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486 *Current Genomics,* **2013,** *14,* **486-501**

Genetic Insights into Sporadic Parkinson's Disease Pathogenesis

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Abstract: Intensive research over the last 15 years has led to the identification of several autosomal recessive and dominant genes that cause familial Parkinson's disease (PD). Importantly, the functional characterization of these genes has shed considerable insights into the molecular mechanisms underlying the etiology and pathogenesis of PD. Collectively; these studies implicate aberrant protein and mitochondrial homeostasis as key contributors to the development of PD, with oxidative stress likely acting as an important nexus between the two pathogenic events. Interestingly, recent genome-wide association studies (GWAS) have revealed variations in at least two of the identified familial PD genes (i.e. *α-synuclein* and *LRRK2*) as significant risk factors for the development of sporadic PD. At the same time, the studies also uncovered variability in novel alleles that is associated with increased risk for the disease. Additionally, *in-silico* meta-analyses of GWAS data have allowed major steps into the investigation of the roles of gene-gene and gene-environment interactions in sporadic PD. The emergent picture from the progress made thus far is that the etiology of sporadic PD is multi-factorial and presumably involves a complex interplay between a multitude of gene networks and the environment. Nonetheless, the biochemical pathways underlying familial and sporadic forms of PD are likely to be shared.

Received on: December 20, 2012- Revised on: September 09, 2013- Accepted on: October 22, 2013

Keywords: Alpha-synuclein, Parkin, LRRK2, PINK1, DJ-1, GWAS, Protein aggregation, Mitophagy.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. According to a recent report, more than 4 million individuals in Europe's five most and the world's ten most populous countries are currently afflicted with PD [1]. In less than 20 years' time (i.e. in 2030), the number of PD sufferers is projected to increase to close to 10 million, which is clearly a worrying trend. Clinically, the disease is attended by a constellation of motoric deficits including bradykinesia (slowness in movements), postural instability, rigidity and tremor that progressively worsen with age, which eventually leads to near total immobility. Although pathological changes are distributed in the PD brain [2], the principal neuropathology that underlies the characteristic motor phenotype of PD patients is unequivocally the loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) of the midbrain. This neuronal loss results in a severe depletion of striatal dopamine (DA) and thereby an impaired nigrostriatal system that otherwise allows an individual to execute proper, coordinated movements. Accompanying the SNpc neuronal loss is the presence of intra-neuronal protein inclusions known as Lewy bodies (LBs) in affected regions of the PD brain, which occurs in numbers that far exceed their occasional presence in the normal brain.

Despite nearly two centuries of research, the etiology of PD remains elusive. However, although most cases of PD occur in a sporadic manner, a subset of PD cases is inheritable and attributable to mutations in specific genetic locus. In particular, the recent identification and functional characterization of several genes linked to these disease-linked loci, including *α-synuclein*, *parkin*, *DJ-1*, *PINK1* and *LRRK2*, have provided tremendous insights into the molecular pathways underlying dopaminergic neurodegeneration. Collectively, these studies implicate aberrant protein and mitochondrial homeostasis as key contributors to the development of PD, with oxidative stress likely acting as an important nexus between the two pathogenic events. Because familial and sporadic forms of PD are often clinically and pathologically quite indistinguishable from each other, the pathogenic mechanisms involved are likely to be shared. Furthermore, recent genome-wide association studies have also revealed a genetic basis for sporadic PD, with two of the genes uncovered (i.e. *α-synuclein* and *LRRK2*) turning out to be familial PD-linked genes. Hence, learning about how dominant or recessive gene mutations cause familial PD could potentially inform us about the molecular pathogenesis of sporadic PD. Here, we shall discuss the contribution of familial PD-linked genes to the disease and their relevance to sporadic PD pathogenesis. We will also provide a brief update on the current knowledge regarding the genetic basis of sporadic PD, although readers are recommended to refer to the accompanying excellent review article on "*Genome-wide association studies in Parkinson's disease*" for more information.

AUTOSOMAL DOMINANT PD-LINKED GENES AND THEIR RELEVANCE TO SPORADIC PD

α-Synuclein (PARK 1 & 4)

SNCA encoding the presynaptic protein α-synuclein is the first causative PD gene identified in a large family of Italian

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1875-5488/13 $58.00+.00

descent with autosomal dominant PD and LB pathology [3]. The gene spans 117 kb at 4q21 and contains 6 exons, encoding a protein of 144 amino acids (Fig. **1**). Two types of disease-causing mutations have been identified in the *SNCA* gene - missense point mutations and whole locus amplification. Since its original discovery in the Italian family, the most common A53T *SNCA* point mutation has been found in several other ethnic groups including Greek [3-7], Korean [8, 9] and Swedish [10] families. Two additional *SNCA* disease-associated missense mutations uncovered to date are A30P [11] and E46K [12]. Whereas patients with the *SNCA* A30P substitution manifest clinical symptoms that closely resembling those with sporadic PD, i.e. with a late age-at-onset and a mild but progressive phenotype [11], E46K carriers display more severe parkinsonism, with an earlier age-at-onset that is accompanied by diffuse LB dementia [12]. More recently, several novel *SNCA* mutations have also been identified that may possibly contribute to sporadic PD. These include the A18T and pA29S substitutions in Polish patients [13] and a pH50Q variation in an English [14] and a Canadian patient [15]. The A18T and pA29S mutations replace highly conserved amino acid residues in the N-terminal amphipathic region of α-synuclein, potentially leading to structural changes. The H50Q mutation is predicted to shift the copper (Cu^{2+}) binding site of α-synuclein to its N-terminus thereby precluding the participation of other portions of the protein in Cu^{2+} binding. This is believed to reduce the affinity of α-synuclein for Cu^{2+} leading to elevated levels of Cu^{2+} that may be toxic to dopaminergic neurons. However, the pathogenicity of these newly discovered mutations remains to be confirmed by studies in cellular and animal experimental systems. Comparatively, multiplications of *SNCA* are more common than missense mutations. A triplication of *SNCA* (PARK4) was first identified in a large PD family [16]. Since then, *SNCA* multiplications have been discovered in several other families [17-25] with the severity of PD correlating with the gene dosage [16, 17, 20, 26].

