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Parkinson's disease: Exit toxins, enter genetics

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Abstract

Parkinson's disease was long considered a non-hereditary disorder. Despite extensive research trying to find environmental risk factors for the disease, genetic variants now stand out as the major causative factor. Since a number of genes have been implicated in the pathogenesis it seems likely that several molecular pathways and downstream effectors can affect the trophic support and/or the survival of dopamine neurons, subsequently leading to Parkinson's disease. The present review describes how toxin-based animal models have been valuable tools in trying to find the underlying mechanisms of disease, and how identification of disease-linked genes in humans has led to the development of new transgenic rodent models. The review also describes the current status of the most common genetic susceptibility factors for Parkinson's disease identified up to today.

Keywords

Genetic risk factors; PARK; Mutation; Animal model; Association study; Linkage study

1. Introduction

Paralysis agitans or Parkinson's disease is well described in the ancient Indian medical treatise *Ayurveda* (Sanskrit: *ayur*, life; *veda*, science) with the oldest material dating from 2000–4000 B.C. and a complete treatise completed around 1000 B.C. According to *Ayurveda*, the disorder was referred to as *Kampavata* (*Kampa*, tremor; *vata*, lack of movements) and manifested symptoms such as rigidity, akinesia, tremors, depression, somnolence, "loss of mind" and mental confusion. It was treated with seeds from *Mucuna pruriens*, a plant in the *Leguminosae* family. At that time the active substance in the plants was unknown, and it was not until the 1930s that the active component L-3,4-dihydroxyphenylalanine (L-dopa) was isolated (Damodaran and Ramaswamy, 1937). However, this finding had limited impact at that time, since the involvement of dopamine in the disease had not yet been discovered.

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For long, Parkinson's disease, as we know it today (Parkinson, 1817), was considered a typical non-genetic disorder. However, the fact that Parkinson's disease has been present since ancient times, presumably without major changes of prevalence caused by the industrial revolution and the increasing use of man-made chemicals as well as the findings of similar prevalences in different populations across the world, suggest that environmental factors play a less important role in Parkinson's disease than previously thought.

Even though the underlying mechanisms of Parkinson's disease remain partly unknown, several hypotheses have been put forward for its causes. Implicated mechanisms involve protein misfolding, mitochondrial and ubiquitin-proteasome dysfunction, oxidative stress, inflammation, apoptosis, exposure to and/or increased vulnerability to environmental toxins and infectious agents. It is unclear, however, how these different pathogenic events, and others yet to be discovered, cause Parkinson's disease. The variable phenotypes observed among Parkinson patients suggest involvement of several different molecular pathways. Moreover, it remains to be resolved if the underlying causes act separately or if they converge into one or only a few final common pathways. All pathogenic events however will affect the survival and/or death of neurons in vulnerable brain areas including the substantia nigra, locus coeruleus and the dorsal motor nucleus of the vagus nerve (Braak et al., 2004).

2. Dopamine neurotoxins

The use of toxin-based animal models has given useful insights into the pathology of Parkinson's disease. Ideally, a valuable and reliable animal model of disease should mimic one or preferably several of the specific features of the human disease. The Parkinson's disease-like rodent models used today can mimic motor dysfunctions, dopamine neuron degeneration, olfactory loss and, albeit to a lesser degree, formation of intracellular inclusion bodies in affected neurons.

2.1. Toxin-based animal models

Two commonly used rodent models of Parkinson's disease are based on administration of 6-hydroxy-dopamine (6-OHDA) (into the brain) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (systemically) in order to rapidly and selectively destroy catecholaminergic neurons. 6-OHDA is a hydroxylated analogue of dopamine (Blum et al., 2001) which was first shown to cause noradrenergic depletion of sympathetic nerves to the heart (Porter et al., 1963, 1965) and destruction of noradrenergic nerves (Tranzer and Thoenen, 1973). In the CNS, 6-OHDA causes destruction of dopaminergic and noradrenergic neurons (Ungerstedt, 1968). The toxin is taken up by dopamine and noradrenaline membrane transporters and accumulates in the cell cytosol. Cell death is caused by formation of reactive oxygen species and mitochondrial respiratory chain deficiency (Blum et al., 2001). The drug does not cross the blood-brain barrier and hence, has to be stereotaxically injected to striatum, substantia nigra, the medial forebrain bundle, or administered directly into the ventricular system. Intrastriatal injection of 6-OHDA can result in a progressive, retrograde partial lesioning, whereas injection into the substantia nigra or medial forebrain bundle results in complete lesioning of the nigrostriatal pathway (Ungerstedt and Arbuthnott, 1970; Ungerstedt, 1971a,b; Sachs and Jonsson, 1975). The

strength of the lesioning is dependent on the site of injection, the amount of 6-OHDA administered and on the species used (Betarbet et al., 2002). Both unilateral (hemiparkinsonian model, where the unlesioned hemisphere serves as an internal control) and bilateral lesioning models are used. Unilateral lesioning causes asymmetrical and quantifiable motor behaviors induced by systemic administration of dopamine receptor agonists, levodopa or dopamine-releasing drugs (Ungerstedt and Arbuthnott, 1970; Hefti et al., 1980). The bilateral model on the other hand, results in parkinsonian motor complications, but due to the need for intensive nursing care of the animals, the use of the model is less common (Cenci et al., 2002). While the 6-OHDA model is widely used in Parkinson's disease research, the model does not recapitulate all pathological features of the disease. For instance, the animals do not develop cytoplasmic Lewy bodies. Moreover, intracerebral injection of 6-OHDA does not affect other brain areas involved in Parkinson's disease such as locus coeruleus, the brain stem or olfactory areas (Betarbet et al., 2002) or cortex cerebri.

