Landscape of genetic testing for monocarboxylate transporter 8 (MCT8) deficiency

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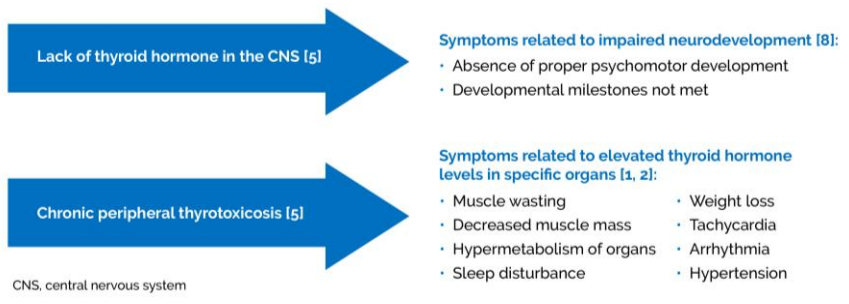
BACKGROUND

- MCT8 deficiency is a rare (<1 in 1 million based on known cases) and profoundly debilitating, chronic, X-linked genetic disorder affecting mainly males [1,2,3]
- It results from dysfunctional activity of monocarboxylate transporter 8 (MCT8), which is a major transporter of thyroid hormone and is widely expressed in human tissues [1,2]
- Two sets of co-existing symptoms occur resulting from early neurodevelopmental impairment and chronic peripheral thyrotoxicosis (**Figure 1**) [1,4,5,6]
- Mutations in the solute carrier family 16-member 2 (*SLC16A2*) gene, which encodes for MCT8 and is located on the X chromosome, are causative [4]
- Owing to its rarity and the heterogeneity of clinical manifestations, diagnosis is frequently missed or delayed. In addition, the absence of *SLC16A2* in multigene panels may prevent a confirmed diagnosis
- No formal guidelines or diagnostic criteria for MCT8 deficiency exist and there remain significant unmet needs in disease awareness, diagnosis, and treatment [4,6,7,8,9]
- We present the findings of a research project which evaluated the current landscape for genetic testing of *SLC16A2* mutations across Europe and the USA

Figure 1: Two sets of co-existing symptoms of MCT8 deficiency



METHODS

- In November 2022, a search of Orphanet and the National Institutes of Health (NIH) Genetic Testing Registry was carried out to identify which laboratories offered genetic testing for mutations in *SLC16A2*.
- Laboratory websites were examined for supplementary information and contacted by email for verification of current data obtained from databases

Orphanet (Europe; a source of information on rare diseases; https://www.orpha.net)
NIH Genetic Testing Registry (USA; a centralized resource for genetic healthcare professionals; https://www.ncbi.nlm.nih.gov/gtr/)

RESULTS

- Laboratories were identified and approached in Belgium, France, Germany, Italy, The Netherlands, Spain, UK and the USA (**Table 1**)

Table 1. Laboratories identified and approached in each country

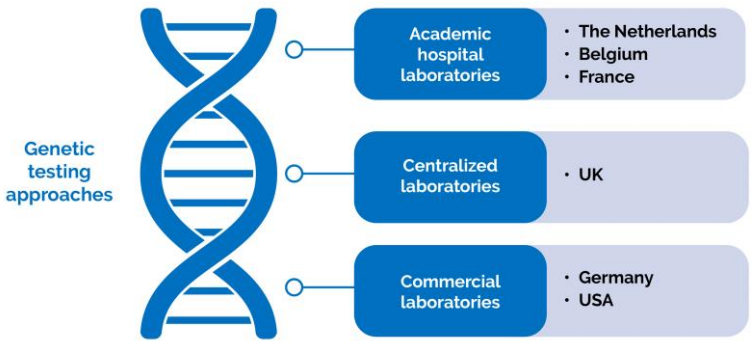
	BE	FR	DE	IT	NL	ES	UK	USA
Laboratories identified (n)	8	24	20	18	7	12	9	19
Laboratories approached for confirmation of information on Orphanet/NIH*	8	24	11	6	4	12	5	16
Extra laboratories approached that did NOT state that they would test for *SLC16A2* on Orphanet, but were considered relevant because they tested for metabolic disorders OR were pediatric centres	/	/	9	12	/	/	4	/
Country representatives of European Board of Medical Genetics (EBMG) also approached (response rate 100%)	Yes	Yes	/	Yes	Yes	Yes	/	/

*That stated these laboratories would test for *SLC16A2*. Not approached if enough information on website, or previously approached by Egetis (in some laboratories in the USA). **Abbreviations:** BE, Belgium; DE, Germany; ES, Spain; FR, France; IT, Italy; NIH, National Institutes of Health; NL, The Netherlands.

