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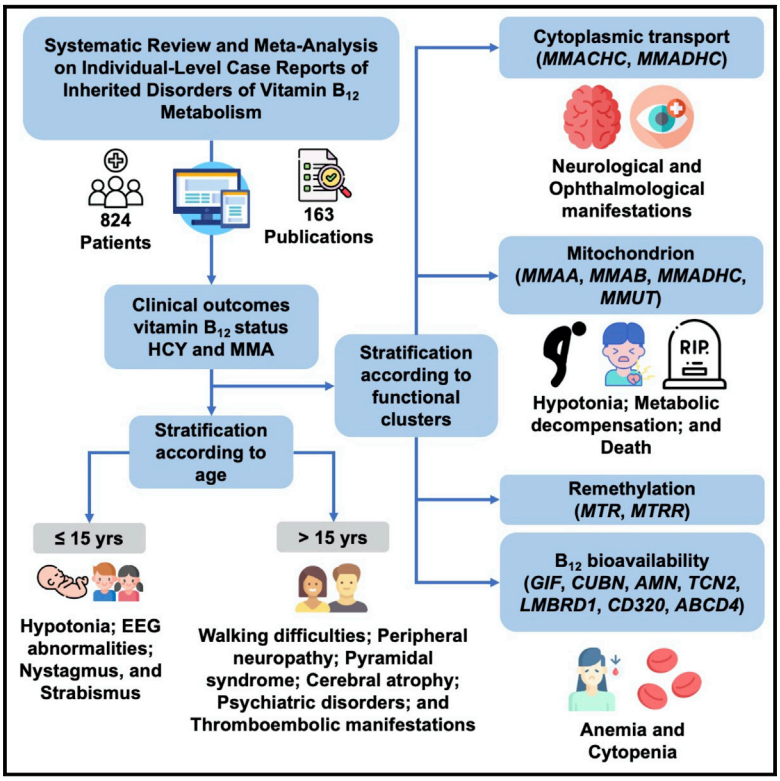
Clinical, phenotypic and genetic landscape of case reports with genetically proven inherited disorders of vitamin B_{12} metabolism: A meta-analysis

Graphical abstract



Highlights

- We analyze 824 individual case reports with genetically proven vitamin B_{12} disorders
- "Cytoplasmic transport" gene cluster is associated with neurological manifestations
- "B_{12} availability" and "remethylation" gene clusters are associated with anemia
- Neurological and thromboembolic manifestations are frequent in adult patients

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In brief

This systematic review by Wiedemann et al. highlights age categories and gene clusters as major determinants of patients' phenotypic landscape in inherited disorders of vitamin B_{12} metabolism. The diagnosis and management of these disorders must be considered in adult patients who present with neurological and thromboembolic manifestations of unknown origin.

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Clinical, phenotypic and genetic landscape of case reports with genetically proven inherited disorders of vitamin B_{12} metabolism: A meta-analysis

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SUMMARY

Inherited disorders of B_{12} metabolism produce a broad spectrum of manifestations, with limited knowledge of the influence of age and the function of related genes. We report a meta-analysis on 824 patients with a genetically proven diagnosis of an inherited disorder of vitamin B_{12} metabolism. Gene clusters and age categories are associated with patients' manifestations. The "cytoplasmic transport" cluster is associated with neurological and ophthalmological manifestations, the "mitochondrion" cluster with hypotonia, acute metabolic decompensation, and death, and the "B_{12} availability" and "remethylation" clusters with anemia and cytopenia. Hypotonia, EEG abnormalities, nystagmus, and strabismus are predominant in the younger patients, while neurological manifestations, such as walking difficulties, peripheral neuropathy, pyramidal syndrome, cerebral atrophy, psychiatric disorders, and thromboembolic manifestations, are predominant in the older patients. These results should prompt systematic checking of markers of vitamin B_{12} status, including homocysteine and methylmalonic acid, when usual causes of these manifestations are discarded in adult patients.

INTRODUCTION

Vitamin B_{12}, also known as cobalamin, is a water-soluble vitamin that influences key biochemical functions involved in DNA synthesis, methylation of DNA, proteins and metabolites, and mitochondrial metabolism through its role as a precursor of methylcobalamin and adenosylcobalamin, which act as cofactors for two target enzymes, cytoplasmic methionine synthase and mitochondrial methylmalonyl-CoA mutase, respectively.[164–166] Vitamin B_{12} is not produced in humans and must be provided by foods of animal origin.[167] The absorption and metabolism of vitamin B_{12} is a complex multistep process reviewed in Green et al.[164] Following ingestion, B_{12} is liberated from food carrier proteins and binds to haptocorrin in the stomach and transferred to gastric intrinsic factor (GIF) when haptocorrin is degraded in the small bowel. The GIF-B_{12} complex is absorbed in the distal ileum through a receptor composed of amnionless (encoded by *AMN* gene) and cubilin (encoded by *CUBN* gene). In blood, B_{12} is transported by haptocorrin and transcobalamin. The circulating B_{12} bound to transcobalamin is available for cellular uptake in most tissues via TcblR/CD320 receptor-mediated endocytosis. B_{12} lysosomal degradation of transcobalamin releases B_{12}, and the vitamin is subsequently exported into the cytosol by LMBD1 and ABCD4. In the cytosol, MMACHC and MMADHC chaperone and orientate B_{12} toward the synthesis of the MeCbl and AdoCbl cofactors in the cytosol and mitochondrion, respectively. At the cytosolic level, methylcobalamin is required for the remethylation of homocysteine into methionine by methionine synthase. This remethylation pathway involves adding a methyl group provided by methyltetrahydrofolate.[164,168] Methionine is the immediate metabolic precursor of S-adenosylmethionine, which is the universal methyl-donor in the transmethylation of DNA, histones, and other proteins and small molecules in mammals.[164,167–169] At the mitochondrial level, adenosylcobalamin serves as a cofactor of methylmalonyl-CoA mutase to catalyze the conversion of L-methylmalonyl-CoA to succinyl-CoA, which represents the final step of the anaplerotic replenishment of the tricarboxylic

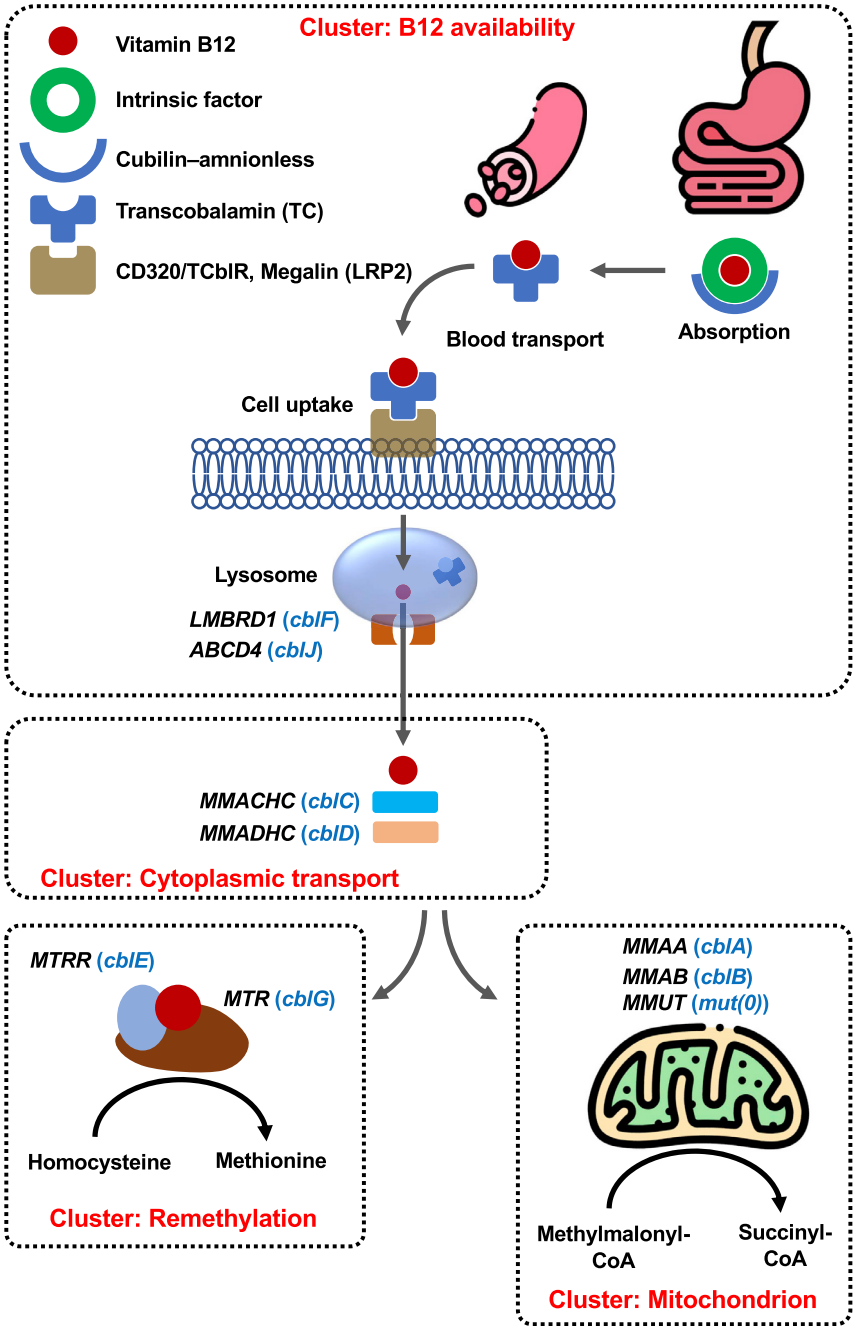

Figure 1. The four clusters are defined according to the function and metabolic consequences of genes involved in inherited disorders of vitamin B_{12} metabolism

The cluster "B_{12} bioavailability" includes gene defects involved in B_{12} absorption, blood transport, and cellular uptake, with an expected abnormal level of blood vitamin B_{12} and/or transport proteins and a combined increase of homocysteine and methylmalonic acid. Note that gene defects in lysosome export may also produce vitamin B_{12} deficit through impaired vitamin B_{12} absorption. The "cytoplasmic transport" cluster includes gene defects of cytoplasmic transport with an expected normal blood level of vitamin B_{12} and/or transport proteins and a combined increase of homocysteine and methylmalonic acid. The "remethylation" cluster includes gene defects of the remethylation pathway of homocysteine with an expected normal blood level of vitamin B_{12} and/or transport proteins and methylmalonic acid and an increased level of homocysteine. The "mitochondrion" cluster of the B_{12} mitochondrion pathway includes gene defects involved in the mitochondrion processing of B_{12} and conversion of L-methylmalonyl-CoA to succinyl-CoA. The complementation groups corresponding to vitamin B_{12} metabolism defects are indicated in blue font (icons made by flaticon, flaticon.com; CC-BY-3.0).

acid cycle by the catabolism of branched-chain amino acids, odd-chain fatty acids, and side chain of cholesterol.[170] The critical metabolic role of B_{12} is illustrated by the broad spectrum of clinical manifestations of inherited disorders of vitamin B_{12} metabolism. Inherited disorders of vitamin B_{12} metabolism are caused by a wide variety of genetic alterations in the genes involved in the absorption, cell trafficking, and intracellular metabolism of vitamin B_{12}.

To date, there is insufficient knowledge regarding the evaluation of the prevalence and classification of the broad spectra of clinical manifestations, biological, electrophysiological, and imaging findings among patients with inherited disorders of vitamin B_{12} metabolism. In particular, no systematic assessment, comparison, and categorization of all disorders have been performed to describe their clinical and metabolic spectrum in relation to age and functional type of gene defects. To address this issue, we defined four functional gene clusters according to the function and metabolic consequences of genes involved in inherited disorders of vitamin B_{12} metabolism, namely "B_{12} bioavailability," "cytoplasmic transport," "remethylation," and "mitochondrion" clusters (Figure 1). Thus, we conducted a systematic review of the literature using a highly sensitive search strategy to identify case reports describing individual-level data of patients with a genetically proven diagnosis of an inherited disorder of vitamin B_{12} metabolism. We performed a meta-analysis to assess the clinical, biological, imaging, and electrophysiological manifestations in the studied population and according to three age categories, <1 year, 1–15 years, and >15 years. We performed phenome-wide association studies to assess the predictors associated with age categories, functional gene clusters, and death. We highlighted specific manifestations according to age and gene clusters, which will help better understand the pathomechanisms that underlie the

two impaired B_{12}-dependent metabolic pathways and better orientate the diagnosis and management of this complex group of inherited metabolic disorders.

