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Research Paper

Attenuated Clinical Forms of Tubulinopathies in Children and Adults: A Series of 24 Individuals

Meghane Durizot, MD [a], Lydie Burglen, MD, PhD [b,c], Catherine Garel, MD, PhD [d], Eléonore Blondiaux, MD, PhD [d], Audrey Riquet, MD [e], Valentine Floret, MD [f], Vincent Desportes, MD, PhD [g], Maria Häänpaa, MD, PhD [h], Maria Irene Valenzuela, MD [i], Anna Maria Pinto, MD, PhD [j], Alessandra Renieri, MD, PhD [k,l,m], Michiel Vanneste, MD [n], Koen Devriendt, MD, PhD [n], Liesbeth de Waele, MD, PhD [o], Lucie Guilbaud, MD, PhD [p], Jean-Marie Jouannic, MD, PhD [p], Madeleine Harion, MD [a], Thierry Billette de Villemeur, MD, PhD [a], Diana Rodriguez, MD, PhD [a], Emmanuelle Lacaze, MD [a], Mathieu Milh, MD, PhD [q], Robin Cloarec, MD [r], Alexandra Afenjar, MD [b,c], Delphine Héron, MD [s,t], Cyril Mignot, MD, PhD [b,t], Stéphanie Valence, MD, PhD [a,t,*]

[a] *APHP Sorbonne Université, Service de Neuropédiatrie, Hôpital Trousseau, Paris, France*
[b] *Département de Génétique, APHP Sorbonne Université, Hôpital Trousseau, Paris, France*
[c] *Department of Clinical Genetics, Centre de Référence Malformations et Maladies Congénitales du Cervelet, Hôpital Armand-Trousseau, Paris, France*
[d] *APHP Sorbonne Université, Service de Radiologie, Hôpital Trousseau, Paris, France*
[e] *Département de Neuropédiatrie, GHICL Université Catholique de Lille, Hôpital Saint Vincent de Paul, Lille, France*
[f] *CHU de Lille, Service de Neuropédiatrie, Hôpital Salengro, Lille, France*
[g] *Centre de Référence des Maladies Rares et Déficience Intellectuelle, HCL Université de Lyon, Service de Neuropédiatrie HFME, Lyon, France*
[h] *Clinical Genetics, Turku University Hospital, Turku, Southwest Finland, Finland*
[i] *Clinical and Molecular Genetics, Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain*
[j] *Clinical Genetics, Policlinico Le Scotte – University Hospital of Siena, Siena, Tuscany, Italy*
[k] *Medical Genetics, University of Siena, Siena, Italy*
[l] *Department of Medical Biotechnologies, Med Biotech Hub and Computer Center, University of Siena, Siena, Italy*
[m] *Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena, Italy*
[n] *Clinical Genetics, University Hospitals Leuven, Leuven, Flemish Brabant, Belgium*
[o] *Neuropediatry, University Hospitals Leuven, Leuven, Flemish Brabant, Belgium*
[p] *Service de Médecine fœtale, APHP Sorbonne Université, Hôpital Trousseau, Paris, France*
[q] *Service de Neurologie Pédiatrique, APHM Aix-Marseille Université, Hôpital de la Timone-Enfants, Marseille, France*
[r] *Centre de Référence Déficiences Intellectuelles et Polyhandicap de causes Rares, APHM Aix-Marseille Université, Hôpital de la Timone-Enfants, Marseille, France*
[s] *Département de Génétique, APHP Sorbonne Université, Hôpital Pitié Salpétrière, Paris, France*
[t] *Department of Pediatric Neurology, Centre de référence Deficiences Intellectuelles de causes rares, Paris, France*

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ABSTRACT

Background: Tubulinopathies are neurodevelopmental disorders caused by pathogenic variants in tubulin-encoding genes, typically presenting with intellectual disability (ID), epilepsy, motor impairments, and distinct brain malformations. While most cases are de novo and severe, recent reports suggest the existence of milder imaging and clinical phenotypes, including familial cases with attenuated symptoms.

Methods: Through international collaboration, clinical, imaging, and molecular data were collected from 24 individuals (≥4 years old) across 16 families with pathogenic or likely pathogenic variants in TUBA1A, TUBB2B, TUBB3, TUBB, or TUBB2A. Patients were selected based on absence of ID and availability of brain MRI. Genetic inheritance patterns and genotype–phenotype correlations were analyzed.

* Communications should be addressed to: Dr. Valence; Service de Neuropédiatrie; Hôpital Trousseau; 26 Avenue du Dr Arnold Netter; Paris 75012, France.
E-mail address: stephanie.valence@aphp.fr (S. Valence).

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Results: Fifteen patients were identified through fetal or pediatric imaging and nine through familial investigations. No cases exhibited severe cortical gyration anomalies. TUBB3 was the most frequently mutated gene (12/24, 50%), and 7 out of 14 total variants were inherited. Two recurrent variants, TUBB3 p.(Pro357Leu) and TUBB p.(Asn52Ser), were associated with non-ID phenotypes in both the current cohort and literature.
Conclusions: This study broadens the spectrum of tubulinopathies to include mild imaging phenotypes with attenuated clinical features in children and adults. Absence of major cortical malformations, inherited mutations, and specific genetic variants may serve as favorable prognostic markers. These findings have important implications for genetic counseling, particularly in prenatal cases.

