To the editor:

Hypomorphic mutation in TTC7A causes combined immunodeficiency with mild structural intestinal defects

Biallelic TTC7A mutations have recently been shown to cause early-onset inflammatory bowel disease or multiple intestinal atresias accompanied by severe combined immunodeficiency (MIA-SCID), a disease usually fatal in infancy without curative treatment.1-4

We studied a patient (P1) born in the thirty-third gestational week (to healthy Turkish consanguineous parents) who suffered from combined immunodeficiency and chronic diarrhea. Two older siblings had previously died of severe diarrhea. Within the first 2 months, P1 suffered from constipation followed by watery diarrhea without identifiable cause. Radiographic colonography revealed normal rectum diameter but hypoplastic descending and sigmoid colon and dilated small intestine and ascending and transverse colon (Figure 1A). Duodenal (Figure 1B) and colonic biopsies (supplemental Figure 1A, available online on the Blood Web site) showed graft-versus-host disease (GVHD)–like lesions. P1 experienced several pneumonia episodes (including Klebsiella pneumoniae septicaemia) and pyelonephritis. Thymic tissue was hypoplastic (Figure 1C). At 3.5 months, P1 exhibited B lymphopenia and hypogammaglobulinemia (supplemental Table 1) requiring immunoglobulin substitution and trimethoprim/sulfamethoxazole prophylaxis. P1 died at age 15 months without an identified causative agent.

Figure 1. Identification and intestinal histopathology of TTC7A-mutated patients. (A) Radiograph colonography with barium enema in P1 showing decreased diameter of the descending and sigmoid colon, dilated small intestine segments, and dilation of ascending and transverse colon. Rectum diameter was normal. (B) Histologic analysis of duodenal biopsy from P1 suggesting GVHD, including erosion and regeneration of the epithelial surface, focal villous atrophy, degeneration of glands, apoptotic content in crypts, and crypt loss accompanied by increase in lamina propria capillaries. (C) Chest radiograph of hypoplastic thymic tissue in P1. (D) Single nucleotide polymorphism–based mapping of the homozygous chromosomal intervals in P1 (red bars). Arrow indicates the chromosomal position of TTC7A locus within the homozygous interval on chromosome 2. (E) Identification and segregation analysis of the point mutation NM_020458:c.T1037C;p.L346P in the TTC7A gene of P1. Chromatograms display the mutation-containing TTC7A sequence in healthy heterozygous parents, 1 representative heterozygous sibling, and P1 who is homozygous for the mutation. All living siblings of P1 were heterozygous for the identified mutation. (F) Chest radiograph of P2 without visible thymic tissue. (G) Intestinal atresia included distal jejunum and the ligament of Treitz and spanned the entire distal colon. Radiographic colonography of P2 showing a small diameter of the pylorus with low passage of contrast agent. Distal intestine ends in a stoma after surgical excision of atretic tissue with no visible lumen in small bowel and colon. (H) Polymerase chain reaction amplification of indicated TTC7A exons from genomic DNA. (I) In vitro proliferation analysis of CD4+ and CD8+ T cells from patients after TCR stimulation. Proliferation history was monitored by flow cytometry–based detection of intracellular violet proliferation dye (VPD) dilution on day 3 (P1; left) and on day 4 (P2; right) after stimulation. Numbers above histograms indicate cell divisions. T-cell activation status was assessed by detection of CD25 on cell surface. HD, healthy donor.
Given the consanguinity, we assumed an autosomal-recessive inheritance and performed homozygosity mapping (Figure 1D) and exome sequencing. Unexpectedly, we identified a perfectly segregating homozygous missense mutation in TTC7A (NM_020458:c.T1037C; p.L346P) (Figure 1E and supplemental Figure 1B). The substitution of the highly conserved TTC7A_Leu346 residue (supplemental Figure 1D) to TTC7A_Pro346 was predicted damaging to TTC7A function by SIFT and PolyPhen-2 prediction algorithms.

Concomitantly, we investigated another patient (P2) with classical MIA-SCID manifesting in lymphopenia with near-absent CD8+ T cells, hypogammaglobulinemia, undetectable thymic tissue (supplemental Figures 1F, 2, and 3B), and extended intestinal atresia (Figure 1G). Molecular analysis revealed a large genomic deletion comprising TTC7A exons 6 through 8, causing frameshift and premature transcriptional stop codon (NM_020458:c.765_1065del; p.N256Qfs*7) (Figure 1H and supplemental Figure 2B-C).

