U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: McDermott DA, Fong JC, Basson CT. Holt-Oram Syndrome. 2004 Jul 20 [Updated 2019 May 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Holt-Oram Syndrome

Synonym: Heart and Hand Syndrome

Deborah A McDermott, MS, CGC,[1] Jamie C Fong, MS, CGC,[2] and Craig T Basson, MD, PhD[3]

Created: July 20, 2004; Updated: May 23, 2019.

Summary

Clinical characteristics

Holt-Oram syndrome (HOS) is characterized by upper-limb defects, congenital heart malformation, and cardiac conduction disease. Upper-limb malformations may be unilateral, bilateral/symmetric, or bilateral/asymmetric and can range from triphalangeal or absent thumb(s) to phocomelia. Other upper-limb malformations can include unequal arm length caused by aplasia or hypoplasia of the radius, fusion or anomalous development of the carpal and thenar bones, abnormal forearm pronation and supination, abnormal opposition of the thumb, sloping shoulders, and restriction of shoulder joint movement. An abnormal carpal bone is present in all affected individuals and may be the only evidence of disease. A congenital heart malformation is present in 75% of individuals with HOS and most commonly involves the septum. Atrial septal defect and ventricular septal defect can vary in number, size, and location. Complex congenital heart malformations can also occur in individuals with HOS. Individuals with HOS with or without a congenital heart malformation are at risk for cardiac conduction disease. While individuals may present at birth with sinus bradycardia and first-degree atrioventricular (AV) block, AV block can progress unpredictably to a higher grade including complete heart block with and without atrial fibrillation.

Diagnosis/testing

The diagnosis of HOS is established in a proband with a preaxial radial ray anomaly and a personal or family history of cardiac septation and/or conduction defects. More than 70% of individuals who meet strict clinical diagnostic criteria have an identifiable heterozygous pathogenic variant in *TBX5*.

Author Affiliations: 1 Consultant, Human Genetics and Genetic Counseling Bedford, New York; Email: mcdermottdeborah@yahoo.com. 2 Memory & Aging Center Department of Neurology University of California, San Francisco San Francisco, California; Email: jamie.fong@ucsf.edu. 3 Vice President, Global Head, Translational Medicine (Cardiovascular and Metabolism) Novartis Institutes for BioMedical Research Cambridge, Massachusetts; Email: craig.basson@novartis.com.

Management

Treatment of manifestations: Management involves a multidisciplinary team of specialists in medical genetics, cardiology, orthopedics, and hand surgery. Treatment for arrhythmias may require medication, surgery, and/or pacemaker implantation. Pharmacologic treatment for individuals with pulmonary hypertension. Cardiac surgery for congenital heart defects is standard; affected individuals and families are also likely to benefit from programs providing social support to those with limb anomalies.

Prevention of secondary complications: A cardiologist can assist in determining the need for anticoagulants and antibiotic prophylaxis for bacterial endocarditis.

Surveillance: Annual EKG for all affected individuals, annual Holter monitor for individuals with known conduction disease, and echocardiogram every one to five years for those with septal defects or as directed by a cardiologist.

Evaluation of relatives at risk: Presymptomatic diagnosis and treatment is warranted in relatives at risk to identify those who would benefit from appropriate cardiac management.

Pregnancy management: Affected women who have not undergone cardiac evaluation should do so prior to pregnancy or as soon as the pregnancy is recognized; those with a known history of a structural cardiac defect or cardiac conduction abnormality should be followed by a cardiologist during pregnancy.

Genetic counseling

HOS is inherited in an autosomal dominant manner. Approximately 85% of affected individuals have HOS as the result of a *de novo* pathogenic variant. Offspring of an affected individual are at a 50% risk of being affected. In pregnancies at 50% risk, detailed high-resolution prenatal ultrasound examination may detect upper-limb malformations and/or congenital heart malformations. Prenatal molecular genetic testing may be used to confirm a diagnosis if the *TBX5* pathogenic variant has been identified in an affected relative.

Diagnosis

Clinical diagnostic criteria for Holt-Oram syndrome have been established and validated through molecular genetic testing [McDermott et al 2005].

Suggestive Findings

Holt-Oram syndrome (HOS) **should be suspected** in individuals with the following limb anomalies, cardiac findings, and family history:

- **Upper-limb malformation** involving the carpal bone(s) and, variably, the radial and/or thenar bones
  - Upper-limb malformations may be unilateral, bilateral/symmetric, or bilateral/asymmetric.
  - An abnormal carpal bone, present in all affected individuals and identified by performing a posterior-anterior hand x-ray [Poznanski et al 1970, Basson et al 1994], may be the only evidence of disease.
- **Congenital heart malformation,** most commonly ostium secundum atrial septal defect (ASD) and ventricular septal defect (VSD), especially those occurring in the muscular trabeculated septum
- **Cardiac conduction disease**
- **Family history** of a first-degree relative with a congenital heart defect or cardiac conduction disease

Note: Congenital malformations involving the following structures or organ systems are not typically within the spectrum of HOS and should prompt the clinician to consider alternate diagnoses: ulnar ray only, kidney, vertebra, craniofacies, auditory system (ear malformations ± hearing loss), lower limb, anus, and eye.

