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Genetic factors associated with dementia in Parkinson's disease (PD)

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Abstract

Parkinson's disease (PD) is a common neurdogenerative condition characterized by both motor and non-motor symptoms. The latter include dementia, the risk factors of which are old age, severity of parkinsonian symptoms, predominance of rigidity, postural instability, hallucinations and mild cognitive deficit documented at the first examinations. Only 5-10% of the cases show dominant or recessive autosomal inheritance, while most patients suffer non-Mendelian or complex forms where genetic factors act in combination with environmental causes. Little is known about the contribution of genetic factors to the development of dementia in PD (PDD). A review of literature on genetic variations eventually producing PDD revealed α-synuclein (PARK1/PARK4) to be the main responsible, in addition to mutations in the glucocerebrosidase (GBA) gene. As for cognitive deterioration in PD, not many associations have been established with genetic polymorphisms and most studies lack a profound assessment of this phenotype. (Gac Med Mex. 2015;151:100-7)

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Introduction

Parkinson's disease (PD) is a very common neurodegenerative condition and its prevalence increases with age. It is estimated to affect nearly 1% of subjects aged 65-69 years with this figure increasing to nearly 3% in those older than 80 years, numbers likely to be doubled by the year of 2030[1]. Clinical manifestations are essentially motor: tremor, rigidity, akinesia, loss of postural reflexes, but numerous non-motor symptoms are also described, including a special type of cognitive deterioration that affects only some patients.

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A late non-motor symptom is represented by dementia, the prevalence of which varies significantly in different series, since it ranges from 23%[2] to up to 83% in cases surviving 20 years with the disease[3]. In general, the time of evolution to develop PD dementia (PDD) is 10 years, although there is also variability between different studies[4]. Over the past two years we have applied neuropsychological tests to 193 patients with PD with a mean of 9 years evolution (standard deviation [SD]: 4.9), and dementia has been found in 39% of the cases (data not published). It has been described as "subcortical"-type dementia with predominance of apathy and failures in executive and visuospatial functions. It differs from Alzheimer's disease"cortical" dementia for not presenting the classical triad of aphasia-apraxia-agnosia[5]. Aarsland et al. informed in their study that 10% of PD patients develop dementia every year[6]. Other study reported that a patient with PD could

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Table 1. Genes positively or negatively associated with the development of PDD

Symbol	Gene	Chromosomal locatization	Type of inheritance	Strength of association	Reference
PARK1/PARK4	*α-synuclein*	4q21	AD	+++	16
PARK8	*LRRK-2*	12q12	AD	+	27
PARK2	*Parkin*	6q25.2-q27	AR	–	71
PARK6	*PINK1*	1p35-6	AR	–	71
PARK7	*DJ-1*	1p36	AR	–	71
PARK9	*ATP13A2*	1p36	AR	++	51
PARK14	*PLA2G6*	22q13.1	AR	+	56
APOE	*APOE2 and 4*	19q16.3	Risk*	?/+	13
GBA	*β-glucocerebrosidase*	1q22	AD/Risk*	++	61
MAPT	*Tau*	17q21.1	Risk*	Inversion +++	67

AD: autosomal dominant; AR: autosomal recessive.
*Risk polymorphisms
+++: definitely associated with PDD.
++: strongly associated.
+: related.
-: not associated with PDD.

develop dementia with a 4 to 6-fold higher probability than an individual without PD[7]. There are several risk factors that predict PDD, including old age, severity of parkinsonian symptoms, and predominance of rigidity, postural instability, gait disturbances, hallucinations and mild cognitive deficit documented in the first examination[8]. However, the association of genetic factors has been reported in very few studies worldwide and little is known on the subject, which is why this review is intended to consolidate the information described to this moment.

Genes and their association with the development of PDD

A positive family history has been found in 20% of the cases of PD and only a minority of them shows a Mendelian ihneritance pattern. The remaining 80% is attributed to PD of the sporadic or idiopatic type[9]. Studies in the past two decades have allowed for responsible loci to be identified in patients with familial PD. Some *PARK* genes have already been associated with PDD, as well as *GBA,* but the myriad of polymorphisms that might also relate to PDD has not yet been studied, in particular those of the *MAPT* and *APOE* genes, which codify for the microtubule-associated protein tau (MAPT) and apolipoprotein E (APOE), respectively, among others.

