RESEARCH ARTICLE OPEN ACCESS

DNAJC12 Disease

Clinical Spectrum and Long-Term Outcomes

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Abstract

Background and Objectives

Autosomal recessive DNAJC12 disease, the most recently identified disorder of biogenic amine synthesis, presents with a broad clinical spectrum and variable outcomes, ranging from asymptomatic patients to early-onset parkinsonism. This study aimed to better outline the clinical phenotype and outcomes of DNAJC12 disease, the prognostic value of the metabolic and genetic biomarkers, and the treatment response.

Methods

We systematically collected clinical, biochemical, and genetic data from 56 patients with DNAJC12 disease in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines: 51 from the literature since the disease was first described and 5 unpublished personal cases.

Results

Three prevalent clinical patterns of presentation and outcome were identified: (1) asymptomatic condition, (2) neurodevelopmental disorders (NDD) leading to intellectual disability with psychiatric issues and dystonia-parkinsonism (D-P) during the second decade of life in some patients, and (3) early-onset static L-dopa–responsive parkinsonism in previously asymptomatic adult patients. Hyperphenylalaninemia was the most consistent metabolic alteration. CSF depletion of homovanillic acid (HVA) and 5-HIAA was detected in 18 and 20 of 29 symptomatic patients, respectively. Three stepwise regression analyses identified significant predictors of clinical outcomes in patients with phenylketonuria (PKU). CSF HVA levels and phenylalanine levels at diagnosis predicted the occurrence of D-P, while 26% of intellectual disability variability was explained by CSF HVA at diagnosis, and 31% of psychiatric disorder variability by later age at diagnosis. The phenotype was consistently associated with only a few *DNAJC12* pathogenic variants, primarily for phenotypes A and C.

Movement disorders responded positively to the various therapies in all symptomatic patients. The preventive effects on NDD and psychiatric problems were less clear.

Discussion

DNAJC12 disease is a new metabolic neurodevelopmental disorder linked to parkinsonism. The combined effects of neurotransmitter depletion and disrupted enzyme proteostasis in dopaminergic and serotoninergic neurons may underlie the early neurodevelopmental presentation and subsequent neurologic and psychiatric disorders.

MORE ONLINE

Supplementary Material

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Glossary

ASR = adult self-report; **D-P** = dystonia-parkinsonism; **HPHE** = hyperphenylalaninemia; **HVA** = homovanillic acid; **MD** = movement disorder; **NDD** = neurodevelopmental disorder; **OGC** = oculogyric crises; **VABS-II** = Vineland Adaptive Behavior Scale, second edition.

Introduction

DNAJC12 disease (DNAJC12d; Mendelian Inheritance in Man [MIM]#606060) was first reported in 2017 as a new autosomal recessive disorder affecting the synthesis of dopamine, serotonine, and related metabolites.[1]

Hyperphenylalaninemia (HPHE), the peripheral marker of this condition and one of the metabolic targets of neonatal screening programs contributed to the increase in the number of diagnosed patients in the past few years. Hypotonia, movement disorders (MD) (dystonia, ataxia), and global developmental delay are presenting features during infancy and childhood. Nevertheless, a broad phenotypic spectrum characterizes the clinical presentation and outcomes of the disease, ranging from asymptomatic patients to late-onset dystonia-parkinsonism (D-P).[1-15] Descriptions of the long-term neurologic, neuropsychological, and psychiatric outcomes in patients with DNAJC12d still need to be explored, as well as the value of potential predictive factors.

Based on the report of new unpublished cases and a systematic review of the literature, this study aims to outline the natural history of this condition and evaluate the role of related genetic and metabolic markers on clinical course and outcomes.

Methods

A systematic review based on the PRISMA guidelines included studies from the first description of the disease in February 2017 to December 2024.[1] A PubMed and Scopus search with descriptions of patients with DNAJC12d was performed using the following keywords: "DNAJC12," "DNAJC12 deficiency," "atypical phenylketonuria." Moreover, we contributed to the resultant cohort with 5 unreported patients from 3 families from an Italian network for rare neurometabolic diseases.

Articles were excluded from the analysis if they reported patients without a molecular genetic diagnosis, did not present data on a patient-by-patient basis, focused on nonhuman studies, or were not written in English.

Results were screened by title, abstract, and full text. Duplicates were excluded. Studies reporting overlapping cohorts were identified by comparing relevant features (i.e., number of patients, clinical, genetic, and biochemical data). The studies with the most extensive reporting were included in our analysis (Figure 1).

Study selection was performed independently by 3 authors (F.M., G.R., and F.N.).

The review protocol has been registered with PROSPERO code CRD420250613940.

The following data were extracted from literature and new cases.

1. Clinical data of patients and their affected relatives: age at last assessment, sex, age at onset, clinical features at presentation, age and clinical status at the diagnosis, response to treatment.
2. Biochemical markers: (1) CSF biogenic amines (homovanillic acid [HVA] and 5-hydroxyindolacetic acid [5-HIAA]), and (2) blood phenylalanine (Phe) concentration at diagnosis; (3) prolactin level during the follow-up.
3. *DNAJC12* genotype: all genetic variants were referenced to the same transcript (NM_021800.3); the pathogenicity of each variant in the patient cohort described here was re-evaluated because of conflicting interpretations reported in ClinVar and PNDdb databases. Variants were revised according to American College of Medical Genetics and Genomics (ACMG) guidelines, Association for Clinical Genomic Science (ACGS) best practice guidelines, and Clingen recommendations for Sequence Variant Interpretation.

Statistical analyses were conducted using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS Inc., Chicago, IL). Normality was assessed with the Kolmogorov-Smirnov test. Continuous variables were compared using independent samples t tests, while categorical variables were analyzed with Fisher exact test. Correlation analyses were performed using Spearman correlation coefficient. The dimensional effect of potential predictive metabolic biomarkers on outcomes was evaluated by linear regression analysis. Missing data were handled by applying case-wise deletion for each analyzed parameter; that is, patients with missing data for a specific variable were excluded from the analysis of that variable only. A p value < 0.05 represented statistical significance for all tests.

