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Genes associated with Parkinson syndrome

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Abstract Genetic findings have changed our views on Parkinson's disease (PD) and parkinsonism, which will be collectively referred to as Parkinsonian Syndrome (PS) in the present manuscript. Mutations in several genes are found to cause monogenic forms of the disorder. Point mutations, duplications and triplications in the α-synuclein gene cause a rare dominant form of PS in families. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene have been identified as a much more common cause for dominant PS, especially in certain ethnic groups, while mutations in the parkin gene, in DJ-1, PINK1 and ATP13A2 cause autosomal recessive parkinsonism of early onset. The monogenic variants are important tools in identifying cellular pathways that also shed light on the molecular pathogenesis of sporadic PS and some of these genes may play a role in the etiology of the common sporadic form of PS. Here we add recent findings to a greatly challenging puzzle.

Key words Parkinson's disease · genetics · LRRK2 · synuclein · parkin · PINK1 · DJ1 · ATP13A2

Introduction

Parkinson disease (PD) is an entity with variable combinations of bradykinesia, rigidity, tremor and postural instability. These symptoms point towards a characteristic pattern of neurodegeneration indicating a loss of nigral dopaminergic neurons. Eosinophilic inclusions, so called Lewy bodies, are found in surviving dopaminergic neurons but also in other parts of the brain, and have been considered to be essential for the pathologic diagnosis of PD. Hardy et al. [22] emphasized the importance of distinguishing the clinical term *parkinsonism* from the clinicopathological entity referred to as PD. Here the term Parkinsonian Syndrome (PS) is used for *parkinsonism*/PD.

Genetic research in the past 10 years, in particular the mapping and cloning of genes which cause inher-

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ited forms of the disorder, has shown that PS is not one disease entity, but rather a heterogeneous group of diseases that are associated with a spectrum of clinical and pathological changes (PARK1 to PARK13 are shown in Table 1). Approximately 5 to 10 % of patients with the clinical picture of PS carry a mutation in one of the known genes that cause autosomal dominant or recessive forms of PS (monogenic PS). A positive family history is not always given, either because of recessive inheritance, or because of reduced penetrance of a dominant mutation. An early age at onset in many (but not all) patients with monogenic PS helps to distinguish inherited from sporadic cases. Although alterations in the genes identified account for only a small number of families, there is some evidence that these genes may also play a role in the much more common sporadic form of the disease. The putative functional interconnection of the encoded proteins in various cellular pathways, i.e. localization at the synapse, mitochondria and lysosomes, protein degradation, and developmental regulation, suggests that these genes could also play a role in sporadic PS.

PS-associated genes at the synapse: α-synuclein, parkin, LRRK2, UCHL1, synphilin

As the name already implies α-*synuclein* (α-SYN, SNCA, PARK1) was initially identified as a synaptic and nuclear protein [49]. Despite intensive studies the exact role of α-SYN at the synapse remains elusive. There is evidence that the protein plays a role in maintenance of synaptic vesicle pools [53] and activity-dependent dopamine release [1]. α-SYN knockout mice have little or no obvious phenotype, but interestingly α-SYN was able to rescue the severe phenotype of knockout mice for the presynaptic cysteine-string protein [8]. In an elegant study from 2006 Larsen et al. [40] provide evidence that α-SYN might modulate synaptic vesicle priming. How does α-SYN relate to PS?

The PARK1 locus was mapped in a large family with dominantly inherited PS and Lewy body pathology [61]. Two additional point mutations have been identified [35, 91] each in a large, dominant family, reflecting the high penetrance of these mutations. α-Synuclein point mutations are very rare and have not been found in sporadic PS [3].

α-SYN is the major fibrillar component of the Lewy body [77] in familial and in sporadic cases. Hypothetically amino acid changes in the α-SYN protein but also duplications and triplications result in an increase of α-SYN levels leading to a tendency of the protein to form oligomers and later fibrillar aggregates although the precise relationship between aggregation, cellular dysfunction and cell death underlying PS is unknown. Recently aggregates have been described to also be present in the presynaptic compartment in addition to cell body and neurites [34]. Increased cellular load of α-SYN protein by 50 to 100 % causes familial PS with high penetrance (multiplication of the gene) [76]. Alterations in regulatory regions of the gene may also be associated with a higher risk to develop the disease. Multiple studies found nucleotide polymorphisms located close to the promoter region and throughout the gene to be associated with sporadic PS (PDGene database). Since α-SYN levels presumably affect synaptic function, it is tempting to speculate that this might lead to early and presymptomatic changes in vulnerable neurons.

