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The role of 22q11.2 deletion syndrome in the relationship between congenital heart disease and scoliosis

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Abstract

BACKGROUND CONTEXT: For over four decades, clinicians and researchers have suggested a relationship between congenital heart disease (CHD) and scoliosis, attributed to either the disease itself or to the long-term effects of cardiac surgery on the immature thoracic cage. However, no study has yet accounted for 22q11.2 deletion syndrome (22q11.2DS), the second most common cause of CHD after Down syndrome. 22q11.2DS has a scoliosis risk of 50%, but within 22q11.2DS a previous report found no significant association between scoliosis and CHD. We, therefore, hypothesized that scoliosis within a CHD cohort would be related to an underlying 22q11.2 deletion.

PURPOSE: To determine the prevalence of scoliosis in CHD patients with and without 22q11.2DS.

STUDY DESIGN/SETTING: Cross-sectional.

PATIENT SAMPLE: A well-characterized existing database of 315 adults with CHD (primarily tetralogy of Fallot), with (n=86) and without (n=229) 22q11.2DS, matched by sex and CHD severity, and excluding other known syndromic diagnoses. We compared the scoliosis prevalence

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of patients with 22q11.2DS and CHD patients to the prevalence of scoliosis in a cohort of adults with 22q11.2DS without CHD based on medical records.

OUTCOME MEASURES: Presence of scoliosis (Cobb angle $\geq 10^\circ$).

METHODS: We systematically determined the presence of scoliosis in all included patients using chest radiographs, blind to genetic diagnosis. Besides 22q11.2DS, we analyzed other suspected risk factors for scoliosis using a regression model: thoracotomy before the age of 12 years, severe CHD type and sex.

RESULTS: The prevalence of scoliosis in adults with CHD and 22q11.2DS (n=46, 53.5%) was significantly greater than in those without 22q11.2DS (n=18, 7.9%, $p<.0001$). The presence of a 22q11.2 deletion (odds ratio [OR] 25.4, 95% confidence interval [95% CI] 11.2–57.4, $p<.0001$), a history of thoracotomy before the age of 12 years (OR 3.5, 95% CI 1.6–8.1, $p=.0027$) and most complex CHD class (OR 2.3, 95% CI 1.1–4.7, $p=.0196$), but not sex, were significant independent predictors of scoliosis. In the 22q11.2DS group, a right-sided aortic arch was associated with a left thoracic scoliotic curve ($p=.036$).

CONCLUSIONS: The prevalence of scoliosis in those with CHD but without a 22q11.2 deletion approximates that of the general population. However, in the CHD population with a 22q11.2 deletion, the prevalence of scoliosis approximates that of others with 22q11.2DS. The pediatric surgical approach and severity of CHD were weaker independent contributors as compared to the 22q11.2 deletion. The results support the importance of a genetic diagnosis of 22q11.2DS to the risk of developing scoliosis in individuals with CHD. The 22q11.2 deletion may represent a common etiopathogenetic pathway for both CHD and scoliosis, possibly involving early laterality mechanisms.

Keywords

22q11.2 deletion syndrome; Chest radiograph; Congenital; Congenital heart disease; Copy number variant; DiGeorge syndrome; Musculoskeletal; Scoliosis; Spine; Thorax radiograph

Introduction

For over four decades, researchers and clinicians have suggested a relationship between congenital heart disease (CHD) and scoliosis (a three-dimensional rotational deformity of the spine and trunk [1,2]), for which several possible mechanisms have been proposed [3-5]. These include biomechanical forces, for example due to altered aortic configuration during development [3,4] or effects of cardiac surgery on an immature thoracic cage disturbing symmetrical growth [6-8].

Scoliosis can have important consequences, including respiratory dysfunction and in severe cases brace therapy or spinal surgery [2]. The majority of patients have adolescent idiopathic scoliosis (AIS), which has an estimated general population prevalence of 1%–9%, and for which the cause is still largely unknown [2,9]. It is widely accepted, however that genetic as well as biomechanical factors play an important role in the etiopathogenesis of AIS. There is a higher concordance of scoliosis in monozygotic twins (73%) and dizygotic twins (36%) than in unrelated individuals [10]. Notably, recent reports indicate that rare pathogenic copy

number variants (CNVs) play a role in the development of AIS [11,12], as they do in CHD [13]. Also, in nature AIS only occurs in fully upright bipedal man [14-16].

