U-Fiber Leukoencephalopathy Due to a Novel Mutation in the TACO1 Gene

Giacomo Sferruzza, MD, Andrea Del Bondio, PhD, Andrea Citterio, PhD, Paolo Vezzulli, MD, Simone Guerrieri, MD, Marta Radaelli, MD, Filippo Martinelli Boneschi, MD, PhD, Francesca Maltecca, PhD, Maria Teresa Bassi, PhD, and Marina Scarlato, MD, PhD

Neurol Genet 2021;7:e573. doi:10.1212/NXG.0000000000000573

Correspondence
Dr. Scarlato
scarlato.marina@hsr.it

Translational activator of cytochrome c oxidase I (TACO1) is a mitochondrial translation factor involved in mitochondria-encoded cytochrome c oxidase subunit I (MT-CO1) synthesis. Loss-of-function mutations in the TACO1 gene cause respiratory chain complex IV deficiency. Clinically heterogeneous human diseases are due to cytochrome c oxidase (COX) deficiency, ranging from Leigh syndrome to myopathy, deafness, or ataxia. Recently, 2 different TACO1 mutations have been identified in 3 families with late-onset Leigh syndrome and a leukoencephalopathy involving predominantly basal ganglia and cystic changes. Here, we report a subject carrying a novel homozygous truncating mutation in the TACO1 gene and presenting an adult-onset slowly progressive spastic paraparesis with cognitive impairment and a subcortical U-fiber leukoencephalopathy.

Case Presentation

The proband is a 50-year-old Italian woman with a 20-year history of slowly progressive spastic gait and mild cognitive impairment. No family history and no clear consanguinity have been reported. She has a daughter, now 24-years-old, healthy. Neurologic examination showed diffuse signs of upper motor neuron involvement and an impairment of executive functions in a context of low cognitive ability setting. Neither involuntary movements nor cerebellar dysfunction signs were present. Optical coherence tomography highlighted a significant bilateral temporal retinal nerve fiber layer thickness reduction. Brain MRI showed a white matter disease with an extensive symmetrical involvement of U-fibers (figure 1A). Laboratory panels (including creatine kinase and lactic acid) and EMG were unremarkable. In a 10-year follow-up, we observed a spastic gait worsening leading to the necessary use of 2 sticks, and a cognitive impairment progression in terms of perseveration and reduced speed in information processing. MRI follow-up displayed a brain atrophy increase.

Genetics and Functional Studies

Whole-exome sequencing was performed on the proband, her healthy sister, and daughter after written informed consent. Two variants in TACO1 and mitochondrial distribution and morphology regulator 1 (MSTO1) were identified in the proband: a novel homozygous truncating change c.676G>T (p.Glu226Ter) in TACO1 and c.833A>G (p.Tyr278Cys) (rs143029385) in MSTO1 (freq. 0.04% in ExAC). None of the variants segregated in the sister, whereas the daughter is a carrier of the TACO1 change (figure 1B). Based on this, we speculated that TACO1 variant might be the disease-causing mutation. Functional studies demonstrated that the newly identified TACO1 mutation is highly pathogenic. Indeed, sodium dodecyl sulfate--
Polyacrylamide gel electrophoresis showed a striking reduction of MT-CO1 in patient fibroblasts compared with the heterozygous daughter and a healthy control (Figure 1C). Destabilized MT-CO1 resulted in a fully compromised assembly of COX, as assessed by blue native polyacrylamide gel electrophoresis on isolated mitochondria from proband and control fibroblasts (Figure 1D). To determine whether COX dysfunction could cause fragmentation of the mitochondrial network in the proband, we assayed mitochondrial morphology by live imaging microscopy in primary fibroblasts (supplemental data, links.lww.com/NXG/A400). Despite a mild reduction of optic atrophy gene 1 long forms, which are the active mediators of mitochondrial fusion (Figure 1C), the proband displayed a mitochondrial network morphology comparable to controls, with the highest percentage of cells showing fused and interconnected organelles (figures e-1 and e-2, links.lww.com/NXG/A397). This finding also demonstrates that the heterozygous MSTO1 variant identified is likely not pathogenic, as it does not affect mitochondrial morphology.

**Discussion**

We reported a novel mutation in the TACO1 gene causing a striking reduction in the MT-CO1 synthesis and compromised COX assembly in fibroblasts. Complex IV, the last enzyme of the mitochondrial respiratory chain, catalyzes electrons transfer to the final acceptor O2 for adenosine triphosphate synthesis. Three of the 14 COX subunits are encoded by mitochondrial DNA (mtDNA), and their synthesis is regulated by different nuclear genes like TACO1.

