RESEARCH ARTICLE

The Phenotypic and Genotypic Spectrum of CSF1R-Related Disorder in China

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ABSTRACT: Background: Colony-stimulating factor 1 receptor (CSF1R)-related disorder (CRD) is a rare autosomal dominant disease. The clinical and genetic characteristics of Chinese patients have not been elucidated.
Objective: The objective of the study is to clarify the core features and influence factors of CRD patients in China.
Methods: Clinical and genetic-related data of CRD patients in China were collected. Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Sundal MRI Severity Score were evaluated. Whole exome sequencing was used to analyze the CSF1R mutation status. Patients were compared between different sexes, mutation types, or mutation locations.
Results: A total of 103 patients were included, with a male-to-female ratio of 1:1.51. The average age of onset was (40.75 ± 8.58). Cognitive impairment (85.1%, 86/101) and parkinsonism (76.2%, 77/101) were the main clinical symptoms. The most common imaging feature was bilateral asymmetric white matter changes (100.0%). A total of 66 CSF1R gene mutants (22 novel mutations) were found, and 15 of 92 probands carried c.2381 T > C/p.I794T (16.30%). The MMSE and MoCA scores (17.0 [9.0], 11.90 ± 7.16) of female patients were significantly lower than those of male patients (23.0 [10.0], 16.36 ± 7.89), and the white matter severity score (20.19 ± 8.47) of female patients was significantly higher than that of male patients (16.00 ± 7.62). There is no statistical difference in age of onset between male and female patients.
Conclusions: The core manifestations of Chinese CRD patients are progressive cognitive decline, parkinsonism, and bilateral asymmetric white matter changes. Compared to men, women have more severe cognitive impairment and imaging changes. c.2381 T > C/p.I794T is a hotspot mutation in Chinese patients. © 2024 International Parkinson and Movement Disorder Society.

Key Words: leukoencephalopathy; colony-stimulating factor 1 receptor; sex difference; phenotype–genotype relationship; China

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Adult-onset leukoencephalopathy with neuroaxonal spheroids and pigmented glia (ALSP), which includes hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD),[1] is a group of hereditary white matter diseases characterized by rapidly progressive cognitive, motor, and psychiatric impairment in midlife.[2] Radiologically, patients typically manifest with bilateral white matter lesions and atrophy of the cortex and corpus callosum. The most significant pathological features are diffuse axonal degeneration and demyelination in the brain, as well as axonal spheroids and pigmented microglia.[3] At present, mutations of colony-stimulating factor 1 receptor (*CSF1R*) are responsible for most autosomal dominant or sporadic ALSP cases with incomplete penetrance,[4,5] and this subgroup of ALSP is named CSF1R-related leukoencephalopathy (CRLE).[6] In different populations with white matter lesions, the prevalence of CRLE is about 3.5%–7%.[2,7] The nomenclature of this disease is continuing to evolve, with the current proposed name being *CSF1R*-related disorder (CRD).[8]

CSF1R encodes a tyrosine kinase transmembrane receptor and is mainly expressed in microglia in the brain,[4] involved in the survival, proliferation, and differentiation of microglia.[9,10] To date, more than 70 different *CSF1R* mutations have been reported worldwide,[11,12] and the majority of *CSF1R* mutations discovered are located in the tyrosine kinase domain (TKD, exons 12–22),[13,14] affecting its autophosphorylation and inactivating tyrosine kinases, thereby influencing the downstream signaling pathways.[5]

CRD has drawn increasing interest globally because of its insidious onset, high disability, and mortality, as well as challenges in diagnosis and treatment. However, current clinical studies mostly focused on Japanese[11,13] and European populations,[15] but there is a lack of systematic understanding of the phenotype and genetic characteristics of this highly heterogenetic disease in China.[2,16] Besides, the influence factors, especially the phenotype–genotype relationship of CRD, are still poorly understood. Therefore, in this cross-sectional study, we enrolled 103 confirmed CRD patients in China, summarized the genetic and phenotypic spectrum of Chinese patients, and further analyzed the sex difference and phenotype–genotype relationship in CRD.

Patients and Methods

Participants

This study is a retrospective cross-sectional study. A total of 103 CRD patients (including 5 cases reported before[14,17-25]) from the China ALSP Collaborative Group (CACG), composed of departments of neurology led by Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, were enrolled from April 1, 2018, to August 15, 2023. Specifically, patients with adult-onset leukoencephalopathy and rapidly progressive cognitive, motor, or/and psychiatric disorders would undergo whole exome sequencing if they were willing to, and they were further asked for the enrollment if they carried heterozygous *CSF1R* variants ("pathogenic" or "likely pathogenic" according to the American College of Medical Genetics and Genomics [ACMG] Standards and Guidelines[26]). All participants were evaluated and consulted by at least two experienced neurologists. Among the 103 patients, 100 are Han Chinese and 3 ethnic minorities (Mongolian, Manchu, and Zhuang).

This study was approved by the Ethics Committee of Shanghai Sixth People's Hospital (approval no.: 2021-219), and registered in the China Clinical Trial Center (registration no.: ChiCTR2100050834).

Clinical and Neuroimaging Assessment

Patient demographic information, initial symptoms, clinical symptoms, neurologic signs, and family history were obtained through patient interviews and review of medical records. Global cognitive performance was assessed using the Mini-Mental State Examination (MMSE)[27] and the Montreal Cognitive Assessment (MoCA).[28] The results of imaging examinations, neurophysiological examinations (electromyography [EMG] and nerve conduction study [NCS], electroencephalogram [EEG]), and cerebrospinal fluid examinations (pressure, protein, glucose, cell count, oligoclonal bands) were reviewed.

Patient imaging data included 3 T brain magnetic resonance imaging (MRI) and brain computed tomography (CT) images. In addition, in vivo positron emission tomography (PET) studies using [18F]-DPA-714 are considered a reliable method to evaluate neuroinflammation that targets on the level of translocator protein,[29] so 21 patients agreed to undergo [18F] DPA714-PET/CT. MRI assessment was made using the Sundal scale, scored independently by two neuroimaging physicians based on MRI images from the medical records.[30] All scales were scored in strict accordance with the scoring criteria.

Whole Exome Sequencing and Data Analysis

A standard phenol/chloroform extraction protocol was used to extract genomic DNA. Exons were captured using Agilent SureSelect v6 reagents. The Illumina HiSeq X Ten platform was used for exome sequencing. Reference human genome assembly hg19 (GRCh37) was used for alignment, recalibration, and variant calling. First, data were initially filtered using public databases of normal human variants (Table S1), excluding all variants with a frequency greater than 5% in the

population. Second, the pathogenicity of nucleotide and amino acid conservation were predicted through related software, including *Mutationtaster* (http://www.mutationtaster.org), *PolyPhen-2* (http://genics.bwh.harvard.edu/pph2), and *SIFT* (http://sift.jcvi.org). Finally, the pathogenicity of the variant was further interpreted and classified according to the ACMG guidelines.[26] Sanger sequencing further confirmed the putative pathogenic variant. All bioinformatics analyses were estimated by two clinical geneticists.

Statistical Analysis

All statistical analyses were performed using *SPSS 26.0* software. Patients were divided into two groups based on sex, mutation type (missense mutation and null mutation), mutation site (Ig domain and TKD domain), and clinical symptoms (motor-predominant and cognitive-predominant). The normally distributed measurement data were presented as mean ± standard deviation (mean ± s), and a t-test was used to compare two groups; the skewed distribution measurement data were presented as the median and interquartile range (Mdn, IQR), and the Mann–Whitney *U* test was used to compare two groups. For comparing two groups with enumeration data, the χ^2 test was used if the sample size (N) was greater than 40 and the theoretical frequency (T) was greater than 5, the χ^2 test with continuity correction was used if $N > 40$ and $T \leq 5$, or Fisher's exact test was used if $N \leq 40$. $P < 0.05$ was considered statistically significant.

Results

Basic Information

A total of 103 patients, 41 men and 62 women, diagnosed with CRD across the country were summarized (Table S2), with a ratio of 1:1.51 (Fig. 1A). Forty-eight patients were with family history (from 36 families, Fig. 1B, supplementary material). The average age of onset was (40.75 ± 8.58) years old (range 22–63 years old), and the peak of onset was between 35 and 45 years old (Fig. 1E). The average course of disease was (2.13 ± 1.69) years, among which 9 patients (8.74%) died (Fig. 1C). The average course of disease from onset to death was (2.8 ± 1.2) years. CRD mainly includes two phenotypes.[31] According to the clinical manifestations, 57 patients were motor-predominant, 43 were cognitive-predominant, and the classification of 3 patients was unknown in this cohort (Fig. 1D). After the family members of the proband were investigated, 36 cases of asymptomatic carriers were found, including 16 men and 20 women. The mean age of carriers was (35.17 ± 16.00) years old (range: 12–68 years). Given that the cumulative incidence was over 95% at age 60 years,[13,14] 14 asymptomatic carriers over 60 years old were found, including 6 men and 8 women.