A link between parkinsonism and mitochondrial dysfunction, a suggested causative event for the disease, was established when the neurotoxic substance MPTP was found to cause severe and irreversible parkinsonism in a small group of drug addicts in California (Langston et al., 1983). The affected individuals displayed several clinical and neuropathological characteristics of Parkinson's disease. MPTP is a lipophilic molecule which readily crosses the blood–brain barrier. In non-dopaminergic neurons (mostly astrocytes) MPTP is converted by monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP) which is oxidized to 1-methyl-4-phenylpyridinium (MPP^+) (Nicklas et al., 1985, 1987; Przedborski and Vila, 2003). The active metabolite MPP^+ is taken up by dopamine neurons through the dopamine transporter (DAT), and acts as an inhibitor of mitochondrial complex I of the respiratory chain (Nicklas et al., 1987; Mizuno et al., 1987). MPTP functions as a potent neurotoxin in both mice and primates, although mice are less sensitive than monkeys (Nicklas et al., 1985; Blum et al., 2001).

It is well known that agricultural chemicals such as the pesticide rotenone can induce specific parkinsonian symptoms (Betarbet et al., 2000, 2002). Structurally and functionally rotenone is related to MPTP and also acts as an inhibitor of mitochondrial complex I (Perier et al., 2003). Studies of rotenone thus add to the evidence that dopamine neurons may be particularly vulnerable to mitochondrial dysfunction. However, while there are some epidemiological studies to indicate that pesticide exposure may increase the risk to develop Parkinson's disease, the relative importance of such exposure for the prevalence of Parkinson's disease worldwide is not clear.

Most toxin-based animal models used today are focused on the nigrostriatal system and the loss of dopamine neurons, which is a prerequisite for understanding the underlying mechanisms of the disease, and for developing symptomatic treatments. However, the animal models are limited in that they do not recapitulate the complete spectrum of symptoms seen in humans, and in particular not the slow and progressive loss of dopamine neurons, which is characteristic of Parkinson's disease.

3. Genetics

Today, the underlying pathology of Parkinson's disease is well explored, but we have limited understanding of the etiology. Long considered a typical non-genetic disorder, the majority of the cases are still classified as idiopathic. However, the view of Parkinson's disease as a sporadic disorder has been subject to dramatic change in recent years. Today, genetic risk factors stand out as the major cause of the disease, possibly in combination with environmental factors. The impact of genetic risk factors has been significantly underestimated in the past and this may be attributed to the late onset of the disease. Inherited diseases with a late-in-life onset are difficult to detect because of failing memory of the patient and his/her relatives, death of relatives, and the patient's prolonged exposure to other possibly disease-causing agents during life. Complex genetic traits and reduced penetrance further complicate the identification of risk factors. A disease phenotype may be caused by a major genetic component, but it does not necessarily imply that only one gene is involved in generating the specific disorder. A disease may be caused by inherited mutations in several genes, some of which give rise to the same phenotype but with a different mode of inheritance. Yet other mutations may convey resistance to disease. This complex situation appears to be another reason why non-genetic causes of Parkinson's disease were in favor for so long. Moreover, it has long been known that infections (Von Economo's disease, *Encephalitis lethargica*) can cause a Parkinson-like disease, as can trauma, which further adds to the complexity. It has been estimated that approximately 10–15% of all Parkinson's disease cases can now be explained by a known genetic component (Bonifati, 2006). We assume this percentage will increase as new genetic markers are continuously being identified.

Even though the genetic involvement in Parkinson's disease has been well established, the findings have gotten limited support from epidemiological studies (Tanner et al., 1999; Sveinbjornsdottir et al., 2000; Wirdefeldt et al., 2004). The risk ratio of disease has been reported to be increased in siblings and the offspring of affected patients, but the concordance between mono- and di-zygotic twins has been found to be lower than expected. Interestingly, positron emission tomography (PET) data from monozygotic twins has shown higher concordance for decreased L-dopa binding, indicating marked inheritance, albeit with other factors influencing the age of onset (Piccini et al., 1999). This opens the possibility that environmental and/or epigenetic factors may also play essential roles in genetically predisposed mutation carriers.

