



The 22q11.2 deletion syndrome as a model for idiopathic scoliosis – A hypothesis



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ABSTRACT

Adolescent idiopathic scoliosis (AIS), defined as a lateral deviation of the spine of at least ten degrees, is a classic enigma in orthopaedics and affects 1–4% of the general population. Despite (over) a century of intensive research, the etiology is still largely unknown. One of the major problems in all existing AIS research is the fact that most patients come to medical attention after onset of the curve. Therefore, it is impossible to know whether current investigated parameters are causative, or an effect of the scoliosis. Moreover, up until now there is no known animal model that captures the core features of AIS. In order to identify causal pathways leading to AIS we propose another approach, which has been of great value in other medical disciplines: To use a subset of the population, with a higher risk for a certain disease as a “model” for the general population. Such a “model” may allow the identification of causative mechanisms that might be applicable to the general population. The 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome and occurs in ~1:3000–6000 children and 1:1000 pregnancies. Nearly half of the population of patients with 22q11.2DS develop a scoliosis that in most cases resembles AIS as far as age at onset and curve pattern. We postulate that within 22q11.2DS certain causal pathways leading to scoliosis can be identified and that these are applicable to the general population.

Introduction

Scoliosis is a three-dimensional (3D) rotational deformity of the spine and trunk which has major consequences for the patient in terms of self-image, pain and the serious impact of possible invasive treatments (brace therapy and/or scoliosis surgery) [1,2]. A scoliosis is defined as a lateral deviation of the spine of at least ten degrees Cobb angle (Fig. 1) [3]. Several known causes for scoliosis exist (congenital and neuromuscular scoliosis). However, the majority of patients have an adolescent idiopathic scoliosis (AIS), for which the cause is, to a large extent, unknown. The majority of AIS patients are healthy and well-functioning up to the age of the pubertal growth spurt. AIS affects 1–4% of the general population and is a classic enigma within orthopaedics [2]. Although recent research has elucidated the role of genetics and the biomechanics of the upright human spine, the true cause of this disorder, and thus the potential for prevention, has remained largely undiscovered [2,4–8]. As a result, surgery is the main treatment option in AIS patients with curves exceeding 45–50 degrees [2,9]. There are two important reasons why there is such a variety of theories and why

the etio-pathogenesis, is still to a large extent unraveled:

1. Patients with AIS are identified as such after the onset of the scoliosis. Therefore, it is impossible to identify causative factors of the curve onset. As a consequence, in current research, it is unknown whether correlated parameters are the cause, the consequence or an epiphenomenon of the scoliosis [2,5].
2. There is no animal that, without experimental intervention, develops a scoliosis. Specific genes are known to play a role in the development of scoliosis, as shown by the curvature developed within e.g. the mutant guppy syndrome curveback or POC-5 zebrafish [10,11]. However, as shown by multiple large genetic studies it is clear that the development of idiopathic scoliosis is not limited to one gene and/or pure mendelian inheritance [2]. On the contrary, the development of idiopathic scoliosis is known to be multifactorial (a combination of genetic, metabolic, the central nervous system, biomechanics and environmental factors) [2]. Thus, in order to investigate the (combination of) multiple pathways leading to scoliosis and to understand the development of idiopathic scoliosis we

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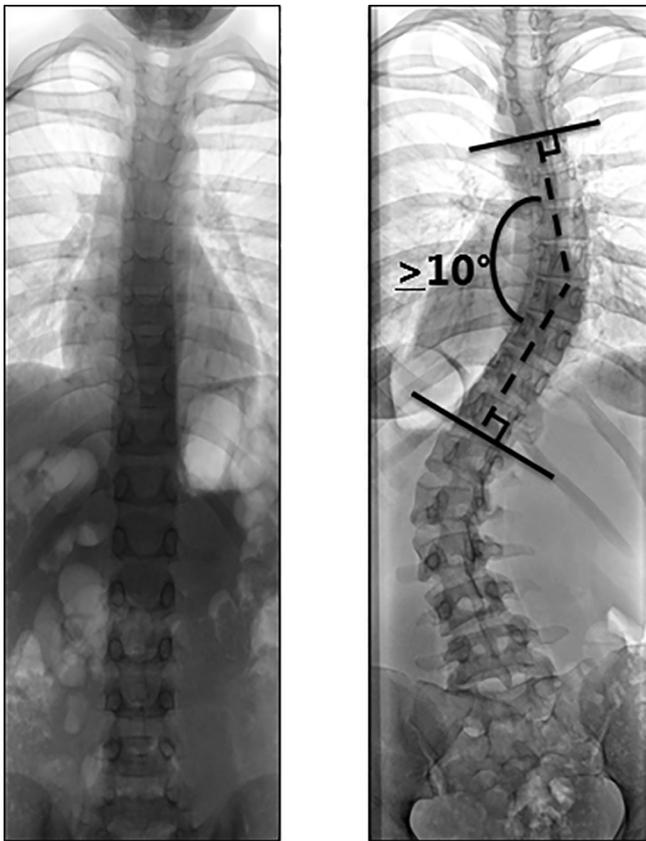


