CORRESPONDENCE

Lifesaving Diagnosis through Prenatal Genomic Sequencing

TO THE EDITOR: Congenital thrombotic thrombocytopenic purpura (TTP) is a rare and potentially lethal thrombotic microangiopathy caused by a quantitative or qualitative deficiency of ADAMTS13 protein. ADAMTS13 cleaves ultralarge von Willebrand factor. Therefore, deficiency results in the accumulation of ultralarge von Willebrand factor multimers, leading to platelet-rich microthrombi and multisystem thrombotic microangiopathy with hemolytic anemia, thrombocytopenia, and end-organ damage.[1]

The phenotypic expression of congenital TTP is highly variable. Biallelic prespacer missense variants have been associated with earlier-onset disease relative to postspacer variants.[2] However, this correlation is inconsistent and most likely relates to the predominance of critical enzymatic domains in the prespacer region.

Congenital TTP can be a severe, early-onset condition for which effective treatment is available with fresh frozen plasma or the recently developed recombinant ADAMTS13.[1] We report the case of a fetus in whom prenatal trio exome sequencing incidentally predicted the presence of congenital TTP, leading to lifesaving management.

A woman who had two previous pregnancies, one of which resulted in a live birth at term, underwent prenatal trio exome sequencing at 31 weeks (+4 days) of gestation after ultrasonographic detection of fetal left ventricular dilatation, a hypertrabeculated and noncompacted left ventricle, and nonspecific skeletal anomalies. The subsequent identification of a pathogenic filamin C (*FLNC*) loss-of-function splice-site variant (c.970-4A→G) was consistent with *FLNC*-related cardiomyopathy. Incidentally identified were compound heterozygous missense variants in *ADAMTS13* (p.L183Q and p.C527S) that were initially classified as likely pathogenic and a variant of uncertain significance, respectively. Both variants localized to prespacer domains (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Genomic analysis revealed that *ADAMTS13* cysteine-527 forms an intrachain disulfide bond with cysteine-508, and the change to a serine in p.C527S is expected to lead to loss of that bond.[3] Mutations involving cysteine-508 have been repeatedly reported in congenital TTP, which allows for a reinterpretation of p.C527S as likely pathogenic.[4] A high risk of neonatal-onset disease was predicted, given the critical enzymatic domain locations of the variants. Although these findings were incidental, the availability of therapy to prevent disease supported reporting.

A discussion among members of a multidisciplinary team led to formulation of a perinatal management plan for delivery at a tertiary center, along with precautions in case of thrombocytopenia, urgent cord-blood testing, and immediate administration of fresh frozen plasma. Recombinant ADAMTS13 was approved by the

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Food and Drug Administration for use only days before delivery and was not locally available.

A male infant was delivered at 38 weeks of gestation. Cord-blood samples were found to have a normal hemoglobin level but marked thrombocytopenia (platelet count, 8×10^9 per liter), hyperbilirubinemia, and ADAMTS13 activity of less than 1%. Fresh frozen plasma (at a dose of 15 ml per kilogram of body weight) was administered within the first hour after birth and continued every 4 to 6 hours with intensive phototherapy instituted for severe hyperbilirubinemia (Fig. 1). Marked thrombocytopenia persisted on day 2 despite 63% ADAMTS13 activity, stable hemoglobin, and a decrease in hyperbilirubinemia. Gastrointestinal bleeding at that time prompted a platelet transfusion. The platelet count stabilized after transfusion and improved after day 5. Infusion of fresh frozen plasma continued until day 12, when the TTP exacerbation resolved (Fig. 1).

No clinical features of functionally significant *FLNC*-related disease were noted on an echocardiogram within the first hour after birth, but a pulmonary-valve thrombus was detected. Chronic thrombosis of the right internal jugular vein was detected on ultrasonography performed on day 1. Additional investigations revealed cerebral punctate hemorrhagic venous infarcts, small subdural hemorrhages, and small hyperechoic hepatic lesions consistent with thrombosed veins. No other causative factors were identified for the thrombi in the pulmonary valve and internal jugular vein, including no central venous instrumentation and no cardiac valvular or functional abnormalities. The early postnatal detection of these anomalies raises the possibility of prenatal onset. The evidence of thrombotic microangiopathy in cord blood at birth is also consistent with peripartum or prenatal onset of microangiopathy.

