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Review Article

Genetics Section

Clinical Features, Molecular Pathogenesis, Diagnosis and Management of Holt-Oram Syndrome: A Narrative Review

HARSH ALLURWAR[1], ANSHIKA AGRAWAL[2], ABHISHEK INGOLE[3], BHAGYESH SAPKALE[4]

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ABSTRACT

Holt-Oram Syndrome (HOS) is a rare autosomal dominant disorder caused by mutations in the TBX5 gene, characterised by radial ray anomalies and congenital cardiac abnormalities. The syndrome, which was described by Holt and Oram in 1960 as a 'heart-hand' syndrome, presents with fully penetrant but variably expressive clinical features affecting the upper limbs and cardiovascular system. This review aims to provide a comprehensive updated overview of HOS regarding clinical spectrum, pathogenesis, diagnosis and differential diagnosis, management approach, along with some emerging therapies, with a highlight on the Indian scenario. This narrative review shows the latest information about the structural and functional roles of TBX5, modifier genes and environmental factors affecting HOS, and early diagnosis through prenatal imaging and molecular testing. Recent studies, like CRISPR/Cas9-engineered models and single-nucleus RNA sequencing, highlighted potential therapeutic targets with transcriptional disruptions. The article also explores Preimplantation Genetic Diagnosis (PGD) in preventing disease transmission and discusses the psychological and functional outcomes of patients with various severities of limb and cardiac involvement. This review is novel in the aspect of recent molecular and translational research with clinical management and prognosis, including some underreported Indian cases with unique challenges for diagnosis and management in such a low-resource healthcare scenario. It also shows the importance of multidisciplinary care and long-term follow-up in cardiac conduction anomalies of HOS. A detailed spectrum of clinical features, emerging therapeutic directions, presented in this review, aims to bridge previous knowledge gaps and also guides future research, clinical strategies for the improved care of individuals with HOS.

Keywords: Heart-hand syndrome, Modifier gene, Preimplantation genetic diagnosis, Radial ray anomalies

INTRODUCTION

Holt-Oram Syndrome (HOS) is an autosomal dominant condition resulting from mutations in the TBX5 gene, with preaxial radial ray anomalies of the upper limb and cardiac defects, the most frequent of which are Atrial Septal Defects (ASDs) and conduction system disease [1]. Holt and Oram in 1960 described it by the name of heart-hand syndrome due to radial ray malformations (e.g., absent or triphalangeal thumbs) and congenital heart diseases, most often ASDs and Ventricular Septal Defects (VSDs) [2]. The disorder is fully penetrant with variable expressivity, so that all those with the genetic defect have some features of the disorder, but the severity and exact features can vary greatly [2,3]. The prevalence of HOS has been estimated as less than one per 100,000 live births [3,4]. Mutations in the TBX5 gene on chromosome 12q24.1 are found in almost 75% of clinically diagnosed individuals [5]. These mutations interfere with normal embryogenesis of the heart and upper limbs [6,7].

Clinical Manifestations in Holt-Oram Syndrome

Upper limb malformation is the hallmark of HOS, and all patients have some type of radial ray defect [5,8]. These defect ranges from mild (clinodactyly and restricted forearm rotation), to severe (hypoplastic or absent thumbs, triphalangeal thumbs, and phocomelia) deformities [5]. Anomalies of the carpal bones are present everywhere and can be the only skeletal expression in certain cases [9]. Severe limb involvement, as well as symmetry, may vary even among individuals belonging to the same family [9,10]. Cardiac manifestations occur in about 75% of patients with HOS and are mainly septal defects, such as ASDs and VSDs [11]. They may range from small to large in size and location and can occur with more severe congenital heart malformations [11]. Also, patients suffer from sinus bradycardia and complete atrioventricular block, which may be independent of structural heart defects [12]. In a few cases, cardiac conduction disease is the only cardiac manifestation [12]. The phenotypic heterogeneity of HOS is not only limited to the heart and limbs; patients might develop extra anomalies, like scoliosis [13]. Clinical features of HOS are described in [Table/Fig-1] [5,8-12].

System/Aspect	Clinical features
Genetics	Autosomal dominant inheritance
Limb anomalies	-Hallmark of HOS -All patients have radial ray defects
Types of limb defects	-Mild: Clinodactyly, restricted forearm rotation -Moderate to severe: Absent/hypoplastic thumbs, triphalangeal thumbs, phocomelia
Carpal bone anomalies	Present in all cases; may be the only skeletal abnormality
Intra-familial variation	Severity and symmetry of limb involvement may vary even within the same family
Cardiac defects	-Present in ~75% of patients -Commonly ASDs and VSDs -May range in size and location -Can be associated with severe cardiac anomalies
Conduction abnormalities	-Sinus bradycardia -Complete atrioventricular block -Can occur independently of structural heart disease -May be the sole cardiac feature
Other features	Rarely, extra anomalies such as scoliosis may be present

[Table/Fig-1]: Clinical features of Holt-Oram syndrome [5,8-12].

