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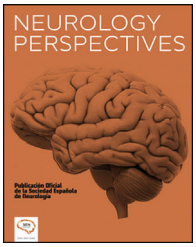

REVIEW ARTICLE

Genetics of Parkinson´s disease: Recessive forms

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Abstract The genes associated with autosomal recessive Parkinson's disease (PD) include the *PRKN*, *PINK1*, and *DJ-1* genes. Homozygous and compound heterozygous carriers of pathogenic variants of these genes tend to display typical characteristics of PD at early ages.
On the other hand, the *ATP13A2*, *FBXO7*, *PLA2G6*, *SYNJ1*, and *DNAJC6* genes are associated with early-onset recessive forms that frequently present with pyramidal signs, ataxia, and oculomotor alterations, with early appearance of levodopa-induced motor fluctuations and dyskinesia. Such non-motor symptoms as depression, psychiatric disorders, hallucinations, and epilepsy are also more frequent in this group.
Among multiple molecular mechanisms involved in these cases, key examples are the dysfunction of mitochondrial and lysosomal processes.
This article presents a brief review intended to inform clinicians about the basic molecular mechanisms and phenotype–genotype relationship of these monogenic forms of PD.

PALABRAS CLAVE
Enfermedad de Parkinson;
genética;
PRKN;
PINK1;
DJ-1;
Autosómico Recesivo

Genética en la efermedad de Parkinson: Formas recesivas

Resumen Los genes asociados a enfermedad de Parkinson (EP) de herencia mendeliana autosómica recesiva incluyen PRKN, PINK1 y DJ-1. Los individuos portadores homocigotos o heterocigotos compuestos de variantes patogénicas en estos genes tienden a manifestar características típicas de la enfermedad de EP a edad temprana.
Por otro lado, los genes ATP13A2, FBXO7, PLA2G6, SYNJ1, y DNAJC6, se asocian a formas recesivas de manifestación precoz, presentan con frecuencia signos piramidales, ataxia y alteraciones oculomotoras, y desarrollan tempranamente, fluctuaciones motoras y disquinesias

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inducidas por levodopa. Alteraciones no motoras como depresión, alteraciones psiquiátricas, alucinaciones y epilepsia son también más frecuentes en este grupo.
Entre los múltiples aspectos moleculares comprometidos en estos casos, destacan la disfunción de procesos mitocondriales y lisosomales.
En este artículo presentamos una breve revisión orientada al clínico sobre los aspectos moleculares básicos y relación fenotipo-genotipo de estas formas monogénicas de la EP.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterised by such motor symptoms as bradykinesia and rigidity resulting from the progressive loss of dopaminergic neurons in the substantia nigra. Common non-motor signs include hyposmia, constipation, REM sleep behaviour disorder, and depression. Age and certain genetic and environmental factors are known risk factors for PD. Pathogenic variants with a demonstrated causal role are rare in the general population, although risk variants are more common. Study of genetic characteristics of PD sheds light on molecular and pathophysiological aspects of the disease and may lead to new therapeutic targets.

PD is diagnosed before 40 years of age in 3%–5% of patients; this is the cut-off point used by some research groups to define early onset (other researchers use a cut-off point of 50 years). Genetics is thought to play a more significant role in early-onset PD.[1]

Homozygous or compound heterozygous autosomal recessive genetic variants demonstrated to cause monogenic early-onset PD with typical or "pure" characteristics include: (1) parkin, or RBR E3 ubiquitin protein ligase (*PRKN*),[2] (2) PTEN-induced kinase 1 (*PINK1*),[3] and (3) parkinsonism-associated deglycase (*PARK7*, also known as *DJ-1*).[4] Although these genes are rare in the general population with PD, they explain approximately 13% of cases with onset before the age of 40–50 years.[5] Specifically, *PRKN* is considered the most common cause of monogenic early-onset parkinsonism.[5] In juvenile cases (onset before 21 years of age), variants of *ATP13A2*, *FBXO7*, *PLA2G6*, *SYNJ1*, and *DNAJC6* may also play a role.

This study reviews the basic molecular mechanisms and relevant clinical characteristics of autosomal recessive monogenic forms of PD.

