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Histogenetic Classification Predicts Outcomes in 130 Adults With Chronic Intestinal Pseudo-Obstruction

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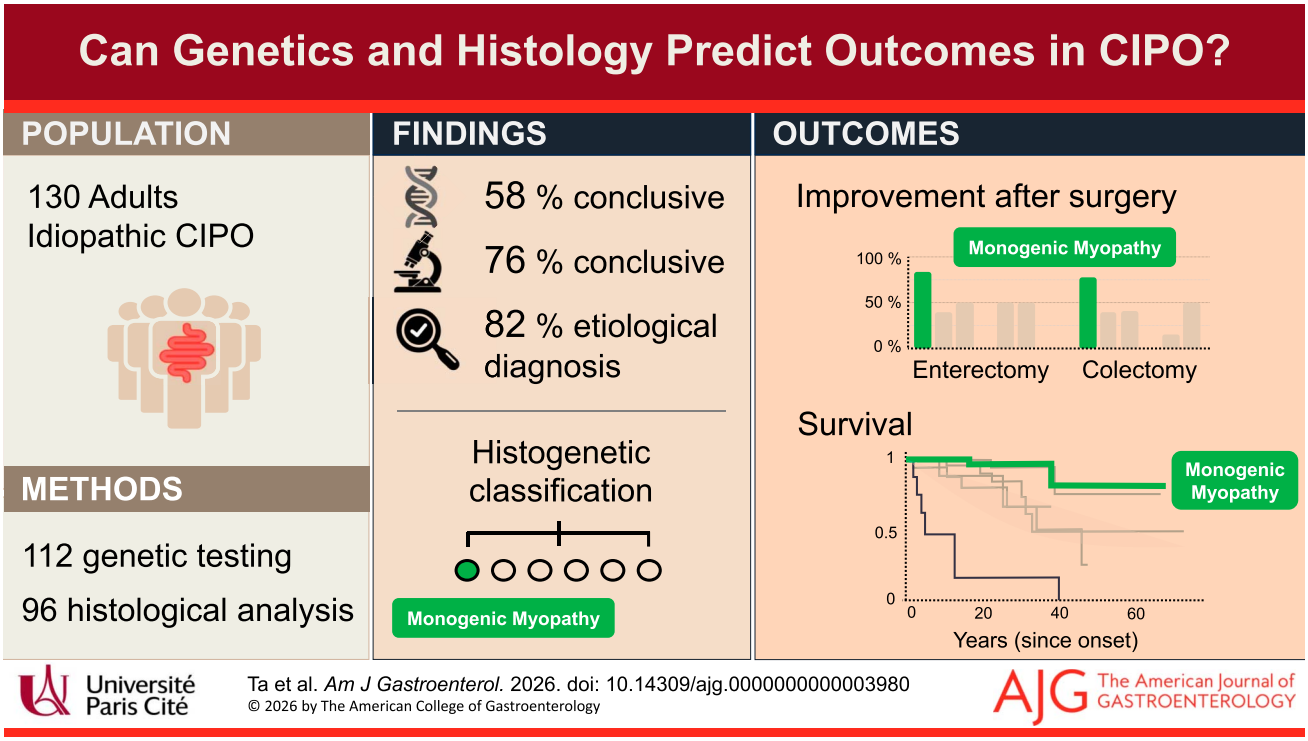
INTRODUCTION: **Chronic intestinal pseudo-obstruction (CIPO) is a rare, heterogeneous disorder associated with severe morbidity. Genetic variants and histopathological lesions have been described, but their combined evaluation has rarely been assessed in adult CIPO cohorts. This study aimed to evaluate the contribution of integrated genetic and histological analyses in adults with CIPO.**



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METHODS: **We conducted a retrospective observational study of adults with CIPO followed at a national tertiary referral center. Patients with CIPO underwent genomic profiling, including next-generation sequencing (NGS) panel, long-range polymerase chain reaction (PCR), whole-exome, and whole-genome sequencing. Centralized histological analysis of full-thickness bowel biopsies and resections was integrated with genomic data to assess their combined impact on disease outcomes.**

RESULTS: **The cohort included 130 patients (75 females, 55 males, aged 19–74 years), followed for up to 64 years. Genetic and histological analyses characterized 82% of the patients (genetic diagnosis: n = 65/112, 58%; histological diagnosis: n = 73/96, 76%), allowing the classification of patients into 6 groups: monogenic myopathy (n = 42), mitochondriopathy (n = 19), unspecified myopathy (n = 26), autoimmune myopathy (n = 8), neuropathy (n = 9), and others (n = 26). Survival and postoperative outcomes differed across groups. In this cohort, patients with monogenic myopathy had the most favorable long-term survival (adjusted hazard ratio: 0.06, 95% CI: 0.01–0.42; *P* = 0.004) and higher rates of improvement after bowel resection compared with other patients.**

DISCUSSION: **Integrated genetic and histological evaluation informed etiological classification in adults with CIPO and may aid clinical decision-making.**

KEYWORDS: CIPO; genetics; histology; survival; prognosis; surgery; *ACTG2*

ABBREVIATIONS: 5-HT_3, 5-hydroxytryptamine receptor 3; 5-HT_4, 5-hydroxytryptamine receptor 4; ACTG2, actin gamma 2; AHS, Alpers–Huttenlocher syndrome; AI M, autoimmune myopathy; AISIMD, familial autoinflammatory syndrome with or without immunodeficiency; ANOVA, analysis of variance; ASMA, alpha-smooth muscle actin; ATP, adenosine triphosphate; BSN, bilateral striatal necrosis; CI, confidence interval; CIPO, chronic intestinal pseudo-obstruction; CMTMA, mitochondrial axonal Charcot-Marie-Tooth disease; CRP, C-reactive protein; CT, computed tomography; CVDPX, X-linked cardiac valvular dysplasia; DNA, deoxyribonucleic acid; ENT, ear, nose, and throat; FGS, FG syndrome; FLNA, filamin A; FMD, frontometaphyseal dysplasia; HES, hematoxylin-eosin-saffron staining; HR, hazard ratio; ICC, interstitial cells of Cajal; IgG, immunoglobulin G; IHC, immunohistochemistry; IMD31C, immunodeficiency-31C; IRB, institutional review board; JAK, Janus kinase; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MaRDI, maladies rares digestives; Mito, mitochondriopathy; MM, monogenic myopathy; MMIHS, megacystis-microcolon-intestinal hypoperistalsis syndrome; MNS, Melnick–Needles syndrome; MRI, magnetic resonance imaging; MT-ATP6, mitochondrially encoded ATP synthase membrane subunit 6; mtDNA, mitochondrial DNA; MT-TL1, mitochondrially encoded tRNA leucine 1 (UUA/G); MT-TV, mitochondrially encoded tRNA valine (GUN); MYH11, myosin heavy chain 11; Neuro, neuropathy; NGS, next-generation sequencing; OPD1, otopalatodigital syndrome type I; OPD2, otopalatodigital syndrome type II; PAS, periodic acid–schiff staining; PCR, polymerase chain reaction; PEO, progressive external ophthalmoplegia; PN, parenteral nutrition; POGZ, Pogo transposable element derived with zinc finger (ZNF) domain; POLG, DNA polymerase gamma; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SCAE, spinocerebellar ataxia with epilepsy; SGO1, Shugoshin 1; SOCS1, suppressor of cytokine signaling 1; SPGM, mitochondrial spastic paraplegia; STAT, signal transducer and activator of transcription; STAT1, signal transducer and activator of transcription 1; TAAD, thoracic aortic aneurysm/dissection; TNGS, targeted next-generation sequencing; TOD, terminal osseous dysplasia; tRNA, transfer ribonucleic acid; TTC37, tetratricopeptide repeat domain 37; TYMP, thymidine phosphorylase; UM, unspecified myopathy; WES, whole-exome sequencing; WGS, whole-genome sequencing

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D906

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INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a rare disorder mimicking mechanical obstruction without physical blockage. Symptoms include severe abdominal pain, bloating, nausea, vomiting, constipation, or diarrhea (1,2), often leading to malnutrition and requiring parenteral nutrition (PN) (3). Diagnosis relies on clinical features and radiographic evidence of small bowel dilation without mechanical obstruction during symptomatic flares. Per international consensus, supplementary tests such as manometry, genetic testing, and histopathology are not mandatory (4–7). Recent reviews have examined the correspondence between genetic and morphological data and their implications for diagnosis and management (8–10). However, genetic testing and histopathological evaluation have rarely been assessed in adult cohorts because of limited awareness of monogenic diseases in adults (11) and risks of invasive transmural biopsies (12,13). This study evaluates genetics and histopathology in a large adult CIPO cohort to address this gap.

