Special Article

Assessment of Chromosome 22q11.2 Deletion in Patients with Isolated Cleft Palate: A Systematic Review of Prospective Studies

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Background: *The prevalence of 22q11.2 deletion in patients presenting with isolated cleft palate has not been systematically assessed.*
Objective: *To assess the evidence in the literature for the prevalence of 22q11.2 deletion in patients who were presenting with isolated cleft palate.*
Material and Method: *A systematic literature search was conducted through PubMed between 1992 and June 2016 using search terms of 22q11.2 deletion OR 22q11 deletion AND cleft palate.*
Results: *Of the six prospective studies reported, 328 patients with isolated cleft palate had been screened with FISH (Fluorescence In Situ Hybridization) test for 22q11.2 deletion. Among the 328 patients, there was one (0.3%) patient with positive FISH test for 22q11.2 deletion. This patient was clinically assessed and did not have an associated malformation or clinically recognized syndrome.*
Conclusion: *The prevalence of 22q11.2 deletion among patients with isolated cleft palate is rather low. Of more than 400 genetic disorders involving occurrences of isolated cleft palate, FISH testing for 22q11.2 deletion in a patient with isolated cleft palate is recommended on clinical suspicion of additional clinical presentations of 22q11.2 deletion syndrome such as conotruncal congenital heart diseases, dysmorphic facies, velopharyngeal insufficiencies, immune deficiencies, hypoparathyroidisms, and neuropsychiatric disorders.*

Keywords: *22q11.2 deletion syndrome, Cardiovascular malformation, Congenital heart disease, Cleft palate, FISH test, Gene*

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Cleft palate is a congenital anomaly resulting in malformation of the palate and it is categorized under orofacial clefts[1,2]. Generally, orofacial clefts are divided into cleft palate (CP), cleft lip (CL), and cleft lip with cleft palate (CLP)[1,2]. Cleft palate is predominantly in females. Among orofacial clefts, the occurrence of associated malformations or syndromes is higher in patients with cleft palate and lower in those with cleft lip[1-4]. The reported prevalence of isolated cleft palate were 0.13 to 2.53 cases per 1,000 live births and were recorded to have associations with more than 400 genetic and syndromic disorders[1,2].

Isolated cleft palate is found in 9 to 11% among patients with chromosome 22q11.2 deletion syndrome of which has classic clinical presentations of cardiovascular malformations, dysmorphic facies, palatal abnormalities (including cleft palate), immune deficiencies, hypoparathyroidism, and neuropsychiatric disorders[5-14].

FISH (Fluorescence In Situ Hybridization) has been used as a diagnostic test of this deletion syndrome[6,9]. The genetic name of 22q11.2 deletion syndrome is preferable to former syndromic names like absent thymus[15], Sedlackova[16], DiGeorge[17], cardiofacial[18], conotruncal anomaly face[19], velocardiofacial (Shprintzen)[20], CATCH 22 (Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcemia with chromosome 22 deletion)[21], and autosomal dominant Opitz G/BBB[22] syndromes.

The 22q11.2 deletion syndrome is one of

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the most common multiple anomaly syndromes with a prevalence of approximately one case per 4,000 live births[5-14]. Clinical management of this syndrome depends on various comorbidities such as congenital heart disease, immune disorders, feeding problems, palatal abnormalities (including cleft palate), developmental and learning disorders, and psychiatric disorders[5-14].

Although there are considerable data on the frequency of 22q11.2 deletion in patients with cardiovascular malformations or congenital heart diseases[5-14], there are very few studies with small numbers of patients examining the frequency of the 22q11.2 deletion in patients with isolated cleft palate[23-28]. This study therefore aimed to identify the frequency of the 22q11.2 deletion in patients with isolated cleft palate worldwide.

Material and Method

Data sources

FISH test has been routinely used to identify the chromosome 22q11.2 deletion syndrome since 1992[6,9]. A systematic literature search was conducted using electronic databases through the PubMed between 1992 and June 2016 using key words and search terms of 22q11.2 deletion OR 22q11 deletion AND cleft palate. The eligible papers in all languages were included and searched. The titles and abstracts of the 188 relevant articles were screened independently by two authors (V.P. and M.P.) to identify potentially relevant articles for which full text publications were retrieved. Reference lists of included papers were screened for additional relevant papers that might have been missed in the database search according to the method previously described[3,4].

Definitions

The diagnosis of the chromosome 22q11.2 deletion syndrome in this present study was confirmed by FISH, or Polymerase Chain Reaction (PCR) analysis.