RESULTS

Literature review

As reported in the PRISMA flow diagram (Figure S1, related to Table 1), the systematic search generated 12,614 citations, of which 678 appeared to be relevant to the systematic review. Of these 678 publications, 515 were excluded based on selection criteria, including 156 studies that lacked a molecular diagnosis (Table S1, related to Table 1). One-hundred and sixty-three publications were eligible for the systematic review and reported individual-level case reports on 824 patients with a genetically proven inherited disorder of vitamin B_{12} metabolism.[1–163]

Description of the whole population of the 824 patients with inherited disorders of vitamin B_{12} metabolism

Among the 824 patients included in the systematic review, the proportion of males was 53% and the median age was 3.7 years (IQR, 0.2–2.0; range, 0–59.0) (Table 1). Seventy-one percent of patients were under 1 year old and 10.3% were over 15 years old. *MMACHC* gene pathogenic variants were the most frequently reported (49.6%, 409/824), followed by *MMUT* (32.6%, 269/824), *MMAA* (6.1%, 50/824), and *MMAB* (3.5%, 29/824) (Table 1). The annotation of the genetic variants retrieved in each of these four genes, including the HGVS nomenclature to report DNA and protein sequences variants and pathogenicity prediction according to the ACMG classification, is reported in Tables S2–S5 (related to Tables 1–4). Neurological manifestations were the most frequently reported and included developmental delay (38.2%, 315/824), hypotonia (17.7%, 146/824), and seizures (10.6%, 87/824). Digestive manifestations were the second most observed category of manifestations and corresponded to feeding intolerance (24.9% 205/824). Acute metabolic decompensation was reported in 13.2% of cases (109/824) and death occurred in 13.1% (108/824).

Phenotypic landscape and predictors of inherited disorders of vitamin B_{12} metabolism according to age category

The number of patients who were less than 1 year old was 509 (71.1% of the whole population). Among them, pathogenic variants on *MMACHC* and *MMUT* were observed in 44.4% (226/509) and 37.7% (192/509) of cases, respectively. In this age subgroup, neurological manifestations were the most frequently reported and included developmental delay (40.5%, 206/509), hypotonia (21.0%, 107/509), and seizures (9.4%, 48/509). Feeding intolerance was reported in 30.6% (156/509) of patients, and 17.1% (87/509) died (Table 2). The number of patients between 1 and 14 years was 133 (median 4.0 years; IQR, 2.0–9.0). In this age category, *MMACHC* deficiency was observed in 57.1% (76/133) and *MMUT* deficiency in 20.3% (27/133). Neurological manifestations were the most frequently reported and included developmental delay (39.1%, 52/133) and peripheral neuropathy (15.8%, 21/133). Cardiovascular manifestations frequently reported were high blood pressure, pulmonary hypertension (8.3%, 11/133), and cardiomyopathy (5.3%, 7/133). The number of patients over 15 years was 74 (median age 20.0; IQR, 18.0–29.0). In this age category, *MMACHC* deficiency was observed in 91.9% of cases (68/74). Neurological manifestations were the most frequently reported in this age category and included walking difficulties 37.8% (28/74), development delay 32.4% (24/74), and peripheral neuropathy 29.7% (22/74). Psychiatric disorders and high blood pressure were reported in 33.8% (25/74) and 12.2% (9/74), respectively.

We evaluated the influence of gradually increasing patient age categories on observed clinical manifestations (Figure 2). We observed a very significant increase in the frequency of neurological manifestations in relation to age categories. This mainly concerned the difficulty in walking and the presence of peripheral neuropathy, pyramidal syndrome, and, to a lesser extent, extrapyramidal syndrome. Likewise, we observed a significant influence of age on the frequency of cerebral atrophy and electroencephalogram abnormalities as well as for psychiatric manifestations. Unlike the neurological and psychiatric manifestations, the ophthalmological manifestations, nystagmus, and strabismus were mainly diagnosed in the first year of life and inversely correlated with age. The frequency of cardiovascular manifestations, including thrombosis and blood pressure, also increased very significantly with age. The increase in systolic blood pressure was not related to renal failure, as the latter was not significantly associated with age (Figure 2).

Phenotypic landscape and predictors of inherited disorders of vitamin B_{12} metabolism according to functional gene clusters

Cytoplasmic transport gene cluster

We classified 416 patients in the cytoplasmic transport gene cluster. The median age was 0.3 years (IQR, 0–10.3) (Table 3). A total of 61.5% (232/377) of the patients were less than 1 year old, 20.4% (77/377) were 1 to 14 years old, and 18.0% (68/377) were 15 years old or more. Among the most frequent neurological manifestations were developmental delay (35.3%, 147/416), hypotonia (15.4%, 64/416), and seizures (14.2%, 59/416). Ophthalmological manifestations were often reported, including nystagmus (16.8%, 70/416) and maculopathy or retinopathy (15.1%, 63/416). Psychiatric disorders occurred in 11.8% of cases (49/416), cardiomyopathy in 5.1% (21/416), and hypertension in 4.6% (19/416). Seventy variants of the *MMACHC* gene were reported (Table S2, related to Tables 1–4). The most frequently reported variants were c.270_271insA (274 occurrences; most frequently observed in the age subgroup 0 to 1 year: 76%, 208/274), c.609G > A (98 occurrences), and c.482G > A (82 occurrences; most frequently observed in the age subgroup 15 years and more: 46%, 38/82). In logistic regression analysis with Bonferroni correction, the following items were significantly associated with an increased risk of belonging to the cytoplasmic transport functional gene cluster when compared with the remaining functional gene clusters, in the descending order of ORs: nystagmus (OR, 27.24; 95% CI: 8.50–87.30); maculopathy or retinopathy (OR, 17.98; 95% CI: 6.48–49.90); psychiatric disorders (OR, 17.98; 95% CI: 5.56–58.18); over 15 years age category (OR, 12.18;

Table 1. Clinical, biological, imaging, and electrophysiological findings of the 824 patients included in the individual patient-level meta-analysis

Demographic data		
Age (years) – n, median (IQR; range)	716	3.7 (0.2–2; 0–59)
Age, 0 to 1 year – n/N, % (95% CI)	509/716	71.1 (67.8–74.4)
Age, 1 to 14 years included – n/N, % (95% CI)	133/716	18.6 (15.7–21.4)
Age, 15 years and more – n/N, % (95% CI)	74/716	10.3 (8.1–12.6)
Male gender – n/N, % (95% CI)	328/620	52.9 (49.0–56.8)
Gene – n/N, % (95% CI)		
MMACHC	409/824	49.6 (46.2–53.1)
MMUT	269/824	32.6 (29.4–35.9)
MMAA	50/824	6.1 (4.4–7.7)
MMAB	29/824	3.5 (2.3–4.8)
MTRR	16/824	2.0 (1.0–2.9)
MMADHC	15/824	1.8 (0.9–2.7)
TCN2	13/824	1.6 (0.7–2.4)
AMN	6/824	0.7 (0.1–1.3)
ABCD4	4/824	0.5 (0.0–0.9)
CBLIF (alias, *GIF*)	3/824	0.4 (0.0–0.8)
LMRD1	3/824	0.4 (0.0–0.8)
MTR	3/824	0.4 (0.0–0.8)
CUBN	2/824	0.2 (0.0–0.6)
CD320	1/824	0.1 (0.0–0.4)
ZF143	1/824	0.1 (0.0–0.4)
Gene clusters[a] – n/N, % (95% CI)		
Cytoplasmic transport[b]	416/823	50.5 (47.1–54.0)
Mitochondrion[c]	353/823	42.9 (39.5–46.3)
B_{12} bioavailability[e]	32/823	3.9 (2.6–5.2)
Remethylation[d]	22/823	2.7 (1.6–3.8)
Clinical findings		
Neurological manifestations – n/N, % (95% CI)		
Developmental delay	315/824	38.2 (34.9–41.6)
Hypotony	146/824	17.7 (15.1–20.3)
Seizures	87/824	10.6 (8.5–12.6)
Walking difficulty	66/824	8.0 (6.2–9.9)
Peripheral neuropathy	64/824	7.8 (5.9–9.6)
Pyramidal syndrome	36/824	4.4 (3.0–5.8)
Extrapyramidal syndrome	30/824	3.6 (2.4–4.9)
Microcephaly	24/824	2.9 (1.8–4.1)
Digestive manifestations – n/N, % (95% CI)		
Feeding intolerance	205/824	24.9 (21.9–27.8)
Multiple organ failure – n/N, % (95% CI)		
Acute metabolic decompensation	109/824	13.2 (10.9–15.5)
Death	108/824	13.1 (10.8–15.4)
Ophthalmologic manifestations – n/N, % (95% CI)		
Nystagmus	74/824	9.0 (7.0–10.9)
Maculopathy or retinopathy	67/824	8.1 (6.3–10.0)
Strabismus	26/824	3.2 (2.1–4.4)
Renal manifestations – n/N, % (95% CI)		
Chronic kidney disease	58/824	7.0 (5.3–8.8)

(*Continued on next page*)

Table 1. *Continued*

Acute kidney failure or hemolytic-uremic syndrome	37/824	4.5 (3.1–5.9)
Psychiatric manifestations – n/N, % (95% CI)		
Psychiatric disorders	52/824	6.3 (4.7–8.0)
Behavior abnormality	24/824	2.9 (1.8–4.1)
Cardiovascular manifestations – n/N, % (95% CI)		
Cardiomyopathy	27/824	3.3 (2.1–4.5)
High blood pressure	21/824	2.6 (1.5–3.6)
Pulmonary hypertension	16/824	1.9 (1.0–2.9)
Thrombosis	13/824	1.6 (0.7–2.4)
Miscellaneous manifestations – n/N, % (95% CI)		
Intrauterine growth restriction	15/824	1.8 (0.9–2.7)
Dermatologic abnormality	7/824	0.8 (0.2–1.5)
Gout	5/824	0.6 (0.0–1.1)
Pregnancy	4/824	0.5 (0.0–1.0)
Biological findings		
Hematology		
Anemia – n/N, % (95% CI)	108/824	13.1 (10.8–15.4)
Cytopenia – n/N, % (95% CI)	45/824	5.5 (3.9–7.0)
Hemoglobin (g/dL) – n, median (IQR)	80	7.8 (6.8–10.4)
Platelet (G/L) – n, median (IQR)	37	158 (83–276)
White blood cell (G/L) – n, median (IQR)	30	5.615 (4.500–7.900)
Biochemistry, blood – n, median (IQR)		
Homocysteine (μmol/L)	288	92 (54–141)
Methionine (μmol/L)	136	13.0 (7.1–21.5)
C3 (μmol/L)	105	9.9 (6.9–14.2)
MMA (μmol/L)	94	19 (4–53)
B_{12} (pmol/L)	52	389 (171–601)
Ammonia (μmol/L)	42	174 (123–350)
Biochemistry, urine – n, median (IQR)		
MMA (mM/mol creatine)	213	1,056 (272–3607)
Imaging and electrophysiological findings – n/N, % (95% CI)		
Brain MRI	175/824	21.2 (19.8–22.7)
Abnormal signal	89/175	50.1 (43.2–58.5)
Cerebral atrophy	52/175	29.7 (23.1–37.1)
MRI without abnormality	46/175	26.3 (19.9–33.5)
Abnormal EMG finding	23/824	2.8 (1.7–3.9)
Abnormal EEG finding[f]	17/824	2.1 (1.1–3.0)
Therapy – n/N, % (95% CI)		
Vitamin B_{12} supplementation	316/824	38.3 (35.0–41.7)
Liver transplantation	16/824	1.9 (1.0–2.9)
Kidney transplantation	14/824	1.7 (0.8–2.6)

MMACHC, metabolism of cobalamin associated C; MMA, methylmalonic acid; MRI, magnetic resonance imaging; EEG, electroencephalography; EMG, electromyography; IQR, interquartile range; Ref, reference values.

[a]One patient had two mutations for the *ZNF143* gene and was not classified in the four gene clusters.

[b]Gene cluster "B_{12} bioavailability" regroups all patients with *CBLIF* (alias, *GIF*), *CUBN*, *AMN*, *TCN2*, *LMBRD1*, *CD320*, or *ABCD4* variants.

