GENEReviews

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Holt-Oram Syndrome

[*Heart and Hand Syndrome*]

Deborah A McDermott, MS, CGC
Greenberg Division of Cardiology
Department of Medicine
Weill Medical College, Cornell
dam2001@med.cornell.edu

Craig T Basson, MD, PhD, FAHA, FACC
Director, Cardiovascular Research
Greenberg Division of Cardiology
Department of Medicine
Weill Medical College, Cornell
ctbasson@med.cornell.edu

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Summary

Disease characteristics. Holt-Oram syndrome (HOS) is characterized by (1) upper-extremity malformations involving radial, thenar, or carpal bones; (2) a personal and/or family history of congenital heart malformation, most commonly ostium secundum atrial septal defect (ASD) and ventricular septal defect (VSD), especially those occurring in the muscular trabeculated septum; and/or (3) cardiac conduction disease. An abnormal carpal bone is present in all affected individuals and may be the only evidence of disease. Seventy-five percent of individuals with HOS have a congenital heart malformation.

Diagnosis/testing. The diagnosis of HOS is based on established clinical criteria and can be confirmed through clinically available molecular genetic testing. More than 70% of individuals who meet strict diagnostic criteria have an identifiable mutation in the *TBX5* gene.

Management. Management of HOS involves a multidisciplinary team approach involving specialists in medical genetics, cardiology, orthopedics, and hand surgery. Affected individuals and families are also likely to benefit from programs providing social support to those with limb anomalies. Surveillance includes annual ECG 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.

Genetic counseling. HOS is inherited in an autosomal dominant manner. Approximately 85% of affected individuals have HOS as the result of *de novo* mutations. Offspring of a proband are at 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 ultrasound findings in families in which the disease-causing mutation has been identified in an affected relative.

Diagnosis

Clinical Diagnosis

The diagnosis of Holt-Oram syndrome (HOS) can be established clinically. The diagnostic criteria have been validated with molecular testing [McDermott et al 2005]. Clinical findings in HOS:

- **An upper-limb malformation involving the carpal bone(s) and, variably, the radial and/or thenar bones**
  - The upper-limb malformations are variably expressed, even within affected families, and may be unilateral, bilateral/symmetric, or bilateral/asymmetric.
  - Abnormalities are often more severe in the left upper limb than in the right upper limb.
  - 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.
  - Upper-limb malformations range from triphalangeal or absent thumb(s) to phocomelia, a malformation in which the hands are attached close to the body, as well as more intermediate presentations resulting from abnormal development of the bones involved.
  - 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.
- **A personal and/or family history of congenital heart malformation**
  - A congenital heart malformation is present in 75% of individuals with HOS.
  - The congenital heart malformations most commonly observed are ostium secundum atrial septal defect (ASD) and ventricular septal defect (VSD), especially those occurring in the muscular trabeculated septum. ASDs and VSDs can vary in number, size, and location. ASDs can present as a common atrium and are often associated with cardiac chamber isomerism (i.e., the defining features of the cardiac chambers, based on their anatomical 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).
  - Other individuals may have complex congenital heart malformations [Sahn et al 1981, Glauser et al 1989, Wu et al 1991, Basson et al 1994, Koishizawa et al 1995, Sletten & Pierpont 1996]; 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.
  - Although 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.

Exclusion criteria. HOS can be excluded in individuals with congenital malformations involving the following structures or organ systems ulnar ray only, kidney, vertebra, craniofacies, auditory system (hearing loss or ear malformations), lower limb, anus, or eye.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. Mutations in *TBX5* account for more than 70% of individuals who meet strict diagnostic criteria for HOS.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Sequencing/mutation scanning.** Molecular genetic testing can be performed by mutation scanning techniques and/or direct sequencing [Terrett et al 1996, Basson et al 1997]. Although DNA sequencing has remained the gold standard for molecular detection of *TBX5*, mutation scanning is an effective alternative, and combined application of both techniques provides high sensitivity [McDermott et al 2005]. More than 70% of individuals who meet the strict diagnostic criteria outlined above (i.e., upper-limb defect and personal and/or family history of structural or conductive heart disease) have a *TBX5* mutation predicted to cause disease [McDermott et al 2005]. Lower mutation 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].
- **Deletion/duplication analysis.** Intragenic deletions involving *TBX5* were detected in about 2% of individuals with HOS who were negative by sequencing/mutation scanning analysis [Borozdin et al 2006]. Therefore, the detection rate of deletion analysis among all individuals with HOS is less than 1%.
- **Array genomic hybridization.** The sensitivity, specificity, and accuracy of this method are not known.

