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Genetics of Parkinson Disease

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1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder second to Alzheimer's disease, affecting 1-2% of individuals over 60 years of age, with a risk that increases with age.

Its phenotypic complexity, characterized by motor (resting tremor, bradikinesia, rigidity and postural instability) and non-motor (autonomic dysfunction and cognitive impairment) symptoms lead to the description of this disorder as a syndrome rather than a monolithic disease. Genetic research in the past 10 years, in particular mapping and cloning of genes which cause the inherited form of the disease, has shown that "Parkinson syndrome" is not one disease entity but rather an atherogeneous group of disorders that are associated with a spectrum of clinical and pathological changes. It is believed to be caused by the interaction of environmental factors and genetic variants acting on the stage of an aging brain.

There is a growing body of evidence that genetic risk factors are of major importance in PD. So far 16 loci have been identified involved in PD.

PD can be referred mostly as sporadic (90-95%) and to a lesser extent as familial (5%)

Familial PD is caused by very rare highly age penetrant mutations, inherited in a Mendelian way (autosomal recessive or dominant). The biological effect of these mutations is sufficient alone for the development of the disease.

Sporadic PD is a complex multifactorial disease in which very common genetic variants play a very modest role singularly while taken all together, interacting with other genes and environmental factors, they can exert an important cumulative effect leading to the development of the disease.

In the last decade pathogenic mutations in five genes (*SNCA*, *LRRK2, PRKN, DJ-1* and *PINK1*) have been linked to familial PD. Recently genome wide association studies, GWAS, across different populations identified other 6 loci involved in the sporadic disease (*MAPT, SNCA*, *HLA-DRB5*, *BST1*, *GAK* and *LRRK2*). Finally a meta-analysis of the 5 previous GWAS discovered 5 new loci in association with the idiopatic disease (*ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11* and *CCDC62/HIP1R*) (International Parkinson Disease Genomics Consortium, 2011)

2. Familial PD

Familial PD is monogenic and caused by rare highly age-dependent penetrant mutations, which follow a Mendelial pattern of inheritance (autosomal dominant or recessive).

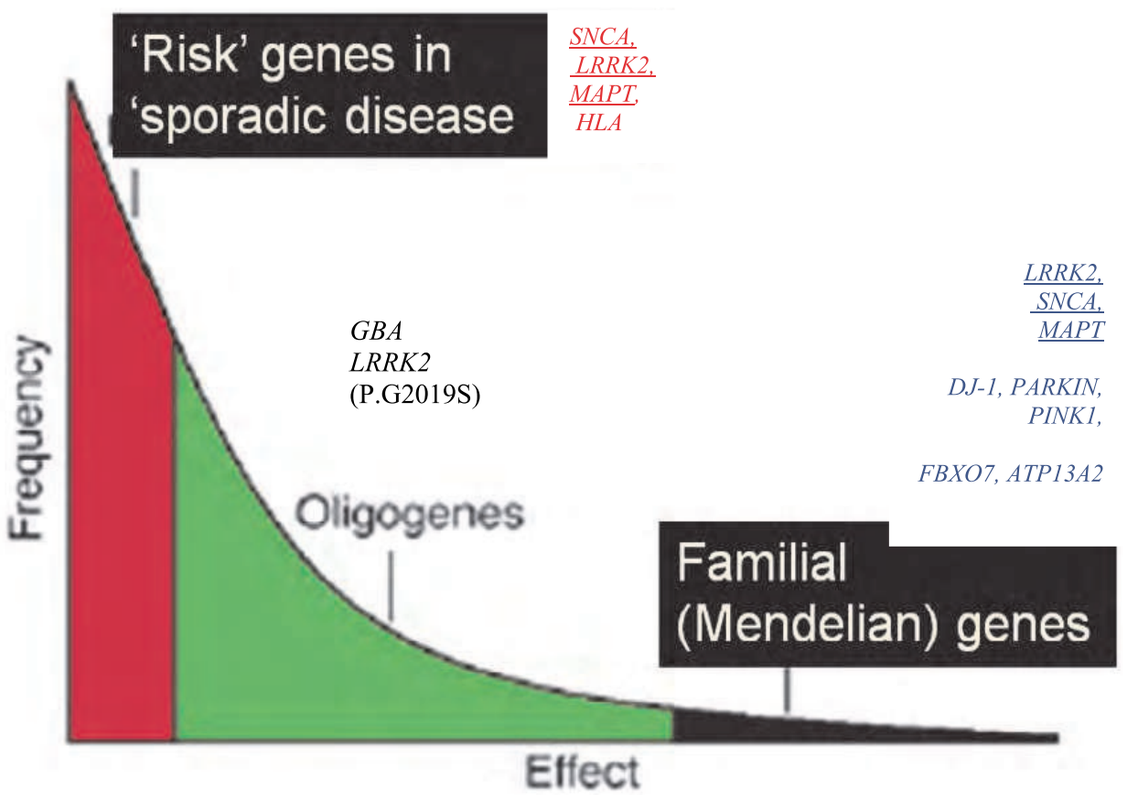

Fig. 1. The hyperbole descrives the relationship between the allelic frequency and the biological effect in the complex traits. The monogenic Mendelian forms are responsible for the familial Parkinson's disease, in which rare mutations can cause, independently from other factors, the disease, with a probability which increases with the age, due to the penetrance. The complex, poligenic, sporadic form is linked to risk factors which can be very common in the population but unable alone to determine the disease without interacting with other factors like genetic or environmental ones. Mutations in several familial (Mendelian) genes have been identified as causal factors for PD. Mutations in *LRRK2*, *SNCA*, *MAPT*, *UCHL1* determine the autosomal dominant disease while the recessive form is caused by mutations in *PARKIN*, *PINK1*, *DJ-1* and to a lesser extent *FBXO7* and *ATP 13A2*. Common variants in *SNCA*, *LRRK2*, *MAPT*, *HLA*, contribute to the development of the idiopatic disease. High-risk factors for the sporadic disease are mutations in *GBA* and *LRRK2* genes, especially among isolated populations like Ashkenazi Jews. Interestingly rare highly penetrant dominant mutations in *SNCA*, *LRRK2* and *MAPT* cause familial parkinsonian syndromes and common variants at the same loci increase susceptibility for PD in the general population.

Locus (chromosomal position)	Gene	inheritance, mutations	age at onset	mutations	clinical phenotype	pathology	comment
PARK1 and PARK4 4q21	Alpha-synuclein SNCA	Autosomal dominant	38-65 years (duplications) 28-48 years (triplications)	Ala30Pro, Gly46Lys and Ala53Thr substitutions; genomic duplications and triplications.	Progressive levo-dopa responsive parkinsonism, associated with cognitive decline, autonomic dysfunction and dementia: progression is more rapid in SNCA triplication cases	Diffuse Lewy bodies disease with prominent nigral and hippocampal (CA2-3) neuronal loss	Genetic and functional data indicated that common promoter and intronic variability are associated with sporadic PD
PARK2, 6q25.2-q27	parkin	Autosomal recessive	30 years on average (range 16-72)	Homozygous and compound heterozygous missense (>57) and exonic deletion/duplication/ triplication mutations	Parkinsonism often presenting with dystonia, with diurnal fluctuations and sleep benefit; typically responsive to very low doses of L-DOPA	Predominantly nigral neural loss, although compound heterozygotes with Lewy bodies and tau pathology are described	Mutations account for 50% of familial juvenile and early-onset parkinsonism, and 18% of sporadic disease (<50 years at onset)
PARK3, 2p13	unknown	Autosomal dominant	60 years			Nigral degeneration with Lewy bodies, plaques and tangles	
PARK5, 4p14	UCHL1	Autosomal dominant and sporadic PD	55-58 years (Ile93Met) Late onset	Linkage for the Ile93Met substitution is equivocal Susceptibility to sporadic PD is associated with a Ser18Tyr polimorphism	Sporadic PD	Indetermined for Ile93Met cases; UCHL1 protein is a prominent component of Lewy bodies	The Ser18Tyr association is supported by meta-analysis and functional data
PARK6, 1p35-p36	PINK1	Autosomal recessive	20-40 years	Missense and exon-deletion mutation	Parkinsonism that progresses slowly and is responsive to low doses of L-DOPA	Undetermined	Rare cause (1-2%) Haploisufficiency might predispose to the disease

