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The role of monogenic genes in idiopathic Parkinson's disease

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Abstract

In the past two decades, mutations in multiple genes have been linked to autosomal dominant or recessive forms of monogenic Parkinson's disease (PD). Collectively, these monogenic (often familial) cases account for less than 5% of all PD, the majority being apparently sporadic cases. More recently, large-scale genome-wide association studies have identified over 40 loci that increase risk of PD. Importantly, there is overlap between monogenic and sporadic PD genes, particularly for the loci that contain the genes *SNCA* and *LRRK2*, which are mutated in monogenic dominant PD. There have also been reports of idiopathic PD cases with heterozygous variants in autosomal recessive genes suggesting that these mutations may increase risk of PD. These observations suggest that monogenic and idiopathic PD may have shared pathogenic mechanisms. Here, we focus mainly on the role of monogenic PD genes that represent pleomorphic risk loci for idiopathic PD. We also discuss the functional mechanisms that may play a role in increasing risk of disease in both monogenic and idiopathic forms.

Keywords

Idiopathic Parkinson's disease; pleomorphic risk loci; genetic risk factors; functional genomics

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects multiple brain regions, resulting in a syndrome that includes symptoms related to neurological control of movement as well as other brain functions including cognition (Langston, 2006). PD is both common and age-related, being rare before the age of 50, affecting about 1% of the population worldwide over the age of 65 years and about 4–5% of the population over 85 years old (de Lau and Breteler, 2006). Since aging remains the largest risk factor for developing PD, the economic and social impact resulting from PD will continue to rise with the overall longevity of many populations (Collier et al., 2011; Driver et al., 2009).

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Historically, other than aging there have been relatively few widely confirmed causal factors that influence lifetime risk of PD, making this a classic sporadic disorder. However, genetic linkage analysis in families, has identified several underlying rare but penetrant pathogenic mutations. To date, 19 *PARK* loci have been designated for different genetic forms of PD and the underlying gene mutation has been identified in 11 of them, with some uncertainty about the accuracy of assignment of several genes in four loci (Hernandez et al., 2016). Although these discoveries have provided important insights into the pathogenesis of PD, the cumulative set of genes only explain up to 5% of all PD cases (Klein and Westenberger, 2012). Therefore, the remaining 95% of PD remain apparently sporadic.

Large genome-wide association studies (GWAS) of PD cases have identified common risk variants that have modest influence on lifetime risk of PD. The first reasonably well-powered PD GWAS identified several loci that contain common variation associated with PD risk (Simón-Sánchez et al., 2009; Satake et al., 2009). Subsequent meta-analyses have confirmed these associations (International Parkinson Disease Genomics Consortium et al., 2011; Nalls et al., 2014) and the latest GWAS, which consists of 37,688 PD cases, 18,618 PD proxies and over 1,400,000 controls, has robustly identified association signals in 92 loci (Nalls et al., 2018). What is particularly interesting in PD, but not generally true in other neurodegenerative diseases, is that the genes that cause disease in families are also represented in the GWAS loci. There are multiple examples of these pleomorphic risk loci, so called because they harbor variants that, likely through slightly different mechanisms, impact both inherited and sporadic PD.

Here, we provide an overview and interpretation of how monogenic genes may play roles in sporadic PD. We will focus mainly on genes that contain deleterious and highly penetrant causal mutations, but also harbor risk variants for idiopathic disease. These genes are particularly important because their presence implies that there are functional pathogenic links between monogenic and idiopathic PD, which in turn has implications for understanding and treating this disorder.

SNCA links protein deposition and genetic risk of PD

The first definitive genetic cause of PD was the discovery of a missense mutation (p.A53T) in *SNCA* (*PARK1*) that was linked to disease in a large family with an autosomal dominant pattern of inheritance (Polymeropoulos et al., 1997). Soon after being linked to monogenic forms of PD, α-synuclein was also identified as the primary component of Lewy Bodies and the major pathological hallmark of PD (Spillantini et al., 1997). Since its initial discovery, several other *SNCA* missense point mutations have been described (p.A30P, p.E46K, p.G51D, p.A53E), all of which are located in the N-terminal region of the protein that normally folds into a helical conformation to bind to neuronal synaptic membranes (Krüger et al., 1998; Zarranz et al., 2004; Lesage et al., 2013; Pasanen et al., 2014). In addition to these point mutations, duplications and triplications of the *SNCA* locus also cause inherited PD (Ibáñez et al., 2004; Chartier-Harlin et al., 2004; Singleton, 2003). Interestingly, individuals carrying triplications present with a more severe and aggressive phenotype than cases with duplications, which are more similar to idiopathic PD (Fuchs et al., 2007), suggesting that SNCA dosage is important in disease pathogenesis.

