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# Adults with 22q11.2 deletion syndrome have a different velopharyngeal anatomy with predisposition to velopharyngeal insufficiency

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## KEYWORDS

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**Summary** *Aim:* To find out if subjects with 22q11.2 deletion syndrome (DS) have a different velopharyngeal anatomy which could cause velopharyngeal insufficiency (VPI).

*Methods:* A prospective study of 16 subjects >16 years of age with 22q11.2 DS, without overt cleft palate and without previous VPI surgery, and 48 healthy controls >18 years of age were included in the study. Speech was recorded and scored blindly by two independent senior speech therapists. All 64 individuals had MRI scans, which were analyzed blindly by a consultant radiologist.

*Results:* Subjects with 22q11.2 DS had a mild degree of weak pressure consonants (mean score); borderline to mild degree of hypernasality and audible nasal emission (mean score). All controls had normal speech. When comparing subjects (22q11.2 DS) to controls, we found the subjects to have the following: A shorter distance between left and right points of origin of the levator veli palatini muscle (LVP) ( $p < 0.0001$ ); a more obtuse angle of origin of the LVP (bilaterally) ( $p < 0.009$ ); a thinner LVP bilaterally and in the midline ( $p < 0.0001$ ); a shorter LVP

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bilaterally ( $p < 0.0001$ ); a shorter velum ( $p = 0.007$ ); a larger osseous pharyngeal depth:velar length ratio ( $p = 0.01$ ); a more obtuse anterior cranial base angle (nasion to sella to basion) ( $p < 0.0001$ ) and posterior cranial base angle (sella to basion to foramen magnum) ( $p < 0.0001$ ); a wider velopharyngeal width ( $p = 0.002$ ) and a larger pharyngeal airway volume ( $p = 0.0007$ ). **Conclusion:** Compared with healthy controls, adults with 22q11.2 DS showed a different velopharyngeal anatomy, which will make these individuals more prone to VPI.

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## Background

The incidence of velopharyngeal insufficiency (VPI) in 22q11.2 deletion syndrome (22q11.2 DS) varies between 27 to 80%.<sup>1,2</sup> In one study 6/16 (37.5%) of cases of isolated VPI (i.e. without an overt cleft palate) had 22q11.2 deletions.<sup>3</sup> 22q11.2 deletion syndrome is the most common genetic cause of VPI.<sup>4</sup> The cause of VPI in 22q11.2 DS patients is complex and often multifactorial (Table 1).

## The levator veli palatini muscle

The levator veli palatini muscle (LVP) is the primary muscle responsible for velar elevation during speech and nonspeech activities such as swallowing.<sup>9</sup> The LVP originates from the lower surface of the petrous portion of the temporal bone. It descends along the inferior surface of the auditory tube and inserts into the midportion of the soft palate, where it blends with levator fibers from the opposite side.<sup>10</sup> The paired levator muscle bundles form a muscular sling to serve velar elevation. Sufficient muscle volume and position of insertion relative to the velum are crucial factors in determining velopharyngeal competence for speech and nonspeech activities.<sup>11,12</sup> Angles of LVP origin (relative to the base of the skull) allow evaluation of appropriate or inappropriate attachment of the muscle for velar function.

Magnetic resonance imaging (MRI) is the only current method that enables visualization of muscles in living subjects. But only two MRI studies have been performed on the levator muscle in 22q11.2 DS,<sup>4,13</sup> studying children. No previous MRI study of the velopharyngeal anatomy (excluding vascular studies) has included adult patients with the 22q11.2 DS.

## Speech

Severe speech disorders are among the most common features associated with the 22q11.2 DS. Systematic speech

errors have been reported.<sup>14-16</sup> Studies report a high percentage of glottal stops in the early speech production of children with 22q11.2 DS, and other cleft type speech characteristics are also common.<sup>14-18</sup>

Few studies have focused on speech in the adult 22q11.2 DS population. Knowledge in this area is therefore limited. Several studies have shown severe articulation problems in young children with the syndrome, but they also show improvement with increasing age.<sup>14,19,20</sup>

## Aim

The purpose of the study was to obtain more detailed anatomical information of the LVP and other relevant craniofacial measurements in adult subjects with the 22q11.2 DS and to compare them with controls, and thereby elucidate factors that can potentially contribute to the aetiology of VPI in these patients. Understanding the anatomy of the speech apparatus in the 22q11.2 DS could potentially bring an improvement in treatment or new treatment modalities. In addition, we wanted to find out the speech characteristics in adult patients with the syndrome, without overt cleft palate and who had not undergone previous VPI surgery.

## Subjects and methods

The Oslo University Hospital is a reference center for individuals diagnosed with 22q11.2 DS in Norway. Patients are almost always referred to the center after genetical diagnosis, not due to a single symptom. The reference center admits both children and adults. To this study we reviewed the registry and found 37 subjects above 16 years of age with 22q11.2 DS. Exclusion criteria for the study were moderate to severe psychiatric disease ( $n = 3$ ); cerebral palsy ( $n = 1$ ); overt cleft palate, previous VPI surgery, adenoidectomy and tonsillectomy ( $n = 11$ ). Subjects and controls who were included in the study were all Caucasians.

## Subjects

Twenty two subjects above 16 years of age with 22q11.2 DS were invited to participate in the study. Sixteen subjects agreed to inclusion (Table 2).

## Controls

Forty nine adult individuals, who were health care providers (physicians, nurses, secretaries and technicians) at the Oslo

**Table 1** Contributing factors to VPI in 22q11.2 DS.

- Adenoid hypoplasia<sup>5</sup>;
- Overt cleft palate and submucous cleft palate<sup>1</sup>;
- Vagus nerve (cranial nerve X) dysfunction<sup>6</sup>;
- Abnormal anatomy and function of the superior pharyngeal constrictor muscle<sup>7</sup>;
- Asymmetry of palate elevation<sup>8</sup>;
- Skull base morphology with tendency toward platybasia, as well as increased velopharyngeal width and a large pharyngeal airway.<sup>4</sup>

**Table 2** Demographic data of subjects and controls.

	Age (yrs)	Height (cm)	Weight (kg)	Male (n)	Female (n)
Subjects (n = 16)					
Mean	31.1	170.5	67.9	11	5
Max	62.5	182	99		
Min	17.6	151	45		
STDEV	15.9	8.6	16.1		
Controls (n = 48)					
Mean	41.1	175.4	73.5	24	24
Max	60.1	200	109		
Min	25.4	154	51		
STDEV	9.4	10.0	12.9		
	$p = 0.0033$	$p = 0.085^*$	$p = 0.16^*$		

\*The comparison in height and weight between subjects and controls has not been corrected for gender.