Locus (chromosomal position)	Gene	inheritance, mutations	age at onset	mutations	clinical phenotype	pathology	comment
PARK7, 1p36	DJ1	Autosomal recessive	20-40 years	Homozygous missense (Leu166Pro) and deletion (del Ex1-5) mutations, and compound heterozygotes	Slowly progressive Parkinsonism, occasionally with behavioural or psychiatric disturbance; rare compound heterozygotes documented with parkinsonism with dementia or amyotrophy	Undetermined	Rare cause (<1%) of cases with onset at <50
PARK8, 12p12	LRRK2	Autosomal dominant and sporadic disease	Between 50 and 70 years (range 32-79)	Many domimant substitutions, notably Arg1441Cys/Gly/His, Tyr1699Cys, Ile2012Thr, Gly2019Ser and Ile2020Thr	Parkinsonism consistent with sporadic PD; dystonia, amyotrophy, gaze palsy and dementia occasionally develop	Heterogeneous pathologic findings: predominantly Lewy body disease; rare cases have also neurofibrillary tangles and/or nigral neural loss	Common coding variation might affect risk in sporadic PD
PARK9, 1p36	ATP13A2			unknown			
PARK10, 1p32	Unknown	Autosomal dominant	50-60 years			No pathology reported	
PARK11, 2q37.1	GIGYF2	Autosomal dominant	late		Parkinsonism consistent with sporadic PD	No pathology reported	
PARK12, Xq21-q25							
PARK13, 2p13	HTRA2						
PARK14, 22q13.1	PLA2G6						
PARK15, 22q12-q13	FBXO7	Autosomal recessive	20-40 years		Parkinsonian-pyramidal syndrome		
PARK16, 1q32	NUCKS1, RAB7L1 SLC41A1						

The classic approaches of linkage analysis and positional cloning have been very successful strategies to identify genes causing the autosomal-dominantly inherited diseases including the major forms of familial PD.
This strategy relies on the availability of large and clinically well-characterized families, usually with at least 8–10 affected family members. By studying the co-segregation of genetic (DNA)markers, the genetic locus of the disease-causing gene in a given family can be narrowed down to a region of several million base pairs (megabases, Mb) of DNA. The statistical method to estimate the likelihood that a particular set of neighbouring DNA markers (a so-called haplotype) are co-inherited with a disease gene as a result of its physical proximity on the chromosome (i.e. that DNA markers and disease gene are 'linked') is called linkage analysis. The most important prerequisite for this type of study, in addition to the availability of sufficiently large families, is the unequivocal classification of affected and unaffected family members. Erroneous classification, which in many age-related complex diseases is a real possibility, will lead to false linkage results (Gasser, 2008). When a disease locus is identified with sufficient confidence (a so-called lod score of >3 is equivalent to a genome-wide p.value of 0.05 and is considered to be significant evidence), all the genes in the identified region have to be sequenced and analysed for potentially disease-causing mutations. Of course, not all of the identified sequence variants in a linked region are pathogenic. This means that either the demonstration of mutations in several independent families co-segregating with a disease is necessary (amounting in effect to a replication of the initial finding) or the careful functional studies in model systems are required to prove pathogenicity.
Mutations in the genes *LRRK2* and *SNCA* are responsible for the autosomal dominant form of the disease through a gain of toxic function. Mutations in *PARKIN*, *PINK1* and *DJ-1* are the most common cause of the autosomal recessive form through a loss of protective function.

3. Autosomal dominant PD

3.1 SNCA (PARK1 and 4, 4p21)

It was the first gene to be inequivocally associated with familial autosomal dominant PD. It encodes for α-synuclein, a small protein, which is aboundantly expressed in the brain and localized mostly to presynaptic nerve terminals. This protein has a central role in the learning process, brain plasticity, vescicular trafficking and dopamine synthesis but many aspects of the normal function of alpha-synuclein are still unknown. There is still no good explanation for the selectivity of neural damage in PD, which is prominent in dopaminergic cells whereas α-synuclein is expressed in many areas of the brain.
Alpha synuclein plays a role in both familial and sporadic form of PD and for this reason can be an interesting target for the development of new therapies.
The protein is linked to the phospolipid membrane strate through the N-terminal edge and to a lesser extent it is free in the cytoplasm. It is hypothesized that a possible pathological role derives from a conformational change that lead to an imbalance between the protein linked to the membrane and that free in the cytoplasm, with a consequent aggregation and fibril formation.
Three missense mutations are causal factor for the familial autosomic dominant form of the disease

- A53T, identified within an Italian family and three Greek families (Polymeropoulous et al., 1997)
- A30P, identified in a German family (Krüger et al.,1998)
- E56K, identified within a Spanish family (Zarranz et al., 2004)

The pathogenic mechanism is supposed to be a conformational change due to the amminoacid substitution in the protein chain, which facilitates α-synuclein aggregation. Clinically, the phenotype is more aggressive with an higher incidence of cognitive impairment and autonomic disfunction. *SNCA* point mutations have so far been found only in large, multigenerational PD families, never in sporadic PD. The phenotype of patients with *SNCA* point mutations is that of L-dopa responsive parkinsonism with a relatively early age at onset, rapid progression, and high prevalence of dementia, psychiatric and autonomic disturbances, reminiscent of Lewy body dementia. Several family members from these kindreds have come to autopsy and they invariably showed cell loss of dopaminergic neurons of the substantia nigra, and severe and widespread Lewy pathology, particularly in the form of Lewy neuritis. The identification of *SNCA* point mutations as a cause of PD soon led to the discovery that the encoded protein, a-synuclein, is the major fibrillar component of Lewy bodies and Lewy neuritis in familial as well as sporadic cases. The currently favoured hypothesis settles that the ammoniacid changes within alpha-synuclein lead to an increased tendency of the protein to form oligomers and later on fibrillar aggregates, representing a 'toxic gain of function'. However, the precise sequence of events which lead from aggregation to cellular dysfunction and cell death is still not obvious. Some studies favour the hypothesis that the mature aggregates (Lewy bodies) are not themselves the toxic moiety, but rather an attempt to the cell to clear small toxic oligomers. A direct link between α-synuclein and PD was further supported by the discovery that multiplications of the wild-type sequence of *SNCA* (duplications and triplications) (Singleton et al., 2003) cause PD with or without dementia in some families. This finding was of major mechanicistic importance because indicates that an increase in wild-type a-synuclein protein expression appears to be toxic to neurons. A dose dependency of this effect is demonstrated by the fact that patients with *SNCA* triplications (4 copies of the gene) have an early age of onset (mean of around 35 years) and high prevalence of dementia, while patients with *SNCA* duplications (3 copies) have a more typical late-onset PD phenotype.

The presence of α-synuclein-containing aggregates in the absence of coding *SNCA* mutations in sporadic disease suggest that other α-synuclein modifications, such as alternative splicing, phosporylation,, alterations in gene expression, or additional interacting genes may contribute to sporadic PD.

Then interaction of α-synuclein with proteins aggregating in other neurodegenerative diseases is coming increasingly into focus. 'Cross-seeding' of α-synuclein and tau has been hypothesized by a recent study. Interestingly this molecular mechanism may turn out to be the biological basis of the recently confirmed and refined association of *MAPT* haplotypes with PD and of an interaction of genetic variants in the *SNCA* and *MAPT* genes.

3.2 LRRK2 (PARK8, 12p21)

The gene spans a genomic region of 144 Kb, with 51 exons encoding LRRK2 or Dardarin, a 2527 amino acids protein, with various conserved domains recognized in its primary ammino-acid sequence. More than 40 variants have been identified in the gene and at least 16 of them are recognized as pathogenic ones. Missense mutations in this gene were found

to cosegregate with the disease in several families and are the most common cause of mendelian PD identified so far. In studies across several populations, 5–15% of autosomal dominant PD families carried mutations in *LRRK2*. One particularly common mutation, a base pair change at position 6055,better known as the 'G2019S-mutation', is responsible for familial PD in up to 7% of cases in different Caucasian populations , but was found, somewhat surprisingly, also in 1–2% of sporadic patients. Even higher G2019S prevalence rates of up to 40%were found in genetically isolated populations,such as the Ashkenazi Jewish and the North-African Arab populations, both in sporadic and familial cases. P.G2019S is the most common mutation among Caucasian patients and it is responsible for the 0.5-2% of the cases of the sporadic disease and for the 5% of the familial cases. This mutation is particularly frequent among the Askenazi Jews and the Arabs from North Africa, where it is responsible for 18-30% of the cases. The substitution has been identified also in the Iberian Peninsula, where it is involved in the 2.5-65% of the cases of the sporadic disease. It seems that the mutation has been originated in North Africa or in the Middle East and probably later it has been spread to Europe and Northern America. It has also been hypothesized a common founder for the p.G2019S substitution probably dated back to the 13th Century. The presence of the mutation in the Middle East and in North Africa lead to guess that the mutation should be even more older. The Fenices were known to be the principal merchants of the ancient world and probably they were responsible for the diffusion of this substitution.