Molecular genetic testing: Research

- **FISH** with specific probes can be effective for detection of large deletions not identified using sequence analysis or mutation scanning [Akrami et al 2001]. Such testing is currently available only through research protocols.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*TBX5* sequence alterations	>70% [1]	Clinical Testing
Mutation scanning			
Deletion/duplication analysis	*TBX5* deletions	<1%	

1. Mutation detection rate in individuals who meet strict diagnostic criteria (i.e., presence of an upper-limb defect and personal and/or family history of structural or conductive heart disease)

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

- Thorough clinical examination and complete family history
- Hand x-rays (posterior-anterior view)
- Echocardiography and electrocardiography
- If a clinical diagnosis of HOS is made, confirmatory diagnostic molecular genetic testing of *TBX5* (Note: Confirmation of the presence or absence of a *TBX5* mutation does not alter management.)

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with germline mutations in *TBX5* [Reamon-Buettner & Borlak 2004].

Clinical Description

Natural History

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

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 no or mild 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.

The natural history of HOS varies from individual to 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.

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

Genotype-Phenotype Correlations

It has been reported that missense mutations 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. Missense mutations 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 mutations 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 defects.

Anticipation

Statistically significant anticipation is not observed in HOS. Because of the variable expressivity of HOS, what appears to be anticipation may reflect ascertainment bias. In small kindreds, the diagnosis of a more severely affected young person can lead to evaluation and subsequent diagnosis of older, more mildly affected individuals [Newbury-Ecob et al 1996]. However, examination of large, multigenerational kindreds with HOS does not support anticipation.

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. Based on limited data, it is estimated to occur in about 1:100,000 live births [Csaba et al 1991].

HOS has been reported from a number of countries worldwide and in individuals of varying racial and ethnic backgrounds [Boehme & Shotar 1989, Yang et al 2000].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The following diagnoses 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]:

Autosomal dominant disorders

- ***SALL4*-related disorders** include Duane-radial ray syndrome (DRRS) and acro-renal-ocular syndrome AROS), two phenotypes previously thought to be distinct entities. DRRS is characterized by uni- or bilateral Duane anomaly and radial ray malformation that can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs; hypoplasia or aplasia of the radii; shortening and radial deviation of the forearms; triphalangeal thumbs; and duplication of the thumb (preaxial polydactyly). Acro-renal-ocular syndrome is characterized by radial ray malformations, renal abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, vesicoureteral reflux, bladder diverticula), ocular coloboma, and Duane anomaly. *SALL4* mutations may rarely cause clinically typical Holt-Oram syndrome (i.e., radial

ray malformations and cardiac malformations without additional features). Additional clinical features include sensorineural and/or conductive deafness.

- **Ulnar-mammary syndrome (UMS)** is caused by mutations in another T-box gene, *TBX3*, which, like *TBX5*, is localized to 12q24.1. These two genes arose via gene duplication. UMS, an autosomal dominant condition, involves primarily the ulnar ray; postaxial polydactyly may be seen. Breast and nipple hypoplasia and delayed puberty are also observed. Although not commonly observed in UMS, congenital heart malformations have been reported. UMS can be diagnosed clinically or by using molecular genetic testing [Bamshad et al 1997, Bamshad et al 1999].
- **Townes-Brocks syndrome (TBS),** referred to by the descriptive name renal-ear-anal-radial syndrome, is caused by mutations in the *SALL1* gene, a putative transcription factor. TBS may be diagnosed using molecular genetic testing [Kohlhase 2000]. It shares a number of features with the VACTERL association, a sporadic disorder of unknown etiology.
- **Heart-hand syndrome II (Tabatznik syndrome)** is characterized by type D branchydactyly (shortening of the distal phalanx of the thumb with or without shortening of the fourth and fifth metacarpals), sloping shoulders, short upper limbs, bowing of the distal radii, and absence of the styloid process of the ulna with supraventricular tachycardia. Affected individuals may also have mild facial dysmorphism, mild mental retardation, and cardiac arrhythmias [Silengo et al 1990]. To date, no causative gene has been identified.
- **Heart-hand syndrome III** is characterized by type C brachydactyly (shortening of the middle phalanges) with an accessory wedged-shaped ossicle on the proximal phalanx of the index fingers. Feet are typically more mildly involved. Intraventricular conduction defects and sick sinus syndrome may also occur [Ruiz de la Fuente & Prieto 1980]. To date, no causative gene has been identified.
- **Long thumb branchydactyly syndrome** is characterized by symmetric elongation of the thumb distal to the proximal interphalangeal (PIP) joint, often associated with index finger brachydactyly, clinodactyly, narrow shoulders, secondary short clavicles, and pectus excavatum. Occasionally,f rhizomelic limb shortening occurs. The cardiac abnormality is often a conductive defect [Hollister & Hollister 1981]. To date, no causative gene has been identified.
- **Familial progressive sinoatrial and atrioventricular conduction disease of adult onset with sudden death, dilated cardiomyopathy, and brachydactyly.** This disorder, possibly a new heart-hand syndrome with involvement of the feet as well, was reported by Sinkovec et al (2005). Linkage to several known disease loci including Holt-Oram syndrome, ulnar-mammary syndrome, brachydactyly type B and Robinow syndrome, and cardiac conduction disease or Brugada syndrome, was excluded in a four-generation pedigree.