Access to recombinant ADAMTS13 was sought on a compassionate basis (from Takeda Development Center Americas). Despite day 1 approval, logistic barriers delayed supply. Prophylaxis with ADAMTS13 (at a dose of 40 IU per kilogram) was initiated on day 15 and continued weekly, without additional TTP exacerbations. On exami-

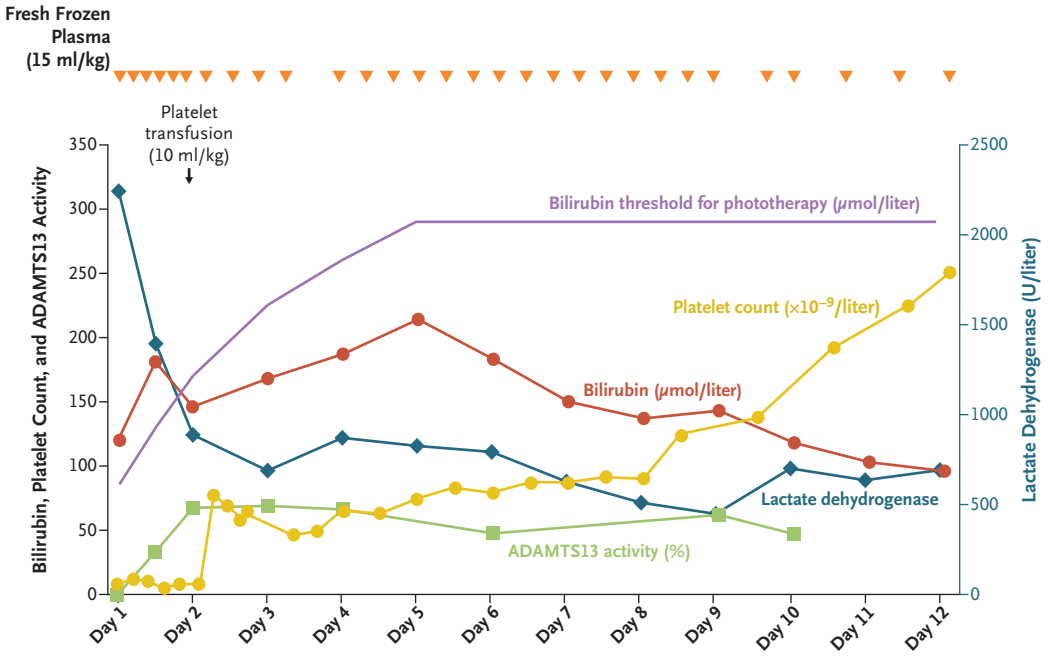

Figure 1. Hematologic and Biochemical Measures and Interventions during Acute Exacerbation of Congenital Thrombotic Thrombocytopenic Purpura (TTP).

Shown is the timeline of treatment during the first 12 days after delivery of an infant born with congenital TTP, a condition that was incidentally predicted by prenatal trio exome sequencing. Values for most measures (including bilirubin, platelet count, and ADAMTS13 activity) are shown on the left y axis, and levels of lactate dehydrogenase are shown on the right y axis. In addition to the daily measure of bilirubin, the bilirubin threshold for the use of phototherapy to treat neonatal jaundice is shown.

nation when the infant was 17 months of age, measures of growth, development, and cardiac, renal, and hepatic function were normal.

This case illustrates the power of prenatal genomics in guiding precision medicine and enabling lifesaving therapy. Prenatal genomic testing has a powerful role not only in the diagnosis of fetal anomalies but also in the reporting of treatable incidental findings. Prenatal incidental findings are ethically complex, especially for variants of uncertain significance or adult-onset disorders. However, parents overwhelmingly want reporting of prenatal incidental findings for early-onset, treatable conditions.[5] Here, a discussion of risks between the managing clinical geneticist and the genomics laboratory pathologist led to deeper curation of the variant of uncertain significance and formal reporting of the risk of congenital TTP, results that highlight the importance of clinicopathological discussions and pretest genetic counseling. At 6 months, in a psychosocial interview that was performed for the PreGen Study (pregen.neura.edu.au), the infant's parents reported that they had no negative effects from such prenatal testing. The inclusion of *ADAMTS13* in reproductive carrier–screening panels could alert clinicians to this condition, although genotype–phenotype correlation remains uncertain for many variants.

This case of congenital TTP in which prenatal genomic sequencing led to lifesaving therapy highlights the technical challenges, ethical concerns, and power of genomic sequencing. As noninvasive techniques for prenatal genomics advance, such findings will become more common, which underlines the need for guidelines for consistent and ethical reporting and development of precision therapeutics.[5]

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Intensive Blood-Pressure Control in Patients with Type 2 Diabetes

TO THE EDITOR: In the Blood Pressure Control Target in Diabetes (BPROAD) trial, Bi et al. (March 27 issue)[1] used the classic design of a prospective randomized trial with an intention-to-treat analysis. However, the target systolic blood pressure of less than 120 mm Hg was met in only approximately 60% of the patients in the intensive-treatment group. In an outcome research study in which the relationship between the blood pressure at study entry and future cardiovascular outcomes was examined, a systolic blood pressure of less than 120 mm Hg provided no benefit with respect to the incidence of cardiovascular events among patients with type 2 diabetes and existing cardiovascular disease.[2]

These results lead to the question of whether a blood-pressure target can serve as a guide in clinical practice. Shouldn't the achieved blood pressure, which accurately reflects the pressure load on the cardiovascular system during follow-up, serve as a guide for the treatment of hypertension? To this end, the investigators need to analyze whether patients in the intensive-treatment group who met the systolic blood-pressure target of less than 120 mm Hg had fewer or more cardiovascular and adverse events (symptomatic hypotension, hyperkalemia, and renal outcomes) than those who did not meet the intended target.

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