacity in dopamine production [8].

This disorder is characterized by a wide range of motor and non-motor symptoms.

Cardinal signs of the disease used in diagnosis are:

Rigidity – Lack of flexibility of muscles that become resistant to movement. It is usually asymmetric [8].

Bradykinesia – Results from dopamine absence in striated muscles that leads to a disequilibrium between excitatory and inhibitory signs. Patients show slow movements and problems in starting movement, as well as in having quick reactions [9]. In an advanced stage of the disease, patients can have movement blockage.

Tremor – This is the most usual symptom. In half the patients, this symptom starts in distal terminals. This sign is observed in rest and decreases with the beginning of any action [10].

Postural instability – Symptom that leads to frequent falls and appears in an advanced stage of the disease [9].

Among the non-motor symptoms of Parkinson's disease, that can develop before the appearance of the first motor signs, are cognitive symptoms that can lead to dementia, partial loss of smell ability, xerostomia, sleep changes (excessive daily dormancy, insomnia, periodic movements during sleep, sleep behavior disturbances), depression, anxiety, fatigue, pain, sexual dysfunction, lack of autonomy (urinary disturbances, hypotension, constipation, hypersudorese), loss of facial expression, speech changes and skin problems (excessive oiliness or intense dryness) [9].

Diagnosis

Current diagnosis of Parkinson is still done through clinical examination. It is based on the detection of alarming motor signs (tremor, rigidity or posture instability) and in clinical, familial and pharmacological history of the patient.

Since symptoms progression is usually slow, within a period of more than twenty years, Hoehn and Yahr [11], developed a scale (Table 1), that helps to understand patient stage of the disease.

To increase diagnosis acuity, a detailed neurological examination together with systemic biochemical analysis are performed, in order to determine the cause of Parkinson.

Diagnosis uncertainty is high (around 10-30%) and misdiagnoses are associated with similarities between symptoms present in other pathologies and Parkinson [12].

Most recent clinical diagnosis criterion, proposed by the *Movement Disorder Society*, try to reach a higher assurance giving more attention to non-motor symptoms of the disorder. In this diagnosis approach, there is a new classification called prodromic phase of Parkinson's disease that is in fact the initial stage of the disorder [12].

The goal of diagnosis in the prodromic phase is early detection by the use of biomarkers and neuro-imaging that have proven their value in the identification of the disease. The most recently identified biomarker is a tissue marker that can be collected through biopsy [12].

Causes of Parkinson

Causes of Parkinson development are still not completely understood. Despite the latest research advances on the disease, facts involved in its development were not yet fully determined and nowadays this disorder is looked at as a multifactorial cascade of events.

Several hypotheses were developed and today, scientists believe that genetic factors as well as environmental and even aging are responsible for the appearance of the disease [10].

Environmental Factors: Several epidemiological factors like environmental and work exposure and lifestyle have been associated with PD development. Table 2 summarizes the main environmental risk factors associated with PD.

Different environmental agents possibly involved in PD development have been studied, like exposure to pesticides, metals, herbicides and toxins. Results are not consensual. Several of these studies were not able to demonstrate the connection between the mentioned exposures and PD

Table 1: Stages of Parkinson's disease according to Hoehn and Yahr [11].

Stage	Characteristics
Stage 1	Symptoms in only one side of the body
Stage 2	Symptoms in both sides of the body
Stage 3	Disequilibrium, physical dependence
Stage 4	Severe incapacity, but still capable of walking or standing up without help
Stage 5	Forced to be in a wheel chair or in bed

Table 2: Main risk factors involved in the development of Parkinson (adapted from Campdelacreu [13]).

Risk level	Environmental agent
Increased Risk (strong evidence)	Pesticides
Increased Risk (weak evidence)	High iron intake, milk consumption (man), chronic anemia
Risk Reducer (strong evidence)	Hyperuricemia, tobacco, coffee
Risk Reducer (weak evidence)	Vitamin E, alcohol, tea, vigorous physical exercice

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development [13]. However, some studies were able to stablish that relationship, since those agents lead to death of dopaminergic neurons [14]. Those studies also relate living in rural habitat, dedication to agriculture and water consumption from wells with PD development [14].