Large variations in genetic testing between regions/countries exists

- The Netherlands, Belgium and France: Strictly regulated testing and exclusively conducted by government-approved (academic) hospital laboratories
- UK: centralized approach across 7 Genomic Laboratory Hubs
- Germany and USA: primarily utilize commercial laboratories for testing of *SLC16A2* **(Figure 2)**

Figure 2. Overview of genetic testing approaches



Confirmation of SLC16A2 inclusion was highest in responses from The Netherlands and lowest in Italy and Spain (Figure 3)

- *SLC16A2* was included in a majority of panels for intellectual disability and spastic paraplegia
- Of panels that included *SLC16A2* testing (only labs confirmed on Orphanet to test for *SLC16A2*), intellectual disability (**Figure 3**) was the most commonly offered panel in the Netherlands (6/7 centers), Belgium (5/8 centers), France (18/24 centers), and Spain (6/12 centers); spastic paraplegia (**Figure 4**) was the most commonly offered panel in Germany (5/11 centers), Italy (3/6 centers), and the USA (9/19 centers)

Figure 3. Countries including *SLC16A2* in panels for intellectual disability

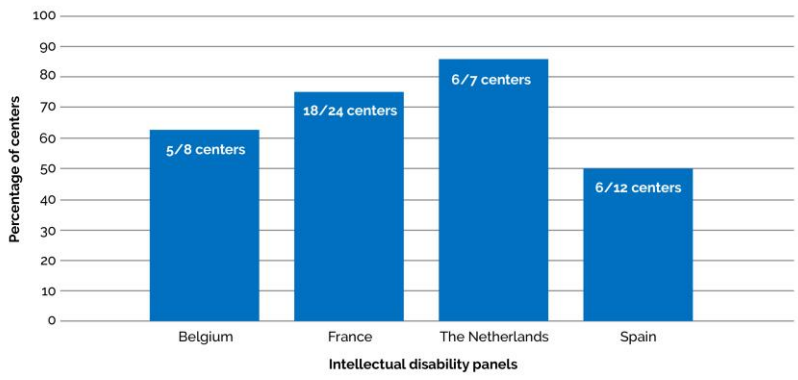
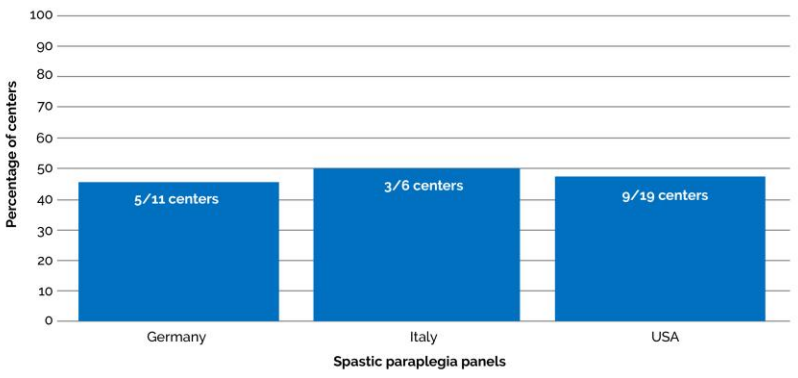


Figure 4. Countries including *SLC16A2* in panels for spastic paraplegia



Variability exists in the inclusion of SLC16A2 in the epilepsy panel in The Netherlands, Belgium, and Spain.

- Panels for leukodystrophy/leukoencephalopathy and autism, including *SLC16A2*, are frequently (6/19) offered in the USA, but are less common in European countries
- In The Netherlands, *SLC16A2* was absent in 3/5 laboratories offering panels related to endocrine or metabolic disorders (including thyroid disorders). For epilepsy, 5 centers in The Netherlands offered the panel, of which 3 included *SLC16A2*
- In both Belgium and Spain, 2/3 centers that confirmed they offer an epilepsy panel included *SLC16A2*
- Commercial laboratories generally offer a wider range of panels, with *SLC16A2* frequently included
- In terms of plans for future testing, most laboratories were willing to discuss adding *SLC16A2* to relevant panels.

TAKE-HOME MESSAGES

- Large variations exist in testing for *SLC16A2* mutations across centers in Europe and the USA. Often, laboratories did offer multigene panels and *SLC16A2* was included variably across and within countries
- This recent analysis can help guide expert groups and patient advocacy organizations in improving diagnostic opportunities for early detection of MCT8 deficiency

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