The 22q11.2 deletion associated with 22q11.2 deletion syndrome (22q11.2DS), formerly known as DiGeorge or velocardiofacial syndrome, is a prime example of a rare pathogenic CNV [17]. The 22q11.2 deletion has an estimated prevalence of 1 in 3000 live births and is characterized by early and later onset conditions, including CHD and scoliosis [17]. In the present study, we used data obtained from an adult CHD cohort to test the hypothesis that the higher prevalence of scoliosis in CHD is related to an underlying 22q11.2 deletion, while accounting for pediatric cardiac surgery and CHD severity.

Methods

Study population

To determine the scoliosis prevalence in the adult (>17 years) CHD population, patients were included from an existing sample followed at a specialized adult CHD hospital [18-21]. All data in this study are part of ongoing studies approved by the local Research Ethics Board.

Fig. 1 shows the sample derivation and individuals included and excluded from the present study. We used data available from an existing database for a well-characterized sample of adults with CHD, including CHD type (mostly tetralogy of Fallot) [20], cardiac surgical history, laterality of aortic arch, and presence of musculoskeletal anomalies [18-21]. CHD complexity was classified as simple, moderate, and severe, following the 2018 guidelines from the American Heart Association and American College of Cardiology [22]. We confined the sample to adults with CHD and sufficient molecular genetic data (mostly standard clinical genetic testing and/or research-based genome-wide microarray) [18-21], to determine presence or absence of a 22q11.2 deletion [17,18]. We used these molecular data to determine individuals confirmed to have the typical chromosome 22q11.2 deletion, that is, at least including the low copy repeat region (LCR)22A-LCR22B and most commonly involving the 2.5 megabase LCR22A-LCR22D region [17,18], (the 22q11.2DS group), and a comparison group comprising those confirmed to have no typical 22q11.2 deletion (the no 22q11.2DS group). The comparison group was selected in a 2–3 to 1 ratio, matching for sex and CHD severity class, by a research-analyst blind to scoliosis status.

Exclusion criteria were absence of a chest radiograph obtained between 17 and 40 years of age, presence of an atypical nested (eg, LCR22B-LCR22D, LCR22C-LCR22D) chromosome 22q11.2 deletion [17,18], congenital spinal anomalies or variants (eg, hemivertebra, butterfly vertebrae, and Klippel-Feil), or a documented genetic or other syndromic disorder other than 22q11.2DS (eg, VACTERL, CHARGE, Klinefelter, Goldenhar, Pallister Killian, hemihypertrophy, or fetal ethanol syndromes) (Fig. 1). After these exclusions the sample comprised 315 adults with CHD, either with or without a 22q11.2 deletion.

Chest radiograph assessment

One trained observer, who was blinded to 22q11.2 deletion status and medical history, assessed the earliest upright chest radiograph available at the adult CHD hospital. The observer first screened each radiograph for the presence of congenital spinal anomalies (if present, patients were excluded, n=15, Fig. 1) and signs of surgery in the past, including sternotomy wires for cardiac surgery (Fig. 2) or spondylodesis material indicating surgically corrected scoliosis. The radiographs were then analyzed according to the Scoliosis Research Society – the observer recorded the number of thoracic vertebrae and (visible) lumbar vertebrae, the presence of scoliosis (a lateral deviation of the spine, defined as a Cobb angle [the angle between the two most tilted vertebrae] $\geq 10^\circ$), the number of curves and the most severe (ie, major) curve, the convexity of the curve, the apex, and the number of involved vertebrae [23,24]. The laterality of the aortic arch was also assessed (Fig. 2) and these data checked against those previously recorded in medical records.

Scoliosis in 22q11.2DS patients without CHD

We also determined the prevalence of scoliosis in a cohort of adults with 22q11.2DS who had no CHD followed at a specialty clinic for adults with 22q11.2DS at the same hospital as those with CHD [18-21]. Inclusion criteria were adults (≥ 17 years) with a 22q11.2 deletion as confirmed by standard molecular methods [25,26] and no CHD present, as determined by echocardiogram (n=136) [27]. We used the same exclusion criteria for the CHD cohort except that, in the absence of comparable chest radiograph data, we determined the presence of scoliosis from medical records that provided documentation of scoliosis, that is, from physical examination and/or spine radiograph. This method was validated by comparing the presence of scoliosis based on such medical records documentation versus that based on direct examination of chest radiographs within the group of 22q11.2DS patients with CHD (data available for n=69 of the total n=86).

