Review Article

Isolated Congenital Vertical Talus: Genetics and Genomics

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Abstract

Congenital vertical talus (CVT) is a distinct orthopedic condition where the bone structure and number are normal in the affected foot, but the orientation of the bones is not correct. The abnormal orientation of the bones in the affected foot is believed to be due to muscle imbalance. There are a shortening and dorsal displacement of the peroneal tendons and tibialis posterior tendon, resulting in the clinical appearance of a severe rigid flatfoot. The underlying etiology of the CVT is unknown, and limited studies have been performed to decipher the genetics of CVT. The purpose of this review is to highlight the key research articles within the CVT genetics and genomics fields that were published previously. Herein, we reviewed the current literature and discussed the genetic studies carried out in families and patients with an isolated form of CVT. It is believed that CVT segregates in an autosomal dominant fashion. Most of the studies used a candidate gene approach to identify CVT causative variants. Variants in growth differentiation factor 5, *HOXD10*, teashirt zinc finger homeobox 1, and skeletal muscle contractile genes have been associated with CVT. An unbiased and hypothesis-free approach of whole-exome sequencing is much needed to unwire the genetic network underlying distal hind limb development and to improve our understanding of the gene regulatory mechanism in this musculoskeletal disorder. Moreover, this review focuses on highlighting the importance of the identification of the genetics of CVT and its implications in early clinical diagnosis and management of patients.

Keywords: Congenital vertical talus, flatfoot, gene regulatory networks, genomics, growth differentiation factor 5, *HOXD10*

Introduction

A large number of musculoskeletal abnormalities exist, which affect the morphology and growth of one or group of bones, muscles, and connective tissues in the skull, trunk, and limbs. These abnormalities ultimately affect the integrity of body position, weight-bearing property, and locomotion. Musculoskeletal abnormalities and disorders of limbs form the largest group of congenital defects.[1] Congenital limb deformity is frequent with variable clinical presentation and can present as an isolated disorder (nonsyndromic) or a part of a syndrome (associated with other extra-musculoskeletal conditions). Congenital vertical talus (CVT) is a rare congenital limb deformity that affects the positioning of the foot.[2] It is characterized by valgus and equinus deformity of the hindfoot, along with the dorsiflexion at the midfoot and abduction of the forefoot.[3] This abduction is caused by a fixed dorsal dislocation of the navicular bone on the head of the talus. Typical CVT is considered as a type I CVT. However, it is termed as CVT type II if the CVT type I includes deformity of the calcaneocuboid joint.[4,5]

The incidence of a CVT is 1 in 10,000, and it affects both males and females in equal proportion.[2,5] CVT is bilateral in approximately 50% of cases.[2,6] CVT rarely occurs as a nonsyndromic condition and in most of the cases exists as a part of a syndrome.[7,8] Syndromic forms of CVT are mostly associated with defects of the central nervous system (arthrogryposis, myelomeningocele, sacral agenesis, and neurofibromatosis), muscle abnormalities (ischiocalcaneal band), acquired deformities (cerebral palsy and spinal muscular atrophy), and certain genetic conditions (Freeman–Sheldon syndrome, Smith–Lemli–Opitz syndrome, Marfan syndrome, Sheldon–Hall syndrome, nail–patella syndrome, Eagle-Barrett syndrome, and split-hand/split-foot malformation).[5,9-18]

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Clinical Presentation of Congenital Vertical Talus

CVT is also frequently termed as "congenital convex pes valgus" or "rocker-bottom foot" deformity.[19-21] CVT is a dislocation of the talonavicular joint characterized by vertical positioning of the talus with a rigid dorsal dislocation of the navicular bone, equinus malformation of the calcaneum, abduction defect of the forefoot, and soft-tissue contracture of the hindfoot and midfoot.[21] The Achilles tendon is contracted, and the calcaneum is in equinus.[22] Radiographic evaluation on the lateral view shows the long axis of the talus to be vertical and lying parallel with the longitudinal axis of the tibia.[22] Forced plantar flexion and forced dorsiflexion lateral radiographs are also required for the confirmation of the CVT diagnosis and to differentiate it from the oblique talus. The forced plantar flexion lateral view shows persistent malalignment of the long axis of the talus and the first metatarsal [Figure 1]. The forced dorsiflexion lateral radiograph exhibits a persistently decreased tibiocalcaneal angle showing fixed hindfoot equinus and shows the persistent malalignment of the long axis of the talus in relation to the navicular bone.[22] A postmortem examination on newborns, as well as findings during surgical corrections, has contributed to our understanding of the pathoanatomy of the CVT.[3,19,23,24] Dorsal and lateral displacements of the navicular bone with respect to the head and neck of the talus were observed. Moreover, the navicular bone becomes hypoplastic and wedge shape due to abnormal articulation with the talus. For a definite diagnosis of a case, it is essential to maintain the foot in extreme plantar flexion to show that the navicular bone is dislocated dorsally on the neck of the talus.[25] Contractures of foot muscles, including tibialis anterior, extensor hallucis brevis, peroneus tertius, peroneus longus, and peroneus brevis, were frequently observed.[22]