[c]Gene cluster "cytoplasmic transport" regroups all patients with *MMACHC* and *MMADHC* variants responsible for combined mitochondrion and remethylation abnormalities.

[d]Gene cluster "remethylation" regroups all patients with *MTR*, *MTRR*, and *MMADHC* variants responsible for remethylation abnormalities.

[e]Gene cluster "mitochondrion" regroups all patients with *MMAA*, *MMAB*, or *MMUT* variants and *MMADHC* variants responsible for mitochondrion abnormalities.

[f]Abnormal EEG pattern other than seizures.

Table 2. Clinical, biological, radiological, and electrophysiological findings of the 824 patients included in the individual patient-level meta-analysis according to age subgroups

	Patients under 1 year	Patients between 1 and 14 years	Patients over 15 years
Demographic data			
Age (years) – n; median (IQR)	509; 0.0 (0.0–0.3)	133; 4.0 (2.0–9.0)	74; 20.0 (18.0–29.0)
Male gender – n/N; % (95% CI)	212/383; 55.4 (50.4–60.4)	52/119; 43.7 (34.7–52.7)	32/65; 49.2 (36.7–61.7)
Gene – n/N; % (95% CI)			
MMACHC	226/509; 44.4 (40.1–48.7)	76/133; 57.1 (48.6–65.7)	68/74; 91.9 (85.5–98.3)
MMUT	192/509; 37.7 (33.5–41.9)	27/133; 20.3 (13.4–27.2)	4/74; 5.4 (1.3–10.7)
MMAA	31/509; 6.1 (4.0–8.2)	8/133; 6.0 (1.9–10.1)	1/74; 1.4 (0.0–4.0)
MMAB	25/509; 4.0 (3.0–6.8)	1/133; 0.8 (0.0–2.2)	0/74; 0.0 (0.0–0.0)
TCN2	12/509; 2.4 (1.0–3.7)	1/133; 0.8 (0.0–2.2)	0/74; 0.0 (0.0–0.0)
MMADHC	10/509; 2.0 (7.6–3.2)	4/133; 3.0 (0.0–0.6)	0/74; 0.0 (0.0–0.0)
MTRR	4/509; 0.8 (0.0–1.6)	3/133; 2.3 (0.0–4.8)	1/74; 1.4 (0.0–4.0)
MTR	3/509; 0.6 (0.0–1.3)	0/133; 0.0 (0.0–0.0)	0/74; 0.0 (0.0–0.0)
ABCD4	2/509; 0.4 (0.0–0.1)	2/133; 1.5 (0.0–3.6)	0/74; 0.0 (0.0–0.0)
LMRD1	2/509; 0.4 (0.0–0.1)	0/133; 0.0 (0.0–0.0)	0/74; 0.0 (0.0–0.0)
CD320	1/509; 0.2 (0.0–0.0)	0/133; 0.0 (0.0–0.0)	0/74; 0.0 (0.0–0.0)
ZF143	1/509; 0.2 (0.0–0.0)	0/133; 0.0 (0.0–0.0)	0/74; 0.0 (0.0–0.0)
AMN	0/509; 0.0 (0.0–0.0)	6/133; 4.5 (0.9–8.1)	0/74; 0.0 (0.0–0.0)
CBLIF (alias, *GIF*)	0/509; 0.0 (0.0–0.0)	3/133; 2.3 (0.0–4.8)	0/74; 0.0 (0.0–0.0)
CUBN	0/509; 0.0 (0.0–0.0)	2/133; 1.5 (0.0–3.6)	0/74; 0.0 (0.0–0.0)
Gene clusters[a] – n/N; % (95% CI)			
Mitochondrion[d]	251/508; 49.4 (45.0–53.8)	37/133; 27.8 (20.1–35.5)	5/74; 6.8 (0.9–12.6)
Cytoplasmic transport[c]	232/508; 45.7 (41.3–50.0)	77/133; 57.9 (49.4–66.4)	68/74; 91.9 (85.5–98.3)
B_{12} bioavailability[b]	17/508; 3.4 (1.8–4.9)	14/133; 10.5 (5.2–15.8)	0/74; 0.0 (0.0–0.0)
Remethylation[e]	8/508; 1.6 (0.5–2.7)	5/133; 3.8 (0.5–7.1)	1/74; 1.4 (0.0–4.0)
Clinical findings			
Neurological manifestations – n/N; % (95% CI)			
Developmental delay	40.5; (36.2–44.7)	52/133; 39.1 (30.7–47.5)	24/74; 32.4 (21.5–43.4)
Hypotony	107/509; 21.0 (17.5–24.6)	16/133; 12.0 (6.4–1.8)	0/74; 0.0 (0.0–0.0)
Seizures	48/509; 9.4 (6.9–12.0)	20/133; 15.0 (8.9–21.2)	11/74; 14.9 (6.6–23.2)
Microcephaly	21/509; 4.1 (2.4–5.9)	1/133; 0.8 (0.0–2.2)	0/74; 0.0 (0.0–0.0)
Walking difficulty	16/509; 3.1 (1.6–4.7)	20/133; 15.0 (8.9–21.2)	28/74; 37.8 (26.5–49.2)
Peripheral neuropathy	16/509; 3.1 (1.6–4.7)	21/133; 15.8 (9.6–22.1)	22/74; 29.7 (19.1–40.4)
Extra pyramidal syndrome	14/509; 2.8 (1.3–4.2)	6/133; 4.5 (0.9–8.1)	8/74; 10.8 (3.6–18.1)
Pyramidal syndrome	10/509; 2.0 (0.9–3.2)	6/133; 4.5 (0.9–8.1)	19/74; 25.7 (15.5–35.9)
Digestive manifestations– n/N; % (95% CI)			
Feeding intolerance	156/509; 30.6 (26.6–34.7)	33/133; 24.8 (17.4–32.2)	3/74; 4.1 (0.0–8.7)
Multiple organ failure – n/N; % (95% CI)			
Death	87/509; 17.1 (13.8–20.4)	10/133; 7.5 (5.2–9.8)	4/74; 5.4 (1.3–10.7)
Acute metabolic decompensation	82/509; 16.1 (12.9–19.3)	12/133; 9.0 (4.1–14.0)	4/74; 5.4 (1.3–10.7)
Ophthalmologic manifestations – n/N; % (95% CI)			
Nystagmus	55/509; 10.8 (8.1–13.5)	6/133; 4.5 (0.9–8.1)	2/74; 2.7 (0.0–6.5)
Maculopathy or retinopathy	52/509; 10.2 (7.6–12.9)	5/133; 3.8 (0.5–7.0)	5/74; 6.8 (0.9–12.6)
Strabismus	23/509; 4.5 (2.7–6.3)	1/133; 0.8 (0.0–2.2)	0/74; 0.0 (0.0–0.0)
Renal manifestations – n/N; % (95% CI)			
Chronic kidney disease	37/509; 7.3 (5.0–9.5)	12/133; 9.0 (4.1–14.0)	7/74; 9.5 (2.6–16.3)
Acute kidney failure or HUS	21/509; 4.1 (2.4–5.9)	14/133; 10.5 (5.3–15.8)	2/74; 2.7 (0.0–6.5)
Cardiovascular manifestations – n/N; % (95% CI)			
Cardiomyopathy	17/509; 3.3 (1.8–4.9)	7/133; 5.3 (1.4–9.1)	2/74; 2.7 (0.0–6.5)

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Table 2. *Continued*

	Patients under 1 year	Patients between 1 and 14 years	Patients over 15 years
Pulmonary hypertension	4/509; 0.8 (0.0–1.6)	11/133; 8.3 (3.5–13.0)	1/74; 1.4 (0.0–4.0)
Thrombosis	3/509; 0.6 (0.0–1.3)	5/133; 3.8 (0.5–7.0)	5/74; 6.8 (0.9–12.6)
High blood pressure	2/509; 0.4 (0.0–0.9)	9/133; 6.8 (2.4–11.1)	9/74; 12.2 (4.5–19.8)
Psychiatric manifestations – n/N; % (95% CI)			
Behavior abnormality	11/509; 2.2 (0.9–3.4)	8/133; 6.0 (1.9–10.1)	4/74; 5.4 (1.3–10.7)
Psychiatric disorders	8/509; 1.6 (0.5–2.7)	18/133; 13.5 (7.6–19.4)	25/74; 33.8 (22.8–44.8)
Miscellaneous manifestations – n/N; % (95% CI)			
Intrauterine growth restriction	8/509; 1.6 (0.5–2.7)	3/133; 2.7 (0.0–4.8)	1/74; 1.4 (0.0–4.0)
Gout	5/509; 1.0 (0.1–1.8)	0/133; 0.0 (0.0–0.0)	0/74; 0.0 (0.0–0.0)
Dermatologic abnormality	1/509; 0.2 (0.0–0.6)	4/133; 3.0 (0.0–6.0)	1/74; 1.4 (0.0–4.0)
Pregnancy	0/509; 0.0 (0.0–0.0)	2/133; 1.5 (0.0–3.6)	2/74; 2.7 (0.0–6.5)
Biological findings			
Hematology			
Anemia – n/N; % (95% CI)	42/509; 8.3 (5.9–10.6)	47/133; 35.3 (27.1–43.6)	11/74; 14.9 (6.6–23.2)
Cytopenia – n/N; % (95% CI)	23/509; 4.5 (2.7–6.3)	18/133; 13.5 (7.6–19.4)	3/74; 4.1 (0.0–8.7)
Hb (g/dL) – n; median (IQR)	25; 7.3 (6.5–10.0)	36; 7.9 (7.0–10.3)	9; 8.9 (7.8–11.6)
WBC (G/L) – n; median (IQR)	16; 4.995 (3.693–7.025)	13; 7.000 (4.900–10.200)	0; —
Platelet (G/L) – n; median (IQR)	15; 83 (21.5–263.5)	20; 199 (122–292.5)	2; 128.5 (82–175)
Biochemistry, blood – n, median (IQR)			
Homocysteine (μmol/L)	137; 92 (50–157)	64; 90 (59–123)	60; 99 (67–117)
Methionine (μmol/L)	77; 117–14	22; 1,912–25	15; 98–16
C3-Carnitine (μmol/L)	69; 10.4 (6.5–14.1)	17; 7.9 (7.1–11.2)	7; 11.2 (7.8–15.5)
MMA (μmol/L)	66; 20 (4–93)	9; 296–14	9; 22 (8–70)
Ammonia (μmol/L)	31; 198 (141–402)	3; 206 (113–232)	6; 3215–54
B_{12} (pmol/L)	21; 362 (181–573)	22; 396 (112–611)	7; 428 (380–738)
Biochemistry, urine – n, median (IQR)			
MMA (mM/mol creatine)	131; 1,940 (550–4,663)	44; 950 (173–2,801)	22; 486 (244–1,009)
Imaging and electrophysiological findings – n/N, % (95% CI)			
Head MRI	61/509; 12.0 (9.2–14.8)	41/133; 30.8 (22.9–38.8)	35/74; 47.3 (35.7–58.9)
Abnormal signal reported	39/61; 64.0 (51.9–76.0)	17/41; 41.5 (26.4–56.5)	9/35; 25.7 (11.2–40.2)
Without abnormality	20/61; 32.8 (21.0–44.6)	5/41; 12.2 (2.2–22.2)	7/35; 20.0 (6.7–33.2)
Cerebral atrophy reported	8/61; 13.1 (4.6–21.6)	22/41; 53.7 (38.4–68.9)	21/35; 60.0 (43.8–76.2)
Abnormal EEG finding reported[f]	61/509; 12.0 (9.2–14.8)	6/133; 4.5 (0.9–8.1)	2/74; 2.7 (0.0–6.5)
Abnormal EMG finding reported	39/61; 64.0 (51.9–76.0)	7/133; 5.3 (1.4–9.1)	14/74; 18.9 (9.8–28.1)
Therapy – n/N, % (95% CI)			
Vitamin B_{12} supplementation	156/509; 30.6 (26.6–34.7)	66/133; 49.6 (45.3–54.0)	56/74; 75.7 (65.7–85.7)
Kidney transplantation	13/509; 2.6 (1.2–3.9)	0/133; 0.0 (0.0–0.0)	1/74; 1.4 (0.0–4.0)
Liver transplantation	15/509; 3.0 (1.5–4.4)	0/133; 0.0 (0.0–0.0)	0/74; 0.0 (0.0–0.0)

MMACHC, metabolism of cobalamin associated C; MMA, methylmalonic acid; HUS, hemolytic-uremic syndrome; Hb, hemoglobin; WBC, white blood cell; MRI, magnetic resonance imaging; EEG, electroencephalography; EMG, electromyography; IQR, interquartile range; Ref, reference values.
[a]One patient had two mutations for the *ZNF143* gene and was not classified in the four gene clusters.
[b]Gene cluster "B_{12} bioavailability" regroups all patients with *CBLIF* (alias, *GIF*), *CUBN*, *AMN*, *TCN2*, *LMBRD1*, *CD320*, or *ABCD4* variants.
[c]Gene cluster "cytoplasmic transport" regroups all patients with *MMACHC* and *MMADHC* variants responsible for combined mitochondrion and remethylation abnormalities.
[d]Gene cluster "mitochondrion" regroups all patients with *MMAA*, *MMAB*, or *MMUT* variants and *MMADHC* variants responsible for mitochondrion abnormalities.
[e]Gene cluster "remethylation" regroups all patients with *MTR*, *MTRR*, and *MMADHC* variants responsible for remethylation abnormalities.
[f]Abnormal EEG pattern other than seizures.