Clinical Features

Parkinsonism is a prominent feature of CRD, including rigidity, bradykinesia, postural instability, and/or resting tremor. About 46.0% (46/100) patients reported parkinsonism as the initial symptom, 38.6% patients presented with cognitive impairment, 11.8% patients were accompanied by dysphagia, and dysarthria was observed in 17.0% patients. Only 8.0% of patients had dizziness or headache as the first symptom. During the course, most patients had dementia (85.1%) and parkinsonism (76.2%), followed by dysarthria (65.4%), personality and behavior changes (57.0%), dysphagia (47.5%), and depression/anxiety (42.0%); very few patients developed emotional liability (22.1%) and epilepsy (13.9%, presented as generalized seizures). Physical examination of the patient revealed that the pyramidal tract was prominently involved (88.4%), including hyperreflexia (72.1%), positive extensor plantar response (68.6%), and increased muscle tone (rigidity and spasticity, 61.6%). In addition, cerebellar ataxia was common (69.7%, 39.5% positive finger-nose test, 30.3% poor alternating movements, 48.7% positive heel–knee-shin test, and 23.7% positive Romberg sign, Table 1); some patients were accompanied by decreased muscle strength (40.0%, 17.6% with unilateral involvement and 22.4% with bilateral involvement, Table 1). Among the 36 patients with decreased muscle strength, one patient had a left muscle strength grade of 0 (Medical Research Council scale), two patients had a lower limb muscle strength grade of 2, and the remaining patients all had mild muscle weakness (grade 4). Besides, some patients underwent cranial nerve physical examination, and 27.6% of patients were found to have positive symptoms and signs (mainly 16.1% of patients had weakened gag reflex, 8.0% had restricted eye movement, and 4.6% had central facial paralysis; the remaining signs are presented in Table 1). A few patients had autonomic dysfunction (15.3%, mainly abnormal urination and defecation, Table 1) and decreased sensation (10.5%) (Fig. 1F).

Some patients received relevant laboratory tests, and the results showed that 31.5% (17/54) of the patients had abnormal EEG, mainly including mildly abnormal EEG (poor rhythm regulation and amplitude modulation, slow wave abnormalities), or epileptiform abnormal discharge. About 34.4% patients had abnormal EMG, mostly manifesting as slowed motor or sensory nerve conduction velocity, decreased nerve conduction amplitude, and nerve conduction delay; one patient showed abnormal bilateral visual conduction pathways (bilateral visual poor differentiation of evoked potential P100 waveform, poor reproducibility, prolonged latency). About 46.5% of

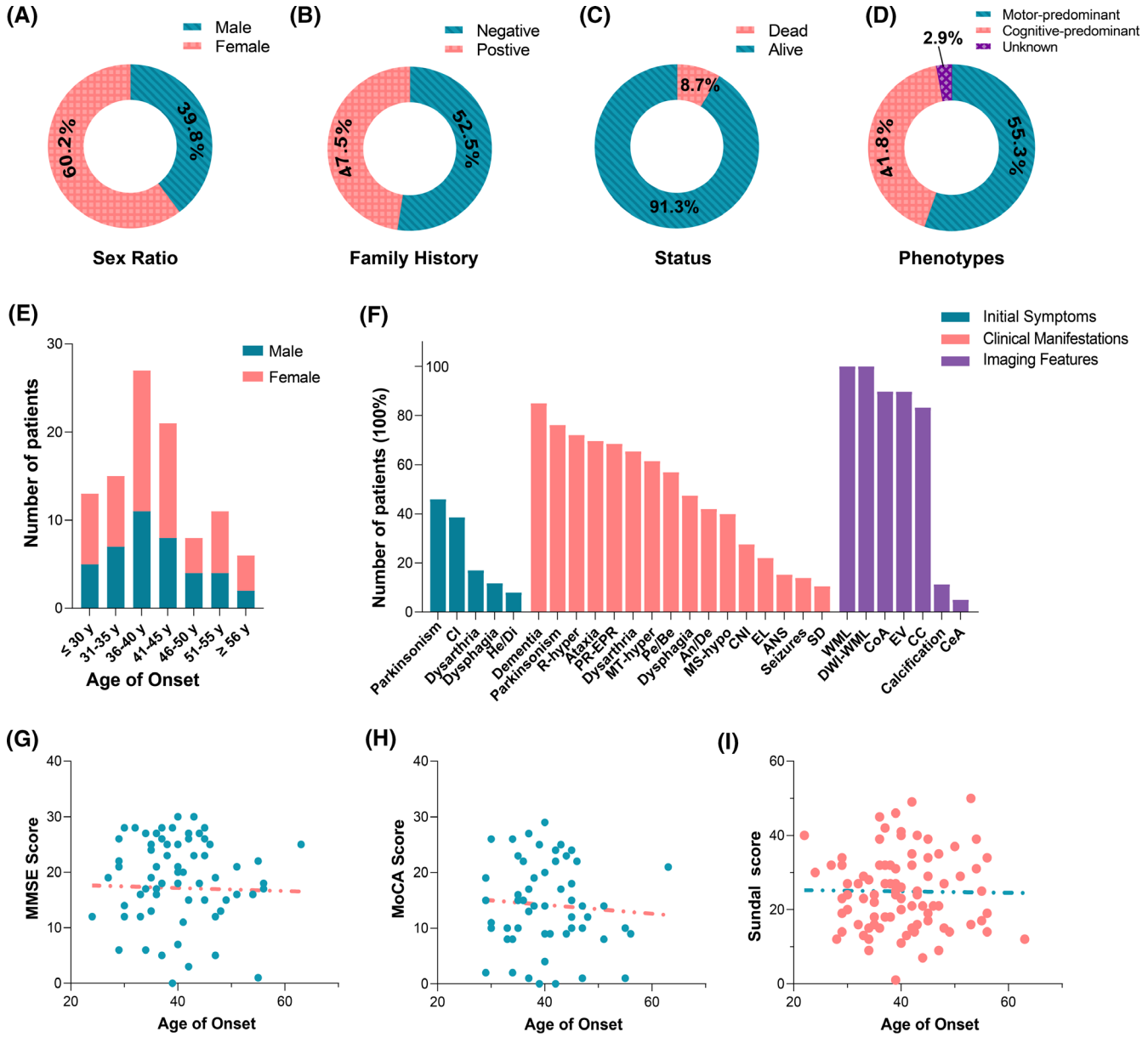

FIG. 1. Clinical features of colony-stimulating factor 1 receptor-related disorder (CRD) patients in China. **(A)** Sex ratio of CRD patients in China. **(B)** Family history of CRD patients in China. **(C)** Status of CRD patients in China. **(D)** Age of onset of Chinese CRD patients. **(E)** Phenotypes of Chinese CRD patients. **(F)** Clinical and imaging features of CRD patients in China. CI: cognitive impairment, PP: pseudobulbar palsy, He/Di: headache/dizziness, Pe/Be: personality/behavior changes, An/De: anxiety/depression; R-hyper: hyperreflexia, PR-EPR: pathologic reflex-extensor plantar response, MT-hyper: increased muscle tone, MS-hypo: decreased muscle strength, CNI: cranial nerve involvement, ANS: autonomic nervous system involvement, SD: sensation disturbance; WML: white matter lesions, DWI-WML: DWI white matter hyperintensity, CoA: cortical atrophy, EV: enlarged ventricles, CC: abnormal signal in the corpus callosum, CeA: cerebellum atrophy. **(G)** The relationship between Mini-Mental State Examination (MMSE) score and age of onset. **(H)** The relationship between Montreal Cognitive Assessment (MoCA) score and age of onset. **(I)** The relationship between Sundal score and age of onset. [Color figure can be viewed at wileyonlinelibrary.com]

patients had abnormalities in test of cerebrospinal fluid, manifesting as increased intracranial pressure (220–240mmH_2O, 230 ± 14.14 mmH_2O), or increased protein content (0.45–0.73 g/L, 0.58 ± 0.13 g/L). A total of 22 patients were examined for cerebrospinal fluid oligoclonal bands, only one patient (P110) was positive, and the rest were negative. Cognitive impairment was evaluated by MMSE and MoCA scores, and the average scores were 20.0 (10.8) and (14.16 ± 7.80), respectively; neither score was correlated with the age of onset (Fig. 1G,H).

