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Are We Listening to Everything the PARK Genes are Telling Us?

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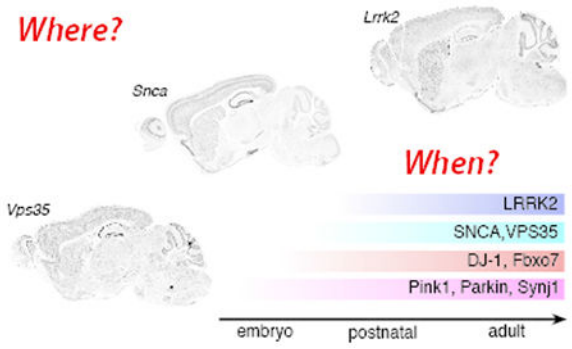
Abstract

The cardinal motor symptoms that define Parkinson's disease (PD) clinically have been recognized for over two hundred years. That these symptoms arise following the loss of dopamine neurons in the substantia nigra has been known for the last fifty. These long-established facts have fueled a broadly held expectation that degenerating dopaminergic neurons alone hold the key to understanding and curing PD. This prevalent expectation is at odds with the observation that many nonmotor symptoms, including depression and cognitive inflexibility among others, can appear years earlier than the overt dopaminergic neuron degeneration that drives motor abnormalities and are not improved by levodopa treatment. Thus, preserving or rescuing dopamine neuron health and function is of paramount importance, but this alone fails to capture the underlying neurobiology of earlier-appearing nonmotor symptoms. Insight into the complete landscape of disease-related abnormalities and the context in which they arise can be gleaned from a more comprehensive consideration of the *PARK* genes that are known to cause PD. Here, we make the case that a full incorporation of research showing when and where *PARK* genes are expressed as well as the impact of gene mutation on function throughout life, in tandem with research studying how dopaminergic neuron degeneration begins, is essential for a full understanding of the multi-dimensional etiology of PD. A broad view may also reveal something about long-term adjustments cells and systems make in response to gene mutation and help to identify mechanisms conferring the resilience or susceptibility of some cells and systems over others.

Graphical Abstract



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Keywords

Parkinson's Disease; *PARK* Genes; nonmotor symptoms; development; critical periods; protein trafficking; protein degradation

Why study genetic forms of Parkinson's Disease?

The idea that PD can have a genetic component is relatively new in the context of a 200-year history. In 1997, point mutations in the gene encoding alpha-synuclein, *SNCA*, were found to cause an autosomal dominant form of PD (Polymeropoulos et al., 1997). Since then, a handful of PARK genes have been identified as monogenic causes of PD (Table 1). PARK genes account for only about 10% of total PD (de Lau and Breteler, 2006), but they are the subject of intensive research efforts with the hope that the PD arising from gene mutation will share features with sporadic PD and lead the way to cures. Laboratory efforts have been focused on (1) producing animal models of the disease that could be used to interrogate disease progression and for testing therapies; (2) gaining an understanding of the functional consequences of particular mutations in order to discover triggers responsible for initiating the disease; and (3) identifying mechanisms shared by PARK proteins that point toward common pathways.

Despite substantial progress towards each of these goals (e.g. Chesselet et al., 2012; Vingill et al., 2016; Cao et al., 2017), to date, no single PD gene mutation has produced a bona fide PD model in laboratory animals having the defining motor deficiencies arising as a consequence of the progressive degeneration of dopaminergic neurons in the SN (Blesa and Przedborski, 2014). This suggests either that PD is a uniquely human disease or that the appropriate conditions (environment, age, etc.) have not yet been met in the animal models (usually rats and mice). The difficulty of identifying suitable rodent models for neurodegenerative diseases is a roadblock that extends well beyond PD, as several lines of evidence indicate that rodents are more resistant to many forms of neurodegeneration than humans and cellular mechanisms underlying neurodegeneration may display species-specific differences (Seok et al., 2013; Kreiner, 2015; Burbulla et al., 2017). Human inducible pluripotent stem cell (hiPSC)-based models are particularly valuable for elucidating human-specific cell biological functions, but they are currently limited as a model for understanding the impact of such cell biology on synaptic circuit function and the behaviors they support. This limitation is partly a reflection of the relative state of immaturity of the neurons, as their gene profiles best match human neurons in their first trimester of life (Brennand et al., 2015) and partly because they do not generate complex circuits, although this may change with continued progress in the generation of 3-d organoid stem cell cultures (Lancaster et al., 2013).

Challenges associated with producing bona fide disease models should not obscure the enormous gains that have been made in understanding the biology of PD-causing genes and the impact of PD-causing gene mutations on the activity and function of neural circuits generally and in systems relevant to PD. In contrast to neural degeneration, basic principles

of cell biology and circuit development in rodents have proven to be good predictors for the function of cells and circuits in humans.

Three PARK Gene Groups in Space and Time

For the purposes of this review, we have placed the *PARK* genes into three groups (I-III) based on pattern of inheritance, age of motor symptom onset, and cellular actions (Table 1). Binning genes into groups inevitably obscures some important nuances and to counter this we highlight some areas of crosstalk between the groups, but the strategy provides a useful construct for discussion.

