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Review

# Correlation between the biochemical pathways altered by mutated parkinson-related genes and chronic exposure to manganese

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ABSTRACT

The studies presented in this review attempt to describe the operative properties of the genes involved in generation of early and late onset of Parkinson's disease or Parkinson-like disorders and how mutation in these genes relate to onset of manganism. These include the genes α-synuclein, parkin, PINK1, DJ-1, ATP13A2, and SLC30A10 which are associated with early-onset of Parkinson's as well as those genes linked with late onset of the disorder which include, LRRK2 and VPS35. Since mutations in these genes and excess Mn potentially disrupt similar cellular processes within the basal ganglia, it is reasonable to hypothesize that the expressed symptoms of Parkinson's disease may overlap with that of manganese (Mn) toxicity. There appears to be four common processes linking the two disorders, as mutations in genes associated with Parkinsonism initiate similar adverse biological reactions acknowledged to stimulate Mn-induced dopaminergic cell death including; (1) disruption of mitochondrial function leading to oxidative stress, (2) abnormalities in vesicle processing, (3) altered proteasomal and lysosomal protein degradation, and (4) α-synuclein aggregation The mutual neurotoxic processes provoked by mutations in these genes in concert with the biological disturbances produced by Mn, most likely, act in synchrony to contribute to the severity, characteristics and onset of both disorders.

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**Contents**



## 1. Introduction

Chronic exposure to Mn can lead to a disorder known as manganism characterized by severe neurological deficits that often resemble the involuntary extrapyramidal symptoms associated with Parkinson's disease. The disorder is most often linked to occupations such as welding, steel and battery manufacturing and Mn mining in which exposure to abnormally high atmosphere levels is a daily occurrence, although, toxicity is also observed in patients with chronic liver disease as hepatic failure precludes the obligatory route required for its elimination (Hauser and Zesiewicz,

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1996; Criswell et al., 2012). Although similar to Parkinsonism, the observed symptoms produced by Mn are somewhat distinct as manganism is characterized by only mild tremors at rest, a masked-like face and a more upright standing position. Most notable is significant loss of balance, limb rigidity, slurred speech, excessive salivation and a distinctive gait often referred to as a cock-like walk. Differences in the neurological deficits expressed between Mn toxicity and Parkinsonism originate with the site of the injury as manganism presumably associates with altered functional behavior of neurons within the globus pallidus as well as dopaminergic neurons in the striatum, whereas, Parkinsonism predominantly correlates with degeneration of dopaminergic neurons in the substantia nigra pars compacta. The distinguishing clinical features resulting from these differences vary considerably even though both conditions significantly alter the signaling output of the basal ganglia.

Although the origins of the lesions between the two disorders are distinct, many of the characteristics of Mn intoxication can coincide or possibly evolve to more Parkinson-like features as there is considerable evidence in the literature suggesting that chronic exposure to Mn may predispose an individual to acquire earlier onset of a Parkinson-like syndrome (Gorell et al., 1999; Hudnell, 1999; Pal et al., 1999; Racette et al., 2001; Kim et al., 2002; Racette et al., 2005). One of the fundamental similarities between the manganism and Parkinsonism results from the fact that Mn is capable of suppressing dopamine release in the striatum generating symptoms which overlap with that observed in Parkinson's disease (Guilarte et al., 2006; Guilarte et al., 2008; Roth et al., 2013). Thus, the classical distinguishing characteristics between the two neurological disorders may, in fact, merge based on the relative magnitude to which Mn inhibits dopamine release. It is important to note that these dopaminergic neurons which originate in the substantia nigra pars compacta remain essentially intact upon chronic exposure to Mn (Olanow et al., 1996). This is particularly significant as Mn has also been reported to accumulate not only in the globus pallidus but also, though to a lesser extent, in both the substantia nigra pars reticulata and pars compacta (Park et al., 2003; Verina et al., 2011; Robison et al., 2012; Zhang et al., 2013) as well as the striatum (Erikson et al., 2005). The fact that these neurons survive and dopamine content within the striatum is essentially unaffected (Guilarte et al., 2006) suggests that the action of Mn on dopamine release is likely to be a local response probably occurring within the presynaptic nerve terminal. The observation that Mn inhibits amphetamine-induced dopamine release implies its actions may be mediated *via* the dopamine transporter (DAT) (Guilarte et al., 2006). In support of this are recent findings demonstrating that Mn promotes internalization of DAT and suppresses dopamine release in DAT transfected HEK cells (Roth et al., 2013). Accordingly, inhibition of dopamine transmission by Mn has the potential to produce a neurological condition resembling that observed in patients with Parkinson's disease which likely contributes to the general pathology seen in manganism.

Similar to other neurological disorders, onset, severity, and individual symptoms expressed in Mn toxicity as well as the progression of the disorder often deviates unpredictably implying underlying genetic variability as a potential origin responsible for the divergence in the pathological lesions and features expressed. This is clearly demonstrated by a study by Sadek et al. (2003) describing a patient who worked as a welder for a total of three years. Within one year after beginning employment, symptoms of Mn toxicity were initially perceived by the individual as a disturbance in his gait which upon continued progression and subsequent neurological testing was diagnosed as manganism. What makes the history for the development of the neurological deficits in this individual so remarkable is the precipitous rate of onset as opposed to the more typical case which requires longer exposure times usually in excess of ten years. The cause for the rapid onset of the neurological deficits in this short a time frame is unknown but, more than likely exposes a genetic predisposition in this individual. Interestingly, within several years of the initial diagnosis of manganism, he developed a unilateral tremor in his right hand more characteristic of Parkinsonism. His family history was only suggestive for older-onset of Parkinson's disease in a maternal great aunt.

The contribution of a genetic component responsible for precipitating the onset of manganism, in some individuals, is further intimated by the reality that not all welders, Mn miners or others exposed to high levels of the metal develop manganism yet exposures are comparable to their fellow workers that acquire the disorder. Clearly, this underscores the potential impact of genetic makeup in contributing to the vulnerability to develop Mn toxicity as well as the specific nature of the symptoms expressed. Assuming susceptibility to develop manganism is, in part, genetically regulated, then the most obvious association linking the two disorders would be the genes linked with early-onset of Parkinson's disease which include parkin (PARK2), DJ-1 (PARK7), PINK1 (PTEN-induced putative kinase 1, PARK6), ATP13A2 (PARK9) and SLC30A10 as well as LRRK2 (leucine-rich repeat kinase 2, PARK8) and VPS35 (vacuolar protein sorting-associated protein 35, PARK17) which associate with late onset of the disorder (Wider and Wszolek, 2007; Lesage and Brice, 2009; Yang et al., 2009; Houlden and Singleton, 2012). By linking mutations of these genes to acquisition of manganism may help clarify why symptoms and features between the two neurological disorders appear to be interrelated and why stress-related events provoked by Mn may accelerate onset of Parkinson-like symptoms.