Nicotine is believed to be a protective factor since it stimulates dopaminergic neurons and inhibits the formation of α-synuclein fibrils, decreasing PD symptoms [14]. Active smokers show a drastic low risk of suffering from PD [15].

Caffeine has shown to be a protective agent against PD development since it is an agonist of adenosine A2A receptors with neuroprotector effect [14].

Individuals with frequent crisis of gout and hence with high plasma levels of uric acid also show low risk of PD development and slow progression of symptoms [14]. Uric acid is a powerful antioxidant with neuroprotector effect [14].

Genetic Factors: Although most PD cases (around 85%) are associated with idiopathic nature or late onset where patients do not demonstrate having inherited the disease from their parents, evidences point out the involvement of genetic factors.

Patients with family history of PD have higher risk of development of this disorder [16]. In these cases, symptoms develop in younger ages.

Biochemical processes involved in the development of Parkinson: It is believed that there are several pathological processes involved in PD development. Explanatory theories of the pathogenesis of PD are based on different conditions: i) abnormal protein aggregation ii) mitochondrial dysfunctions; iii) oxidative stress; iv) neuroinflammation; v) excitotoxicity. All these processes lead to degenerescence of dopaminergic neurons of nigra substance and consequent reduction of dopamine production.

i) Abnormal protein aggregation: In most cases the pathogenic process starts with α-synuclein deposition in dopaminergic neurons that will give rise to eosinophilic cytoplasmic inclusions known as Lewy's bodies [17]. The protein α-synuclein is a small lipophilic molecule present at high levels in CNS. Lewy's bodies contain not only this protein but also parkin, ubiquitin and neurofilaments [18].

Accumulation of this protein in Lewy's bodies can be explained by the lack of action of the ubiquitin-proteasome system, responsible for protein degradation. In CNS, if ubiquitination and consequent α-synuclein degradation do not occur, lead to storage of this protein over time [17]. This fact explains the higher prevalence of the disease in elderly populations.

ii) Mitochondrial Dysfunctions: Neurons of PD patients frequently show failure and oxidative damage in complex I of the electron transport chain [19]. Changes in complex I (NADH-ubiquinone oxidoreductase) of nigra substance cells, can lead to decreased ATP synthesis that will result in neuronal degeneration [20].

Besides oxidative damage, several mitochondrial toxins block complex I leading to Parkinsonism in humans and laboratory animals [21]. Toxin 1-methyl-4-phenyl-1,2,3,6-tetrahidropiridin (MPTP), given to lab mice, leads to dopaminergic neurons death of nigra substance [22]. MPTP can induce all motor symptoms of the disease since it inhibits mitochondrial complex I.

Mitochondrial dysfunctions can also result from the direct or indirect action of genes associated with familial forms of PD. The gene coding for α-synuclein has a terminal sequence with mitochondrial target [23]. Cytosol acidification or over-expression of α-synuclein can lead to accumulation of this protein in mitochondria [24].

The *Parkin* gene, when mutated, leads to mitochondrial deficiency and to decreased resistance to oxidative stress [25,26]. The protein codified by this gene is involved in autophagy of non-functional mitochondria. In this way, a mutation in this gene can conduct to accumulation of deficient mitochondria [27].

Mutations in *LRRK2* gene are the most common cause of PD with familial origin or of sporadic appearance [28]. Around 10% of total amount of protein codified by the *LRRK2* gene is located in the external mitochondrial membrane [29].

The presence of mutations in the *PINK1* mitochondrial gene, identified in several families with recessive transmission of PD, gives stronger evidences of the role of mitochondrial dysfunctions in the development of the disease. Mice having this gene deficient show problems in production and release of dopamine [30], altered mitochondrial respiration and increased sensitivity to oxidative stress [31]. Gene over-expression or loss of function of PINK 1 protein leads to anti-apoptotic activity [32]. Moreover, studies in *Drosophila* and HeLa cells (immortal cells of carcinogenic lineage) indicate that the *PINK 1* mutant gene leads to morphologic changes of mitochondria [33-36].

Data showing that *PINK1* gene interacts with the mitochondrial machinery of fission or fusion supports the hypothesis that this gene affects several mitochondrial functions since it interferes with mitochondrial dynamics [37,38].

iii) Oxidative stress: The oxidative stress theory was developed after the analysis of *post-mortem* brain tissues from individuals with PD, where the loss of color of nigra substance was observed.

