

Recurrent *Mycobacterium avium* Osteomyelitis Associated With a Novel Dominant Interferon Gamma Receptor Mutation

Anthony Villella, MD*; Capucine Picard, MD‡; Emmanuelle Jouanguy, PhD‡; Stéphanie Dupuis‡; Stacey Popko, MDS; Nazha Abughali, MD||; Howard Meyerson, MD*; Jean-Laurent Casanova, MD, PhD‡; and Robert W. Hostoffer, DO¶

ABSTRACT. *Mycobacterium avium* causes infections in immunocompromised individuals. Recurrent infection with this organism has been associated with a deletion at the 818 residue of the interferon- γ receptor (IFN- γ R). This mutation produces a truncated receptor without an intracytoplasmic tail, resulting in diminished signaling. We describe a substitution at the 832 residue of the IFN- γ R causing a similar truncated receptor in a 7-year-old girl with recurrent *M avium* osteomyelitis. *Pediatrics* 2001;107(4). URL: <http://www.pediatrics.org/cgi/content/full/107/4/e47>; *Mycobacterium avium*, interferon gamma receptor mutation.

ABBREVIATIONS. MAC, *Mycobacterium avium* complex; IFN- γ R, interferon- γ receptor; Ig, immunoglobulin; STAT1, Signal Transducers and Activators of Transcription 1.

M*ycobacterium avium* complex (MAC) is the name given to *M avium* and *Mycobacterium intracellulare*—2 nearly indistinguishable organisms classified as atypical mycobacteria or nontuberculous mycobacteria.¹ These organisms, like *Mycobacterium tuberculosis*, are aerobic, pleomorphic, weakly Gram-positive bacilli that are acid-fast positive.² MAC is a minimally virulent, intracellular pathogen and is ubiquitous in soil, water, vegetables, and animals.³ It is rarely associated with disease in normal hosts other than localized lymphadenitis in childhood.⁴ Systemic infections and infections of the bone by this organism are typically found in immunocompromised hosts, such as patients infected with the human immunodeficiency virus.²⁻⁵ Recurrent infections with this and other similar intracellular organisms have recently been described with rare genetic defects of the interferon- γ receptor (IFN- γ R).⁶⁻¹³ Various mutations have been described that result in either complete or partial deficiency of either of the 2 chains of the receptor showing a recessive or dominant inheritance.

From the *University Hospitals, Case Western Reserve University, Cleveland, Ohio; ‡Laboratory of Human Genetics of Infectious Diseases, Necker-Enfants Malades Medical School, Paris, France; §Private practice, Miami, Florida; ||Metro Health Center, Cleveland, Ohio; and ¶Private practice, South Euclid, Ohio.

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Address correspondence to Robert W. Hostoffer, DO, FACOP, FAAP, University Suburban Health Center, Suite 231, 1611 South Green Rd, South Euclid, OH 44121. E-mail: k.hostoffer@worldnet.att.net

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Jouanguy et al⁸ described a series of patients with recurrent or disseminated mycobacterial infections with a single small deletion at the 818 residue of the IFN- γ R1, resulting in a reading frame shift and a subsequent downstream stop codon. Translation of the gene product resulted in a truncated receptor. We describe a patient with recurrent *M avium* osteomyelitis with a truncated IFN- γ R1 secondary to a unique and not previously described nucleotide substitution at position 832.

CASE REPORT

A 7-year-old white female presented with left wrist pain and swelling. Radiographic studies showed a destructive lesion in the midshaft of the left radius. Bone scan showed increased reactivity in the left radius, with additional activity in the right femur. Open biopsy revealed chronic osteomyelitis, but no organisms were isolated. The patient did not receive antimicrobial therapy and the lesion resolved spontaneously. Six months later, the patient was evaluated again with complaints of right heel pain and swelling. Radiographic studies showed both lytic and sclerotic lesions of the calcaneus. She was treated with nonsteroidal antiinflammatory agents and slowly improved.