Establishing the Diagnosis

The diagnosis of Holt-Oram syndrome **is established** in a proband with either a preaxial radial ray anomaly and a personal or family history of cardiac septation and/or conduction defects or, if clinical findings are insufficient, a heterozygous pathogenic (or likely pathogenic) variant in *TBX5* identified by molecular genetic testing (see Table 1).

Molecular testing approaches can include **single-gene testing** and – if the phenotype includes features that are atypical for Holt-Oram syndrome – a **multigene panel**. Though rare, chromosome rearrangements involving 12q24 have been reported in individuals with Holt-Oram syndrome [Li et al 1997, Basson et al 1999].

- **Single-gene testing.** Sequence analysis of *TBX5* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *TBX5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Holt-Oram Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TBX5	Sequence analysis [3]	>70%[4]
	Gene-targeted deletion/duplication analysis [5]	<1% [6]

Table 1. continued from previous page.

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Individuals meeting the strict diagnostic criteria of upper-limb defect and personal and/or family history of structural or conductive heart disease have a heterozygous *TBX5* pathogenic variant predicted to cause disease [McDermott et al 2005, Debeer et al 2007]. Lower pathogenic variant detection rates (30%-40%) reported in some studies likely result from the inclusion of individuals who would not meet the strict diagnostic criteria outlined above [Cross et al 2000, Brassington et al 2003].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Deletion of one or more exons or the entire gene was detected in about 2% of individuals with HOS who did not have a pathogenic variant identified by sequence analysis/variant scanning [Borozdin et al 2006].
7. That current molecular analysis fails to identify a heterozygous pathogenic variant in *TBX5* in up to 30% of individuals with HOS suggests the presence of pathogenic variants in noncoding regions or regulatory regions around *TBX5* [McDermott et al 2005, Debeer et al 2007].

Clinical Characteristics

Clinical Description

Holt-Oram syndrome is characterized by upper-limb defects, congenital heart malformation, and cardiac conduction disease [Holt & Oram 1960].

Upper-limb malformations may be unilateral, bilateral/symmetric, or bilateral/asymmetric and can range from triphalangeal or absent thumb(s) to phocomelia, a malformation in which the hands are attached close to the body; intermediate presentations resulting from abnormal development of the bones involved may also be observed. Other upper-limb malformations can include unequal arm length caused by aplasia or hypoplasia of the radius, fusion or anomalous development of the carpal and thenar bones, abnormal forearm pronation and supination, abnormal opposition of the thumb, and sloping shoulders and restriction of shoulder joint movement.

While all individuals have an upper-limb defect, the broad range of severity of these findings is such that some individuals with the mildest upper-limb malformations and mild or no congenital heart malformation may escape diagnosis. These individuals may only be diagnosed when a more severely affected relative is born or when symptoms develop in middle age as a result of cardiac abnormalities such as pulmonary hypertension, high-grade atrioventricular block, and/or atrial fibrillation. Cardiac conduction disease can be progressive.

A congenital heart malformation is present in 75% of individuals with HOS and most commonly involves the septum. Atrial septal defect (ASD) and ventricular septal defect (VSD) can vary in number, size, and location. ASDs can present as a common atrium and are often associated with cardiac chamber isomerism; that is, the defining features of the cardiac chambers, based on their anatomic location, are altered (e.g., what may be considered right atrium based on its anatomic location may not have the atrial appendage morphology typical of the right atrium).

Some individuals with severe congenital heart malformation may require surgery early in life to repair significant septal defects [Sletten & Pierpont 1996].

Other individuals may have complex congenital heart malformations [Faria et al 2008, Baban et al 2014, Barisic et al 2014]; conotruncal malformations, though observed in HOS, are not common and may be caused by other genetic defects.

Cardiac conduction disease. Individuals with HOS with or without a congenital heart malformation are at risk for cardiac conduction disease. While individuals may present at birth with sinus bradycardia and first-degree atrioventricular (AV) block, AV block can progress unpredictably to a higher grade including complete heart block with and without atrial fibrillation.