Imaging Features

Brain MRI showed white matter changes in 100% of patients (Fig. 2A and white matter hyperintensities in diffusion-weighted imaging (DWI) sequences, Fig. 2B). The second most common imaging changes included

TABLE 1 *Clinical and genetic characteristics of colony-stimulating factor 1 receptor (CSF1R)-related disorder in China*

Variable	Total	Sex				Mutation Type			
		Male	Female	Value	*P*	Missense	Null	Value	*P*
Total (N[%])	103/103 (100.0)	41/103 (39.8)	62/103 (60.2)	-	-	74/103 (71.8)	29/103 (28.2)	-	-
AAO (mean ± s)	40.75±8.58	40.76±8.21	40.74±8.89	0.008[d]	0.993	40.58±8.75	41.16±8.26	-0.309[d]	0.758
AAD (Mdn[IQR])	41.0 (7.0)	43.0 (–)	40.0 (8.5)	−0.516[e]	0.606	39.0 (6.0)	43.5 (-)	−1.464[e]	0.143
Duration (Mdn[IQR])	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	−0.214[e]	0.831	2.0 (2.0)	1.5 (1.5)	−0.604[e]	0.546
Family history (N[%])	48/101 (47.5)	18/41 (43.9)	30/60 (50.0)	0.363[a]	0.547	36/72 (50.0)	12/29 (41.4)	0.616[a]	0.433
Initial symptoms (N[%])									
Cognitive impairment	39/101 (38.6)	16/41 (39.0)	23/60 (38.3)	0.005[a]	0.944	22/72 (30.6)	17/29 (58.6)	6.870[a]	0.009★
Parkinsonism	46/100 (46.0)	19/40 (47.5)	27/60 (45.0)	0.060[a]	0.806	36/72 (50.0)	10/28 (35.7)	1.656[a]	0.198
Dysphagia	12/102 (11.8)	9/61 (14.8)	3/41 (7.3)	0.6988[b]	0.407	8/73 (11.0)	4/29 (13.8)	0.004[b]	0.952
Dysarthria	17/100 (17.0)	13/60 (21.7)	4/40 (10.0)	2.315a	0.128	10/72 (13.9)	7/28 (25)	1.064[b]	0.302
Headache/dizziness	8/100 (8.0)	2/40 (5.0)	5/60 (10.0)	0.277[b]	0.598	8/72 (100.0)	0	2.040[b]	0.066
Clinical features during the course of disease development (N[%])									
Personality/behavior	57/100 (57.0)	18/41 (43.9)	39/59 (66.1)	4.864[a]	0.027★	42/71 (59.2)	15/29 (51.7)	0.464[a]	0.496
Cognitive impairment	86/101 (85.1)	34/41 (82.9)	52/60 (86.7)	0.269[a]	0.604	60/72 (83.3)	26/39 (89.7)	0.249[b]	0.618
Anxiety/depression	42/100 (42.0)	17/40 (42.5)	25/60 (41.7)	0.007[a]	0.934	30/71 (42.3)	12/29 (41.4)	0.006[a]	0.936
Parkinsonism	77/101 (76.2)	30/41 (73.2)	47/60 (78.3)	0.358[a]	0.549	54/72 (75.0)	23/29 (79.3)	0.212[a]	0.645
Seizures	14/101 (13.9)	6/41 (14.6)	8/60 (13.3)	0.035[a]	0.853	9/72 (12.5)	5/29 (17.2)	0.093[b]	0.76
Dysphagia	48/101 (47.5)	19/41 (46.3)	29/60 (48.3)	0.039[a]	0.844	34/72 (47.2)	14/29 (48.3)	0.009[a]	0.924
Dysarthria	53/81 (65.4)	19/31 (61.3)	34/50 (68.0)	0.381[a]	0.537	33/57 (57.9)	20/24 (83.3)	4.832[a]	0.028★
Emotional liability	17/77 (22.1)	8/32 (25.0)	9/45 (20.0)	0.272[a]	0.602	13/55 (23.6)	4/22 (18.2)	0.047[b]	0.828
Cranial nerve involvement	24/87 (27.6)	11/39 (28.2)	13/48 (27.1)	0.014[a]	0.907	17/61 (27.9)	7/26 (26.9)	0.008[a]	0.928
Blurry vision	1/87 (1.1)	1/39 (2.6)	0	1.619[c]	0.448	1/61 (1.6)	0	0.715[c]	1
Restricted eye movement	7/87 (8.0)	3/39 (7.7)	4/48 (8.3)	0[b]	1	4/61 (6.6)	3/26 (11.5)	0.123[b]	0.725
Horizontal nystagmus	2/87 (2.3)	1/39 (2.6)	1/48 (2.1)	0.022[c]	0.882	1/61 (1.6)	1/26 (3.8)	0.362[c]	0.511
Central facial paralysis	4/87 (4.6)	2/39 (5.1)	2/48 (4.2)	0[b]	1	3/61 (4.9)	1/26 (3.8)	0[b]	1
Peripheral facial paralysis	1/87 (1.1)	1/39 (2.6)	0	1.619[c]	0.448	0	1/26 (3.8)	2.443[c]	0.299

(Continues)

TABLE 1 *Continued*

Variable	Total	Sex				Mutation Type			
		Male	Female	Value	*P*	Missense	Null	Value	*P*
Sensorineural deafness	1/87 (1.1)	1/39 (2.6)	0	1.619[c]	0.448	1/61 (1.6)	0	0.715[c]	1
Weakened gag reflex	14/87 (16.1)	5/39 (12.8)	9/48 (18.8)	0.560[a]	0.454	11/61 (18.0)	3/26 (11.5)	0.190[b]	0.633
Shrugging or turning head weakly	2/87 (2.3)	2/39 (5.1)	0	3.267[c]	0.198	2/61 (3.3)	0	1.440[c]	1
Tongue deviation	2/87 (2.3)	0	2/48 (4.2)	2.417[c]	0.5	1/61 (1.6)	1/26 (3.8)	0.362[c]	0.511
Decreased muscle strength	34/85 (40.0)	15/39 (38.5)	19/46 (41.3)	0.071[a]	0.79	25/59 (42.4)	9/26 (34.6)	0.453[a]	0.501
Left upper limb	13/85 (15.3)	6/39 (15.4)	7/46 (15.2)	0[a]	0.983	8/59 (13.6)	5/26 (19.2)	0.117[b]	0.732
Left lower limb	23/85 (27.1)	8/39 (20.5)	15/46 (32.6)	1.565[a]	0.211	19/59 (32.2)	4/26 (15.4)	2.587[a]	0.108
Right upper limb	11/85 (12.9)	4/39 (10.3)	7/46 (15.2)	0.461[a]	0.497	7/59 (11.9)	4/26 (15.4)	0.009[b]	0.924
Right lower limb	26/85 (30.6)	17/46 (37.0)	9/39 (23.1)	1.915[a]	0.238	21/59 (35.6)	5/26 (19.2)	2.276[a]	0.131
Unilateral limb	15/85 (17.6)	4/46 (8.7)	11/39 (28.2)	5.528[a]	0.019★	10/59 (16.9)	5/26 (19.2)	0[b]	1
Bilateral limbs	19/85 (22.4)	15/46 (32.6)	4/39 (10.3)	6.076[a]	0.014★	15/59 (25.4)	4/26 (15.4)	1.048[a]	0.306
Increased muscle tone	53/86 (61.6)	23/39 (59.0)	30/47 (63.8)	0.212[a]	0.645	39/61 (63.9)	14/25 (56.0)	0.472[a]	0.492
Hyperreflexia	62/86 (72.1)	29/39 (74.4)	33/47 (70.2)	0.182[a]	0.67	41/61 (67.2)	21/25 (84.0)	2.484[a]	0.115
Pathologic reflex-extensor plantar response	59/86 (68.6)	28/39 (71.8)	31/47 (66.0)	0.337[a]	0.561	41/61 (67.2)	18/25 (72.0)	0.189[a]	0.664
Sensation disturbance	8/76 (10.5)	4/35 (11.4)	4/41 (9.8)	0[b]	1	7/53 (13.2)	1/23 (4.3)	0.562[b]	0.454
Ataxia	53/76 (69.7)	21/35 (60.0)	32/41 (78.0)	2.914[a]	0.088	35/55 (63.6)	18/21 (85.7)	3.510[a]	0.061
Left finger-nose test	30/76 (39.5)	10/35 (28.6)	20/41 (48.8)	3.228[a]	0.072	16/55 (29.1)	14/21 (66.7)	8.981[a]	0.003★
Right finger-nose test	30/76 (39.5)	10/35 (28.6)	20/41 (48.8)	3.228[a]	0.072	16/55 (29.1)	14/21 (66.7)	8.981[a]	0.003★
Left heel-knee-shin test	22/76 (28.9)	8/35 (22.9)	14/41 (34.1)	1.170[a]	0.279	15/55 (27.3)	7/21 (33.3)	0.271[a]	0.602
Right heel-knee-shin test	23/76 (30.3)	8/35 (22.9)	15/41 (36.6)	1.686[a]	0.194	16/55 (29.1)	7/21 (33.3)	0.130[a]	0.719
Left alternate motion	37/76 (48.7)	13/35 (37.1)	24/41 (58.5)	3.459[a]	0.063	25/55 (45.5)	12/21 (57.1)	0.831[a]	0.362
Right alternate motion	37/76 (48.7)	14/35 (40.0)	23/41 (56.1)	1.958[a]	0.162	25/55 (45.5)	12/21 (57.1)	0.831[a]	0.362
Romberg sign	18/76 (23.7)	8/35 (22.9)	10/41 (24.4)	0.025[a]	0.875	13/55 (23.6)	5/21 (23.8)	0[b]	1
ANS	13/85 (15.3)	7/38 (18.4)	6/47 (12.8)	0.519[a]	0.471	8/60 (13.3)	5/25 (20.0)	0.200[b]	0.655
Frequent urination	1/85 (1.2)	1/38 (2.6)	0	1.625[a]	0.447	1/60 (1.7)	0	0.702[c]	1
Urgent micturition	1/85 (1.2)	1/38 (2.6)	0	1.625[a]	0.447	1/60 (1.7)	0	0.702[c]	1