Introduction

Tubulinopathies encompass a wide range of congenital brain malformations and neurological disorders resulting from likely pathogenic/pathogenic variants (LP/PVs) in genes encoding different tubulin isotypes. To date, dominant pathogenic variants have been reported in 6 genes (*TUBA1A, TUBB2B, TUBB, TUBB3, TUBB2A,* and *TUBG1*).[1] The associated phenotypes share common imaging features such as cerebral cortical anomalies, ranging from lissencephaly to dysgyria, dysmorphic or hypertrophic basal ganglia due to ectopic corticospinal tract, anomalies of the corpus callosum (CC), and cerebellar and brainstem hypoplasia/dysplasia. Clinically, most patients reported to date presented with severe developmental delay, moderate to severe intellectual disability (ID), motor dysfunction, and frequent refractory epilepsy. The severity of the clinical phenotype correlates in part with the causal gene and with the extent of brain malformations.[1-3] Only a few point mutations are known to be consistently associated with specific phenotype, such as p.(Arg402Cys)[3,4] and p.(Arg402His)[3,5] in *TUBA1A*-related lissencephaly or p.(Glu410Lys) in *TUBB3* causing congenital fibrosis of the extraocular muscles and complex midline defects.[6]

In addition to the classic phenotypes, milder forms of tubulinopathies have been described in a few patients with mild cognitive impairment and without epilepsy, whose brain magnetic resonance imaging (MRI) scans do not show major cortical disorder.[7-12] Notably, inherited variants have been reported, suggesting either incomplete penetrance, a parental mosaicism, or a mild parental phenotype.[13-16]

Recently, Hagege et al. described a mild imaging phenotype in fetuses.[14] This phenotype includes midline distortion, CC anomalies, ventricular asymmetry, frontal horn and sulcus anomalies, and brainstem anomalies—without major gyration defects or microcephaly. In a study of 34 fetuses, termination of pregnancy (TOP) was performed in 70% of cases. However, molecular analyses, often performed post-TOP, revealed that variants in tubulinopathy-related genes were inherited in 50% of cases from an asymptomatic parent with a poorly documented phenotype.

Our objective was to refine the concept of "mild tubulinopathies" from a clinical perspective, by describing both neurological and imaging manifestations in children and adults without ID harboring a tubulin LP/PV.

Materials and Methods

Thanks to a *collaborative call* through the European Rare Disease Network ITHACA, we collected data from patients with tubulinopathies fulfilling the following criteria: (1) age greater than 4 years; (2) with an LP/PV (class 4 or 5 American College of Medical Genetics and Genomics) in the *TUBA1A, TUBB2B, TUBB3, TUBB2A, TUBG1,* or *TUBB* gene; and (3) without ID or with limited intellectual impairment. The last criterion was met (1) if the Full-Scale Intellectual Quotient (FSIQ) was >70 as assessed by Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition for children aged 4 to 6 years; (2) if standardized psychometric tests (Wechsler Intelligence Scale for Children-Fifth Edition or Wechsler Adult Intelligence Scale) excluded ID (FSIQ >70); and (3) for individuals who did not undergo formal psychometric assessment: normal schooling in children and teenagers or vocational autonomy in adults. All participants were asked to complete a data collection sheet. Brain MRI scans, when performed, were reviewed by a radiologist (C.G.) and a neuropediatrician (S.V.) and analyzed according to the classical cardinal signs of tubulinopathies (gyration defect, dysmorphic and/or fused basal ganglia, abnormal CC, and cerebellar and brainstem abnormalities),[1] taking into account the recently described major and minor criteria of mild tubulinopathy.[14] Major criteria included midline distortion, ventricular asymmetry, dilatation and/or distortion, abnormal sulcation, and dysmorphic and/or dilated frontal horn(s). Minor criteria included absence or asymmetry of the olfactory sulci and classical posterior fossa abnormalities, such as cerebellar dysgenesis/hypoplasia, anteroposterior diameter of the pons $\leq$5th centile, abnormal bulging of the pons, and brainstem asymmetry.

All patients and/or their legal representatives were provided an informed consent form explaining the procedures and objectives of the study. This study was approved by the Research Ethics Committee of the Société Française de Pédiatrie on 25 July, 2023 (CERSFP_2023_154).

Results

Description of the population

We collected data from 24 patients from 16 unrelated families, including 16 males (67%) and 8 females (33%). At the last follow-up, the median age was 9 years (range 4 to 39 years), with 11 patients being adults (>18 years). The median age at genetic diagnosis was 13 years (range 10 months-77 years).

Clinical-imaging phenotypes

Tables 1 and 2, based on data collection, summarize the clinical and imaging characteristics of the patients.

Circumstances of diagnosis of tubulinopathy

Our series includes 13 index cases referred for the diagnosis of pre- or postnatal signs. Their ages at last follow-up were 2.5 to 33 years (median 9 years). Eleven individuals were diagnosed following a family segregation study. Their ages were 0.8 to 77 years (median age 33 years).