Due to its relatively high frequency, the p.G2019S mutation offers for the first time the possibility of looking at gene–gene interactions. Three Spanish patients simultaneously harbouring heterozygous mutations in *LRRK2* and in the parkin gene did not present with an earlier age at onset or a more severe disease. The G2019S mutation also seems to be fully dominant, as homozygous mutation carriers have been identified who also do not differ from heterozygotes with respect to disease severity or age of onset.

Another, even more common *LRRK2* variant, G2385R, has been found in the Asian population in 6–10% of sporadic PD patients, as opposed to 3–5% of controls. Consequently, this variant confers a relative risk of about 2 to 3 of developing PD,suggesting that different alterations in one and the same gene may act as a high-penetrance disease-causing mutation or as a genetic risk variant in sporadic populations.To date, more than 20 potentially pathogenic mutations in *LRRK2* have been identified, but in only six of them pathogenicity can be considered to be highly likely (R1441C, R1441G,R1441H, Y1699C, G2019S and I2020T), because of firm evidence of cosegregation in affected families and functional data suggesting an alteration of kinase activity.The most extensive clinicogenetic study so far estimated the overall frequency of *LRRK2* mutations in the European population to be 1.5%in sporadic and 4%in familial cases, with a geographic gradient decreasing from Mediterranean countries (Spain, Portugal, Italy) to northern countries. The average age of onset was 58 years, with a wide range from the mid-20s (rarely) to over 90 years. The clinical picture was that of typical asymmetric L-dopa responsive parkinsonism that was indistinguishable by any single criterion from PD in individuals without *LRRK2* mutations. As a group, the disease appeared to be somewhat more benign in patients with mutations in *LRRK2*, with slower progression and a lower frequency of dementia and psychiatric complications.

In contrast to the finding that α-synuclein stains Lewy bodies and tau stains neurofibrillary tangles and grains, LRRK2 immunocytochemistry has so far failed to highlight any specific,

neurodegenerative lesion , and it is unclear how LRRK2 substitutions result in neuropathology. *LRRK2* mutations may therefore be an upstream event in the cascade leading to neurodegeneration with different pathologies.

LRRK2 is widely expressed in the brain, with highest levels in the striatum and the hippocampus but a relatively low abundance in the substantia nigra; it can also be detected in other organs, such as the spleen, the lung and the liver. It has been found in the cytoplasm as well as associated with membranes. Its function and the mechanism by which LRRK2 mutations cause neuronal degeneration are unknown. By sequence homology, LRRK2 can be assigned to the group of recently identified ROCO proteins and contains a protein kinase domain of the mitogen-activated kinase class, suggesting a role in intracellular signalling pathways. Although the natural substrate of LRRK2 is unknown, cell culture studies using generic substrates or LRRK2 autophosphorylation paradigms suggested that at least some pathogenic mutations seem to be associated with an increase, rather than a loss, of kinase activity, and that kinase activity appears to be necessary for neurotoxicity in vitro. This discovery raises the interesting possibility that kinase inhibition may be a potential therapeutic strategy. An interesting aspect of LRRK2-associated PD is its heterogeneous pathology. Post-mortem changes in patients with *LRRK2* mutations are those of typical Lewy-body PD in most cases, but also include diffuse Lewy-body disease, nigral degeneration without distinctive histopathology and, rarely, even aggregates of the microtubule-associated protein tau, suggestive of progressive supranuclear palsy or frontotemporal dementia. Different pathological findings were even reported in a single family with an R1441C mutation. *LRRK2* mutations may therefore be an upstream event in the cascade leading to neurodegeneration with different pathologies. However, the vast majority of patients with a G2019S mutation, in whom pathology has been reported, seem to conform to the typical α-synuclein Lewy-body type of PD. No direct link between LRRK2 and α-synuclein has so far been demonstrated. α-synuclein does not seem to be phosphorylated by LRRK2.

Despite its still poorly understood role in pathogenesis, LRRK2-associated PD is of particular interest since it is the first example of a mendelian form of PD that is common enough to provide the opportunity to study the development

of the disease in a sizeable population. Longitudinal studies in presymptomatic mutation carriers may reveal premotor changes by clinical, biochemical or imaging methods, indicating the very early phases of the neurodegenerative process. It is in this population that studies exploring neuroprotective or preventive measures are most promising to yield first results

3.3 UCHL1 (Park 5, 4p14)

The ubiquitin C-terminal hydrolase-L1 (*UCH-L1*) was first identified as an abundant (1–2% of total brain protein), neuronspecific protein encoded by a 9.5 kb gene product (Day and Thompson, 1987; Doran et al., 1983). UCH-L1 is a de-ubiquitinating enzyme that removes carboxy-terminal ubiquitin *UCH-L1* from substrates but does not break bonds within polyubiquitin complexes and results in the recycling of ubiquitin. In addition,UCHL1 protein is found in several pathological structures including Lewy bodies and some Alzheimer's neurofibrillary tangles (Lowe

et al., 1990). Furthermore, recent studies have identified a single dominant mutant (I93M) in two members of a PD-affected family. Inversely, a polymorphism in *UCH-L1* (S18Y) has

been suggested to reduce the risk of developing sporadic PD. Interestingly, another study hypothesizes that UCHL1 may possess two enzymatic activities, hydrolase and ligase activity. Overexpression of UCH-L1 variant I93M resulted in an accumulation of α-synuclein. Furthermore, they suggest that this accumulation is due to an ubiquitination of α-synuclein by dimerized UCH-L1. However, the S18Y polymorphic variant of UCH-L1 has reduced ligase activity but normal hydrolase activity,
which may explain the 'protective' effect of the S18Y polymorphism. With evidence of UCH-L1 and parkin being involved in certain forms of familial PD, this gives credence to the involvement of the UPS in PD. However, it is unclear how UCH-L1 can promote the specific neurodegeneration of dopaminergic neurons in familial PD and what role it plays in the sporadic form.

4. Autosomal recessive PD

The strategies of linkage mapping and positional cloning can also be used to identify loci in genes responsible for autosomal-recessive monogenic diseases. This mode of inheritance is characterized typically by the occurrence of the disease in siblings while the parents are obligatory heterozygous mutation carriers and usually remain healthy. Autosomal-recessive PD has clinically been first recognized and characterized in Japan (Ishikawa and Tsuji, 1996). Sibling pairs with PD often have much earlier age of onset compared with patients with the sporadic disease, which is why the term 'autosomal-recessive juvenile parkinsonism'(AR-JP): has been coined. Since families with a recessive disease are usually much smaller than multigenerational dominant pedigrees, linkage analysis is only successful if several families mapping to the same locus are included into a study.
So far, mutations in three genes have been identified in clinically 'pure' forms of autosomal recessive PD: *PARKIN* (PRKN, or PARK2), *PINK1* (PARK6) and *DJ-1*(PARK7). *PRKN* encodes for parkin, a cytoplasmatic protein which functions in the cellular ubiquitination/protein degradation pathway as an ubiquitin ligase. *DJ-1* and *PINK1* encode for mitochondrial proteins. Genetics mutations in these genes cause PD through the loss of the wild-type protein neuroprotective function, leading to oxidative stress, iron accumulation and mitochondrial dysfunction.
They cause PD with earlier onset (<45 years) and slower progression compared to idiopatic PD. Three additional recessive genes have been added to the list more recently-*ATP13A2*, *PLA2G6* and *FBXO7*- which all also cause, when mutated, an early-onset disease with parkinsonism, but also with additional features such as dystonia, which often is seen as the first symptom, dementia, oculomotor disturbances and spasticity.