(Continues)

TABLE 1 *Continued*

Variable	Total	Sex				Mutation Type			
		Male	Female	Value	*P*	Missense	Null	Value	*P*
Difficulty urinating	1/85 (1.2)	1/38 (2.6)	0	1.625[a]	0.447	0	1/25 (4.0)	2.476[c]	0.294
Uracratia	9/85(10.6)	4/38 (10.5)	5/47 (10.6)	0[b]	1	5/60 (8.3)	4/25 (16.0)	0.435[b]	0.509
Constipation	2/85 (2.4)	1/38 (2.6)	1/47 (2.1)	0.023[c]	1	2/60 (3.3)	0	1.413[c]	0.235
Fecal incontinence	4/85(3.9)	2/38 (5.3)	2/47 (4.3)	0[b]	1	2/60 (3.3)	2/25 (8.0)	0.132[b]	0.716
Sweatless	1/85 (1.2)	1/38 (2.6)	0	1.625[a]	0.447	1/60 (1.7)	0	0.702[c]	1
Cognitive assessment									
MMSE (Mdn[IQR])	20.0 (10.8)	23.0 (10.0)	17.0 (9.0)	−2.018[e]	0.044★	21.0 (9.0)	16.0 (14.0)	−1.280[e]	0.2
MoCA (mean ± s)	14.16±7.80	16.36±7.89	11.90±7.16	2.197[d]	0.032★	15.02±8.75	41.16±8.26	1.413[d]	0.164
Brain imaging features (N[%])									
White matter lesion	97/97 (100.0)	41/41 (100.0)	56/56 (100.0)	-	-	68/68 (100.0)	29/29 (100.0)	-	-
Thinning of the corpus callosum	80/96 (83.3)	34/41 (82.9)	46/55 (83.6)	0.009[a]	0.926	51/67 (80.6)	26/29 (89.7)	0.632[b]	0.426
Cerebellum	5/98 (5.1)	2/41 (4.9)	3/57 (5.3)	0[b]	1	5/69 (7.2)	0	0.971[b]	0.325
Enlarged ventricles	87/98 (89.7)	37/41 (90.2)	50/56 (89.3)	0[b]	1	60/68 (88.2)	27/29 (93.1)	0.128[b]	0.721
Cortical atrophy	88/98 (89.8)	37/41 (90.2)	51/57 (89.5)	0[b]	1	60/69 (88.2)	28/29 (96.6)	1.138[b]	0.286
Calcifications	8/71 (11.3)	6/30 (20.0)	2/41 (4.9)	2.294[b]	0.107	5/10 (10.0)	3/21 (14.3)	0.012[b]	0.912
MRI severity scores									
Total score scores (mean ± s)	24.40±10.66	21.93±10.57	26.55±10.37	−2.070[d]	0.041★	23.92±10.62	25.38±10.84	−0.604[d]	0.548
WMLs scores (mean ± s)	18.24±8.31	16.00±7.62	20.19±8.47	−2.425[d]	0.017★	17.76±8.32	19.21±8.35	−0.764[d]	0.447
Atrophy scores (mean ± s)	5.69±2.91	5.54±3.24	5.83±2.62	−0.469[d]	0.64	5.69±3.00	5.69±2.78	0.008[d]	0.994
Auxiliary inspections (N[%])									
EMG and/or NCS abnormal	11/32 (34.4)	4/10 (40.0)	7/22 (31.8)	0.202[c]	0.653	9/23 (39.1)	2/9 (22.2)	0.860[c]	0.354
EEG abnormal	17/54 (31.5)	5/25 (20.0)	12/29 (41.4)	2.845[a]	0.092	12/38 (31.6)	5/16 (31.3)	0.001[a]	0.981
CSF abnormal	20/43 (46.5)	13/18 (72.2)	7/25 (28.0)	8.226[a]	0.004★	14/33 (42.4)	6/10 (60.0)	0.377[b]	0.539
Oligoclonal banding negative	21/22 (95.5)	10/11 (90.9)	11/11 (100.0)	0[b]	1	14/14 (100)	7/8 (87.5)	0.084[b]	0.772

Variable	Mutation site				Phenotypes			
	Ig domain	TKD	Value	*P*	Motor-predominant	Cognitive-predominant	Value	*P*
Total (N[%])	11/103 (10.7)	92/103 (89.3)	-	-	57/100 (57.0)	43/100 (43.0)	-	-

(Continues)

