**Supplementary File 1. Detailed description of the new 14 cases of *PLA2G6*-related parkinsonism reported in this study.**

**Case 1**

A 33-year-old white British female presented complaining of her head and trunk pulling backwards. These symptoms appeared over few months during her first cycle of *in vitro* fertilization. Her perinatal and developmental history was unremarkable. She had polycystic ovary syndrome with anovulatory infertility, and an ovarian dermoid cyst removed at age 25 with negative serum anti-NMDAR antibody testing. She reported difficulty in holding a pen and a tightening feeling in her right hand (not entirely task-specific) since age 27. There was a history of sleep disturbances suggestive of REM sleep behavior disorder (RBD). Her parents and two youngest siblings were in good health. Dystonia slowly became generalized (facial grimacing, limb involvement). She experienced balance difficulties with occasional falls and developed anxiety and depression with suicidal ideation. On examination at age 36, she showed retrocollis and extensor truncal dystonia, parkinsonism (rest tremor in her limbs, bradykinesia, and rigidity), brisk reflexes, and mild limb dysmetria. She used a walking stick. Laboratory tests and initial brain MRI were unremarkable, and genetic tests of *TOR1A*, *LRRK2*, *PRKN* and *PINK1* negative. Her follow-up brain MRI with SWI sequences (Supplementary File 1A) showed only cerebellar atrophy (Supplementary File 1B), and a DaTscan detected bilaterally reduced tracer uptake in the striatum (Supplementary File 1C). Neuropsychological tests at age 37 revealed attentional dysfunction with associated memory difficulty. She had no benefit from trihexyphenidyl and a mild response to ropinirole, whereas low-dose levodopa resulted in worsening of dystonia and tremor as well as early dyskinesias. She had a good, albeit unsustained, response to apomorphine. At age 38, she underwent bilateral deep brain stimulation (DBS) of the GP internus (GPi), with improvement of her truncal dystonia and abrupt cessation of dyskinesias, which allowed to increase her levodopa daily dose. Trio whole-genome sequencing (WGS) and targeted resequencing demonstrated she was a compound heterozygote for the maternally inherited variant NM\_003560.4:c.956C>T (p.Thr319Met) and the paternally inherited variant NM\_003560.4:c.1061T>C (p.Leu345Pro). Neurological examination at age 41 is provided in the Video. Myoclonic jerks were present on re-assessment at age 43.

**Case 2**

This 36-year-old white British woman was in good health until age 29, when she developed a parkinsonian syndrome with executive dysfunction and personality changes. She became withdrawn, apathetic, and emotionally labile, being tearful with relatively little provocation. Her short-term memory was impaired, and she was occasionally disoriented in time and place. She denied sleep disturbances but had a tendency to talk in her sleep. She had nocturia and occasional urinary incontinence. There was no history of hallucinations, disinhibition or hyperorality. Her family history was unremarkable. Brain MRI scan with SWI sequences initially showed subtle iron deposition in the basal ganglia. At age 31 her Montreal Cognitive Assessment (MoCA) score was 25/30, with impairments of verbal fluency, attention, and delayed recall; she was rather impulsive during assessment. Genetic tests of *HTT*, *PANK2*, and *WDR45* were negative. She was started on levodopa with quite good response. However, she became pregnant during the early course of her condition. She therefore discontinued levodopa until 16 weeks, and experienced worsening of her motor function at this time. Levodopa response waned after her uneventful pregnancy, and she developed lower limb dyskinesias with small doses. Since age 33 her gait deteriorated with intoeing, and she manifested balance difficulties with falls typically backwards. On reassessment at age 34, she was mainly wheelchair-bound and showed gaze impersistence with saccadic intrusions on smooth pursuit, twitchy facial movements, and chin tremor. Tongue movements were slow, and she had difficulty holding the tongue protruded, as well as moderate dysarthria and occasional facial grimacing. Her trunk appeared stiff with anterocollis. There was action myoclonus of the outstretched hands, which was confirmed of cortical origin on neurophysiology, mild dystonic posturing of her fingers, and inversion of her left foot. There was bradykinesia on finger-tapping bilaterally and brisk reflexes with bilateral ankle clonus. She had an unsteady gait with reduced stride length. Her follow-up MRI revealed stable iron deposition (Supplementary File 1D) but progressive cerebral and cerebellar atrophy. Trio WGS and subsequent Sanger sequencing revealed she was a compound heterozygote for the maternally inherited variant NM\_003560.4:c.238G>A (p.Ala80Thr) and paternally inherited variant NM\_003560.4:c.1924A>G (p.Thr642Ala) in *PLA2G6*.

