Parkinsonism and Related Disorders 20S1 (2014) S23–S28

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Genetics of Parkinson's disease – state of the art, 2013

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ARTICLE INFO

Keywords:
Parkinson's disease
Parkinsonism
Genetics
SNCA
LRRK2
VPS35
Parkin
PINK1
DJ-1
ATP13A2
PLA2G6
FBXO7
DNAJC6
SYNJ1

SUMMARY

In the past 15 years there has been substantial progress in our understanding of the genetics of Parkinson's disease (PD). Highly-penetrant mutations in different genes (*SNCA*, *LRRK2*, *VPS35*, *Parkin*, *PINK1*, and *DJ-1*) are known to cause rare monogenic forms of the disease. Furthermore, different variants with incomplete penetrance in the *LRRK2* and the *GBA* gene are strong risk factors for PD, and are especially prevalent in some populations. Last, common variants of small effect size, modulating the risk for PD, have been identified by genome-wide association studies in more than 20 chromosomal loci.

Here, I first outline the evolution of the research strategies to find PD-related genes, and then focus on recent advances in the field of the monogenic forms, including *VPS35* mutations in autosomal dominant PD, and *DNAJC6* and *SYNJ1* mutations in recessive forms of juvenile parkinsonism. Additional genetic determinants of PD likely remain to be identified, as the currently known mutations and variants only explain a minor fraction of the disease burden. There is great expectation that the new DNA sequencing technologies (exome and whole-genome sequencing) will bring us closer to the full resolution of the genetic landscape of PD.

1. Introduction

The genetic studies of the past 15 years have revolutionized the Parkinson's disease (PD) research field, and primed the development of innovative theories for its pathogenesis. The identification of mutations in the *SNCA* gene, causing rare inherited forms of the disease, led to the discovery of the α-synuclein protein as the main component of the Lewy bodies (LBs) [1]. Misfolding and aggregation of this protein into neurotoxic species, and cell-to-cell spread are currently considered central in the pathogenesis. Mutations in another gene, *LRRK2*, are a much more frequent cause of PD [2], but how these fit into the α-synuclein cascade remains unknown. Early-onset forms of parkinsonism are caused by mutations in an increasing number of genes, but whether these are part of the same pathogenetic pathways of the late-onset forms, remains doubtful. Genome-wide association studies identified common variants in more than 20 loci (including *SNCA* and *LRRK2*), modulating the risk of developing PD [3], but these variants only explain another minor fraction of the disease burden, suggesting that further genetic determinants remain to be discovered. Here, I briefly discuss the main research strategies to find PD-related genes, and then focus on the monogenic forms, highlighting the more recent advances in this area.

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2. Finding genes for PD – the research approaches

Most of the progress in this field has come from unbiased research strategies – the systematic scanning of the entire human genome without *a-priori* hypotheses on the nature of the causal gene or the pathogenetic mechanisms (Fig. 1). Traditional family-based genome-wide **linkage mapping** studies, followed by positional cloning, are well-suited and powerful for the identification of highly-penetrant "disease-causing" mutations, assuming that DNA samples from large families segregating the disease are accessible. In the case of PD, a clear Mendelian inheritance is rarely seen, and large families with several affected individuals with DNA available are also rare. The situation is easier in the forms with a recessive pattern of inheritance, because the analysis of only 2–3 affected siblings born from consanguineous parents might be informative enough to find a causative gene using homozygosity mapping. Further complications include the occurrence of incomplete penetrance, phenocopies, and variable clinical (or pathological) expressivity. Despite these difficulties, the meticulous analysis of large PD families proved successful in the identification of genes bearing highly-penetrant mutations that "cause" PD (Table 1). Perhaps not surprisingly, all these Mendelian mutations are rare, confirming that in most cases, PD does not behave as a Mendelian trait. The *LRRK2* gene is not an exception: the "common" Gly2019Ser (G2019S) mutation, present in up to 40% of PD cases in some populations, has a strongly reduced penetrance and should not be considered as a classical Mendelian mutation [4]. However, even if the Mendelian mutations are rarely causing PD,