The *SNCA* locus was first implicated as a common genetic risk factor when polymorphisms in REP1, a variable repeat microsatellite sequence located upstream of the *SNCA* promoter, were associated with idiopathic PD (Maraganore et al., 2006). Subsequently, at least three independent single nucleotide polymorphisms (SNPs) across the SNCA locus have now been associated with increased risk for PD by GWAS (Pihlstrøm et al. 2018; Simón-Sánchez et al., 2009; Nalls et al., 2014; Chang et al., 2017; Nalls et al., 2018). Additionally, a recent GWAS in Dementia with Lewy Bodies (DLB), a synucleinopathy with overlapping symptoms, identified only one of the three independent signals at the 5' end of *SNCA* as contributing to disease risk (Guerreiro et al., 2018). These distinct patterns of associations with PD and DLB at the SNCA locus suggest that these variants have different effects on SNCA gene regulation.

While the *SNCA* locus harbors multiple types of genetic variation associated with PD risk, an important question is whether there is convergence of these variants on disease processes or whether each type of variation causes disease by different mechanisms (Nalls et al., 2014). Several non-coding risk variants have been demonstrated to play a role in regulating *SNCA* expression levels in various model systems. For example, the *SNCA*-REP1 allele has been shown to increase human *SNCA* mRNA and protein levels in a transgenic mouse model (Cronin et al., 2009). Recently, a study employing a CRISPR/Cas9 strategy in human induced pluripotent stem cells (iPSCs), found that an intronic SNP in *SNCA* associated with PD by GWAS is located in an enhancer that contributes to the regulation of *SNCA* expression (Soldner et al., 2016). More recently, it was suggested that one of the lead SNPs from the PD GWAS is a major functional SNP and is predicted to act by increasing SNCA expression in the brain (Pihlstrøm et al. 2018). If we consider that inherited PD can be influenced by the number of copies of *SNCA* without coding variation, then we might expect that higher expression level of *SNCA* controlled by common genetic variants would influence sporadic PD risk. If this is true, then sporadic disease caused by common non-coding variants may be a subtler form of the multiplication cases.

As opposed to variants that influence expression level, coding missense point mutations in *SNCA* have a variety of structural effects on the protein that include changes in the ratio of tetrameric to monomeric species, formation of oligomeric aggregates and loss of membrane binding. Which of these activities is critically important for neuronal damage in PD is not resolved, as each have been shown to cause cellular damage. However, as the main neuropathological and clinical phenotypes in point mutations and multiplication mutations overlap, it seems likely that there are some common mechanisms that underlie disease pathogenesis. However, the likelihood of cognitive impairment, psychosis and related phenotypes in SNCA mutation carriers correlates with the type of the mutation. Missense mutation carriers are least likely to display these non-motor phenotypes while individuals with a locus triplication are most likely to exhibit severe forms of disease, and phenotypes in duplication carriers often lie in between these two ends of this range (Tambasco et al. 2016). Another, more specific example of common mechanisms between different types of PD is given by the *LRRK2* locus that we will discuss below.

Variation at the *LRRK2* polymorphic risk locus nominates common mechanisms in sporadic and monogenic PD

Mutations in *LRRK2* were first identified as the cause of *PARK8*-linked autosomal dominant PD in multiple families in 2004 (Paisán-Ruíz et al., 2004; Zimprich et al., 2004). By 2008, 46 point mutations, excluding those commonly found in controls, had been identified in *LRRK2* (Biskup and West, 2009) and by 2010 the total number of exonic variants had expanded to 121 (Ross et al., 2011). Of these variants, only six, p.R1441C/G/H, p.Y1699C, p.G2019S and p.I2020T, have reliably been shown to segregate with disease in extended pedigrees (Paisán-Ruíz et al., 2004; Zimprich et al., 2004; Di Fonzo et al., 2005; Nichols et al., 2005). *LRRK2* p.G2019S, the most common disease associated variant, causes monogenic PD with an age-and population-dependent incomplete penetrance. Penetrance estimates range from a lower bound of 16.7% in the Ashkenazi population to an upper estimate of 85% by the age of 80 (Lee et al., 2017; Kachergus et al., 2005). This lack of complete penetrance explains the relatively high number of apparently idiopathic cases that carry the p.G2019S allele, with particularly high frequencies in Ashkenazi Jewish and North African populations (Gilks et al., 2005; Ozelius et al., 2006; Lesage et al., 2005). Other *LRRK2* mutations also show incomplete penetrance (Gosal et al., 2007; Ruiz-Martínez et al., 2010), suggesting that while all of the variants initially found in families increase risk substantially, they do not invariably lead to disease.

