



# A Novel Kindred with MyD88 Deficiency

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To the Editor,

Monogenic deficiency of myeloid differentiation primary response gene 88 (MyD88), like interleukin (IL)-1 receptor-associated kinase 4 (IRAK4) deficiency, results in impairment of the canonical Toll-like receptor (TLR) and IL-1 receptor (IL-1R) signaling pathways [1–4]. Both MyD88 and IRAK-4 deficiency manifest as increased susceptibility to invasive infection as well as deep tissue (mostly tonsillitis) and skin infections with a narrow range of pathogens, typically with *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Invasive infections with viruses, mycobacteria, parasites, and fungi have not been described in human MyD88 deficiency, although one patient had Bacillus Calmette-Guérin (BCG) adenitis after vaccination with BCG [2, 3, 5]. Early childhood mortality from infection is as high as 50% [2], but clinical suspicion and the prompt start of antibiotic prophylaxis and immunoglobulin (Ig) substitution therapy can improve survival beyond the teenage years, when the incidence of invasive infection decreases markedly, potentially due to compensation by a mature adaptive immune system [2, 3]. If left untreated, IRAK-4 deficiency and MyD88 deficiency can also result in irreversible organ damage from recurrent invasive and deep tissue infection (Supplementary ref. E1). We here present a patient carrying a homozygous deleterious mutation in *MYD88*, who experienced viral infections and

recurrent mucocutaneous candidiasis in addition to the classical invasive and superficial pyogenic infections.

## Case Description

A 4-year-old boy suffering from recurrent invasive infections was referred to our center for immunological evaluation. He was the first child of non-consanguineous Romanian parents, descendants from the same small village. His family history was remarkable for a maternal cousin who suffered from meningitis at the age of 4 months; two cousins of his mother who succumbed at age 4 years and 9 years of pneumonia and meningitis, respectively; the son of a cousin of his paternal grandfather who died of fulminant meningitis at the age of 3 years; a paternal great-great-uncle who suffered from meningitis; and notions of consanguinity ascending five generations on the paternal side. The family pedigree is summarized in Fig. 1A. Born at 38 weeks and 4 days after an uncomplicated pregnancy, the patient presented with omphalitis and delayed separation of the umbilical cord 4 weeks after birth. At the age of 4 months, he suffered from a skin abscess on his chest and peritonitis caused by *P. aeruginosa*, with gut perforation requiring resection and ileostomy. At 18 months, he suffered from a basilar pneumonitis. At the age of 3 years, he was admitted for bilateral pneumonia with cough, moderate respiratory distress and high fever for 3 days (Fig. 1B). His laboratory analyses were normal except for elevated CRP (118 mg/L) and transient neutropenia (nadir 1100 neutrophils/ $\mu$ L, 1 week after the onset of symptoms); Coronavirus NL63 and Influenza A virus were detected in the respiratory fluids by culture and/or PCR. He received oxygen therapy for 2 days and promptly responded to treatment with ceftriaxone and oseltamivir. A month later he was assessed again for cellulitis and a cutaneous abscess caused by *S. aureus*. Between these episodes, he reportedly suffered from recurrent throat infections and cough without fever, multiple warts (*verruca vulgaris*) on the face that were surgically removed, and various episodes of oral candidiasis outside the context of antibiotic treatment. No further

