CORRESPONDENCE

Rapid Sequencing-Based Diagnosis of Thiamine Metabolism Dysfunction Syndrome

TO THE EDITOR: Approximately 30 years after the start of the Human Genome Project, we sequenced the genome of an infant with encephalopathy in just over 11 hours. The results led to a clinical diagnosis of thiamine metabolism dysfunction syndrome 2 (THMD2) 16.5 hours after a blood sample was obtained and 13 hours after we initiated sequencing, which informed treatment of the infant, thereby illustrating the fulfillment of the promise of the Human Genome Project to transform health care.

A 5-week-old, previously healthy male infant was admitted after 2 hours of inconsolable, atypical crying and irritability (Fig. 1). Examination revealed downward eye deviation when he cried. Computed tomography of the head showed multiple large, bilateral hypodensities. Ten years earlier, his parents, who were first cousins, had had a child with a similar neurologic presentation that rapidly progressed to epileptic encephalopathy; the child died at 11 months of age without an etiologic diagnosis, despite extensive evaluation.

Infantile encephalopathy is associated with approximately 1500 genetic diseases, many of which are clinically indistinguishable but have unique, effective treatments. Without prompt treatment, permanent neurologic injury or death occurs in many infants with these diseases. A resemblance to common conditions, such as hypoxic ischemic encephalopathy, can lead to inappropriate or delayed treatment. These considerations prompted us to seek a diagnosis through genome sequencing. With written informed consent from the parents, we obtained blood samples 17 hours after admission (Fig. 1) and performed genome sequencing, using standard and prototypic methods in parallel.[2,3] We used the criteria of the American Society of Medical Genetics to evaluate the pathogenicity of a frameshift variant (c.597dup; p.His200fs) in *SLC19A3* (ClinVar accession number, VCV000533549.2) and make a provisional diagnosis of THMD2 14 hours 33 minutes after his blood sample arrived at the genome center. (*SLC19A3* encodes a thiamine transporter.) This provisional diagnosis was clinically confirmed 49 minutes later.

Video electroencephalography showed numerous seizures occurring in the interim. Thiamine and biotin administration was started 37.5 hours after admission, and phenobarbital administration was started 2 hours later. One 15-second seizure was recorded thereafter. Six hours later, the patient was alert, calm, and bottle feeding. Standard, trio genome sequencing confirmed the diagnosis. After a further 24 hours passed without seizures, the patient was discharged. He is now thriving at 7 months of age.

Early infantile, "Leigh-like" THMD2 is characterized by rapid neurologic deterioration and, if untreated, childhood death.[4,5] We believe that the patient's sibling died in infancy from THMD2, given the carrier status of both parents and the