Additional risk variants have been identified in other populations, with p.R1628P and p.G2385R being the most common in Asian populations (Funayama et al., 2007; Farrer et al., 2007; Tan et al., 2010; Gopalai et al., 2014). Interestingly, a protective variant of *LRRK2*, p.R1398H, has also been identified in multiple populations (Chen et al., 2011; Heckman et al., 2014). The effect size of these variants is quantitatively less than p.G2019S, having a less than two-fold effect on PD risk.

LRRK2 encodes a large multi-domain protein consisting of 2527 amino acids. Interestingly, all proven monogenic pathogenic mutations are clustered in the ROC (ras of complex proteins), COR (C-terminal of Roc) and kinase domains. Pathogenic mutations either work by decreasing the GTPase activity encoded by the ROC-COR tandem bidomain (West et al., 2005; Lewis et al., 2007; Berwick et al., 2017) or by increasing the activity of kinase domain (West et al., 2005; Greggio et al., 2006; West et al., 2007). The protective allele p.R1398H is also located in the COR domain and has been shown to decrease kinase activity of the protein (Tan et al., 2010; Nixon-Abell et al., 2016). An exception to these general observations, is the risk variant p.G2385R which is located in a C-terminal WD40 domain and shows lower steady state protein levels and altered protein binding due to changes in protein structure (Rudenko et al., 2012; Ho et al., 2016; Rudenko et al., 2017; Carrion et al., 2017). Speculatively, the lower steady state levels may help negate the pathogenic effects and explain why this variant is only risk factor rather than a more penetrant allele like p.G2019S.

Perhaps counter-intuitively, the lower GTPase activity of several pathogenic mutations is likely to enhance overall LRRK2 function as hydrolysis of GTP to form GDP is typically an inactivation event for GTPases. Thus, it has been postulated that while different mutations

have slightly different biochemical mechanisms, they rapidly converge with consistent direction of effect on immediate downstream biology (Cookson, 2010). This contention has received support from experiments arising from an understanding that LRRK2 interacts with several small RAB family GTPases. First, LRRK2 interacts with a specific RAB at the *trans*-Golgi network (TGN) and all pathogenic mutations enhance the recruitment of LRRK2 to the TGN relative to WT, with the risk factor variant p.G2385R having an intermediate effect (Beilina et al., 2014). Second, LRRK2 can phosphorylate a series of RAB proteins and in cells (but not *in vitro*) all mutations enhance RAB phosphorylation (Steger et al., 2016). Therefore, all pathogenic coding mutations appear to have consistent effects on cellular events that are likely linked to intracellular membrane sorting, a well-defined function of RABs.

In early GWAS studies, the *LRRK2* locus was noted to have potential association signal in both European and Japanese populations. However, the association did not pass correction for genome-wide significance in the European population and so was labeled as a suggestive association (Simón-Sánchez et al., 2009; Satake et al., 2009). As GWAS study sizes have significantly increased, it has become evident that there is a common non-coding risk variant at the *LRRK2* locus (Nalls et al., 2014). The most recent meta-GWAS identified rs76904798 as the most significantly associated SNP in the *LRRK2* region with a p-value of 1.52×10^{-28} (Nalls et al., 2018). It has been suggested that this specific PD risk variant is associated with higher expression of *LRRK2* mRNA, being an example of an expression quantitative trait locus (eQTL) (Ryan et al., 2017). Although this result needs to be confirmed in additional sample series, it suggests that non-coding risk factor variants act in the same direction as pathogenic alleles, i.e., by increasing overall LRRK2 activity. Thus, as for *SNCA*, the pleomorphic risk locus containing *LRRK2* likely has several genetic variants that lead to disease by similar mechanisms.

Heterozygous mutations in recessive genes may increase PD risk

Pathogenic mutations in *PRKN, PINK1, DJ1, ATP13A2, PLA2G6, FBXO7*, and *DNAJC6* are causes of recessive, predominantly early-onset PD (EOPD) (Hauser et al., 2017). In each case, disease is associated with homozygous or compound heterozygous loss of function mutations in the same gene. In many ways, the phenotypes associated with recessive gene mutations are distinct from sporadic PD. Recessively inherited forms of PD are rare and often found in consanguineous pedigrees that may have other symptoms in addition to those characteristic of typical PD. Furthermore, unlike most PD cases, mutations in these genes result in early onset disease, sometimes as early as teenage years. EOPD cases tend to progress more slowly than typical sporadic PD or dominant gene mutations. Finally, autopsy examination of brains from EOPD suggests that α-synuclein deposition does not always occur, unlike sporadic PD where Lewy pathology is required for a definitive diagnosis (Mori et al., 1998; Hayashi et al., 2000; van de Warrenburg et al., 2001; Farrer et al., 2001; Sasaki et al., 2004; Samaranch et al., 2010). However, this data is complicated to interpret as *LRRK2* PD cases also show variable protein deposition pathology despite high clinical overlap (Kalia et al., 2015; Poulopoulos et al., 2012).

