REVIEW

Genotype–Phenotype Correlations for ATX-*TBP* (SCA17): MDSGene Systematic Review

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ABSTRACT: Spinocerebellar ataxia type 17 or ATX-*TBP* is a CAG/CAA repeat expansion disorder characterized by marked clinical heterogeneity. Reports of affected carriers with subthreshold repeat expansions and of patients with Parkinson's disease (PD) with expanded repeats have cast doubt on the established cutoff values of the expansions and the phenotypic spectrum of this disorder. The objective of this systematic review was to explore the genotype–phenotype relationships for repeat expansions in *TBP* to delineate the ATX-*TBP* phenotype and reevaluate the pathological range of repeat expansions. The International Parkinson and Movement Disorder Society Genetic Mutation Database (MDSGene) standardized data extraction protocol was followed. Clinically affected carriers of reported ATX-*TBP* expansions were included. Publications that contained repeat sizes in screened cohorts of patients with PD and/or healthy individuals were included for a separate evaluation of cutoff values. Phenotypic and genotypic data for 346 ATX-*TBP* patients were curated. Overall, 97.7% of the patients had ≥41 repeats, while 99.6% of patients with PD and 99.9% of healthy individuals had ≤42 repeats, with a gray zone of reduced penetrance between 41 and 45 repeats. Pure parkinsonism was more common in ATX-*TBP* patients with 41 to 45 repeats than in the group with ≥46 repeats, which conversely more often presented with a complex phenotype with mixed movement disorders. An updated genotype–phenotype assessment for ATX-*TBP* is provided, and new repeat expansion cutoff values of reduced penetrance (41–45 expanded repeats) and full penetrance (46–66 expanded repeats) are proposed. These adjusted cutoff values will have diagnostic and counseling implications and may guide future clinical trial

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Introduction

Spinocerebellar ataxia (SCA) type 17 (SCA17), currently referred to as ATX-*TBP* by the International Parkinson and Movement Disorder Society Task Force on Genetic Nomenclature in Movement Disorders,[1] is an autosomal dominant cerebellar ataxia caused by a polyglutamine-encoding CAG/CAA repeat expansion within the TATA box-binding protein (*TBP*) gene.[2,3] The average age of onset is in the fourth or fifth decade of life, and the typical phenotype includes cerebellar ataxia associated with one or more of the following clinical manifestations: chorea, dystonia, parkinsonism, pyramidal signs, cognitive impairment, and psychiatric symptoms such as psychosis and depression.[4,5] ATX-*TBP* is one of the Huntington's disease–like syndromes.[6,7]

In 2010, the cutoff values for repeat expansions within *TBP* reported by the European Molecular Genetics Quality Network best practice guidelines for molecular genetic testing of SCAs[8] were set as normal (25–42 CAG/CAA repeats), reduced penetrance (RP; 43–48 repeats), and full penetrance (FP; 49–66 repeats), respectively. However, establishing an unequivocal cutoff for a disease-causing repeat expansion has been a challenging task in ATX-*TBP* because many reports suggested that the threshold for pathological expansions is lower.[9-13] Also, atypical phenotypes have been reported for ATX-*TBP*, such as the (inconsistent) finding of repeat expansions in patients considered to have Parkinson's disease (PD),[14-17] casting doubt on the breadth of the phenotypic spectrum of ATX-*TBP*. These controversial findings motivated us to systemically evaluate the reported ATX-*TBP* patients to study the full phenotypic spectrum, extract potential genotype–phenotype correlations, and reconsider the cutoff values for expanded *TBP* repeats.