TABLE 1 *Continued*

Variable	Mutation site				Phenotypes			
	Ig domain	TKD	Value	*P*	Motor-predominant	Cognitive-predominant	Value	*P*
AAO (mean ± s)	40.00±11.34	40.40±8.22	1.267[d]	0.208	39.32±8.24	42.36±8.69	−1.787[d]	0.077
AAD (Mdn[IQR])	-	41.0 (7.0)	-	-	40.8 (8.0)	41 (-)	0[e]	1
Duration (Mdn[IQR])	2.0 (4.0)	2.0 (2.0)	−1.067[e]	0.286	2.0 (1.0)	1.5 (2.0)	−0.219[e]	0.827
Family history (N[%])	2/10 (20.0)	46/91 (50.5)	2.258[b]	0.133	22/57 (38.6)	25/42 (59.5)	4.247[a]	0.039★
Initial symptoms (N[%])								
Cognitive impairment	6/10 (60.0)	33/91 (36.3)	1.257[b]	0.262	5/56 (8.9)	34/43 (79.1)	50.121[a]	<0.001★
Parkinsonism	4/9 (44.4)	42/91 (46.2)	0[b]	1	42/56 (75.0)	4/42 (9.5)	41.311[a]	<0.001★
Dysphagia	2/10 (20)	10/92 (10.9)	0.112[b]	0.738	9/57 (15.8)	3/43 (7.0)	1.803[a]	0.179
Dysarthria	3/9 (33.3)	14/91 (15.3)	0.814[b]	1	12/56 (21.4)	5/42 (11.9)	1.518[a]	0.218
Headache/dizziness	0	8/91 (8.8)	0.080[b]	0.777	7/56 (12.5)	1/42 (2.4)	2.067[b]	0.15
Clinical features during the course of disease development (N[%])								
Personality/behavior	4/10 (40.0)	53/90 (58.9)	0.653[b]	0.419	31/56 (55.4)	26/43 (60.5)	0.260[a]	0.619
Cognitive impairment	9/10 (90.0)	77/91 (84.6)	0[b]	1	45/57 (78.9)	40/43 (93.0)	3.809[a]	0.051
Anxiety/depression	4/10 (40.0)	38/90 (42.2)	0[b]	1	21/57 (36.8)	20/42 (47.6)	1.158[a]	0.282
Parkinsonism	7/10 (70.0)	70/91 (76.9)	0[b]	1	53/57 (93.0)	23/43 (53.5)	20.960[a]	<0.001★
Seizures	4/10 (40.0)	10/91 (11.0)	4.154[b]	0.042★	6/57 (10.5)	7/43 (16.3)	0.717[a]	0.397
Dysphagia	5/10 (50.0)	43/91 (47.3)	0[b]	1	30/57 (52.6)	17/43 (39.5)	1.688[a]	0.194
Dysarthria	6/7 (85.7)	47/74 (63.5)	0.585[b]	0.444	38/49 (77.6)	15/32 (46.9)	8.054[a]	0.005★
Emotional liability	0/5 (0.0)	17/72 (23.6)	0.453[b]	0.501	13/47 (27.7)	4/30 (13.3)	2.185[a]	0.139
Cranial nerve involvement	3/10 (30.0)	21/77 (27.3)	0[b]	1	18/53 (34.0)	6/34 (17.6)	2.760[a]	0.097
Blurry vision	0	1/77 (1.3)	0.246[c]	1	1/53 (1.9)	0	0.999[c]	1
Restricted eye movement	0	7/77 (9.1)	1.787[c]	1	6/53 (11.3)	1/34 (2.9)	0.996[b]	0.318
Horizontal nystagmus	0	2/77 (2.6)	0.494[c]	1	0	2/34 (5.9)	3.832[c]	0.15
Central facial paralysis	0	4/77 (5.2)	1.002[c]	1	4/53 (7.5)	0	1.244[b]	0.265
Peripheral facial paralysis	0	1/77 (1.3)	0.246[c]	1	0	1/34 (2.9)	1.897[c]	0.391
Sensorineural deafness	0	1/77 (1.3)	0.246[c]	1	1/53 (1.9)	0	0.999[c]	1
Weakened gag reflex	2/10 (20.0)	12/77 (15.6)	0[b]	1	11/53 (20.8)	3/34 (8.8)	2.184[a]	0.139

(Continues)

TABLE 1 *Continued*

Variable	Mutation site				Phenotypes			
	Ig domain	TKD	Value	*P*	Motor-predominant	Cognitive-predominant	Value	*P*
Shrugging or turning head weakly	0	2/77 (2.6)	0.494[c]	1	2/53 (3.8)	0	2.013[c]	0.518
Tongue deviation	0	2/77 (2.6)	0.494[c]	1	2/53 (3.8)	0	2.013[c]	0.518
Decreased muscle strength	2/9 (22.2)	32/76 (42.1)	0.627[b]	0.429	25/52 (48.1)	9/33 (27.3)	3.641[a]	0.056
Left upper limb	2/9 (22.2)	11/76 (14.5)	0.015[b]	0.904	9/52 (17.3)	4/33 (12.1)	0.419[a]	0.517
Left lower limb	2/9 (22.2)	21/76 (27.6)	0[b]	1	17/52 (32.7)	6/33 (18.2)	2.154[a]	0.142
Right upper limb	1/9 (11.1)	10/76 (13.2)	0[b]	1	8/52 (15.4)	3/33 (9.1)	0.261[b]	0.609
Right lower limb	1/9 (11.1)	25/76 (32.9)	0.919[b]	0.338	19/52 (36.5)	7/33 (21.2)	2.234[a]	0.135
Unilateral limb	1/9 (11.1)	14/76 (18.4)	0.007[b]	0.935	11/52 (21.2)	4/33 (12.1)	1.133[a]	0.287
Bilateral limbs	1/9 (11.1)	18/76 (23.7)	0.188[b]	0.665	14/52 (26.9)	5/33 (15.2)	1.612[a]	0.204
Increased muscle tone	6/10 (60.0)	47/76 (61.8)	0[b]	1	42/53 (79.2)	11/33 (33.3)	18.128[a]	<0.001★
Hyperreflexia	10/10 (100.0)	52/76 (68.4)	2.951[b]	0.086	43/53 (81.1)	19/33 (57.6)	5.608[a]	0.018★
Pathologic reflex-extensor plantar response	8/10 (80.0)	51/76 (67.1)	0.215[b]	0.643	42/53 (79.2)	17/33 (51.5)	7.261[a]	0.007★
Sensation disturbance	1/6 (16.7)	7/70 (10.0)	0[b]	1	4/47 (8.5)	5/50 (16.7)	0.522[b]	0.47
Ataxia	5/6 (83.3)	48/70 (68.6)	0.086[b]	0.77	36/46 (78.3)	17/30 (56.7)	4.012[a]	0.045★
Left finger-nose test	4/6 (66.7)	26/70 (37.1)	0.970[b]	0.325	19/46 (41.3)	11/30 (36.7)	0.163[a]	0.686
Right finger-nose test	4/6 (66.7)	26/70 (37.1)	0.970[b]	0.325	20/46 (43.5)	10/30 (33.3)	0.782[a]	0.376
Left heel-knee-shin test	2/6 (33.3)	20/70 (28.6)	0[b]	1	15/46 (32.6)	7/30 (23.3)	0.760[a]	0.383
Right heel-knee-shin test	2/6 (33.3)	21/70 (30.0)	0[b]	1	16/46 (34.8)	7/30 (23.3)	1.128[a]	0.288
Left alternate motion	1/6 (16.7)	36/70 (51.4)	1.463[b]	0.227	26/46 (56.5)	11/30 (36.7)	2.865[a]	0.091
Right alternate motion	1/6 (16.7)	36/70 (51.4)	1.463[b]	0.227	27/46 (58.7)	10/30 (33.3)	4.675[a]	0.031★
Romberg sign	1/6 (16.7)	17/70 (24.3)	0[b]	1	14/46 (30.4)	4/30 (13.3)	2.938[a]	0.087
ANS	1/10 (10.0)	12/75 (16.0)	0.001[b]	0.978	8/53 (15.1)	5/32 (15.6)	0[b]	1
Frequent urination	0	1/75 (1.3)	0.252[c]	1	1/53 (1.9)	0	0.952[c]	1
Urgent micturition	0	1/75 (1.3)	0.252[c]	1	1/53 (1.9)	0	0.952[c]	1
Difficulty urinating	1/10 (10.0)	0	4.372[c]	0.118	1/53 (1.9)	0	0.952[c]	1

(Continues)

TABLE 1 *Continued*

Variable	Mutation site				Phenotypes			
	Ig domain	TKD	Value	*P*	Motor-predominant	Cognitive-predominant	Value	*P*
Uracratia	0	9/75 (12.0)	0.374[b]	0.541	4/53 (7.5)	5/32 (15.6)	0.654[b]	0.419
Constipation	0	2/75 (2.7)	0.507[c]	1	2/53 (3.8)	0	1.918[c]	0.525
Fecal incontinence	0	4/75 (5.3)	1.027[c]	1	1/53 (1.9)	3/32 (9.4)	1.104[b]	0.293
Sweatless	0	1/75 (1.3)	0.252[c]	1	1/53 (1.9)	0	0.952[c]	1
Cognitive assessment								
MMSE (Mdn[IQR])	5 (27.5)	20.0 (9.0)	−0.902[e]	0.367	21.0 (9.0)	17.5 (14.0)	−1.606[e]	0.108
MoCA (mean ± s)	-	14.76±7.25	-	-	15.32±7.1	12.67±8.55	1.259[d]	0.214
Brain imaging features (N[%])								
White matter lesion	11/11 (100.0)	86/86 (100.0)	-	-	52/52 (100)	43/43 (100)	-	-
Thinning of the corpus callosum	10/11 (90.9)	70/85 (82.4)	0.082[b]	0.774	46/52 (88.5)	33/42 (78.6)	1.695[a]	0.193
Cerebellum	3/11 (27.3)	2/87 (2.3)	7.950[b]	0.005★	4/52 (7.7)	0 (0)	1.809[b]	0.179
Enlarged ventricles	8/11 (72.7)	79/86 (91.9)	2.069[b]		47/52 (90.4)	40/43 (93.0)	0.008[b]	0.928
Cortical atrophy	9/11 (81.8)	79/87 (90.8)	0.159[b]	0.69	49/52 (94.2)	38/43 (88.4)	0.426[b]	0.514
Calcifications	3/8 (37.5)	5/63 (7.9)	3.601[b]	0.058	5/45 (11.1)	3/25 (12.0)	0[b]	1
MRI severity scores								
Total score scores (mean ± s)	26.10±11.92	24.18±10.55	0.534[d]	0.594	26.92±10.29	21.68±10.53	2.319[d]	0.023★
WMLs scores (mean ± s)	20.90±8.29	17.90±8.31	1.077[d]	0.285	19.96±8.30	16.26±8.01	2.083[d]	0.04★
Atrophy scores (mean ± s)	4.70±3.83	5.82±2.78	−1.148[d]	0.254	6.33±2.68	5.13±2.94	1.976[d]	0.051
Auxiliary inspections (N[%])								
EMG and/or NCS abnormal	0	11/29 (37.9)	2.687[c]	0.101	10/21 (47.6)	1/11 (9.1)	3.196[b]	0.074
EEG abnormal	3/7 (42.9)	14/47 (29.8)	0.067[b]	0.796	7/29 (24.1)	9/24 (37.5)	1.113[a]	0.292
CSF abnormal	2/4 (50.0)	18/39 (42.6)	0[b]	1	13/27 (48.1)	6/15 (40.0)	0.258[a]	0.611
Oligoclonal banding negative	2/3 (66.7)	19/19 (100.0)	1.176[c]	0.136	14/14 (100.0)	7/8 (87.5)	0.084[b]	0.772