Clinical assessment data (for the cohort of patients personally examined and, where available, from the literature review).

Neuropsychological, Neurologic, and Psychiatric Assessment

Intellectual development was assessed using the IQ score (Wechsler Preschool and Primary Scale of Intelligence [WPSSI-III] for patients aged 3–6 years)[16]; Wechsler Intelligence Scale for Children [WISC-IV] for patients aged 6–16 years[17]; Wechsler Adult Intelligence Scale [WAIS-IV] for adults ≥17 years).[18] IQ scores >70 were deemed normal.

Executive Function

The Brief Rating Inventory of Executive Function (BRIEF - child, adolescent, and adult version) was used to explore executive functions. BRIEF T-scores greater than 65 were considered clinically significant for executive dysfunction.[19-21]

Adaptive Functioning

Adaptive functioning was assessed as a standardized measure through the Vineland Adaptive Behavior Scale, Second Edition (VABS-II), which is a semistructured parent interview. VABS-II standard scores have a mean of 100 (SD SD ± 15), with lower scores associated with greater impairment.[22]

Motor Function

Motor function was assessed using Section III of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale.[23]

Emotional and Behavioral Profile

The Achenbach System of Empirically-Based Assessments was used to assess emotional and behavioral profile. Psychiatric symptoms were measured using either the Child Behavior Checklist (CBCL, age 6–18 years) completed by patients or their parents, or the Adult Self-Report (ASR), comprising 112 (CBCL) or 126 (ASR) items rated on a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true/often true). Scoring yielded a total problem score, 2 broadband scores (internalizing and externalizing problems), and 8 syndrome scales [anxious/depressed, withdrawn/depressed, somatic complaints, rule-breaking problems, aggressive syndrome scale, social problems (CBCL) or intrusive problems (ASR), thought problems, and attention problems] based on the 2001 profile. Both raw and standardized T scores were generated for total, internalizing, and externalizing symptoms (T scores ≥65 classified as clinically significant; 60–64 as "borderline") and for each syndrome scale (T scores ≥70 classified as clinically significant; 65–70 as "borderline" for emotional or behavioral problems).[24]

Finally, all patients first reported in this study underwent a psychiatric interview. Alterations were classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revised (DSM-5-TR) criteria.

Standard Protocol Approvals, Registrations, and Patient Consents

The local ethics committee approved the study (Prot. 0779/2023, Rif. 3627).

The 5 unpublished patients or their parents (for minors) signed a written informed consent form to participate in this study.

Data Availability

The data sets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

Case Series

ID50

This 54-year-old woman (ID50), the second of 6 offsprings of nonconsanguineous Italian parents, was born at term after an uneventful pregnancy. A global developmental delay was observed during infancy and early childhood (she walked independently at the age of 26 months and spoke her first words at the age of 30 months). At the age of 7 years, she was diagnosed with mild intellectual disability. Because of a mild increase in blood Phe, she started a Phe-restricted diet until the age of 12 years. Clinical conditions remained stable in the following 2 decades, while progressive motor difficulties and behavioral problems emerged around age 40 years. On examination at 53 years, she exhibited bradykinesia, limb rigidity, spontaneous and exercise-induced dystonic limb posture, and postural and action tremor (MDS-UPDRS-section III = score of 40). She had moderate intellectual disability (WAIS-IV edition: full-scale IQ [FIQ] = 40), generalized anxiety disorder, and psychosis with poor adaptive skills (Vineland Adaptive Behavior Scale-II: communication domain = 22; daily living skills domain = 22; socialization domain = 20; composite score = 20).

Under selegiline and L-dopa/carbidopa treatment, she experienced a mild improvement in bradykinesia, dystonia, and anxiety disorder. Sapropterin dihydrochloride supplementation (16 mg/kg/d) obtained a blood decline of Phe (164 μmol/L, r.v. 51–98, Table 1).

ID51

Patient ID51, the older brother of ID50, was born in Italy and diagnosed with global developmental delay (GDD) at age 24 months and Attention-Deficit/Hyperactivity Disorder (ADHD) at 5 years. Clinical conditions remained stable until age 46 years, when he progressively developed bradykinesia, rest and action tremors, and rapid deterioration of his gait, which led him to a wheelchair within a few months (MDS-UPDRS-section III = score of 60 points). A brain MRI was normal, and a DaTScan showed a mildly reduced signal in the right putamen. He was diagnosed with PD. Despite dopaminergic therapy, at age 47 years, he experienced progressive weight loss, constipation, emotional lability, insomnia, restless legs syndrome, and, over the next 3 years, cognitive deterioration with speech apraxia and

