

## Supplementary figure 1 | Survey on patient-oriented outcomes for treatment of MCT8 deficiency.

The survey was designed in close collaborations with patient families. It includes (i) a section on the clinical abilities and impairments of the patient, (ii) a list of therapy wishes of parents, and (iii) a list of anticipated therapy wishes of the affected child. Free text is allowed in all sections. The survey should be answered by each parent separately. It was distributed *via* a German self-help group and *via* the Italian Leukodystrophy Center C.O.A.L.A. (Center for Diagnosis and Treatment of Leukodystrophies).

Version from 17.01.2023

### Survey on therapy targets for children with MCT8 deficiency.

Dear Parents,

Patients with MCT8 deficiency show in most cases a severe developmental disorder and additionally symptoms of varying severity such as movement disorders (dystonia, spasticity), dysphagia, underweight, a fast heartbeat and hypertension.

Various therapies have been under development since 2008. Currently, the modified thyroid hormone "Triac" is being tested. In addition, there are and will soon be further trials with other active substances for the treatment of MCT8 deficiency.

We would like to involve you as affected families in order to plan these therapy studies in the future as close to the patient as possible and to incorporate your needs into the trial design. In this survey, we would like to find out (1) how the child is developing and what complications he is suffering from, and (2) what therapeutic goals you would expect and desire from a new therapy. The survey was designed together with two families of patients with MCT8 deficiency.

Participation in this survey is voluntary and you may withdraw at any time. We ask each parent individually to complete and submit a questionnaire. Please return the completed questionnaire to the following email address:

████████████████████

If you would like to be informed about the result after the survey has been evaluated, please provide us with your contact details:

██  
██  
██

We thank you for your assistance!

Sincerely yours,

██

Age of patient: \_\_\_\_\_

In the first step, we ask questions about your child's current development and illnesses:

**Which developmental steps has your child already learned at the current time and what complications does he suffer from?**

Please select an applicable option between "0 = does not apply at all" and "4 = always applies". Under items 33-37, you can list your own abilities or complications that apply to your child and were not suggested under items 1-32.

Below we have formulated statements to try to assess your expectations of a new therapy:

**At a minimum, what changes in your child would you expect from therapy?**

Please tick a maximum of five answers from items 1-34. Under items 35-39, you can additionally formulate your own therapy goals that were not suggested under items 1-34.

- |   |                          |
|---|--------------------------|
| 1. My child is learning to sit.   | <input type="checkbox"/> |
| 2. My child falls asleep faster.  | <input type="checkbox"/> |
| 3. My child is developing normal blood pressure.                                      | <input type="checkbox"/> |
| 4. My child is learning to understand simple questions (e.g., "Do you want to eat?"). | <input type="checkbox"/> |
| 5. My child is developing less heartburn/reflux.                                      | <input type="checkbox"/> |
| 6. My child is learning to swallow better.  | <input type="checkbox"/> |
| 7. My child is learning to respond positively to music.                               | <input type="checkbox"/> |
| 8. My child is learning to hold his head.   | <input type="checkbox"/> |
| 9. My child is learning to grasp objects.   | <input type="checkbox"/> |
| 10. My child is learning to communicate using assistive devices.                      | <input type="checkbox"/> |
| 11. Stiffness/cramps in my child's arms/legs are decreasing.                          | <input type="checkbox"/> |
| 12. My child is more cheerful.  | <input type="checkbox"/> |
| 13. My child is learning to speak sentences.  | <input type="checkbox"/> |
| 14. My child is learning to walk.   | <input type="checkbox"/> |
| 15. My child is gaining weight.   | <input type="checkbox"/> |
| 16. My child learns to understand complicated questions.                              | <input type="checkbox"/> |
| 17. My child develops fewer infections that are treated in the hospital.              | <input type="checkbox"/> |
| 18. My child is learning to communicate with sounds.                                  | <input type="checkbox"/> |
| 19. My child is more alert during the day.  | <input type="checkbox"/> |
| 20. My child has less constipation.   | <input type="checkbox"/> |
| 21. My child learns to control the upper body better.                                 | <input type="checkbox"/> |
| 22. My child is less likely to develop untargeted, sudden movements.                  | <input type="checkbox"/> |
| 23. My child's hip coverage (dislocation) is improving.                               | <input type="checkbox"/> |
| 24. My child has a normal MRI of the head.  | <input type="checkbox"/> |
| 25. My child is learning to eat with a spoon or fork.                                 | <input type="checkbox"/> |
| 26. My child does not develop a crooked back (scoliosis).                             | <input type="checkbox"/> |
| 27. My child is learning to communicate with gestures.                                | <input type="checkbox"/> |
| 28. My child is learning to use the toilet.   | <input type="checkbox"/> |
| 29. My child's heartbeat is normalizing.  | <input type="checkbox"/> |
| 30. My child is learning to speak words.  | <input type="checkbox"/> |
| 31. My child does not need a feeding tube.  | <input type="checkbox"/> |
| 32. My child is learning to sleep through the night.                                  | <input type="checkbox"/> |
| 33. My child is developing normal laboratory values overall.                          | <input type="checkbox"/> |
| 34. My child develops normal thyroid hormone levels in the blood.                     | <input type="checkbox"/> |
| 35. _____   | <input type="checkbox"/> |
| 36. _____   | <input type="checkbox"/> |
| 37. _____   | <input type="checkbox"/> |
| 38. _____   | <input type="checkbox"/> |
| 39. _____   | <input type="checkbox"/> |