★$P < 0.05$ represents a difference, Mann-Whitney *U* test was used to compare means of groups of variables skewly distributed and were summarized by median (Mdn) and interquartile range (median [interquartile range, IQR]).
[a]$\chi 2$ test.
[b]$\chi 2$ test with continuity correction.
[c]Fisher.
[d]t test.
[e]Mann–Whitney *U* test.
Abbreviations: AAD, age of death; AAO, age of onset; ANS, autonomic nervous system involvement; Calcifications, calcifications on CT scan; Cerebellum, abnormal signal in cerebellum or cerebellar atrophy; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; WMLs scores, white matter lesions scores.

cortical atrophy (89.8%, Fig. 2A), enlarged ventricles (89.7%, Fig. 2A), and corpus callosum thinning or abnormal signal (83.3%, Fig. 2A). Only a small proportion of patients had cerebellar atrophy (5.1%, Fig. 2A, Patient 4). The MRI features of CRD patients showed high heterogeneity, including: (1) predominant atrophy but little white matter lesions (Figs. 2A and 3, Patient 1); (2) predominant leukoencephalopathy in frontoparietal lobes (Fig. 2A, Patient 2); (3) predominant leukoencephalopathy in temporooccipital lobes (Fig. 2A, Patient 3); (4) diffusive leukoencephalopathy (Fig. 2A, Patient 4).

Besides, some patients showed typical point-like calcification on head CT (11.3%, 8/71, Fig. 2C,D). Compared to healthy controls, patients with CRD showed diffusive hypometabolism, especially in the frontoparietal lobes in [^{18}F]FDG-PET/CT (Fig. 2E) and extensive neuroinflammation, especially in the thalamus and midbrain revealed by [^{18}F]DPA714-PET/CT (Fig. 2F). The severity of the patient's MRI was scored (24.40 ± 10.66) points, of which the white matter lesion score was (18.24 ± 8.31) points, and the atrophy score was (5.69 ± 2.91) points. There was no statistically significant correlation between patients' Sundal scores and age of onset (Fig. 1I).

CSF1R Mutations

A total of 66 CSF1R variants were detected in 92 probands, 22 of which were unreported variants (Fig. 4A, red font). All *CSF1R* variants can be divided into 41 missense mutations and 25 null mutations (including 5 nonsense mutations, 4 full-frame mutations, 8 frameshift mutations, and 8 splicing mutations) (Fig. 4B). Among all probands, the exon with the highest mutation frequency was exon 18 (34.78%, 32/92) (Fig. 4C), and c.2381 T > C/p. I794T was the most common mutation, as 15 of the 92 (16.30%) probands carried this mutation. The six most common mutations are shown in Figure 4D.

Sex Differences in Chinese CRD Patients

This study summarized the sex differences in CRD in China (Table 1). Compared with male patients, female patients had a higher incidence of personality/behavioral changes ($P = 0.027$) and a lower rate of CSF abnormalities ($P = 0.004$). Decreased muscle strength in unilateral limb is more common in female patients, whereas in male patients bilateral limbs are more likely to be affected ($P = 0.019$). The MMSE and MoCA scores of female patients were significantly lower than those of male patients ($P = 0.044$, $P = 0.032$). Moreover, female patients had significantly higher white matter severity scores than male patients ($P = 0.041$).

Differences between Motor and Cognitive-Predominant Chinese CRD Patients

Participants were also categorized based on their predominant symptoms. Compared to motor-predominant ones, cognitive-predominant patients were prone to have a family history ($P = 0.039$), and they had lower scores on Sundal scores ($P = 0.023$), especially in white matter lesion score ($P = 0.040$).

Phenotype–Genotype Relationship of CRD in China

The results of the relationship between phenotypes and genotypes are summarized in Table 1. Compared to patients with missense mutations, patients with null mutations had a higher proportion of cognitive impairment as the initial manifestation ($P = 0.009$). There were no statistical differences between patients with null mutations and those with missense mutations in terms of other clinical manifestations, neurological signs, laboratory tests, and imaging findings. Compared to patients with TKD mutations, those with Ig domain mutations were more likely to develop epilepsy during the course of the disease ($P = 0.042$). From an imaging perspective, the proportion of cerebellar atrophy in patients with Ig domain mutations was significantly higher than in patients with TKD mutations ($P = 0.005$).

Discussion

In this study, we demonstrated the phenotypic and genetic spectrum of 103 Chinese patients with *CSF1R*-related disorder (CRD). Besides, we analyzed sex differences and phenotype–genotype relationship in CRD, which might provide new clues for clinical diagnosis and treatment, as well as underlying mechanisms.

Chinese patients showed different features in clinical manifestations compared to foreign cohorts in previous studies, which mostly focused on Japanese and European populations.[11,13,15] For example, the proportion of cognitive impairment (38.6%) was the highest among the first manifestations, followed by parkinsonism (44.3%).[13] However, in our cohort, patients were more likely to start with parkinsonism rather than cognitive decline. Similarly, during the course of CRD, the proportion of parkinsonism (76.2%) was also higher than that reported in the foreign population (60.7%). Because it has been revealed that motor-predominant patients responded better to hematopoietic stem cell transplantation (HSCT), which was the only potential therapeutic effects to stabilize disease progression and improve survival,[31,32] Chinese patients might have better response to HSCT from this prospective.