Table 3. Clinical, biological, radiological, and electrophysiological findings of the 824 patients included in the individual patient-level meta-analysis according to functional gene clusters

	Cytoplasmic transport[a]	Mitochondrion[b]	B_{12} bioavailability[d]	Remethylation[c]
Demographic data				
Age (years) – n, median (IQR)	377; 0.3 (0.0–10.3)	293; 0.1 (0.0–0.7)	31; 0.3 (0.2–2.1)	14; 0.3 (0.1–5.0)
Age, 0 to 1 – n/N, % (95% CI)	232/377; 61.5 (56.6–66.5)	251/293; 85.7 (81.6–89.7)	17/31; 54.8 (36.3–73.4)	8/14; 57.1 (56.5–79.5)
Age, 1 to 14 years included – n/N, % (95% CI)	77/377; 20.4 (16.3–24.5)	37/293; 12.6 (8.8–16.5)	14/31; 45.2 (26.6–63.7)	5/14; 35.7 (7.0–64.4)
Age, 15 years and more – n/N, % (95% CI)	68/377; 18.0 (14.1–21.9)	5/293; 1.7 (0.2–3.2)	0/31; 0.0 (0.0–0.0)	1/14; 7.1 (0.0–22.6)
Male gender – n/N, % (95% CI)	196/361; 54.3 (49.1–59.5)	116/214; 54.2 (47.5–60.9)	11/31; 35.5 (17.6–53.3)	5/14; 35.7 (7.0–64.4)
Clinical findings				
Neurological manifestations – n/N, % (95% CI)				
Developmental delay	147/416; 35.3 (30.7–39.9)	142/353; 40.2 (35.1–45.4)	15/32; 46.9 (28.6–65.2)	10/22; 45.5 (22.9–68.1)
Hypotony	64/416; 15.4 (11.9–18.9)	75/353; 21.2 (17.0–25.5)	2/32; 6.3 (0.0–15.1)	4/22; 18.2 (0.7–35.7)
Seizures	59/416; 14.2 (10.8–17.5)	$2^2/_3$ 53; 6.2 (3.7–8.8)	1/32; 3.1 (0.0–9.5)	4/22; 18.2 (0.7–35.7)
Peripheral neuropathy	49/416; 11.8 (8.7–14.9)	3/353; 0.9 (0.0–1.8)	4/32; 12.5 (0.4–24.6)	8/22; 36.4 (14.5–58.2)
Walking difficulty	46/416; 11.1 (8.0–14.1)	8/353; 2.3 (0.7–3.8)	9/32; 28.1 (11.7–44.6)	3/22; 13.6 (0.0–29.2)
Pyramidal syndrome	25/416; 6.0 (3.7–8.3)	9/353; 2.6 (0.9–4.2)	0/32; 0.0 (0.0–0.0)	2/22; 9.1 (0.0–22.1)
Microcephaly	18/416; 4.3 (2.4–6.3)	2/353; 0.6 (0.0–1.4)	1/32; 3.1 (0.0–9.5)	2/22; 9.1 (0.0–22.1)
Extra pyramidal syndrome	12/416; 2.9 (1.3–4.5)	15/353; 4.3 (2.1–6.4)	1/32; 3.1 (0.0–9.5)	2/22; 9.1 (0.0–22.1)
Digestive manifestations– n/N, % (95% CI)				
Feeding intolerance	85/416; 20.4 (16.5–24.3)	97/353; 27.5 (22.8–32.2)	19/32; 59.4 (41.4–77.4)	3/22; 13.6 (0.0–29.2)
Ophthalmologic manifestations – n/N, % (95% CI)				
Nystagmus	70/416; 16.8 (13.2–20.4)	0/353; 0.0 (0.0–0.0)	0/32; 0.0 (0.0–0.0)	3/22; 13.6 (0.0–29.2)
Maculopathy or retinopathy	63/416; 15.1 (11.7–18.6)	4/353; 1.1 (0.0–2.2)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)
Strabismus	26/416; 6.3 (3.9–8.6)	0/353; 0.0 (0.0–0.0)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)
Psychiatric manifestations – n/N, % (95% CI)				
Psychiatric disorders	49/416; 11.8 (8.7–14.9)	2/353; 0.6 (0.0–1.4)	0/32; 0.0 (0.0–0.0)	1/22; 4.6 (0.0–14.0)
Behavior abnormality	22/416; 5.3 (3.1–7.5)	1/353; 0.3 (0.0–0.8)	0/32; 0.0 (0.0–0.0)	1/22; 4.6 (0.0–14.0)
Multiple organ failure – n/N, % (95% CI)				
Death	31/416; 7.5 (4.9–10.0)	74/353; 21.0 (16.7–25.2)	0/32; 0.0 (0.0–0.0)	2/22; 9.1 (0.0–22.1)
Acute metabolic decompensation	13/416; 3.2 (1.5–4.8)	93/353; 26.3 (21.7–31.0)	2/32; 6.3 (0.0–15.1)	1/22; 4.6 (0.0–14.0)
Cardiac or hemodynamic manifestations – n/N, % (95% CI)				
Cardiomyopathy	21/416; 5.1 (2.9–7.2)	4/353; 1.1 (0.0–2.2)	1/32; 3.1 (0.0–9.5)	0/22; 0.0 (0.0–0.0)
High blood pressure	19/416; 4.6 (2.6–6.6)	2/353; 0.6 (0.0–1.4)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)
Pulmonary hypertension	13/416; 3.2 (1.5–4.8)	3/353; 0.9 (0.0–1.8)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)
Thrombosis	10/416; 2.4 (0.9–3.9)	1/353; 0.3 (0.0–0.8)	1/32; 3.1 (0.0–9.5)	1/22; 4.6 (0.0–14.0)
Renal manifestations – n/N, % (95% CI)				
Acute kidney failure or HUS	24/416; 5.8 (3.5–8.0)	12/353; 3.4 (1.5–5.3)	1/32; 3.1 (0.0–9.5)	1/22; 4.6 (0.0–14.0)
Chronic kidney disease	16/416; 3.9 (0.0–8.8)	36/353; 10.2 (7.0–13.4)	6/32; 18.8 (4.5–33.0)	0/22; 0.0 (0.0–0.0)
Miscellaneous manifestations – n/N, % (95% CI)				
Intrauterine growth restriction	9/416; 2.2 (0.8–3.6)	2/353; 0.6 (0.0–1.4)	3/32; 9.4 (0.0–20.1)	1/22; 4.6 (0.0–14.0)
Pregnancy	3/416; 0.7 (0.0–1.5)	1/353; 0.3 (0.0–0.8)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)
Dermatologic abnormality	2/416; 0.5 (0.0–1.2)	1/353; 0.3 (0.0–0.8)	4/32; 12.5 (0.4–24.6)	0/22; 0.0 (0.0–0.0)
Gout	0/416; 0.0 (0.0–0.0)	5/353; 1.4 (0.2–2.7)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)

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Table 3. *Continued*

	Cytoplasmic transport[a]	Mitochondrion[b]	B_{12} bioavailability[d]	Remethylation[c]
Biological findings				
Complete blood count				
Anemia – n/N; % (95% CI)	52/416; 12.5 (9.3–15.7)	16/353; 4.5 (2.4–6.7)	25/32; 78.1 (63.0–93.3)	15/22; 68.2 (47.0–89.3)
Cytopenia – n/N; % (95% CI)	23/416; 5.5 (3.3–7.7)	8/353; 2.3 (0.7–3.8)	11/32; 34.4 (17.0–51.8)	3/22; 13.6 (0.0–29.2)
Hemoglobin (g/dL) – n; median (IQR)	37; 8.4 (7.1–10.4)	7; 9.2 (7.6–10.2)	18; 7.4 (5.4–11.2)	18; 7.5 (6.3–8.5)
WBC (G/L) – n; median (IQR)	8; 3.945 (2.520–6.295)	6; 8.870 (5.250–16.800)	15; 5.980 (4.600–7.300)	1; 7.900 (–)
Platelets (G/L) – n; median (IQR)	15; 144 (87–231)	6; 313 (276–419)	14; 103 (55–198)	2; 165 (–)
Blood metabolic findings – n, median (IQR)				
Homocysteine (μmol/L)	237; 99 (65–146)	11; 6.0 (5.1–9.3)	22; 4,726–60	18; 93 (71–136)
Methionine (μmol/L)	105; 127–21	5; 2,514–33	9; 1,915–21	17; 125–21
MMA (μmol/L)	72; 103–25	20; 270 (136–1040)	2; 148–17	0; –
C3-Carnitine (μmol/L)	58; 7.8 (5.8–11.2)	43; 13.0 (9.8–19.1)	3; 5.7 (4.2–8.8)	0; –
Vitamin B_{12} (pmol/L)	24; 501 (399–767)	6; 348 (216–750)	17; 149 (82–375)	5; 151 (105–240)
Ammonia (μmol/L)	7; 54 (26–108)	35; 199 (141–367)	0; –	0; –
Urine metabolic findings– n, median (IQR)				
MMA (mM/mol creatine)	109; 710 (216–2045)	95; 2,903 (603–5699)	9; 154 (70–804)	0; –
MRI, EEG, and EMG findings – n/N, % (95% CI)				
Head MRI	100/416; 24.0 (19.9–28.2)	62/353; 17.6 (13.6–21.6)	4/32; 12.5 (0.4–24.6)	8/22; 26.5 (11.5–41.4)
Abnormal signal reported	47/100; 47.0 (37.2–56.8)	36/62; 58.0 (46.7–71.3)	1/4; 25.0 (0.0–67.4)	4/8; 50.0 (15.4–84.6)
Cerebral atrophy reported	42/100; 42.0 (32.3–51.7)	4/62; 6.4 (0.3–12.8)	2/4; 50.0 (1.0–99.0)	4/8; 50.0 (15.4–84.6)
Without abnormality	17/100; 17.0 (9.6–24.4)	25/62; 40.3 (28.6–53.3)	1/4; 25.0 (0.0–67.4)	2/8; 25.0 (0.0–55.0)
Abnormal EMG finding reported	20/416; 4.8 (2.7–6.9)	0/353; 0.0 (0.0–0.0)	1/32; 3.1 (0.0–20.8)	2/22; 9.1 (0.0–22.1)
Abnormal EEG finding reported[e]	14/416; 3.4 (1.6–5.1)	1/353; 0.3 (0.0–0.8)	0/32; 0.0 (0.0–0.0)	2/22; 9.1 (0.0–22.1)
Therapy – n/N, % (95% CI)				
Vitamin B_{12} supplementation	191/416; 45.9 (41.1–50.7)	73/353; 20.4 (15.6–25.2)	30/32; 93.8 (84.9–100.0)	21/22; 95.5 (86.0–100.0)
Liver transplantation	0/416; 0.0 (0.0–0.0)	16/353; 4.5 (2.4–6.7)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)
Kidney transplantation	0/416; 0.0 (0.0–0.0)	14/353; 4.0 (1.9–6.0)	0/32; 0.0 (0.0–0.0)	0/22; 0.0 (0.0–0.0)

MMACHC, methylmalonic aciduria and homocystinuria type C protein; MMA, methylmalonic acid; MRI, magnetic resonance imaging; EEG, electroencephalography; EMG, electromyography.

One patient had two mutations for the *ZNF143* gene, which is not classified in these gene clusters.