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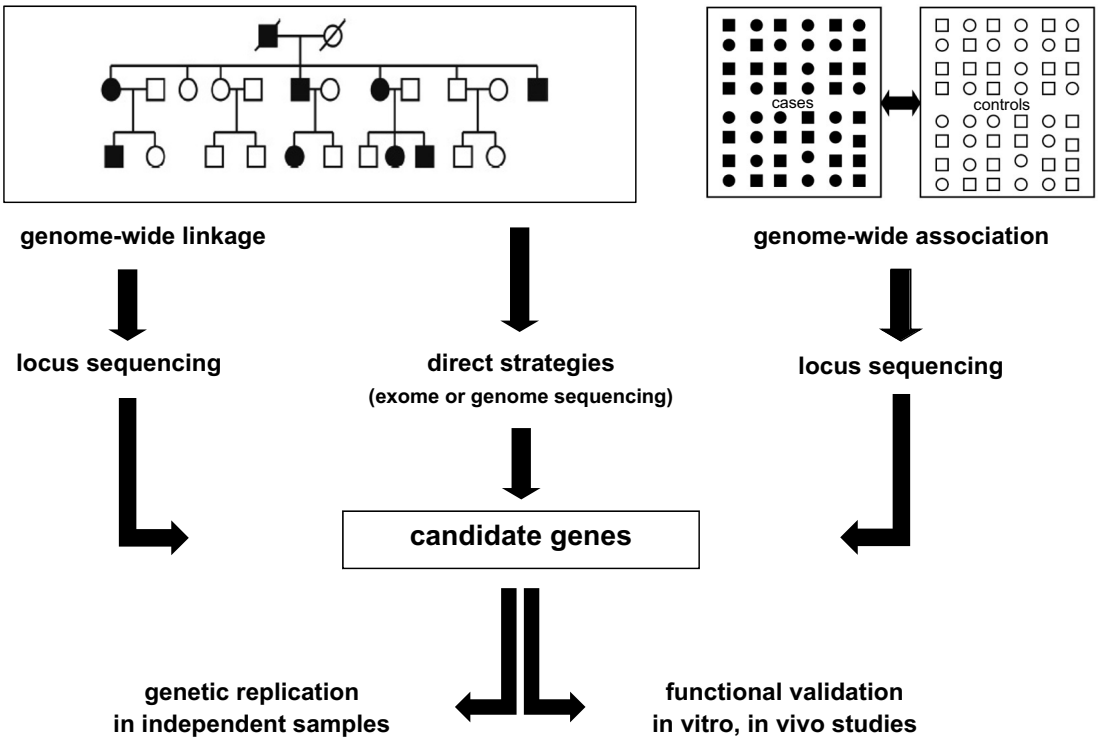

Fig. 1. Schematic representation of the current research strategies for finding genes related to human diseases.

Table 1
Confirmed genes implicated in monogenic parkinsonisms

Gene	Inheritance	Strategy	Pathological features	Clinical phenotype	Reference(s)
SNCA	Dominant	GW-linkage	LBs, atypical in some cases (MSA-like)	Earlier-onset PD, aggressive course	Polymeropoulos et al., 1997
LRRK2	Dominant	GW-linkage	Pleomorphic, typical LBs in most cases	Typical, late-onset PD	Zimprich et al., 2004; Paisan-Ruiz et al., 2004
GBA	Dominant	Candidate gene	Typical LBs	Typical, late-onset PD	Neudorfer et al., 1996; Aharon-Peretz et al., 2004
VPS35	Dominant	Exome sequencing	Unknown	Typical, late-onset PD	Zimprich et al., 2011; Vilariño-Güell et al., 2011
Parkin	Recessive	GW-linkage	No LBs in most cases	Early-onset PD, slow course	Kitada et al., 1998
PINK1	Recessive	GW-linkage	LBs (only 1 brain available)	Early-onset PD, slow course	Valente et al., 2004
DJ-1	Recessive	GW-linkage	Unknown	Early-onset PD, slow course	Bonifati et al., 2003
ATP13A2	Recessive	GW-linkage	Ceroid lipofuscinosis (only 1 brain available)	Juvenile onset, atypical	Ramirez et al., 2004
PLA2G6	Recessive	GW-linkage	Typical LBs, brain iron accumulation	Juvenile onset, atypical	Paisan-Ruiz et al., 2009
FBXO7	Recessive	GW-linkage	Unknown	Juvenile onset, atypical	Shojaee et al., 2008; Di Fonzo et al., 2009
DNAJC6	Recessive	Linkage/Exome sequencing	Unknown	Juvenile onset, atypical	Edvardson et al., 2012; Köroğlu et al., 2013
SYNJ1	Recessive	Linkage/Exome sequencing	Unknown	Juvenile onset, atypical	Krebs et al., 2013; Quadri et al., 2013