Group I comprises six genes, *PARKIN, PINK1, DJ-1, FBXO7, VPS13C* and *ATP13A2.* Mutations identified in these genes produce autosomal recessive forms of PD that appear to be loss of function. Symptoms typically emerge much earlier than sporadic PD and as early as the first decade of life, consistent with a developmental disorder. All of the encoded proteins in this group act in cellular pathways that are relevant for marking and clearing defective mitochondria or for maintaining mitochondrial health, and this has been the subject of multiple reviews (Abou-Sleiman et al., 2006; Farrer, 2006; Corti and Brice, 2013; Itoh et al., 2013; Scarffe et al., 2014; Menzies et al., 2015; Ryan et al., 2015). Briefly summarized, PARKIN, PINK1 and FBXO7 work coordinately to promote mitophagy (Clark et al., 2006; Springer et al., 2006; Yang et al., 2006; Narendra et al., 2008; Narendra et al., 2010; Pompilio and Kacelnik, 2010; Burchell et al., 2013; Bingol and Sheng, 2016). In parallel, Parkin can also regulate mitochondrial biogenesis indirectly by controlling levels of the transcriptional repressor, PARIS (Shin et al., 2011). DJ-1, VPS13C and ATP13A2 appear to act in pathways that lie upstream (DJ-1 and ATP13A2) or in parallel (VPS13C) to the others indirectly regulating mitochondrial health (Canet-Aviles et al., 2004; Park et al., 2014; Moscovitz et al., 2015; Lesage et al., 2016; Burbulla et al., 2017) or degradation (Dehay et al., 2012; Kong et al., 2014; Tsunemi and Krainc, 2014). Whether direct or indirect, the actions of this cohort of genes on mitochondria dovetail with data showing that neurotoxins known or suspected to cause PD-like motor dysfunction including MPTP, rotenone and paraquat interfere with mitochondrial metabolism (Martinez and Greenamyre, 2012). Early disease onset suggests the impact of these genes is direct and cumulative. In this light it is interesting that *PARKIN* mutations rarely produce Lewy Bodies, the neuronal cytoplasmic inclusions that are the pathological hallmark of sporadic Parkinson's Disease (Postuma et al., 2015), suggesting that some mechanisms may lie downstream of or can bypass production of Lewy pathology.

In situ hybridization data show that Group I genes are expressed broadly and almost homogeneously throughout the brain (Fig. 1) and body (www.proteinatlas.org; Uhlen et al., 2015; Allen Institute; Lein et al., 2007) beginning prior to birth and continuing through life (Fig. 2). On its surface, this pattern contradicts the apparent selectivity of PD symptoms. However, with respect to dopaminergic neurons, specificity may arise from intrinsic properties since strong data support that their tonic pacemaking activity is uniquely dependent on calcium currents that render them vulnerable to oxidative stress (Puopolo et al., 2007; Guzman et al., 2010; Burbulla et al., 2017). Selective vulnerability of dopamine neurons could also reflect the huge bioenergetic demands of maintaining extensive and

uniquely complex axonal arbors (Bolam and Pissadaki, 2012). Conversely, the broad expression pattern of Group I genes suggests that most cells may be able to tolerate or can functionally compensate for loss of gene function. Additional populations may not die, but may suffer consequences mediated by the mutations. A recent study by Vingill and colleagues (Vingill et al., 2016) pinpoints the relevance of restricted populations of cells to particular disease symptoms while also highlighting the presence of pathology that sits outside the usual suspects. In mice, conditional deletion of *Fbxo7* from forebrain glutamatergic neurons produces pyramidal tract–like motor impairments such as hindlimb clasping beginning at two months of age (Vingill et al., 2016) and consistent with symptoms seen in humans lacking FBXO7 (Di Fonzo et al., 2009). In contrast, conditional deletion in dopaminergic and noradrenergic neurons produces PD-like deficits in motor coordination and mobility beginning at six months. Germline *Fbxo7* knockout mice display motor deficits consistent with combining the impairments observed in the two conditional mutants, but the phenotypes are more severe, the age of onset much earlier and death ensues by P28 (Vingill et al., 2016). Thus, while gene mutations in restricted cell populations are sufficient to produce particular symptoms, germline knockout reveals additional effects that extend well beyond the conditional phenotypes and which are likely contributed by other cell populations that also normally express FBX07.

In addition to their impact on mitochondria, most Group I genes play additional roles that would also be expected to affect cell health. For example, FBX07, also regulates proteasome assembly (Vingill et al., 2016), Parkin-mediated ubiquitination targets several non-mitochondrial proteins, including Kainate receptors, to the proteasome (Shimura et al., 2000; Maraschi et al., 2014), DJ-1 has chaperone activity (Shendelman et al., 2004; Zhou and Freed, 2005), and ATP13A2 plays an important role in the normal regulation of lysosome function and α-synuclein clearance (Dehay et al., 2012; Kong et al., 2014; Tsunemi and Krainc, 2014). These data suggest that mechanisms supporting protein homeostasis are also negatively impacted by the loss of Group I proteins in a variety of cells, and would be expected to be deleterious, or at the very least, to exacerbate the impact of cellular stressors.

Group II contains *SNCA, LRRK2* and *VPS35* (Table 1). The genes *DNAJC13* or *TMEM230* may also be part of this group, but they were identified in the same extended family dataset and have yet to be confirmed, so we have excluded them here (Vilarino-Guell et al., 2014; Deng et al., 2016). Group II genes cause autosomal dominant, late-onset forms of PD. Disease symptoms and progression closely resemble idiopathic PD, making this group particularly relevant for understanding PD in general. The members of this group show interesting anatomical and cellular expression patterns that are more restricted than Group I genes and help to define cell populations most relevant to PD. Group II gene expression is most enriched in cerebral cortex and neostriatum, the major postsynaptic targets for SN dopaminergic neurons, underscoring the idea that retrograde signaling from postsynaptic targets may be relevant to the degeneration of dopamine-expressing neurons (for review, see Bjorklund et al., 1997; Volta et al., 2015; Tagliaferro and Burke, 2016). Group II genes also show a striking increase in expression during synaptogenesis (Fig. 2) in a pattern that is consistent with them playing roles in shaping neural circuits. This developmental^ late onset of expression is also consistent with research showing that Group

II proteins are largely dispensable for earlier events in brain development such as regionalization and neuronal cell migration (Abeliovich et al., 2000; Herzig et al., 2011; Wang et al., 2012). All of the encoded Group II proteins regulate intracellular membrane trafficking.