TABLE 1.
Clinical Characteristics

Patient ID	Family 1		Family 2*			Family 3	Family 4	Family 5		Family 6	Family 7	
	P1†	P2	P3	P4	P5	P6†	P7†	P8†	P9	P10†	P11†	P12
Gene (variant) *Diagnostic tool*	***TUBB3*** *(p.Arg46Gln)* *Gene panel for cerebellar malformations*		***TUBB3*** *(p.Pro357Leu)* *Gene panel for cerebellar malformations*			***TUBB3*** *(p. Pro357Leu)* *Exome*	***TUBB3*** *(p. Val255Ile)* *Exome*	***TUBB3*** *(p.Val76Ile)* *Exome*		***TUBB3*** *(p. Glu205Lys)* *Exome*	***TUBB3*** *(p.Glu328Lys)* *Gene panel for cerebral malformations*	
Transmission	Inherited (P2)	NA	NA	Inherited (P3)	Inherited (P3)	*De novo*	*De novo*	Inherited (P9)	NA	NA (duo)	Inherited (P12)	NA
Sex	F	M	F	M	F	M	M	M	M	M	M	M
Age at genetic diagnosis	21 y	55 y	33 y	6 y	10 m	2 y 6 m	6 y	33 y	77 y	9 y	2 y 8 m	32 y
Initial first signs/ diagnostic discovery mode	18 m (motor delay)	Family genetic investigation	Family genetic investigation (MTP)	Antenatal	Antenatal	Antenatal	4 m (no head holding)	Primary school academic challenges	Family genetic investigation	Primary school academic challenges	10 m (motor delay)	Family genetic investigation
Age of sitting	12 m	NA	NA	NA	NA	NA	12 m	9 m	NA	NA	9 m	NA
Age of walking	28 m	NA	NA	20 m	22 m	4 y	24 m	14 m	NA	15 m	26 m	NA
Language delay	-	-	NA	+	+	+	+	-	NA	-	-	-
Age at last follow-up	19 y	57	37 y	6 y	4 y 3 m	6 y	7 y	33 y	77 y	9 y	4 y 6 m	32 y
Head circumference at last follow-up (S.D.)	2	NA	−1	−1	0	−1.5	−2.9	−0.35	NA	NA	+2.1	+2,5
Neuromotor disorders	Cerebello spastic, hemiparesis	-	-	-	-	Widened base of support	Spastic diparesis	-	NA	-	Ataxic	Ataxic
Mirror movements	NA	-	+	+	+	+	-	+	+	-	-	-
Epilepsy (type, age)	-	-	-	-	-	-	-	Absences, 29 y	NA	-	-	-
Education	Higher technician's diploma	High school education	Professional aptitude certificate	ORD	ORD	ORD	ORD	ORD	Studied until 14 y	ORD	ORD	NA
Professional integration	Na	Airport agent	Manual work	na	na	na	Na	Waiter	Carpenter and glazier	na	na	Landscaper
Neuropsychologic assessment	WISC-IV (12 y 3 m)	NA	WAIS (36 y)	WPPSI-IV (6 y)	WPPSI-IV (4 y 3 m)	WISC-V (6 y 3 m)	NA	NA	NA	WISC-V (8 y 5 m)	SON test (4 y 6 m)	-
FSIQ	89	NA	74	82	87	86	NA	NA	NA	74	79	-

Patient	Family 8		Family 9*	Family 10		Family 11	Family 12	Family 13	Family 14*		Family 15	Family 16
	P13†	P14	P15	P16†	P17	P18†	P19†	P20†	P21	P22	P23†	P24†
Gene (variant) *Diagnostic tool*	***TUBB*** p.(Asn52Ser) *Gene panel for cerebellar malformations*		***TUBB*** p. (Asn52Ser) *Exome*	***TUBB*** p.(Lys58Arg) *Exome*		***TUBA1A*** p. (Leu117Phe) *Exome*	***TUBA1A*** p. (Val118Met) *Exome*	***TUBA1A*** p. (Tyr103Cys) *Exome*	***TUBB2B*** *(p.Met299Ile)* *Exome*		***TUBB2B*** p. (Ile210Asn) *Exome*	***TUBB2A*** p. (Gly142Ala) *Gene panel for cerebellar malformations*
Transmission	Inherited (P14)	NA	NA	Inherited (P17)	NA	*De novo*	*De novo*	*De novo*	Inherited (P22)	NA	*De novo*	*De novo*
Sex	M	M	F	F	F	M	M	M	F	F	M	M
Age at genetic diagnosis	14 y	47 y	39 y	7 y	33 m	9 y	6 y	5 y	28 y	NA	13 y	4 y
Initial first signs/ diagnostic discovery mode	12 m (motor delay)	Family genetic investigation	Family genetic investigation (MTP)	9 m (motor delay)	Family genetic investigation	20 m (motor delay)	Antenatal	Antenatal	Family genetic investigation (MTP)	Family genetic investigation	Primary School academic challenges	18 m (motor delay)
Age of sitting	9 m	NA	NA	>9m	NA	NA	10 m	NA	NA	NA	NA	8 m
Age of walking	22 m	NA	NA	22 m	NA	20 m	24 m	20 l	NA	NA	12 m	3 y
Language delay	+	NA	-	+	NA	+	+	+	NA	NA	-	-
Age at last follow-up	14 y	NA	39 y	11 y	NA	9 y	6 y	6 y	NA	NA	13 y	5 y
	+2.5	NA	NA	+1.5	NA	−1	NA	NA	NA	NA	NA	+0.5

(*continued on next page*)

Table 1 (*continued*)

Patient	Family 8		Family 9*	Family 10		Family 11	Family 12	Family 13	Family 14*		Family 15	Family 16
	P13†	P14	P15	P16†	P17	P18†	P19†	P20†	P21	P22	P23†	P24†
Head circumference at last follow-up (S.D.)												
Neuromotor disorders	Cerebellar ataxia	NA	-	-	NA	-	Ataxia, oculomotor apraxia	Oculomotor, coordination difficulties	NA	NA	-	Choreo dystonia
Mirror movements	-	NA	NA	-	NA	-	-	-	NA	NA	-	-
Epilepsy (type, age)	-	NA	-	Single status epilepticus, 2 y	-	-	-	Absences, 29 y	NA	-	-	-
Education	ORD	Post-secondary education	Post-secondary education	SPE	Professional aptitude certificate	SPE	ORD	ORD	Post-secondary education	NA	ORD	NA
Professional integration	NA	Tertiary sector	Tertiary sector	NA	NA	NA	NA	NA	Tertiary sector	NA	NA	NA
Neuropsychologic assessment	K- ABC (5 y 11 m)	NA	NA	NA	NA	WPPSI (6 y)	NA	NA	NA	NA	NA	WPPSI (6 y)
FSIQ	84	NA	NA	NA	NA	70	NA	NA	NA	NA	NA	75