Fig. 1. A scoliosis (right image) is diagnosed as a curve ≥ 10 degrees.

have to investigate man: Only humans carry the body's center of gravity straight above the pelvis due to a pelvic and lumbar lordosis. All other animals, quadrupedal and bipedal alike, carry the body's center of gravity in front of the pelvis. Man has a unique

biomechanical loading of the spine that introduces dorsal shear forces, that have been shown to cause a loss of rotational stability (Fig. 2) [8,12,13].

There is a large gap of knowledge in the etio-pathogenesis of scoliosis, which needs to be bridged in order to reach the next step in scoliosis care: Primary prevention (prevent the development of scoliosis) and/or secondary prevention (identify the patients in an early stage in order to prevent surgery). Therefore, we propose another possibility, which has been of great value in other medical disciplines: To prospectively investigate a subset of the population, with a higher risk for a certain disease, as a model for the general population. For AIS, patients with the 22q11.2 deletion syndrome (22q11.2DS) could be such a population to study, since 50% develops a scoliosis and the majority of patients has a scoliosis resembling AIS as far as age at onset and curve pattern [14].

In humans, 22q11.2DS, is the most common microdeletion syndrome with a prevalence of ~ 1 in 3–6 thousand live births and 1 in 1000 unselected pregnancies [15–18]. Patients with 22q11.2DS, prior to the identification of the chromosomal etiology, may have been diagnosed with a variety of clinical described entities such as the Di-George syndrome, velocardiofacial syndrome or conotruncal anomaly face syndrome [19]. The clinical features associated with this condition vary greatly within and between individuals [20]. Numerous clinical features are now known to be associated with 22q11.2DS including common conditions such as congenital heart disease (CHD, 25–60%), endocrinopathies such as hypocalcemia (55%), immunodeficiency (77%), cognitive deficits ($> 95\%$) and psychiatric illness including schizophrenia (25%), and less frequently associated problems such as congenital diaphragmatic hernia and imperforate anus [20,21]. On the other hand, the clinical features of 22q11.2DS can be relatively mild and the diagnosis tends to be missed. In fact, we treated multiple patients for presumed AIS that later turned out to suffer from 22q11.2DS. Scoliosis is present in about 50% of patients with 22q11.2DS, compared to about 1–4% in the general population [14,22]. We postulate that the population of individuals with 22q11.2DS can be used as a model to study scoliosis in a unique, prospective manner, starting from genetic

