

Genetics of Holt-Oram syndrome

Holt-Oram syndrome (HOS) is an autosomal dominant disorder, characterized by congenital heart and upper limb malformations. Although genetically heterogeneous, HOS is frequently linked to the gene TBX5, in which mutations have been detected in affected individuals. In many patients with HOS, however, conventional methods have failed to reveal a mutation in TBX5, suggesting that some of the “missing” mutations may be due to exonic deletions. We applied Multiplex Amplifiable Probe Hybridization (MAPH) to genomic DNA from patients in which the mutation at TBX5 was unknown. A large novel deletion was detected encompassing exons 3-9 in two related patients. Although the causative mutation is still unknown in many HOS patients, this observation supports a haploinsufficiency mechanism for HOS.