Abbreviations:
F = Female
FSIQ = Full-Scale Intellectual Quotient
M = Male
MTP = Medical termination of pregnancy
NA= Not available
na= Not applicable
ORD = Ordinary schooling
P = Patient
SON = Snijders-Oomen Nonverbal Intelligence Test (SON test)
SES = Special Education School
WAIS = Wechsler Adult Intelligence Scale
WISC = Wechsler Intelligence Scale for Children
WPPSI = Wechsler Preschool and Primary Scale of Intelligence
+ = Present
- = Absent
* Index case was the first MTP fetus.
† Index cases.

TABLE 2.
Imaging Characteristics

Patient	Gene (Variant)	Age at Brain MRI	Classical Signs of Tubulinopathies (Bahi Buisson et al., 2016)[24]					Others Signs of "Mild" Tubulinopathies (Hagege et al., 2022)
			Gyration	Basal Ganglia	Corpus Callosum	Cerebellum	Brainstem	
P1	TUBB3 p.(Arg,46Gln)	14 y and 20 y	Frontal left dysgyria	dysm, fus	Short	Vermis <3rd p., right dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild dist, asym LV, dysm fH
P3	TUBB3 p.(Pro357Leu)	31 y	N	fus	short and dysgenetic	right dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH
P4	TUBB3 p.(Pro357Leu)	2 m	N	dysm, fus	Short and dysgenetic	left dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH
P5	TUBB3 p.(Pro357Leu)	34 GW	N	dysm, fus	Short	N	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH
P6	TUBB3 p.(Pro357Leu)	8 d	N	dysm, fus	N	N	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH
P7	TUBB3 p.(Val255Ile)	2.5 y	bilat frontal dysgyria	dysm, fus	Short, thin and dysgenetic	Vermis <3rd p., left dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH, hypoplastic olfactive sulci
P8	TUBB3 p.(Val76Ile)	29 y	N	fus	Dysgenetic	Dysgenetic vermis <3rd p.	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV
P9	TUBB3 p.(Val76Ile)	77 y	N	dysm, fus	Na	Na	asym brainstem	Mild-dist, asym LV
P10	TUBB3 (p.(Glu205Lys)	5 y	N	fus	Dysgenetic	Dysgenetic vermis <3rd p., right dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., asym brainstem	Mild-dist, asym LV, dysm fH
P13	<I>TUBB</I> (p.asn52Ser)	5 y	N	dysm	Dysgenetic	Right dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb	Mild-dist, asym LV, dysm fH, asym olfactive sulci
P14	<I>TUBB</I> (p.asn52Ser)	40 y	N	dysm	Dysgenetic	Vermis <3rd p., right dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH
P16	<I>TUBB</I> (p.Lys58arg)	2.5 y	N	dysm, fus	Dysgenetic	Vermis <3rd p., left dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH
P17	<I>TUBB</I> (p.(Lys58arg)	34 y	N	fus (right)	N	Vermis< 3rd p., left dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb, asym brainstem	Mild-dist, asym LV, dysm fH, hypoplastic olfactive sulci
P18	<I>TUBA1A</I> p.(Leu117Phe)	9 y	N	dysm, fus	Short, dysgenetic	Vermis <3rd p., left dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb	Mild-dist, asym LV, dysm fH
P19	TUBA1A (p.Val118met)	5 y	N	dysm	Dysgenetic	Vermis <3rd p., right dysgenetic cerebellar hemisph	ant-post diameter of pons <5th p., abnormal bulb	Mild-dist, asym LV, dysm fH
P20	<I>TUBA1A</I> (p.Tyr103Cys)	3 m	NA	NA	NA	NA	NA	Mild-dist, asym LV, dysm fH
P21	<I>TUBB2B</I> (p.Met299Ile)	28 y	N	fus	Short, dysgenetic	N	ant-post diameter of pons <5th p., abnormal bulb	Mild-dist, asym LV, dysm fH
P23	<I>TUBB2B</I> (p.Ile210Asn)	13 y	N	dysm, fus	Dysgenetic	N	asym brainstem	Mild-dist, asym LV, asym olfactive sulci
P24	<I>TUBB2A</I> (p.Gly142Ala)	2 y	Left frontal dysgyria	N	N	N	asym brainstem	Mild-dist, asym LV, dysm fH

Abbreviations:
ant-post = Anteroposterior
asym = Asymmetric
bilat = Bilateral
dist = Distortion
dysm = Dysmorphic
fH = Frontal horn
fus = Fused
GW = Gestational weeks
hemisph = Hemisphere
LV = Lateral ventricle
MRI = Magnetic resonance imaging
N = Normal
na = Nonavailable
NA = Not available
P = Patient
p. = Percentile

Fetuses with tubulinopathy. In 5 cases (4 families), the first signs of the disease were observed prenatally. Patient (P) 6 and P19 were referred for a complex brain malformation discovered prenatally, and P20 had isolated midline distortion on fetal brain imaging. In Family 2 (Fig 1), the index case was a fetus with cerebral malformation (TOP without genetic analysis). His mother (P3) had 2 other term pregnancies characterized by the discovery of cerebral malformations (P4 and P5). The genetic diagnosis of tubulinopathy was established postnatally in these 2 children as well as in their mother.