[a]Gene cluster "cytoplasmic transport" regroups all patients with *MMACHC* and *MMADHC* variants responsible for combined mitochondrion and remethylation abnormalities.

[b]Gene cluster "mitochondrion" regroups all patients with *MMAA*, *MMAB*, or *MMUT* variants and *MMADHC* variants responsible for mitochondrion abnormalities.

[c]Gene cluster "remethylation" regroups all patients with *MTR*, *MTRR*, and *MMADHC* variants responsible for remethylation abnormalities.

[d]Gene cluster "B_{12} bioavailability" regroups all patients with *CBLIF* (alias, *GIF*), *CUBN*, *AMN*, *TCN2*, *LMBRD1*, *CD320*, or *ABCD4* variants.

[e]Abnormal EEG pattern other than seizures.

95% CI: 5.21–28.46); behavior abnormality (OR, 11.31; 95% CI: 2.64–48.41); high blood pressure (OR, 9.69; 95% CI: 2.24–41.88); abnormal EMG finding (OR, 6.80; 95% CI: 2.01–23.07); peripheral neuropathy (OR, 3.49; 95% CI: 1.92–6.33); seizures (OR, 2.33; 95% CI: 1.44–3.75); and homocysteine (for each 10 μmol/L increment) (OR, 1.14; 95% CI: 1.07–1.22) (Figure 3A; Table S6, related to Tables 1–4). When compared with the B_{12} bioavailability gene cluster as a reference comparator, the following items were significantly associated with an increased risk of belonging to the cytoplasmic transport functional gene cluster, in the descending order of ORs: vitamin B_{12} (for each 100 pmol/L increment) (OR, 2.58; 95% CI: 1.44–4.63) and homocysteine (for each 10 μmol/L increment) (OR: 1.30; 95% CI: 1.14–1.49) (Table S6, related to Tables 1–4).

Mitochondrion gene cluster

We classified 353 patients in the mitochondrion gene cluster. The median age was 0.1 years (IQR, 0–0.7). A total of 85.7% of the patients were under 1 year old (251/293), 12.6% were between 1 and 14 years old (37/293), and 1.7% were over 15 years old (5/293) (Table 3). Development delay (40.2%, 142/353) and hypotonia (21.2%, 75/353) were the most frequently reported manifestations. Acute metabolic decompensation occurred in 26.3% (93/353) of the patients and digestive manifestations occurred in 27.5% (97/353). Death was reported in 21.0% (74/353) of cases. Few ophthalmological manifestations

Table 4. Comparison of the characteristics and clinical, biological, and imaging findings between the 161 patients with *CblC* from the E-HOD registry and the 416 patients within the "cytoplasmic transport" cluster from the individual patient data meta-analysis

	E-HOD registry – *CblC* n = 161	Individual patient data meta-analysis, "cytoplasmic transport" cluster, n = 416	p value
Patients' characteristics			
Gender (male) – n/N, %	93/161, 57.7	196/361, 54.3	0.47
Pre-clinically diagnosed – n/N, %	47/161, 29.2	38/416[a], 9.1	<0.0001
Age at first symptoms (years) – n, median (IQR)	93, 0.1 (0.0–0.3)	377, 0.3 (0.0–10.3)	NS
Mutations reported – n/N, %	117/191, 61.3	416/416, 100	<0.0001
Clinical findings – n/N, %			
Thromboembolic events			
Stroke	3/113, 2.7	8/416, 1.9	0.60
Thromboembolic manifestations	5/113, 4.4	10/416, 2.4	0.26
Renal manifestations			
Hemolytic uremic syndrome	17/113, 15.0	24/416, 5.8	0.001
Chronic kidney disease	2/113, 1.7	16/416, 3.9	0.25
Cardiac disease			
Cardiomyopathy/cardiac malformation	5/113, 8.8	21/416, 5.1	0.14
Cardiac arrest/heart failure/death	2/113, 1.7	31/416, 7.5	0.02
Arterial hypertension	3/113, 2.7	19/416, 4.6	0.37
Digestive and liver manifestations			
Feeding problems	68/113, 60	85/416, 20.4	<0.0001
Hepatomegaly	9/113, 8.0	6/416, 1.4	0.0002
Acute manifestation			
Metabolic crises	20/113, 18	13/416, 3.2	<0.0001
Ophthalmological manifestations			
Eye disease (optic nerve disease)	20/113, 18	100/416, 24.0	0.18
Nystagmus	NR in E-HOD registry	70/416, 16.8	no data for comparison
Maculopathy or retinopathy	NR in E-HOD registry	63/416, 15.1	no data for comparison
Strabismus	NR in E-HOD registry	26/416, 6.3	no data for comparison
Psychiatric manifestations			
Psychiatric disorders	6/113, 5	49/416, 11.8	0.04
Behavior abnormality	NR	22/416, 5.3	no data for comparison
Neurological manifestations			
Muscular hypotonia	38/113, 34	64/416, 15.4	<0.0001
Developmental delay	26/113, 23	147/416, 35.3	0.01
Seizures	19/113, 17	59/416, 14.2	0.46
Brain malformation	3/113, 3	not reported in the study	no data for comparison
Microcephaly	9/113, 8	18/416, 4.3	0.11
Hydrocephalus	5/113, 4	not reported in the study	no data for comparison
Myelopathy	4/113, 3	49/416; 11.8	0.006
Peripheral neuropathy	NR in E-HOD registry	49/416; 11.8	no data for comparison
Walking difficulty	NR in E-HOD registry	46/416; 11.1	no data for comparison
Pyramidal syndrome	NR in E-HOD registry	25/416; 6.0	no data for comparison
Extrapyramidal syndrome	NR in E-HOD registry	12/416; 2.9	no data for comparison
Laboratory findings			
Homocysteine before treatment μmol/L – n, median (IQR)	139, 123 (65–197)	237, 99 (65–146)	NS
Anemia – n/N, %	32/113, 28	52/416, 12.5	0.0001

(*Continued on next page*)

Table 4. *Continued*

Imaging findings			
Abnormal MRI signal reported	NR in E-HOD registry	47/100; 47.0	no data for comparison
Cerebral atrophy reported on MRI	NR in E-HOD registry	42/100; 42.0	no data for comparison
Abnormal EMG findings reported	NR in E-HOD registry	20/416; 4.8	o data for comparison

NR, not reported; NS, not significant.

[a]The 38 children diagnosed by Newborn Screening are described in Table S9. List of publications including patients with an inborn error of vitamin B_{12} metabolism diagnosed by newborn screening. Related to Tables 1–4.

or cardiological manifestations were noticed. Cerebral atrophy on brain MRI was only noticed in 6.4% of the case (4/62), whereas an abnormal signal was reported in 58.0% (36/62). Liver transplantation was performed in 4.5% of cases (16/353). Among the 190 *MMUT* variants described, c.572C > A (27 occurrences) and c.655A > T (21 allele occurrences) were the most frequent (Table S3, related to Tables 1–4). The pathogenic c.433C > T variant was the most frequent among the 31 *MMAA* variants, with 27 allele occurrences (Table S4, related to Tables 1–4). Most of the variants reported in *MMAB* were pathogenic and associated with early onset (Table S5, related to Tables 1–4). In logistic regression analysis with Bonferroni correction, the following items were significantly associated with an increased risk of belonging to the mitochondrion functional gene cluster, when compared with the remaining functional gene clusters in the descending order of ORs: acute metabolic decompensation (OR, 0.15; 95% CI: 5.84–17.63); 0 to 1 year age category (OR, 3.83; 95% CI: 2.62–5.62); death (OR, 3.51; 95% CI:2.27–5.44); C3-carnitine (μmol/L) (OR, 1.24; 95% CI: 1.12–1.38); MMA, urine (for each per 500 mmol/mol creatinine increment) (OR, 1.17; 95% CI: 1.09–1.25); and MMA, blood (for each per 10 μmol/L increment) (OR, 1.14; 95% CI: 1.07–1.23) (Figure 3B; Table S6, related to Tables 1–4).

B_{12} bioavailability gene cluster

We classified 32 patients in the B_{12} bioavailability gene cluster. The median age was 0.3 years (IQR, 0.2–2.1). A total of 54.8% (17/31) of the patients were less than 1 year old and 45.2% (14/31) were in the 1–14-year-old subgroup (Table 3). Anemia was the most frequently reported manifestation (78.1%, 25/32), followed by feeding intolerance (59.4%, 19/32) and development delay (46.9%, 15/32). No seizures were noticed, and no other abnormal EEG patterns were reported. No ophthalmological or psychiatric manifestations were observed. Only one patient with cardiological manifestation was reported. Chronic kidney disease was observed in 18.8% (6/32), dermatologic abnormalities in 12.5% (4/32), and intrauterine growth restriction in 9.4% (3/32). Cytopenia was noticed in 34.4% (11/32) despite B_{12} supplementation in as much as 93.8% (30/32) of patients. In logistic regression analysis with Bonferroni correction, the following items were significantly associated with an increased risk of belonging to the B_{12} bioavailability functional gene cluster when compared with the remaining functional gene clusters in the descending order of ORs: cytopenia (OR, 11.66; 95% CI: 5.21–26.12); walking difficulty (OR, 5.04; 95% CI: 2.23–11.40); feeding intolerance (OR, 4.79; 95% CI: 2.32–9.88); 1 to 14 years age category (OR, 3.91; 95% CI: 1.88–8.15); and vitamin B_{12} (per 100 pmol/L) (OR, 0.57; 95% CI: 0.39–0.82) (Table S6, related to Tables 1–4; Figure S2A, related to Tables 1 and 3).

Remethylation gene cluster

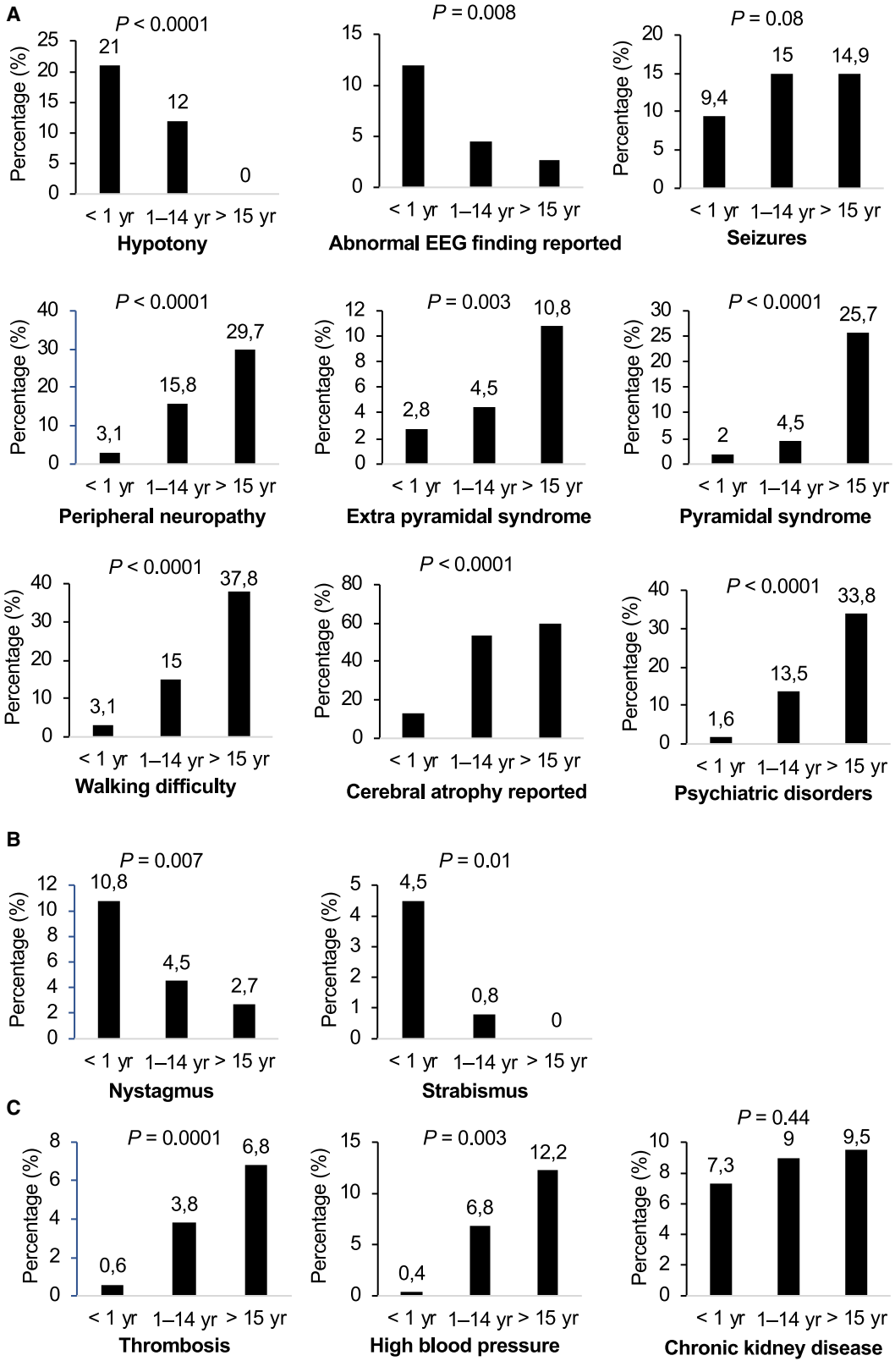
We classified 22 patients in the remethylation cluster. The median age was 0.3 years (IQR, 0.1–5.0), with 57.1% (8/14) reported as younger than 1 year, and only one patient older than 15 years (7.1%) (Table 3). As expected, anemia was a predominant manifestation observed in 68.2% (15/22). Neurological manifestations were also frequently observed, with 45.5% (10/22) of the patients exhibiting developmental delay, 36.4% (8/22) peripheral neuropathy, and 18.2% (4/12) seizures and hypotonia. A total of 9.1% (2/22) of the patients had abnormal EEG finding reported and 9.1% (2/22) had abnormal EMG finding reported. A total of 95.5% (21/22) of the patients were supplemented with vitamin B_{12}. In logistic regression analysis with Bonferroni correction, only peripheral neuropathy (OR, 7.60; 95% CI: 3.06–18.89) was significantly associated with an increased risk of belonging to the remethylation functional gene cluster when compared with the remaining functional gene clusters (Table S6, related to Tables 1–4; Figure S2B, related to Tables 1 and 3).