3.1. Parkinson's disease genetics from a historical perspective

An early documented observation of a genetic component in Parkinson's disease was made by Leroux (Leroux, 1880), who in 1880 suggested a link between heritable factors and increased disease susceptibility (Farrer, 2006). More than half a century later, Allen reported familial forms of parkinsonism inherited as a dominant trait in North Carolina, USA (Allen, 1937), and Henry Mjönes described autosomal dominantly inherited cases in Sweden (Mjönes, 1949). In 1996 a pioneering genetic finding was made by Polymeropoulos and colleagues who found genetic linkage in an Italian family with an autosomal dominant form of Parkinson's disease (Polymeropoulos et al., 1996). The ground-breaking discovery was

strengthened by identification of a missense mutation in the *SNCA* gene (encoding the α-synuclein protein) in the affected family members (Polymeropoulos et al., 1997), and subsequent identification of α-synuclein as one of the major components of Lewy bodies (Spillantini et al., 1997). After the identification of the first chromosomal locus linked to Parkinson's disease (PARK1), fourteen more chromosomal loci (PARK2-15) with suggested linkage to disease have been identified, although for some of these loci a specific gene implicated in Parkinson's disease is yet to be found (Lesage and Brice, 2009). Some of the genes linked to monogenic forms of Parkinson's disease have also been identified as risk factors for sporadic forms of the disease. Through identification of families carrying mutations in PARK genes, the weight of evidence has now shifted towards genetic or, possibly gene-environmental interactions, as the causes of Parkinson's disease. A genetic variant can be a mutation or a single nucleotide polymorphism (the latter is present at a frequency of >1% in the population), a deletion, an insertion, a whole gene rearrangement or a copy number variation. Disease-associated genetic variants can be present both in coding and non-coding parts of the gene. Still, the mechanism by which intronic variability predisposes to disease is obscure, although altered transcriptional regulation, mRNA stability and regulation by miRNAs, as well as alternative splicing, have been suggested (Wang et al., 2008).

3.2. Linkage studies

Thanks to today's increased longevity, families with several affected generations can be studied, enabling easier identification of chromosomal regions carrying a disease-causing gene. Identification of candidate genes through linkage analysis is a hypothesis-free method which is based on the segregation of a genetic marker with a known genomic location through several generations in a family. Linkage analyses are most successful for chromosomal loci with high penetrance, whereas analyses of mutations with low-penetrance and diseases with complex traits are more difficult to perform. Linkage or co-segregation is presented as the logarithm of the odds (LOD) score, in which a high positive score shows evidence for linkage whereas a negative score shows evidence against (Dawn and Barrett, 2005). Calculation of LOD scores requires information about the mode of disease inheritance (i.e. dominant or recessive), allele frequencies, and a full marker map for each chromosome.

3.3. Association studies

Association studies are based on the hypothesis that a genetic variant associates with increased or decreased risk of disease. The studies are carried out using sample sets consisting of unrelated patients and controls. Specific candidate genes must be chosen, and can be identified through linkage analyses or they can be genes with a particular relevance for the dopamine system, for mitochondrial function, protein aggregation or any other function for which a hypothesis can be formulated about a possible involvement in the specific disease. Variable findings are frequently reported from association studies, sometimes due to small sample sizes. A way to increase reliability in association analyses is to investigate larger samples from genetically diverse populations. However, geographically distinct populations may differ in terms of mutation frequencies such that large samples may also mask locally significant disease-associated mutations. A single association study has

limited power to detect true susceptibility genes, and has to be replicated in other populations in order to improve statistical significance. Other strategies to increase reliability are to perform retrospective meta-analyses of multiple independent studies or collaborative multi-center studies with standardized methodologies and diagnostic criteria. In the field of Parkinson's disease, collaborative analyses have led to the identification of the promoter polymorphism NACP-Rep1 in *SNCA* and the inversely associated missense mutation S18Y in *UCH-L1* as risk/protective susceptibility factors (Maraganore et al., 2004, 2006).

In order to deliver valid and reproducible results from an association study, standardized methodological and statistical approaches are needed. In terms of the study groups, the number of cases and controls has to be sufficient for the study to have enough power and the groups should also be matched for age and gender. Moreover, careful consideration has to be taken when diagnosing and classifying patients and controls. A correct diagnosis (in both study groups) is essential, since both positive and negative diagnostic errors impair statistical analyses. Further adding to the complexity of association studies is the presence of population-specific gene–gene interactions, genes with different modes of inheritance, population stratification and presence of phenocopies.

With a large number of polymorphisms available in public databases and the development of high-throughput techniques for genotyping, the interest in using whole-genome association studies to unravel genetic susceptibility factors is increasing. The method is based on the scanning of a large number of genetic markers across the complete genome in order to find genetic variations associated with disease. Given the large number of genes and mutations implicated in Parkinson's disease, it appears evident that multiple methodological approaches are required for identification of susceptibility factors. Moreover, studies of both isolated and heterogeneous populations are important in order to identify pathogenic mutations in different parts of the world.