The natural history of HOS varies by individual and largely depends on the severity of the congenital heart malformation. Potential complications (which can be life threatening if not recognized and appropriately managed) include congestive heart failure, pulmonary hypertension, arrhythmias, heart block, atrial fibrillation, and infective endocarditis.

Genotype-Phenotype Correlations

It has been reported that pathogenic missense variants at the 5' end of the T-box (which binds the major groove of the target DNA sequence) are associated with more serious cardiac defects.

Pathogenic missense variants at the 3' end of the T-box (which binds the minor groove of the target DNA) result in more pronounced limb defects. Caution is warranted, however, in applying these population-based associations to individuals in whom pathogenic variants may not predict specific phenotypes [Basson et al 1999, Brassington et al 2003].

In addition, genotypes do not appear to predict the progressive hemodynamic course associated with any particular cardiac septal defect.

Penetrance

The upper-limb malformations in HOS are fully penetrant.

Congenital heart malformations occur in approximately 75% of affected individuals [Basson et al 1999]. Conduction defects may occur in the presence or absence of structural heart defects.

Nomenclature

HOS has been referred to as heart-hand syndrome, a nonspecific designation that could apply to any number of conditions with involvement of these structures.

Prevalence

HOS is the most common of the heart-hand syndromes. The estimated prevalence of HOS is between 0.7 and 1 per 100,000 births [Elek et al 1991, Barisic et al 2014].

HOS has been reported from a number of countries worldwide and in individuals of different backgrounds [Boehme & Shotar 1989, Yang et al 2000, Barisic et al 2014, Kimura et al 2015].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with heterozygous germline pathogenic variants in *TBX5* [Reamon-Buettner & Borlak 2004].

Variants in *TBX5* enhancers have been implicated in the pathogenesis of nonsyndromic ASDs or VSDs, the predominant cardiac malformations in individuals with HOS [Smemo et al 2012].

Differential Diagnosis

Diagnoses summarized in Table 2 can be considered when anomalies involving the ulna, lower limbs, kidneys, genitourinary system, vertebrae, craniofaces, and auditory or ocular systems are present [Newbury-Ecob et al 1996, Allanson & Newbury-Ecob 2003, Bressan et al 2003].

Table 2. Disorders to Consider in the Differential Diagnosis of Holt-Oram Syndrome (HOS)

Disorder/Condition	Gene(s) / Genetic Mechanism	MOI	Clinical Description	Comments
Duane-radial ray syndrome	*SALL4*	AD	• Uni- or bilateral Duane anomaly • Radial ray malformation (e.g, thenar hypoplasia, thumb hypoplasia, aplasia, duplication or triphalangeal thumb, radius hypoplasia or aplasia, shortening & radial deviation of forearms)	• *SALL4* pathogenic variants may rarely cause what appears to be clinically typical HOS (i.e., radial ray malformations & cardiac malformations). • Further clinical investigations frequently demonstrate features considered exclusionary of HOS (e.g., renal anomalies, Duane anomaly, sensorineural hearing loss).
Acro-renal-ocular syndrome		AD	• Radial ray malformations • Renal abnormalities • Ocular coloboma • Duane anomaly	
Ulnar-mammary syndrome (OMIM 181450)	*TBX3*	AD	• Primarily involves ulnar ray (e.g., postaxial polydactyly) • Breast & nipple hypoplasia & delayed puberty • Congenital heart malformations (not commonly observed)	
Townes-Brocks syndrome	*SALL1*	AD	• Triad of: imperforate anus; dysplastic ears (overfolded superior helices & preauricular tags) frequently associated w/ sensorineural &/or conductive hearing impairment; & thumb malformations (duplication, hypoplasia, or triphalangeal thumbs) • Renal impairment incl ESRD w/or w/out structural abnormalities • Congenital heart disease • Foot malformations (flat feet, overlapping toes) • Genitourinary malformations • ID in ~10% of affected persons	

Table 2. continued from previous page.