It was also observed decreased levels of glutathione, an antioxidant of the CNS, resulting from the diminished activity of mitochondrial complex I. In these conditions, there is an increase in oxygen reactive species and consequent decrease of glutathione levels [39]. This decrease can result from diminished synthesis due to inhibition of glutathione reductase or from increased levels of glutathione bisulfite [40].

A decrease in polyunsaturated fatty acid levels was observed that allows to understand the occurrence of a big number of lipid peroxidation reactions [41,42]. Brain contains a very high

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level of polyunsaturated fatty acids and this makes it especially susceptible to oxidative stress and, consequently to lipid peroxidation reactions. Since some of the lipid peroxidation products are chemically reactive, it is believed that they are responsible for the observed tissue damage. The process of dopamine synthesis leads, on its own, to oxidative stress since it produces oxygen reactive species to whom dopaminergic neurons are susceptible [43].

Dopamine is an unstable molecule that suffers self-oxidation giving rise to dopamine quinones and free radicals. This reaction is catalyzed by metals, oxygen or enzymes like tyrosinase [44]. Other enzymes, like MAO and catechol O-methyl transferase (COMT) are also involved in dopamine metabolism. MAO-A and MAO-B, localized in the outer membrane of mitochondria, degrade the excess of dopamine in cytosol by catalyzing its oxidative deamination [45]. In normal conditions, dopamine levels are regulated by MAO-A oxidative metabolism, localized mainly in catecholaminergic neurons [46].

However, with neuronal degeneration that takes place during aging and in PD, an increase in MAO-B occurs, localized in glial cells, becoming the main enzyme to metabolize dopamine [47,48] that is received by astrocytes by sodium dependent and independent mechanisms [49,50].

Products of dopamine metabolism catalyzed by MAO-B are 3,4-dihidroxiphenyl-acetaldehyde, ammonium and H_2O_2. Hydrogen peroxide is highly permeable, entering in neighboring dopaminergic neurons where it can react with Fe^{2+} to form hydroxyl radical [51].

Induction of MAO-B in astrocytes of adult transgenic mice leads to selective and progressive loss of dopaminergic neurons [52]. Dopamine oxidation products (dopamine quinones), can also contribute to neurodegeneration [53]. These quinones can suffer cyclization forming aminochrome that is highly reactive and leads to the formation of superoxide anion and to depletion of cell NADPH.

Aminochromes can combine with proteins like α-synuclein [54], and are precursors of neuromelanine, a brain pigment that can contribute to neurodegeneration by induction of neuroinflammation [55].

Transport and storage of dopamine can also contribute to the increase of reactive oxygen species production and consequent cell dysfunction. Usually, dopamine is captured by storage vesicles through active transport that requires monoamine 2 transporter (VMAT2), preparing its release after depolarization. Therefore, VMAT2 allows to keep controlled dopamine levels, preventing ROS formation. In this way, dopaminergic neurons having genetic or pharmacological VMAT2 blockage are more susceptible to toxic agents [56].

Mitochondrial dysfunction, caused by the various mentioned factors, is also a source of oxidative stress.

iv) Neuroinflammation: PD neuronal loss is also related to chronic neuroinflammation. This process is controlled by microglia, innate immunological cells and by the main immune cells of CNS.

Reactions of microglia were observed in the nervous system of PD patients of sporadic [57], and familial origin [58]. Microglia is activated in response to lesions or toxicity and originates oxidant compounds like nitric oxide and superoxide anion that might contribute to oxidative stress. If microglia is over-activated or if this activation is chronic, it will generate an exaggerated neuroinflammation state and uncontrolled neuroinflammatory responses [59]. These processes will end up in a neurodegeneration cycle.

v) Excitotoxicity: This theory states that the increase in excitatory neurotransmitters activity, like glutamate, resulting from lack of dopamine, can increase the amount of calcium ion inside the cell. This can lead to biochemical processes that culminate in cell death [20].

Genes in Parkinson disease

For a long time PD was seen as having only sporadic origin, without considering a genetic contribution for its complex pathogenesis. However, in 1997, Polymeropoulos *et al.* identified mutations responsible for the appearance of the disorder, in the gene coding for α-synuclein (SNCA) [60]. This finding changed the way the scientific community looks to PD and led to the beginning of genetic research of the disease.