An underlying neuromuscular disease must be ruled out in isolated CVT.[7] In order to rule out isolated CVT, any evidence of flexion contractures or ulnar deviation of the fingers, as well as limitation of motion at other joints, must be excluded. Radiographic assessment is enough to establish the diagnosis. CVT has been associated with certain defects of the central nervous system, multiple malformation syndromes, *in utero* deformations, and some gross chromosomal defects.[4] However, the precise etiology of CVT is still unknown.

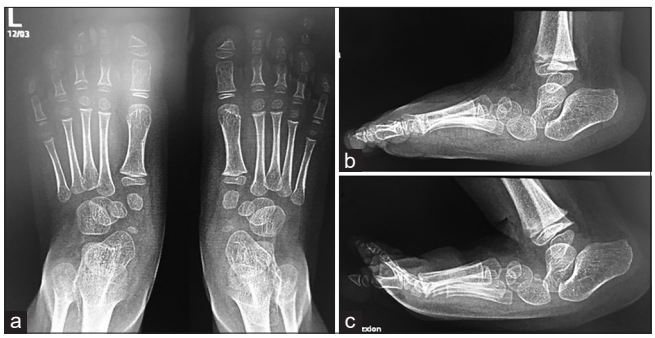

Figure 1: (a) Anteroposterior of 3-year-old girl feet. (b and c) Lateral view demonstrates the malalignment of the first ray with the talus bone. The long axis of the talus passes planter to the metatarsal axis

Treatment of Congenital Vertical Talus

CVT is treated surgically as well as nonsurgically. The main aim of the treatment is to resume the normal function of the foot by correcting the anatomic relationship among talus, navicular bone, and calcaneum. Most commonly employed nonsurgical treatment methods involve conservative therapies, such as manipulation and serial casting.[26] This method is used to improve the deformity and thus decrease the complexity of the surgical procedure.[25] However, these methods are not always successful in this deformity.[6] The surgical procedure involves correction between the ages of 6 and 12 months. Mostly, a single-stage surgery is used to obtain the necessary correction.[25,27,28] The use of consecutive plaster cast treatment (serial cast correction) to slowly reduce the talonavicular joint, followed by minimal surgical interventions, has shown good early results in the treatment of CVT.[26,29]

Transmission of Congenital Vertical Talus

Isolated forms of CVT have been reported to transmit in families. In most of the familial cases of CVT, an autosomal dominant inheritance has largely been considered as a transmission pattern.[7,30-33] Families with asymptomatic parents have also been reported.[32] However, in cases where both parents are asymptomatic, the inheritance pattern can also be considered as an autosomal recessive. Nevertheless, in such cases, carriers were presumed to be nonpenetrant. Definite inheritance pattern could not be determined in familial CVT due to small family size, the rarity of the problem, incomplete penetrance of the phenotype, and lack of thorough clinical evaluation of carriers.

Genetics of Congenital Vertical Talus

The contribution of genetic factors in the etiology of CVT is evident from the fact that 50% of isolated CVT patients have affected first-degree relatives.[30] Several families with more than one affected individual segregating CVT have been reported. Moreover, the association of CVT with well-established genetic syndromes strengthens the hypothesis of genetic factors underlying CVT. The segregation of CVT in families suggests a major role of a single gene variant(s) in an individual family. In this context, defects in signaling pathways and the associated molecular components involved in the development of the skeleton might be the dominant players and an underlying cause of CVT.

Genetic Models Used to Decipher the Genetics of Congenital Vertical Talus

Genetic association, as well as candidate gene variant approaches, has been used to identify the genetic factors

underlying CVT. Moreover, a genome-wide linkage analysis study design has also been used to decode the genetics of CVT.

