Study Population

	Cohort I (1980-1989)	Cohort II (1990-1999)	Cohort III (2000-2009)	Cohort IV (> 2010)	Total
cblA					
n	4	4	13	7	28
Mean age [years]	31.3	17.4	9.5	2.3	11.9
Sex: f:m					11:17
mut^0					
n	1	16	50	28	95
Mean age [years]	27.2	18.3	9.1	2.0	8.7
Sex: f:m					45:50

Diagnostic work-up

	Both	Enzyme Studies	Mutation Analysis	Family History
cblA n	9 (32%)	3 (11%)	16 (57%) 5 new mutations	0 (0%)
mut^0 n	31 (33%)	7 (7%)	53 (56%) 6 new mutations	4 (4%)

Dietary treatment

|	*cblA*	*mut0*
no diet	19% (5/26)	
Calculated diet	73% (19/26)	98% (87/89)
Aminoacid supplements	27% (7/26)	69% (61/88)
Avoid food with high protein content	8% (2/26)	2% (2/89)
NG feeding	11% (3/27)	14 % (12/88)
PEG feeding	4% (1/27)	26% (23/88)

Drug therapy

	cbl A	mut^0
Hydroxocobalamin Treatment − orally − subcutaneous − Intramuscular	7% [1/14] 7% [1/14] 86% [12/14]	n=4 n=0 n=5
Carnitine [mg/kg/day] Median ± range	52.4 ± [11.5-102.6]	70.9 ± [19.3-200.0]