PATIENTS AND METHODS

Patients

This retrospective, observational cohort study included patients followed in the Gastroenterology Department of Beaujon Hospital (Clichy, France) between January 1, 2007, and December 1, 2023. The department serves as a national referral center, specialized in rare digestive diseases, providing care to patients from all regions of France (Centre des Maladies Rares Digestives, MaRDI). Inclusion criteria were age older than 18 at enrollment, chronic/recurrent obstructive symptoms with radiological evidence of dilated bowel loops (air-fluid levels, no occluding lesion), and genetic and/or

Table 1. Characteristics of patients

	Overall (n = 130)	MM (n = 42)	Mito (n = 19)	UM (n = 26)	AI M (n = 8)	Neuro (n = 9)	Others (n = 26)	*P* value
Age (yr, median, range)	35 (19–77)	31 (19–75)	34 (19–59)	32 (21–77)	39 (31–70)	56 (39–71)	34 (24–73)	0.004
Female sex—no. (%)	75 (58)	23 (55)	11 (58)	18 (69)	2 (25)	3 (33)	18 (69)	0.131
Age at symptom onset (yr, median, range)	6 (0–69)	1 (0–43)	12 (3–56)	6 (0–59)	34 (0–69)	33 (6–49)	6 (0–50)	<0.001
Complete functional obstruction on the first admission—no. (%)	82 (63)	33 (79)	7 (37)	17 (65)	5 (63)	7 (78)	13 (50)	0.024
Pediatric admission <18 yr—no./total no. (%)	57/71 (80)	32/33 (97)	5/8 (63)	11/15 (73)	1/1 (100)	0/1 (0)	8/13 (62)	0.010
Adult admission ≥18 yr—no./total no. (%)	25/59 (42)	1/9 (11)	2/11 (18)	6/11 (55)	4/7 (57)	7/8 (88)	5/13 (39)	0.014
Age at diagnosis (yr, median, range)	22 (0–71)	8 (0–66)	20 (0–59)	20 (0–71)	36 (0–70)	44 (22–71)	26 (0–67)	< 0.001
Follow-up duration (yr, median, range)	18 (0.9–64)	25 (6–41)	11 (0.9–28)	19 (1–41)	4 (1–41)	18 (5–28)	16 (2–64)	< 0.001
Symptoms observed during the initial evaluation—no./total no. (%)								
Pyloric stenosis	6 (5)	6 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.063
Constipation	55/129 (43)	14 (33)	9/18 (50)	12 (46)	1 (13)	4 (44)	15 (58)	0.193
Diarrhea without constipation	22/129 (17)	2 (5)	3/18 (17)	6 (23)	5 (63)	2 (22)	4 (15)	0.005
Vomiting	63/129 (49)	23 (55)	6/18 (33)	16 (62)	5 (63)	4 (44)	9 (35)	0.242
Volvulus	12 (9)	5 (12)	0 (0)	2 (8)	0 (0)	1 (11)	4 (15)	0.512
Symptoms during the follow-up—no./total no. (%)								
Chronic abdominal pain	29 (22)	7 (17)	5 (26)	6 (23)	4 (50)	2 (22)	5 (19)	0.478
Dysphagia	29/118 (25)	5/40 (13)	7/16 (44)	7/22 (32)	2/8 (25)	5/8 (63)	3/24 (13)	0.009
Volvulus	28/129 (22)	10 (24)	0 (0)	6/25 (24)	2 (25)	2 (22)	8 (31)	0.118
Lower GI bleeding	31/129 (24)	17 (41)	3 (16)	4/25 (16)	2 (25)	0 (0)	5 (19)	0.062
Urinary symptoms	52 (40)	27 (64)	9 (47)	9 (35)	1 (13)	0 (0)	6 (23)	<0.001
Cardiopathy	39 (30)	14 (33)	3 (16)	12 (46)	3 (38)	1 (11)	6 (23)	0.194
Epilepsy	9 (7)	1 (2)	2 (11)	1 (4)	0 (0)	1 (11)	4 (15)	0.269
Cognitive impairment	7 (5)	1 (2)	6 (32)	0 (0)	0 (0)	0 (0)	0 (0)	<0.001
Sensorimotor neuropathy	14 (11)	0 (0)	12 (63)	0 (0)	0 (0)	2 (22)	0 (0)	<0.001
Ear, nose, throat (ENT) impairment	9 (7)	0 (0)	6 (32)	1 (4)	0 (0)	1 (11)	1 (4)	0.001
Ophthalmic impairment	9 (7)	0 (0)	8 (42)	0 (0)	0 (0)	0 (0)	1 (4)	<0.001
Leukoencephalopathy (MRI)	8/80 (10)	0/24 (0)	7/15 (47)	0/14 (0)	0/5 (0)	0/5 (0)	1/17 (6)	<0.001

AI M, autoimmune myopathy; Mito, mitochondriopathy; MM, monogenic myopathy; Neuro, neuropathy; UM, unspecified myopathy.

histological evaluation. To focus on initially idiopathic cases, exclusion criteria included identifiable etiologies at initial assessment: Hirschsprung disease, spinal cord injury, neurofibromatosis, multiple endocrine neoplasia type 2B, scleroderma, dermatomyositis, lupus, amyloidosis, radiation enteritis, and Ehlers-Danlos syndrome. Informed consent was obtained from all patients alive or from a family member when the patient was deceased. Our Institutional Review Board (IRB) approved the study (IRB 00006477).

Clinical data and outcomes

All data were collected from the Beaujon Hospital database. Follow-up started from the first admission to pediatric or adult units and ended at the last visit to our center before December 1, 2023. Complete functional obstruction was defined as a clinical and imaging-based diagnosis characterized by small bowel dilation on radiographic studies (e.g., abdominal X-ray or CT scan) without evidence of mechanical obstruction. CIPO diagnosis was based on clinical and imaging criteria per international consensus. The age at diagnosis was calculated from the patient's birth date to the first recorded CIPO reference in the medical records. Surgical outcomes were assessed at 1 year, 5 years, and at subsequent visits after surgery, with improvement defined by meeting at least 2 of the following criteria: (i) reduction in pain and analgesic use, (ii) antibiotic discontinuation, (iii) reduction in hospitalizations and occlusion episodes per year compared with the