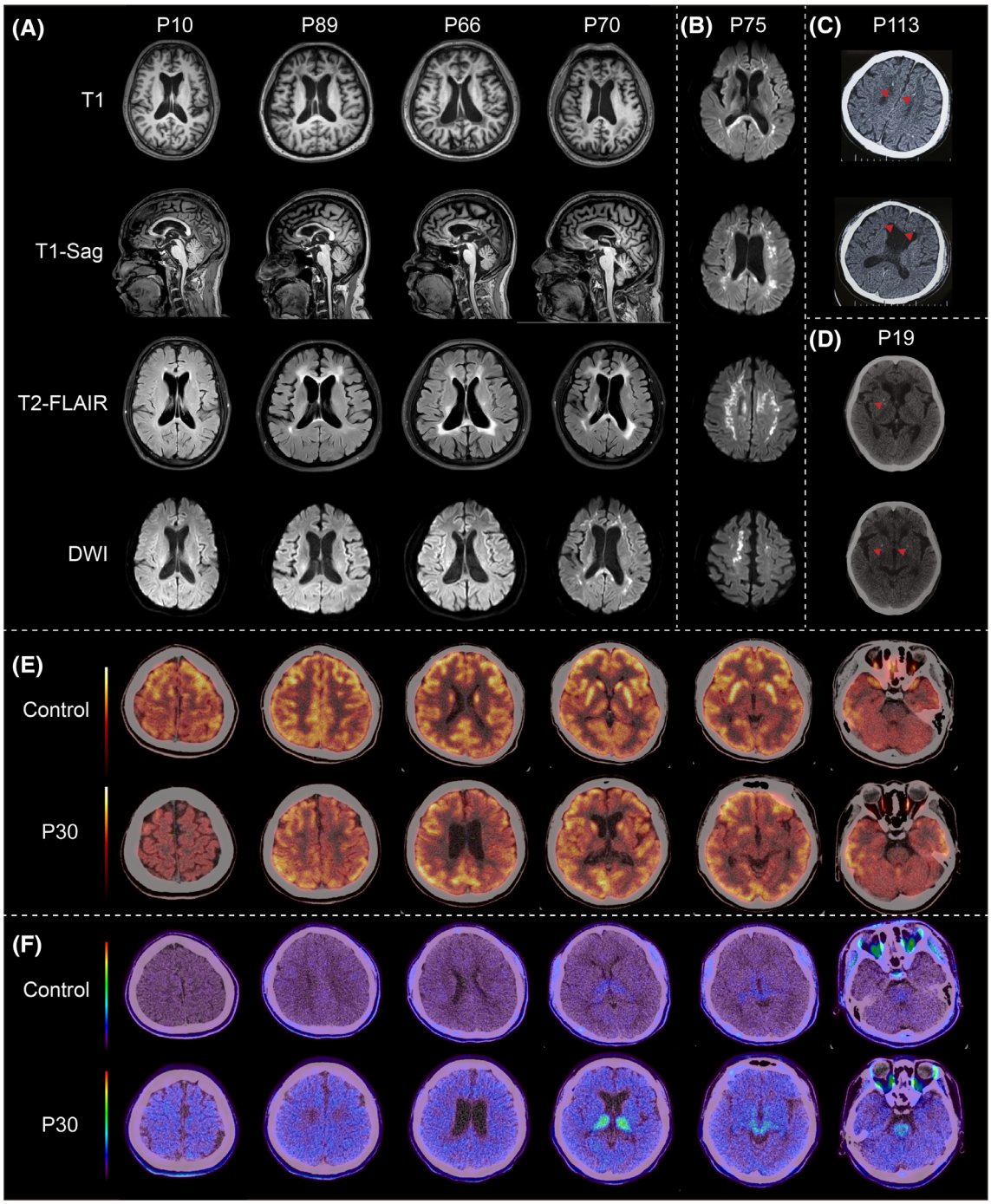

FIG. 2. Radiological features of colony-stimulating factor 1 receptor-related disorder (CRD) patients in China. **(A)** MRI characteristics. P10 was featured with enlarged ventricles, but little white matter lesion. He is a 40-year-old man with an age of onset (AAO) of 39, carrying c.2381 T > C/p.I794T mutation and characterized with cognitive decline. P89 was featured with frontoparietal white matter lesions, with prominent cognitive decline but no influence in movement; she is a 51-year-old female woman, 2-year duration, carrying the c.2703_2706del/p.T902Sfs mutation. P66 was characterized with temporooccipital demyelination, consistent with prominent parkinsonism in clincial manifestations; she is a 50-year-old woman carrying c.2473G > C/p.E825Q mutation with an AAO of 48. P70 with diffuse leukoencephalopathy manifested with both dementia and movement disorders, is a 39-year-old man, and carries c.2680_2692del/p.895_897del with 2-year duration. **(B)** Extensive diffusion-weighted imaging (DWI) hyperintensities in white matter of a CRD patient (P75). Male, 41 years old, carried c.2391 T > G/p.F797C mutation with prominent cognitive decline with an AAO of 40. **(C)** Punctuate calcification in white matters near the anterior horns of ventricles revealed by CT (triangles). Male (P113), 35 years old, with c.1939_1941del/p.V647del mutation. He started manifest with significant cognitive decline and parkinsonism at 35 and underwent MRI 9 months after onset. **(D)** Punctuate calcification in basal ganglia revealed by CT (triangles). Female (P19), 34 years old, carries c.2330G > A/p.R777Q mutation, mainly manifesting parkinsonism with an AAO of 33. **(E)** Diffuse hypometabolism in frontoparietal lobes revealed by [^{18}F]FDG-PET/CT. **(F)** Extensive neuroinflammation in the thalamus and the midbrain revealed by [^{18}F]DPA714-PET/CT. Images of (E) and (F) are all from a 39-year-old woman (P30) carrying the c.2567A > C/p.Y856S mutation with a duration of 2 years. The main clinical symptoms are bradykinesia and abnormal posture and balance. [Color figure can be viewed at wileyonlinelibrary.com]

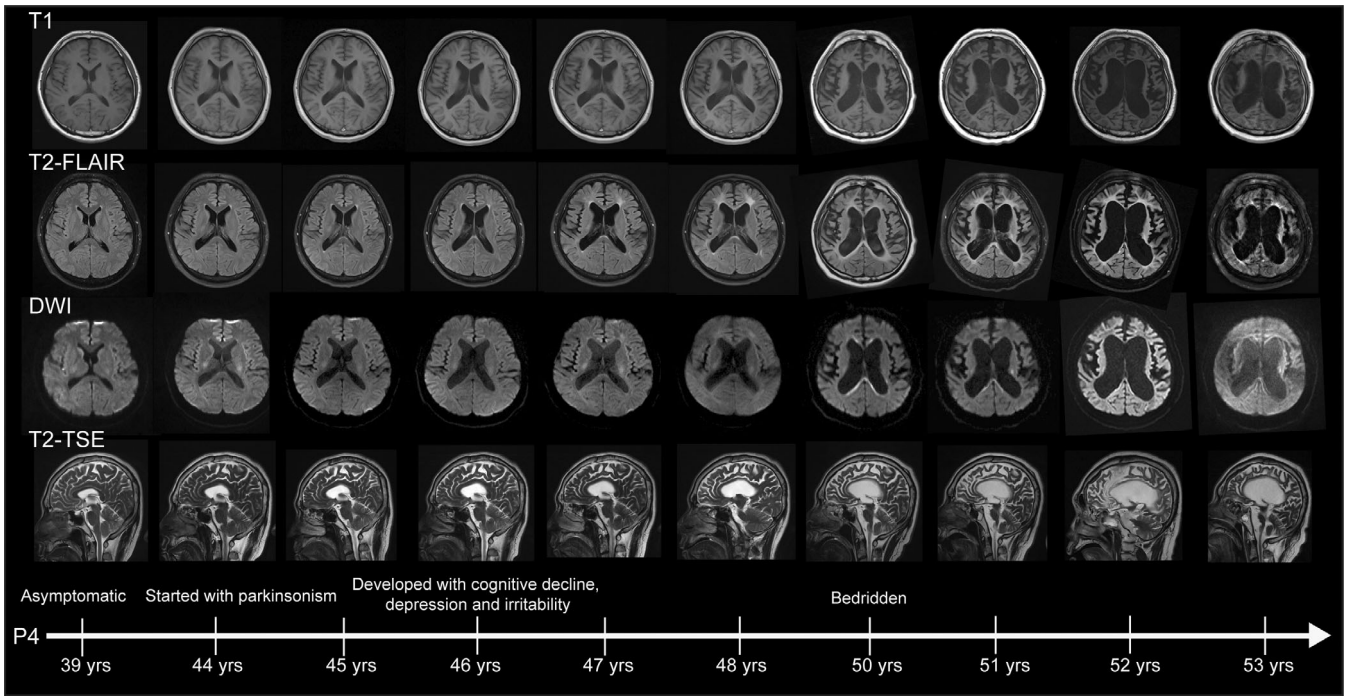

FIG. 3. Dynamic follow-up of magnetic resonance imaging (MRI) of a male CRD (colony-stimulating factor 1 receptor-related disorder) patient (P4) carrying the c.2342C > A/p.A781E mutation from asymptomatic stage to bedridden stage. The patient developed clinical symptoms at the age of 44, manifesting as parkinsonism. Two years later, he developed cognitive impairment, and his personality and behavior changed, manifesting into anxiety and irritability. Six years after the onset of the disease, the patient was completely bedridden.

Besides, autonomic involvement and peripheral neuropathy were rarely reported in patients from other regions, whereas in our cohort, 15.3% had autonomic symptoms and 34.4% were with peripheral EMG and/or CNV abnormality. These results, which indicate the clinical heterogeneity, also support the nomenclature of this illness as CSF1R-related disorder rather than CSF1R-related leukoencephalopathy.[8] However, it should be noted that these autonomic or peripheral abnormalities were all mild and non-specific to this disease. Besides, these autonomic dysfunctions in patients mostly occurred after cognitive decline and/or parkinsonism in late or terminal stage of the illness, and were closely related to cognitive deficit and/or parkinsonism.