**Table 3** Speech Variables and Rating Scales for Perceptual Speech Analysis.

Hypernasal resonance/hyponasal resonance/audible nasal emission/weak pressure consonants

(0) = Not Present

(1) = Mild and Consistent

(2) = Moderate and Consistent

(3) = Severe and Consistent

University Hospital, were invited to participate in the study. One control had to be excluded due to abnormal findings in the pharynx on MRI. Forty eight healthy controls were finally included.

For achieving a normal gender cohort of the control group, an equivalent distribution of males and females were included.

### Speech protocol

In the present study, perceptual assessments were made according to the Swedish Articulation and Nasality Test, SVANTE.<sup>20</sup> The Norwegian version, which is phonetically balanced for the Norwegian language, was used in the present study (SVANTE-N). The test includes a word part, a sentence part and a spontaneous speech part, and is constructed to systematically assess articulation and nasal resonance deviation. Hypernasality, hyponasality, audible nasal emission and weak pressure consonants were scored on a four point scale (Table 3).

Audio-recordings were performed with the audio software Audacity (Dominic Mazzoni, [dominic@audacityteam.org](mailto:dominic@audacityteam.org)), soundcard Edirol UA-25 (Shizuoka, Japan). Microphone AKG c520 (Vienna, Austria) was used. Recordings were made in quiet rooms.

The recordings were independently scored by two calibrated senior speech therapists, specialized in cleft palate speech, and blinded to the individuals being subjects or controls.

### Protocol for palatal assessment

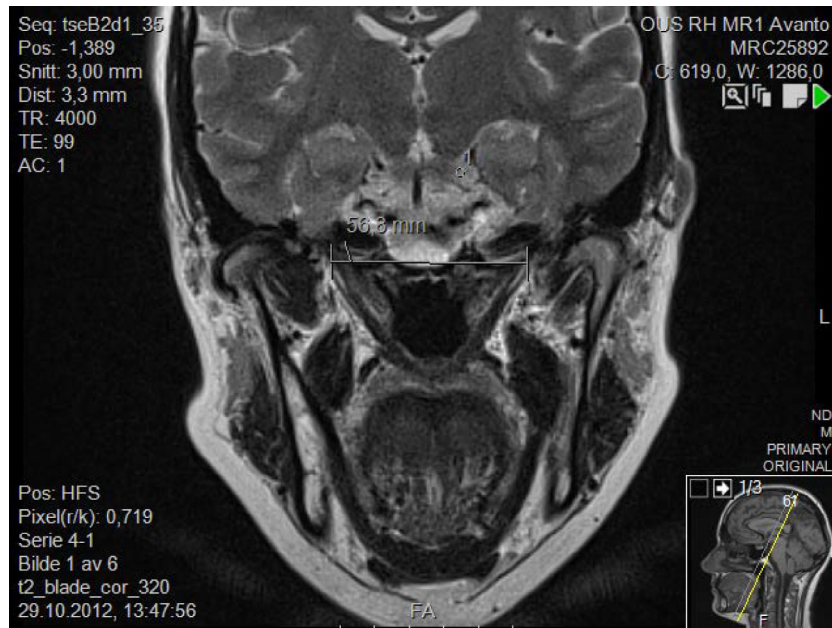
Oral examination was performed by the senior cleft surgeon (CF) and the movement of the pharyngeal wall and the soft palate was examined by oral inspection during phonation

/a/. The three cardinal signs of submucous cleft palate (SMCP) were evaluated; bifid uvula, midline notching at the posterior edge of the hard palate and separation of the soft palate musculature in the midline with intact mucosa. The palate was inspected for any other pathology.

### MRI protocol

A static (non-dynamic) MRI study was performed. The MRI session took 10–20 minutes to complete. All MRI examinations were performed with a 1.5 Tesla Avanto scanner (Magnetom Sonata, Siemens, Erlangen, Germany). A twelve channel head array coil was used with the subject/control in supine position. A sagittal T1 SPACE sequence, a coronal oblique T2 BLADE, and an axial T2 turbo spin echo sequence were used. Several measurements of the LVP were performed in the oblique coronal planes, similar to that described by Ha et al<sup>9</sup>: *The distance between the left and right points of origin of the LVP (Figure 1); the angle of origin (left and right sides) of the LVP (Figure 2); the length of the LVP (left and right sides) from the origin [on the inferior surface of the petrous temporal bone in front of the lower opening of the carotid canal] to the midpoint of the velum (Figure 3); the maximal thickness of the right, left and midpoint of the LVP (Figure 4).* In addition, the following craniofacial measures were analyzed: *Hard palate length* (anterior to posterior nasal spine); *osseous pharyngeal depth* (linear distance between the posterior nasal spine to the anterosuperior body of C1); *velar length* (posterior nasal spine to tip of velum, measured through the midline of the velum) (Figure 5); *osseous pharyngeal depth:velar length ratio*; *anterior cranial base angle* [nasion (the middle point of the frontonasal suture) to sella (the point at the center of the sella turcica) to basion (the midpoint of the anterior border of the foramen magnum)] (Figure 6); *posterior cranial base angle* (sella to basion to the midpoint of the posterior border of the foramen magnum) (Figure 7); *SNA* (angle between a line drawn from sella to nasion (SN) and the point of the deepest concavity of the anterior maxilla); *SNB* (angle between SN and the point of the deepest convexity of the anterior mandible); *palate width* (linear distance between the free gingival lingual margin of the posterior cusp of the 2nd molar tooth of one side to the same region on the contralateral side); *pharyngeal width* (distance between the innermost aspects of the lateral pharyngeal walls at the level of the anterior prominence of C1) (Figure 8); *cranial length* (measured in a straight