Subjects and Methods

Search Strategy and Eligibility Criteria

We conducted a systematic literature search and data extraction procedure following the PRISMA guideline[18] and the standardized International Parkinson and Movement Disorder Society Genetic mutation database (MDSGene, https://www.mdsgene.org/) protocol.[19,20] The search term for the literature search in PubMed up to June 12, 2020, and updated in April 20, 2022, is listed in Supporting Information Methods S1. Articles in English were assessed for eligibility using the title, abstract, or full text, as necessary. Every publication with genetic and clinical data describing at least one clinically affected carrier of a heterozygous CAG/CAA repeat expansion in the *TBP* gene was included in this study. Data from asymptomatic individuals were not extracted. Patients with biallelic repeat expansions and with pathogenic variants or repeat expansions in other genes were excluded from the analysis. A patient was considered clinically affected if there was documented presence of gait and/or limb ataxia, or in the absence of ataxia (eg, pure parkinsonism or chorea associated with dementia) if the patient was explicitly labeled as clinically affected by the authors. Additional cerebellar symptoms, such as dysarthria and/or eye movement abnormalities, were supportive, but not mandatory. In parallel, publications containing data on CAG/CAA repeat size ranges in the *TBP* gene in cohorts of patients with PD and/or healthy individuals were included for a separate analysis of the best cutoff values for molecular genetic testing of SCAs.[8] All eligible articles were screened for references to additional articles on affected patients. The data collection process of demographic, genetic, clinical, and imaging data was conducted according to the standard protocol.[19] A list of the extracted clinical variables is provided in Supporting Information Methods S2. All available information was combined in case a patient had been reported more than once in subsequent publications. Similarly, clinical features that were described differently in the literature were combined into a single term following the Human Phenotype Ontology terminology (eg, cognitive decline, cognitive impairment, memory impairment, dementia, and intellectual disability were combined into mental deterioration). Discrepancies were resolved by discussion among coauthors involved in the data extraction process until reaching consensus. Patients with ataxia were evaluated for the presence of other associated clinical features or were categorized as pure ataxia if no other clinical manifestations were present, except for postural instability, head titubation, dysarthria, dysphagia, diplopia, nystagmus, and/or saccadic eye movement abnormalities. Similarly, patients were categorized as pure parkinsonism, chorea, dystonia, or myoclonus if ataxia or other movement disorders were absent (other clinical manifestations, such as mental deterioration or behavioral abnormalities, were allowed to be present).

