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Polygenic Threshold Model with Sex Dimorphism in Clubfoot Inheritance: The Carter Effect

By Lisa M. Kruse, BS, Matthew B. Dobbs, MD, and Christina A. Gurnett, MD, PhD

Investigation performed at Washington University School of Medicine and Shriners Hospital for Children, St. Louis, Missouri

Background: Idiopathic clubfoot is approximately twice as common in males than in females. The reason for this discrepancy is unclear but may represent an inherent difference in the susceptibility to the deformity. If this difference is due to genetic factors it is predicted that in order to inherit clubfoot, females need to have a greater number of susceptibility genes than males. Females would also be more likely to transmit the disease to their children and have siblings with clubfoot. This phenomenon is known as the Carter effect, and the presence of such an effect supports a multifactorial threshold model of inheritance.

Methods: Ninety-seven multiplex families with more than one individual with idiopathic clubfoot were studied. The study included 1093 individuals: 291 with clubfoot and 802 unaffected relatives. Rates of transmission by the thirty-seven affected fathers and twenty-six affected mothers were calculated, and the prevalence among siblings was determined in the nuclear families of affected persons.

Results: Within these multiplex families, the prevalence of clubfoot was lowest in daughters of affected fathers (eight of twenty-four) and highest in sons of affected mothers (eleven of thirteen). Affected mothers transmitted clubfoot to 59% of their children (nineteen of thirty-two children), whereas affected fathers transmitted idiopathic clubfoot to 37% of their children (twenty-six of seventy children) (p = 0.04). Siblings of an affected female also had a significantly higher prevalence of clubfoot than siblings of an affected male (46% [fifty-four of 117] compared with 34% [sixty-seven of 197]; p = 0.03).

Conclusions: This study demonstrates the presence of the Carter effect in idiopathic clubfoot. This effect can be explained by a polygenic inheritance of clubfoot, with females requiring a greater genetic load to be affected.

Idiopathic clubfoot is an isolated congenital deformity of the foot and distal part of the leg that is present before birth and consists of four components: equinus, hindfoot varus, forefoot adductus, and cavus. Clubfoot deformity may be associated with myelodysplasia, arthrogryposis, or multiple congenital abnormalities, but it is most commonly idiopathic. Although the exact genetic mechanism of clubfoot has not yet been determined, a multifactorial and possibly polygenic causation has been suggested.

Evidence of a genetic etiology of idiopathic clubfoot is provided by the observation that concordance among monozygotic twins is greater than that of dizygotic twins. Parent-to-child transmission of idiopathic clubfoot has been noted in 20% of pedigrees of families with multiple affected members, suggesting a potential genetic mechanism. Effects of ethnicity on prevalence also suggest a genetic basis. The prevalence of clubfoot is one to two per 1000 live births in whites, but there is a lower prevalence in Chinese (0.39 per 1000 live births) and a higher prevalence in Hawaiians and Maoris (6.5 to seven per 1000 live births).

Nearly all studies have demonstrated a higher prevalence of clubfoot in males than in females. Male:female ratios of idiopathic clubfoot range from 2.5:1 to 1.6:1, although it is nearly 4:1 in Australian Aborigines. A male bias was also consistent across a series of eighty-four patients with nonidiopathic clubfoot, despite these individuals having diverse neuromuscular and genetic causes of the clubfoot.

Investigations of clubfoot inheritance patterns have been inconclusive, but their findings have supported a single major gene effect. In two separate studies, complex segregation analysis suggested a single major gene with low penetrance. The male:female ratio of idiopathic clubfoot, however, has been consistent across multiple studies.

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analyses suggested a single incompletely dominant disease gene with unmeasured factors contributing to incomplete penetrance\textsuperscript{6,7}. In a different study, segregation analysis suggested a recessive mixed model\textsuperscript{8}, and a complex segregation analysis of Pacific and Maori people showed a single dominant gene with 33% penetrance\textsuperscript{9}. However, in more than a decade since these studies were performed, no single gene causing idiopathic clubfoot has been discovered.