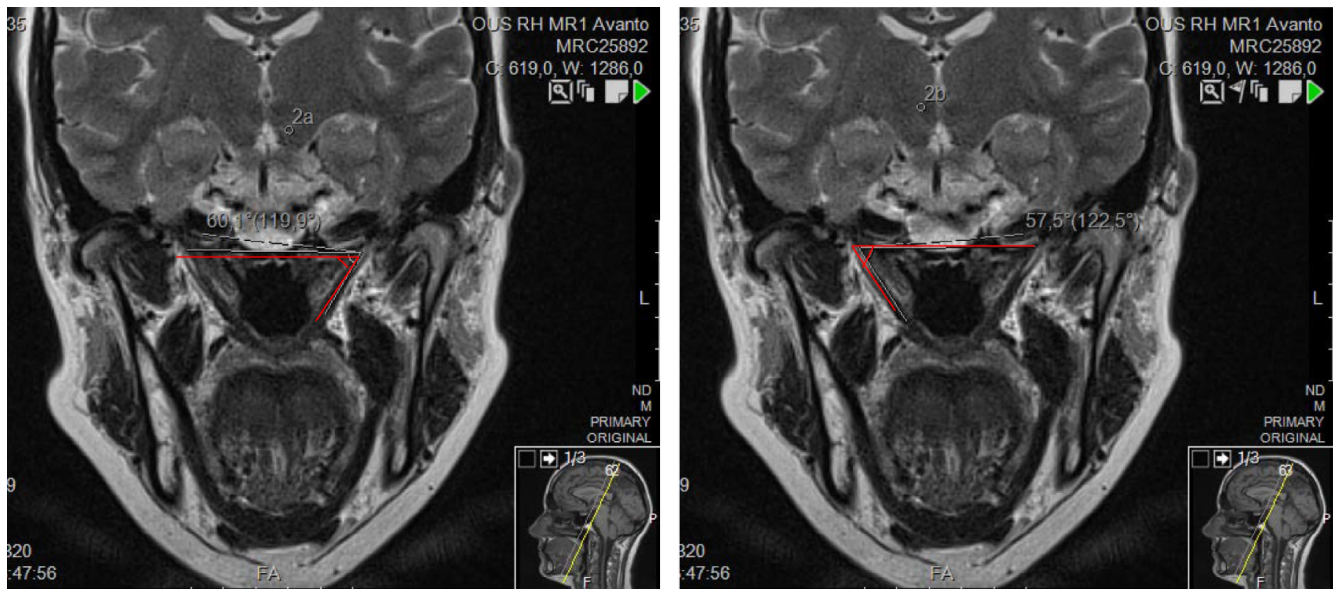
The distance between the left and right points of origin of the LVP is measured from its origin on the inferior surface of the petrous temporal bone on one side to the contralateral side.



**Figure 1** Distance between left and right points of origin of the levator veli palatini muscle (LVP).

Left side

Right side



**Figure 2** The angle of origin of the levator veli palatini muscle.

line from nasion to sella to occiput); *cranial width* (measured at a perpendicular line of that from nasion to sella to occiput); *pharyngeal airway volume* (anterior boundaries are the posterior border of the vomer, posterior nasal spine, soft palate, base of tongue, and anterior wall of pharynx; posterior boundary is the posterior pharyngeal wall; the lateral boundary is the lateral walls of the pharynx; the inferior boundary is a horizontal plane of the base of the epiglottis; the superior boundaries are the highest point of the nasopharynx, coinciding with the posterior choanae

and consistent with the anterior boundary) (**Figure 9**); *area of the choanae* at the posterior part of the nasal septum, measured parallel to the posterior part of the septum in an oblique angle (**Figure 10**).

A senior consultant radiologist (IA) did the measurements on a diagnostic workstation, Sectra (PACS IDS 5 11.4 P1, Sectra Imtec AB, Linköping, Sweden), except for the length of the LVP, the cranial width and the pharyngeal airway volume, which were measured on Toshiba Vitrea fx, version 6.7.1 (Vital Images, Minnesota, USA).



The length of the LVP (left and right sides) is measured from its origin on the inferior surface of the petrous temporal bone to the midpoint of the velum.

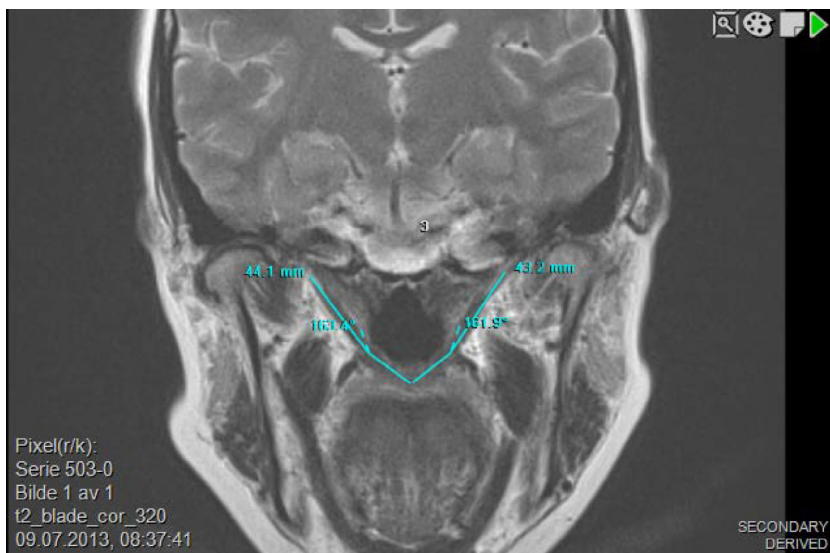
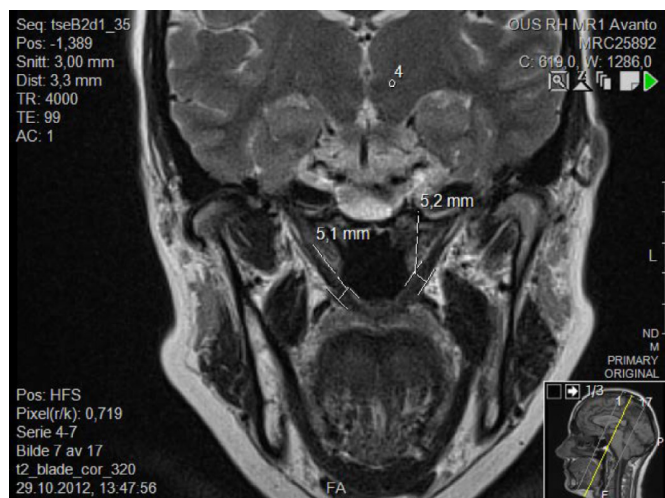


Figure 3 The length of the levator veli palatini muscle (LVP).