4.1 PARKIN (PARK2, 6q25.2-q27)

Juvenile cases of parkinsonism in siblings were first recognized in Japan. The first genetic locus for autosomal- recessive juvenile parkinsonism (AR-JP), as this form of PD was called, was mapped to chromosome 6.
Mutations were then identified in a large gene in that region that was called parkin. Clinically, these patients suffer from L-dopa-responsive parkinsonism and often develop early and severe L-dopa-induced motor fluctuations and dyskinesias. Some show diurnal fluctuations, with symptoms becoming worse later in the day. Dystonia at onset of the disease is common. *Parkin* mutations turned out to be a common cause of parkinsonism

with early onset, particularly in individuals with evidence of recessive inheritance. Nearly 50% of families from a population of sibling pairs with PD had *parkin* mutations. Also, *parkin* mutations are responsible for the majority of sporadic cases with very early onset (before age 20), and are still common (25%) when onset is between 20 and 35. Prevalence is almost certainly well below 5% in those with onset later than 45. Several studies have described the clinical spectrum of *parkin*-associated parkinsonism. Mean age at onset in a European population was 32 years; progression of the disease was usually relatively slow, but L-dopa-associated fluctuations and dyskinesias occurred frequently. Dystonia (usually in a lower extremity) at disease onset was found in about 40% of patients, and brisk reflexes of the lower limbs were present in 44%. Psychiatric abnormalities have been recognized in PD patients with *parkin* mutations but there are no systematic studies to determine whether this is a characteristic feature associated with *parkin*-mutations. Phenotype– genotype studies implicate that the type of mutation may influence the clinical phenotype to a certain degree: patients with at least one missense mutation showed a faster progression of the disease with a higher UPDRS (United Parkinson's Disease Rating Scale) motor score than carriers of truncating mutations. Missense mutations in functional domains of the *parkin* gene resulted in earlier onset. It is still controversial whether heterozygous mutations in the *parkin* gene can cause parkinsonism or can confer an increased susceptibility for typical late-onset PD. There is evidence from imaging studies that heterozygous carriers of *parkin* mutations have reduced uptake of fluorodopa in the basal ganglia. Furthermore, families with heterozygous mutation carriers manifesting symptoms of PD have been described. On the other hand, the frequency of heterozygous mutations in the *parkin* gene was found to be similar in elderly healthy individuals, as compared to a cohort with late-onset typical PD and in a large family reported recently, 12 heterozygous carriers of a particular *parkin* mutation (ex3delta40) were asymptomatic. Also, in a group of families with PD showing anticipation (late-onset PD in the parent generation and early-onset PD in the offspring) genotyping results did not support the explanation that the presence of single or compound heterozygous *parkin*-mutations contribute to this phenomenon. Therefore, at present the data are still insufficient to confidently judge the role of single heterozygous *parkin* mutations in the development of PD. Knowledge on the neuropathology of molecularly confirmed cases of AR-JP is still based on only a few cases. Severe and rather selective degeneration of neurons in the substantia nigra and the locus coeruleus, usually with absence of Lewy bodies, has been described.

As mutations in *parkin* cause parkinsonism, in all likelihood by a loss-of-function mechanism, the study of the normal function of parkin provides insight into the molecular pathogenesis of the disorder. Several groups have now shown that parkin, a protein found in the cytosol but also associated with membranes, functions in the cellular ubiquitination/protein degradation pathway as a ubiquitin ligase. It has been hypothesized that the loss of parkin function may lead to the accumulation of a nonubiquitinated substrate that is deleterious to the dopaminergic cell but, due to its nonubiquitinated nature, does not accumulate in typical Lewy bodies. Several proteins have been shown to interact with parkin. However, the putative toxic protein, which has been hypothesized to accumulate due to the lack of *parkin* in patients (or in knock-out animals) has not yet been identified. However, novel functions of *parkin* are being identified, and it is possible that they may be of equal or even greater relevance to the pathogenesis of PD. For example, it has been shown that parkin does not only mediate the well-studied ubiquitinylation via lysin48 (K48), which directs ubiquitinylated proteins for

proteasomal degradation, but also via lysin63 (K63), which may play a role intracellular signaling processes and also in Lewy body formation. A recent study revealed a decreased abundance of a number of proteins involved in mitochondrial function or oxidative stress, accompanied by a reduction in respiratory capacity of striatal mitochondria, a decreased serum antioxidant capacity and increased protein and lipid peroxidation These novel findings indicate that proteasomal dysfunction, although supported by several lines of evidence, might not be the sole mechanism contributing to neurodegeneration in *parkin*-related disease. Whatever the mechanism, increasing evidence suggests an important role of *parkin* for dopamine neuron survival. Overexpression of wildtype rat parkin could protect against the toxicity of mutated human A30P α-*SYN* in a rat lentiviral model of PD. The *parkin* mediated neuroprotection was associated with an increase in hyperphosphorylated α-*SYN* inclusions, suggesting a key role for parkin in the genesis of Lewy bodies. Recently, two biochemical modifications of Parkin (*S*-nitrosylation and dopamine quinine-adduct formation) were identified in cellular studies and human brain specimens. These data indicated that reduced E3-ligase activity of the wild-type Parkin protein (rather than an autosomal recessive mutation in the two *Parkin* alleles) could also occur as a result of the principal pathogenetic process that is responsible for the development of sporadic PD.

4.2 PINK1 (PARK6, chr.1p35-1p36)

The new locus was identified in a large Italian family and it causes familial recessive PD in 1-9% of the cases. The phenotype was similar to that seen with *PRKN* mutations and characterised by early-onset parkinsonism (range 32 to 48 years), with slow progression and sustained response to L-dopa. In this and two other consanguineous PARK6- linked families, two different mutations in the gene *PINK1* (encoding PTEN-induced putative kinase 1) were identified. Several studies confirmed the presence of *PINK1* mutations in patients with early-onset PD. Most mutations were missense mutations in conserved regions, but whole-gene deletions have also been described. Almost all described patients with *PINK1* mutations have slow disease progression and a good response to L-dopa. As in *PRKN* related disease, except for the earlier average age of onset, no single feature can separate *PINK1*-related disease from idiopathic PD. There are some indications that *PINK1*-mutated patients have a higher prevalence of psychiatric disturbances, particularly anxiety and depression, which is only relatively rarely observed in *PRKN*-related cases . Wild-type PINK1 is thought to function as a protein kinase with possible activity inside the mitochondria, thereby strengthening the hypothesized link between mitochondrial dysfunction and oxidative stress in PD pathogenesis.

4.3 DJ-1 (PARK7, chr.1p36)

The third locus for AR-JP, PARK7, was mapped also to chromosome 1p36, in a Dutch family, and the gene was identified as the oncogene *DJ-1*. Again, the phenotype closely resembles that found in patients with *PRKN* and *PINK1* mutations, but this statement is based on a small number of identified patients.Mutations in the gene are responsible for 1-2% of the AR-JP. However, one recessive family, which carries two homozygous mutations in the *DJ-1* gene, has been described with early-onset parkinsonism, dementia and amyotrophic lateral sclerosis, suggesting that the clinical phenotype associated with mutations in this gene, although rare, may be rather wide.

There are now eight recessive loci, which can lead to EOPD syndromes. These are the classical recessive loci, *PRKN* (PARK2), *PINK1* (PARK6), *DJ-1* (PARK7). Loss of function mutations at *PRKN*, *PINK1*, and *DJ-1* nearly always give rise to a pure parkinsonian phenotype which has an early onset, a benign course, sleep benefit and a good and prolonged response to L-dopa. The lifespan of mutation carriers is only marginally reduced and there have been no reports of brain iron accumulation. All three proteins have functions related to mitochondrial biology and *PRKN* mutations are usually not associated with Lewy bodies. More recently, five other genes, *ATP13A2* (PARK9), *PLA2G6* (PARK14), *FBX07* (PARK15) and *SPG11* and the *PANK2*, have been identified that cause early-onset forms of parkinsonism associated with a variety of other signs and symptoms, including, in variable combinations, dystonia, ataxia, spasticity and dementia.

4.4 ATP13A2 (PARK9, 1p36)

It was the first of these genes to be characterized, encoding a predominantly neuronal P-type ATPase, in a recessively inherited early-onset parkinsonian syndrome described as 'Kufor- Rakeb syndrome' . Patients with this disease have rapidly progressive parkinsonism, spasticity, vertical upgaze palsy and dementia. The substrate and function of the protein is unknown. The wild-type protein was found to be located in the lysosome of transiently transfected cells, while the unstable truncated mutant proteins were retained in the endoplasmic reticulum and degraded by the proteasome. It can be speculated that either overload of the proteasomal protein degradation machinery or lysosomal dysfunction due to the absence of sufficient levels of ATP13A2 protein might lead to neurodegeneration. In fact, there is increasing evidence for an important role of the lysosome in the aetiology of PD: α-synuclein is degraded by chaperone mediated autophagy, and mutations in the gene encoding lysosomal glucocerebrosidase are an important cause of PD. Nevertheless, a direct involvement of the lysosome in the neurodegenerative process in Kufor-Rakeb syndrome and its potential bearing for PD remains speculative at this time

4.5 PLA2G6 (PARK14, 22q13.1)

Another interesting addition to the recessive genes causing parkinsonian syndromes that may give important insight into underlying pathogenetic processes is the gene for phospholipase A2 group VI (*PLA2G6*). Mutations in this gene have been identified in two recessive childhood-onset disorders: infantile neuroaxonal dystrophy (INAD) and neurodegeneration with brain iron accumulation (NBIA). There is brain iron accumulation in some patients with INAD, so when gene mapping identified a common locus in families with these disorders on chromosome 22, it was reasonable to suspect that the disorders may be allelic. In fact, a large number of mutations were identified, including missense changes, small deletions with and without frameshift, nonsense mutations and large deletions. As patients with two null mutations tended to have the most severe phenotype, a loss of function mechanism can be assumed. Interestingly, in addition to axonal swellings throughout the cortex, striatum, cerebellum, brainstem and spinal cord, the pathological picture also includes a-synuclein positive Lewy bodies, and thus these disorders share this important pathological feature with PD. Lewy bodies are also found in another form of neurodegeneration with brain iron accumulation (NBIA type 1; formerly called Hallervorden–Spatz disease), caused by mutations in the gene for pantothenate kinase 2 (*PANK2*). Therefore, there seems to be an interesting but still little understood link between

iron accumulation (which is also found in PD proper), a-synuclein aggregation, and neurodegeneration with parkinsonian symptoms.While the 'classic' phenotype of NBIA types 1 and 2 is that of a young-onset progressive extrapyramidal-pyramidal syndrome with visual disturbance through optic atrophy or pigmentary retinopathy, mutations in both genes can be associated with a parkinsonian syndrome of later onset. Recently, *PLA2G6* mutations have been identified in patients with adult-onset L-dopa-responsive dystonia–parkinsonism, pyramidal signs and cognitive/psychiatric features, and cerebral and cerebellar atrophy on magnetic resonance imaging but lack of iron in the basal ganglia.

