Received: 2 July 2018 | Revised: 6 September 2018 | Accepted: 7 September 2018

DOI: 10.1002/ajmg.a.40649

WILEY AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

Club foot in association with the 22q11.2 deletion syndrome: An observational study

Jelle F. Homans[1] | Terrence B. Crowley[2] | Erin Chen[2] | Daniel E. McGinn[2] | Vincent F. X. Deeney[3,4] | Ralph J. B. Sakkers[1] | Richard S. Davidson[3,4] | René M. Castelein[1] | Donna M. McDonald-McGinn[2,4]

[1]Department of Orthopaedic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[2]Division of Human Genetics and 22q and You Center, The Children's Hospital of Philadelphia (CHOP), Philadelphia, Pennsylvania

[3]Department of Orthopaedic Surgery, The Children's Hospital of Philadelphia (CHOP), Philadelphia, Pennsylvania

[4]The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Correspondence
Donna M. McDonald-McGinn, Division of Human Genetics and 22q And You Center, The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA1 9104.
Email: mcginn@email.chop.edu

Funding information
K2M; Koninklijke Nederlandse Akademie van Wetenschappen, Grant/Award Number: Ter Meulen Grant (Travel grant)

The 22q11.2 Deletion Syndrome (22q11.2DS) occurs in ~1:3,000–6,000 individuals. Features less typically associated with 22q11.2DS, such as orthopedic manifestations, may be overlooked or may not lead to appropriate diagnostic testing. Club foot has a general population prevalence of ~1:1,000 and has been occasionally described in association with 22q11.2DS. Our hypothesis is that the prevalence of club foot is higher in patients with 22q11.2DS. We performed a retrospective review in two specialized 22q11.2DS centers to determine the prevalence of club foot. "True club foot" requires treatment (either conservative or surgical), therefore we only included those patients with proof of treatment. We investigated whether congenital heart disease (CHD) and/or cleft palate were associated with the presence of club foot within 22q11.2DS. The records of 1,466 patients were reviewed. Of these, 48 (3.3%) had confirmation of club foot (95% Confidence Interval: 2.4–4.3): 22 (46%) had a bilateral, 12 (25%) left, and 14 (29%) right club foot. Within our study, neither a CHD and/or a cleft palate were associated with a club foot. The prevalence of club foot in 22q11.2DS is 30 times higher than that observed in the general population. This suggests the diagnosis of club foot, especially in the face of other typically associated abnormalities of 22q11.2DS, should provoke consideration of 22q11.2DS as an underlying diagnosis, particularly in the neonatal setting.

KEYWORDS

club foot, orthopedics, 22q11.2 deletion syndrome, 22q11.2DS, clubfoot, pes equinovarus

1 | INTRODUCTION

The 22q11.2 Deletion Syndrome (22q11.2DS) is the most common microdeletion syndrome in humans, with a prevalence of one in 3,000–6,000 live births and one in 1,000 pregnancies (Botto et al., 2003; Devriendt, Fryns, Mortier, van Thienen, & Keymolen, 1998; Goodship, Cross, LiLing, & Wren, 1998; Grati et al., 2015; Oskarsdóttir, Vujic, & Fasth, 2004; Du Montcel, Mendizabai, Ayme, Levy, & Philip, 1996) Within a subset of the 22q11.2DS patients, congenital anomalies need treatment in the neonatal period of their life. The most severe congenital anomalies include congenital heart disease (CHD), for example, Tetralogy of Fallot, and palatal deficiencies such as cleft palate.(McDonald-McGinn et al., 2015) However, these are just a few of the large number of (congenital) clinical characteristics that can be part of the 22q11.2DS. (Bassett et al., 2011; McDonald-McGinn et al., 2015) Recently, 69 orthopedic manifestations have been described as being part of the 22q11.2DS. One of these manifestations, (congenital) club foot, has attained little attention so far (Homans et al., 2017).