Other chromosomal loci (including *PARK3, PARK10, PARK11*) have been identified by genome-wide approaches, and these regions might harbor further (still unknown) genes for typical, late-onset Parkinson's disease.
Parkinsonism might occur in a number of disparate genetic neurodegenerative disorders, in which the phenoytype is usually dominated by other signs and symptoms. These include DNA-repeats expansion disorders (e.g. *SCA2*, *SCA3*, *SCA7*, Huntington's disease), frontotemporal lobe degenerations (*MAPT*, *GRN*, *c9orf72*), Wilson's disease, manganese-transport disease (*SLC30A10*), neurodegenerations with brain iron accumulation (*FTL*, *c19orf12, WDR45*), spastic paraplegias (*SPG11*), mitochondrial disorders (*POLG1*), chorea-acanthocytosis, X-linked dystonia-parkinsonisms, Niemann–Pick disease type C, and others.

their identification has been very important in pinpointing molecular players and pathways that are involved in the disease pathogenesis in general. More recent successes illustrate that the genome-wide linkage strategy maintains intact its validity, even in the era of the next-generation sequencing technology, and additional monogenic forms of PD might be discovered in the future.

Intensive efforts have been dedicated in the past 5 years to **genome-wide association studies (GWAS)**. Here, the goal is to

identify genetic variants that are common in the population, have very small effect sizes (odds ratios <1.5), and "modulate the risk of" (rather than cause) disease. GWAS require large numbers of cases and well-matched population controls. More than 20 susceptibility loci for PD have been identified (reviewed in [3]) and others are expected to result from larger GWAS and meta-analyses. Although the effect size of these variants is not large enough to inform disease prediction or diagnostics in the clinical practice, the GWAS loci are important. Each of these might lead to novel important molecular players for PD in general. Moreover, the impact of carrying several risk variants might be higher, due to additive or synergic effects. However, the estimates suggest that also the common variants explain only a small fraction of the disease heritability [5]. Thus, the rare mutations of large effect and the common variants of small effect each explain only a minor fraction of the disease burden. One possibility is that the "missing heritability" lies in a different type of variants, that are not common enough to be detected by GWAS, and not penetrant enough to be found by family-based linkage approaches. Indeed, variants of this type include Gly2019Ser in *LRRK2* [4], and several variants in *GBA* [6], the most common variants known so far in PD. Their odds ratios are similar (in the range of 5–8), in keeping with strongly reduced penetrance. Variants of this type might exist in several, still unknown, genes and their prevalence might also be population-specific (like that of *LRRK2*-Gly2019Ser and the *GBA* variants).

There are great expectations that further genetic discoveries for PD will result from the **next-generation sequencing** (**NGS**) technologies, which enable much higher sequencing capacity at lower cost [7]. Sequencing of entire human genomes remains challenging for the average laboratory. Instead, sequencing only the coding fraction of the genome (the **exome**, ~2% of the genome) has rapidly become a routine technology for finding disease-related genes. For example, one can now rapidly sequence the entire chromosomal region delimited by a linkage mapping or a GWAS strategy, or sequence only the exons contained therein. Moreover, the NGS technologies enable a range of novel strategies for directly tackling the disease-related variants, without a prior linkage or GWAS study (reviewed in [8]). One strategy consists in sequencing the exome of distant relatives of a family (e.g. two cousins), and filtering the results for shared novel, potentially disease-causing variants. Candidate variants are then followed up in independent, large samples to identify the same or other mutations in the same gene and support pathogenicity. This approach has led recently to the identification of *VPS35* mutations in autosomal dominant PD [9,10]. It is expected that additional genes will soon be identified using this and other NGS-based strategies. Furthermore, the continuous drop in sequencing costs already makes it possible to perform large case–control studies at the level of the exome; soon, this design will be feasible for entire genomes. However, while the generation of sequence data is increasing exponentially, our capacity of interpretation of the functional effects of novel identified variants (pathogenicity) is lagging behind. Moreover, complex ethical issues arise, particularly concerning the "incidental" findings (pathogenic variants in genes different from those representing the object of the initial study) [11].