Metabolic characteristics according to the presence of anemia, neurological manifestations, or both or neither of these two manifestations

Hematological manifestations associated with neurological manifestations were mainly observed in the B_{12} bioavailability gene cluster with a combined increase of homocysteine and methylmalonic acid and decreased methionine. The methionine concentration was significantly higher in cases with anemia and without neurological manifestations than in those with anemia and neurological manifestations or neurological manifestations only. The concentrations of urinary methylmalonic acid were significantly lower in cases with anemia associated with neurological manifestations than those with neurological manifestations without anemia (Table S7, related to Tables 1–4).

Assessment of predictors associated with death

In logistic regression analysis with Bonferroni correction, the following items were significantly associated with an increased risk of death, in the descending order of ORs: pulmonary hypertension (OR, 7.08; 95% CI: 2.60–19.29); mitochondrion functional gene cluster (OR, 3.51; 95% CI: 2.27–5.44); pathogenic variants on the *MMUT* gene (OR, 3.47; 95% CI: 2.29–5.25); acute metabolic decompensation (OR, 3.29; 95% CI: 2.04–5.31); and 0 to 1 year age category (OR, 2.84; 95% CI: 1.58–5.12). Conversely, the following predictors were significantly associated with a decreased risk of death, in the descending order of ORs: pathogenic variants on the *MMACHC* (OR, 0.36;



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95% CI: 0.23–0.56); cytoplasmic transport functional gene cluster (OR, 0.35; 95% CI: 0.23–0.55); head MRI performed (OR, 0.34; 95% CI: 0.17–0.67); and nystagmus (OR, 0.08; 95% CI: 0.01–0.60) (Table S8, related to Tables 1–4; Figure S3, related to Tables 1 and 3).

DISCUSSION

Our study investigated the clinical and metabolic characteristics of a group of rare diseases of metabolism, in this case of vitamin B_{12}, by a systematic extraction of more than 800 individual reports of genetically proven cases, using the names of diseases and related genes and protein/enzymes. We extracted all the manifestations described in the reports and built a database that allowed us to characterize the main clinical, imaging, and biological metabolic manifestations of these diseases according to patient age and functional gene cluster groups. So far, the characteristics of this group of diseases have been reported in narrative reviews or registry studies focused on pediatric recruitment and only part of inborn errors of intracellular metabolism of vitamin B_{12}. We classified the patients into age categories defined in function of clinical practice and medical care.[171] During the first year of life, clinical manifestations of inherited disorders may be severe and require pediatric expertise.[172] The >15 years period of life includes late adolescence (15–19 years) and young adulthood (20–24 years). In this period, pediatric expertise is less necessary, and most cases are in adult care and examined by family physicians.[171,173] Our study highlighted the strong association of manifestations with age and functional gene clusters. We showed that clinical manifestations diagnosed in late adolescence/adulthood differ from those usually observed in pediatric practice. We pointed out the need to revise the rationale for investigating the cause of these manifestations, for which the involvement of inborn errors of intracellular metabolism of vitamin B_{12} is probably often overlooked in medical practice.

Our study shows that patients older than 15 years had a distinct clinical presentation and exhibited genetic variants with less pathogenicity than newborns and children. In particular, we observed a strong association of specific neurological and cardiovascular manifestations with age, as shown in Figure 2. Some manifestations also predominated explicitly in one of the four functional gene clusters. They could reflect specific pathomechanisms related to impaired methionine synthesis or methylmalonyl-CoA catabolism. For example, peripheral neuropathies and psychiatric manifestations were predominantly reported in the remethylation cluster, episodes of acute metabolic decompensation and renal or hemolytic-uremic syndrome manifestations in the mitochondrion cluster, and cardiovascular and ophthalmological manifestations in the cytoplasmic transport cluster. Anemia was the predominant outcome reported in the clusters related to B_{12} availability and remethylation pathways (Table 2).

Hematological findings were primarily reported in children and were not as frequent as reported in reviews dedicated to manifestations of inborn errors of vitamin B_{12}.[164,174,175] In the B_{12} bioavailability cluster, we observed that cases with anemia and no neurological manifestation had higher methionine and lower methylmalonic acid and no difference in homocysteine compared with those with neurological manifestation and no anemia (Table S7, related to Tables 1–4). These metabolic differences illustrate the need to study the molecular mechanisms that could specifically trigger anemia versus neurological manifestations, including the cobalamin partitioning toward methionine synthase and methylmalonyl-CoA mutase, the interactome of methionine synthase with methionine synthase reductase, *MMCHC*, and *MMADHC*, and the cellular status in methionine.[176,177] The cellular status in folate could play a role in the increased methylmalonic acid concentration observed in cases of the B_{12} bioavailability cluster with neurological manifestations since a high folate status increases methylmalonic acid in subjects with low blood concentrations of B_{12}.[178]

Neurological manifestations, such as walking difficulties, peripheral neuropathy, and pyramidal syndrome, were observed in almost one-third of patients over 15 years and were strongly dependent on age. MRI brain imaging clearly showed an age-related increase of cerebral atrophy, with over 60% of cases reported in adulthood, compared with only 13% in newborns (Table 2; Figure 2). These data are consistent with cohort studies of elderly subjects, which showed a link between vitamin B_{12} status and brain atrophy during aging and a preventive effect of vitamin B_{12} therapy.[179,180] These manifestations are linked to the impaired endogenous synthesis of methionine rather than to the catabolism of methylmalonyl-CoA. Indeed, they were mainly observed in patients in the remethylation and cytoplasmic transport functional gene clusters, but not in those in the mitochondrial cluster, as shown in Table S6 (related to Tables 1–4). These results are consistent with recent experimental studies on cellular models, patients' fibroblasts, and animal models. In these studies, the cellular deficit in B_{12} altered the nucleo-cytoplasmic transport and splicing of mRNAs and increased reticulum stress.[181–183] The altered shuttling of RNAs results from the decrease in SIRT1 (Sirtuin 1, also known as NAD-dependent protein deacetylase sirtuin-1) expression and imbalanced phosphorylation and methylation of RNA binding proteins, including ELAV1 (ELAV-like RNA binding protein 1, also known as human antigen R).[184] It produces an altered expression of genes needed for neurodevelopment and neuroplasticity and inhibits neuronal proliferation and differentiation.[181,185,186] Deficiency also increases neuronal apoptosis and homocysteinylation of proteins involved in neurodegeneration, including the Tau protein.[187] Unlike neurological manifestations, ophthalmological manifestations

Figure 2. Influence of age in the manifestations reported by the Cochran-Armitage test for trend in the three age categories, "0 to 1 year," "1 to 14 years," and "over 15 years"

(A) Neuropsychiatric manifestations include hypotony, abnormal EEG findings, seizures, peripheral neuropathy, extrapyramidal syndrome, pyramidal syndrome, walking difficulty, and cerebral atrophy reported on head MRI.

(B) Ophthalmological manifestations include nystagmus and strabismus.

(C) Cardiovascular and renal manifestations include thrombosis, blood pressure, and chronic kidney disease.

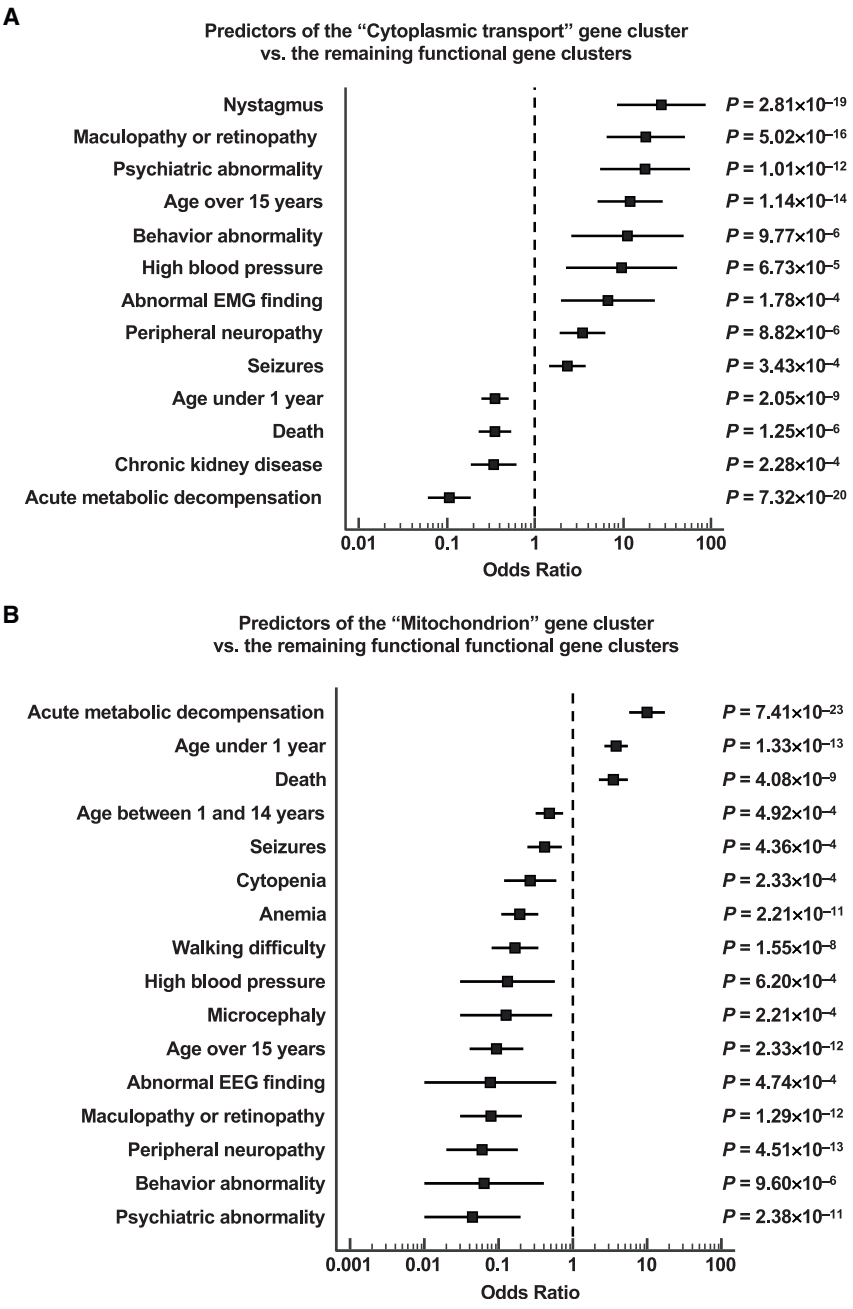

Figure 3. Predictors of inherited disorders of vitamin B12 metabolism according to "Cytoplasmic transport" and "Mitochondrion" functional gene clusters

(A) Forest plot illustrating the logistic regression analysis results that assessed the predictors of the "cytoplasmic transport" gene cluster compared with the remaining functional gene clusters. Only binary variables are shown in the Forest plot. The gene cluster "cytoplasmic transport" regroups all patients with *MMACHC* variants and *MMADHC* variants responsible for combined mitochondrion and remethylation abnormalities. The black square represents the OR and the horizontal line indicates the 95% CI.

