四川大学学报（医学版）
Journal of Sichuan University (Medical Sciences)

Available online at http://www.jsu-mse.com

Research Article

探索马蹄内翻足的遗传和病理生物学途径：简短叙述性综述

***Yasir Naseem Khan* [1,2] *Mohammad Imad A. Mustafa Mahmud*[1]**

[1]Department of Basic Medical Sciences, Faculty of Medicine, Islamic International University, Malaysia
[2] Department of Basic Medical Sciences, College of Medicine, Al-Rayan National College, Al-Madina, Al-Munawara, Saudi Arabia

通信作者，E-mail: ynkhanlughmani@gmail.com

Received: 2024-01-25 ◆ *Reviewed: 2024-09-20*
Accepted: 2024-11-30 ◆ *Publication: 2024-12-25*

【摘要】：

背景：马蹄内翻足(TEV)，通常称为马蹄足，是一种常见的先天性足部畸形，其特征是多种骨软骨组织异常，包括后足内翻（距下关节外翻或内翻）、前足内收（跖骨内收）、足弓过大（高弓足）和踝关节背屈受限（马蹄足）。TEV的发病率为每1000个活产婴儿中0.5至2.0个，其病因被认为涉及遗传和环境因素的复杂相互作用。尽管人们早已认识到TEV的确切病因，但其确切病因在很大程度上仍不清楚。各种遗传学研究，包括候选基因关联研究、拷贝数变异分析、连锁分析、全外显子组测序和全基因组测序，已经确定了与TEV发病机制有关的特定基因。然而，现有文献仍然不足以查明家族性病例的确切遗传原因，因为大多数研究都集中在散发病例上，许多遗传因素仍处于推测阶段。方法：本叙述性综述综合了现有关于导致TEV的环境、分子和遗传因素的文献，同时阐明了其发展所涉及的病理生物学机制。结果：有证据表明，TEV表现出与常染色体显性和隐性遗传以及不完全外显率的常染色体显性遗传一致的家族分离模式，强调了遗传因素的重要作用。值得注意的是，同卵双胞胎(32%)的TEV一致率明显高于异卵双胞胎(2.9%)，这强化了该疾病的遗传基础。结论：根据我们的综述结果，TEV同时源于遗传倾向和环境影响，这些因素会破坏下肢细胞骨架的正常有丝分裂。为了加深我们对TEV的了解，迫切需要进行大规模、多中心合作研究，采用先进的遗传技术，例如采用单核苷酸多态性扫描的全基因组关联研究(GWAS)和广泛家庭队列中的连锁分析。

【关键词】：马蹄内翻足，遗传，病理学

Exploring the Genetic and Pathobiological Pathways of Talipes Equinovarus: a Short Narrative Review

【Abstract】:

Background: Talipes equinovarus (TEV), commonly referred to as clubfoot, is a prevalent congenital foot deformity characterized by a combination of osteochondral tissue anomalies including hindfoot varus (supination or inversion of the subtalar joint), forefoot adduction (metatarsus adductus), exaggerated midfoot arch (cavus), and restricted ankle dorsiflexion (equinus). The incidence of TEV ranges from 0.5 to 2.0 per 1000 live births, and its etiology is believed to involve a complex interplay of genetic and environmental factors. Despite its long-standing recognition, the precise cause of TEV remains largely unknown. Various genetic studies, including candidate gene association studies, copy number variation analyses, linkage analyses, whole-exome sequencing, and whole-genome sequencing, have identified the specific genes implicated in TEV pathogenesis. However, the existing literature remains insufficient to pinpoint the exact genetic causes of familial cases, as most investigations have concentrated on sporadic instances, leaving many speculative genetic factors. **Methods**: This narrative review synthesizes the existing literature on the environmental, molecular, and genetic factors contributing to TEV while elucidating the pathobiological mechanisms involved in its development. **Results**: Evidence suggests that TEV exhibit familial segregation patterns consistent with both autosomal dominant and recessive inheritance, as well as autosomal dominant inheritance with incomplete penetrance, underscoring the significant role of genetic components. Notably, the concordance rate for TEV was markedly higher in monozygotic twins (32%) than in dizygotic twins (2.9%), reinforcing the genetic underpinning of the condition. **Conclusions**: According to our review outcomes, TEV simultaneously originates from genetic predispositions and environmental influences that disrupt normal mitotic division of the cytoskeleton in the lower limbs. To advance our understanding of TEV, there is a pressing need for large-scale, multicenter collaborative studies employing advanced genetic techniques, such as genome-wide association studies (GWAS) with single nucleotide polymorphism scans and linkage analysis in extensive family cohorts.

【Keywords】: Talipes equinovarus, genetics, pathology

1. Introduction

Skeletal disorders include a series of conditions in which the development and architecture of the chondro-osseous tissue are adversely affected, leading to deformities of the musculoskeletal system. TEV is one of the most common congenital abnormalities affecting the limbs, characterized by deformity of the foot with four components of osteochondral tissues, namely, the hind foot varus, forefoot (metatarsus) adducts, exaggerated midfoot arch (cavus), and equinus [1], [2]. The resulting deformities are shown in Figure 1.

图 **1**

Fig.1 ***An infant with bilateral club foot (Courtesy of orthopedic unit, District headquarter hospital Rawalpindi Pakistan)***

The prevalence of TEVs varies from 0.5 to 2.0 per 1000 live births [3]. In low- to middle-income countries, TEV incidence varies between 0.15 and 2.03/1000 live births [4]. The incidence of TEV is high in the Māori population in New Zealand, which can be explained by the genetic load carried by closed societies [5]. Approximately 80 % of all reported cases of TEV are classified as isolated clubfoot, also called non-syndromic, while the other 20% are associated with other clinical abnormalities, and are thus called syndromic.

Syndromic TEV is more commonly associated with myelomeningocele and distal arthrogryposis, multiple epiphyseal dysplasia, Larsen syndrome (LS), Lambert syndrome, and Ehlers-Danlos syndrome (EDS) [6], [8], as shown in Figure 2. Studies performed on isolated TEV have been carried out during childhood; however, no data are available for these cases in adulthood to elaborate on the presence of delayed presentations of other features. The male-to-female ratio is 2:1, which is not variable in different societies [3]. As explained in [7], the polygenic and multifactorial pattern of inheritance in which females are also more likely to transmit clubfoot to their children, leads to the Carter effect. The clubfoot can be unilateral (30-40%) or bilateral (60-70%). TEVs manifest a large variety of biomolecular genetic defects that are influenced by environmental factors [8].

Historically, TEV were also described by Hippocrates during his era [9]. Egyptian Pharaoh Tutankhamen in 1332 was also shown to suffer from clubfoot [10]. A 17th-century painting of a dubbed *clubfoot child* by Jusepe de Ribera remains at the Musee du Lauvre [11]. Since ancient times, considerable work and advancements have been made in the management of TEVs.

However, the primary cause of this deformity remains unclear. In this review, we focus on the molecular genetic factors and pathobiological mechanisms underlying TEV.