3. The autosomal dominant forms of PD

Mutations in three genes (*SNCA*, *LRRK2, VPS35*) are conclusively established as a cause of autosomal dominant forms of PD. The evidence for a fourth gene, *EIF4G1*, remains inconclusive. Last, heterozygous mutations in the *GBA* gene are important and strong risk factors for PD and diffuse Lewy-body disease (DLB).

3.1. SNCA

Mutations in the *alpha-synuclein* gene (*SNCA*) are rare and include point mutations and whole-locus multiplications (duplications or triplications). Duplications are detected in ~1–2% of the PD families compatible with autosomal dominant inheritance. Triplications and point mutations are exceedingly rare: the Ala53Thr mutation has been found in a few families of Greek ancestry and occasionally elsewhere (including Asia); Ala30Pro and Glu46Lys have been detected so far in single families, of German and Spanish origin, respectively. The brain pathology is characterized by abundant α-synuclein-positive neuronal inclusions (LBs and Lewy neurites, LNs), but the associated clinical spectrum is broad, ranging from classical PD to more atypical and aggressive phenotypes (including myoclonus, severe autonomic dysfunction and dementia in addition to parkinsonism), and resembling DLB or multiple system atrophy (MSA). The patients with *SNCA* duplications often display a classical PD phenotype, whereas the more rare cases carrying triplications display more severe phenotypes, in keeping with a direct relationship between *SNCA* gene dosage and disease severity. The *SNCA* mutations usually display a high penetrance, but instances of reduced penetrance have been reported, particularly for the *SNCA* duplications.

Two novel missense mutations have been recently identified in this gene in PD patients. The first mutation, c.150T>G, leads to the **p.His50Gln** (H50Q) missense change in the α-synuclein protein. This mutation was identified in one English patient with sporadic, pathologically-confirmed PD (onset age 71) [12], and in one Canadian case of English–Welsh ancestry, with PD (onset age 60) and a positive family history for parkinsonism and dementia [13]. Co-segregation studies are not available. Haplotype data in these two patients are compatible with the mutation originating from a common founder. The strongest argument in favour of pathogenicity is that the His50Gln mutation is located in the same alpha-helix, between another two definitely pathogenic mutations, Glu46Lys and Ala53Thr. Furthermore, the mutation was found in two PD patients, and not in ethnically-matched controls (875 tested in one study). However, caution is warranted: co-segregation data are not available; one of the two patients was reported as sporadic (though this is compatible with a reduced penetrance); the mutation is predicted as benign by some of the popular *in silico* tools; and the same variant is present in one out of 6503 individuals in the Exome Variant Server (http://evs.gs.washington.edu/EVS/). Further data, either from genetic or functional studies, are therefore needed, to clarify whether His50Gln is a PD-causing mutation or a benign neutral rare variant.

The second mutation, c.152G>A, occurs just two nucleotides downstream in the *SNCA* open reading frame, leading to the **p.Gly51Asp** (G51D) missense change in the protein [14,15]. This mutation was shown to co-segregate with disease in a total of five patients, in two independent families of French and British origins, is absent from all the control databases, replaces a highly conserved amino acid, again positioned between two other PD-causing mutations Glu46Lys and Ala53Thr, and is predicted to be damaging *in silico*. The same Gly51Asp mutation was also reported (even if only in abstract form) in a Japanese kindred with autosomal dominant parkinsonism and dementia. There is therefore solid evidence to consider Gly51Asp as a disease-causing mutation. This conclusion is supported by the atypical clinical and pathological associated phenotypes, which bear similarities to those of Ala53Thr and *SNCA*-triplication cases. The onset of parkinsonian symptoms in the carriers of Gly51Asp occurred often before the age of 40, even before 20 in one (juvenile parkinsonism); the response to levodopa is moderate, and the disease progression is very rapid, with death in less than 10 years from onset in some. Additional features, such as

pyramidal signs, cognitive deterioration, psychiatric disturbances, myoclonus and seizures, are present. All these features resemble those in patients with Ala53Thr or *SNCA*-triplications. The pathology in the carriers of Gly51Asp is characterized by brain atrophy, more severe in the fronto-temporal lobes, severe neuronal loss in sites typical for PD, but also in the striatum, hippocampus and cerebral cortex, with abundant and pleomorphic α-synuclein-positive inclusions, some resembling LBs and LNs but others similar to the glial and neuronal cytoplasmic inclusions of the MSA. Therefore, similarly to Ala53Thr and *SNCA*-triplications, the Gly51Asp-associated phenotypes support the view that seemingly different synucleinopathies (PD, DLB, and MSA) share pathogenetic pathways, and offer opportunities for mechanistic insights.