Parkin (PRKN, PARK2) was the first gene identified for an autosomal recessive form of PS. Parkin protein localizes, although not predominantly, to the synapse and associates with membranes [36, 17]. In general parkin is a cytoplasmic protein and functions in the cellular ubiquitination/protein degradation pathway as an ubiquitin ligase [73, 95]. Interestingly parkin is involved in the modulation and in the turnover of several presynaptic proteins (summarized by Moore [52]). α-SYN and the α-SYN-binding synaptic protein synphilin are two prominent examples. In addition parkin has been shown to modulate the function of a G-protein coupled receptor (GPR37) that interacts with the dopamine transporter DAT [48].

Mutations within parkin were identified in patients with very early onset of the disease. This form of PS was also called autosomal recessive juvenile parkinsonism (AR-JP). Clinically, patients suffer from L-dopa-responsive parkinsonism and often develop early and severe levodopa-induced motor fluctuations and dyskinesias [31]. Nearly 50 % of sibling pairs with evidence of recessive inheritance and the majority of sporadic cases with very early onset were found to have parkin mutations [47]. Parkin mutations are rare in sporadic cases with onset later than 45 years. As mutations in parkin most probably cause parkinsonism by a loss-of-function mechanism, the study of the normal function of parkin is crucial to uncover the molecular pathogenesis of the disorder.

Another locus for a dominant form of PS was first mapped in a Japanese family on chromosome 12 and named PARK8 [19]. Missense mutations in the gene for leucine-rich repeat kinase 2 (*LRRK2*) [57, 96] were found to be disease causing. LRRK2-associated PS is remarkable for several reasons. First, mutations in the LRRK2 gene are clearly the most common cause of inherited PS discovered so far. In a number of studies across several different populations 4 % of all families with PS carry the common G2019S mutation within LRRK2 with highest frequencies of up to 40 % in the Ashkenazi Jewish population [25]. A common variant, G2385R, was found in approximately 9 % of Chinese patients with PS [18, 82], but also in about 3 % of controls, suggesting that specific mutations in the LRRK2 gene may act more as

Table 1 Summary of PARK1-PARK13 expression patterns (for references, please see text)

Locus/ gene	Inheritance	Onset	Pathology	Map position	Gene	Tissue specificity	Cellular localization in neurons	Expression during development
PARK1	Dominant	40's	nigral degeneration with Lewy-bodies	4q21	α-synuclein	expressed everywhere except liver	presynaptic terminal, nucleus	embryonic expression, all tissues
PARK2	Recessive	20–40	nigral degeneration without Lewy-bodies,	6q25	Parkin	brain, heart, muscle, testis	ubiquitous	embryonic expression, all tissues
PARK3	Dominant	60's	nigral degeneration with Lewy-bodies, Plaques and tangles in some	2p13	?	?	?	?
PARK4	Dominant	30's	nigral degeneration with Lewy-bodies, vacuoles in neurons of the hippocampus	4q21	α-synuclein triplications and duplications	expressed everywhere except liver	presynaptic terminal, nucleus	embryonic expression, all tissues
PARK5	Dominant	~50	no pathology reported	4p14	ubiquitin C-terminal hydrolase L1	brain, neuroendocrine system, ovary	cell body and processes	embryonic expression, especially studied in NPCs
PARK6	Recessive	30–40	no pathology reported	1p35-37	PINK1	highly expressed in heart, skeletal muscle, testis, lower levels in brain, placenta, liver, kidney, pancreas, prostate, ovary and small intestine	mitochondrial, cytoplasmic	embryonic expression in testis, otherwise unknown
PARK7	Recessive	30–40	no pathology reported	1p38	DJ-1	pancreas, kidney, skeletal muscle, liver, testis, heart, lower levels in brain, placenta	cytoplasmic, nuclear, mitochdrial	unknown
PARK8	Dominant	~60	variable α-synuclein and tau pathology	12cen	LRRK2	ubiquitous	ubiquitous	embryonic expression in various tissues
PARK9	Recessive	20–40	no pathology reported	1p36	ATP13A2	ubiquitous	lysosome	unknown
PARK10	Dominant (?)	50–60	no pathology reported	1p32	?	?	?	?
PARK11	Dominant (?)	Late	no pathology reported	2q34	GIGYF2	heart, liver, kidney, brain and lung	?	?
PARK12	X-linked	Late	no pathology reported	Xq31	?	?	?	?
PARK13	?	Late	no pathology reported	2p12	OmiHtrA2	expressed everywhere	inner membrane space of mitochondria	embryonic expression in various tissues