Review

Genes associated with autosomal recessive early-onset Parkinson's disease with typical manifestations

PRKN

Function of the parkin protein. Parkin belongs to a protein family with a preserved ubiquitin-like (UBL) domain and RING ("really interesting new gene") finger motifs. Parkin functions as a multifunctional cytosolic E3 ubiquitin ligase, and catalyses the transfer of ubiquitinated molecules to multiple substrates. Through mono- and poly-ubiquitination chains linked by lysine-48 or lysine-63, the protein is involved in signalling protein degradation and in non-degradation processes. Parkin indirectly mediates PGC-1α, which regulates the expression of genes involved in mitochondrial biogenesis and antioxidant activity.

PRKN and *PINK1* encode proteins involved in a quality control system that "checks" the autophagy of depolarised and defective mitochondria (mitophagy). Parkin is self-inhibited in normal conditions, and is activated to induce mitophagy. This process is triggered by accumulation of PINK1, a serine–threonine kinase located on the mitochondrial outer membrane. PINK1 is involved in the phosphorylation of ubiquitin molecules, triggering the recruitment of parkin due to its affinity for phosphorylated ubiquitin. By binding to phosphorylated ubiquitin, PINK1 is able to phosphorylate parkin at the UBL domain, activating its catalytic action. The generation of new mitochondria-bound ubiquitin molecules and their phosphorylation by PINK1 results in a positive feedback mechanism, with further recruitment of parkin. Parkin-mediated ubiquitination of mitochondrial proteins leads to the recruitment of mitophagy receptors. *PRKN* and *PINK1* have also been linked to processes other than autophagy, such as the production of mitochondrial-derived vesicles that transport damaged cargo, and the suppression of mitochondrial antigen presentation.[6]

PRKN molecular mechanisms associated with Parkinson's disease. The simplest explanation of the pathophysiological mechanism associated with this gene is physiological loss of function of parkin, resulting in accumulation of substrates, and mitochondrial dysfunction due to the alteration of the genetic pathway shared with *PINK1*.[7]

PRKN variants. Pathological variants of *PRKN* include substitutions of individual base pairs, small deletions, splice-site mutations, and deletions of hundreds of nucleotides.[8]

The penetrance of homozygous and heterozygous/compound heterozygous *PRKN* variants is estimated at 100% and 1%–25%, respectively[8]; these are considered the most common cause of early-onset PD, accounting for 4.6%–10.5% of cases, depending on the population studied.[9]

PRKN-PD phenotype. Mean age of onset of *PRKN*-PD is 31 years. Onset is early (20–40 years) in 62% of cases, late (>40 years) in 22%, and juvenile (<20 years) in 16%.[5]

Generally, patients with *PRKN*-PD respond well to low doses of dopaminergic drugs.[10] A review found that 94% of patients respond well to levodopa.[5]

Dystonia, dyskinesia, and motor fluctuations were reported in 18%, 19%, and 15% of cases, respectively. Strikingly, up to 46% presented dystonia not induced by levodopa.[5] However, dystonic gait disorders were reported as the initial symptom in 5 out of 18 patients.[11] Gait disturbances secondary to biphasic dyskinesia are also a more frequent initial symptom in *PRKN*-PD.[12] Levodopa-induced motor fluctuations and dystonia are more frequent in homozygous or compound heterozygous carriers than in heterozygous carriers of *PRKN* variants (94% vs 69% and 70% vs 40%, respectively).[13]

In a review, tremor was reported in 31% of patients with *PRKN*-PD, and was absent in 3%. This information was not reported in the remaining 66%.[5] Postural instability is reported in 17%.[5] Atypical manifestations are rare, with antero-/retrocollis, pyramidal signs, spasticity, and alien hand syndrome being reported in only 3% of cases (n=32).[5]

The prevalence of cognitive impairment is estimated at 1.5%–13%,[14] similar to the rate reported in the population aged over 65 years.[15]

Psychotic symptoms are reported in 17/45 and depression in 48% of patients with *PRKN*-PD.[15,16] Presence of at least one symptom of impulse control disorder seems to appear at approximately the same rate as in idiopathic PD, although compulsive shopping, binge eating, and punding/hobbyism are more common in *PRKN*-PD.[17] Autonomic dysfunction occurs in 32% of patients with *PRKN*-PD.[15] Table 1 summarises the phenotypes of autosomal recessive monogenic PD.