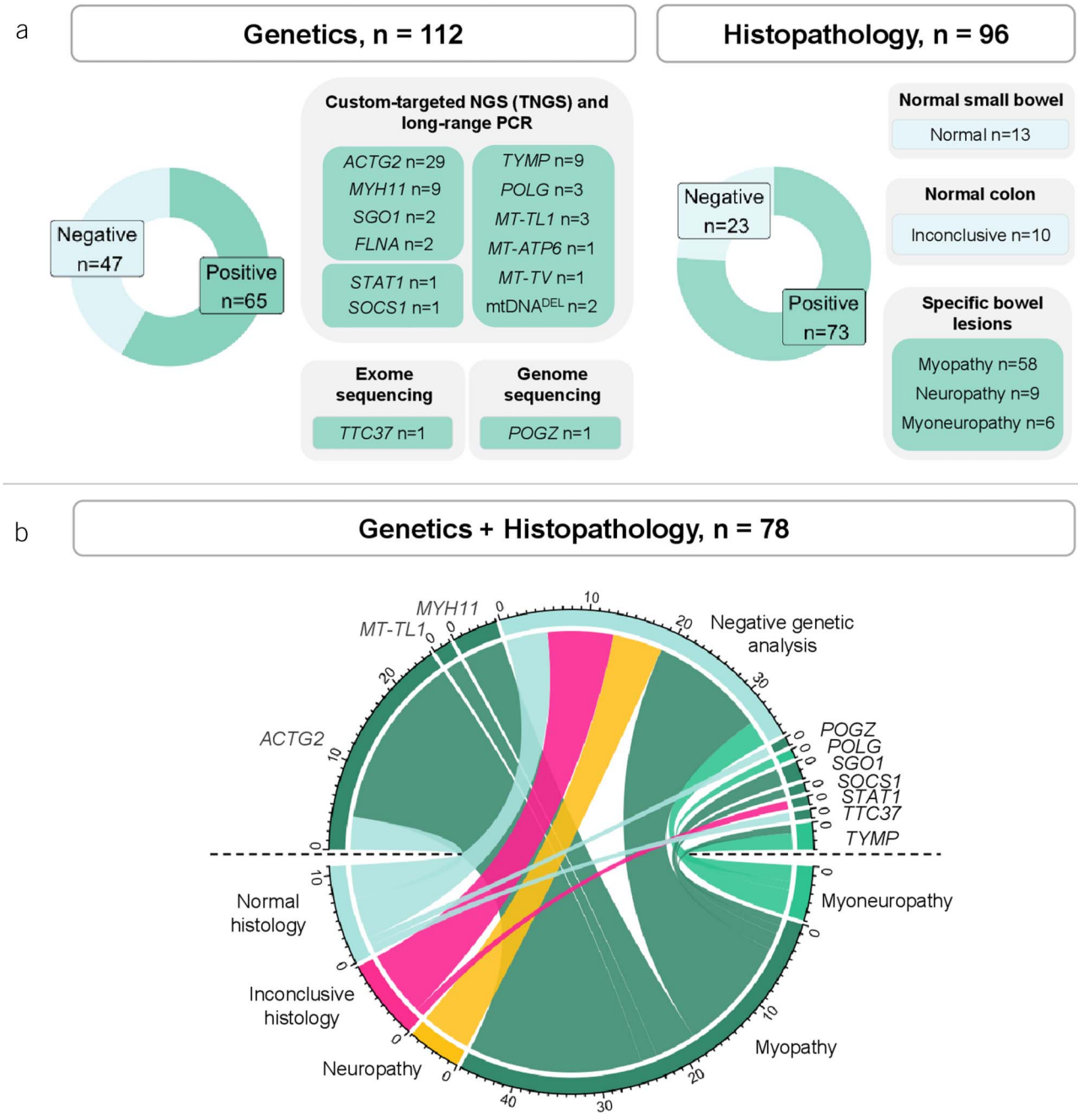

Figure 1. Methodology and histogenetic results. (**a**) Genetic and histological analyses. (**b**) Integration of genetic and histological results. TNGS, targeted next-generation sequencing.

previous year, and (iv) improvement in general condition based on clinical reports and weight gain.

Histological analysis

Full-thickness biopsies and bowel resections underwent histopathologic analysis. All intestinal samples (formalin-fixed and paraffin-embedded) were analyzed using hematoxylin-eosin-saffron, periodic acid Schiff, and picrosirius stainings, and by immunohistochemistry (performed using an automated immunohistochemical stainer according to the manufacturer's instructions; BenchMark, Ventana, Tucson, AZ). Immunohistochemical staining details are provided in the Supplementary Data (http://links.lww.com/AJG/D906).

Two gastrointestinal pathologists analyzed the samples (14) and classified per London Classification (15): myopathic (enteric muscle lesions) and neuropathic (myenteric hypoganglionosis <30 ganglion cells/cm on Hu C/D immunohistochemistry, based on previous studies (14,16)). In the absence of a small bowel sample, histological assessment of the colon alone was considered inconclusive if no specific lesions according to the London Classification were seen.

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes or frozen intestinal tissues and sequenced using targeted next-

Table 2. Mutated genes identified in this adult CIPO cohort

Gene	Full name	Function	Zygosity[a]	Genetic mode	Number of patients	Present clinical syndromes	Absent clinical syndromes[b]	Number of deaths
ACTG2	Actin gamma 2	Provides instructions for making gamma-2 actin, part of the actin family involved in smooth muscle contraction	Heterozygous	Autosomal dominant	29	Visceral myopathy (n = 21)	MMIHS	0
FLNA	Filamin A	Cross-links actin filaments to transmembrane integrins, building and stabilizing cytoskeleton	Hemizygous (men)	X-linked dominant	2	Periventricular nodular heterotopia (n = 1)	CVDPX, FGS, FMD, MNS, OPD1, OPD2, TOD	0
MT-ATP6	Mitochondrially encoded ATP synthase membrane subunit 6	Essential component of ATP synthase for mitochondrial energy production	Heteroplasmy	Mitochondrial (maternal)	1	NARP syndrome	BSN, LHON, LS	0
MT-TL1	Mitochondrially encoded tRNA leucine 1 (UUA/G)	Transfer RNA that helps assemble leucine into proteins in mitochondria	Heteroplasmy	Mitochondrial (maternal)	3	Maternally inherited diabetes-deafness syndrome (n = 2); MELAS syndrome (n = 1)		1
MT-TV	Mitochondrially encoded tRNA valine (GUN)	Transfer RNA that helps assemble valine into proteins in mitochondria	Heteroplasmy	Mitochondrial (maternal)	1		CMTMA, SPGM	0
MYH11	Myosin heavy chain 11	Encodes smooth muscle myosin heavy chain, a component of the contractile unit in smooth muscle cells	Heterozygous Compound heterozygous	Autosomal dominant Autosomal recessive	9	Visceral myopathy (n = 6)	TAAD, MMIHS	1
POGZ	Pogo transposable element derived with the ZNF domain	Zinc finger protein involved in kinetochore assembly and mitotic sister chromatid cohesion	Heterozygous	Autosomal dominant	1	White-Sutton syndrome		0
POLG	DNA polymerase gamma	Responsible for replication of the mitochondrial genome	Homozygous Compound heterozygous	Autosomal recessive	3	Mitochondrial neurogastrointestinal encephalopathy-like (n = 3)	AHS, PEO SANDO, SCAE	2
SGO1	Shugoshin 1	Plays a central role in chromosome cohesion during mitosis	Homozygous	Autosomal recessive	2	Chronic atrial and intestinal dysrhythmia (n = 1)		1
SOCS1	Suppressor of cytokine signaling 1	Negative regulator of the JAK/STAT signaling pathway	Heterozygous	Autosomal dominant	1		AISIMD	0

Table 2. (*continued*)

Gene	Full name	Function	Zygosity[a]	Genetic mode	Number of patients	Present clinical syndromes	Absent clinical syndromes[b]	Number of deaths
STAT1	Signal transducer and activator of transcription 1	Involved in immune system functions, including defense against pathogens and regulation of immune responses	Heterozygous	Autosomal dominant	1		IMD31C	1
TTC37	Tetratricopeptide repeat domain 37	Involved in RNA metabolism and protein folding	Homozygous	Autosomal recessive	1	Trichohepatoenteric syndrome		0
TYMP	Thymidine phosphorylase	Catalyzes the phosphorylation of thymidine or deoxyuridine, essential in the nucleotide salvage pathway for mtDNA replication	Homozygous Compound heterozygous	Autosomal recessive	9	Mitochondrial neurogastrointestinal encephalopathy (n = 9)		3

