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SLC41A1 and TRPM7 in magnesium homeostasis and genetic risk for Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system with a clinically heterogeneous presentation that includes progressive loss of dopaminergic (DA) neurons in the substantia nigra. A minority of PD cases are familial and are caused by mutations in single genes. Most cases, however, are idiopathic PD, a complex multifactorial disorder with environmental and genetic contributors to etiology. Here, we first briefly summarize published evidence that among environmental contributors is dietary deficiency of magnesium. We then review genetic data suggesting that mutations in genes encoding two proteins contributing to cellular magnesium homeostasis confer risk for PD or other Parkinsonian conditions. First, the gene encoding magnesium transporter SLC41A1 is, among others, a candidate for the causative gene in the PARK16 locus where variation is associated with risk for idiopathic Parkinsonian disease. Studies of the function of SLC41A1 in animal models are needed to test whether this protein has a role in maintenance of dopaminergic neurons. Second, in a small study, a hypomorphic variant of TRPM7, a magnesium-permeable channel, was over-represented in cases of amyotrophic lateral sclerosis/ Parkinson dementia complex versus controls from the same ethnic group. Although this association was not detected in a second study, in zebrafish Trpm7 is necessary for terminal differentiation and reduction of toxin-sensitivity in dopaminergic neurons. Overall, epidemiological results support the possibility that mutations in genes relevant to magnesium homeostasis would alter PD risk, but deeper genetic analyses of PD patients are necessary to confirm whether *SLC41A1* and *TRPM7* are among such genes.

Abbreviations

Parkinson's Disease (PD), cerebrospinal fluid (CSF), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium (MPP+), dopaminergic (DA), Amyotrophic lateral sclerosis/Parkinsonian dementia complex (ALS/PDC)

Magnesium levels are lower than normal in brains of PD patients and animal models of PD

Several studies have used spectroscopic methods to measure magnesium levels in postmortem brain tissue from PD patients, or in serum and CSF of living patients (Table 1). In one, using inductively coupled plasma atomic emission spectrometry, magnesium levels were found to be lower in the cortex, white matter, basal ganglia, and brainstem of PD brains in comparison to control brains[1]. In another, phosphorus magnetic resonance spectroscopy showed that average cytosolic free magnesium was lower in the occipital lobes of 13 PD patients than in those of 16 healthy age-matched controls[2].

Sample Size	Sample Type	Mg^{2+} Levels	*Free or Total Mg^{2+}	Citation
4 PD 5 control	Brain tissue (26 regions)	Reduced by an average of 191.6 µg/g in all regions (PD vs control)	Total	1
13 PD 16 control	Brain tissue (occipital lobe)	143 ± 11 mM (PD) vs 181 ± 23 mM (control)	Free	2
9 PD 12 control	Brain tissue (caudate nucleus)	471 ± 28 µg/g (PD) vs 530 ± 11 µg/g (control)	Total	3
91 PD 18 control	CSF	Diagnosed <1 year = 26.9 ± 3.0 µg/mL Diagnosed >8 years = 20.9 ± 1.7 µg/mL	Total	4
91 PD 18 control	Blood	31.7 ± 4.7 µg/mL (PD) vs 26.5 ± 4.8 µg/mL (control)	Total	4
20 PD 15 control	CSF	31.6 ± 3.6 µg/mL (PD) vs 29.6 ± 6.5 µg/mL (control) – No significant difference	Total	5
13 PD 4 control	Brain tissue (substantia nigra)	No significant difference (exact values not reported)	Total	6

Table 1: *The measurement of free or total Mg^{2+} was deduced by the technology used and was not explicitly stated by the authors

Atomic absorption and atomic emission spectroscopy was applied to four brain regions from 9 PD patients and 12 controls; lower concentrations of magnesium were present specifically in the caudate nucleus of Parkinsonian brains[3]. A further study found that magnesium levels in the CSF correlated inversely with duration and severity of PD, whereas levels of magnesium in the blood of PD patients were slightly higher than normal[4]. The authors noted that blood magnesium levels may be more sensitive to short term variation affected by diet than the levels in the CSF. However, in two other studies of similar scale magnesium levels were not significantly lower in the CSF[5] or brain tissue[6] of PD patients versus controls, consistent with variable pathogenic mechanisms among cases of PD .

