LIG4 Syndrome: A Rare Form of Combined Immunodeficiency Presenting with Infantile Onset Myelodysplasia. Case Report and Review of Literature

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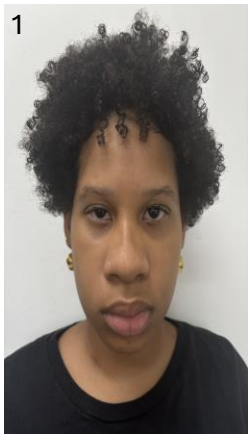
INTRODUCTION

LIG4 encodes for an important DNA repair system protein named DNA ligase IV andbiallelic pathogenic variants in this gene are associated with LIG4 syndrome,characterized by a variable degree of combined immunodeficiency which includes thephenotypes of neurodevelopment disorders, febrile episodes and recurrent infections,autoimmune disorders like eczema and psoriasis, endocrinopathies and increased riskof blood dyscrasias and myelodysplastic syndromes. We present a case report of an18-year-old woman with compatible phenotype and biallelic variants in LIG4.



CASE REPORT

Woman, 18 years old was referred to the clinical genetics department by the hematology department with the initial clinical suspicion of Fanconi anemia. She presented nausea and vomiting at age 3 associated with thrombocytopenia evolving into chronic anemia as well. At age 9 she had myelodysplastic syndrome that was treated with bone marrow transplantation. At age 16, she presented with secondary amenorrhea and hypergonadotropic hypogonadism and mixed hyperlipidemia. Clinical evaluation evidenced microcephaly with a “bird like” facies and oral swab exome sequencing was ordered for etiological clarification. Exome analysis evidenced composite heterozygous variants in LIG4 [c.1904del p.(Lys635Argfs*10); c.56T>G p.(Leu19Trp)] the former classified as pathogenic and the latter classified as VUS.

Figure 1 and 2: Photographs of the patient face evidencing facial dysmorphological features

DISCUSSION AND CLOSING COMMENTS

LIG4 syndrome is a rare condition with high phenotype expressivity. Individuals affected may present with variable forms of combined immunodeficiency, including a “seckel-like" phenotype, hypogonadism, developmental delay, autoimmune eczema or psoriasis and an increased risk of blood dyscrasias and myelodysplasia. Due to conflicting interpretation of c.56G>T variant on ClinVar and literature reports, the variant was reported as VUS. Moreover, the phase of the variants was unknown, thus challenging the molecular diagnosis of this patient. Segregation analysis of this variant may help reclassify the variant and stablish the molecular diagnosis.

We described a case study of a combined immunodeficiency presenting with early onset myelodysplasia and endocrinological disorders in combination, due to DNA repair complex defects. The description elucidation of clinical features and its variability along with natural history should enhance the clinical suspicion of this disorder and help clinical diagnosis and management in further cases.

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