#### Thickness on right and left sides



#### Thickness in midline

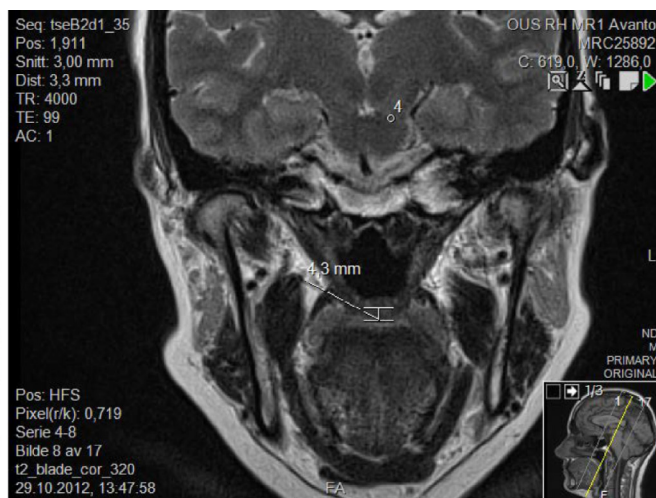


Figure 4 The maximal thickness of the levator veli palatini muscle.

### Statistical analysis

We conducted power and sample-size analysis based on 16 included subjects and assumptions of mean difference between subject and control groups expressed as Cohen's *d* effect size. Cohen's *d* effect size is the difference between two means divided by the standard deviation of the data, where Cohen's *d* of 0.2, 0.5 or 0.8 corresponds to small, medium or large effect size, respectively. We estimated the number of controls necessary to detect a Cohen's *d* effect size of 0.8 with 80% statistical power, because we wanted a study able to at least statistically detect major differences between subject and controls. It was found sufficient with three times as many controls as subject, i.e. 16 subjects and 48 controls, in our study.

The means from the two speech therapists' perceptual scorings of each patient are reported.

The unpaired t-test was used to compare data on craniofacial measurements between subjects and controls. *P*-values < 0.05 were considered to be significant. All statistical analysis was performed using GraphPad software 2016, Inc., La Jolla, CA, USA.

### Results

The subjects (22q11.2 DS) were significantly younger than the controls (Table 2). Even though the subjects consisted predominantly of males (68.8%) compared to the controls (50%), their body height showed a trend (non-significant) of being shorter ( $p = 0.09$ ).

Velar length is measured from the posterior nasal spine (PNS) to the tip of the velum.

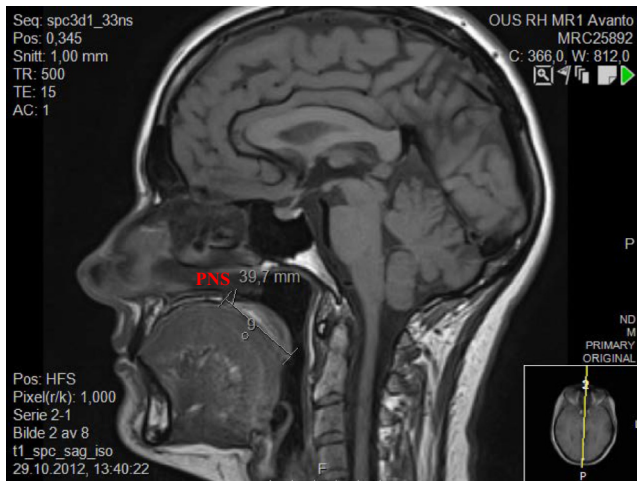


Figure 5 Velar length.

The angle between the nasion (N) to sella (S) to basion (B) points.

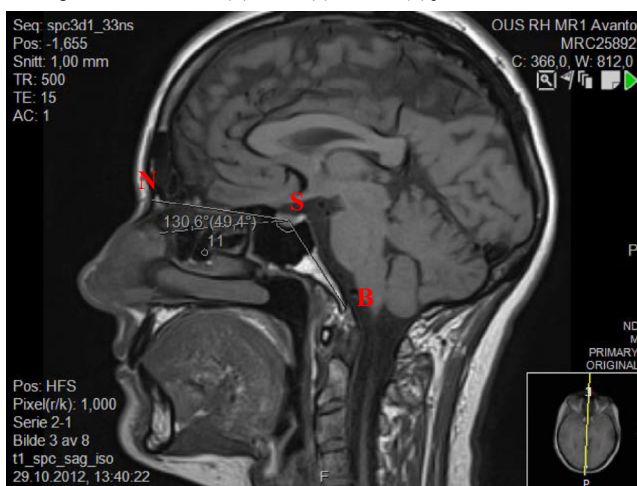


Figure 6 Anterior cranial base angle.

## Speech

Subjects with 22q11.2 DS had a mild degree of weak pressure consonants; borderline to mild degree of hypernasality and audible nasal emission (mean scores), as illustrated in Table 4. Only three of 16 subjects (18.8%) had normal scores in spontaneous speech.

All controls had normal speech.

## Palatal assessment

Palatal assessment revealed a palpable notch in the midline of the posterior end of the hard palate in six of 16 subjects (37.5%) compared to seven of 48 controls (14.6%). The size of the notch was minimal [grade 1]<sup>21</sup> in all cases, except in one subject in whom the notch was of moderate size [grade 2].<sup>21</sup> None of the controls had a visible separation of the LVP compared to one of the subjects (6.3%), who had a small diastasis of the LVP and also a minimal notch. This subject

The angle between the sella (S) to basion (B) to the midpoint of the posterior border of the foramen magnum (F).

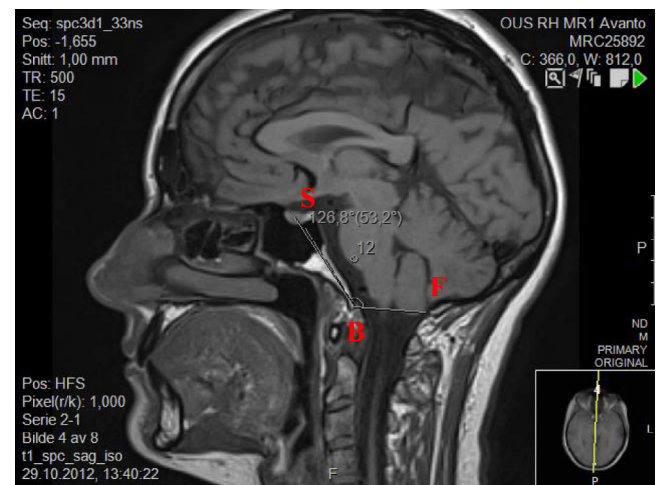


Figure 7 Posterior cranial base angle.

fulfilled our requirements for an occult SMCP diagnosis. His perceptual speech evaluation revealed a borderline degree of weak pressure consonants and no other speech deviations.

Neither controls nor subjects had a bifid uvula.

None of the controls had an asymmetrical elevation of the velum compared to three of the subjects (18.8%). In addition, one of 16 subjects (6.3%) had a severe asymmetry of the posterior nasal spine and median palatine suture, displaced to one side.