This review is intended to focus on the function and properties of the most studied genes which have been linked to either early or late onset of Parkinsonism and to illustrate how the proposed mechanism of action for each may possibly relate to onset and severity of Mn toxicity.

## 2. PARK1 (α-synuclein)

Aggregation of α-synuclein in the brain is a central pathological feature of several neurodegenerative disorders classified as synucleinopathies which include Parkinson's disease (Marques and Outeiro, 2012). α-Synuclein is present in neurons as well as glial cells where it preferentially localizes to presynaptic terminals and is most abundant in the neocortex, hippocampus, striatum, thalamus, and cerebellum. It has been associated with a diverse array of activities including functioning of the ubiquitin–proteasome system (Bennett et al., 1999, Chu et al., 2009), maintenance of synaptic functionality (Watson et al., 2009), dopamine-mediated toxicity (Abeliovich et al., 2000; Tabrizi et al., 2000; Periquet et al., 2007), vesicle trafficking defects (Bonini and Giasson, 2005) and regulation of oxidative stress (Junn and Mouradian, 2002). Selective toxicity for dopamine neurons has been suggested to be caused by the actions of reactive oxidative products of dopamine on α-synuclein function and aggregation (Pham et al., 2009). Aggregated α-synuclein is a major constituent of Lewy bodies associated with Parkinsonism and mutations are linked with familial Parkinson's disease (Spillantini et al., 1997; Baba et al., 1998; Schulz-Schaeffer, 2010). The fact that the other early and late onset genes associated with Parkinson's disease have the potential to influence aggregate formation implies α-synuclein is a central element associated with dopaminergic cell death.

α-Synuclein is a 140 amino acid protein whose primary sequence is divided into three regions: the amphipathic N-terminal region, the hydrophobic central region and the largely acidic C-terminal region (Maroteaux et al., 1988). Native α-synuclein is normally a monomeric random coil protein which assumes various conformations that

hinder the amyloidogenic sequence from forming aggregates. Interactions between the N- and C-terminal sequences of the native protein inhibit binding of the different monomers presumed to be responsible for oligomerization and aggregation (Deleersnijder et al., 2013) thus, provides an intrinsic auto-inhibitory mechanism that when disrupted supports α-synuclein oligomer formation (Bertoncini et al., 2005).

As noted above, oxidative stress has also been suggested to participate in the neurotoxic actions of α-synuclein as a number of studies have determined that mitochondrial dysfunction as being related to dopaminergic cell degeneration in Parkinson's disease (Nakamura, 2013). α-Synuclein accumulation in mitochondria is enhanced in Parkinson's disease brains linking it to its neurotoxic actions (Devi et al., 2008). α-Synuclein protein has a noncanonical mitochondrial targeting sequence in its N terminal region presumably responsible for its translocation to mitochondria (Devi et al., 2008; Devi and Anandatheerthavarada, 2010). α-Synuclein appears to interact directly with mitochondrial membranes to regulate mitochondrial activity (Banerjee et al., 2010; Nakamura et al., 2011) as it has been reported to interact with complex I, ultimately promoting the production of ROS.

The question addressed in this review is whether alterations in α-synuclein activity or aggregation can provoke early development of manganism and whether exposure to Mn can further stimulate the neurotoxic events induced by altered α-synuclein function in dopaminergic neurons which lead to early onset of Parkinsonism. A number of studies have attempted to address these questions using both *in vivo* and various *in vitro* model systems. Mn has been reported to increase expression of both mRNA and α-synuclein protein as well as promote its oligomerization (Xu et al., 2013). In PC12 cells, Mn exposure was similarly found to induce overexpression of α-synuclein while siRNA knockdown of α-synuclein reversed Mn-induced cytotoxicity (Cai et al., 2010). Additionally, Mn induced the activation of ERK1/2 in PC12 cells whereas the MEK1 inhibitor, PD98059, which inhibits the activation of ERK, attenuated both the overexpression of α-synuclein and cytotoxicity. Mn-induce oxidative neuronal damage and α-synuclein oligomerization were also shown to be partially alleviated by the pretreatment with reduced glutathione and aggravated by $H_2O_2$ pretreatment (Xu et al., 2013). The mechanism for Mn toxicity in rat mesencephalic cells (MES 23.5) overexpressing α-synuclein was suggested to involve the translocation of NF-κB to the nucleus which was inhibited by both antioxidants and inhibitors of p38 MAP kinase (Prabhakaran et al., 2011). Mn also promoted increased toxicity in SKN-MC neuroblastoma cells stably expressing the human dopamine transporter when transfected with human α-synuclein (Pifl et al., 2004). In addition, α-synuclein-positive cells were found to increase in the gray matter of Cynomolgus macaques in Mn-exposed animals and some of these neurons displayed loss of Nissl staining along with α-synuclein-positive aggregates (Verina et al., 2013). Another study compared the effect of Mn in male transgenic C57BL/6J mice expressing human α-synuclein or a doubly mutated human α-synuclein to their non-transgenic littermates (Peneder et al., 2011). Results of this study revealed that Mn decreased dopamine turnover in the striatum of mice transgenic for human wild type α-synuclein but not in mice expressing two mutant species, nor in non-transgenic littermates although Mn failed to induce signs of neurodegeneration of nigrostriatal dopamine neurons.

The findings described above provide substantial evidence there may be mutual and possibly additive deleterious interactions between Mn and mutated α-synuclein which potentially can facilitate dopaminergic cell death and therefore, may promote early onset of idiopathic Parkinsonism or possibly even manganism. The overall importance of this is reinforced by the fact that many of the other known genes linked to Parkinsonism influence α-synuclein function and aggregation within the dopaminergic neurons.

## 3. PARK2 (parkin)

Parkin (Park2) is one of over 600 identified E3 ligases each being responsible for ubiquitination of a diverse and select set of proteins which serves to regulate both their biological activity and degradation *via* the proteasomal pathway (Dev et al., 2003, Lim et al., 2005). The parkin gene consists of 12 exons and encodes a protein of 465 amino acids with a molecular weight of approximately 52 kDa. It is present in multiple sites within the cell, being localized to the cytosol, trans-Golgi complex, mitochondria and the cytoplasmic surface of secretory vesicles (Shimura et al., 1999). Numerous missense mutations in the parkin gene have been reported to alter its activity through a number of different mechanisms resulting in aberrant ubiquitination leading to the impairment of the protein function and degradation as well as destabilization of parkin itself. The mechanism by which parkin promotes dopaminergic cell death is likely to be multifaceted and involve a number of interdependent processes all of which are contingent on divergence in the operative function of parkin to selectively ubiquitinate proteins. This relates to the fact that parkin is normally recruited to depolarize mitochondria in order to foster their elimination by autophagy (mitophagy) (Narendra et al., 2008) with the intent to preserve cellular redox balance. Translocation of parkin to damaged mitochondria results in the selectively ubiquitination of several outer mitochondrial membrane proteins causing their rapid degradation through the proteasomal pathway thus, promoting elimination of mitochondria (Narendra et al., 2010, Chan and Chan, 2011). Phosphorylation of parkin by PINK1 is essential for its recruitment to mitochondria and, with the support of DJ-1, required for activation of its ubiquitin ligase activity (Xiong et al., 2009; Geisler et al., 2010; Matsuda et al., 2010; Narendra et al., 2010; Vives-Bauza and Przedborski, 2010; Lazarou et al., 2013). PINK1 not only phosphorylates parkin but also phosphorylates ubiquitin thereby stimulating parkin's E3 ligase promoting both increased auto-ubiquitination and substrate ubiquitination of mitochondrial proteins (Kane et al., 2014; Kazlauskaite et al., 2014; Koyano et al., 2014; Shaw, 2014). Although DJ-1 is part of this complex and appears to promote activation of parkin's ubiquitin ligase activity, its role in this process has not been clearly defined.