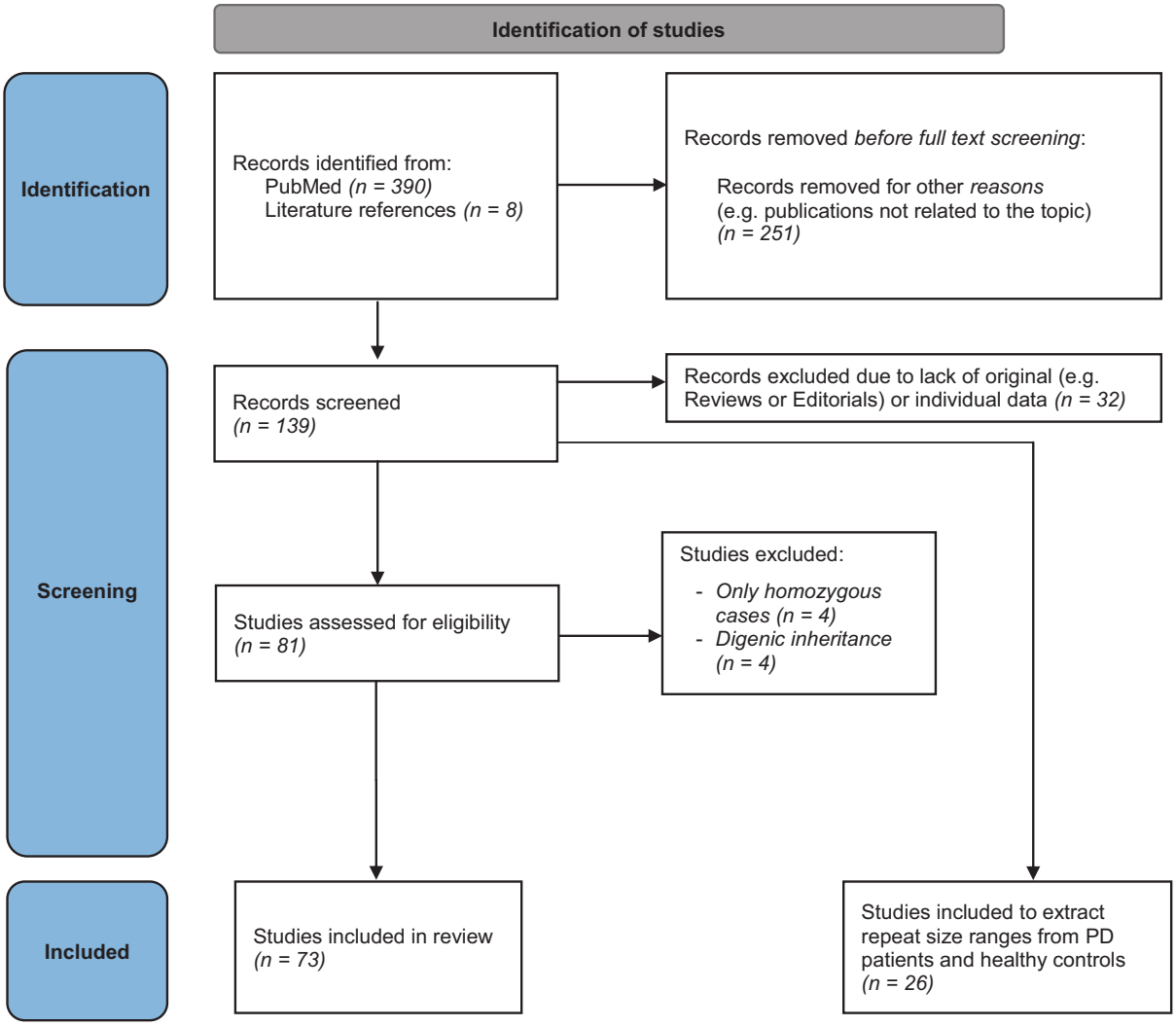

FIG. 1. Flow diagram of the review process. PD, Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

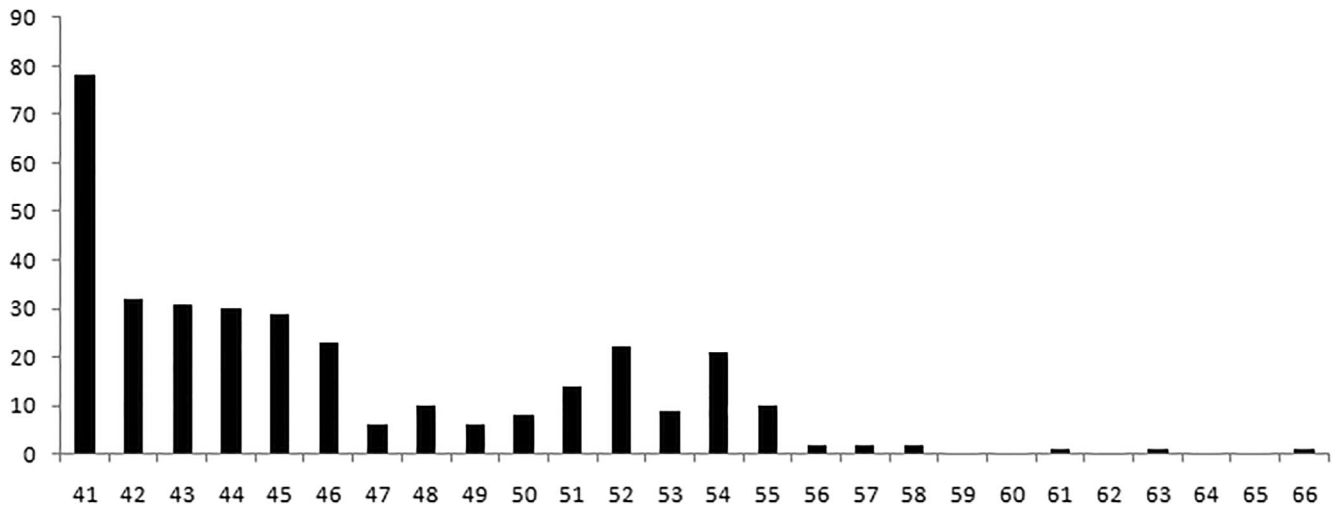

FIG. 2. Distribution of the number of patients reported per CAG/CAA repeat size in the expanded allele. *x* axis: number of CAG/CAA repeats; *y* axis: number of patients. Eight patients with 33, 34, or 38 repeats were excluded as explained in the Results section.