Table 1 Biochemical Markers and Genotype of Patients With DNAJC12 Disease

ID/Sex	Phenotype	Blood Phe at diagnosis (μmol/L)	Prolactin level (ng/mL)	CSF HVA nmol/L (nv)	CSF 5-HIAA nmol/L (nv)	Genotype	References
1 M[a]	B	410	23.4*	192 (295–932)	28 (114–336)	c.[298-968_503-2603del]; [298-968_503-2603del]	1
2 F[a]	A	275	38	390 (310–1,100)	76 (150–800)	c.[298-968_503-2603del]; [298-968_503-2603del]	1
3 F[b]	B	460	25.4	44 (133–551)	5 (74–163)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	1
4 M[b]	B	84	10.8	47 (133–551)	2.2 (74–163)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	1
5 M	B	145	22.1*	80 (364–870)	2.8 (220–560)	c.[215G>C]; [215G>C]; p.[Arg72Pro]; [Arg72Pro]	1
6 F	B	503	5.3	27 (220–560)	148 (90–237)	c.[298-968_503-2603del];[298-968_503-2603 del]	1
7 M[c]	B	500	NA	108 (133–551)	28 (50–300)	c.[85delC]; [596G>T]; p.[Gln29LysfsTer38]; [Ter199LeuextTer42]	1
8 F[c]	B	433	NA	86 (133–551)	20.3 (74–163)	c.[85delC]; [596G>T]; p.[Gln29LysfsTer38]; [Ter199LeuextTer42]	2
9 F[d]	A	526	NA	NP	NP	c.[214C>T]; [214C>T]; p.[Arg72Ter]; [Arg72Ter]	2
10 M[d]	A	509	NA	NP	NP	c.[214C>T]; [214C>T]; p.[Arg72Ter]; [Arg72Ter]	2
11 M	A	420	NA	NP	NP	c.[214C>T]; [214C>T]; p.[Arg72Ter]; [Arg72Ter]	2
12 M	B	NA	NA	NP	NP	c.[187A>T]; [187A>T]; p.[Lys63Ter]; [Lys63Ter]	3
13 F[e]	C	449	45.6; 15.6*	37 (115–455)	7 (51–204)	c.[79-2A>G]; [79-2A>G]; p.[Val 27TrpfsTer14]; [Val 27TrpfsTer14]	3,9 Pt 1
14 M[e]	C	NA	NA	NP	NP	c.[79-2A>G]; [79-2A>G]; p.[Val 27TrpfsTer14]; [Val 27TrpfsTer14]	3
15 M	B	564	NA	119 (100–800)	13 (50–300)	c.[298-953_503-2589del]; [298-953_503-2589del]; p[?];[?]	25
16 M[f]	B	249	12.7	NP	NP	c.[58_59delGG]; [58_59delGG]; p.[Gly20MetfsTer2]; [Gly20MetfsTer2]	4
17 M[f]	B	538	NA	119 (167–563)	10 (67–189)	c.[58_59delGG]; [58_59delGG]; p.[Gly20MetfsTer2]; [Gly20MetfsTer2]	4
18 M	B	185	6.97[+]	NP	NP	c.[262del]; [262del]; p.[Gln88SerfsTer6]; [Gln88SerfsTer6]	5
19 M	B	223.14	NA	NP	NP	c.[306C>G]; [182delA]; p.[His102Gln]; [Lys61ArgfsTer6]	6
20–33?	A	97–363 (range)	14.6 (mean)[+]	NP	NP	c.[524G>A]; [524G>A]; p.[Trp175Ter]; [Trp175Ter]	7
34?	A	158	11.7[+]	NP	NP	c.[298-2A>C]; [524G>A]; p.[?]; [Trp175Ter]	7
35?	B	442	NA	NP	NP	c.[502+1G>C];[524G>A]; p.[?];[Trp175Ter]	7
36?	A	324	NA	NP	NP	c.[502+1G>C];[524G>A]; p.[?];[Trp175Ter]	7
37?	B	266	NA	NP	NP	c.[309G>T]; [524G>A]; p.[Trp103Cys]; [Trp175Ter]	7
38?	B	204	NA	NP	NP	c.[309G>T]; [524G>A]; p.[Trp103Cys]; [Trp175Ter]	7
39 M	A	318	NV	NP	NP	c.[404del]; [404del]; p.[Arg135LysfsTer21]; [Arg135LysfsTer21]	8

Continued

Table 1 Biochemical Markers and Genotype of Patients With DNAJC12 Disease *(continued)*

ID/Sex	Phenotype	Blood Phe at diagnosis (μmol/L)	Prolactin level (ng/mL)	CSF HVA nmol/L (nv)	CSF 5-HIAA nmol/L (nv)	Genotype	References
40 F	B	410	NV	332 (364–870)	9 (155–359)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	8
41 F	A	258	NA	NP	NP	c.[158-1G > A]; [336delG]; p.[Val53AspfsTer15]; [Met112IlefsTer44]	11
42 M	B	247	NA	259 (345–716)	24 (100–245)	c.[78 + 1del]; [78 + 1del]; p[?]; [?]	12
43 F[g]	A	168	NA	238.8 (294–1,115)	31 (129–520)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	10
44 F[g]	A	479	NA	164.6 (218–852)	15.9 (66–338)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	10
45 M	A	288	NA	270.6 (233–928)	31.4 (74–345)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	10
46 F	A	521	NA	160.6 (218–852)	15.32 (66–338)	c.[158-2A>T]; [158-2A>T]; p[?]; [?]	10
47 F[i]	B	236	8.6*	275 (236–867)	19 (97–367)	c.[58_59del]; [58_59del]; p.[Gly20MetfsTer2]; [Gly20MetfsTer2]	13, Pt 2
48 F[i]	B	496	13.5*	133 (137–582)	5 (68–220)	c.[58_59del]; [58_59del]; p.[Gly20MetfsTer2]; [Gly20MetfsTer2]	13, Pt3
49 F	B	160	42.4	215 (294–1,115)	26 (129–520)	c.[235C>T]; [235C>T]; p. [Arg79Ter]; [Arg79Ter]	14
50 F[h]	B	419	41.4*	NP	NP	c.[167_168del]; [167_168del]; p.[Phe56SerfsTer1]; [Phe56SerfsTer1]	Unpublished; Pt 4
51 M[h]	B	241	36.8*	NP	NP	c.[167_168del]; [167_168del]; p.[Phe56SerfsTer1]; [Phe56SerfsTer1]	Unpublished, Pt 5
52 F[h]	B	382	33.3*	NP	NP	c.[167_168del]; [167_168del]; p.[Phe56SerfsTer1]; [Phe56SerfsTer1]	Unpublished; Pt 6
53 M	B	529	31*	107 (137–582)	33 (68–220)	c.[132C>G]; [132C>G]; p.[Asp44Glu]; [Asp44Glu]	Unpublished; Pt 7
54 F[e]	C	250	70*	NP	NP	c.[79-2A>G]; [595T>C]; p.[Val 27TrpfsTer14]; [Ter199ArgextTer42]	9,25 Pt 8
55 F	A	179	NA	NP	NP	c.[131A>G]; [410_413del]; p.[Asp44Gly]; [Lys137ArgfsTer18]	Unpublished; Pt 9
56 M	B	233	119	248 (295–932)	75 (114–336)	c.[214C>T]; [185C>A]; p.[Arg72Ter]; [Ala62Glu]	15