SNCA encodes α-synuclein (Maroteaux and Scheller, 1991), which is the main component of Lewy bodies (Spillantini et al., 1997). *SNCA* mutation, duplication or triplication in humans is associated with the generation of Lewy Bodies (Singleton et al., 2003; Singleton and Gwinn-Hardy, 2004) and data from animal models support that α-synuclein mutation, and in particular, increased levels, produce Lewy pathology (Fernagut and Chesselet, 2004). Lewy pathology can also develop in the absence of endogenous *SNCA* mutation and can originate outside the central nervous system from exogenously introduced α-synuclein fibrils and propagate extracellularly like a prion-mediated disease (Kordower et al., 2008; Volpicelli-Daley et al., 2011; Luk et al., 2012; Brundin and Melki, 2017). Aggregated exogenous α-synuclein oligomers can also interfere with lysosomal (Decressac et al., 2013) and mitochondrial function (Luth et al., 2014).

α-Synuclein is enriched in brain and erythroid cells (Nakai et al., 2007). Within the brain, it is expressed almost exclusively in neurons (Gokce et al., 2016), and highest levels are observed in olfactory bulb, cerebral cortex, dorsal and ventral striatum, hippocampus, and SN (Fig. 1). α-Synuclein and its closely related family members, β- and γ-synucleins, concentrate in presynaptic terminals, loosely associated with vesicle membranes (Iwai et al., 1995; Fortin et al., 2005) where they appear to negatively regulate vesicle tethering to one another and to the presynaptic active zone (Vargas et al., 2017). It is likely that it is through these interactions and effects on membrane curvature (Lautenschlager et al., 2017) that synucleins modulate vesicle endo- and exocytosis. Mice lacking all three isoforms show slower synaptic vesicle endocytosis (Vargas et al., 2014) and increased exocytosis (Greten-Harrison et al., 2010; Anwar et al., 2011), while overexpression attenuates release of both synaptic and large dense core vesicles (Larsen et al., 2006; Nemani et al., 2010; DeWitt and Rhoades, 2013). At dopaminergic terminals α-synuclein A30P mutation or overexpression can also impede vesicle release (Nemani et al., 2010; Janezic et al., 2013; Taylor et al., 2014) and in hippocampal neurons, alter vesicle tethering (Vargas et al., 2017). In contrast to these relatively modest effects, strong, repetitive stimulation in the presence of excess α-synuclein in *a* lamprey nerve preparation nearly eliminates normal endocytosis (Busch et al., 2014), and in mouse neurons, action potential dependent activity promotes α-synuclein secretion (Yamada and Iwatsubo, 2018). Thus, it may be that synucleins exert their greatest influence over particular kinds of synaptic activity, regulating trafficking events that are especially important for maintaining sustained, highly demanding activity as well as producing widespread responses (Diogenes et al., 2012; Shrivastava et al., 2015).

Mutant or overexpressed SNCA can also produce a blockade of ER to Golgi vesicle trafficking that appears to be a pathological gain in function because it is not consistent with results from SNCA knockout preparations and it targets cellular domains that extend beyond the normal expression pattern of SNCA, which is highly restricted to presynaptic terminals. In mammalian cells the blockade can be relieved by overexpression of Rab1, Rab3A or Rab8A, small GTPases that are important for directing and regulating vesicle traffic (Outeiro

and Lindquist, 2003; Cooper et al., 2006; Gitler et al., 2008). Collectively, the data support a role for mutant or overexpressed SNCA in regulating vesicle traffic within and outside of synaptic terminals.

LRRK2 encodes a very large 286kDa multifunctional protein having interactive kinase and GTPase domains. PD causing mutations cluster in these two enzyme domains and most of them increase the phosphorylation of LRRK2 substrates (West et al., 2005; Greggio et al., 2006; Smith et al., 2006; West et al., 2007; Steger et al., 2016). Within the nervous system, LRRK2 is enriched in forebrain neurons (Gokce et al., 2016), with particularly high levels in cerebral cortex, dorsal and ventral striatum (Fig. 1). Expression levels are far lower in dopaminergic neurons in mice (West et al., 2014) and humans (Sandor et al., 2017). The regional distribution pattern displayed by LRRK2 mRNA is very similar to α-synuclein and more restricted than most *PARK* genes (Fig. 1), highlighting brain regions likely to be particularly important for PD symptoms. LRRK2 is also expressed at high levels in kidney and lung and in peripheral immune cells, including monocytes, dendritic cells and lymphocytes (Gardet et al., 2010; Hakimi et al., 2011; Thevenet et al., 2011). Significantly, its levels rise in immune cells, including brain microglia, upon stimulation (Gardet et al., 2010; Thevenet et al., 2011; Moehle et al., 2012). LRRK2 appears to act as a pro-inflammatory agent consistent with point mutations near or within *LRRK2* that have been linked to inflammatory bowel disease and leprosy (Barrett et al., 2008). Since PD is associated with inflammation (Whitton, 2007; Dzamko et al., 2015), immune actions of LRRK2 are likely to be as relevant as neuronal mechanisms.