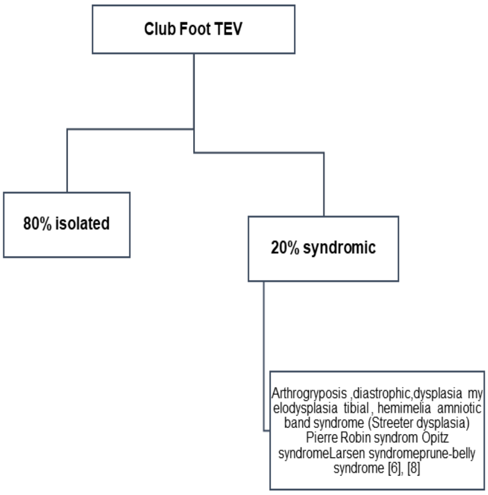

图 **2**
Fig.2 Presentation of TEV

2. Methodology

2.1. Etiology

Despite multiple theories, the exact cause of this deformity remains unclear. It is multifactorial, in that environmental and genetic factors are thought to play significant roles [12]. Some environmental factors, such as maternal psychological distress during pregnancy, alcohol use, parental age, parental education, and birth season were excluded because of the lack of significant statistical association [13]. Hippocrates postulated that increased intrauterine pressure compressing the lower limbs during the intrauterine life of a fetus plays a role in the development of this deformity. However, later studies showed that congested fetuses with oligohydramnios, twin pregnancy, large babies, and primigravida fetuses are not affected by clubfoot [14]. Moreover, it has also been proved that TEV can be diagnosed even in the second trimester of pregnancy before the intrauterine pressure rises [15]. The most common and congruous environmental factor involved in the etiology of this anomaly is the exposure of women to tobacco smoke during pregnancy [16]. Previous studies have shown that tobacco smoke is biotransformed via modulation of the N-acetylation genes, *NAT1* and *NAT2*. This is supported by studies showing that variations in *the NAT1 and NAT2* genes are associated with TEV [18]. Moreover, decreased acetylation activity of *the NATE 2* gene polymorphism was also found to be associated with TEV [17]-[18]. Additionally, genetic variations in smoking metabolism genes were studied in relation to clubfoot, where it was found that perturbation of *the CYP1A1 gene results in* adverse effects on the development of the lower limb [16].

Because TEVs segregate in families with both autosomal dominant and recessive modes of inheritance, the concordance rate is higher in monozygotic twins (32%) than in dizygotic twins (2.9%) [19]-[21]. Various genetic technologies have been used to identify genetic defects involved in the development of TEVs. Candidate association studies, copy number variation analysis, linkage analysis, whole-genome sequencing, and whole-exome sequencing have indicated the involvement of certain genes in the development of TEVs [12]. However, the genetic molecular regulatory network underlying TEVs has yet to be identified. Other studies have shown that TEV is a multifactorial deformity of the lower limb, in which genetic factors are predominant but modifiable by environmental factors [22]-[23].

2.2. Gross TEV **Phenotypic Abnormalities**

In TEVs, the tibia and fibula bones are slightly shortened because of the incomplete developmental process [24]–[25]. Hence, distal tibial metaphyseal fractures due to diastasis in the tibiofibular joint have been reported in several cases during forced dorsiflexion and eversion of the ankle joint [26]-[28]. Relations between the talus bone and other abnormal bones are divided into different subgroups, such as medical subluxation of the navicular bone on the talar head and medial subluxation of the cuboid bone over the calcaneal head, which ultimately leads to restriction of movements in the ankle joint [26]-[27]. However, some bone anomalies in TEV, such as small dome-shaped deformations, are associated with a better range of movements of the ankle joint [29].

Congenital hypoplasia of the calf muscles after TEV treatment has also been reported [30]. The total number of muscle fibers was normal, but they showed type 1 fiber atrophy, type 2b deficiency, and an increased number of type 2c muscle fibers, suggesting abnormal development of these muscle fibers in TEV cases [31].

2.3. TEV Genetics

Usually, mutations in genes encoding contractile proteins of skeletal myofibrils, such as *MYBPH*, *TPM2*, *TNNT3*, *TPM1*, *MYH13*, and *MYH3* are involved in TEVs [32]-[33]. However, Gurnett et al. in their study of 31 patients, of whom 20 had familial clubfoot TEV, could not detect mutations in the TNNT3, MYH3, and TPM2 genes [33]. However, he found several previously undescribed single-nucleotide polymorphisms of unknown importance.

3. Results

3.1. Genes implicated in TEVs

3.1.1. PITX- Gene

PITX1 participates in the development of hind limbs, primarily in the legs and feet. The first brachial arch, an embryonic structure at the base of the brain, has also been found to preferentially express *PITX1* [34]-[35]. A study of six probands of Ghanaian parents reported the co-occurrence of orofacial clefts (congenital malformations of the face and palate) and clubfoot with variable genetic causes [36]. Defects in the bronchial arches explain this co-occurrence. Most studies have shown that genetic defects in *PITX1* can cause lower limb developmental deformities such as developmental hip dysplasia, patellar hypoplasia, tibial hemimelia, preaxial polydactyly, and bilateral TEV [37]-[41]. Moreover, copy number variations and haploinsufficiency of PITX1 play crucial roles in the development of isolated clubfoot [42]-[43].

3.1.2. TBX4-Gene

In the T-box family, T-box factor 4 (*TBX4*) is a known transcription factor and its expression has been expressed in multiple organs and tissues [44]. Knockout studies have revealed that *the TBX4 gene plays* a significant role in the development of the lower limbs and respiratory pathways [45]. Hence, mutations in TBX4 lead to skeletal dysplasia and pulmonary hypertension due to developmental lung diseases [37]. Specifically, mutations in *TBX4* have been reported in patients with pulmonary developmental disorders and lower-limb deformities [46]. Moreover, microduplication of the 17q23.1q23.2 region involving TBX4 has been identified in familial cases of TEV [47].

3.1.3. HOX (homeobox A, C, D) gene

The HOX family participates in patterning [48]. Genes in the HOX cluster (*HOXA-D*) control the development of the lower-limb axis. Members of the HOXD cluster, *HOXD12* and HOXD13, are involved in the development of TEV [49]. Transmission defects in HOXA and HOXD apoptosis gene clusters have also been found in TEVs [50]. Moreover, microdeletion of the *5'* region of *HOXC* contributes to the development of both the vertical talus and TEV [51].

3.1.4. Filamin B (FLNB)

FLNB is a cytoplasmic protein that regulates intracellular communication and signaling by cross-linking the protein actin, thus allowing direct communication between the cell membrane and cytoskeletal network, thereby controlling and guiding proper skeletal development. *FLNB* mutations may lead to boomerang dysplasia atelosteogenesis I and III and Larsen syndrome [52]-[55]. Although a mutation in filamin B can cause a complex syndrome, three novel missense mutations in this gene have been identified in the development of TEV [56]. The deletion of *FLNB E1792del* has also been documented in isolated clubfoot patients [57].

3.1.5. COL9A1

Type IX collagen proteins are produced by the COL9A1 gene, which helps in strengthening connective tissues, ligaments, tendons, cartilage, bone, and skin [58]. A study of a Chinese population showed that the COL9A1 rs35470562 variant may contribute to the development of TEVs [59]. As demonstrated in [60], the high expression of a protein from the COL9A1 gene in the rs1135056-encoding region may increase susceptibility to TEVs.