3.4. Autosomal dominant PARK genes

3.4.1. α-Synuclein (PARK1 and PARK4)—The first finding strengthening the involvement of genetic risk factors in Parkinson's disease was the identification of the PARK1 locus on chromosome 4q21, linking to familial forms of the disease (Polymeropoulos et al., 1996). The finding of a chromosomal region linked to Parkinson's disease was confirmed by identification of the point mutation A53T in the *SNCA*/α-synuclein gene in Italian and Greek families with autosomal dominant inheritance of the disease (Polymeropoulos et al., 1997). In the following years a Korean A53T-mutated Parkinson's disease family (Ki et al., 2007) and two unrelated German and Spanish families, carrying the point mutations A30P and E46K respectively, were found (Kruger et al., 1998; Zarranz et al., 2004), as well as whole *SNCA* gene multiplications (PARK4) (Singleton et al., 2003; Chartier-Harlin et al., 2004; Farrer et al., 2004; Ibanez et al., 2004; Nishioka et al., 2006; Fuchs et al., 2007; Ahn et al., 2008; Ikeuchi et al., 2008; Ross et al., 2008). Parkinson patients with a gene duplication exhibit a 1.5 fold increase in α-synuclein levels whereas an *SNCA* triplication causes a two-fold increase in protein levels (Farrer et al., 2004), showing that the gene dose is critical in causing the disease. Polymorphisms in non-coding regions of

SNCA have also been shown to contribute to the risk of sporadic Parkinson's disease (Mueller et al., 2005; Mizuta et al., 2006; Westerlund et al., 2008), as has the *SNCA* promoter variability NACP-Rep1 (Maraganore et al., 2006). Mutated forms of the protein may be more likely than wild-type protein to aggregate, resulting in formation of insoluble protein inclusions.

Compelling evidence from biochemical studies and animal models has also strengthened the involvement of α-synuclein in Parkinson's disease. The α-synuclein protein has, together with a number of other proteins, been identified as a constituent of Lewy bodies (Spillantini et al., 1997), the intracellular inclusions found in brain stem and cortical areas of Parkinson patients. α-Synuclein was originally identified as a precursor protein of the non-β-amyloid component (NAC) of Alzheimer's disease amyloid plaques (Ueda et al., 1993). It is highly expressed in the human brain, including the cerebral cortex, hippocampus and cerebellum, where it is localized to presynaptic nerve terminals. Because of its extensive neuronal expression in the brain, abnormal aggregation or disruption of α-synuclein function may have similarly widespread consequences. However, α-synuclein is not essential for survival, since α-synuclein knockout mice are viable and fertile (Abeliovich et al., 2000). The complete function of α-synuclein is not yet understood, although the protein has been implicated in learning, synaptic vesicle mobilization, presynaptic functions and maintenance of the synaptic vesicle pool (Murphy et al., 2000; Cabin et al., 2002; Chandra et al., 2004). Moreover, the suggested mechanism by which α-synuclein causes neurodegeneration is obscure, but formation of protofibrils or fibrils has been suggested (Goedert, 2001). Interestingly, a protective role of Lewy bodies as a scavenger of misfolded proteins has also been suggested. The recent observation that embryonic dopamine neurons grafted to patients with Parkinson's disease may develop Lewy bodies (Kordower and Brundin, 2009) adds yet another dimension to the possible roles of α-synuclein in Parkinson pathology.

3.4.2. UCH-L1 (PARK5)—Mutations in ubiquitin carboxyl-terminal esterase L1 (*UCH-L1*) at the PARK5 locus have been suggested to cause autosomal dominant Parkinson's disease. Linkage to chromosome 4p14 has been established, however the finding has been questioned since it has only been found in rare cases from a single Parkinson's disease family. An I93M mutation was found in a Parkinson's disease family of German ancestry (Leroy et al., 1998) and this finding has later been followed by identification of the more common S18Y variant (Lincoln et al., 1999), which is associated with a reduced risk of Parkinson's disease (Maraganore et al., 1999; Zhang et al., 2000; Wintermeyer et al., 2000; Satoh and Kuroda, 2001; Momose et al., 2002; Wang et al., 2002; Elbaz et al., 2003; Carmine et al., 2007). However, the finding of an inverse association of S18Y with Parkinson's disease has also been questioned since contradictory results or lack of association has been reported (Mellick and Silburn, 2000; Levecque et al., 2001; Savettieri et al., 2001). UCH-L1, also known as the neuronal marker PGP9.5, constitutes a key component of the ubiquitin-proteasome system, removing abnormal and misfolded proteins, and generating free ubiquitin monomers (Wilkinson et al., 1989). The presence of variable sites in the *UCH-L1* gene may result in a dysfunctional protein and subsequent aggregation of misfolded proteins. UCH-L1 shows high and specific expression in all central and peripheral neurons (Doran et al., 1983). It comprises up to 2% of the total soluble brain

proteins (Wilkinson et al., 1989) and hence, it is one of the most abundant proteins in the brain. It has also been identified as one of the components of the proteinaceous inclusion bodies in the remaining neurons in substantia nigra of Parkinson patients (Lowe et al., 1990).

