RESEARCH ARTICLE

Genetic analysis of *IRF2BPL* in a Taiwanese dystonia cohort: The genotype and phenotype correlation

Pin-Shiuan Chen[1,#], Ying-Fa Chen[2,3,#], Jian-Ying Chiu[4] (iD), Meng-Chen Wu[1,5], Chun-Hwei Tai[1], Yung-Yee Chang[2,3], Min-Yu Lan[2,3], Ni-Chung Lee[6] (iD) & Chin-Hsien Lin[1,7,8,9] (iD)

[1]Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
[2]Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[3]Center for Parkinson's Disease, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[4]Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan
[5]Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan
[6]Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan
[7]College of Medicine, National Taiwan University, Taipei, Taiwan
[8]Institute of Molecular Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
[9]Department of Biomedical Engineering, National Taiwan University, Taipei, Taiwan

Abstract

Objective: *IRF2BPL* mutation has been associated with a rare neurodevelopmental disorder with abnormal movements, including dystonia. However, the role of *IRF2BPL* in dystonia remains elusive. We aimed to investigate *IRF2BPL* mutations in a Taiwanese dystonia cohort. **Methods**: A total of 300 unrelated patients with molecularly unassigned isolated ($n = 256$) or combined dystonia ($n = 44$) were enrolled between January 2015 and July 2023. The *IRF2BPL* variants were analyzed based on whole exome sequencing. The in silico prediction of the identified potential pathogenic variant was performed to predict its pathogenicity. We also compared the clinical and genetic features to previous literature reports. **Results**: We identified one adolescent patient carrying a de novo heterozygous pathogenic variant of *IRF2BPL*, c.379C>T (p.Gln127Ter), who presented with generalized dystonia, developmental regression, and epilepsy (0.33% of our dystonia cohort). This variant resides within the polyglutamine (poly Q) domain before the first PEST sequence block of the IRF2BPL protein, remarkably truncating the protein structure. Combined with other patients with *IRF2BPL* mutations in the literature ($n = 60$), patients with variants in the poly Q domain have a higher rate of nonsense mutations ($p < 0.001$) and epilepsy ($p = 0.008$) than patients with variants in other domains. Furthermore, as our index patient, carriers with substitutions before the first PEST sequence block have significantly older age of onset ($p < 0.01$) and higher non-epilepsy symptoms, including generalized dystonia ($p = 0.003$), and ataxia ($p = 0.003$). **Interpretation**: *IRF2BPL* mutation is a rare cause of dystonia in our population. Mutations in different domains of *IRF2BPL* exhibit different phenotypes.

Introduction

Dystonia is a clinically and genetically diverse movement disorder marked by sustained or intermittent muscle contractions, resulting in abnormal, frequently repetitive movements or postures. It may manifest as isolated dystonia, in which dystonia represents the sole motor symptom, or as combined dystonia, which encompasses dystonia occurring alongside other neurological manifestations, such as parkinsonism, myoclonus, epilepsy, ataxia, or developmental delay.[1] Currently, more than 30 dystonia-causative genes have been identified.[1,2] The co-occurrence of dystonia combined with neurodevelopmental delay implicates causative genetic variants related to neurodevelopment, with a pathogenic substitution frequency of up to 45% in complex dystonia syndrome.[3]

These genetic discoveries shed light on the molecular mechanisms involved in dystonia, including endoplasmic reticulum function and protein trafficking, presynaptic and postsynaptic neurotransmitter signaling, and gene transcription modulation during neurodevelopment.[4] The recognition that multiple dystonia-related genes coalesce in shared biological pathways is a crucial advance in understanding dystonia and will aid in the development of mechanism-targeted therapeutic strategies.

Rare heterozygous pathogenic variants in the interferon regulatory factor 2-binding protein-like gene (*IRF2BPL*) have been associated with a progressive neurodevelopmental disorder characterized by severe regression, speech abnormalities, epilepsy, ataxia, and a variety of movement disorders.[5,6] These movement disorders mainly encompass dystonia and ataxia, though some patients may present with a pure epileptic encephalopathy without movement presentations, with symptoms mainly developing between childhood and adolescence.[5,6] The expression of IRF2BPL is ubiquitous, including in the central nervous system. Although its precise functions remain largely unclear, various studies have shown its potential involvement in neuronal development and maintenance,[7] transcription of gonadotropin-releasing hormone,[8,9] modulation of the ubiquitin-proteasome system in the nucleus,[10,11] and acting as an E3 ubiquitin ligase that targets β-catenin for proteasomal degradation.[6,10,12] These reports have drawn attention to the possibility that IRF2BPL may contribute to dystonia, especially combined dystonia. However, the exploration of *IRF2BPL* mutation in patients with dystonia is limited. To date, the literature has documented several cases with *IRF2BPL* mutation, mostly in the presence of epilepsy and developmental delay. Here, we investigated *IRF2BPL* mutations in a Taiwanese dystonia cohort with molecularly unidentified dystonia to elucidate the frequency and genotype–phenotype correlation of *IRF2BPL* mutations, focusing on non-epilepsy symptoms.