AHS, Alpers-Huttenlocher syndrome; AISIMD, familial autoinflammatory syndrome with or without immunodeficiency; ATP, adenosine triphosphate; BSN, bilateral striatal necrosis; CIPO, chronic intestinal pseudo-obstruction; CMTMA, mitochondrial axonal Charcot-Marie-Tooth disease; CVDPX, X-linked cardiac valvular dysplasia; FGS, FG syndrome; FMD, frontometaphyseal dysplasia; IMD31C, immunodeficiency-31C; LHON, Leber hereditary optic atrophy; LS, Leigh syndrome; MMIHS, megacystis-microcolon-intestinal hypoperistalsis syndrome; MNS, Melnick-Needles syndrome; mtDNA, mitochondrial DNA; OPD1, otopalatodigital syndrome type I; OPD2, otopalatodigital syndrome type II; PEO, progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SCAE, spinocerebellar ataxia with epilepsy; SPGM, mitochondrial spastic paraplegia; STAT, signal transducer and activator of transcription; TAAD, thoracic aortic aneurysm/aortic dissection; TOD, terminal osseous dysplasia.
[a]Zygosity of the variants identified in this cohort.
[b]"Absent clinical syndromes" refer to established clinical syndromes associated with the mutated genes identified in our adult CIPO cohort, which are not present in our patients.

generation sequencing (TNGS), whole-exome sequencing (WES), or whole-genome sequencing (WGS). In patients with suspected mitochondrial disorder, mitochondrial DNA (mtDNA) deletions were investigated in skeletal muscle biopsies using long-range polymerase chain reaction (PCR). The complete list of genes in the TNGS panel and methodologies for TNGS (17), WES, WGS, and long-range PCR are provided in the Supplementary Data (http://links.lww.com/AJG/D906). All damaging variants were classified per American College of Medical Genetics guidelines (18). All identified variants were validated by Sanger sequencing and familial segregation analyses when DNA samples from family members were available.

Statistical analysis

Fisher exact tests and logistic regression assessed associations. An ANOVA test was used to assess differences in parametric numerical data between groups. Nonparametric numerical variables were compared between groups using the Kruskal-Wallis test. Survival was analyzed using Cox proportional hazards models in R (v4.3.0), with time from symptom onset to death or last follow-up. The histogenetic group was the main predictor, adjusted for key clinical covariates. Univariable and multivariable hazard ratios were estimated, with model fit assessed by concordance and global tests; $P < 0.05$ was considered significant. No multiplicity adjustment method for inferences was prespecified. Confidence interval (CI) widths were not adjusted for multiplicity, and the CIs should therefore not be used for hypothesis testing. Statistical analyses and figures were performed using RStudio Desktop (version 2025.09.2+418; Posit Team, 2025, Boston, MA; https://posit.co).

RESULTS

Clinical presentation

Of 130 patients with CIPO (Table 1, Table S1, http://links.lww.com/AJG/D906), 75 were female (58%) and 55 were male (42%), with a median age of 35 years (range: 19–74). The median age at symptom onset was 6 years (range: 0–69). The cohort included 71 adult patients (55%) transitioning from pediatric to adult care, and 59 patients (45%) admitted for the first time in adult departments. On first admission to pediatric or adult units, 82 patients (63%) presented with complete functional obstruction, as defined in the Methods section. Pediatric admissions showed a high prevalence of complete functional obstruction (80%, Table 1), while first-time adult admissions displayed a wider range of clinical presentations (58%), frequently resulting in misdiagnoses before evaluation at our referral center. Twenty-four patients with severe chronic constipation were initially diagnosed with colonic inertia. Twenty women with repeated vomiting and/or low weight in their teenage years were initially diagnosed with anorexia nervosa. Twelve patients with acute severe diarrhea, weight loss, and dehydration were initially diagnosed with infectious enteritis (n = 5), Crohn's disease (n = 4),