3.4.3. Leucine-rich repeat kinase 2 (PARK8)—A large number of genetic variants (most of them missense mutations) have been found in the 51 exon long leucine-rich repeat kinase 2 (*LRRK2*) gene. Among the variable sites, seven have been shown to be pathogenic, and they are all located in protein domains of high functional importance (Lesage and Brice, 2009). Together, the *LRRK2* mutations constitute the most common known genetic cause of Parkinson's disease identified to date, accounting for up to 10% of the familial Parkinson cases with autosomal dominant inheritance and 3.6% of the sporadic cases. The *LRRK2* gene is located at the PARK8 locus on chromosome 12p11.2-q13.1 (Funayama et al., 2002) which is linked to autosomal dominant Parkinson's disease (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). Since the discovery of *LRRK2* mutations in Basque Parkinson families, the gene and its variable sites have been extensively studied. The G2019S mutation alone is responsible for approximately 1–2% of the "sporadic" Parkinson cases and 2–6% of all familial Parkinson cases. However in certain populations, like Ashkenazi Jews and North African Arabs, mutation frequencies up to 30–40% have been reported (Lesage et al., 2006, 2008; Ozelius et al., 2006; Ishihara et al., 2007; Orr-Urtreger et al., 2007; Hulihan et al., 2008). Studies have also revealed presence of the G2019S mutation in healthy control individuals (Lesage et al., 2005, 2006; Farrer et al., 2005; Kay et al., 2005; Carmine et al., 2006; Clark et al., 2006; Ozelius et al., 2006; Change et al., 2008) as well as in other neurological disorders (Chen-Plotkin et al., 2008). The penetrance of the G2019S mutation varies with ethnicity, and it has been estimated by the International LRRK2 Consortium to be around 28% at the age of 59 and 74% at the age of 79 (Healy et al., 2008). Moreover, the G2019S mutation is believed to have evolved from a few common founders (Zabetian et al., 2006a, b). Another common *LRRK2* variant, the G2385R polymorphism, has been found to be present in 10% of Asian Parkinson cases but only 4% of matched control individuals. Although a significant risk factor among Asians, this particular polymorphism is rare or even absent in most other populations (Berg et al., 2005; Di Fonzo et al., 2006; Tan et al., 2008) and previous large scale whole-genome association studies have failed to identify G2385R as a risk factor for Parkinson's disease. Some missense mutations in *LRRK2* have been associated with an increased kinase activity (West et al., 2005; Gloeckner et al., 2006) as well as with generation of inclusion bodies and cell death *in vitro*, whereas mutations eliminating the kinase activity, have been found to inhibit formation of aggregates (Greggio et al., 2006). Patients carrying mutations in *LRRK2* exhibit typically late onset, L-dopa-responsive Parkinson's disease, although somewhat surprisingly with varying pathology between, and even within families, for example presence or absence of Lewy bodies. The LRRK2 protein, also known as dardarin, consists of several domains including ARM (Armadillo), ANK (Ankyrin repeat), a leucine-rich repeat (LRR), Roc, COR (C-terminal of Roc), MAPKKK (mitogen-activated protein kinase kinase kinase) and WD40 repeats (Zimprich et al., 2004; Lesage and Brice, 2009). LRRK2 has been suggested to be implicated in apoptosis, regulation of neuronal survival, maintenance of neurites and protein–protein interactions. LRRK2 is localized to membranous and vesicular structures

such as mitochondria, vesicles, lysosomes and endosomes (Biskup et al., 2006). Using *in situ* hybridization to localize transcriptional activity at the cellular level, it is striking to find that none of the many genes so far linked or associated to Parkinson's disease is specifically expressed in dopamine neurons, as compared to other cells in the brain or elsewhere. LRRK2 is not an exception, although it does differ from other "Parkinson's disease genes" by being markedly, but not exclusively, expressed in the striatal dopamine target area (Galter et al., 2006).

3.5. Autosomal recessive PARK genes

3.5.1. Parkin (PARK2)—The *PRKN* gene encoding the Parkin protein harbors a number of genetic variants including insertions, deletions and point mutations and these variable sites have been identified in populations of all ethnic origins. Mutations in the *PRKN* gene constitute the most common cause of early onset Parkinson's disease, responsible for up to 50% of the cases. The number of mutations in this gene is inversely associated with disease onset and mutations are thus rare in patients with late onset Parkinson's disease. Patients with *PRKN* mutations exhibit a clinical phenotype resembling sporadic disease. Interestingly, neuropathological findings from patients carrying mutations in *PRKN*, rarely show presence of Lewy bodies, although nigrostriatal cell loss may occur. The *PRKN* gene is located at the PARK2 locus, mapped to chromosome 6q25.2-q27 and causes an autosomal recessive early onset form of Parkinson's disease (Kitada et al., 1998). The function of the ubiquitin E3 ligase encoded by the *PRKN* gene is to add ubiquitin onto specific substrates, thereby targeting them for proteasomal degradation. It has been suggested that loss-of-function mutations in the gene can cause abnormal accumulation of Parkin substrates, such as α-synuclein and synphilin-1. The important role of Parkin in the ubiquitin proteasome pathway strengthens the involvement of protein degradation and aggregation as a major causative event of Parkinson's disease.