Seven of 16 subjects (43.8%) had normal findings on palatal assessment compared to 41 of 48 controls (85.4%).

## MRI

When comparing subjects (22q11.2 DS) to controls (Tables 5 and 6), we found the subjects to have the following differences: A shorter distance between left and right points of origin of the LVP ( $p < 0.0001$ ); a more obtuse (larger) angle of origin of the LVP (left and right side) ( $p < 0.009$ ); a thinner LVP (left and right side) and in the midline ( $p < 0.0001$ ); a shorter velum ( $p = 0.007$ ); a shorter LVP muscle (left and right side) ( $p < 0.0001$ ); a larger osseous pharyngeal depth:velar length ratio ( $p = 0.01$ ); a more obtuse anterior cranial base angle ( $p < 0.0001$ ) and posterior cranial base angle ( $p < 0.0001$ ); a wider pharyngeal width ( $p = 0.002$ ); a shorter cranial length ( $p = 0.03$ ) and a larger pharyngeal airway volume ( $p = 0.0007$ ).

The area of the choanae showed a trend towards being larger in the syndromic group ( $p = 0.09$ ).

The hard palate length; the osseous pharyngeal depth; the SNA; the SNB; the palate width; and the cranial width were **not** significantly different between the two groups ( $p > 0.17$ ).

## Discussion

This study has added anatomical information to explain the complex aetiology of VPI in patients with 22q11.2 DS.

Pharyngeal width is the distance between the innermost aspects of the lateral pharyngeal walls at the level of the anterior prominence of C1.

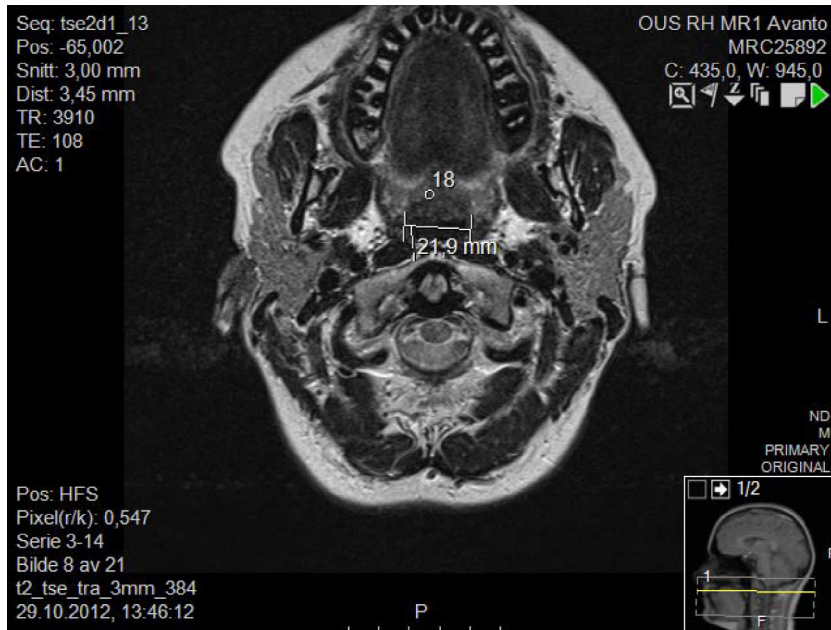


Figure 8 Pharyngeal width.

A 3-D reconstruction of the pharyngeal airway volume.

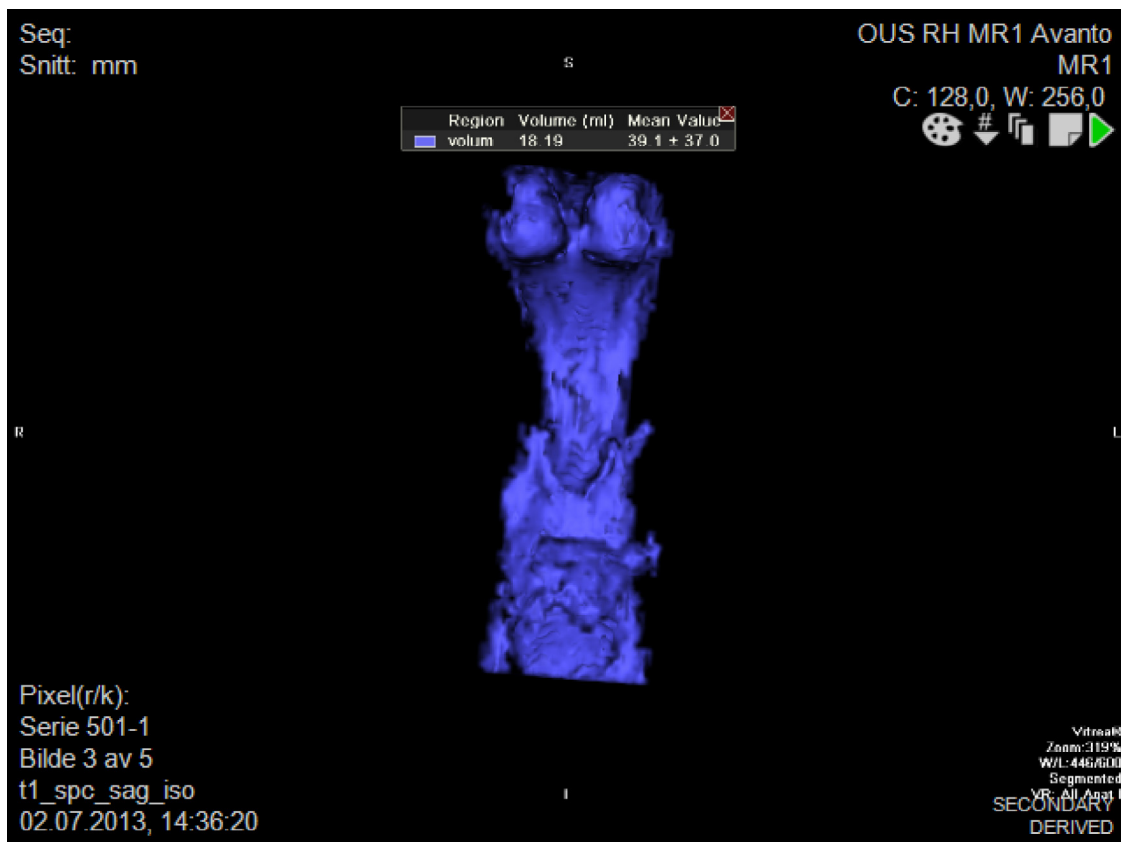


Figure 9 Pharyngeal airway volume.



