Novel XLF/Cernunnos mutation linked to severe combined immunodeficiency, microcephaly and abnormal T and B cell receptor repertoires

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Abstract

Background: During the process of generating diverse T and B cell receptor (TCR and BCR, respectively) repertoires, double strand DNA breaks are produced. Subsequently, these breaks are corrected by a complexed system led mainly by the non-homologous end-joining (NHEJ). Mutations in proteins involved in this process, including the XLF/ Cernunnos gene, cause severe combined immunodeficiency syndrome (SCID) along with neurodevelopmental disease and susseptability to inoizing radiation. Objective: To provide new clinical and immunological insights on XLF/Cernunnos deficiency, arising from a newly diagnosed patient with severe immunodeficiency. Methods: A male infant, born to consanguineous parents, suspected of having primary immunodeficiency underwent immunological and genetic work up. This included a thorough assessment of T cell phenotyping and lymphocyte activation by mitogen stimulation tests, whole exome sequencing (WES), TCR repertoire Vβ repertoire via flow cytometry analysis and TCR and BCR via next generation sequencing (NGS). Results: Clinical findings included microcephaly, recurrent bacterial viral pneumonia and failure to thrive. Immune workup revealed lymphopenia, reduced T cell function and hypogammaglubolinemia. A skewed TCR Vβ repertoire, TCR gamma (TRG) repertoire and BCR repertoire were determined in the patient. Genetic analysis identified a novel autosomal recessive homozygous missense mutation in XLF/Cernunnos c. A580Ins.T; p. M194fs. The patient underwent a successful hematopoietic stem cell transplantation (HSCT). Conclusions: A novel XLF/Cernunnos mutation is reported in a patient presented with SCID phenotype that displayed clonally expanded T and B cells. An adjusted HSCT was safe to ensure full T cell immune reconstitution.

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