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Initial metabolic crisis
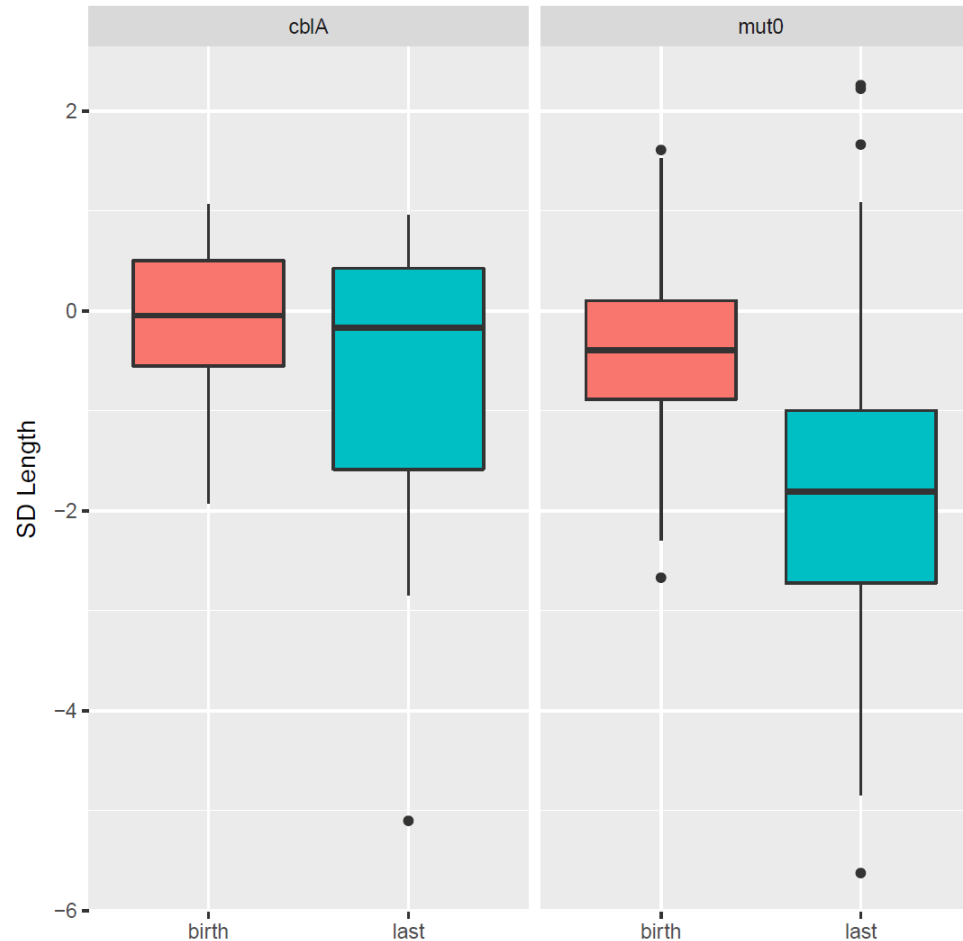
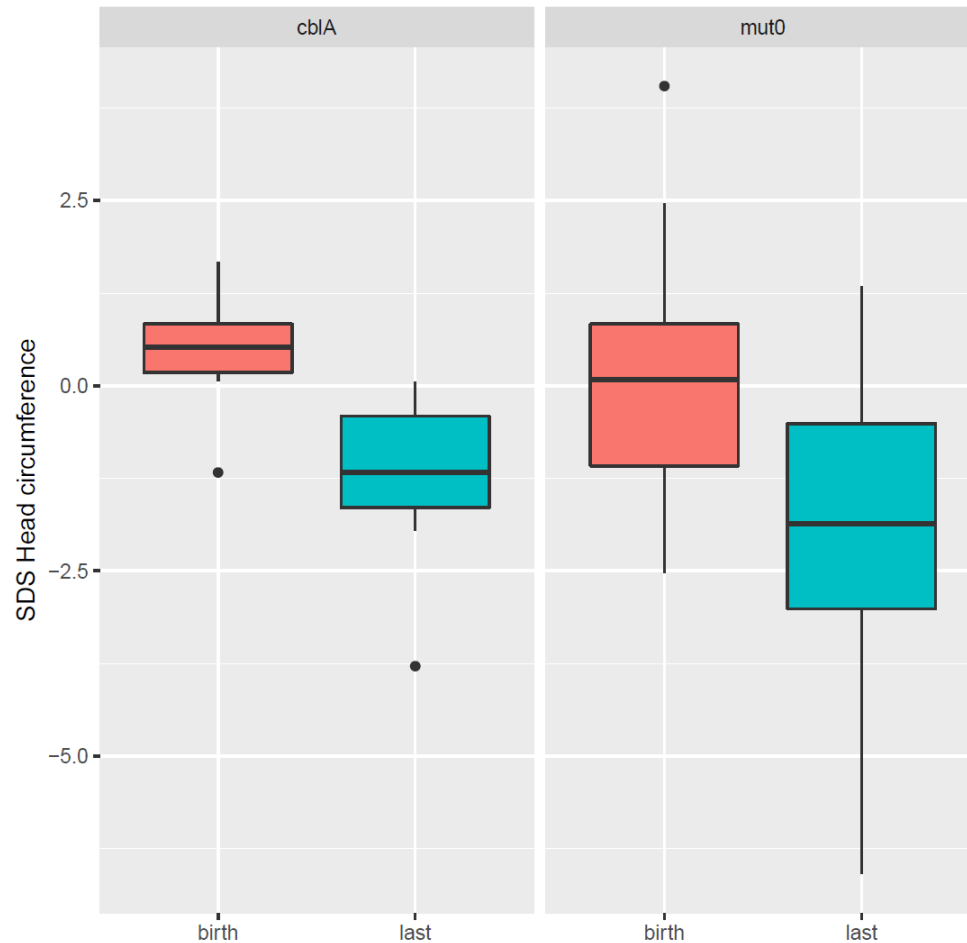|	cblA	mut0
Median age at first symptoms [days]	24.5 * [Q1 = 3.75; Q3= 180]	5 [Q1 = 2; Q3= 133]
Median age at diagnosis [days]	21 [Q1 = 5.75; Q3= 265.5]	12 [Q1 = 4.0; Q3= 180]
Mode of diagnosis [%]: Symptomatic screening High risk family screening Neonatal screening Prenatal testing	64.3 17.9 17.9 0 [n= 28]	78.9 4.2 12.6 2 [n= 93]
Mean diagnostic delay (symptomatic screening) [days]	91 * [±274, 0-1065]	28 [±69, 0-276]
Median [Q1; Q3] NH3 [µmol/l] pH BE Lactate[mmol/l] within first crisis	247 [155; 446] 7.24 [7,08; 7,30] -18.2 [-11,1; - 24,0] 2.5 [2,3; 4,2]	255 [156; 497] 7.24 [7,10; 7,33] -16.2 [-11,2; -21,6] 2.4 [1,6; 3,8]