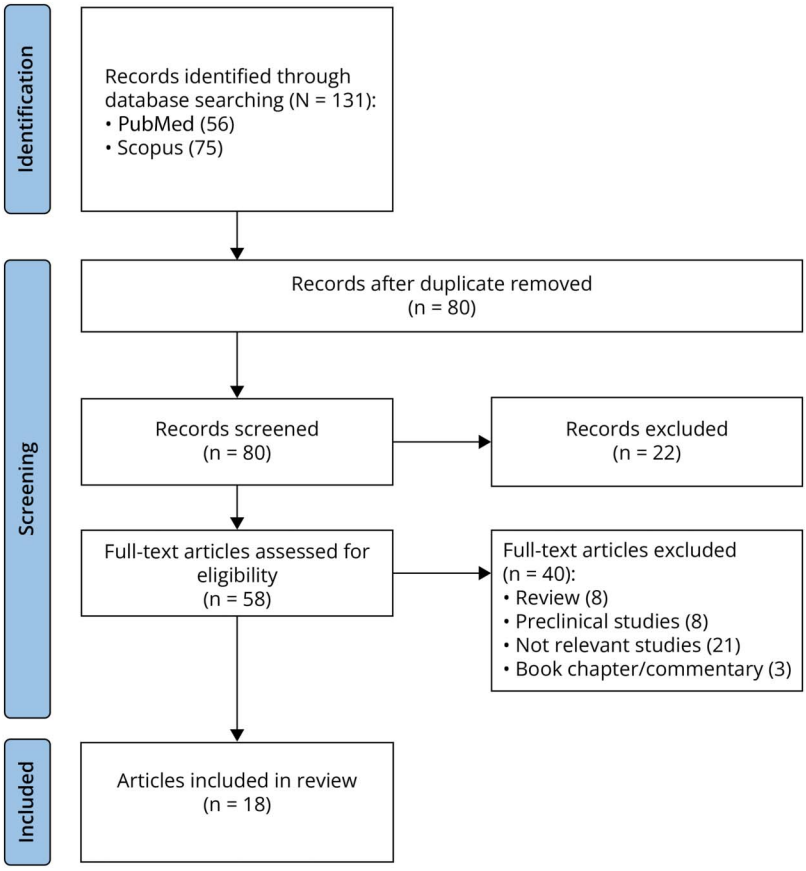
Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid; A = phenotype A; B = phenotype B; C = phenotype C; HVA = homovanillic acid; NA = not available; NP = not performed; nv = normal value; Phe = phenylalanine.
[a,b,c,d,e,f,g,h,i]Siblings; * = prolactin level under treatment; + = not possible to define if the value is before or after treatment. Reference = the reference to the original study from which the data were extracted is provided in brackets.

mood disorders. A mild increase in blood phenylalanine was detected (241 μmol/L). On examination, at age 52 years, the patient presented with symmetric parkinsonism, pervasive anxiety, and restlessness. L-dopa/benserazide and sapropterin dihydrochloride supplementation dramatically improved parkinsonian and psychiatric symptoms while normalizing blood Phe.

ID52

This 46-year-old woman (ID52), the fourth offspring of the same couple, was born at term in Italy after an uneventful pregnancy. In the neonatal period, she was diagnosed with PKU because of an increase in blood Phe detected by the neonatal screening program and began a Phe-restricted diet. Nevertheless, her psychomotor development was delayed, leading to stable mild intellectual disability. On examination, at age 46 years, she exhibited mild symmetric parkinsonism (MDS-UPDRS-section III = score of 34 points) and exercise-induced dystonia of the lower limbs. She had mild intellectual disability (FIQ = 54), low adaptive functioning (Vineland Adaptive Behavior Scale-II: communication domain = 33; daily living skills domain = 52; socialization domain = 35; composite score = 38), a generalized anxiety disorder, and executive dysfunctions (BRIEF: Shift subscale: score of 79; Emotional control subscale: score of 79; Plan/Organization subscale = score of 66).

Figure 1 Study Flow Diagram Showing Selection of Articles for Analysis



Selegiline and sapropterin dihydrochloride treatment improved MD and reduced blood Phe level (170 μmol/L).

ID53

The patient (ID53) was born in Italy following an uneventful pregnancy and delivery. At age 18 months, a GDD was observed. At age 8 years, he presented with severe intellectual disability and autism spectrum disorder, along with clumsiness and mild limb dystonia. General physical examination revealed hypochromic skin lesions on the trunk and limbs. Metabolic alterations included increased blood Phe (529 μmol/L) and decreased CSF HVA and 5-HIAA. Brain MRI was normal. He recently started treatment with sapropterin dihydrochloride and 5-hydroxytryptophan.

ID55

This young girl (ID55) was born in Italy by a normal pregnancy. She tested positive for mild HPHE at newborn screening (Phe: 179 μmol/L). At age 9 years, a retrospective genetic analysis of unsolved cases of HPHE detected *DNAJC12* alterations. On the examination, cognitive profile was normal (WISC-IV: Verbal Comprehension Index [VCI] = 86; Perceptual Reasoning Index [PRI] = 89; Working Memory Index [WMI] = 79; Processing Speed Index [PSI] = 115; FIQ = 88), as well as executive functions (BRIEF: Behavior Regulation Index = 41; Metacognition Index = 47, and Global Executive Composite = 45). Concomitant blood Phe was 313 μmol/L.

