Movement Disorders
CLINICAL PRACTICE
REVIEW

Genetic Movement Disorders Commonly Seen in Asians

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Abstract: The increasing availability of molecular genetic testing has changed the landscape of both genetic research and clinical practice. Not only is the pace of discovery of novel disease-causing genes accelerating but also the phenotypic spectra associated with previously known genes are expanding. These advancements lead to the awareness that some genetic movement disorders may cluster in certain ethnic populations and genetic pleiotropy may result in unique clinical presentations in specific ethnic groups. Thus, the characteristics, genetics and risk factors of movement disorders may differ between populations. Recognition of a particular clinical phenotype, combined with information about the ethnic origin of patients could lead to early and correct diagnosis and assist the development of future personalized medicine for patients with these disorders. Here, the Movement Disorders in Asia Task Force sought to review genetic movement disorders that are commonly seen in Asia, including Wilson's disease, spinocerebellar ataxias (SCA) types 12, 31, and 36, Gerstmann-Sträussler-Scheinker disease, *PLA2G6*-related parkinsonism, adult-onset neuronal intranuclear inclusion disease (NIID), and paroxysmal kinesigenic dyskinesia. We also review common disorders seen worldwide with specific mutations or presentations that occur frequently in Asians.

Starting in the 1980s, advancements in genomics technologies have resulted in the discovery of genetic factors underlying many rare and non-rare diseases among different populations.[1] Genetic diseases often cluster in different ethnic groups with unique clinical presentations or red flags. Recognition of a particular clinical phenotype, combined with information about the ethnic origin of the patients, could lead to an early and correct diagnosis.

There have been a few studies showing differences in both the clinical phenotypes and genetic causes or risk factors of movement disorders between Asian and Western patients.[2] Some of the disorders may be more common in some populations, or it may be just a specific genetic variant that is more common.

In this article, we review the genetic movement disorders that are considered to be commonly seen in Asians. We also include disorders that are commonly seen worldwide with

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certain specific variants or presentations occurring frequently in Asians.

Methodology

We searched PubMed from 1969 through March 31, 2022 and used references from relevant articles. Search terms included "Parkinson's disease" (PD), "parkinsonism", "ataxia", "dystonia", "chorea", "tremor", "myoclonus", "movement disorders", and "Creutzfeldt-Jakob" with "Asians" or "Asia" without language restrictions. From the search, it was found that comprehensive epidemiological data for non-PD movement disorders in Asia were largely lacking. Hence, the disorders nominated to be included in this review had to be derived by consensus among experts who are members of the Movement Disorders in Asia Task Force (TF) of the International Parkinson and Movement Disorder Society—Asian and Oceanian Section (MDS-AOS). This group comprised representatives from most of the major regions in Asia: East Asia (China, Japan, Taiwan, South Korea), the Indian subcontinent (India), South-East Asia (Thailand, Malaysia, the Philippines), Central Asia (Kyrgyzstan), and the Middle East (Saudi Arabia). Based on their knowledge of the published literature and clinical practice experience, genetic disorders that are widely accepted to be common in Asia, or have been more frequently reported in these populations, were selected. The final reference list was generated by giving priority to the articles directly related to the topic, articles with the latest information, and comprehensive reviews.

Result

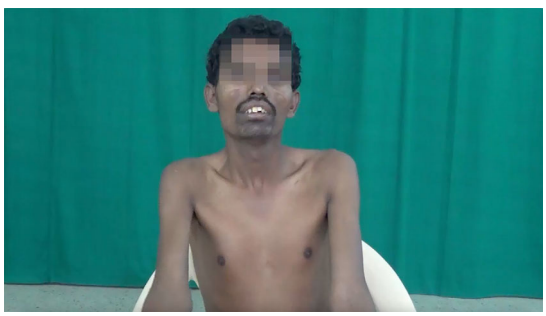
A total of 14 genetic movement disorders were found to be common in Asians: Wilson's disease (WD), spinocerebellar ataxias (SCA) types 12, 31, and 36, Gerstmann-Sträussler-Scheinker disease (GSS), *PLA2G6*-related parkinsonism, adult-onset neuronal intranuclear inclusion disease (NIID), paroxysmal kinesigenic dyskinesia (PKD), X-linked dystonia-parkinsonism (XDP), dentatorubral-pallidoluysian atrophy (DRPLA), Woodhouse-Sakati syndrome, benign adult familial myoclonic epilepsy (BAFME), Kufor-Rakeb disease, and tremulous dystonia associated with variant of the calmodulin-binding transcription activator 2 (*CAMTA2*) gene. The latter six conditions have previously been reviewed by the TF (submitted). In this study, we will focus on the first eight disorders listed above. We also discuss the unique presentation of parkinsonism in Asian patients with SCA2 and SCA17, highlight the common genetic variants in PD-causative genes in Asian patients, and discuss the differences between Asian and Western patients for all the disorders where possible. Key differences in the prevalence, risk factors, and clinical aspects of PD between Asians and Western patients have been previously reviewed.[2]

Wilson's Disease

WD is an autosomal recessive (AR) disorder of copper metabolism caused by variants in the *ATP7B* gene on chromosome 13.[3] Prevalence studies in Asian countries have been done in Chinese (5.9/100,000),[4] Korean (3.8/100,000; allelic variants-1.3/10,000),[5] Japanese (1:20,000 to 1:30,000; allelic variants-1.2/10,000)[6] and Taiwanese (1.8/100,000) populations.[7] The disease appears to be especially commonly encountered by physicians in India. WD affected 7.6% of patients in a study of hepatobiliary-spectrum disorders in North India and about 15–20 new cases are registered annually in a WD clinic in South India.[8,9] These relatively large numbers of patients are postulated to be due in part to high rates of consanguinity[8]; however, systematic epidemiological studies remain lacking.

The clinical presentation of WD is heterogeneous, ranging from asymptomatic to acute or chronic liver involvement and neuropsychiatric illnesses.[10] Previous studies reported that the age of onset in Indian patients may be earlier compared to those from Europe and South America.[11,12]

Hepatic presentations are common in younger age groups and neuropsychiatric features predominate in later-onset cases (Video 1).[10] Large cohort studies from Asia, including India, Korea and China, on WD clinical features, show that neuropsychiatric presentations account for 22–77% of the studied populations.[13–15] Kayser–Fleischer rings are reported in 97–100% of neurological cases, 14–87% of hepatic presentations and up to 60% of asymptomatic patients, in the Indian population.[9] Magnetic resonance imaging (MRI) of the brain is a cornerstone for the diagnosis and monitoring of neurological forms of WD.[16] A study in 100 Indian patients showed a variety of MRI features: classical T2-weighted hyperintensity in the putamen (72%), caudate (61%), thalamus (58%) and/or midbrain (49%); T2-weighted pallidal hypointensity (34%); "face of the giant panda" sign (12%); central pontine myelinolysis (7%); T1-weighted striatal hyperintensity (6%); and bright claustral sign (4%) (Fig. 1).[17] Sequential MRI study



Video 1. Wilson's Disease. A 33-year-old man with a seven-year history of tremulousness involving bilateral upper limbs and head. He has a past history of jaundice and upper gastrointestinal bleeding. There is a family history of severe liver dysfunction and subsequent demise of his sister. The video shows severe rest and postural tremor of both upper limbs (right more than left) as well as dystonia of the limbs when outstretched. The tremor is a Holmes tremor and is of "wing-beating" type. *Courtesy: Prof. Pramod Kumar Pal.* Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737

demonstrated imaging improvement in up to 70% of patients after copper-chelating therapy.[18]