Table 2 lists the most common genes involved in TEV development.

表 **2**
Table 2 Genes involved in TEV development

Genes	Associated with other phenotypes	References
PITX- gene	Orofacial clefts Developmental hip dysplasia Patella hypoplasia Tibial hemimelia Preaxial polydactyly	37,38,39,40,41,42, 43
***TBX4*- gene**	Skeletal dysplasia Pulmonary hypertension Coxodopatellar syndrome Amelia	37, 44,45,
HOX A	Severe limb and genital abnormalities	49, 50,51
FLNB	Dysplasia atelosteogenesis I–III and Larsen syndrome	52, 53,54,55,57
COL9A1	Osteoarthritis Epiphyseal dysplasia Stickler syndrome	58, 59,60

4. Discussion

Recently, mutations in several candidate genes or SNPs have been hypothesized to be involved in the molecular genetic basis of TEV, but the main mechanism remains elusive [9], [61]–[62]. TEV inheritance in heterogenic families is associated with multiple genetic factors. These genetic factors and their regulatory sequences are further influenced by a few environmental factors, complicating their discovery. A neurovascular hypothesis is proposed to identify the common denominator. Spinal anomalies and spina bifida, which are frequently observed in TEV deformities, are associated with neurodegenerative disorders [63]–[64]. A study on sciatic nerve defects in a chicken and mouse model of the TEV phenotype found that upregulation of *LIMK1* causes peroneal muscular atrophy [65]. Vascular insufficiency and occlusion of the vascular tree at the sinus tarsi canal of the ankle and foot are found in the limbs of patients affected by TEV [66]-[67]. The finding of joint laxity in patients with TEV supports the theory of connective tissue defect [65]. Calcaneus and talar bone anomalies with reduced fetal movement also support the concept of physiological deformity of the foot [1], [68]. All these mechanisms for developing TEVs are related to genes that are key players in cytoskeleton formation. A healthy and genetically maintained cytoskeleton in the feet during intrauterine life is important for foot maturity. Any disruption to the physical properties or shape of the cytoskeleton of bones, muscles, ligaments, and soft tissues may lead to a deformed foot.

Since its description by Hippocrates in 400 BC, a search for possible causes was initiated. Data on segregation analysis suggested the “major genes” involved in the development of TEVs. However, because of the heterogeneity of genetic causes, the candidate gene approach failed to reveal the exact number of causative variants in both isolated and syndromic TEV phenotypes. Moreover, according to [69], the genetics of isolated and syndromic clubfeet were classified, and it was concluded that FLNB is involved in both types. As shown in Table 2, genes involved in clubfoot are also involved in other disease processes. Studies published on clubfoot management reported that additional features appear even after surgical intervention in clubfoot patients during adulthood [70]. A case report [71] in a 56 year of age suggested additional features, such as degenerative changes in the hindfoot and thoracolumbar scoliosis with degenerative spondyloarthrosis in the thoracolumbar spine segments. Sequencing analysis in one study failed to detect genetic variants of *TBX4, PITX1, HOXD12,* and *HOXD9* in two Pakistani families [72]. They suggested that mutations might be present in the regulatory regions of these genes. A literature review of a large number of studies proved that relapse of the disease process occurs even after corrective surgery because of tissue deposition, indicating that pathobiological factors persist and cause the issues [73]-[74].

Recently, more advanced techniques have become available to obtain promising results regarding the underlying causes of TEV. Among all the reported genetic studies using different techniques, next-generation sequencing (NGS), including whole-genome sequencing and whole-exome sequencing (WES), has become popular in common clinical diagnosis, as well as in research on gene identification in inherited diseases. To obtain the most effective results, it is useful to combine these techniques with a linkage analysis [75].

5. Conclusions

TEV is a multifactorial condition characterized by genetic disruption of multiple molecules in the cytoskeleton, which is affected by exposure to adverse environmental and genetic factors. The available literature shows a deficit in high-profile studies, as many studies focusing on the genetic causes of this deformity lack speculative harmony in proving the exact genetic cause in both isolated and syndromic types of talipes equinovarus. Therefore, refinement of existing genes of isolated clubfoot and clubfoot-associated phenotypes in early and late adulthood will lead to more effective genotype determination and improved diagnostic capabilities and management options. Hence, large-scale, multicenter collaborative studies using genetic techniques such as GWAS with SNP scans for linkage analysis are required for families affected by TEV. Furthermore, inheritance patterns and penetrance will help to identify novel genes involved in this disorder. The discovery of genetic factors will revolutionize the management of TEV and eliminate the disability of patients who often persist.

Nonetheless, we would like to put forward the hypothesis that genes implicated in clubfoot not only cause clubfoot but also lead to multiple symptoms, and the affected patients are suffering from syndromic clubfoot. Therefore, we need to thoroughly investigate affected individuals to determine the possibility of other syndromes. In other words, the classification of club feet into isolated and syndromic types must be revised.

Declarations

Author Contributions

Yasir Naseem Khan wrote the initial draft of the article under the supervision of **Mohammad Imad. Mohammad Imad** reviewed and suggested the changes required for publication. All the authors contributed equally to the study and approved the final manuscript.

Ethical Approval and Consent to participate

The Research Ethics Committee of the Islamic International University, Malaysia, granted all necessary clearance and ethical approval.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors would like to thank Dr. Uzma Khan from the Department of Clinical Sciences, Al Rayan College of Medicine, Al Rayan National College, Madina Munawarra for her useful suggestions and guidance during the final stage of the study.

References

[1] PAVONE V, CHISARI E, VESCIO A, et al. The etiology of idiopathic congenital talipes equinovarus: a systematic review. J Orthop Surg Res, 2018, 13(1): 206, doi: 10.1186/s13018-018-0913-z

[2] IPPOLITO E, & PONSETI IV. Congenital club foot in the human fetus. A histological study. J Bone Joint Surg Am.,1980, 62(1): 8-22.

[3] CHING GH, CHUNG CS, & NEMECHEK RW.

Genetic and epidemiological studies of clubfoot in Hawaii: ascertainment and incidence. Am J Hum Genet, 1969, 21(6): 566-580.

[4] SMYTHE T, KUPER H, MACLEOD D, et al. Birth prevalence of congenital talipes equinovarus in low-and middle-income countries: a systematic review and meta-analysis. Trop Med Int Health, 2017, 22(3): 269-285, doi: 10.1111/tmi.12833

[5] TODD MR, KODOVARU SS, ANTONIOU G, & CUNDY PJ. Clubfoot deformity in the Solomon Islands: Melanesian versus Polynesian ethnicity, a retrospective cohort study. J Child Orthop, 2020, 14(4): 281-285, doi: 10.1302/1863-2548.14.190172

[6] GURNETT CA, BOEHM S, CONNOLLY A, et al. Impact of congenital talipes equinovarus etiology on treatment outcomes. Dev Med Child Neurol 2008, 50(7): 498-502, doi: 10.1111/j.1469-8749.2008.03016.x

[7] KRUSE LM, DOBBS MB, & GURNETT CA. Polygenic threshold model with sex dimorphism in clubfoot inheritance: the Carter effect. J Bone Joint Surg. Am., 2008, 90(12): 2688-2694, doi: 10.2106/jbjs.g.01346 .