Short after this discovery new genes were associated to PD, located in different chromosomic regions. This led to the perception of PD being a polygenic disease. Since then several other genes involved in PD development were identified as well as monogenic forms of PD and several genetic risk factors.

Highly penetrant mutations in genes like *SNCA*, *Parkin*, *DJ-1*, *PINK1*, *LRRK2* and *VPS35* produce rare monogenic forms of the disease. Studies have shown that incomplete penetrance of *LRRK2* and *GBA* genes are strong risk factors for PD. Additionally, more than twenty common gene variants were associated with risk of PD development.

Investigation of Mendelian forms of the disorder gave precious information concerning the physiopathology of most common idiopathic forms of the disease. Despite these findings, the process that leads to the appearance of risk alleles is still not known. In the next years, the challenge is to understand the way gene variants are involved in changes of biological processes. In this way, it will be possible to investigate new diagnostic and therapeutic possibilities.

Monogenic forms

Understanding the monogenic forms of PD gives a broader vision concerning the genetic architecture of the disorder. Apparently, there is a correlation between genes having mutations leading to PD and the ones having risk factors (Table 3).

Table 3: Genes involved in monogenic forms of PD and genetic risk *loci* (adapted from Hernandez *et al.* [61]).

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Mutations in three genes, *SNCA* (*PARK1*; codifies α-synuclein), *LRRK2* (*PARK8*; codifies dardarin) and *VPS35* (codifies the vacuolar protein 35) are associated with autosomic dominant forms of PD [61]. Mutations in six genes, *PINK1* (*PARK6*; PTEN-induced 1 kinase), *DJ-1* (*PARK7*), Parkin (*PARK2*), *ATP13A2* (*PARK9*), *FBXO7* and *PLA2GB* are associated with autosomic recessive forms of the disease [61].

Monogenic forms of PD are responsible for 30% of familial cases and 3-5% of sporadic cases of the disorder [62].

Autosomic dominant forms of Parkinson disease

i). α-synuclein (SNCA): As previously mentioned, α-synuclein (*SNCA*) gene was the first to be linked with PD. This gene is located in the long arm of chromosome 4 (4q21) [60].

The A53T missense mutation in this gene was identified in an Italian and a Greek families, having autosomal dominant forms of PD [60]. This mutation was latter reported in other families with the same holotype, supporting the possibility of a common Mediterranean ancestral [63,64].

Later on, Spillantini *et al.* found out that α-synuclein is the main component of Lewy's bodies [18]. This discovery gave a strong contribution to the perception of the processes occurring in brains of PD patients with a sporadic form. Only four other mutations were identified in this gene in families having dominant forms of PD: A30P [65], E46K [66], G51D [67,68] and H50Q [69,70].

Patients with this type of mutations show a broad clinical phenotype from classic forms of PD to atypical symptoms that include not only parkinsonism but also myoclonia, severe autonomous dysfunction and dementia.

Mutation A53T is responsible for PD development in younger ages, for its rapid progression and for prevalence of symptoms like dementia and psychiatric disorders [65].

Mutation A30P seems to be linked with late onset of the disease and an attenuated phenotype while mutation E46K is associated to a phenotype similar to patients having Lewy body's dementia [66].

The recently described mutation, G51D, is presented as a co-segregator of diseases in French, Japanese and

Table 3: Genes involved in monogenic forms of PD and genetic risk loci (adapted from Hernandez et al. [61]).

