Clinical Immunology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Letter to the Editor

Novel biallelic TRNT1 mutations resulting in sideroblastic anemia, combined B and T cell defects, hypogammaglobulinemia, recurrent infections, hypertrophic cardiomyopathy and developmental delay

Keywords:
TRNT1
B cells
T cells
Hypogammaglobulinemia

To the Editor

Bi-allelic mutations in *TRNT1*, encoding tRNA nucleotidyltransferase 1, were recently described to be responsible for a syndrome of sideroblastic anemia, B-cell immunodeficiency, developmental delay, and periodic fevers (SIDF) [1–2]. To date, 23 patients have been described, underscoring the rarity of this disorder [1–6]. Features of this disease include early-onset, recurrent febrile episodes associated with microcytic anemia, B cell lymphopenia, hypogammaglobulinemia, and developmental delay [1–2]. Additional features may include gastrointestinal disease, seizures, splenomegaly, ataxia, and retinitis pigmentosa [4]. Defects that impair the TRNT1-mediated addition of cytosine and adenosine (CCA) residues to the end to mitochondrial and cytosolic tRNA result in defective mitochondrial translation essential for respiratory chain function [3,7,8]. While TRNT1 is a ubiquitous tRNA nucleotidyl transferase, T cell abnormalities have been reported rarely in SIFD. We report a male patient affected with SIFD harboring novel bi-allelic mutations in *TRNT1* and T and B cell abnormalities.

The proband was born to non-consanguineous parents of Italian descent, with a birth weight of 2.2 kg at 38 weeks of gestation (<3rd percentile). The family history was notable for a brother who died at the age of nine months due to suspected sepsis and hypertrophic cardiomyopathy (Fig. 1A). The proband presented at three months of age with fever and a *Klebsiella oxytoca* urinary tract infection (Fig. 1B). Subsequently, he developed recurrent febrile episodes associated with respiratory or gastrointestinal symptoms; an infectious etiology was identified in some, but not all, of his fevers (Fig. 1B). Cardiac ultrasound demonstrated hypertrophic cardiomyopathy. Testing for metabolic disorders was unremarkable, and a muscle biopsy failed to reveal evidence of a neuromuscular disorder. At ten months of age, the patient was found to have hypogammaglobulinemia, prompting immunoglobulin replacement. At 21 months of age, the patient continued to have failure to thrive, with a weight of 9.17 kg (<3rd percentile) and mild neurodevelopmental delay. Laboratory evaluation was notable for a severe microcytic anemia and bone marrow aspiration revealed sideroblasts without ring formation. The proband had normal numbers of lymphocytes, but reduced percentages of naive and $CD19^{+}CD27^{+}$ memory B cells, markedly elevated terminally differentiated $CD19^{+}$-$CD38^{hi}CD27^{hi}CD21^{lo}$ B cells, and a progressive decrease in plasma cells (Supplemental Table 1). From 21 to 24 months of age, the patient demonstrated a reduction of $CD4^{+}$ T cells, although T cell proliferation to mitogens was intact (Supplemental Table 1). Both thymic and bone marrow B cell output were reduced in the index patients, indicated by severely decreased T cell receptor excision circles (TRECS) and kappa-deleting recombination excision circles (KRECS), respectively (Supplemental Table 1), indicating either defective T and B cell development or impaired exit of mature lymphocytes from central lymphoid organs. The patient had decreased levels of IgG despite intravenous immunoglobulins (Supplemental Table 1). During follow-up at a regional hospital, the patient continued to have more frequent febrile episodes, and one-dose steroid treatment was started at the age of 22 months for such episodes, as treatment of a presumed auto-inflammatory disorder. The patient presented at the regional hospital at age 26 months with a sepsis-like episode complicated by multi-organ failure and died shortly thereafter; no infectious agent was identified.

Whole exome sequencing (WES) of the patient revealed two heterozygous mutations in *TRNT1* (c.565 T>C, p.Ile155Thr; c.608 G>A, p.Arg203Lys) (Fig. 1C). Each parent harbored one of the *TRNT1* mutations, indicating bi-allelic inheritance in the proband. The PHRED-like scaled C-score of the $TRNT1^{I155T}$ and the $TRNT1^{R203K}$ are 28.4 and 29.8, respectively, indicating that these variants are in the most deleterious 0.1% of all variants in the human genome [9]. The $TRNT1^{I155T}$ mutation has not been reported in the EXAC or 1000 Genomes databases, and the $TRNT1^{R203K}$ has a minor allelic frequency of 8.6×10^{-6} in the EXAC database, and neither has been reported in patients with SIFD. Both the I155 and the R203 residues are within the enzyme's active site. Modeling the I155T mutation suggests that replacing the hydrophobic I155 with a hydrophilic threonine within a pocket of hydrophobic residues will may affect substrate binding at this region (Fig. 1D). The model of $TRNT1^{R203K}$ indicates that the mutant lysine residue is approximately 0.3 Å further from K244 than R203, potentially weakening the interaction between neighboring alpha-helices (Fig. 1D).