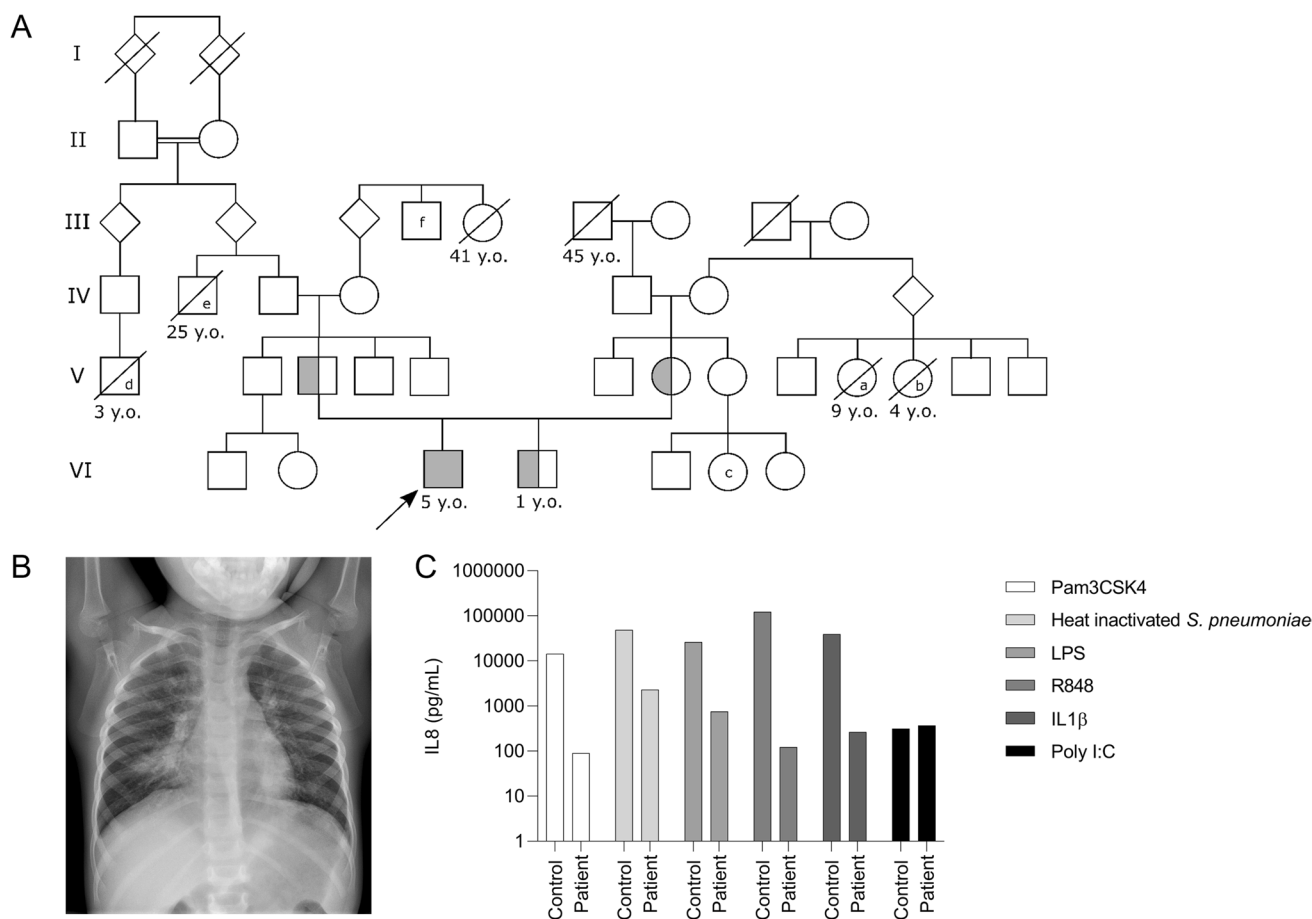
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**Fig. 1** **A** Family tree showing consanguinity in the II generation on the paternal side. Squares indicate males, circles females, and rhombuses unknown gender. Fully shadowed symbols represent homozygosity for the MyD88 mutation E66del, half-shadowed symbols heterozygosity. The index patient is indicated with an arrow. Remarkable family history: (a) died of meningitis, (b) died of pneumonia, (c) suffered from meningitis aged 4 months, (d) died from fulminant meningitis, (e) died from vasculitis, (f) suffered from meningitis. **B**

episodes of candidiasis were observed after age 3.5 years. He received the measles-mumps-rubella vaccination without adverse effects, but did not receive the varicella-zoster vaccine and to date did not suffer from chickenpox. At the age of 4 years, he was admitted with fever, vomiting, lethargy, and positive meningeal signs upon examination. His laboratory tests revealed elevated C reactive protein (CRP 52 mg/dL, raising to 201 mg/L after 24 h), relative neutrophilia (7500/ $\mu$ L, 87.3% of the white blood cells), lymphopenia (820/ $\mu$ L), and mild thrombocytopenia (72,000/ $\mu$ L). Analyses of the cerebrospinal fluid (CSF) showed 976 WBC/ $\mu$ L, 100 red blood cells/ $\mu$ L, increased proteins (1 mg/ml), markedly decreased glucose (1.7 mg/dL with a blood glucose of 161 mg/dL), and the CSF culture was positive for *S. pneumoniae*. He was successfully treated with an intravenous course of ceftriaxone and recovered without sequelae.

Chest X-ray of the patient at the age of 3 years showing bilateral lung infiltrates during Coronavirus NL63 and Influenza A virus pneumonia. **C** Production of IL-8 is impaired in the patient's cells after 24-h stimulation with several TLR ligands. Basal levels from the unstimulated condition have been subtracted from the represent results. Pam3CSK4: TLR1/2 agonist; heat-inactivated *S. pneumoniae*: TLR2 agonist; LPS: lipopolysaccharide, TLR4 agonist; R848: resiquimod, TLR7/8 agonist; IL-1 $\beta$ : IL-1R ligand; poly I:C: TLR3 agonist