The lack of a specific disease-causing gene as well as the sex discrepancy in the absence of sex-linked inheritance suggests a polygenic inheritance model with a dimorphic sex threshold for the affected phenotype. In this model, females require a greater number of, or more potent, susceptibility genes than males to inherit clubfoot and therefore would be predicted to have a higher rate of transmission of the affected phenotype to their children. This is known as the Carter effect (a multifactorial threshold model with sex dimorphism for liability)\textsuperscript{10}. The Carter effect is more evident in families with multiple affected individuals than it is in families with a single affected member because of a greater genetic load present in these families. The Carter effect was originally described in pyloric stenosis\textsuperscript{11}, but it has also been shown in multiple sclerosis\textsuperscript{12}, familial malignant melanoma\textsuperscript{13}, and atopy\textsuperscript{14}. It is widely cited as evidence of polygenic inheritance or genetic-environment interaction. Our hypothesis is that idiopathic clubfoot is a polygenically inherited disorder requiring females
to have a higher genetic load to be affected. Evidence of the Carter effect would be a higher rate of idiopathic clubfoot in offspring and siblings of affected females compared with the rate in offspring and siblings of affected males.

Materials and Methods

This retrospective prognostic study was performed with the approval of the Washington University Human Protection Research Office, and all participants signed an approved informed-consent form. We searched a database of family pedigrees of probands treated for clubfoot at St. Louis Children’s Hospital and Shriners Hospital for Children in St. Louis from 2000 to 2007. The inclusion criteria and a description of the pedigree are shown in Figure 1. Pedigrees were constructed in a prospective manner at the time of the patients’ initial visit or a follow-up appointment, and family history was discussed on subsequent visits to decrease recall bias. On the basis of a detailed interview of all patients by a trained research nurse, a three-generation pedigree was generated for all individuals with a family history of limb abnormalities. Thirty-one percent (ninety-seven) of 318 idiopathic clubfoot pedigrees had more than one affected individual. Patients were considered to be affected if they had rigid hindfoot varus, hindfoot equinus, forefoot adduction, and forefoot cavus deformities that were present from birth and required intervention. All patients were evaluated in a prospective manner by a single pediatric orthopaedic surgeon at the time that the pedigree was created.

Patients were considered to be syndromic if the clubfoot was associated with multiple congenital abnormalities or had occurred as part of a diagnosed syndrome; those patients were then excluded from the study. A family history of clubfoot was confirmed by a detailed interview of the index patient and his or her guardians and through evaluation of the family members’ medical records when available, as it was not practical to examine each family member. Individuals were considered to be affected if they had a diagnosis of clubfoot requiring intervention, including surgery, bracing, or cast treatment. Individuals were considered to be possibly affected if they had a foot deformity whose description was consistent with clubfoot in that both forefoot and hindfoot deformities were present and bracing or corrective shoes were required. All ethnicities were included in this study, although the majority of the families (>80%) were white.

In order to calculate differential transmission rates of idiopathic clubfoot, multiplex families were divided into nuclear families, and each person was entered into a spreadsheet. This information included data regarding each person’s parents, children, and siblings to ensure that individuals who were both parents and children were not double counted. The sex of ten unaffected individuals and three affected individuals was not known.

### Statistical Methods

Unless otherwise indicated, p < 0.05 was considered significant. The Pearson chi-square test was used to compare sex ratios. The effect of the parents’ affected status (whether or not they had clubfoot) on the total number of children that they had was determined with use of Kruskal-Wallis one-way analysis of variance followed by post hoc analysis with the Student t test. The Bonferroni method was used to correct for multiple comparisons. Potential bias of the sex or affected status of the parent on the sex and affected status of the children was determined with the Pearson chi-square test. Transmission rates were calculated as a percentage with a 95% confidence interval, assessed for sig-
significance with the Pearson chi-square test, and compared by calculating odds ratios with 95% confidence intervals. All statistical analyses were completed with use of Microsoft Excel 2007 (Redmond, Washington) and SISA (Single Interactive Statistical Analysis)\(^1\).