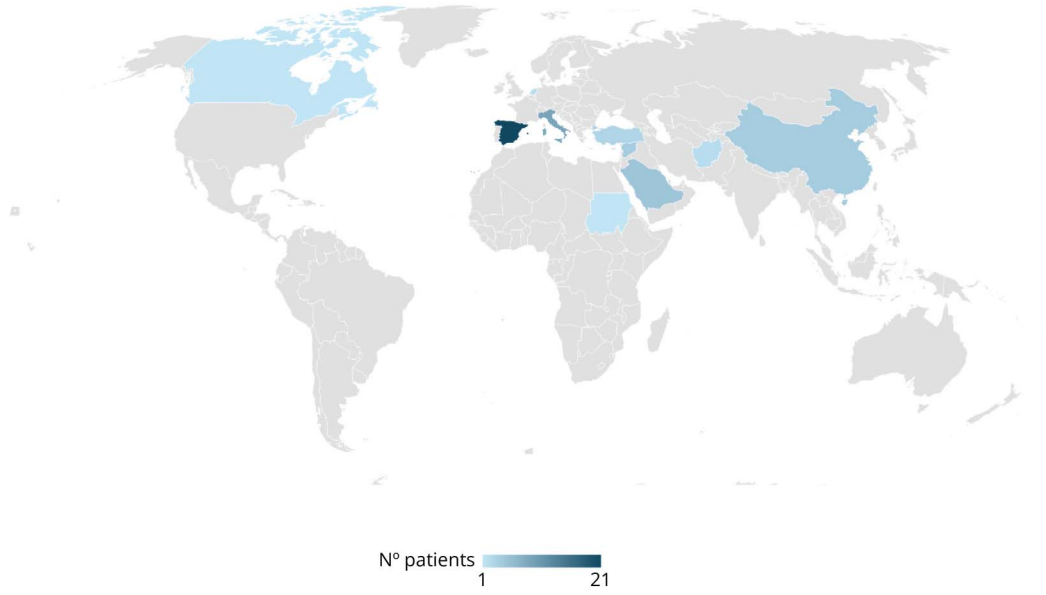
Clinical, Biochemical, and Genetic Data

A systematic literature search identified 18 original papers (2017 to November 2024), cumulatively reporting 51 patients with DNAJC12d. With our 5 unpublished cases, we could collect data from 56 patients (18 F, 19 M, and 19 unreported) (Table 1, Figure 2).

The mean age at the time of the diagnosis and publication were 8.28 years (range 1 month-53 years) and 15 years (range 1 month-73 years), respectively.

Twenty-nine of 56 patients were clinically affected, with a mean age at disease onset being 6 years (range 14 days–51 years): 3 of 29 had neonatal onset, 21 of 29 had infantile onset (0–18 months), 2 of 29 had childhood onset (18 months-11 years), and 3/29 had adulthood presentation (>18 years). The remaining 27 patients were clinically asymptomatic when published. Clinical presentation included neurodevelopmental disorders (NDD), MD, and a single case of epilepsy (eTable 1). Twenty-six of 29 patients were diagnosed with neurodevelopmental disorder at the time of the first

Figure 2 Geographical Distribution of the Patients With DNAJC12 Disease



observation (language disorder = 5; global developmental delay = 10; intellectual disability = 4; autism spectrum disorder = 5; attention deficit hyperactivity disorder = 4). In 17 patients, comorbid MD included focal/segmental dystonia affecting limbs (6/17), parkinsonism (2), oculogyric crises (OGC) in 2, and mild ataxia/dyskinetic MD in 2. Axial hypotonia concurred in 6 patients (Figure 3).

Overt psychiatric disturbances were reported in 2 (mood disorder = 2; anxiety disorder = 1).

Regarding metabolic alterations, HPHE was detected in 54 of 56 patients (M±SD = 305.47 ± 141.70; range = 97–564 μmol/L; r.v. 60–120). Prolactin was increased in 14 of 24 patients (M±SD = 26.02 ± 25.33; range = 6.3–119 ng/mL; r.v. 2–18 ng/mL in male and 2–29 ng/mL in female).

Twenty-one of 29 symptomatic patients underwent CSF sampling at the diagnosis to analyze biogenic amine concentrations: decreased HVA was detected in 18 and 5-HIAA in 20 patients. The lowest values were reported in a patient with parkinsonism (ID13).[25]

Three different regression analyses (step-wise model) were performed to identify significant predictors of clinical outcome (age at diagnosis, Phe at birth, HVA, 5-HIAA, and HVA/5-HIAA ratio in CSF). CSF HVA at diagnosis and phenylalanine levels at birth have a significant influence on the occurrence of MD at the last examination ($R^2 = 0.480$, $p = 0.003$).

Moreover, 26% of ID variability at the last examination was explained by the HVA CSF level at diagnosis ($R^2 = 0.265$, $p = 0.030$), and 31% of psychiatric disorder variability at the last examination was explained by later age at diagnosis ($R^2 = 0.315$, $p = 0.005$).