	never applies	rarely applies	some- times applies	applies more often	always true
	0	1	2	3	4
1. My child can sit.	0	0	0	0	0
2. My child has trouble falling asleep.	0	0	0	0	0
3. My child has high blood pressure.	0	0	0	0	0
4. My child can understand simple questions (e.g., "Do you want to eat?").	0	0	0	0	0
5. My child has heartburn/reflux.	0	0	0	0	0
6. My child has a swallowing disorder.	0	0	0	0	0
7. My child responds positively to music.	0	0	0	0	0
8. My child can hold his head.	0	0	0	0	0
9. My child can grasp objects.	0	0	0	0	0
10. My child communicates with assistive devices.	0	0	0	0	0
11. My child suffers from stiffness/cramps in arms/legs.	0	0	0	0	0
12. My child has a positive mood.	0	0	0	0	0
13. My child can speak sentences.	0	0	0	0	0
14. My child can walk.	0	0	0	0	0
15. My child suffers from underweight.	0	0	0	0	0
16. My child can understand complicated questions.	0	0	0	0	0
17. My child often suffers infections that are treated in the hospital.	0	0	0	0	0
18. My child communicates with sounds.	0	0	0	0	0
19. My child is very tired during the day.	0	0	0	0	0
20. My child has constipation.	0	0	0	0	0
21. My child can control the upper body well.	0	0	0	0	0
22. My child suffers from untimely, sudden movements.	0	0	0	0	0
23. My child has a poor hip coverage (-luxation).	0	0	0	0	0
24. My child has an abnormal MRI of the head.	0	0	0	0	0
25. My child can eat with a spoon or fork.	0	0	0	0	0
26. My child has a crooked back (scoliosis).	0	0	0	0	0
27. My child communicates with gestures.	0	0	0	0	0
28. My child can use the toilet.	0	0	0	0	0
29. My child's heartbeat is elevated.	0	0	0	0	0
30. My child can speak words.	0	0	0	0	0
31. My child has a feeding tube.	0	0	0	0	0
32. My child has trouble sleeping through the night.	0	0	0	0	0
33.	0	0	0	0	0
34.	0	0	0	0	0
35.	0	0	0	0	0
36.	0	0	0	0	0
37.	0	0	0	0	0

Last, we would like to try to assess which therapy goals the patients themselves would choose:

**What improvement would your child be most excited about?**

Please list the three most important items from the previously mentioned list (items 1-39).