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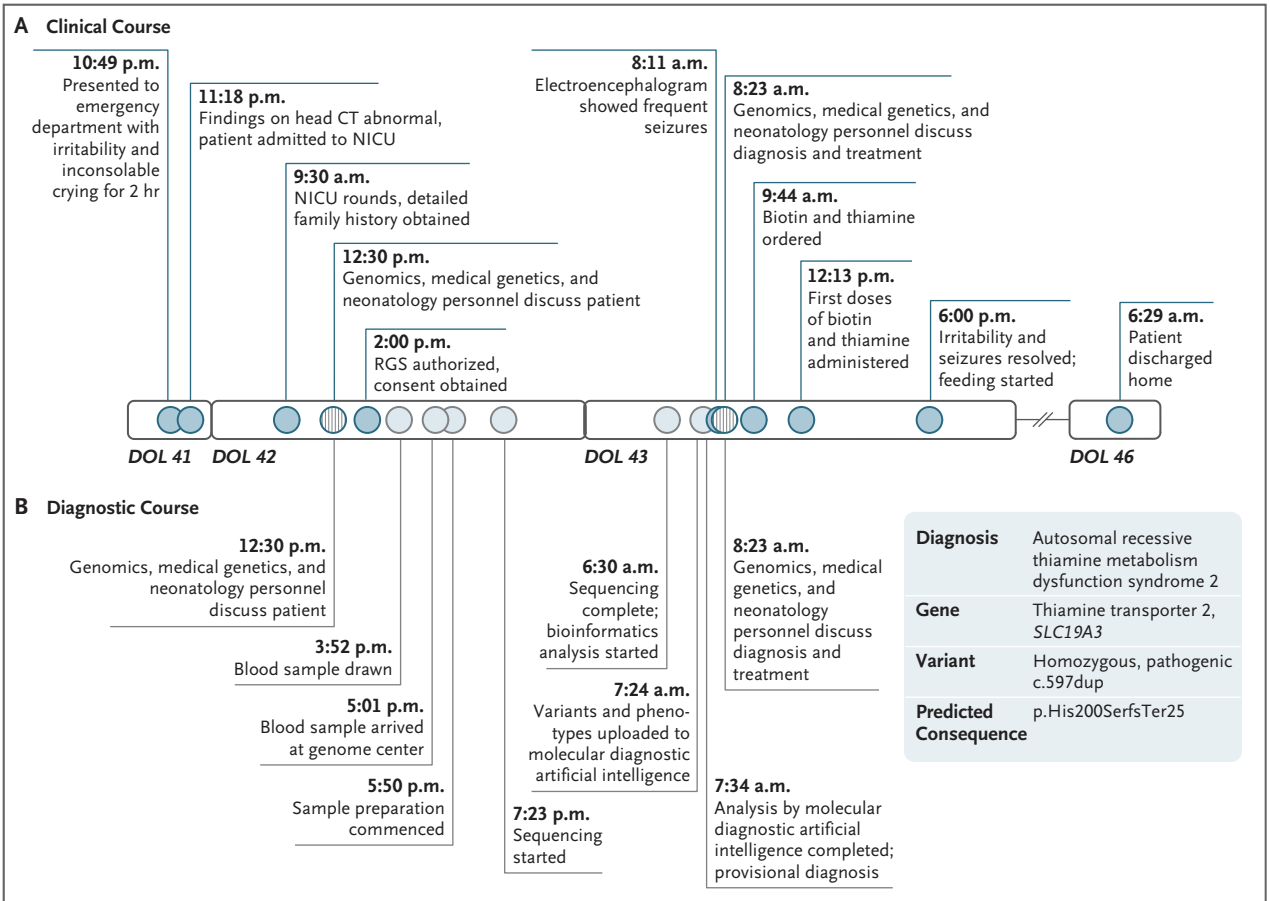

Figure 1. Clinical and Diagnostic Course in the Patient and His Sibling.

The homozygous frameshift variant in the thiamine transporter 2 gene *SLC19A3* that was detected in the patient had previously been reported as pathogenic both in a child with a similar presentation[1] and in the ClinVar database (accession number, VCV000533549.2). Circles along the timeline indicate events that occurred during the clinical course (darker blue) and the diagnostic course (lighter blue). Circles with vertical lines indicate points of interaction among neonatology, genomics, and medical genetics personnel. CT denotes computed tomography, DOL day of life, NICU neonatal intensive care unit, and RGS rapid genome sequencing.

similarity of radiographic and neurologic findings (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

This case illustrates the potential for decreased suffering and improved outcomes through the implementation of rapid genome sequencing in a multidisciplinary, integrated, precision medicine delivery system.[1] Such a system includes identification of infants with suspected genetic diseases on the day of admission, rapid genome sequencing as a first-tier test, communication of results in a manner that facilitates prompt transition from empirical to etiologically informed treatment, and implementation within a learning health care system.[1] Currently, rapid genome sequencing is being implemented in Australia, England, Germany, and Wales and in Medicaid pilot programs in California, Florida, and Michigan.

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Cross-Reactive Neutralizing Antibody Responses Elicited by SARS-CoV-2 501Y.V2 (B.1.351)

TO THE EDITOR: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 501Y.V2 lineage (also known as B.1.351), first identified in South Africa in October 2020,[1] has mutations that confer increased resistance to plasma from convalescent patients and vaccine recipients, as well as to some monoclonal antibodies.[2-4] However, the immune response to 501Y.V2 is unknown. Similarly, the ability of antibodies elicited by 501Y.V2 infection to cross-react with other variants is unknown, but such cross-reactivity would have implications for the ability of second-generation vaccines based on the 501Y.V2 spike protein to protect against infection with the original and emerging SARS-CoV-2 lineages.[5]

We characterized the SARS-CoV-2 infections in a cohort of patients with coronavirus disease 2019 (Covid-19) who were hospitalized in the Groote Schuur Hospital, Cape Town (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), after the emergence and dominance of 501Y.V2 in South Africa. Blood samples were obtained from 89 patients between December 31, 2020, and January 15, 2021; of these patients, 28 (31%) were randomly selected for SARS-CoV-2 sequencing, all of whom were shown by phylogenetic analysis to be infected with 501Y.V2 (Fig. S1A). Furthermore, at this time, the epidemic in Cape Town (Fig. S1B) and in South Africa as a whole