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A novel mutation of IL21R in a patient with common variable immunodeficiency

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Introduction:

Interleukin-21 (IL-21) is a recently discovered member of the common gamma-chain (γc) group of cytokines. The IL-21 cytokine regulates lymphocyte proliferation, B-Cell differentiation, Natural Killer (NK) cell cytotoxicity and Th17 cell differentiation.[1,2] Gene defects in IL-21 and its receptor, Interleukin-21 receptor, (IL-21R) have been linked to primary immunodeficiency diseases (PID). Mutations in the IL-21R gene have been shown to cause combined immunodeficiency by compromising the function of both the innate and adaptive immune systems.[3] IL-21 binds to the gamma chain of IL-21R and initiates the Janus kinase/signal transducers and activators of transcription signaling (JAK/STAT) pathway for the proper transfer of signals.[1,2] Mutations of the γc portion of this complex in humans results in X-linked severe combined immunodeficiency (XSCID). The hallmark of this disease is reduced T-Cells and NK cells, but ample B-Cells which lack function. Similarly, studies have proved mutations in IL-21R has devastating effects on plasma cells, memory B-Cell generation and immunoglobulin class switching and has been linked to common variable immunodeficiency (CVID). Currently there have been eight reported patients from five different families with a unique homozygous mutation in IL-21R as a cause of CVID. We describe the first case of a novel heterozygous IL21R gene mutation in a patient with CVID.

Case Presentation:

A 70-year-old male with a past medical history of multiple recurrent infections presented to the outpatient allergy and immunology clinic. He failed several rounds of antibiotics and often required longer antibiotic courses to eradicate infections prompting immune deficiency testing. The immunological workup was initiated, and labs revealed a low serum IgG of 383 mg/dL (normal: 600-1450 mg/DL), IgA of 43 mg/dL (normal: 70-320 mg/dL), and IgM of 36 mg/dL (normal: 50-300 mg/dL). The patient was also noted to have low pneumococcal serotypes which were nonresponsive to pneumococcal vaccinations. An immunodeficiency profile indicated B-lymphopenia with CD-19 of 5% (normal 6-9%) and absolute count of 0.041 (reference 0.07-0.9). These findings demonstrated the diagnosis of CVID, and a primary immunodeficiency genetic panel was ordered for specific evaluation.

The Invitae™ test results revealed heterozygous mutation in the IL-21R gene. A mutation was found on exon 6, with methionine, a neutral and non-polar amino acid, replaced by isoleucine, another nonpolar and neutral amino acid at codon 205 of the IL-21R protein (p.Met205Ile).

CVID is a broad term encompassing many immunoglobulin deficiencies that are found in patients with similar clinical presentations.[4] Patients with CVID have symptoms that affect many organ systems including hematological, dermatological, and gastrointestinal systems.[5] This immunodeficiency is characterized by a low level of immunoglobulins and has been genetically characterized by many different abnormalities affecting multiple immune pathways.[4] There have been several different serum biomarkers and genetic mutations seen in CVID patients

including elevated BAFF/APRIL, mutation in TACI, and reduced BCMA.[6]

IL-21R was discovered in 2000 by a group of Parrish-Novak at Zymogenetics and Warren Leonard from the National Institutes of Health. The IL-21/Il-21R signaling pathway plays a significant role in humoral immune responses. Mutations of IL-21R show reductions in total and antigen specific IgG resulting in a blunted antigen response and have been linked to combined immunodeficiencies.[7] Eight unique mutations in IL-21R have been identified by exome in families, all of which have been recessive homozygous mutations. These patients suffer from recurrent bacterial infections and gastrointestinal infections, prominently cryptosporidium with chronic cholangitis. The clinical presentation includes chronic diarrhea, mycobacterial infections, failure to thrive, tinea corporis, herpes labialis, candida and hypogammaglobulinemia.[8]

Conclusion:

CVID is a broad diagnosis with various presenting symptoms and etiologies. Genetic analysis ca be done to determine the genetic cause of this disease, which is spread over many different types and locations of disease-causing mutations. We present a novel heterozygous IL-21R mutation in a patient with the diagnosis of CVID.

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