The diagnosis of neurologic WD is usually based on clinical presentation, biochemical evaluation, and brain imaging, but sometimes needs genetic confirmation. Variant "hotspots" in *ATP7B* have been reported to vary by geographic region (Table S1).[19] The p.R778L variant is common in East Asians (30% in China,[20] 40% in Taiwan[21] and Korea[22]) with patients having an earlier onset and predominantly hepatic presentation than those with other genetic variants.[23] The p.P992L variant is the second most common variant in East Asians with a variant frequency of 14.6% in Chinese WD patients.[20] However, no single mutation appears to be dominant in India.[17] In contrast, the p.H1069Q variant has an allelic frequency of 30–70% among Caucasians but is rare in Asians. Most carriers with the p.H1069Q variant have a mean onset age of 20–22 years and a predominantly neurological phenotype.[24] Singh et al. in India have further noted hepatosplenomegaly and extrapyramidal features like bradykinesia, rigidity and dystonia to be associated with truncating variants, and tremors with missense variants.[25]

A large Indian cohort showed improvement in clinical symptoms in 76% (176/225) of patients after a mean duration of 46 months of treatment (Video 2).[13] Treatment response and longitudinal tracking can be best done with the Global Assessment Scale (GAS) for WD.[26]

Spinocerebellar Ataxia Type 12; SCA-*PPP2R2B*

SCA12 is a rare autosomal dominant cerebellar ataxia (ADCA) characterized by CAG trinucleotide repeat expansions in the 5′ region of the *PPP2R2B* gene on chromosome 5q31–5q32, which encodes for a brain-specific regulatory subunit of the protein phosphatase PP2A.[27,28]

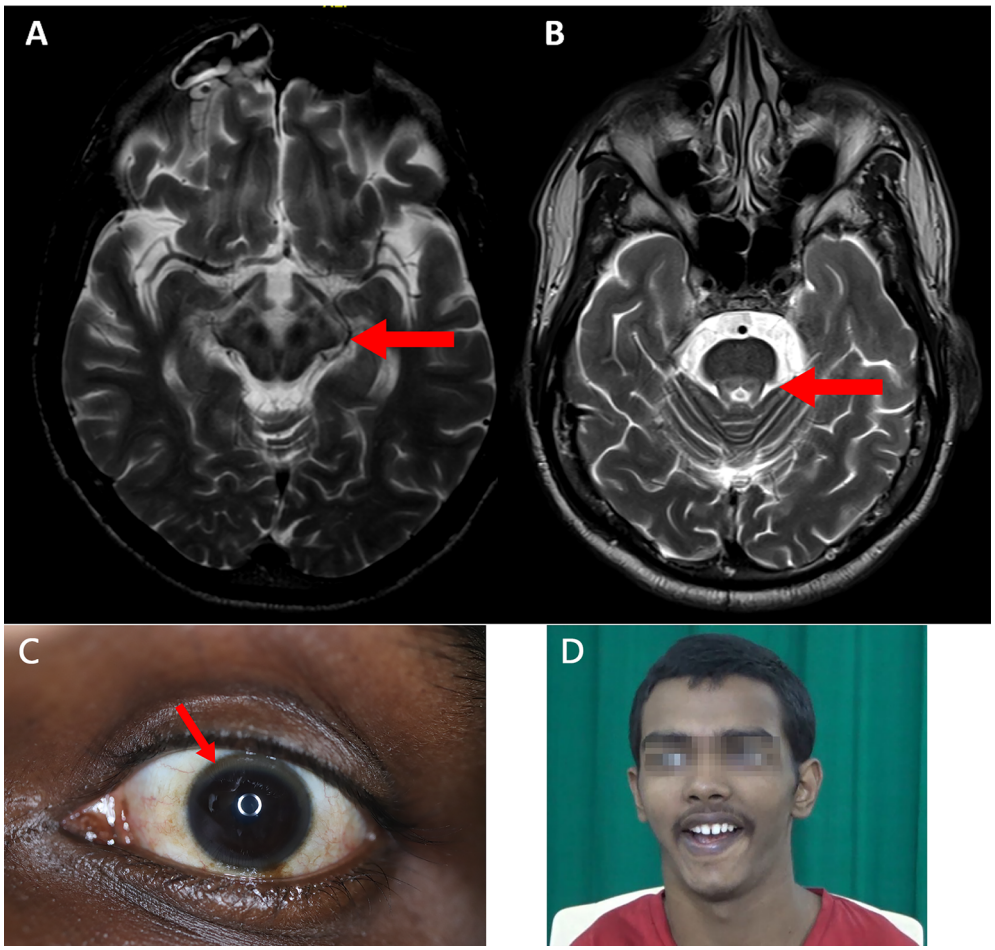
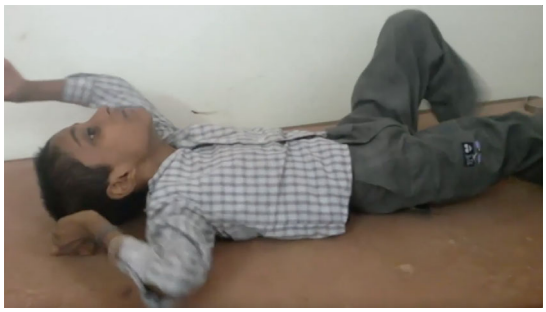
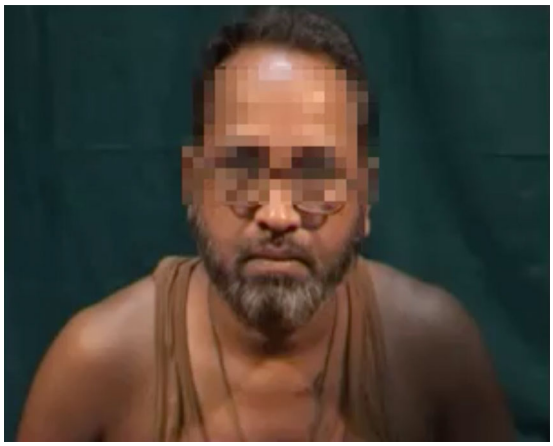


FIG. 1. Wilson's disease. Brain MRI T2-weighted images demonstrating the classic "double panda" sign: (A) Giant panda sign (B) Miniature panda. (C) Kayser-Fleischer (KF) ring which occurs due to deposition of copper in Descemet's membrane. (D) Classic Wilson's face is shown which is characterized by a facetious smile, pseudo-laughter, open mouth, dull look, and staring expression in variable combinations. *Courtesy: Prof. Pramod Kumar Pal.*



Video 2. Wilson's disease, pre- and post-treatment. Segment 1: Shows a child with Wilson's disease who is confined to the bed and anarthric with generalized choreo-dystonic movements. Segment 2: The same child after initiation of decoppering therapy shows significant improvement, with ability to speak and walk independently. Some residual generalized chorea and dystonic features are still noted. *Courtesy: Dr. Prashanth Lingappa Kukkle.*
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737