Club foot (Figures 1 and 2), can be identifiable in utero (Figure 3) and it contains four characteristic features which can be remembered through the acronym CAVE: cavus (a high medial longitudinal arch), forefoot adductus, hindfoot varus, and hindfoot equinus (Figure 1) (Dobbs & Gurnett, 2009; Horn & Davidson, 2010; Werler et al., 2013). The prevalence of congenital isolated club foot in the general

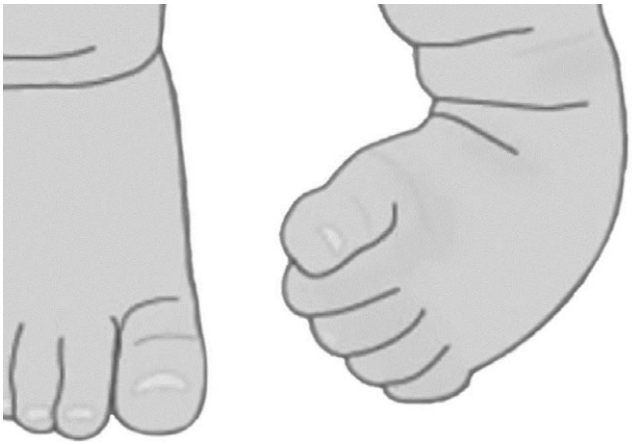

FIGURE 1 An illustration of a left club foot. The four characteristics of club foot can be seen: Cavus (a high medial longitudinal arch), forefoot adductus, hindfoot varus, and hindfoot equinus

population differs among multiple ethnic populations, but is approximately 1.2–6 per 1,000 individuals. Within the group of patients with isolated club foot the male:female ratio is 2:1 and half of the patients have a bilateral club foot (Cartlidge, 1983; Krogsgaard et al., 2006; Parker et al., 2009; Stone, Martis, & Crawford, 2017; Werler et al., 2013). In studies on club foot within 22q11.2DS the prevalence ranges from 1.1 to 13.3%, which seems to be higher as compared to the general population (Homans et al., 2017). However, none of these studies had club foot as their primary outcome nor was it explained how the club foot was diagnosed (Homans et al., 2017). Currently, it is unknown whether the club foot within 22q11.2DS is typically associated with other severe congenital anomalies, such as CHD and cleft palate or whether the club foot can occur as a single entity. CHD and/or cleft palate will lead to genetic testing and subsequently bring the diagnosis of 22q11.2DS into light. However, if the prevalence of club foot within 22q11.2DS is increased and it occurs without the presence of these congenital malformations, a club foot in combination with other, subtle, 22q11.2DS phenotypic features might lead to the suspicion of 22q11.2DS.

First, we wanted to investigate the prevalence of club foot within 22q11.2DS. Second, we investigated whether club foot within 22q11.2DS is associated with CHD and/or cleft palate. Our hypothesis was that the prevalence of club foot is higher in 22q11.2DS as compared to the general population. Moreover, since scoliosis within 22q11.2DS is not associated with CHD and the prevalence of club foot is increased in other syndromes (e.g., Down Syndrome) we hypothesized that the club foot within 22q11.2DS is not associated with CHD and/or cleft palate (Homans et al., 2018; Stoll, Dott, Alembik, & Roth, 2015).

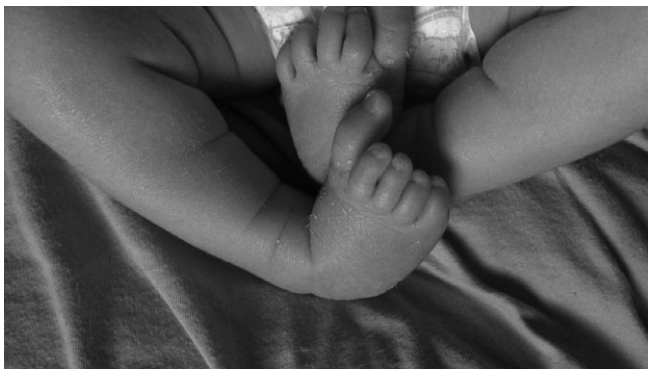

FIGURE 2 A 22q11.2DS patient with a bilateral club foot

2 | MATERIALS AND METHODS

After Institutional Review Board approval was obtained, a retrospective analysis based on longitudinal collected data was performed in two specialized 22q11.2DS centers. The research was conducted according to the STROBE criteria (von Elm et al., 2008). The patients were evaluated by the multidisciplinary team at the "22q and You" center at the Children's Hospital of Philadelphia (CHOP, inclusion: January 1999–June 2018) or by the multidisciplinary 22q team at the University Medical Center Utrecht (UMCU, inclusion: January 2014–May 2018). All patients were diagnosed with a 22q11.2 deletion using fluorescent in situ hybridization, array comparative genomic hybridization, multiplex ligation probe amplification, or chromosomal microarray. Patients with a known genetic disorder in addition to the 22q11.2 deletion were excluded.