The pronounced immunodeficiency despite mild structural intestinal defects in P1 prompted us to compare the lymphocyte compartments of P1 and P2. Both showed B-cell lymphopenia and hypogammaglobulinemia (supplemental Table 1) despite the presence of naïve, marginal zone–like and class-switched memory B cells (supplemental Figure 3A). Increased proportion of transitional B cells in P1 indicated a partial developmental block (supplemental Figure 3A) reminiscent of the tonic BCR- or BAFF-signaling defects resulting in decreased B-cell survival and hypogammaglobulinemia.5,6 TTC7A is required for tethering of phosphatidylinositol 4-kinase, catalytic, alpha (PI4KCA) to the plasma membrane,2 which in turn phosphorylates phosphatidylinositol into phosphatidylinositol(4,5)P2, a second messenger in the phospholipase C gamma-2 (PLCγ2) and phosphatidylinositol 3'-kinase (PI3K) signaling cascades downstream of lymphocyte antigen receptors.7

P1 had unremarkable T-cell counts (supplemental Table 1), CD4+ and/or CD8+ T-cell distribution (supplemental Figure 3B), and T-cell repertoire (supplemental Figure 1E). Maternal cells were absent. A significant proportion of CD4+ T cells in P2 but not in P1 expressed CD25 activation marker, possibly as a compensatory mechanism that would otherwise lead to proliferative expansion8 (supplemental Figure 3B). Cell-surface expression of CD44, CD62L, and CD69 and neutrophil counts and oxidative burst were normal (not shown).

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TTC7A deficiency was recently identified as the molecular cause for MIA with or without accompanying SCID.1,3 The hallmark feature of TTC7A deficiency was varying degree of intestinal aberrations. The mildest case presented with intestinal aberrations consisting of bloody diarrhea, apoptotic enterocolitis, and acute GVHD-like symptoms, but no atresias, and the extent of the observed lymphopenia remained unclear.2 P1 had B-lymphopenia, hypogammaglobulinemia, and functional T-cell defects, but intestinal structural aberrations were mild and GVHD-like signs were discrete. Collectively, the clinical spectrum of TTC7A deficiency is considerably more variable than previously appreciated, which should alert physicians to consider TTC7A mutational analysis in (S)CID patients.

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\[ \text{TTC7A}^{\text{Lau346}} \text{-mutant T cells,}^{1,1} \text{underlining the phenotypic variability of TTC7A-mutant immunodeficiency.} \]

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The efficacy of ibrutinib in the treatment of Richter syndrome

Richter syndrome (RS) is defined as the transformation of chronic lymphocytic leukemia (CLL) to a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).1 Traditional anthracycline- or platinum-based chemotherapy is associated with complete response (CR) rates of <20%, and median survival after transformation is <12 months.2 Although stem cell transplantation has been shown to improve outcomes in RS,3 fewer than 15% of patients are able to proceed to transplantation because of primary refractory disease.4

Ibrutinib, a Bruton’s tyrosine kinase inhibitor, has shown remarkable efficacy in relapsed/refractory CLL.5 In a pivotal phase 1B/2 study of ibrutinib in 85 pretreated CLL patients, the overall response rate (ORR) was 71%. Despite this remarkable activity, 7 patients experienced RS at the time of progression.5 A subsequent phase 3 study (n = 391) comparing ibrutinib to ofatumumab in relapsed/refractory CLL found no difference in the rate of transformation to RS between treatment arms.6 Although some have interpreted these results to imply that ibrutinib has no activity in RS, we describe here the successful use of ibrutinib in patients with RS. The Mayo Clinic Institutional Review Board approved this study.

Table 1 shows the characteristics of 4 CLL patients who developed biopsy-proven DLBCL. The median time to transformation from CLL was 4.3 years (range, 3.1 to 11.4 years). In the only patient with available testing to determine clonality (patient 3), the DLBCL was clonally related to the underlying CLL. At the time of transformation, 3 patients were initially treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHEOP) with a suboptimal response. Subsequent regimens in these 3 patients included rituximab, ifosfamide, carboplatin, and etoposide (R-ICE; n = 3 patients; 1 patient had no response). Subsequent regimens in these 3 patients were able to proceed to transplantation because of primary refractory disease and included rituximab, ifosfamide, carboplatin, and etoposide (R-ICE; n = 1 patient; rituximab, cytarabine, cisplatin, and dexamethasone (R-DHAP; n = 1); and rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (R-EPOCH; n = 1) with no response. Because of a lack of efficacious standard treatment options for refractory RS, ibrutinib was initiated in these 3 patients. The fourth patient, with heavily pretreated CLL harboring a 17p deletion, was felt to be a poor candidate for anthracycline-based therapy and began treatment with ibrutinib at the time of RS diagnosis.

The median duration of ibrutinib therapy for these patients was 6.1 months (range, 2.8 to 10.8 months). All patients experienced an improvement in constitutional symptoms. According to the 2007 revised response criteria for malignant lymphoma,7 1 patient had a CR and 2 patients had a partial response. The fourth patient was started on low-dose ibrutinib (140 mg per day) because of concomitant voriconazole use (metabolized through the CYP3A4 pathway); he subsequently died of pulmonary mucormycosis (diagnosed prior to ibrutinib initiation) after 15 weeks of therapy and prior to repeat imaging to allow for response assessment. The patient who achieved a CR is currently receiving ibrutinib (duration of therapy, 134(6):1354-1364.

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References

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