

Letter to the Editor

Myeloid differentiation primary response gene 88 (MyD88) deficiency in a large kindred*To the Editor:*

Myeloid differentiation primary response gene 88 (MyD88) deficiency is a disorder of the innate immune system. Only one study of the human deficiency has been published, and the disorder is believed to be among the rarer primary immune deficiencies.¹ We studied a large consanguineous kindred after identifying the proband after *Pseudomonas* species-induced meningitis. Our cases differ from the previously published series in that the protein was absent, infections began in the neonatal period, and *Pseudomonas* species infections dominated the clinical picture. Seven family members with confirmed MyD88 deficiency were identified, and another 2 are suspected to have had MyD88 deficiency. This kindred extends the spectrum of what is known regarding MyD88 deficiency. Recognition of this disorder or the related IL-1 receptor-associated kinase 4 (IRAK-4) deficiency is important because children present early in infancy and do not have a febrile response to infection, leading to delayed diagnosis of infection and serious consequences.²

The proband (B1) presented at 8 days of age with disseminated *Pseudomonas aeruginosa*. This subsequently evolved into endophthalmitis and meningitis. He did not have a fever or an increased white cell count at presentation. He was started on intravenous immunoglobulin (IVIG) on the basis of a family history strongly suggestive of immune deficiency and had only 1 urinary tract infection subsequently. He is now 2 years old. After resolution of his

endophthalmitis, he had extensive testing for an immune deficiency, including measures of reactive oxygen production, T-cell proliferation, immunoglobulin production, and function. The single notable finding was a Toll-like receptor (TLR) assay (ARUP Laboratories, Salt Lake City, Utah) that was unresponsive to most stimuli. TNF- α , IL-6, and IL-1 β levels are measured after culture with various TLR ligands in this assay. The patient's responses were less than 10% of the lower limit of the control range. Subsequently, a Western blot demonstrated absent MyD88, and sequencing revealed a stop codon in exon 1 (Fig 1).

Three of the parents of this kindred are siblings. Two married their first cousins. The third married her father's first cousin. The proband's older siblings had also presented with infections in early infancy. To distinguish the family units, they are labeled A, B, and C in Table I. Two of the proband's siblings had similar histories. One had a *Pseudomonas* species-induced abscess and ecthyma at 5 months of age. This patient also had pneumonia at 1 year of age and then a streptococcal bacteremia at 3 years of age. Another sibling had urinary tract infections, *Pseudomonas* species-induced abscesses, group A streptococcal bacteremia, and a peritonsillar abscess. She likewise did not demonstrate typical febrile responses to infection or mount an increased white cell count in response to infection. She carries the same mutation as her brother. These patients have been maintained on IVIG since infancy, with apparent improvement in the infection pattern.

Other family members with different parents also had evidence of immunodeficiency. Patient A4 had group B streptococcal meningitis at 17 days of age. Three pseudomonal skin infections

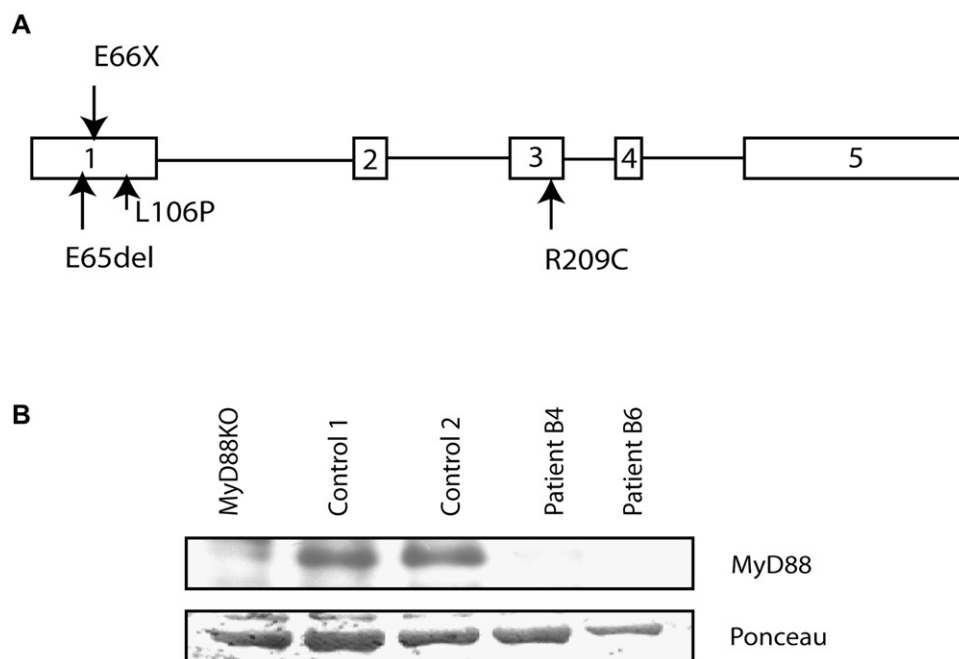


FIG 1. Identification of MyD88 deficiency. **A**, The sequencing of the *MYD88* gene revealed a homozygous stop codon in exon 1 (E66X). The gene was fully sequenced in both directions from the proband. Mutations from a previous report are shown below the gene for reference 1. The numbering has been adjusted from the original report to correspond to the dominant ATG initiation, which is consistent with GenBank. **B**, A Western blot was performed for MyD88. Selected family members are shown. The lanes marked B4 and B6 correspond to family members B4 and B6, respectively, in Table I.