Children with tubulinopathy. In 10 index cases, the first signs were observed postnatally. In 7 of 10 children, the disease first manifested as a motor delay, including absent head holding at 4 months (n = 1/7) and unachieved sitting or walking after 8 months (n = 5/7) or 18 months (n = 7/7), respectively. In 3 of 10 patients, learning difficulties in school requiring specific accommodations raised the first concerns.

Familial segregation analyses. In 9 adult individuals, the molecular diagnosis of tubulinopathy was confirmed through segregation analysis. In particular, in Family 9 and Family 14, the molecular diagnosis was carried out following TOP of affected fetuses. Initially, the variants were classified as variant of uncertain significance because the parents were asymptomatic. However, in Family 9, the p.(Asn52Ser) variant was later reclassified as pathogenic, as it had been previously reported in the literature. In Family 14, the reclassification was based on the recurrence of brain malformations in 2 fetuses, along with MRI findings in P21 consistent with a mild form of tubulinopathy (Fig 1).

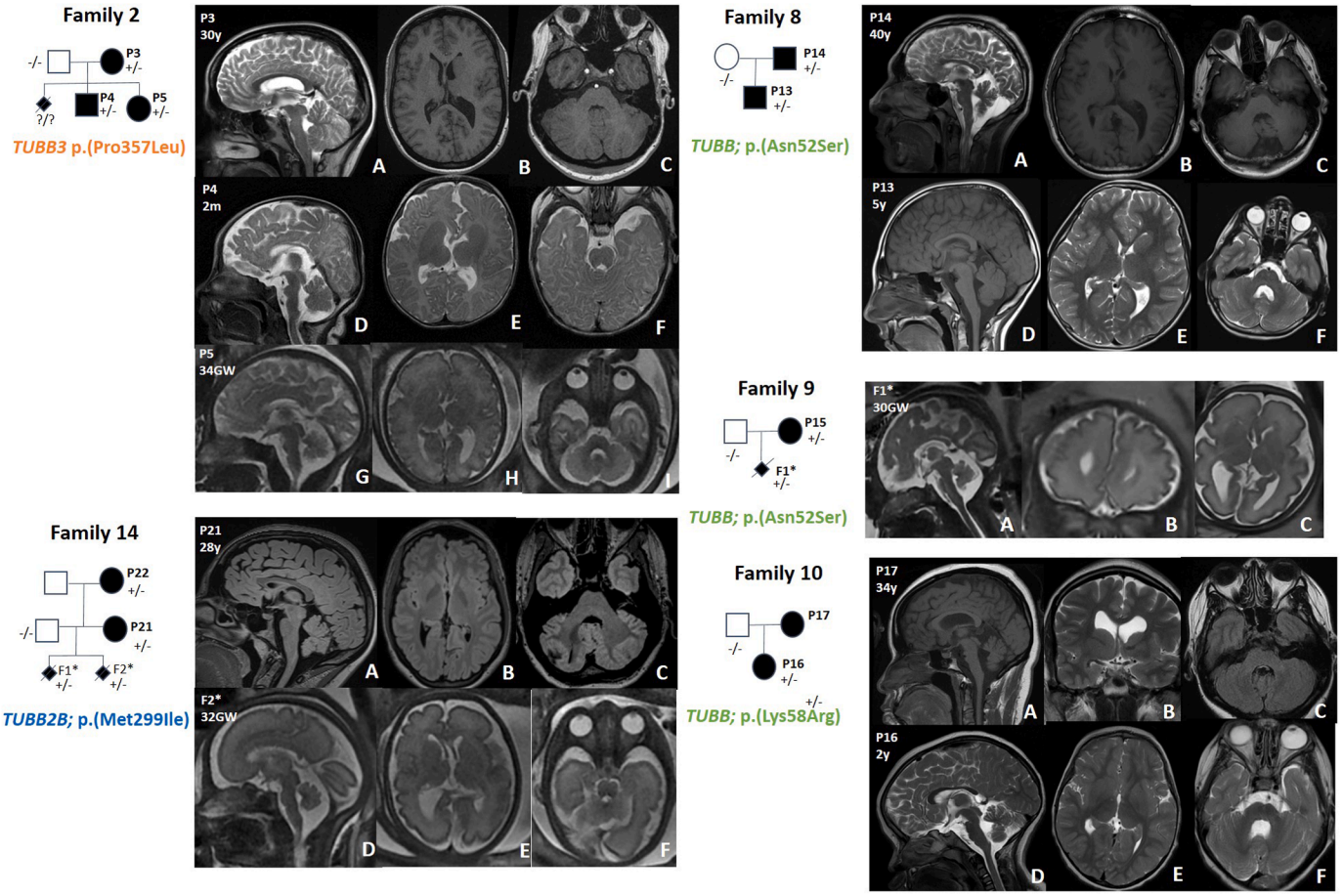

FIGURE 1. Brain magnetic resonance imaging of inherited form of mild tubulinopathies. Family 2 (P3, P4, and P5): the sagittal slices (A, D, G) show reduced anteroposterior diameter of the pons (<5th percentile) with abnormal bulging and dysgenetic corpus callosum; the axial slices (B, C, E, F, H, I) reveal midline distortion and dysmorphic and fused basal ganglia, asymmetry of the lateral ventricles, dysmorphic frontal horns, and brainstem asymmetry. Family 14 (P21 and F2*: index case [fetus, termination of pregnancy (TOP)], not included in the study): the sagittal slices (A, D) show reduced anteroposterior diameter of the pons (<5th percentile) with abnormal bulging; the axial slices (B, C, E, F) reveal midline distortion, right fused basal ganglia (B), dysmorphic (E) and asymmetric lateral ventricles (E), and brainstem asymmetry. Family 8 (P14 and P15): the sagittal slices (A, D) show reduced anteroposterior diameter of the pons (<5th percentile) with abnormal bulging and dysgenetic corpus callosum; the axial sections (B, C, E, F) reveal midline distortion and dysmorphic and fused basal ganglia, asymmetry of the lateral ventricles, dysmorphic frontal horns, and brainstem asymmetry. Family 9 (P15 and F1*: index case [fetus, TOP] not included in the study): the sagittal, coronal, and axial slices (A, B, C) show reduced anteroposterior diameter of pons (<5th percentile), midline distortion, dysmorphic and fused basal ganglia, asymmetry of the lateral ventricles, and dysmorphic frontal horns. Family 10 (P17 and P16): the sagittal slices (A, D) show reduced anteroposterior diameter of pons (<5th percentile) with abnormal bulging and dysgenetic corpus callosum (D); the axial (C, F, E) and coronal slices (B) reveal mild midline distortion, dysmorphic and fused basal ganglia, asymmetry of the lateral ventricles, dysmorphic frontal horns, and brainstem asymmetry. Family 10 (P17 and P16): Sagittal sections (A, D) show an abnormal anteroposterior diameter of the pons (<5th percentile), a similarly abnormal bulging, and a dysgenetic corpus callosum (D); axial (C, F, E) and coronal sections (B) reveal a slight midline distortion, dysmorphic and fused basal ganglia, asymmetry of the lateral ventricles, dysmorphic frontal horns, and brainstem asymmetry. The color version of this figure is available in the online edition.