(B) Forest plot illustrating the results of the logistic regression analysis that assessed the predictors of the "mitochondrion" gene cluster in comparison with the remaining functional gene clusters. Only binary variables are shown in the Forest plot. The gene cluster "mitochondrion" regroups all patients with *MMAA*, *MMAB*, or *MUT* variants and *MMADHC* variants responsible for mitochondrion abnormalities. OR, odds ratio; EMG, electromyography; EEG, electroencephalography. The black square represents the OR and the horizontal line indicates the 95% CI.

are mainly observed in patients whose diagnosis is made in the first year of life.[188,189] Like the neurological manifestations, they are mainly observed in combined deficits produced by altered intracellular metabolism of B_{12} or bioavailability but not in the mitochondrial cluster of methylmalonyl-CoA catabolism, suggesting that the underlying pathomechanisms are presumably the consequence of the impaired remethylation pathway.

Cardiovascular manifestations, such as thromboembolic disorders, cardiomyopathy, and hypertension, accounted for the main clinical characteristics of cases over 15 years. They were underestimated in previous reviews and registries, which evaluated mostly cases reported in pediatrics (Table 4).[174,175] The thromboembolic manifestations were infrequent in the first year of life and were strongly associated with age (Figure 2). They may be related to the dramatic increase of homocysteine. The negative results of interventional studies to lower homocysteine in cases with mild hyperhomocysteinemia (<30 μmol/L) have confused the debate regarding the management of patients with intermediate to severe hyperhomocysteinemia.[190] In contrast, the association between vitamin B_{12} and thromboembolic events was recently highlighted in a study of patients with hyperhomocysteinemia >30 μmol/L hospitalized for thromboembolic and other cardiovascular manifestations among 1,006 patients consecutively recruited in a regional university hospital center.[191] Hyperhomocysteinemia was related to vitamin B_{12} deficiency in 40% and mutations in one or more genes of vitamin B_{12} metabolism in 11% of studied patients.[191] The increase in systolic blood pressure was also closely associated with age (Figure 2). It was not explained by chronic renal failure, as the latter was not associated with age. The link between systolic blood pressure and homocysteine level has been well documented in interventional studies targeting MTHFR by riboflavin supplementation.[192,193] In contrast, increased systolic blood pressure is not reported in the literature on inborn errors of vitamin B_{12}, probably because the published series of cases are focused on newborns and children.[183] The age-related increase

of blood pressure is consistent with experimental data in rats, in which vitamin B_{12} and folate deficiency during pregnancy produced hypertension, arterial remodeling, and cardiomyopathy through homocysteinylation of extracellular matrix proteins and altered angiotensin-AT2 and TGFB1 pathways in pups.[194–197]

Acute metabolic decompensations were observed not only in the first year of life but also later with an associated risk of death. These results illustrate the need for the careful monitoring of patients in adulthood. Our data point out also the predominance of acute metabolic decompensation and death in the mitochondrion functional gene cluster (Table S6, related to Tables 1–4). This illustrates the dramatic consequences of the impaired adenosylcobalamin-dependent methylmalonyl-CoA conversion into propionyl-CoA. This reaction is the last step of a crucial anaplerotic pathway, which fuels the metabolites resulting from the catabolism of branched-chain amino acids, odd-chain fatty acids, and the side chain of cholesterol into the tricarboxylic acid cycle.[198] The frequent occurrence of decompensation and death among patients classified in the mitochondrion cluster is also found in Mut knockout (KO) mice, where most homozygous pups do not survive after 24 h of life.[199,200] A hemizygous knockin (KI) mouse model (Mut-KO/KI), which combines a KI missense mutation with a KO allele, produces failure to thrive and kidney dysfunction, consistent with the mild phenotype observed in adult patients.[201] Adding a 51% protein diet produced a more severe phenotype with behavioral, cardiovascular, and hematological abnormalities, suggesting the influence of diet, particularly on adult cases.[202]

The diagnosis at an age older than 15 years concerned 18% of all cases with *MMACHC* mutations and could be related in part to the lower pathogenicity of genetic variants (Table S2, related to Tables 1–4). Among the ten most frequent genetic variants, seven were annotated as pathogenic and produced a truncated protein with presumed dramatic consequences on the intracellular transport and processing of vitamin B_{12}. Consistently, these mutations were predominantly reported in newborns (Table S2, related to Tables 1–4). In contrast, most cases diagnosed at an age older than 15 years had either the p.Arg161Gln frequent missense pathogenic mutation or missense mutations classified as likely pathogenic. Similarly, the patients of the mitochondrion cluster older than 15 years had genetic variants classified as likely pathogenic or of uncertain significance in *MMUT*, *MMAA*, and *MMAB* genes (Table S3–S5, related to Tables 1–4)

In our opinion, some key results of our study should be translated into clinical practice. We showed that neurological manifestations, such as hypotonia, EEG abnormalities, microcephaly, nystagmus, and strabismus, could evoke an inherited disease of vitamin B_{12} metabolism even in the absence of anemia in pediatric practice. In contrast, walking difficulty, peripheral neuropathy, extrapyramidal syndrome, depression, and cerebral atrophy are much more frequent in patients over age 15 years. These patients are cared for by neurologists and internists who must be aware of the diagnosis of inherited disease of vitamin B_{12} metabolism. Our results also show that cardiovascular manifestations are dramatically more frequent in adults than in children presenting with inherited disorders of vitamin B_{12} metabolism. The association of increased systolic blood pressure with age is a heretofore unrecognized manifestation in this group of inherited metabolic diseases. The thromboembolic manifestations observed in the absence of classic risk factors of thrombophilia should lead to a search for hyperhomocysteinemia in association with an inherited error of vitamin B_{12} metabolism, as was shown very recently in an observational study.[191] These rare diseases may be underestimated or even ignored in the usual practice of cardiovascular medicine. US and European Societies of Cardiology do not recommend including hyperhomocysteinemia as a risk factor of cardiovascular disease. Consequently, cardiologists lack consideration and/or knowledge to diagnose and treat patients with intermediate and severe hyperhomocysteinemia related to an inherited error of vitamin B_{12} metabolism. The neurological and cardiovascular clinical profiles should prompt clinicians to systematically check the metabolic markers of vitamin B_{12} status, including homocysteine and methylmalonic acid, when the usual causes of these manifestations are discarded. Genetic analyses could be integrated into the diagnostic workup of these patients, particularly among those with extreme clinical phenotypes and/or a familial clustering. In this setting, clinical-exome sequencing-based approaches could be used as a straightforward first-tier diagnostic strategy in patients for whom a diagnosis of inherited disorders of vitamin B_{12} metabolism is suspected.[203] Identifying an underlying genetic error of vitamin B_{12} metabolism could allow a personalized therapeutic approach to achieve partial or total restoration of metabolic alterations with potential long-term benefits.[191]

The present meta-analysis has several strengths. First, we report an individual patient data meta-analysis that collected original data from 824 patients to assess the phenotypic landscape of patients with inherited disorders of vitamin B_{12} metabolism and to look for clinical, biological, imaging, and electrophysiological predictors significantly associated with age category, functional gene clusters, and death. The report of 74 adults, 133 children, and 509 newborns allowed us to assess the course and specificity of the manifestations according to age. By comparison, the most extensive registry study involved 248 patients seen primarily in pediatric departments.[175] Second, the reported data covered the 15 genes known to be involved in hereditary disorders of vitamin B_{12} metabolism, allowing to perform updated annotation and pathogenicity prediction on more than 300 genetic variants reported on the four most frequently observed genes (*MMACHC*, *MMUT*, *MMAA*, and *MMAB*). In contrast, the largest registry study of the literature reported only on patients with *cblC*, *cblG*, *cblE*, *cblD*, and *cblJ* diseases.[175] Third, the meta-analysis of individually reported cases allowed the compilation of unselected patients, thereby reducing the risk of population heterogeneity. We did not consider studies of registries and case series with aggregated data to avoid any bias related to the study designs. This approach allowed us to consider manifestations that were not reported in registries, including nystagmus, maculopathy, retinopathy, peripheral neuropathy, walking difficulty, pyramidal syndrome, extrapyramidal syndrome, and cerebral atrophy reported on MRI.

We acknowledge several limitations. First, we used data extracted from available case reports through a systematic retrospective search, with the risk of missing data. For example, laboratory findings were not available for all patients. Second, the low number of case reports of inherited disorders of vitamin

B_{12} absorption did not allow to evaluate whether they presented a clinical profile distinct from the other disorders of the B_{12} availability cluster. The number of cases was lower than expected in regard to a recent study of our reference center for rare metabolic diseases, which showed mutations in *GIF*, *AMN*, and *CUBN* genes as the leading causes of hyperhomocysteinemia due to vitamin B_{12} deficiency.[191] Moreover, the diagnosis of Imerslund-Gräsbeck disease is probably underestimated since the Schilling test is no longer available. Likewise, the determination of the soluble intrinsic factor receptor in the urine has limited use despite its diagnostic value in the different subsets of the disease.[204–206] Third, we reported the single literature case with *ZNF143* mutation but not cases with mutations in *HCFC1*, *THAP11*, and *PRDX1*. These genes are not directly involved in vitamin B_{12} metabolism and their mutations produce manifestations related to altered expression of *MMACHC* and/or other genes. HCFC1 is a transcriptional co-regulator that interacts with THAP11 and ZNF143 DNA-binding proteins to jointly regulate the expression of target genes that include MMACHC.[207–209] The HCFC1/THAP11 complex also acts as a transcriptional regulator of ribosome biogenesis during development.[210] Mutations in any of the two genes produce decreased *MMACHC* expression with milder metabolic and more severe neurological manifestations than *MMACHC* mutations. Some mutations can also result in complex syndromes exhibiting aspects of both *cblC* disease and ribosomopathies. In addition, some variants in *HCFC1* produce X-linked intellectual disability even in the absence of metabolic abnormalities of inherited disorders of vitamin B_{12} metabolism. The single case in the literature of two mutations in the *ZNF143* gene had combined methylmalonic acidemia and hyperhomocysteinemia and bilateral cleft palate, microcephaly, severe neurological manifestations, and a ventricular septal defect.[209] *PRDX1* is a gene neighboring *MMACHC*. Mutations in *PRDX1* produce the epi-*cblC* type of inherited disorders of vitamin B_{12} metabolism.[147] This disorder is due to an epimutation at the *MMACHC* promoter, which results from *PRDX1* splicing mutations with an aberrant extension of antisense transcription through the *MMACHC* promoter.[147] The antisense readthrough transcripts also encompass the promoter of the *TESK2* neighboring gene, resulting in the silencing of both *MMACHC* and *TESK2* genes.[211] So far, 20 cases have been reported, with a much higher frequency of severe metabolic decompensation than in patients with *MMACHC* mutations.[212] The fourth limit of our systematic review is the exclusion of case reports not written in English, which could have potentially led to selection bias. However, a previous study that examined non-English publications' influence on combined estimates of published meta-analyses did not reveal a significant effect after excluding non-English publications.[213] Fifth, we did not use machine learning and natural language processing methods that could represent attractive tools to decrease the manual burden during the literature collection and review process. However, these methods are limited by their potential bias toward a low detection rate.[214] Furthermore, machine learning methods did not apply to some old publications without a digital format that were included in our systematic review.

In conclusion, our meta-analysis and phenome-wide association study of the clinical, phenotypic, and genetic landscape of 824 patients with a genetically proven diagnosis of an inherited disorder of vitamin B_{12} metabolism pointed out inborn errors of vitamin B_{12} metabolism as potential etiologies deserving consideration in the diagnostic algorithm of atypical neurological manifestations and thromboembolic disorders not explained by classical etiologies in children and adult cases. We highlighted a high frequency of inherited disorders of vitamin B_{12} metabolism in patients older than 15 years. Compared with younger cases, adults harbored fewer pathogenic mutations and had a higher prevalence of cardiovascular manifestations, including thromboembolic outcomes and increased blood pressure. Neurological manifestations were also strongly dependent on age, with a predominance in gene clusters that impair the remethylation pathway. In contrast, metabolic decompensation and death were predominant in clusters that impair the adenosylcobalamin-dependent methylmalonyl-CoA conversion into propionyl-CoA, regardless of age.