A growing body of research supports that LRRK2 kinase activity regulates vesicle trafficking (e.g. Piccoli et al., 2011; Matta et al., 2012; MacLeod et al., 2013; Beilina et al., 2014), but mechanistic detail is sparse. The most direct evidence for this role comes from the identification of several Rab family members as *in vivo* substrates for LRRK2-mediated phosphorylation (Steger et al., 2016). Phosphorylated Rabs have reduced affinity for most Rab effectors and would be predicted to negatively regulate traffic (Steger et al., 2016). Increased LRRK2-mediated Rab phosphorylation can also interfere with the generation of primary cilia (Dhekne et al., 2018; Madero-Perez et al., 2018). Functional studies of LRRK2 knockout/knockdown or loss of function support that LRRK2 can regulate synaptic vesicle recycling with several studies supporting that LRRK2 promotes endocytosis (Matta et al., 2012; Arranz et al., 2015) and others that it regulates exocytosis (Piccoli et al., 2011). Such differences may be reconciled by recent work showing that LRRK2 regulation of synaptic vesicle recycling is mediated differently according to neuron type (Pan et al., 2017). LRRK2 can also regulate postsynaptic expression of AMPA receptors (Parisiadou et al., 2014; Sweet et al., 2015) an activity that normally utilizes a likely LRRK2 substrate, Rab8 (Gerges et al., 2004). At early postnatal ages in mice that carry a *Lrrk2-G2019S* knockin mutation, the most common *LRRK2* PD mutation (Paisan-Ruiz et al., 2013), spiny projection neurons (SPNs) in dorsal striatum show a substantial increase in glutamatergic activity and altered dendritic spine size (Beccano-Kelly et al., 2014; Matikainen-Ankney et al., 2016; Volta et al., 2017). Such excessive synaptic activity is driven in part by increased cortical activity (Beccano-Kelly et al., 2014; Matikainen-Ankney et al., 2016; Volta et al., 2017), and reflects mostly action potential based activity rather than spontaneous vesicle fusion (Matikainen-Ankney et al., 2016). The enhanced activity displayed by these circuits is transient, but is

concurrent with synaptogenesis (Matikainen-Ankney et al., 2016; Volta et al., 2017), thus leading to the prediction that abnormalities in striatal synaptic activity, first detectable at early postnatal ages, could have lasting consequences for the function of basal ganglia circuits (Kozorovitskiy et al., 2012).

LRRK2 mutation, and in particular, its increased kinase activity, additionally appears to increase levels of cellular stress and to impact pathways that normally clear misfolded proteins and damaged organelles. LRRK2 overexpression can promote apoptosis (Skibinski et al., 2014) and reduce chaperone-mediated autophagy (Orenstein et al., 2013), effects that are exacerbated by the G2019S mutation (Orenstein et al., 2013; Skibinski et al., 2014). LRRK2 may also normally regulate macroautophagy since LRRK2-KO mice and mice exposed to LRRK2 kinase inhibitors for long periods accumulate protein aggregates and macroautophagy intermediates in kidney where LRRK2 is expressed at exceptionally high levels. Recent work using transgenes in *Drosophila* also suggests that dLRRK phosphorylation of EndoA may positively regulate macroautophagy of synaptic vesicles (Soukup et al., 2016). These activities are not well understood, but they have gained a substantial level of enthusiasm in the field because they place LRRK2 in pathways important for clearing α-synuclein aggregates and defective mitochondria in ways that could be synergistic with the pathways outlined for the Group I genes. Conversely, recent work shows that Parkin stabilizes endocytic zones and regulates surface expression of AMPA receptors (Cortese et al., 2016), suggesting certain Parkin activities may also converge on LRRK2-dependent trafficking pathways (Parisiadou et al., 2014).

VPS35 mutations underlie the most recently discovered autosomal dominant form of PD (Wider et al., 2008). Its expression is enriched in the forebrain, but broader than LRRK2 or α-synuclein (Fig. 2). VPS35 functions as part of the retromer complex, which together with sorting nexins and Rab7a directs cargo from endosomes to the plasma membrane or to the trans-Golgi (Bonifacino and Hurley, 2008; Williams et al., 2017). Maintaining appropriate levels of VPS35 appears to be crucial as either too much or too little can alter trafficking or impair lysosome function and produce mitochondrial fragmentation (Miura et al., 2014; Wang et al., 2014; Munsie et al., 2015; Tang et al., 2015; Wang et al., 2016). Such data suggest a possible link to Group I's cellular stress pathways, but there is no evidence that altered levels of VPS35 play a role in PD (Ishizu et al., 2016). The most prevalent mutation, D620N, does not change protein stability (McGough et al., 2014; Tsika et al., 2014; Zavodszky et al., 2014; Munsie et al., 2015; Ishizu et al., 2016), but instead appears to interfere with retromer's interaction with the WASH complex, which drives generation of F-actin patches at endosomes (McGough et al., 2014; Zavodszky et al., 2014). Perhaps most relevant to the disease are data suggesting that the impact of the D620N mutation may be specific to particular cargos (Choy et al., 2014; Follett et al., 2014; McGough et al., 2014; Tian et al., 2015; Temkin et al., 2017), including proteins relevant to autophagy suggesting a point of interaction with LRRK2 or Group I proteins (Zavodszky et al., 2014; Tang et al., 2015). Such specificity could explain the late onset and could account for anatomical and cell type specificity of the disease, although earlier changes conferred by VPS35 mutation have been described. For example, a recent study has shown that VPS35-D620N knockin mice already display altered striatal dopamine release and turnover by three months of age (Cataldi et al., 2018). Specificity may also be driven by the more restricted localization of

LRRK2. Recent work supports that VPS35-D620N potentiates LRRK2 kinase activity suggesting the mutation is gain of function and in the same pathway as LRRK2 (Mir et al., 2018).