TABLE I. Clinical characteristics

Kindred designation		Diagnosis and age	Response to TLR stimulation
Mother A		Healthy	Normal
Father A		Healthy	Normal
A1		Healthy	Normal
A2		Healthy	Normal
A3		Healthy	Normal
A4		Group B <i>Streptococcus</i>–induced meningitis, 17 d <i>Pseudomonas aeruginosa</i>–induced ecthyma, 5 mo <i>Pseudomonas aeruginosa</i> debridement, 6 mo <i>Pseudomonas aeruginosa</i> wound flap, 7 mo <i>Staphylococcus aureus</i>–induced bacteremia (line), 10 mo <i>Acinetobacter baumannii</i> (line), 16 mo <i>Streptococcus pneumoniae</i>–induced cellulitis/bacteremia, 2 y Adenitis, 4 y Submandibular abscess, 5 y	Absent
A5		Viral gastroenteritis, 6 mo	Normal
A6		Healthy	Normal
Mother B		Healthy	Normal
Father B		Healthy	Absent
B1		<i>Pseudomonas aeruginosa</i> (disseminated), 8 d <i>Pseudomonas aeruginosa</i>–induced endophthalmitis, 13 d <i>Staphylococcus similans</i>–induced urinary tract infection, 10 mo	Absent
B2		Healthy	Normal
B4		<i>Pseudomonas aeruginosa</i>–induced abscess, 5 mo <i>Pseudomonas aeruginosa</i>–induced ecthyma/bacteremia, 6 mo Pneumonia/bronchiolitis, 13 mo Nutritionally deficient <i>Streptococcus/Corynebacterium</i> species, 32 mo	Absent
B6		<i>Escherichia coli</i>–induced urinary tract infection, 2 and 4 mo <i>Pseudomonas aeruginosa</i>–induced abscess, 16 mo Group A <i>Streptococcus</i>–induced abscess/bacteremia, 3 y	Absent
Mother C		Healthy	Normal
Father C		Healthy	Absent
C1		<i>Streptococcus pneumoniae</i> –induced meningitis	Deceased
C2		<i>Streptococcus pneumoniae</i> –induced meningitis	Deceased
C3		Periorbital cellulitis, 2 y	Normal
C4		Viral syndrome, 2 mo	Normal
C5		<i>Staphylococcus aureus</i>–induced adenitis/bacteremia, 6 mo Cellulitis, 16 mo Cellulitis, 20 mo	Absent
C6		Healthy	Normal

Confirmed MyD88-deficient patients are shown in boldface.

occurred before 1 year of age, and *Streptococcus pneumoniae*–induced cellulitis and bacteremia occurred at 2 years of age. Two episodes of adenitis occurred at 4 and 5 years of age. Patient C5 had staphylococcal bacteremia at 6 months of age and painful hand and arm swelling without evidence of erythema or induration at 16 months of age. At 20 months of age, cellulitis of the hand and arm had notable erythema and induration. Both patients had been maintained on IVIG since infancy.

Two deceased family members (C1 and C2) are presumed to have had MyD88 deficiency based on the clinical picture. Both died in early infancy of *S pneumoniae*–induced meningitis. Two adult family members (fathers B and C) lack TLR responses but have no past medical history of life-threatening bacterial infections either can recall. It is unclear how these subjects survived their early childhood, unless they had infectious events they do not remember; however, asymptomatic IRAK-4–deficient subjects have been described.

TLR pathway defects are a unique set of primary immunodeficiencies in which cytokine expression is impaired because of

poor nuclear factor κ B activation.³ The 2 major immune deficiencies in this pathway are IRAK-4 and MyD88 deficiency.⁴ MyD88 deficiency has been described as a mimic of IRAK-4 deficiency, which is associated with streptococcal, staphylococcal, and pseudomonal infections predominantly. IRAK-4 deficiency is more strongly associated with *Streptococcus* and *Staphylococcus* species than *Pseudomonas* species but shares the minimal febrile response to infection with MyD88 deficiency.^{5,6} This extended kindred had a very pronounced history of systemic and cutaneous pseudomonal infections. Whether this relates to the unique nature of the kindred, the specific mutation, or undefined aspects in the environment is not known. Several members of this kindred were started on IVIG replacement therapy before a full understanding of their immune deficiency. They appeared to have had a clinical response, and there are theoretical reasons to believe that IVIG could be of benefit in patients with MyD88 and IRAK-4 deficiency.⁷ For example, patients appear to do better with age, suggesting that a mature adaptive immune system can compensate for this defect in the innate immune system.

A second reason is the demonstration of a defect in functional antibody production in MyD88-deficient mice.⁸ However, this kindred extends our knowledge of MyD88 deficiency and highlights the need for awareness when treating infants with streptococcal, staphylococcal, and pseudomonal infections, particularly when the infant has an atypical host response to infection.

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