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Effect of coronary artery disease risk SNPS on serum cytokine levels and cytokine imbalance in premature coronary artery disease

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Background: Coronary Artery Disease (CAD) occurs almost a decade earlier in the South Asian population as compared to the West. Inclusion of genetic information can prove to be a robust measure to improve early risk prediction of PCAD. Aim was to estimate the genotypic distribution and risk allele frequencies of 13 Coronary Artery Disease (CAD) risk Single Nucleotide Polymorphisms in loci identified by the CARDIoGRAMplusC4D consortium namely MIA3 rs17465637;9p21 rs10757274; CXCL12 rs1746048; APOA5 rs662799; APOB rs1042031; LPA rs3798220; LPA 10455872; MRAS rs9818870; LPL rs328; SORT1 rs646776; PCSK9 rs11591147; APOE rs429358; APOE rs7412 in Pakistani PCAD patients and controls and to determine the differential serum cytokine levels (IL18,IL10,IL6, TNFalpha, IL18:IL10 & TNFalpha:IL10 ratios) with respect to the genotypic distribution of these selected SNPs.

Material & Methods: The study design was case-control and it was conducted in National University of Sciences and Technology, Islamabad in collaboration with the Cardiovascular Genetics Institute, University College London, UK. Subjects (n=340) with >70% stenosis in at least a single major coronary artery on angiography were taken as PCAD cases along with 310 angiographically verified controls. ELISA was performed for measuring the concentrations of serum IL18, TNFA, IL6 and IL10. Genotyping was done using TAQMAN and KASPar assays.

Results: The risk allele frequencies (RAF) of APOE rs7412, CXCL12 rs1746048, 9p21 rs10757274, MIA3 rs17465637 and SORT1 rs646776 were markedly higher in the PCAD cases as compared to the controls. APOE rs429358 had the greatest influence among the selected GWAS/CARDIoGRAMplusC4D consortium CAD risk SNPs by significantly altering the serum levels of TNFalpha, IL10 and TNFalpha:IL10 ratio followed by APOE rs7412 and CXCL12 rs1746048 which significantly altered the serum levels of IL18; TNFalpha and IL18; IL18:IL10 ratio respectively. The cytokine imbalance denoted by IL18:IL10 was statistically significantly greater in the risk allele carriers MIA3 rs17465637 and CXCL12 rs1746048 while TNFalpha:IL10 ratio was raised markedly in the risk allele carriers of APOE rs429358; MRAS rs9818870 and LPL rs328.

Conclusion: The association of the selected SNPs with differential serum cytokine levels especially the cytokine imbalance points towards their potential causal role in the immune inflammatory pathogenic pathway of PCAD.

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