Neurological phenotype

All patients had achieved independent walking at a median age of 22 months (range 1 to 4 years) (Table 1). All index cases, as well as P4 and P5, underwent clinical examination. Four of them had varying degrees of neuromotor impairment: ataxic gait, right hand hemiparesis, choreo-dystonic gait, and spastic paresis. Head circumference was available for 13 individuals; only one had microcephaly (<−2 S.D.). Six patients had mirror movements. Three patients (P8, P16, and P19) had epileptic seizures presenting as focal seizures, absence seizures, and a single status epilepticus.

Among the adult familial segregation cases, clinical data were often lacking. Neuromotor disorder was excluded in only 4 individuals.

Intellectual functioning, schooling, and professional integration

Nine patients had a neuropsychologic assessment during childhood at a median age of 6 years because of learning difficulties (details in Supplemental data). None had a FSIQ ≥100; the mean FSIQ was 81, the lower FSIQ was 70. Among the unassessed patients, 5 were in regular classes, indicating good intellectual functioning, and one was in a special education class because of learning difficulties.

Data were available for 8 of 9 adults with tubulinopathy diagnosed during familial segregation studies. None had obvious ID, but academic difficulties were retrospectively reported in 3 of them. Neuropsychologic assessment was performed in P3 only and showed an FSIQ of 79. Three other individuals achieved post-secondary education and worked in the tertiary sectors, indicating efficient intellectual functioning. Five others had high school or vocational training certificates and were professionally integrated with manual works. Data were not available for P22.

Overall, 9 of 23 individuals were completely asymptomatic, with a typical school career or higher education achievements.

Imaging findings

Table 2 describes the main imaging phenotypes according to the genetic variant identified in our study. Figure 1 illustrates the familial forms (Families 2, 8, 9, 10, and 14). MRI data for the remaining patients are available in the Supplemental data.

Nineteen individuals underwent pre- or postnatal MRI at a median age of 9 years (range: 30 gestational weeks to 77 years). All sequences could be analyzed for 17 MRI showing no severe gyration abnormalities (polymicrogyria or lissencephaly) but focal dysgyria in 3 patients (3 of 17). Classic malformations of tubulinopathies were present in all 17 MRI, particularly cerebellum and brainstem abnormalities (16 of 17), abnormal basal ganglia (16 of 17), and CC dysgenesis (14 of 17). Regarding the signs of mild tubulinopathies, all patients showed at least 2 major signs, with the most common being midline distortion (19 on 19) and ventricular asymmetry (17 on 19).