**Case 3**

This 25-year-old Indian female born to non-consanguineous parents became progressively slow, fearful, and depressed since the third month of her first pregnancy at age 21. Her past medical history and family history were unremarkable. Recent sleep disturbances suggestive of RBD were reported. She suffered from urinary urgency with occasional incontinence but denied constipation. She had never experienced hallucinations. On examination, she presented with an asymmetrical akinetic-rigid syndrome with prominent rigidity in her lower limbs and mild gait and limb ataxia. On the 10th day postpartum, her symptoms rapidly deteriorated with diffuse severe rigidity, hypophonia, dysphagia, and psychiatric disturbances. She was initially diagnosed with catatonia and received four cycles of electroconvulsive therapy. On clinical reassessment (Video), she presented with an akinetic rigid syndrome associated with axial and limb dystonia and some cerebellar features. Her mother noticed some deterioration of her short-term memory. There were no pyramidal signs. Her tandem gait was impaired, and she had mild bilateral ataxia on finger-nose testing. Investigations including routine laboratory testing, iron profile, serum copper and ceruloplasmin, serum vasculitis, paraneoplastic and neuronal antibodies, and CSF analysis were unremarkable. EEG was normal and brain MRI revealed mild cerebellar atrophy but no signs of mineralization on T2-weighted sequences. 99mTc-TRODAT-1 SPECT (Supplementary File 1E) showed asymmetrical severe decrease in tracer uptake in the striatum (putamen>caudate). A next-generation sequencing (NGS) gene panel for young-onset Parkinson’s disease detected the missense variants NM\_003560.4:c.673C>T (p.His225Tyr) and NM\_003560.4:c.2311G>A (p.Asp771Asn) in *PLA2G6*. The patient was started on levodopa with an optimal response but experienced severe dyskinesias after approximately eight months of treatment (Video).

**Case 4**

This 22-year-old Indian male was born to non-consanguineous parents and had normal birth and developmental milestones. Since age 15, he developed aggressiveness and disinhibited behaviors, experienced episodes of fear and emotional lability, and showed deterioration of his scholastic performance. He suffered from urinary frequency and urgency, with occasional incontinence, and constipation. There was no history of anosmia, RBD, and orthostatic hypotension. His elder brother manifested psychiatric features, including suicidal ideation, and parkinsonism, since age 17, and died at age 27 without a definite diagnosis. Examination at age 18 (Video) revealed an asymmetric akinetic-rigid syndrome (left>right) with impaired postural reflexes. He had bilateral postural tremor in the upper limbs with superimposed myoclonic jerks. Eye movements assessment showed broken pursuits and slow saccades in the horizontal plane. Deep tendon reflexes were brisk with presence of striatal toes. Sensory system and cerebellar examination were unremarkable. Brain MRI with SWI sequences revealed cerebro/cerebellar atrophy (Supplementary File 1F-G) and no evidence of iron deposition. 18F-DOPA PET showed asymmetrically decreased tracer uptake (Supplementary File 1H). He had a modest response to levodopa with early occurrence of dyskinesias predominantly affecting the lower limbs almost a year after starting levodopa with a dose of 100mg three times daily. He also exhibited mild dystonia affecting his left upper limb late into his illness. Whole exome sequencing (WES) detected the homozygous variant NM\_003560.4:c.2222G>A (p.Arg741Gln) in *PLA2G6*.

**Case 5**

This 20-year-old Indian male, product of consanguineous marriage, presented with a 4-year history of progressive gait disturbance and behavioral issues, including aggressiveness, abusive behaviors, and overreligiosity. His past medical history was unremarkable. There was no history of anosmia, sleep disturbances, and orthostatic hypotension. His sister was similarly affected at age 20 with predominant behavioral features, aggressiveness, and obsessive-compulsive disorder. She later developed cervical dystonia and parkinsonism and died by age 23 without formal diagnosis. His examination at age 19 showed spastic paraparesis along with parkinsonian features (bradykinesia and impaired postural reflexes), cranio-cervical dystonia, and motor perseveration. Spasticity, brisk deep tendon reflexes, and bilateral ankle clonus were present. He had extensor plantar response bilaterally. Cerebellar and sensory examination was unremarkable. Saccades were slow in the horizontal plane. He also had occasional myoclonic jerks in the upper limbs on extending his hands. Pull test revealed impaired postural reflexes. His Mini Mental State Examination (MMSE) was 26/30 with subtle impairment in frontal lobe functions and impaired calculation abilities. Brain MRI showed cerebellar atrophy but no iron deposition on SWI sequences. One year into his illness his parkinsonism and postural instability worsened, and he started having episodes of urinary incontinence. 18F-DOPA PET showed moderate-severe reduction in tracer uptake over the caudate and putamen asymmetrically. He was started on levodopa and developed severe dyskinesias three months after treatment initiation at the dose of 300mg daily. Pramipexole was therefore initiated with improvement of dyskinesias. WES detected the homozygous variant NM\_003560.4:c.2222G>A (p.Arg741Gln) in *PLA2G6*.