PINK1

Function of the PINK1 protein and molecular mechanisms associated with Parkinson's disease. See sections

Table 1 Summary of the phenotypes of different forms of autosomal recessive monogenic parkinsonism.

Gene	*PRKN*	*PINK1*	*DJ-1*	*ATP13A2*	*PLA2G6*	*FBXO7*	*DNAJC6*	*VPS13C*
Locus	PARK2	PARK6	PARK7	PARK9	PARK14	PARK15		
Early onset	+	+	+					+
Juvenile onset				+	+	+	+	
Response to levodopa	+	+	+ ~50%	+	+ At onset	+	+	+ At onset
Motor fluctuations/early dyskinesia	+	+	+	+ Early	+ Early	+ Early	+ Early	+
Dystonia	+ LL	+	+	+	+	+ TEV	+	
Tremor	+	+	+	+				+
Postural instability				+				
Pyramidal signs				+ SP phenotype	+	+	+	+
Neuropathy				+	+			
Ataxia					+		+	
Myoclonus/mini-myoclonus				+ FFF mini-myoclonus				
Oculomotor alterations				+ VGP	+ OC	+ OA, VGP		
Epilepsy					+		+	
Early-onset dementia/intellectual disability			+	+	+	+	+	+
Severe neuropsychiatric disorders/ early-onset psychosis	+	+	+	+ Psychosis	+ Psychosis	+	+	+
Autonomic dysfunction	+						+ Early	+ Early
Early dysarthria/dysphagia				+	+ Anarthria			
Abnormal neuroimaging findings				+ Atrophy, BIA	+ Cerebellar atrophy, BIA			

+: expected in this disease. BIA: brain iron accumulation; FFF: facial–faucial–finger; LL: lower limbs; OA: oculomotor apraxia; OC: oculogyric crises; SP: spastic paraparesis; TEV: talipes equinovarus; VGP: vertical gaze palsy.
*** This table is based on the authors' interpretation of the literature.

"Function of the parkin protein" and "PRKN molecular mechanisms associated with Parkinson's disease".

PINK1 variants. Dozens of variants have been described, with the majority being nonsense point mutations. Penetrance is age-dependent, although, as with *PRKN*, it seems to be complete in carriers of biallelic pathogenic variants.

The prevalence of these mutations is not known. They are thought to be the second most frequent cause of early-onset PD, and account for 3.7% of cases, ranging from 0.6% in European populations to 13.5% in Asian populations.[9]

PINK1-PD phenotype. The mean age of onset of *PINK1*-PD is 32 years (onset is early, late, and juvenile in 62%, 22%, and 15% of cases, respectively). Tremor is present in 51% of patients and absent in 9% (data not reported in 40%).[5] Postural instability is observed in 26%.[5]Ninety-nine percent of patients respond well to levodopa, with 39% presenting dyskinesia, 21% dystonia, and 34% motor fluctuations. Dyskinesia and dystonia are related to levodopa treatment in 85% and 24% of cases, respectively. Dystonia is not associated with levodopa in 59% of cases,[5] and was the initial symptom in 3 out of 4 patients with early-onset PD who were homozygous for *PINK1* variants.[18]

After exclusion of cases with missing data, patients with *PINK1*-PD presented cognitive impairment in 14%–33% of cases and psychotic symptoms in 2 out of 41 cases.[15,16] Depression was reported in 59%, and autonomic dysfunction in 46%.[15]

DJ-1

Function of the DJ-1 protein. *DJ-1* encodes a small protein that is ubiquitously expressed as a homodimer in the cytoplasm, mitochondria, and nucleus. DJ-1 reacts to oxidative stress, sensing, and neutralising reactive oxygen species. It also has chaperone, protease, and glycosylase functions. Furthermore, it is a transcription regulator and RNA-binding protein, and regulates mitochondrial function, autophagy, and norepinephrine and dopamine homeostasis.[19]

Molecular mechanisms associated with Parkinson's disease. The L166P variant is expressed as a monomer, losing its physiological functions and acquiring pro-apoptotic properties, with reduced lysosomal activity and mitochondrial damage.[19]

DJ-1 variants. *DJ-1* variants are rare, accounting for 1%–2% of sporadic cases of early-onset PD, although they are thought to represent approximately 5% of cases of early-onset PD in the Indian population.[20]

DJ-1–PD phenotype. Mean age of onset of *DJ-1*–PD is 27 years. Onset is early, juvenile, and late in 83%, 13%, and 4% of cases, respectively.

