

**Supplemental Table 1. Initial presentation of the nine pre-symptomatic patients with MTHFR deficiency**

	Total number of patients with available data (N)	Number	Median (range)
<b><u>Demographic data</u></b>			
Gender (Female/Male)	9	6/3	
<b><u>Pregnancy and neonatal period data</u></b>			
Normal pregnancy	7	6	
Gestational age (weeks)	5		39 (39-39)
Birth weight (grams)	6		3373 (2800 – 4300)
Head circumference (cm)	5		34 (32 – 35)
<b><u>Diagnosis data</u></b>			
Age at diagnosis (years)	9		5 (0-52)
Laboratory data at time of diagnosis			
Plasma total homocysteine concentration ( $\mu\text{mol/L}$ ) <sup>a</sup>	7		200 (23 – 278)
Plasma methionine concentration ( $\mu\text{mol/L}$ ) <sup>b</sup>	1		7

<sup>a</sup> reference laboratory concentration <10  $\mu\text{mol/L}$ ; <sup>b</sup> reference laboratory concentration 17-43  $\mu\text{mol/L}$

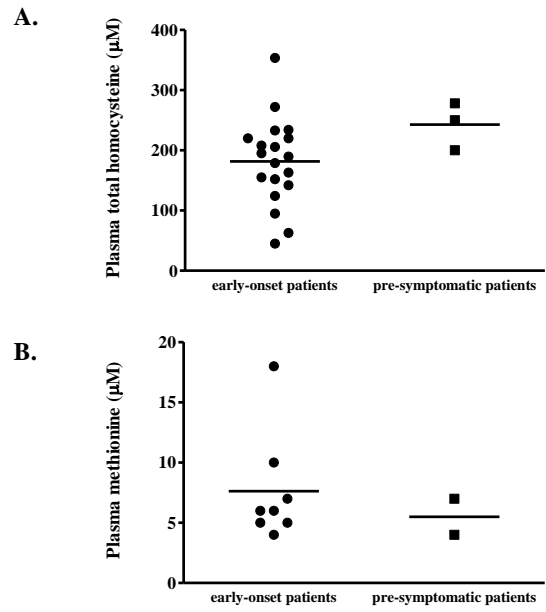
**Supplemental Table 2. Brain MRI and EEG data at diagnosis**

ID	Brain MRI at diagnosis										EEG at diagnosis		
	Dilated ventricles	External CSF spaces dilated	Cortex atrophy	Myelination delay	Deep gray matter structure abnormality	White matter T2/FLAIR hyperintensity	Pontine or cerebellar hypoplasia	Corpus callosum agenesis	Brainstem abnormality	Thrombosis or stroke	EEG at diagnosis	Abnormal basal rhythm	Paroxysmal abnormalities
9	yes	yes	yes	no	yes	yes	no	no	yes	no	yes	yes	yes
10	no	no	no	yes	yes	yes	no	no	no	no	yes	yes	no
19	yes	yes	yes	yes	no	NA	yes	yes	no	no			
20	yes	no	yes	no	no	NA	yes	yes	no	yes			
25											yes	no	no
26	yes	yes	yes	yes	no	no	yes	no	no	no	yes	yes	yes
29	no	no	no	yes	no	yes	yes	no	no	no	yes	yes	yes
30	yes	yes	yes	no	no	no	yes	no	no	no	yes	yes	yes
31	no	no	no	no	no	no	no	no	no	no	yes	yes	yes
32	yes	yes	no	no	no	no	no	no	no	no	yes	yes	yes

**Supplemental Table 3. Presentation of the nine pre-symptomatic patients with MTHFR deficiency, at their last follow-up visit**

	Total number of patients with available data (N)	Number	Median (range)
<b><u>Treatment modalities</u></b>	5		
Betaine		5	174.5 (44 – 284) <sup>a</sup>
B9 (folinic acid)		4	3.7 (0.28 – 9.24) <sup>a</sup>
B9 (folic acid)		3	0.095 (0.07 – 0.1) <sup>a</sup>
B12 (hydroxocobalamin)		4	0.019 (0.007 – 0.028) <sup>b</sup>
B12 (cyanocobalamin)		2	0.0182 (0.018 – 0.018) <sup>a</sup>
B6 (pyridoxine)		2	5.5 (5.5 – 5.5) <sup>a</sup>
Riboflavine		1	0.28 <sup>a</sup>
L-Methionine		2	7.5 (5.7 – 9.2) <sup>a</sup>
L-Carnitine		0	
5-Methyltetrahydrofolate		0	
<b><u>Clinical data</u></b>			
Age at the last follow-up visit	9		11.5y (3m - 58 y)
Microcephaly	4	0	
Analytic neurologic examination data			
Pyramidal syndrome	9	0	
Hypotonia	9	0	
Extrapyramidal syndrome	9	0	
Gait abnormalities	9	0	
Muscle strength abnormalities	9	0	
Clinical epilepsy	9	0	
Neurodevelopmental outcome data			
Gross motor abnormalities	9	0	
Interactions abnormalities	9	1	
Fine motor abnormalities	9	0	
Language abnormalities	2	0	
Special educational needs	9	1	
Visual problems	9	1	
Feeding problems	9	0	
Other affected organ systems			
Thromboembolic events	9	0	
Abnormal liver size	8	0	
Cardiac disease	8	0	
Psychiatric disease	6	1	
<b><u>Laboratory data</u></b>			
Plasma total homocysteine concentration (μmol/L) <sup>c</sup>	8		84.5 (6.8 - 163)
Plasma methionine concentration (μmol/L) <sup>d</sup>	6		21 (13 - 24)

<sup>a</sup> daily oral dose in mg/kg/day; <sup>b</sup> intramuscular dose in mg/kg/day; <sup>c</sup> reference laboratory concentration <10 μmol/L; <sup>d</sup> reference laboratory concentration 17-43 μmol/L



**Supplemental Figure 1: Plasma total homocysteine (A) and methionine (B) concentrations at the time of diagnosis in early-onset MTHFR patients (circle) versus pre-symptomatic patients (square)**