The area of the choanae is measured parallel to the posterior part of the septum in an oblique angle.

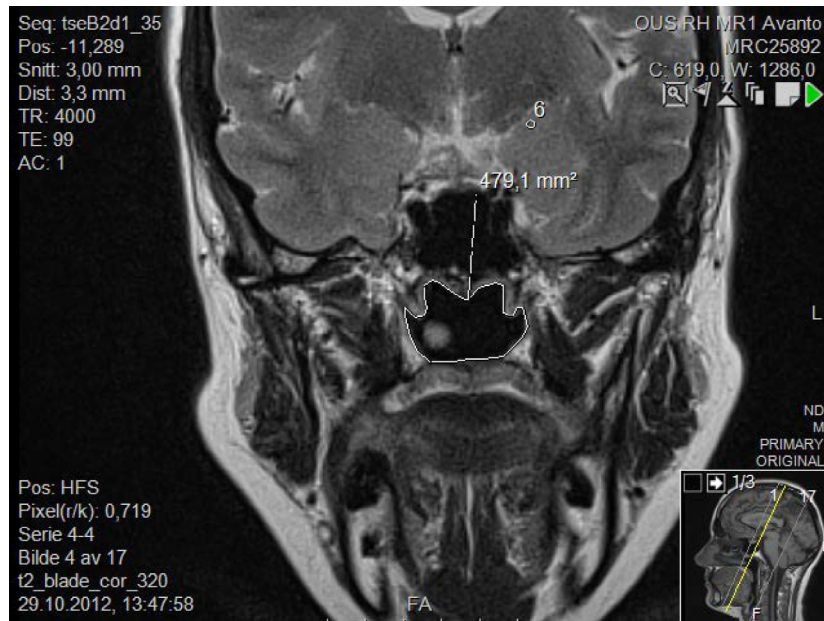


Figure 10 Area of the choanae.

Table 4 Perceptual speech analysis of audio recordings from subjects on a 4 point scale (0–3).

	Hypernasality	Hyponasality	Audible nasal emission	Weak pressure consonants
Single Words				
Mean	0.5	0.1	0.3	1.1
Max	2.0	0.5	2.0	3.0
Min	0.0	0.0	0.0	0.0
SD	0.8	0.2	0.6	1.0
Sentences				
Mean	0.5	0.1	0.4	1.2
Max	2.0	0.5	2.0	3.0
Min	0.0	0.0	0.0	0.0
SD	0.8	0.2	0.7	1.0
Spontaneous Speech				
Mean	0.5	0.1	0.4	1.2
Max	2.0	0.5	2.0	3.0
Min	0.0	0.0	0.0	0.0
SD	0.7	0.2	0.7	1.0

## Speech

Subjects with the 22q11.2 DS had a mild degree of weak pressure consonants, borderline to mild degree of hypernasality and audible nasal emission (mean scores). One of the main characteristics of the syndrome is muscular hypotonia,<sup>20</sup> which will most likely be related to the anatomical findings of the LVP in this study. Weak pressure consonants in particular seem to be caused by hypotonic musculature and have been previously described in the adult population with the 22q11.2 DS.<sup>15,16</sup>

Over 80% of our subjects had speech deviations in spontaneous speech. This is interesting, as none of the subjects in the study had an overt cleft palate or had had previous VPI surgery.

All controls had normal speech.

## Palatal assessment

Unexpectedly, palatal assessment revealed a small palpable notch in the posterior end of the hard palate in seven of 48 healthy controls (14.6%). However, this did not affect their speech and is not considered to be part of an undiagnosed SMCP. Hence, a small palpable notch as an isolated finding is probably of little clinical importance. The prevalence of a palpable notch in the posterior part of the hard palate in the Caucasian population is unknown and warrants further study. The finding was more frequent in the syndromic group (37.5%) and is likely to be part of the syndrome, as palatal anomalies have been reported in 69% of 181 cases with the 22q11.2 DS.<sup>1</sup> In our study, nine of 16 (56%) subjects had a palatal anomaly on oral examination. However in our study individuals with



**Table 5** Measurements of the levator veli palatini muscle (LVP).

	Distance between left and right points of origin of LVP (mm)	Angle of origin left side of LVP	Angle of origin right side of LVP	Length of LVP, left side (mm)	Length of LVP, right side (mm)	Maximal thickness of left LVP (mm)	Maximal thickness of right LVP (mm)	Maximal thickness of LVP in midline (mm)
<b>Subjects</b>								
Mean	45.1	67.3	69.0	37.5	37.8	3.2	3.4	1.4
Max	54.0	77.0	82.2	44.4	47.9	5.8	5.8	5.0
Min	37.5	49.0	51.4	28.4	26.7	2.0	2.0	0.0
STDEV	4.7	8.0	10.5	4.2	5.8	1.1	0.9	1.4
<b>Controls</b>								
Mean	54.6	62.4	61.7	45.3	45.5	4.7	4.7	3.9
Max	66.3	88.0	84.8	55.8	56.6	6.4	6.2	5.8
Min	44.6	54.6	52.4	33.1	33.9	3.2	3.0	2.2
STDEV	4.7	5.6	5.2	4.7	4.5	0.7	0.7	1.0
	$p < 0.0001$	$p = 0.0087$	$p = 0.0005$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$

overt cleft palate and previous VPI surgery were excluded. Therefore the frequency of such anomalies is expected to be significantly higher in the population with 22q11.2 DS as a whole.

One subject with a minimal notch of the hard palate and a small diastasis of the LVP, fulfilled our requirements for an occult SMCP diagnosis. As expected with an occult SMCP his speech revealed only a borderline speech deviation.

## MRI

There is no previous study on adults with the 22q11.2 DS to compare our data with. Comparison to previous studies with related measurements is presented in Table 7. It is important to note that variables may be measured differently in different studies, which does not allow for a uniform comparison between studies.

When comparing subjects (22q11.2 DS) to controls in our study, we found the subjects to have multiple anatomical differences that would increase their risk of VPI. Perhaps the most important factors were those related to the LVP. The individuals with the 22q11.2 DS had significantly shorter and thinner LVPs. Park et al<sup>13</sup> conducted a prospective study, which included 17 children with the 22q11.2 DS and nine children with nonsyndromic SMCP. Children with nonsyndromic SMCP had a significantly thicker LVP compared to patients with 22q11.2 DS ( $p < 0.001$ ). In addition, the subjects in our study had a significantly larger angle of origin of the LVP, bilaterally. Its importance is not fully understood, but can at least partially be explained by the fact that the distance between left and right points of origin of the LVP was significantly shorter. Kuehn et al<sup>31</sup> used MRI to image the levator muscle before and after primary palatoplasty. It was noted that by dissecting the levator fibres from the hard palate and releasing the anterolateral attachments in the region of the pterygoid hamuli, the course of the muscle will be rendered steeper relative to its origin at the base of the skull, which was described to be a "likely" favorable outcome in improving the leverage for velar elevation.