Methods

Participants

A total of 300 unrelated patients with molecularly unassigned isolated or combined dystonia from the movement disorder clinics of National Taiwan University Hospital and Kaohsiung Chang Gung Memorial Hospital were enrolled in this study between January 2015 and July 2023. For patients with combined dystonia, dystonia would be the main feature alongside other movement disorder features. Patients with secondary causes, such as neuroleptic agent-induced tardive dystonia, cerebral palsy, posttraumatic dystonic syndrome, and structural brain lesions with gadolinium contrast enhancement on brain MRIs (including brain tumor, demyelinating lesions, and infectious or autoimmune encephalitis), were excluded. We excluded patients with mutations in known causative genes related to familial dystonia or parkinsonism listed in our previous panel sequencing.[13] We also excluded patients having pathogenic variants in other known dystonia genes based on the current exome data (Table S1).

Among the 300 recruited patients, 37 had an age at onset of symptom <20 years, and 61 patients had a family history of dystonia Of these latter, 23 had a family inheritance pattern compatible with autosomal-dominant inheritance and the remaining 38 patients had an autosomal recessive inheritance pattern with affected siblings or at least one other first- and/or second-degree relative with dystonia. None of the patients were from a consanguineous family. All participants provided written informed consent, and the study was approved by the institutional ethics review board of National Taiwan University Hospital and Kaohsiung Chang Gung Memorial Hospital.

Whole exome sequencing

Genomic DNA was isolated from 10 ml of venous blood obtained from all participants following a standard protocol.[13] Whole exome sequencing was performed for all enrolled patients on the Illumina NovaSeq 6000 sequencer.[14] The paired-end reads were trimmed of the sequencing adaptor sequences and low-quality bases (Q < 30, Phred scale). After trimming, the sequences were aligned to the human reference genome (GRCh37/hg19). Average on-target coverage of at least 30X was obtained for all included samples.

Variant analysis

We excluded genetic variants that did not alter coding sequences and variants with a minor allele frequency >0.001 in control subjects in one or more reference databases, specifically the Single-Nucleotide Polymorphism Database (dbSNP144; https://www.ncbi.nlm.nih.gov/snp), 1000 Genomes Project,[15] Exome Aggregation Consortium (ExAC version 0.3), The Genome Aggregation Database (gnomAD, $n = 123{,}136$ exomes and 15,496 whole-genome sequences; http://gnomad.broadinstitute.org/), and The Taiwan biobank (https://taiwanview.twbiobank.org.tw/index, $n = 1517$ exomes).[16] We analyzed variants that were annotated as missense, splice donor, splice acceptor, start-lost, stop-gained, stop-loss, or frameshift substitution by ANNOVAR software. To predict the function of the variant in the coding region, we used PROVEAN,[17] SIFT,[18] PolyPhen-2,[19] MutationTaster,[20] and CADD[21] to predict the possible impact of the variant on the protein structure. Missense variants with PolyPhen-2 scores <0.95

and SIFT scores >0.05 were excluded. The Varsome version 10.0 tool platform (Varsome, https://varsome.com) was applied to classify pathogenicity based on the American College of Medical Genetics and Genomics interpretation criteria.[22] Variants meeting the criteria were then subjected to Sanger sequencing to confirm the nucleotide change.

Sanger sequencing

The potentially pathogenic variants were ascertained by Sanger sequencing. Genomic DNA samples from the index patients were sequenced as described previously.[6]

Systematic review of previous reports of patients with IRF2BPL mutation

We searched the PubMed database for all published studies in English that contained the terms "*IRF2BPL* mutation," "*IRF2BPL* pathogenic variant," "*IRF2BPL* likely pathogenic variant," "*C14orf4* mutation," "*C14orf4* pathogenic variant," and "*C14orf4* likely pathogenic variant." We selected case reports, case series, or original articles of patients with genetically confirmed *IRF2BPL*-related mitochondrial complex I deficiency published in 2000–2023. Next, we summarized the clinical, genetic, and imaging characteristics of different genotypes and compared them to the patients enrolled in this study to delineate the genotype and phenotype correlations of this rare disorder.

Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM) and nominal variables as numbers and percentages. Continuous variables were compared by the Mann–Whitney U-test, whereas categorical data were examined using Fisher's exact test due to small sample number in some compassion groups. Multiple comparisons were adjusted using Bonferroni's correction for the significance level of p value. The threshold p value for statistical significance in the multiple clinical feature comparisons was set at 0.009. Baseline characteristics were compared between different genotype groups using analysis of variance or the Kruskal–Wallis test when appropriate. All analyses were performed in Stata software (StataCorp LLC, College Station, TX).

In silico modeling

Both the wild-type sequence and mutated variant of IRF2BPL were obtained from the SWISS MODEL (https://swissmodel.expasy.org/). Subsequently, we performed an in silico comparison of these two models to predict potential alterations in the three-dimensional protein structure after mutation.

Results

The mean age at onset among the 300 enrolled patients was 43.42 ± 18.57 years, and 39.67% were men. A total of 256 (85.33%) patients presented with isolated dystonia, and the remaining 44 (14.67%) patients had combined dystonia with concomitant myoclonus [$n = 12$ (27.27%)], parkinsonism [$n = 25$ (56.82%)], ataxia [$n = 4$ (9.09%)], or epilepsy and developmental delay [$n = 3$ (6.82%)]. Notably, 3 patients had two non-dystonia features, that is, epilepsy and developmental delay. For patients with combined dystonia, the dystonia was mostly generalized in distribution.

Among the 300 enrolled participants, 1 patient presenting with generalized dystonia combined with epilepsy and neurodevelopment regression was found to carry a de novo heterozygous nonsense c.379C>T (p.Gln127Ter) mutation in *IRF2BPL*. None of the patients with non-epileptic dystonia ($n = 297$) had a pathogenic variant in *IRF2BPL*. This index patient is an 18-year-old female, the only child born from non-consanguineous healthy parents, and had no family history of neurological diseases. Initially, she achieved motor development milestones well, though she exhibited speech delay. At the age of 4 years, she gradually developed strabismus and regressed in motor skills. Starting at the age of 13 years, she experienced ataxic gait, generalized dystonia, and generalized tonic–clonic seizures. At 18 years of age, a neurological examination revealed reduced cognitive function, left eye esotropia, generalized dystonia, bilateral lower limb myoclonus (more severe on the right side), and a mixed dystonic and ataxic gait. Brain MRI revealed thinning of the corpus callosum without signal changes or structural lesions in the bilateral basal ganglia (Fig. 1A). Awake electroencephalography (EEG) showed generalized epileptic discharges mixed with focal epileptic activity (Fig. 1B). A ^{99m}Tc-TRODAT single-photon emission computed tomography scan did not show reduced dopamine transporter uptake at the bilateral basal ganglia (Fig. 1C).

The patient underwent laboratory testing, including a complete blood count, liver function test, renal function tests, ceruloplasmin, autoimmune profiles, urine organic acid analysis and plasma tandem mass analysis of metabolites, which were all unremarkable. We then performed whole exome sequencing for the index patient and identified a pathogenic nonsense variant in *IRF2BPL*, c.379C>T (p.Gln127Ter), in a heterozygous state (Fig. 2A). Direct Sanger sequencing verified this substitution in the index
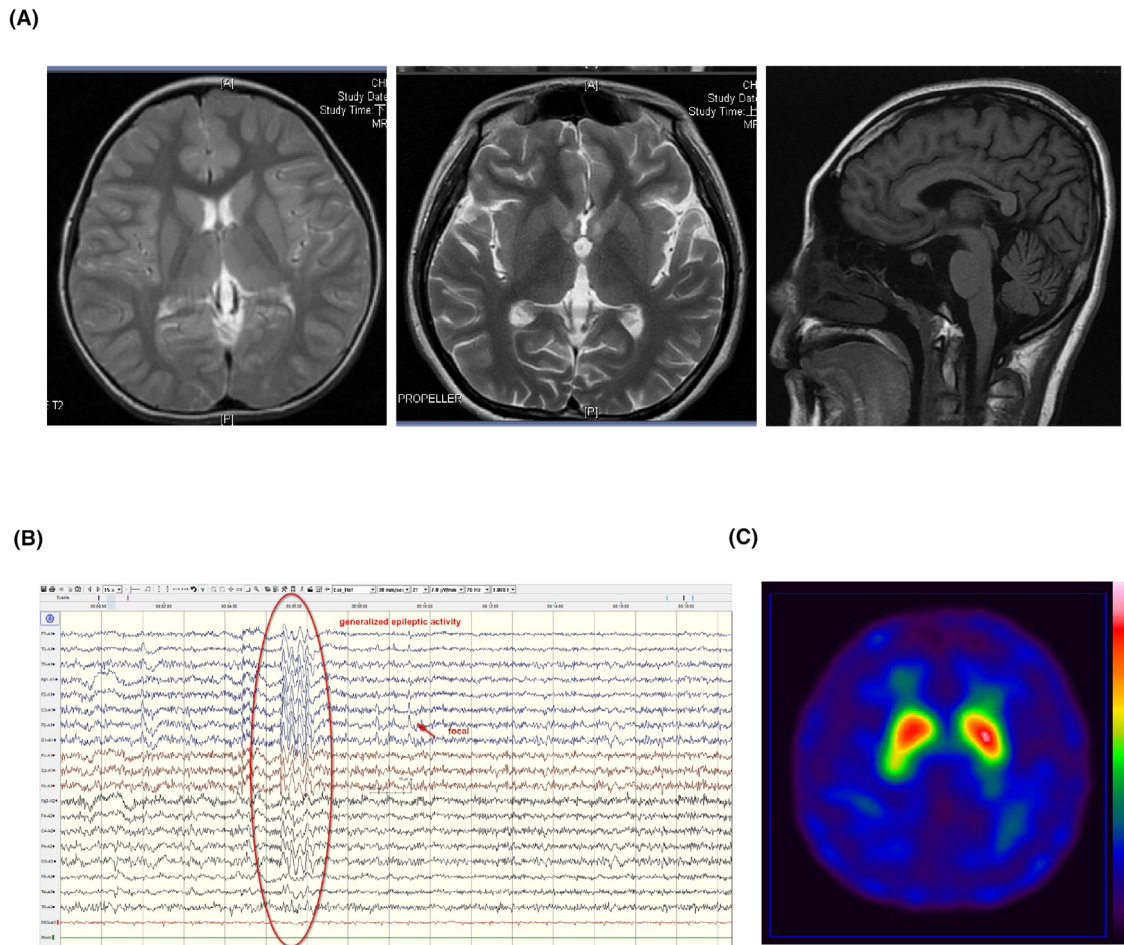
(A)