[8] TUKKER AM, ROYAL CD, BOWMAN AB, & MCALLISTER KA. The impact of environmental factors on monogenic mendelian diseases. Toxicol Sci, 2021, 181(1): 3-12, doi: 10.1093/toxsci/kfab022

[9] SANZARELLO I, NANNI M, & FALDINI C. The clubfoot over the centuries. J Pediatr Orthop B, 2017, 26(2): 143-151, doi: 10.1097/bpb.0000000000000350

[10] DARNELL JC, & MANASSA C. Tutankhamun's armies: Battle and conquest during ancient Egypt's Late Eighteenth Dynasty. John Wiley & Sons; 2007.

[11] ABUL K, MISIR A, & BUYUK AF. Art in Science: Jusepe de Ribera's *Puzzle in The Clubfoot*. Clin Orthop Relat Res, 2018, 476(5): 942-945, doi 10.1007/s11999.0000000000000267

[12] BASIT S, & KHOSHHAL KI. Genetics of clubfoot; recent progress and future perspectives. Eur J Med Genet, 2018, 61(2): 107-113, doi: 10.1016/j.ejmg.2017.09.006

[13] DODWELL E, RISOE P, & WRIGHT J. Factors associated with increased risk of clubfoot: a Norwegian national cohort analysis. J Pediatr Orthop, 2015, 35(8): e104-109, doi: 10.1097/BPO.0000000000000449

[14] ANAND A, & SALA DA. Clubfoot: Etiology and treatment. Indian J Orthop 2008, 42(1): 22-28, doi: 10.4103/0019-5413.38576

[15] PAGNOTTA G, MAFFULLI N, AURELI S, et al. Antenatal sonographic diagnosis of clubfoot: a six-year experience. The J Foot Ankle Surg. 1996, 35(1): 67-71, doi: 10.1016/s1067-2516(96)80015-9

[16] SOMMER A, BLANTON SH, WEYMOUTH K, et al. Smoking, the xenobiotic pathway, and clubfoot. Birth Defects Res A Clin Mol Teratol, 2011, 91(1): 20-28, doi: 10.1002/bdra.20742

[17] HECHT JT, ESTER A, SCOTT A, et al. NAT2 variation and idiopathic talipes equinovarus (clubfoot). Am. J Med Genet A, 2007, 143(19): 2285-2291, doi: 10.1002/ajmg.a.31927

[18] SHARP L, MIEDZYBRODZKA Z, CARDY AH, et al. The C677T polymorphism in the methylenetetrahydrofolate reductase gene (MTHFR), maternal use of folic acid supplements, and risk of isolated clubfoot: A case-parent-triad analysis. Am J Epidemiol, 2006, 164: 852-861, doi: 0.1093/aje/kwj285

[19] BARKER S, CHESNEY D, MIEDZYBRODZKA Z, & MAFFULLI N. Genetics and epidemiology of idiopathic congenital talipes equinovarus. J Pediatr Orthop, 2003, 23(2): 265-272.

[20] YAMAMOTO H. A clinical, genetic, and epidemiologic study of congenital club foot. Jap J Hum Genet, 1979, 24(1): 37-44, doi: 10.1007/bf01890110

[21] YANG H, CHUNG CS, NEMECHEK RW, & RAO DC. A genetic analysis of clubfoot in Hawaii. Genet Epidemiol, 1987, 4(4): 299-306, doi: 10.1002/gepi.1370040408

[22] BACINO CA, & HECHT JT. Etiopathogenesis of equinovarus foot malformations. Eur J Med Genet, 2014, 57(8): 473-479, doi: 10.1016/j.ejmg.2014.06.001

[23] ENGELL V, NIELSEN J, DAMBORG F, et al. Heritability of clubfoot: a twin study. J Child Orthop, 2014, 8(1): 37-41, doi: 10.1007/s11832-014-0562-7

[24] SCHLIGHT D. The pathological anatomy of talipes equino-varus. Austr N Z J Surg, 1963, 33(1): 1-11.

[25] WAISBROD H. Congenital club foot: an anatomical study. J Bone Joint Surg. Br., 1973, 55(4): 796-801.

[26] VOLZ R, PAULSEN M, & MORCUENDE J. Distal tibia/fibula fractures following clubfoot casting report of four cases. Iowa Orthop J, 2009, 29: 117-120.

[27] CRAWFORD AH. Clubfoot controversies: complications and causes for failure. Inst Course Lect, 1996, 45: 339-346.

[28] NOONAN KJ, MEYERS AM, KAYES K. Leg length discrepancy in unilateral congenital clubfoot following surgical treatment. Iowa Orthop J, 2004, 24: 60-64.

[29] KOLB A, WILLEGGER M, SCHUH R, et al. The impact of different types of talus deformation after treatment of clubfeet. Int Orthop, 2017, 41(1): 93-99, doi: 10.1007/s00264-016-3301-5

[30] IRANI RN, & SHERMAN MS. The pathological anatomy of idiopathic clubfoot. Clin Orthop Relat Res, 1972, 84: 14-20, doi: 0.1097/00003086-197205000-00004

[31] HANDELSMAN JE, & GLASSER R. Muscle pathology in clubfoot and lower motor neuron lesions. In SIMONS GW. (Ed.) The Clubfoot. (pp. 21-31). Springer, New York, NY. doi: 10.1007/978-1-4613-9269-9_5

[32] WEYMOUTH KS, BLANTON SH, BAMSHAD MJ, et al. Variants in genes that encode muscle contractile proteins influence risk for isolated clubfoot. Am J Med Genet A, 2011, 155(9): 2170-2179, doi: 10.1002/ajmg.a.34167

[33] GURNETT CA, ALAEE F, DESRUISSEAU D, et al. Skeletal muscle contractile gene (TNNT3, MYH3, TPM2) mutations not found in vertical talus or clubfoot. Clin Orthop Relat Res, 2009, 467(5): 1195-1200, doi: 10.1007/s11999-008-0694-5

[34] IPPOLITO E, & GORGOLINI G. Clubfoot pathology in fetus and pathogenesis. A new pathogenetic theory based on pathology, imaging

findings and biomechanics—a narrative review. Ann Transl Med, 2021, 9(13): 1095, doi: 10.21037/atm-20-7236

[35] SZETO DP, RODRIGUEZ-ESTEBAN C, RYAN AK, et al. Role of the Bicoid-related homeodomain factor Pitx1 in specifying hindlimb morphogenesis and pituitary development. Genes Dev, 1999, 13(4): 484-494, doi: 10.1101/gad.13.4.484

[36] GOWANS LJ, AL DHAHERI N, LI M, et al. Co-occurrence of orofacial clefts and clubfoot phenotypes in a sub-Saharan African cohort: Whole-exome sequencing implicates multiple syndromes and genes. Mol Genet Genom Med, 2021, 9(4): e1655, doi: 10.1002/mgg3.1655

[37] HAARMAN MG, KERSTJENS-FREDERIKSE WS, & BERGER RM. The ever-expanding phenotypical spectrum of human TBX4 mutations: from toe to lung. Eur Respir J, 2019, 54(2): 1901504, doi: 10.1183/13993003.01504-2019