Statistical Analyses

Statistical analyses comparing demographic, genetic, clinical, and imaging data between groups of patients were performed with the SPSS statistical package (version 25; IBM Corp., Armonk, NY, USA). Descriptive data are presented as mean ± standard deviation or proportions out of the total number of non-missing observations. Proportions for the clinical features at disease onset were calculated in relation to the total sample of each group instead of the total number of non-missing observations because it better reflects how symptoms at disease onset are commonly reported. The Shapiro–Wilk test was used to assess the normal distribution of the data. Analysis of variance was used to assess between-group differences in quantitative variables that were normally distributed; otherwise, the Mann–Whitney *U* test was used. Chi-square test was conducted for categorical variables, and Bonferroni post hoc comparisons test was used when three groups of patients were compared. According to the statistical

TABLE 1 *Main characteristics of ATX-TBP patients according to the newly proposed clusters*

Characteristics	RP-rev (41–45 repeats), n = 200 [missing data]	FP-rev (46–66 repeats), n = 138 [missing data]	*P* value
Genetic data			
CAG/CAA expanded repeats (mean ± SD; range)	42.5 ± 1.5; 41–45 [0]	51.2 ± 3.7; 46–66 [0]	**<0.001**
CAG/CAA normal allele (mean ± SD; range)	36.8 ± 1.3; 32–40 [42]	36.9 ± 1.7; 32–40 [70]	0.5
Interrupted repeat alleles	58 (86.6%) [133]	42 (70.0%) [78]	**0.019**
Demographic data			
Female sex	83 (46.4%) [11]	68 (53.1%) [10]	0.4
Race	118 [82]	53 [85]	
Asian	100 (84.7%) [82]	18 (34.0%) [82]	**<0.001**
White	17 (14.4%)	22 (41.5%)	**<0.001**
Mixed/other	1 (0.9%)	12 (22.6%)	**<0.001**
Native American	0 (0%)	1 (1.9%)	0.5
Family history	46 (31.3%) [53]	87 (79.8%) [29]	**<0.001**
Age at disease onset (any first symptom), years	47.2 ± 14.1 [106]	34.5 ± 12.7 [25]	**<0.001**
Age at movement disorder onset, years	47.8 ± 14.1 [113]	33.8 ± 12.0 [34]	**<0.001**
Age at onset of any other clinical feature, years	38.2 ± 11.5 [178]	32.8 ± 12.0 [109]	0.1
Age at examination, years	57.5 ± 12.9 [37]	42.5 ± 13.4 [49]	**<0.001**
Disease duration, years	7.1 ± 8.2 [111]	10.7 ± 8.3 [34]	**0.003**
Clinical features at disease onset[a]			
Ataxia	33 (16.5%)	40 (29.0%)	**0.005**
Behavioral abnormality	12 (6.0%)	23 (16.7%)	**0.002**
Mental deterioration	4 (2.0%)	17 (12.3%)	**<0.001**
Chorea	5 (2.5%)	10 (7.2%)	**0.036**
Parkinsonism	7 (3.5%)	1 (0.7%)	0.1
Dystonia	2 (1.0%)	7 (5.1%)	**0.027**

[a]Proportions for the clinical features at disease onset were calculated in relation to the total sample of each group instead of the total number of non-missing observations because it better reflects how symptoms at disease onset are commonly reported. Statistically significant values are shown in bold.
Abbreviations: FP-rev, full penetrance-revised; RP-rev, reduced penetrance-revised; SD, standard deviation.