**Case 6**

This 33-year-old Indian male born to consanguineous parents had a 4-year history of levodopa- responsive asymmetric akinetic-rigid syndrome without rest tremor. He reported falls since two years after the onset of parkinsonian symptoms. His family history was unremarkable. He suffered from anxiety and depression with crying episodes only in the off periods. There were significant sleep problems with history suggestive of RBD. Other non-motor symptoms included fatigue, pain and urinary issues with occasional incontinence. Anosmia, bowel dysfunction and orthostatic hypotension were not reported. He had mild cognitive impairment (MMSE score 27/30) with apathetic behavior. Eye movement examination revealed square wave jerks and saccadic pursuits. His postural reflexes were impaired. Cerebellar and sensory examination was normal. Brain MRI showed cerebellar atrophy but no iron deposition on SWI sequences. 18F-DOPA PET detected severely reduced tracer uptake in the bilateral striatum (putamen>caudate), asymmetrically. He developed dyskinesias five months after starting levodopa. On NGS gene panel for early-onset parkinsonism, he was found to carry the homozygous variant NM\_003560.4:c.1937C>T (p.Pro646Leu) in *PLA2G6*.

**Case 7**

This 28-year-old Indian female with no history of parental consanguinity manifested asymmetric parkinsonism with rest tremor, postural instability, depressive episodes with suicidal ideation, and emotional lability since age 25. She had urinary disturbances, including frequency, urgency, and occasional incontinence, and constipation. There was no history of anosmia nor elements suggestive of RBD. Her family history was unremarkable. Examination revealed pyramidal signs, including lower limb spasticity (Modified Ashworth score 2) and brisk reflexes. Cerebellar and sensory examination was normal. Eye movement examination revealed normal pursuits with slightly slow saccades. She also exhibited bilateral postural tremor in the hands with superimposed action-induced myoclonic jerks. She had no orthostatic hypotension. Parkinsonism responded to levodopa, but she developed levodopa-induced dyskinesias within 2 months since treatment initiation. Her MMSE score was 26/30 with mild impairment of frontal lobe functions. Brain MRI revealed cerebellar atrophy, with no iron deposition on SWI sequences. 18F-DOPA PET detected asymmetrically reduced uptake in the striatum. WES detected the two variants NM\_003560.4:c.2370T>G (p.Tyr790\*) and NM\_003560.3:c.1511C>T (p.Ser504Leu) in *PLA2G6*.

**Case 8**

A 21-year-old Indian male born to non-consanguineous parents had normal birth and development. At age 17, he started developing a progressive akinetic-rigid syndrome with rest tremor in his arms. On examination, his saccadic movements were slow, and he had upper-limb and axial rigidity as well as spasticity in his lower limbs. There were brisk tendon reflexes and bilateral Babinski sign. Over few years, he also developed gait difficulty, postural instability, and generalized myoclonic jerks. There were cognitive and psychiatric issues, including disorientation, attention deficit, apathy, executive dysfunction, progressive reduction in spontaneous speech till mutacism, and emotional lability, as well as urinary incontinence two years into the disease course. Myoclonic jerks appeared few years into the disease course. He was wheelchair-bound at age 20. He had visual hallucinations. A single generalized tonic-clonic seizure was reported. Serum ferritin and ceruloplasmin were unremarkable, and no acanthocytes were detected. EEG showed intermittent generalized epileptiform discharges. Nerve conduction studies (NCS) were unremarkable. On brain MRI, there was evidence of mainly frontotemporal and cerebellar atrophy, with mild iron deposition in the substantia nigra (SN), putamen, and GP (Supplementary File 1I). Brain 18F-fluorodeoxyglucose(FDG)-PET was normal. Parkinsonism was levodopa- responsive, with early appearance of dyskinesias.