In a prospective study of 240 patients, progression of dementia was compared in subjects with familial PD versus a group with sporadic PD. The results showed that patients with familial PD have an earlier onset of the disease ($p = 0.001$), but develop significantly less dementias than patients with sporadic PD ($p = 0.02$)[11]. However, some forms of familial PD have shown clinical findings that differ from those encountered in sporadic PD. This is why clarifying the cognitive characteristics of patients carrying different mutations reported in literature to this moment is intended (Table 1).

PARK1/PARK4K (α-synuclein)

The α-synuclein gene *(SNCA)* is found in the locus PARK1/PARK4 located in the long arm of chromosome 4 (4q21). Mutations in this gene result in PD with a dominant autosomal inheritance pattern. SNCA is a protein found in presynaptic terminals in the brain of mammals. Its function is not yet well clarified, but several studies suggest it intervenes in the release of presynaptic vesicles[12]. Not only mutations have been described in the gene sequence, but duplications and triplications of the *SNCA* gene are favored. Normal α-synuclein tends to form the aggregates found in Lewy bodies (LB). These typical PD cytoplasmic inclusions (although no pathognomonic) influence on the death of dopaminergic neurons[9]. A longitudinal study identified 4 patients with the E46K mutation in *SNCA,* two of them with clear cognitive deficit, although all 4 subjects presented progressive deterioration of cognitive functions in at least

one of the performed tests[10]. In a larger study of 140 patients diagnosed with PD, LB aggregation was positively correlated with dementia ($p \leq 0.001$)[13]. Other studies have demonstrated that patients with higher numbers of LB have 20 times more probability to develop dementia versus PD patients without or with little LB disease ($p = 0.002$)[14,15]. PD patients who carry *SNCA* triplication have more severe disease progression and worse cognitive deficit than those with duplicated *SNCA*[12,16], although the sole duplication of *SNCA* carries the risk of dementia development[17]. With these claims, it can be concluded that the development of dementia is "dose-dependent" with regard to the amount of mutated *SNCA* or LB. It is important to mention that α-synuclein mutations can be found not only in the familial forms, but also in sporadic cases[9,13].

PARK8 (LRRK-2)

The *LRRK-2* (leucine-rich repeat kinase 2) gene is located in the *PARK8* locus and it is found on the long arm of chromosome 12 (12q12). In a manner similar to PARK1/PARK4, mutations in LRRK-2 show autosomal dominant inheritance. The *LRRK-2* gene codifies for a protein named "dardarin" that has a domain with tyrosine kinase activity. This domain participates in signalling cascades with functions in the cytoskeleton dynamics[18]. Mutations in *LRRK-2* are the most common cause of late-onset autosomal dominant PD, although in a Mexican series of 319 patients, only 3 cases were found with the R1441G, R1441H and G2019S mutations, out of which the last two were reported as "sporadic"[19]. The most common mutation is G2019S, which is present in 1-2% patients with European-origin PD, in 20% in Ashkenazi Jewish-origin PD and in up to 40% in Berber Arab-origin PD[9]. In a recent study, 60 healthy patients with a close relative with PD were assessed, out of which 30 tested positive for the G2019S mutation. All of them underwent the MoCA test[20], among others, to assess mental functions, and a significant loss of executive functions ($p = 0.04$) was demonstrated in "presymptomatic" carriers of the mutation[21]. Other retrospective study of 3 patients with the G2019S mutation showed that two of them had long-term cognitive deficit[22]. Conversely, in a cohort analyzed by Ban Sassi et al. in 2012, cognitive deficit was compared in 55 patients with the G2019S mutation and 55 EP patients that were not carriers of the mutation. The authors did not find any difference, since both groups had similar deficit, predominantly visuospatial and in executive tasks mainly, but they did specify that patients with the G2019S mutation had the worst score in the geriatric depression scale ($p = 0.04$) compared with those non-mutated[23]. Similarly, Belarbi et al. (2010) did not find differences with regard to cognitive deficit among their 106-patient cohort: 34 with the mutation and 72 without it. However, they described higher incidence of psychiatric manifestations in patients with the mutation, especially depression ($p = 0.04$)[24]. Shanker et al. (2011) demonstrated in a cohort that patients with the G2019S mutation are more likely (odds ratio [OR] = 6.0) to develop psychiatric conditions compared with those without the mutation[25]. Finally, we found other two contradicting studies that report that patients with *LRRK-2* mutations have a more benign course ($p = 0.0016$) with regard to cognitive deficit compared to other forms of PD[26,27].

