Type of file: table
Label: 1
Filename: 315374_Table1.doc

Supplementary Table 1. Ophthalmologic complications in patients with cblC disease

PATIENT No.	Classification	Age diagnosis (years)	Age findings (years)	Normal Exam	Visual inattention	Nystagmus	Normal fundus	Maculopathy	Optic nerve	Retinopathy	ERG	Other	Visual acuity OD (logMAR)	Visual acuity OS (logMAR)	Reference	Genotype
EARLY-ONSET																
1	2	0.1	0.1					Pigment mottling							Traboulsi	
2	1	0.1	0.1	*			*								Schimel	
3	1	0.1	0.1	*			*								Gerth	c.547_548delGT/ 547_548delGT
4	2	0.1	0.1					Pigment mottling							Geraghty	c.271dupA/271dupA
5	2	0.1	0.1					Pigment mottling							Kind	
6	1	0.1	0.1	*			*								DeBie	c.271dupA/271dupA
7	1	0.1	0.1	*			*								Mitchell	c.331C>T/271dupA
1	3	0.1	0.2		*	*					Decreased				Traboulsi	
8	1	0.2	0.2	*			*								Mamlok	
9	2	0.1	0.2		*			Pigment mottling			Normal				Mitchell	c.331C>T/271dupA
10	3	0.2	0.2		*			Pigment mottling	Pallor		30*/37**				Bartholomew	c.271dupA/271dupA
11	2	0.2	0.2					Pigment mottling							Bartholomew	c.271dupA/271dupA
12	3	0.3	0.3		*							Roving eye movement			Beauchamp	
13	1	0.1	0.3	*			*								Gerth	c.331C>T/666C>A
14	2	0.3	0.3		*			Pigment mottling		RP					Brandstetter	c.331C>T/271dupA
6	3	0.1	0.4			*					Decreased				DeBie	c.271dupA/271dupA
1	3	0.1	0.5					BEM	Temporal pallor			Narrowed retinal vessels			Traboulsi	
1	2	P	0.						Slight						Patton	

5			5						pallor									
2	2	0.1	0.5						Mild pallor		Decreased						Schimel	
16	2	0.1	0.5	*							Decreased						Schimel	
5	2	0.1	0.5		*		*				Normal						Kind	
6	3	0.1	0.5							RP							DeBie	c.271dupA/271dupA
17	2	0.6	0.6		*	*	*										Frattini	c.271dupA/616C>T
18	3	0.1	0.6					BEM									Schimel	
19	2	0.1	0.6							Mild RP							Carmel	
20	2	0.2	0.6		*		*					Wandering eye movements					Robb	
10	2	0.2	0.6					Mild BEM			77*/96**						Bartholomew	c.271dupA/271dupA
21	3	0.3	0.7					Degeneration									Smith	
22	3	0.7	0.7					Maculopathy			42§						Tsina	c.271dupA/271dupA
3	2	0.1	0.8														Gerth	c.547_548delGT/547_548delGT
1	2	0.1	0.9														Traboulsi	*improvement
23	3	0.1	1		*				Atrophy		Normal						Patton	
24	3	0.1	1							RP							Ellaway	c.271dupA/271dupA
9	3	0.1	1					BEM		Peripheral RP							Mitchell	c.331C>T/271dupA
20	2	0.2	1					Foveal pigmentation									Robb	
25	1	0.5	1.1	*			*										Enns	c.331C>T/615C>G
4	3	0.1	1.1							RP							Geraghty	c.271dupA/271dupA
9	3	0.1	1.3								Cone dysfunction						Mitchell	c.331C>T/271dupA
11	3	0.2	1.3							RP							Bartholomew	c.271dupA/271dupA
2	2	0.	1.		*			Progressive			50*/62**/						Robb	

0		2	6								150***						
25	3	0.5	1.7							RP		Sclerotic retinal arterioles			Enns	c.331C>T/615C>G
21	3	0.3	1.7						Atrophy						Smith		
20	3	0.2	1.7							RP posterior pole					Robb		
22	3	0.7	1.8								40§				Tsina	c.271dupA/271dupA	
18	3	0.1	2					Progression BEM							Schimel		
20	4	0.2	2.7		*	*			Pale	Progressive RP			1	1	Robb		
22	3	0.7	2.8								30§				Tsina	c.271dupA/271dupA	
21	4	0.3	3										LB	LB	Smith		
15	3	P	3						Pale				0.9	0.9	Patton		
26	3	0.5	3						Pale						Patton		
10	3	0.2	3					BEM	Pale				0.78	0.78	Bartholomew	c.271dupA/271dupA	
13	2	0.1	3.5									Retinal nerve fiber loss	0.2	0.2	Gerth	c.331C>T/666C>A	
3	3	0.1	3.7					Atrophy			Progressive CRD		0.5	0.5	Gerth	c.547_548delGT/ 547_548delGT	
22	2	0.7	3.9								100§				Tsina	*Improved with therapy	
27	3	0.1	3.9			*		Maculopathy	Atrophy		RCD				Gerth	c.547_548delGT/ 547_548delGT	
12	4	0.3	4.5							RP			LB	LB	Beauchamp		
10	4	0.2	5						Pale	Diffuse RP		Narrowed retinal vessels	1	0.9	Bartholomew	c.271dupA/ 271dupA	
23	4	0.1	8										1	0.8	Patton		
18	4	0.1	10										1	1	Schimel		
27	3	0.1	13					Maculopathy	Atrophy	RP	RCD				Gerth	c.547_548delGT/ 547_548delGT	
LATE-ONSET																	
28	2	4	4	*						Discrete pigmentary changes	Normal				Van Hove	c.82-9_12delTTTC/ 271dupA	