Mutations in **Group III** genes (Table 1), *DNAJC6* and *SYNJ1*, cause autosomal recessive forms of PD that are early onset, severe, and accompanied by cognitive decline (Edvardson et al., 2012; Koroglu et al., 2013; Krebs et al., 2013; Quadri et al., 2013; Olgiati et al., 2014; Olgiati et al., 2016), combining aspects of neurodevelopmental and neurodegenerative disorders. Both Synaptojaninl and Auxilin (the product of *DNAJC6)* are broadly expressed throughout the brain, but levels are highest in cortical neurons beginning before birth (Fig. 1, 2) (Gokce et al., 2016). They both regulate the removal of clathrin coats from internalized presynaptic vesicles and PD-mutation interferes with this process. Mice expressing mutant *SYNJ1* (R258Q knockin) accumulate clathrin coated vesicles in presynaptic terminals and show increased levels of Auxilin as well as Parkin (Cao et al., 2017). Data from Drosophila NMJ suggest that mutant Synaptogjaninl may also reduce presynaptic autophagy (Vanhauwaert et al., 2017). Mice lacking Auxilin (*DNAJC6* mutations are complete loss of function) accumulate clathrin coated vesicles at synapses, similar to *SYNJ1* mutants, and empty clathrin cages (Yim et al., 2010). Synaptojaninl and Auxilin act in the same pathway, but they do not compensate for one another: increased levels of Auxilin do not rescue mutant Synaptojaninl phenotypes and Synaptojaninl levels remain normal in the absence of Auxilin (Yim et al., 2010).

While these two forms of PD are accompanied by severe cognitive symptoms that are not observed in most PD, they highlight that endocytic trafficking, like mitochondrial health and clearance, is a common PD-sensitive pathway. Additionally, Parkin ubiquitinates (Trempe et al., 2009; Cao et al., 2014) and LRRK2 is suspected to phosphorylate Endophilin, Synaptojaninl and Auxilin (Matta et al., 2012; Arranz et al., 2015; Islam et al., 2016; Soukup et al., 2016; Nguyen and Krainc, 2018).

GBA1 is not classified as a PARK gene, but mutations in *GBA1* are the most common genetic risk factor for PD and warrant special emphasis. It encodes an enzyme that is expressed throughout the brain and body and is found on lysosomal membranes where it breaks down glucocerebroside (Willemsen et al., 1987). Homozygous loss of function mutations produce Gaucher's disease, a lysosomal storage disorder in which enzyme substrates accumulate and produce pathology in a wide variety of organs. Mutations (typically heterozygous) in *GBA1* also appear in PD patients where they are five times more commonly observed than in healthy controls (reviewed in Sidransky and Lopez, 2012). Pathological *GBA1* mutations all appear to decrease enzyme activity. A study of the distribution of active glucocerebrosidase suggests that activity normally varies considerably between brain regions and cell types (Herrera Moro Chao et al., 2015). This likely underlies particular symptoms and apparent differences in cellular vulnerability. *GBA1* mutation can reduce α-synuclein clearance, and significantly, increased levels of α-synuclein appear to decrease the enzyme's activity (reviewed in Wong and Krainc, 2016). How GBA1 mutations integrate with other causes of PD is not well understood, but they clearly point to the importance of normally functioning recycling and degradative pathways.

Brain circuits are affected by PARK genes throughout life

The late-life onset of dopamine neuron degeneration and subsequent motor symptoms of PD that dominate the clinical presentation have been somewhat tacitly viewed as a pathophysiological process that co-opts neuronal circuit function at the onset of the prodromal phase, usually later in life (Hawkes, 2008). However, as emphasized above, all of the *PARK* genes are expressed in the brain during development and throughout adulthood (Fig. 1, 2). Thus, PD-causing gene mutations are positioned to shape developing brain circuits, potentially changing fundamentally a variety of interconnected cell and synaptic networks throughout life, including and beyond the onset of neuronal degeneration. This is important, because it is well established that cortical and subcortical circuits display periods of heightened sensitivity to patterns and levels of synaptic activity during postnatal development that can permanently alter circuit structure and function (Wiesel and Hubei, 1963a; b). For example, during early postnatal life in mice, selectively silencing SPNs in dorsal striatum projecting directly to the SN (D_1R expressing) leads to decreased synaptic input to both silenced SPNs as well as to neighboring unmanipulated SPNs projecting to the globus pallidus (D_2R expressing). Selectively silencing pallidal-projecting SPNs has the opposite effect on both SPN subtypes. These effects are mediated through a multistep circuit and the consequences are long-lasting (Kozorovitskiy et al., 2012). Consequences can also be synapse specific. Embryonic day 9.5 deletion of Huntingtin in cerebral cortex, where it is most enriched, increases the pace of synaptogenesis in both cortical layer 5 neurons and in their dorsal striatum targets, but in adults, the resulting glutamatergic synapses are weaker in cortex and stronger in striatum than in control neurons (McKinstry et al., 2014). Even when the expression of mutant Huntingtin is restricted to development, ending at P21, at 9 months of age, mice show striatal neuron degeneration, motor deficits and altered corticostriatal plasticity similar to mice expressing mutant Huntingtin over the entire lifespan (Molero et al., 2016). Thus, by maturity, disease symptoms may emerge directly, as a cumulative consequence of these changes; indirectly, due to compensatory mechanisms; or they may arise independently, in response to an additional insult. Regardless, it is important to consider that PD-related symptoms may arise within an environment of cells, synapses and circuits that differ in important ways from an environment that had developed in the absence of mutation.

A consideration of LRRK2-G2019S knockin mice, where the mutant protein is expressed at normal physiological levels throughout life, illustrates these and related points. Elevated activity at glutamatergic synapses in striatum that is evident at three postnatal weeks is transient (as described in the section above), but synaptic responses in LRRK2-G2019S striatum remain functionally different than WT synapses into adulthood. In young adult G2019S mice, baseline AMPAR currents at glutamatergic synapses in nucleus accumbens, a part of the ventral striatum important for reward and motivation and implicated in the pathophysiology of depression (Carlezon et al., 2005; Bosch-Bouju et al., 2016; Han and Nestler, 2017), are mediated by a different composition of AMPAR subunits with fewer that are calcium permeable (CP) in comparison with WTs (Matikainen-Ankney et al., 2018). Dynamic trafficking of CP-AMPARs is an important, mechanistic component of persistent forms of synaptic plasticity (Plant et al., 2006; Ma et al., 2018; Zhou et al., 2018). Thus,