Notwithstanding the difference between missense mutations and gene multiplication, both types of variation essentially result in the same pathogenic outcome, i.e. accumulation and aggregation of the α-synuclein protein. Notably, α-synuclein is typically unfolded (or intrinsically disordered) in its native state and is prone to misfolding because of its flexibility to adopt different conformations. Importantly, α-synuclein is a major component of LBs, which immediately suggests its role in sporadic PD pathogenesis (given that the inclusion body is a signature and a post-mortem diagnostic criterion for sporadic PD). Supporting this, *SNCA* duplications were reported in several cases of apparently sporadic PD patients [23, 24, 27-29]. Apart from gene multiplication, a longer allele resulting from complex dinucleotide repeat polymorphism in the promoter region of *SNCA* (NACP-Rep1) that increases expression of *SNCA in vitro* has also been associated with increased PD risk [30-36]. Many studies have further demonstrated a strong association between specific haplotypes in the *SNCA* locus and sporadic PD, suggesting that variations at the *SNCA* locus increases PD susceptibility [37-40]. More recently, using differential co-expression analysis to compare gene expression data sets from age-matched unaffected-control and PD patient SN at biopsy, Rhinn *et al.* [41] have identified an α-synuclein transcript isoform with a longer 3′UTR, aSynL. An elevated aSynL to total α-synuclein transcript ratio was found to be highly correlated with the PD brain, which appears to be specific to the disease as the correlation was not seen in other neurological disorders including Huntington's disease and Fronto-temporal dementia. Moreover, a common variant in the *SNCA* 3′ UTR associated with increased PD risk, rs356168, promoted the accumulation and translation of aSynL transcripts. Interestingly, the presence of intracellular DA can further enhance the relative abundance of aSynL transcripts through alternative poly-adenylation site selection, the modification of which can be regulated by two SNPs, rs356165 and rs78991202. *In vitro* assays using primary cortical neurons demonstrated that environmental risk factors associated with cellular oxidative stress and increased PD risk such as aging, exposure to rotenone or MPTP all increased the aSynL:total ratio. Conversely, nicotine exposure, which is associated with decreased PD risk, reduces this ratio. Intriguingly, the presence of the extended 3' UTR in aSynL transcript was observed to be sufficient to alter the

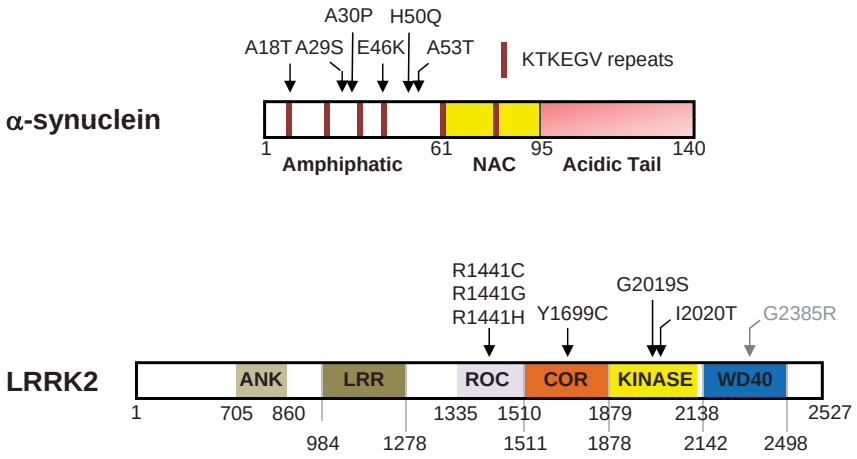

Fig. (1). Autosomal dominant PD-linked genes. Schematic depiction of the protein structure of α-synuclein and LRRK2 showing the various domains and the location of disease-associated missense mutations - including the G2385R "Asian risk variant" for LRRK2. (NAC, Non-amyloid component; ANK, Ankyrin-like repeats; LRR, Leucine-rich repeats; ROC, Ras of complex proteins - a GTPase domain; CPR, C-terminal of ROC).

accumulation of α-synuclein protein, which shifted away from synaptic terminals and towards mitochondria and soma structures, a phenomenon that is apparently reminiscent of PD pathology. Overall, the findings from this study suggest a potential convergent mechanism by which diverse genetic and environmental risk factors can lead to disease pathology through their influence on the abundance of α-synuclein transcripts. However, the precise mechanism by which alteration in transcript 3' UTR could affect protein localization and compartmentalization remains to be elucidated.

Even in the absence of genetic variation, it is obvious that any exogenous or endogenous event that could promote the accumulation/aggregation of α-synuclein would in theory be able to mimic the outcome of *SNCA* disease-associated variants. Not surprisingly, several groups have demonstrated in different experimental model systems that various exogenous neurotoxicants linked to PD, including pesticides, herbicides and metal ions, significantly accelerate the aggregation of α-synuclein [42-44]. Similarly, impairments in the protein quality control systems in the cell including those impacting on the chaperone, ubiquitin-proteasome and autophagy machineries can accelerate the accumulation and aggregation of α-synuclein [45]. In turn, α-synuclein accumulation and aggregation can act in a reciprocal fashion to promote derangements of these protein homeostasis apparatus, and thereby perpetuating a vicious cycle. Accumulated/aggregated α-synuclein that are not efficiently removed by the cell can physically disrupt cellular topography and/or interfere with normal cellular physiology, including provoking ER stress [46], mitochondrial dysfunction [47] and defective neurotransmission [48], which if prolonged, would eventually lead to the neuronal demise. Interestingly, cytosolic DA in dopaminergic neurons can interact with α-synuclein to form adducts that stabilize α-synuclein oligomeric intermediates [49]. These α-synuclein species are capable of forming pore-like structure to permeabilize membranes and vesicles, a physical disruption that no doubt can result in serious cellular injuries. Taken together, it is clear that α-synuclein plays an important role in both familial and sporadic forms of PD.

LRRK2 (PARK 8)

The LRRK2 gene comprises of 51 exons that encode a large multi-domain protein kinase of 2,527 amino-acid, which is capable of exhibiting a GTP-dependent phosphorylation activity (Fig. **1**) [50, 51]. Mutations in LRRK2 gene are currently recognized to be the most common genetic cause of familial PD worldwide (~7%) [52] with disease-associated mutations being represented in all functional domains of the protein [50, 53-55]. Importantly, LRRK2 mutations also contribute to sporadic PD. Clinically, LRRK2-related PD overlaps considerably with that of sporadic PD in terms of age of onset (typically late), motor symptoms, and responsiveness to DA replacement therapies [52, 56]. However, the neuropathology of LRRK2 patients can be quite heterogeneous in terms of the nature of inclusion bodies, which could be in the form of α-synuclein-positive LBs, tau-positive neurofibrillary tangles, ubiquitin-positive nuclear or cytoplasmic inclusions. In some cases, inclusion bodies are absent altogether.