Somatic outcome: weight
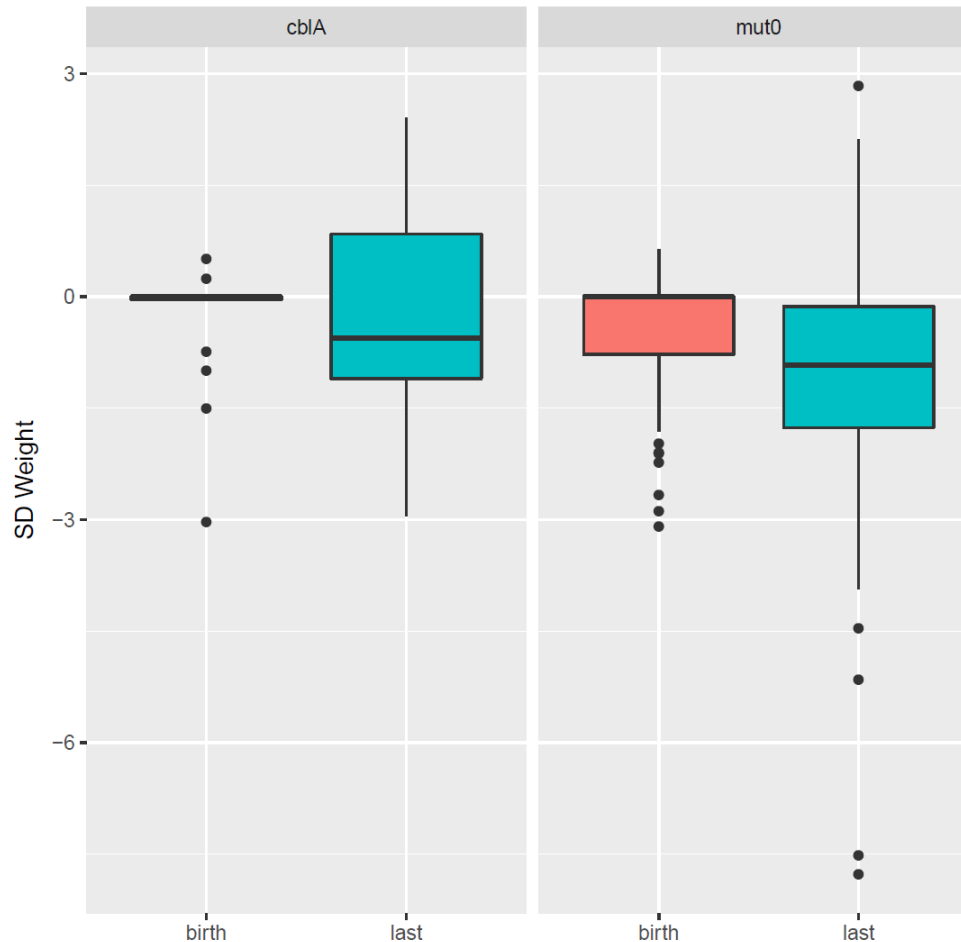
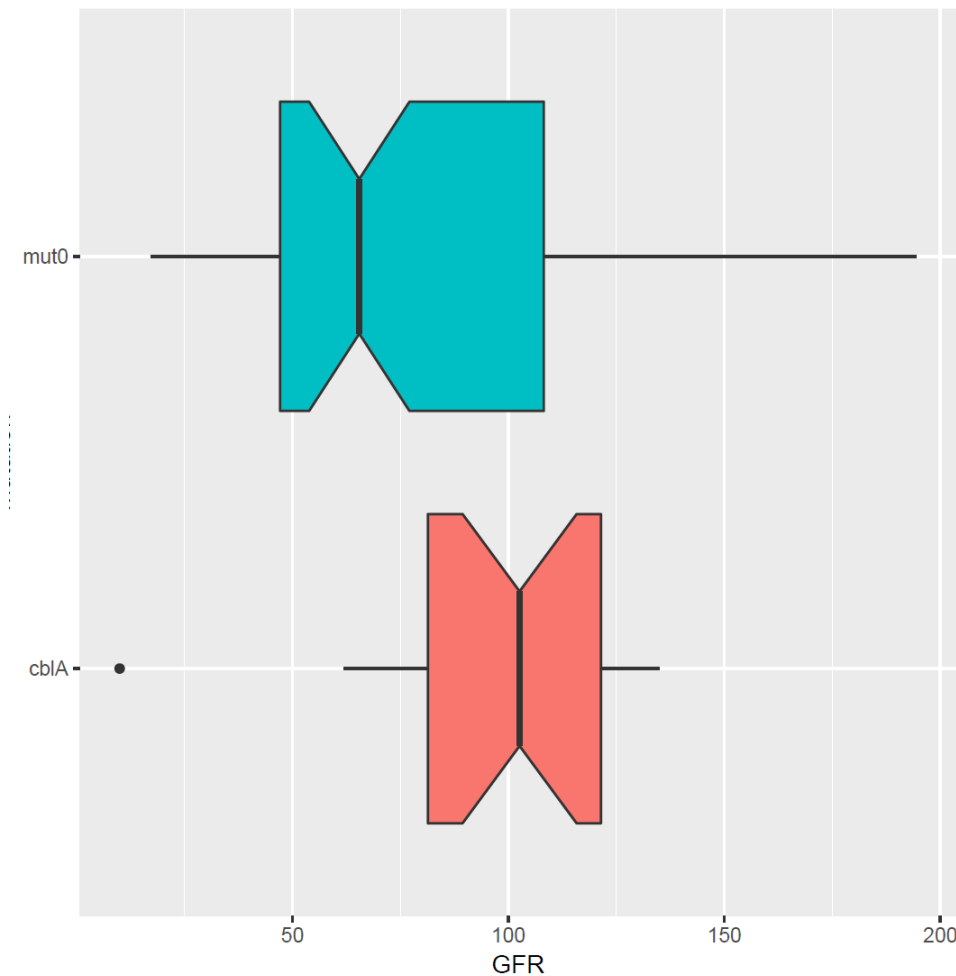Welch Two Sample t-test: t = 2.0328, df = 38.249, p-value = 0.04905