Deficiencies of dietary magnesium have also been noted in patients with PD. A case-control study in Japan found that higher iron, magnesium, and zinc intake was associated with reduced risk of PD and that the inverse association remained after adjustment for intake of other elements[7]. Another found that lower intake of protein, folate, magnesium, and phosphorus was associated with lower olfactory acuity – an early symptom of both PD and Alzheimer's – in both PD patients and controls[8]. Amyotrophic lateral sclerosis/Parkinsonian dementia complex (ALS/PDC), observed at high incidence among the Chamorro population on Guam especially in the 1950s, has been attributed to nutritional deficiencies in calcium and magnesium[9]. In the Kii Peninsula of Japan, as on Guam, an increased risk for ALS/PDC was associated with significantly lower levels of manganese in food and magnesium in drinking water[10]. Moreover, declining incidence of the disease in Guam coincided with a shift towards a more Western diet richer in magnesium and calcium[11]. However, despite the correlation of low dietary magnesium and risk for ALS/PDC, a study in 1995 did not detect significantly different levels of free magnesium in urine and blood of 12 ALS/PDC patients and 12 Chamorro controls[12]. We conclude that the etiology of most Parkinsonian disorders is complex, and nutritional deficiency may contribute to it in some cases.

Several animal- and cell-based experiments support a neuroprotective effect of magnesium. Rats treated with 6-hydroxydopamine (a common PD animal model) had lower levels of magnesium and other elements compared to control[13]. Rats that were fed a low magnesium diet continuously for one year (including during the prenatal period) displayed a marked reduction in both levels of serum magnesium and numbers of dopaminergic neurons of the substantia nigra at one year of age[14]. In another study, mice fed a low magnesium diet for six weeks developed catalepsy and had a reduction in the amount of tyrosine hydroxylase-positive neurons in the substantia nigra compared to controls[15].

The link between reduced magnesium levels and elevated risk for PD may be oxidative stress, a long-suspected culprit PD-related neurodegeneration (recently reviewed[16]). Low magnesium levels have been linked to oxidative stress in traumatic brain injury[17]. Magnesium supplementation in a canine model of cardiac infarction lowered ascorbate free radical levels[18]. The dopaminergic toxin MPTP specifically inhibits complex I of the electron transfer chain and greatly increases the production of free radicals[19]. Work from the Oka group showed that a reduction in magnesium levels elevates ROS and sensitizes PC12 cells to MPTP[20], and that overexpression of the magnesium transporter SLC41A2 can protect against MPTP-induced death[21]. In summary, results from epidemiology, animal studies, and cell lines all implicate magnesium as a contributing factor in at least some forms of Parkinsonism.

Mutations in genes encoding proteins involved in magnesium homeostasis

Given the evidence connecting lower-than-normal magnesium levels to elevated risk for PD, it might be expected that mutations in genes encoding regulators of magnesium homeostasis would predispose individuals

to PD. The levels of intracellular and extracellular free magnesium are nearly identical (roughly 0.5-1.2 mM)[22], although levels of total cytoplasmic magnesium are considerably higher than those of free magnesium (around 5 mM), with the majority complexed with ATP[22]. Although numerous ion channels and transporters have been implicated in control of magnesium homeostasis in eukaryotic cells, including TRPM7, MAGT1, CNNM2, SLC41 paralogs, ACDP paralogs, NIPA paralogs, and HIP14 paralogs[23], to our knowledge, only two are implicated in inherited risk for any parkinsonian disorder, i.e., SLC41A1 and TRPM7.