Video 3. Spinocerebellar Ataxia Type 12; SCA-*PPP2R2B*. A 48-year-old man with an eight-year history of shaking of the hands and gait imbalance, with a diagnosis of SCA12. The video shows a coarse amplitude postural tremor of both upper limbs (right more than left) when these are held in front of the chest with shoulders abducted and elbows flexed, rest tremor of the left fourth and fifth fingers, mild head tremor, mild dystonia of the hands (spooning), finger-nose-incoordination especially on the left side, inability to perform tandem walking, and tremulousness of both lower limbs while walking. *Courtesy: Prof. Pramod Kumar Pal.*
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737

The gene was first identified in 1999 in a large German kindred.[27] Following the discovery, a study in North India involving 77 families with ADCA phenotype found that SCA12 variants accounted for approximately 7% of the cohort (six patients from five families), and was the third most prevalent SCA, after SCA1 and SCA2.[29] The same group subsequently reported 15 new families.[30] The mean onset age was in the fourth decade, ranging from 26–56 years.[30] These families were from an endogamous population (Agarwal community) originating from Haryana, a Northern Indian region, suggesting a common founder. The mean CAG repeat length in *PPP2R2B* in the expanded allele was 53.3 ± 6.1 (40–72) with no correlation between the CAG repeat size and the age at symptom onset.[31] Overall, SCA12 accounts for around 16% of ADCA in Northern India, which is considerably higher compared to series from other populations.[30,32]

Apart from Northern Indian cases, few SCA12 cases have been reported from elsewhere.[33–35] A study among 120 French and 27 Indian families with ADCA without common variants identified one Indian family with SCA12, but none in the French families.[36] In other Asian populations, none of 82 index patients from Thailand,[33] 1 of 430 ADCA families from China,[34] and 1 of 204 ataxic patients from Singapore had SCA12.[35]

The most common clinical presentations of SCA12 are upper extremity action tremor and gait ataxia (Video 3), followed by varied features including pyramidal dysfunction (hyperreflexia and positive Babinski sign), parkinsonism, dystonia, and cognitive decline.[31,32,37] Brain MRI usually reveals mild to moderate atrophy of the cerebellum, with more severe atrophy in the vermis compared to the cerebellar hemispheres, as well as in the cerebral cortex with or without subcortical white matter changes.[37]

The diagnosis of SCA12 requires genetic analysis. Since the majority of patients present with upper extremity action tremor and variable degrees of ataxia, SCA12 should be carefully differentiated from essential tremor (ET) and other late-onset tremor-ataxia syndromes, for example, Fragile X-associated tremor ataxia syndrome (FXTAS).[37] There is no disease-modifying treatment available for SCA12, but beta-blockers or GABAergic medications are used for symptomatic relief of the upper limb action tremor.

Spinocerebellar Ataxia Type 31; SCA-*BEAN1*

SCA31, caused by a large insertion containing pentanucleotide repeats (TGGAA)n in overlapping introns of the *BEAN1* and *TK2* genes, is largely restricted to the Nagano district of Japan where it accounts for approximately 42% of ADCA, with a strong founder effect.[38–41] The abnormal repeat insertion forms abnormal RNA structures, called RNA foci, preferentially in the nuclei of Purkinje cells in affected patients.[38] The length of the SCA31 repeat insertion correlates inversely with the age of onset and shows a pattern of genetic anticipation.

The prevalence of SCA31 ranges between 8–17% of ADCA in other parts of Japan.[40,42,43] It is rare or absent outside Japan with only one case reported so far in a Chinese patient.[44,45] The clinical phenotype of SCA31 is one of late-onset and relatively pure cerebellar ataxia. A natural history study prospectively enrolling 44 patients with genetically-proven SCA31 showed that the patients developed ataxic symptoms at the age of 58.5 ± 10.3 years, were confined to wheelchair at 79.4 ± 1.7 years, and

died at 88.5 ± 0.7 years.[42] As with other SCAs, therapy is supportive.

Spinocerebellar Ataxia Type 36; SCA-*NOP56*

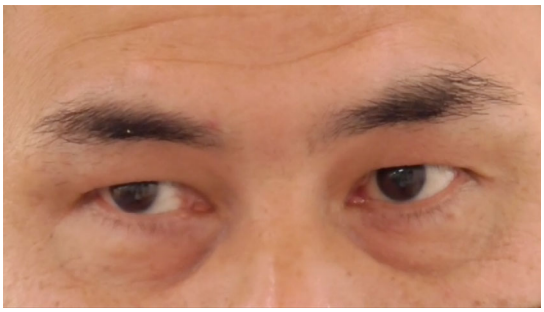
SCA36, another SCA that is rather specifically connected to Asia, is a slowly progressive late-onset autosomal dominantly (AD) inherited disease that is caused by a hexanucleotide repeat expansion in *NOP56*.[46–48] This gene encodes a nucleolar protein 56 which is involved in ribosomal RNA methylation and pre-rRNA processing.[49] This ataxic syndrome was first described in two Japanese patients,[50] and later from the Galicia region in Northwestern Spain.[47] SCA36 is now reported worldwide, but most cases are found in Western Japan and Spain.[51] In Western Japan, SCA36 was initially named "Asidan" ataxia as many patients with SCA36 lived in the Chugoku region near the Asida river,[46] while in Spain, SCA36 was named "Costa de Morte ataxia".[47] SCA36 is the most frequent spinocerebellar ataxia in the Galicia region, representing 6.3% of adult-onset ataxia, followed by SCA2 (4.4%), SCA1 (1.9%), SCA3 (1.9%), and SCA7 (1.3%).[47] In Japan, the prevalence of SCA36 is lower than other SCA subtypes and represents 0.6–3.6% of adult-onset ataxia.[52] SCA36 was reported to contribute to 3% of Italian families with ADCA without one of the commonly-tested SCAs. Otherwise, SCA36 does not appear to be common in other Asian countries, eg, 0.6% (3/512) of SCA patients in Taiwan,[53] or other world regions, including Greece (none in 98 index patients) and the USA (0.7%, 4/577),[54,55] although cases could also be underdiagnosed since this form of ataxia is currently not included in most genetic ataxia panels.

SCA36 is characterized by a late-onset cerebellar ataxia with a mean onset age in the fourth-to-fifth decades, combined with signs of lingual atrophy and fasciculations, and sensorineural hearing loss.[46,47] Notably, even though lingual atrophy is prominent in the later stage of the disease, dysphagia is rarely present.[52] Mild cognitive impairment of a fronto-subcortical pattern has been reported in patients with SCA36.[47] Brain MRI findings range from mild cerebellar vermis atrophy to diffuse cerebellar atrophy. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan can show hypometabolism in the vermis and cerebellar hemispheres.[56]

The treatment for SCA36 remains supportive, including speech therapy and communication devices for those with dysarthria.