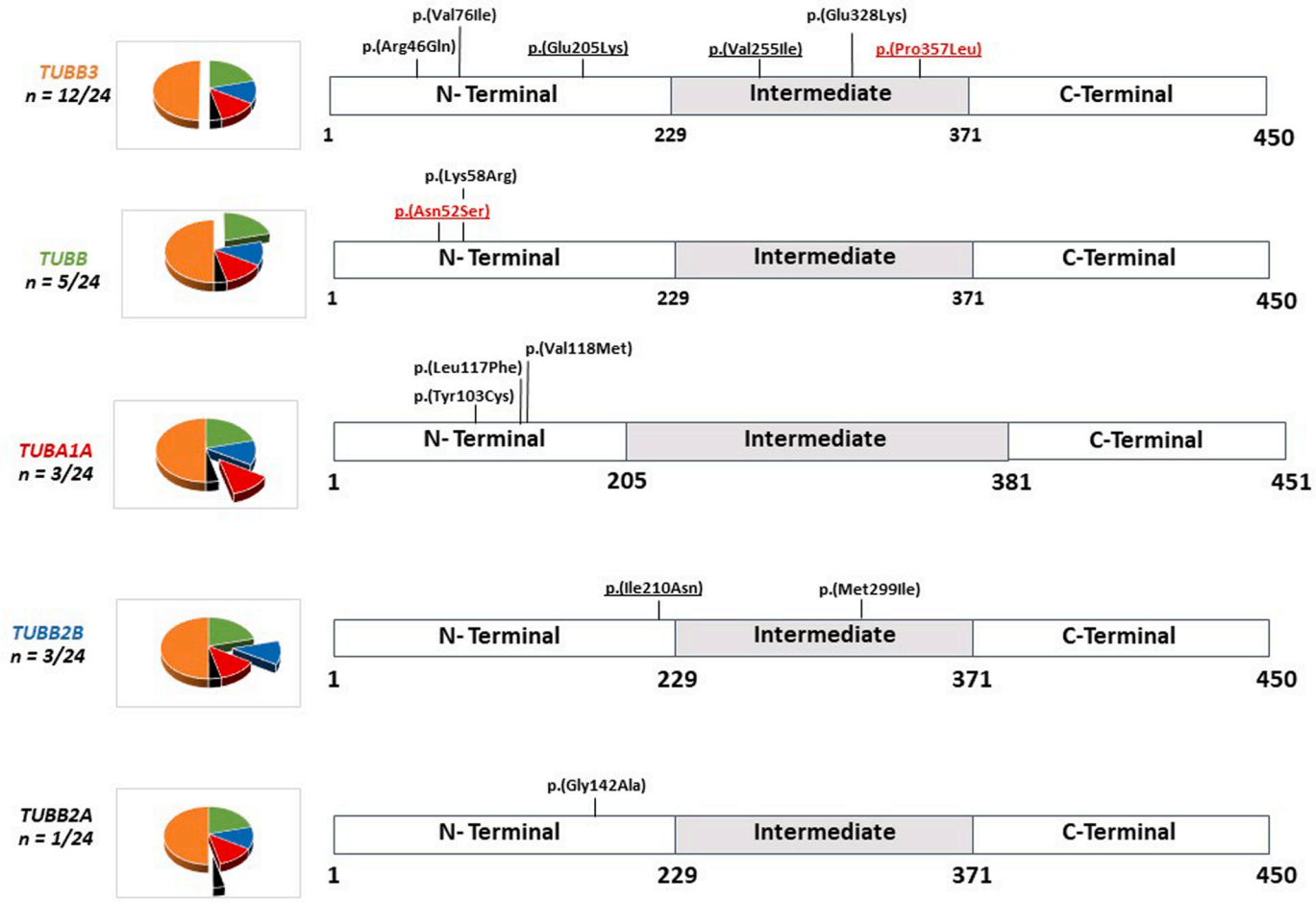

FIGURE 2. Functional domains of TUBB3, TUBB, TUBA1A, TUBB2B, and TUBB2A, and the distribution of mutations in our series. Variants shown in red represent those previously reported with a consistently attenuated phenotype, whereas underlined variants indicate differences in phenotype between our series and the literature. The color version of this figure is available in the online edition.

Molecular data and genotype-phenotype correlation

We identified a total of 14 different heterozygous variants. All of them were located in the N-terminal or intermediate domains of tubulins. Seven were *de novo,* and 7 were inherited (Fig 2). Five of these variants have been previously reported.[15-19]

In decreasing order of frequency, the genes involved were *TUBB3* (6 variants, 12 individuals, 7 families) *TUBB* (two variants, 5 individuals, 3 families), *TUBB2B* (two variants, 3 individuals, 2 families), *TUBA1A* (3 variants, 3 individuals, 3 families), and *TUBB2A* (one variant, one individual, one family).

TUBB3: Of the 6 LP/PVs 4 were inherited (4 of 7 families). We found the p.(Pro357Leu) substitution, which was previously described,[15] in 2 unrelated families. Three additional variants, p.(Glu205Lys), p.(Val255Ile), and p.(Arg46Gln), have also been reported as likely pathogenic in the literature and in ClinVar,[16,18] whereas two were novel, p.(Glu328Lys) and p.(Val76Ile).

Notably, 50% (6 of 12) of the individuals exhibited mirror movements. Among the inherited variants, no significant intrafamilial phenotypic variability was observed, except in Family 1: P1 and her brother, excluded from this study due to profound ID, carried the same *TUBB3* p.(Arg46Gln) variant inherited from their asymptomatic father. P1's brain MRI disclosed radiological signs of tubulinopathy but no severe gyration anomalies (see Supplemental data).

TUBB: The p.(Asn52Ser) variant was recurrent in 2 families, inherited in both cases, and has been previously described once.[17] The p.(Lys58Arg) variant was inherited and is novel.

TUBA1A: All 3 LP/PVs, p.(Tyr103Cys), p.(Leu117Phe), and p.(Val118Met), occurred *de novo* and have not been previously reported.

TUBB2B: The p.(Met299Ile) variant is new and occurred *de novo;* the p.(Ile210Asn) variant was inherited and previously described.[19]

TUBB2A: The p.(Gly142Ala) variant occurred *de novo* and was found in the only patient of the series with choreo-dystonia.

Discussion

Inherited tubulinopathies are rarely documented in the literature; however, advances in fetal imaging over the past decade have enabled prenatal identification of “mild” imaging forms of tubulinopathies, often inherited from asymptomatic or paucisymptomatic parents.[14,20] This fact suggests that mild imaging forms of tubulinopathies may be underdiagnosed. Our series included pathogenic variants across most genes associated with tubulinopathies, excluding *TUBG1,* with *TUBB3* variants comprising 50% of the diagnoses. Notably, half of the variants in our cohort were inherited, differing from prior studies, in which most cases of tubulinopathy were attributed to *de novo* variants (>95%, per Bahi-Buisson et al.[1]).