Statistical analysis

Descriptive statistics were performed using Fisher exact test and if normally distributed (determined with Shapiro-Wilk's test) the means of continuous variables were compared using independent samples *t* test. Mann-Whitney *U* tests were used if distribution was non-normal. The main analysis used a logistic regression model to assess possible contributory factors to the development of scoliosis in CHD – presence of a 22q11.2 deletion, sex, CHD severity class, and thoracotomy under age of 12 years. The variance inflation factor and tolerance methods were used to determine that there was no multicollinearity between variables. Post-hoc chi-square (χ^2) tests and degrees of freedom (*df*) for the regression model and odds ratios (OR) and 95% confidence intervals (95% CI) for every predictor were reported. Statistical analysis was done in SPSS 25.0 for Windows (IBM, Armonk, NY, USA) and/or SAS. The statistical significance level was set at 0.05, two-tailed.

Results

A total of 315 patients with a CHD formed the main sample studied 86 with and 229 without 22q11.2DS (Table 1). By design, there was no significant between-group sex or CHD severity class differences. Mean age at chest radiography was significantly older in the no

22q11.2DS group (Table 1). Although the majority of patients had a sternotomy before the age of 12 years, a significantly greater proportion of those in the no 22q11.2DS group had thoracotomy whereas the 22q11.2DS group was enriched for those who had no cardiac surgery before age 12 years or where there was uncertainty about the surgical approach (Table 1).

Scoliosis in adults with CHD

Of the 64 individuals with scoliosis within the CHD cohort studied, the scoliosis prevalence was significantly greater in the 22q11.2DS group ($n=46$, 53.5%, 95% CI: 42.7–64.2) than in the no 22q11.2DS CHD group ($n=18$, 7.9%, 95% CI: 4.3–11.4; $p<.0001$).

The logistic regression model was highly significant ($X^2=94.6$, $df=4$, $p<.0001$). Consistent with our hypothesis, the presence of a 22q11.2 deletion was the most significant predictor of scoliosis (OR 25.4, 95% CI: 11.2–57.4; $p<.0001$), followed by thoracotomy before the age of 12 years and CHD severity (Table 2). A secondary analysis using the same predictors (except 22q11.2 deletion) but restricting to the 229 adults with CHD and no 22q11.2DS, showed that the regression model remained significant ($X^2=13.4$, $df=3$, $p=.0039$) but only thoracotomy before the age of 12 years was a significant predictor of scoliosis (OR 4.4, 95% CI: 1.5–13.2; $p=.0078$); CHD severity was nonsignificant (OR 2.0, 95% CI: 0.7–5.6, $p=.183$). A further secondary analysis examined the model to predict scoliosis in only 22q11.2DS patients ($X^2=8.6$, $df=3$, $p=.035$); this showed no significant predictors for scoliosis, with a trend only for CHD severity ($p=.057$).

Table 3 presents further details of the scoliosis in this cohort; there were no significant differences found between the two groups on the parameters assessed. Only a minority had scoliosis surgery, nonsignificantly fewer in the 22q11.2DS than the no 22q11.2DS group (Table 3). Six of those who did not have scoliosis surgery had thoracic scoliosis with a Cobb angle greater than 45°, all in the 22q11.2DS group; no individual in the no 22q11.2DS group had a Cobb angle over 40° (Table 3). The median number of visible lumbar vertebrae was 2, with an interquartile range of 2–3. Based on the chest radiographs, we were able to determine eight individuals with lumbar scoliosis (Table 3).

Scoliosis convexity and aortic arch laterality

With respect to the 51 adults with CHD and thoracic scoliosis, the majority had the typical scoliotic curve convexity to the right, with no significant difference between the 22q11.2DS and no 22q11.2DS groups (Table 3). Amongst the 35 individuals with 22q11.2DS and a major thoracic scoliotic curve, there were 21 with a normal left-sided aortic arch, 15 (71%) of whom had a right convex scoliosis curve. There were 14 with a right-sided aortic arch, 5 (36%) with a right convex scoliosis curve, demonstrating a significant association between right-sided aortic arch and left convex thoracic curve ($p=.036$).