Gerstmann-Sträussler-Scheinker Disease

GSS is an extremely rare, AD-inherited disease, caused by pathogenic variants in the prion protein (*PRNP*) gene.[57] GSS was first described in an AD inheritance family with the 25-year-old index patient developing cerebellar ataxia and psychosis, eventually dying 6 years after onset. Neuropathological examination revealed prominent cerebellar atrophy with molecular layer "senile" plaques, along with cerebral cortical atrophy.[58] Numerous missense variants have been reported in *PRNP* with the most prevalent being p.P102L.[59] Octapeptide repeat insertions, particularly longer (>7) insertions in the *PRNP* gene, can also cause GSS.[60] Although GSS is an AD disorder, up to 30% of patients have no apparent family history.[61]



Video 4. Gerstmann-Sträussler-Scheinker (GSS). A 44-year-old man with a two-year history of gradually progressive gait disturbance. His uncle and mother had similar symptoms, and the uncle was clinically diagnosed as having Gerstmann-Sträussler-Scheinker disease. On neurological examination, he has saccadic pursuit eye movements in horizontal and vertical directions and dysmetria and decomposition on finger-nose test and heel–knee test. The deep tendon reflexes are generally decreased, and the plantar reflex extensor on the left. Neither rigidity nor spasticity is seen. Due to severe postural instability, he is not able to walk independently. Genetic analyses revealed the *PRNP* p.P102L variant, and no pathological variants for SCA1, SCA2, SCA3, SC6, SCA7, SCA10, SCA17, SCA31 and DRPLA. *Courtesy: Assoc. Prof. Shinsuke Fujioka.*
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737

The prevalence of GSS is estimated at 1–10 per 100,000,000 people.[61] One review reported that GSS accounted for approximately 7.9% of genetic prion diseases in European countries and about 10–20% in East Asian countries including Japan, Korea and China.[62,63] The p.P102L variant causing GSS is one of the most common *PRNP* variants in Japan and Korea, but is rare in China.[62,63] Another common GSS-associated variant in Japanese, p.P105L, is also rare in Chinese,[63] while the p.A117V variant is common in Europeans.[61]

Clinically, GSS presents with progressive ataxia and lower limb hyporeflexia, followed by cognitive decline and dementia (Video 4).[64] The age of onset is in the fourth-to-fifth decades, although two patients with p.P102L were reported to develop symptoms in their twenties.[65] The average disease duration is 40 to 50 months after clinical onset.[66] Some genotype–phenotype correlations are emerging. For example, prominent cognitive decline without cerebellar ataxia as the initial presentation has been reported with p.Q212R.[67] Parkinsonism and psychiatric features such as delusions, paranoia, and hallucinations can be seen in half of the patients with the p.P102L variant.[66,68] Less than a quarter of patients with the p.P102L variant developed a sporadic Creutzfeldt–Jakob disease (sCJD)-like phenotype with rapidly progressive dementia.[69] Recently, a large cohort study enrolling 218 Chinese genetic prion disease patients revealed that GSS p.P102L variant patients had a long survival compared to those with other variants.[63] Patients with the p.P105L variant can present with late-onset spastic

paraparesis.[70] These observations demonstrate that different variants at different positions in *PRNP* result in different phenotypes of GSS, which vary substantially in their ethnic prevalence and clinical manifestations.

An integrated evaluation is needed to diagnose GSS, including cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), brain MRI, and genetic analysis. The sensitivity of the real-time quaking-induced conversion (RT-QuIC) test in CSF is approximately 75% in GSS,[71] while it was 92% in sCJD with 100% specificity.[72] EEG periodic synchronous discharges are uncommonly seen (<10%), and there are no specific MRI findings for GSS, although up to 30% of cases show fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) abnormalities similar to sCJD with increased signal intensity in the cortex (cortical ribboning) and basal ganglia.[73] GSS is often misdiagnosed as other degenerative cerebellar ataxias, especially at the early stage. Genetic analysis of the *PRNP* gene is needed to confirm the diagnosis. Management is supportive.

DYT/PARK-*PLA2G6*-Related Parkinsonism

PLA2G6-associated neurodegeneration (PLAN) is an AR neurodegenerative disorder caused by variants in *PLA2G6*.[74] The clinical phenotypes of PLAN are heterogeneous: infantile neuroaxonal dystrophy (INAD), with psychomotor regression or delay between the ages of 6–36 months; atypical neuroaxonal dystrophy (ANAD), with prominent language difficulty and autistic-like traits between ages 1.5–6.5 years[75,76]; hereditary spastic paraparesis between ages 9–66 years[77,78]; and early-onset dystonia-parkinsonism in the second to third decades of life.

A total of 101 *PLA2G6*-mutated cases with parkinsonism have been documented worldwide.[74,79–88] The majority of the patients ($n = 86$) were from Asia, mainly China and Taiwan ($n = 36$).[89,90] Among the Asian cases, 51.8% were males and mean age of onset was 25.1 ± 9.1 years compared to 20.8 ± 9.2 years in Caucasians. The most common manifestations at onset were parkinsonism and dystonia in 62.5% of the Asian patients. Psychiatric features (eg, severe depression or anxiety, psychosis), the second most common manifestations, presented more frequently in Caucasian (40%) than in Asian (21.3%) patients.

The "classical" scenario of early-onset *PLA2G6*-related dystonia-parkinsonism includes various movement disorders: parkinsonism (100%), dystonia (68.3%), cerebellar ataxia (36.2%), pyramidal signs (63.6%), psychiatric symptoms (76.8%) and cognitive decline (59.7%).[79,91] Besides these, autonomic features (including urinary disturbances, constipation, sexual dysfunction and orthostatic hypotension) were observed in 71.9% (23/32) of Asian patients and 75% (3/4) of Caucasian patients.[91] Brain MRI showed cerebral atrophy (especially generalized or frontotemporal lobe) in 52.6% and cerebellar atrophy in 39.1% of Asian cases, whereas only 13.2% of cases reported iron accumulation in the basal ganglia, which is less than in INAD and ANAD patients (26.7%).[92]

Pathogenic *PLA2G6* variants impair iPLA2β function via a variety of loss-of-function mechanisms.[93] The most frequent variant in Chinese is homozygous p.D331Y,[89,94] suggesting a common founder effect. The p.R741Q variant is mainly reported in Indian, Saudi Arabian and Pakistani populations, and p.R635Q in Japanese patients.[91] These above-mentioned variants were rarely reported in Caucasian patients.

The neuropathological findings of patients with *PLA2G6* variants are also heterogenous, including Lewy bodies in the substantia nigra and locus ceruleus (similar to idiopathic PD),[95] co-existing Alzheimer's disease-like pathology in temporal lobe structures, abundant gliosis, and some may also have excessive iron accumulation in the substantia nigra and basal ganglia.[96]

Parkinsonism responded to levodopa in 98.4%, while levodopa-induced dyskinesias were reported in 86.8% and appeared within the first year of treatment in most cases. Early occurrence of dyskinesias and exacerbation of psychiatric symptoms after levodopa initiation are considered tell-tale signs of *PLA2G6*-related parkinsonism.[79] Motor and non-motor symptoms and fluctuations responded well to subthalamic nucleus (STN) and globus pallidus internus (GPi) deep brain stimulation (DBS) in a few patients who have received the treatment, in both Asians and Caucasians.[79,85,97–99]

Adult-Onset NIID and *NOTCH2NLC*-Related Disorders

NIID has been reported since the 1960s, but was rarely diagnosed as this required brain autopsy or invasive (eg, rectal or sural nerve) biopsies.[100,101] The recent recognition of cases based on MRI findings and skin biopsy (showing eosinophilic ubiquitin-positive and p62-positive intranuclear inclusions in adipocytes, fibroblasts, and sweat glands) paved the way for more widespread recognition of the condition, particularly among Japanese adult patients.[100]