**Results**

From the ninety-seven multiplex families, 1093 individuals met the inclusion criteria for the study: 262 (24%) had definite idiopathic clubfoot, twenty-nine (3%) had possible idiopathic clubfoot, and 802 (73%) were unaffected (Fig. 1). The median pedigree size (and standard deviation) was 12 ± 7 individuals (range, three to thirty-two individuals). The frequencies of the numbers of affected individuals in the families with multiple affected individuals are shown in Figure 2. There were sixty-three nuclear families with one affected parent and 268 nuclear families with neither parent affected. There were no families in which both parents were affected. Of the 102 children in families with an affected parent, forty-five (44%) were affected and fifty-seven (56%) were unaffected.

The ratio of males to females did not differ within affected and unaffected groups when compared according to the affected status of the parent (Table I). The male:female ratio of affected individuals was 1.64:1 (179:109) and the male:female ratio of unaffected individuals was 0.97:1 (391:401).

The total number of children in the nuclear family did not depend on the parents’ affected status or the affected or unaffected parents’ sex except that affected mothers had fewer children than did affected fathers or unaffected parents (Table II). Kruskal-Wallis one-way analysis of variance showed a difference between the number of children produced by each parental type \((p = 0.05)\). Post hoc analysis with the Student t test showed that the number of children did not differ between unaffected fathers and mothers \((p = 0.40)\), between unaffected fathers and affected fathers \((p = 0.49)\), or between unaffected mothers and affected fathers \((p = 0.80)\). However, affected mothers had significantly fewer children than did affected fathers \((p = 0.003)\), unaffected fathers \((p = 0.0001)\), and unaffected mothers \((p = 2 \times 10^{-5})\).

Affected mothers were more likely to have affected sons than were unaffected mothers \((p = 0.007, \text{odds ratio} = 4.9 [95\% \text{confidence interval} = 1.4 \text{ to } 29.1])\) (Table III), but the affected status of the father appeared to have no significant

### Table II Relationship Between the Sex and Status of the Parent and the Number of Children*

<table>
<thead>
<tr>
<th></th>
<th>1 Child</th>
<th>2 Children</th>
<th>&gt;2 Children</th>
<th>Total No. of Children</th>
<th>Mean No. of Children (and Stand. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unaffected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>162 (55%)</td>
<td>77 (26%)</td>
<td>55 (19%)</td>
<td>524</td>
<td>1.8 ± 1.2</td>
</tr>
<tr>
<td>Mother</td>
<td>158 (52%)</td>
<td>72 (24%)</td>
<td>65 (22%)</td>
<td>551</td>
<td>1.9 ± 1.3</td>
</tr>
<tr>
<td><strong>Affected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>17 (46%)</td>
<td>11 (30%)</td>
<td>9 (24%)</td>
<td>71</td>
<td>1.9 ± 1.1</td>
</tr>
<tr>
<td>Mother</td>
<td>20 (77%)</td>
<td>5 (19%)</td>
<td>1 (4%)</td>
<td>33</td>
<td>1.3 ± 0.5</td>
</tr>
</tbody>
</table>

*The number of children did not differ significantly between unaffected fathers and mothers \((p = 0.40)\), between unaffected fathers and affected fathers \((p = 0.49)\), or between unaffected mothers and affected fathers \((p = 0.80)\). Affected mothers had significantly fewer children than did affected fathers \((p = 0.003)\), unaffected fathers \((p = 0.0001)\), and unaffected mothers \((p = 2 \times 10^{-5})\).

