Holt-Oram Syndrome

Genetics

-TBX5, SALL4

-AD, 85% de novo

Clinical findings

-Malformation of the carpal bone(s) (100%)

-Radial and/or thenar bones (left often more severe than right)

-Thumb anomaly

-Congenital heart malformation (75%): most often atrial septal defect (ASD) and ventricular septal defect (VSD), cardiac conduction disease, arrhythmia (even if no CHD)

Etiology

-Most common heart-hand syndrome; 0.7 and 1 per 100,000 births

Pathogenesis

-TBX5 protein product is TF with important role in cardiogenesis and limb development

-Mutant TBX5 mRNAs degrades rapidly or transcripts with diminished DNA binding —> decreased gene dosage

Genetic testing/diagnosis

-TBX5 sequencing (>70%), Del/Dupl analysis (<1%)

-More than 70% of ind. with clinical diagnosis have heterozygous pathogenic variant in TBX5

-Rarely: SALL4 mutations result in similar syndrome

Others

-Variants at the 5' end of T-box (which binds the major groove of the target DNA sequence) with more serious cardiac defects vs. missense variants at 3' end of the T-box (which binds the minor groove of the target DNA) result in more pronounced limb defects