

studied, a heterozygous missense mutation was found in the *IL17F* gene. The mutant allele was found in 2 apparently healthy family members, which suggests incomplete clinical penetrance, and in all of the affected members of the kindred. This mutant protein was tested in a cell line and was nonfunctional.

CONCLUSIONS. Mutations in IL-17–family genes that cause functional deficiency of this pathway are associated with CMCD.

REVIEWER COMMENTS. This is an excellent example of bench-to-bedside medicine and illustrates the utility of murine models of immunity in the search for causes of human disease. These findings provide definitive evidence that IL-17A and IL-17F are essential for protective immunity to *C albicans* and, to a lesser extent, *S aureus* in the nails, skin, and oral and genital mucosa and provide new opportunities for designing novel treatments for this chronic immunologic disorder. It is also important to consider that elevated levels of IL-17 have been associated with various chronic inflammatory conditions, which raises the possibility that anti-IL-17 treatment strategies now under development could lead to increased susceptibility to infections with *C albicans* or *S aureus*.

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Douglas F. McMahon, MD
James E. Gern, MD
Madison, WI

Hypomorphic *Rag* Mutations Can Cause Destructive Midline Granulomatous Disease

De Ravin SS, Cowen EW, Zarembek KA, et al. *Blood*. 2010;116(8):1263–1271

PURPOSE OF THE STUDY. To describe a new clinical phenotype in patients who inherit mutations in the recombination activation gene (*Rag*) necessary for effective immunoglobulin and T-cell receptor gene rearrangement.

STUDY POPULATION. This was a case report of a 14-year-old patient referred with a 1-year history of extensive granulomatous destruction of the midface structures and a past history of myasthenia gravis treated with thymectomy. The patient had a sister who died at 5 years of age of staphylococcal sepsis; she also had a history of ptosis that the authors suggested might have reflected undiagnosed myasthenia gravis.

RESULTS. The patient underwent extensive immunologic and genetic testing for both autoimmune disease and immunodeficiency disorders that revealed compound heterozygous mutations in *Rag*. These mutations resulted in ~50% loss of Rag enzyme functional activity. The immunologic studies revealed relatively normal T

and B cells and normal immunoglobulin levels and T-cell diversity but markedly decreased FoxP3⁺ T-regulatory cells.

CONCLUSIONS. Immune dysregulation with granulomatous hyperinflammation and autoimmunity can result from hypomorphic mutations in the gene encoding Rag.

REVIEWER COMMENTS. This study adds to the phenotypic range of disease that is now associated with mutations in the *Rag* gene, which now include classical severe combined immunodeficiency, Omenn syndrome, combined immunodeficiency with expansion of γ - δ T cells, granulomatous disease, and autoimmunity. Readers are encouraged to refer to a recent review in which phenotypic variability based on cases with RAG1 deficiency was demonstrated (Valayannopoulos V, de Blic J, Mhlaoui N, et al. *Pediatrics*. 2010;126[5]; available at: www.pediatrics.org/cgi/content/full/126/5/e1242). Recognition of variable phenotypes with mutations in a gene associated with primary immunodeficiency disorders has become a common phenomenon, which clearly suggests that practitioners must be aware that “textbook” descriptions of gene defects associated with primary immunodeficiencies only present part of the full story and that the potential for phenotypic variability is significant.

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Thomas A. Fleisher, MD
Bethesda, MD

Clinical Disease Caused by *Klebsiella* in 2 Unrelated Patients With Interleukin 12 Receptor β 1 Deficiency

Pedraza S, Lezana JL, Samarina A, et al. *Pediatrics*. 2010;126(4). Available at: www.pediatrics.org/cgi/content/full/126/4/e971

PURPOSE OF THE STUDY. To describe a new infectious disease phenotype in patients who inherit mutations in the interleukin 12 (IL-12) signaling pathway.

STUDY POPULATION. In this report the authors documented sepsis with *Klebsiella pneumoniae* in 2 unrelated patients with complete defects in the IL-12 receptor β 1.

METHODS. This was a chart review with case reports.