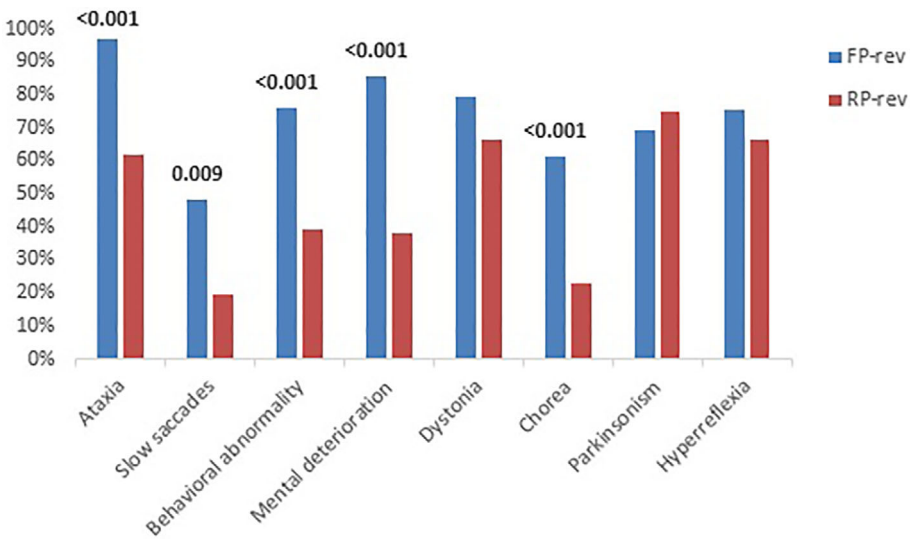

FIG. 3. Schematic representation of the main clinical features during overall disease course. *x* axis: percentage of patients; *y* axis: clinical features according to reduced penetrance-revised (RP-rev) group and full penetrance-revised (FP-rev) group. [Color figure can be viewed at wileyonlinelibrary.com]

distribution, Spearman's rank correlation coefficient was used to correlate variables. The critical α value was conventionally set at 0.05.

Results

The flow diagram of the review process is depicted in Figure 1. The literature search yielded a total of 390 citations, of which 139 were screened after removing publications not related to the topic. A total of 73 studies were eligible for data extraction on patients with repeat expansions in *TBP* and are listed in Supporting Information Results S1. From these publications, clinical and genetic data were obtained from 346 patients. The distribution of the CAG/CAA repeats in the expanded allele is shown in Figure 2. The mean CAG/CAA repeat numbers in the expanded allele were higher in patients with ataxia, chorea, or dystonia than in those without these movement disorders (Supporting Information Table S1). In contrast, it was lower in patients with pure ataxia, pure parkinsonism, or pure dystonia than in those without pure movement disorders (Supporting Information Table S1). The number of CAG/CAA repeats in the expanded allele was inversely correlated with the age at disease onset ($r = -0.45$; $P < 0.001$), irrespective of the presenting symptom being ataxia or another movement disorder ($r = -0.51$; $P < 0.001$) or any other clinical feature (eg, mental deterioration) ($r = -0.37$; $P = 0.01$). The number of CAG/CAA repeats in the nonexpanded (normal) allele (≤40 repeats) was not correlated with the age at disease onset ($r = 0.15$; $P = 0.1$). Interruptions in the CAG/CAA repeat expansions were not correlated with age at disease onset (n = 102; $r = 0.07$; $P = 0.49$) or with the presence of ataxia (n = 124; $r = -0.14$; $P = 0.12$) or other clinical features.

Following the European Molecular Genetics Quality Network best practice guidelines for molecular genetic testing of SCAs,[8] the current standard, we initially classified the included patients into three groups: a normal or nonpathogenic (NP) group including 118 patients with 33 to 42 CAG/CAA repeats, an RP group with 129 patients carrying 43 to 48 expanded repeats, and an FP group including 99 patients with 49 to 66 expanded repeats. Patients in the NP group had a higher frequency of Asian ethnicity (93.8% vs. 70.0% in the RP group and 25.0% in the FP group; $P < 0.001$), a lower frequency of a positive family history of ATX-*TBP* (17.5% vs. 53.7% in the RP group vs. 84.2% in the FP group; $P < 0.001$), and a later age at disease onset (47.7 ± 14.6 vs. 42.7 ± 13.2 years in the RP group and 31.8 ± 13.1 years in the FP group; $P < 0.001$). According to these current cutoff values, the main clinical features of ATX-*TBP* patients are shown in Supporting Information Table S2.

The comparison of the CAG/CAA repeat sizes in patients with ATX-*TBP* and patients with PD and healthy individuals (the latter two groups are shown in Supporting Information Table S3) demonstrated that: (1) 338/346 (97.7%) ATX-*TBP* patients had ≥41 repeats (8 patients with 33, 34, or 38 repeats that lacked the typical above-mentioned ATX-*TBP* phenotypic characteristics were all reported in a single article,[21] and an alternative cause of genetic ataxia cannot be ruled out); (2) almost all patients with PD (11,742/11,757, 99.9%) and healthy individuals (16,748/16,759, 99.9%) had ≤42 repeats in the *TBP*

TABLE 2 *Relationship between ataxia and other movement disorders by newly proposed clusters*