The consequence of parkin's role in altering mitochondrial function and survival likely results from stimulation of oxidative stress and the ensuing elevation of apoptotic signaling pathways (Joselin et al., 2012; Wang et al., 2012) as overexpression of parkin reduces ROS production by enhancing mitochondrial membrane potential (Hyun et al., 2005). In contrast, tissue-specific mitochondrial defects although observed early in life of PARK2$^{-/-}$ mice, were only mildly associated with altered respiration, with minimal effect on mitochondrial membrane potential as complex I defects and prominent oxidative damage were minimal (Damiano et al., 2014). Mitochondrial inner membrane potential in PARK2$^{-/-}$ mice was found to be similar to that of wild-type mice but showed increased sensitivity to uncoupling in the ageing striatum. Although there was some suggestion of oxidative stress in the striatum in the parkin knock-out animals as indicated by increased mitochondrial glutathione content and oxidative adducts, the functional role of these changes in maintaining mitochondrial integrity remains to be determined.

The discussion presented above reveals there is substantial overlap between parkin-induced changes in mitochondrial function and the activation of the ensuing apoptotic signals which foster both dopaminergic cell death and Mn toxicity. Thus, it is not surprising that overexpression of parkin can prevent dopaminergic cell death induced by a number stress promoting agents including

Mn (Higashi et al., 2004, Roth et al., 2010). For example, overexpression of parkin in human SHSY5Y and CATH.a cells prevent Mn-induced cell death whereas human lymphocytes containing an inactive mutant form of the ligase display greater loss of mitochondrial activity compared to control cells possessing wild-type parkin as assessed by decreases in ATP production (Roth et al., 2012). Mn also augmented oxidative stress and the ensuing apoptotic signals in the parkin mutant cell line as indicated by enhanced ROS formation and caspase 3-activation. In another study (Aboud et al., 2012), human induced pluripotent stem cells derived from mutant parkin subjects displayed significantly higher levels of ROS generation upon exposure to Mn than cells obtained from control subjects suggesting that inheritance of a Parkinson's disease genetic risk factor may increase susceptibility to provoke Mn toxicity. Thus, it is reasonable to assume that the degree to which mutant parkin results in mitochondrial dysfunction and the age of onset for the critical loss of dopaminergic activity, more than likely, can impact on the appearance of Parkinson-like symptoms associated with excess exposure to Mn. In a reciprocal manner, Mn, by promoting degeneration of mitochondria, likely can facilitate mitophagy generated by mutant parkin.

In addition to its influence on mitochondrial integrity, there is an additional mechanism by which parkin can directly influence Mn toxicity. This relates to the ability of parkin to influence transport of Mn into cells (Roth et al., 2010). Several different transport systems have been identified for cellular uptake of Mn, though the general consensus presumes that the primary process utilizes divalent metal transporter 1 (DMT1, also called NRAMP2 and SLC11A2) (Garrick et al., 2006, Roth, 2006, 2009). Four isoforms of DMT1 have been identified in mammalian cells encoded by a single gene. The isomers differ both in their N- and C-terminal residues with two mRNA isoforms possessing an iron response element (IRE) motif downstream from the stop codon which presumably regulates DMT1 message levels *via* binding of the iron response proteins, IRP1 and IRP2. Transcriptionally regulated splice variants, exon 1A and 1B, have also been identified on the proximal N-terminal end of the message (Hubert and Hentze, 2002). Expression of the 1B isoforms is impacted by post-translational processing *via* the ubiquitin/proteasomal degradative pathway (Paradkar and Roth, 2006, 2007; Brasse-Lagnel et al., 2011; Garrick et al., 2012). Studies have reported that parkin is the E3 ligase responsible for the ubiquitination and the subsequent proteasomal degradation of the 1B isoforms of DMT1 (Roth et al., 2010). This is consistent with the findings that several different cell lines overexpressing parkin display decreased levels of the transporter as well as reduced transport and increase toxicity of Mn whereas cells expressing a native mutant construct of parkin as well as brains from parkin-knockout rats display increased levels of the transporter. Thus, mutations in the parkin are expected to lead to increase cellular transport of Mn and facilitate Mn toxicity. Accordingly, mutations in parkin may not only lead to early onset of Parkinson's disease but may also be responsible for increased uptake of Mn and propensity to develop Mn toxicity.

## 4. PARK6 (PINK1)

PINK1 (PTEN-induced putative kinase 1) is a 581 amino acid protein containing an N-terminal mitochondrial-targeting sequence, a transmembrane domain and a highly conserved serine/threonine kinase sequence which is structurally similar to the $Ca^{2+}$/calmodulin family of proteins (Valente et al., 2004). PINK1 is an integral mitochondrial membrane protein whose kinase domain faces the outer surface making it available to substrates within the cytoplasm (Gandhi et al., 2006, Muqit et al., 2006). Several mitochondrial proteins have been identified as downstream targets as it directly phosphorylates these proteins resulting in altered mitochondrial function, oxidative damage and degradation of parkin-dependent E3 ligase-dependent proteins. By protecting neurons from oxidative stress, PINK1 is presumed to play a major role in preserving mitochondrial morphology and activity (Yang et al., 2006; Exner et al., 2007; Haque et al., 2012). Within the mitochondria, degradation of PINK1 is elicited by a variety of proteases including LON serine protease located within the mitochondrial matrix which ultimately controls parkin activity (Thomas et al., 2014).