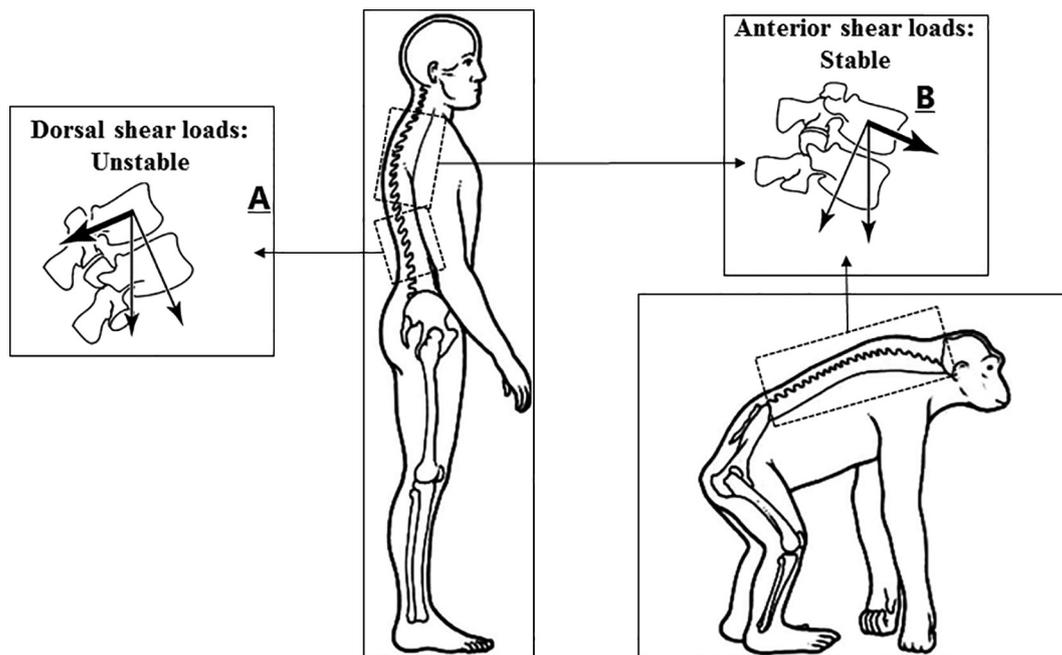


Fig. 2. There are unique differences between human and all other animals. Humans have the center of gravity straight above the pelvis, while all other animals (including the bipedal ones) carry the body's center of gravity in front of the pelvis, leading to different biomechanical circumstances. Certain parts of the human spine experience dorsally directed shear loads (A), while other parts and all other animals only have anteriorly directed shear loads (B). The dorsal shear loads have been shown to decrease rotational stability in the affected segments. Compiled from Castelein et al. [12].

risk to the emergence of first signs of (spine) abnormalities. We hypothesize that these insights will be informative for our understanding of the causal pathways leading to scoliosis in the general population.

Lessons learned from other high-risk populations

In the field of gynecology, the Sjögren-Larsson syndrome is proposed as a model for preterm labor and in the field of psychiatry 22q11.2DS is regarded as a model for idiopathic schizophrenia [23,24]. The 22q11.2 deletion is found to be the most prevalent and strongest single genetic risk factor for developing schizophrenia. The correlation between 22q11.2DS and schizophrenia has long been established; multiple studies confirm that approximately one out in four patients with 22q11.2DS develop schizophrenia [20,23,25]. On the other hand, within the general population, out of all patients with schizophrenia only one in 100–200 have the 22q11.2 deletion [20,26]. This led to establishment of the International 22q11.2DS Brain and Behavior Consortium (a large group of international experts representing 22 clinical and five genomic sites) that aims to identify causal mechanisms leading to schizophrenia in 22q11.2DS and elaborating on that, investigate if these causal mechanisms are applicable to the general population. The large a-priori chance of conversion to schizophrenia in 22q11.2DS, leads to a dramatic decrease in required sample size to identify causative mechanisms of schizophrenia within 22q [27]. Using this approach, multiple studies showed that several parameters, such as prematurity, lower global neurocognitive performance, poorer pre-morbid functioning and a decrease in intelligence quotient years before the onset of schizophrenia, pose an increased risk of developing schizophrenia at a later stage [25,27,28].

Obviously, preterm labor and schizophrenia are two disorders very distinct from scoliosis, however the onset of all three are thought to be multifactorial. By the use of a model as proposed, we can prospectively study one or more causative factors within a subgroup, and possibly extrapolate these findings to the general population [2,20,24].

Neuromuscular versus idiopathic scoliosis

Neuromuscular scoliosis is a distinct spinal curvature which is caused by a disorder of the muscles and/or central nervous system. Common causes are cerebral palsy, myelodysplasia, spinal muscular atrophy (SMA) or Duchenne's muscular dystrophy [29]. These patients do not have the ability to maintain postural balance, are often wheelchair bound, and develop a C-curved scoliosis already at a very early stage of development (Fig. 3). Both the underlying condition, the age at onset and the curve type are very different from AIS. Moreover, in neuromuscular scoliosis (e.g. Duchenne and spinal muscular atrophy) the risk of curve progression and subsequent surgical treatment is much higher as compared to AIS [2,30].

Scoliosis within 22q11.2DS

Scoliosis is an important part of the multi-morbidity seen in association with 22q11.2DS, with a prevalence of about 50% [14]. In 22q11.2DS, as well as in the general population, scoliosis usually develops during the growth spurt [2,14]. Moreover, the majority of patients with 22q11.2DS have an idiopathic-like curve pattern. Lastly, although during development gross motor milestones like crawling, cruising, walking are slightly behind peers and siblings, patients with 22q11.2DS, in general are fully ambulant [31].

This leads to our hypothesis that within 22q11.2DS causal pathways resulting in scoliosis can be identified and that these may also play a role in the general population.