According to data compiled from linkage and association analyses, at least 128 mutations have been identified in the protein coding exons of LRRK2 gene, the majority of which result in base substitutions (http://www.molgen.vib-ua.be/PDmutDB) [57, 58]. The highest frequency of mutations are located in exon 31 that encodes part of the ROC domain (50% of mutations accounting for 17.2% of cases) but the most penetrant mutations are found in exon 41 that encodes the kinase domain (33.3% of mutations accounting for 82.4% of cases). A recent large scale screen for LRRK2 mutations in 14,002 European subjects using deep sequencing has further increased the number of exonic mutations [59]. However, despite the large number of documented LRRK2 gene variations, pathogenicity has been firmly established only for R1441C, R1441G, Y1699C, G2019S, and I2020T substitutions. Among these, the G2019S substitution is the most frequent pathogenic mutation, causing 4–5% of familial and 1–2% of sporadic PD in populations of European descent, 30–40% of both familial and sporadic PD in Arab-Berber patients from North Africa and 10–30% in Ashkenazi Jews [60, 61]. This missense mutation is however rare among Asians. Instead, the LRRK2 G2385R risk variant occur more frequently in Asian populations [62]. In addition to risk variants, apparently protective alleles for PD have also been identified in the LRRK2 locus. For example, the variants R1398H and N551K have been found to associate with reduced PD risk in a multicenter Chinese study [61, 63].

Whereas protein aggregation typifies the features of aberrant α-synuclein species, elevated kinase and decreased GTPase activities are thought to underlie pathogenic LRRK2 mutations [64-71]. Consistent with this, LRRK2 mutations occurring outside of the catalytic domains do not appear to segregate with the disease. Accordingly, the inhibition of LRRK2 kinase activity (in theory) should be able to mitigate the toxicity of disease-associated LRRK2 mutants. Indeed, several recent studies using commercially available kinase inhibitors such as GW-5074 that are capable of suppressing LRRK2 kinase activity have demonstrated that this is the case, i.e. the strategy proved to be beneficial against LRRK2 G2019S-induced neurodegeneration both *in vitro* and *in vivo* [72-74]. More recently, Yao *et al.* [75] have described the use of a more potent and selective LRRK2 inhibitor originally developed by the Gray group [76] on a *C. elegans* model of LRRK2. They found that the inhibitor can rescue dopaminergic neurodegeneration and associated behavioral impairments in transgenic worms expressing human R1441C- and G2019S-LRRK2 but not in worms expressing inhibitor-resistant version of the LRRK2 mutants. Together, these results provide robust support to the proposal that elevated LRRK2 kinase activity underlies it neurotoxicity. Given this, the intuitive question to ask is what is/are the LRRK2 substrates whose hyperphosphorylation presumably drives mutant LRRK2-induced neurotoxicity? This is a hot topic that is currently being pursued by many labs around the world. Several LRRK2 candidate substrates have recently been proposed, such as the cytoskeletal-associated ERM (ezrin/radixin/moesin) family members [77], MAPK kinase family members [78], Ste20 serine/threonine kinase families [79], eukaryotic translation initiation factor 4E-binding protein (4E-BP) [80] and peroxiredoxin 3 (PRDX3) [81]. Although the various candidate proteins are interesting and

may be functionally relevant to PD, it is perhaps fair to say that their authenticity as *bona fide* substrates of LRRK2 is currently contentious. Indeed, the "best" substrate of LRRK2 at this moment appears to be the protein itself, which is capable of autophosphorylation.

Notwithstanding the above, whether and how the activity of LRRK2 might be elevated in cases of sporadic PD in cases where the protein is not mutated remains to be elucidated. In other words, can potential mis-regulation of the wild type protein contribute to sporadic PD pathogenesis? We and others have demonstrated that the mere elevation of wild-type LRRK2 expression, which presumably would lead to a mathematical increase in the activity, is insufficient to promote neurotoxicity (at least in the *Drosophila* model system) [82-84], although Liu *et al*. have reported otherwise [85]. However, wild type LRRK2-expressing cells treated with hydrogen peroxide exhibit significant cell death relative to untreated cultured cells, suggesting that exogenous factors can modulate LRRK2-associated toxicity [86]. In Asian populations, the polymorphic G2385R variant is known to increase the risk for PD. Although the variant behaves in large part like the wild type protein, we have shown using the *Drosophila* system that G2385R-expressing flies exposed to rotenone display marked degeneration in several DA neuronal clusters that are otherwise unaffected by normal aging [82]. Again, a possible interplay between the wild type protein and the environment is implicated here and may be relevant to sporadic PD pathogenesis. Interestingly, LRRK2 is present (albeit occasionally) as a component of LB [87], suggesting its potential interaction with α-synuclein. The relationship between LRRK2 and α-synuclein is however complex. For example, whereas some studies suggest that the loss of LRRK2 function reduces the aggregation and thereby toxicity of α-synuclein [88], others have demonstrated the accumulation of α-synuclein-positive inclusions (albeit in kidneys) following the ablation of LRRK2 in animals [89]. Yet another study found that neither deletion of LRRK2 nor the overexpression of human G2019S-LRRK2 has significant impact on the neurodegenerative phenotypes displayed by A53T α-synuclein transgenic mice, including premature lethality, pre-symptomatic behavioral deficits and α-synuclein or glial neuropathology [90]. Thus, unlike α-synuclein whose expression enhancement and/or impaired clearance can mimic the effects brought about by disease-associated mutations, a similar scenario for wild type LRRK2 in sporadic PD (particularly in relation to LB formation) is less straightforward to appreciate.

AUTOSOMAL RECESSIVE PD-LINKED GENES AND THEIR RELEVANCE TO SPORADIC PD

Parkin (PARK 2) and PINK1 (PARK 6)

First identified as the genetic cause of autosomal recessive juvenile Parkinsonism [91], *Parkin* mutations are now recognized as the most common known cause of early-onset PD (EOPD) accounting for about 50% of familial and 18% of sporadic EOPD cases in Europeans [92, 93]. A recent review of 43 previous studies comprising 3952 patients from various ethnic backgrounds attributed *Parkin* mutations to 15.5% and 4.3 % of familial and sporadic EOPD cases, respectively [94]. Interestingly, another recent study on EOPD in Mexican-metizo populations found *Parkin* mutations in as high as 61% of sporadic cases [91], suggesting that loss of Parkin function may be relevant to sporadic PD pathogenesis. To date, over 275 different mutations or genetic variants have been identified in the *Parkin* gene including deletions, insertions, exon rearrangements, amplification, as well as missense mutations (http://www.hgmd.org) (Fig. **2**). Among these, gene deletions represent the most common causative *Parkin* mutations [95-98] with mutation hotspots clustered around exons 3 and 4 [95, 99]. The unusually high rate of mutation in the *Parkin* locus may be due to its location within the common fragile site, FRA6E [100]. Aside from coding mutations, genetic variants in the non-coding regions of *Parkin* have also been associated with PD susceptibility [101]. Notably, a SNP (parkin −258G; rs9347683) in the promoter region of the *Parkin* gene has been implicated by several groups as a risk factor in older PD patients [101, 102], although at least one other study involving a large Caucasian cohort have failed to identify an association [103].