Autosomal recessive disorders

- **Fanconi anemia (FA)** is characterized by physical abnormalities, bone marrow failure, and increased risk of malignancy. Physical abnormalities, present in 60%-75% of affected individuals, include short stature; abnormal skin pigmentation; malformations of the thumbs, forearms, skeletal system, eyes, kidneys and urinary tract, ear, heart, gastrointestinal system, oral cavity, and central nervous system; hearing loss; hypogonadism; and developmental delay. Progressive bone marrow failure with pancytopenia typically presents in the first decade, often initially with thrombocytopenia or leukopenia. FA is caused by mutation in one of at least 11 genes; The diagnosis of FA rests upon the detection of chromosomal aberrations (breaks,

rearrangements, radials, exchanges) in cells after culture with a DNA interstrand cross-linking agent such as diepoxybutane (DEB) or mitomycin C (MMC).

- **Thrombocytopenia-absent radius syndrome (TAR)** is characterized by bilateral absence of the radii and thrombocytopenia. Thumbs are always present in individuals with TAR. Other findings (particularly hematologic and neurologic) and frequent involvement of the lower limbs differentiate TAR from HOS [Greenhalgh et al 2002].

Chromosomal etiology

- **22q11.2 deletion syndrome (del 22q11.2)** is characterized by a range of findings including congenital heart disease (74% of affected individuals) (particularly conotruncal malformations) and other features not seen in HOS such as palatal abnormalities (69%), learning difficulties (70%-90%), and immune deficiency (77%). About 6% of individuals exhibit upper-extremity anomalies including pre- and postaxial polydactyly, which may result in misdiagnosis of HOS. Del 22q11.2 is diagnosed using fluorescence in situ hybridization (FISH).

Disorders of unknown cause

- **VACTERL** is an acronym for **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 or during intercourse with a partner who has recently used the drug puts 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) [McDermott et al 2005, Matthews & McCoy 2003].
- **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 at Initial Diagnosis to Establish the Extent of Disease

Limb

- Limb involvement is determined by physical examination.
- If limb involvement is not grossly obvious, upper-limb and hand radiographs can be performed to detect subtle anomalies of the carpal bones.

Cardiac

- Chest radiography may demonstrate enlarged pulmonary arteries caused by pulmonary hypertension or cardiomegaly and/or evidence of congestive heart failure.
- Echocardiography is the procedure of choice to define the presence of septal defects or other structural cardiac anomalies.
- ECG is also recommended for the detection of cardiac conduction disease.

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 such as pollicization (creation of a thumb-like digit by moving another digit into the thenar position) in the case of thumb aplasia/hypoplasia, for improved function. 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

ECG is indicated annually or more often in individuals diagnosed with a conduction defect, as well as in individuals at risk for developing a conduction defect.

ECG should be combined with annual Holter monitor in individuals with known conduction disease to assess progression.

Depending on the nature and significance of potential septal defects, echocardiogram surveillance may be requested every one to five years by the managing cardiologist.

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.

Testing of Relatives at Risk

Genetic testing or a clinical diagnosis of HOS can be useful in identifying at-risk family members for the institution of appropriate cardiac management; genetic counseling is useful in predicting recurrence risk for future offspring of affected individuals.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Holt-Oram syndrome 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 *de novo* gene mutation. One series reported that up to 85% of cases are caused by *de novo* mutations [Csaba et al 1991].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include echocardiography, ECG, 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* mutation in the proband has been identified.