Study selection

The present review included prospective reports on prevalence of 22q11.2 deletion in cohorts of patients with isolated cleft palate. The authors excluded studies limited to clinical features, case reports without a mention of the 22q11.2 deletion, and retrospective studies. Two authors (V.P. and M.P.) performed the search independently using these inclusion and exclusion criteria. Disagreements were resolved by discussion.

When a study was eligible for inclusion, two authors (V.P. and M.P.) independently verified the data to check for accuracy.

Data extraction

Using a standardized data extraction form, data on locations, number of patients with isolated cleft palate, number of patients with 22q11.2 deletion, were extracted.

Quality assessment

Studies were assessed on completeness of data and origins of the data.

Statistical analysis

Prevalence rates were presented with percentage.

Results

The search combination in the databases identified 188 relevant articles. A through evaluation of these articles using the inclusion and exclusion criteria led to the exclusion of 179 articles leaving nine papers that met the inclusion criteria. Of the nine papers remained, after critical review of the full text, four papers were excluded due to retrospective data. After the full paper review, five papers of which contained relevant data. Of these papers, one additional paper was found after reference checking. This additional paper was not initially retrieved by the original search because it was not indexed in the searched database. Thus, six papers were eligible for this systematic review (Fig. 1).

There were six prospective studies reporting the frequency of 22q11.2 deletion in patients with isolated cleft palate[23-30]. Three hundred twenty eight patients with isolated cleft palate were included in this present review, one of whom had positive FISH test for 22q11.2 deletion. This patient was clinically assessed and did not have an associated malformation or syndrome. The present study revealed that the prevalence of 22q11.2 deletion in patient with isolated cleft palate was relatively low (0.3%) (Table 1).

Discussion

Based on the six studies[23-28] included in this present review, there were 328 patients with isolated cleft palate. Only one of these patients had a positive FISH test for 22q11.2 deletion. This patient was clinically assessed and did not have an associated malformation or syndrome. Therefore, this study revealed that the prevalence of 22q11.2 deletion in patient with isolated

cleft palate was relatively low (0.3%). The present study supports the recommendation that routine FISH testing for 22q11.2 deletions in all patients with isolated cleft palate is not recommended[23-28].

At the fourth week of embryologic development, neural crest cells migrate and form tissues of the pharyngeal arch systems, including parts of the palate/pharynx, aortic arch and its branches, cardiac outflow tract, thymus, and parathyroid gland. The separation of nasal and oral cavity development occurs around the sixth or seventh week of development.

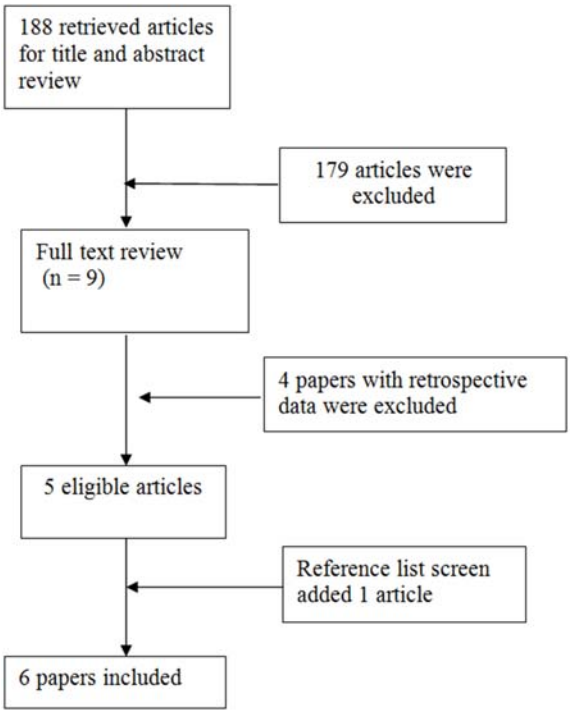

Fig. 1 Overview of included studies.

Later, palatal cell differentiates into bony and muscular parts of the hard and soft palate. The fusion processes of the palate are complete by the 10th week of embryogenesis[1,2]. However, the important developmental gene, *TBX1*, which is thought to be responsible for many associated features of 22q11.2 deletion syndrome such as congenital heart defects and palatal defects, is not a major risk factor for isolated cleft palate[29]. Over 400 genetic disorders which isolated cleft palate occurs have been reported and studies have suggested that many candidate genes may be responsible[1,2,29].

Patients with isolated cleft palate, who show additional clinical presentations of 22q11.2 deletion syndrome such as velopharyngeal insufficiencies (nasal reflux of fluid during swallowing, hypernasality during speech, and submucous cleft palate), conotruncal congenital heart disease, dysmorphic facies, mental retardation, and psychiatric disorder, should be checked with FISH testing for 22q11.2 deletion[30,31].