### Table III Relationship Between the Sex and Status of the Parents and Children

<table>
<thead>
<tr>
<th></th>
<th>Father (N = 331)</th>
<th>Mother (N = 328)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected (N = 37)</td>
<td>Unaffected (N = 294)</td>
</tr>
<tr>
<td><strong>Daughters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>8/24 (33%)</td>
<td>80/255 (31%)</td>
</tr>
<tr>
<td>Unaffected</td>
<td>16</td>
<td>175</td>
</tr>
<tr>
<td>P value</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td><strong>Sons</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>18/40 (45%)</td>
<td>129/268 (48%)</td>
</tr>
<tr>
<td>Unaffected</td>
<td>22</td>
<td>139</td>
</tr>
<tr>
<td>P value</td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>
effect on the risk to his sons ($p = 0.71$). Neither the affected status of the father ($p = 0.84$) nor the affected status of the mother ($p = 0.22$) significantly influenced the affected status of the daughters. The sex and affected status of the parent did not alter either the expected 1:1 male:female ratio of all offspring or the 1.6:1 ratio of affected offspring (Table I).

Rates of transmission by affected parents were determined to evaluate for the presence of the Carter effect. Affected mothers transmitted the clubfoot phenotype to their children more often than did affected fathers ($p = 0.04$) (Table IV). Affected mothers transmitted clubfoot to eleven of thirteen sons (84.6% [95% confidence interval = 82.7% to 86.6%]), whereas affected fathers transmitted clubfoot to eighteen of forty sons (45.0% [95% confidence interval = 43.8% to 46.2%]). The risk of transmission to all children was increased 5.55-fold (95% confidence interval = 1.05 to 5.88-fold) if the affected parent was the mother (as opposed to the father), and the risk of transmission to sons was increased 10.0-fold (95% confidence interval = 1.31 to 33.3-fold) if the affected parent was the mother (as opposed to the father). There was no significant difference in the transmission to daughters ($p = 0.46$), although there was a trend toward a higher transmission from affected mothers (eight of eighteen, or 44.4% [95% confidence interval = 41.7% to 47.1%]) compared with transmission from affected fathers (eight of twenty-four, or 33.3% [95% confidence interval = 31.5% to 35.1%]).

The Carter effect was also investigated by determining the prevalence of clubfoot among siblings of affected individuals (Table V). Siblings of affected females were found to be more likely to be affected (fifty-four of 117, or 46.2% [95% confidence interval = 45.7% to 46.6%]) than were siblings of affected males (sixty-seven of 197, or 34.0% [95% confidence interval = 33.8% to 34.2%]) ($p = 0.03$).

### Discussion

Previous studies have shown that the relatives of female individuals with clubfoot have a higher risk of having clubfoot than relatives of male individuals with clubfoot,[1,2] and this finding suggested the possibility of a multifactorial threshold model of inheritance. Because clubfoot is diagnosed and treated early in life and is a relatively rare disorder, in none of these studies were there sufficient data on older affected individuals to determine disease transmission rates. The current study demonstrates that, in familial cases, females with clubfoot are 5.55 times more likely than affected males to transmit idiopathic clubfoot to their children ($p = 0.04$). This observation is consistent with the Carter effect: individuals of the less commonly affected sex carry a higher genetic load and are therefore more