Clinical Outcome

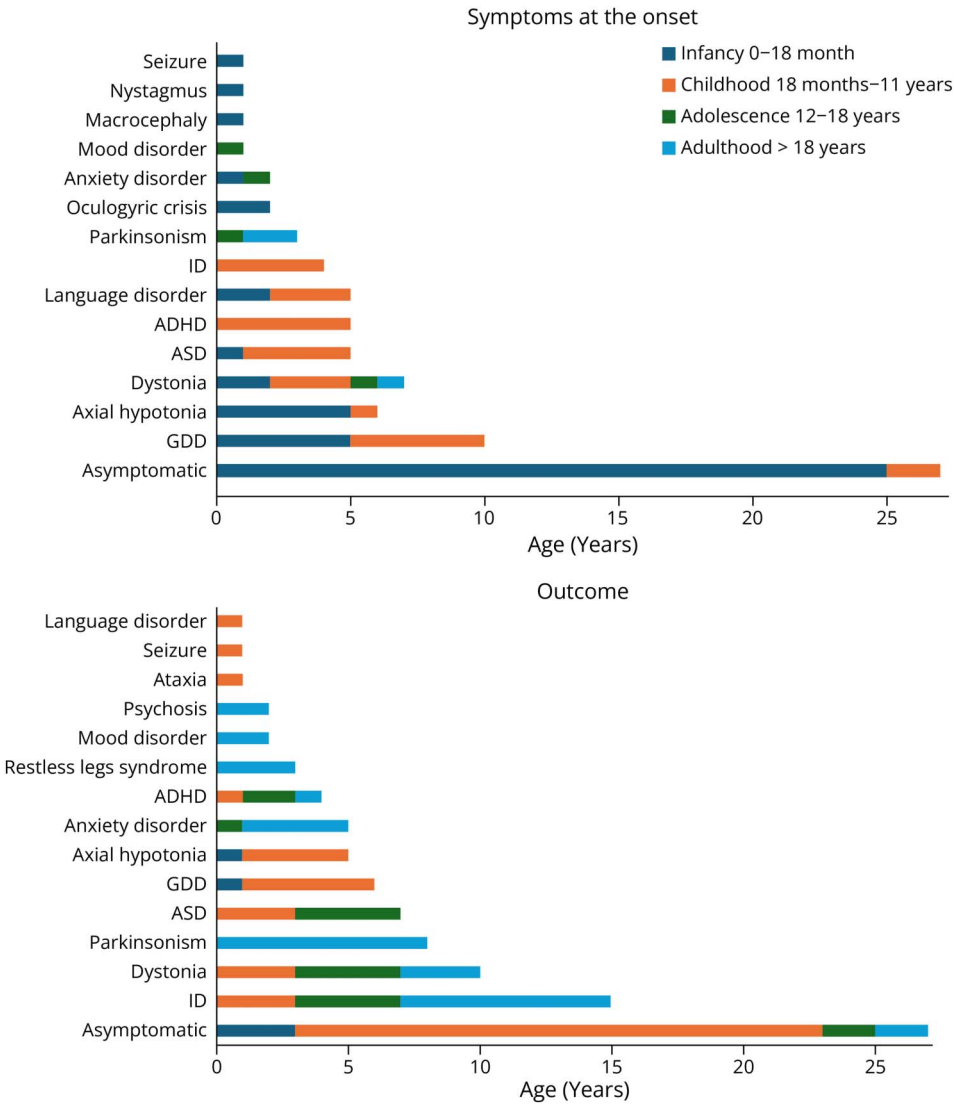
Clinical data were classified according to predefined categories: asymptomatic, presence of a neurodevelopmental disorder, or movement disorder. The timing of symptom onset, when present, was also recorded.

Twenty-seven asymptomatic patients remained unaffected after a few days to many years of follow-up, with age at the last evaluation ranging from 0 months to 40 years (mean 6.15 years). Some of them were treated with sapropterin (10) to correct HPHE, L-dopa/carbidopa (8), 5-hydroxytryptophan (6), folinic acid (2), and Phe restricted diet (1). The oldest untreated patient was a 40-year-old woman with typical development.[7] Concerning 29 symptomatic patients at the diagnosis, the mean age at follow-up was 41.4 years (range 0.7–73 years), 21 were still suffering from global developmental delay (6) that in the older ones led to intellectual disability (as assessed by formal IQ assessment or clinical evaluation) (mild ID = 10; moderate ID = 3; severe ID = 2; eTable 1, Figure 3).

MDs were detected in 17 of 29 patients (eTable 1). Dystonia and ataxia/dyskinesia remained stable in 7 and 2 patients, respectively.[1,2,4,7,13,26] In 9 of 17 patients, the disease progressed in the second decade or later with parkinsonism and D-P in 3 patients with restless leg syndrome (ID13, 51 and 54).[9] One patient still complained of OGC.[7]

In 3 patients, D-P emerged later in adulthood after previous good health remaining stable after 6–28 years of follow-up.

Figure 3 Symptoms at the Onset and Outcome



MDS-UPDRS-section III was available in 3 patients with a mean score of 39.33 (SD ± 5.03; range 34–44).

Seven participants (ID 48, 50-55, eTable 1), assessed by the authors, underwent a standardized neuropsychological assessment. In 6 patients who completed a full IQ test, IQ ranged from 40 to 88 (M ± SD = 62.33 ± 18.59). Four of 5 who completed BRIEF and VABS-II questionnaires scored above the cutoff value for clinically relevant symptoms on at least 1 subscale (Inhibit, Shift, Emotional Control, Initiate, Working Memory) and all VABS-II domains, respectively.

Six patients or their relatives completed CBCL/ASR questionnaires. Five scored above the cutoff value for clinically relevant symptoms in the Internalizing Problems Scale, Anxiety, and Somatic Problems subscales (1 subject).

On the whole, 10 of 29 patients (34.5%; 5 M, 4 F, 1 unreported) met the criteria for a psychiatric diagnosis, including generalized anxiety disorder (6), attention deficit hyperactivity disorder (4), mood disorders (2), and psychosis (2).

In summary, according to the clinical presentation and outcome, 3 different phenotypes have emerged from the patients with DNAJC12d diagnosed so far.

1. Clinically unaffected patients;
2. Patients suffering from early NDD with or without dystonia leading later, from the second decade of life to D-P;
3. Patients asymptomatic during childhood and early adolescence later developing static L-dopa–responsive D-P.

To summarize the present clinical evidence, we can outline 3 main phenotypic patterns.

Phenotype A

Twenty-seven of 56 patients with DNAJC12d (48.2%) were clinically unaffected. In a few of them, the clinical follow-up needs longer to ascribe them to this group. HPHE was detected in all. The newborn screening program for PKU identified 12 of 27, and 9 underwent early treatment: 8 with sapropterin/BH4 (5–10 mg/kg/d) plus L-dopa/carbidopa (10 mg/kg/d in pt 2) and 5-hydroxytryptophan in 5, folinic acid in 2, Phe-restricted diet in 1. None of these patients underwent CSF sampling.

Table 1 shows the genotypes consistently associated with this phenotype so far.