Misfolding and aggregation of the α-synuclein protein into neurotoxic species is at the center of the current pathogenetic theories for PD. The more recent discovery that α-synuclein aggregates develop in dopaminergic neurons transplanted in the brain of PD patients, and further data from in vitro and in vivo animal studies, suggest that misfolded α-synuclein conformers have prion-like properties, and are able to induce a cascade of protein misfolding, and to spread from cell to cell in the brain (reviewed in [16]). These recent, important evidences need to be taken in consideration and to be incorporated into our theories of pathogenesis in a way that also fits with the results of the genetic studies.

There might be several points in the initiation and propagation of the α-synuclein misfolding, determined by Mendelian mutations, or modulated by genetic variants. For example, the GBA mutations might impair the lysosomal clearance of misfolded α-synuclein; in turn, misfolded α-synuclein might further inhibit the GBA activity, thereby creating a positive feedback loop that enhances the accumulation and spread of misfolded proteins and toxicity [17]. How the *LRRK2* mutations fit into this model remains unclear.

3.2. LRRK2

Mutations in the *leucine-rich repeat kinase 2 (LRRK2)* are the most common, known cause of autosomal dominant PD. The *LRRK2* gene encodes a large protein with two enzymatic domains (GTPase and kinase) and multiple protein–protein interaction domains. Seven mutations (Asn1437His, Arg1441Cys, Arg1441Gly, Arg1441His, Tyr1699Cys, Gly2019Ser, and Ile2020Thr) are considered disease-causing. For other variants a pathogenic role remains possible but is not proven. *LRRK2* mutations explain up to ~10% of the PD patients with familial, autosomal dominant inheritance. Gly2019Ser is by far the most common mutation (see below), followed by Arg1441Cys. However, Gly2019Ser has strongly incomplete penetrance, which explains why this founder mutation is detectable in patients with familial but also in some with sporadic PD. This mutation is frequent in PD patients from southern Europe (especially Portugal, Spain, and Italy) but very common among Arab patients from North Africa and Ashkenazi Jewish patients. Dopaminergic neuronal loss and gliosis in the *substantia nigra* are common pathological features in patients with *LRRK2* mutations, and classical LBs are found in the majority of them. However, in some cases only tau-positive or ubiquitin-positive inclusions are seen. Overall, the clinical characteristics of patients with *LRRK2* mutations are those of classical PD, but the onset age range is broad.

The Gly2019Ser mutation is present on a single ancestral haplotype in the North-African and Middle-Eastern populations, where the mutation might have originated approximately four millennia ago. It is tempting to speculate that the spread of this mutation over time and space is not simply the result of chance (genetic drift), but of selective evolutionary forces. PD symptoms start in most cases after the reproductive period of the life. Furthermore, and more importantly, the average life expectancy in the previous centuries was shorter than the age of typical PD symptomatic onset. The mutation might have conferred some evolutionary advantage early in life, or during development. One possibility is that the mutation enhances the resistance to environmental pathogens, particularly intracellular microbial agents. This theory is supported by recent evidence for a role of the LRRK2 protein in the immune system [18]; *LRRK2* common variants have also been identified in GWAS as modulators of risk for leprosy and inflammatory bowel disease. These roles are thought to be mediated by the LRRK2 involvement in the phagocytosis of the immune system cells, a process with analogies to the neuronal endocytosis (both involving cell membrane remodelling and membrane trafficking). One can also speculate that the function of LRRK2 in the immune system, and its modifications due to the Gly2019Ser mutation, could be mechanistically linked to the susceptibility to PD.