Testing the hypothesis

In order to test the hypothesis that the scoliosis in patients with

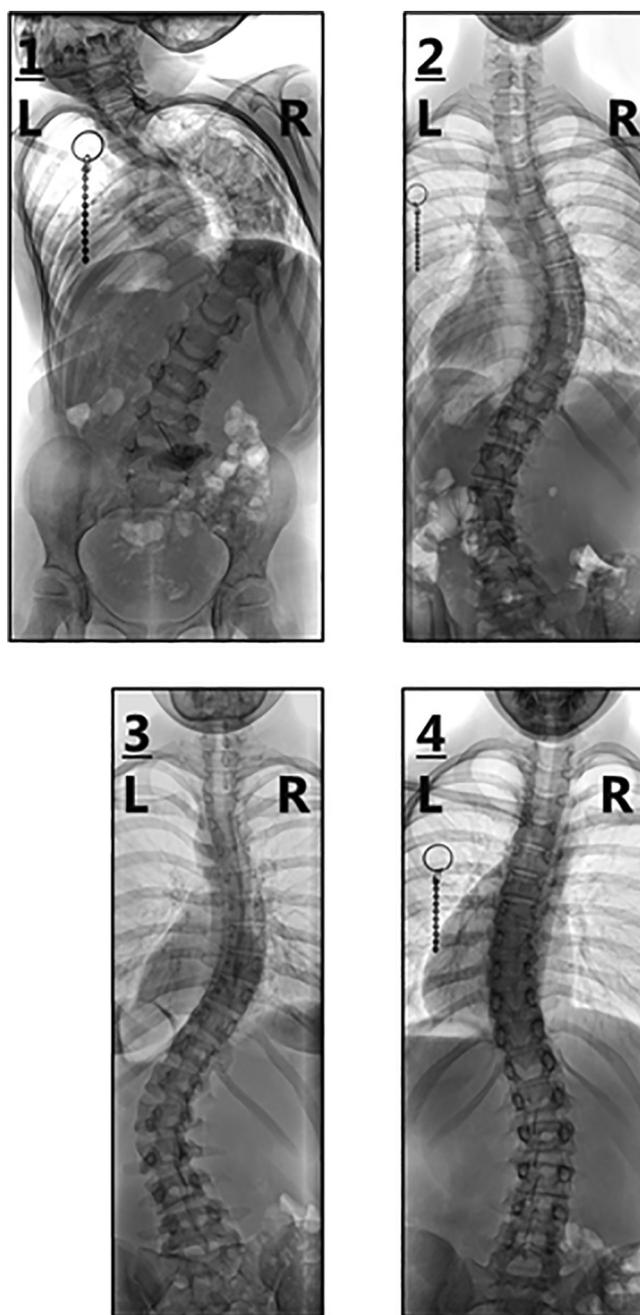


Fig. 3. 1: A five year old spinal muscular atrophy patient with a scoliosis neuromuscular scoliosis (C-shape, right thoracic) 2: A 14 year old patient with an adolescent idiopathic scoliosis (S-shape, right thoracic, left lumbar) 3: A 16 year old 22q11.2 Deletion Syndrome patient with a scoliosis (S-shape, right thoracic, left lumbar) 4: A seven year old 22q11.2 Deletion Syndrome patient with a scoliosis (S-shape left thoracic, right lumbar).

22q11.2DS can serve as a model for idiopathic scoliosis, four important factors, of the development of idiopathic scoliosis, should be determined within the 22q11.2DS population:

1. Does the scoliosis in 22q11.2DS behave like AIS?
2. What is the prevalence of intraspinal anomalies in 22q?
3. What is the neuromuscular status of 22q11.2DS patients as compared to AIS?
4. What is the condition of essential soft tissue structures, such as the intervertebral discs (IVD)?

Does the scoliosis in 22q11.2DS behave like AIS?