Locus name	Gene	Locus	Coded Protein	Disease	Type of transmission
Park1	SNCA	4q21-22	α-synuclein	PD of EO	AD
Park2	Parkin	6q25.2-q27	Parkin	PD of EO	AR
Park3	Unknown	2p13	Unknown	Classic PD	AD
Park4	SNCA	4q21-q23	α-synuclein	PD of EO	AD
Park5	UCHL1	4p13	C terminal of ubiquitin hydrolase	Classic PD	AD
Park6	PINK1	1q35-p36	PTEN-induced kinase 1	PD of EO	AR
Park7	DJ-1	1p36	DJ-1	PD of EO	AR
Park8	LRRK2	12q12	Dardarin	Classic PD	AD
Park9	ATP13A2	1p36	Lysosomal type 5 ATPase	atypical PD with dementia and spasticity	AR
Park10	unknown	1p32	unknown	Classic PD	Risk locus
Park11	unknown	2q36-37	GYF 2 protein; GRB	PD of LO	AD
Park12	unknown	Xq21-q25	unknown	Classic PD	X linked
Park13	HTRA2	2p12	Serine peptidase HTRA 2	Classic PD	AD
Park14	PLA2G6	22q13.1	Phosphorylase A2	Distonia-parkinsonism of LO	AR
Park15	FBX07	22q12-q13	"F-box" protein 7	Pyramidal Parkinsonism syndrome of AP	AR
Park16	unknown	1q32	unknown	Classic PD	Risk locus
Park17	VPS35	16q11.2	Vacuolar protein 35	Classic PD	AD
Park18	EIF4G1	3q27.1	Initiation factor 4 ɣ-1 of eukaryotic translation	Classic PD	AD
Park19	DNAJC16	1p31.3	DNAJ/HSP40	Atypical juvenile PD	AR
Park20	SYNJ1	21q22.11		Atypical juvenile PD	AR
Park21	DNAJC13	3q22.1		PD of LO	AD
-----	SNCA		α-synuclein		Risk locus
-----	LRRK2		LRRK2		Risk locus
-----	GBA		Glucocerebrosidase		Risk locus

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British families [67-71]. This mutation was not detected in the control group and it is predicted to be of the functional type. These data supports the idea that this is a pathogenic mutation associated with a clinical phenotype similar to the one produced by mutation A53T. Mutation H50Q, detected in a patient with family history of Parkinson and dementia and in another patient with late sporadic PD appearance, was also not detected in the control group [69,70]. However, it is still too early to assume that this mutation is pathogenic since co-segregation studies are not yet available and functional studies present limitations.

Duplications and triplications of the coding region of the *SNCA* gene were also associated with familial cases of PD [72,73]. A direct relationship seems to exist between the number of α-synuclein gene copies and the age of onset and progression of the disease as well as the severity of the symptoms. In fact, α-synuclein gene triplication was associated with early onset of the disease and to its fast progression characterized by dementia and diminished lifespan. Patients having duplications of this gene develop an attenuated clinical phenotype [72] and these are said to be the most common cause of familial and sporadic forms of PD [74,75].

A recent study revealed that patients with four copies of α-synuclein gene (resulting from duplication of both alleles or from one allele triplication) present, according with *Unified Parkinson's Disease Rating Scale*, a faster progression of the disease when compared with patients having three copies of that gene [76]. Consequently, the increase in α-synuclein levels seems to decrease the age of onset of PD and increase its severity.

These mutations are rare and multiplications of the gene were detected in only 1-2% of families having autosomic dominant PD.

Besides advances in PD genetics, normal functions of α-synuclein are still not completely understood. This protein is mainly found in the cytosol linked to lipid rafts (plasma membrane domains with high content of cholesterol and sphingolipids that concentrate specific receptors and molecules involved in cell signaling), in a sort of interaction that is required due to its involvement in synapse processes [77]. This protein interacts with members of the family proteins Rab and SNARE, pointing out its involvement in vesicle trafficking [78,79]. Another work that reinforces α-synuclein intervention in synaptic process was developed by Nemani *et al.* and shows that over-expression of human *SNCA* gene in mice inhibits synaptic transmission [80]. These researchers also observed synaptic inhibition as a result of over-expression of A53T and E46K mutations but not of A30P [80].

Experiments were performed using human *SNCA* gene mutations in mice and it was observed that mutations favoring low molecular weight oligomer formation, that attach to membranes (E35K and E57K), lead to a higher number of dopaminergic neurons death in nigra substance than the ones stimulating fast fibril formation (A30P and A53T) [81].

This findings demonstrate the importance of *SNCA* gene in intracellular trafficking, membrane interaction and synaptic activity. However, more research is required to fully understand the mechanisms underlying the normal function of the gene and the disease.

ii). LRRK2: The discovery, in 2004, of *LRRK2* gene mutations in families with autosomal dominant transmission of PD, was the turnover point in the field of PD genetics. These mutations were the first frequent genetic changes found in familial and sporadic forms of PD. This supports the theory of the existence of a common pathway involved in pathogenesis of both forms of the disease [82,83].