Although the classical definition of recessive disease genes is that carriers of one risk allele are not affected, it has been reported that heterozygous mutations in some of these genes may act as risk factors for sporadic PD (Klein et al., 2007). One possible mechanism for this proposal is that heterozygous nonsense mutations predispose an individual to PD through partial loss of function. However, it is more likely that some individuals have a second undiscovered mutation or structural genetic variant that might explain their disease and be consistent with compound heterozygosity. None of the published PD GWAS, including the largest and most recent meta-analysis (Nalls et al., 2018), have identified a recessive PD gene as a risk locus. Most likely these variants are not detected because they are too rare for identification by GWAS or on their own they do not act as risk variants for PD. Most of the EOPD mutations are too rare to have been studied in the heterozygous state however for two of the most commonly mutated autosomal recessive PD genes (*PRKN* and *PINK1*) there are some reports that heterozygous mutations have a potential role in development of PD, and each will be discussed separately below.

PRKN (PARK2)

Mutations in *PRKN* are diverse in nature, owing to its large genomic size of 1.3Mb on chromosome 6 and recognition as a common fragile site in the genome (Smith et al., 2006). PD-linked *PRKN* mutations consist of homozygous or compound heterozygous point mutations as well as partial deletions or duplications (Abbas et al., 1999). Parkin mutations are the most common cause of EOPD with frequency estimations ranging from 4.6% to 10.5%, depending on the population (Abbas et al., 1999; Leroy et al., 1998; Taghavi et al., 2017). *PRKN* encodes the cytosolic E3 ubiquitin ligase parkin which is recruited to the mitochondrial membrane when phosphorylated by PINK1 to induce mitophagy (Kane et al., 2014).

Several studies have suggested that *PRKN* variants increase risk for sporadic PD (Lincoln et al., 2003; Lücking et al., 2000; Lesage et al., 2008; Clark et al., 2006; Wang et al., 1999; Hedrich et al., 2002) and/or influence age at onset (Foroud et al., 2003; Sun et al., 2006). However, others have shown that heterozygous mutations and structural genetic variants are observed with the same frequency in cases and healthy controls (Kay et al., 2007; Lincoln et al., 2003; Lücking et al., 2000; Kay et al., 2007). These conflicting studies make the role of heterozygous *PRKN* mutations in disease development uncertain. A meta-analysis of 4,538 cases and 4,213 controls that screened for *PRKN* copy number variants (CNVs) supported the idea that heterozygous carriers of CNVs containing coding exons had increased risk of developing PD compared to non-carriers (Huttenlocher et al., 2015). Additionally, although neuroimaging and electrophysiological findings associated with PD have shown some premorbid changes in heterozygous mutation carriers, such as reduced fluorodopa uptake in the striatum, these individuals have not been reported to be clinically diagnosed with PD (Khan et al., 2002; Hilker et al., 2001; Khan et al., 2005; Inzelberg et al., 2005).

One argument that has been advanced to explain the presence of heterozygous mutations in *PRKN* in apparently sporadic disease is that these variants might be associated with dominant inheritance but with diminished penetrance, suggesting that partial loss of function mutations would lead to milder forms of PD. Several studies have been performed in

families, with the expectation that heterozygous carriers would also have PD, but these studies have yielded conflicting results. Some have reported that heterozygous relatives of *PRKN*-linked cases suffer from mild parkinsonism (Klein et al., 2000; Farrer et al., 2001) but not a full PD-like phenotype. However, others have not replicated any observations of parkinsonism in heterozygous carriers (Wang et al., 2013). Due to its large genomic size and diversity of mutations it is possible that some mutations in the second allele remain undetected in apparently heterozygous individuals.

PINK1 (PARK6)

The *PARK6* locus was initially mapped to chromosome 1 in three different consanguineous families (Valente et al., 2001; Valente et al., 2002). Upon sequencing candidate genes in the region, *PINK1* was confirmed to contain homozygous missense mutations (Valente et al., 2004a). Additional missense mutations have since been identified in several other consanguineous pedigrees (Hatano et al., 2004). It has been estimated that *PINK1* mutations are found in 3.7% of EOPD cases worldwide, with frequencies ranging from 0.6% in European descent cases to 13.5% in Asian populations (Kilarski et al., 2012).