Scoliosis in adults with 22q11.2DS without CHD

There was a clinical history of scoliosis in 61 of 136 adults with 22q11.2DS and no CHD (44.9%, 95% CI: 36.8%–53.2%) based on medical records data. Of the 69 patients with 22q11.2DS and a CHD, where data from both medical records and direct examination of

radiography were available to assess for the presence of scoliosis, there was agreement in presence/absence of scoliosis for 61 individuals (88.4%), supporting the validity of the medical records method.

Discussion

For the past four decades, the role of CHD in development of scoliosis has been noted as a partial explanation of the enigma of scoliosis pathogenesis. However, in no previous study was a major risk factor for both entities taken into account: the 22q11.2 deletion. The present study provides the first evidence of the significant impact of the 22q11.2 deletion in the development of scoliosis in a cohort of adult CHD patients. Importantly, the prevalence of scoliosis in the no 22q11.2DS CHD cohort was found to be nearly similar to the prevalence of scoliosis in the general population [2,9].

The results are consistent with previous studies reporting high prevalence of scoliosis in 22q11.2DS of about 50% [28], compared with general population expectations of about 1%–9% [2,9]. The scoliosis prevalence in the general population varies greatly, with estimates from 0.5% to 5.2% based on physical examination [29]. However, in two independent studies using chest radiographs and a definition of scoliosis as a Cobb angle of $\geq 10^\circ$, the scoliosis prevalence in the general population was reported as 9.3% and 13.4%, respectively [9,30]. The scoliosis prevalence of 8% we found in the no 22q11.2DS CHD population in this study thus appears comparable to that of the general population when assessed radiographically. Taken together, the results may indicate that in previous studies unrecognized 22q11.2DS could be a confounder for reported associations between CHD and the development of scoliosis.

AIS is more common in females [31], whereas we found that in 22q11.2DS, the prevalence of scoliosis is about equal between females and males, consistent with previous reports [28]. In the general population, early onset scoliosis (age <10 years) comes closer to a 1:1 female:male ratio [32,33]. Prospective studies in 22q11.2DS, investigating the differences between males and females in the development of scoliosis and between patients with and without a scoliosis, might therefore help shed light on the scoliosis development in the general population [34].

The type of scoliosis, both in the 22q11.2DS and no 22q11.2DS group is comparable to that of the general population, with the majority having a major thoracic curve [35]. This finding supports the hypothesis that the 22q11.2 deletion population, which has a high risk to develop an idiopathic-like scoliosis, can be used as a model to study the development of scoliosis [28,34].

Recent studies have suggested a general role for CNVs in the development of AIS [11,12]. Sadler et al. reported that 16p11.2 duplications explain nearly 1% of AIS cases, in a study restricted to patients without major development impairment or major congenital anomalies [12]. Given that the 22q11.2DS population is characterized by broad phenotypic heterogeneity, with developmental impairment and congenital anomalies (eg, CHD) as common features, many patients with 22q11.2DS and scoliosis may have been excluded

from the Sadler et al. study. Nonetheless they reported two patients with 22q11.2DS in their cohort of 1,197 AIS patients, reinforcing the importance of considering clinical genetic testing by microarray in AIS, as in CHD [13].

In the present study, for the main regression model, and in the secondary analysis of the no 22q11.2DS group, pediatric thoracotomy was a significant predictor of scoliosis. This could be explained by the fact that a thoracotomy is an asymmetrical procedure on an immature thoracic cage, which may lead to a disturbance of symmetrical growth and an increased scoliosis risk, as proposed by others [6-8]. However, in the literature, results are mixed as to whether and which type of cardiac surgery, including sternotomy, is associated with scoliosis risk [4,6-8,36]. Further studies, taking genetic syndrome status into account, are needed.

A right-sided aortic arch is rare with an estimated incidence of 0.1% in the general population, yet in 22q11.2DS a right-sided aortic arch is relatively common [37]. In the present study of CHD, in patients with 22q11.2DS we found that a right-sided aortic arch was associated with a left convex curve in patients with a major thoracic scoliosis. There was a similar finding in a previous study of 119 CHD patients where all eight scoliosis patients with a right-sided aortic arch had a left convex thoracic curve [4]. This phenomenon may be explained by the principle of inverted organ anatomy and spinal lateralization. In patients with scoliosis, one study found that scoliotic curve convexity was predominantly to the right in patients with normal organ anatomy (situs solitus), and to the left in patients with situs inversus totalis [38]. Also, laterality of the center of mass in the thorax is related to slight spinal rotation in the opposite direction in patients without scoliosis [39]. Although no causality can be concluded based on these former studies, our findings make the biomechanical theory of an aortic arch to the right side increasing the chance of a left convex scoliotic curve appear plausible.