Although initially described as a recessive disorder, emerging evidence suggest that heterozygous *Parkin* mutations may also confer increased susceptibility to PD [104-107]. Indeed, single heterozygous mutations have been found to account for 43% and as high as 85% of *Parkin*-related EOPD cases [105, 106]. Further, first degree relatives of *Parkin*-associated PD patients who are carriers of heterozygous mutations were estimated to have a 4.1-fold higher risk of PD compared to non-carrier relatives [107]. Whilst *Parkin* haplo-insufficiency may explain for the increased risk for PD associated with single parkin mutations, the possibility that some *Parkin* heterozygous mutations may be pathogenic, although contentious, cannot be completely excluded. Moreover, certain missense mutations seem to be inherited in an autosomal dominant manner [108] and can apparently exert toxic effects when expressed *in vivo* [109].

Under normal conditions, parkin functions as an E3 ligase associated with the ubiquitin-proteasome system, a major proteolytic machinery that identifies and degrades unwanted intracellular proteins. Importantly, several groups have demonstrated that disease-associated parkin mutations compromise its role as an E3 enzyme [110-112]. A logical and popular hypothesis that ensued is that loss of parkin function could lead to a toxic accumulation of one or several of its substrates, thereby leading to neurodegeneration. This has led to intense effort by many laboratories around the world to identify the substrate(s) involved, with no less than 25 substrates (or putative substrates) of parkin being identified to date [113]. Like the situation with LRRK2 substrates, the authenticity of several of the reported parkin substrates remains questionable. Along the way, some surprises also came up in that parkin turned out to be a unique, multifunctional E3 ligase capable of mediating both proteasome-dependent (i.e. K48-linked) and proteasome-independent (i.e. K63-linked and mono) ubiquitination, with the latter modifications sub-serving different cellular roles including endocytosis and aggresome formation [114]. Importantly, we now know that parkin also plays an essential role in removing damaged mitochondria from the cell via a specialized form of autophagy known as "mitophagy" [115]. Parkin collaborates with PINK1 to do this and it is hardly surprising to note in retrospect that parkin and PINK1 models often exhibit shared mitochondrial features.

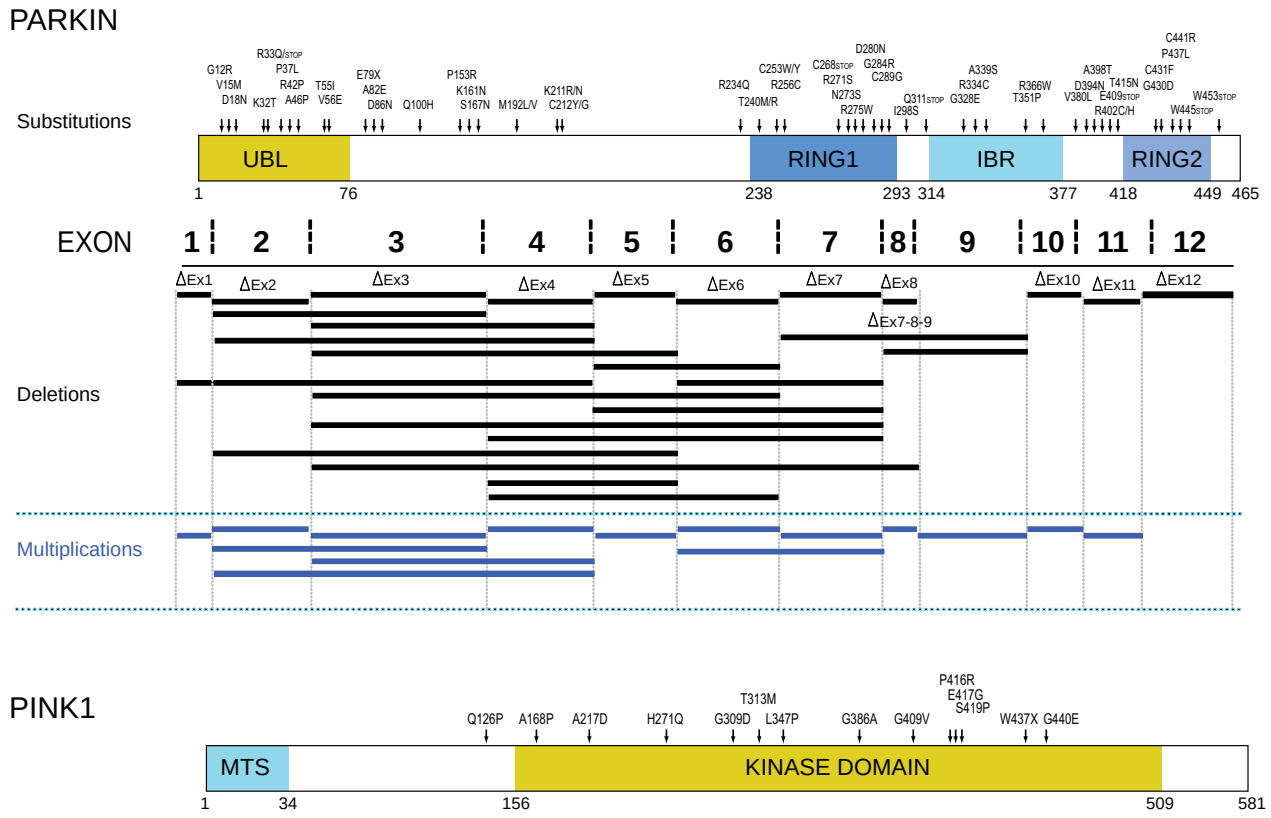

Fig. (2). Autosomal recessive PD-linked genes. Schematic depiction of the protein structure of parkin and PINK1 showing the various domains and the location of disease-associated mutations. (UBL, Ubiquitin-like domain; RING, Really Interesting New Gene domain; IBR, In-between RING domain; MTS, Mitochondrial targeting sequence).

Like parkin, mutations in the PTEN-induced putative kinase 1 (PINK1) gene on chromosome 1p35-36 (PARK6) also cause autosomal recessive EOPD [116]. Thus far, 138 PINK1 mutations have been reported of which 28 are classified as pathogenic (http://www.molgen.vib-ua.be/PDmutDB) [57, 58] causing mainly loss-of-function mutations comprising of substitutions, frame-shifts, truncations, splice site mutations and deletions [58] (Fig. **2**). Pathogenic PINK1 mutations are estimated to be ~20 times more common in Asian patients than in white patients (13.5% versus 0.6%) [94]. In addition to familial PD, PINK1 mutations account for 1–4% of sporadic EOPD. Similar to *Parkin*, a number of heterozygous variations have also been identified in familial and sporadic PD patients [117, 118]. These heterozygous carriers show a spectrum of disease phenotypes, ranging from severe parkinsonism to mild dopaminergic deficits [119-121].