**Case 9**

Case 8’s 24-year-old sister also had unremarkable birth and developmental history. At age 22, she presented with behavioral abnormalities (excessive irritability, aggressiveness), emotional lability, generalized bradykinesia, and abnormal posturing of her hands and feet. She had deterioration of her gait and balance over a six-month period and started to fall backwards daily around 18 months after symptom onset. She was not able to sit straight due to truncal dystonia and tendency to retropulsion. On examination, she presented with emotional lability and impairment of her working memory and verbal fluency. There was hypomimia, and eye movement assessment showed square wave jerks and slow saccades. She had truncal dystonia and asymmetric abnormal posturing of the extremities, limb rigidity, and brisk reflexes, with flexor plantar responses. Her gait was characterized by foot dragging and striatal toes. Sensory and cerebellar examination was normal. Serum ceruloplasmin and ferritin were normal, no acanthocytes were detected. Abdominal US excluded organomegaly, and NCS were unremarkable. Brain MRI showed cortical and cerebellar atrophy, as well as mild iron deposition in the bilateral SN, caudate, and putamen. WES detected both siblings (Cases 8-9) were homozygotes for the variant NM\_003560.4(*PLA2G6*):c.2222G>A (p.Arg741Gln). Parkinsonism responded to levodopa.

**Case 10**

A 26-year-old female, born to consanguineous Pakistani parents, presented with a 3-year-history of anxiety and “unusual emotional states” which started during her first pregnancy. Since approximately the same period, she noticed intermittent tremor of her right hand and then progressively over time a combination of slowing of movement, poor balance, and emotional lability. Brain MRI at age 24 was unremarkable as well as serum copper and ceruloplasmin, slit lamp examination, and CSF analysis. She was initially diagnosed with postpartum depression and a possible functional motor disorder. On examination (age 26), she had facial hypomimia, restriction and slowing of both vertical and horizontal saccades, and difficulty with rapid tongue movements. She had bilateral severe bradykinesia, rest tremor affecting the right arm and stimulus-sensitive action myoclonus, particularly in the legs. Reflexes were pathologically brisk throughout with crossed adductor responses. She walked with a short-stepped gait, having difficulty initiating and stopping movement. She turned with multiple steps and was very unsteady. There were no cerebellar signs. Formal neuropsychometry (age 26) revealed global intellectual underfunctioning. Follow-up brain MRI at age 26 revealed some increase in CSF spaces abnormal for her age. She was started on rotigotine and levodopa but developed dyskinesias within the first three months of treatment. WES detected the homozygous variant NM\_003560.4(*PLA2G6*):c.2222G>A (p.Arg741Gln), which was documented in the heterozygous state in her parents. She was lost to follow-up at age 27 and died of unknown cause at age 36.

**Case 11**

Case 10’s younger sister developed depression and anxiety at age 21, with increasing difficulty in attending university. She was told to be frequently tearful but also to laugh inappropriately at times. On first examination (age 23), she was hypomimic and had slowing of vertical saccades. She had bilateral bradykinesia with action-induced myoclonus in her limbs. She walked with a cautious, short-stepped gait, taking multiple steps on turning. She was clearly unsteady and had positive pull test indicating severely impaired postural reflexes. She was initially started on ropinirole, with no benefit, and then on rotigotine and levodopa, with very good response. Citalopram was also added for her mood disorder. The patient developed some dyskinetic movements within the first month of treatment with levodopa (150mg daily). Formal psychometry at age 24 was overall suggestive of cortical and subcortical involvement, revealing impaired global memory, cognitive speed, and attention. There was also evidence of weak executive function and comprehension. She underwent CSF examination, which was unremarkable except for low homovanillic acid (HVA), 5-hydroxyindoleacetic acid, and tetrahydrobiopterin. Brain MRI showed mild symmetrical biparietal atrophy, but no other abnormalities. Sanger sequencing confirmed she was homozygote for the variant NM\_003560.4:c.2222G>A (p.Arg741Gln) in *PLA2G6*. She was lost to follow-up at age 26 but remained alive at age 33.