3.5.2. PINK1 (PARK6)—Mutations in the tumor suppressor PTEN induced putative kinase 1 (*PINK1*) gene causes autosomal recessive early onset Parkinson's disease (<50 years) and a typical parkinsonian phenotype. *PINK1* is localized to the PARK6 locus on chromosome 1p35-36, originally mapped in European Parkinson's disease families by Valente and coworkers in 2004 (Valente et al., 2001). In addition to the familial cases carrying mutations in *PINK1*, mutations have also been found in rare, possibly sporadic early onset cases (Valente et al., 2004b). Findings from genetic studies have identified several mutations in *PINK1*, distributed throughout the gene, in populations of different geographical origins including Europe, Asia and North America. The protein encoded by the *PINK1* gene is a serine-threonine kinase which has been suggested to be protective against stress induced by mitochondrial dysfunction (Valente et al., 2004a). Moreover, PINK1 has a mitochondrial targeting motif which makes it prone to accumulation in the mitochondrial inter-membranous space.

3.5.3. DJ-1 (PARK7)—Genetic variability in the *DJ-1* gene, located on chromosome 1p36 at the PARK7 locus, causes autosomal recessive early onset parkinsonism (van Duijn et al., 2001). However, mutations in the gene are rare, accounting for only 1% of the early onset cases (Abou-Sleiman et al., 2003; Lockhart et al., 2004). Besides the characteristic early

onset, patients carrying mutations in *DJ-1* display a slowly progressing disease with good response to levodopa. A genetic link between *DJ-1* and Parkinson's disease was first presented by Bonifati and colleagues, who found a missense mutation (L166P) and a homozygous deletion of exons 1–5 in the gene (Bonifati et al., 2003). Presence of the L166P mutation causes altered protein folding properties (Olzmann et al., 2004), resulting in a less stable protein (Miller et al., 2003) along with decreased protein levels (Lockhart et al., 2004). Further genetic screening of *DJ-1* has resulted in identification of several variable sites containing deletions, missense and nonsense mutations (Abou-Sleiman et al., 2003; Hague et al., 2003; Hedrich et al., 2004).

DJ-1 has been suggested to be a sensor of oxidative stress since it shifts its isoelectric point to a more acidic form following oxidative stress (Mitsumoto and Nakagawa, 2001; Bandopadhyay et al., 2004). In agreement with this, wild-type DJ-1 can reduce the motor abnormalities and dopamine neuron death caused by 6-OHDA in rats (Inden et al., 2006). Moreover, involvements of DJ-1 in apoptosis, protein folding, chaperone activity and transcriptional regulation have also been proposed. The *DJ-1* gene is conserved across species and is present in nervous as well as in peripheral tissues. The protein is localized to the nucleus and cytoplasm (Nagakubo et al., 1997; Zhang et al., 2005), but it relocalizes to mitochondria under oxidizing conditions (Canet-Aviles et al., 2004; Blackinton et al., 2005).

3.5.4. ATP13A2 (PARK9)—Mutations in the ATPase type 13A2 gene on the PARK9 locus on chromosome 1p36 (Hampshire et al., 2001) have been linked to autosomal recessive parkinsonism in families with Kufor-Rakeb syndrome (Najim al-Din et al., 1994; Hampshire et al., 2001). The patients have juvenile onset atypical parkinsonism, accompanied by pyramidal cell degeneration and cognitive dysfunctions, features not commonly seen in Parkinson's disease. More recently, genetic variants in *ATP13A2* were associated with a more typical early-onset parkinsonism in Brazil and Italy (Di Fonzo et al., 2007).

3.6. Genetic risk factors

PARK genes may harbor less severe mutations that do not *per se* cause disease, but merely increase risk. For instance, this appears to be the case for *LRRK2*. *GBA*, glucocerebrosidase originally implicated in Gaucher's disease, may constitute risk of both familial and sporadic Parkinson's disease (see Lees et al., 2009). Current data suggest mutations in *GBA* may constitute a relatively common cause/risk factor. Located at 1q21, *GBA* encodes a lysosomal protein which cleaves the beta-glucosidic linkage of glycosylceramide, an intermediate formed during glycolipid metabolism. In addition, variants in a large number of other non-PARK genes have been associated with increased risk to develop Parkinson's disease in case–control studies. These genes are too many to be dealt with individually in this review. However, the evidence from the hypothesis-driven association studies, the linkage studies and the emerging whole genome-wide studies taken together provides a strong case for genetic factors as the dominating cause of Parkinson's disease.

The large and increasing number of genes in which mutations have been found that increase, or sometimes decrease (e.g. UCH-L1) risk to develop Parkinson's disease is bewildering.

However, it is possible to group the implicated genes. Several are important for mitochondrial function, sometimes assumed to participate in the same metabolic pathways, other genes are important for detoxification and/or protection against oxidative stress. Yet others are involved in protein degradation, proteasome or lysosomal functions. It is striking that none of the genes implicated to date is specifically expressed in dopamine neurons (see Fig. 1). Instead, many of the implicated genes have rather general neuronal or cellular functions in and outside of the brain, suggesting that dopamine neurons are more susceptible to stress than other neurons, and, by the same token, explaining why many other neuron systems are eventually damaged in Parkinson's disease. Clearly, from an etiologic standpoint, "Parkinson's disease" is *de facto* the definition of several different types of neurodegenerative diseases.