Three years from her initial presentation, she sustained a minor trauma to her left arm and complained of right calcaneus pain. Radiographic images showed osteomyelitis with numerous sinus tracts in both areas. Open biopsies of her left radius and right calcaneus were performed and the specimen cultures grew *M avium* complex from both. She was treated with rifampin, ethambutol, and clarithromycin. After several months of this regimen, the lesions resolved.

She was subsequently evaluated for an immunodeficiency. Serum immunoglobulins (Ig) showed a mildly elevated IgG total and IgG1 subclass with a mildly lowered IgG2. Total T-cell numbers as well as T-cell subpopulations were normal. B cells and natural killer cells were normal in number and percentage. Mitogen stimulation with concanavalin A and phytohemagglutinin were normal. Antigen stimulation with *Candida* was normal. Serology was negative for *Cytomegalovirus*, Epstein-Barr virus, and *Toxoplasmosis*. After consent was obtained for genetic testing, DNA sequencing of her IFN- γ R1 gene showed a single base substitution of thymidine for guanine at position 832, resulting in an immediate stop codon in 1 of the patient's 2 IFN- γ R1 alleles. The subsequent translated mutant protein would be predicted to lack most of its cytoplasmic tail (Fig 1). Evaluation of the patient's parents and siblings showed no other members with the substitution, suggesting that the mutational event occurred de novo in a parental germline. Cell surface expression of the IFN- γ R1 on both T lymphocytes and monocytes was increased as compared with normal control (Fig 2). This increase in surface expression has been noted previously in patients heterozygous for other similarly truncated IFN- γ R1 proteins and may be attributable in part to impaired recycling of the mutated receptor.⁸

To facilitate the evaluation of the function of this patient's IFN- γ R1, we derived an Epstein Barr virus-transformed B-cell line from peripheral blood. The response of these cells to IFN- γ was assessed by monitoring the nuclear translocation of Signal Trans-

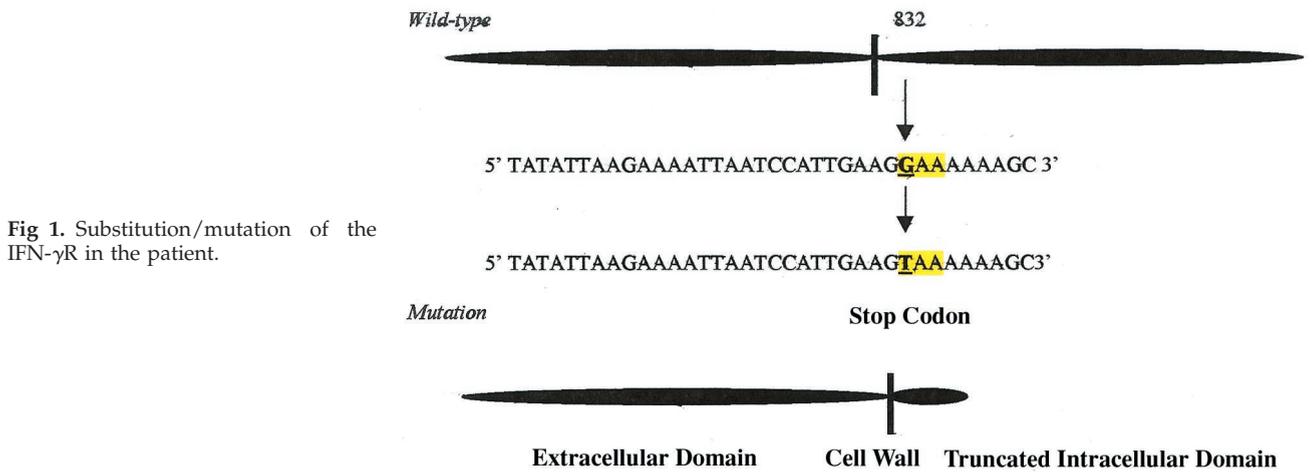


Fig 1. Substitution/mutation of the IFN- γ R in the patient.