As noted above, PINK1 is responsible for the phosphorylation of parkin which is essential for parkin's recruitment to mitochondria and, with the support of DJ-1, critical for activation of its ubiquitin ligase activity (Xiong et al., 2009; Geisler et al., 2010; Matsuda et al., 2010; Narendra et al., 2010; Vives-Bauza and Przedborski, 2010; Lazarou et al., 2013). Recently, PINK1 has also been shown to be responsible for phosphorylating ubiquitin at Ser65 which is essential for activation of ligase activity (Kane et al., 2014; Kazlauskaite et al., 2014; Koyano et al., 2014; Shaw, 2014). These findings demeonstrate that PINK1-dependent phosphorylation of both parkin and ubiquitin is critical for full stimulation of parkin E3 ligase activity.

Like the other early onset genes, the average age of inception of PINK1-linked Parkinson's disease is in the early thirties. As a functional part of the parkin E3 ligase complex with parkin, PINK1 knockdown also leads to proteasomal dysfunction, accompanied by increased formation of α-synuclein aggregates (Clark et al., 2006; Pallanck and Greenamyre, 2006; Park et al., 2006; Yang et al., 2006; Exner et al., 2007; Liu et al., 2009), a primary constituent of Lewy bodies typically observed in dopaminergic neurons associated with Parkinson's disease.

These observations lead to the basic question addressed in this review as to whether mutations in PINK1 can potentiate symptoms and possibly promote premature development of manganism. The fact that mutations in PINK1 promote degeneration of mitochondria and induce oxidative stress, clearly support the conclusion that deficiencies have the potential to influence onset and progression of Mn toxicity. In addition, by normally stimulating parkin activity, it is likely that functionally inactive PINK1 mutants will cause a decrease in parkin E3 ligase activity which will have the deleterious consequence of reducing ubiquitination and degradation of the major Mn transporter, DMT1, thus increasing uptake of Mn (Roth et al., 2010). Accordingly, the combined actions of the two processes on mitochondrial function and oxidative stress strongly reinforce the probability that mutations in PINK1 have the potential to facilitate Mn-induced toxicity. At the same time it is not unreasonable to hypothesize that exposure to Mn can also exacerbate mitochondrial degeneration caused by mutations in PINK1 and thus, provide additional stress to dopaminergic cells leading to premature onset of Parkinson-like symptoms.

## 5. PARK7 (DJ-1)

DJ-1 (PARK7) plays an essential role in the cellular defensive mechanisms by maintaining and protecting normal biological responses against oxidative stress (Wilhelmus et al., 2012). Deletions and point mutations in DJ-1 which lead to loss of function are the third most frequent identifiable genetic cause of early onset of autosomal recessive Parkinson's disease (Bonifati et al., 2003) behind that of parkin and PINK1 (Abou-Sleiman et al., 2003; Hedrich et al., 2004). DJ-1 functions by regulating and preserving mitochondria function (Taira et al., 2004) and therefore, either a deficiency or malfunction of DJ-1 has the potential to stimulate ROS formation leading to oxidative insults promoting premature degeneration of dopaminergic neurons.

DJ-1 is a 20 kDa protein ubiquitously expressed in both brain and peripheral tissue which forms a stable dimer in solution. Parkinson's disease mutations, which hinders dimerization,

abolishes its neuroprotective activity, suggesting that dimerization may be critical to its normal function. Although DJ-1 protein predominates in the cytosol, minor portions are also present in the nucleus and mitochondria (Zhang et al., 2005). DJ-1 redistributes to the mitochondria under conditions of oxidative stress, where it is presumed to act as a neuroprotective intracellular redox sensor (Canet-Aviles et al., 2004) and thus, is important in maintaining mitochondrial homeostasis (Ashley et al., 2009, Junn et al., 2009).

There is increasing evidence that DJ-1 activity is regulated by the MAP kinase pathway based on the observation that its expression is increased through activation of ERK 1/2 (Lev et al., 2009). Thus, increased ROS produced by oxidative stress initiated by mitochondrial damage or oxidation of dopamine can result in the phosphorylation of both ERK 1/2 which subsequently has the indirect effect of protecting dopaminergic cells *via* upregulation of DJ-1. In addition to its direct neuroprotective actions, DJ-1 has also been shown to form a complex with parkin and PINK1 to stimulate ubiquitination and degradation of parkin substrates, including parkin itself (Moore et al., 2005, Xiong et al., 2009, Sha et al., 2010, Vives-Bauza et al., 2010). Whether the three proteins actually form a distinct complex, however, has been challenged (Thomas et al., 2011), though decreased expression of either Pink1or DJ-1 results in reduced ubiquitination of endogenous parkin which subsequently causes a reduction in the degradation and increased accumulation of other parkin substrates.

Whether any of the responses caused by mutations in DJ-1 can parallel and/or, exacerbate the toxic events provoked by Mn and, in a reciprocal fashion potentiate early onset of Parkinson-like symptoms induced by Mn is not an unlikely scenario since they both elicits their toxic response *via* impairment of mitochondrial activity. A recent report (Lee et al., 2012) has further indicated that Mn can actually decrease both protein and RNA expression of DJ-1 potentially provoking similar neurotoxic activity induced by mutant DJ-1. The fact that both mutant DJ-1 and Mn cause a decrease in ATP production and a decrease in mitochondrial transmembrane potential as well as increased opening of the mitochondrial permeability transition pore minimally implies there is likely to be amplification of these deleterious activities when Mn is present in patients exhibiting homozygous mutations in DJ-1 (Gavin et al., 1999; Roth, 2006; Milatovic et al., 2007; Giaime et al., 2012). In addition to inhibiting mitochondrial function, Mn has also been shown to affect the MAP kinase pathway as it can result in activation of ERK 1/2, p38 and JNK and thus, potentially impact on DJ-1 activity (Hirata et al., 1998; Roth et al., 2000; Cordova et al., 2012). Also as noted above, the proposed interaction of DJ-1 with parkin is likely to have an influence on Mn toxicity as prior studies have revealed that parkin is the E3 ligase responsible for ubiquitination of the major Mn transporter, DMT1 (Roth et al., 2010). Mechanistic differences, however, do exist between the actions of the DJ-1 and Mn as striatal synaptosome preparations from DJ-1$^{-/-}$ mice exhibit increases in the dopamine transporter, DAT (Manning-Bog et al., 2007) whereas, Mn results in a decrease of surface levels of DAT as well as decreased DA uptake and amphetamine-induced DA efflux in HEK cells transfected with the transporter (Guilarte et al., 2006; Guilarte et al., 2008; Roth et al., 2013). The reduction in surface levels of DAT by Mn was shown to be caused by internalization of the transporter in these cells (Roth et al., 2013). Despite these differences, the majority of the evidence clearly supports the premise that mutations in DJ-1 are likely to exacerbate the neurotoxic actions of Mn and ultimately lead to premature onset of manganism.