PARK2 (Parkin)

Mutations in *PARK2* are more frequently associated (77%) with early-onset and autosomal recessive inheritance forms of PD[28.] *PARK2,* whose locus is in 6q25.2-6q27, codifies for a protein named "Parkin", which is an E3 ubiquitin ligase that marks certain proteins for adequate degradation. It also intervenes in mitochondrial DNA maintenance and repair[29,30]. Autosomal recessive-type juvenile PD has certain differences with regard to classical PE, although both are consistent with the akinesia-rigidity-resting tremor triad[31]. Neuropathological findings in a patient with homozygous deletion in axon 4 of the gene were: neuronal loss and gliosis in the medial and ventrolateral portion of the substantia nigra pars compacta and locus coeruleus, although without LB being found. The patient did not show any signs of cognitive deterioration or dementia at clinical evaluation[32]. Although mutations in *PARK2* do not seem to cause cognitive loss (Mini-mental test was normal in 24 subjects), they do associate with different psychiatric manifestations[33]. It is important to mention that the locus of the gene predisposing to the development of schizophrenia gene (6q25) is adjacent to the *PARK2* locus (6q25.2), which might explain the high prevalence of psychiatric disease in patients with mutated Parkin[24]. However, other study suggests a correlation between *PARK2* mutation and the development of attention deficit hyperactivity disorder ($p < 0.001$)[35]. Although attention deficit usually does not translate into cognitive deterioration, it certainly can affect executive tasks.

A genetic study in our institution described different abnormalities in this gene in 34 patients with PD and onset at between 16 and 44 years of age. Three of them have variations in sequences, whereas 31 cases

exhibit exonic rearrangements: heterozygous deletions in 8 cases, homozygous in 6 cases and composed heterozygous in 15 cases with deletions/duplications. Interestingly, earlier age of onset is associated with greater familial aggregation, whereas onset close to 40 years of age is found in sporadic cases[36]. A priori, no cases with dementia are reported, but no in-depth neuropsychological studies are planned in these cases.

PARK6 (PINK1)

The *PINK1* (PTEN-induced putative kinase 1) gene is found at the 1p35-36 locus. Its mutations have a low incidence and it is associated with early-onset PD, with autosomal recessive inheritance pattern[37]. *PINK1* mutations are found in 1-8% of early-onset PD sporadic cases[38]. PINK1 is a kinase with an N-terminal sequence that protects against mitochondrial dysfunction through the fision/fusion pathway. It also acts in the same cascades as Parkin (PARK2) for the maintenance of mitochondrial quality[39].

Albanese et al. informed on clinical findings of 21 patients with mutation in *PINK1.* Their study shows that most of their patients have slow progression of the disease, good response to levodopa, bradykinesia and predominance of rigidity[40]. In a case report of a Japanese patient, deletions in exons 6 and 8 of the *PINK1* gene are found and, clinically, they are characterized by the presence of hallucinations, depression and dementia, in addition to classical parkinsonian symptoms[41]. As the mutations in Parkin *(PARK2),* mutations in *PINK1* reported in some studies are associated with higher prevalence of psychiatric disease[42,43]. Psychiatric manifestations were described in 61% of patients from a large family n = 20) with monogenic PD with mutation in *PINK1,* whereas these are only present in 20% of the subjects without mutation[43]. Although mutations in *PINK1* have not been adequately studied with regard to cognitive deficit in PD, it has certainly been concluded, in the previously mentioned studies, that they confer higher probability to develop psychiatric disease. Due to the same pathway of action shared by *PINK1* and Parkin, the correlation of both with the development of psychiatric disease can be understood. Funayama et al. further support this fact with a study where the correlation of psychiatric disease is suggested in patients with the digenic mutation *PINK1-PARK2,* although their sample is very modest and they claim they need a larger number of cases to obtain more significant results[44].