As the first study to report the scoliosis prevalence in CHD patients, while taking 22q11.2DS into account this study had several advantages but also some limitations. The study was based on a relatively large existing database of CHD patients, in which all patients had genetic testing to confirm or rule out the 22q11.2 deletion [18-21]. Moreover, in order to find the prevalence of scoliosis not caused by congenital spinal malformations, patients with a congenital spinal malformation were excluded. However, since the radiographs were made in order to visualize the thorax, the radiographs capture only the first several (lumbar) spine in most cases (median two visible lumbar vertebrae). Therefore, it might be possible that patients with an undetectable lumbar congenital malformation remain in the sample. Also, the eight adults with 22q11.2DS and lumbar scoliosis in the study sample may be an underestimation of the true number of patients with a lumbar scoliosis in the sample. However, since the lumbar spine is partly visible and the most common type of scoliosis is thoracic scoliosis, it is likely that these numbers are low. We excluded radiographs of patients under age 17 years and older than 40 years, in order to find the definitive prevalence of scoliosis. The younger age group may not yet have developed a scoliosis, whereas scoliosis in the older age group may be related to degenerative scoliosis [40]. We also excluded patients with other syndromic forms of CHD; scoliosis is known to occur more often in other syndromes [41].

In the present study, available data for 136 adults with 22q11.2DS but no CHD indicated a scoliosis prevalence of 45% based on medical records data. This may be an underestimate given that the determination of scoliosis, either at an age still at risk for the development of scoliosis or based on physical examination, could lead to lower scoliosis prevalence than radiographic determination in an adult population. Importantly however, within the 22q11.2DS subgroup with CHD, we demonstrated a high level of agreement (88.4%) between medical records data and chest radiograph methods of determining scoliosis.

There may be other risk factors for the development of scoliosis we did not assess. For example, the methods used would not rule out the presence of neurologic anomalies, although we expect that number to be small in 22q11.2DS [17].

In conclusion, the results of this study support the importance of clinical genetic testing for 22q11.2 deletions in patients with CHD, and the relevance of 22q11.2DS, in understanding the risk for scoliosis in the CHD population. With respect to the CHD population without 22q11.2DS, the scoliosis prevalence is comparable to that of the general population, with a slightly increased risk for those who underwent a thoracotomy as a child. These findings suggest that the 22q11.2 deletion may represent a common genetic pathway for the development of CHD and of scoliosis. Future studies using this genetic model may help determine the pathogenesis of both these complex developmental conditions.

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References

- [1]. Nicoladoni C Anatomie und mechanismus der skoliose In: Kocher König, von Mikulicz, editors. Bibliotheca medica. Stuttgart, Germany: Verlag von erwin nagele; 1904.
- [2]. Cheng JC, Castelein RM, Chu WC, Danielsson AJ, Dobbs MB, Grivas TB, et al. Adolescent idiopathic scoliosis. *Nat Rev Dis Prim* 2015;1: 1–20. 10.1038/nrdp.2015.30.
- [3]. Beals R, Kenney K, Lees M. Congenital heart disease and idiopathic scoliosis. *Clin Orthop Relat Res* 1972;89:112–6. [PubMed: 4646251]
- [4]. Jordan CE, White RI, Fischer KC, Neill C, Dorst JP. The scoliosis of congenital heart disease. *Am Heart J* 1972;84:463–9. [PubMed: 5075085]
- [5]. Lui GK, Saidi A, Bhatt AB, Burchill LJ, Deen JF, Earing michael G, et al. Diagnosis and management of noncardiac complications in adults with congenital heart disease: a scientific