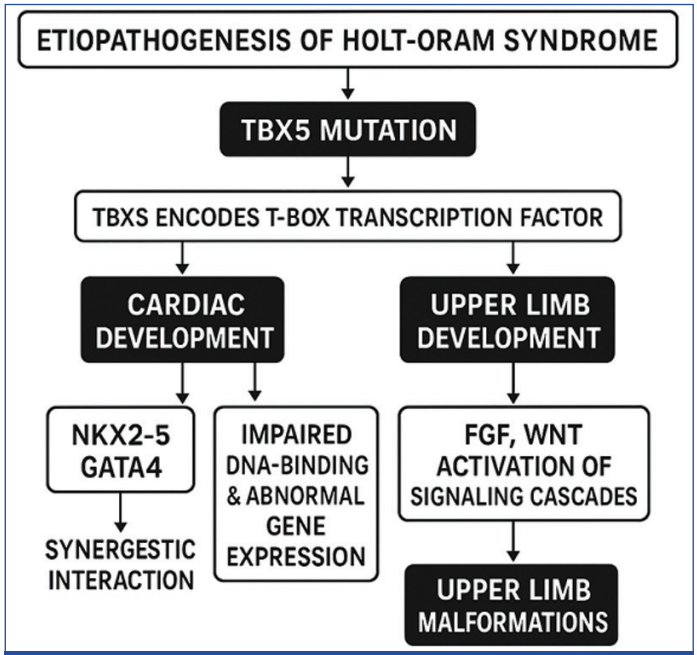
Etiopathogenesis of Holt-Oram Syndrome

The etiopathogenesis of HOS mostly revolves around mutations in the gene TBX5 at chromosome 12q24.1, which encodes a T-box transcription factor required for the development of upper limbs and heart [14,15]. Interference with the TBX5 gene by mutations causes the phenotypic expression as observed in HOS patients

[15]. The TBX5 protein has a conserved T-box DNA-binding domain [residues 56-236], which helps it to bind specific DNA sequences and regulate downstream gene expression for embryogenesis [16]. Structural analysis particularly reveals mutations disrupting the conformation and stability of this domain, particularly missense mutations, which impair transcriptional activity and DNA-binding affinity of TBX5 [17,18].

At the molecular level, TBX5 acts with other transcription factors like NKX2-5 and GATA4 for inducing cardiomyocyte differentiation, cardiac septation and conduction system development of the heart [19,20]. Certain missense mutations in TBX5 impair its DNA-binding activity, function of transcription, and binding to NKX2-5, leading to abnormal cardiac expression of the gene and structural cardiac abnormalities [19,21]. In the development of the limb, TBX5 is expressed in anterior lateral plate mesoderm required for the initiation of the forelimb bud, thereby acting upstream of the Fibroblast Growth Factor 10- Fibroblast Growth Factor Receptor 2 (FGF 10-FGFR2) signalling axis [22]. It also activates signalling pathways, like FGF, Wnt, causing differentiation and growth of limbs [22]. TBX5 mutations interfere with these pathways and further lead to upper limb malformations from thumb aplasia to phocomelia [23]. TBX5 is involved in the regulation of pre-mRNA splicing, indicating that its mutations might exert more global effects on gene expression than transcriptional regulation alone [15,23].

Recent research highlights the role of modifier genes and environmental factors for variable expressivity observed in HOS [24]. For example, variants in TBX3, MEF2C, and other cardiac gene regulatory networks modulate the phenotype of HOS accordingly [24,25]. Additionally, epigenetic mechanisms, like methylation, altered histone acetylation, can influence TBX5 target expression of gene [25]. Environmental stressors like hypoxia, maternal diabetes during the process of embryogenesis, also exacerbate cardiac and limb defects in genetically predisposed individuals, although direct evidence remains limited [26]. Etiopathogenesis of HOS is depicted through [Table/Fig-2] [14-26].