[38] GURNETT CA, ALAEE F, KRUSE LM, et al. Asymmetric lower-limb malformations in individuals with homeobox PITX1 gene mutation. Am J Hum Genet, 2008, 83(5): 616-622, doi: 10.1016/j.ajhg.2008.10.004

[39] ROSENFELD JA, DRAUTZ JM, CLERICUZIO CL, et al. Deletions and duplications of developmental pathway genes in 5q31 contribute to abnormal phenotypes. Am J Med Genet A, 2011, 155(8): 1906-1916, doi: 10.1002/ajmg.a.34100

[40] KLOPOCKI E, KÄHLER C, FOULDS N, et al. Deletions in PITX1 cause a spectrum of lower-limb malformations including mirror-image polydactyly. Eur J Hum Genet, 2012, 20(6): 705-708, doi: 10.1038/ejhg.2011.264

[41] ALVARADO DM, BUCHAN JG, FRICK SL, et al. Copy number analysis of 413 isolated talipes equinovarus patients suggests role for transcriptional regulators of early limb development. Eur J Hum Genet, 2013, 21(4): 373-380, doi: 10.1038/ejhg.2012.177

[42] ALVARADO DM, MCCALL K, AFEROL H, et al. Pitx1 haploinsufficiency causes clubfoot in humans and a clubfoot-like phenotype in mice. Hum Mol Genet, 2011, 20(20): 3943-3952, doi: 10.1093/hmg/ddr313

[43] WANG J, LIN Y, DUAN J, et al. Silent gene Pitx1 reveals the potential pathogenesis of clubfoot. Int J Clin Exp Med, 2020, 13(7): 4879-4888.

[44] AGULNIK SI, GARVEY N, HANCOCK S, et al. Evolution of mouse T-box genes by tandem duplication and cluster dispersion. Genetics, 1996, 144(1): 249-254, doi: 10.1093/genetics/144.1.249

[45] NAICHE LA, & PAPAIOANNOU VE. Loss of Tbx4 blocks hindlimb development and affects vascularization and fusion of the allantois. Development, 2003, 130(12): 2681-2693, doi: 10.1242/dev.00504

[46] BONGERS EM, DUIJF PH, VAN BEERSUM SE, et al. Mutations in the human TBX4 gene cause small patella syndrome. Am J Hum Genet, 2004, 74(6): 1239-1248, doi: 10.1086/421331

[47] PETERSON JF, GHALOUL-GONZALEZ L, MADAN-KHETARPAL S, et al. Familial microduplication of 17q23. 1–q23. 2 involving TBX4 is associated with congenital clubfoot and reduced penetrance in females. Am J Med Genet A, 2014, 164(2): 364-369, doi: 10.1002/ajmg.a.36238

[48] MARK M, RIJLI FM, & CHAMBON P. Homeobox genes in embryogenesis and pathogenesis. Pediatr Res, 1997, 42(4): 421-429, doi: 10.1203/00006450-199710000-00001

[49] WANG F, DU M, WANG R, et al. Molecular mechanism of Hoxd13-mediated congenital malformations in rat embryos. Int J Clin Exp Pathol, 2015, 8(12): 15591-15598.

[50] ESTER AR, WEYMOUTH KS, BURT A, et al. Altered transmission of HOX and apoptotic SNPs identify a potential common pathway for clubfoot. Am J Med Genet A, 2009, 149(12): 2745-2752, doi: 10.1002/ajmg.a.33130

[51] ALVARADO DM, MCCALL K, HECHT JT, et al. Deletions of 5′ HOXC genes are associated with lower extremity malformations, including clubfoot and vertical talus. J Med Genet, 2016, 53(4): 250-255, doi: 10.1136/jmedgenet-2015-103505

[52] Wu H, Wang Y, Chen X, et al. Cell-Dependent Pathogenic Roles of Filamin B in Different Skeletal Malformations. Oxid Med Cell Longev, 2022, 2022: 8956636, doi: 10.1155/2022/8956636

[53] BICKNELL LS, MORGAN T, BONAFE L, et al. Mutations in FLNB cause boomerang dysplasia. J Med Genet, 2005, 42(7): e43, doi: 10.1136/jmg.2004.029967

[54] FARRINGTON-ROCK C, FIRESTEIN MH, BICKNELL LS, et al. Mutations in two regions of FLNB result in atelosteogenesis I and III. Human Mutat, 2006, 27(7): 705-710, doi: 10.1002/humu.20348

[55] ZHANG D, HERRING JA, SWANEY SS, et al. Mutations responsible for Larsen syndrome cluster in the FLNB protein. J Med Genet. 2006, 43(5): e24, doi: 10.1136/jmg.2005.038695

[56] YANG H, ZHENG Z, CAI H et al. Three novel missense mutations in the filamin B gene are associated with isolated congenital talipes equinovarus. Hum Genet, 2016, 135(10): 1181-1189, doi: 10.1007/s00439-016-1701-7

[57] QUIGGLE A, CHARNG WL, ANTUNES L, et al. Whole exome sequencing in individuals with idiopathic clubfoot reveals a recurrent Filamin B (FLNB) deletion. Clin Orthop Relat Res, 2022, 480(2): 421-430, doi: 10.1097/corr.0000000000001957

[58] BLUMBACH K, NIEHOFF A, PAULSSON M, & ZAUCKE F. Ablation of collagen IX and COMP disrupts epiphyseal cartilage architecture. Matrix Biol, 2008, 27(4): 306-318, doi: 10.1016/j.matbio.2007.11.007

[59] ZHAO XL, WANG YJ, WU YL, & HAN WH. Role of COL9A1 genetic polymorphisms in development of congenital talipes equinovarus in a Chinese population. Genet Mol Res. 2016, 15(4), doi: 10.4238/gmr15048773

[60] LIU LY, JIN CL, CAO DH, et al. Analysis of association between COL9A1 gene and idiopathic congenital talipes equinovarus. Yi Chuan, 2007, 29(4): 427-432, doi: 10.1360/yc-007-0427

[61] CARDY AH, BARKER S, CHESNEY D, et al. Pedigree analysis and epidemiological features of idiopathic congenital talipes equinovarus in the United

Kingdom: a case-control study. BMC Musculoskelet Disord, 2007, 8(1): 62, doi: 10.1186/1471-2474-8-62

[62] MUSTARI MN, FARUK M, BAUSAT A, & FIKRY A. Congenital talipes equinovarus: A literature review. Ann Med Surg, 2022, 81: 104394, doi: 0.1016/j.amsu.2022.104394

[63] BRAY JJ, CROSSWELL S, & BROWN R. Congenital talipes equinovarus and congenital vertical talus secondary to sacral agenesis. BMJ Case Rep, 2017, 2017: bcr2017219786, doi: 10.1136/bcr-2017-219786

[64] SWAROOP VT, & DIAS L. Orthopaedic management of spina bifida—part II: foot and ankle deformities. J Child Orthop, 2011, 5(6): 403-414, doi: 10.1007/s11832-011-0368-9