Similarly to *PRKN*, several lines of evidence suggest that heterozygous *PINK1* mutations can act as risk factors for idiopathic PD (Rogaeva et al., 2004; Bonifati et al., 2005; Abou-Sleiman et al., 2006; Valente et al., 2004b). A recent study reported that carrying one copy of the rare p.G411S mutation in PINK1 increases risk of PD to a greater degree than other disease-associated variants (Puschmann et al., 2017). The p.G411S variant significantly decreases PINK1 kinase activity in neurons and the average age at disease onset is significantly younger in p.G411S mutation carriers than in non-carriers. Some clinical examinations of heterozygous relatives of homozygous *PINK1* carriers have shown signs of mild parkinsonism (Criscuolo et al., 2006; Hedrich et al., 2006; Hiller et al., 2007; Djarmati et al., 2006). However, not all heterozygous relatives present with such symptoms. Similar to *PRKN* mutations, therefore, whether *PINK1* alleles cause disease by haploinsufficiency or a low-penetrance dominant mechanism is uncertain. However, a meta-analysis of approximately 1,000 cases and 400 controls for heterozygous *PINK1* variants found no significant difference in frequencies between the populations (Marongiu et al., 2008). The conflicting evidence at this locus suggests a role for *PINK1* in idiopathic PD but more data is needed to validate this correlation.

Deciphering whether heterozygous variants in recessive genes are risk factors for idiopathic PD is important for the understanding the etiology of disease. Among individuals with PD, the number of carriers of heterozygous mutations in recessive genes surpasses the number of homozygous or compound heterozygous carriers, suggesting that they could be susceptibility factors or disease modifiers. These genes might also contribute to the heritability of idiopathic PD in a subset of carriers making them possible drug targets. Conversely, it is also possible that other mutations have been missed in *PRKN* or *PINK1* or that there is a secondary mutation in an unknown modifier gene. Theoretically, non-coding variation at either of these loci that reduce expression on the unaffected allele may result in a PD phenotype if only the mutant allele is expressed. In the coming years, well powered

human genetic studies will be decisive in robustly uncovering the role of heterozygous variants in recessive genes and their effect in PD.

Genome-wide association studies link sporadic and monogenic parkinsonism

There is growing evidence that the multiple pathways identified in monogenic PD also play a role in sporadic PD, showing that they are not separate entities and several genes might interact to regulate downstream common targets. This type of pleomorphism can be extrapolated to several PD related loci identified by GWAS including *ACMSD, CSMD1, GCH1,* and *VPS13C*. These candidate loci contain common variants linked to sporadic forms of PD, and putative rare pathogenic variants have also been described in monogenic cases with either PD or a parkinsonism syndrome.

Supporting the link between monogenic and sporadic etiologies, mutations in *GCH1* have been found to segregate in families with a combination of members with adult-onset parkinsonism or dopa-responsive dystonia following an autosomal dominant pattern of inheritance with incomplete penetrance (Hagenah et al., 2005). Prompted by this observation, a follow-up large exome sequencing study showed that known *GCH1* pathogenic mutations are more frequent in sporadic PD cases than in controls and are associated to a 7-fold increase in the risk for developing PD (Mencacci et al., 2014). These results were also supported by the latest PD meta-analysis which also nominated this locus at a significant level.

Another example of possible shared etiologies comes from a recent screening of individuals in a three generation pedigree affected with familial cortical myoclonic tremor and epilepsy, which pointed to p.Trp26Stop in *ACMSD* as a disease-segregating and predicted pathogenic mutation (Martí-Massó et al., 2013). Interestingly, one family member also exhibited parkinsonism and *ACMSD* is in a region associated with sporadic PD by GWAS (International Parkinson Disease Genomics Consortium et al., 2011). Subsequently, the *ACMSD* p.Glu298Lys mutation was detected in a single individual with late onset sporadic PD (Vilas et al., 2017) suggesting that rare variants within *ACMSD* may cause PD. Another genetic study performed in two unrelated families with PD identified two novel, heterozygous variants in the *CSMD1*, each resulting in mutation of a highly conserved amino acid, suggesting that they may cause PD (Ruiz-Martínez et al., 2017). The most convincing example, *VPS13C* was first reported as a susceptibility risk locus for PD (Nalls et al., 2014). Later, homozygous and compound heterozygous truncating mutations were found to cause a very severe type of autosomal recessive PD (Lesage et al., 2016). The shared role of these genes in monogenic and sporadic PD requires further validation in large well-powered studies but indicates that loci associated with sporadic forms of PD may also contain very rare variants that can cause monogenic PD.