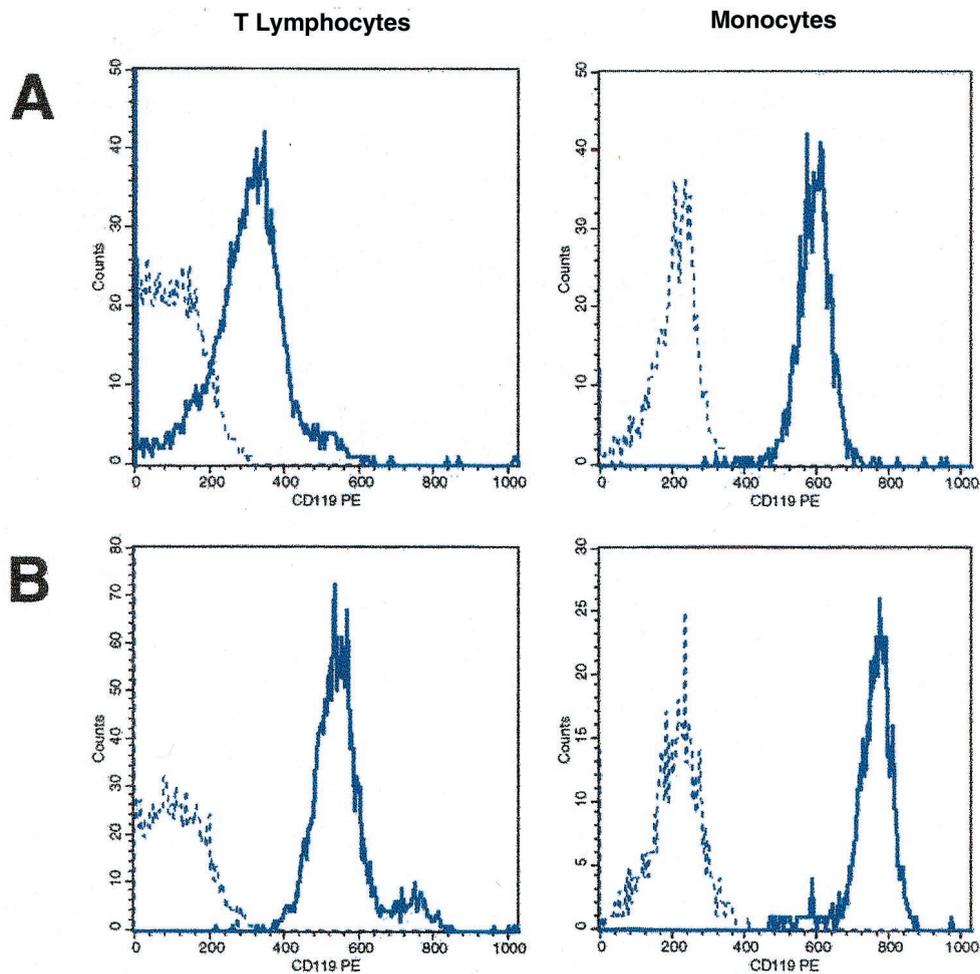


Fig 2. Direct immunofluorescent staining with monoclonal antibodies was performed on aliquots of heparinized peripheral blood collected from patient and control as described previously.¹⁴ Expression of IFN- γ R1, as assessed by the mAb GIR-218, on CD3+ (T lymphocytes) and CD14+ (monocytes) cells is shown in a normal control, A, and the patient, B. The negative control (isotype matched) is shown as the dashed line.

ducers and Activators of Transcription 1 (STAT1) by using an electrophoretic mobility shift assay. The intensity of the radioactive bands are an indirect measure of the nuclear translocation of STAT1. Markedly reduced STAT1 nuclear translocation was observed after exposure to IFN- γ (Fig 3), indicating a significantly impaired signal transduction through the IFN- γ R1 in this patient. The methods used for molecular analysis, surface expression, and signaling were performed as previously described.^{8,14}