Nowadays, more than one hundred mutations in *LRRK2* gene were identified, linked with autosomal dominant forms of PD, representing about 10% of familial cases and a significant fraction of sporadic forms [84].

Although several mutations in this gene were already identified, their pathogenicity is only known for seven of them (R1441C, R1441G, R1441H, Y1699C, G2019S, I2020T and N1437H). These pathogenic mutations are present in exons that code for the Ras group of complex proteins, the C-terminal of these proteins or its kinase domain. Prevalence of *LRRK2* gene mutations varies considerably among populations [85,86].

G2019S mutation, that leads to aminoacid substitution, is responsible for 40% of familial and sporadic cases of PD in Arabic individuals from the north of Africa [87], 30% of familial forms in Jewish populations from central and oriental Europe [88], 6% familial cases in Europe [89,90] and 3% sporadic forms in Europe and North America [91]. It is a very rare mutation in Asian populations. It is believed that this mutation was transmitted by a common ancestral, coming from the north of Africa and widespread due to Jewish emigration [88,92]. Moreover, penetrance of this mutation seems to be dependent on age, since it is 28% for ages around 59 years, 51% at 69 years and increases to 74% at ages of 79 years [92].

Remaining six pathogenic mutations are much less frequent, however, R1441G mutation is common in Basque country with a prevalence of 15% in PD patients of this region [93]. Age of PD onset is variable, oscillating between the forth and ninth life decade.

Mutations in *LRRK2* gene lead to symptoms like pathology of Lewy bodies and taupathy with tangled neurofibrils [83]. This symptom diversity suggests that the gene is involved in several cell processes and might be a main component of diverse signaling pathways, crucial for the correct function of neurons.

Still the pathological mechanisms resulting from *LRRK2* gene mutations that lead to PD continue under investigation since the coded protein is very complex.

iii). VPS35: Sequencing techniques allowed the identification of the D620N mutation on the gene coding the vacuolar protein 35 (VPS35). This mutation is responsible for late onset PD with autosomal dominant transmission [94].

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VPS35 gene is present in chromosome 16 (16q11.2) and the codified protein (a homolog of vacuolar protein 35), is a subunit of the "Retromer" complex involved in endosomal-lysosomal transport [95].

Distribution of *VPS35* gene mutations varies according with ethnicity. Mutation D620N is more frequent in Jewish Yemenis (1,67%), in France (1,2%) in Tunisia (0,5%), but it has never been found in Canadians, Norwegians, Polish, Irish, Thai, Germans, Chinese, Belgians from the Flanders region, South-Africans or Indians and is uncommon in Greeks [96,97]. Mutations in this gene only rarely cause PD and contribute for 1% of the familial form and 0,2% of the sporadic form [94,98].

Some studies are trying to see if these mutations change catepsin D trafficking, a protein involved in α-synuclein degradation [99,100].

Autosomic recessive forms of Parkinson disease

Several studies have identified mutations in six genes that are responsible for PD with autosomal recessive transmission: *PARK2* (codes for parkin), *PINK1* (*PARK6*; PTEN-induced kinase 1), *DJ-1* (*PARK7*), *ATP13A2* (*PARK9*; ATPase type 13A2), *PLA2G6* (*PARK14*; phosphorylase A2, group VI) and *FBXo7* (*PARK15*; Protein 7 of "F-box") [61]. Mutations in these genes lead to PD of early onset in a small number of patients.

i). Parkin: One year after the discovery of α-synuclein gene mutations, changes in another gene, *Parkin* gene, were found in a Japanese family with juvenile Parkinson disease with autosomal recessive transmission [101]. These mutations are responsible for PD of early onset [102] and are present in 77% of sporadic forms with onset before 20 years of age [103].

So far, more than one hundred mutations in this gene have been identified, including deletions, insertions, duplications, triplications and point mutations. Most mutations in *Parkin* gene (54%) are big deletions or duplications of one or several exons, one third are single nucleotide changes and 13% are minor deletions [104].

Patients with *Parkin* gene mutations, with the exception of very young ages, show clinical symptoms not distinguishable from idiopathic PD, with good response to levodopa but with early motor fluctuations. These mutations lead to a considerable loss of neurons in nigra substance, casual pathologies of Tau proteins and, in most cases, to *post-mortem* absence of Lewy bodies [105]. The explanation for this last symptom is the fact that PD resulting from *Parkin* mutations has a very early onset [106].