3.3. VPS35

In 2011 two groups reported the identification of the same missense mutation (p.Asp620Asn) in the *vacuolar protein sorting 35* (*VPS35*) gene, as a novel cause of autosomal dominant PD [9,10]. This was the first PD gene found by a direct NGS-based strategy: exome sequencing in affected relatives pairs from large families of Austrian and Swiss origins, respectively. Although there was no prior linkage support, and only one disease-segregating mutation was detected, the overall evidence supporting a disease-causing role for this mutation is robust: the Asp620Asn mutation co-segregates with PD in the two original and a few additional large families, while it was not found in thousands of controls. Moreover, it replaces a highly conserved amino acid, and is predicted to be deleterious by bioinformatics tools. A series of subsequent studies confirmed the presence of this specific mutation in familial PD cases with dominant inheritance (and rarely in sporadic PD) from Caucasian and Japanese series, but also confirmed it to be rare (<1/500 PD). However, in France and Japan, the frequency was about 1/100 of autosomal dominant PD, a figure comparable to the frequency of *SCA2* or *SNCA* duplications. Despite intensive screening, additional definitely pathogenic mutations have not been found. The phenotype associated with the Asp620Asn mutation is that of typical PD, with asymmetric onset, good L-dopa response, and motor complications, but with a slightly earlier onset age (on average at the beginning of the sixth decade of life). Severe cognitive or psychiatric disturbances are rare. Also in the case of this mutation, the penetrance is incomplete. Haplotype analyses suggest that the Asp620Asn mutation has arisen independently, supporting the possibility of a mutational hot spot. The brain pathology in carriers of this mutation remains unknown. Despite its rarity, this novel form might provide further important pathogenetic clues. This gene encodes a subunit of the retromer complex, which is involved in the retrograde transport between endosomes and the trans-Golgi network, and is linked to the traffic and recycling of synaptic vesicles and proteins. Here, there are further, intriguing links to the pathways of *LRRK2*, *parkin* [19], *SNCA*, and the recently identified genes *DNAJC6* and *SYNJ1*. Taken together, these findings support the contention that endosomal trafficking and recycling of synaptic vesicles are involved in the pathogenesis.

3.4. EIF4G1

Mutations in the *eukaryotic translation initiation factor 4 gamma 1* (*EIF4G1*) gene have been nominated as a further cause of autosomal dominant PD by a genome-wide linkage approach in a large French family, where the missense p.Arg1502His mutation was initially

identified [20]. Further screening revealed the same and another missense mutation, p.Ala502Val, in a few small families. However, several subsequent studies have failed to replicate those initial findings: mutations were not identified in PD, while, contrary to the initial results, some carriers of these two mutations were detected in healthy controls. It is possible that *EIF4G1* mutations are a rare cause of, or a risk factor for, PD, but this remains to be conclusively demonstrated.

3.5. GBA

Dominantly-inherited, heterozygous mutations in the *glucocerebrosidase* (*GBA*) gene are a frequent and strong risk factor for PD [6]. Some mutations are prevalent in specific ethnic groups, such as the Asn370Ser mutation among Ashkenazi Jews. According to current estimates of size effect (pooled OR >5) the *GBA* mutations display a much lower penetrance than the classical (Mendelian) mutations. However, an accurate estimate of ORs and penetrance is currently possible only for the most common *GBA* mutations. The patients with *GBA* pathogenic mutations have typical PD with possibly a slightly earlier onset age.

4. Autosomal recessive, early-onset typical parkinsonism

Homozygous or compound heterozygous mutations in each of the following three genes: ***parkin*** (*PRKN*, PARK2), *PTEN induced putative kinase 1* (***PINK1***, PARK6), and *Parkinson protein 7* (***DJ-1***, PARK7) can cause autosomal recessive forms of early-onset parkinsonism, usually without atypical clinical signs. Mutations in these three genes are identified worldwide, including point mutations and large rearrangements, leading to deletions or multiplications (these latter being especially frequent in the *parkin* gene). Dosage assay is therefore required, in addition to sequencing, for a sensitive mutational screening. Mutations in *parkin* are the most common, and explain up to half of familial PD, compatible with recessive inheritance, and ~15% of the sporadic PD with onset before 45 years. Mutations in the *PINK1* and *DJ-1* gene are less common (~1–8%, and 1–2% of early-onset cases, respectively. LBs have not been detected in most cases carrying *parkin* disease-causing mutations, suggesting pathogenetic differences between the autosomal recessive and the typical forms of PD. However, a first patient with pathogenic *PINK1* mutations was recently reported with LB-positive pathology [21]. The pathology in patients with *DJ-1* mutations remains unknown. The clinical phenotype associated with *parkin* mutations is characterized by early-onset parkinsonism, good and prolonged response to levodopa and a benign course. The average onset age is in the early 30s in most patients, but late-onset cases have been described up to 70 years of age [22]. Marked cognitive or vegetative disturbances are rare. There are no specific clinical features that distinguish patients with *parkin* mutations from those with *PINK1* and *DJ-1* mutations, or other early-onset PD forms. Rare atypical presentations have also been described, and a wide variability in onset age and phenotype might be observed even within the same family. The parkin protein has ubiquitin-ligase activity, which is abolished by the disease-causing mutations. The PINK1 protein contains a kinase domain and is localized to the mitochondria. The parkin and PINK1 proteins are functionally linked, with PINK1 acting upstream of parkin. Together, they are important to tag damaged mitochondria for degradation by autophagy [23].