4.6 FBXO7 (PARK15, 22q12-q13)

Finally, mutations in a novel and still poorly characterised gene, *FBXO7*, have been found in members of two families with early-onset, progressive parkinsonism and pyramidal tract signs, a phenotype that had been described clinically as the pallidopyramidal syndrome. Loss of function mutations in *FBX07* appear to give a phenotype which resembles *PRKN* mutation associated phenotype but the disease is generally less benign and has a reduced life expectancy, pyramidal signs and late cognitive problems. This overlap of phenotypes related to *FBX07* and *PRKN* mutations is consistent with the related functions of these two genes and their likely common disease pathway. Like PRKN, F-box proteins, such as FBXO7, are components of the modular E3 ubiquitin protein ligases. The genetic heterogeneity was surprising given their initially common clinical features

5. Role of heterozygous mutations in 'recessive' genes

A considerable percentage of patients with PD was shown to carry a single heterozygous mutation in the *Parkin*, *DJ1* or *PINK1* genes, raising the intriguing question of whether the much more frequent heterozygous mutations in 'recessive' genes might act as susceptibility factors for PD. Several ways lead to explore the potential role of these mutations. First, the frequency of single heterozygous mutations in ethnically matched PD cases and controls could be compared. According to recent reports, heterozygosity for *Parkin* mutations was similar between patients and controls, whereas heterozygous *PINK1* mutations were rarer in controls. Lincoln *et al*. indicated that there was no elevation in PD risk for people who carry a single mutant *Parkin* allele. In most studies, however, healthy controls are not subjected to detailed neurological and neuroimaging examinations, leaving open the possibility that mild clinical (or preclinical) changes could have been present but were not screened for. As recently shown for *Parkin* and *PINK1* families, subtle, but unequivocal, clinical signs of possible or probable PD can be found on careful motor examination in a considerable number of the heterozygous mutation carriers who consider themselves asymptomatic. Furthermore, it could be argued that at least some of the controls had not yet reached the age of their disease onset. Second, the heterozygous offspring of homozygous or compound heterozygous mutation carriers could be examined in a prospective manner, an approach that is currently being used in several cohorts. The probability that a second mutation might have been overlooked in these carriers is much lower than the probability of a mutation being missed in sporadic cases of PD. Last, further functional studies of the affected allele carriers would be highly valuable. Haploinsufficiency, leading to a functional loss of heterozygosity or a dominant-negative effect of some mutant alleles, could explain why a second mutation cannot (and need not) be found for some mutations in the above-

mentioned recessive genes. Although the role of heterozygous mutations in the development of clinical signs currently remains a matter for debate, there is growing evidence that they are associated with pre clinical changes. PET studies have revealed reduced [18F]fluoro-dopa uptake by nerve terminals in the striatum of heterozygotes; there are also structural neuroimaging changes that indicate an increased deposition of metals in the substantia nigra, and there is reorganization of striatocortical motor loops with detectable changes in connectivity patterns.These collective data have important implications. Some carriers of heterozygous mutations might be in the preclinical period of PD, thereby affording unique opportunities to examine the relative risk associated with the affected allele and to study the natural history of the disease. This group also represents an ideal study population to be used not only to investigate compensatory mechanisms, facilitating the development of a sensitive surrogate marker, but also to detect the earliest PD-specific changes, allowing the development of urgently needed clinical biomarkers. Finally, these individuals could provide a small, but important, target population in which to evaluate the 'proof of principle' of a therapeutic intervention in future neuroprotection trials.

6. Sporadic PD

Sporadic PD is multifactorial, complex and polygenic, generally determined by several common non-coding genetic variants, each of them play a role as a very modest risk factor singularly but with an important cumulative effect taken all together, interacting with environmental factors, other genes or functional variants, controlling the expression, splicing, phosphorylation, influencing the age at onset, severity and progression of the syndrome.

Association studies have been widely used in an attempt to identify common genetic variations that carry a mild to moderately increased risk to develop a disease. Over the years, literally hundreds of studies have been published, but unfortunately, only very few of them have produced robust and reproducible results. Several are the reasons which can justify the failure of this approach: most studies were greatly underpowered in relation to the small increases in the relative risk that today are known to be conferred by common genetic variants (usually the odds ratios are in the range of 1.2–2, with some exceptions, for example apolipoprotein E for AD). Then the choice of candidate genes was often based on rather arbitrary rationales with very weak experimental or epidemiologic evidence. As the gene-mapping studies in monogenic diseases have shown, newly identified genes most often could not have been predicted based on the current knowledge of pathogenesis. Furthermore in most studies only arbitrarily chosen individual genetic variants were investigated, thus it was a priori unlikely that the causative variant or a variant in high linkage disequilibrium, tagging the risk-conferring variant, would be among those studied. Finally, it is not easy to match patient and control cohorts with respect to their genetic background. Often, due to different recruiting strategies, these cohorts differ in their genetic composition (a problem called undetected population stratification, which today can be easily resolved in GWAS, see below). Due to different allele frequencies in different populations, spurious associations can be detected.

In the idiopatic cases an attempt is made to evaluate the PD population as a whole, using association studies and non parametric linkage methodology and trying to define risk alleles that contribute to the sporadic form of the disease.

Common genetic variants in *SNCA* can increase the susceptibility for idiopatic PD, while the *LRRK2* p.G2019S mutation can cause sporadic PD. Recently GWAS discovered new genes associated with PD: *GBA*, *MAPT*, *GAK, BST1, HLA, LONGO1*and *LONGO2, PARK16, SYNPHILIN.*

6.1 SNCA (PARK1-4, 4q21)

Previous studies have found associations between Parkinson's disease and polymorphisms located within both the α-synuclein gene promoter and other gene regions. Particularly interesting is a complex polymorphic dinucleotide repeat polymorphism (NACP-REP1), located 10 kb upstream of the transcriptional start site of *SNCA*. In this case the number of dinucleotide repeats are directly linked to an higher risk to develop PD. Indeed the 263 haplotype is associated to the disease while the 259 one has a protective effect.

The *SNCA* gene consists in two haplotype blocks (genetic regions usually inherited as a single block, with a high degree of Linkage disequilibrium). The first block ranges from the promoter region to intron 4 while the second block includes exons 5 and 6 and the 3'-untraslated region. The second block gives the strongest association signal with PD. Becasuse the SNP variability is noncoding and not within a region of species-conserved sequence identity or a miRNA binding site, the biologic mechanism remain unclear. Alternative splicing, phosporilation, expression modification or even linkage disequilibrium with another functional variant within the gene have been hypothesized as possible mechanisms. Gene expression may also be influenced by epigenetic interactions, including methylation, recently implicated in the downregulation of *SNCA* gene expression, which may warrant further investigation.

6.2 LRRK2 (PARK8,12q12)

Even if mutation in *LRRK2* are the most common cause of familial autosomal dominant PD, the p.G2019S substitution is of special significance as it is frequently identified not only in autosomal dominant, but also sporadic PD. Thus, being the most common cause of PD. The mutation is particularly frequent in PD patients residing in, or having genealogical ties to North Africa or the Middle East. This phenomenon can be explained by the fact that most *LRRK2* p.G2019S substitution carriers originate from a common founder.