## 6. PARK8 (LRRK2)

LRRK2 (leucine-rich repeat kinase 2) is a widely expressed 2527 amino acid protein that is present in many organs and tissues including the brain (Mata et al., 2006). Full-length LRRK2 is mainly occurs in the cytoplasm, with partial localization in mitochondria and membranes, such as endoplasmic reticulum and synaptic vesicles (Biskup et al., 2006). It is a relatively complex gene encoding a multi-domain protein that includes a LRR (leucine-rich repeat) region and two catalytically active domains, a serine/threonine kinase with sequence homology to MAPKKK, and a GTPase domain belonging to the Ras-GTPase superfamily of GTPases, more specifically to the ROC subfamily. LRRK2 functions upstream of canonical MAPKK and therefore, acts to phosphorylate several essential MAPKs including p38 and JNK which mediate oxidative cell stress, neurotoxicity and apoptosis (Gloeckner et al., 2009; Hsu et al., 2010). There is an inter-play between the LRRK2 GTPase function and its kinase function, with the majority of the data suggesting ROC sequence functions as an upstream modulator of the kinase domain. Clearly, the ROC domain is important for the functioning of LRRK2 as mutations located in this sequence have been found to be linked to Parkinson's disease (Zimprich et al., 2004; Deng et al., 2008). Recent studies have also revealed the presence of a variety of other multiple genetic mutations associated with decreased kinase activity as being linked to susceptibility to develop both familial and sporadic Parkinson's disease (Jaleel et al., 2007; Bardien et al., 2011; Ross et al., 2011; Wu et al., 2012).

Because of the structural and functional complexity of LRRK2, the mechanisms by which mutations elicits Parkinsonism are likely to involve multi-interactive signaling systems as variants have been reported to influence mitochondrial function (Saha et al., 2009), protein homeostasis (Tong et al., 2010) as well as a number of signaling pathways within neurons (Habig et al., 2008). Microarray analysis has indicated that down-regulation of LRRK2 can lead to changes in genes involved in actin cytoskeleton-related processes which are known to influence neurite outgrowth, synaptic plasticity, and axonal/dendritic transport (Habig et al., 2008). Other studies have reported that LRRK2 deficiency may possibly play an essential role in regulating protein homeostasis during aging resulting in impairment of autophagy/lysosomal pathway leading to α-synuclein accumulation and aggregation (Tong et al., 2010). Recent studies have, also indicated that LRRK2 can interact with α-synuclein and possibly be responsible for aggregate formation (Lin et al., 2009; Tong et al., 2010; Greggio et al., 2011; Kondo et al., 2011) as well as cause a decrease in the dopamine transporter, DAT (Adams et al., 2005; Nandhagopal et al., 2008) impairing dopamine-stimulated neurotransmission (Tong et al., 2009). These latter observation are particularly significant with respect to Mn toxicity, as several reports indicate that Mn also perturbs dopaminergic function (Sriram et al., 2010; Peneder et al., 2011) and inhibits amphetamine-induced dopamine release (Guilarte et al., 2006; Guilarte et al., 2008) as well as promote mitochondria degeneration (Gavin et al., 1999; Gunter et al., 2009). Thus, LRRK2 displays a number of critical functions many of which can affect or be affected by Mn.

Several different mutations in LRRK2 have been identified and, although some mutations impair activity, others, in contrast, promote increased activity (Jaleel et al., 2007; Santpere and Ferrer, 2009). For example, the most prevalent LRRK2 mutant species, G2019S, promoting Parkinsonism actually exhibits increased kinase activity (Covy and Giasson, 2009; Bravo-San Pedro et al., 2013). Interestingly, a recent study (Mamais et al., 2013) has suggested that difference in the biochemical properties of aggregated α-synuclein is produced in G2019S linked Parkinson's disease patients when compared to those with idiopathic Parkinson's disease despite a similar histopathological presentation. What is most significant is the observation that Mn stimulates phosphorylation activity of the G2019S mutant protein whereas it inhibits wild-type kinase activity normally activated by Mg (Covy and Giasson, 2010; Lovitt et al., 2010).

LRRK2 mutations have also been suggested to have the potential to sensitize microglia cells toward a pro-inflammatory state in response to a variety of noxious agents. The mechanism for this is not fully elucidated but may include the modulation of vesicle trafficking involved in the release of inflammatory mediators, delivery of membrane receptors, and/or phagocytotic processes within microglia (Shin et al., 2008; Matta et al., 2012). This is based on the findings from both *in vivo* and *in vitro* studies reporting that LRRK2 overexpression or knockdown affects both vesicular endocytosis and exocytosis (Cirnaru et al., 2014). LRRK2 has also been shown increase transcriptional activity of the inflammatory mediator, NF-κB, by increasing phosphorylation levels of IκBα (Hongge et al., 2014) whereas knockdown of the LRRK2 gene in microglia results in a significant reduction of NF-κB expression (Russo et al., 2014).

Related to this is the observation implicating LRRK2 kinase activity in the dysregulation of excitatory synapse as alterations in synaptic activity occurred following mutant LRRK2 overexpression in the postsynaptic compartment of mammalian neurons (Plowey et al., 2014). Results from this study suggest that activation of endogenous NMDA receptors as a contributing factor in mutant LRRK2-induced dendrite degeneration. Thus, secretion of pro-inflammatory agents *via* its effect on the release of excitatory neurotransmitters facilitates neuronal death caused by LRRK2 mutations. This is significant as the area of the brain initially affected by Mn, the globus pallidus, receives glutaminergic input from the subthalamic nuclei suggesting that palladial neurons expressing the LRRK2 mutation may be more sensitive to the neurotoxic properties of Mn. This is also mechanistically important as Mn has been reported to inhibit glutamate uptake into astrocytes (Karki et al., 2013). Related to this is the observation that Mn can stimulate the inflammatory response by exciting production of microglia in the substantia nigra of non-human primates (Verina et al., 2011).

Recent studies have confirmed that when LRRK2 is silenced with an shRNA, Mn can potentiate oxidative stress leading to cell death as indicated by activation of both ROS and JNK (Roth and Eichhorn, 2013). In contrast, Mn was shown to reduced phosphorylation of p38 consistent with the fact that p38 is a likely a downstream substrate of LRRK2 (Kim et al., 2012). Unlike the other genes associated with Mn toxicity, LRRK2 is an autosomal dominant gene and therefore, potentially differentiates a population of individuals that upon exposure to excess Mn can develop early symptoms of manganism even in the absence of overt signs of Parkinson's disease (Gloeckner et al., 2009; Covy and Giasson, 2011). Thus, mutations in LRRK2 not only play an essential role in development of Parkinson's disease but also has the potential to result in the generation of manganism as well.