risk alleles rather than as high penetrance disease genes. Clinical signs and symptoms of LRRK2-related disease closely resemble typical sporadic PS. Many groups immediately started to study altered function of mutated LRRK2 which is of great importance for the understanding of molecular pathways leading to PS. One year after the first description of mutated LRRK2 West et al. [89] was the first to succeed in cloning the 51 exon long gene and most interestingly showed that mutated overexpressed protein has increased kinase activity in vitro. Endogenous LRRK2 is ubiquitiously expressed within neurons and associates with membranes and lipid rafts [4, 23]. The protein is found in presynaptic terminals where it associates with vesicles and endosomes. A deletion mutant for C.elegans *lrk-1* (lrk-1 is similar to mammalian LRRK1, a homolog of LRRK2), points towards a function in localizing synaptic vesicle proteins to terminals [68]. Recently it was shown that LRRK2 regulates synaptic vesicle endocytosis by directly interacting with the early endosome marker protein Rab5 [74].

UCHL1 stands for ubiquitin carboxy-terminal hydrolase L1 and is already suggesting one function of the protein (UCHL1, PARK5). A mutation (I93M) was identified in affected members of one single family of German ancestry [42]. To date, no other *bona fide* pathogenic mutations of this gene have been found. Whether UCHL1 really is a PS gene is not yet clear. Interestingly loss of UCHL1 function leads to neurodegeneration in mice [67]. Recently UCHL1 has been shown to improve cognitive impairment by strengthening synapses through the transcription factor CREB in a model of Alzheimer's disease [21].

Although not one of the canonical PARK genes, the presynaptic protein *synphilin 1* and its isoform 1A have been associated with PS [16]. Synphilin is an interactor of α-SYN and is modulated by parkin [10]. Synphilin is widely expressed with highest levels in brain, heart and placenta. One alteration within synphilin (R621C) had been identified in two German patients with sporadic PS [51], but recently this variant and two other variants (V44A and E706Q) were also found in controls [54]. Mouse models will hopefully shed light on the function of the protein.

PS-associated genes and mitochondria: *α-synuclein, parkin, PINK1, Omi/HtrA2, DJ-1, POLG1*

α-SYN has long been known to modulate mitochondrial function [13, 27], but the mechanism remains unknown. In a recent study Devi et al. [15] demonstrate the localization of α-SYN to the inner membrane of mitochondria. They identified a cryptic mitochondrial targeting signal in the N-terminus of the protein. In addition they provide evidence that accumulated α-SYN might interfere with complex I function. α-SYN may act as a modulator of oxidative stress [84] and α-SYN knockout mice are resistant to mitochondrial toxins [33].

Parkin has a role in mitochondrial morphogenesis during spermiogenesis [65]; it enhances mitochondrial biogenesis in proliferating cells through transcription and replication of mitochondrial DNA [39] and rescues mitochondrial dysfunction in PINK1 (PARK6) deficient flies [11]. Recently loss of parkin has been shown to worsen mitochondrial damage in α-SYN overexpressing mice [79].

Mutations in the *PINK1*-gene have been identified as a cause for autosomal recessive early-onset parkinsonism [86]. This gene is particularly interesting within the context of the findings linking PS to mitochondrial dysfunction and oxidative stress, as PINK1 encodes a primarily mitochondrial protein kinase. Mutations in the PINK1-gene are much less common than parkin mutations, and probably account for only 1 to 4 % of early-onset cases [24, 38, 66, 87].

The kinase PINK1 has been shown to be in a linear pathway upstream of parkin [11]. More recently the function of PINK1 was linked to the fission and fusion machinery in Drosophila and mammalian cell mitochondria [62, 90]. The first substrate of PINK1 to be reported was the mitochondrial chaperone TRAP1 (TNF receptor associated protein 1). By phosphorylation of TRAP1 PINK1 suppresses cytochrome c release from mitochondria and therefore protects against oxidative stress induced cell death. PS linked mutations within PINK1 impair its protective activity [63]. Another interesting finding has been described by Plun-Favreau et al. [60]. In a PINK1-dependent manner HtrA2 is phosphorylated upon activation of the p38 stress sensing pathway.

