CORRESPONDENCE

Serious Ivermectin Toxicity and Human *ABCB1* Nonsense Mutations

TO THE EDITOR: The discoverers of ivermectin, a broad-spectrum parasiticide that is widely used in humans and animals, were awarded the Nobel Prize in Physiology or Medicine in 2015.[1] This drug is reputed to be remarkably safe thanks to its ability to be effluxed by the ATP-binding cassette subfamily B member 1 (ABCB1) transporter (also known as MDR1 and P-glycoprotein) in the blood–brain barrier.

In some breeds of dogs such as collies, which are homozygotes for a nonsense mutation in *ABCB1*, and in *Abcb1*-knockout mice, ivermectin induces neurologic disorders that can be fatal.[2,3] Few cases of neurologic disorders after ivermectin treatment have been reported in humans, and data are lacking on such a deleterious mutation in the human gene *ABCB1*.[4]

We report the case of a 13-year-old boy admitted to the pediatric intensive care unit for impaired consciousness. He had received a single oral dose of ivermectin (0.23 mg per kilogram of body weight) to prevent scabies infection 2 hours 30 minutes before the onset of impaired consciousness. His condition worsened 6 hours after he received ivermectin, with persistent neurologic signs, including coma, ataxia, pyramidal signs, and binocular diplopia, as well as abdominal pain and vomiting. He was monitored for 48 hours; during this period, he had a fluctuating Glasgow score and normal results on paraclinical tests. He fully recovered after 48 hours (see the Supplementary Data 1 section in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Ivermectin intoxication was suspected, since encephalopathy and coma are well-known side effects of ivermectin treatment in animals and the usual causes of coma had been ruled out. *ABCB1* sequencing identified the child as a compound heterozygote for two nonsense mutations: NC_000007.13(NM_000927.4):c.2380C→T (a cytosine-to-thymine transition in exon 20) and NC_000007.13(NM_000927.4):c.3053_3056delTTGA (a 4-bp deletion in exon 25) (Fig. 1A). Genetic analysis performed in the patient's family confirmed allelic segregation (Fig. 1B). Each *ABCB1* mutation generated a premature stop codon that predicted two incomplete copies of the transporter, both of which lacked the C-terminal nucleotide-binding domain that is essential for drug-transport activity.[5] The loss of ABCB1 activity in the child would have resulted in a failure of brain protection and probably would have induced high exposure of the central nervous system to ivermectin and the toxic effects observed.

We describe two human *ABCB1* nonsense mutations associated with a loss of function in a patient who had an adverse reaction to ivermectin

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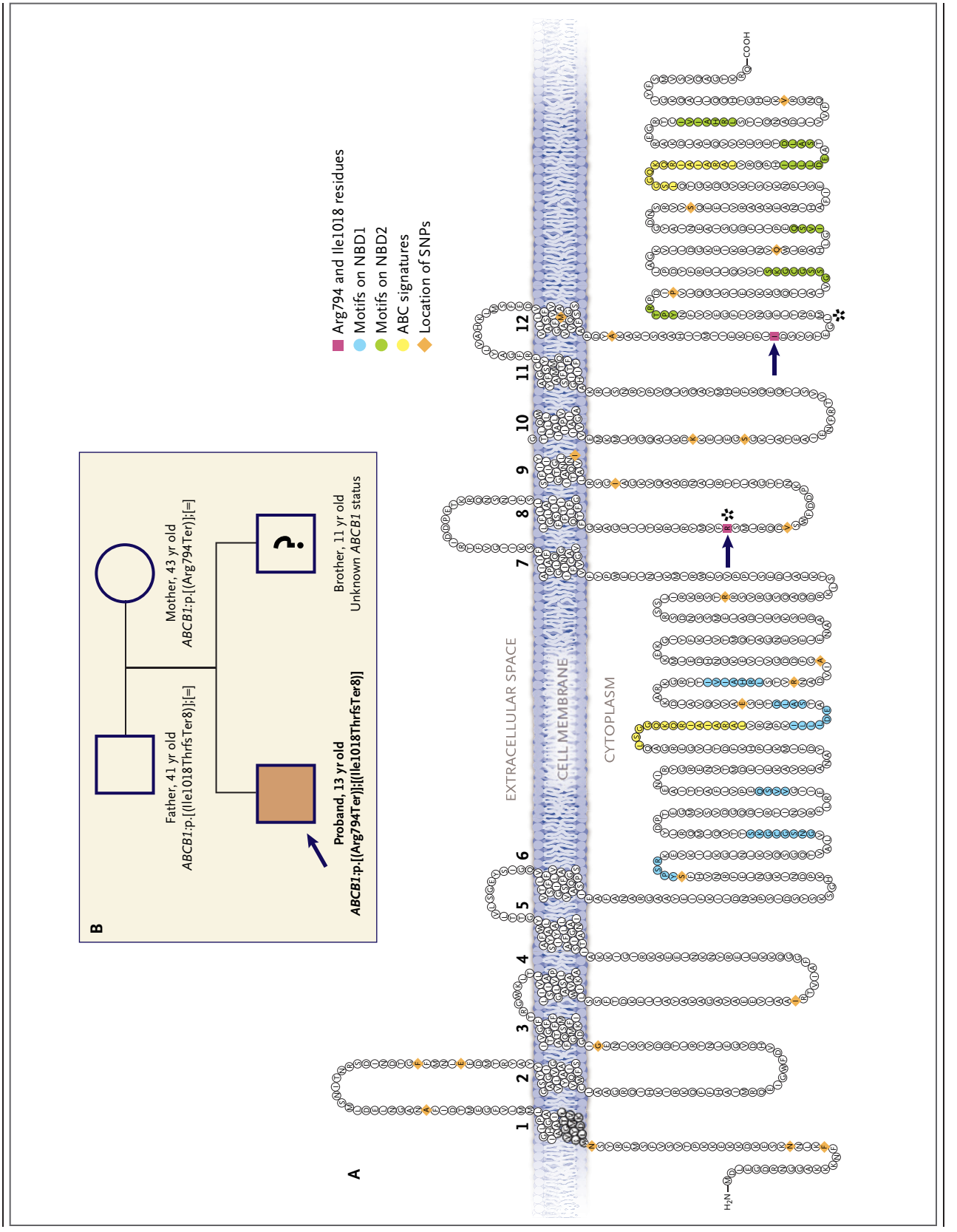

