Journal of Microbiology, Immunology and Infection (2019) 52, 504—506

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Correspondence

Mycobacterium abscessus infection in a boy with X-linked anhidrotic ectodermal dysplasia, immunodeficiency

KEYWORDS
IKBKG;
Mycobacterium;
NEMO;
Primary immunodeficiency;
X-linked anhidrotic ectodermal dysplasia;
Immunodeficiency (EDA-ID)

Dear Editor,

X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID, OMIM 300291) is characterized by the abnormal development of ectoderm and susceptibility to infection. It is due to *nuclear factor-kappa B essential modulator (NEMO)*, also known as *inhibitor of nuclear factor kappa B kinase subunit gamma (IKBKG)*, hypomorphic mutations which reduce nuclear factor-kappa B (NF-κB) activation. Most mothers with incontinentia pigmenti (IP) have heterozygous *NEMO/IKBKG* loss of function mutation, a skewed X-inactivation and male fetuses lethality during pregnancy.[1]

A male infant with features of sparse hair and thin skin had suffered from recurrent infections since age one month, including *Enterobacter cloacae* and *Staphylococcus aureus*. (Figure S1). Patient's mother, grandmother and aunts had IP (Fig. 1). Immunology work up at age one month showed decreased lymphocyte and $CD3^+$ T counts, low levels of immunoglobulin M and decreased lymphocytes proliferation response (Supplementary Table). He received regular intravenous immunoglobulin and trimethoprim-sulfamethoxazole prophylaxis. *Mycobacterium abscessus* blood stream infection with septic emboli over left foot and scalp developed at age six months (Supplementary Figure S1). Infection was controlled by intravenous amikacin, imipenem, linezolid and subcutaneous recombinant interferon-γ (Imukin®). He died at one year old for *Klebsiella pneumoniae* brain abscess *and Burkholderia cepacia sepsis*.

A hemizygous c.520_523dupCAGG mutation on *NEMO/IKBKG* gene (NM_003639.3) was identified, which affects our patient, his older brother, mother, aunt and grandmother. RT-PCR of the patient showed two PCR amplicons (Fig. 1). The full-length amplicon confirmed a duplication of CAGG in exon 5 (p.A174Qfs*15). This mNRA with a premature stop codon might undergo nonsense mediated decay and result in a loss of function. The shorter amplicon showed skipping of exon 5 which is predicted to cause a truncated protein. Similar abnormal splice mutation (skipping exon 4, 5, 6) has been shown to cause a partial abolition of NF-κB in patients with XL-EDA-ID by lacking coiled-coil motif responsible for the interaction of the NEMO with IκB kinase (IKK)-1 and IKK-2 subunits.[2]

The c.520_523dupCAGG *NEMO/IKBKG* mutation is the second common mutation in the IP families in Taiwan.[3] Only four *NEMO/IKBKG* mutations of XL-EDA-ID son and IP mother have ever been reported, which affect zinc finger domain on exon 10 that is required for NF-κB activation in response to pro-inflammatory cytokines and cause severe immunodeficiency.[4]

The ability of *M. bovis* BCG to stimulate the release of interleukin-12 and *M. bovis* BCG clearance by PBMCs were significantly decreased in our patient, compared to controls (Supplementary Figure S2 and S3). A broad spectrum of innate and adaptive immunodeficiencies are associated with hypomorphic *NEMO/IKBKG* mutation and an impaired NF-κB activation. IL-12 production defects in monocytes have been shown to be T-cell dependent, which results in defective IFN- γ secretion by T cells and Mycobacterium susceptibility.[4]

Non-tuberculosis Mycobacteria (NTM) infections are common, with insidious onset but often disseminating