Mutations in *MAPT* can cause parkinsonism and are risk factors for Parkinson's disease

Although *MAPT*, which encodes the neuronal structure protein tau, is not considered a PARK gene there are several lines of evidence that link this gene to PD. Rare pathogenic variants in *MAPT* have been identified in several neurodegenerative diseases including tauopathies such frontotemporal dementia (FTD) (Hutton et al., 1998) and PSP (Spillantini et al., 1998; Clark et al., 1998; Haussmann et al., 2017; Poorkaj et al., 2002). Individuals carrying these *MAPT* mutations often present with a typical behavioral FTD phenotype as well as motor symptoms resembling parkinsonism (Wszolek et al., 2006).

The *MAPT* gene is found within a region of high linkage disequilibrium (LD) that covers ~1 Mb of chromosome 17. Two major *MAPT* haplotypes have been identified, H1 and H2, that are inverted relative to each other and each have several sub-haplotypes (Steinberg et al., 2012). Common variants within the H1 haplotype have been associated with PD (Nalls et al., 2014) and several other neurodegenerative diseases, including FTD (Verpillat et al., 2002), PSP (Höglinger et al., 2011) and AD (Jun et al., 2016; Desikan et al., 2015). It is noteworthy that *MAPT* is the only risk locus that is shared between Alzheimer's disease (AD) and PD. A recent study has shown that PD patients who are homozygous for the H1 haplotype have a significantly increased burden of Lewy bodies in the neocortex compared to cases with the H2 haplotype (Robakis et al., 2016).

There are several transcripts of *MAPT* expressed in the CNS and multiple eQTLs have been identified that are associated with differences in alternate transcript levels (Blauwendraat et al., 2016; Ramasamy et al., 2014; Myers et al., 2007). A specific SNP within the H1 haplotype has been suggested to be involved in the regulation of exon 3 retention and thus there may be splicing quantitative traits as well eQTLs at this locus (Lai et al., 2017). This is a potential disease mechanism as exon 3 retention may change the interaction partners of tau protein. Overall, these findings show that the *MAPT* locus is highly pleomorphic, although the genetic and molecular underpinnings of its association with PD remain to be determined.

Mutations in *GBA* increase risk of PD

Mutations in *GBA*, encoding the glucocerebrosidase enzyme, were first identified as the cause of the autosomal recessive lysosomal storage disorder Gaucher disease in the 1980s (Tsuji et al. 1987). Currently over 300 GBA mutations have been identified which typically result in a reduced enzyme activity (Montfort et al. 2004). Clinically, Gaucher disease patients can display parkinsonian symptoms, and many studies have identified an increased frequency of heterozygous GBA mutations in PD cohorts (Aharon-Peretz et al., 2004; Clark et al., 2007). Subsequently, large multicenter studies identified a significant increase of *GBA* coding variants in both PD and DLB cases compared to controls and that the genetic influence of GBA is higher in DLB than PD (Sidransky et al. 2009; Nalls et al., 2013). Others have shown that PD patients who are *GBA* mutation carriers are more likely to develop cognitive impairment and dementia (Cilia et al. 2016) that is independent of Alzheimer disease pathology (Tsuang et al., 2012). Additionally, mutations in *GBA* are

associated with an earlier age of onset of PD compared to non-carriers (Clark et al. 2007; Alcalay et al., 2012, Blauwendraat et al., 2018)

Heterozygous coding variants in GBA are therefore a common genetic cause of PD and they have also been associated with sporadic PD by GWAS (Nalls et al., 2014; Chang et al., 2017; Nalls et al. 2018). Although GBA coding variants explain the majority of the GBA GWAS signal there also appears to be independent non-coding signal (Blauwendraat et al., 2018; Berge-Seidl et al., 2017; Nalls et al., 2018). Interestingly, some coding variants like p.E365K are associated with PD and have a significant effect on glucocerebrosidase activity (Alcalay et al., 2015) but do not cause Gaucher disease in homozygous state. Reduction of functional glucocerebrosidase has been shown to result in an accumulation of SNCA protein in neurons (Cullen et al. 2011; Du et al. 2015) highlighting the importance of functional lysosomes in healthy aging (Robak et al. 2017). All of this evidence points to GBA as a significant, but low penetrant, risk factor for PD with alleles that may or may not cause Gaucher's disease.