In 2019, abnormally increased GGC-repeat expansions in the 5′ untranslated region (UTR) of the *NOTCH2NLC* gene were identified to be the cause of NIID, largely among Japanese and other Asian patients.[101–103] Since then, the phenotype has expanded and *NOTCH2NLC* variants were found in 5.6% of mainland Chinese families with ET[104]; 1.3% of typical sporadic PD cases in Singapore (all cases were ethnic Chinese)[105] and in China (1.1%, 11/1011)[106]; and were also reported to be the most frequent genetic cause of adult-onset leukoencephalopathy in Japan and Taiwan.[107,108] In contrast, *NOTCH2NLC* variants appear to be extremely rare in Caucasians.[101,109,110] A recent literature search revealed no more than a dozen adult-onset NIID (and a similar number of juvenile-onset) cases reported from Europe, North America, and Australia since 2000.[101] Interestingly, a recent analysis of NIID cases of European ancestry (confirmed on post-mortem brain examination; $n = 11$) found no case of expanded repeats in *NOTCH2NLC*, suggesting that NIID may be genetically heterogeneous between Asians and Caucasians.[111]

In the "classical" scenario of adult-onset NIID, onset is usually in mid- or later life and features commonly include cognitive decline or dementia, various movement disorders (including parkinsonism,

tremor, cerebellar ataxia), muscle weakness, peripheral neuropathy, and autonomic dysfunction, with limb weakness vs. dementia being more prominent in younger- vs. older-onset patients, respectively.[100] Cases may be sporadic or AD in inheritance (sometimes displaying genetic anticipation).[104] Apart from age, variable clinical expressivity may be caused by genetic factors such as the length of the GGC repeats, interruptions (eg, of GGA) in the repeat tracts, or other unknown modifiers.[104,112] For example, clinical NIID cases typically have >65 (and up to about 500) repeats (vs. <40 in healthy controls),[105] and typical sporadic PD cases were mostly reported to have intermediate-length expansions (40–60 GGC repeats).[105,106] Interestingly, the Chinese familial ET cases had repeat sizes of 60–250, but did not have other NIID features.[104]

Brain MRI could offer diagnostic clues with the characteristic features of high signal intensity in the corticomedullary/gray-white matter junction on DWI (Fig. 2A,B). FXTAS (also caused by expanded trinucleotide repeats, but in *FMR1*) has been highlighted as a mimic of NIID (and vice versa), in terms of clinical, radiological (Fig. 2C,D) and also histological findings.[101,113,114] However, it appears that FXTAS is quite rare in Asian populations (Chinese, Japanese, Koreans, and Singaporeans).[2,101]

Like most other genetic neurodegenerative disorders, NIID has no specific treatment besides supportive and symptomatic therapy.

Paroxysmal Kinesigenic Dyskinesia; PxMD-*PRRT2*; PKD-*PRRT2*

Paroxysmal dyskinesias are a rare heterogeneous group of conditions.[115,116] They are classified into three main subtypes based on triggering factors: PKD, paroxysmal non-kinesigenic dyskinesia

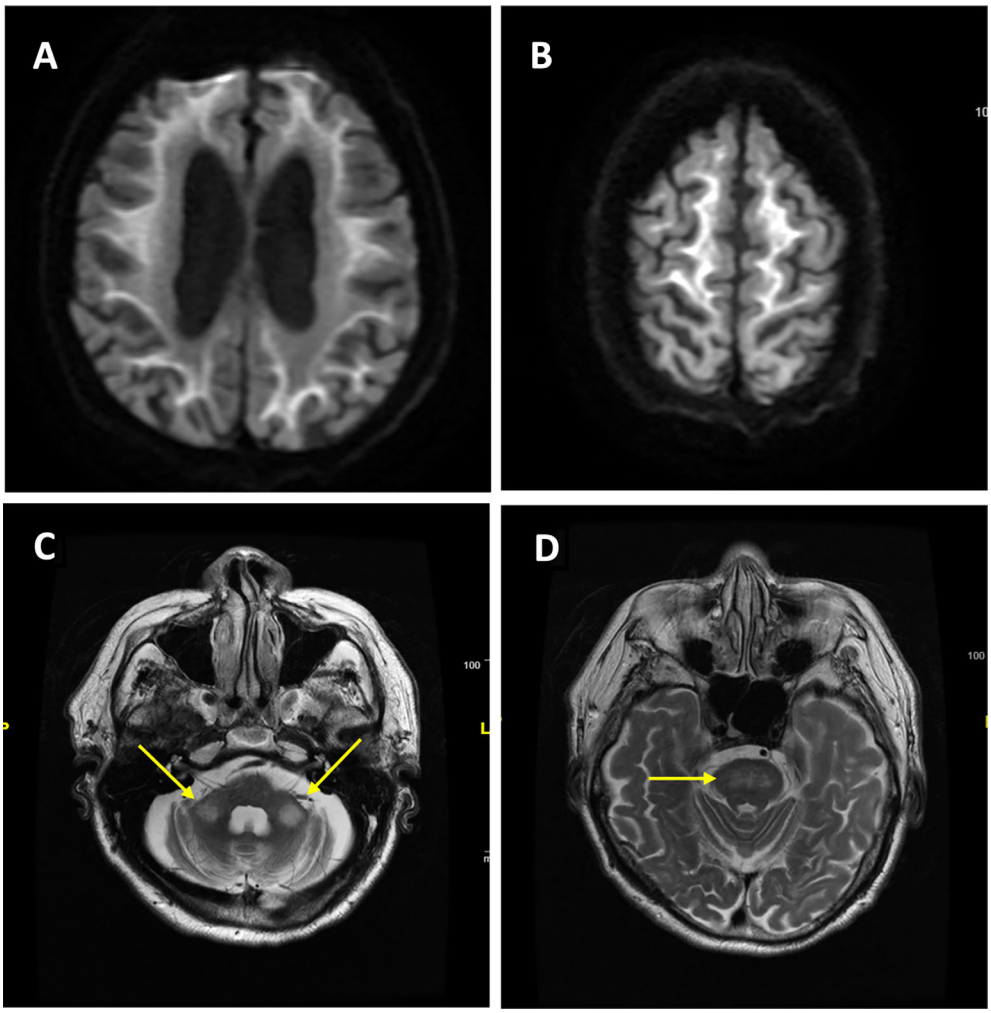


FIG. 2. Representative brain MRI from a patient with genetically proven neuronal intranuclear inclusion disease (NIID). (A, B) Characteristic high-intensity signal along the corticomedullary junction in the cerebral hemispheres on diffusion-weighted imaging (DWI). High-intensity signal on T2-weighted images in bilateral middle cerebellar peduncles (arrows, C) and pons (D), which may mimic the radiological features of FXTAS. This was Malaysian Patient #1 in Lim et al., Ishiura et al.[101,102] *Courtesy: Prof. Shen-Yang Lim.*

(PNKD) and paroxysmal exercise-induced dyskinesia (PED).[117,118] The prevalence of PKD, which is the most common form of paroxysmal dyskinesias, was estimated to be 1:150,000 in the general population, with a suggestion that it may be more common in Asians, especially Chinese and Japanese, although direct comparisons of prevalence among various ethnic groups are not available.[119,120] In studies from Malaysia and Singapore, which are multi-racial Southeast Asian countries, a preponderance of Chinese (over Malay and Indian) cases has been observed (65–90% Chinese).[121–123] The first multicenter study in Asia was reported by Japanese investigators who analyzed 150 patients with a clinical diagnosis of PKD comprising 53 sporadic cases and 97 affected individuals from 32 pedigrees with a majority compatible with AD inheritance.[124] The mean age of onset was 8.8 years with male predominance (80%). Attacks were precipitated by sudden voluntary movements, startle, or emotional stress, lasted between seconds to 5 min, and upper limbs were most affected. Treatment with carbamazepine or phenytoin was effective in 95% of patients.