DISCUSSION

M avium complex most commonly causes infection in patients with human immunodeficiency virus, chronic lung disease, and prolonged use of corticosteroid.¹⁵⁻¹⁷ Additionally and recently, several patients with mycobacterial infection have been deter-

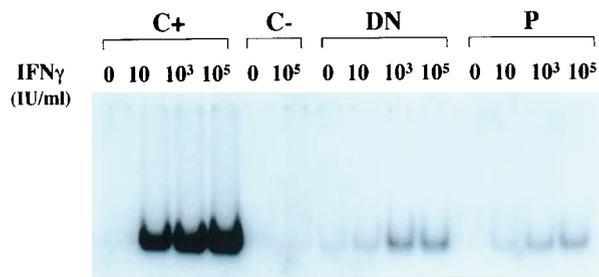


Fig 3. An electrophoretic mobility shift assay was performed using 10- μ g nuclear extracts of EBV-transformed B cells from a healthy control (C+), a child with complete recessive IFN- γ R1 deficiency (C-), a child with partial dominant IFN- γ R1 deficiency 818del4 (DN), and the patient (P) stimulated with variable concentrations of IFN- γ (IU/mL) for 30 minutes. Nuclear extracts were incubated with a radiolabeled IFN- γ activated sequence probe and the samples were separated by acrylamide electrophoresis.⁸

mined to be homozygous for a mutation of the IFN- γ R1.⁶⁻¹⁴ Although *M avium* has been the major pathogen, other severe infections have occurred in these patients.⁷ This immune defect seems to translate phenotypically to a selective susceptibility to intramacrophagic organisms and, perhaps, uncovers a part of the immune system that lacks a redundant host response. In addition, this deficiency may allow the patient to be open to severe viral infections such as herpes viruses, parainfluenza virus type 3, and respiratory syncytial virus, as shown by Dorman et al.¹³

Jouanguy et al⁸ investigated 18 patients with infections with bacille Calmette-Guerin and mycobacteria. In this study, however, only 4 of 18 patients had MAC disease limited to bone alone.⁸ They were able to identify 14 mutations at a single site on the IFN- γ R1 gene in these patients. All of the mutations isolated occurred at the 818 residue position and produced a reading frame shift that resulted in a premature stop codon downstream that halted transcription of the receptor protein. The resulting incomplete IFN- γ R1 lacked the intracellular component on the R1 subunit responsible for cell signaling, with 1 normal wild-type allele and 1 mutant allele. Dominant inheritance was inferred in the kindreds reported.

Analysis of our patient's IFN- γ R1 revealed a unique mutation at position 832. This mutation was a substitution of T for G that immediately led to translation of a premature stop codon and resulted in a similarly truncated IFN- γ R1 (Fig 1). This mutation at 832, designated E278X, has 9 intracytoplasmic residues (YIKKINPLK), whereas the 818delT consisted of 6 (YIKKIH) and the 818del4 consisted of 7 (YIKKIH). The substitution/mutation was not found in other family members. Therefore, in the genetic differential diagnosis of patients with these reported clinical symptoms and hyperexpression of the IFN- γ R1, the search for the mutation cannot be limited only to 818T and 818del4, but must also include E278X.

In our patient's case, because some of the cell

surface IFN- γ R1 are functionally present, it is, therefore, conceivably possible to administer exogenous IFN- γ to flood the existing functional and nonfunctional receptor sites during an episode of osteomyelitis. This would then ensure an optimal immunologic response from the patient's cells, potentially expediting infectious resolution.

This case stresses the importance of analyzing and coupling not just the immediate past medical history involving a patient's chief complaint, but also history that may span several years. It also exemplifies the fact that genetic mutations need not affect the host directly at birth, and care must be taken not to immediately eliminate genetic mutations from the differential diagnosis. In addition, individual differences in susceptibility to the same pathogens may be caused by subtle defects in the immune system that remain unrecognized. With the aid of modern technology in the laboratory and the explosion of knowledge in the field of genetics, these immune disorders can be increasingly uncovered by the observant clinician with access to a sophisticated laboratory.

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