Regarding motor symptoms, tremor is observed in 63% of patients, dystonia in 46% (induced by levodopa in 2/14 cases), dyskinesia in 23% (mostly induced by levodopa), and postural instability in 40%.[5] Hyperreflexia has been reported in at least 4 cases. Forty-five percent of patients respond well to levodopa.[5] Non-motor symptoms include psychotic symptoms in (3/4 cases), depression (66%), and autonomic dysfunction (28%).[15]

Genes associated with autosomal recessive Parkinson's disease with atypical phenotypes

ATP13A2

Function of the ATP13A2 protein. ATP13A2 belongs to the P-type ATPase family of proteins, the majority of which are cation transporters. ATP13A2 regulates the metabolism and prevents the accumulation of divalent metals, preventing their cytotoxicity.[21] It has been suggested that it may also play a role in preventing intracellular accumulation of α-synuclein by modulating clearance via the autophagy–lysosomal pathway.[22]

Molecular mechanisms associated with Parkinson's disease Patient-derived cell models have shown low concentrations of intracellular free zinc ions, impaired expression of zinc transporters, and abnormal sequestering of zinc in vesicles associated with the autophagy–lysosomal pathway. This would have an impact on mitochondrial energy production and lysosomal proteolysis.[22]

ATP13A2 variants. More than 10 homozygous or compound heterozygous pathogenic variants have been reported to affect the protein's transmembrane domains.[21] These variants would result in loss of function of ATP13A2 through such mechanisms as nonsense-mediated mRNA decay, mislocalisation, and premature protein degradation by the proteasomal system.[22]

Rare *ATP13A2* variants have been associated with susceptibility to PD in exome sequencing studies.[23]

ATP13A2-PD phenotype. Disorders related to *ATP13A2*, initially known as Kufor-Rakeb syndrome, have been assigned to various classifications: atypical parkinsonism (Kufor-Rakeb syndrome or *ATP13A2*-PD),[24] neuronal ceroid lipofuscinosis,[25] neurodegeneration with brain iron accumulation,[26] autosomal recessive spastic paraplegia-78,[27] and juvenile amyotrophic lateral sclerosis.[28]

Symptoms generally appear before 20 years of age,[29,30] and the rate of progression is variable, ranging from relatively rapid deterioration over a space of months, to slower progression taking decades.[26,29,31] These diseases typically present with some degree of parkinsonism, with half of the cases presenting hand tremor,[22] which is more frequent in carriers of the T12M variant.[31] Postural reflexes are often absent.[32] Patients may initially respond well to levodopa, but soon develop peak dose dyskinesia and hallucinations, especially in cases associated with the G504R, T12M, or G533R variants[31,33] In other cases, levodopa is poorly tolerated.[24,32]

Approximately, half of patients developed dystonia over the course of the disease, with limb involvement and in some cases risus sardonicus.[22]

Pyramidal signs and spasticity, predominantly in the lower limbs, are also frequent. Vertical gaze palsy and facial–faucial–finger mini-myoclonus are common signs,[22] with other authors considering tongue tremor and chin

trembling to be equivalent to the characteristic mini-myoclonus.[26]

The clinical picture often includes dysarthria, dysphagia, cognitive impairment, behavioural alterations, psychosis, and hallucinations.[26,31,32] Ataxia and axonal sensorimotor neuropathy may also be present.[22,31] Table 1 summarises the phenotypes of autosomal recessive monogenic PD.

Neurodegeneration with brain iron accumulation/ hereditary dystonia/*PLA2G6*-PD

Function of the phospholipase A2 group VI protein. The *PLA2G6* gene encodes phospholipase A2 group VI, a protein that plays a fundamental role in regulating inflammatory processes, the immune response, cell membrane homeostasis, mitochondrial function, and membrane remodelling. The protein protects mitochondria against apoptotic stimuli and has a neuroprotective effect in dopaminergic neurons.