### Table IV Rates of Transmission of Idiopathic Clubfoot from Affected Parents to Their Children

<table>
<thead>
<tr>
<th>No. (%) to Whom Clubfoot Transmitted</th>
<th>No. (%) to Whom Clubfoot Not Transmitted</th>
<th>P Value</th>
<th>Odds Ratio (Female vs. Male)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father affected</td>
<td>26/70 (37.1%)</td>
<td></td>
<td>36.5% to 37.8%</td>
<td></td>
</tr>
<tr>
<td>Mother affected</td>
<td>19/32 (59.4%)</td>
<td>0.04</td>
<td>5.55</td>
<td>1.05 to 5.88</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father affected</td>
<td>8/24 (33.3%)</td>
<td></td>
<td>31.5% to 35.1%</td>
<td></td>
</tr>
<tr>
<td>Mother affected</td>
<td>8/18 (44.4%)</td>
<td>0.46</td>
<td>2.50</td>
<td>0.45 to 5.55</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father affected</td>
<td>18/40 (45.0%)</td>
<td></td>
<td>43.8% to 46.2%</td>
<td></td>
</tr>
<tr>
<td>Mother affected</td>
<td>11/13 (84.6%)</td>
<td>0.01</td>
<td>10.0</td>
<td>1.31 to 33.3</td>
</tr>
</tbody>
</table>

*The total number of children differs from the sum of the females to whom clubfoot was not transmitted and the males to whom clubfoot was not transmitted because the sex of seven children of affected parents was unknown.

### Table V Differential Prevalence of Idiopathic Clubfoot in Siblings

<table>
<thead>
<tr>
<th>No. (%) of Siblings Affected</th>
<th>No. of Siblings Not Affected</th>
<th>P Value</th>
<th>Odds Ratio (Female vs. Male)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male affected</td>
<td>67/197 (34.0%)</td>
<td></td>
<td></td>
<td>33.8% to 34.2%</td>
</tr>
<tr>
<td>Female affected</td>
<td>54/117 (46.2%)</td>
<td>0.03</td>
<td>1.67</td>
<td>1.04 to 2.63</td>
</tr>
</tbody>
</table>
likely to transmit the disease to their offspring\(^\text{11}\). The Carter effect assumes that there is a greater threshold for disease expression in the less affected sex but does not specify the mechanism of this reduced threshold. In the case of clubfoot, the difference in the threshold could be due to multiple environmental or genetic factors, including sex-related differences in the rate of limb development or hormonal interactions with genes.

As predicted by the Carter effect, the prevalence of clubfoot was lowest in daughters of affected males (eight of twenty-four, or 33%) and highest in sons of affected mothers (eleven of thirteen, or 85%). The rate of transmission of clubfoot by affected mothers to sons was higher than would be expected with a fully penetrant autosomal dominant condition, which would be transmitted 50% of the time. Because of the lower prevalence of clubfoot in females and the selection of multiplex families for this study, the clubfoot transmission rates were calculated for a relatively small cohort (twenty-six affected females) and thus may be an overestimate of the actual rate in a larger population. The high transmission rate suggests several possible mechanisms, including multigenic, mitochondrial, or other environmental factors (including in utero effects). Previous studies have shown no evidence of inheritance through the maternal lineage\(^\text{5-8}\) (suggesting mitochondrial transmission) or of in utero crowding in the etiology of clubfoot\(^\text{1}\). Despite the lack of evidence, we cannot rule out these mechanisms, and it is possible that mitochondrial inheritance or in utero effects contribute to the etiology of clubfoot in some families. However, multigenic inheritance of clubfoot is more likely, given the presence of the Carter effect. The high rate of transmission of clubfoot to sons may reflect the presence of multiple risk alleles in the mother, with fewer risk alleles required for disease expression in her male offspring. The supposition that daughters require a greater number of risk alleles than sons is reflected by the nearly two-fold-lower rate of transmission to female offspring by affected females as compared with the rate of transmission to male offspring. Caution must be taken when translating these inheritance rates for the purposes of genetic counseling, as the rates determined in this study are reflective only of multiplex families (those who have more than one affected individual). These families are an excellent source for the study of familial cases, but they may be inherently different, with regard to inheritance risk, from families with a single sporadic affected individual.