baseline differences between genotypes in AMPAR stoichiometry would predict defects in lasting forms of synaptic plasticity. Corticostriatal synapses normally display bidirectional plasticity--long-term potentiation (LTP), a strengthening of synaptic signals which is postsynaptically mediated (Kreitzer and Malenka, 2008; Ma et al., 2018), and long-term depression (LTD), a weakening of synaptic strength that is pre-synaptically mediated (Calabresi et al., 1992; Choi and Lovinger, 1997; Kreitzer and Malenka, 2007). Consistent with the prediction, LRRK2-G2019S mice are unable to express corticostriatal LTP, a deficit evident in both D_1R- and D_2R-SPNs. This deficit is evident at three postnatal weeks and sustained into adulthood (Matikainen-Ankney et al., 2018). Additionally, D_2R-SPNs abnormally display LTD following an LTP induction protocol. Thus, normally bidirectional striatal synaptic plasticity in WTs is instead abnormally unidirectional in G2019S striatum.

As might be predicted from impaired striatal synaptic plasticity, LRRK2-G2019S mice exhibit significant differences in striatal-dependent behavioral responses that depend on a full-range of synaptic modifications. Chronic social defeat stress (CSDS) is a validated rodent model of depression in which mice are subjected to brief, daily periods of physical subordination by a larger male aggressor mouse, then tested for their social interaction with a novel social target. WT mice that undergo CSDS exhibit one of two social behaviors when tested for social interaction--about half of the mice are "susceptible", meaning they display significant social avoidance and anhedonia-like behaviors that can be reversed by chronic antidepressants, while the rest are "resilient", meaning that despite defeat experience, they remain socially interactive (Golden et al., 2011). Susceptible WT mice acquire significant numbers of CP-AMPARs at synapses in the nucleus accumbens during social defeat, which in turn is thought to drive, at least in part, subsequent social avoidance behavior (Vialou et al., 2010). Resilient WT mice, in contrast, retain an AMPAR response profile that is more-or-less similar to unstressed control mice. Surprisingly, young adult LRRK2-G2019S mice are almost completely (~94%) resilient to CSDS (compared to 57% resilient WT mice), remaining highly socially interactive despite defeat experience, and concomitantly fail to acquire CP-AMPARs (Matikainen-Ankney et al., 2018). Thus, the G2019S mutation promotes resilience to chronic social stress in young adulthood which very likely reflects striatal synapses unable to display the full range of experience-dependent synaptic plasticity. In the absence of CSDS, G2019S and WT mice are indistinguishable on a variety of tasks across several behavioral domains, including motor coordination, anxiety, exploratory activity, self-care and anhe donia-like behaviors, consistent with other studies of different G2019S knockin lines of mice (reviewed in (Volta and Melrose, 2017). This could indicate that behavioral differences from WT mice become evident only under extreme, experience-dependent challenges, such as CSDS, and while the significance of a high degree of behavioral resilience to social stress in young adult LRRK2-G2019S mice is uncertain, it is possible this represents some kind of compensatory response. Since depression is a prominent comorbid non-motor symptom of PD (Ishihara and Brayne, 2006; Gaig et al., 2014), it is also possible that the behavioral resilience observed in young adult G2019S mice would give way to susceptibility later in life, an idea supported by transgenic mice overexpressing *LRRK2*-G2019S, which after 8 - 10 months of age show a profound deficit in hippocampal LTD (Sweet et al, 2015) and display anxiety and depression-like behaviors (Lim et al., 2018). It is unclear what would mediate the transition from adaptive resilience to

maladaptive susceptibility and depression, but progressive changes in dopamine or other systems could play a role.

In addition to LRRK2-G2019S, several other mouse models of PD gene mutations have also yielded significant changes in normal brain synaptic plasticity in young adults. For example, mice lacking either Parkin or Pink1 show impaired striatal LTP and LTD (Kitada et al., 2007; Kitada et al., 2009). DJ-1 knockout mice show a selective loss of striatal LTD (Goldberg et al., 2005), and hippocampal neurons in mice expressing VPS35-D620N show deficits in LTP and reduced activity dependent incorporation of CP-AMPARs (Temkin et al., 2017). Taken together, these data strongly suggest that mechanisms of synapse plasticity that rely on AMPA receptor trafficking are particularly sensitive to PD gene mutation. They also support that PD gene mutations regulate brain development and function and most likely alter the landscape in which disease symptoms appear. Even more likely, they contribute to the disease, but in the absence of DA neuron degeneration, pursuit of these results has been less than aggressive and it remains an area of research that has great promise.

What's Next?

Strong evidence supports that many of the PARK gene mutations change neural circuits and have a sustained influence on non-motor behaviors. This is likely to be true for all PARK gene mutations and similar to other brain disorders having genetic and experience dependent components (Caspi and Moffitt, 2006). Shared biological roles played by Group I genes justifies current focused efforts on understanding relationships between mitochondrial health and PD. At the same time, nearly all cells express Group I genes throughout the lifespan and nearly all Group I genes are multifunctional, having roles outside of mitochondrial health (and some of these roles are also shared). A broader view may reveal, for example, why most cells are resistant to PD pathology. Shared biological pathways and/or shared distribution patterns shown by Group II and Group III genes highlight the importance of membrane trafficking, endocytosis and mechanisms supporting sustained neural activity in cerebral cortex and dorsal striatum in addition to dopaminergic neurons. LRRK2 appears to have a highly restricted set of substrates, VPS35 may traffic an equally restricted set of proteins and work collaboratively with LRRK2, and α -synuclein and LRRK2 may selectively impact particular types of activity. These restricted roles may be important clues to cellular systems susceptible to cellular stress. The actions of Group III proteins for which disease onset is very early, underscore the relevance of endocytosis, and members of all three Groups as well as GBA1 are important for regulating autophagy and managing protein turnover. It is also worth highlighting that actions of PARK genes within the nervous system can be strongly influenced by interactions with other systems, and in particular, the immune system (Kannarkat et al., 2013; Dzamko et al., 2015). Additional work studying cross-talk will further the understanding of neural circuits and non-neural systems that contribute to or are impacted by PD and provide new insights into novel, targeted treatment strategies.