3.7. Transgenic animal models

Based on the findings that mutations in human genes can cause Parkinson's disease, a number of animal models have been developed in attempts to mimic the characteristic features of the disease (see Terzioglu and Galter, 2008). Like drug-induced models, these genetically modified animal models have contributed to the understanding of the disease. Following the identification of α-synuclein as a cause of Parkinson's disease in the 1990s, several transgenic mouse models based on this gene have been developed, including mice over-expressing human α-synuclein, mice carrying the point mutations found in familial Parkinson's disease (A30P and/or A53T) and mice which are null mutants for the gene. Since the α-synuclein gene dose appears critical in Parkinson's disease, a number of α-synuclein over-expressing lines have also been generated. The mice show varying degrees of behavioral and pathological disturbances, and the most pronounced phenotypes are observed in the high expressing lines. However, only a few of the over-expressing lines show alterations in the nigrostriatal pathway that worsen with age (Masliah et al., 2000; Richfield et al., 2002; Rockenstein et al., 2002). Interestingly, α-synuclein knock-out mice have reduced striatal dopamine levels (Abeliovich et al., 2000) and they show decreased rearing and a reduced reserve vesicle pool (Cabin et al., 2002). The latter is in line with the suggested involvement of α-synuclein in maintenance of synaptic vesicles. Moreover, α-synuclein null mutant mice show resistance to MPTP exposure (Dauer et al., 2002; Schluter et al., 2003; Drolet et al., 2004).

Identification of *LRRK2* mutations as the most common cause of Parkinson's disease has lead to a high demand for *LRRK2* transgenic mouse models, which are currently being developed. A desirable model would carry mutations in functionally important domains, like for instance the Roc and kinase domains, or in other sites known to be mutated in Parkinson patients.

Parkin knock-out mice have been generated by deleting different exons in the gene, resulting in a loss of Parkin function (Goldberg et al., 2003; Itier et al., 2003; von Coelln et al., 2004; Perez and Palmiter, 2005). The mouse lines have variable phenotypes with only modest behavioral effects, and none of the lines show loss of nigrostriatal neurons. However, Parkin knock-out mice do show changes in striatal dopamine release and synaptic dysfunction making them suitable for studying the early phases of Parkinson's disease.

Studies of *DJ-1* transgenic mice are useful for understanding sporadic forms of Parkinson's disease. Targeted deletion of exon 2 or insertion of a truncating mutation in exon 1 of the *DJ-1* gene, results in reduced spontaneous or drug-induced locomotor activity in mice (Kim et al., 2005; Goldberg et al., 2005). As is the case for Parkin mice, *DJ-1* knock-out mice also fail to show loss of nigrostriatal dopamine neurons. Another mouse model based on the linkage of a recessively inherited PARK gene with Parkinson's disease, is the PINK1 knock-out mouse which shows a decrease in evoked dopamine release in striatum and deficits in corticostriatal plasticity (Kitada et al., 2007).

Recently, conditional knock-out models of Parkinson's disease were generated, in which a gene of interest is flanked by two LoxP sites for recombination. By breeding mice carrying a floxed gene on each allele, with a mouse expressing Cre-recombinase under a particular promoter, the gene of interest can be conditionally knocked out. In MitoPark mice, one such example, the mitochondrial transcription factor A (*TFAM*) has been selectively deleted in dopamine neurons. The animals are generated by crossing *TFAM* floxed mice with mice expressing Cre-recombinase under the DAT promoter (Ekstrand et al., 2007). TFAM is a nuclear encoded protein which is essential for transcription and replication of mitochondrial DNA (Kang et al., 2007), which encodes some of the subunits of the mitochondrial respiratory chain. Loss of TFAM activity in MitoPark mice thus results in impaired oxidative phosphorylation specifically in dopamine neurons. Interestingly, these mice show several parkinsonian features including a progressive loss of dopamine neurons in substantia nigra, reduced striatal dopamine levels, reduced locomotor activity and formation of intracellular aggregates, and the mice die prematurely (Ekstrand et al., 2007).

4. Concluding remarks

In recent years, genetic risk factors have become increasingly important in the search for possible causes of Parkinson's disease. Genetic variations are present at 0.1% of the human genome, and these differences determine not only properties, but also susceptibility to disease. Mutation frequencies may vary considerably between populations. A factor found to be linked to, or associated with disease in one geographically or genetically confined family or population, can be present at another frequency or completely absent in another sample set. These population-specific differences make identification of genetic risk factors complex, and they also point at the importance of mapping genetically diverse materials. Characterization of genes and their variable sites is essential for understanding the pathways in which they are involved and also for identifying their interacting moieties. The heterogenic nature of Parkinson's disease with regard to both age of onset, symptoms and pathology is compatible with an involvement of multiple genes and pathways rather than a single gene or mutation.

