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WHOLE EXOME SEQUENCING ENABLES A MOLECULAR DIAGNOSIS IN >10% OF EARLY ONSET OR FAMILIAL SLE

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Introduction: Systemic lupus erythematosus is an autoimmune disease characterized by the production of antinuclear antibodies and an increase in type I interferons. The exact cause of the disease is unknown, but genetic and environmental factors are thought to play a role. Over the past decade, we have been able to explore the Mendelian contribution to juvenile-onset SLE (jSLE) and show that 7% of jSLE is monogenic using a panel approach[1,2].
Objectives: The aim of this study was to explore a cohort of juvenile or familial lupus with a pangenomic approach to assess the diversity of genes involved in lupus and to evaluate the diagnostic rate of exome sequencing.
Methods: We selected patients from the National Lupus Biobank who met at least one of the following criteria: (1) male sex, (2) disease onset < 12 years, (3) family history of autoimmune disease, and performed whole exome sequencing in 118 families. In a diagnostic approach, we used in silico panels and then explored the dataset to identify novel genes involved in lupus.
Results: We identified pathogenic or probable pathogenic variations according to the American College of Medical Genetics classification in genes associated with inborn errors of immunity in 7 patients (ADAR, C1QA, PSTPIP1, IRAK4, PTPN11, COPA, IKZF3). A genetic diagnosis involving a gene never associated with lupus (MAN1B1, ETV6) was identified in 2 patients, explaining part of the phenotype but not the lupus. In addition, a research approach revealed numerous candidate genes, including SOCS1, PTPN2, and DOCK11, which were confirmed as responsible for the disease by collaborative and functional studies[3,4].
Conclusion: This study confirms the value of exome sequencing in pre-selected lupus patients with a diagnosis rate of more than 10% of monogenic SLE. It demonstrates the superiority of exome over panel in lupus, with genetic diagnosis of unexpected genes and the possibility of discovery-based approaches. Finally, the striking element is the high proportion of novel genes involved, demonstrating the dynamics of genetic discovery in this field.
Patient Consent: Yes, I received consent
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Disclosure of Interest: None declared