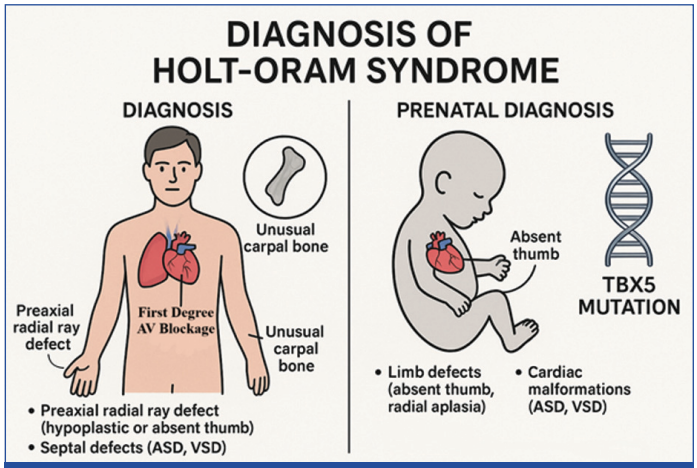


[Table/Fig-2]: Etiopathogenesis of Holt-Oram syndrome [14-26].

Diagnosis of Holt-Oram Syndrome

Diagnosis of HOS is clinical, based on preaxial radial ray defects like hypoplastic/absent thumbs or radii with personal or family history of cardiac septation defects and atrioventricular blockages [27]. An unusual carpal bone is found in all cases and cardiac manifestations are also frequent [28,29]. Sinus bradycardia and first-degree AV block, advances later to complete heart blockage with or without atrial fibrillation [28,30]. High-resolution foetal ultrasonography performed at 13 to 20 weeks of gestation can identify all limb deformities as well as cardiac malformations (ASDs and VSDs) in prenatal diagnosis of HOS [31,32].

Once a pathogenic TBX5 mutation has been found in one family, prenatal molecular testing can be carried out on foetal DNA to establish the diagnosis [33]. Where the familial mutation is not known, ultrasonography and foetal echocardiography are advised to detect typical limb and cardiac abnormalities [33]. Preimplantation Genetic Diagnosis (PGD) and In Vitro Fertilisation (IVF) provide a means for the prevention of transmission of HOS in at-risk couples [34]. PGD allows selection of embryos without the TBX5 mutation, further aiding in IVF [34,35]. In spite of these diagnostic tools, prenatal detection rates are still suboptimal [4]. A European registry study found that more than 60% cases were not suspected prenatally, yet presented with anomalies of HOS, highlighting the need for prenatal screening [4]. Diagnosis of HOS is depicted in [Table/Fig-3] [4,27-35].



[Table/Fig-3]: Diagnosis of Holt-Oram syndrome [4,27-35].

Differential Diagnosis of Holt-Oram Syndrome and Related Disorders

It is important to distinguish HOS from other syndromes that have overlapping features for proper diagnosis and management [36]. HOS have overlapping skeletal and cardiac abnormalities with Okihiro syndrome, Thrombocytopenia Absent Radius (TAR) syndrome, Fanconi anaemia, and thalidomide embryopathy [17,37]. Distinct clinical features, however, are helpful in distinguishing such disorders. For example, Okihiro syndrome typically shows Duane anomaly and hearing loss, whereas TAR syndrome features the presence of thumbs, radial aplasia with thrombocytopenia [38,39]. Fanconi anaemia features radial deficiency, haematologic dysfunction, and excess chromosomal breakage [40]. Thalidomide embryopathy is associated with in utero exposure to thalidomide and results in limb abnormalities without a hereditary origin [41]. In contrast, HOS usually comprises radial ray abnormalities with hypoplasia or aplasia of the thumb and congenital heart malformation, but not hematologic complications or exposure history [8,36]. Differential diagnosis of HOS is described in [Table/Fig-4] [8,17,36-41].

Management of Holt-Oram Syndrome

HOS management requires a multidisciplinary team of cardiologists, orthopaedic surgeons, and genetic counsellors [42,43]. Treatment plans for cardiac manifestations, e.g., ASDs and VSDs, and conduction defects include surgical repair of structural defects along with arrhythmia management, which consists of medication or pacemaker placement [42]. Usage of His-bundle pacing in patients with conduction problems has proved valuable, helping to maintain the rhythm of their hearts [8]. Orthopaedic and rehabilitative therapy is individualised to the degree of limb abnormality [44]. Surgical intervention is helpful to repair skeletal deformities and occupational therapy to restore limb function [44]. The effectiveness of an emerging