Clinical features	RP-rev (41–45 repeats), n = 200 [missing data]	FP-rev (46–66 repeats), n = 138 [missing data]	*P* value
Pure ataxia	17 (14.5%) [83]	17 (13.7%) [14]	0.5
Pure parkinsonism	70 (55.1%) [73]	3 (7.7%) [99]	**<0.001**
Pure chorea	10 (8.3%) [79]	2 (3.1%) [73]	0.1
Pure dystonia	3 (25.0%) [188]	2 (4.5%) [94]	0.1
Pure myoclonus	0 (0%) [196]	1 (14.3%) [131]	0.6

Note: Pure ataxia: ataxia in the absence of other clinical features, except for postural instability, head titubation, dysarthria, dysphagia, diplopia, nystagmus, or saccadic eye movement abnormalities. Pure parkinsonism, chorea, dystonia, and/or myoclonus if ataxia was absent. Statistically significant values are shown in bold.
Abbreviations: FP-rev, full penetrance-revised; RP-rev, reduced penetrance-revised; SD, standard deviation.

gene; and (3) there is a *gray zone* between 41 and 45 repeats with RP, because 64/12,845 (0.5%) healthy subjects were reported within this range of repeats. In other words, in the data we extracted, we found no firm evidence of *TBP*-related disease in those with repeats of ≤40, and no healthy subjects with repeats greater than 45. These findings led us to reconsider the cutoff values for ATX-*TBP*, as previously mentioned, and motivated us to compare the data from the included patients following a new set of CAG/CAA repeat size clusters as follows: 41 to 45 expanded repeats (RP-revised [RP-rev]) group and 46 to 66 expanded repeats (FP-revised [FP-rev] group). As shown in Figure 2, the most frequent CAG/CAA repeat lengths in the expanded allele in the RP-rev and FP-rev groups were 41 and 46, respectively. Table 1 shows the main genetic, demographic, and clinical data. The full data are presented in Supporting Information Table S4 (clinical manifestations at disease onset) and Supporting Information Table S5 (clinical characteristics during the course of the disease). Figure 3 shows a schematic representation of the prevalence of the main clinical features present up to time of evaluation in both the RP-rev and FP-rev groups (mean disease duration was 7.1 ± 8.2 vs. 10.7 ± 8.3 years, $P = 0.003$, respectively). Patients in the RP-rev group more commonly manifested pure parkinsonism than patients in the FP-rev group (Table 2). A complementary analysis of the frequency of combined movement disorders confirmed that ataxia combined with other movement disorders was more frequent in the FP-rev group (48.5%) than in the RP-rev group (20.9%) ($P < 0.001$). Different types of movement disorders combinations for the two groups are given in Supporting Information Table S6. Also, mental deterioration and behavioral abnormalities were significantly more common in the FP-rev group, both at onset and during the further course of the disease.

Asian race was more common in the RP-rev group than in the FP-rev group, and exploring the influence of Asian race on the main clinical features in the RP-rev group showed that ataxia, mental deterioration, and chorea were less frequent in Asian patients than in non-Asians, whereas parkinsonism was more common in Asian patients (Supporting Information Table S7).

Analysis of the imaging studies showed that the FP-rev group had more frequent cerebellar, brainstem, and cerebral atrophy than the RP-rev group (Supporting Information Table S8). Patients with pure parkinsonism had less frequent cerebellar atrophy than patients with parkinsonism combined with ataxia (8.2% vs. 75.0%, $P < 0.001$, respectively).

Discussion

This systematic review provides a comprehensive evaluation of genotype–phenotype relationships in a large sample of 346 reported ATX-*TBP* patients. Based on the analysis of CAG/CAA repeat sizes in ATX-*TBP* patients, patients with PD, and healthy controls, we identified three new clusters of repeat expansion sizes that might lead to reconsidering the diagnostic cutoffs for ATX-*TBP*.[8] These findings allowed us to propose the following allele classification: (1) normal or NP expansion for alleles ≤40 repeats, (2) RP-rev for alleles ranging from 41 to 45 repeats, and (3) FP-rev for alleles ranging from 46 to 66 repeats. It must be acknowledged that the definition of normal and pathogenic size ranges remains problematic, especially if the data available are based on case reports or case series or small cohort studies in racially or ethnically different populations and with variable methodological repeat expansion testing accuracies obtained usually by repeat-spanning polymerase chain reaction–based methods.[8] Also, although some studies have explicitly included a clinical reexamination of supposedly healthy subjects with an RP-rev expansion,[17] this was not the case for the majority.[14-16,22-26] Notably, when applying the current diagnostic cutoffs for ATX-TBP,[8] a substantial number of patients in the NP group had clinical manifestations, reinforcing the necessity to reestablish the repeat size cutoffs. In contrast, none of the patients with alleles ≤40 repeats presented the typical ATX-*TBP* phenotypic characteristics.