6.2.1 The LRRK2 c.6055G>A (p.G2019S) mutation

P.G2019S is located in the mitogen-activated protein kinase (MAP) domain of the LRRK2 protein. The identification of p.G2019S substitutions as the most common cause of both familial and sporadic PD has been a major breakthrough. The frequency of p.G2019S substitutions differ remarkably throughout the world. This is due to a common founder for most p.G2019S carriers, originating from the Middle East or North Africa. Two large studies on Lrrk2 p.G2019S parkinsonism conclude that the phenotype of Lrrk2 p.G2019S can not be distinguished from idiopathic PD. There are some indications of a more benign course of p.G2019S parkinsonism compared to idiopathic PD with a slower disease progression and less cognitive impairment. However, methodological issues may have contributed to these observations. The penetrance of Lrrk2 p.G2019S has been much debated over the last years. Hulihan et al. investigated sporadic PD in Tunisia and found a lifetime penetrance of 45% (95% CI: 20–100%) for p.G2019S substitution carriers. Healy et al. additionally included hereditary patients and estimated that 74% had PD by age 79 years. Interestingly,

homozygous p.G2019S carriers do not have more severe disease than heterozygous carriers, this lack of gene-dose effect is consistent with the hypothesis that the p.G2019S substitution increases kinase activity. The pathology of p.G2019S parkinsonism is consistent with LBD in most, but not all cases.

6.3 GBA (1q21)

GBA is responsible to cause Gaucher Disease, GD, when the mutation is present in homozigosity. Patients with GD and relatives have an increased susceptibility for PD (2-3 fold), susceptibility which can increase among different populations like Ashkenazi Jews (5-6 fold), when the mutation in the gene is present in heterozigosity. *GBA* encodes a lysosomal enzyme that cleaves glucocerebroside. As α-synuclein is in part degraded by chaperone-mediated lysosomal pathway, it is conceivable that *GBA* mutations may increase the risk for PD by altering cellular α-synuclein homeostasis. It is supposed that the pathologic effect is due to the lack of the physiologic function or gain of a toxic one. Neuropathologically, Lewy bodies are present in the hippocampal region, corresponding to Braak stages 5 and 6, indicating that the dementia can be very similar to Lewy bodies dementia. Phenotipically GBA mutations carriers present the clinical features of sporadic PD with an higher and more severe incidence of dementia, olphactory disfunction, bradikinesia and a lower frequency of rigidity.

6.4 MAPT (17q21.1)

MAPT, encodes for the microtubule associated protein tau. Risk alleles of the associated SNPs are in LD with the H1 haplotype. An association between *MAPT* locus and PD could seem surprising, given the classic separation of synucleinopathies and tauopathies but the role of *MAPT* in neurodegenerative diseases is well established and this association is biologically plausible, despite the lack of neuropathology in PD. The combination of risk variants in *MAPT* and *SNCA* doubles the risk of developing PD, supporting the idea that related pathways contribute to neurodegenerative diseases. Finally, although we do not understand the relationship between the *MAPT* locus and Parkinson disease, it is worth remembering that while *LRRK2* mutations usually give rise to a-synuclein pathology, they sometimes give rise to tangle pathology (Zimprich et al., 2004) and that, while *MAPT* mutations usually give rise to tangle pathology, they sometimes give rise to Lewy body pathology.
An association to *MAPT* is absent in the Asian population.

6.5 GAK (4p16)

GAK (cyclin G associated kinase, a cell cycle regulator) is a serine thereonine kinase. It is a particularly promising candidate because it is one of 137 genes shown to be differentially espressed in PD, with an 1.56 fold change in expression in the substantia nigra pars compacta of PD patients compared to controls. Protective role postulated: decreased in expression or depletion enhance alpha-synuclein toxicity.

6.6 BST1 (4p15)

BST1(bone marrow stromal cell antigen) catalyses the formation of cyclic ADP-ribose (cADPR). cADPR mobilizes calcium (Ca2+) from ryanodine sensitive intracellular Ca2+, stored in the endoplasmic reticulum. Distruption of the Ca2+ homeostasis has recently been

proposed of a possible cause of selective vulnerability of dopaminergic neurons in PD. Associated SNPs in the *BST1* region may modify ADP-ribosylcyclase activity, thus leading to Ca2+ dyshomeostasis in dopaminergic neurons.

6.7 HLA (HLA-DRA; HLA-DQ;HLA-DR (6p21.3)

The *HLA* variant that displayed the strongest statistical association with Parkinson's disease, rs3129882, is a noncoding polymorphism in intron 1 of *HLA-DRA*. The protein chains encoded by the closely linked *HLA-DRA* and *HLA-DRB* form the class II HLA-DR antigens that are expressed by antigen-presenting cells, including microglia in the brain, and which interact with T-cell receptors. HLA-DRB chains are highly variable and have been associated with numerous disorders, including multiple sclerosis, which, like Parkinson's disease, is a progressive neurodegenerative disorder. HLA-DRA, on the other hand, is practically monomorphic and therefore has not been investigated for disease association. The conventional explanation for this finding is that PD is associated with a classical polymorphic HLA antigen and that rs3129882 is a proxy for this antigen. Alternatively, the association of Parkinson's disease with an intronic *DRA* variant may reflect involvement of regulatory elements, which would be in line with Parkinson's disease–specific overexpression of DR antigens in substantia nigra. The evidence for genetic association of PD with HLA region, particularly when obtained from a hypothesis free-GWAS, where the entire genome is scanned without pre-existing bias towards any particular genes, lends strong and independent support to the involvement of neuroinflammation and humoral immunity in Parkinson's disease pathogenesis. Studies have shown elevated DR expression in the brain and cerebrospinal fluid of individual with PD. The sustained presence of reactive DR positive microglia has been observed in the substantia nigra of individuals with PD, as well as animals and humans affected with 1-methyl-4-phenyl-1,2,3,6,-tetrahydropiridine-induced (MPTP) parkinsonism. It is postulated that chronic immune activation and neuroinflammation occurs in response to an initial trigger, possibly related to alpha-synuclein accumulation, and produces neurotoxins and oxidative damage that could kill neurons. From a therapeutic perspective, vaccination aimed neutralizing neuroimmune dysfunction was recently shown to attenuate neurodegeneration in a Parkinson's disease model: further, NSAID use is associated with reduced reduced risk of developing PD in humans. The newly discovered association of PD with HLA region highlights the involvement of an important biological pathway in the etiology of the disease and point to a potential drug target that will stimulate research toward new therapies.

6.8 LINGO1 and LINGO2 (15q24.3)(9p21.2)

A significant overlap between the diagnoses of PD and essential tremor (ET) is frequently observed. In retrospective analyses, 6-20% of ET patients have been described to exhibit signs of Parkinsonism. A recent prospective study demonstrated that patients with ET have a four-fold elevated risk to develop PD over an observational period of 3.3 years. Conversely, a diagnosis of ET was proposed to be 5 to 10 times more likely in subjects with PD than in controls. Furthermore it has been demonstrated that the risk of ET in first-degree relatives of patients with PD is significantly elevated. A neuropatholgical study demonstrated the occurrence of Lewy bodies in the brainstem in an older subset of ET patients. Genetic variation in the leucine-rich repeat and Ig domain containing Nogo receptor interacting protein1, (LINGO1) and its paralog (LINGO2) was recently associated

with an increased risk of developing essential tremor (ET) and Parkinson's disease (PD). LINGO1 plays a role in early brain development and oligodendrocyte differentiation. Because of its presumed role in neural survival and myelination, LINGO1 has been targeted in vivo and in vitro in model of spinal cord injury, autoimmune encephalitis and PD.

6.9 PARK16(1q32)

The PARK16 region contains five functionally interesting candidate genes for PD etiology. *SLC41A1* is a magnesium (Mg2+) transporter. It is of interest that Mg2+ deficiency is thought to be an environmental risk factor for the amyotrophic lateral sclerosis (ALS)-parkinsonism/dementia complex. Furthermore, *RAB7L1* is a small GTP-binding protein that plays an important role in regulation of exo-and endocytotic pathways, and *NUCKS1* is a nuclear protein containing several consensus phosphorylation sites for casein kinase II and cyclin-dependent kinases of unknown function.

Although pathogenic mutations and risk alleles within the PARK16 locus seem to be rare in European ancestry populations, further molecular analyses within different populations are required to examine its biochemical role in PD.

6.10 Synphilin

The presynaptic protein synphilin 1 and its isoform 1A have been associated with PD. Synphilin is an interactor of α-synuclein and is modulated by parkin. Synphilin is widely expressed with highest levels in brain, heart and placenta.