Disorder/Condition	Gene(s) / Genetic Mechanism	MOI	Clinical Description	Comments
Heart-hand syndrome II (Tabatznik syndrome) [1]	Not identified	AD	• Type D brachydactyly (shortening of distal phalanx of the thumb ± shortening of 4th & 5th metacarpals) • Sloping shoulders • Short upper limbs, bowing of distal radii, absence of styloid process of the ulna • Cardiac arrhythmias (e.g., supraventricular tachycardia) • Mild dysmorphic facial features • Mild ID	
Heart-hand syndrome III (Spanish type) (OMIM 140450)	Not identified	AD	• Type C brachydactyly (shortening of the middle phalanges) w/accessory wedge-shaped ossicle on proximal phalanx of index fingers • Feet typically more mildly affected • Intraventricular conduction defects (e.g., sick sinus syndrome)	
Long thumb brachydactyly syndrome (OMIM 112430)	Not identified	AD	• Symmetric elongation of thumb distal to proximal interphalangeal joint • Index finger brachydactyly • Clinodactyly • Narrow shoulders • Secondary short clavicles • Pectus excavatum • Cardiac abnormality is often a conduction defect.	
Heart-hand syndrome, Slovenian type (OMIM 610140)	*LMNA*	AD	• Familial progressive sinoatrial & atrioventricular conduction disease of adult onset w/sudden death • Dilated cardiomyopathy • Brachydactyly • Feet also involved	
Fanconi anemia	>20 genes [2]	AR AD XL	• Short stature • Abnormal skin pigmentation • Malformations of thumbs, forearms, eyes, ears, oral cavity, genitourinary system, heart, gastrointestinal system, central nervous system • DD • Progressive bone marrow failure w/ pancytopenia typically presenting in 1st decade, often initially w/ thrombocytopenia or leukopenia • Increased risk for malignancy	

Table 2. continued from previous page.

Disorder/Condition	Gene(s) / Genetic Mechanism	MOI	Clinical Description	Comments
Thrombocytopenia-absent radius syndrome (TAR)	*RBM8A* [3]	AR	• Bilateral absence of radii w/presence of both thumbs • Thrombocytopenia (<50 platelets/nL), generally transient	Other findings in TAR, (esp hematologic & neurologic) & frequent involvement of lower limbs differentiate TAR from HOS.
22q11.2 deletion syndrome (del22q11.2)	Deletion of 22q11.2 DGCR	AD	• Congenital heart disease • ~6% of persons exhibit upper-extremity anomalies incl pre- & postaxial polydactyly, which may → misdiagnosis of HOS.	Other features in del22q11.2 incl palatal abnormalities (69%), learning difficulties (70%-90), & immune deficiency (77%), distinguish del22q11.2 from HOS.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DGCR = DiGeorge chromosome region; ESRD = end-stage renal disease; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Silengo et al [1990]

2. Genes known to be associated with Fanconi anemia: *BRCA2*, *BRIP1*, *ERCC4*, *FANCA*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *FANCM*, *MAD2L2*, *PALB2*, *RAD51*, *RAD51C*, *RFWD3*, *SLX4*, *UBE2T*, *XRCC2*

3. The diagnosis of TAR syndrome is established in a proband with bilateral absent radii, present thumbs, and thrombocytopenia. Identification of a heterozygous null allele (most often a minimally deleted 200-kb region at chromosome band 1q21.1) *in trans* with a heterozygous *RBM8A* hypomorphic allele on molecular genetic testing confirms the diagnosis.

Other Diagnoses to Consider in the Differential Diagnosis of HOS

Disorders of unknown cause

- **VACTERL** (*v*ertebral defects, *a*nal atresia, *c*ardiac malformation, *t*racheo-*e*sophageal fistula with esophageal atresia, *r*enal anomalies, and *l*imb anomalies)

Teratogen exposure

- **Thalidomide.** Exposure to thalidomide in pregnancy places the fetus at risk for severe upper- and lower-limb defects (e.g., phocomelia, amelia), cardiac defects, and malformations in other systems not observed in HOS (renal, ocular, auditory, gastrointestinal, and craniofacial) [Matthews & McCoy 2003, McDermott et al 2005, Vianna et al 2013].
- **Valproate.** Exposure to valproate, particularly in the first trimester, places the fetus at risk for major congenital defects including congenital heart defects that can overlap those seen in HOS; however, the other malformations seen (e.g., polydactyly, spina bifida) are not features of HOS [McDermott et al 2005, Wyszynski et al 2005].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Holt-Oram syndrome (HOS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Holt-Oram Syndrome

System/Concern	Evaluation	Comment
Musculoskeletal	Physical examination for limb involvement	Hand & upper-limb radiographs may be recommended by orthopedist to aid in management of radial ray malformations.
Cardiac	Chest radiography	To identify enlarged pulmonary arteries caused by pulmonary hypertension or cardiomegaly &/or evidence of congestive heart failure
	Echocardiography	To identify septal defects or other structural cardiac anomalies
	EKG	To identify cardiac conduction disease
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

The management of individuals with HOS optimally involves a multidisciplinary team approach with specialists in medical genetics, cardiology, and orthopedics, including a specialist in hand surgery.

A cardiologist can assist in determining the need for antiarrhythmic medications and surgery. Individuals with severe heart block may require pacemaker implantation. Pharmacologic treatment for affected individuals with pulmonary hypertension may be appropriate. Individuals with pulmonary hypertension and/or structural heart malformation may require tertiary care center cardiology follow up. Cardiac surgery, if required for congenital heart defect, is standard.