The most common genetic variant underlying PKD is c.649dupC (p.Arg217fs) in *PRRT2*, which was responsible for 76.4% of *PRRT2* variant carriers in a Chinese study.[120,125] A review of 1444 cases of patients with *PPRT2* variants showed that 58.5% of PKD-*PRRT2* were Asians, mainly Chinese, followed by Caucasians (33.9%).[120] *PRRT2* variant carriers presented with earlier onset, longer attack duration, and greater complexity (such as having bilateral involvement or a history of infantile convulsions), compared to non-*PRRT2* carriers. The clinical phenotypes include an evolving continuum from benign familial infantile epilepsy, to PKD and paroxysmal headache disorders such as hemiplegic migraine.[117,120] The excellent response of PKD to antiepileptic medications, and the recent identification of epilepsy-related genes (including *SCN8A*, *KCNMA1*, *DEPDC5*, *KCNA1*, and *CHRNA4*) in pure or complicated PKD suggest that PKD and epileptic disorders might share similar pathogenesis.[126–128] As such, implications for clinical practice are starting to emerge, with revised clinical diagnostic criteria incorporating genetic diagnosis, and treatment recommendations.[129]

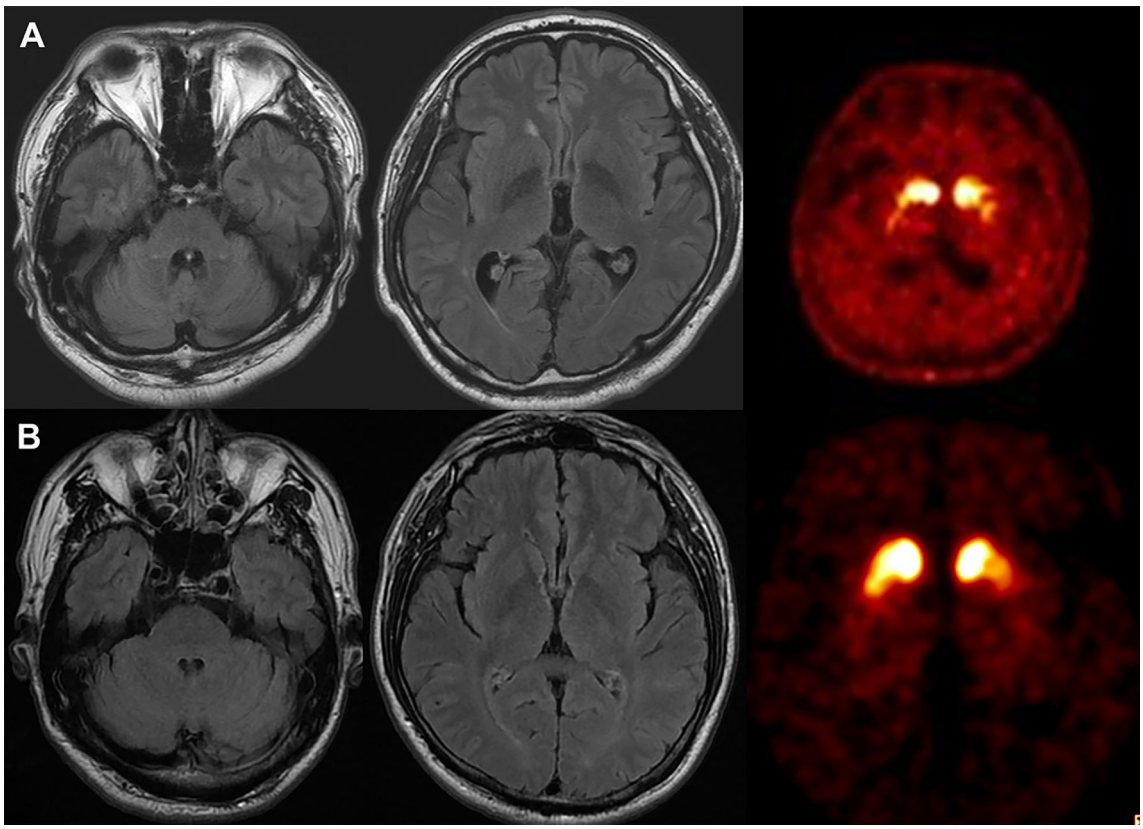


FIG. 3. SCA2 and SCA17 presenting with parkinsonism. (A) Brain MRI and ^{18}F-FP-CIT PET images of a patient with SCA2 (26/36 expansions) presenting with excellent levodopa-responsive symmetric parkinsonism with onset at the age of 43 years. There is mild degree pontocerebellar atrophy, but he has no overt ataxia. Dopamine transporter availabilities are reduced bilaterally with anteroposterior gradient. Notably, the patient's family members showed marked clinical heterogeneity. His father and sister manifested severe ataxia and his elder brother has predominantly parkinsonism. (B) Brain MRI and ^{18}F-FP-CIT PET images of a patient with SCA17 (36/44 expansions) presenting with levodopa-responsive parkinsonism with onset at 52 years of age. No clear evidence of cerebellar atrophy is seen, and FP-CIT bindings are bilaterally reduced in the striatum with anteroposterior gradient. *Courtesy: Prof. Jee-Young Lee and Prof. Beomseok Jeon.*

Issues of Parkinsonism in SCA2 and SCA17 in Asian Populations

Parkinsonism is not rare in ADCA patients with abnormally expanded trinucleotide repeats. SCA2, caused by abnormal CAG repeat expansion in *ATXN2*, is the most frequent SCA that can present with parkinsonism, and can mimic PD.[130,131] Pathologically, nigral dopaminergic neuronal loss exceeds that seen in PD,[132] with brainstem Lewy body pathology variably found.[132,133] Interestingly, midbrain dopaminergic loss appears to be a universal phenomenon in SCA2 regardless of the presence or absence of parkinsonism.[134] Dopamine transporter imaging findings can resemble those of PD with asymmetric and preferential involvement of the posterior putamen, although the dopaminergic denervation is often symmetrical involving the entire striatal regions (Fig. 3A).[134,135]

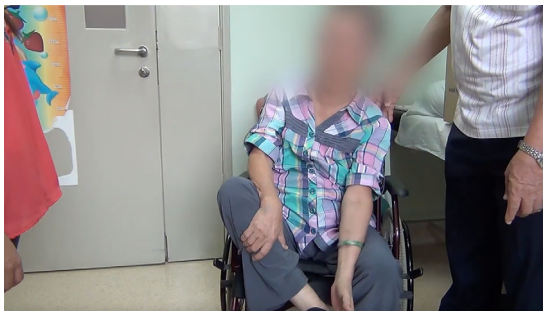
The manifestation of parkinsonism in SCA2 is heterogeneous and it is thought to be more prevalent in Asians compared to other populations, although systematic epidemiological studies are lacking. Studies in sporadic PD populations reported a SCA2 frequency of 2.2% among Singaporean Chinese[136] and 0.4% in Koreans and Taiwanese[134,137]; whereas familial PD populations had frequencies of 1.5–8.7% in mainland China and Taiwan,[138,139] 2–2.5% in Italy and France,[135,140] and 0.9–1.5% in the USA.[131,141]

