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IS VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2 (VEGFR2) INVOLVED IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)? A COMBINED STRUCTURAL BIOLOGICAL AND GENETIC APPROACH

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Background The VEGFR2 directly regulates the formation of blood vessels, a process dependent upon the function of specialised cell-types including vascular endothelial cells. *VEGFR2* gene polymorphisms have been correlated with vascular diseases such as Coronary Heart Disease (CHD).

Aim In view of the premature atherosclerosis observed in SLE, the authors sought to clarify the structural/functional consequences of two common polymorphisms in *VEGFR2* in SLE and determine whether these polymorphisms are associated with risk of SLE by influencing endothelial cells.

Materials and methods Three-dimensional (3D) homology modeling of the mutation V297I was based on the 3D structure of domains D2 and D3 of *VEGFR2* in complex with VEGF-C, while mutation Q472H was investigated by homology modeling on the KIT ectodomain structure. The V297I (rs2305948) and Q472H (rs1870377) single nucleotide polymorphisms (SNPs) in *VEGFR2* were genotyped with Taqman technology in 250 SLE patients and 241 healthy controls from a Greek population (Cretan). The replication sample set for the rs1870377 SNP consisted of 253, 184 and 77 patients with SLE of African-, European- and Hispanic-American origin, respectively, as well as geographically/ethnically-matched controls.

Results Modeling revealed that amino acid position #297 is located on the D3 Ig-like domain of the extracellular region of *VEGFR2* on a surface loop and polymorphism V297I affects the efficiency of trans-autophosphorylation and cell signaling. On the other hand, position #472 is located on the surface of the D5 domain and mutation Q472H affects homotypic contacts of membrane proximal Ig-like domains. This finding prompted us to examine whether these polymorphisms contribute to SLE risk or vascular damage. No significant difference was observed in the frequency of the minor allele **A** of rs1870377 when SLE patients were compared with controls either in the Greek population or in the 3 replication groups analysed. No association was detected between rs2305948 SNP and SLE when tested in the Greek population.

Conclusions Although structural data suggest that both *VEGFR2* SNPs may contribute to SLE pathogenesis by impairing cell signaling, none of the SNPs analysed was associated with increased susceptibility to SLE. Experiments in progress address the role of these polymorphisms on the number of circulating endothelial cells and their possible influence to vascular injury observed in the disease.