nonimmune cells such as neurons are nonetheless essential for host defense against invading pathogens.

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Timothy P. Moran, MD, PhD
Brian P. Vickery, MD
Durham and Chapel Hill, NC

Loss-of-Function Mutations in the IL-21 Receptor Gene Cause a Primary Immunodeficiency Syndrome

Kotlarz D, Ziętara N, Uzel G, et al. *J Exp Med*. 2013;210 (3):433–443

PURPOSE OF THE STUDY. This report of 2 unrelated kindreds with newly recognized mutations in the inteleukin-21 receptor gene (IL-21R) highlights the molecular basis and phenotype of a new form of immunodeficiency.

STUDY POPULATION. Two sets of kindreds were studied. The first set included a 4-year-old boy and a 10-year-old sister born from consanguineous Lebanese parents with phenotypes characterized by recurrent respiratory infections and chronic cryptosporidial gastrointestinal infection and associated chronic cholangitis, biliary fibrosis, and cirrhosis. A second unrelated set included an 8-year-old boy and a 13-year-old boy from consanguineous Columbian parents who had a phenotype similar to that of the first set, including recurrent respiratory infections, chronic cryptosporidial gastrointestinal infection, and hepatobiliary disease.

METHODS. In addition to reviewing each patient's clinical course and basic immune evaluation, subjects underwent exome and candidate gene sequencing with directed molecular investigation into the cellular mechanism of the identified mutations.

RESULTS. All 4 patients had recurrent respiratory and gastrointestinal infections characterized by underlying B- and T-cell defects with variable natural killer cell dysfunction. Cryptosporidial infections were universal. Sequencing revealed 2 unique and unrelated homozygous recessive loss-of-function mutations in the IL-21R gene. Unlike patients with a common γ-chain deficiency, which affects several interleukin receptors, including IL-21R, the subjects in this study did not meet criteria for severe combined immunodeficiency. Patients seemed to have impaired T-cell response and memory B-cell development, thought to account for the observed increase in infections. The mechanism of cirrhosis is less clear and may be secondary to chronic infections. All patients have had grave clinical courses: 1 died of complications from liver transplant, another died of complications of hematopoietic stem cell transplant (HSCT), and the other 2 are alive but too ill to undergo HSCT.

CONCLUSIONS. This study details the phenotypes and molecular investigation of the first reported patients with IL-21R deficiency, providing insight into the role of IL-21R in immune function. The poor clinical outcome of these patients highlights the importance of early primary immunodeficiency recognition, potentially enabling HSCT before development of irreversible secondary morbidities.

REVIEWER COMMENTS. As has been the case with previously discovered primary immunodeficiencies, this small case series reveals a glimpse into a specific aspect of immune function. In this case, we have learned that the IL-21R pathway is important for T- and B-cell responses protecting from respiratory and gastrointestinal infections, especially with *Cryptosporidium*. The case series also imparts the critical importance of identifying primary immunodeficiency early in life so that the best opportunity for successful HSCT can be provided.

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David R. Scott, MD
Susan Laubach, MD
San Diego, CA

Ribosomal Protein SA Haploinsufficiency in Humans With Isolated Congenital Asplenia

Bolze A, Mahlaoui N, Byun M, et al. *Science*. 2013;340 (6135):976–978

PURPOSE OF THE STUDY. To identify a potential genetic basis for isolated congenital asplenia.

STUDY POPULATION. Thirty-three patients from 23 kindreds with a history of congenital asplenia, including multiplex kindreds that suggested an autosomal dominant inheritance pattern.

METHODS. Genomic DNA was initially obtained from at least 1 member of each kindred and subjected to whole exome sequencing followed by testing of remaining subjects.

RESULTS. Eighteen (55%) of the 33 subjects from 8 of the 21 kindreds were identified with 7 different heterozygous missense mutations of the gene encoding the ribosomal protein SA (RPSA). The mutations affect highly conserved nucleotides in mammals, vertebrates, and yeast and showed complete penetrance in that all individuals carrying the mutation had isolated congenital asplenia.

CONCLUSIONS. Heterozygous mutations in RPSA underlie all isolated congenital asplenia in the multiplex families studied (but not all subjects with isolated congenital asplenia). RPSA is involved in preribosomal processing, but its role in splenic development is unknown at this time. There were no other definable defects observed in these patients. Interestingly, another mutation affecting

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