6.11 Omi/HtrA2 (PARK 13, 2p12)

In vitro and *in vivo* studies strongly implicate loss of Omi/HtrA2 protein in disrupted mitochondrial homeostasis and subsequent cell death. Moreover, recent pathoanatomical studies indicate that Omi/HtrA2 represents a consistent pathological marker for neurodegeneration in different α-synucleinopathies (Kawamoto et al.,2008). Loss of Omi/HtrA2 function may contribute to a broader spectrum of neurodegeneration, as decreased levels of Omi/HtrA2 were demonstrated in brains of Huntington's disease patients. Therefore, while some genetic association studies provide no consistent support for an association of *Omi/HtrA2* and PD, functional studies suggest that further study of this gene in the context of neurodegenerative disorders is justified. We cannot exclude the possibility that other neurodegenerative diseases besides PD may be influenced by *Omi/HtrA*2 variations.

Recent discoveries from meta-analysis study of previous GWAS, identified 11 loci that surpassed the threshold for genome-wide significance ($p<5x10(-8)$). Six were already known loci (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK* and *LRRK2*) and 5 were newly identified loci (*ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11* and *CCDC62/HIP1R*) (International Parkinson's Disease Genomic Consortium, 2011)

ACMSD is involved in picolinic and quinolinic acid homoeostasis and is a possible therapeutic target for several disorders that affect the CNS. The locus identified near *STK39* has been associated with autism and infl ammatory status, although there have been no reports of this locus contributing to neurodegenerative phenotypes. The *LAMP3* locus might modulate neurosecretory function in PC12 cell lines.

HLA-DRB5 is involved in multiple sclerosis, immunocompetence, and histocompatibility. The association with Parkinson's disease at *HLA-DRB5* supports the theory that inflammatory factors are associated with the pathogenesis of PD.

7. Pathogenic pathways

Familial and sporadic PD present similar clinical features, which reinforce the hypothesis that common pathways might be at the basis of a so analogous phenotype. Generally dystonia appears as the first symptom in the familial cases, while gait impairment and postural instability are one of the first manifestation for the sporadic ones. Evidence is emerging that some of the pathways covered in the rare monogenic forms of PD: dysfunction or impairment of the ubiquitin-proteosome system and/or mytochondria, may play a direct role in the etiology of the common sporadic disorder and genetic variation contribute to the risk of developing PD.

So far, the proteins that have been linked to parkinsonism by genetic studies have roles in:

- mitochondrial function (α-synuclein, *PARKIN*, *PINK1*, *DJ-1*, *FBXO7*, *Omi/HtrA2*, *POLG1*)
- lysosome (*GBA*, *ATP13A2*)
- the ubiquitin–proteosome system (*PARKIN* and *UCHL1*)
- vescicle dynamics (α-synuclein),
- MAPKKK signaling (*LRRK2*),
- oxidative stress
- microtubule stability (*MAPT*)
- embryonic development (α-synuclein, *PARKIN*, *UCHL1*, *LRRK2*, *Omi/HtrA2*, *NURR1*, *PITX3*)

These disparate functions might overlap as they all lead to the age-associated dysfunction and death of dopaminergic neurons that characterize PD. However, the relationships between these functions are not direct and the connections between them are not immediately evident.

7.1 Mitochondrial dysfunction (α-synuclein, *PARKIN*, *PINK1*, *DJ-1*, *FBXO7*, *POLG1*, *Omi/HtrA2*)

The pathway that has come most clearly out of the analysis of the Mendelian genes is a mitochondrial damage repair pathway. α-synuclein has long been known to modulate mitochondrial function, but the mechanism remains unknown. A possible role in mitochondrial signaling has been hypothesized. Parkin enhances transcription and replication of mitochondrial DNA in proliferating cells. Furthermore, Parkin, an E3 ubiquitin ligase, and PINK1, a mitochondrial kinase, are involved in the elimination of damaged mitochondria. DJ-1, and possibly FBX07, another ubiquitin ligase, are also likely to play a role in the mitochondrial pathway. DJ-1 can protect the cell against oxidative stress and can also translocate to the mitochondria. (Cookson 2010). The similar phenotype can confirm a common role of these genes in the mitochondrial pathway (Paisan-Ruiz et al., 2010; Valente et al., 2004;Yamamura 2010).

POLG1 is a mitochondrial DNA polymerase (Polymerase gamma 1) of the inner membrane that synthesizes, replicates and repairs mitochondrial DNA. Several mutations within POLG1 have been associated with parkinsonism in addition to other clinical phenotypes.

HtrA2 also known as Omi (HtrA2/Omi) is serine protease localized to the inner membrane space of mitochondria. A variation within Omi (G399S) was found in four patients with late-

onset PD and a polymorphism (A141S) has been suggested to be a risk factor in Germans. Furthermore, a possible implication has been demonstrated by animal models: knocking out Omi in mice leads to neurodegeneration with features of motor neuron dysfunction, ataxia and parkinsonism with striatal damage.
In addition MPTP can damage in a selective way dopamine neurons and mitochondria causing parkinsonism. (Langston 1989).

7.2 Lysosome pathway (*GBA*, *ATP13A2*)

A second pathway that is likely to be involved in Parkinson disease clearly involves the lysosomes. Proteins with short half-lives are mostly degraded by the proteasome whereas most cytosolic proteins with half lives longer than 10 hours are degraded by the autophagy- lysosome pathway. Glucosecerebrosidase, GBA, and ATP13A2 are lysosomal enzymes. A role of GBA protein in PD is suggested by the clinical observation of association of PD with Gaucher's disease. Patients with this well characterized recessive neurometabolic disease, caused by mutation in the glucocerebrosidase gene (*GBA*) have a high prevalence of PD. Screening of PD patients for *GBA* mutations found a higher number of heterozygous mutations carriers as compared to healthy controls. *GBA* encodes a lysosomal enzyme that cleaves glucocerebroside. As α-synuclein is in part degraded by chaperone-mediated lysosomal pathway, it is possible that *GBA* mutations may increase the risk for PD by altering cellular α -synuclein homeostasis. Within the chaperone-mediated lysosomal uptake pathway α-synuclein binds lysosomal membrane receptors before being selectively translocated into the lysosome. Mutant α-synuclein also binds to receptors, but instead of being translocated sufficiently blocks not only its own uptake but also uptake of other substrates. Mutations in ATP13A2, a lysosomal ATPase, cause autosomal-recessive early onset PD further linking lysosomes to neurodegeneration

7.3 Ubiquitin proteosome pathway (*PARKIN*, *UCHL1*)

The ubiquitin proteasome pathway has been strongly implicated in PD pathogenesis. *Parkin* functions as an E3 ubiquitin ligase. Some disease causing mutations within parkin impair its ligase activity leading to intracellular accumulation of parkin substrates. Accumulation of potentially toxic proteins might be especially detrimental for vulnerable neurons like dopaminergic neurons. Furthermore a missense mutation has been described in *UCHL1*, a deubiquitylating enzyme. The I93M substitution decreases UCHL1 enzymatic activity in vitro. Deubiquitylation is an important process to recycle ubiquitin monomers from proteins that have been targeted to the proteasome. In addition overexpressed wildtype or mutant α-synuclein has been shown to inhibit proteasome function in vitro and in vivo, even if not directly involved in the proteosomal pathway.

7.4 Embryonic development (α-synuclein, *PARKIN*, *UCHL1*, *LRRK2*, *Omi/HtrA2*, *NURR1*, *PITX3*)

α-synuclein is important not only in brain but also in peripheral tissues during normal human prenatal development. From 15 to 23 gestational weeks α-synuclein is expressed in almost all fetal human organs while in adult human tissues an high alpha-synuclein expression can be observed only in the brain.

Parkin expression is correlated with cell maturation and implicates a physiological role of parkin in various types of neurons. *UCHL1* is highly expressed in cultured NPCs (neural progenitor cells) as well as in embryonic brain in general. UCHL1 has been shown to be involved in regulating morphology of NPCs and in mediating neurogenesis. Involvement of *LRRK2* in neurite outgrowth might explain high expression levels in the first two or three weeks after birth. *Omi/HtrA2* is found in various fetal tissues. Loss of Omi/HtrA2 (mouse mutant mnd2, motor neuron degeneration2) leads to muscle wasting, neurodegeneration, involution of the spleen and thymus, and death by 40 days of age. Since dopaminergic neurons have long been central to PD research and genes involved in development of these cells deserve special attention. Dominant mutations in *Nurr1* have been reported in families with late onset PD. Nurr1, a member of the nuclear receptor superfamily of transcription factors is critically involved in the development of ventral midbrain dopaminergic neurons. Mutations within *Nurr1* have not been found again, association studies turned out to be negative in most studies. In addition (mice deficient for *PITX3*), a homeobox transcription factor, which is expressed from E11 to adulthood, fail to develop dopaminergic neurons of the substantia nigra . Taken together several PD associated genes are expressed during development. The potential involvement of these genes in early stages of the disease remains to be determined. Additionally PD is by no means restricted to dopaminergic neurons. It will be of great interest to identify genes with involvement in developmental stages of several cell types affected in PD.