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When and where are Parkinson's disease (PARK) genes expressed in the brain? How do PARK gene mutations impact the development and function of neural circuits? Here we discuss how spatial and temporal expression data when coupled with emerging cellular mechanisms provide important clues for detecting, understanding and treating this disease.

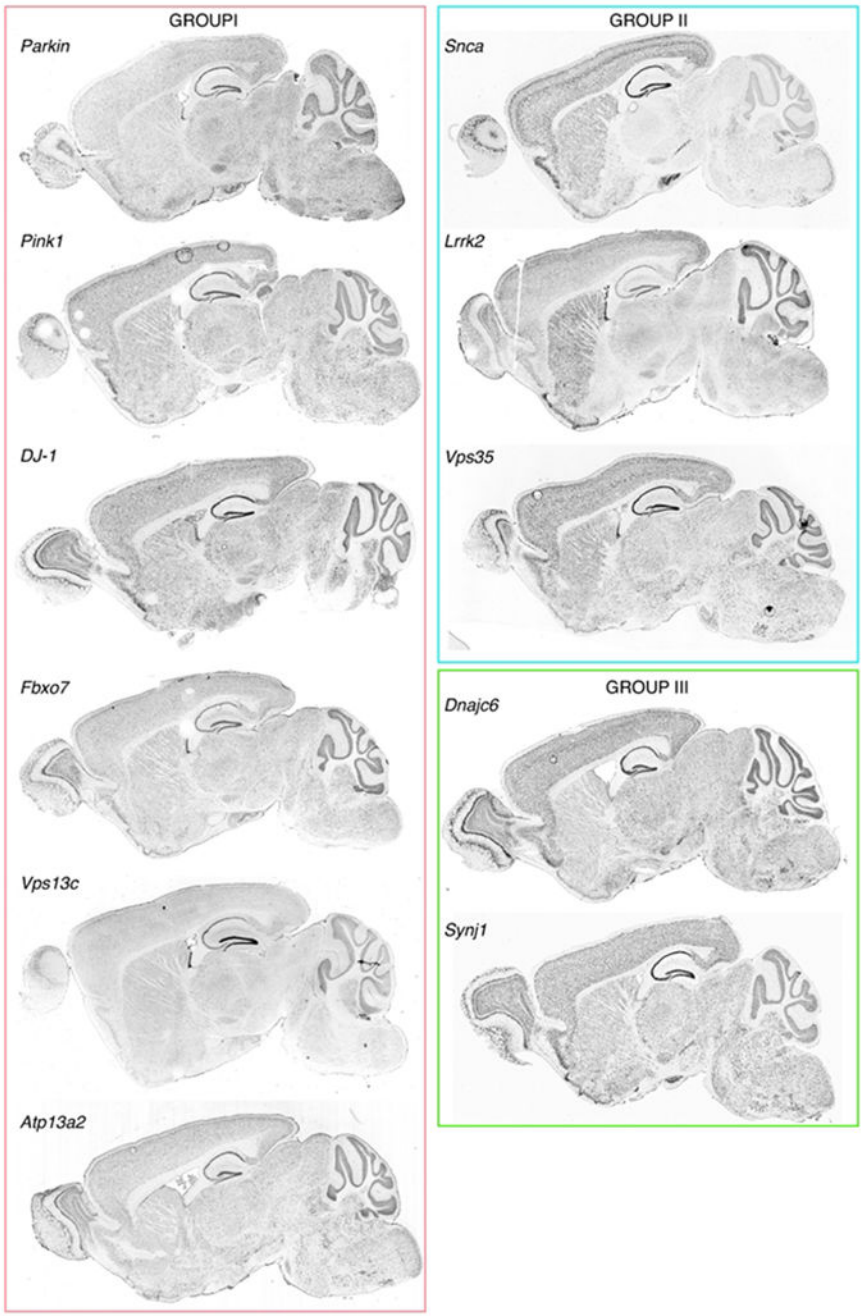

Fig. 1. Where PARK genes are expressed.

In situ hybridization showing regional distribution patterns of the PARK gene transcripts indicated in adult mice. All data shown are from the Allen Mouse Brain Atlas (Lein et al., 2007). Groups are defined and colored as indicated in Table 1 and text.