## 7. PARK9 (ATP13A2)

Mutations in ATP13A2/PARK9 (ATPase type 13A2) have been reported to cause Kufor-Rakeb syndrome, a juvenile recessive neurodegenerative disorder distinguished by progressive L-DOPA-responsive Parkinsonism (Ramirez et al., 2006; Park et al., 2011; Eiberg et al., 2012). Patients display generalized brain atrophy with evidence of reduced nigrostriatal dopaminergic function consistent with the observation that ATP13A2 is enriched in the substantia nigra (Ramirez et al., 2006; Gitler et al., 2009; Ramonet et al., 2012). Mutations of ATP13A2 promote its re-localization from intracellular vesicular compartments to the endoplasmic reticulum where it is subsequently degraded *via* the proteasomal ER-associated degradation pathway (Ugolino et al., 2011; Ramonet et al., 2012). Homozygous mutations of ATP13A2 have been reported to cause juvenile-onset Parkinsonism (10–22 years) whereas heterozygous modifications are linked with early-onset Parkinsonism (<50 years) (Ning et al., 2008; Santoro et al., 2010; Chien et al., 2011; Podhajska et al., 2012).

Human ATP13A2 gene encodes a 1180 amino acid transmembrane-spanning domain protein encompassing a P5 subfamily of P-type transport ATPases (Schultheis et al., 2004). Mutations in the gene lead to altered lysosomal function including impaired lysosomal acidification, decreased proteolytic processing of lysosomal enzymes, reduced degradation of lysosomal substrates, diminished lysosomal-mediated clearance of autophagosomes and the subsequent accumulation of toxic α-synuclein aggregates (Gitler et al., 2009; Usenovic et al., 2012; Usenovic and Krainc, 2012). Consistent with the latter observation is the fact that orthologs of ATP13A2 can protect against cellular toxicity provoked by overexpression of α-synuclein in primary neurons from midbrain dopaminergic cells (Gitler et al., 2009). Loss of ATP13A2 function is also associated with increased mitochondrial fragmentation and increased production of ROS implying that it normally functions in the maintenance of mitochondria (Gusdon et al., 2012). Thus, similar to the other genes related to early onset of Parkinsonism, mutant ATP13A2 disruption of α-synuclein degradation and the subsequent production of α-synuclein aggregates within the dopaminergic cell as well as provocation of mitochondrial degeneration may represent common cytotoxic mechanisms linking these genes.

ATP13A2 has also been suggested to play a role in the active transport of cations across lysosomal membranes in mammalian cells (Gitler et al., 2009; Schmidt et al., 2009; Tan et al., 2011; Ramonet et al., 2012), though the activity and metal specificity has not been adequately determined. This transport function in yeast, is significant as deletion of the ATP13A2 ortholog, ykp9, confers sensitivity to growth in the presence of heavy metals, including Cd, Mn, Ni and Se (Schmidt et al., 2009). Consequently, overexpression of Ypk9 can protect cells from Mn toxicity whereas Parkinson's disease-linked and ATPase-dead mutants fail to prevent metal-dependent cell death (Gitler et al., 2009; Chesi et al., 2012). The mechanism by which Ypk9 prevents heavy metal toxicity is not known, though it has been reported to involve cellular trafficking and cell cycling. These data suggest that Ypk9 preserves cell viability in the presence of Mn and other heavy metals possibly *via* its role in sequestration of the metals within vacuoles of cells whereas the harmful mutant species lack this ability. This possibly results from reduced transport of Mn into these vesicles or disruption of the normal vesicle trafficking or possibly by suppressing digestion of essential proteins within the lysosomes. As anticipated, expression of ATP13A2 is capable of preventing Mn toxicity along with a reduction in the levels of intracellular Mn (Tan et al., 2011). Interestingly, ATP13A2 expression was shown to be up-regulated by Mn in this study which is consistent with the up-regulated protein levels observed in surviving substantia nigra dopaminergic neurons from Parkinson' disease brains (Ramonet et al., 2012) suggesting that ATP13A2 may provide an inducible protective function to cells. The function of ATP13A2, however, as a heavy metal transporter has recently been challenge based on the relationship to other ATPases (van Veen et al., 2014). The authors of this paper hypothesize that AT13A2 might act as flippase involved in lipid dynamics during vesicle formation and membrane fusion events.

Another recent study reported that ATP13A2 is localized to multi-vesicular bodies, a late endosomal compartment involved in lysosomal activity and delivery of endocytosed proteins to the lysosome. ATP13A2 was also shown to function as a Zn/Mn pump within this compartment as indicated by increased sensitivity to both cations from ATP13A2 knockdown cells (Kong et al., 2014). Reduced ATP13A2 expression resulted in decrease levels of vesicular Zn and Mn suggesting that ATP13A2 facilitates transport of these cations into these vesicles

Overexpression of ATP13A2 was also shown to reduce intracellular α-synuclein levels and increase α-synuclein externalization in exosomes whereas ATP13A2 knockdown decreased α-synuclein externalization. These authors propose that ATP13A2 can modulate metal levels in these multi-vesicular bodies and thus, regulate biogenesis of exosomes capable of containing α-synuclein. Supporting this is another recent study demonstrating that loss of function of ATP13A2 leads to dyshomeostasis of intracellular Zn that in turn contributes to lysosomal dysfunction and accumulation of α-synuclein (Tsunemi and Krainc, 2014)

In summary, there is compelling evidence to suggest that mutant forms of ATP13A2 have the ability to potentiate Mn toxicity though the actual mechanism has not been firmly delineated. Supporting this is a recent study implicating ATP13A2 variants as potential risk factors for the neurotoxic actions of Mn in humans (Rentschler et al., 2012). Since ATP13A2 is selectively localized to dopaminergic neurons in the substantia nigra, the actions of the variants will have little direct impact on the direct toxic actions of Mn activity in the globus pallidus. Nevertheless, the combination of excess Mn suppressing dopamine release in the striatum and its cooperative noxious actions in cells expressing mutated ATP13A2 may potentially exacerbate or promote earlier onset of the Parkinson-like symptoms in individuals exposed to high levels of the metal.