The authors also mention using MRI as a prognostic indicator before surgery. Ha et al<sup>9</sup> described how a large angle of origin indicates a more vertical course and therefore a more lateral insertion into the soft palate; as such, the points of application of force may not be optimal for elevating the soft palate. That is, a more medial, centralized application of force would appear to be more effective in elevating the bulk of the soft palate toward the posterior pharyngeal wall.

Our subjects also had other craniofacial differences that may increase their risk of VPI. These included a significantly wider pharyngeal width (but with no significant difference in palate width); a significantly larger pharyngeal airway volume; a significantly larger osseous pharyngeal depth:velar length ratio with a significantly shorter velum (but with no significant difference in the osseous pharyngeal depth). In addition, a significantly more obtuse anterior and posterior cranial base angle may also increase the risk of VPI, as these angles will affect the positioning of the overlying soft tissue, and hence the angle of the posterior pharyngeal wall. A more obtuse anterior and posterior cranial base angle will most likely be associated with a more obtuse posterior pharyngeal wall and an increase in the "need ratio" for velopharyngeal closure. Ruotolo et al<sup>4</sup> did a retrospective study on five children with the 22q11.2 DS, and compared these to a control population consisting of 123 unaffected patients, who had undergone MRI for reasons other than VPI assessment. In parallel to our study, it was found that the syndromic patients have a significantly larger osseous pharyngeal depth:velar length ratio ( $p < 0.04$ ); a non-significant difference in the osseous pharyngeal depth ( $p = 0.10$ ); a significantly more obtuse anterior and posterior cranial base angle ( $p < 0.001$ ); a significantly wider pharyngeal width ( $p < 0.001$ ); and a significantly larger pharyngeal airway volume ( $p < 0.001$ ). Different from our study, Ruotolo et al found no significant difference in the velar length ( $p = 0.47$ ), but a significantly shorter hard palate length in patients with the 22q11.2 DS ( $p = 0.007$ ). Ruotolo et al described how patients with the 22q11.2 DS demonstrated platybasia, along with changes in angulation of the upper cervical spine, deepening of the velopharynx and increase in the velar "need ratio" in affected patients.

**Table 6** Craniofacial measurements.

	Hard palate length (ant. to post. nasal spine) (mm)	Osseous pharyngeal depth (post. nasal spine to body of C1) (mm)	Osseous pharyngeal depth:velar length ratio	Velar length (post. nasal spine to tip of velum) (mm)	Anterior cranial base angle (nasion to sella basion)	Posterior cranial base angle (sella to basion to foramen magnum)	SNA angle (sella to nasion to deepest concavity of ant. Maxilla)	SNB angle (sella to nasion to deepest convexity of the ant. Mandible)	Palate width (right to left margin of 2nd molar teeth) (mm)	Velopharyngeal width (innermost aspects of lateral pharyngeal walls) (mm)	Cranial length (nasion to sella to occiput) (mm)	Cranial width (mm)	Pharyngeal airway volume (cm <sup>3</sup> )	Area of the choanae (mm <sup>2</sup> )
<b>Subjects</b>														
Mean	49.6	33.5	1.0	33.4	136.7	141.1	87.3	83.7	35.4	22.9	171.7	134.9	19.5	477.3
Max	56.1	38.6	1.3	50.8	157.5	165.4	97.4	96.3	39.5	33.9	187.3	142.9	29.5	684.2
Min	42.8	26.0	0.7	24.8	119.6	114.6	79.0	75.8	31.2	9.8	156.7	126.2	10.68	347.9
STDEV	4.0	3.8	0.2	6.9	11.6	13.3	4.9	5.4	2.9	6.8	8.7	4.1	5.3	99.7
<b>Controls</b>														
Mean	49.5	32.9	0.9	37.5	126.8	128.6	86.6	83.6	34.8	18.2	177.9	137.1	15.2	434.0
Max	58.0	45.5	1.2	45.8	136.6	155.9	94.7	92.6	41.6	30.6	197.2	155.5	27.0	714.2
Min	40.1	25.5	0.7	28.3	118.4	116.8	77.1	72.8	29.0	10.4	156.5	125.5	9.15	296.8
STDEV	4.7	4.0	0.1	4.4	4.4	7.3	4.1	3.9	2.6	4.2	9.8	5.9	3.7	83.5
	<i>p</i> = 0.94	<i>p</i> = 0.61	<i>p</i> = 0.011	<i>p</i> = 0.0073	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> = 0.58	<i>p</i> = 0.94	<i>p</i> = 0.44	<i>p</i> = 0.0017	<i>p</i> = 0.028	<i>p</i> = 0.18	<i>p</i> = 0.0007	<i>p</i> = 0.092