(B)

(C)

Figure 1. Neuroimaging and electroencephalogram studies of the index patient with *IRF2BPL* c.379C>T (p.Gln127Ter) mutation. (A) T2-weighted axial view and T1-weighted sagittal view of brain MRI. (B) electroencephalogram. (C) ^{99m}Tc-TRODAT single-photon emission computed tomography scan.

patient but not in the proband's asymptomatic parents (Fig. 2B). The variant is absent in the population database gnomAD and is classified as pathogenic according to ACMG guidelines.[22] Given the deleterious nature of the c.379C>T (p.Gln127Ter) variant and its absence in population databases, it was considered a de novo likely pathogenic variant for the index patient.

The mutated nucleotide is located within the N-terminus polyglutamine (poly Q) domain of *IRF2BPL* (Fig. 2C), which is known to form the protein's coiled-coil structure. IRF2BPL contains two highly conserved domains, including a coiled-coil DNA-binding domain (IRF2BP zinc finger domain) at the N-terminus and a C3HC4-type RING finger domain at the C-terminus.[7] Between the two conserved domains is a variable region that contains a potential nuclear targeting signal, as well as poly Q and polyalanine tracts. IRF2BPL also contains three putative PEST (proline, glutamic acid,

serine, and threonine-rich) sequences, suggesting that this protein is post-translationally regulated.[23] Based on the in silico computational protein modeling, nucleotide 127 is predicted to be located on the poly Q domain, and the nonsense substitution markedly truncates the protein (Fig. 3A,B). The c.379C>T (p.Gln127Ter) variant is predicted to cause premature termination of the protein at amino acid 127/796, resulting in loss of the nuclear localization sequence and the C-terminal C3HC4 type ring finger domain, which is predicted to affect the cellular localization and function of IRF2BPL protein.