As mentioned earlier, multiple lines of evidence suggest that parkin and PINK1 function together in the same pathway to tag and target defective mitochondria for degradation by mitophagy (For a recent review, please refer to [122]). Briefly, a key initial event that occurs upon mitochondrial depolarization is the selective accumulation of PINK1 in the outer membrane of the damaged organelle. Normally, PINK1 accumulation in healthy mitochondria is prevented by the sequential proteolytic actions of mitochondrial proteases that rapidly cleave the protein to generate an unstable 53 kDa PINK1 species that is usually degraded by the proteasome. In depolarized mitochondria, PINK1 stabilization on the outer membrane enables the protein to recruit parkin to the organelle. Mitochondrial-localized parkin then becomes activated and promotes the ubiquitination and subsequent degradation of many outer membrane proteins including the pro-fusion mitofusin proteins, the elimination of which is thought to prevent unintended fusion events involving damaged mitochondria and thereby their re-entry into undamaged mitochondrial network from occurring. Mitophagy induction then occurs.

Given the pivotal role of parkin/PINK1 pathway in mitochondrial quality control, it is conceivable that deficiency in parkin or PINK1 function can result mitochondrial dysfunction, as in the case with several parkin/PINK1-related PD models. A role for mitochondrial dysfunction in the pathogenesis of PD is rather compelling. Through post-mortem analysis performed as early as 1989, several groups have recorded a significant reduction in the activity of mitochondrial complex I as well as ubiquinone (co-enzyme Q10) in the SN of PD brains [123-125]. Moreover, mitochondrial poisoning recapitulates PD features in humans and represents a popular strategy to model the disease in animals [126]. Similarly, impairment of mitochondrial homeostasis via genetic ablation of TFAM, a mitochondrial transcription factor, in dopaminergic neurons of mice (named MitoPark mouse) results in energy crisis and neurodegeneration [127]. Thus the question here is not about whether mitochondrial dysfunction is relevant to sporadic PD but rather how parkin

and PINK1 may be involved in sporadic forms of the disease in the absence of apparent disease-causing mutations.

Unlike dominant mutations that represent a gain of new function, the role of recessive genes like parkin and PINK1 in sporadic PD is probably easier to envisage. For example, any intrinsic or extrinsic events that could result in the loss of function in the wild type protein can potentially mimic the outcome of loss-of-function mutations. Further, in view of the suggested contribution of genetic haplo-insufficiency to disease risk, it is reasonable to assume that the down-regulation of normal parkin (or PINK1) function mediated by such events need not result in the total abolition of its enzymatic activity to elicit a pathogenic effect. At least for parkin, several groups including ours have demonstrated that such disease mutation-mimicking events do happen. For example, we and others have found that a wide variety of PD-linked stressors, including those that produce oxidative and nitrosative stress, induce parkin solubility alterations and thereby its aggregation in a manner analogous to that brought about by several of its missense mutations [128-130]. Remarkably, DA also modifies parkin in a similar and rather selective fashion [128, 129, 131]. Accordingly, detergent-insoluble parkin accumulates in the PD brain [128, 129, 131]. As optimal level of soluble parkin is important for neuronal survival, the immobilization of the parkin within aggregates would not only deprive the protein of its function but also effectively reduce the pool of functional parkin available to the cell. Like haploinsufficiency, the biochemical depletion of soluble parkin levels is expected to increase the vulnerability of susceptible neurons to degeneration. Interestingly, normal parkin in the brain also becomes progressively more detergent-insoluble with aging (Pawlyk *et al.*, 2003), which may provide an explanation to why age represents a risk factor for PD.

Besides stress-induced modifications, parkin phosphorylation is another post-translational modification that can lead to its inactivation. Notably, casein kinase 1 (CK1) or cyclin-dependent kinase 5 (Cdk5)-mediated serine phosphorylation of parkin results in the down-regulation of its activity [132, 133], and compound phosphorylation of parkin by both kinases further leads to its aggregation [134]. While the physiological role of parkin phosphorylation remains unclear, it is conceivable that aberrant CK1 or Cdk5 activity can promote loss of parkin function and play a role in sporadic PD pathogenesis. Supporting this, parkin phosphorylation is elevated in distinct regions of sporadic PD brains and correlates with increased levels of p25, the activator of CDK5 [134]. In addition to serine phosphorylation, tyrosine phosphorylation of parkin at residue 143 (Y143) by the src family kinase member, c-Abl can similarly inactivates its enzyme activity and compromises its protective function both *in vitro* and *in vivo* [135]. Consistent with this, c-Abl appears activated and parkin is hyper-phosphorylated at Y143 in human post-mortem sporadic PD brains [135]. Taken together, it is apparent that loss of parkin function is not limited to those induced by disease-causing mutations, but also includes several biochemical modifications that can either alter the catalytic function of the E3 ligase directly, or indirectly through promoting its aggregation. Collectively, these mutation-independent modifications that inactivate parkin activity provide a mechanism for parkin dysfunction that is arguably relevant to the pathogenesis of sporadic PD.

DJ-1 (PARK 7)

Mutations in the DJ-1 gene are comparatively rare, accounting for about 0.4% of early-onset autosomal recessive PD [94]. The phenotype is characterized by slow progression and good response to levodopa, closely resembling the phenotypes caused by *Parkin* or *PINK1* mutations. The first disease mutations identified in DJ-1 were a large homozygous exonic deletion and a homozygous missense mutation, L166P, detected in consanguineous families from the Netherlands and Italy, respectively [136]. Since the identification of these prototype mutations, several other mutations and genetic variants have been reported for DJ-1 (http:// www.molgen.vib-ua.be/PDmutDB) including deletions, nucleotide substitutions in 5' untranslated or non-coding regions, and missense mutations [95, 137-146]. Many of these mutations and variants appear to be population-specific [147-152]. In a meta-analysis of studies spanning the last decade, DJ-1 mutations were found to be twice more likely to be present in familial than in sporadic PD, although this was not statistically significant due to the low number of cases [94].

