Abstract ID:- 39

Abstract Topic:- Complex traits and polygenic disorders

Abstract Title:- High-resolution HLA sequencing identified novel association at C*15:02 and suggested clinical relevance of DPB1*04:01 for ANCA-associated granulomatosis with polyangiitis: A pilot study on a north Indian cohort from Delhi

Presenting author name :- Harinder Singh

Presenting author institute:- Central University of Punjab

Co-authors name:- Sabyasachi Senapati, BK Thelma, Narender Verma, Uma Kumar

Co-authors institute:-Central University of Punjab, University of Delhi South Campus, New Delhi , All India Institute of Medical Sciences, New Delhi

Aims:-Granulomatosis with polyangiitis (GPA) is a prevalent subtype of ANCA-associated vasculitis, a rare autoimmune disorder that primarily affects individuals with a genetic predisposition. Previous investigations using candidate allele typing and genome-wide association studies have uncovered various HLA alleles associated with GPA. Nevertheless, no established method for diagnosing GPA or predicting its risk is currently based on HLA typing. This study aims to employ HLA sequencing-based genotyping in a cohort of North Indian individuals with GPA to discover new and clinically significant associations with the disease.

Methods:- PR3-ANCA-positive 40 GPA patients and 40 healthy controls from the north Indian state of Delhi were recruited for the study. High-resolution genotyping for HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1was performed using next-generation sequencing. Appropriate statistics were applied to test allelic and haplotypic association with GPA. Molecular docking of susceptibility HLA alleles with known super antigen epitopes was performed. The association of substituted amino acid residues located at the antigen binding domain of HLA protein was evaluated.

Results:- Genetic association of five HLA alleles were identified with GPA. The novel association was identified for C*15:02 ($p=0.04$; OR=0.27). The strongest association was observed for DPB1*04:01 ($p<0.0001$; OR=6.2), previously reported in European studies. 35 out of 40 GPA subjects had at least one allele of DPB1*04:01, and its significant risk was previously not reported from the Indian population. Significantly associated haplotypes DRB1*03:01~DQB1*02:01~DPB1*04:01 ($p=0.02$; OR=3.46) and DRB1*07:01~DQB1*02:02~DPB1*04:01 ($p=0.04$; OR=3.35) were the most frequent in the GPA patients. Molecular docking confirmed a strong interaction between the HLA and three epitopes of Staphylococcus aureus's reported super antigen TSST-1.

Conclusions:- DPB1*04:01 was replicated as a significant predisposing allele for GPA. Our study highlighted its applicability for screening and diagnosis of GPA. Large multi-centric study and genotype-phenotype correlation analysis among GPA patients will enable establishing HLA-based GPA diagnosis and modelling of the disease to understand the pathogenesis better.

Keywords:- HLA typing, GPA, DPB1*04:01, Haplotypes