SLC41A1

The PARK16 locus was initially identified in a pair of GWAS of PD disease patients of European and Japanese descent[24,25]. This locus harbors 6 genes, three of which – *NUCKS1, SLC41A1*, and *RAB7L1* – are considered candidates for the causative gene. *SLC41A1* encodes a protein distantly related to the bacterial MgtE magnesium transporters[26]. Because of the connections between magnesium homeostasis and PD risk, *SLC41A1* is good candidate for the causative gene. Supporting *SLC41A1* as the causative gene, a SNP within *SLC41A1* (rs11230569) was associated with a lower risk of PD in independent studies of Iranian and Chinese cohorts[27,28]. Interestingly, although this SNP is synonymous, the GTex study of expression quantitative trait loci (eQTL) shows that it is associated with altered expression of *SLC41A1* (but not of *RAB7L1* or *NUCKS1*) in several tissues[29]. The SLC41A1 coding variant p.A350V was identified in one of a cohort of 454 PD cases, but absent in 483 controls[30]. It is also missing among 60,706 individuals in the ExAc database, strengthening the case that *SLC41A1* is the causative gene in the PARK16 locus[31]. Patch clamp recordings of HEK293 cells forced to express SLC41A1 A350V indicated that this variant is over-active, resulting in a reduction of cellular magnesium levels[32]. In a separate study, a variant in *SLC41A1* (R244H) was identified in one case of early onset PD, but not in 479 PD patients with age of onset over 50 or in 525 normal controls[33] (a frequency of less than 1 in 10,000 alleles currently represented in the ExAc study[31]). When this variant was cloned and expressed in HEK293-derived cells, it was still able to correctly localize to the plasma membrane but was less effective at magnesium efflux than the wildtype protein[33]. A final study found one noncoding and two coding variants in *SLC41A1*, but not in *RAB7L1*, that were found amongst 205 PD patients yet not in 210 controls[34].

Nonetheless, it is by no means certain that *SLC41A1* is the causative gene in PARK16. For instance, *RAB7L1* encodes a protein that can bind and alter the activity of the strongly-PD associated LRKK2 protein[35]. Moreover, the GTex study found that, in contrast to some other SNPs in PARK17, rs947211 (associated with PD in GWAS of both European and Asian populations[36]) is an eQTL for *RAB7L1* and *NUCKS1* in many tissues, and for *SLC41A1* in just one[29]. It has been discussed that there may be more than one pathogenic gene in this locus[30]. Animal model studies of SLC41A1 function *in vivo* – for instance in mouse or zebrafish mutants or in cell line models of dopaminergic neurons – would help to assess the likelihood that *SLC41A1* is indeed a causative gene for PD.

TRPM7

Transient receptor potential melastatin-like 7 (*TRPM7*) encodes an ion channel with a C-terminal kinase domain. The channel is permeable to magnesium, calcium, zinc, and other trace metals. Channel activity is inhibited by intracellular magnesium, and is stimulated by PIP2 and perhaps by stretch (reviewed in [37]). Early studies in tissue culture showed that TRPM7 is essential for cell proliferation and viability[38,39]. Cells depleted of TRPM7 had lower-than-normal levels of intracellular magnesium, and supplementation of the culture media with magnesium rescued cell growth and viability[38], indicating that TRPM7 regulates cellular magnesium homeostasis. Later loss-of-function studies, through targeted mutation or morpholino-mediated knockdown, reveal that TRPM7 is essential for morphogenesis of mice and frogs[40,41]. Overexpression of SLC41A2, a magnesium transporter closely related to SLC41A1 discussed above, rescued morphogenesis in frog embryos depleted of TRPM7, indicating that the essential function of TRPM7 during morphogenesis is also regulation of cellular magnesium homeostasis[41]. Tissue specific knockout in mice reveals that TRPM7 is also necessary for differentiation of thymocytes[40], sensory neurons, melanocytes, and potentially other cell types[42]. Interestingly, cellular magnesium homeostasis was not grossly perturbed in thymocytes or T-lymphocytes lacking TRPM7[40]. Because TRPM7 is permeable to ions other than magnesium, and because it has a kinase domain that can be cleaved and migrate to the nucleus[43] the role of TRPM7 in some developmental or physiological contexts may be independent of its function as a magnesium channel. For instance, studies in cultured neurons and rats indicate that excessive flow of calcium and possibly zinc through TRPM7 is toxic to neurons[44,45]. In summary, TRPM7 is a combined channel and kinase that is necessary for cell migration, proliferation, survival, and differentiation, but which also mediates a toxic influx of divalent cations in certain physiologic conditions.