Figure 1 (facing page). Two Predicted Truncated Proteins Generated by Nonsense Mutations of Human *ABCB1*.

Panel A shows the location of the altered residues on the two-dimensional structure of human ABCB1 (NP_000918.2). The protein contains 1280 residues (circles), organized in 12 transmembrane domains, and canonical nucleotide-binding domains 1 and 2 (NBD1 and NBD2) with two symmetric ATP-binding sites, essential for coupling ATP hydrolysis to drug efflux pump activity. ABC-specific conserved sequence motifs (i.e., A loop, Walker A, Q loop, ABC signature [yellow], Walker B, D loop, and H switch) in the NBD1 domain (blue) and NBD2 domain (green) are shown. The altered residues (Arg794 and Il1018) are indicated by arrows. The p.(Arg794Ter) substitution generates a stop codon (asterisk) and a truncated protein of 793 residues. The p.(Ile1018ThrfsTer8) deletion causes a frameshift starting from the Ile1018 codon and a new reading frame ending 8 amino acids downstream, resulting in a truncated protein of 1024 residues. The topologic plot was generated with the use of Protter software. SNP denotes single-nucleotide polymorphism. Panel B shows the results of the family *ABCB1* genetic study. Genetic screening of *ABCB1* (NC_000007.13, NM_000927.4) was undertaken in three members of the family with the use of next-generation sequencing (Agilent SureSelectQXT reagent for Illumina MiSeq). The mutations detected were p.(Arg794Ter) and p.(Ile1018ThrfsTer8) in exons 20 and 25, respectively. These mutations were subsequently confirmed with the use of Sanger sequencing. The proband (arrow) had inherited the chromosome bearing the c.2380C→T allele from his mother and the chromosome with the c.3053_3056delTTGA deletion from his father. Genetic analysis was not performed in the younger brother because of ethical reasons. The equal sign denotes a normal allele.

after the administration of a usual dose. The seriousness of the intoxication in the child implies that caution is warranted regarding medical prescriptions of ivermectin and other ABCB1 substrates (see the Supplementary Data 2 section in the Supplementary Appendix). Our findings highlight the importance of pharmacovigilance and the benefit of *ABCB1* genotyping to identify clinically significant *ABCB1* mutations related to a well-circumscribed phenotype and to explain an unexpected response to a drug.

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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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New-Onset Diabetes in Covid-19

TO THE EDITOR: There is a bidirectional relationship between Covid-19 and diabetes. On the one hand, diabetes is associated with an increased risk of severe Covid-19. On the other hand, new-onset diabetes and severe metabolic complications of preexisting diabetes, including diabetic ketoacidosis and hyperosmolarity for which exceptionally high doses of insulin are warranted, have been observed in patients with Covid-19.[1-3] These manifestations of diabetes pose challenges in clinical management and suggest a complex pathophysiology of Covid-19–related diabetes.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19,