

## Letter to the Editor

**A homozygous mutation of RTEL1 in a child presenting with an apparently isolated natural killer cell deficiency**

To the Editor:

Although the genetic and immunologic basis of human natural killer (NK) cell defects in the context of certain subtypes of severe combined immunodeficiencies is well characterized, it is not as well defined in the setting of other human genetic syndromes associated with specific NK cell deficiency or dysfunction.<sup>1</sup> We previously reported<sup>2</sup> a case of fatal varicella associated with isolated NK lymphocyte deficiency: a 23-month-old girl born from consanguineous Druze parents who developed severe varicella infection with encephalitis. Aside from the decreased number of NK cells and abrogated NK cell cytotoxic activity, her immunologic workup was otherwise normal (including total white cell count, lymphocyte number, T- and B-cell immunophenotyping, total immunoglobulin level, and specific antibody titers). There were no signs of bone marrow failure, skin abnormalities, or other clinical phenotypes. Unfortunately, the child died at the age of 2.5 years. Recently, with the whole-exome sequencing technique, DNA from the patient and family were analyzed. The index case exhibited a homozygous mutation in the regulator of telomere elongation helicase 1 (RTEL1) gene: c.3791G>A; p.R1264H (Fig 1). Her parents and her unaffected sibling are heterozygous carriers of this mutation. The list of variants (heterozygous, homozygous, and compound heterozygous) identified by whole-exome sequencing can be found in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). RTEL1 is an essential helicase that is crucial for telomere maintenance and DNA repair.<sup>3</sup> It is also essential for the disassembly of T loops during DNA replication.<sup>4</sup> Walne et al<sup>5</sup> and Ballew et al<sup>6</sup> reported biallelic mutations of *RTEL1* in a subset of patients with features of Hoyeraal-Hreidarsson syndrome, a variant causing severe dyskeratosis congenita that is characterized by various disorders, including bone marrow failure, intrauterine growth retardation, developmental delay, cerebellar hypoplasia, and usually short telomeres.<sup>6</sup> Severe immunodeficiency is an additional prominent feature of these patients, including NK cell deficiency in most cases.<sup>6</sup> Further studies regarding RTEL1 subdomains function are required to better understand its role in bone marrow maturation. More than 10 mutations have been described so far. Interestingly, the mutation found in our case is a highly prevalent founder mutation in the Ashkenazi Jewish population previously described homozygous in 2 patients with Hoyeraal-Hreidarsson syndrome.<sup>7</sup> To our knowledge, this is the first description of selective NK cell deficiency in association with biallelic RTEL1 mutations because they have been so far described only in a subset of individuals with Hoyeraal-Hreidarsson syndrome with a tightly overlapping phenotype. Our finding of this mutation in RTEL1 further expands the clinical importance of RTEL1 in the immune system, which was not a main feature of this genetic defect in the past. It also points once more the crucial role of whole-exome sequencing in the identification of novel form of primary immunodeficiency, allowing both basic researchers and clinicians to better understand the immune system and to develop better therapeutic options. Unfortunately, because our patient died many years ago, the most advanced phenotyping methods were not

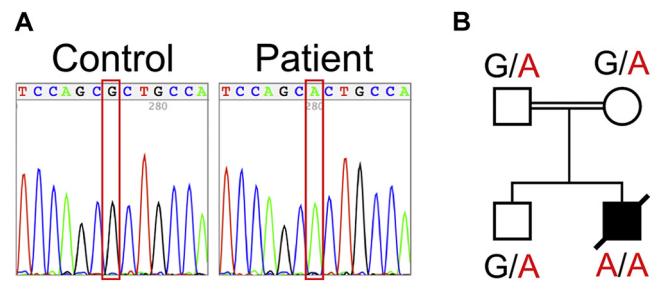


**FIG 1.** A, Sanger sequencing profiles showing the homozygous RTEL1 c.3791G>A mutation in genomic DNA extracted from whole blood of a patient and a wild-type control. B, Familial pedigree of the proband. The proband is indicated in black.

used. Recently, it was shown that CD56<sup>bright</sup> and CD56<sup>dim</sup> NK cell correspond to sequential steps in NK cell differentiation.<sup>8</sup> The investigation of future RTEL1 patient with this phenotype assay, as well as measuring the proliferation and apoptosis of NK cells, might allow one to identify the exact step of differentiation in which the mutation causes its deleterious effect. Our observation is reminiscent of the GATA2 mutation that was identified 25 years after the originally first reported and most cited case with an apparently selective NK deficiency.<sup>9</sup> This patient had since developed many other cytopenias, similar to the other patients with GATA2 defect with common key features of multiple cytopenias due to bone marrow failure.<sup>9</sup> Although in GATA2 deficiency NK cell number and function are impaired,<sup>1</sup> it seems that, in our case, the low NK cell number resulted in the absence of function. The idea that NK deficiency may be the first presentation of at least some inherited forms of bone marrow failure may therefore be of general significance. It is probably not coincidental that another form of isolated NK cell deficiency turned out to be caused by mutations in MCM4, which is involved in DNA replication.<sup>10</sup> NK cells may be highly vulnerable to such genetic lesions. Although NK deficiency cases are rare, the investigation of these rare patients is very important to better understand the developmental pathways and function of NK cells. For example, from the recent reports of MCM4 mutations, we learned about the critical role of the minichromosome maintenance helicase complex in NK cell development.<sup>8</sup> Our observation has important clinical and research implications. As for the practicing immunologist, encountering patients with an apparently isolated NK cell deficiency requires a thorough and recurrent evaluation of the patient global bone marrow function. NK defects may be followed by other cytopenias. Furthermore, one should always search for mutations in genes known to be involved in bone marrow failure, such as RTEL1 and GATA2, in cases of apparently isolated NK cell deficiency.

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