A missense variant of *TRPM7, T1482I,* was reported to be present in 5 of 22 Guamanian ALS/PDC patients and absent from 23 age-matched controls from the same ethnic group, i.e., the indigenous Chamorros[46]. The *TRPM7* T1482I variant was shown to have a lower peak current and to be more sensitive to inhibition by intracellular magnesium than the reference variant[46]. However, a separate study on

a similar scale (25 patients and 27 age-matched regional controls) in the Kii peninsula, where this disease is also prevalent, detected no association between the disease and the mutation causing the T1482I variant[47]. Moreover, in the ExAc study, this variant represented 8.7% of *TRPM7* alleles sequenced, and many homozygotes were detected[31]. Importantly, the frequency of the T1482I variant among the Chamorros and among individuals in the Kii peninsula is unknown. Nonetheless, the genetic evidence that this predisposes people to Parkinsonian conditions, except perhaps in conditions of low dietary magnesium, is weak.

In this context it is interesting that the phenotype of zebrafish *trpm7* loss-of-function mutants, identified in several chemical mutagenesis screens, support a role for TRPM7 in the differentiation, and possibly survival, of dopaminergic neurons. Unlike mouse and Xenopus embryos deficient in TRPM7, zebrafish *trpm7* mutants undergo early morphogenesis normally[48,49]. However, at 5 days post fertilization, loss-of-function mutants exhibit significantly less spontaneous swimming than their wildtype and heterozygous siblings[50]. Motility is elevated by application of L-DOPA (a dopamine precursor), implicating a dysfunctional DA system[50]. Indeed, histology revealed that whereas the number of precursors expressing *Dopamine transporter* (*dat*) is normal in *trpm7* mutants, only about half of the normal number of TH-positive neurons are present in mutants[50]. These results indicate that in zebrafish Trpm7 is necessary for terminal differentiation of at least a subset of dopaminergic neurons. In addition, residual TH-positive neurons in *trpm7* mutant zebrafish larvae are hypersensitive to the toxic effects of MPTP and MPP+ [50], consistent with the possibility that Trpm7 is necessary for the maintenance of dopaminergic neurons, not just their differentiation. Supporting this possibility, overexpression of a channel dead variant of TRPM7 in SH-SY5Y cells – which are dopaminergic – blocks proliferation and survival[50].

Outstanding questions for future research

Ever increasing sample sizes and sequencing depth of PD patients and controls – including whole genome sequences – will yield increasing power and resolution of genetic studies, strengthening or weakening the case for *SLC41A1, TRPM7*, and potentially other magnesium transporters and channels as causative genes for PD. Meanwhile, efforts to illuminate the roles of SLC41A1 and TRPM7 in the development, function, and maintenance of dopaminergic neurons will benefit from studies in cell lines and in animal models, including zebrafish. Cell lines are more tractable than *in vivo* models for physiology and some pharmacology experiments. However, animal models offer the ability to study dopaminergic neurons in their normal context; for studies of Trpm7 *in vivo*, the zebrafish mutant is particularly useful as the mouse mutant is embryonic lethal. Future studies in animal models may answer questions including: Why are dopaminergic neurons compromised to a greater degree than other cell types by a given variant of SLC41A1 or TRPM7? Do both loss and gain-of-function variants of SLC41A1 disrupt the dopaminergic system, as indicated by human genetic studies? What is the connection between TRPM7 function, magnesium homeostasis, and the physiology and development of dopamine neurons? In this context, does TRPM7's kinase domain contribute, beyond modulating the sensitivity of the channel to inhibition by internal magnesium[37]? TRPM7 may contribute to maintaining ion homeostasis in intracellular vesicles, including synaptic vesicles[51], and defects in vesicle trafficking are proposed to play a major role in PD[52]. Another possibility is that, by maintaining correct magnesium levels, Trpm7 protects against buildup of ROS, particularly in the context of the oxidative chemistry of dopamine synthesis[20]. And finally, in which cell type is SLC41A1 (or TRPM7) required to maintain healthy dopaminergic neurons?

Conclusion

To date there is little evidence that sequence variants near genes encoding magnesium transporters contribute a large portion of heritable risk for idiopathic PD, although they may contribute a measure of such risk. By contrast the evidence that magnesium homeostasis is relevant to the survival and function of dopaminergic neurons is relatively strong. Therefore, regulatory pathways governing magnesium homeostasis are worth investigating as therapeutic targets for PD.

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