This gene is present in chromosome 6 (6q25.2-27), and codes for ubiquitin E3 ligase [107]. This enzyme is mainly expressed in nervous system, being involved in proteasome degradation [108]. Loss of function resulting from *Parkin* gene mutations leads to inactivation of its role as ligase E3, to lack of target protein ubiquitination and, as a consequence, toxic accumulation of proteins that should be degraded by the ubiquitin/proteasome *Parkin* dependent pathway [108]. The accumulation of these toxic aggregates seems to have a crucial role in PD pathogenesis namely concerning neuron degradation of nigra substance. Other data supports the importance of ligase E3 in PD and show that *Parkin* gene mutations can lead to mitochondrial damage [25].

A model was proposed where *Parkin* gene interacts with *PINK1* gene, also associated with PD. Koyano et al. found out that protein PINK1 is responsible for phosphorylation of parkin and ubiquitin, through recruitment of parkin to depolarized mitochondria, activating ligase E3 and promoting the elimination of damaged mitochondria [109].

Another model trying to explain parkin activation deals with the alternating stage of Ubl/ubiquitin. This model states that phosphorylation of ubiquitin (its pUb domain) and of the Ubl domain of parkin is a crucial step on parkin activation in mitochondria. After initial phosphorylation of ubiquitin present in proteins of the mitochondrial membrane, performed by PINK1, parkin is recruited and its Ubl domain dissociates. This Ubl domain recently released is now phosphorylated by PINK1, leading to translocation of parkin to the surface of damaged mitochondria. Since parkin lost its Ubl domain, its affinity to pUb domain increases together with its ubiquitin ligase activity that will mark and eliminate mitochondrial membrane proteins [27,110,111].

ii). PINK1: In 2004, the *Park6 locus* was mapped on chromosome 1p35-p36 on an Italian family with PD of autosomal recessive transmission [112]. One *missense* recessive mutation (G309D) and one nonsense recessive mutation (W437X) were detected in Spanish and Italian families with PD [112]. After these discoveries, several missense, nonsense and frameshift mutations as well as deletions of multiple exons were associated with the *PINK1* gene (*PTEN-induced putative kinase 1*) in families of different ethnicities [112-114].

PINK1 gene mutations are considered the second most common cause of early onset PD with autosomal recessive transmission [113,115]. These mutations were detected in 2-4% of early onset PD in Caucasian patients and in 4-9% in Asian patients with the same form of PD [102].

Patients with *PINK1* gene mutations develop early onset PD, slow progression and show atypical traits like dystonia, pyramidal signs and psychiatric co-morbidities (anxiety and depression [113].

PINK1 gene codes for a mitochondrial kinase [112]. This protein is responsible for parkin phosphorylation, regulating destruction of damaged mitochondria [111,116].

It has been shown that over-expression of the wildtype *PINK1* gene, but not of its G309D mutation, is able to avoid death from apoptosis induced by stress [112]. The role of these two genes (*PINK1* and *Parkin)* in mitofagia confirms their importance for good neuronal function and can be an ideal therapeutic target in patients with early onset PD.

ii. DJ-1: DJ-1 gene mutations are responsible for 1-2% of juvenile Parkinson, with autosomal recessive transmission [117].

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It is believed that this gene is a protective factor against oxidative stress and mitochondrial damage, probably working in a common pathway with parkin and PINK1 proteins. Requejo-Aguilar et al. associated the DJ-1 gene to cell metabolism and proliferation regulation through PINK1 [118]. In fact, this gene is pointed out as a positive regulator of PINK1 gene transcription [118]. Moreover, loss of function of DJ-1 gene contributes to increased oxidative stress and dopaminergic neurodegeneration, characteristic of PD.

iii. ATP13A2, PLA2G6 and FBXO7: Very rare and atypical forms of autosomal recessive PD are caused by mutations in three genes: *ATP13A2* (codes for ATPase type 13A2), *PLA2G6* (codes for phospholipase A2, group VI) and *FBXO7* (codes for F-box protein 7).

