CHARACTERIZATION OF A MUTATION IN THE ZONA PELLUCIDA MODULE OF ENDOGLIN THAT CAUSES HEREDITARY HEMORRHAGIC TELANGIECTASIA.

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Hereditary hemorrhagic telangiectasia (HHT) is a vascular rare disease characterized by nose and gastrointestinal bleeding, skin and mucosa telangiectasias, and arteriovenous malformations in internal organs. HHT shows an autosomal dominant inheritance and a worldwide prevalence of approximately 1:5000 individuals. In >80% of patients, HHT is caused by mutations in either ENG (HHT1) or ACVRL1 (HHT2) genes, which code for the membrane proteins Endoglin and Activin A Receptor Type II-Like Kinase 1 (ALK1), respectively, both belonging to the TGF-beta/BMP signaling pathway. In this work, we describe a novel mutation in exon 9 of ENG (c.1145 G > A) found in five affected members of a family, all of them with characteristic symptoms of HHT. This mutation involves Cys382 residue of the Endoglin protein (p.Cys382 > Tyr) in the zona pellucida (ZP) module of its extracellular region. This is a critical residue involved in a conserved intrachain disulphide bond and in the correct folding of the protein. In fact, transfection studies in human cells using Endoglin expression vectors demonstrated that the p.Cys382 > Tyr mutation results in a marked reduction in the levels of the Endoglin protein. These results demonstrate the pathogenic role for this variant in HHT1 and confirm the key function of Cys382 in Endoglin expression.