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Titel des Beitrags: Whole-exome sequencing links caspase recruitment domain 11 (CARD11) inactivation to severe combined immunodeficiency.

Abstract: Primary immunodeficiencies represent model diseases for the mechanistic understanding of the human innate and adaptive immune response. They are clinically highly relevant per se because in patients with severe combined immunodeficiency (SCID), infections caused by opportunistic pathogens are typically life-threatening early in life. We aimed at defining and functionally characterizing a novel form of SCID in an infant of consanguineous parents who presented with life-threatening Pneumocystis jirovecii pneumonia using a comprehensive immunologic and whole-exome genetic diagnostic strategy. Analysis of leukocyte subpopulations was performed by using multicolor flow cytometry and was combined with stimulation tests for T-cell function. The search for a disease-causing mutation was performed with diagnostic whole-exome sequencing and systematic variant categorization. Reconstitution assays were used for validating the loss-of-function mutation. The novel entity of SCID was characterized by agammaglobulinemia and profoundly deficient T-cell function despite quantitatively normal T and B lymphocytes. Genetic analysis revealed a single pathogenic homozygous nonsense mutation of the caspase recruitment domain 11.
(CARD11) gene. In reconstitution assays we demonstrated that the patient-derived truncated CARD11 protein is defective in antigen receptor signaling and nuclear factor \( \beta \) activation. We show that an inactivating CARD11 mutation links defective nuclear factor \( \beta \) signaling to a novel cause of autosomal recessive SCID.

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