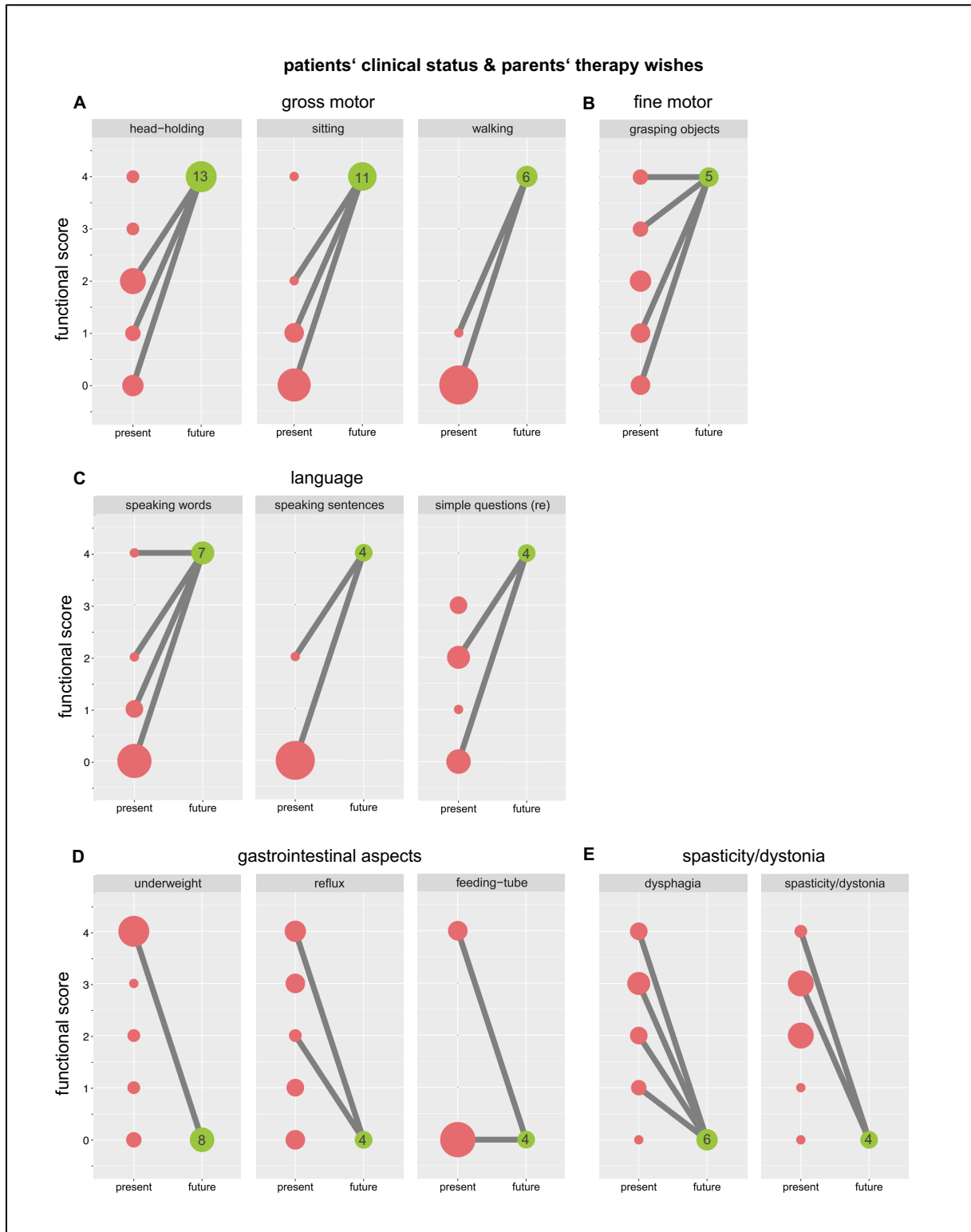
1. \_\_\_\_\_

2. \_\_\_\_\_

3. \_\_\_\_\_

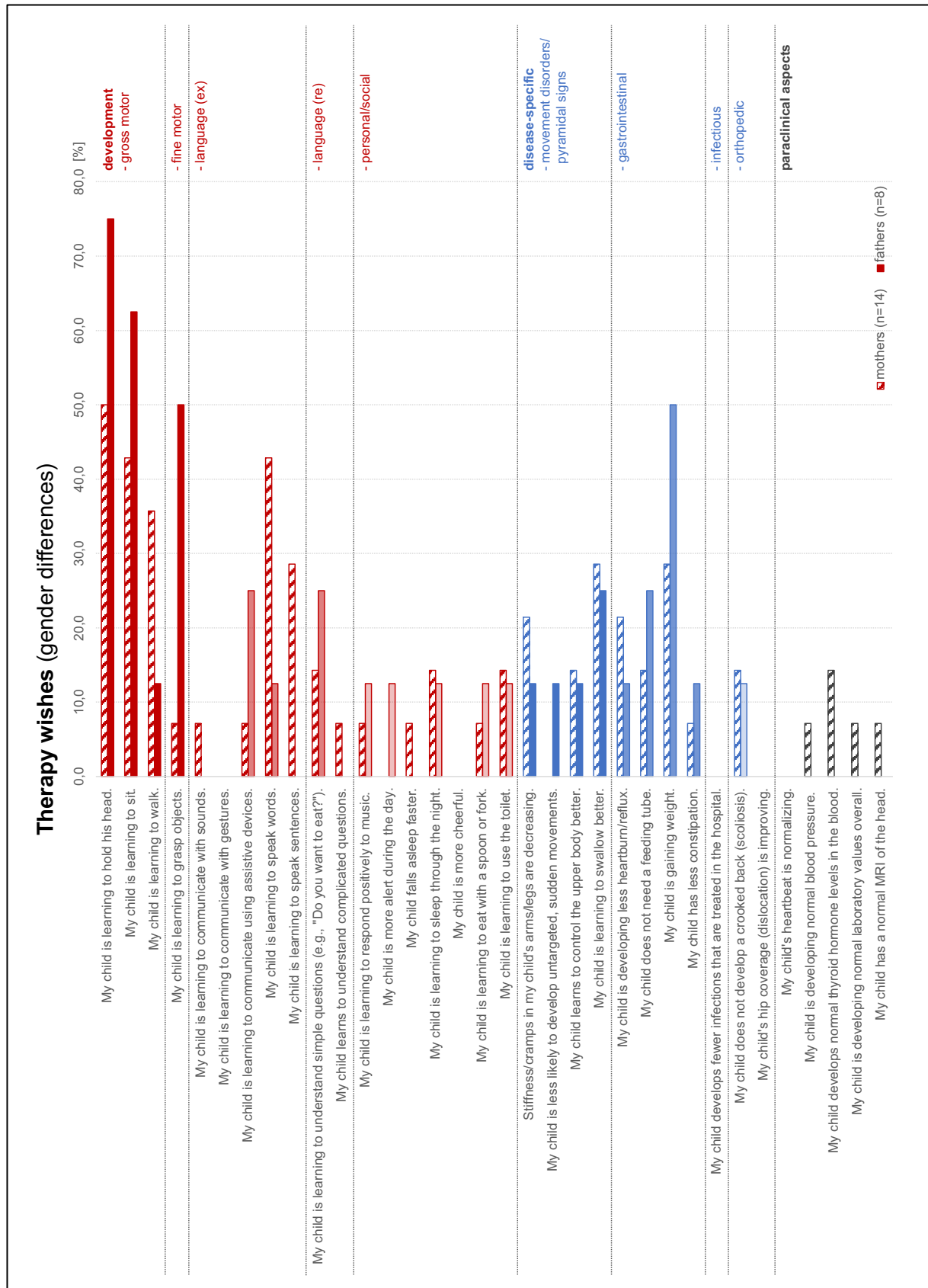
**Supplementary figure 2 | Phenotype spectrum of AHDS patients and parental therapy wishes.**

Actual clinical abilities (“present”) and impairments of patients were classified by parents in functional scores grade 0 (“never applies”), grade 1 (“rarely applies”), grade 2 (“sometimes applies”), grade 3 (“applies more often”), or grade 4 (“always true”). The patients’ phenotype (coral bubbles) is related to the parental expectations for minimal treatment effects (“future”, green bubbles, absolute numbers, total n=22). Gray lines visualize the effect of clinical status on therapy wishes: e.g. parents of patients with secure head control (**A**, 4/22, 18%, grade 3 or 4) did not choose and *vice versa* only parents of patients with underweight (**D**, 13/21, 62%, grade 4) chose improvement of the respective aspects “head control” and “underweight”.



### Supplementary figure 3 | Patient-oriented outcomes for treatment of MCT8 deficiency (gender differences).

In close collaborations with patient families, we designed a questionnaire asking for the favorite five therapy goals, which, if achieved at minimum, would make a change in their everyday life. We obtained results from 15 families (filled in questionnaires of 14 mothers and 8 fathers). TOP 12 therapy goals are labeled with stars and mainly included improvement in motor and verbal development (red) and of disease-specific complications (blue) as movement disorders/pyramidal signs and gastrointestinal aspects. Paraclinical aspects (gray) were least important.



**Supplementary figure 4 | Gross motor development in AHDS patients after Triac treatment *versus* natural history control.**

The raw data [GMFM88 scores] of a cross sectional natural history control (blue)<sup>14</sup> and of 12-months Triac-treated patients (red)<sup>22</sup> were digitized from published figures with ImageJ and merged as jittered points for comparison. Both groups showed fundamental impairment of gross motor skills with scores rarely beyond 20% of normal ranges. More data will be needed to interpret the effect of Triac on the neurological development of patients. Statistical differences in between groups were determined with the Mann-Whitney-U-Test. A p-value <0.05 was considered as statistically significant.