5. Autosomal recessive, juvenile atypical parkinsonism

Recessive mutations in several genes can cause neurodegeneration with very early (juvenile) onset, usually with other clinical signs in addition to parkinsonism. PARK9 (also termed Kufor–Rakeb syndrome), is characterized by juvenile, levodopa-responsive parkinsonism, pyramidal signs, dementia and supranuclear gaze palsy, and is caused by recessive mutations in the *ATPase type 13A2* (***ATP13A2***) gene. The *ATP13A2* gene encodes a lysosomal membrane transporter. Recently, one family with pathologically-proven neuronal ceroid lipofuscinosis turned out to carry *PARK9* mutations [24]. Similar pathology was reported in association to mutations in the canine homolog of the *ATP13A2* gene. While additional data are warranted, these evidence suggest that PARK9 is a disease distinct from PD.

Recessive mutations in the *phospholipase A2, group VI* (***PLA2G6***) gene, described initially as the cause of infantile neuroaxonal dystrophy and neurodegeneration associated with brain iron accumulation, were later identified in patients with levodopa-responsive dystonia-parkinsonism, pyramidal signs and cognitive/psychiatric features, with onset in early adulthood. Additional disease-causing homozygous and compound heterozygous mutations have since been reported in other Japanese and Chinese patients with very early-onset atypical parkinsonism. MRI shows brain atrophy with or without iron accumulation. Brain pathology in patients with *PLA2G6* mutations revealed widespread LBs [25], suggesting links with the typical PD.

Mutations in the *F-box only protein 7* gene (***FBXO7***) cause PARK15, a recessive form of juvenile parkinsonism with pyramidal disturbances. Initially nominated in one Iranian kindred with predominant pyramidal signs, the involvement of *FBXO7* was conclusively demonstrated by different mutations found in Italian and Dutch families with prominent juvenile parkinsonism with varying degrees of levodopa response. Subsequently, the same truncating mutation present in the Italian family was identified in unrelated families from Turkey and Pakistan. The brain pathology in patients with *PARK15* remains unknown. However, we recently reported FBXO7 immunoreactivity in the LBs of typical PD, and in glial cytoplasmic inclusions of multiple system atrophy, suggesting an involvement of this protein in the pathogenesis of the common forms of synucleinopathies [26]. The *FBXO7* gene encodes two protein isoforms, which are part of larger ubiquitin-ligase complexes, but have poorly characterized functions. We also recently reported a vertebrate model of PARK15 in the zebrafish. This model reproduces features of PD, including loss of dopaminergic neurons and dopamine-dependent motor deficit.

During the past year, mutations in another two genes, ***DNAJC6*** and ***SYNJ1***, were identified as the cause of autosomal recessive, juvenile parkinsonism. Exome sequencing combined with genome-wide homozygosity mapping were the keys to these discoveries, highlighting the great potential of these modern tools for gene finding, particularly in consanguineous families. *DNAJC6* mutations were initially nominated as the disease cause in a Palestinian family [27], and later confirmed in a Turkish family [28]. In the case of *SYNJ1*, the same homozygous mutation, p.Arg258Gln, was identified independently in two families of Iranian and Italian origins [29,30]. *DNAJC6* encodes auxilin, and *SYNJ1* encodes synaptojanin 1, two proteins with distinct, but very close roles in the post-endocytic recycling of synaptic vesicles. Abnormalities at the same level have been implicated in PD from different studies, including some on the pathogenesis of disease caused by the *LRRK2*, *VPS35*, *SNCA*, and *parkin* mutations. Thus, the mutations in *DNAJC6* and *SYNJ1* define two novel rare causes of parkinsonism, but might also provide further insights for the pathogenesis of the common forms of PD.

Acknowledgements

I wish to thank the patients and family relatives for their contribution, and the many neurologists, who have been involved

in our studies on the genetics of PD over many years. This work was supported by a research grant from the Stichting Parkinson Fonds (The Netherlands).

Conflict of interests

The author has no conflict of interest to declare.

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