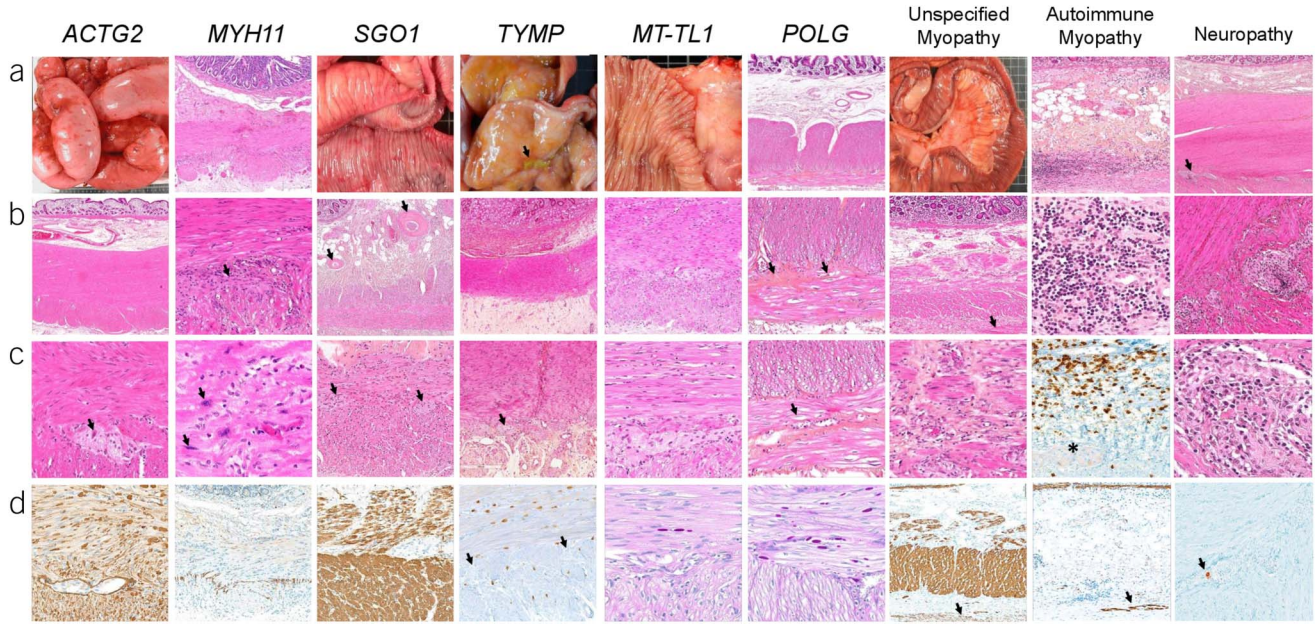

Figure 2. Histopathological findings in bowel specimens. In patient 25 (33 M, *ACTG2* mutation), subtotal enterectomy revealed (**a**) dilated small bowel loops; (**b**) thick muscularis propria with atrophic mucosa, no inflammation (×5 HES); (**c**) normal myenteric plexus (arrow) with myocyte eosinophilic inclusions (×20 HES); and (**d**) ASMA IHC showing disrupted actin with globules (×20). Patient 119 (54 F, *MYH11* mutation) showed (**a**) jejunal degenerative myopathy with outer muscularis propria atrophy (×5 HES), (**b**) preserved myenteric plexus (arrow ×10 HES), (**c**) myocyte shrinkage and nuclear dystrophy (arrows ×30 HES), and (**d**) preserved ICC on CD117 IHC (×5). Patient 3 (30 M, *SGO1* mutation) exhibited (**a**) dilated bowel with normal mucosa; (**b**) inner muscularis propria atrophy, arteriolar medial degeneration with hyaline deposition (arrows, ×5 HES); (**c**) myocytes with clear cytoplasm and bland nuclei, normal myenteric plexuses (arrows, ×10 HES); and (**d**) actin loss in the inner layer on ASMA IHC (×20). Patient 87 (22 M, *TYMP* mutation) presented (**a**) Crohn's-like enteritis with strictures and erosions (arrow); (**b**) severe outer muscularis propria atrophy without fibrosis/inflammation (×5 HES); (**c**) normal myocytes, sparse plexuses with hypoganglionosis (arrow) (×10 HES); and (**d**) no ICC on CD117 IHC around plexuses (arrows), only mast cells (×10). Patient 78 (57 M, *MT-TL1* mutation) had (**a**) normal mucosa, unremarkable intestinal wall (×10 HES); (**b** and **c**) myocytes had faint cytoplasmic lipofuscin deposits, normal myenteric plexus (×20 HES); and (**d**) periodic acid Schiff (PAS) staining showed isolated muscle inclusions in the inner layer (×30 PAS). In patient 65 (26 F, *POLG* mutation), jejunal wall exhibited (**a**) degenerative myopathy with outer muscularis propria atrophy, no fibrosis/inflammation (×5 HES); (**b**) rare myenteric plexuses with hypoganglionosis, fibrotic plexus replacement (arrows) (×10 HES); (**c**) vacuolated myocytes contained grey inclusions (arrow, ×10 HES); and (**d**) PAS stained the grey inclusions (×20 PAS). Patient 17 (72 M, unspecified myopathy) showed (**a**) dilated bowel with normal mucosa, (**b**) degenerative myopathy with inner muscularis propria atrophy and an additional muscle coat (arrow) (×5 HES), (**c**) irregular myocyte nuclei (×20 HES), and (**d**) desmin IHC showed inner atrophy and an additional muscle coat (arrow, ×20). Patient 14 (30 M, autoimmune myopathy) had (**a**) lymphocytic ileiomyositis causing complete muscularis propria atrophy (×5 HES), with (**b**) lymphocytes replacing myocytes (×30 HES); (**c**) predominant $CD8^+$ T cells, unaffected myenteric plexuses (*, ×20 HES); and (**d**) desmin IHC showed myocyte remnants (arrow, ×5). Patient 109 (36 F, neuropathy) displayed (**a**) inflammation involving all myenteric plexuses, thick normal muscularis propria (×5 HES); (**b**) rare ganglion cells with (**c**) plasma cells and lymphocytes (×40 HES); and (**d**) anti-Hu IHC showed diffuse hypoganglionosis (arrow on a ganglion cell remnant, ×10). ASMA, alpha-smooth muscle actin; HES, hematoxylin-eosin-saffron; ICC, interstitial cells of Cajal; IHC, immunohistochemistry; PAS, periodic acid Schiff.

and lymphoma/myeloma (n = 3) due to an IgG monoclonal peak. Misdiagnosed patients received antibiotics, corticosteroids, or empiric chemotherapy (e.g., R-CHOP) before being admitted to our department. The median age at formal diagnosis was 22 years (range: 0–71) (Table 1). The median follow-up period was 18 years, with a range spanning from 0.9 to 64 years.

Genetic testing and histological analysis

Genetic testing through TNGS (n = 110), WES (n = 2), and WGS (n = 11) was conducted on peripheral blood cells (n = 109) and frozen intestinal tissues (n = 3) from 112 patients. Long-range PCR was conducted on muscle samples from 4 patients with extradigestive symptoms suggestive of mitochondrial disorders. Pathogenic mutations were identified in 65 patients of 112 patients (58%), encompassing 13 genes (Figure 1a, Table 2) and multiple mtDNA deletions (Figure 1a). The 3 most frequently mutated genes were *ACTG2* (n = 29), *MYH11* (n = 9), and *TYMP* (n = 9). Table S2 (http://links.lww.com/AJG/D906) provides the exact mutations, including their nomenclature, zygosity, and novelty compared with prior literature. Patient phenotypes associated with *MT-ATP6, MT-TV, STAT1, TTC37*, and *POGZ* are detailed in the Supplementary Data (http://links.lww.com/AJG/D906). For these rare associations, additional data are required to confirm causality.

Among the 14 adults who experienced a functional obstruction after the age of 50, 7 (50%) had mutations, located in *MYH11* (n = 2), *ACTG2* (n = 1), *SOCS1* (n = 1), *MT-TL1* (n = 1), *MT-TV* (n = 1), and multiple mtDNA deletions (n = 1). Among the 20 patients who were initially diagnosed with anorexia nervosa, 10 (50%) had mutations in *TYMP* (n = 6), *ACTG2* (n = 2), *MYH11* (n = 1), and *POLG* (n = 1). A distinctive onset mimicking Crohn's disease was observed in patients carrying *TYMP* mutations, who were initially hospitalized for acute gastroenteritis (n = 7/9), with fever and elevated C-reactive protein levels (n = 4/9). Radiological and

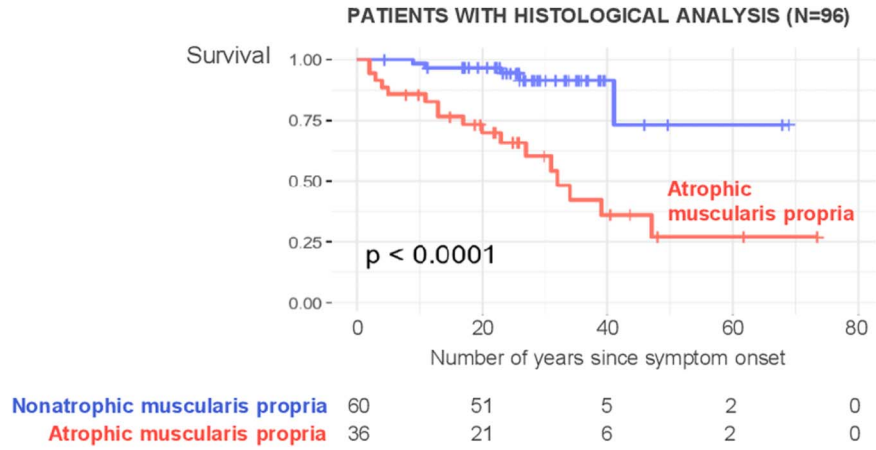

Figure 3. Impact of atrophic muscularis propria on survival. The log-rank survival analysis shows the outcomes of patients diagnosed with atrophic muscularis propria (n = 36, red line) compared with those who showed nonatrophic muscularis propria (n = 60, blue line).

endoscopic examinations revealed ulcerations and strictures in the bowel or rectum (n = 4/9) and/or gastroduodenal dilation (n = 4/9). Genetic testing was inconclusive in 47 patients (inconclusive TNGS without subsequent WGS n = 37, inconclusive WGS n = 10).

A total of 96 patients underwent histological analysis (Figure 1a). The number of specimens per patient ranged from 1 to 6 (Figure S1, http://links.lww.com/AJG/D906), resulting in a cumulative total of 148 bowel specimens centrally analyzed (Table S3, http://links.lww.com/AJG/D906). Specific lesions were found in 73 patients (76%), revealing visceral myopathy (n = 58), visceral neuropathy (n = 9), and mixed myoneuropathy (n = 6) (Figure 1a, Table S4, http://links.lww.com/AJG/D906). No isolated mesenchymopathy was detected because CD117/ICC abnormalities were associated with myopathies and/or neuropathies (Table S5, http://links.lww.com/AJG/D906). Figure 1b depicts the correspondence between histological findings and genetic data. Figure 2 shows the histopathological lesions associated with monogenic diseases (*ACTG2*, *MYH11*, *SGO1*, *TYMP*, *MT-TL1*, *POLG*) compared with other cases. Atrophic muscularis propria, defined as the partial or complete loss of muscularis propria tissue, was significantly correlated with poor survival ($P < 0.0001$, Figure 3). Patients with myopathy associated with *ACTG2* and *MT-TL1* mutations did not show atrophic muscularis propria.