Molecular mechanisms associated with Parkinson's disease. It has been suggested that *PLA2G6* may be involved in PD-associated neurodegeneration due to the excessive generation of reactive oxygen species and iron accumulation associated with dysfunction of the protein, a common finding in PD. *PLA2G6* deficiency also results in elevated α-synuclein expression in neuronal mitochondria.[34]

PLA2G6 variants. *PLA2G6* variants include nonsense mutations, protein-truncating variants, fragment deletions, and copy number variants. The link between phenotypes and genotypes suggests that changes at specific sites have different effects on protein activity. Most studies find that frequent *PLA2G6* variants appear not to constitute a risk factor for sporadic PD, with weak evidence of an association in Asian populations.[35]

PLA2G6 parkinsonism phenotype. Phospholipase A2 group VI-associated neurodegeneration (PLAN), an autosomal recessive syndrome of neurodegeneration with brain iron accumulation, is caused by *PLA2G6* variants. This syndrome encompasses such phenotypes as classical infantile neuroaxonal dystrophy and atypical neuroaxonal dystrophy. Both phenotypes often present with ataxia, rigidity, spasticity, dystonia, myoclonic seizures, intellectual disability, and vision problems. In some cases, MRI reveals cerebellar atrophy and iron accumulation in the substantia nigra, the globus pallidus, and sometimes in the striatum (particularly in adult patients).[40,41]

PLA2G6 was shown in 2008 to be the causal gene in adult-onset dystonia-parkinsonism (PARK14).[36]

Age of onset of *PLA2G6* parkinsonism is early (mean of 19±11 years), but the disease may appear at older ages.[29,37,38] Limb tremor has been described as an initial symptom.[39] Response to levodopa may be associated with early development of dyskinesia,[39] and treatment tends to lose its efficacy or to be associated with psychosis. These patients may present ataxia, dysarthria, dysphagia, and pyramidal signs.[38] Vertical gaze palsy, apraxia of eyelid opening,[29] and levodopa-associated oculogyric crises have also been reported.[38,39] Cognitive impairment, psychosis, and psychiatric complaints are also frequent.[37,38]

FBXO7

Function of the FBXO7 protein. FBXO7 belongs to the F-box family of proteins, interchangeable subunits on the Skp, Cullin, F-box containing (SCF) E3 complex. By binding to cullin-1 and RING-box, it forms a multimeric E3 ubiquitin ligase in which FBXO7 acts as the ubiquitin-recruiting unit. *FBXO7* has recently been reported to play a role in the autophagy of damaged mitochondria in *PINK1*-PD, promoting the recruitment and ubiquitination of parkin.[42,43]

Molecular mechanisms associated with FBXO7 and Parkinson's disease. Loss of *FBXO7* expression results in inhibition of the recruitment of parkin to depolarised mitochondria, leading to dysfunction in the mitophagy process.[43]

FBXO7 variants. Several *FBXO7* variants have been described. For instance, the R498X variant, reported in multiple cases of familial PD, reduces the protein's capacity to recruit parkin, and the T22M and R378G variants affect binding sites; no functional studies have yet been performed for the I87T, D328R, or R481C variants. The non-coding IVS-329C>T variant has been linked to moderate risk of PD.[44]

FBXO7 parkinsonism phenotype. Patients display heterogeneous phenotypes, mostly presenting with parkinsonism and signs of pyramidal involvement.

Symptoms usually appear between 10 and 30 years of age,[29] although late onset (41–52 years) has also been reported.[30,45] Levodopa was effective in 81.3% of cases (13/16), and was frequently associated with dyskinesia, motor fluctuations, and behavioural problems.[29,31,46,47] Dystonic characteristics are observed in more than half of patients.[31] Ten (10) out of 16 cases of *FBXO7* parkinsonism presented action tremor.[29,47] Pyramidal signs are reported in over 56% of patients,[47] and are frequently associated with spasticity and talipes equinovarus from childhood.[46] Oculomotor apraxia and vertical gaze palsy are common, as are psychiatric disorders. Cognitive impairment is reported in over 43% of patients.[47] Tics and chorea have also been described.