Syndrome	Key skeletal features	Cardiac features	Hematologic features	Other distinct features	Etiology
Holt-Oram Syndrome (HOS)	Radial ray abnormalities; thumb hypoplasia/aplasia	Congenital heart malformations; arrhythmias	None	May present with isolated cardiac conduction disease	Genetic (TBX5 mutations)
Okihiro syndrome	Radial ray defects	Possible cardiac anomalies	None	Duane anomaly [eye movement disorder]; hearing loss	Genetic (SALL4 mutations)
TAR syndrome	Radial aplasia with thumbs present	Possible structural defects	Thrombocytopenia	Platelet levels improve with age	Genetic (RBM8A mutations)
Fanconi anaemia	Radial defects; possible thumb abnormalities	Occasional heart defects	Hematologic dysfunction; anaemia; pancytopenia	Chromosomal breakage; increased cancer risk	Genetic (various FA genes)
Thalidomide embryopathy	Limb malformations; phocomelia	Rare or secondary cardiac anomalies	None	History of in utero thalidomide exposure	Teratogenic exposure, not inherited

[Table/Fig-4]: Differential diagnosis of Holt-Oram syndrome [8,17,36-41].

combined home and clinic-based occupational therapy programme consisting of orthosis construction, passive range of motion therapy, and modified constraint-induced movement therapy is proven useful for managing HOS, particularly in infants undergoing pollicisation surgery [45]. This integrated strategy results in the enhancement of hand function and alignment in patients with bilateral radial defects [44,45].

Emerging therapies targeting HOS: CRISPR/Cas9-engineered human pluripotent stem cell models having TBX5 mutations are being developed, which mimic HOS in vitro, providing powerful platforms for testing gene correction techniques [46]. Single-nucleus RNA sequencing (snRNA-seq) of cardiac tissue of HOS patients has uncovered TBX5-dependent transcriptional pathways responsible for conduction and cardiac metabolism, highlighting molecular targets for the development of drugs [47]. Additionally, new TBX5 variants are being studied to identify mutation-specific mechanisms for future precision therapies, such as splicing modulators, protein-stabilising agents [48,49]. Gene therapy and novel molecular interventions remain investigational, but their success depends upon expanding knowledge of TBX5 pathophysiology and its interaction with transcription factors such as NKX2-5 and GATA4 [8,43].

Genetic counselling to manage HOS: Genetic counselling is at the heart of HOS management because its autosomal-dominant pattern of inheritance renders each child of an affected parent at a 50% risk, despite ~85% of probands resulting from de novo TBX5 mutations [50]. Proper counselling thus starts with molecular diagnosis: identification of pathogenic TBX5 mutations with strict clinical criteria, and further negative testing can help risk assessment for relatives and prevent anxiety [50]. Foetal echo and high-resolution ultrasound to detect radial-ray and cardiac abnormalities are done at the first or second trimester [51]. Couples who wish to avoid pregnancy termination can have pre-implantation genetic testing with in-vitro fertilisation; proof-of-concept cases reveal biopsy-genotyped embryos without the familial TBX5 mutation resulting in normal births [52].

Current Limitations and Areas of Uncertainty in Holt-Oram Syndrome

Multiple areas of uncertainty and gaps in current knowledge of HOS are persistent, despite advancements in HOS. A major gap remains in the correlation of genotype-phenotype observed among individuals with similar TBX5 mutations, complicating further clinical prediction and management [53]. The variable expressivity and reduced penetrance in familial cases suggest the influence of non-identified modifier genes, epigenetic and environmental factors, which remain largely unexplored and poorly defined [26,54]. Although TBX5 mutations account for most of the clinically diagnosed cases, a significant number of patients remain mutation-negative, indicating possible involvement of non-coding regions, undiscovered genes [55].

Current studies of TBX5 variants are derived from in vitro models; these do not fully replicate the complex in vivo developmental processes and are also limited in number [56]. The lack of large-scale cohort studies and population-specific data hampers epidemiological estimates and outcome prognostication in low-resource settings like the rural parts of India [56,57]. Prenatal diagnosis is also not proper, reflecting a gap in sonographic expertise, diagnostic guidelines, and variable manifestations of limb and heart [33,49]. Molecular therapies show promise, but their clinical results are unknown due to ethical issues, limited trials and technical barriers in gene editing [46]. In HOS, addressing knowledge gaps by functional assay, genomic studies, and research is beneficial to improve the accuracy of diagnosis, risk prediction, and personalised therapy [4,54].

Long-Term Prognosis and Clinical Outcomes of Holt-Oram Syndrome

The long-term prognosis of HOS depends on the nature, progression of cardiac conduction abnormalities than on structural heart defects [58]. ASDs and VSDs are often managed successfully in childhood; the conduction defects, such as sinus node dysfunction and atrioventricular block, may be progressive and require long-term cardiac surveillance [54,58]. Patients without overt structural defects can also develop arrhythmias later in life, so continuous electrocardiographic monitoring into adulthood is important [59]. Implantation of permanent pacemakers has shown good outcomes in patients with progressive conduction disease, and His-bundle pacing also emerged as a preferred technique in preserving physiologic cardiac function [8,59].