Six groups of patients

Overall, genetics and histopathology characterized 106 patients (82%, Figure 4a). Integrated findings stratified patients into 6 groups: monogenic myopathy (n = 42, 32%), mitochondriopathy (n = 19, 15%), unspecified myopathy (n = 26, 20%), autoimmune myopathy (n = 8, 6%), neuropathy (n = 9, 7%), and others (n = 26, 20%). Figure 4a outlines the methodology for classifying patients using serology, genetics, and histopathology. Table S6 (http://links.lww.com/AJG/D906) provides the list of all patients, their corresponding classifications, and family histories.

Figure 4b illustrates the age distribution of patients at the onset of digestive symptoms. Patients categorized in 3 groups as monogenic myopathy, unspecified myopathy, and "others" showed symptom onset in early childhood. Most patients in the mitochondriopathy group experienced symptom onset during their teenage years (n = 11/19, between 8 and 17 years old). Patients in the autoimmune myopathy and neuropathy groups experienced symptom onset in adulthood (n = 7/8 and n = 7/9, respectively).

The natural history of CIPO

Dilation throughout the digestive tract, assessed on imaging at baseline and at different time points, differed between myopathic and neuropathic patients (Figure 4c). At the initial assessment, neuropathic patients presented with either megaesophagus (44%) or small bowel dilation (56%), while myopathic patients showed a potential dilation of both the small bowel and colon. Over time, 67% of neuropathic patients developed biliary and pancreatic ductal dilation, while this phenomenon was not observed in myopathic patients. Patients classified as "others" initially showed a megacolon followed by secondary small bowel dilation, justifying the diagnosis of CIPO (Figure 4c, Table S7 [http://links.lww.com/AJG/D906]).

Survival analyses showed that, for CIPO patients who were initially admitted to adult units, the probability of surviving more than 10 years after symptom onset was 89% (95% CI: 82%–98%). Patients who were initially hospitalized in pediatric units and transitioned into adulthood had a 99% probability of surviving more than 10 years after the age of 18 (95% CI: 96%–100%).

Survival differed significantly across the 6 groups (Figure 4d; log-rank $P < 0.0001$). Patients with autoimmune myopathy had the poorest prognosis (mortality of 88%, 63% died within 5 years of symptom onset). Intermediate severity was observed in mitochondriopathy, neuropathy, and unspecified myopathy. Monogenic myopathy and "others" showed favorable long-term survival outcomes. In the exploratory multivariable analysis adjusting for key clinical factors (Table 3), monogenic myopathy was independently associated with favorable survival (adjusted HR: 0.06, 95% CI: 0.01–0.42; $P = 0.004$).

Responses to treatments

The medications administered are detailed in Table 4. Patients with autoimmune myopathy and mitochondriopathy showed the highest rates of dependence on opioids (25% and 21%, respectively). In addition, 42% of the patients with mitochondriopathy required analgesics for neuropathic pain. Conversely, most patients with monogenic myopathy did not need analgesic medication for chronic abdominal pain (Table 1).

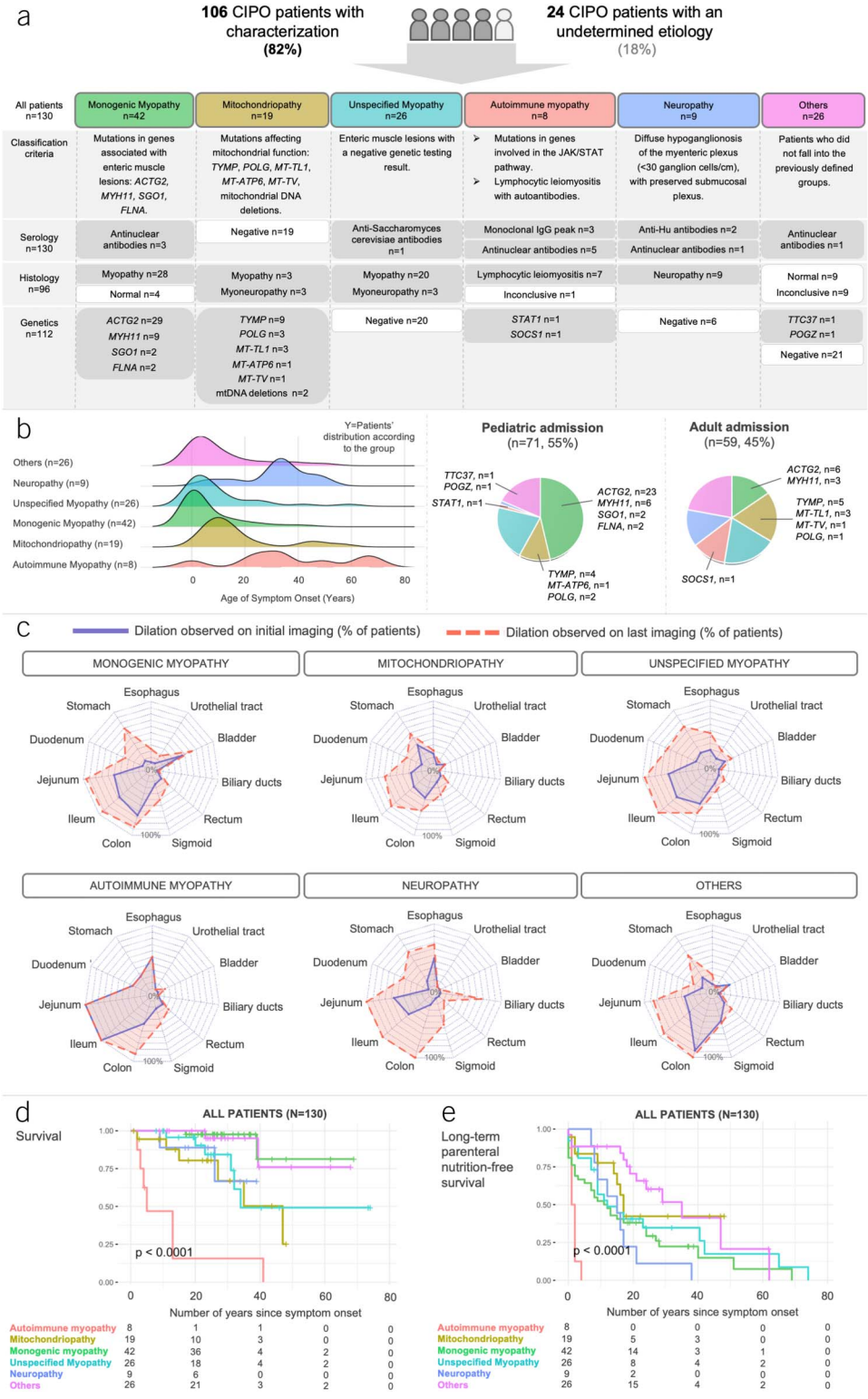

Figure 4. Six groups of CIPO patients. (**a**) Classification of patients into 6 groups. Three patients without histological analysis were classified into the unspecified myopathy group, based on the histological findings of their siblings. These patients had symptoms that were clinically identical to those of their siblings and negative genetic testing results. (**b**) Distribution of patients according to the age at digestive symptom onset in each group. (**c**) Spider charts showing the progression of dilation in the digestive and urinary tracts in the 6 groups. Each line of the spider web diagram represents a 10% increment in patients' population, from the center (0%) to the outer edge (100%). The solid blue line indicates the percentage of patients showing dilation of the segment of interest at the time of initial imaging. By contrast, the dashed orange line shows the percentage of patients with dilation observed in the same segment at the last imaging assessment. (**d**) Log-rank survival analysis of the 6 groups from the onset of digestive symptoms. (**e**) Log-rank survival analysis representing long-term parenteral nutrition-free survival rates in the 6 groups from the onset of digestive symptoms. CIPO, chronic intestinal pseudo-obstruction; mtDNA, mitochondrial DNA.