The orthopedic team may be able to guide individuals in decisions regarding surgery for improved upper-limb and hand function as well as physical and occupational therapy options. Those individuals born with severe upper-limb malformations may be candidates for surgery to improve function, such as pollicization (creation of a thumb-like digit by moving another digit into the thenar position) in individuals with thumb aplasia/hypoplasia [Vaienti et al 2009]. Children with severe limb shortening may benefit from prostheses as well as from physical and occupational therapy.

Individuals and families are also likely to benefit from programs providing social support to those with limb anomalies.

Prevention of Secondary Complications

A cardiologist can assist in determining the need for anticoagulants and antibiotic prophylaxis for bacterial endocarditis (SBE).

Surveillance

Table 4. Recommended Surveillance for Individuals with Holt-Oram Syndrome

System/Concern	Evaluation	Frequency
Cardiac	EKG	Annually in those at risk of developing a conduction defect
	EKG combined w/Holter monitor	Annually in those w/known conduction disease to assess progression
	Echocardiogram	Every 1-5 yrs; may be recommended by managing cardiologist depending on nature & significance of potential septal defects.

Agents/Circumstances to Avoid

Certain medications may be contraindicated in individuals with arrhythmias, cardiomyopathy, and/or pulmonary hypertension. People with such disorders require individual assessment by a cardiologist.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from appropriate cardiac management. Evaluations can include:

- Molecular genetic testing if the *TBX5* pathogenic variant in the family is known;
- Echocardiography, EKG, and hand x-rays (anterior/posterior view) if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnant women with HOS who have a known history of a structural cardiac defect or cardiac conduction abnormality should be followed by a multidisciplinary team (including a cardiologist) during pregnancy. Affected women who have not undergone cardiac evaluation should do so prior to pregnancy if possible, or as soon as the pregnancy is recognized.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Holt-Oram syndrome (HOS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with HOS have an affected parent.
- A proband with HOS often has the disorder as the result of a heterozygous *de novo TBX5* pathogenic variant. Up to 85% of cases are caused by a *de novo* pathogenic variant [Elek et al 1991], while approximately 15% of cases are familial [Barisic et al 2014].
- Recommendations for the evaluation of parents of a proband with an apparent heterozygous *de novo* pathogenic variant include echocardiography, EKG, and hand x-rays (anterior/posterior view) to

determine their affected status. Alternatively, molecular genetic testing can be performed on the parents if the *TBX5* pathogenic variant in the proband has been identified.

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Presumed parental germline mosaicism has been reported [Braulke et al 1991].
- The family history of some individuals diagnosed with HOS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may be mildly/minimally affected.

Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or has the *TBX5* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Significant intrafamilial clinical variability is observed.
- If the parents are clinically unaffected and the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to the sibs of a proband appears to be low but slightly greater than the general population risk of approximately 1/100,000 because of the possibility of parental germline mosaicism.

Offspring of a proband

- Offspring of a proband are at 50% risk of inheriting the *TBX5* pathogenic variant.
- Because of the effects of modifying genes and the significant variable expressivity observed in individuals with HOS, both among and within families with the same *TBX5* pathogenic variant, the phenotype of affected offspring cannot be accurately predicted.

Other family members. The risk to other family members depends on the status of the proband's parents; if a parent is affected/has the pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Specific risk issues. Specific clinical risks of concern for at-risk family members are those related to life-threatening cardiac issues including congestive heart failure, arrhythmias, heart block, atrial fibrillation, pulmonary hypertension, and infective endocarditis.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *TBX5* pathogenic variant in the family.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

For pregnancies known to be at increased risk for HOS

- Once the *TBX5* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.
- If the *TBX5* pathogenic variant is identified in a fetus, molecular genetic testing should be followed by detailed ultrasound (US) evaluation.
- If the pathogenic variant in the family is not known, US examination evaluating for characteristic limb and cardiac manifestations (including fetal echocardiogram) is recommended. Note: A normal ultrasound examination does not eliminate the possibility of HOS in the fetus.

For pregnancies not known to be at increased risk for HOS. If a routine US examination has identified limb and cardiac manifestations characteristic of HOS, consider prenatal molecular genetic testing from a clinical laboratory that offers testing for *TBX5* or custom prenatal testing for other disorders in the differential diagnosis (see Differential Diagnosis).

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Because of the significant variable expressivity observed in individuals with HOS both among and within families with the same pathogenic variant, the severity of upper-limb defects and congenital heart malformations cannot be accurately predicted by molecular genetic testing alone.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**

  Holt-Oram syndrome

- **American Heart Association**

  Phone: 800-242-8721

  www.americanheart.org

- **REACH**

  Helping children with upper limb differences live life without limits.