Sibs of a proband

- The risk to sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected or has a disease-causing mutation, the risk to the sibs of inheriting the disease-causing mutation is 50%.
- When the parents are clinically unaffected and the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to the sibs of a proband appears to be low (similar to the general population risk, on the order of 1/100,000).
- When the disease-causing mutation found in the proband cannot be detected in the DNA isolated from peripheral blood samples of either parent, the two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been confirmed, it remains a possibility [Braulke et al 1991].

Offspring of a proband

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

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

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.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA, particularly in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Ultrasound (US) examination. In pregnancies at 50% risk, detailed high-resolution prenatal ultrasound examination may detect upper-limb malformations and/or congenital heart malformations [Tongsong & Chanprapaph 2000, Sepulveda et al 2004].

Note: Although Tongsong & Chanprapaph (2000) and Sepulveda et al (2004) both report the use of US in the prenatal diagnosis of HOS, the diagnosis of HOS was not confirmed by molecular genetic testing in either study.

A normal ultrasound examination does not eliminate the possibility of HOS in the fetus.

Molecular genetic testing. Prenatal testing for HOS may be most useful in families with a known mutation to confirm ultrasound findings. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal molecular genetic testing can be performed.

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

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) for Holt-Oram syndrome may be an option for some at-risk couples for whom the disease-causing mutation has been identified in the proband [He et al 2004]. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Holt-Oram Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
TBX5	12q24.1	T-box transcription factor TBX5

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Holt-Oram Syndrome

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

Table C. Genomic Databases for Holt-Oram Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
TBX5	TBX5	6910 (MIM No. 601620)	TBX5

For a description of the genomic databases listed, click here.

Normal allelic variants: *TBX5* is a member of the T-box family of transcription factors [Basson et al 1997, Li et al 1997]. The T-box, which is the DNA binding region, is highly conserved across species and among members of the T-box family of transcription factors. The *TBX5* gene consists of nine coding exons. At least two alternatively spliced isoforms modify the coding region to add or remove the terminal exon, whose presence modifies *TBX5* activity but is not necessarily required [Basson et al 1999, Ghosh et al 2001].

Pathologic allelic variants: Most HOS results from an altered *TBX5* gene dosage. Well over 30 mutations have been described in *TBX5*. While most mutations are private mutations, at least two recurrent mutations have been reported, suggesting that these may be "hot spots." Disease-causing mutations may be missense or nonsense mutations; large deletions have also been reported [Basson et al 1997, Basson et al 1999, Cross et al 2000; Akrami et al 2001; Brassington et al 2003, Heinritz et al 2005, McDermott et al 2005].

Normal gene product: T-box transcription factor TBX5 functions as a transcription factor that has an important role in both cardiogenesis and limb development. In vitro and in vivo animal models support a role for TBX5 in cellular arrest signaling pathways during cardiac growth and development, particularly in cardiac septation. In vivo studies also support a role for TBX5 in forelimb specification and outgrowth. TBX5 can interact with other transcription factors including NKX2.5 and GATA 4, 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].

Abnormal gene product: It is hypothesized that most nonsense and frameshift mutations lead to mutant *TBX5* mRNAs that are degraded with resulting haploinsufficiency. Some missense mutations result in transcripts that have diminished DNA binding activity. Both result in a reduced *TBX5* gene dose, which leads to disease [Hatcher & Basson 2001].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Holt-Oram syndrome

American Heart Association
National Center
7272 Greenville Avenue
Dallas TX 75231
Phone: 800-AHA-USA-1 (800-242-8721)
www.americanheart.org

Reach: The Association for children with Hand or Arm Deficiency
PO Box 54
Helston
Cornwall TR13 8WD
United Kingdom
Phone: (+44) 0845 1306 225
Fax: (+44) 0845 1300 262
Email: reach@reach.org.uk
www.reach.org.uk

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Mori AD, Bruneau BG. TBX5 mutations and congenital heart disease: Holt-Oram syndrome revealed. Curr Opin Cardiol. 2004;19:211–5. [PubMed: 15096952]

Chapter Notes

Revision History

- 22 November 2006 (cd) Revision: array genomic hybridization and deletion/duplication testing clinically available
- 21 September 2006 (me) Comprehensive update posted to live Web site
- 20 July 2004 (me) Review posted to live Web site
- 23 December 2003 (cb) Original submission