Table 3. Univariable and multivariable Cox proportional hazards analyses of factors associated with overall survival in chronic intestinal pseudo-obstruction

Variable	Univariable HR (95% CI)	Univariable *P* value	Multivariable HR (95% CI)	Multivariable *P* value
Patient groups				
Autoimmune myopathy	1 (Reference)	—	1 (Reference)	—
Monogenic myopathy	0.02 (0.00–0.11)	<0.001***	0.06 (0.01–0.42)	0.004**
Mitochondriopathy	0.18 (0.06–0.56)	0.003**	2.00 (0.26–15.66)	0.510
Unspecified myopathy	0.12 (0.04–0.37)	<0.001***	0.91 (0.14–5.80)	0.924
Neuropathy	0.13 (0.03–0.63)	0.012*	0.11 (0.01–0.83)	0.032*
Others	0.04 (0.01–0.18)	<0.001***	0.54 (0.06–5.07)	0.592
Sex (male)	1.94 (0.88–4.28)	0.102	2.50 (0.73–8.58)	0.145
Age at symptom onset	1.06 (1.03–1.08)	<0.001***	1.05 (1.02–1.09)	0.003**
Surgery number	1.01 (0.89–1.15)	0.859	0.97 (0.79–1.20)	0.803
Dependence on parenteral nutrition	8.23 (1.11–60.85)	0.039*	11.51 (1.11–119.26)	0.041*
Use of laxatives	0.43 (0.20–0.95)	0.038*	0.34 (0.09–1.34)	0.124
Use of antidopaminergics	1.29 (0.58–2.84)	0.535	0.83 (0.20–3.48)	0.799
Use of motilin agonist	1.49 (0.68–3.30)	0.322	3.42 (0.89–13.08)	0.073
Use of 5-HT_3 antagonist	1.34 (0.46–3.91)	0.593	1.06 (0.21–5.26)	0.947
Use of 5-HT_4 agonist	0.99 (0.34–2.90)	0.987	1.30 (0.24–7.16)	0.763
Use of acetylcholinesterase inhibitors	1.19 (0.53–2.71)	0.672	1.39 (0.25–7.76)	0.705
Use of trimebutine	0.24 (0.07–0.79)	0.020*	0.15 (0.03–0.72)	0.018*
Use of somatostatin analogs	2.10 (0.90–4.87)	0.085	1.27 (0.37–4.31)	0.707
Use of antibiotics	10.64 (1.44–78.76)	0.021*	6.09 (0.69–54.09)	0.105

5-HT, 5-hydroxytryptamine.
*< 0.05.
**< 0.01.
***< 0.001.

Two patients with germline mutations in the Janus kinase (JAK)/signal transducer and activator of transcription pathway received JAK inhibitors. To date, the patient with the *SOCS1* mutation (previously documented (19)) is still successfully managed with this targeted treatment strategy.

Long-term PN was administered to 72% of patients. The long-term PN-free survival is shown in Figure 4e. Patients with mitochondriopathy who required long-term PN (n = 9/19, 47%) were at higher risk of mortality compared with patients with mitochondriopathy who did not require PN (Figure S2 [http://links.lww.com/AJG/D906], $P = 0.0068$). Conversely, most patients with monogenic myopathy were on long-term PN (81%) and showed a favorable outcome (Figure 4d).

Surgery was performed in 109 patients, with a median number of 4 surgeries per patient (range: 1–15). Patients with monogenic myopathy who underwent colectomy, including ileocolectomy, partial colectomy, and total colectomy (n = 22/42, mutations in *ACTG2* n = 19 and *MYH11* n = 3), experienced more frequent improvement after colectomy (n = 17/22, 77%, odds ratio: 5.48, 95% CI: 1.77–19.86; $P = 0.0036$) compared with other patients. Patients with monogenic myopathy who underwent enterectomy (n = 23/42, mutations in *ACTG2* n = 18, *MYH11* n = 3, and *SGO1* n = 2), experienced more frequent improvement after enterectomy (n = 19/23, 83%, odds ratio: 6.46, 95% CI: 1.97–26.49; $P = 0.0016$) compared with other patients.

Five patients underwent multivisceral transplantation due to multiorgan failure (Table 4). Three patients died 8 years, 62 days, and 2 days after transplantation (Table S8, http://links.lww.com/AJG/D906). Two patients carrying *ACTG2* mutations survived and did not require PN for 5 and 23 years after transplantation. Their digestive and urinary symptoms completely disappeared.

Twenty-five patients died at a median age of 36 years (range: 21–82) after a median follow-up of 12 years because of malnutrition, infections, transplant rejection, cancer, thromboembolic, and cardiac complications.

DISCUSSION

This study provides the most comprehensive clinical, genetic, and histopathological characterization of adult CIPO reported to date, based on a large cohort managed in a tertiary referral center. The centralized and longitudinal follow-up of this cohort enabled detailed phenotyping and the integration of genomic and histopathological data, yielding etiological diagnosis in 82% of patients.

Genetic testing yielded successful results in a significant proportion of adult patients (n = 65/112, 58%), including 7 of 14 adults who experienced functional obstruction after the age of 50. These results emphasize that monogenic CIPO is not exclusively a pediatric condition but can also appear in adults. These findings must be contextualized within a tertiary-care population over-represented by severe, refractory disease. The high diagnostic

Table 4. Patients' outcomes

	Overall (n = 130)	MM (n = 42)	Mito (n = 19)	UM (n = 26)	AI M (n = 8)	Neuro (n = 9)	Others (n = 26)	*P* value
Drug use duration exceeding 1 yr—no./total no. (%)								
Laxatives	56/72 (78)	15/19 (79)	10/10 (100)	8/13 (62)	2/2 (100)	4/7 (57)	17/21 (81)	0.192
Antidopaminergics	10/38 (26)	3/11 (27)	1/2 (50)	2/7 (29)	1/4 (25)	2/6 (33)	1/8 (13)	0.901
Motilin agonist	19/44 (43)	3/13 (23)	2/2 (100)	3/9 (33)	3/4 (75)	1/4 (25)	7/12 (58)	0.141
5-HT_3 antagonist	5/12 (42)	1/5 (20)	2/2 (100)	0/1 (0)	—	0/2 (0)	2/2 (100)	—
5-HT_4 agonist	3/16 (19)	2/5 (40)	0/2 (0)	0/2 (0)	—	0/1 (0)	1/6 (17)	—
Acetylcholinesterase inhibitors	17/35 (49)	3/9 (33)	4/4 (100)	0/2 (0)	1/2 (50)	2/6 (33)	7/12 (58)	0.149
Trimebutine	26/40 (65)	9/14 (64)	1/1 (100)	6/11 (55)	—	2/3 (67)	8/11 (73)	—
Somatostatin analogs	27/58 (47)	6/16 (38)	4/7 (57)	5/10 (50)	3/6 (50)	1/6 (17)	8/13 (62)	0.543
Antibiotics	48/72 (67)	17/26 (65)	5/7 (71)	3/10 (30)	5/7 (71)	4/7 (57)	14/15 (93)	0.034
Enteral nutrition (%)	6 (5)	1 (2)	2 (11)	2 (8)	0 (0)	0 (0)	1 (4)	0.738
Parenteral nutrition (%)	94 (72)	34 (81)	9 (47)	20 (77)	8 (100)	9 (100)	14 (54)	0.002
Volume per day (mL, mean ± SD)	2,422 ± 1,154	2,477 ± 1,250	2,271 ± 1,001	2,497 ± 1,178	2,370 ± 1,600	2,362 ± 1,057	2,299 ± 986	0.995
Number of days per week (mean, range)	6 (1–7)	6 (1–7)	7 (5–7)	6 (4–7)	7 (5–7)	6 (2–7)	5 (2–7)	0.061
Inability to maintain oral feeding—no. (%)	16 (12)	2 (5)	4 (21)	4 (15)	4 (50)	0 (0)	2 (8)	0.013
Analgesics for neuropathic pain—no. (%)	20 (15)	1 (2)	8 (42)	5 (19)	0 (0)	3 (33)	3 (12)	< 0.001
Dependence on opioids—no. (%)	17 (13)	4 (10)	4 (21)	4 (15)	2 (25)	1 (11)	2 (8)	0.554
Improvement after surgery—no./total no. (%)								
Ileostomy	42/55 (76)	21/24 (88)	3/3 (100)	9/16 (56)	1/3 (33)	3/4 (75)	5/5 (100)	0.054
Jejunostomy	17/29 (59)	7/9 (78)	2/2 (100)	5/10 (50)	0/3 (0)	2/2 (100)	1/3 (33)	0.086
Small bowel resection	35/62 (56)	19/23 (83)	2/5 (40)	7/14 (50)	0/6 (0)	3/6 (50)	4/8 (50)	0.004
Colon resection	33/65 (51)	17/22 (77)	2/5 (40)	5/12 (42)	0/3 (0)	1/7 (14)	8/16 (50)	0.013
5-yr survival after multivisceral transplantation (%)	3/5 (60)	2/2 (100)	—	1/3 (33)	—	—	—	—
Death (%)	25 (19)	2 (5)	6 (32)	6 (23)	7 (88)	2 (22)	2 (8)	< 0.001
Age at death (yr, median, range)	36 (21–82)	35 (30–40)	39 (29–59)	31 (21–70)	37 (31–82)	56 (40–71)	47 (33–60)	0.752