PARK7 (DJ-1)

The *PARK7K* gene codifies for an antioxidant protein named DJ-1 and is localized in the 1p36 locus. It is associated with early-onset PD, with autosomal recessive inheritance pattern and with sporadic cases (in 1-2%)[45]. The DJ-1 protein has a function in mitochondrial protection against oxidative stress, and forms, together with Parkin and PINK1, the ubiquination complex, the function of which is to degrade wrongly folded Parkin substrates[46,47]. Mutations in *DJ-1* are clinically characterized by slow disease progression, good response to levodopa, PD early onset and for not having atypical signs. These patients can present blepharospasm, leg dystonia and psychiatric disturbances, although none of these symptoms is exclusive to DJ-1, since they are also found with *PINK1* and *Parkin* mutations[46]. To this moment, DJ-1 mutations have not been associated in PD patients with any selective cognitive function condition.

PARK7 (DJ-1)

The *PARK9* gene, whose locus is found in 1p36, as *PINK1* and DJ-1, codifies for a protein known as type 13A2 ATPase (ATP13A2)[48]. The ATP13A2 function is as yet not well known, but it is involved in neurodegeneration; apparently, it is driven by a loss of lysosomal function and abnormal protein aggregation[49]. Mutations of this gene cause PD in a rare form known as Kufor-Rakeb syndrome (KRS), which follows an autosomal recessive inheritance pattern[50]. This syndrome is characterized by juvenile-onset, rigid-akinetic PD, progressive cognitive deterioration, vertical gaze palsy, pyramidal syndrome, mini myoclonus, insomnia and good response to levodopa[51]. To date, only few studies report families with KRS around the world[49-54], but basically all show the same clinical characteristics, predominantly including early-onset PD and cognitive deterioration. Moreover, Behrens, et al. describe magnetic resonance pathological findings in KRS patients, including global atrophy and lenticular nucleus iron deposition[51].

PARK 14 (PLA2G6)

The *PARK14* gene is found in locus 22q13.1 and codifies for a protein known as "phospholipase A2 group 6" (PLA2G6), which catalizes fatty acids elimination from phospholipids. Its mutations cause autosomal recessive PD and are associated with neurodegenerative conditions such as infantile neuroaxonal dystrophy and neurodegeneration with brain iron accumulation[55].

In 2009, Paisan-Ruiz et al. described the association of *PLA2G6* with an early-onset, autosomal recessive form of dystonia-parkinsonism[56].

The phenotype of patients with this familial Parkinson has been described, and they tend to present the disease very early, between 10 and 26 years of age, with good response to levodopa, severe akinesia and rigidity, widespread dystonia and cognitive deficit[57]. The same report also presents a female patient with mutation in *PLA2G6,* which started at 26 years of age with progressive cognitive loss, tremor, slow movements, problems with balance and language ability and, finally, widespread dystonia. Initially, she had a good response to levodopa, but, gradually, she lost responsiveness to the drug. At 34 years she was already postrated in bed when convulsive crises added to her condition.

APOE4

The apolipoprotein E epsilon 4 allele (ε4) has been considered the most important risk factor in neurodegenerative conditions such as PD. The *APOE* gene is localized in the 19q13.2 chromosome. This gene has been studied in the Mexican population in 229 PD patients, associating the ε4 polymorphism with the development of the disease (OR = 1.73; p = 0.011)[58]. A recent meta-analysis in more than 1,000 subjects with and without PD, reveals a slight majority of dementia in cases with *APOE* ε 4 genotype (OR = 1.16; 95% confidence interval [CI]: 1.03-1.31), whereas when subjects with and without PDD are compared, there is an over-representation of the ε4 polymorphism in cases with dementia (OR = 1.74; 95% CI: 1.36-2.23). However, a 5-year follow-up of a representative cohort of 107 patients did not show higher incidence of dementia in the *APOE* ε 4 genotype[59]. On the other hand, we only found one postmortem study in 140 cases with PD that significantly associates *APOE* ε 4 with dementia (OR = 4.19)[13].