"True club foot" needs treatment (either conservative or surgical) and therefore, in order to prevent false positive cases (e.g., patients with another (congenital) malformation of the foot), we only included patients whom had proof of treatment of the club foot and thus the clinical diagnosis of club foot (Dobbs & Gurnett, 2009; Horn & Davidson, 2010; Werler et al., 2013).

Baseline characteristics (age, gender, presence and type of CHD, and the presence of a cleft palate) were collected. Cerebral palsy and spina bifida are known to have a strong association with club foot and therefore the 22q11.2DS cases were screened for these anomalies (Dobbs & Gurnett, 2009; Werler et al., 2013). The 22q11.2DS patients with a club foot were compared with the non-club foot 22q11.2DS patients with respect to the presence of CHD and cleft palate. These characteristics were chosen since these congenital anomalies would definitely lead to hospital referral (and genetic testing) within the first

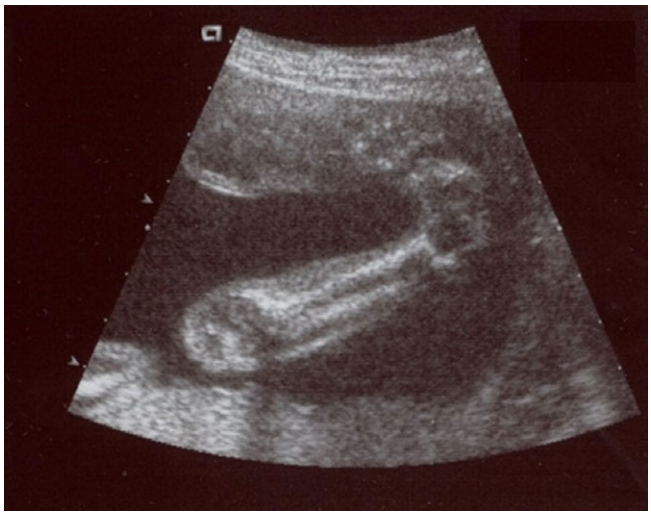

FIGURE 3 A 22q11.2DS patient with a prenatal ultrasound of a club foot

year and subsequently reveal the 22q11.2DS diagnosis. The CHDs were graded according to the grading scale described by Billett and colleagues: Simple, moderate, or complex and for further analyses they were dichotomized (present or absent) (Billett, Cowie, Gatzoulis, Vonder Muhll, & Majeed, 2008). Cleft palate was considered a dichotomous outcome; present or absent.

3 | STATISTICAL ANALYSIS

The 95% confidence intervals (CI) for the prevalence estimates were calculated. Baseline differences between the patients with and without club foot were compared with the two-tailed Fisher's exact test. All statistical analyses were conducted with the Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). A p value of <.05 was considered statistically significant.

There was missing data on CHD and cleft palate within the group of patients without a club foot and there was no missing data within the group of patients with a club foot. In order to investigate whether the missing data had influence on the statistical significance of the findings on the possible association between CHD and/or cleft palate and club foot we performed a sensitivity analysis: First, we imputed the missing data as "event" (e.g., presence of CHD or cleft palate). Second, we imputed the missing data as "no event" (e.g., no CHD/cleft palate). Next, we performed the Fishers exact test multiple times in which we either considered all the missing data as "event" or "no event".

4 | RESULTS

4.1 | Prevalence of club foot

At the time of analysis, the CHOP database consisted of 1,332 patients evaluated in the 22q and You Center (a multidisciplinary clinic for patients with a chromosome 22q11.2 abnormality). All patients were seen by a clinical geneticist and/or an orthopedic surgeon. Seventy-four percent of the CHOP cohort was Caucasian. Within the UMCU cohort 134 patients were seen by the pediatrician and orthopedics (ethnicity unknown). The total cohort consisted of 1,466 patients of whom 51.0% were male. Out of the total cohort 48 patients (3.3%) had a confirmed club foot (95% CI: 2.4–4.3). Out of this group, two patients had cerebral palsy and one patient had spina bifida. Thirty-seven patients were male (77%, 95% CI: 63–87%, $p < .005$) which corresponds to a male:female ratio of 3.4:1. Twenty-two patients (46%, 95% CI: 31–61%) had bilateral club feet (ratio: 1:0.8) and the remainder had either a left ($n = 12$) or right ($n = 14$) club foot (left:right ratio of 1:1.2).