Phenotype A includes 23 homozygous and 4 compound heterozygous genotypes. The most frequent alteration is the nonsense pathogenic variant c.524G>A (p.Trp175Ter), identified in 14 homozygous patients (Table 1). Blood Phe at diagnosis was under 240 μmol/L. RNA analysis disclosed a marked reduction in transcript levels and the absence of detectable protein in fibroblasts.[7]

Other homozygous genotypes involve 3 individuals carrying nonsense pathogenic variant p.Arg72Ter (blood Phe 433–526 μmol/L at the diagnosis),[2] 4 splice-site pathogenic variant c.158-2A > T (blood Phe 168–521 μmol/L), 1 the large, likely pathogenetic deletion c.298-968_503-2603del (blood Phe 275 μmol/L), and 1 frameshift pathogenic variant p.Arg135LysfsTer21(blood Phe 275 μmol/L).

The compound heterozygous patients harbored splice site/nonsense variants, splice site/frameshift variants, or missense and frameshift variants. No missense variants were detected in homozygosity in this phenotypic group. The blood Phe was under 300 μmol/L in all.

Phenotype B

Twenty-six patients (phenotype B in Table 1) presented with a late infantile or early childhood onset neurodevelopmental disorder (language impairment, global developmental delay, autism spectrum disorder, intellectual disability, ADHD), axial hypotonia, OGC, and multifocal to generalized dystonia, with or without pyramidal signs.

In 23 patients, early NDD and dystonia plateau in the following years. In 8 patients (ID6, 7, 15, 16, 17, 37, 48, 56) neurodevelopmental disorder (GDD, autism spectrum disorder [ASD], ADHD) and in 2 neurologic deterioration antedated the later emergence of multifocal dystonia, during the second decade of life.

In 6 patients (ID3, 12, 50, 51, 52, 53) of the 9 with neurologic regression to parkinsonism/D-P, GDD and ID preceded the emergence of the movement disorder after the second decade.

Four patients (ID1, 19, 38, 47) were treated 3–17 months after disease onset and experienced a dramatic response to treatment, with normal (ID19) and near-normal neurologic outcomes (ID1, 38, 47).

Remarkably, patient 47, now age 5 years, who was diagnosed and treated presymptomatically, later developed a mild language impairment. Moreover, a recently published child (ID56) presented with a delay of expressive language progressing toward ASD, despite early supplementation of neurotransmitter precursors and CSF normalization of HVA and 5-HIAA.[15]

The Phe level at the diagnosis was lacking in patient ID12.

CSF was analyzed in 21 patients: HVA was reduced in 17 and 5-HIAA in 19 (Table 1).

In phenotypic group B, the distribution of homozygous and compound heterozygous individuals is also unbalanced, with 19 and 7 patients, respectively. Among the homozygous individuals, frameshift variants are the most common genotype, identified in 8 of 19 patients. This contrasts with group A, where most homozygous individuals (17 of 23) carry nonsense variants, followed by 3 with splicing variants, 3 with large deletions, and a few with missense or nonsense variants. The compound heterozygous genotypes in group B show considerable variability. The nonsense likely pathogenetic variant c.524G>A (p.Trp175Ter) is found in 3 patients in combination with either the splice site pathogenetic variant c.502+1G>C or the missense likely pathogenetic variant c.309G>T (p.Trp103Cys). Additional genotypes include a nonsense likely pathogenetic variant (c.214C>T) in trans with a missense VUS (c.185C>A, p.Ala62Glu), as well as a frameshift likely pathogenetic variant (c.85del) in trans with a stop-loss likely pathogenetic variant (c.596G>T). Blood Phe in this ranged 204–500 μmol/L (Table 1, eFigure 1).

Phenotype C

Three patients (ID13, 14, 54) suffered from early-onset static L-dopa–responsive D-P in previously asymptomatic patients, emerging between age 21 and 51 years.

Patient ID13 was diagnosed with early-onset parkinsonism at 32 years. She had mild progression of motor and nonmotor symptoms over 30 years and experienced mild peak-dose L-dopa–induced dyskinesias that disappeared by fractioning the L-dopa dose. Neuropsychological assessment (at age 55 years) revealed a borderline intellectual ability (IQ = 71). DaTSCAN at age 57 years was normal.

Patient ID14 had mild nonprogressive parkinsonism emerging at age 51 years and psychotic symptoms without overt cognitive dysfunction. DaTSCAN at age 54 years was normal.

Patient ID 54 showed a clinical history of idiopathic hyperprolactinemia and galactorrhea, only partially responsive to

cabergoline treatment, that progressed at age 22 years in a parkinsonism and restless legs syndrome with anxiety disorder. DaTSCAN was not reported.

All patients carried the same *DNAJC12* splice-site likely pathogenetic variant, c.79-2A>G, which leads to exon 2 skipping and results in a frameshift that introduces a premature stop codon (p.Val27TrpfsTer14).[3] The variant occurred in a homozygous state in 2 individuals, specifically ID13 and ID14. In another individual, ID42, this variant was found in a compound heterozygous state, paired with a stop-loss VUS (c.595T>C, p.Ter199ArgextTer) (eFigure 1).

Discussion

DNAJC12 belongs to the family of proteostasis chaperones. It is highly expressed in the brain and liver and is a specific cochaperone of HSP70 members. This protein complex has a particular tropism for proteins such as phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxylase, which have a remarkable tendency to unfold and precipitate in cell-damaging aggregates. Through an interaction cycle with their client protein, the complex DNAJC12/HSP70 prevents unfolding and aggregation of these enzymes or addresses them to demolition, preventing protein precipitation.[27,28]

DNAJC12d has been recently identified as a new autosomal recessive disorder of neurotransmitter synthesis leading to brain depletion of dopamine and serotonin.[1] Since the first report, DNAJC12d has been diagnosed in about 51 patients, with a growing number of patients intercepted by neonatal screening programs. The lack of a definitive genotype-phenotype correlation, the high percentage of asymptomatic patients, and the limited follow-up of the patients so far diagnosed affect the choice of treatment in presymptomatic patients and the possibility of predicting the long-term prognosis. Like other defects of biogenic amine metabolism,[29] DNAJC12d belongs to the growing number of conditions causing neurodevelopmental and MDs ("metabolic NDD"). To extract from the current clinical, metabolic, and genetic data possible biomarkers predictive of the disease outcome, we systematically collected the clinical records from 51 patients reported in the literature. Moreover, we directly examined 9 Italian patients, 5 of whom were unpublished.