DJ-1 encodes a 189 amino acid protein of the evolutionarily conserved ThiJ/PfPI superfamily of molecular chaperones and proteases [153, 154]. The protein is thought to operate as an atypical peroiredoxin-like peroxidase that is capable of scavenging mitochondrial H_20_2 [155]. Notably, a pool of DJ-1 is known to be localized to the mitochondria [155, 156] and increased levels of H_20_2 in mitochondria can be isolated from DJ-1 knockout mice [157]. Accordingly, the absence of DJ-1 may predispose dopaminergic neurons to oxidative stress-induced degeneration. Indeed, DJ-1-deficient animals are hypersensitive to pharmacological inducers of oxidative stress [158-163]. Consistent with this, dopaminergic neurons derived from *in vitro* differentiated DJ-1-deficient embryonic stem cells display decreased survival and increased sensitivity to oxidative stress [164]. Importantly, ablation of DJ-1 expression results in the amplification of basal oxidant stress in SN dopaminergic neurons [165]. As prolonged oxidative stress is intimately associated with protein aggregation and mitochondrial defects, it is not surprising to note that DJ-1 is also involved in both of these processes linked to PD. Several groups have demonstrated that DJ-1 may prevent α-synuclein aggregation [166, 167] and concomitantly mitigate the harmful effects of pathogenic α-synuclein mutants [168, 169]. More recently, DJ-1 was also reported to act in concert with parkin and PINK1 to regulate mitochondria dynamics [170-172]. Loss of DJ-1 led to fragmentation of mitochondria and increased autophagy in a mechanism dependent on oxidative stress which can be rescued by parkin and PINK1 overexpression.

Although exactly how DJ-1 function might be compromised in sporadic PD is unclear, the fact that DJ-1 mutations cause familial PD is perhaps the most direct genetic evidence supporting the oft-proposed role of oxidative stress in PD pathogenesis. There is certainly ample support from post-mortem studies to suggest that the redox state in the PD brain is in disequilibrium. For example, several groups have reported that markers for lipid peroxidation (including 4-hydroxynonenal and malondialdehyde), protein carbonyl modifications and even DNA and RNA oxidation are markedly elevated in the SN of post-mortem PD brains [173-176], and that these ROS-induced events are accompanied by a dramatic depletion of reduced glutathione (presumably leading to a considerably weakened antioxidant defense system)

[177]. Furthermore, DA itself can generate ROS via auto-oxidation or monoamine oxidase-catalyzed reactions. The participation of DJ-1, a redox-related protein, in PD is therefore one that aligns well with the oxidative stress hypothesis.

OTHER FAMILIAL PD-LINKED GENES AND THEIR RELEVANCE TO SPORADIC PD PATHOGENESIS

UCHL1 (PARK 5)

More than a decade ago, a missense mutation (I93M) in UCHL1, a deubiquitinating enzyme, was reported in a pair of German siblings with inherited PD [178]. Notably, the I93M UCHL1 mutant display markedly reduced ubiquitin hydrolase activity *in vitro*; suggesting that impaired polyubiquitin hydrolysis leading to a shortage of free ubiquitin might also promote the accumulation of toxic proteins and contribute to neuronal death. The relevance of UCHL1 I93M mutation in PD pathogenesis is however unclear as its occurrence to date is restricted to the pair of German siblings [178], although the discovery back then helped fuelled the hypothesis that disruption of the ubiquitin-proteasome system may underlie dopaminergic neuronal death in PD.

ATP13A2 (PARK 9)

ATP13A2 encodes for lysosomal P-type ATPase and loss of function mutations in this gene are causative of a juvenile and early-onset form of parkinsonism that is also characterized by pyramidal degeneration and dementia [179]. In patient-derived fibroblasts as well as in ATP13A2-silenced primary mouse neurons, deficient ATPase function results in impaired lysosomal degradation capacity that concomitantly enhanced the accumulation and toxicity of α-synuclein [180], which can otherwise be degraded by autophagy via the lysosome [181]. Importantly, silencing of endogenous α-synuclein ameliorated the toxicity in neurons depleted of ATP13A2, suggesting that ATP13A2-induced parkinsonism may be contributed by α-synuclein accumulation amid functional impairments of the lysosome. Supporting this, overexpression of wild type ATP13A2 suppresses α-synuclein-mediated toxicity in *C. elegans* while knockdown of ATP13A2 expression promotes the accumulation of misfolded α-synuclein in the animal [182]. Together, these studies demonstrate a functional link between ATP13A2-related lysosomal dysfunction and α-synuclein in promoting neurodegeneration. That ATP13A2 mutations are causal of the disease would provide a functional link between lysosomal dysfunction (thereby aberrant protein homeostasis) and PD pathogenesis.

GIGYF2 (PARK 11)

The *Grb10-Interacting GYF Protein-2* (*GIGYF2*) gene was proposed to be the causative gene for the PARK11 locus [183]. However, several follow-up studies by others in various populations have failed to replicate the data, which raises considerable doubt on the causal role of GIGYF2 [184]. Notably, abrogation of GIGYF2 function in zebrafish neither result in a drastic cell loss in diencephalic dopaminergic neuron clusters nor render them more vulnerable to the toxicity of the parkinsonian neurotoxin MPTP [185]. Thus, at this moment, GIGYF2 does not appear to play a major role in PD.

Omi/HtrA2 (PARK 13)

Although mutations of Omi/HtrA2 have been suggested to cause parkinsonism [186], their relevance to PD is also contentious because the purported disease-causing mutation is present in control population at similar frequencies (e.g. Omi/HtrA2 G399S) [187]. However, a recent study revealed that non-coding heterozygous Omi/HtrA2 mutations occurring in the non-coding regulatory regions of the gene segregate exclusively with patient populations [188], suggesting that aberrant Omi/HtrA2 expression may increase the risk for PD. Supporting this, loss of Omi/HtrA2 mitochondrial serine-protease function results in the alterations of mitochondrial morphology that include increased mitochondrial fusion leading to elongation of the organelle [189, 190], which again implicates a role for mitochondrial dysfunction in PD pathogenesis.

PLA2G6 (PARK 14)

Recently, *PLA2G6* was reported as the causative gene for PARK14-linked autosomal recessive early-onset dystonia-parkinsonism in Asian families [191], a finding that was reproduced by others in other Asian families [192, 193]. Affected individuals exhibit adult-onset, levodopa–responsive parkinsonism. PLA2G6 belongs to the calcium-independent phospholipases A2 family, members of which are involved in reactions that result in the release of arachidonic acid and other fatty acids. Recent evidence demonstrated that disease-causing mutations impair the catalytic activity of PLA2G6-mediated phospholipids-hydrolyzing function [193], suggesting the interesting possibility that aberrant lipid metabolism may also contribute to PD pathogenesis.