To further delineate the potential genotype and phenotype correlations of the rare mutations in *IRF2BPL*, we combined our data with results from previous studies to clarify whether dystonia or other non-epilepsy clinical characteristics are observed in patients having mutations in the poly Q domain of *IRF2BPL*. Combining 60 patients with *IRF2BPL* mutations previously described in the
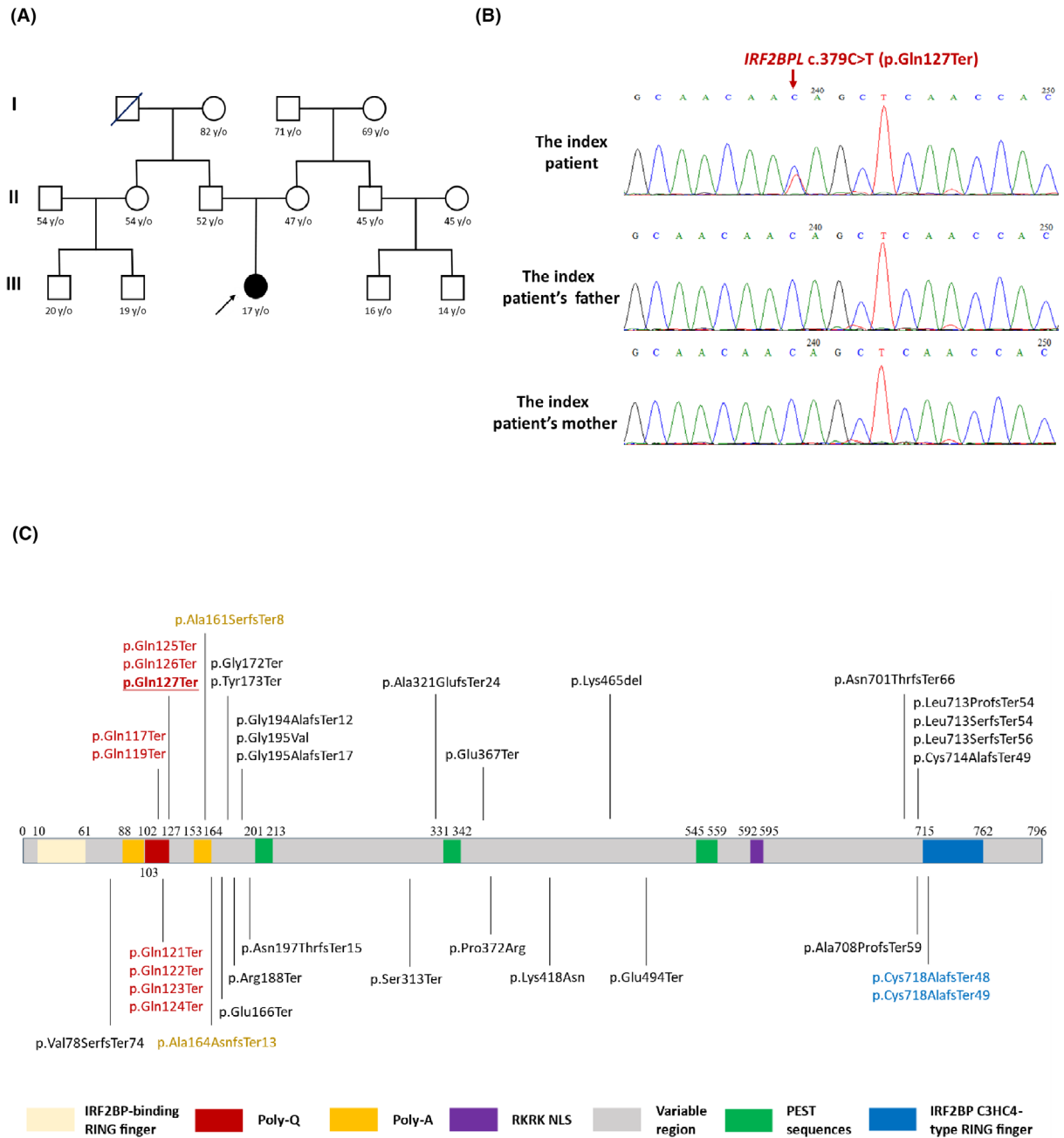
Figure 2. Family pedigree and genetic analysis of the index patient. (A) Pedigree of the index patient. Open symbol: unaffected; filled symbol: affected; arrow: proband. (B) Sanger sequencing traces confirm the de novo heterozygous c.379C > T (p.Gln127Ter) mutation in *IRF2BPL*. (C) Reported pathogenic variant, including the reported p.Gln127Ter variant (underlined) identified in the current study on the individual protein domain of IRF2BPL.

literature and the patient reported in the present study (Table S2),[5–7,9–11,24–38] we created four subgroups (Table 1) based on the locations of the identified mutations in the protein: the N-terminal poly Q domain

($n = 29$), poly A domain ($n = 2$), variable region ($n = 28$), and the C-terminal C3HC4 type ring finger domain ($n = 2$). Among these patients, only four individuals were documented to have affected parents with heterozygous