Future directions

Remarkable progress has been achieved in the understanding of the genetic architecture underlying monogenic and idiopathic PD in the past twenty years. Over 15 genes now have been identified to cause monogenic forms of PD and over 40 independent loci are associated with increased risk of sporadic PD. It is becoming clear that some genes exist that contain both deleterious and highly penetrant coding mutations as well as coding and non-coding variants that increase risk for idiopathic disease. This data is prima facie evidence suggesting a pathophysiological link between monogenic and idiopathic forms of PD. Monogenic and sporadic cases of PD are often clinically indistinguishable and it is clear that both forms share common genetic determinants. It is likely that the monogenic and sporadic dichotomy will break down in the coming years, when stratifying and redefining disease subtypes improves.

Despite the considerable success in identifying the genetic components associated with disease risk, a major challenge remains to understand the mechanisms by which pleomorphism affects biological function to contribute to PD risk. Observations at both the *LRRK2* and *SNCA* loci suggest that risk factors act in a similar manner to more penetrant mutations, in both cases by providing an enhancement of function but in a quantitatively smaller manner. This has important implications for disease-modifying treatments as it suggests that strategies to limit toxicity of dominant PD gene products might be helpful for sporadic PD.

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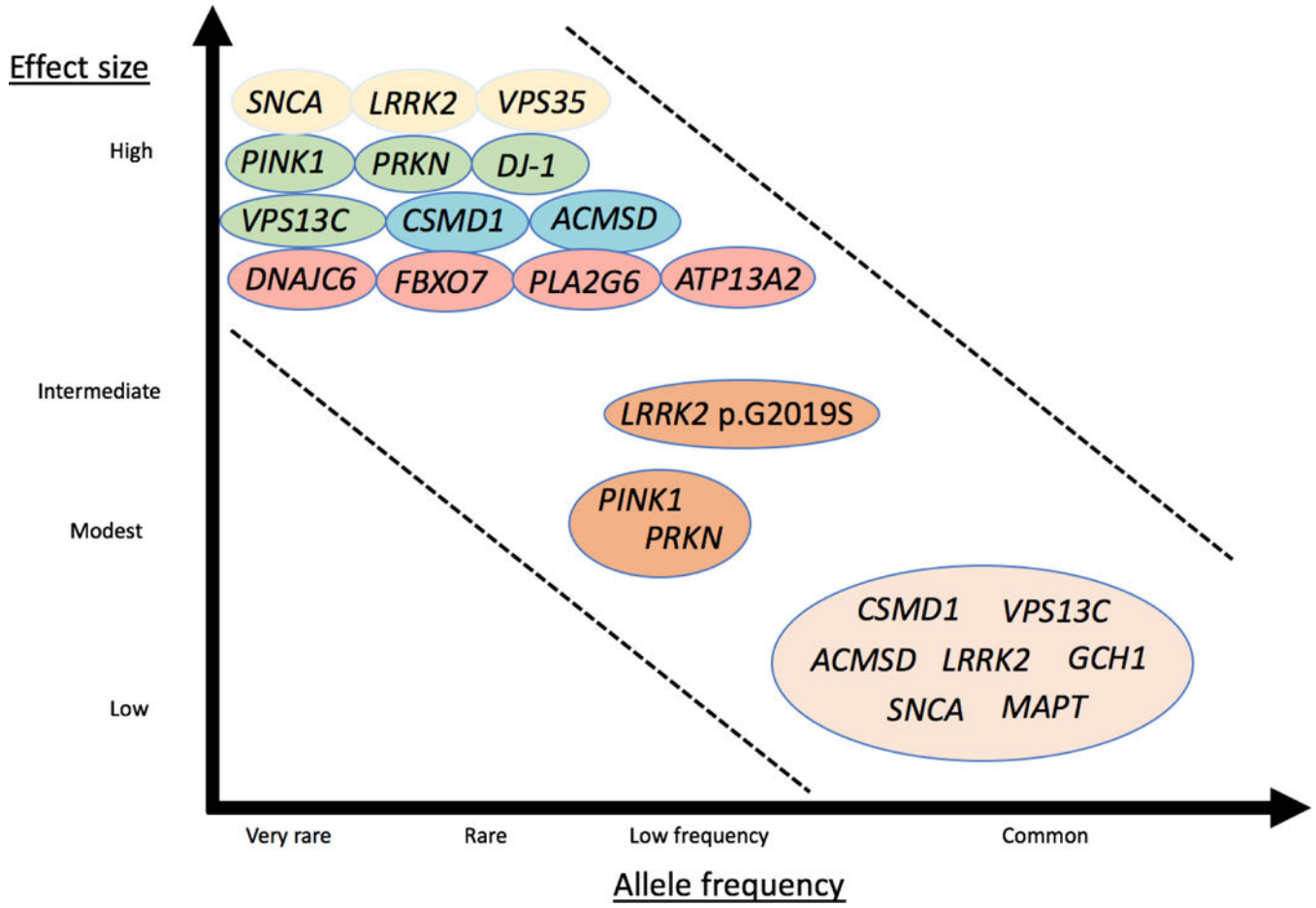

Figure 1.