FBXO7 (PARK 15)

The FBXO7 gene, which encodes the F-box protein 7 (FBXO7) was recently reported to be the cause of autosomal recessive, early-onset parkinsonian-pyramidal syndrome that was previously mapped to PARK15 [194]. The finding has been replicated by others in at least two other families [195]. PARK15 patients exhibit parkinsonism (that respond well to levodopa therapy) that is often accompanied by pyramidal disturbances. FBXO7 is a member of the F-box-containing protein family, which typically function as part of the SCF (Skp1, Cullin1, F-box protein) ubiquitin ligase complexes involved in ubiquitin-mediated proteasomal degradation. Loss of FBXO7 function, like parkin, is therefore expected to disrupt protein homeostasis. Using the zebrafish model system, Zhao *et al.* performed a morpholino (MO)-based knock-down of the sole FBXO7 orthologous gene in the fish and observed that the morphants display dopaminergic neuronal loss and dopamine-dependent locomotor defects, which mirrors the characteristics of PD [196]. In an exciting recent development, Burchell and colleagues demonstrated that overexpression of FBXO7 can rescue loss of parkin function [197]. However, the protective mechanism involves the role of Fbxo7 in mitochondrial rather than protein homeostasis. Apparently, FBXO7 augments the translocation of parkin to damaged mitochondria during mitophagy, which promotes the process. In contrast, disease-associated mutations in FBXO7 interfere with parkin-mediated mitophagy.

VPS35 (PARK 17)

Using exome sequencing, a new and powerful sequencing platform, two recent studies independently identified a p.D620N mutation in the vacuolar protein sorting 35

(VPS35) gene as a possible cause for an autosomal dominant form of PD in families of Caucasian descent [198, 199]. Following this, a large multi-center study to determine the frequency and pathogenicity of VPS35 variants in PD in diverse populations worldwide has replicated the finding in familial cases and also identified the same variation in sporadic PD cases [200]. Functionally, VPS35 is a component of the retromer complex that associates with the cytosolic face of endosomes and mediates retrograde transport between endosomes and the trans-Golgi network. It is conceivable that VPS35 mutations can impair endosomal-lysosomal trafficking and consequently disrupt neuronal homeostasis.

GENETIC BASIS OF SPORADIC PD

By virtue of its sporadic nature of occurrence, the etiology of the common form of PD is often thought to be intractable. Moreover, the presumed involvement of environmental factors further complicates the picture. However, most would agree (especially these days) that hitherto unknown composite genetic susceptibility is likely to underlie sporadic PD pathogenesis. To address this, twin studies are particularly useful in distinguishing between the influence of genetics or the environment on the risks of a disease. If genetic factors predominate in etiology of a disease, it is expected that concordance in monozygotic (MZ) twins will be greater than dizygotic (DZ) twins. Using striatal ^{18}F[DOPA] positron emission tomography (PET) scan to detect dopaminergic dysfunction in asymptomatic co-twins of twin pairs with mostly sporadic and late-onset PD, Pecinni *et al.* [201] found a three-fold higher concordance rate for PD in MZ twins (55%) than in DZ twins (18%), suggesting a significant genetic contribution. Furthermore, when monitored over a period of 7 years, asymptomatic MZ co-twins all showed progressive loss of dopaminergic function and 4 developed clinical PD while none of the DZ twin pairs became clinically concordant. Similarly, recent longitudinal study carried out on Swedish twins with predominantly sporadic PD revealed concordance rates of 11% for MZ and 4% for same-sexed DZ twin pairs, with an overall heritability estimate of 34% [202].

Besides twin studies, the recent application of high-throughput whole genome and exome analysis technologies augmented by powerful bioinformatics has proved invaluable in the identification of novel susceptibility loci involved in apparent sporadic PD. Recent genome-wide association studies (GWAS) on European [203-206] and Asian [207] populations have identified *SNCA* and *MAPT* as consistent risk loci as well as implicated *BST1* (bone marrow stromal cell antigen 1) [207], *GAK* (cyclin G-associated kinase) *DGKQ* (diacylglycerol kinase, theta 110 kDa) [36], and *HLA-DR* (encoding a MHC class II cell surface receptor) [208]. More recently, meta-analyses of GWAS information have collectively identified and replicated a raft of additional risk loci including *GBA, ACMSD, STK39, NMD3, STBD1, GPNMB, FGF20, MMP16, STX1B, ITGA8, RIT2/SYT4, MCCC1/LAMP3, SYT11/RAB25,* and *CCDC62/HIP1R* [209-212]. Previously identified risk associated SNPs in PARK16 locus were mapped to the *RAB7L1* gene (a member of the Ras oncogene family) in two studies [209, 212]. Importantly, these studies additionally validated associations at *SNCA*, *LRRK2*, *MAPT*, *BST1*, *GAK* and *HLA-DR* (discussed in the next section).

Despite the success of GWAS in uncovering novel genetic variants in PD, it is predicted that many more variants remained to be discovered to account for vast heritable variations seen in PD. There is general consensus now that PD is a complex, polygenic disease and inherent risks may be expressed as quantitative trait loci (QTLs). In this respect, genome wide complex trait analysis [213, 214], a method that considers the collective effect of all SNPs regardless of the size of their influence rather than the association of individual SNPs with a particular trait, may prove useful for a more exhaustive screen for PD risk variants [215]. Indeed, the application of GCTA has led to the identification of *SCARB2* and *SREBF1/RAI1* as new loci, and *USP25* and *RIT2/SYT4* as potential novel regions [216]. The study also replicated seven previously reported loci *LRRK2*, *SNCA*, *GBA*, *MAPT*, *MCCC1/LAMP3*, *GAK/DGKQ* and *SLC41A1*. *RIT2* was later replicated in a meta-analysis [211]. Another challenging task is to ascribe functional meaning to these associations. To this end, groundbreaking efforts have begun to establish the relationship between SNPs identified by GWAS and gene expression levels. Latourelle *et al.* [217] examined the association between 67 SNPs in the *SNCA*, *MAPT*, *GAK/DGKQ*, *HLA* and *RIT2* loci observed to be strongly associated to PD risk [211] and gene expression levels in 26 PD and 24 control cortical brain samples in an effort to identify disease related expressed quantitative trait loci (eQTLs). *Cis*-acting effects of the SNPs were examined by looking at their influence on all probes within 250 kb of each locus. Several SNPs in the *MAPT* region show significant association to multiple nearby probes, including those targeting LOC644246, duplicated genes LRRC37A and LRRC37A2, DCAKD and also the HLA region on chromosome 6. When *trans*-effects of the SNPs were examined by observing their effects on the expression of 39,122 probes on a whole human genome microarray, an additional 23 SNP-probe associations reaching statistical significance were uncovered for SNPs in the *SNCA*, *MAPT* and *RIT2* regions. This approach provides insights into potential novel mechanisms underlying the observed SNP associations with PD etiology.