(A)   **(B)**
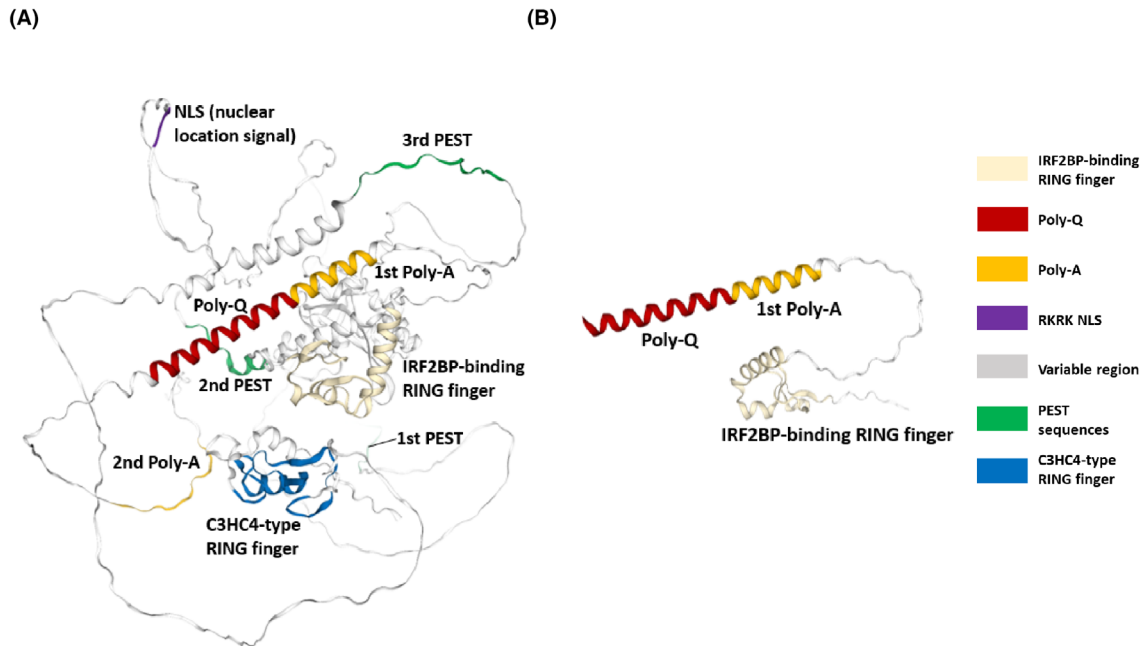

Figure 3. In silico protein structures of wild-type and mutant IRF2BPL. (A) The mutated nucleotide of p.Gln127 is located within the N-terminal coiled-coilstructure of the poly Q domain of the IRF2BPL protein. (B) The truncated mutant IRF2BPL protein harboring the nonsense p.Gln127Ter mutation.

variant following an autosomal-dominant inheritance trait, indicating a high rate of de novo mutation in this gene. Of note, the majority of patients have nonsense variants or small deletions causing frameshift mutations, while only two patients possess missense pathogenic variants (Table S2). Since a previous study has demonstrated no association between either the neurological features or the MRI findings with mutation type,[10] we thus categorized patients based on the locations of the identified mutations in the protein structure of IRF2BPL, despite the varying mutation types. Compared with the other three groups, patients with mutations in the poly Q domain all had nonsense mutations, whereas mutations within the poly A and C3HC4 domains were exclusively frameshift mutations ($p < 0.001$, Table 1). Moreover, patients with pathogenic variants in the poly Q domain had a higher frequency of epilepsy (poly Q domain: $13/14 = 92.86\%$ vs. poly A domain: $1/2 = 50\%$ vs. variable region: $12/25 = 48.0\%$ vs. C3HC4 domain: $1/2 = 50\%$, $p = 0.008$). Within the variable region, patients with mutations clustering in the N-terminus before the first PEST (proline, glutamic acid, serine, and threonine-rich) sequence block had a later age of onset ($p = 0.002$) and lower initial developmental delay ($p = 0.04$) but higher occurrence of motor regression ($p < 0.001$), dystonia ($p = 0.003$), and ataxia ($p = 0.003$) compared to mutations located after the first PEST sequence block (Table 2).

These observations highlight the crucial role of the N-terminus of *IRF2BPL*, especially the poly Q domain and sequences before the first PEST sequence block.

Discussion

We described the screening of *IRF2BPL* in a large Taiwanese dystonia cohort. The low prevalence within the cohort suggests that *IRF2BPL* mutations are a rare cause of dystonia in our population, even in the subgroup with combined dystonia. Compared with prior reports, our study revealed that mutations across various domains of *IRF2BPL* exhibit distinct phenotypic spectrum. N-terminal pathogenic variants, mostly nonsense mutations, are associated with later age at onset and non-epileptic symptoms, encompassing dystonia and ataxia. Our results extend the current knowledge and provide further insights into the phenotype–genotype correlation of rare mutations in *IRF2BPL*.

IRF2BPL mutations are a rare cause of dystonia in our population. The simultaneous presence of dystonia and neurodevelopmental delay or regression has long been acknowledged to involve causative genetic variants associated with neurodevelopment, with a pathogenic substitution rate of up to nearly half of complex dystonia syndrome.[3] The causative genes related to neurodevelopment involved in dystonia combined with

Table 1. Clinical and genetic features in patients with *IRF2BPL* mutations in different protein domain derived from previous literature and the current study.