Overall, life expectancy and quality of life of HOS individuals are generally favourable in the absence of complex cardiac anomalies [54]. Cognitive development remains unaffected; timely orthopaedic interventions and rehabilitative therapies help many individuals attain functional independence [45,60]. Studies on upper limb defects highlighted that HOS cases mainly had subtle skeletal anomalies and remained undiagnosed until adolescence or adulthood [4]. Additionally, normal deliveries and pregnancies were successful in women with HOS, provided cardiac function is monitored carefully [61]. These suggest that personalised treatment, interdisciplinary follow-up, and the long-term prognosis for the majority of patients with HOS can be optimistic [58,62].

Accurate data on mean survival age for HOS are limited; evidence from population-based and clinical-genetic cohort studies suggests that survival into adulthood is usual, especially with moderate cardiac involvement [4,57]. A EUROCAT registry study of 73 European HOS cases (1990-2011) found that despite ~25% having complex congenital heart disease, first-week survival was "very good" in patients [63]. Long-term life expectancy is primarily affected by the severity of cardiac defects and conduction abnormalities, with modern approaches causing many to live well into adulthood [54]. Impact on quality of life by upper limb abnormalities is good to excellent, with proper multidisciplinary care, psychological support, which fosters independence and positive psychosocial outcomes [54,58].

Indian Clinical Spectrum of Holt-Oram Syndrome

In the case of a 4-month-old male Indian child reported by Shankar B et al., with bilateral radial aplasia, absent thumbs, atrial septal defect, tricuspid atresia, and a fatal cerebrovascular event

pointed towards HOS [64]. Pulmonary stenosis, tricuspid atresia, atrial septal aneurysm with right-to-left shunting, and an inlet VSD were seen on Echocardiography [64]. Along with future Fontan surgery, a modified Blalock-Taussig (BT) shunt was planned [64]. Patient developed a parietal infarct and seizures, later treated by anticoagulants, but died due to a seizure episode [64]. In a case of a 1-year-old Indian male child reported by Arunachalam VS et al., born preterm from a non-consanguineous marriage, presented with dyspnoea and poor weight gain [65]. He had upper right limb deformities like absent thumb, radial aplasia relating to HOS and right lung agenesis, dextroposition of the heart, and a large ostium secundum ASD with moderate pulmonary hypertension [65]. Imaging resulted in posterior herniation of the left lung into the right side of the hemithorax [65]. Surgical ASD closure was done, which led to clinical improvement, reduced pulmonary hypertension and a 40% weight gain over 6 months [65].

A 26-year-old Indian female reported by Kumar B and Agstram S presented with both upper limb deformities (absent thumbs with polydactyly) since birth and exertional dyspnoea for 5 years [29]. Features of HOS were ostium secundum ASD, right heart chamber dilation, first-degree AV blockage, and block in the right bundle branch [29]. Despite being advised surgical ASD closure, she remained on medical management due to financial issues, but showed a stable condition later after a 2-year follow-up [29]. Family genetic screening showed similar limb deformities in her child without involvement of the heart [29]. A 31-year-old Indian male with HOS reported by Rana M et al., with a history of repaired ASD and bilateral thumb anomalies, was scheduled for tongue carcinoma resection with radical neck dissection [63]. He had atrial fibrillation, a pulse deficit, and a left ventricular ejection fraction of 30-35% [63]. Preoperative evaluation resulted in radial aplasia and the absence of the radial artery, which required invasive femoral artery monitoring [63]. A subclavian pacemaker sheath was used to avoid the risk of arrhythmias [63]. Postoperative recovery was good, and he was discharged on the sixth day [63]. These cases of the Indian scenario highlight phenotypic variability and severity of HOS, and the need for multidisciplinary intervention, family screening to manage cardiopulmonary and skeletal abnormalities.

CONCLUSION(S)

Holt-Oram Syndrome (HOS) includes upper limb malformation and congenital heart disease due to mutations in the TBX5 gene. Since both its symptoms and clinical features overlap with many other syndromes, it is important to be alert and check for the syndrome by full genetic testing and involve many doctors in care. Proper management of this condition is based on customised treatment for the bones and heart, along with effective genetic counselling. There is a need for more studies to better understand the causes of HOS and increase the success of early treatment and plans related to its prevention.

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PARTICULARS OF CONTRIBUTORS:
1. Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Professor, Department of Preventive and Social Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
4. Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Harsh Allurwar,
Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College,
Datta Meghe Institute of Higher Education and Research,
Wardha-442001, Maharashtra, India.
E-mail: allurwarharsh@gmail.com

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