The serine protease HtrA2 also known as Omi (*HtrA2/Omi*) is localized to the inner membrane space of mitochondria [81]. Knocking out Omi in mice leads to neurodegeneration with features of motor neuron dysfunction, ataxia and parkinsonism with striatal damage [29]. Subsequently a variation within Omi (G399S) was found in four patients with late-onset PS and a polymorphism (A141S) has been suggested to be a risk factor in Germans [80]. In a recent study by Sanchez and Singleton [75] both variations were not associated with PS, although the authors did not exclude small genetic risk at the Omi/HtrA2 locus (PARK13).

Mutations in the *DJ-1* gene (PARK7) are another rare cause of autosomal recessive parkinsonism [6, 26]. The clinical picture with early-onset and slow progression is similar to the other recessive Parkinson syndromes. The normal function of DJ-1 and its role in dopamine cell degeneration is unknown, but there is evidence linking DJ-1 to oxidative stress response and mitochondrial function (summarized in [71]). Studies of the intracellular distribution of DJ-1 demonstrate that it is not only cytoplasmic but also present in the inner membrane

space and matrix of mitochondria [93]. Canet-Aviles et al. [7] have shown that wild-type DJ-1 translocates to the outer mitochondrial membrane upon oxidative stress which is associated with neuroprotection.

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 (see POLG mutation database).

PS-associated genes and the proteasome: *Parkin, UCHL1, α-synuclein*

The ubiquitin proteasome pathway has been strongly implicated in PS pathogenesis. *Parkin* functions as an E3 ubiquitin ligase [28, 73, 95]. Some disease causing mutations within parkin impair its ligase activity leading to intracellular accumulation of parkin substrates (reviewed by Lim and Tan [45]). Accumulation of potentially toxic proteins might be especially detrimental for vulnerable neurons like dopaminergic neurons as one example. However, parkin may have additional functions. For example it has been shown that parkin not only mediates ubiquitinylation via lysin48 (K48), which directs ubiquitinylated proteins to proteasomal degradation, but also via lysin63 (K63), which may play a role intracellular signaling processes and also in Lewy body formation [44].

Impairment of degradation of proteins through the proteasome has been further implicated in PS after a missense mutation has been described in *UCHL1*, a deubiquitylating enzyme. The I93M substitution decreases UCHL1 enzymatic activity in vitro [42]. Deubiquitylation is an important process to recycle ubiquitin monomers from proteins that have been targeted to the proteasome.

Although not directly involved in proteosomal degradation of proteins overexpressed wildtype or mutant α-*SYN* has been shown to inhibit proteasome function in vitro and in vivo [9, 78, 83, 94].

PS-associated genes and the lysosome: *α-synuclein, ATP13A2, GBA*

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 (recently reviewed by Pan et al. [58]). α-*SYN* levels increase after lysosomal inhibition suggesting that α-SYN is not only cleared by the proteasome [12]. Within the chaperone-mediated lysosomal uptake pathway α-SYN binds lysosomal membrane receptors before being selectively translocated into the lysosome. Mutant α-SYN also binds to receptors, but instead of being translocated sufficiently blocks not only its own uptake but also uptake of other substrates [12].

Mutations in *ATP13A2*, a lysosomal ATPase, cause autosomal-recessive early onset PS further linking lysosomes to neurodegeneration [64].

A role of another lysosomal protein in PS is suggested by the clinical observation of association of PS 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 PS. Screening of PS patients for GBA mutations found a higher number of heterozygous mutations carriers as compared to healthy controls [2]. GBA is a lysosomal enzyme that catalyzes the breakdown of the glycolipid glucosylceramide to ceramide and glucose.

PS-associated genes and embryonic stages of development: *α-synuclein, parkin, UCHL1, LRRK2, Omi/HtrA2, Nurr1, PITX3, microRNAs*

Western blot analysis from various human tissues from 15 to 23 gestational weeks show that α-*SYN* expression can be observed in all fetal human organs examined. In adult human tissues high expression of α-SYN is only maintained in brain. Within other organs expression levels were greatly reduced [46]. This suggests that α-SYN is important not only in brain but also in peripheral tissues during normal human prenatal development.

Parkin mRNA and protein is detected at embryonic day (E) E10/12 in mice and shows a widespread distribution in CNS and other organs with marked increase during midgestational development (E15-18) within the CNS followed by a steady increase until adulthood. Parkin expression is correlated with cell maturation and implicates a physiological role of parkin in various types of neurons [37].

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. In vitro studies with NPCs suggest that UCHL1 mediates neurogenesis in embryonic brain by regulating progenitor cell morphology [70].