5-HT, 5-hydroxytryptamine; AI M, autoimmune myopathy; JAK, Janus kinase; Mito, mitochondriopathy; MM, monogenic myopathy; Neuro, neuropathy; STAT, signal transducer and activator of transcription; UM, unspecified myopathy.

yield in our cohort may not be extrapolatable to patients managed in secondary or community-based settings.

Consistent with several reports on CIPOs' atypical initial presentations (20–23), only 63% of our patients had a functional obstruction at the time of their first admission. This percentage was even lower in adult departments (42%), confirming the difficulty of making an early diagnosis. Longitudinal follow-up showed that the disease often follows a progressive course, with different segments of the gastrointestinal tract becoming dilated over time. In the "others" group, megacolon often preceded secondary small bowel dilation. This dynamic course likely contributes to the high rate of initial misdiagnoses observed in our cohort (e.g., colonic inertia and anorexia nervosa). Therefore, enhancing awareness and early diagnosis of CIPO remains a critical unmet medical need.

As next-generation sequencing becomes increasingly accessible, the identification of variants of uncertain significance and inconclusive results is expected to rise. In our study, histopathological evaluation played an important role in corroborating genetic findings and strengthening diagnostic confidence. However, the feasibility and diagnostic performance of this integrated approach depend on access to specialized pathology expertise and may not be achievable across varied healthcare systems. This limitation further emphasizes that our results reflect the capabilities of a specialized referral center rather than routine practice.

Nevertheless, implementation of this strategy for patients with suspected CIPO could significantly reduce the time from symptom onset to confirmed diagnosis (median age: 6 and 22 years, respectively). Our integrated data set offers novel insights into histogenetic classification and prognosis in CIPO. However,

incomplete overlap between genetic and histological assessments, and variability in tissue sampling (range: 1–6), introduce potential information bias. Patients with limited or absent histological evaluation may have been underclassified. These limitations underscore the need for future studies with standardized, comprehensive genetic and histopathological evaluation.

Disease progression in our cohort was frequently associated with the emergence of additional gastrointestinal and extradigestive manifestations, including volvulus, lower gastrointestinal bleeding, dysphagia, fecal incontinence, and neurological, cardiac, or urinary involvement. These observations reflect the overlap between CIPO and multisystem disorders and support the necessity of multidisciplinary and coordinated longitudinal follow-up to optimize patient assessment and guide management decisions.

Our findings also refine the prior association of Heneyke et al (1999) (24) between myopathies and poor outcomes in CIPO. Although atrophy of the muscularis propria was strongly associated with a worse prognosis ($P < 0.0001$), patients with monogenic myopathies showed favorable long-term survival (adjusted HR: 0.06, 95% CI: 0.01–0.42; $P = 0.004$) and significant improvement after bowel resection. These observations suggest that prognosis may depend on specific lesions or mechanisms rather than histological category alone. However, diagnostic approaches, surgical indications, and management strategies evolved substantially over the 16-year inclusion period. Heterogeneity in surgical indications may therefore have introduced selection bias toward patients more likely to respond. Therefore, these results should be interpreted with caution and should not be extrapolated to broader CIPO populations without validation. However, the heterogeneity of postoperative outcomes across the remaining groups argues against selection bias as the principal determinant of our findings. The benefit of bowel resections observed in monogenic myopathies may be attributed to the localized expression of the implicated genes in the gastrointestinal tract, rather than a uniform expression across the entire body (25,26).

Although retrospective and single-center, this study's strength lies in its large and unique cohort, with patients undergoing systematic regular follow-up. The cohort primarily consists of severely ill patients because management in our tertiary center is largely driven by intestinal failure, requiring PN. This represents a significant selection bias because included patients exhibited a more severe phenotype than those described in previous publications (1,27). However, this bias highlights the importance of genetic screening for this severely affected population because it enables genetic counseling, particularly in the context of family planning, pregnancy management, and preventing disease transmission to offspring. In addition, survivor bias cannot be excluded. The most severe patients (e.g., pediatric cases) may not have survived to evaluation at our adult referral center, potentially leading to an overestimation of survival.

In conclusion, integrating genetic and histological analyses enabled the characterization of 82% of the 130 adult patients admitted to our tertiary referral center between 2007 and 2023. The identification of monogenic diseases in late-onset adult CIPO underscores the importance of genetic testing. This approach refines prior efforts to align genetic and morphological data by proposing a classification with direct implications for therapeutic decision-making and survival. Although rigorous validation in independent CIPO cohorts free of the identified biases is required before any broad clinical application, these findings showed that favorable survival is possible even in severe disease and highlight the need for a scientifically grounded classification to inform personalized care and future clinical trials.

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CONFLICTS OF INTEREST

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Specific author contributions: M.-C.T.: conducted the study, writing, data collection, data interpretation, visualization. D.C.-H.: data interpretation, reviewing. L.B.: reviewing. A.A.: reviewing. M.B.: data collection. D.B.: data interpretation. B.C.: data collection. O.C.: reviewing. E.E.-D.: reviewing. O.G.: reviewing. F.L.: reviewing. C.L.: data collection. Y.N.: reviewing. J.R.: data collection. C.T.: data collection. F.C.-H.: conducted the study, data interpretation, visualization, reviewing. F.J.: conducted and planned the study, data collection, data interpretation, reviewing.

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Study Highlights

WHAT IS KNOWN

- ✓ Chronic intestinal pseudo-obstruction (CIPO) represents significant challenges in diagnosis and management.
- ✓ Genetic variants and histopathological lesions have been described.
- ✓ Integrated genetic-histological evaluation in adults remains incompletely characterized.

WHAT IS NEW HERE

- ✓ Integrated genetic and histological analyses characterized 82% of adults with CIPO in a large referral cohort.
- ✓ Distinct histogenetic groups showed different survival and postoperative outcomes.
- ✓ Adults with monogenic myopathy had better survival compared with other adult patients with CIPO.

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