DNAJC6

Function of the DNAJC6 protein. *DNAJC6* encodes auxilin, which is expressed selectively in neurons. Auxilin acts as a co-chaperone to recruit HSC70 to clathrin-coated vesicles. Its main function is in endocytosis, which is crucial in regulating signalling pathways via receptor and ligand internalisation, which is necessary for axon and dendrite growth. It is also involved in post-endocytic recycling of synaptic vesicles, and stimulates ATPase activity in many cell processes.

Molecular mechanisms associated with DNAJC6 and Parkinson's disease. Experimental models have demonstrated an association between degeneration of dopaminergic neurons, pathological α-synuclein aggregation, increased intrinsic neuronal firing frequency, and mitochondrial and lysosomal dysfunction.[48] Evidence from affected patients suggests dyshomeostasis downstream from auxilin, GAK, and dopaminergic proteins.[49]

DNAJC6 variants. Homozygous or compound heterozygous *DNAJC6* variants result in loss of function of the protein. The variants reported to date include splice site mutations, large multi-exon deletions, protein-truncating variants, and nonsense mutations.

DNAJC6 parkinsonism phenotype. These patients develop parkinsonism at an early age (10–42 years),[30] presenting rapid progression associated with resting and postural tremor.[50] Some respond well to levodopa, but present motor and psychiatric adverse effects. Patients eventually present ataxia and postural instability, reaching a stage where they need a wheelchair or are unable to leave bed, with anarthria and global akinesia at 10–15 years of progression.[50] Some patients present generalised or intermittent dystonia.[38,50] Carriers of the D331Y variant present PD, although tremor is less frequent.[38] Reported symptoms include intellectual disability, pyramidal signs, severe dysarthria, and epilepsy.[50] The D331Y and M358I variants are associated with autonomic dysfunction.[38]

VPS13C

Function of the VPS13C protein. VPS13C belongs to a family of large VPS13 proteins (VPS13A–D), which are essential in vesicular transport. Early studies linked VPS13 with delivery of proteins to the lysosome. It has been suggested that the protein may also play a role in PINK1/parkin transport, delivering damaged mitochondrial cargo directly to lysosomes in response to mitochondrial stress. Several other reports suggest that, like *PINK1* and *PRKN*, *VPS13C* is involved in mitochondrial maintenance.[51]

Molecular mechanisms associated with VPS13C and Parkinson's disease. Loss of function of VPS13C would cause perinuclear redistribution of mitochondria, mitochondrial fragmentation, and a reduction in mitochondrial transmembrane potential, increasing mitophagy in response to mitochondrial damage, mediated by PINK1/parkin.

VPS13C variants. Nonsense variants, splice site mutations, and structural variations have been reported in 6 individuals from France and Turkey.[52] Such polymorphisms as rs2414739 may act as genetic risk factors for PD.[53]

VPS13C parkinsonism phenotype. Parkinsonism associated with *VPS13C* variants manifests early (25–46 years of age) and responds to levodopa. However, progression is particularly aggressive, frequently with loss of treatment response,[30,54] and some patients present motor fluctuations and dystonia. Limb tremor, axial symptoms, cognitive impairment, dysautonomia, pyramidal signs, and weakness are reported in 2/3 patients. The majority of patients are unable to leave bed by 15 years after symptom onset.[54]

Conclusions

The causal genes involved in recessive forms of parkinsonism participate in various pathways and cell processes fundamental to PD pathophysiology. Specifically, pathogenic *PRKN* and *PINK1* variants are associated with dysfunctional mitophagy. Such other genes as *DJ-1*, *PLA2G6*, *VPS13C*, and *ATP13A2* are related to mitochondrial homeostasis. Others, such as *DNAJC6*, are involved in vesicle trafficking, and especially endocytosis. From a clinical perspective, patients with *PRKN*-PD present a classical early-onset phenotype, as do those with *PINK1*-PD and *DJ-1*–PD, who rarely present atypical symptoms. On the other hand, the remaining genetic forms addressed in this review manifest with complex phenotypes and atypical characteristics including pyramidal signs, dystonia (constituting the so-called pallidopyramidal syndrome), ataxia, myoclonus, oculomotor alterations, epilepsy, and psychiatric disorders. Establishing phenotype–genotype relationships and identifying the molecular pathways involved in autosomal recessive PD constitute the groundwork for advancing towards precision medicine.

Data protection

The authors declare that no patient data appear in this article.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

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