A Novel Splicing Mutation in the ACVRL1/ALK1 Gene as a Cause of HHT2

Una nueva mutación de empalme en el gen ACVRL1/ALK1 como causa de HHT2

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ABSTRACTO: Hereditary Hemorrhagic Telangiectasia (HHT) is a rare disorder of vascular development. Common manifestations include epistaxis, telangiectasias and arteriovenous malformations in multiple organs. Different deletions or nonsense mutations have been described in the ENG (HHT1) or ACVRL1/ALK1 (HHT2) genes, all affecting endothelial homeostasis. A novel mutation in ACVRL1/ALK1 has been identified in a Peruvian family with a clinical history compatible to HHT. Subsequently, 23 DNA samples from oral exchanges (buccal swaps) of the immediate family members were analyzed together with their clinical histories. A routine cDNA PCR followed by comparative DNA sequencing between the founder and another healthy family member showed the presence of the aforementioned specific mutation. The single mutation detected (c.525 + 1G > T) affects the consensus splice junction immediately after exon 4, provokes anomalous splicing and leads to the inclusion of intron IV between exons 4 and 5 in the ACVRL1/ALK1 mRNA and, therefore, to ALK1 haploinsufficiency. Complete sequencing determined that 10 of the 25 family members analyzed were affected by the same mutation. Notably, the approach described in this report could be used as a diagnostic technique, easily incorporated in clinical practice in developing countries and easily extrapolated to other patients carrying such a mutation