On comparisons of phenotypes according to these new clusters, we found that patients in the FP-rev group (46–66 expanded repeats) more frequently exhibit the characteristic, complex clinical picture of ATX-*TBP*, characterized by ataxia combined with chorea and other neurological features, including mental deterioration, behavioral abnormalities, and slow saccadic eye movements, as well as an earlier disease onset and a

positive family history of ATX-*TBP*, in comparison with patients in the RP-rev group (41–45 repeats). In some publications, nonataxia movement disorders such as dystonia were more frequently found in patients with larger CAA/CAG repeat expansions (eg, ≥50) within the *TBP* gene,[3,27-31] whereas parkinsonism and chorea were typically found in patients with shorter repeat sizes.[29,32-34] However, a sizable phenotype–genotype correlation study performed on 30 ATX-*TBP* patients was unable to identify any particular phenotypic trait for particular CAG/CAA repeat compositions or lengths.[35] In addition, our analysis of 346 patients does not support the existence of a particular movement disorder associated with a specific repeat size cluster, except for chorea that was more frequent in the FP-rev group. In other words, dystonia was also observed in patients with small expansions,[27,33,36,37] and parkinsonism and chorea were also present in patients with large expansions.[4,30,38-41] ATX-*TBP* patients with parkinsonism showed, in some cases, a phenotype resembling typical PD with response to dopaminergic therapy and, in other cases, a clinical picture indistinguishable from multiple system atrophy (MSA-C or MSA-P) with partial or no response to dopaminergic therapy and, in some, characteristic imaging findings of MSA, such as the hyperintense putaminal rim or the hot cross bun sign.[13,32,33,39,42-46] Dopaminergic single-photon emission computed tomography/positron emission tomography imaging studies demonstrated presynaptic and postsynaptic dopaminergic deficits involving the nigrostriatal pathway. However, presynaptic dopaminergic dysfunction was not consistently found,[29] which might explain the limited or absent response to dopaminergic therapy in some ATX-*TBP* patients with parkinsonism.[42,45] The limited information on the response of parkinsonian signs to dopaminergic therapy hampered further analyses. Notably, we found that patients with pure parkinsonism were more likely to have repeat expansions in the RP-rev range, were of Asian ethnicity, and had less frequently a positive family history and cerebellar atrophy than patients in whom parkinsonism was combined with ataxia.

Patients with RP or small-range (41–49 repeats) CAG/CAA expansions were recently reviewed by others and were found to have a highly variable clinical presentation, ranging from pure cerebellar ataxia to a PD-like phenotype.[47] Gait ataxia was the most frequent feature. Unlike our study, this review did not include patients with larger expansions (≥50 repeats). Still, the authors did extract phenotypic variables from some screening studies for *TBP* expansions in patients with PD, which we included only for CAG/CAA repeat sizes analysis of the reported cutoff values. Instead, we have evaluated phenotypic traits of patients considered to have an ATX-*TBP* mutation who could exhibit parkinsonism as part of their clinical picture. Of importance in ATX-*TBP* patients with RP, a recent study excitingly showed a genetic factor that modulates the penetrance of intermediate *TBP* alleles: patients with 41 to 46 repeat expansions almost universally (30/31 cases) carried a heterozygous pathogenic variant in the ATX-*STUB1* gene (MIM #607207), whereas such variants were absent in all 12 patients with 47 to 54 repeat expansions and in 37 healthy individuals with repeat sizes in the RP range.[48] All patients with the combined RP-*TBP/STUB1* genotype exhibited a phenotype similar to that of patients with ≥47 repeat expansions that lacked heterozygous pathogenic variants in the *STUB1* gene. Further studies are required to confirm this digenic inheritance pattern for ATX-*TBP*,[48-50] but these data suggest monogenic dominant disorder for *TBP* alleles with ≥47 repeats and a digenic *TBP/STUB1* disease for intermediate *TBP* expansions. Although rare, the coexistence of *TBP* expansions and expanded alleles in other ataxia genes has also been reported, such as combined *TBP/ATXN3* repeat expansions.[51] Also, a patient with PLA2G6-related neurodegeneration and 42 repeat expansions in the *TBP* gene was recently reported who exhibited a phenotype consisting of ataxia, spasmodic torticollis, parkinsonism responsive to levodopa, and pyramidal signs and who showed marked cerebellar atrophy.[52] These data also point to a limitation of our work, because we included reported carriers of RP *TBP* alleles in whom the presence of *STUB1* or other genetic variants has not been investigated, rendering this at present a counseling challenge.