[65] COLLINSON JM, LINDSTRÖM NO, NEVES C, et al. The developmental and genetic basis of ‘clubfoot’ in the peroneal muscular atrophy mutant mouse. Development. 2018, 145(3): dev160093, doi: 10.1242/dev.160093

[66] TAILOR A, JURKOVIC D, BOURNE TH, et al. Sonographic prediction of malignancy in adnexal masses using multivariate logistic regression analysis. Ultrasound Obstet Gynecol, 1997, 10(1): 41-47, doi: 10.1046/j.1469-0705.1997.10010041.x

[67] MERRILL LJ, GURNETT CA, SIEGEL M, et al. Vascular abnormalities correlate with decreased soft tissue volumes in idiopathic clubfoot. Clin Orthop Relat Res, 2011, 469(5): 1442-1449, doi: 10.1007/s11999-010-1657-1

[68] HESTER TW, PARKINSON LC, ROBSON J, et al. A hypothesis and model of reduced fetal movement as a common pathogenetic mechanism in clubfoot. Med Hypotheses, 2009, 73(6): 986-988, doi: 10.1016/j.mehy.2009.04.056

[69] SADLER B, GURNETT CA, & DOBBS MB. The genetics of isolated and syndromic clubfoot. J Child Orthop, 2019, 13(3): 238-244, doi: 10.1302/1863-2548.13.190063

[70] BRODSKY JW. The adult sequelae of treated congenital clubfoot. Foot Ankle Clin, 2010, 15(2): 287-296, doi: 10.1016/j.fcl.2010.03.002

[71] MILENKOVIC SS, MITKOVIC MM, & MITKOVIC MB. Neglected Congenital Clubfoot in an Adult 56 Years Old Patient. J Foot Ankle Surg (Asia Pacific), 2021, 8(3): 152-154, doi: 10.5005/jp-journals-10040-1163

[72] KHAN YN, HUMA Z, KHAN U, BASIT S. Mutation screening of genes associated with congenital talipes equinovarus in Pakistani families. J Musculoskelet Surg Res, 2020, 4(1): 25-30 doi: 10.4103/jmsr.jmsr_94_19

[73] RAMSEIER LE, SCHOENIGER R, VIENNE P, & ESPINOSA N. Treatment of late recurring idiopathic clubfoot deformity in adults. Acta Orthop Belg, 2007, 73(5): 641-647.

[74] JOHNSON JE, FORTNEY TA, LUK PC, et al. Late Effects of Clubfoot Deformity in Adolescent and Young Adult Patients Whose Initial Treatment Was an Extensive Soft-tissue Release: Topic Review and Clinical Case Series. J Am Acad Orthop Surg Glob Res Rev, 2020, 4(5): e1900126, doi: 0.5435/jaaosglobal-d-19-00126

[75] ALHARBY E, ALBALAWI AM, NASIR A, et al. A homozygous potentially pathogenic variant in the PAXBP1 gene in a large family with global developmental delay and myopathic hypotonia. Clin Genet, 2017, 92(6): 579-586, doi: 10.1111/cge.13051

参考文献

[1] PAVONE V、CHISARI E、VESCIO A 等。特发性先天性马蹄内翻足的病因：系统综述。J Orthop Surg Res，2018，13(1)： 206， doi：10.1186/s13018-018-0913-z

[2] IPPOLITO E 和 PONSETI IV。 人类胎儿的先天性马蹄足。 组织学研究。J Bone Joint Surg Am.，1980，62(1)：8-22。

[3] CHING GH、CHUNG CS 和 NEMECHEK RW。 夏威夷马蹄足的遗传和流行病学研究：确定和发病率。Am J Hum Genet，1969，21(6)：566-580。

[4] SMYTHE T、KUPER H、MACLEOD D 等。 低收入和中等收入国家先天性马蹄内翻足的出生患病率：系统评价和荟萃分析。Trop Med Int Health， 2017，22(3)：269-285，doi：10.1111/tmi.12833

[5] TODD MR、KODOVARU SS、ANTONIOU G 和 CUNDY PJ。 所罗门群岛马蹄内翻足畸形： 美拉尼西亚人与波利尼 西亚人种， 一项回顾性队列研究。 J Child Orthop, 2020, 14(4): 281-285, doi: 10.1302/1863-2548.14.190172

[6] GURNETT CA, BOEHM S, CONNOLLY A, 等。 先天性马蹄内翻足病因对治疗结果的影响。Dev Med Child Neurol 2008, 50(7): 498-502, doi: 10.1111/j.1469-8749.2008.03016.x

[7] KRUSE LM, DOBBS MB, 和 GURNETT CA。 马蹄足遗传中具有性别二态性的多基因阈值模型：Carter 效应。J Bone Joint Surg. Am., 2008, 90(12): 2688-2694, doi: 10.2106/jbjs.g.01346 .

[8] TUKKER AM, ROYAL CD, BOWMAN AB, 和 MCALLISTER KA. 环境因素对单基因孟德尔疾病的 影响 . Toxicol Sci, 2021, 181(1): 3-12, doi: 10.1093/toxsci/kfab022

[9] SANZARELLO I, NANNI M, 和 FALDINI C. 几个世纪以来的马蹄足。 J Pediatr Orthop B, 2017, 26(2): 143-151, doi: 10.1097/bpb.0000000000000350

[10] DARNELL JC 和 MANASSA C。 图坦卡蒙的军队： 古埃及第十八王朝晚期的战斗与征服. 约翰·威利父子公司；2007。

[11] ABUL K、MISIR A 和 BUYUK AF。 科学中的艺术： Jusepe de Ribera 在《马蹄足》中的谜题。 Clin Orthop Relat Res, 2018, 476(5): 942-945, doi 10.1007/s11999.0000000000000267

[12] BASIT S 和 KHOSHHAL KI。 马蹄足遗传学； 最新进展和未来展望。Eur J Med Genet, 2018, 61(2): 107-113, doi: 10.1016/j.ejmg.2017.09.006

[13] DODWELL E、RISOE P 和 WRIGHT J。 与马蹄足风险增加相关的因素：挪威国家队列分析。 J Pediatr Orthop, 2015, 35(8): e104-109, doi: 10.1097/BPO.0000000000000449

[14] ANAND A, 和 SALA DA. 马蹄足： 病因与治疗。 Indian J Orthop 2008, 42(1): 22-28, doi: 10.4103/0019-5413.38576

[15] PAGNOTTA G, MAFFULLI N, AURELI S, 等. 马蹄足的产前超声诊断：六年经验。The J Foot Ankle Surg. 1996, 35(1): 67-71, doi: 10.1016/s1067-2516(96)80015-9

[16] SOMMER A, BLANTON SH, WEYMOUTH K, 等。吸烟、外来生物途径和马蹄足。出生缺陷研究 A Clin Mol Teratol , 2011 , 91(1): 20-28 , doi: 10.1002/bdra.20742

[17] HECHT JT, ESTER A, SCOTT A, 等。NAT2 变异和特发性马蹄内翻足（马蹄足）。Am. J Med Genet A, 2007, 143(19): 2285-2291, doi: 10.1002/ajmg.a.31927