Young patients with isolated cleft palate should be followed-up because of the additional feature of 22q11.2 deletion such as learning disability or psychiatric problem. Whenever, if there is a clinical suspicion, a 22q11.2 deletion need to be identified[30,31].

Conclusion

The prevalence of 22q11 deletion among patients with isolated cleft palate is rather low. FISH testing for 22q11.2 deletion in a patient with isolated cleft palate is recommended on clinical suspicion of additional clinical presentations of 22q11.2 deletion syndrome such as velopharyngeal insufficiencies (nasal reflux of fluid during swallowing, hypernasality during speech, and submucous cleft palate),

Table 1. FISH (Fluorescence In Situ Hybridization) test for 22q11.2 deletion assessment in patients with isolated cleft palate

Study (year)	Country	Number of patients with cleft palate	Number of patients with positive FISH test (%)
Prabodha et al (2012)[23]	Sri Lanka	162	0 (0.0)
Barisic et al (2008)[24]	Croatia	58	0 (0.0)
Reish et al (2003)[25]	Israel	9	0 (0.0)
Ruiter et al (2003)[26]	Netherlands	45	1 (2.2)
Mingarelli et al (1996)[27]	Italy	38	0 (0.0)
Driscoll et al (1995)[28]	United States	16	0 (0.0)
Total	Worldwide	328	0 (0.3)

FISH = Fluorescence In Situ Hybridization

conotruncal congenital heart disease, dysmorphic facies, mental retardation, and psychiatric disorder.

What is already known on this topic?

The prevalence of 22q11.2 deletion among patients with isolated cleft palate is rather low.

What this study adds?

FISH testing for 22q11.2 deletion in a patient with isolated cleft palate is recommended on clinical suspicion of additional clinical presentations of 22q11.2 deletion syndrome such as velopharyngeal insufficiencies (nasal reflux of fluid during swallowing, hypernasality during speech, and submucous cleft palate), conotruncal congenital heart disease, dysmorphic facies, mental retardation, and psychiatric disorder.

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Potential conflicts of interest

None.

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ความชุกของ chromosome 22q11.2 deletion ในผู้ป่วยเพดานโหว่: การศึกษาทบทวนอย่างเป็นระบบในรายงาน prospective studies

วิภาวี ปะนะมณฑา, กุณฑล วิชาจารย์, ยุทธพงศ์ วงศ์สวัสดิวัฒน์, มนัส ปะนะมณฑา, สุธีรา ประดับวงษ์, บวรศิลป์ เชาวน์ชื่น

ภูมิหลัง: *ความชุกของ chromosome 22q11.2 deletion ในผู้ป่วยเพดานโหว่อย่างเดียว ยังไม่มีการศึกษาอย่างเป็นระบบ*

วัตถุประสงค์: *เพื่อศึกษาความชุกของ chromosome 22q11.2 deletion ในผู้ป่วยเพดานโหว่อย่างเดียว โดยศึกษาอย่างเป็นระบบจากรายงานวิจัยที่ศึกษาแบบ prospective*

วัสดุและวิธีการ: *รวบรวมงานวิจัยที่รายงานความชุกของ chromosome 22q11.2 deletion ในผู้ป่วยเพดานโหว่อย่างเดียวจากรายงานในฐานข้อมูล PubMed ตั้งแต่ปี พ.ศ. 2535 ถึง เดือนมิถุนายน พ.ศ. 2559*

ผลการศึกษา: *จากงานวิจัยทั้งหมด 6 รายงาน ผู้ป่วยเพดานโหว่อย่างเดียวมีจำนวน 328 รายและพบผู้ป่วยที่มี 22q11.2 deletion จำนวน 1 (ร้อยละ 0.3) ราย*

สรุป: *ความชุกของ chromosome 22q11.2 deletion ในผู้ป่วยเพดานโหว่อย่างเดียวพบได้ค่อนข้างน้อย มีความผิดปกติทางพันธุกรรมที่เกี่ยวข้องมากกว่า 400 ชนิดของการเกิดเพดานโหว่อย่างเดียว การคัดกรอง 22q11.2 deletion ในผู้ป่วยเพดานโหว่อย่างเดียวควรกระทำเมื่อมีอาการอื่นของ 22q11.2 deletion ร่วมด้วยเช่น โรคหัวใจพิการแต่กำเนิดชนิด conotruncal defects, ลักษณะใบหน้าที่ผิดปกติ, ความผิดปกติของเพดานปากและคอ, ภูมิคุ้มกันบกพร่อง, ภาวะแคลเซียมในเลือดต่ำหรือความผิดปกติของจิตประสาทเป็นต้น*