  United Kingdom

  Phone: 0845 1306 225; 020 3478 0100

  www.reach.org.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Holt-Oram Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TBX5	12q24.21	T-box transcription factor TBX5	TBX5 database	TBX5	TBX5

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Holt-Oram Syndrome (View All in OMIM)

142900	HOLT-ORAM SYNDROME; HOS
601620	T-BOX TRANSCRIPTION FACTOR 5; TBX5

T-box transcription factor TBX5 functions as a transcription factor that has an important role in both cardiogenesis and limb development. TBX5 can interact with other transcription factors including NKX2.5 and GATA4, and these interactions may participate in regulating cardiogenesis. Appropriate balance between expression of TBX5 and other T-box transcription factors may be required for specification of cardiac and limb structures during embryogenesis [Hatcher et al 2001, Rallis et al 2003, Ghosh et al 2009, Maitra et al 2009, Rothschild et al 2009, Camarata et al 2010a, Camarata et al 2010b, Nadeau et al 2010].

It is hypothesized that most nonsense and frameshift pathogenic variants lead to mutated *TBX5* mRNAs that are degraded, resulting in haploinsufficiency. Some missense pathogenic variants result in transcripts that have diminished DNA-binding activity. Both result in reduced functional TBX5, which leads to disease [Hatcher & Basson 2001]. By contrast, studies reporting pathogenic variants predicting either an elongated TBX5 or an intragenic *TBX5* duplication suggest the possibility of a dominant-negative effect on downstream targets [Böhm et al 2008, Patel et al 2012]. Researchers who recently elucidated the crystal structure of the *TBX5* T-box domain in its DNA-unbound and DNA-bound forms have identified an inducible C-terminal element within the T-box domain that may be required for the interaction of *TBX5* with DNA [Stirnimann et al 2010].

Mechanism of disease causation. Loss of function or dominant-negative interference with function

Chapter Notes

Revision History

- 23 May 2019 (sw) Comprehensive update posted live
- 8 October 2015 (me) Comprehensive update posted live
- 4 April 2013 (me) Comprehensive update posted live
- 4 January 2011 (me) Comprehensive update posted live
- 22 November 2006 (cd) Revision: array genomic hybridization and deletion/duplication testing clinically available
- 21 September 2006 (me) Comprehensive update posted live
- 20 July 2004 (me) Review posted live
- 23 December 2003 (cb) Original submission

References

Literature Cited

Allanson JE, Newbury-Ecob RA. Holt-Oram syndrome: is there a "face"? Am J Med Genet. 2003;118A:314–8. PubMed PMID: 12687661.

Baban A, Pitto L, Pulignani S, Cresci M, Mariani L, Gambacciani C, Digilio MC, Pongiglione G, Albanese S. Holt-Oram syndrome with intermediate atrioventricular canal defect, and aortic coarctation: functional characterization of a de novo TBX5 mutation. Am J Med Genet A. 2014;164A:1419–24. PubMed PMID: 24664498.

Barisic I, Boban L, Greenlees R, Garne E, Wellesley D, Calzolari E, Addor MC, Arriola L, Bergman JE, Braz P, Budd JL, Gatt M, Haeusler M, Khoshnood B, Klungsoyr K, McDonnell B, Nelen V, Pierini A, Queisser-Wahrendorf A, Rankin J, Rissmann A, Rounding C, Tucker D, Verellen-Dumoulin C, Dolk H. Holt-Oram syndrome: a registry-based study in Europe. Orphanet J Rare Dis. 2014;9:156. PubMed PMID: 25344219.

Basson CT, Cowley GS, Solomon SD, Weissman B, Poznanski AK, Traill TA, Seidman JG, Seidman CE. The clinical and genetic spectrum of the Holt-Oram syndrome (heart-hand syndrome). N Engl J Med. 1994;330:885–91. PubMed PMID: 8114858.

Basson CT, Huang T, Lin RC, Bachinsky DR, Weremowicz S, Vaglio A, Bruzzone R, Quadrelli R, Lerone M, Romeo G, Silengo M, Pereira A, Krieger J, Mesquita SF, Kamisago M, Morton CC, Pierpont ME, Muller CW, Seidman JG, Seidman CE. Different TBX5 interactions in heart and limb defined by Holt-Oram syndrome mutations. Proc Natl Acad Sci U S A. 1999;96:2919–24. PubMed PMID: 10077612.

Boehme DH, Shotar AO. A complex deformity of appendicular skeleton and shoulder with congenital heart disease in three generations of a Jordanian family. Clin Genet. 1989;36:442–50. PubMed PMID: 2591070.