RESULTS. The first patient was born to unrelated parents and developed BCGitis after BCG vaccination in infancy followed by nontyphoidal salmonellosis. Both infections were difficult to treat despite multiple appropriate antimicrobial agents administered over 26 months. This was followed by development of disseminated *Mycobacterium bovis* infection, which also responded poorly to multi-drug antimicrobial agents along with interferon γ therapy. The patient’s condition worsened, and he developed

systemic infection with *Candida albicans* and with *K pneumoniae*, which ultimately proved to be fatal despite aggressive and appropriate antimicrobial therapy. The second patient was born to consanguineous parents and did not receive the BCG vaccine, but at the age of 14 months she developed multiple adenopathies that stained for *Nocardia nova*; she also developed a positive blood culture for *K pneumoniae*. The initiation of appropriate antimicrobial agents and interferon γ resulted in resolution of her infections.

CONCLUSIONS. *Klebsiella* infections should be considered in patients with IL-12 receptor $\beta 1$ deficiency. In addition, IL-12 receptor $\beta 1$ should be considered in patients with unexplained klebsiellosis.

REVIEWER COMMENTS. This is another example of the expanding range of microbial pathogens that can be observed in patients with defects that affect the IL-12 pathway. The historical observation that these patients primarily are affected by mycobacterial and salmonella infections needs to be modified to include mucocutaneous disease with *C albicans* seen in up to 25% of these patients and now also *Klebsiella* infection. This again points out that clinicians should be wary of not considering a specific defect caused by an infectious organism that does not fit with the initial or "classical" description of infections associated with a genetic defect. These disorders should be considered a "work in progress" in terms of the clinical phenotype. As with all rare diseases, it is best to consult with an experienced clinical immunologist when a child presents with an unusually severe or persistent infection.

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Thomas A. Fleisher, MD
Bethesda, MD

Clinical Features and Outcome of Patients With IRAK-4 and MyD88 Deficiency

Picard C, von Bernuth H, Ghandil P, et al. *Medicine (Baltimore)*. 2010;89(6):403-425

PURPOSE OF THE STUDY. To describe the clinical features and outcomes of patients with autosomal recessive defects in the interleukin 1 receptor-associated kinase 4 (IRAK-4) and the myeloid differentiation factor 88 (MyD88).

STUDY POPULATION. The authors provided the cumulative data of 48 patients with IRAK-4 deficiency and 12 patients with MyD88 deficiency from 37 kindreds in 15 countries.

METHODS. The data for this report were collected on the basis of a detailed questionnaire filled out by the physician who cared for the enrolled patient.

RESULTS. The leading threat to these patients was invasive pneumococcal disease, which was seen in 41 of the 60 patients (68%) and caused 72 documented invasive infections (52.2%). Invasive infections with *Pseudomonas aeruginosa* and *Staphylococcus aureus* were observed in 13 patients each. Noninvasive infections, typically involving the skin and lungs associated with *Pseudomonas aeruginosa* and *Staphylococcus aureus*, were also seen frequently (52 of 60 patients). Signs of inflammation (fever, elevated C-reactive protein level) are usually weak or delayed. It is important to note that there were no instances of severe viral, fungal, or parasitic infections. The clinical outcome to date has been poor; there have been 24 infection-related deaths (38%), and in 10 cases death was associated with the first invasive episode. Antibiotic prophylaxis, antipneumococcal vaccination, and/or immunoglobulin infusions seem to have a beneficial effect on outcomes. It is also important to note that there were no deaths after the age of 8 years and no invasive infections after the age of 14 years, which indicates that once a child with these defects reaches adolescence, there might be little risk for infection and prophylactic therapy might not be needed at that point.

CONCLUSIONS. The authors concluded that patients and families should be informed of the risk of developing life-threatening infections, and empiric antibacterial treatment and immediate medical consultation were strongly recommended in cases of suspected infection or moderate fever. Prophylactic measures in childhood were considered beneficial until spontaneous improvement occurs in adolescence.

REVIEWER COMMENTS. This is the most complete account to date of the clinical features and outcome of these 2 defects, both of which target critical signaling pathways in the innate immune system involving Toll-like receptors and the interleukin 1 receptor. The authors clearly defined these signaling pathways as playing a critical role in the host defense against invasive bacterial infection earlier in life. This also suggests that the full maturation of adaptive immunity involving T and B cells that occurs during later childhood compensates for the innate defect and prevents susceptibility to invasive bacterial infection after reaching adolescence. The consistent finding that the inflammatory response is somewhat diminished represents a clinical clue in these disorders, and the therapeutic recommendations clearly seem to alter what is otherwise a serious primary immunodeficiency in terms of mortality.

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Thomas A. Fleisher, MD
Bethesda, MD

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Thomas A. Fleisher

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