HLA-DR GENES AND NEUROINFLAMMATION IN SPORADIC PD

In recent years, the role of neuroinflammation in the pathogenesis of PD has gained considerable attention and recognition. The link between CNS inflammation and PD pathology was first proposed by McGeer *et al.* [218], who detected the upregulation of HLA antigens and the presence of activated microglia in post-mortem SN of sporadic PD patients, a finding subsequently corroborated by several other groups [219, 220]. Reactive microgliosis, or self-perpetuating microglial activation, in the midbrain of PD patients was confirmed by PET imaging [221]. Importantly, the extent of microglial activation in the midbrain has a positive correlation with the severity of motor symptoms in early PD and a negative correlation with dopaminergic (DA) fiber density in the striatum. Under normal circumstances, activated microglia play essential roles in neuronal survival by scavenging dead cells and cellular debris as well as secreting trophic and anti-inflammatory factors that have neuroprotective functions. However, when microglia become aberrantly overactivated, they can trigger deleterious effects to DA neu-

rons by the excess production of a number of cytotoxic factors such as nitric oxide (NO), superoxide, prostaglandin E2 and pro-inflammatory cytokines such as tumour necrosis factor-α (TNFα) and interleukin-1β (IL-1β).

Histological and experimental evidence for the role of the immune system in PD pathogenesis is corroborated by a growing body of genetic evidence. Polymorphisms in genes encoding for the immune molecules tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1) have been implicated as risk factors for PD [222, 223]. Clues of the possible associations between HLA-A, -B and -DQB1 with PD first emerged in the early 1980's from studies using low resolution genotyping in small patient cohorts [224, 225]. More recently, large-scale GWAS identified genetic susceptibility loci for late-onset sporadic PD in the HLA-DR regions in population of European ancestry - rs3129882 variant in HLA-DRA and chr6:32588205 variant in HLA-DRB5 [208, 210]. The rs3129882 variant was replicated in Han Chinese from mainland China [226]. Surprisingly, however, the rs3129882 variant was found to be inversely associated with PD risk in ethnic Chinese populations from South Asia [227]. This possibly underscores the polymorphic heterogeneity of the HLA region even amongst populations with seemingly recent common ancestry. Two regions within HLA-DRB1 have been found to be associated with PD risk - rs660895 in French patients [228] and *0301 in Han Chinese [229]. Both studies concurred in the finding that allele(s) within HLA-DRB1*04 is associated with lowered PD risk. A meta-analysis involving 195,205 individuals from various ethnic regions showed a higher frequency of HLAD RB1*0301 and a lower frequency of HLA-DRB1*0406 in populations of European descent than in Asians, prompting the speculation that this might account for the higher prevalence of sporadic PD in the former populations [229]. Although risk associations have been clearly established, the mechanistic contribution of HLA polymorphism to PD development remains to be elucidated.

CONCLUDING REMARKS

Taking stock of the information accrued thus far regarding the function of the various identified PD-linked genes, it is apparent some biochemical pathways are consistently implicated in disease pathogenesis (Table **1**). These include the ubiquitin-proteasome and autophagy pathways whose aberrations promote protein misfolding and aggregation (e.g. in α-synuclein, parkin, ATP13A2 and UCH-L1-related cases), mitochondrial-related pathways (e.g. in parkin, PINK1, Omi/HtrA2 and perhaps LRRK2-related cases), redox pathways (e.g. in DJ-1-related cases) and pathways involving aberrant protein phosphorylation (e.g. in LRRK2-related cases). Undoubtedly, new pathways (e.g. endosome and lipid metabolism pathways) will emerge following a better understanding of the genetics underpinning the disease. However, it is important to recognize that these pathways often act in a reciprocal fashion to influence one and another and that each of the PD-linked gene product when dysfunctional can impact on multiple pathways either directly or indirectly. For example, it is now clear that parkin function is relevant to both protein and mitochondrial homeostasis. Further, a role for LRRK2 in mitochondrial dysfunction has also been implicated recently [230]. Thus, PD pathogenesis would appear to be a result of a tapestry of events rather than of a single pathogenic pathway, which may explain in part why neuroprotective strategies directed at a single target/event gener-

Table 1. PD-linked Genes

Locus	Position	Gene	Inheritance	Function	Implications
PARK1 & 4	4q21-23	*α-synuclein (SNCA)*	Dominant	Unclear (presynaptic protein)	Protein aggregation
PARK2	6q25.2-27	*Parkin*	Recessive	Ubiquitin ligase	Aberrant protein & mitochondrial homeostasis
PARK3	2p13	*Unknown*	Dominant	-	
PARK5	4p14	*UCHL1*	Dominant	Ubiquitin hydrolase	Aberrant protein homeostasis
PARK6	1p35-36	*PINK1*	Recessive	Putative serine/threonine kinase	Aberrant mitochondrial homeostasis
PARK7	1p36	*DJ-1*	Recessive	Redox sensor	Oxidative stress
PARK8	12p11.2-q13.1	*LRRK2*	Dominant	Putative serine/threonine kinase	Aberrant phosphorylation
PARK9	1p36	*ATP13A2*	Recessive	Lysosomal P-type ATPase	Aberrant protein homeostasis
PARK10	1p32	*Unknown*	Unknown	-	
PARK11	2q37.1	*GIGYF2?*	Dominant	-	
PARK12	Xq21-q25	*Unknown*	Unknown	-	
PARK13	2p12	*Omi/HtrA2*	Dominant	Mitochondrial serine protease	Aberrant mitochondrial homeostasis?
PARK14	22q13.1	*PLA2G6*	Recessive	Phosopholipase	Aberrant lipid homeostasis?
PARK15	22q12-q13	*FBXO7*	Recessive	Component of SCF E3 complex	Aberrant protein homeostasis?
PARK16	1q32	*Unknown*	Unknown	-	
PARK17	16p12.1-q12.1	*VPS35*	Dominant	-	Aberrant endosomal recycling?

ally failed to produce clear benefits to the PD patient, notwithstanding that most trials are conducted with patients at a more advanced stage of the disease where substantial neuronal loss has already taken place and that the remaining surviving population of SN neurons have been chronically stressed. Nonetheless, we have learnt a great deal about the mechanisms underlying dopaminergic neuronal death in PD over the last 15 years as a result of intense effort in the identification and functional characterization of PD-linked genes. We anticipate that new and important insights regarding the genetic basis of PD will continue to be uncovered as technologies evolve to become more powerful in interrogating the genome, and along with this, the progressive clarification of the pathways underlying disease pathogenesis that would be of therapeutic value.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Research Foundation – Competitive Research Program, Singapore Millennium Foundation, A*STAR Biomedical Research Council (LKL) and the National Medical Research Council – New Investigator Grant (CC) and Exploratory/ Development Grant (LKL).

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