Moreover, little is known about the neurocognitive outcomes of familial cases, affected fetuses who were live-born, or “asymptomatic” parents carrying these variants. This study, involving 24 patients, presents the first series of individuals without ID, displaying an “attenuated” clinical phenotype compared with the severe neurological presentation typically reported in patients carrying a pathogenic variant in tubulin genes. The aim is to better characterize this attenuated clinical phenotype associated with “mild” imaging tubulinopathies.

Motor and/or language delay were common in our cohort, yet these features did not necessarily predict ID in children with tubulinopathies. Intellectual functioning of individuals varied from borderline to normal, with the majority displaying learning disabilities, whereas approximately 40% could be considered functionally asymptomatic. Thus, our findings demonstrate that a tubulinopathy diagnosis does not inherently imply ID or cognitive impairment.

Our study further reveals that even asymptomatic carriers of LP/PVs in tubulin genes often present radiological signs suggestive of tubulinopathy. Most of the cerebral malformations associated with tubulinopathies were observed in these individuals without ID, with the notable exception of severe gyration anomalies (lissencephaly, microlissencephaly, polymicrogyria, or pachygyria). This fact underscores the absence of major gyration anomalies as a key factor for favorable cognitive prognosis. However, in the case of dysgyria, cognitive prognosis remains highly uncertain.

Our findings advocate for parental MRI screening when a variant of unknown significance is found in a fetus or child but inherited from a parent. Although it may be tempting to dismiss the variant's pathogenicity, identifying cerebral malformations in the parent can provide strong evidence for its clinical relevance.

TUBB3 was the most frequently involved gene in our cohort, consistent with the existing literature, where the *TUBB3*-related tubulinopathies are known to be occasionally reported as familial cases[1,15,16,21] with milder clinical and radiological phenotypes, often accompanied with mirror movements.[22] Notably, certain *TUBB3* variants in our study appear to correlate with a moderate phenotype and better neuropsychologic outcomes. For instance, the *TUBB3* p.(Pro357Leu) variant was identified in 4 of our patients with mirror movements, with 2 additional patients (aged 6 and 2 years) reported by Oegema et al.[15] with the same variant but without ID or mirror movements. Similarly, the p.(Asn52Ser) in *TUBB* was present in 3 patients in our cohort and has been associated with mild learning disabilities and compatible MRI findings by Sferra et al.[17] These 2 variants appear to produce a relatively homogeneous phenotype with a better neuropsychologic prognosis.

Conversely, other variants have been linked to more severe phenotypes. The *TUBB3* p.(Glu205Lys) was previously described by Poirier et al.[16] in 2 unrelated families involving 4 individuals. These individuals exhibited mild to severe ID, and MRI scans revealed polymicrogyria with other signs of tubulinopathies. One of them also had prolonged epileptic seizures; the *TUBB3* p.(Val255Ile) was previously reported by de Boer et al.[18] The authors described a case involving a 16-year-old patient with a *de novo* variant, who presented with severe ID. MRI findings included hypoplasia of the CC and reduced volume of the supratentorial white matter; the *TUBB2B* p.(Ile210Asn) was previously described by Jaglin et al.[19] in a 13-year-old boy with severe motor impairment (tetraparesis), severe ID, and generalized seizures. The MRI showed an asymmetric polymicrogyria.

These described patients in the literature with severe phenotype presented with major cortical abnormalities such as polymicrogyria on MRI, again suggesting that cortical involvement is an important element for the intellectual prognosis.

We also confirmed the well-documented possibility of intrafamilial variability,[13,15] as highlighted in Family 1. In this family, the 19-year-old son with profound ID was excluded from analysis due to phenotypic differences, despite an MRI revealing no specific anomalies to account for his severe presentation compared with his sibling, who shared the same *TUBB3* p.(Arg46Gln) variant inherited from their asymptomatic father. Although fragile X syndrome and pathogenic variants in *OPHN1* were excluded, and array comparative genomic hybridization results were normal, further high-throughput genomic analysis is required to exclude other contributory genetic factors.

Environmental factors, cellular or molecular events affecting the phenotype, and factors modifying gene expression are all possible explanations for these variable presentations. Further research in this area is needed to understand the mechanism of phenotype variability in tubulinopathies.[23-25]

In summary, mild forms of tubulinopathies, characterized by the absence of severe intellectual deficits and cardinal signs on brain imaging, are rare, poorly documented, and probably underdiagnosed.

However, advances in fetal imaging techniques are leading to an exponential increase in the identification of "mild" tubulinopathies, some of which are inherited from asymptomatic or paucisymptomatic parents with an attenuated phenotype. Recognizing these "mild" imaging forms is crucial not only for accurate genetic counseling but also for providing refined prognostic information. We propose an innovative approach to prenatal management when cerebral anomalies suggestive of mild tubulinopathies are detected: systematically offering cerebral MRI to couples alongside the genetic study to avoid overlooking inherited forms.

Prognostic information must remain cautious; however, continued data collection from patients in the coming years may allow us to further refine the neurological prognosis.

CRediT authorship contribution statement

Meghane Durizot: Writing – original draft. **Lydie Burglen:** Data curation. **Catherine Garel:** Methodology, Funding acquisition, Data curation. **Eléonore Blondiaux:** Funding acquisition, Data curation. **Audrey Riquet:** Conceptualization. **Valentine Floret:** Data curation. **Vincent Desportes:** Data curation. **Maria Häänpaa:** Data curation. **Maria Irene Valenzuela:** Data curation. **Anna Maria Pinto:** Data curation. **Lucie Guilbaud:** Data curation. **Jean-Marie Jouannic:** Data curation. **Emmanuelle Lacaze:** Data curation, Formal analysis. **Cyril Mignot:** Data curation. **Stéphanie Valence:** Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2025.06.003.

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