Genetic modifications have been suggested as one of the possible mechanisms for the pure parkinsonian phenotype of SCA2. Pathogenic alleles with one or more CAA interruptions and low-range CAG repeat expansions are reported to be linked to parkinsonism in SCA2.[134,135,142] A report on quite long-lasting (up to 34 years) PD phenotype with pure parkinsonism in a Korean SCA2 family without anticipation across generations (40 repeats with four CAA interruptions) supported the hypothesis of CAA interruption in contributing

TABLE 1 *Variant frequency in Parkinson's disease (PD)-causative genes with autosomal dominant inheritance in Asian patients with PD*

AD inheritance			
LRRK2	Heterozygous missense variants	Similar to sporadic late-onset PD (Video 5)	23 of 1402 (1.6%) Japanese PD patients had variants including 7 (0.5%) with p.G2019S, 7 (0.5%) with p.I2020T, 5 (0.4%) with p.R1441H, and 4 (0.3%) with p.R1441G[157]; 4 of 324 (1.2%) Taiwanese EOPD or FPD patients had variants, including p.R1441H and p.I2012T[149]; 2 of 662 (0.3%) Chinese EOPD had the p.R1441C variant[158] who, together with other p.R1441C patients in Singapore and Malaysia, were suggested to have a common founder.[156]
	p.R1628P polymorphism	Similar to sporadic PD	A meta-analysis revealed that p.R1628P was a risk variant for PD in Asians with an OR of 1.83.[159]
	p.G2385R polymorphism	Similar to sporadic PD	A meta-analysis revealed that p.G2385R was a risk variant for PD in Asians with an OR of 2.27.[159]
	Risk variants identified from GWAS	Similar to sporadic PD	A Japanese GWAS study identified five risk variants (rs1994090, rs7304279, rs4768212, rs2708453 and rs2046932) for PD.[160] A large East Asian study demonstrated that rs1384236 is a risk variant for PD in Asians.[161]
	p.N551K-p.R1398H haplotype	Similar to sporadic PD	An Asian cohort study showed a protective association in Malays with an OR of 0.45; and meta-analysis of Chinese patients showed a protective effect (OR: 0.79, 95% CI: 0.67–0.92).[162]
CHCHD2	Heterozygous missense variants	Similar to sporadic PD	A large Japanese cohort identified two families having p.T61I variant, one family having p.R145Q and another one with a splice-site variant (300 + 5G > A).[163] A meta-analysis showed p.P2L to be a risk variant for PD among Chinese.[164]
UQCRC1	Heterozygous missense variants	Early-onset parkinsonism with polyneuropathy	A large East Asian cohort study identified two Taiwanese families and one Japanese family having *UQCRC1* missense or splicing variants.[165] A subsequent large Chinese study identified risk variants in *UQCRC1* in sporadic PD.[166] The pathogenic variants of *UQCRC1* were not identified in European populations.[167,168]

Abbreviations: AD, autosomal dominant; EOPD, early-onset Parkinson's disease; FPD, familial Parkinson's disease; OR, odds ratio.



Video 5. *LRRK2* R1441C variant. This Malaysian patient of Chinese ancestry was diagnosed with Parkinson's disease (PD) at the age of 58 years, later found to be associated with the *LRRK2* p.R1441C variant. Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) was performed at the age of 67 years to treat progressively worsening OFF periods (medication effect lasting only 2–3 hr, with disabling OFF symptoms characterized by akinesia, tremors and painful foot dystonia—described further in Lim et al. Patient 2).[156] This video was taken 6 weeks after the DBS surgery, and the patient has come in OFF-medication for her 1st DBS programming session. The patient is in a wheelchair and is able to take several small steps but requires close supervision. Limb movements are bradykinetic and there is an obvious "striatal toe" on the right side. *Courtesy: Prof. Shen-Yang Lim.*
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737

to the pure parkinsonism phenotype.[143] However, CAA interruption was not the only factor determining phenotype,[144,145] suggesting other genetic modifiers could play a role in the manifestation of parkinsonism in different populations. Heterogeneous observations suggest that genetic modifiers may be different across populations, which may explain the heterogeneity in the frequency of pure parkinsonism and in the relevant numbers of genetic interruptions and expansions in SCA2 among different ethnic populations. In a large Chinese cohort study, the presence or absence of parkinsonism was independent of the severity of ataxia.[145]

In addition to SCA2, levodopa-responsive parkinsonism has been reported in SCA types 3, 6, 8, and 17.[130] SCA17 is caused by abnormal CAG/CAA repeat expansion in the TATA-binding protein (*TBP*) gene. The association with parkinsonism is commonly found in Asian populations.[130] SCA17 patients can present with an atypical parkinsonian syndrome and show poor levodopa response resembling multiple system atrophy or progressive supranuclear palsy.[146] However, SCA17-pure parkinsonism cases are also reported in Korean, Taiwanese Chinese, and Thai populations.[33,147–149] There has been no reported pathologic study of SCA17-parkinsonism, but dopamine transporter imaging showed heterogeneous features as bilateral severely reduced uptake or diffuse reduction without anterior–posterior gradient, or resembling typical PD (Fig. 3B). Reduced copy number of CAG in the *TBP* gene may be related to a pure parkinsonian presentation,[147] but the cutoffs remain unclear, and variable movement disorders have been reported with small-expanded alleles.[150,151] One study investigated the frequency of low-range repeat expansions between parkinsonian patients and normal controls but reported no difference between the groups.[152] Therefore, further studies are required to reveal the exact mechanism of pure parkinsonism in SCA17.

PD-Causative Genetic Variants in Asian Populations

Approximately 10% of PD can be attributed to a monogenic cause, and the heritable component of PD due to common

Video 6. *GBA1* p.L483P variant and also the *LRRK2* Asian variant p.R1628P. Parkinson's disease in this patient was diagnosed at the age of 44 years. She underwent bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) at the age of 57 years. The video, taken at the age of 59 years, was in the stimulation-ON, medication-ON (3.5 hr post-dose) condition. Parkinsonian signs including bradykinesia can be observed, of mild-to-moderate severity. She is able to stand up quickly and walk independently without an aid (albeit slowed, with reduced arm swing bilaterally), and is able to recover during pull test. However, she has difficulty following simple verbal/gestural commands, with Montreal Cognitive Assessment (MoCA) score of only 9/30. The patient was later found to have the *GBA1* p.L483P (p.L444P) variant (which could be an explanation for her dementia), and also the *LRRK2* "Asian variant" p.R1628P. *Courtesy: Prof. Shen-Yang Lim.*
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737

genetic variability is estimated to be around 22%.[153] *LRRK2* variants, the most frequently implicated genetic factor in familial and sporadic PD, display significant ethnic variation. In particular, the *LRRK2* p.G2019S variant is very common (up to around 40% of PD cases) in North African Berber Arabs and Ashkenazi Jews and to some extent in Europeans, but very rare in Asians.[154,155] In contrast, p.G2385R and p.R1628P (so-called *LRRK2* Asian variants) are common genetic risk factors in Asian PD (Table 1), each being present in around 5–10% of some Asian PD populations such as Han Chinese, vs. approximately half of that in the respective general populations.[2] Although overall the clinical features of *LRRK2*-related parkinsonism appear to be comparable to idiopathic PD (Video 5), several studies have reported that patients with the p.G2019S variant are more likely to be women and less likely to have non-motor symptoms, including olfactory impairment, cognitive dysfunction, and rapid eye movement sleep behavior disorder.[169,170] A recent meta-analysis revealed that patients with the p.G2385R variant have lower motor symptom severity and better cognitive function, but a higher tendency to develop levodopa-related motor complications than those without this genetic substitution.[171] In addition, heterozygous variants in *GBA1* also increase the risk of PD in both Eastern and Western populations, although specific variants (eg, p.L483P which is associated with a more aggressive phenotype (Video 6)) may be over-represented in Asian populations (Table 2). Interestingly, a recent study suggested that combined *LRRK2* p.G2019S and *GBA1* variants were not associated with worse disease progression, although no information was available on *LRRK2* Asian variants.[197] *PINK1* variants have also been commonly reported in Asians. Specifically,