29	1	6	6	*			*							0.1	0.1	Gerth	c.394C>T/394C>T
30	1	6	7.2	*			*									Gerth	c.3G>A/3G>A
31	2	11	11	*						Discrete pigmentary changes						Van Hove	c.82-9_12delTTTC/271dupA
32	1	12	16	*			*									Gerth	c.394C>T394C>T
33	2	14	14						Mild pallor							Shinnar	c.394C>T394C>T
34	1	16	16	*			*									Roze	c.271dupA/347T>C
35	1	20	20													Bodamer	c.271dupA/482G>A
29	1	6	15	*										0.02	0.04	Gerth	c.394C>T/394C>T
30	1	6	19	*										0	0.2	Gerth	c.3G>A/3G>A
30	2		21	*											0.32	Gerth	c.3G>A/3G>A

*Flicker (cones) Normal: 60-100 uV; **Cones % of normal (80 uV); ***Scotopic (rods) 300-400 uV; § Rod % normal (300) b wave (postreceptor)
MP: Macular pigmentation; BEM: Bull's eye maculopathy; ERG: electroretinogram; OP: Optic pallor; RP: Retinitis pigmentosa; VF: Visual fixation

Type of file: table
Label: 2
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Supplementary Table 2. Outcome of patients with cblC disease and their therapeutic regimens.

Classification	Age (years)	Cbl form/ frequency / Dose 1 mg/day unless specified (Age modified)	Other Medications (Age added)	Developmental delay	Neurologic complications	Death (age)	Other	Reference	Genotype
5	0.1	CNCbl				7 weeks	? HUS	Mudd	NR
5	0.3	CNCbl			White matter disease	4 months	Diffuse pulmonary thromboembolism	Brandstetter	c.271dupA/331C>T
4	0.1	CNCbl ∏					HUS, required ventilation, transfusions	Sharma	c.271dupA/271dupA
2	0.1	OHCbl daily					Resolution HUS	Same patient as above	
3	5	OHCbl 5X/week		Delay	Diffuse white matter disease		No recurrence	Same patient as above	
2	0.1	OHCbl daily ∏	Betaine, folic, carnitine				Daily OHCbl: resolution seizures, successful VSD repair	Tomaske	NR
3	1	OHCbl 2X/week	Betaine, folic	Mild	Hypotonia, cortical atrophy			Same patient as above	
2	0.3	OHCbl daily	Betaine, folinic, carnitine		Regained conciousness, seizures controlled, improved muscle tone			Harding	c.328_331delAAC/ 328_331delAACC
2	0.2	OHCbl daily ∏	Betaine		Neurological improvement		Resolution microangiopathic hemolysis	Francis	c.457C>T/481C>T
3	0.5	OHCbl 2/week	Betaine, folic, carnitine, protein restriction 2 g/kg/day	Normal motor			Resolution cardiomyopathy; Growth 3rd centile at 7 months	DeBie	c.271dupA/271dupA
2	0.5	OHCbl 1/day	Carnitine, folinic	Motor delay			Resolution HUS	Kind	NR
2	1.2	OHCbl daily	Carnitine. Betaine added late	Delay	Hypotonia		Normal growth Tracks but nystagmus with	Urbon	NR

