European Respiratory Society
Annual Congress 2012

Abstract Number: 5147

Publication Number: 4553

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Genetics **Keyword 2:** Pulmonary hypertension **Keyword 3:** Epidemiology

Title: Polymorphisms in angiotensin converting enzyme gene are associated with risk of development of and disease severity in scleroderma-related pulmonary arterial hypertension

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Body: Background: While 8-12% of patients with scleroderma (SSc) will develop pulmonary arterial hypertension (PAH), little is known about risk factors for this complication.Angiotensin converting enzyme (ACE) is associated with endothelial dysfunction and may play a role in susceptibility to vascular disease in SSc.We sought to identify polymorphisms in ACE gene that may contribute to risk of PAH in SSc.Methods: A case-control study was performed in 916 patients of European descent.Of 458 SSc patients,103 had right heart catheterization-proven PAH; the remainder did not have significant respiratory disease.Three single nucleotide polymorphisms (SNPs) in ACE gene [rs4293, rs3730025, rs4311], previously shown to be associated with cardiovascular disease, were examined.The relative frequency of SNPs and their relationship to presence of PAH and severity of PAH were assessed using Cochran-Armitage trend test with PLINK and linear regression for association between genotype and hemodynamics.Results: A strong association was found between SNP rs3730025 and risk of PAH (P=0.009).Carriers of G allele of rs4293 had increased cardiac index (ß=0.458, P=0.005) and decreased pulmonary vascular resistance (ß=-0.137, P=0.018).Conclusion: In this SSc cohort, a coding SNP in ACE gene was strongly associated with presence of PAH.Further, presence of SNP rs4293 was associated with preserved cardiac function in SSc-PAH.Given the role of these SNPs in the function of ACE and the relationship between ACE and vascular function, further studies are warranted to investigate the role of these SNPs in the pathogenesis of PAH in SSc.