In order to investigate whether the 22q11.2DS is comparable with AIS, both the curve pattern and the progression rate of patients with 22q11.2DS should be compared with AIS. This is illustrated by the fact that within neuromuscular scoliosis both of these factors are very different as compared to AIS. The majority of patients with 22q11.2DS has an idiopathic-like curve scoliosis pattern and a relatively mild scoliosis as shown by the fact that 16% of all 22q11.2DS scoliosis patients eventually require scoliosis surgery [14,32]. In AIS, 13.2% of the patients require brace and/or surgical treatment (2.4% of all the AIS patients require surgical treatment) [33]. It is not possible to compare the progression rate of AIS and 22q11.2DS scoliosis based on need for surgical treatment. With the introduction of brace therapy, the need for scoliosis surgery in AIS decreased dramatically [34]. In 22q11.2DS, associated symptoms such as CHD and psychological status, can influence the compliance for brace therapy. Therefore, we should focus on the rate of progression. According to a recent systematic review by Negrini et al. the pooled estimated progression prevalence (defined as > 5 degrees curve progression) within juvenile and adolescent idiopathic scoliosis was 49% and the rate of scoliosis progression ranged from 2.2 to 9.6 degrees per year. We hypothesize that the patients with 22q11.2DS with an idiopathic-like curve have a comparable progression rate as in idiopathic scoliosis.

What is the prevalence of intraspinal anomalies in 22q?

In a recent systematic review it was shown that, approximately ten percent of all AIS patients have intraspinal anomalies as shown on MRI [35]. In some cases this is linked to the development of scoliosis (e.g. a tethered cord) and subsequently in that case it is not deemed as AIS. However, how the majority of the intraspinal anomalies found in AIS relate to the development of idiopathic scoliosis remains unclear [35]. Therefore, there is no consensus on whether all AIS patients, prior to surgery, should receive an MRI or only the patients with atypical curves or abnormal neurologic findings [35]. From the point of view of our hypothesis it would be preferable if the scoliosis patients with 22q11.2DS have a similar percentage and/or a similar sort of intraspinal anomalies as AIS patients and not anomalies that are directly related to scoliosis development. However, it is currently unknown whether patients with 22q11.2DS, with an idiopathic-like curve, have a similar rate of intraspinal anomalies as compared to the AIS population.

What is the neuromuscular status of 22q11.2DS patients as compared to AIS?

Although AIS patients are -by definition- considered to be normal apart from their spinal deformity, various subtle differences that may be cause or effect, with the normal population have been described. As discussed, there is a large difference between AIS patients and neuromuscular scoliosis patients with regards to their postural balance and body control. However, in AIS, there are small differences with respect to the neuromuscular status as compared to the general, non-scoliotic population. For example, in a gait analysis study, there was a significantly higher postural instability in AIS that included limb load symmetry, sway length and velocity in anteroposterior and latero-lateral directions [36]. Once again, it cannot be determined if these differences are the cause or the effect of the disorder. It is currently unknown whether the subtle neuromuscular differences (as present in AIS) also occur between patients with 22q11.2DS with and without a scoliosis. More research should be performed on the possible neuromuscular differences in patients with 22q11.2DS with and without scoliosis, in order to, analyse whether these differences are causative or an effect of the scoliosis.

What is the condition of essential soft tissue structures, such as the intervertebral discs (IVD)?

In AIS patients, it was demonstrated that the curves were characterized by a much greater deformation in the intervertebral discs (IVD) as compared to the vertebral bodies [37,38]. The increase in curve magnitude, during adolescent skeletal growth and maturation, occurs mostly through disc wedging during the rapid growth spurt and vertebral wedging occurs later and to a lesser extent [39]. In other words, within the general population it is known that the intervertebral disk plays an important role in the development of scoliosis. Yet, whether there are primary IVD differences between the population that does and does not develop a scoliosis is unknown. In 22q11.2DS, we should analyze the possible disc property differences of patients with and without scoliosis. Hereafter, with intensive monitoring of the 22q11.2DS patients starting at a young age, we have the opportunity to analyze possible differences in the disc properties before the onset of the scoliosis.

Patients with 22q11.2DS are prone to develop scoliosis; in 22q11.2DS nearly half of the patients develop scoliosis, while within the general population scoliosis occurs in 1–4%. The major question is why do 50% of the patients with 22q11.2DS develop scoliosis and moreover what are the differences between the 22q11.2DS patients with and without a (progressive) scoliosis. There may be small differences between the patients with 22q11.2DS and the general population (e.g. a slight delay in milestone development). Yet, as opposed to AIS, in 22q11.2DS we have the opportunity to compare the parameters before the onset of the scoliosis and thus truly determine whether these parameters are the cause or the consequence of the scoliosis. Our hypothesis is that the 22q11.2DS scoliosis behaves the same as compared to AIS and by prospectively identifying differences between the 22q11.2DS patients with and without a scoliosis, we can identify causal mechanisms between these groups and subsequently expand these findings to the general population.