							fixation		
1	0.75	OhCbl 4/week Started prenatally	Betaine, folic	None			No complications	Spada	NR
2	0.2	OHCbl daily ∏			Considerable neurologic improvement		Improvement marrow megaloblastic changes	Carmel	NR
4	0.6	OHCbl 3X every 2 weeks			Seizures		Neutrophil hypersegmentation	Same patient as above	
2	0.15	OHCbl IV daily ∏					Dramatic clinical improvement	Ribes	NR
3	3.6	At 8 months of age ∏ followed by trials MeCbl oral OHCbl ∏	Folic acid, protein restriction, Betaine added at 20 months	IQ 65	Infrequent seizures, microcephaly		Failure to thrive	Same as above	
5	0.6	Oral OHCbl	Betaine		Progressive impairment	1 year		Frattini	c.271dupA/616C>T
4	3	OHCbl NON-COMPLIANCE	Betaine				cor pulmonale	Profitlich	NR
5	3	OHCbl 1/week ∏ MeCbl ∏ CNCbl ∏ No compliance	Betaine, methionine		Seizures, white matter disease, severe demyelinating polyneuropathy	15 years		Smith	NR
2	0.4	Prenatal OHCbl 3-5/week	Betaine				Foveal hyperpigmentation	Huemer	NR
4	2	OHCbl 0.5 mg 3/week ∏ daily at 17 months	Protein restriction. added betaine at 15 months		Choreoatetosis Grey and white matter disease		Initial resolution hematological abnormalities and improvement neurological status	Enns	c.331C>T/615C>G
3	1	OHCbl 0.5 mg daily ∏ 0.75 mg 3X/week	Betaine, folinic	Delay			Pigmentary retinopathy	Ellaway	c.271dupA/271dupA
3	1.25	OHCbl daily	Betaine, folic acid	DQ 80			Retinopathy Normal growth	Bartholomew	c.271dupA/271dupA
3	4.4	OHCbl daily	Betaine, folic acid	IQ 77			Retinopathy Growth <5th centile	Bartholomew	c.271dupA/271dupA
3	0.9	OHCbl 2/week					Pigmentary retinopathy	Robb	NR

Classification	Age (years)	Cbl form/ frequency / Dose 1 mg/day unless specified (Age modified)	Other Medications	Cognitive	Neurologic complications	Death (age)	Other	Reference	Genotype
1	11	OHCbl IM 1 mg/day	Folic acid, betaine (1 month later)	Back to normal	Resolution EEG findings and behavioral changes		When weaned to OHCbl 4/week - worsened considerably	Augoustides	c.271dupA/394C>T
5	13	None				13 years	Sister of the above	Augoustides	c.271dupA/394C>T
1	12	OHCbl SQ 5 mg/day	Betaine				Resolution thrombotic microangiopathy.	Van Hove	c.82-9_12delTTTC/ 271dupA
1	4	OHCbl SQ 5 mg/day	Betaine				Resolution thrombotic microangiopathy.	Van Hove	c.82-9_12delTTTC/ 271dupA
5	16	OHCbl ORAL	Betaine, methionine			21 years	Cerebrovascular complications	Brunelli	NR
2	16	OHCbl IV 2 ∏	Betaine, folinic, carnitine		Recovery of strength and resolution of psychotic symptoms			Roze	c.271dupA/T347C
4	20	OHCbl 2 mg/month	Betaine, folinic, carnitine		Severe myelopathy, neuropathy		Deep venous thrombosis	Same patient as above	
3	24	OHCbl IM 1 mg/day	Betaine, folinic, carnitine		Proximal weakness, mild improvement in gait		Mild improvement	Roze	c.271dupA/T347C
2	42	OHCbl IM 2 mg 3X/week	Betaine, folate, carnitine		Seizure-free, better work performance and executive functioning			Boxer	c.394C>T/394C>T
2	42	OHCbl IM daily	Betaine, folinic	Complete recovery	Recovered partial autonomy and ability to walk		Disappearance psychiatric symptoms	Thauvin-Robinet	c.271dupA/565C>A
1	40	OHCbl IM daily	Betaine, folinic				No recurrence thromboembolic	Thauvin-Robinet	c.271dupA/365A>G

							complications		
3	20	OHCbl 2 mg IM daily	Carnitine, low protein diet		Full recovery mental and upper extremity function. Residual diplegia		24 hours after initiation treatment: weaned off ventilator	Bodamer	c.271dupA/482G>A
2	14	OHCbl daily	Folate	Resolved dementia	Resolution EEG abnormalities. Residual mild myelopathy			Shinnar	c.394C>T/394C>T
5	32	No treatment				34	Progressive weakness to quadriplegia	Powers	c.271dupA/440G>C
5	44	No treatment				45	Pulmonary embolism	Powers	c.271dupA/440G>C
3	30	OHCbl 0.5 mg/day (during acute event), then 10 mg/week			Remained wheelchair-bound		Weaned from respirator	Gold	NR
4	4	CNCbl			Semi-comatose, multifocal epileptic activity			Mitchell	c.271dupA/394C>T
2	3	OHCbl 3-7X/week		Average student	Emotional instability, hyperreflexia			Same as above	
2	20	OHCbl daily	Betaine, carnitine, low-protein	Grade A student	Remarkable improvement in gait – mild gait distubances		Had diffuse brain atrophy on MRI before treatment	Ben-Omran	c.394C>T/394C>T
3		OHCbl daily		Learning difficulties	Persistent psychotic behavior, improved weakness			Ben-Omran	c.394C>T/394C>T
2	14	OHCbl daily	Betaine added late	Learning difficulties	Seizure-free, off psychotic medications			Same patient as above	