[18] SHARP L, MIEDZYBRODZKA Z, CARDY AH, 等。亚甲基四氢叶酸还原酶基因 (MTHFR) 的 C677T 多态性、母亲使用叶酸补充剂和孤立性马蹄足的风险：病例-父母-三联分析。Am J Epidemiol, 2006, 164: 852-861, doi: 0.1093/aje/kwj285

[19] BARKER S, CHESNEY D, MIEDZYBRODZKA Z, 和 MAFFULLI N。 特发性先天性马蹄内翻足的遗传学和流行病学。 J Pediatr Orthop, 2003, 23(2): 265-272。

[20] YAMAMOTO H. 先天性马蹄足的临床、 遗传和流行病学研究。 Jap J Hum Genet, 1979, 24(1): 37-44, doi: 10.1007/bf01890110

[21] YANG H, CHUNG CS, NEMECHEK RW, 和 RAO DC。 夏威夷马蹄足的遗传分析。Genet Epidemiol, 1987, 4(4): 299-306, doi: 10.1002/gepi.1370040408

[22] BACINO CA, 和 HECHT JT。 马蹄内翻足畸形的病因学。 欧洲医学遗传学杂志, 2014, 57(8): 473-479, doi: 10.1016/j.ejmg.2014.06.001

[23] ENGELL V、NIELSEN J、DAMBORG F 等。 马蹄足的遗传性：双胞胎研究。儿童骨科杂志，2014, 8(1): 37-41, doi: 10.1007/s11832-014-0562-7

[24] SCHLIGHT D. 马蹄内翻足的病理解剖学。Austr N Z J Surg，1963，33(1)：1-11。

[25] WAISBROD H. 先天性马蹄足：解剖学研究。J Bone Joint Surg. Br.，1973，55(4)：796-801。

[26] VOLZ R、PAULSEN M 和 MORCUENDE J. 马蹄足铸造后胫骨/腓骨远端骨折四例报告。Iowa Orthop J，2009，29：117-120。

[27] CRAWFORD AH. 马蹄足争议： 并发症和失败原因。Inst Course Lect， 1996， 45： 339-346。

[28] NOONAN KJ、MEYERS AM、KAYES K。 单侧先天性马蹄足手术治疗后腿长差异。Iowa Orthop J, 2004，24：60-64。

[29] KOLB A、WILLEGGER M、SCHUH R 等。 不同类型的距骨变形对马蹄足治疗的影响。Int Orthop，2017，41(1)：93-99，doi：10.1007/s00264-016-3301-5

[30] IRANI RN 和 SHERMAN MS。 特发性马蹄足的病理解剖 学 Clin Orthop Relat Res, 1972, 84: 14-20, doi: 0.1097/00003086-197205000-00004

[31] HANDELSMAN JE 和 GLASSER R。 马蹄足和下运动神经元损伤的肌肉病理学。SIMONS GW。 （编辑）马蹄足。（第 21-31 页）。 Springer， 纽约， NY。doi: 10.1007/978-1-4613-9269-9_5

[32] WEYMOUTH KS、BLANTON SH、BAMSHAD MJ 等。 编码肌肉收缩蛋白的基因变异影响孤立性马蹄足 的风险。 Am J Med Genet A, 2011, 155(9): 2170-2179, doi: 10.1002/ajmg.a.34167

[33] GURNETT CA, ALAEE F, DESRUISSEAU D, 等. 垂直距骨或马蹄足中未发现骨骼肌收缩基因 (TNNT3、MYH3、 TPM2) 突变。临床矫形与康复研究，2009, 467(5): 1195-1200, doi: 10.1007/s11999-008-0694-5

[34] IPPOLITO E, 和 GORGOLINI G. 胎儿马蹄足病理和发病机制。 基于病理学、 影像学发现和生物力学的新型致病理论——叙述性综述。 Ann Transl Med, 2021, 9(13): 1095, doi: 10.21037/atm-20-7236

[35] SZETO DP, RODRIGUEZ-ESTEBAN C, RYAN AK, 等。 Bicoid 相关同源域因子 Pitx1 在指定后肢形态发生和垂体发育中的作用。 Genes Dev, 1999, 13(4): 484-494, doi: 10.1101/gad.13.4.484

[36] GOWANS LJ, AL DHAHERI N, LI M, 等。 撒哈拉以南非洲人群中颌面裂和马蹄足表型共现：全外显子组测序提示多种综合征和基因。 Mol Genet Genom Med, 2021, 9(4): e1655, doi: 10.1002/mgg3.1655

[37] HAARMAN MG、KERSTJENS-FREDERIKSE WS 和 BERGER RM。人类 TBX4 突变的不断扩大的表型谱从脚趾到肺。欧洲呼吸杂志，2019，54(2): 1901504，doi: 10.1183/13993003.01504-2019

[38] GURNETT CA、ALAEE F、KRUSE LM 等。同源框 PITX1 基因突变个体的不对称下肢畸形。 Am J Hum Genet, 2008, 83(5): 616-622, doi: 10.1016/j.ajhg.2008.10.004

[39] ROSENFELD JA, DRAUTZ JM, CLERICUZIO CL, 等。 5q31 中发育途径基因的缺失和重复导致 异常表型。 Am J Med Genet A, 2011, 155(8): 1906-1916, doi: 10.1002/ajmg.a.34100

[40] KLOPOCKI E, KÄHLER C, FOULDS N, 等。PITX1 基因缺失可导致一系列下肢畸形， 包括镜像多指畸形。 Eur J Hum Genet, 2012, 20(6): 705-708, doi: 10.1038/ejhg.2011.264

[41] ALVARADO DM, BUCHAN JG, FRICK SL, 等。413 名孤立性马蹄内翻足患者的拷贝数分析表明转录 调控因子在早期肢体发育中起着作用。Eur J Hum Genet, 2013, 21(4): 373-380, doi: 10.1038/ejhg.2012.177

[42] ALVARADO DM, MCCALL K, AFEROL H, 等。Pitx1 单倍体不足导致人类马蹄足和小鼠马蹄足样 表型。 Hum Mol Genet, 2011, 20(20): 3943-3952, doi: 10.1093/hmg/ddr313

[43] WANG J, LIN Y, DUAN J, 等。 沉默基因 Pitx1 揭示马蹄足的潜在发病机制. Int J Clin Exp Med, 2020, 13(7): 4879-4888.