Numerous working models have been proposed to integrate the complexities of environmental, biochemical, genetic and neuropathological evidence. However, a more simplicistic model of PD pathogenesis depicts a progressive imbalance between the forces that promote degeneration of at risk neurons by increasing mitochondrial dysfunction and oxidative stress during the aging process, and those that encompass individual or integrated cellular-defense mechanism.

Genetic therapy should move forward, aiming to restabilize the balance between these antagonist forces: enhancing the neuroprotective ones (*PRKN, DJ-1, PINK1*) and/or stopping and silencing potentiallty harmful effects ones (*SNCA*, *LRRK2*)

8. Pathological mechanisms in neurodegenerative diseases

Parkinson's disease is a progressive neurodegenerative disease which shares genetic influences and pathways with other neurodegenerative diseases like Alzheimer's disease (AD). Specifically, common pathways involve protein aggregation and neuroinflammatory process.

Several lines of investigation have now converged to show that the etiologies of AD and PD share common mechanisms (Bossy-Wetzel et al., 2004). One of the commonalities between AD and PD is the extra and intracellular accumulation of protein aggregates rich in β-pleated sheet conformation, representing the hallmarks of these two slowly progressive neurodegenerative disorders. Such protein aggregates might arise, in part, as a consequence of impaired proteasomal and/or autophagic removal of the damaged proteins (Taylor et al., 2002; Bence et al., 2001). The conformational change that results in the accumulation of misfolded proteins — amyloid-β (Aβ) and tau in AD and α-synuclein in PD — is associated with progressive dysfunction and death of cells in selected brain areas, determining clinical presentation. The intermediate forms of pathogenic proteins such as oligomers and protofibrils are thought to have cytotoxic effects on neurons. There

is considerable overlap in the mechanisms by which oligomeric Aβ and α-synuclein damage and kill neurons that may include: oxidative stress and free radical formation, impaired bioenergetics and mitochondrial dysfunction, disruption of neuronal Golgi apparatus and transport, molecular chaperones, neurotrophins and "neuroinflammatory" processes.

While variability in several genes may influence the risk for developing one disease, single genes often affect the risk for more than one trait. This diversity is best exemplified by variability in the tau and alpha-synuclein (*SNCA*) proteins, which alter risk of PD (*MAPT* and *SNCA*), progressive sopranuclear palsy corticobasal degeneration (*MAPT*), and multiple system atrophy (*SNCA*).

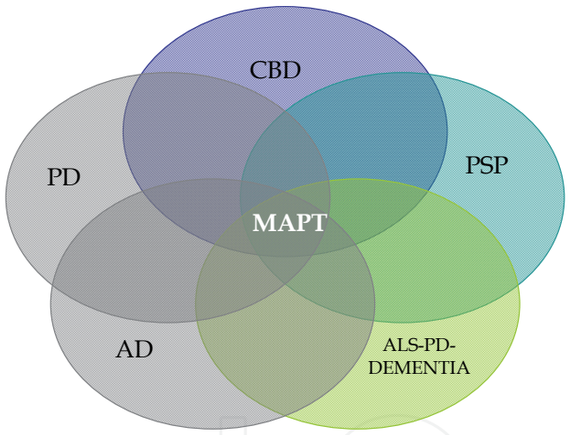

Fig. 2. Mutations and variants in the *MAPT* gene, encoding for tau protein, are involved in several neurodegenerative diseases, tauopathies: progressive sopranuclear palsy, PSP, corticobasal degeneration, CBD, Alzheimer disease, AD, Als-PD-dementia complex of Guam and Parkinson's disease.

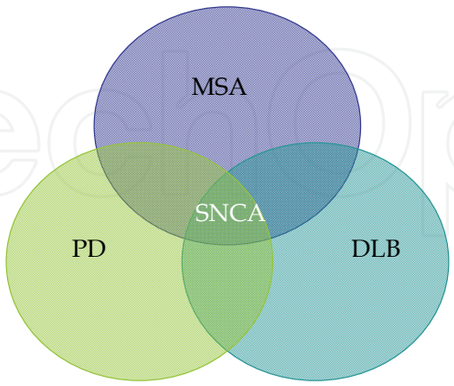

Fig. 3. Mutations and variations in the *SNCA* gene, encoding for α-synuclein, are involved in several neurodegenerative diseases, synucleinopathies: Parkinson's disease, PD, Multi system atrophy, MSA, Dementia with Lewy Bodies, DLB

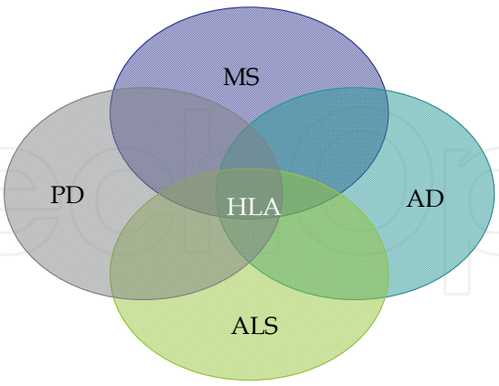

Fig. 4. Variations in the *HLA*, the major histocompatibility complex gene, are involved in several neurodegenerative diseases: Parkinson's disease, PD, Alzheimer disease, AD, Multiple sclerosis, MS, Amiotrofic Lateral Sclerosis, ALS.

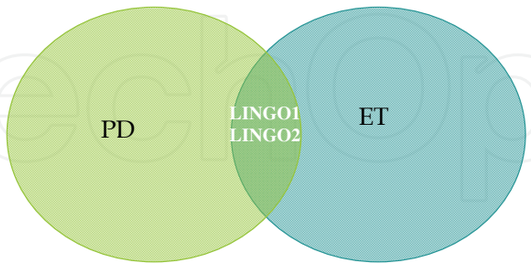

Fig. 5. Variations in *LINGO1* and *LINGO2* are risk factors for Parkinson's disease, PD, and essential tremor, ET.

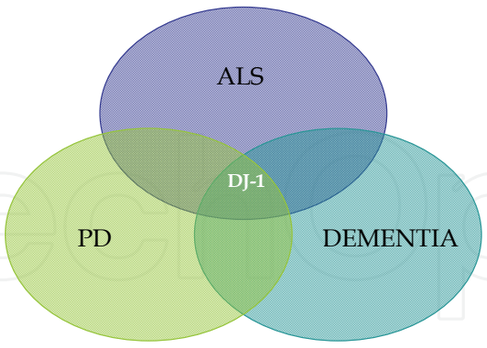

Fig. 6. Mutations in *DJ-1* can be involved in several neurodegenerative diseases: Parkinson's disease, PD, dementia and Amyotrophic Lateral Sclerosis, ALS.

Ultimately, a joint GWA study of a pooled population of individuals with Alzheimer's disease and Parkinson's disease might be a powerful approach to identify common genetic susceptibility factors for these diseases. One interesting model is that tau acts as a downstream factor involved in both β-amyloid and α-synuclein toxicity, with neurofibrillary tangles only forming in the presence of amyloid. Therefore, β-amyloid and α-synuclein might reinforce each other's effect on neurodegeneration in the aging population, and the relative proportions of each pathology could correlate with the extent of dementia or parkinsonism, respectively. Recent studies suggest that environmental factors may contribute to neurodegeneration through the induction of epigenetic modifications, such as DNA methylation, and chromatin remodeling, which may induce alterations in gene expression programs. Epigenetics, which refers to any process that modifies gene activity without changing the actual DNA sequence, and leads to modifications that can be transmitted to daughter cells, is a relatively novel area of research that is currently attracting a high level of interest. Epigenetic modulation is present since the prenatal stages, and the aging process is now accepted to be associated with a loss of phenotypic plasticity to epigenetic modifications. Since aging is the most important risk factor for idiopathic AD and PD, it is expected that epigenetic alterations on DNA and/or chromatin structure may also accumulate during neurodegeneration, explaining to some extent the etiology of these chronic and progressive disorders.

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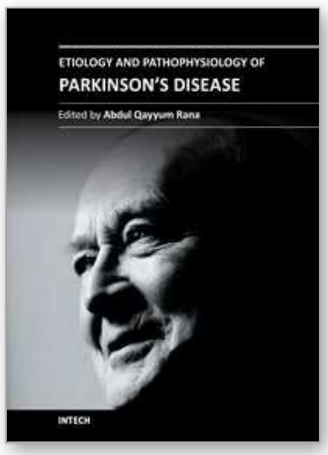

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This book about Parkinsonâ€™s disease provides a detailed account of etiology and pathophysiology of Parkinsonâ€™s disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinsonâ€™s disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinsonâ€™s disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinsonâ€™s disease.

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