FREQUENCY OF PATHOGENIC, “RISK FACTOR”, AND UNCERTAIN SIGNIFICANCE VARIANTS IN 378 BRAZILIAN PATIENTS WITH SUSPECTED AUTOINFLAMMATORY SYNDROMES

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BACKGROUND

Autoinflammatory syndromes (AIS) are a group of rare monogenic diseases that have recently been described. The syndrome is characterized clinically by recurrent episodes of fever and systemic inflammation affecting multiple organs and systems. Mutations in IL1RN, LPIN2, MEFV, MVK, NLRC4, NLRP12, NLRP3, TNFRSF1A, PSTPIP1 and NOD2 genes cause the called AIS: Deficiency of interleukin-1 receptor antagonist (DIRA), Majeed Syndrome, Familial Mediterranean Fever (FFM), Hyper IgD syndrome (HIDS), cryopyrinopathies (CAPS), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) and BLAU Syndrome, respectively. The aim of the present study was described the frequency of pathogenic variants, variants classified as “risk factor” and variants of uncertain significance (VUS) in IL1RN, LPIN2, MEFV, MVK, NLRC4, NLRP12, NLRP3, TNFRSF1A, PSTPIP1 and NOD2 genes.

MATERIALS AND METHODS

We reviewed the genetic results of 378 patients analyzed by Next Generation Sequence (NGS) in our laboratory. The genes were sequenced on the MiSeq or NextSeq (Illumina) platforms with 100% coverage and 50X of depth. Variant classification was carried out using the ACMG criteria, and using Infevers database as a reference. Variants previously known as “risk factors”, or of incomplete clinical penetrance, were added to the classification.

RESULTS

A total of 378 patients, 187 females and 191 males, were enrolled in the analysis. In total, 37 (9.79%) patients had pathogenic variants that defined the molecular diagnosis. The variants were found mainly in the IL1RN (1), MEFV (8), MVK (11), NLRP12/NLRP3 (5), NOD2 (4), PSTPIP1 (2) and TNFRSF1A (6) genes. In 25 (6.61%) patients low-penetrance variants classified as risk factors were found. Another 10 (2.64%) patients were carriers for pathogenic variants in heterozygosity in the MEFV and MVK genes. Finally, 94 (24.87%) of the patients presented variants of unknown significance (VUS) in IL1RN, LPIN2, MEFV, MVK, NLRC4, NLRP12, NLRP3, TNFRSF1A, PSTPIP1 and NOD2 genes.

CONCLUSION

In summary, 62 (16.40%) patients had pathogenic or risk factor variants associated with autoinflammatory syndromes. The precise diagnosis of AIS through the knowledge of the clinical manifestations as well as the genetic characteristics offer better therapeutic possibilities for the patients.