## 8. PARK17 (VPS35)

One of the newest genes linked with autosomal recessive late onset Parkinsonism is VPS35 (vacuolar protein sorting-associated protein 35). This gene encodes a protein which is a component of a large heteropentameric complex, termed the retromer complex, involved in retrograde transport of proteins from endosomes to the trans-Golgi network (Bonifacino and Rojas, 2006). The basic structure includes a sorting nexin dimer, comprised of either sorting nexins 1 or 2 and 5 or 6, as well as a cargo-recognition trimer, composed of VPS26, VPS29 and VPS35 (Bonifacino and Hurley, 2008). It has been suggested that pathogenic mutation in VPS35 may function by disrupting recognition sites required for the binding to essential cargo proteins (Zimprich et al., 2011) and can promote endosomal alterations and trafficking defects that may partly explain its action in Parkinson's disease (Follett et al., 2014). Recently, a number of studies have identified patients with mutations in VPS35 that present with late onset autosomal-dominant Parkinson disease characterized with tremor-predominant symptoms (Vilarino-Guell et al., 2011; Zimprich et al., 2011; Sharma et al., 2012). An association of VPS35 component of the retromer complex with Parkinson's disease-associated defects in LRRK2 was recently reported as causing endolysosomal and Golgi apparatus sorting defects and deficiency (MacLeod et al., 2013). Although, there is currently no study that has directly linked VSP35 to Mn toxicity, it has been reported that VSP35 is linked to the recycling of the major Mn transport protein, DMT1 (Tabuchi et al., 2000). It appears that VPS35 binds exclusively to the cytoplasmic tail of the –IRE species of DMT1, as binding is dependent on a specific hydrophobic motif which is necessary for its endosomal recycling. Both the –IRE isoform of DMT1 and VPS35 were shown to colocalize with transferrin receptor-positive endoscopes and depletion of VPS35 led to missorting of the transporter to the lysosome-associated membrane protein, LAMP2-positive vesicles, though, this did not result in alteration of the levels of DMT1. Thus, it is difficult to predict whether mutations in the gene can actually alter endosomal or surface levels of DMT1 or whether the missorted vesicles display differences in there capacity to transport Mn. Interestingly, prior studies have reported that the major signal for internalization and recycling of the –IRE species of DMT1 resides in its carboxyl terminus and that removal of this signal leads to a default lysosomal targeting (Lam-Yuk-Tseung et al., 2005). Since four different isoforms of DMT1 exist, it is also difficult to speculate how changes in only the –IRE species will affect the overall uptake of Mn in any given cell type. Interestingly, the –IRE species is suggested to predominate in neuronal cells implying that mutated VPS35 may have its greatest influence on Mn trafficking in nerve cells (Ingrassia et al., 2012). In a similar fashion, it is not known whether Mn accumulated in neurons can disrupt the actions of VPS35 on recycling of DMT1. This is an important concern as Mn has recently been reported to promote internalization of the dopamine transporter, DAT, and thus, Mn may influence internalization of other surface proteins which may be regulated by VPS35.

## 9. SLC30A10

One of the most recently identified genes linking Parkinsonism and manganism is SLC30A10 which displays an autosomal recessive pattern for inheritance of the disorder (Tuschl et al., 2012b; Quadri et al., 2012; DeWitt et al., 2013). Based on the gene family classification, SLC30A10 was originally categorized as a Zn transport, although it is presently recognized as a member of the divalent cation transporter superfamily responsible for transport of Fe, Cu, Zn, and Mn. It, along with ferroportin, has been suggested to be involved in the export of metals and recent studies have further implicated it as having an important and selective role in the efflux of Mn (Stamelou et al., 2012; DeWitt et al., 2013). This is based on structural analysis of its amino acid sequence which differs from other Zn transporters (Quadri et al., 2012). Further establishing SLC30A10 as an essential Mn transporter are studies demonstrating that human wild-type SLC30A10 but not mutated constructs can rescue Mn sensitive yeast (Tuschl et al., 2012b).

The gene for SLC30A10 contains four exons which encodes an ~52 kD protein of 485 amino acid membrane bound protein possessing six proposed transmembrane domains containing both a cytoplasmic N and C-termini (Quadri et al., 2012). Expression of normal SLC30A10 predominates in the liver and neuronal cells within the CNS. Highest expression levels in brain are observed in the globus pallidus, subthalamic nucleus, and deep cerebellar nuclei with reduced levels seen in the putamen and other diencephalic and cortical areas whereas, the lowest levels are in the hippocampus and cerebellar cortex.

The phenotype associated with mutations of SLC30A10 is rather broad and include neurologic, hepatic, and hematologic deficits. The magnitude of the defects and age of onset of the expressed symptoms of the disorder vary considerably. A recent paper (Lechpammer et al., 2014) has described a detailed pathological analysis of a patient with a homozygous SLC30A10 mutation, who was first diagnosed at the age of 14 and subsequently died at the age 38 years. Mn levels from various brain regions in this individual relative to control samples were elevated, especially in basal ganglia which increased approximately 16-fold whereas Zn and Fe content remained unchanged compared to that in control subjects. SLC30A10 immunoreactivity was reported to be reduced in the residual globus pallidus neurons and the basal ganglia showed yellow–gray mottling, predominately in the globus pallidus. There was severe bilateral neuronal loss in the medial and lateral globus pallidus which displayed an increased number of activated microglia along with reactive astrocytosis, myelin loss, and spongiosis. Similar but milder pathology was also observed in the putamen, caudate nucleus, thalamus, and cerebellum.

Identification of the disorder as being linked to SLC30A10 was based on a recent study utilizing two consanguineous families with neurologic disorders including juvenile-onset dystonia, adult-onset parkinsonism, severe hypermanganesemia, polycythemia, and chronic hepatic disease, including steatosis and cirrhosis

(Quadri et al., 2012). Two different homozygous frameshifts within SLC30A10 were identified as mutations segregated with the disease. The clinical manifestations of the disorder were also assessed in individuals from eight different families having homozygous missense or truncation mutations leading to a nonexistent or non-functional protein product in SLC30A10 (Tuschl et al., 2012a). This study provided evidence defining this disorder as an autosomal recessive genetic defect based on the findings that heterozygous family members lack any of the presenting symptoms. The study also provided evidence of the variability of the disorder even between family members as onset of the symptoms for the affected individuals ranged between 2 and 57 years of age, with many of the cases presenting in childhood. The diverse array of symptoms and onset for the appearance of the disorder probably reflect a rather complex multi-component system responsible for the precise phenotype displayed. The interplay of the effects of liver failure along with neuronal damage in the globus pallidus and other neuronal systems in the CNS may be responsible for the assortment of symptoms expressed. It should be noted that while mutations in SLC30A10 resulted in Parkinsonism from increased accumulation of Mn in the CNS, affected individuals did not express loss of dopamine terminals in the striatum (Quadri et al., 2012; Tuschl et al., 2012a; Lechpammer et al., 2014). In addition, individuals with the SLC30A10 mutation are not responsive to L-DOPA or dopamine agonist therapy as in idiopathic Parkinsonism.

The importance of the findings establishing the link between SLC30A10 and manganese toxicity has broad implications for understanding of manganese homeostasis and pathophysiology in humans. The direct association between Mn accumulation in the globus pallidus and the ensuing degeneration of neurons in individuals possessing nonfunctional mutations of SLC30A10 clearly provides some of the strongest evidence to date demonstrating the deleterious and selective actions of Mn on the CNS. Because these mutations are also linked to onset of Parkinsonism, the entirety of these findings provides additional evidence linking the two debilitating neurologic disorders.