LRRK2 mRNA can be detected around mouse embryonic day 15 with steady increase before birth in lung and kidney. In brain protein levels increase dramatically between postnatal day 0 and four weeks of age [5, 43]. Involvement of LRRK2 in neurite outgrowth might explain high expression levels in the first two or three weeks after birth.

α-SYN, parkin, LRRK2, DJ-1, Pink1 knockout mouse models are viable and fertile suggesting either dispensability of the gene product or redundancy due to crucial function. DJ-1 and Pink1 expression during early development has not been studied yet.

Omi/HtrA2 is found in various fetal tissues [55]. Loss of Omi/HtrA2 (mouse mutant mnd2, motor neuron degeneration 2) leads to muscle wasting, neurodegeneration, involution of the spleen and thymus, and death by 40 days of age [29].

Dopaminergic neurons have long been central to PS research and genes involved in development of these cells enjoy special attention. In 2002 Le et al. [41] reported dominant mutations in *Nurr1* in families with late onset PS. As a member of the nuclear receptor superfamily of transcription factors, Nurr1, is critically involved in development of ventral midbrain dopaminergic neurons [69, 92]. Mutations within Nurr1 have not been found again, association studies turned out to be negative in most studies (PDGene database).

Mice deficient for *PITX3*, a homeobox transcription factor, which is expressed from E11 to adulthood, fail to develop dopaminergic neurons of the substantia nigra [56]. Polymorphisms within in PITX3 have been positively and negatively associated with PS (PDGene database).

Abeliovich and his group [32] were the first to show that the *microRNA* miR-133b regulates maturation and function of midbrain dopaminergic neurons. Specifically expressed in these neurons miR-133b acts in a feedback circuit together with PITX3.

Taken together several PS associated genes are expressed during development. The potential involvement of these genes in early stages of the disease remains to be determined. Additionally PS 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 PS.

Association studies in sporadic PS patients

Most of the genes and mutations described in the previous paragraphs have been identified by genetic linkage analyses in individual families, implying that the mutations are disease causing with high penetrance. Nevertheless, specific mutations or variants in these genes have also been shown to act as risk alleles for the sporadic disease, rather than being truly causative.

The most commonly used procedure to search for risk alleles in sporadic disease is the association study, i.e. comparing the frequency of putative risk-alleles in cohorts of patients and controls. Many candidate genes have been studied in this way. Unfortunately, the vast majority of initially positive findings have failed to be reproducible. The cause for this poor record of association studies is probably the fact that most attempts have been underpowered, looking only at a few hundred patients and controls, which also carries the risk of false positive results, due to random fluctuations of allele frequencies and poorly matched controls. Interestingly, recent progress in whole genome association studies using high density array technologies provides the opportunity to generate much larger data sets by pooling different studies.

So far, the only risk alleles for sporadic PS that seem to be robustly reproducible across different populations appear to be single nucleotide variants in the 5' and 3' region of the α-synuclein gene (PDGene database), and several variants in the Tau gene [85], remarkably both genes that also harbor high penetrance disease causing mutations.

A specific polymorphism in the 3' untranslated region of FGF20 might modulate not only its own expression but also expression levels of α-synuclein through variation of a microRNA binding site [88] and many other potential risk factors have been described. Future studies will show if minor effects might be potentiated by combining risk factors and/or PS associated genes, or by looking at genes of one pathway with strong relevance to disease pathogenesis.

Another dominant locus had initially been mapped as a high penetrance disease gene in several large families on chromosome 2p13 (PARK3 [20]) but the gene has not yet been identified. Clinical features closely resemble those of sporadic PS. Interestingly, however, two independent recent reports implicate the PARK3-locus as a disease modifying locus influencing age at onset in two sib pair cohorts with PS [14, 59], and a European sib pair study also identified a linkage peak in this region [50]. A further study refined this association to a region containing the sepiapterine reductase gene [30], which was confirmed in another study [72]. Sepiapterine reductase is involved in dopamine synthesis. This finding may indicate that the SPR gene is modifying age of onset of PS.

Due to space limitations several other genes could not be discussed here. We apologize to all authors whose important contributions are not mentioned within this article.

Conclusion

Although genes that are linked to monogenic forms of PS and other closely related neurodegenerative diseases are, at first glance, not related to a common cause, recent genetic, pathologic and molecular studies have strengthened the evidence that the different genes and pathways could interact at several levels. These findings support the existence of several common pathogenic mechanisms at different sites within the cell and throughout different developmental stages.

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