GBA

Mutations in the *GBA* gene cause Gaucher's disease, which is characterized by a defect in the storage of lysosomal glycolipids. Gaucher's disease patients' close relatives have been shown to be at high risk of developing parkinsonian syndrome[60]. A sample of 128 Mexican patients has been studied and the L444P has been found in 7 cases, out of which 6 show different psychiatric manifestations, such as depression, anxiety and obsessive-compulsive disorder, and in 3, dementia or cognitive deterioration is documented. The comparison between cases with and without mutation in *GBA* showed a predominance of neuropsychiatric manifestations in the first group with an OR of 1.82[61]. A recent cohort study, where 33 patients have PD with mutations in *GBA* and 60 have EP without the mutation shows that the patients with the mutation have worse progression to cognitive deficit than those non-mutated (p = 0.035)[62]. Although only a few studies associate PD cognitive deficit or dementia with the *GBA* mutation (Table 2), there are enough grounds to continue investigating these mutations, as well as this gene's polymorphisms[63].

COMT

Genetic influences of the catechol-O-methyltransferase gene *(COMT),* a monoamine degradation enzyme, were suspected in two occasions, as well as the role of the dopaminergic system, before the conduction of a longitudinal study in 212 subjects with PD. In particular, the *COMT* Met/Met genotype, found in 56 cases, was studied, failing to associate it with increased cognitive deterioration[64].

MAPT

In a study of PDD genetic determinants, the *MAPT* H1 haplotype was analyzed, since tauopathy was evidenced in some cases of PD autopsy and upon genome-wide studies that confirm the presence of this gene in PD[70]. Only memory was found to be affected, but not other areas of cognition[64]. In this study*, APOE* ε 4 was also not associated with severe cognitive deterioration.

Discussion

In this brief review, we focus on the study of the most relevant genes in current literature with regard to their association with the loss of cognitive functions in PD.

The first genes identified as responsible of familial PD correspond to α-*synuclein* mutations, which result in its aggregation and are the main component of the LBs. These inclusions are known for being responsible of dementia with LB and are strongly related to PDD[14]. Dementia is also known to depend on duplication or triplication of the gene and, therefore, the effect, early onset and dementia seem to depend on the gene or protein dose[12,16]. In support of pathological findings of α-synuclein as a dementia-generator in Parkinson, a study conducted by Hurtig et al. finds 90% specificity and 91% sensitivity of these findings, when comparing PD brains with and without dementia. The authors conclude that

Table 2. Studies focused on the gene-PDD relationship

Gene	Type of study	Sample	Results	Reference	Level of evidence/ degree of recommendation[68,69]
PARK1/ PARK4	Postmortem study	92 PDD vs. 48 PD without dementia	Presence of LB positively correlated with dementia with OR = 4.06 (95% CI = 1.9-8.8)	Irwin, 2012[12]	2++ B
	Large family with PDD	Large family	Genetic variability in *SNCA* contributes to the risk for developing PD	Singleton, 2003[11]	C
PARK2 (Parkina)	Case reports	First large series of 24 cases	Sensitivity to levodopa and psychosis. No dementia	Khan, 2003[33]	D
	Comparative study (early-onset PD, HyY III and late onset)	240 (6 with 29 familial forms mutations)	Dementia only in non-inherited forms (p = 0.02)	Somme, 2011[11]	C
	Genetic study	31 cases with mutations	Exonic rearrengements and early onset predominance	Guerrero, 20126	2+ C
PARK 8 (LRRK2)	Observational in healthy subjects from a family with G2019S mutation	60 (30 vs. 30)	G2019S mutation carriers show deterioration in executive functions in Stroop's test (p = 0.007)	Thaler, 2012[21]	2+ C
PARK 9	Observational	5 cases	Juvenile cognitive deficit	Behrens, 2010[51]	D
	Observational		Many families with KRS present dementia and parkinsonism	Hampshire, 2001[48]	D
APOE	1. Case-control 2. Cohort	1,040 subjects 528 with PD 107 cohort	Higher incidence of dementia in *APOE4* (p = 0.017 and 0.001)	Williams-Gray, 2009[59]	2++ B
GBA	Case-control	93 (33 vs. 60)	Higher deterioration of non-verbal memory in 33 patients with mutations vs. 60 without mutation (p < 0.001)	Alcalay, 2012[62]	C
	Cohort	262 with PD mutations n = 4 Polymorphisms n = 11	More marked dementia in carriers of a mutation (p = 0.003)	Winder-Rhodes, 2013[64]	C

α-synuclein labelling is better indicator of dementia than neurofibrillary degeneration, dystrophic neurites and amyloid plaques[14]. It will be interesting to explore the encephalic burden in LB with α-synuclein using functional imaging specific biomarkers and in cerebrospinal fluid, a project we are currently designing.

