Published in final edited form as:

J Pediatr Orthop B. 2012 January ; 21(1): 7–9. doi:10.1097/BPB.0b013e328349927c.

Genetics of Clubfoot

Matthew B DOBBS^{1,2} and Christina A GURNETT^{1,2,3}

¹Department of Orthopaedic Surgery, Washington University School of Medicine, St. Louis, Missouri, U.S.A

²Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, U.S.A

³Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, U.S.A

⁴St. Louis Shriners Hospital for Children, St. Louis, MO

Abstract

Modern advances in genetics have allowed investigators to begin to identify the complex etiology of clubfoot. It has become increasingly apparent that clubfoot is a heterogeneous disorder with a polygenetic threshold model explaining its inheritance patterns. Several recent genetics studies have identified a key developmental pathway, the PITX1-TBX4 transcriptional pathway, as being important in clubfoot etiology. Both PITX1 and TBX4 are uniquely expressed in the hindlimb which helps explain the foot phenotype seen with mutations in these transcription factors. Future studies are needed to develop animal models to determine the exact mechanisms by which these genetic abnormalities cause clubfoot and to test other hypotheses of clubfoot pathogenesis.

Clubfoot is one of the most common congenital birth defects, with an estimated birth prevalence of 1 per 1000 live births [1]. In 20% of cases, clubfoot is associated with distal arthrogryposis, congenital myotonic dystrophy, myelomeningocele, amniotic band sequence, or other genetic syndromes such as trisomy 18 or chromosome 22q11 deletion syndrome [2,3], while in the remaining cases the deformity is isolated and the exact etiology is unknown [4]. Recent studies, however, are beginning to shed light on the importance of early limb developmental pathways in clubfoot etiology.

Many theories of clubfoot pathogenesis, including intrauterine immobility, neurological, vascular, and connective tissue fibrosis, have been proposed based on specific anatomic abnormalities [5]. Vascular anomalies, consisting most commonly of anterior tibial artery hypoplasia, are present in >80% of clubfoot patients though the genetic basis of this abnormality is unknown [6,7]. It has also been observed that unilateral clubfoot is associated with a smaller calf circumference compared to the unaffected limb, resulting in quantitative muscle differences in two series of patients with unilateral clubfoot [8,9]. Despite quantitative muscle differences, electrophysiological studies of muscle and nerve are most often normal in clubfoot, and histological evaluations of muscle biopsies from clubfoot lower extremities typically show nonspecific abnormalities [10–12]. A mild leg length discrepancy can be seen in clubfoot patients indicating effects on skeletal growth as well [13]. These widespread anatomic abnormalities suggest that clubfoot is either etiologically heterogeneous or that a single primary cause may be responsible for all of the effects seen on bone and soft tissue.

Important insight into the pathogenesis of clubfoot is being revealed through genetic studies. A genetic basis for isolated clubfoot is supported by the fact approximately 25% of all patients with isolated clubfoot report a positive family history for clubfoot [14]. The role for genetic factors in clubfoot is also supported by a twin study that demonstrates a higher concordance rate for identical twins compared to fraternal twins (33% versus 3%) [4]. Further evidence for a genetic basis for clubfoot is the differences in clubfoot prevalence across ethnic populations, with the lowest prevalence in Chinese (0.39 cases per 1000 live births) and highest in the Hawaiians and Maoris (7 per 1000)[15,16]. The ratio of isolated clubfoot among males to females is 2:1 and is consistent across ethnic groups [15].

Based on complex inheritance patterns, isolated clubfoot is unlikely to be due to mutations within a single gene but instead is multifactorial and/or polygenic in nature [1,14]. An argument against a single gene cause of isolated clubfoot is the fact that there is a sex discrepancy, males more commonly affected than females, in the absence of sex-linked inheritance. A polygenic inheritance model with a dimorphic sex threshold for the affected phenotype would explain this discrepancy. Support for this polygenic threshold model for clubfoot inheritance has been shown by demonstration of the Carter effect: individuals of the less commonly affected sex carry a higher genetic load and are therefore more likely to transmit the disease to their offspring [17]. The physiological cause of this sex dimorphism, in which males are twice as likely to be affected as females, is currently unknown.

There is some evidence to suggest that the common disease-common variant hypothesis applies to clubfoot [18], in which inheritance of common genetic variants (i.e. single nucleotide polymorphisms present at an allele frequency of > 5%), each conferring a small increase in risk, contributes to clubfoot susceptibility. Common genetic variants (polymorphisms) near HOX homeobox genes [19], insulin-like growth factor binding protein 3 (IGFBP3) (MIM 146732) [20], and caspase genes [21] have all been reported to be associated with isolated clubfoot. However, these genetic variants are all of relatively small effect and need to be replicated in larger cohorts to confirm their importance in clubfoot susceptibility.

An alternative to the common disease-common variant hypothesis is that clubfoot may be explained better by the common disease-rare hypothesis in which rare genetic variants (with allele frequencies of <5%) each confer a moderate risk with higher penetrance [22]. Recent studies supporting this hypothesis have identified a key developmental pathway important in clubfoot etiology, the PITX1-TBX4 transcriptional pathway responsible for early limb development [23,24]. A missense mutation in PITX1 (MIM 602149), a bicoid-related homeodomain transcription factor, was identified in a large multi-generational family with predominantly isolated clubfoot segregating with reduced penetrance [23]. Since the PITX1 gene is expressed predominantly in the hindlimb and not the forelimb, this is the first gene implicated in clubfoot to explain the specific involvement of the foot.

Though mutations in PITX1 are not a common cause of isolated clubfoot, recurrent chromosome 17q23 copy number variants involving the T-box transcription factor TBX4, a transcriptional target of PITX1 [24–26], are responsible for ~5% of all patients with familial isolated clubfoot[24]. Both duplications and deletions of the chromosome 17q23 region result in clubfoot, highlighting the critical importance of TBX4 gene dosage. Similar to PITX1, TBX4 is uniquely expressed in the hindlimb, explaining the foot phenotype. The chromosomal microarray (CMA) genetic study can detect the chromosome 17q23 copy number variants, which are clinically significant for their possible association with both severe, treatment-refractory clubfoot and hip dysplasia [24].

The implication of genes specifically involved in hindlimb development in clubfoot etiology makes other commonly hypothesized genes for clubfoot, such as the muscle contractile genes implicated in distal arthrogryposis less likely, as mutations in these genes cause both upper and lower extremity involvement and have not been identified in isolated clubfoot patients [27,28]. Future studies are needed to develop animal models to determine the exact mechanisms by which these genetic abnormalities cause clubfoot and to test other hypotheses of clubfoot pathogenesis.

Acknowledgments

FUNDING

This work was supported by grants from the National Institute of Health, The Children's Discovery Institute, The March of Dimes Basil O'Connor Starter Scholar Research Award, St Louis Children's Hospital Foundation, Shriners Hospital for Children, The Orthopaedic Research and Education Foundation, Pediatric Orthopaedic Society of North America, and the Mallinckrodt Institute of Radiology.

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