To date, this is the third TACO1 homozygous mutation reported. In the first and second one, a juvenile-onset Leigh-like disease was described with wide symptom variability also within the same family. We expanded the clinical
and neuroradiologic spectrum associated with TACO1 mutations, reporting a non-Turkish woman with a novel clinical and neuroradiologic phenotype. Subcortical arcuate U-fibers are among the slowest and latest myelinating fibers, with a reduced rate of myelin turnover; therefore, they are generally spared in other inherited leukodystrophies, except for Alexander and Canavan disease. In mitochondrial disorders, white matter involvement is a common feature. Usually, lesions caused by mtDNA point mutation predominantly affect deep gray matter with minor peripheral white matter involvement, whereas diffuse necrotic or cystic changes associated with brain atrophy are frequently observed in patients with Leigh disease due to mutation in nuclear genes encoding for complex I or IV and assembly factor. Late-onset and slow progressing neurologic manifestations make the described case an uncommon variant of COX deficiency spectrum disorder and are apparently in contrast with functional data showing a markedly reduced COX activity in fibroblasts. This discrepancy highlights the complex protein interactions involved in COX synthesis and assembly, which are probably tissue and development specific.

Acknowledgment
The authors thank the patient and her family for participating in the study and Valentina Baderna for the technical support in functional studies.

Study Funding
This work was supported by Italian Ministry of Health, RF-2016-02361610 (F.M.) and RC 2018-2020 (M.T.B.), and by the Fondazione Regionale per la Ricerca Biomedica, grant ID, Care4NeuroRare (M.T.B.).

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures.

Publication History
Received by Neurology: Genetics September 29, 2020. Accepted in final form January 12, 2021.

Appendix
(continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrea Del Bondio, PhD</td>
<td>IRCCS San Raffaele Scientific Institute, Milan, Italy</td>
<td>Major role in the acquisition of data and revised the manuscript</td>
</tr>
<tr>
<td>Andrea Citterio, PhD</td>
<td>Scientific Institute IRCCS E. Medea, Bosso Parini, Italy</td>
<td>Major role in the acquisition of data and revised the manuscript</td>
</tr>
<tr>
<td>Paolo Vezzulli, MD</td>
<td>IRCCS San Raffaele Scientific Institute, Milan, Italy</td>
<td>Major role in the acquisition of data and revised the manuscript</td>
</tr>
<tr>
<td>Simone Guerrieri, MD</td>
<td>IRCCS San Raffaele Scientific Institute, Milan, Italy</td>
<td>Major role in the acquisition of data and revised the manuscript</td>
</tr>
<tr>
<td>Marta Radaelli, MD, PhD</td>
<td>Papa Giovanni XXII, Bergamo, Italy</td>
<td>Acquired the data and revised the manuscript</td>
</tr>
<tr>
<td>Filippo Martinelli Boneschi, MD, PhD</td>
<td>University of Milan, Milan, Italy Fondazione IRCCS Ca' Granda Policlinico, Maggiore Policlinico, Milan, Italy</td>
<td>Acquired the data and revised the manuscript</td>
</tr>
<tr>
<td>Massimo Filippi, MD, PhD</td>
<td>IRCCS San Raffaele Scientific Institute, Milan, Italy</td>
<td>Acquired the data and revised the manuscript</td>
</tr>
<tr>
<td>Francesca Maltecca, PhD</td>
<td>IRCCS San Raffaele Scientific Institute, Milan, Italy</td>
<td>Drafting/revision of the manuscript for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
</tr>
<tr>
<td>Maria Teresa Bassi, PhD</td>
<td>Scientific Institute IRCCS E. Medea, Bosso Parini, Italy</td>
<td>Drafting/revision of the manuscript for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
</tr>
<tr>
<td>Marina Scarlato, MD, PhD</td>
<td>IRCCS San Raffaele Scientific Institute, Milan, Italy</td>
<td>Drafting/revision of the manuscript for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
</tr>
</tbody>
</table>

References
U-Fiber Leukoencephalopathy Due to a Novel Mutation in the TACO1 Gene
Giacomo Sferruzza, Andrea Del Bondio, Andrea Citterio, et al.

*Neurol Genet* 2021;7;
DOI 10.1212/NXG.0000000000000573

This information is current as of March 9, 2021
| Updated Information & Services | including high resolution figures, can be found at: http://ng.neurology.org/content/7/2/e573.full.html |
| References | This article cites 7 articles, 0 of which you can access for free at: http://ng.neurology.org/content/7/2/e573.full.html##ref-list-1 |
| Subspecialty Collections | This article, along with others on similar topics, appears in the following collection(s):  
  All Clinical Neurology [link]  
  All Genetics [link]  
  Mitochondrial disorders [link]  
  MRI [link]  
  Spastic paraplegia [link] |
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://ng.neurology.org/misc/about.xhtml#permissions |
| Reprints | Information about ordering reprints can be found online: http://ng.neurology.org/misc/addir.xhtml#reprintsus |

*Neurol Genet* is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.