Punctate calcification is one of the characteristic manifestations of CRD. Calcifications mostly occur in the white matter area of the frontal lobe near the anterior horn of the ventricles. They can be present in both patients and asymptomatic carriers with relatively stability in size and location, and they basically do not worsen, remit, or disappear with the course of the disease. However, compared with Japanese patients (53.8%),[13] the proportion of punctate calcifications in the brain was significantly lower in our patients (11.3%). This may be related to the wide application of thin-layer CT. In the retrospective study in Japan, the patients mostly received 1-mm thin-layer CT scans, whereas in this study, the CT scans conducted in the patients were all plain scans. Besides, sagittal reconstructions of CT and 7 T MRI are helpful to demonstrate calcifications.[33,34]

In addition, the DWI sequences of all patients in this study showed constant high signals in bilateral abnormal white matter, suggesting that abnormalities on the DWI sequences are an important clue for the diagnosis and differential diagnosis of CRD. DWI is more sensitive to reflect the changes in the microstructure of the white matter and can detect the changes in the white matter at an earlier stage than the T2-FLAIR sequences.

Our study revealed that many female patients were affected than male patients with a ratio of 1.51:1, and female patients manifested with more severe clinical and radiological manifestations, with lower cognitive scores, and higher white matter severity score. Previous studies also revealed that in patients from other countries, women had an earlier onset of (40 ± 10) years compared to men ([47 ± 11] years). Sex differences in CRD may be related to many factors. For one thing, as a primary microgliopathy,[4] significant sex differences in microglia development, maintenance of neurological homeostasis, and immune response[35] may lead to differences in the risk of pathogenesis and the pathogenic mechanisms of this genetic defect in different sexes. Besides, like other neurologic diseases with sex differences such as Parkinson's disease, Alzheimer's disease,[36] autism,[37] such differences may be closely

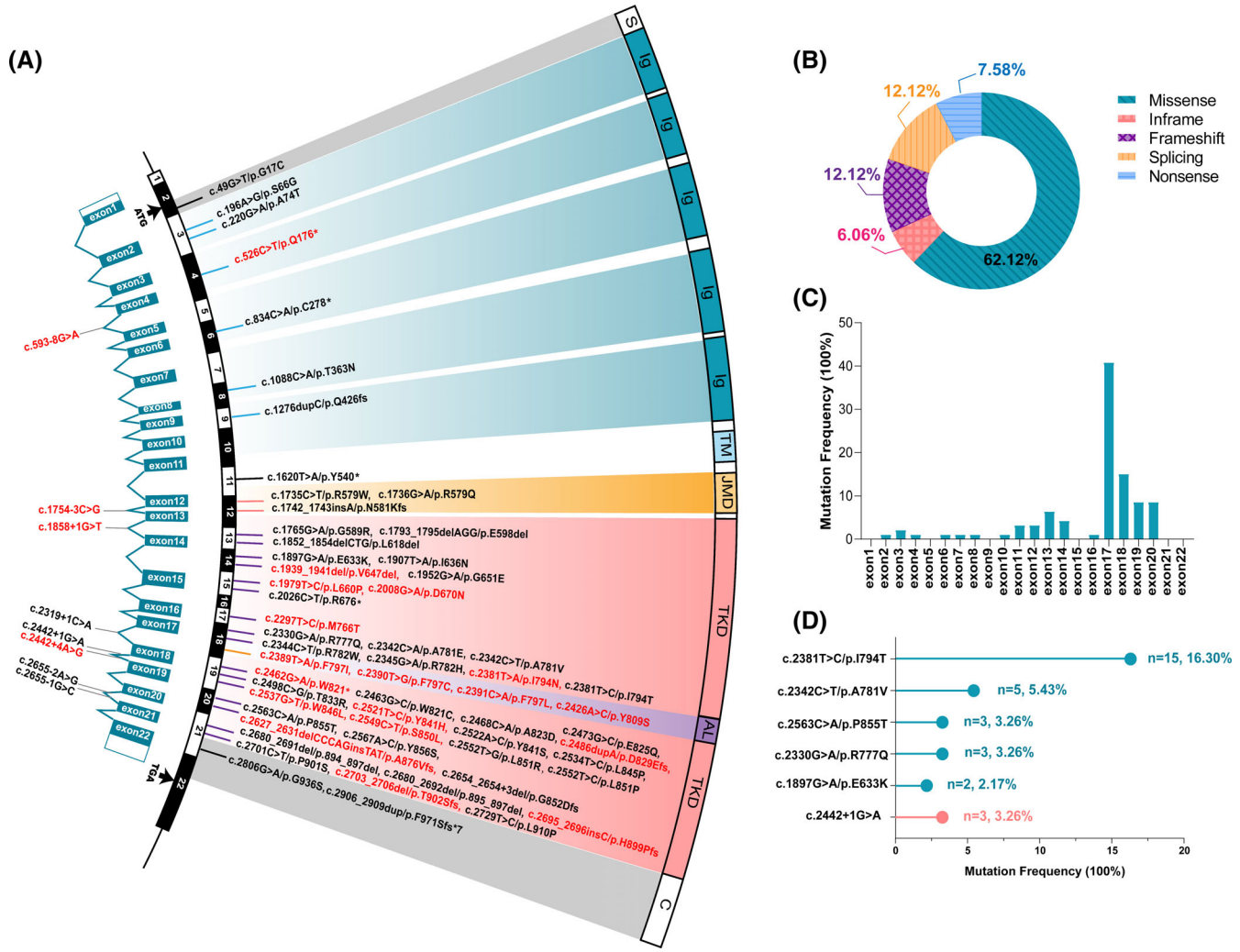

FIG. 4. Genetic characteristics of CRD (colony-stimulating factor 1 receptor-related disorder) patients in China. **(A)** Schematic representation of colony-stimulating factor 1 receptor (CSF1R) variants. *CSF1R* gene has 22 exons (transcript: NM_005211), including N-terminal signal peptide sequence (S), immunoglobulin-like domain (Ig), transmembrane domain (TM), juxtamembrane domain (JMD), tyrosine kinase domain (TKD, including an activation loop [AL]) and C-terminal sequence (C). The novel mutations are shown in red font, and previously reported mutations are shown in black fonts. **(B)** Mutation types of CSF1R gene in this study. **(C)** Mutation frequency of different CSF1R gene exons in probands. **(D)** The top six CSF1R variants with mutation frequency among the probands in this study. [Color figure can be viewed at wileyonlinelibrary.com]

related to sex hormone levels and metabolic levels.[38] Further studies on sex differences may help reveal the underlying mechanisms of CRD.

The *CSF1R* gene has a total of 22 exons and encodes a class of tyrosine kinase receptors, the colony-stimulating factor-1 receptors. Similar to past studies, the 66 mutations identified in this study are mainly located in the TKD domain. This region is an important structure for securing autophosphorylation and downstream signaling. c.2381 T > C/p.I794T had the highest mutation frequency of 17.9% (10/56), suggesting that this locus is a hotspot mutation in Chinese patients. In addition, this mutation has been reported in many countries and regions, including North America, Europe, Japan, and Korea.[4,39]

Our study revealed that motor-predominant patients showed less severe MRI performance with lower proportion with family history compared to cognitive-predominant ones, but no differences in ages of onset or durations at the point of MRI evaluation. Similarly, it has been reported before that HSCT might be more effective on motor-predominant patients.[31] Together, motor-predominant phenotypes might be an indicator of better prognosis.

The main limitation of this study is that this was a retrospective study and some data, especially electrophysiological and CSF analysis, were not complete. More long-term prospective cohort studies, especially those on asymptomatic *CSF1R* carriers, are needed in the future to better illustrate the natural history and characteristics of CRD. Furthermore, all patients in our cohort only underwent 3 T MRI, whereas 7 T MRI has showed its potential to demonstrate calcifications. Moreover, electrophysiological examinations were

performed in different laboratories under different machines and/or different normative data; thus further standard studies were called for confirmation. No patients enrolled underwent HSCT at the point of evaluation; therefore further clinical trials were needed to illustrate the efficacy and safety of HSCT. In addition, there were deaths in this retrospective cohort, but due to relevant policies and customs, we did not perform autopsies, which is a limitation of this study. Besides, based on our preliminary results, it seems that Chinese patients have different features compared to patients from other countries. Systematic review and meta-analysis are required to further confirm our results, and accordingly, the diagnostic criteria need to be modified to make them more applicable for Chinese patients. ■

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Data Availability Statement

Data will be made available on request.

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A. conception and study design; B. data collection or acquisition; C. statistical analysis; D. interpretation of results; E. drafting, editing or revising of the text.

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