	Poly Q domain (N = 29)	Poly A domain (N = 2)	Variable region (N = 28)	C3HC4 domain (N = 2)	p Value
Age of onset, years	9.51 ± 8.14	7.75 ± 5.25	7.27 ± 8.73	3.25 ± 1.75	0.06
Male sex (n, %)	6 (46.1%, n = 13)	1 (50%)	13 (46.43%)	1 (50%)	0.99
Ethnicity					
Asian	1 (3.45%)	0	4 (14.29%)	0	0.43
Western	28 (96.55%)	2 (100%)	23 (82.14%)	2 (100%)	0.41
Unknown	0	0	1 (3.57%)	0	0.52
Mutation type					
Frameshift	0	2 (100%)	13 (46.43%)	2 (100%)	<0.001***
Nonsense	29 (100%)	0	13 (46.43%)	0	<0.001***
Missense	0	0	2 (7.14%)	0	0.33
Main clinical features					
Initial global developmental delay	6 (27.27%, n = 22)	0	11 (42.31%, n = 26)	1 (50%)	0.48
Motor regression	5 (22.73%, n = 22)	2 (100%)	10 (38.46%, n = 26)	0	0.09
Language regression	2 (10%, n = 20)	0	7 (26.92%, n = 26)	0	0.44
Dystonia	11 (39.29%, n = 28)	1 (50%)	8 (34.78%, n = 23)	0	0.82
Ataxia	25 (86.21%)	1 (50%)	14 (50%, n = 24)	1 (50%)	0.04*
Pyramidal signs	16 (55.17%)	1 (50%)	12 (50%, n = 24)	1 (50%)	0.94
Epilepsy	13 (92.86%, n = 14)	1 (50%)	12 (48%, n = 25)	1 (50%)	0.008**
Brain MRI findings					
Normal	4 (28.57%, n = 14)	2 (100%)	11 (52.38%, n = 21)	1 (50%)	0.22
Cerebral or cerebellar or brainstem atrophy	5 (35.71%, n = 14)	0	9 (42.86%, n = 21)	1 (50%)	0.78
Corpus callosum atrophy	4 (28.57%, n = 14)	0	1 (4.76%, n = 21)	0	0.25

*$p < 0.05$;
**$p < 0.01$.
***$p < 0.001$.

neurodevelopmental delay include *IRF2BPL*.[3,7] In this study, we did not identify any likely pathogenic variants in the aforementioned genes but one de novo mutation in *IRF2BPL*. However, *IRF2BPL* is not a major contributing genetic factor in our dystonia patients, even those with combined dystonia. Due to the rarity of *IRF2BPL*-related disorder, the information from previously reported cases implicated *IRF2BPL* in a severe pediatric phenotype characterized by developmental delay and epilepsy in patients with de novo mutations, although inherited *IRF2BPL* variants have also been reported in patients with late-onset progressive dystonic and ataxic syndrome.[5–7] Consistent with our observation, one documented case with the same de novo mutation as our index patient, c.379C>T (p.Gln127Ter) variant, has been reported.[7] Both our index patient and the previously described case exhibited initially normal neurodevelopment, followed by motor regression, occurrence of ataxia, dystonia, and epilepsy. Notably, ataxia or dystonia preceded the onset of epilepsy in both cases. With the high occurrence of de novo mutations, the absence of a family history in dystonia patients should not preclude the molecular diagnosis of *IRF2BPL* mutations.

Pathogenic variants have been reported throughout *IRF2BPL*. One study has proposed that nonsense variants are associated with the phenotypes of severe developmental delay or regression and movement disorders, whereas missense substitutions are associated with epilepsy,[7] but conflicting results exist.[10] Another study revealed that the mutation type (nonsense or missense variations) is not related to either clinical presentation or MRI findings.[10] In the current study, we characterized the clinical presentations based on the protein domains in which the mutations were located. Our analysis revealed that patients carrying pathogenic variants in the poly Q domain exhibited a higher frequency of epilepsy compared to those harboring mutations in other domains. Notably, all mutations identified within the poly Q domain were nonsense mutations leading to a truncated IRF2BPL protein. Furthermore, mutations located before the first PEST block had significantly later onset, less developmental delay, and more frequent non-epilepsy features of dystonia and ataxia compared to mutations close to the C-terminus. We hypothesized that mutations close to the N-terminus in the poly Q domain or before the first PEST block will result in a truncated protein with loss of the nuclear

Table 2. Clinical and genetic characteristics in patients with *IRF2BPL* mutations located before and after first PEST region on the variable domain.