## 10. Others

The above discussion attempts to delineate genes acknowledged to be risk factors for development of Parkinsonism and their potential to influence the onset and progression of Mn toxicity. It should be noted there are a number of large case-control genome-wide and meta-analysis studies that have identify polymorphisms in a number of other genes that also significantly correlate with the development of Parkinson's disease. These include GBA (β-glucocerebrosidase) (Swan and Saunders-Pullman, 2013), MAPT (microtubule-associated protein tau) (Lill et al., 2012), GAK (cyclin-G-associated kinase) (Rhodes et al., 2011), EIF4G1 (eukaryotic translation initiation factor 4-gamma) (Chartier-Harlin et al., 2011), HLA (human leukocyte antigen) and the transport protein (Puschmann et al., 2011) as well as several others. In several cases, identification and functionality of genes linked to Parkinsonism within the human chromosomes have not been adequately characterized and thus, the pathogenicity caused by mutations in these genes requires additional basic and clinical studies to further corroborate the relationship with expression of Parkinson-like features as well as Mn toxicity. Regardless of the characteristics of the symptoms presented, at this point it is difficult to predict *a priori* whether any of these genes will also segregate with progression of manganism though based on the other risk factors already linked to Parkinsonism, there is a reasonable probability that some if not all will also correlate with provocation of Mn toxicity.

## 11. Conclusion

The typical person has approximately a 2.5% chance of developing Parkinson's disease in their lifetime, and the risk for people whose close relatives have the disorder is increased to about 6–10% indicative of the fact that onset can be genetically controlled. The information provided in Table 1 attempts to summarize the data presented in this review related to the biochemical and pathophysiological defects accompanying mutations in genes known to induce Parkinson's disease and their potential contribution to generate Mn toxicity. As noted in this Table, there appears to be several common themes linking the two disorders, as mutations in genes associated with early and late onset of Parkinsonism induce similar adverse physiological responses acknowledged to provoke neuronal cell death. There are essentially four basic elements correlating mutated Parkinson's disease genes with Mn toxicity; (1) oxidative stress induced by disruption of mitochondrial function, (2) abnormalities in vesicle processing, (3) alteration in proteasomal and lysosomal protein degeneration, and (4) altered aggregation of α-synuclein. Clearly,

**Table 1**

| Gene | Cytotoxic mechanism |
|---|---|
| α-Synuclein | Mutations disrupt synaptic functionality, dopamine-mediated toxicity, vesicle trafficking defects, mitochondrial membranes regulation of mitochondrial activity and oxidative stress; disruption of dopamine oxidative products alter α-synuclein function and aggregation, mitochondrial α-synuclein is enhanced in Parkinson's disease brains implying a responsibility for its neurotoxic actions, disrupts mitochondrial complex I promoting production of ROS. |
| Parkin | Mutations disrupt ubiquitination of a variety of proteins including outer mitochondrial membrane proteins; disrupts cellular redox within mitochondria causing depolarization of mitochondria, regulated by PINK and DJ-1, stimulates oxidative stress and pursuant elevation in apoptotic signaling pathways, mutations lead to increased transport of Mn by DMT1 |
| PINK1 | Mutations lead to disruption of phosphorylation of mitochondrial proteins including parkin causing altered mitochondrial function, stress-induced mitochondrial apoptosis, lowered mitochondrial membrane potential and opening of the permeability transition pore promoting increased intramitochondrial calcium levels, excess production of ROS; interacts with parkin |
| DJ-1 | Mutations disrupt cellular defensive mechanisms regulating and preserving mitochondria function promoting oxidative stress, forms complex with parkin and PINK1, disrupts ubiquitin parkin activity to facilitate elimination of a variety of proteins |
| LRRK2 | Mutations lead to disruption of mitochondrial function, protein degradation, actin cytoskeleton-related processes, impairment of autophagy–lysosomal pathway involved in α-synuclein accumulation and aggregation, endolysosomal and Golgi apparatus sorting defects, decrease in the DA transporter, DAT, and promotes oxidative stress. |
| ATP13A2 | Mutations lead to lysosomal alterations including impaired lysosomal acidification, reduced proteolytic processing of lysosomal substrates and diminished lysosomal-mediated clearance of autophagosomes, disruption of mitochondria leading to ROS production, disruption of α-synuclein degradation, promotes cation (Mn) transport |
| VPS35 | Mutations promote disruption of retrograde transport of proteins from endosomes to the trans-Golgi network, mutations may function by disrupting recognition sites required for the binding to essential cargo proteins, endolysosomal and Golgi apparatus sorting defects and deficiency; associated in the recycling of the major Mn transport protein, DMT1. |
| SLC30A10 | Mutations lead to decreased export of Mn promoting increase levels within neuronal cells especially within the globus pallidus thus directly linking Mn accumulation with onset of manganism. |

these are not mutually exclusive events as each has the potential to influence the others behavior and performance. The operative effects generated by alterations in the biological processes associated with these four systems is likely to lead to provocation of manganism as each has previously been implicated as contributing to the Mn toxicity. In a reciprocal fashion, the fact that Mn can independently impact on each of these processes further implicates it in possibly potentiating the degenerative actions of mutant forms of Parkinson-related genes and thus, has to be considered as a potential risk factors provoking onset of Parkinsonism. The contribution of genetic mutations described above to eliciting Parkinsonism, based on our current knowledge, is actually relatively small and therefore, suggest that other factors such as diet or environmental agents, possibly in combination with genetic abnormalities, as contributing to onset and severity of the disorder. Clearly, the evidence presented above implies that chronic exposure to Mn has the potential to foster Parkinsonism in individuals expressing Parkinson-related gene mutations. Whether it can actually provoke idiopathic Parkinsonism in the absence of these or other genetic mutations is questionable but remains to be determined. Nevertheless, the one mutual element linking the two disorders is the altered output from the basal ganglia potentially resulting in enhancement and acceleration of the neurological pathology observed. Difference in the symptoms seen between the two disorders may reflect selective impairment to other neurological pathways in the brain.

Although the major focus of this review relates to the severe and debilitating extrapyramidal features of Parkinsonism and manganism, it should be noted that both disorders are associated with behavioral and cognitive dysfunction suggesting that a variety of neurotransmitter systems may be affected in the CNS independent of changes in the response to dopamine. In the case of Mn toxicity, these symptoms are most evident during the early stages of the disorder prior to the appearance of the more discernable and severe dystonic symptoms although these behavioral complications persist throughout the course of the disorder. Which neurotransmitter systems are responsible for the behavioral component of manganism has not been adequately evaluated but prior studies have reported Mn-induced changes in glutaminergic (Karki et al., 2013), GABAminergic (Yang et al., 2011, Fordahl and Erikson, 2014) and cholinergic (Finkelstein et al., 2007) systems in the brain not unlike the systems linked with similar neurobehavioral deficits in Parkinsonism (Nie et al., 2013, Buchanan et al., 2014). Whether the physiological consequences of the mutant genes described in this review combined with exposure to excess Mn can result in amplification of these behavioral or cognitive complexities needs to be examined.

## Conflict of interest

The authors declare that there are no conflicts of interest.

## Transparency document

The Transparency document associated with this article can be found in the online version.

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