**Case 12**

This 24-year-old German male with no history of parental consanguinity presented with subjective unsteadiness, slowness of movements and fatigue at age 22. His past medical and family history was unremarkable. The patient did not report any affective symptoms. On examination, he showed asymmetric parkinsonism with marked bradykinesia, rigidity, mild rest tremor and moderate kinetic and postural tremor of the upper limbs. There were mild cerebellar signs with saccades and mild dysmetria. There were no pyramidal signs nor sensory deficits, but mild postural instability. His neuropsychological assessment revealed impairment of attention as well as mnesic and executive functions, with significant fluctuations in his performances during the assessment. Brain MRI showed atrophy of the cerebellum and gyrification exceeding the age limit (Supplementary File 1L). His DaTscan showed bilaterally reduced tracer uptake in both striata (Supplementary File 1M). EEG and somatosensory evoked potentials (SEP) were unremarkable. On neurophysiology, he had unilaterally reduced motor evoked potentials (MEP) in lower-limb assessment after cortical stimulation, which reveals subclinical pyramidal dysfunction. He showed optimal response to levodopa, with improvement of gait, bradykinesia, and tremor. On an NGS gene panel for early-onset parkinsonism, he was found to carry the variants NM\_003560.4:c.1021G>A (p.Ala341Thr) and NM\_003560.4:c.1898C>T (p.Ala633Val) in *PLA2G6*, which were detected in the heterozygous state in his father and mother, respectively.

**Case 13**

This 24-year-old Indian male presented at age 22 with a one-year history of personality changes, including irritability and stubbornness, and a few-month history of gait difficulty and slowness in his daily life activities. His perinatal history and motor developmental milestones were unremarkable. He had mild intellectual disability and poor scholastic performance since childhood. The patient was the youngest of three children born to a consanguineous marriage. His parents and 25-year-old sister were in good health, whereas his eldest brother experienced progressive gait difficulty and global slowness since age 17, became bedridden at age 19, and died at age 25 with no formal diagnosis. On examination, the patient was hypomimic and dysarthric. He had mild blepharospasm and gaze-evoked nystagmus. He had global bradykinesia, with pill-rolling tremor. Muscle strength, sensory and autonomic assessment was normal. He had brisk reflexes throughout. He scored 24/30 on MMSE. Blood tests, including copper and ceruloplasmin, NCS, EMG, and ophthalmological assessment were normal. Brain MRI showed cerebral atrophy with frontal predominance and mild cerebellar atrophy, with no mineralization of the basal ganglia on T2\* and SWI sequences (Supplementary File 1N-O-P). WES revealed the proband carried the variant NM\_003560.4:c.2222G>A (p.Arg741Gln) in *PLA2G6* in the homozygous state, while segregation analysis detected the same variant in the heterozygote state in his parents and sister. Parkinsonism was levodopa-sensitive.

**Case 14**

This 36-year-old male was born to a first-cousin couple of Pakistani origin. He presented at age 32 with a 6-month history of slowly progressive leg stiffness leading to walking and balance difficulties. Over the first year since symptom onset, he also developed leg tremor and required support for ambulation. He denied swallowing difficulty, bladder and bowel issues, sleep disturbances, and hallucinations. Although he looked quiet and withdrawn, the patient and his family denied recent cognitive and behavioral changes. His past medical history was unremarkable. One of his younger brothers and his younger sister were previously diagnosed with PLAN manifesting as prominent parkinsonian syndrome and ataxic syndrome with mild parkinsonism, respectively.8,12 On examination, he had mild facial hypomimia and normal eye movements. On walking, there was mild extension truncal dystonia. He had increased muscle tone in his legs and right arm. He was slow on tapping tasks with his hands but more with his feet. Deep tendon reflexes were markedly brisk throughout, and there was bilateral ankle clonus. Routine blood tests were unremarkable. Brain MRI (age 33) showed mild generalized atrophy in the supra- and infratentorial compartments. On SWI, there was mildly decreased signal in the SN bilaterally and subtle loss of the appearances of the nigrosome (swallow tail sign). His DaTscan revealed abnormal tracer distribution in the striatum, with relative reduced activity in the putamen bilaterally, worse on the left (Supplementary File 1Q). Formal cognitive assessment at age 33 revealed marked impairment of processing speed, reduced recognition and recall of visual information, visual constructional difficulty, and reduced executive function, overall indicating marked sub-cortical and milder anterior cognitive compromise with the suggestion of greater right hemisphere involvement. *PLA2G6* targeted sequencing detected the variant NM\_003560.4:c.2239C>T p.(Arg747Trp) in the homozygous state, as previously detected in his affected siblings. He received baclofen 60mg daily, procyclidine 15mg daily, levodopa 100mg daily, and botulinum toxin injections in his lower limbs. Dyskinesias mainly affecting his jaw were observed few months after starting levodopa.