Böhm J, Heinritz W, Craig A, Vujic M, Ekman-Joelsson BM, Kohlhase J, Froster U. Functional analysis of the novel TBX5 c.1333delC mutation resulting in an extended TBX5 protein. BMC Med Genet. 2008;9:88–94. PubMed PMID: 18828908.

Borozdin W, Bravo Ferrer Acosta AM, Bamshad MJ, Botzenhart EM, Froster UG, Lemke J, Schinzel A, Spranger S, McGaughran J, Wand D, Chrzanowska KH, Kohlhase J. Expanding the spectrum of TBX5 mutations in Holt-Oram syndrome: detection of two intragenic deletions by quantitative real time PCR, and report of eight novel point mutations. Hum Mutat. 2006;27:975–6. PubMed PMID: 16917909.

Brassington AM, Sung SS, Toydemir RM, Le T, Roeder AD, Rutherford AE, Whitby FG, Jorde LB, Bamshad MJ. Expressivity of Holt-Oram syndrome is not predicted by TBX5 genotype. Am J Hum Genet. 2003;73:74–85. PubMed PMID: 12789647.

Braulke I, Herzog S, Thies U, Zoll B. Holt-Oram syndrome in four half-siblings with unaffected parents: brief clinical report. Clin Genet. 1991;39:241–4. PubMed PMID: 2070544.

Bressan MC, McDermott DA, Spencer RH, Basson CT. TBX5 genetic testing validates strict clinical criteria for Holt-Oram syndrome. Circulation. 2003;108:358:A1675

Camarata T, Kremery J, Snyder D, Park S, Topczewski J, Simon HG. Pdlim7 (LMP4) regulation of Tbx5 specifies zebrafish heart atrio-ventricular boundary and valve formation. Dev Biol. 2010a;337:233–45. PubMed PMID: 19895804.

Camarata T, Snyder D, Schwend T, Klosowiak J, Holtrup B, Simon HG. Pdlim7 is required for maintenance of the mesenchymal/epidermal Fgf signaling feedback loop during zebrafish pectoral fin development. BMC Dev Biol. 2010b;10:104. PubMed PMID: 20950450.

Cross SJ, Ching YH, Li QY, Armstrong-Buisseret L, Spranger S, Lyonnet S, Bonnet D, Penttinen M, Jonveaux P, Leheup B, Mortier G, Van Ravenswaaij C, Gardiner CA. The mutation spectrum in Holt-Oram syndrome. J Med Genet. 2000;37:785–7. PubMed PMID: 11183182.

Debeer P, Race V, Gewillig M, Devriendt K, Frijns JP. Novel TBX5 mutations in patients with Holt-Oram syndrome. Clin Orthop Relat Res. 2007;(462):20–6. PubMed PMID: 17534187.

Elek C, Vitéz M, Czeizel E. Holt-Oram syndrome. Orv Hetil. 1991;132:73–4. PubMed PMID: 1996196.

Faria MH, Rabenhorst SH, Pereira AC, Krieger JE. A novel TBX5 missense mutation (V263M) in a family with atrial septal defects and postaxial hexodactyly. Int J Cardiol. 2008;130:30–5. PubMed PMID: 18706711.

Ghosh TK, Song FF, Packham EA, Buxton S, Robinson TE, Ronksley J, Self T, Bonser AJ, Brook JD. Physical interaction between TBX5 and MEF2C is required for early heart development. Mol Cell Biol. 2009;29:2205–18. PubMed PMID: 19204083.

Hatcher CJ, Basson CT. Getting the T-box dose right. Nat Med. 2001;7:1185–6. PubMed PMID: 11689880.

Hatcher CJ, Kim MS, Mah CS, Goldstein MM, Wong B, Mikawa T, Basson CT. TBX5 transcription factor regulates cell proliferation during cardiogenesis. Dev Biol. 2001;230:177–88. PubMed PMID: 11161571.

Holt M, Oram S. Familial heart disease with skeletal malformations. Br Heart J. 1960;22:236–42. PubMed PMID: 14402857.

Kimura M, Kikuchi A, Ichinoi N, Kure S. Novel TBX5 duplication in a Japanese family with Holt-Oram syndrome. Pediatr Cardiol. 2015;36:244–7. PubMed PMID: 25274398.

Li QY, Newbury-Ecob RA, Terrett JA, Wilson DI, Curtis AR, Yi CH, Gebuhr T, Bullen PJ, Robson SC, Strachan T, Bonnet D, Lyonnet S, Young ID, Raeburn JA, Buckler AJ, Law DJ, Brook JD. Holt-Oram syndrome is caused by mutations in TBX5, a member of the Brachyury (T) gene family. Nat Genet. 1997;15:21–9. PubMed PMID: 8988164.