TABLE 2 *Variant frequency in Parkinson's disease (PD)—causative genes with autosomal recessive inheritance and risk gene in Asian patients with PD*

Gene	Variants	Phenotypes	Variant frequency in cohort studies
AR inheritance			
PARK2	Missense variants or exonic deletions (especially exons 2 to 5)[149,172,173]	Early to juvenile-onset levodopa-responsive PD (average 26.1 yr)[2,172]	5 of 189 (2.6%) Korean patients with EOPD or FPD[174]; 15 of 324 (4.6%) Taiwanese patients with EOPD or FPD[149]; 9 of 240 (3.8%) Han Chinese patients with sporadic or familial EOPD,[175] 83 of 1676 (5.0%) Han Chinese patients with EOPD or FPD[173]; 137 of 1204 (11.4%) Japanese FPD patients.[176]
PINK1	Missense variants	Early-onset levodopa-responsive PD (average 30–50 yr) (Video 7)	2 of 47 (4.3%) Japanese AR-inheritance families and 1 of 190 (0.5%) sporadic PD patients[178]; None of 324 Taiwanese patients with EOPD or FPD[149]; 7 of 1676 (0.4%) Han Chinese patients with EOPD or FPD[173]; 3 of 289 (1.0%) mixed Asian populations of PD patients[179]; 6.9% of Malay EOPD patients had homozygous p.L347P variants.[177] 7 of 273 (2.6%) EOPD patients from New Zealand had homozygous p.L347P variants.[180]
PLA2G6	Missense variants	Early-onset parkinsonism and may be combined with atypical features	3 of 29 (10.3%) Japanese patients with EOPD[91]; 2 of 324 (0.6%) Taiwanese patients with EOPD or FPD[149]; 9 of 1676 (0.5%) Han Chinese patients with EOPD or FPD.[173] The p.D331Y variant was almost exclusively found in Chinese patients, suggesting a common founder effect in this population.[89]
Risk Gene			
GBA1	Heterozygous variants	A younger onset age and more severe motor and non-motor features,[181–187] for *GBA1* p.L483P (old nomenclature p.L444P) variant[184,187–190] (Video 6)	An international multicenter cohort showed an increased risk for PD in those carrying p.N370S (OR 3.96) and p.L483P (OR 6.73), but p.N370S variant is uncommon among Asians while p.L483P is a pan-ethnic variant.[191] A meta-analysis found that p.R159W (old nomenclature p.R120W) increased the risk of PD (OR 14.93) specifically in East Asians.[127] In East Asians, p.L483P (OR 12.43), RecNciI (a recombinant allele containing p.L483P) and A495P (also known as V499V) increased the risk of PD (OR 3.56).[127] The p.L483P variant has been reported to be the most common *GBA1* variant in some Asian populations.[173,192–196]

Abbreviations: AR, autosomal recessive; EOPD, early-onset Parkinson's disease; FPD, familial Parkinson's disease.

Video 7. *PINK1* p.L347P variant. A case of young-onset Parkinson's disease with *PINK1* p.L347P variant in an Indonesian Malay woman (Patient 1 in reference Tan et al.[177]). The patient started having slowness of movement, tremor and stiffness at age 26 years and developed severe motor fluctuations and dyskinesia within months of levodopa therapy initiation. She was dependent on her caregivers by age 34 years. The video was taken 15 min after taking levodopa/benserazide 150 mg/37.5 mg and shows severe generalized choreo-ballistic movements leading to difficulty in sitting and standing, and tongue protrusion. This troublesome dyskinesia typically lasts for about 2 hours after each dose of medication, during which the patient moves around at home by bottom shuffling. *Courtesy: Assoc. Prof. Ai Huey Tan.*
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13737

the p.L347P variant appears to be a common cause of AR early-onset PD in Southeast Asia and the Pacific Islands (proposed to reflect ancient migratory patterns of Austronesian races), and displays marked clinical heterogeneity ranging from mild PD (or even dopa-responsive dystonia without parkinsonism), to cases with extremely severe motor complications (Video 7).[177,180,198]

In recent years, several novel PD-causative or related genes have been identified, notably in Asian populations. Variants in the *CHCHD2* gene were linked to a late-onset AD form of PD (PARK22) in a large Japanese cohort.[163] The authors identified two families having the p.T61I variant, one family having the p.R145Q variant, and another with a splice-site variant (300 + 5G > A).[163] Their phenotypes were similar to idiopathic PD with good levodopa response. A further meta-analysis showed the p.P2L substitution to be a risk variant for PD.[164] Although the aforementioned variants were not found in a large European cohort of PD patients, three other rare variants (p.A32T, p.P34L, and p.I80V) were identified[199] and a homozygous missense variant (p.A71P) was reported in a young-onset Caucasian PD patient.[200]

Variants in *UQCRC1* were reported in a large East Asian PD cohort, including two Taiwanese families (p.Y314S and p.I311L) and one Japanese family (concomitant splicing variant, c.70-1G4A, and a frameshift insertion, p.Ala25Glyfs*27).[165] The Taiwanese family presented with early-onset, levodopa-responsive parkinsonism with polyneuropathy. A subsequent large Chinese study identified risk variants in *UQCRC1* in sporadic PD.[166] PD-related variants in *UQCRC1* have not so far been observed in European populations.[167,168]

Conclusion

Asian patients have unique disease-causing variants which may come from founder effects, and high rates of consanguinity are also likely to be contributory in specific regions. Furthermore, many patients may present with characteristic phenotypes, in part related to the genetic variants that are more common or almost exclusively found in specific Asian groups. However, access to genetic testing facilities varies vastly between regions in Asia and may skew some of the results.[201]

Recent advances in understanding the pathogenic mechanisms of PD and related movement disorders have shed light on the development of disease-modifying or mechanism-targeted therapies. Therefore, it is becoming increasingly imperative that clinicians are aware of and have knowledge about genetic disorders that are more commonly encountered in different ethnic groups. Improved recognition of particular phenotypic characteristics, coupled with information about the ethnic origin of patients, would point to specific genetic testing and lead to earlier diagnosis for better prognostication and, potentially, genetics-based, mechanism-targeted, therapies. All these issues underscore the need for further improvements in infrastructure and services, and concerted efforts in training and research involving cross-collaborations between clinicians and researchers in Asia, and the rest of the world.

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Author Roles

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Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

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C.H.L.: 1A, 1B, 3A, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of institutional review board was not required for this review. Written informed consent from patients was obtained for all the supplementary videos. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

TABLE S1: Common variants in *ATP7B* gene in Asian patients with WD