4.2 | Congenital anomalies and club foot

The presence of a CHD or a cleft palate was not associated with a club foot (Table 1). Second, a separate category was made (the presence of either a CHD, a cleft palate, or both) and this category could not be identified as a risk factor for club foot as well. Third, there was no association between CHD, cleft palate, and the multiple subcategories of club foot (bilateral, left, or right club foot).

4.3 | Missing data

In the group without club foot there was missing data on the presence of CHD and cleft palate: 140 patients (9.5%) and 73 patients (5.0%), respectively. First, the missing data were imputed as "event": the p values were .154, 1.00, .125 for CHD, cleft palate, and CHD and/or cleft palate, respectively. Second, the missing data were imputed as "no event": the p values were 1.00, .446, and 1.00, respectively. Subsequently, our sensitivity analysis revealed that the missing data had no effect on the statistical significance as shown in Table 1.

5 | DISCUSSION

The 22q11.2DS is the most common microdeletion syndrome and is characterized by broad phenotypic heterogeneity including multiple congenital anomalies, such as tetralogy of Fallot and cleft palate (Bassett et al., 2011; McDonald-McGinn et al., 2015). Due to these conditions, often requiring urgent medical/surgical attention, possible orthopedic features tend to be overshadowed, as shown by the fact that there are no studies on the treatment of orthopedic manifestations within 22q11.2DS (Homans et al., 2017; Homans et al., 2018). Club foot has occasionally been mentioned in previous research, but no studies had club foot as their primary outcome of interest (Homans et al., 2017). Our research has shown that club foot is definitely associated with the 22q11.2DS with a prevalence of 3.3%. The majority (74%) of the CHOP cohort is Caucasian and since the prevalence of club foot within the general Caucasian population is ~1:1,000 patients, the prevalence of club foot occurs approximately 30 times more often within 22q11.2DS as compared to the general Caucasian population. Moreover, the bilateral:unilateral and male:female ratio are comparable with the general population (Krogsgaard et al., 2006; Parker et al., 2009; Stone et al., 2017; Werler et al., 2013). Last, we did not find a relation between the presence of club foot and the presence of a CHD and/or a cleft palate. We choose CHD and cleft palate since these major congenital anomalies would definitely lead to genetic testing and subsequently reveal the diagnosis of 22q11.2DS. However, it is important to note that 58.3% and 22.9% of the patients with club foot had a CHD or cleft palate, respectively.

Within our cohorts, there were multiple patients that were diagnosed with 22q11.2DS at a later age; however, they could have been diagnosed with 22q11.2DS in the neonatal period because of the combination of a club foot at the prenatal ultrasound and other congenital malformations. One patient, whose father had a history of repaired ventricular septal defect and cleft palate, was discharged to home from an outside hospital neonatally, without genetic testing and proper physical examination. Afterwards, this patient was transferred emergently to our hospital, in cardiac extremis due to a previously unrecognized diagnosis of an interrupted aortic arch type B (a malformation associated with 22q11.2DS). Another patient was found prenatally to have a club foot, but no other features. Postnatally the child had stridor but no doctor considered the diagnosis (or any

TABLE 1 Congenital anomalies in association to club foot

	Patients without club foot	Patients with club foot	*p* value
Presence of a CHD	837 (65.5%)	28 (58.3%)	.354
Presence of a cleft palate	257 (19.1%)	11 (22.9%)	.462
Presence of either a CHD or a cleft palate	903 (72.9%)	32 (66.7%)	.327

Note. Categorical values are expressed as the number and the ratio in %. CHD = congenital heart disease.

diagnosis for that matter). When the child was a toddler, he was finally referred to the clinical geneticist and 22q11.2DS was confirmed.

In this study, we looked at a possible relationship between one of the most extreme associated congenital clinical features of the 22q11.2DS (CHD and/or cleft palate) in relation to the club foot. However, this is just a small portion of all the associated anomalies within 22q11.2DS (Bassett et al., 2011; McDonald-McGinn et al., 2015). Stone et al. performed a long-term study on the associated anomalies found in patients with presumed idiopathic club foot (Stone et al., 2017). These features include developmental and mild cardiovascular abnormalities, abnormalities that are also part of the 22q11.2DS. In other words, if a patient with a club foot is identified, it could be important to identify whether the patient truly has an idiopathic club foot or other possible (mild) syndromic features as well. For example, if a patient has associated anomalies such as developmental delay, characteristic facial features, and/or a CHD, careful examination should follow to determine whether the combination of symptoms leads to the suspicion of the 22q11.2DS and/or another syndrome (McDonald-McGinn et al., 2015).