Based on current clinical data, we outlined 3 clinical patterns of disease presentation and course: (1) asymptomatic patients (except for HPHE); (2) patients with early NDD progressing toward D-P from the second decade of life on, and (3) adult-onset, relatively static L-dopa–responsive parkinsonism in previously asymptomatic patients.

The occurrence of parkinsonism in patients with DNAJC12d evokes observations made in the autosomal dominant form of *CGH1* defect, a disorder that affects the same metabolic pathway as DNAJC12. The higher-than-expected occurrence of PD in some *CGH1* pedigrees suggested a possible pathogenetic link between this gene and PD.[30] No evidence of nigrostriatal degeneration imaging has been reported in 2 of the 3 examined patients with adult-onset parkinsonism associated with DNAJC12d. In a patient with phenotype B (ID12), described as nonprogressive juvenile parkinsonism,[3,31] ^{18}Fluoro(F)-Dopa PET imaging at ages 56 and 73 years detected a nonprogressive reduction in the tracer uptake. The raclopride PET striatum/background ratio was within the normal range. A reduced symmetrical striatal dopamine transporter (DAT) density was also detected in our ID50 patient with a static L-dopa–responsive parkinsonism. PD is a neurodegenerative condition resulting from the loss of dopaminergic neurons in the ventrolateral region of the substantia nigra and the accumulation of Lewy bodies in the brainstem (nigral cells and locus coeruleus).[32,33] By contrast, DNAJC12d is a metabolic disorder causing dopamine depletion in the nigrostriatal pathway because of secondary tyrosine hydroxylase (TH) deficiency.[7,34] The progression of neuroimaging alterations, rather than their occurrence, coupled with disease progression despite treatment, would help discriminate between static parkinsonism and PD. Based on current data, no evidence exists that DNAJC12d may result in PD. Apart from the derangement of neurotransmitter synthesis, further studies should investigate the long-term impact on neuronal cells, if any, of increased unfolding, aggregation, and precipitation of proteins, depending on DNACJ12 proteostasis function failure.

Regarding biochemical markers, mild HPHE is a common, although nonspecific, biomarker of DNAJC12d. CSF HVA and 5-HIAA depletions were detected in 80% and 90% of the symptomatic patients undergoing CSF sampling, respectively. Therefore, the diagnostic value of CSF examination is limited to patients showing alterations, and it cannot rule out the disease in those who do not. CSF HVA at diagnosis and phenylalanine levels at birth marginally influence the occurrence and outcome of MD. The age at diagnosis correlates with the presence of psychiatric disorders, which are prominent in adults with phenotype B.

The genetic background reveals that many potentially pathogenic allele variants remain without known consequences at the transcript level. Notably, 44 of 56 patients were homozygous for pathogenic/likely pathogenetic variants. Nonsense pathogenetic variants such as p.Trp175Ter and p.Arg72Ter are associated with HPHE as the only symptom. Other variants, including splice-site pathogenetic variant c.158-2A>T and large deletion c.298-968_503-2603del, also occur in homozygous states in different patient groups and lead to undetectable levels of the DNAJC12 protein.[7]

In group A, most patients carry homozygous variants, while a smaller percentage have compound heterozygous variants. The data show that nonsense variants are particularly common, making up a substantial portion of the alleles, with the c.524G>A (p.Trp175Ter) variant being the most frequent.

This pattern suggests a strong association between these nonsense variants and the clinical phenotype observed in this group.

Group B is characterized by a more diverse genetic profile, with no single variant being predominant, although some like p.Gly20MetfsTer2 (pathogenetic), p.Phe56SerfsTer13 (likely pathogenetic), and c.158-2A>T (pathogenetic) recur in more than 1 patient. This group shows a higher occurrence of frameshift and missense variants, accounting for 37% and 15% of alleles, respectively. By contrast, the splicing and nonsense variants are less common. This variability in genetic changes suggests that multiple genetic factors can contribute to the phenotype observed in group B.

Group C consists of 3 patients, all of whom have the splice-site pathogenetic variant c.79-2A>G. This variant leads to exon skipping and a frameshift (Val27TrpfsTer14). It is found in homozygous form in 2 patients and a compound heterozygous form with a stop-loss VUS (p.Ter199ArgextTer42) in 1 patient. This variant occurs in 5 of 6 alleles in this group, indicating a strong link between this genetic variant and the C phenotype. The VUSs reported in this study merit reclassification as pathogenic or likely pathogenic.

Concerning therapy, although controlled studies on pharmacologic treatment are lacking, sapropterin/tetrahydrobiopterin supplementation normalizes HPHE while dopamine precursors improve and may prevent the occurrence of MD in DNAJC12d. How long this treatment may be effective in preventing or improving NDD requires further observations. Despite early neurotransmitter precursor treatment and CSF HVA and 5-HIAA normalization, a child was recently reported to have developed ASD.[15] Low dosage of pramipexole, in addition to L-dopa treatment, was effective in improving restless legs syndrome in 2 adult patients with parkinsonism and D-P, respectively.[9]

In conclusion, the DNAJC12d is a neurodevelopmental disorder associated with dystonia and parkinsonism in various combinations depending on the age at presentation. Second, at least as far as MDs are concerned, it is a potentially treatable metabolic condition with a self-limiting, nonprogressive course. Finally, HPHE, which occurs in almost all patients, provides the advantage of an early presymptomatic diagnosis through a neonatal screening program. The pathogenesis of the disease and genotype-phenotype correlations are topics for further studies.

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