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

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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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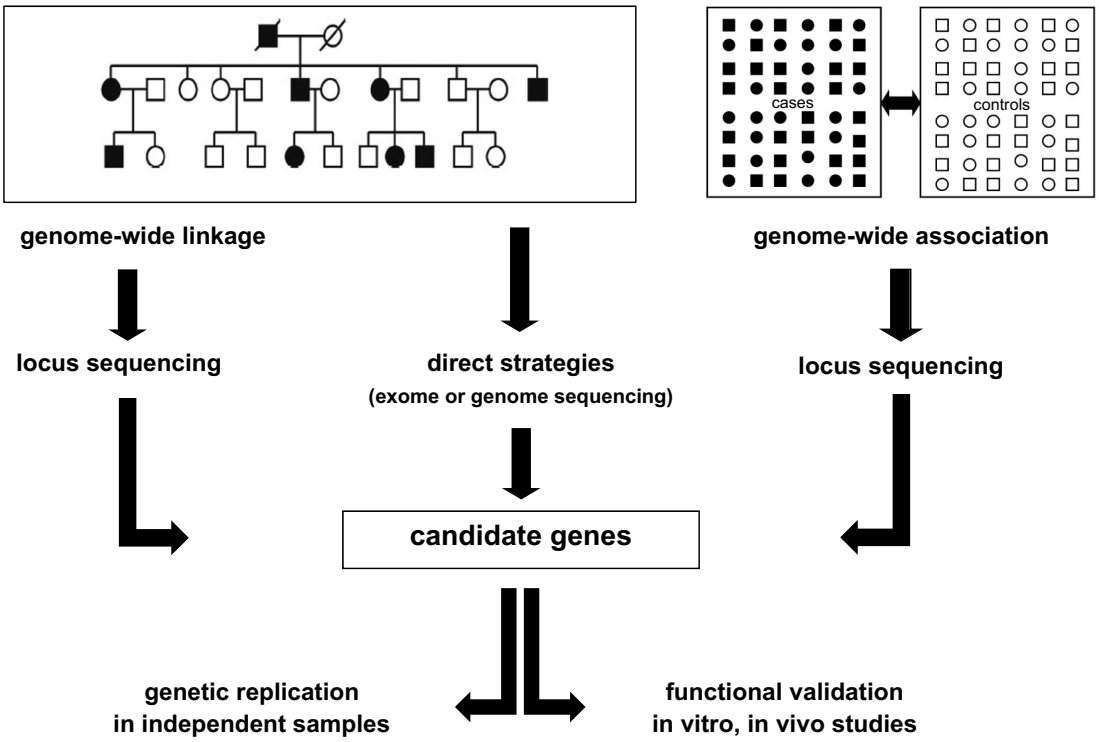

Fig. 1. Schematic representation of the current research strategies for finding genes related to human diseases.

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