Candidate Gene Sequencing

Cartilage-derived morphogenetic protein-1 (growth differentiation factor 5)

Cartilage-derived morphogenetic protein-1 (CDMP1) is also known as growth differentiation factor 5. *CDMP1* encodes a ligand for the transforming growth factor-beta (TGF-β) superfamily of proteins. Binding of CDMP1 ligand with the TGF-β receptors leads to the recruitment and activation of a group of transcription factors and thus controls gene expression in various cell types and subsequently plays a role in the development of cartilage, joints, and the growth of neuronal axons.[35-38] Mutations in *CDMP1* cause severe upper- and lower-limb malformations, including Grebe-type acromesomelic dysplasia, Hunter-Thompson-type chondrodysplasia, Du Pan syndrome, and brachydactyly type C.[35,39-46] Some reports also showed that CVT is a part of a spectrum of skeletal malformations due to CDMP1 heterozygous mutations.[35,42] Candidate gene sequencing approach was used in families with CVT, and a heterozygous mutation (c.1312C>T; p.R438C) in *CDMP1* was identified in a North American family with isolated CVT.[47] The data have not been replicated, and this is the only report available. The authors of this review have performed *in silico* analysis of the variant (c.1312C>T) and found that the variant is in the active domain of the *CDMP1* and is predicted to be likely disease causing. For instance, it is predicted to be deleterious by sorting intolerant from tolerant (SIFT) (score 0), probably damaging by PolyPhen-2 (score 1), and damaging by MetaLR (score 0.738) tools (unpublished data).

HOXD10

HOXD10 gene encodes a homeobox DNA-binding domain containing protein. The HOXD10 protein is expressed in the limb buds during development and is known to play a role in differentiation and limb development functions by acting as a sequence-specific transcription factor.[48,49] Mutations in the *HOXD10* gene have been associated with Wilms' tumor,[9] esophageal squamous cell carcinoma,[42] and CVT.[33,34,43,44] A missense mutation (c.956T >A; p.Met319Lys) in the homeodomain recognition helix of HOXD10 was detected in all affected individuals of an extended family with isolated CVT.[34] This mutation was previously reported in a family with bilateral CVT and Charcot–Marie–Tooth disease.[50,51] The authors of this review have performed *in silico* analysis of the variant (c.956T>A) and found that the variant is pathogenic (ClinVar) and clinically significant. It is expected to be deleterious by SIFT (score 0), possibly damaging by PolyPhen-2 (score 1), and damaging by MetaLR (score 0.9496) tools (unpublished data). However, a significant number of families with isolated CVT are negative for mutations in the coding as well as 5' and 3' untranslated regions of the *HOXD10* gene.[52] This shows that *HOXD10* mutations are not a common cause of isolated CVT. Therefore, downstream spatiotemporal transcriptional targets of the *HOXD10* gene must be characterized and screened in CVT families. *HOXD10* target genes expressing in the developing limb may be the excellent candidate genes for CVT.

Copy Number Variation and Congenital Vertical Talus

The deletion of the distal part of the long arm of chromosome 18 (18q deletions) is known to cause the 18q-deletion syndrome. The 18q-deletion syndrome phenotype has been described well and varies greatly among individuals with 18q deletions.[53,54] Variations in clinical features in patients with distal 18q deletions are due to the difference in the size of the deletion. Various studies have used chromosomal microarray to identify the precise genotype–phenotype correlation in patients with 18q deletions.[53-61] The region was narrowed to a 5.8 Mb segment (69.1–74.9 Mb) for lower-limb deformities, including CVT.[60] It was further narrowed to 1.70 Mb (72.2–73.9 Mb) containing just five genes (*ZNF407, ZADH2,* teashirt zinc finger homeobox 1 (*TSHZ1*), *C18orf62,* and *ZNF516*) in patients with bilateral CVT features only [Figure 2].[62] Further analysis of the deletions using patient data from the DECIPHER database (http://decipher.sanger.ac.uk/) and data published by Feenstra *et al*. (2007) refined the region to 1.02 Mb (72.9–73.5). This region contains only *TSHZ1* and *C18orf62* genes [Figure 2].

Teashirt zinc finger homeobox 1 and *C18orf62*

TSHZ1 encodes a transcriptional factor containing atypical DNA-binding domain.[63,64] It is predicted to be involved in the developmental processes through transcriptional regulation of target genes.[64] Based on the expression pattern of the *TSHZ1* in human tissues and its role in murine skeletal growth and development, the gene *TSHZ1* was considered as a likely candidate gene for the bilateral CVT phenotype in 18q-deletion syndrome.[62] A recent study has identified a 2.5 Mb deletion (chr18: 72.8–75.4) in a patient with syndromic features, including bilateral CVT using array