Unlike *SNCA,* the phenotype of the dardarin mutation *(LRRK2)* yields conflicting results[23] that deserve to be

completed by more data obtained from cohorts and serial cognitive studies.

As for the "three musketeers"[65], represented by *Parkin, PINK1* and *DJ-1,* they are a trio of enzymatic protein-codifying genes with a combined effect that confers neuroprotection. Indeed, mitochondrial calcium buffering and oxygen free-radicals production was corroborated in biogenesis, driving the trio to ensure mitochondrial and, therefore, neuronal quality control. No cognitive deterioration is reported, but other neuropsychiatric manifestations in patients carrying mutations in these genes. Recently, the effects of mutations in *GBA* were studied and, in patients studied in our institution, we have found the L444P mutation to be a dementia driver[61]. The CORE-PD cohort study on early symptoms already showed in 2010, in spite of a normal Mini-mental test in both groups, that patients carrying the mutation had more intellectual difficulties. Of note, two years later, neuropsychological tests were made, which allowed for cognitive deterioration to be verified[62]. An anatomopathological study of 4 cases carrying a mutation in *GBA* shows LB diffuse disease[66] and, again, it suggests that a more diffuse LB pattern, i.e., also involving the cerebral cortex, is responsible of DPP.

As a final consideration, we were surprised on how little genetic risk factors for DPP have been studied, without forgetting the myriad of gene polymorphisms that might be involved. With regard to these risk factors, we would propose as our first candidate the study of the tau protein, and in particular of an inversion polymorphism of *MAPT* previously associated with cognitive deterioration[67], but that also, when associated with another single-nucleotide polymorphism, also of *MAPT,* participates in the development of PD itself.

The recent implementation of genome-wide screening studies reveals that at least 20 genes are involved in the development of PDD[9], but the most recently reported, which are also in our sights after this review, remain essentially *SNCA, GBA* and *MAPT*[9,67.70].

Conclusions

SNCA mutations are infrequent, but there are very solid evidences (class 1+ and 2++) with level of recommendation A on their association with Lewy disease and PDD. Wlth regard to gene duplications and triplications that result in an increase of the load of wild-type α-synuclein, these phenomena entail an excess of protein that surpasses the clearance mechanisms. Triplication cases are clearly associated with dementia.

PARK9 mutations, which affect the lysosomal membrane protein ATP13A2, are responsible of an early-onset Parkinson, with pyramidal syndrome and dementia, and a toxic role has been suggested for the mutated protein causing wrongful folding of α-synuclein in cortical neurons. The doubt on the existence of LB and Lewy neurites remains up to this moment in cases of *PARK14,* early-onset with cognitive deterioration, and in cases of *PARK17,* in the form of late onset with dementia.

LRRK-2 most frequent mutation, G2019S, reveals in autopsies typical Lewy disease and a very symilar phenotype to idiopatic PD.

Conversely, *Parkin* gene mutations, identified in more than half of early-onset PD cases, are not associated with severe cognitive deterioration and neither with LB. Currently, there is a quite elevated level of evidence of 2+.

Synucleinopathies are not the sole responsible for PDD, since their highest expression is dementia with LB, but other neuropathological substrates have also been documented, such as findings in Alzheimer's disease (senile plaques and neurofibrillary tangles) and amyloid angiopathy.

Over the past 10 years, advances in the understanding of genetic determinants of PDD have become apparent in both some highly penetrating monogenic forms of the disease and in variants with incomplete penetrance of the *LRRK-2* and *GBA* genes, whereas other variations such as polymorphisms have been identified in only a few genome-wide association studies. Essentially, the *APOE* ε 4 genotype and the *MAPT* H1p haplotype are mentioned. But many of the currently available studies lack the elements that confer consistency to the results; namely, serial neuropsychological studies and neuropathological findings.

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