[44] AGULNIK SI, GARVEY N, HANCOCK S, 等。 通过串联重复和簇分散进化小鼠 T-box 基因. Genetics, 1996, 144(1): 249-254, doi: 10.1093/genetics/144.1.249

[45] NAICHE LA, 和 PAPAIOANNOU VE. Tbx4 的缺失会阻碍后肢发育并影响尿囊的血管形成和融合。发展，2003, 130(12): 2681-2693, doi: 10.1242/dev.00504

[46] BONGERS EM、DUIJF PH、VAN BEERSUM SE 等。人类 TBX4 基因突变会导致小髌骨综合征。 Am J Hum Genet, 2004, 74(6): 1239-1248, doi: 10.1086/421331

[47] PETERSON JF、GHALOUL-GONZALEZ L、MADAN-KHETARPAL S 等。 17q23 的家族性微重复。1–q23。 2 涉及 TBX4 与先天性马蹄足和女性外显率降低有关。Am J Med Genet A， 2014， 164(2): 364-369， doi: 10.1002/ajmg.a.36238

[48] MARK M、RIJLI FM 和 CHAMBON P。 同源框基因在胚胎发生和发病机制中的作用。儿科研究，1997，42(4): 421-429， doi: 10.1203/00006450-199710000-00001

[49] WANG F，DU M，WANG R，等。Hoxd13 介导大鼠胚胎先天性畸形的分子机制。国际临床实验病理学杂志，2015，8（12）：15591-15598。

[50] ESTER AR, WEYMOUTH KS, BURT A, 等。HOX 传递的改变和凋亡的 SNP 确定了马蹄足的潜在共同途径。Am J Med Genet A, 2009, 149(12): 2745-2752, doi: 10.1002/ajmg.a.33130

[51] ALVARADO DM, MCCALL K, HECHT JT, 等。 5′HOXC 基因缺失与下肢畸形有关， 包括马蹄足和垂直距骨。 J Med Genet, 2016, 53(4): 250-255, doi: 10.1136/jmedgenet-2015-103505

[52] Wu H, Wang Y, Chen X, 等。细丝蛋白 B 在不同骨骼畸形中的细胞依赖性致病作用。Oxid Med Cell Longev， 2022， 2022： 8956636， doi： 10.1155/2022/8956636

[53] BICKNELL LS、MORGAN T、BONAFE L 等。FLNB 突变导致回旋镖发育不良。J Med Genet，2005， 42(7)： e43， doi：10.1136/jmg.2004.029967

[54] FARRINGTON-ROCK C、FIRESTEIN MH、BICKNELL LS 等。 FLNB 两个区域的突变导致骨形成 I 和 III。 Human Mutat, 2006, 27(7): 705-710, doi: 10.1002/humu.20348

[55] ZHANG D, HERRING JA, SWANEY SS, 等。 导致拉尔森综合征的突变集中在 FLNB 蛋白中。J Med Genet. 2006, 43(5): e24, doi: 10.1136/jmg.2005.038695

[56] YANG H, ZHENG Z, CAI H 等。 细丝蛋白 B 基因中的三种新的错义突变与个体先天性足内翻畸形有关。Hum Genet， 2016， 135(10)： 1181-1189， doi： 10.1007/s00439-016-1701-7

[57] QUIGGLE A、CHARNG WL、ANTUNES L 等。特发性马蹄足患者的全外显子组测序揭示了复发性 Filamin B (FLNB) 缺失。 临床骨科研究， 2022， 480(2) ： 421-430 ， doi ： 10.1097/corr.0000000000001957

[58] BLUMBACH K、NIEHOFF A、PAULSSON M 和 ZAUCKE F。 IX 型胶原蛋白和 COMP 消融会破坏骨骺软骨结构。 Matrix Biol, 2008, 27(4): 306-318, doi: 10.1016/j.matbio.2007.11.007

[59] ZHAO XL, WANG YJ, WU YL, & HAN WH. COL9A1 基因多态性在中国人群先天性马蹄内翻足发生发展中的作用. Genet Mol Res. 2016, 15(4), doi: 10.4238/gmr15048773

[60] LIU LY, JIN CL, CAO DH, 等. COL9A1 基因与特发性先天性马蹄内翻足的关联分析. Yi Chuan, 2007, 29(4): 427-432, doi: 10.1360/yc-007-0427

[61] CARDY AH, BARKER S, CHESNEY D, 等. 英国特发性先天性马蹄内翻足的系谱分析和流行病学特征：病例对照研究。BMC Musculoskelet Disord, 2007, 8(1): 62, doi: 10.1186/1471-2474-8-62

[62] MUSTARI MN, FARUK M, BAUSAT A, 和 FIKRY A. 先天性马蹄内翻足：文献综述。 Ann Med Surg, 2022, 81: 104394, doi: 0.1016/j.amsu.2022.104394

[63] BRAY JJ、CROSSWELL S、和 BROWN R。 先天性马蹄内翻足和先天性垂直距骨继发于骶骨发育不全。BMJ Case Rep, 2017, 2017: bcr2017219786, doi: 10.1136/bcr-2017-219786

[64] SWAROOP VT 和 DIAS L。脊柱裂的矫形治疗 - 第二部分： 足部和踝部畸形。 J Child Orthop, 2011, 5(6): 403-414, doi: 10.1007/s11832-011-0368-9

[65] COLLINSON JM、LINDSTRÖM NO、NEVES C, 等。 腓骨肌萎缩突变小鼠“马蹄足”的发育和遗传基础。发展。 2018, 145(3): dev160093 ， doi: 10.1242/dev.160093

[66] TAILOR A、JURKOVIC D、BOURNE TH 等。 使用多元逻辑回归分析对附件肿块恶性肿瘤进行超声预测。 Ultrasound Obstet Gynecol, 1997, 10(1): 41-47, doi: 10.1046/j.1469-0705.1997.10010041.x

[67] MERRILL LJ、GURNETT CA、SIEGEL M 等。 血管异常与特发性马蹄足软组织体积减少相关。临床骨科相关研究， 2011， 469(5): 1442-1449， doi: 10.1007/s11999-010-1657-1

[68] HESTER TW、PARKINSON LC、ROBSON J 等。 胎动减少是马蹄足常见致病机制的假设和模型。Med Hypotheses, 2009, 73(6): 986-988, doi: 10.1016/j.mehy.2009.04.056

[69] SADLER B, GURNETT CA, 和 DOBBS MB. 孤立性和综合征性马蹄足的遗传学。J Child Orthop, 2019, 13(3): 238-244, doi: 10.1302/1863-2548.13.190063

[70] BRODSKY JW. 经治疗的先天性马蹄足 的成人后遗症。 Foot Ankle Clin， 2010， 15（2）：287-296，doi：10.1016/j.fcl.2010.03.002

[71] MILENKOVIC SS、MITKOVIC MM 和 MITKOVIC MB。 一名 56 岁成年患者被忽视的先天性马蹄内翻足。J Foot Ankle Surg（亚太），2021，8（3）：152-154，doi：10.5005/jp-journals-10040-1163

[72] KHAN YN、HUMA Z、KHAN U、BASIT S。 巴基斯坦家庭中与先天性马蹄内翻足相关的基因突变筛查。肌肉骨骼外科研究杂志, 2020, 4(1): 25-30 doi: 10.4103/jmsr.jmsr_94_19

[73] RAMSEIER LE、SCHOENIGER R、VIENNE P 和 ESPINOSA N。 成人晚期复发性特发性马蹄内翻足畸形的治疗。 比利时矫形学报，2007，73(5)：641-647。

[74] JOHNSON JE、FORTNEY TA、LUK PC 等。 青少年和青年患者马蹄足畸形的后期影响，其初始治疗为大面积软组织松解：专题回顾和临床病例系列。J Am Acad Orthop Surg Glob Res Rev， 2020， 4(5)：e1900126， doi：0.5435/jaaosglobal-d-19-00126

[75] ALHARBY E、ALBALAWI AM、NASIR A 等。 一个患有全面发育迟缓和肌病性肌张力低下的大家族中存在 PAXBP1 基因的纯合潜在致病变异。Clin Genet，2017，92(6)：579-586，doi：10.1111/cge.13051