**Table 7** Summary of related measurement from previous studies.

	Current study				Ruotolo et al, 2006 <sup>4</sup>						Park et al, 2015 <sup>13</sup>			Butterfield et al, 2015 <sup>28</sup>	Perry et al, 2016 <sup>29</sup>	Jordan et al, 2017 <sup>30</sup>
	Subjects	Controls	Violaris et al, 1994 <sup>22</sup>	Ettema et al, 2002 <sup>23</sup>	Subjects	Controls	Ha et al, 2007 <sup>9</sup>	Bae et al, 2011 <sup>24</sup>	Perry et al, 2014 <sup>25</sup>	Perry et al, 2014 <sup>26</sup>	Perri et al, 2014 <sup>27</sup>	Subjects	Controls			
	16 subjects with 22q11.2 DS 11 male + 5 female Caucasian	48 healthy adults 24 female + 24 male Caucasian	70 adult patients 38 females + 32 males investigated for cranial pathology Ethnicity not specified	10 healthy adults 5 female + 5 male Caucasian	5 children with 22q11.2 DS Age 2 to 7 years 3 girls + 2 boys Ethnicity not specified	123 children without a history of VPI Age 4 to 7 74 boys + 49 girls Ethnicity not specified	4 adult male with repaired cleft palate 3 Caucasian + 1 Hispanic	10 healthy adults 5 female + 5 male Caucasian	10 healthy adult male Caucasian	30 healthy adults 15 female + 15 male Caucasian	85 healthy adults 49 female + 36 male Caucasian	17 children with 22q11.2 DS Age 4 to 9 years 9 boys + 8 girls Ethnicity not specified	9 children Nonsyndromic SMCP Age 4 to 13 years 8 boys + 1 girl Ethnicity not specified	12 adults with class I or II occlusion 6 female + 6 male Ethnicity not specified	30 healthy adults 15 female + 15 male Caucasian Ethnicity not specified	38 healthy adults 18 female + 20 male Ethnicity not specified
	Mean values															
Distance between left and right points of origin of LVP (mm)	45.1	54.6		53.6			53	53.1		56.3						
Angle of origin, right and left side combined (°)	68.2	62.1		62.5			65	58		58						
Length of LVP, left and right side combined (mm)	37.7	45.4		45.3			41	42.5		46.2						
Maximal thickness of LVP, left and right side combined (mm)	3.3	4.7					3.8				2.1	3.7				
Hard palate length (ant. to post. nasal spine) (mm)	49.6	49.5			38.5	43.6		52.4	60.6	59.8						
Osseous pharyngeal depth (post. nasal spine to ant. body of C1) (mm)	33.5	32.9			36.8	33.8										
Osseous pharyngeal depth:velar length ratio	1.0	0.9			1.3	1.2										
Velar length (post. nasal spine to tip of velum) (mm)	33.4	37.5			28.1	29.3		33.6	37.6							36.1
Anterior cranial base angle (nasion to sella to basion) (°)	136.7	126.8			144.8	131.6									126.5	
Posterior cranial base angle (sella to basion to foramen magnum) (°)	141.1	128.6			162.6	136.9										
Palate width (right to left margin of 2nd molar teeth) (mm)	35.4	34.8						38.9	37							
Velopharyngeal width (innermost aspects of lateral pharyngeal walls) (mm)	22.9	18.2			21.1	13.6										19.7
Cranial width (mm)	134.9	137.1									136.8					
Pharyngeal airway volume (cm <sup>3</sup> )	19.5	15.2			6.9	2.9								13.5		
Area of the choanae (mm <sup>2</sup> )	477.3	434.0	540													

Values for right and left muscle measures are averaged to provide comparison to other studies. Averaged values for men and women are reported.



Obstructive sleep apnoea (OSA) is not commonly seen in patients with the 22q11.2 DS after a superiorly based pharyngeal flap.<sup>32</sup> A significantly larger pharyngeal airway volume will reduce the chance of OSA in these patients. Also, the area of the choanae showed a trend of being larger in the syndromic group ( $p = 0.092$ ). However, the advantage of a larger pharyngeal airway volume may be diminished by the fact that these patients often have a degree of muscular hypotonia.

Although the cranial width was not significantly different, the cranial length was significantly shorter in our syndromic subjects ( $p = 0.03$ ), which may imply a different cerebral volume. The latter may or may not be associated with muscular hypotonia, which needs further study.

The SNA and SNB angles were not significantly different between the two groups in our study ( $p > 0.43$ ). Cleft palate patients who undergo maxillary advancement achieve an increase in the SNA angle. Pereira et al<sup>33</sup> concluded from a systematic review that there is conflicting evidence on the impact on resonance, nasalance and velopharyngeal function and urged for further research.

### Other findings

Even though the subjects group consisted predominantly of males (68.8%) compared to the control group (50%), their body height showed a trend (non-significant) of being shorter ( $p = 0.09$ ). In a study by Tarquinio et al,<sup>34</sup> adult height was significantly lower in 22q11.2 DS compared to the normal population.

### Surgical implications

Our findings of a thinner and shorter LVP in subjects with the 22q11.2 DS suggest that the chance of an efficient intravelar veloplasty is reduced, as the LVP is known to be the main workforce for velar elevation during speech. A significantly wider pharyngeal width means a larger pharyngeal opening to close by an already significantly shorter velum, which also reduces the chance of a successful intravelar veloplasty. However, one cannot conclude to say that an intravelar veloplasty would be in vain in these patients, as cleft palate patients without the 22q11.2 DS are also known to have hypoplastic LVPs<sup>35</sup> and still achieve excellent speech results.<sup>36</sup> In the case of an SMCP with diastasis of the LVP in the 22q11.2 DS patient, it seems likely that an intravelar veloplasty would improve the angle of origin of the levator by becoming steeper. In addition, retropositioning of the LVP should also increase its leverage for velar elevation. Our findings may, at least in theory, favour a surgical treatment that not only corrects the positioning of the LVP in SMCP and cleft palate, but also produces lengthening of a shorter velum in the 22q11.2 DS patients. Mehendale et al<sup>37</sup> found 11 of 25 patients (44%) with the 22q11.2 DS, who had undergone a radical intravelar veloplasty, subsequently required further VPI surgery. In a systematic review by Spruijt et al,<sup>38</sup> it was concluded that based on outcomes research (level 2c evidence) and poor quality cohort studies (level 4 evidence), a Grade C recommendation could be made to minimize the morbidity of further surgery for patients with 22q11.2 DS

and VPI, by choosing to perform a pharyngoplasty directly. Only performing a palatoplasty resulted in a greater need for further surgery. However, higher level evidence is needed to confirm or refute these findings.

One should be extremely cautious when considering patients with the 22q11.2 DS for fat transplantation to the posterior pharyngeal wall,<sup>39,40</sup> as an estimated 49–55% of these patients are reported to have a medial deviation of at least one internal carotid artery,<sup>41</sup> which may put these patients at increased risk of fat embolism.

### Weaknesses of the study

A weakness of the study is the selection of the control group consisting of health care providers, which may introduce selection bias, as such a cohort most often represents individuals from social class I and II. Another weakness is the small number of subjects studied, which may not be representative for the adult population with the 22q11.2 DS.

There was a larger proportion of male in the subject group (68.8%) compared to the control group (50%). This disproportion will most likely underestimate some of the differences between the two groups. In a study by Perry et al,<sup>29</sup> LVP muscle measures varied significantly based on sex. Compared with women, men demonstrated a significantly longer levator muscle and a significantly larger distance between the muscle origins at the skull base.

### Conclusions

Adults with the 22q11.2 DS showed a significantly different velopharyngeal anatomy, which will make these individuals more prone to VPI.

### Ethical approval

The study was approved by the Regional Ethics Committee of South-Eastern Norway; reference 2010/3004.

### Conflict of interest

None.

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