- statement from the American Heart Association. *Circulation* 2017;136:e348–92. 10.1161/CIR.0000000000000535. [PubMed: 28993401]
- [6]. Gilsanz V, Boechat IM, Birnberg FA, King JD. Scoliosis after thoracotomy for esophageal atresia. *AJRAmerican J Roentgenol* 1983;141: 457–60.
- [7]. Durning RP, Scoles PV, Fox OD. Scoliosis after thoracotomy in tracheoesophageal fistula patients. A follow-up study. *J Bone Jt Surg - Ser A* 1980;62:1156–9. 10.2106/00004623-198062070-00015.
- [8]. Roclawski M, Sabiniewicz R, Potaz P, Smoczynski A, Pankowski R, Mazurek T, et al. Scoliosis in patients with aortic coarctation and patent ductus arteriosus: does standard posterolateral thoracotomy play a role in the development of the lateral curve of the spine? *Pediatr Cardiol* 2009;30:941–5. 10.1007/s00246-009-9469-3. [PubMed: 19597861]
- [9]. Urrutia J, Besa P, Bengoa F. A prevalence study of thoracic scoliosis in Chilean patients aged 10–20 years using chest radiographs as a screening tool. *J Pediatr Orthop Part B* 2018;27:159–62. 10.1097/BPB.0000000000000466.
- [10]. Kesling K, Reinker K. Scoliosis in twins. A meta-analysis of the literature and report of six cases. *Spine (Phila Pa 1976)* 1997;22: 2009–14. [PubMed: 9306532]
- [11]. Buchan JG, Alvarado DM, Haller G, Aferol H, Miller NH, Dobbs MB, et al. Are copy number variants associated with adolescent idiopathic scoliosis? *Clin Orthop Relat Res* 2014;472:3216–25. 10.1007/s11999-014-3766-8. [PubMed: 25005481]
- [12]. Sadler B, Haller G, Antunes L, Bledsoe X, Morcuende J, Giampietro P, et al. Distal chromosome 16p11.2 duplications containing SH2B1 in patients with scoliosis. *J Med Genet* 2019;1–7; e-pub 10.1136/jmedgenet-2018-105877.
- [13]. Costain G, Silversides CK, Bassett AS. The importance of copy number variation in congenital heart disease. *NPJ Genom Med* 2016;14:1–11. 10.1038/npjgenmed.2016.31.
- [14]. Castelein RM, van Dieën JH, Smit TH. The role of dorsal shear forces in the pathogenesis of adolescent idiopathic scoliosis - a hypothesis. *Med Hypotheses* 2005 ;65:501–8. 10.1016/j.mehy.2005.03.025. [PubMed: 15913901]
- [15]. Janssen MMA, de Wilde RF, Kouwenhoven J-WM, Castelein RM. Experimental animal models in scoliosis research: a review of the literature. *Spine J* 2011;11:347–58. 10.1016/j.spinee.2011.03.010. [PubMed: 21474088]
- [16]. Kouwenhoven JW, Smit TH, van der Veen AJ, Kingma I, van Dieën JH, Castelein RM. Effects of dorsal versus ventral shear loads on the rotational stability of the thoracic spine: a biomechanical porcine and human cadaveric study. *Spine (Phila Pa 1976)* 2007;32:2545–50. 10.1097/BRS.0b013e318158cd86 [PubMed: 17978652]
- [17]. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Prim* 2015;1:1–19. 10.1038/nrdp.2015.71.
- [18]. Van L, Heung T, Graffi J, Ng E, Malecki S, Mil S Van, et al. All-cause mortality and survival in adults with 22q11.2 deletion syndrome. *Genet Med* 2019;1–8. e-pub 10.1038/s41436-019-0509-y.
- [19]. Chin-yeo NJ, Costain G, Swaby J, Silversides CK, Bassett AS. Reproductive fitness and genetic transmission of tetralogy of Fallot in the molecular age. *Circ Cardiovasc Genet* 2014;7:102–9. 10.1161/CIRCGENETICS.113.000328. [PubMed: 24563425]
- [20]. Silversides CK, Lionel AC, Costain G, Merico D, Migita O, Liu B, et al. Rare copy number variations in adults with tetralogy of Fallot implicate novel risk gene pathways. *PLoS Genet* 2012;8:1–14. 10.1371/journal.pgen.1002843.
- [21]. Piran S, Bassett AS, Grewal J, Swaby J-A, Morel C, Oechslin EN, et al. Patterns of cardiac and extracardiac anomalies in adults with tetralogy of fallot. *Am Heart J* 2011;161:131–7. 10.1016/j.ahj.2010.09.015. [PubMed: 21167345]
- [22]. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation* 2018AD;139:e698–800. 10.1161/CIR.0000000000000603.
- [23]. O'Brien M, Kulklo T, Blanke K, Lenke L. Radiographic measurement manual. 2008.