Limitations of this study include the relatively small number of affected parent-child pairs. This could have resulted in a loss of significance in certain groups in the study. For example, there did not appear to be a significant difference between affected mothers and fathers with regard to their rate of transmission of clubfoot to daughters (\(p = 0.46\)), although the data trended toward higher rates of transmission by the mothers. The inability to detect a significant difference may have been due to the paucity of affected female-child pairs secondary to both the lower prevalence of clubfoot in females and the reduced fecundity of affected females with clubfoot. Although not described in previous studies, we found that females affected with clubfoot had significantly fewer children than either unaffected parents or affected males (\(p < 0.01\)). Future studies including larger numbers of patients are necessary to further investigate this phenomenon, as it may have implications with regard to understanding both the social and the genetic aspects of clubfoot deformity. The inability to detect parent-of-origin effects on daughters may also have been related to the threshold model of multigenic inheritance. Although an affected mother may carry a higher genetic load, all of these genes are not necessarily passed on to her daughters, and the received genetic load may not place the daughter above the genetic threshold necessary to cause phenotypic deformity.

Because multigenic disorders may result in phenotypic variation, we included idiopathic clubfeet of varying severity in our study and considered individuals with positional talipes to be affected. New methodologies such as the Dimeglio score\(^\text{16,9}\), the Pirani score\(^\text{16,9}\), and neurophysiological studies (i.e., nerve conduction studies and electromyography) have improved clubfoot phenotyping, but it remains to be determined whether milder foot deformities, including positional clubfoot, are part of a spectrum that includes the more severe phenotype, or whether the milder deformities represent entirely different entities. Our observation of an increased frequency of these milder foot deformities in families with idiopathic clubfoot suggests that they may be genetically related. For these reasons, we included these patients, who accounted for <10% of the total number of affected patients. Although bilateral rather than unilateral deformity may be another marker of severity and subsequently of increased genetic load, we chose not to include these data in our study as a surrogate for severity because, in the absence of accepted markers of severity (Dimeglio or Pirani scores), we did not want to introduce an unproven bias. We hypothesize that a more severe phenotype may reflect a greater genetic load and that these individuals would be more likely to pass the deformity on to their offspring. Future studies that include measures of severity would allow us to investigate this hypothesis and may provide further information for clinicians and families regarding risk prognostication.

Past epidemiological studies provide further evidence of the polygenic nature of clubfoot disorder. Wynne-Davies observed that “the rapid fall in incidence of TEV to near the general population level in third-degree relatives is more characteristic of polygenic inheritance with a threshold beyond which there is a risk of malformation.”\(^\text{12}\) The finding of a Carter effect in idiopathic clubfoot provides further evidence of a multifactorial threshold model of inheritance. Although complex segregation analyses have provided an argument for a single-gene hypothesis for clubfoot, these studies either needed to include the effects of unmeasured factors\(^\text{2-8}\) or were performed in a small population of Maori people isolated to New Zealand—an ethnic population that is well recognized as having a greater prevalence of idiopathic clubfoot and, therefore, possibly having a stronger single-gene effect or a different mechanism than other ethnic groups. More than a decade of searching has revealed a number of genes that are associated with idiopathic
clubfoot and that have been hypothesized to play a role in susceptibility, such as HOXD12/HOXD13, NAT2, and a variety of apoptotic genes including CASP10. The identification of multiple susceptibility genes through association studies also suggests that single-gene inheritance of clubfoot is unlikely. Given the complex inheritance and the likelihood that multiple susceptibility genes are responsible for idiopathic clubfoot, a genome-wide association study may be the most promising method of discovering major and minor susceptibility genes contributing to clubfoot. Genome-wide association studies compare the allele frequencies of >500,000 single nucleotide DNA polymorphisms (SNPs) between thousands of patients and controls. They have recently resulted in the discovery of new and novel genes associated with complex disorders such as multiple sclerosis, rheumatoid arthritis, osteoporosis, and diabetes and have the potential to do the same for musculoskeletal conditions in the near future. Performing a genome-wide association study for the purpose of identifying susceptibility genes for idiopathic clubfoot will require collaborative efforts within the orthopaedic community in order to obtain the large number of well-characterized patient DNA samples (>1000) necessary for a successful study.

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