	Variable region (N = 28)		
	Before first PEST region (N = 15)	After first PEST region (N = 13)	*p* Value
Age of onset, years	11.11 ± 10.05	2.40 ± 1.48	0.002**
Male sex (*n*, %)	6 (40%)	7 (53.85%)	0.71
Ethnicity			
Asian	3 (20%)	1 (7.69%)	0.60
Western	12 (80%)	11 (84.62%)	0.99
Unknown	0	1 (7.69%)	0.46
Mutation type			
Frameshift	6 (40%)	7 (53.85%)	0.71
Nonsense	9 (60%)	4 (30.77%))	0.15
Missense	0	2 (15.38%)	0.21
Main clinical features			
Initial global developmental delay	3 (21.43%, *n* = 14)	8 (66.67%, *n* = 12)	0.04*
Motor regression	10 (71.43%, *n* = 14)	0 (*n* = 12)	<0.001**
Language regression	6 (42.86%, *n* = 14)	1 (8.33%, *n* = 12)	0.08
Dystonia	8 (61.54%, *n* = 13)	0 (*n* = 10)	0.003**
Ataxia	12 (85.7%, *n* = 14)	2 (20%, *n* = 10)	0.003**
Pyramidal signs	9 (64.29%, *n* = 14)	3 (30%, *n* = 10)	0.21
Epilepsy	4 (28.57%, *n* = 14)	8 (72.73%, *n* = 11)	0.05
Brain MRI findings			
Normal	5 (41.67%, *n* = 12)	6 (66.67%, *n* = 9)	0.39
Cerebral or cerebellar or brainstem atrophy	7 (58.33%, *n* = 12)	2 (22.22%, *n* = 9)	0.18
Abnormal corpus callosum	1 (8.33%, *n* = 12)	0 (*n* = 9)	0.98

Data are the number (%) or the mean ± SD. *p*-Values that compare individual characteristics between four groups with different genotypes were evaluated with Fisher's exact test. Variables without a normal distribution were compared with the Kruskal–Wallis test.
*$p < 0.05$;
**$p < 0.01$.

localization signal and C-terminal C3HC4 RING domain, which will lead to neuronal impairment. The C-terminal C3HC4 RING domain belongs to the E3 ligase family and is associated with protein ubiquitination and degradation.[11,39] Dysregulation of the ubiquitin system not only contributes to neurodegenerative diseases, but also results in delayed neurodevelopmental processes.[11,40] The c.379C>T (p.Gln127Ter) mutation in our patient is situated within the poly Q domain of *IRF2BPL*. Computational modeling revealed alterations in the tertiary structure of the protein, supporting our hypothesis and suggesting an impact on the function of IRF2BPL. Several studies have investigated potential mechanisms associated with *IRF2BPL* mutations. One study demonstrated that cells with the truncated *IRF2BPL* mutation had decreased levels of ubiquitinated proteins.[11] Other research utilized astrocytes reprogrammed from patient skin fibroblasts and found partial mis-localization of IRF2BPL to the cytoplasm, along with reduced astrocyte-mediated neuronal support and abnormal energy metabolism.[41] Recently, loss of IRF2BPL in in vivo Drosophila and zebrafish models revealed increased WNT transcription.[7] Another study using RNA-Seq data showed that some WNT ligands, including WNT5A, WNT16, WNT9B, and WNT10B, are upregulated in astrocytes differentiated from *IRF2BPL* mutated patients' induced pluripotent stem cells.[41] The Wnt canonical pathway controls multiple biological processes throughout development and adult life. Growing evidence suggests that deregulation of the Wnt canonical pathway is involved in the pathogenesis of neurodegenerative diseases. Further functional studies are required to determine whether loss of IRF2BPL transcriptional regulation activity directly causes differential expression of neurodevelopmental genes.

In conclusion, *IRF2BPL* mutation is a rare cause of dystonia in our population. Mutations in different domains of *IRF2BPL* result in a phenotypic spectrum. Further functional studies are needed to delineate the pathogenicity of mutant *IRF2BPL* in neuron dysfunction.

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Author Conributions

Study concept and design: PS Chen, YF Chen, and CH Lin. Acquisition of data: PS Chen, YF Chen, JY Chiu, MC Wu, CH Tai, YY Chang, MY Lan, NC Lee, and CH Lin. Analysis and interpretation of data: PS Chen and CH Lin. Drafting of the manuscript: PS Chen. Critical revision of

the manuscript for important intellectual content: CH Lin. Obtained funding: CH Lin. Study supervision: CH Lin.

Conflict of Interest

All authors report no conflict of interests.

Data Availability Statement

The data supporting the findings of this study are available on request from the corresponding author.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1.