Somatic outcome: length

Welch Two Sample t-test: t = 3.085, df = 33.544, p-value = 0.00406

Somatic outcome: head circumference

Welch Two Sample t-test: t = 1.8677, df = 33.665, p-value = 0.07053

Renal complications

Mann Whitney U-Test: W = 1093.5, p-value = 0.006921

	cblA	*mut⁰*
CRF	8 % (2/23)	45.7 % (32/69)
Dialysis	8% (2/23)	3 % (3/88)
Hypertension	4% (1/23)	15 % (11/73)
Kidney transplantation	N= 0	N= 5

Neurological outcome

	cblA	mut^0
Seizures	0 % (0/27)*	11% (10/90)
Movement disorder	4 % (1/27)*	30% (29/89)

	cblA	mut^0
Regular school	78 % (14/18)	49% (24/49)
Professional training	100 % (3/3)	?
Live independently	100% (4/4)	?

Methylmalonic Acid: last visit
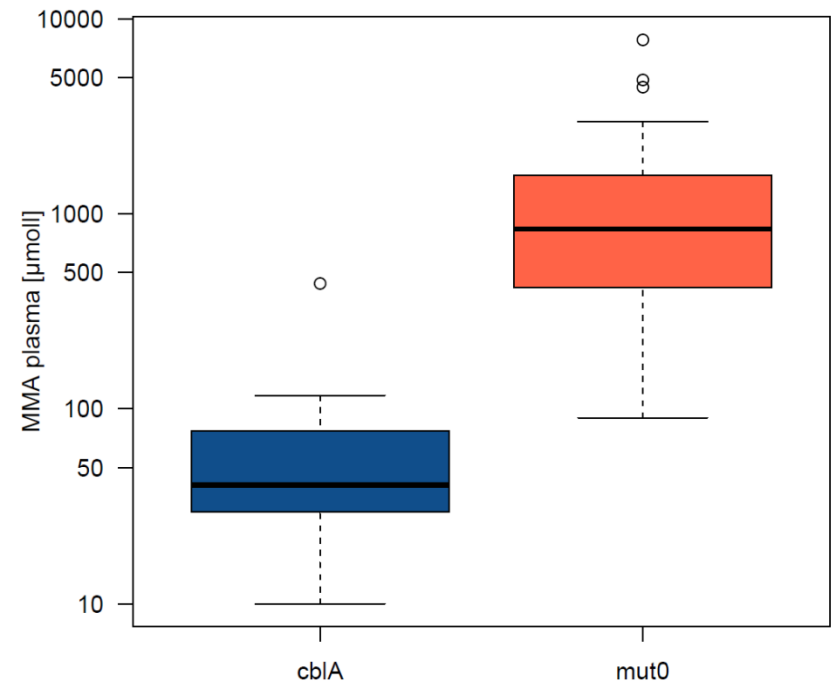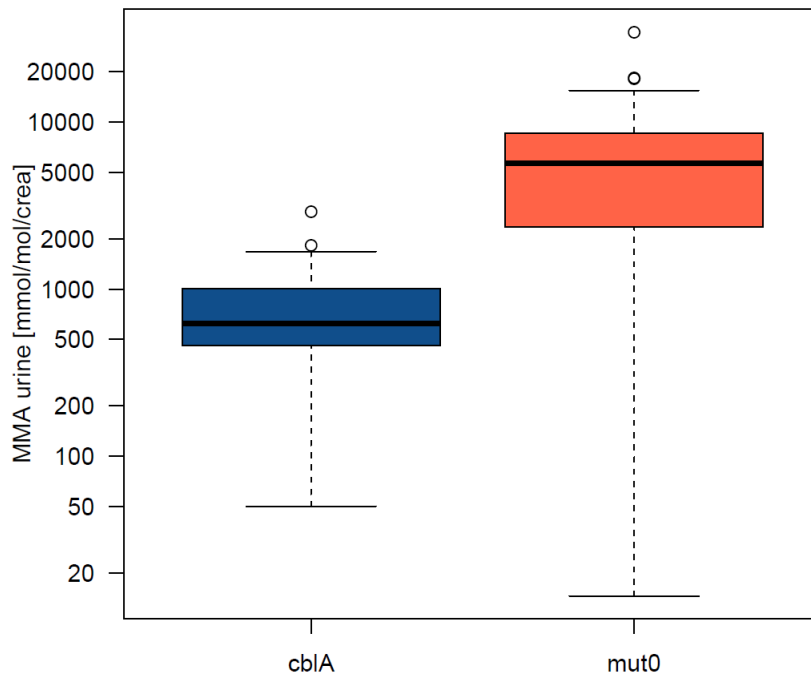
Wilcoxon rank sum test with continuity correction:
W = 88, p-value = 2.191e-06 (urine)
W = 14, p-value = 7.859e-10 (plasma)

Summary

✓ Data of 28 *cblA* and 95 *mut*^{0} patients, mostly confirmed by mutation analysis (revealing new mutations)

✓ 86% of *cblA* patients are treated with hydroxocobalamin *im* and 73% follow a calculated diet with aminoacid supplements in 27%

✓ Weight and length in both groups show reduced z scores and become significantly lower in *mut*^{0} patients towards last visit

✓ Metabolic crisis is the predominant symptom leading to diagnosis: Biochemical disturbances within the first crisis are similar in both groups, while diagnosis is made significantly later *in cblA* patients

✓ GFR is significantly higher in *cblA*, consecutively CRF and related complications are significantly less frequent and renal function can be preserved even in older patients

✓ Neurological complications were predominantly found in the *mut*^{0} subgroup

✓ MMA levels in urine and plasma are sigificantly lower in *cbl A*

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Participating centers

	N cblA	N mut0
Amsterdam, Netherlands	1	2
Barcelona San Joan de Deu, Spain	0	4
Birmingham, UK	1	2
Bruxelles, University Hospital Vrije, Belgium	2	0
Bucharest, Romania	0	1
Copenhagen, Denmark	3	3
El Palmar, Spain	0	4
Heidelberg, Germany	6	13
Innsbruck, Austria	2	1
Kumamoto City, Japan	0	1
Lille, France	0	2
London Evelina Children?s Hospital, UK	1	0
London Evelina Childrens Hospital, UK	0	2
London, Great Ormond Street, UK	1	1
Malaga, Spain	0	2
Marseille, France	1	5
Novi Beograd, Serbia	1	3
Padova, Italy	0	7
Paris Hopital Necker-Enfants Malades, France	3	16
Paris Hopital Robert Debre, France	0	2
Prague 2, Czech Republic	1	4
Reutlingen, Germany	0	2
Rome, Italy	1	0
Taipei City, Taiwan	2	7
Washington, USA	0	3
Zagreb, Croatia	2	5
Zurich, Switzerland	0	3
Total	28	95

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