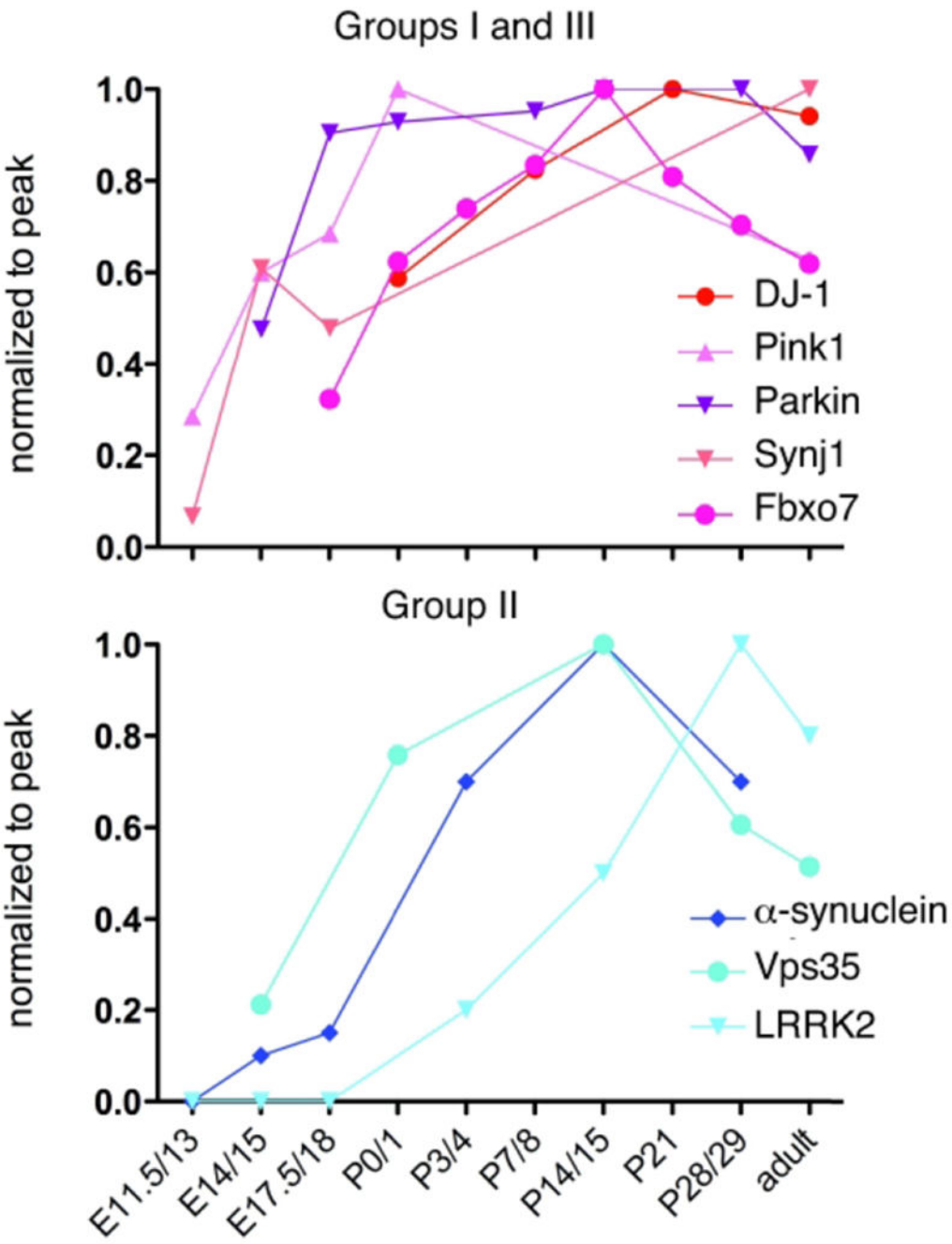

Fig. 2. When PARK genes are expressed.

Data from published papers was normalized to peak expression and then plotted in order to provide a gross comparison of the timing of expression of PARK genes(Petersen et al., 1999; Kuhn et al., 2004; Westerlund et al., 2008; Wang et al., 2012; Giesert et al., 2013; Beccano-Kelly et al., 2014; Bjorkblom et al., 2014; Choi et al., 2016). Colors are assigned by Groups defined in Table 1.

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TABLE 1

	GENE	Inheritance	Mutation	Typical age of onset (years)	Progression	Prominent symptoms outside of the motor symptoms defining PD	Response to L-DOPA	Lewy Pathology	Citations
Group I	*PARKIN/ PARK2*	AR	probable loss of function	24-40	slow	dystonia; depression; anxiety; autonomic	Yes	Rare	Kitada et al, 1998; Kahn et al, 2003
	PINK1/PARK6	AR	probable loss of function	18-56	slow	dystonia; depression; anxiety; autonomic	Yes	Yes (n=1)	Hatano et al, 2004; Valente et al, 2004; Steinlechner et al, 2007; Samaranch et al, 2010
	DJ-1/PARK7	AR	probable loss of function	24-40	slow	dystonia; anxiety	Yes	Yes (n=1)	Bonifati et al, 2003; Taipa et al, 2016
	ATP13A2/ PARK9	AR	probable loss of function	10-18	rapid	Kufor Rakeb Syndrome. supranuclear gaze palsy,spasticity,cognitive decline,pyramid atrophy; psychotic episodes.	Yes	Yes	Ramirez et al, 2006
	FBXO7/ PARK15	AR	probable loss of function	35-50	slow	dystonia; spasticity; pyramidal symptoms	Yes (non pyramidal)	?	Di Fonzo et al, 2009
	VPS13C/ PARK23	AR	probable loss of function	25-46	rapid	dysautonomia; cognitive decline; incontinence	Yes	Yes (n=1)	Lesage et al, 2016
Group II	*SNCA/PARK1 and PARK4*	AD	mutation; duplication; change and/or gain of function triplication; gain of function	35-65 30's	variable rapid	cognitive decline; depression; sleep disorders dementia; paranoia; hallucinations	Yes Yes	Yes Yes	Polymeropoulos et al, 1997; Ibanez et al, 2004; Chartier-Harlin et al, 2004 Singleton et al, 2003
	LRRK2/PARK8	AD	change or gain of function	50-65	slow	depression; sleep disorders; cognitive decline	Yes	not always	Paisan-Ruiz et al, 2004; Zimprich et al, 2004
	VPS35/PARK17	AD	partial loss of function	50-52	slow		Yes	No (n=1)	Vilarino-Guell et al, 2011; Zimprich et al, 2011
Group III	*DNAJC6*/ auxillin/ *PARK19*	AR	probable loss of function	10-42	rapid	seizures; pryamidal symptoms;intellectual disability	Mixed	?	Edvardson et al, 2012
	SJI/ synaptojanin/ *PARK20*	AR	partial loss of function	20-30	rapid	generalized seizures; cognitive decline; supranuclear gaze palsy	Yes but develop dyskinesia	?	Krebs et al, 2013