- [24]. Kane WJ. Scoliosis prevalence: a call for a statement of terms. *Clin Orthop Relat Res* 1977;126:43–6.
- [25]. Bassett AS, Chow EWC, Husted J, Weksberg R, Caluseriu O, Webb GD, et al. Clinical features of 78 adults with 22q11 deletion syndrome. *Am J Med Genet Part A* 2005;138 A:307–13. 10.1002/ajmg.a.30984. [PubMed: 16208694]
- [26]. Bassett A, Van L, Butcher N, Chow E, Ogura L, Costain G. Fetal growth and gestational factors as predictors of schizophrenia in a high risk genetic subtype. *Biol Psychiatry* 2015;77:326S–7S.
- [27]. Bassett AS, McDonald-McGinn DM, Devriendt K, Digilio MC, Goldenberg P, Habel A, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. *J Pediatr* 2011;159:332–9. 10.1016/j.jpeds.2011.02.039. [PubMed: 21570089]
- [28]. Homans JF, Baldew VGM, Brink RC, Kruyt MC, Schlösser TPC, Houben ML, et al. Scoliosis in association with the 22q11.2 deletion syndrome: an observational study. *Arch Dis Child* 2019;104:19–24. 10.1136/archdischild-2018-314779. [PubMed: 29627765]
- [29]. Konieczny MR, Senyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. *J Child Orthop* 2013;7:3–9. 10.1007/s11832-012-0457-4. [PubMed: 24432052]
- [30]. Chen JB, Kim AD, Allan-Blitz L, Shamie AN. Prevalence of thoracic scoliosis in adults 25 to 64 years of age detected during routine chest radiographs. *Eur Spine J* 2016;25:3082–7. 10.1007/s00586-015-4215-4. [PubMed: 26329652]
- [31]. Luk KDK, Lee CF, Cheung KMC, Cheng JCY, Ng BKW, Lam TP, et al. Clinical effectiveness of school screening for adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2010;35:1607–14. 10.1097/BRS.0b013e3181c7cb8c. [PubMed: 20453727]
- [32]. Chiu YL, Huang TJ, Hsu RW. Curve patterns and etiologies of scoliosis: analysis in a university hospital clinic in Taiwan. *Chang Yi Xue Za Zhi* 1998;21:421–8.
- [33]. Figueiredo UMM, James JIPI. Juvenile idiopathic scoliosis. *J Bone Jt Surgery British* 1981;63-B:61–6.
- [34]. Homans JF, Reuver S De, Breetvelt EJ, Vorstman JAS, Deeney VFX, Flynn JM, et al. The 22q11.2 deletion syndrome as a model for idiopathic scoliosis – a Hypothesis. *Med Hypotheses* 2019;127:57–62. 10.1016/j.mehy.2019.03.024. [PubMed: 31088649]
- [35]. Lenke LG, Betz RR, Harms J, Bridwell KH, Clements DH, Lowe TG, et al. Adolescent idiopathic scoliosis: a new classification to determine extent of spinal arthrodesis *J Bone Jt Surgery American* Vol 2001;83-A:1169–81.
- [36]. Feiz HH, Afrasiabi A, Parvizi R, Safarpour A, Fouladi RF. Scoliosis after thoracotomy/ sternotomy in children with congenital heart disease. *Indian J Orthop* 2012;46:77–80. 10.4103/0019-5413.91639. [PubMed: 22345811]
- [37]. D'Antonio F, Khalil A, Zidere V, Carvalho JS. Fetuses with right aortic arch: a multicenter cohort study and meta-analysis. *Ultrasound Obstet Gynecol* 2016;47:423–32. 10.1002/uog.15805. [PubMed: 26643657]
- [38]. Schlösser TPC, Semple T, Carr SB, Padley S, Loebinger MR, Hogg C, et al. Scoliosis convexity and organ anatomy are related. *Eur Spine J* 2017;26:1595–9. 10.1007/s00586-017-4970-5. [PubMed: 28180983]
- [39]. de Reuver S, Brink RC, Homans JF, Kruyt MC, van Stralen M, Schlösser TPC, et al. The changing position of the center of mass of the thorax during growth in relation to pre-existent vertebral rotation. *Spine (Phila Pa 1976)* 2019;44:679–84. 10.1097/BRS.0000000000002927. [PubMed: 30395092]
- [40]. Silva FE, Lenke LG. Adult degenerative scoliosis: evaluation and management. *Neurosurg Focus* 2010;28:1–10. 10.3171/2010.1.focus09271. [PubMed: 20369435]
- [41]. Levy BJ, Schulz JF, Fornari ED, Wollowick AL. Complications associated with surgical repair of syndromic scoliosis. *Scoliosis* 2015;10:1–16. 10.1186/s13013-015-0035-x. [PubMed: 25628756]

Fig. 1.
Flowchart of the sample studied.