Mutations in *ATP13A2* gene lead to rare, juvenile onset, Kufor-Rakeb syndrome, characterized by weak response to levodopa treatment and to atypical symptoms like distonia and supranuclear paralysis [119,120]. At least eleven families with numerous different missense, nonsense and deletion mutations in this gene have been identified. Phenotype intensity is highly variable among patients and seems to be related to the type of inherited mutation [121].

This gene codes for a member of the ATPases family. ATP13A2 is a multifunctional protein with ten transmembrane domains that seem to have a role in the endosome-lysosome dynamics [122,123], in proper mitochondrial function [124,125], and in cell protection against toxicity induced by metals like manganese (Mn^{2+}) and zinc (Zn^{2+}) [126,127]. These studies also indicate that ATP13A2 protein is present in Lewy bodies of PD patients [123], and over-expression of this gene prevents α-synuclein accumulation in neurons [126,127]. These mutations are the rarer cause of Parkinson.

PLA2G6 gene mutations cause autosomal recessive PD associated with distonia and a good response to levodopa [106]. The accumulation of iron in brain is characteristic of the majority of affected individuals [128]. These mutations were also associated with neurodegeneration with iron accumulation in brain and to Karak syndrome, both severe forms of childlike neurodegeneration [129,130]. PD associated with this gene has recessive transmission or dominant when there are several missense mutations [131,132].

PLA2G6 gene codes for a protein called phosphorylase A2 of group VI with seven ANK (ankirin) repeats, a lipase domain and a calmodulin linking domain [106]. This protein is responsible for glycerophospholipid hydrolysis [106]. Fibroblast analysis of a patient with the R747W mutation in *PLA2G6* gene showed the presence of mitochondrial damage [133].

Shojaee and collaborators were the first to identify *FBXO7* gene mutations in an Iranian family with pyramidal Parkinson of juvenile autosomal recessive transmission [134]. Patients of other families with similar symptoms, carry three different mutations in the same gene in the homozygous or heterozygous form [135].

This gene codes for F-box protein 7 that interacts directly with *Parkin* and *PINK1* gene, in maintenance of mitochondrial health and in mitofagia [136,137]. These studies show that the *FBXO7* gene is involved in parkin translocation to mitochondria, in response to cellular stress [136,137].

Several other genes and *loci* were associated with Mendelian forms of PD: *PARK3* [138], *PARK5* (UCHL1) [139], *PARK10* [140], *PARK11* [141], *PARK12* [141], *PARK13* (HTRA2) [142], *PARK16* [143], *PARK18* (EIF4G1) [144,145] and *PARK21* (DNAJC13) [146].

Genetic risk: Development of diseases with complex genetic risk like PD probably results from a combination of genetic, environmental and lifestyle factors. Two theories try to explain the genetic components of PD: the existence of a rare variant of a common disease (RVCD) and the existence of a common variant of a common disease (CVCD) [61]. The RVCD theory states that the risk component that contributes to complex PD is a rare genetic variant, and rare alleles are the ones having a frequency of 1% or less. This hypothesis also says that less common variants are abundant in human population and, due to recent demographic growth, it is not easy to remove them through natural selection.

The CVCD hypothesis proposes that the significant risk proportion for the common form of the disease is mediated by genetic variants that are also common (this means variants with allele's frequency above 1% in the population) [147,148]. These variants are common and, for this reason, have been present in the population during a significant period of time. Alleles highly functional and deleterious suffered negative selection and for this do not manifest in the common form of the disease. This theory accepts that the effect of individual alleles for a deleterious trait is not significant but being numerous and, through cumulative effect, might contribute to the trait.

Discussion and Conclusions

Pathogenesis of Parkinson disease is still not completely understood by the scientific community and it is still a big challenge for researchers.

During the last decade, the existence of a genetic component for PD development was unquestionably confirmed. Although this certainty, genetic contribution is responsible for only a small percentage of diagnosed PD cases. The great majority of patients have PD forms associated to sporadic causes.

PD is step by step seen as a multifactorial pathology and, it is assumed that for its appearance environmental, genetic and even aging factors are involved. For this reason, it is easy to understand that PD cases will go on increasing since the population is getting older.

In the near future, new challenges are the discovery of more risk factors and their consequences at the biological level to PD development.

The ultimate goal would be to build a genetic map that relates different risk variant and that contributes to diagnosis

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and to the development of drugs that act specifically on PD and not only on symptoms control.

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