Given the significant infectious history, he was referred for an immunological workup. The analyses revealed normal blood count, normal lymphocyte subpopulations, normal complement activity via classic and alternative pathway, IgG3 subclass deficiency, partial IgA deficiency with normal total IgG and IgM, normal neutrophil oxidative burst and adhesion, moderate iron deficiency, and elevated vitamin B12 (results are summarized in Supplementary Table S1). Inherited congenital asplenia was ruled out by abdominal ultrasound and absence of Howell-Jolly bodies on peripheral blood smear. In vitro cytokine production by the patient's peripheral blood mononuclear cells (PBMCs) was assessed by measuring IL-8 following stimulation of TLR1, 2, 3, 4, 7/8, and IL-1R (Fig. 1C, methods are described in the Supplementary material). IL-8 secretion was severely impaired in the patient compared to the control for all tested stimuli except for PolyI:C, which is MyD88 independent. Flow

cytometry showed normal distribution of T and B cell subpopulations with lower proportion of monocytes and NK cells compared to healthy controls. Effector T cell, T follicular helper, and T helper 17 (Th17) frequencies were lower in the patient than in a healthy control (Supplementary Fig. S1) (E2). A targeted primary immunodeficiency panel identified a homozygous mutation in *MYD88*, c.196-198del-GGA (p.E66del, previously known as E52del), previously reported as pathogenic and causing extreme reduction of protein expression [1] (E3). Whole exome sequencing did not reveal any other variants compatible with the phenotype. The patient was in good clinical condition and did not experience recurrent infections after the start of Ig replacement therapy and antibiotic prophylaxis with amoxicillin until the age of 5 years, when he was admitted to a hospital with COVID-19 pneumonia requiring oxygen therapy for 4 days. His viral load on nasopharyngeal swab was high ( $> 10^7$  copies/mL) and a chest CT scan showed diffuse ground-glass opacities and infiltrates involving 50% of the lung parenchyma on estimate. He was treated empirically with antibiotics and recovered clinically from the infection within 10 days. His SARS-CoV-2 PCR became negative a month after admission.

## Discussion

We report the clinical and immunological features of a patient of Romanian origin with MyD88 deficiency due to the homozygous mutation E66del. Contrary to mouse models, invasive viral, fungal, or parasitic infections have not been described in patients with IRAK4 or MyD88 deficiency, although a child with biallelic mutations in both *MYD88* and *CARD9* was reported with persistent Epstein-Barr virus (EBV) viremia [1–3, 5] (E3, E4). Eleven kindreds with MyD88 deficiency have been described so far, all except two from European countries (Italy, Spain, France, Portugal, Turkey, Serbia, USA, Oman). Homozygous E66del has been reported in seven of them, of which at least three are of Romani descent (traditional itinerant ethnic group originating from northern India and living mostly dispersed in Europe and the Americas) [1, 2] (E3, E4). A founder effect could thus explain the high prevalence of E66del among the affected patients and the scattering of the variant across Europe. Unfortunately, we were not able to sequence all family members.

The current patient manifested influenza and coronavirus NL63 pneumonia requiring hospitalization and antiviral treatment at the age of 3 years, COVID-19 pneumonia requiring oxygen therapy at the age of 5 years, and reportedly suffered from recurrent oral candidiasis past the age of 1 year, beyond the predominant phenotype of invasive and superficial pyogenic infections typical of MyD88 deficiency.

No defect in Th17 number or any known pathogenic variants underlying chronic mucocutaneous candidiasis or severe viral infection could be identified. Recently, three siblings aged 13 to 16 years with MyD88 deficiency were reported to have been admitted to the ICU for COVID-19 pneumonia, two of them with a severe form requiring intubation and ventilation in one case and extracorporeal membrane oxygenation (ECMO) in the other, and two additional adolescent MyD88-deficient siblings were admitted with COVID-19 and interstitial pneumonia (Supplementary Table S2, E5, E6). The two children requiring intubation or ECMO were treated with tocilizumab, remdesivir, and hydroxychloroquine, and all the patients survived. Interestingly, these patients and the patient reported here all suffered from viral pneumonia and not from the multi-system inflammatory syndrome, which is more common among children.

However, whether the observation of viral and fungal infections is coincidental or intrinsically due to the underlying MyD88 defect, will need to be verified in future prospective studies. The main message of this study is that any child presenting with invasive pneumococcal disease or invasive/cutaneous infections with *S. pneumoniae*, *S. aureus* or *P. aeruginosa* should alert the physician to the possibility of an underlying inborn error of the TIR pathway and prompt the initiation of antimicrobial prophylaxis, prior to identification of the genetic defect, as a life-saving intervention in the patient.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10875-022-01240-6>.

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**Author Contribution** GB and IM were the principal investigators and drafted the manuscript; LM performed experimental work and genetic analysis; AC performed genetic analysis; AD, IM were involved in the clinical care. All the authors revised and corrected the manuscript.

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**Data Availability** Not applicable.

**Code Availability** Not applicable.

## Declarations

**Ethics Approval** This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee for Research of Leuven University Hospitals.

**Consent to Participate** The subject has given consent to participate.

**Consent for Publication** The subject has given consent for findings based on his samples and history to be published.

**Conflict of Interest** IM receives the CSL-Behring Chair of Primary Immunodeficiencies in Children, paid to Institution.

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\*Further references are in the supplementary material.