Here, we report two novel mutations in *TRNT1* in a patient with a clinical phenotype consistent with SIFD, including recurrent fevers, sideroblastic anemia, hypogammaglobinemia, and developmental delay. While T and B cell lymphopenia have been reported in the only surviving adult patient with SIFD [10], to our knowledge, the reduction in TRECs and/or KRECs has not been previously reported in SIFD. The measurement of TRECs is increasingly available worldwide due to the feasibility and low cost of this test [11], indicating that this test may serve as screening test for this clinically heterogeneous disease. Since hematopoietic stem cell transplantation has been shown to be curative in one case [1,2], early diagnosis of this disorder is critical. Future studies

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https://doi.org/10.1016/j.clim.2017.11.008

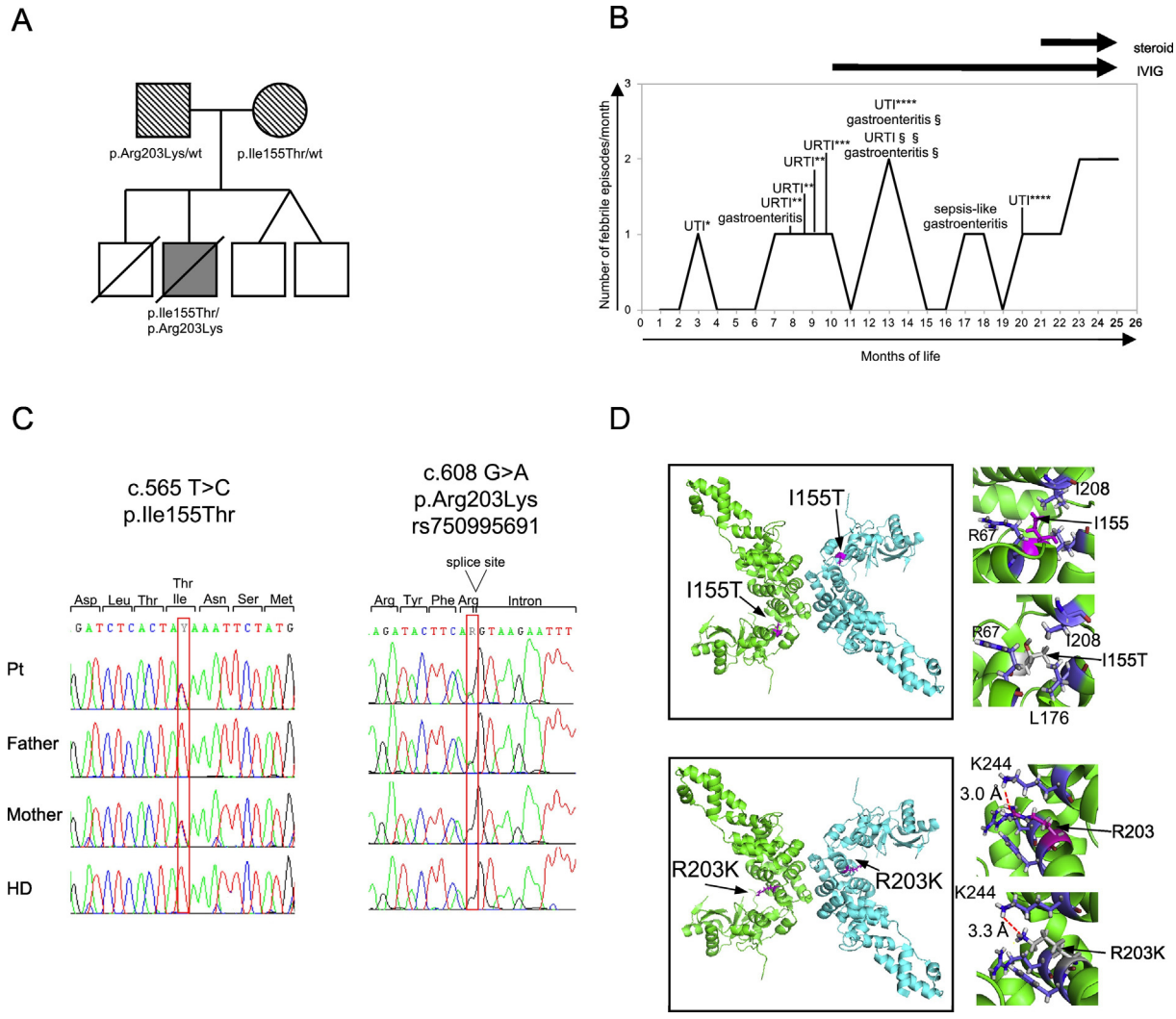

Fig. 1. Clinical, immunological and genetic findings of the index patient. A. Pedigree depicting the healthy parents (striped box and circle) and the affected patient (grey box). B. Graphical representation of the proband's febrile episodes UTI: urinary tract infection; URTI: upper respiratory tract infection; * Klebsiella oxytoca; ** Rhinovirus; ***Moraxella chatarralis; **** *Escherichia coli*; § Rotavirus; §§ VRS, Metapneumovirus, Bocavirus C. Chromatographs of the *TRNT1* mutations in the index patient, healthy parents, and healthy control. D. Ribbon diagrams of the TRNT1^{I155T} and the TRNT1^{R203K} mutations, based on mitochondrial CCA-adding tRNA Nucleotidyltransferase.

are needed to determine the widespread applicability of this finding as a marker for SIFD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2017.11.008.

Funding

The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement no 201549 (EURO-PADnet HEALTH-F2-2008-201549) and from the Italian Ministeria Grantl GR-2010-2315762. The research leading to these results also received funding from the "Fondazione C. Golgi", Brescia, Italy and the Jeffrey Modell Foundation.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the patients, the patients' families and the nurses for all their efforts.

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17 November 2017
Available online xxxx

Please cite this article as: V. Lougaris, et al., Clin. Immunol. (2017), https://doi.org/10.1016/j.clim.2017.11.008