In this study, we excluded some reported, rare cases with homozygous CAG/CAA repeat expansions in the *TBP* gene.[35,53-58] Notably, a more severe phenotype and faster disease progression in comparison with the heterozygous patients was described in most of these homozygous patients,[35,54,55,57] indicating that a gene dosage effect may contribute to enhanced phenotypic severity because it occurs in some other SCA subtypes, such as ATX-*ATXN3* and ATX-*CACNA1A*.[59-61]

Anticipation, known as the tendency for clinical features to worsen and/or appear at a younger age because of expansion of the repeat from generation to generation, is unusual in ATX-*TBP* compared with other SCA subtypes, such as ATX-*ATXN1*,[62] ATX-*ATXN2*,[63] ATX-*ATXN3*,[64] and ATX-*ATXN7*.[65] The occasional presence of CAA interruptions within the *TBP* CAG repeat configuration stabilizes the repeat in germline transmission.[66-68] By contrast, uninterrupted alleles are unstable, associated with anticipation, and show an expansion bias that increases with paternal age.[67,69] In our analysis, we found that larger CAA/CAG repeats in the expanded allele were inversely correlated with the age at disease onset. We found that interruptions were frequent in the FP-rev group but significantly less than in the RP-rev group. We observed no modifying effect on onset age or other clinical features for the presence

versus absence of interruptions. In addition, larger repeat sizes in the expanded allele were associated with ataxia combined with other movement disorders, such as chorea or dystonia, whereas smaller expansions were more commonly present in patients with pure ataxia, pure parkinsonism, or dystonia (without ataxia). The presence of interruptions was also not associated with a particular clinical feature, contrary to, for example, parkinsonism in ATX-*ATXN2*.[70-72] This may explain the observation of a similar frequency of parkinsonism between the RP-rev and the FP-rev groups, despite more common interruptions in the former group. In contrast with other SCA subtypes, such as ATX-*ATXN1*, ATX-*CACNA1A*, and ATX-*ATXN7* that exhibit an interaction between the expanded and normal alleles in *trans* and age at onset,[73] we found that the number of CAG/CAA repeats in the nonexpanded (normal) allele was not correlated with the age at disease onset.

A limitation of this study is the high proportion of missing data due to incomplete descriptions of patients in the literature, as was also highlighted in previous MDSGene systematic reviews for PD genes[19,74] or dystonia genes.[75] This problem does not allow a precise and reliable analysis or interpretation of less common clinical features. Still, in our opinion, it does not affect the interpretation of results for the most frequent clinical manifestations of ATX-*TBP* and the main conclusions of this study. The fact that the dataset of this review mostly consists of case reports and family studies, which are less prone to missing data compared with mutational screening studies, reinforces the assumption that the missing data are probably because these data (eg, certain clinical manifestations) were absent in the reported patients. Lastly, the lack of knowledge of the *STUB1* status in the RP-rev group is another limitation as mentioned earlier.

Taken together, this MDSGene systematic review on ATX-*TBP* provides a comprehensive overview of demographic, genetic, clinical, and imaging findings and proposes new repeat expansion ranges of RP (41–45 expanded repeats) and FP (46–66 expanded repeats) that are relevant for diagnostic purposes. Any patient who presents with features of the wide ATX-*TBP* spectrum (varying from the classic clinical picture of ataxia combined with another movement disorder, psychiatric problems, or cognitive decline to more atypical features such as prominent or predominant pure parkinsonism) and who has 46 to 66 repeats in the ATX-*TBP* gene can be considered to have TBP-related disease. For such patients with 41 to 45 repeats expansions, additional evidence is needed, eg, through segregation studies, exclusion of alternative (genetic) diagnoses, and perhaps the presence of *STUB1* variants. ■

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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