A desirable outcome of genetic studies is identification of candidate genes which can be used as biomarkers for early and reliable diagnosis. However, identification of new genetic markers may also lead to the demand for individual genetic testing of healthy relatives at risk. Genetic testing of healthy individuals is controversial and requires cautious considerations of potential risks. Another important goal of genetic studies would be identification of new drug targets for improved therapy with fewer side effects. While the

pharmacological and surgical treatments used in Parkinson's disease today are effective in improving motor complications, they have limited or no effects on depression, hallucinations, dementia or the autonomic and sleep disturbances seen in Parkinson patients. Importantly, there is currently no treatment that stops the progressive loss of dopamine neurons or modifies the rate of progression. Extended knowledge about disease-causing genes may aid in finding pathogenic mechanisms, suitable for therapeutic intervention.

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Abbreviations

ATP13A2	ATPase type 13A2
LRRK2	leucine-rich repeat kinase 2
PINK1	PTEN induced putative kinase 1
SNCA	synuclein alpha
TFAM	mitochondrial transcription factor A
UCH-L1	ubiquitin C-terminal esterase L1

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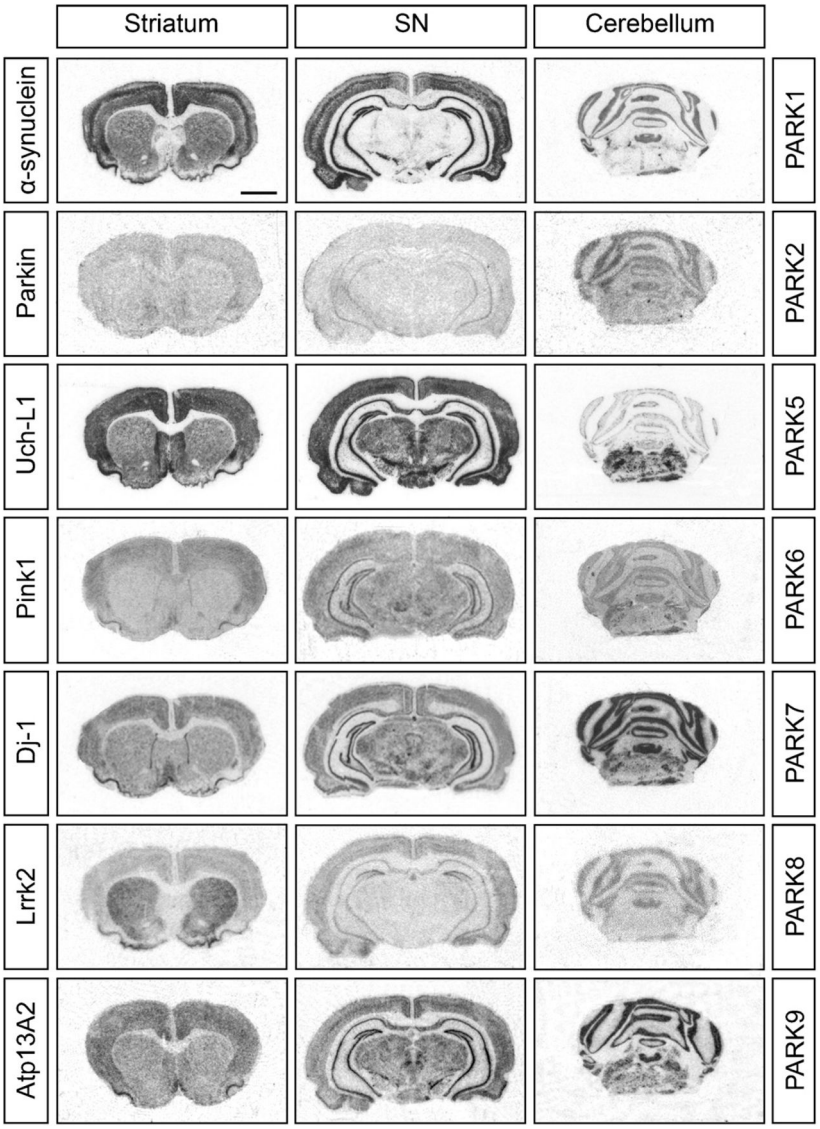

Fig. 1.

mRNA expression patterns in the rat brain (at the level of striatum, substantia nigra/hippocampus and cerebellum) of the PARK genes α-synuclein/*SNCA* (PARK1), Parkin/*PRKN* (PARK2), *Uch-L1* (PARK5), *Pink1* (PARK6), *Dj-1* (PARK7), *Lrrk2* (PARK8) and *Atp13a2* (PARK9) revealed by *in situ* hybridization and radioactively labeled oligo probes. All PARK genes presented in the figure have been implicated in the pathogenesis of Parkinson's disease. Despite being involved in a common disease, they show variable levels and patterns of expression. *Uch-L1* for instance is expressed by all neurons, *α-synuclein/SNCA* show high expression in substantia nigra, striatum and cortical areas whereas *Lrrk2* shows particularly high expression in striatum, the target area of dopamine neurons. Interestingly none of the candidate genes shows a restricted expression in the dopamine system only.