Maitra M, Schluterman MK, Nichols HA, Richardson JA, Lo CW, Srivastava D, Garg V. Interaction of Gata4 and Gata6 with Tbx5 is critical for normal cardiac development. Dev Biol. 2009;326:368–77. PubMed PMID: 19084512.

Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. Clin Ther. 2003;25:342–95. PubMed PMID: 12749503.

McDermott DA, Bressan MC, He J, Lee JS, Aftimos S, Brueckner M, Gilbert F, Graham GE, Hannibal MC, Innis JW, Pierpont ME, Raas-Rothschild A, Shanske AL, Smith WE, Spencer RH, St John-Sutton MG, van Maldergem L, Waggoner DJ, Weber M, Basson CT. TBX5 genetic testing validates strict clinical criteria for Holt-Oram syndrome. Pediatr Res. 2005;58:981–6. PubMed PMID: 16183809.

Nadeau M, Georges RO, Laforest B, Yamak A, Lefebvre C, Beauregard J, Paradis P, Bruneau BG, Andelfinger G, Nemer M. An endocardial pathway involving Tbx5, Gata4, and Nos3 required for atrial septum formation. Proc Natl Acad Sci. 2010;107:19356–61. PubMed PMID: 20974940.

Newbury-Ecob RA, Leanage R, Raeburn JA, Young ID. Holt-Oram syndrome: a clinical genetic study. J Med Genet. 1996;33:300–7. PubMed PMID: 8730285.

Patel C, Silcock L, McMullan D, Brueton L, Cox H. TBX5 intragenic duplication: a family with an atypical Holt-Oram syndrome phenotype. Eur J Hum Genet. 2012;20:863–9. PubMed PMID: 22333898.

Poznanski AK, Gall JC Jr, Stern AM. Skeletal manifestations of the Holt-Oram syndrome. Radiology. 1970;94:45–53. PubMed PMID: 5410358.

Rallis C, Bruneau BG, Del Buono J, Seidman CE, Seidman JG, Nissim S, Tabin CJ, Logan MP. Tbx5 is required for forelimb bud formation and continued outgrowth. Development. 2003;130:2741–51. PubMed PMID: 12736217.

Reamon-Buettner SM, Borlak J. TBX5 mutations in non-Holt-Oram syndrome (HOS) malformed hearts. Hum Mutat. 2004;24:104. PubMed PMID: 15221798.

Rothschild SC, Easley CA 4th, Francescatto L, Lister JA, Garrity DM, Tombes RM. Tbx5-mediated expression of Ca(2+)/calmodulin-dependent protein kinase II is necessary for zebrafish cardiac and pectoral fin morphogenesis. Dev Biol. 2009;330:175–84. PubMed PMID: 19345202.

Silengo MC, Biagioli M, Guala A, Lopez-Bell G, Lala R. Heart-hand syndrome II. A report of Tabatznik syndrome with new findings. Clin Genet. 1990;38:105–13. PubMed PMID: 1976459.

Sletten LJ, Pierpont ME. Variation in severity of cardiac disease in Holt-Oram syndrome. Am J Med Genet. 1996;65:128–32. PubMed PMID: 8911604.

Smemo S, Campos LC, Moskowitz IP, Krieger JE, Pereira AC, Nobrega MA. Regulatory variation in TBX5 enhancer leads to isolated congenital heart disease. Hum Mol Genet. 2012;21:3255–63. PubMed PMID: 22543974.

Stirnimann CU, Ptchelkine D, Grimm C, Müller CW. Structural basis of TBX5-DNA recognition: the T-box domain in its DNA-bound and -unbound form. J Mol Biol. 2010;400:71–81. PubMed PMID: 20450920.

Vaienti L, Zilio D, Ravasio G, Gazzola R, Marchesi A. The pollicization of the index finger in the aplasia of the thumb. Pediatr Med Chir. 2009;31:258–61. PubMed PMID: 20333885.

Vianna FSL, Schueler-Faccini L, Leite JC, de Sousa SH, da Costa LM, Dias MF, Morelo EF, Doriqui MJ, Maximino CM, Sanseverino MT. Recognition of the phenotype of thalidomide embryopathy in countries endemic for leprosy: new cases and review of the main dysmorphological findings. Clin Dysmorphol. 2013;22:59–63. PubMed PMID: 23448904.

Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology. 2005;64:961–5. PubMed PMID: 15781808.

Yang J, Hu D, Xia J, Yang Y, Ying B, Hu J, Zhou X. Three novel TBX5 mutations in Chinese patients with Holt-Oram syndrome. Am J Med Genet. 2000;92:237–40. PubMed PMID: 10842287.

License