Fig. 2.

Findings during chest radiography assessment. In the case of a history of sternotomy, sternal wires can be visible from a coronal view (a) and sagittal view (b) of the chest radiograph.

While the aortic arch is normally left sided (c), in this group of CHD patients the aortic arch is sometimes right-sided (d). Dashed guidelines are drawn over Figures 2c and 2d to indicate the aortic arch position.

Characteristics of the 315 adults with congenital heart disease (CHD) studied, comparing those with and without 22q11.2 deletion syndrome (22q11.2DS)

Table 1

Variables	22q11.2DS (n=86)	No 22q11.2DS* (n=229)	p Value
Female sex (%)	39 (45.4%)	108 (47.2%)	.8009*
Mean age in years at time of thoracic radiograph (SD)	22.7 (5.0)	26.9 (6.4)	<.0001
CHD severity class [†]			
Mild-moderate	56 (65.1%)	139 (60.7%)	0.5163*
Severe	30 (34.9%)	90 (39.3%)	
Cardiac surgery before age 12 years [‡]			
Sternotomy only	55 (64.0%)	124 (54.2%)	0.1270
Thoracotomy (with/without sternotomy)	15 (17.4%)	83 (36.2%)	.0016
No cardiac surgery or uncertain cardiac surgical approach	16 (18.6%)	22 (9.6%)	.0339

Significant findings are indicated in bold font.

* By design, the no 22q11.2DS group was matched a priori to the 22q11.2DS group by sex and CHD severity class.

[†] CHD severity class was determined following the 2018 guidelines from the American Heart Association and American College of Cardiology [22]; mild and moderate severity classes were combined given small numbers for the mild subgroup.

[‡] The surgical approach was determined based on the medical records. The patients could either fall in the sternotomy only group (first category), the lateral thoracotomy group with or without a sternotomy (second category) or in the group in which it was uncertain whether the patients had surgery paediatric cardiac and/or it was uncertain what kind of surgical approach was used (third category).

Table 2
Factors contributing to scoliosis risk in 315 adults with congenital heart disease (CHD)

Predictor variables	Total (n=315)	Scoliosis (n=64, 20.3%)	No scoliosis (n=251, 79.7%)	Logistic regression analysis		
				OR	95% CI	p
22q11.2 deletion syndrome	86	46 (53.5%)	40 (46.5%)	25.4	11.2–57.4	<.0001
Thoracotomy before age 12 years	98	24 (24.5%)	74 (75.5%)	3.5	1.6–8.1	.0027
Severe CHD	120	32 (26.7%)	88 (73.3%)	2.3	1.1–4.7	.0196
Female sex	147	35 (23.8%)	112 (76.2%)	1.7	0.9–3.3	.1309

OR, Odds ratio; 95% CI, 95% confidence intervals.

Significant findings are indicated in bold font.

Likelihood ratio for regression model: $\chi^2 = 94.6$, df=4, $p < .0001$.

Radiographic parameters of the scoliosis in the 64 adults with scoliosis in the CHD cohort studied, comparing those with and without 22q11.2 deletion syndrome (22q11.2DS)

Table 3

Variables	22q11.2DS with scoliosis (n=46)	No 22q11.2DS with scoliosis (n=18)	p Value
Major scoliosis curve type (total n=64)			
Cervicothoracic	0 (0%)	1 (5.6%)	.2812
Thoracic	35 (76.1%)	16 (88.9%)	.3200
Thoracolumbar	3 (6.5%)	1 (5.6%)	1.0000
Lumbar	8 (17.4%)	0 (0%)	.0930
Scoliosis surgery	6 (13.0%)	5 (27.8%)	.2667
Subset with major thoracic scoliosis without surgery (n=41)	(n=30)	(n=11)	
Median degree of Cobb angle (IQR)	21.3 (17–41)	23.7 (20–28)	.9758
Range	11–111	13–40	
Median number of vertebrae involved (IQR)	6 (5–7)	6 (6–8)	.3309
Range	4–9	4–8	
Apex of curve (vertebra)	T6 (T4–T8)	T8 (T6–T9)	.0675
Range	T3–T9	T3–T10	

IQR, interquartile range; T, level of thoracic vertebra.