https://doi.org/10.1016/j.jmii.2018.04.009

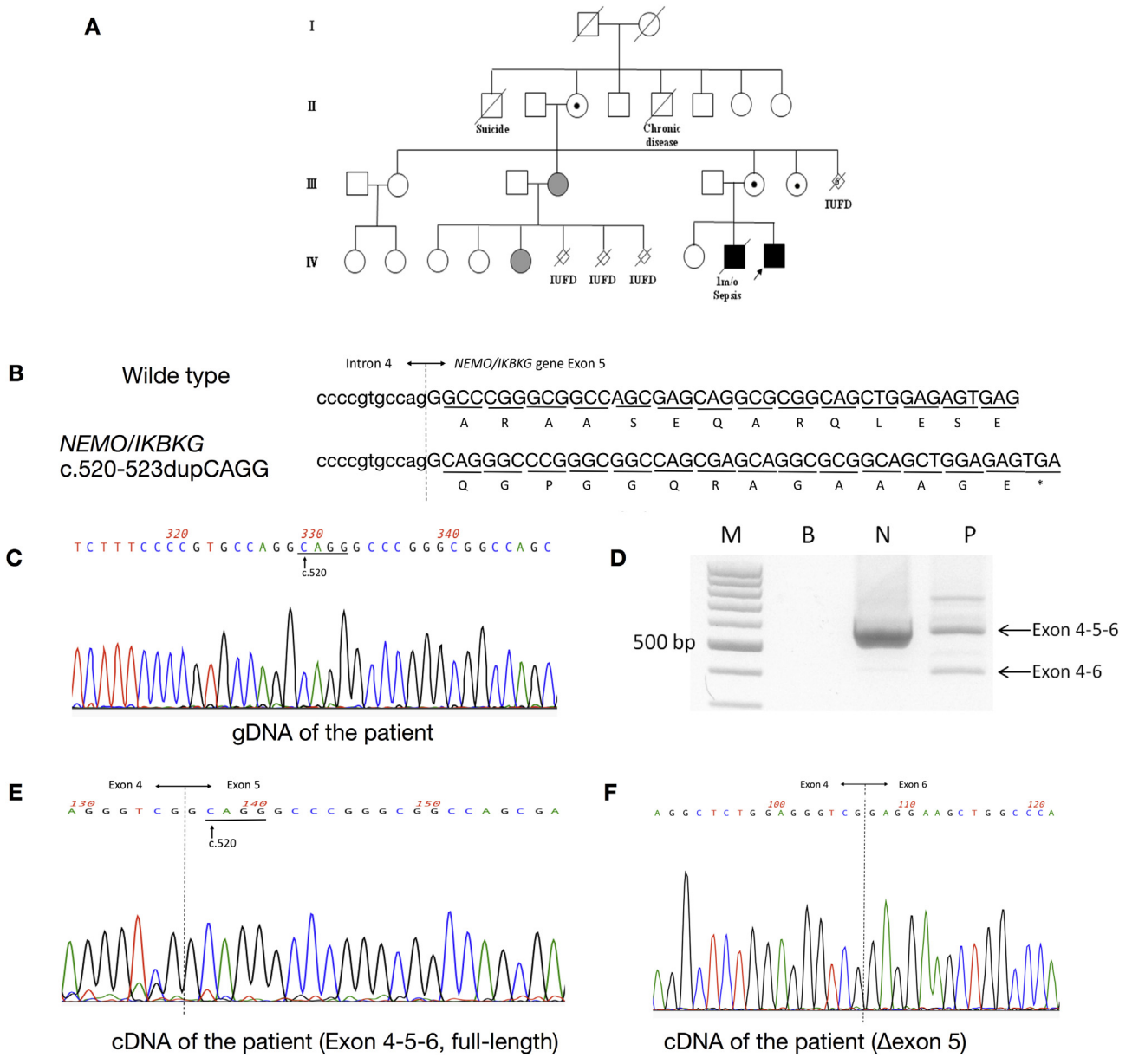

Figure 1. Pedigree and *NEMO/IKBKG* genotypes of the patient with X-linked EDA-ID. (A) The pedigree of the family is illustrated. Male patients in black squares carried a hemizygous c.520_523dupCAGG *NEMO/IKBKG* mutation and XL-EDA-ID. The proband is indicated by an arrow. Female with a heterozygous c.520_523dupCAGG *NEMO/IKBKG* mutation and incontinentia pigmenti (IP) are represented by black dots. Female patients in grey circles were diagnosed as IP clinically without genetic testing. Abbreviation: intrauterine fetal deaths, IUFD. (B) The DNA and corresponding amino acids sequences of the wild-type and *NEMO/IKBKG* c.520_523dupCAGG mutation on exon 5 (p.A174QfsX15) are shown. (C) Genomic DNA sequencing of *NEMO/IKBKG* gene on the patient showed a hemizygous c.520_523dupCAGG mutation. (D) Aberrant PCR amplicons detected in the patient by gel electrophoresis. B, blank; M, 100 bp marker; N, normal control; P, patient. (E) Sequencing of the full-length cDNA of the patient showed a duplication of CAGG in exon 5. (F) Sequencing of the shorter amplicon of the patient showed exon 5 skipping without disrupting open reading frame after exon 6.

and carry a poor prognosis in XL-EDA-ID. There are few reports of successful treatment using recombinant IFN-γ for disseminated NTM infection in patients with XL-EDA-ID. Early diagnosis and hematopoietic stem cells transplant for severe phenotypes are important for a better outcome.[5]

Acknowledgements

This study was funded by grants from the National Taiwan University Hospital (104-2850) and from National Science Council (NSC 98-2314-B002017-MY3).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmii.2018.04.009.

References

1. Zonana J, Elder ME, Schneider LC, Orlow SJ, Moss C, Golabi M, et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet* 2000;**67**:1555–62.
2. Orstavik KH, Kristiansen M, Knudsen GP, Storhaug K, Vege A, Eiklid K, et al. Novel splicing mutation in the NEMO (IKK-gamma) gene with severe immunodeficiency and heterogeneity of X-chromosome inactivation. *Am J Med Genet A* 2006;**140**:31–9.
3. Lee NC, Huang CH, Hwu WL, Chien YH, Chang YY, Chen CH, et al. Pseudogene-derived IKBKG gene mutations in incontinentia pigmenti. *Clin Genet* 2009;**76**:417–9.
4. Fusco F, Pescatore A, Conte MI, Mirabelli P, Paciolla M, Esposito E, et al. EDA-ID and IP, two faces of the same coin: how the same IKBKG/NEMO mutation affecting the NF-kappaB pathway can cause immunodeficiency and/or inflammation. *Int Rev Immunol* 2015;**34**:445–59.
5. Hanson EP, Monaco-Shawver L, Solt LA, Madge LA, Banerjee PP, May MJ, et al. Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. *J Allergy Clin Immunol* 2008;**122**:1169–77. e16.

Hsin-Hui Yu
Tien-Chuan Hu
Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

Ni-Chung Lee
Yin-Hsiu Chien
Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan

Yao-Hsu Yang
Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

Wuh-Liang Hwu
Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan

Bor-Luen Chiang*
Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan

*Corresponding author. Department of Medical Research, National Taiwan University Hospital, No. 7 Zhongshan S. Rd, Zhongzheng Dist., Taipei, 100, Taiwan. Fax: +886 2 2311 9087.
E-mail address: gicmbor@ntu.edu.tw (B.-L. Chiang)

6 April 2018
Available online 31 August 2018