Discussion

Scoliosis has severe consequences for the patient in terms of self-image and pain and in severe cases possible cardiopulmonary compromise [1,40]. Moreover, surgical treatment as well as brace therapy, that consists of rigid and constraining braces that have to be worn extensively in an emotionally vulnerable period of life, is a severe burden on the patient. Last, apart from the impact of the spinal deformity on the quality of life of the patient, scoliosis patients are also a considerable economic burden to society: it is the spinal deformity most frequently seen by general practitioners, pediatricians and orthopedic surgeons, and current therapies are very costly [2,41,42]. Therefore, the ultimate goal of scoliosis care is to prevent the development and/or deter progression, thereby eliminating the need for brace/surgical treatment.

The first step to prevent the development of scoliosis within a patient is to identify the etio-pathogenesis of this deformity. It is well recognized that the development of scoliosis is multifactorial, and in order to truly elucidate its cause, new approaches are needed [2].

The identification of causal pathways leading to scoliosis within 22q11.2DS, will lead to a large improvement in care for the population of patients with 22q11.2DS, both in primary and secondary prevention. At the same time, we hypothesize that the causative mechanisms leading to scoliosis within 22q11.2DS are applicable to the general population and thereby, this can lead to the improvement of care for a disease troubling 1–4% of the general population. The majority of patients with 22q11.2DS have an idiopathic-like curve scoliosis pattern and a relatively mild scoliosis as shown by the fact that 16% of all patients with 22q11.2DS eventually require scoliosis surgery.^{12,30} To investigate the differences between 22q11.2DS patients with and without a scoliosis and with a non progressive and (rapid) progressive

scoliosis will be the next step. Within the 22q11.2DS population we have the opportunity to analyze metabolic, the central nervous system, biomechanics and environmental factors, but also genetic factors: Possible differences within the deletion and/or genetic variances outside of the 22q11.2 deletion.

From a scientific perspective, a limitation of the 22q11.2DS population as a model for the general population could be that CHD are common (25–60%) in 22q [14,20,21]. The limitation would be that already four decades ago, a correlation between the appearance of congenital heart defects (CHD) and the development of scoliosis in the general population was shown [43–45]. Multiple theories were formed for why CHD leads to a scoliosis. First, different biomechanical forces, due to altered aortic configuration, could possibly cause an increased risk in developing scoliosis [43,44]. Second, surgery on an immature thoracic cage may result in altered growth and an increased scoliosis risk [45–47]. Yet, in a recent study, no relation between a thoracotomy/sternotomy for CHD and scoliosis was found [48]. In other words, there are conflicting results on the correlation between CHD and scoliosis. Moreover, in none of these studies genetic testing of (all) the patients was performed. Subsequently, it is unknown whether (a subset of) the included patients in these studies may have had 22q11.2DS [43–47]. This is important because 22q11.2DS is the second greatest risk factor for CHD and the symptoms of 22q11.2DS can be subtle leading to underdiagnoses of 22q11.2DS [19,20]. Interestingly, in a recent study, in which all the patients had the 22q11.2DS diagnosis there was no association between CHD and scoliosis [14]. In other words, it is possible that actually 22q11.2DS was the reason that these patients developed both a CHD and a scoliosis.

Patients with 22q11.2DS are at an increased (~25 times fold) risk for the development of scoliosis. The major question is what are the factors that determine whether a scoliosis develops, or not. Moreover, what are the factors that lead to a progressive scoliosis that necessitates surgery in 16% of the 22q11.2DS patients. Within 22q11.2DS we have the opportunity to truly investigate this multifactorial pathway and in the end, possibly, extrapolate them to the general population.

Disclosure of funding

Jelle F. Homans: Receives a small exploratory research grant from the Scoliosis Research Society

Steven de Reuver: None to declare

Elemi J. Breetvelt: None to declare

Jacob A.S. Vorstman: None to declare

Vincent F.X. Deeney: None to declare

John M. Flynn receives personal fees from Biomet, other from Wolters Kluwer Health – Lippincott Williams & Wilkins, outside the submitted work. AAOS: Board or committee member American Board of Orthopaedic Surgery, Inc.: Board or committee member Orthopedics Today: Editorial or governing board Pediatric Orthopaedic Society of North America: Board or committee member Scoliosis Research Society: Board or committee member.

Donna M. McDonald-McGinn: None to declare

Moyo C. Kruyt: Receives a K2M research grant

René M. Castelein: Receives a K2M research grant and a small exploratory grant from the Scoliosis Research Society

Conflict of interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.03.024>.

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