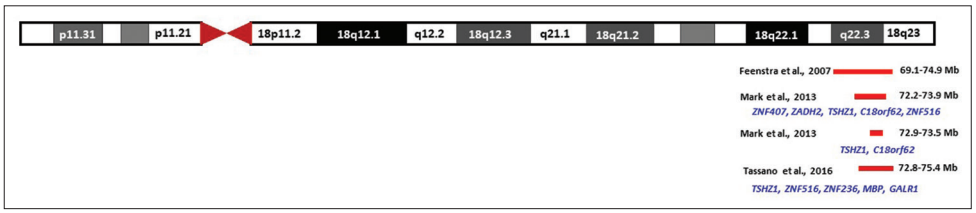

Figure 2: Schematic representation of the congenital vertical talus critical genomic region in 18q deletion

comparative genomic hybridization.[65] The region overlaps with the previously identified region and has *TSHZ1* as the only common gene [Figure 2]. Therefore, *TSHZ1* is the most plausible candidate gene for CVT in the 18q-deletion syndromes. The second gene in the 1.02 Mb (72.9–73.5) critical region on chromosome 18 is *C18orf62 or* small integral membrane protein 21 (*SMIM21*). *SMIM21* is an uncharacterized protein-coding gene. Expression data are lacking, and pathogenic variations in this gene have not been associated with any human disease. Moreover, this gene is not present in the smallest common deletions identified by Mark *et al*. and Tassano *et al*.[62,65] Therefore, up till now, the impact of the heterozygous deletion of *SMIM21* on the clinical features of CVT is unclear.

Skeletal Muscle Contractile Genes in Congenital Vertical Talus

Contractile genes encode a component of the contractile apparatus of skeletal myofibers. It is known that the muscle biopsy specimens from patients with CVT have abnormalities in skeletal muscles, including the small size of the muscle fiber and predominant abnormal fiber type.[66] Mutations in skeletal muscle contractile genes (*MYH3, MYH8, TPM2, TNNI2,* and *TNNT3*) are responsible for distal arthrogryposis (DA).[66-70] The DA syndrome is a group of abnormalities manifested as nonprogressive congenital contractures mainly involving the distal parts of the limbs.[71-73] The foot phenotype described in individuals with DA is similar to the foot features in isolated CVT.[71] Therefore, it is proposed that the contractile genes responsible for DA might also be involved in more common distal limb defects, including CVT.[74] This assumption is supported by the fact that variations in skeletal muscle contractile genes influence the risk of clubfoot, another distal limb anomaly.[69] Therefore, skeletal muscle contractile genes must be considered in the etiology of CVT. However, the resequencing of coding exons of three contractile genes (*MYH3, TNNT3*, and *TPM2*) failed to identify any pathogenic variant in CVT patients.[74] Failure to identify the CVT-causing variants in contractile genes has been attributed to the low number of samples tested.[74]

Discussion

CVT occurs both in isolated and syndromic forms. Therefore, it is important to rule out the CVT-associated clinical features while assessing individuals with apparently isolated forms of CVT. Extra-musculoskeletal features may also exist with CVT, including neurological malformations. Approximately half of the CVT cases are associated with abnormalities of various systems including muscles, skeleton, and nervous system.[2,9,11,13,14,31,75-78]

The role of genetic variations in the etiology of CVT is evident from the fact that CVT has the tendency to aggregate and segregate in families. Moreover, the autosomal dominant inheritance model has been widely suggested emphasizing Mendelian segregation and monogenic factor within a family. Furthermore, isolated CVT patients with a first-degree relative have been reported in 50% of the cases.[30] The genetic factors underlying CVT are not fully penetrant, and a variable expression has been observed in multiple families segregating CVT.[7,34] Although genetic variants are implicated in CVT, the effect of these variants in the pathogenesis of CVT is estimated to be small to moderate in size and may vary from population to population.

Variants in *HOXD10* and *CDMP1* have been associated with CVT. However, the replication studies are largely missing. The deletion of *TSHZ1* gene has also been implicated in isolated CVT, though heterozygous knockout mice failed to recapitulate human phenotype.[64] Several studies failed to identify defects in genes associated with CVT. This emphasizes that CVT is a genetically heterogeneous phenotype, and large-scale studies are required to decipher the gene network underlying CVT phenotype. We suggest whole-exome sequencing in those families where at least 2 individuals with CVT are available. Once an underlying gene CVT is identified, the gene can be screened in isolated cases. Besides, in isolated cases, copy number variation detection using dense SNP array might lead to detect indels underlying CVT.

Ethical approval

The study was approved by the ethical review committee of the college of medicine, Taibah University Almadinah Almunawwarah.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their consent for the images and other clinical information to be reported in the journal. The parents understand that the name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Authors' contributions

SB conceived the idea; YNK collected and organized the literature and wrote the initial draft; SB wrote the final draft of the article. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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