Continuum of genes of different phenotypic effect sizes and allele frequencies. Colors symbolize modes of inheritance: dominant (yellow), recessive (green), recessive atypical parkinsonism (pink), possibly disease-causing genes (blue), dominant with incomplete penetrance (orange), risk loci (light orange). Modified from McCarthy et al., 2008 (McCarthy et al. 2008).

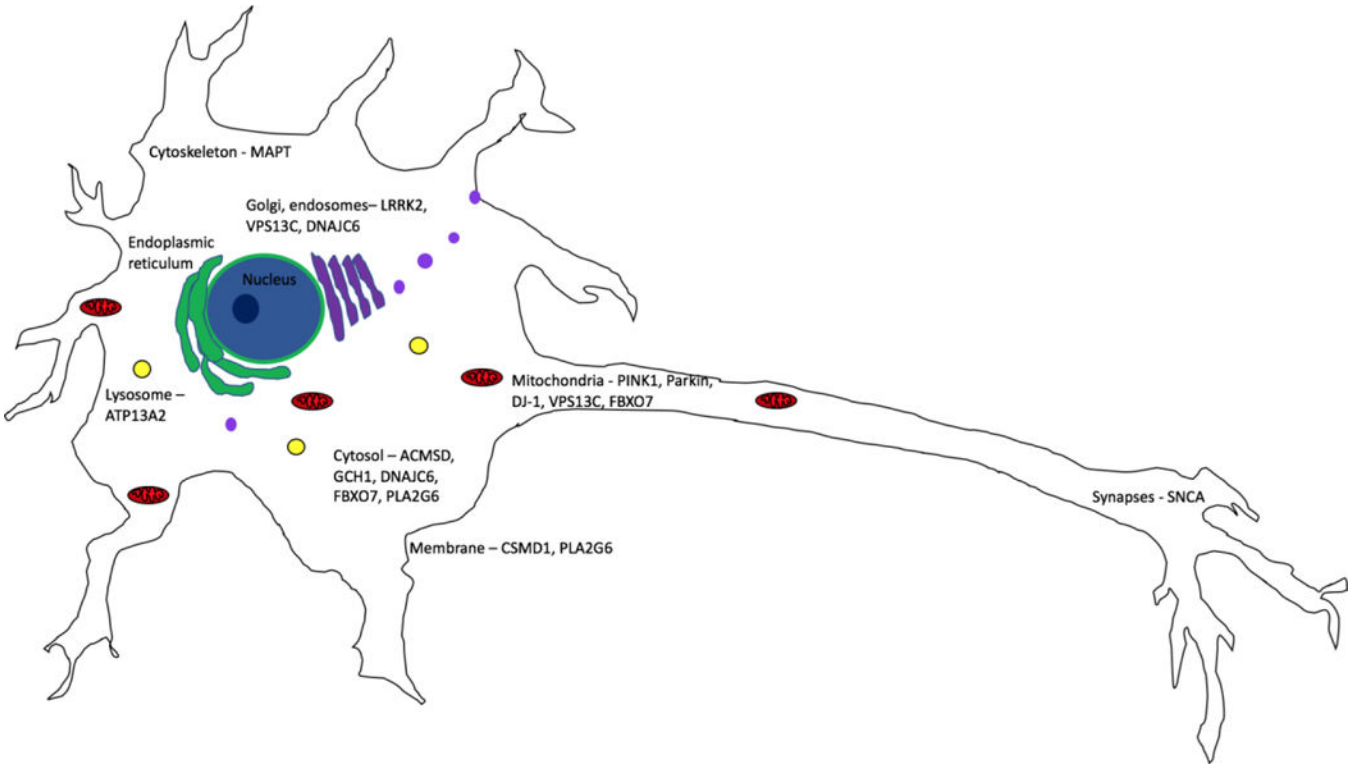

Figure 2.

Subcellular localization of genes predicted to be involved in sporadic Parkinson's disease. The most common subcellular localization for genes associated with sporadic PD is in the cytosol, mitochondria, and in organelles involved in vesicular trafficking, Golgi Network and endosomes.