Limitations of the study

This systematic review has several limitations: (1) we used data extracted from available case reports through a systematic retrospective search, with the risk of missing data; (2) we did not use machine learning and natural language processing methods that could represent attractive tools to decrease the manual burden during the literature collection and review process; (3) the low number of case reports of inherited disorders of vitamin B_{12} absorption did not allow to evaluate whether they presented a clinical profile distinct from the other disorders of the "B_{12} availability" cluster; (4) we excluded non-English case reports, which could have potentially led to selection bias.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND SUBJECT DETAILS
- METHOD DETAILS
  - Study aims
  - Electronic search query
  - Study selection
  - Data extraction
  - Main outcomes and measures
  - Functional gene clusters
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2022.100670.

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AUTHOR CONTRIBUTIONS

Literature review and data extraction, A.W., A.O., N.L., M.T., M.J., J.-P.M., B.A., P.D., T.A., and M.F.; data synthesis, A.W.; drafting/revision of the manuscript, A.W., A.O., F.F., and J.-L.G.; analysis and interpretation of data, A.W., A.O., F.F., and J.-L.G.; data synthesis and statistical analysis, A.O.; study concept, J.-L.G.; literature review, A.W.; all authors approved the final draft.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Not used.		
Bacterial and virus strains		
Not used.		
Biological samples		
Not used.		
Chemicals, peptides, and recombinant proteins		
Not used.		
Critical commercial assays		
Not used.		
Deposited data		
All papers that were used for data extraction are indicated in ref.[1–163]		
PubMed link to access to the 163 publications retained in the systematic review: ==https://pubmed.ncbi.nlm.nih.gov/?term=8968736+9554742+10923046+11350191+12438653+12402345+12064907+12555939+12948746+14689755+12971424+15292234+15754282+15781199+16186538+15931548+15714522+16247646+16750411+16714133+17431913+17768669+17597648+17410422+17445044+17874135+17853453+18385497+18848477+17668238+17957493+18164228+18956254+18245139+19821145+19375370+19248038+19700356+19914430+19058814+19767224+19136951+20830523+19700743+20610126+20556797+20524213+21835369+21153419+20446115+21873889+21671183+22854512+22922874+21545677+23141461+22447314+22560872+23776111+23580368+23751327+24044590+24095221+23707710+23479330+23753090+23711287+24059531+23430521+23686626+23503767+24330302+23954310+24011988+25322992+25155779+24210589+24599607+25125334+24126030+24853097+25398587+25367534+24563082+24961826+24464670+25772322+24512365+26658511+24813872+25687216+25750861+25982642+26454439+25526710+25894566+25511120+26253414+24974159+25091368+26318470+26040326+25771389+26174677+25567501+26370686+26283149+26077484+25234635+25914105+26464686+26149271+27602322+26608391+26825575+26952825+26997947+26581066+27167370+26563984+28536607+26449400+26979128+27683594+27349184+25978498+26830710+27014578+25856670+28835862+28481040+29068997+27591164+28101778+28666289+28811685+28327205+27858373+27252276+27748010+28218226+27824740+29558000+30080956+30103768+29379858+29302025+29433791+30197982+29996803+28610805+30530444+29294253+29942494+29098535+30334532+29374341+29924026+30728829+30466947+30863077+30782345+31092259&sort=		
Experimental models: Cell lines		
Not used.		
Experimental models: Organisms/strains		
Not used.		
Oligonucleotides		
Not used.		
Recombinant DNA		
Not used.		
Software and algorithms		
MedCalc, version 19.5.3 (MedCalc Software, Ostend, Belgium)		https://www.medcalc.org/
SVS (v8.8.1; Golden Helix, Inc., Bozeman, MT, USA)		https://www.goldenhelix.com
Other		
Not used.		

RESOURCE AVAILABILITY

Lead contact

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Materials availability

This study did not generate new unique reagents.

Data and code availability

- This work used data extracted in ref.[1–163] and did not generate any novel standardized datasets
- This paper does not report original code and the extracted information are presented in Tables 1–3 and S1–S9
- Any additional information required to reanalyze the data reported in this work paper is available from the Lead Contact upon request

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Please see Section: "Description of the whole population of the 824 patients with inherited disorders of vitamin B12 metabolism".

METHOD DETAILS

Study aims

The aims of the study were: 1) to assess the clinical, biological, genetic cause, imaging, and electrophysiological findings among patients with inherited disorders of vitamin B_{12} metabolism in the whole population, according to previously established age categories (<1 year; 1–15 years; and >15 years)[171–173] and functional gene clusters; 2) to look for clinical, biological, imaging, and electrophysiological predictors significantly associated with functional gene clusters and death.

Electronic search query

We conducted the literature search on MEDLINE-indexed literature using the PubMed search engine from the National Center for Biotechnology Information (www.pubmed.gov) (January 1966 to August 2019) to identify case reports describing individual-level data of patients with a genetically proven diagnosis of an inherited disorder of vitamin B_{12} metabolism. We developed a highly sensitive electronic query using keywords, indexed terms, medical subject headings (MeSH), and free text words (e.g., gene names, complementation groups, disease name, metabolites, enzymes) to elaborate three electronic search panels: **Panel #1** addressed the concepts of vitamin B_{12}, one-carbon metabolism, hyperhomocysteinemia, or methylmalonic acidemia; **Panel #2** addressed the concepts related to genetic diseases; and **Panel #3** addressed the concepts of inborn errors metabolism. The detailed electronic strategy reporting the plain text query, the electronic search query, and the NCBI translations for each panel are available in the Supplemental Methods. We built the electronic search strategy using the three electronic panels, as follows: Panel #1 AND (Panel #2 OR Panel #3) to identify from all the publications that were related to genetic disorders or inborn errors of metabolism those reporting case reports of patients with an inherited disorder of vitamin B_{12} metabolism. Additional articles were retrieved from primary search references. EndNote X7.8 was used for reference management.[215] This systematic review was performed in compliance with the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) Statement.[216]

Study selection

We retained a case report in the systematic review if it reported clinical findings and molecular diagnosis of an inherited disorder of vitamin B_{12} metabolism. The exclusion criteria were as follows: i) non-English language publication; ii) editorial, narrative review, or congress abstract; iii) study reporting aggregated data without individual-level data; iv) case report without a molecular diagnosis; v) genome-wide association studies or genetic association studies on candidate gene of gene panels for the potential association with vitamin B_{12} and/or one-carbon metabolism markers; and vi) studies reported in animals.

Data extraction

Two investigators (AW, AO) reviewed the titles and abstracts of all citations identified by the literature search. Ten investigators reviewed eligible articles (AW, NL, MT, MJ, JPM, BA, PD, TA, MF, AO). All data directly related to the disease were extracted without any filter. The following data were extracted and assigned to 10 domains: **Domain #1**: **Case report characteristics** (Author, Year, Country); **Domain #2**: **Patient's demographics** (Age, Gender); **Domain #3: Clinical manifestations** expressed as binary outcomes (Group 1: Intrauterine growth restriction, Microcephaly; **Group 2**: Cardiomyopathy, Thrombosis; **Group 3**: Feeding intolerance; **Group 4**: Acute metabolic decompensation; **Group 5**: Maculopathy, Retinopathy, Nystagmus; **Group 6**: Hypotonia, Pyramidal syndrome, Extrapyramidal syndrome, Walking difficulty, Peripheral neuropathy, Seizures, Development delay, Absence of neurologic disorders; **Group 7**: Arterial hypertension, Acute renal failure, Hemolytic–uremic syndrome, Chronic renal failure; **Group 8**: Hyperpigmentation; **Group 9**: Gout). **Domain #4**: **Laboratory findings** expressed as continuous outcomes [vitamin B_{12} (pmol/L); methionine (μmol/L); homocysteine (μmol/L); methylmalonic acid (μmol/L); C3-carnitine (μmol/L); ammonia (μmol/L); urinary methylmalonic acid (mmol/mol of creatinine)]; **Domain #5**: **Molecular diagnosis** according to the Human Genome Variation Society (HGVS) nomenclature to report DNA and protein sequences variants, using the GRCh37 built and the reference sequence (RefSeq) database. Two investigators (AW, AO) manually curated and annotated each variant to assess its pathogenicity according to the standards and

guidelines of the American College of Medical Genetics and Genomics[217] using the VarSome tool,[218] ClinVar,[219] and bibliographical evaluation. We used the gnomAD Exomes database (Version: 2.1.1)[220] to report the alternative allele frequencies of the reported variants considering the whole studied population. **Domain #7: Electrophysiological evaluation** expressed as binary outcomes (electroencephalography abnormality, electromyography abnormality); **Domain #8: Magnetic resonance findings** expressed as binary outcomes (cerebral atrophy, T2 signal hyperintensity in the white substance); and **Domain #9: Therapy and patient's evolution** expressed as binary outcomes (Vitamin B_{12} supplementation, liver transplantation, kidney transplantation, and death).

Main outcomes and measures

The systematic review's primary outcome was to report on the clinical, laboratory, electrophysiological, and magnetic resonance findings of subjects diagnosed with an inherited disorder of vitamin B_{12} metabolism. **Main clinical findings:** intrauterine growth restriction; microcephaly; cardiomyopathy; thrombosis; feeding intolerance; acute metabolic decompensation; maculopathy; retinopathy; nystagmus; hypotonia; pyramidal syndrome; extrapyramidal syndrome; walking difficulty; peripheral neuropathy; seizures, developmental delay; hypertension; acute renal failure; hemolytic–uremic syndrome; chronic kidney failure; hyperpigmentation; gout; **Laboratory findings:** vitamin B_{12}; methionine, homocysteine, C3-carnitine; ammonia; blood and urinary methylmalonic acid; genetic diagnosis; **Electrophysiological evaluation:** electroencephalographic abnormality; electromyographic abnormality; **Magnetic resonance findings:** cerebral atrophy, T2 signal hyperintensity in the white substance; **Therapy and patient's evolution:** vitamin B_{12} supplementation, liver transplantation, kidney transplantation, and death.

Functional gene clusters

We classified the patients into four functional gene clusters according to the affected gene. The ''B_{12} bioavailability'' gene cluster regrouped all patients with *CBLIF* (alias, *GIF*), *CUBN*, *AMN*, *TCN2*, *LMBRD1*, *CD320*, or *ABCD4* variants. The ''cytoplasmic'' gene cluster regrouped all patients with *MMACHC* variants and those on *MMADHC* that are responsible for combined mitochondrion and remethylation abnormalities.[221–223] The ''Remethylation'' gene cluster regrouped all patients with *MTR* or *MTRR* variants and those on *MMADHC* that are responsible for remethylation abnormalities.[221–223] The ''Mitochondrion'' gene cluster regrouped all patients with *MMAA*, *MMAB*, or *MUT* variants and those on *MMADHC* that are responsible for mitochondrion abnormalities.17,18,19

QUANTIFICATION AND STATISTICAL ANALYSIS

Categorical variables were summarized as frequency counts and percentages with the 95% confidence interval (95% CI). Quantitative variables were expressed as medians and interquartile range (IQR, 25^{th} and 75^{th} percentiles). We studied the influence of age, reported in the three age categories, on patients' manifestations using the Cochran–Armitage test for trend. We used univariate logistic regression with Bonferroni correction to look for the clinical, biological, imaging, and electrophysiological predictors significantly associated with functional gene clusters: ''B_{12} bioavailability'' vs. remaining functional gene clusters, ''Mitochondrion'' vs. remaining functional gene clusters, ''Cytoplasmic transport'' vs. remaining functional gene clusters, ''Remethylation'' vs. remaining functional gene clusters, and ''Cytoplasmic transport'' vs. ''B_{12} bioavailability''). For each predictor, we reported the beta coefficient, the standard error, and the odds ratio (OR) with the corresponding 95% confidence interval (95% CI). We also assessed the predictors significantly associated with death. All statistical analyses were conducted using MedCalc, version 19.5.3 (MedCalc Software, Ostend, Belgium) and SVS (v8.8.1; Golden Helix, Inc., Bozeman, MT, USA).