In patients with idiopathic club foot the etiology is unknown (Horn & Davidson, 2010). It has been related to the intra-uterine position, environmental factors such as smoking, or abnormal muscle, soft tissue, bone and vascular malformations (Dobbs & Gurnett, 2009; Horn & Davidson, 2010). Moreover, there is definitely a genetic component regarding the development of club foot within 22q11.2DS: multiple genes (e.g., *PITX1*, *TBX4*) are associated with the development of club foot and within identical twins there is 33% concordance (Basit & Khoshhal, 2018; Horn & Davidson, 2010). Interestingly, *TBX1* is one of the deleted genes within the 22q11.2 region.

Multiple (family) studies on club foot have provided (genetic) insights in the development of idiopathic club foot (Basit & Khoshhal, 2018). Despite this valuable research, the etiology of club foot is still largely unknown and therefore we propose an alternative possibility in order to gain more knowledge on the development of idiopathic club foot. Given the fact that the club foot male:female ratio and bilateral:unilateral ratio in 22q11.2DS are comparable to the general population and the fact that there was no relation with CHD and/or cleft palate it seems to be that the 22q11.2 deletion itself is an risk factor for developing an "idiopathic-like" club foot. Since the prevalence of club foot within 22q11.2DS is increased, further research on the club foot within 22q11.2DS could lead to more insight in the prenatal differences and possible risk factors for developing a club foot. Subsequently, this might provide insights in the development of club foot in the general population analogous to schizophrenia research within 22q11.2DS (McDonald-McGinn et al., 2015).

There are a number of limitations within our study. First, this study was performed retrospectively and we only classified patients as having a club foot if we could find proof of the treatment. As a result, we excluded patients without a letter of orthopedic treatment. However, patients could have received the treatment in an outside hospital after referral to one of our specialized 22q11.2DS centers. Therefore, the prevalence of 3.3% could be an underestimation of the true prevalence of club foot within 22q11.2DS. Conversely, the study was conducted in two tertiary expertise centers for 22q11.2DS. Therefore, it is possible that patients with major conditions, such as club foot, could have been referred to the CHOP or UMCU. However, in none of the referral letters the club foot was the specific cause for referral to one of the specialized centers. Moreover, we only looked at the association between the major congenital phenotypic features (CHD and cleft palate) and club foot. In order to further determine whether other associated features within the first year, such as feeding difficulties and seizures, are associated with club foot a 22q11.2DS prospective study should be performed. At last, we had 9.5% missing data regarding CHD and 5.0% missing regarding cleft palate, for which we performed a sensitivity analysis, which showed that our findings were robust.

6 | CONCLUSION

The 22q11.2DS is a challenging condition, characterized by a high diversity in (congenital) phenotypic features. Club foot is definitely one of these features, since the prevalence is approximately 30 times higher as compared to the general population. Moreover, the major congenital phenotypic features, CHD and cleft palate, which will lead to referral to the hospital and the clinical geneticist, could not be identified as risk factors for club foot within the 22q11.2DS.

FINANCIAL DISCLOSURE

Jelle F. Homans received the Ter Meulen Grant of the Royal Netherlands Academy of Arts and Sciences in order to travel to the Children's Hospital of Philadelphia for data collection. The research was supported by a research grant of K2M.

ORCID

Jelle F. Homans https://orcid.org/0000-0003-0172-7335

Terrence B. Crowley https://orcid.org/0000-0002-3272-5458

REFERENCES

Basit, S., & Khoshhal, K. I. (2018). Genetics of clubfoot; recent progress and future perspectives. *European Journal of Medical Genetics*, *61*, 107–113.

Bassett, A. S., McDonald-McGinn, D. M., Devriendt, K., Digilio, M. C., Goldenberg, P., Habel, A., … Vorstman, J. (2011). Practical guidelines for managing patients with 22q11.2 deletion syndrome. *The Journal of Pediatrics*, *159*, 332–339.

Billett, J., Cowie, M. R., Gatzoulis, M. A., Vonder Muhll, I. F., & Majeed, A. (2008). Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: Cross-sectional, population-based study with case-control analysis. *Heart*, *94*, 1194–1199.

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A., … Campbell, R. M. (2003). A population-based study of the 22q11.2 deletion: Phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics*, *112*, 101–107.

Cartlidge, I. J. (1983). Club foot in the Polynesian: An epidemiological survey. *The New Zealand Medical Journal*, *13*, 515–517.

Devriendt, K., Fryns, J. P., Mortier, G., van Thienen, M. N., & Keymolen, K. (1998). The annual incidence of DiGeorge/velocardiofacial syndrome. *Journal of Medical Genetics*, *35*, 789–790.

Dobbs, M. B., & Gurnett, C. A. (2009). Update on clubfoot: Etiology and treatment. *Clinical Orthopaedics and Related Research*, *467*, 1146–1153.

Goodship, J., Cross, I., LiLing, J., & Wren, C. (1998). A population study of chromosome 22q11 deletions in infancy. *Archives of Disease in Childhood*, *79*, 348–351.

Grati, F. R., Molina Gomes, D., Ferreira, J. C. P. B., Dupont, C., Alesi, V., Gouas, L., … Vialard, F. (2015). Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenatal Diagnosis*, *35*, 801–809.

Homans, J. F., Baldew, V. G. M., Brink, R. C., Kruyt, M. C., Schlösser, T. P. C., Houben, M. L., … McDonald-McGinn, D. M. (2018). Scoliosis in association with the 22q11.2 deletion syndrome: An observational study. *Archives of Disease in Childhood*, *1*, 1–6.

Homans, J. F., Tromp, I. N., Colo, D., Schlösser, T. P. C., Kruyt, M. C., Deeney, V. F. X., … Castelein, R. M. (2017). Orthopaedic manifestations within the 22q11.2 deletion syndrome: A systematic review. *American Journal of Medical Genetics, Part A*, *1*, 1–17.

Horn, B. D., & Davidson, R. S. (2010). Current treatment of clubfoot in infancy and childhood. *Foot and Ankle Clinics*, *15*, 235–243.

Krogsgaard, M. R., Jensen, P. K., Kjær, I., Husted, H., Lorentzen, J., Hvass-Christensen, B., … Sonne-Holm, S. (2006). Increasing incidence of club foot with higher population density: Incidence and geographical variation in Denmark over a 16-year period - An epidemiological study of 936,525 births. *Acta Orthopaedica*, *77*, 839–846.

McDonald-McGinn, D. M., Sullivan, K. E., Marino, B., Philip, N., Swillen, A., Vorstman, J. A. S., … Bassett, A. S. (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*, 15071.

Oskarsdóttir, S., Vujic, M., & Fasth, A. (2004). Incidence and prevalence of the 22q11 deletion syndrome: A population-based study in Western Sweden. *Archives of Disease in Childhood*, *89*, 148–151.

Parker, S. E., Mai, C. T., Strickland, M. J., Olney, R. S., Rickard, R., Marengo, L., … Meyer, R. E. (2009). Multistate study of the epidemiology of clubfoot. *Birth Defects Research, Part A: Clinical and Molecular Teratology*, *85*, 897–904.

Stoll, C., Dott, B., Alembik, Y., & Roth, M. P. (2015). Associated congenital anomalies among cases with Down syndrome. *European Journal of Medical Genetics*, *58*, 674–680.

Stone, P., Martis, W., & Crawford, H. (2017). Idiopathic congenital talipes equinovarus; not always an isolated anomaly. A review of long-term outcomes. *The Journal of Maternal-Fetal & Neonatal Medicine*, *31*, 2693–2698.

Du Montcel, S. T., Mendizabai, H., Ayme, S., Levy, A., & Philip, N. (1996). Prevalence of 22q11 microdeletion. *Journal of Medical Genetics*, *33*, 719–719.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2008). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Journal of Clinical Epidemiology*, *61*, 344–349.

Werler, M. M., Yazdy, M. M., Mitchell, A. A., Meyer, R. E., Druschel, C. M., Anderka, M., … Mahan, S. T. (2013). Descriptive epidemiology of idiopathic clubfoot. *American Journal of Medical Genetics, Part A*, *161A*, 1569–1578.

How to cite this article: Homans JF, Crowley TB, Chen E, et al. Club foot in association with the 22q11.2 deletion syndrome: An observational study. *Am J Med Genet Part A*. 2018; 176A:2135–2139. https://doi.org/10.1002/ajmg.a.40649