# Special Article

# Birth Prevalence of Chromosome 22q11.2 Deletion Syndrome: A Systematic Review of Population-Based Studies

Vipawee Panamonta MD*, Khunton Wichajarn MD**,
Arnkisa Chaikitpinyo MD**, Manat Panamonta MD**,
Suteera Pradubwong MSN***, Bowornsilp Chowchuen MD****

** Taksin Hospital, Bangkok, Thailand*
*** Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
**** Division of Nursing, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
***** Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

***Background:*** *A birth prevalence of chromosome 22q11.2 deletion syndrome among population-based reports has been documented to vary, however, a systematic assessment is lacking.*
***Objective:*** *To assess the evidence in the literature for the birth prevalence of chromosome 22q11.2 deletion syndrome.*
***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 prevalence.*
***Results:*** *Of the six studies reported, there were 156 patients with 22q11.2 deletion syndrome found in total study populations of 1,111,336 live births. According to countries, the birth prevalence of this deletion syndrome (95% confidence interval) from United States, Belgium, Sweden, United Kingdom, France, and Singapore were 1.68 (1.22-2.26), 1.56 (1.33-1.72), 1.36 (0.91-2.08), 1.30 (0.45-2.15), 1.03 (0.53-2.23), and 1.02 per 10,000 live births, respectively. Estimates of minimum prevalence rates on the basis of the presence of this syndrome in cohorts of patients with cardiovascular malformations were from one in 4,000 to one in 7,092 live births.*
***Conclusion:*** *This systematic review indicates that the 22q11.2 deletion syndrome is rather common. The findings can help physicians, health care planners and other health professionals to plan and manage better care of these patients.*

***Keywords:*** *22q11.2 deletion syndrome, Cardiovascular malformation, Congenital heart disease, Palatal abnormality, Birth prevalence*

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A 22q11.2 deletion syndrome has the classic clinical manifestations of cardiovascular malformations (including congenital heart disease), dysmorphic facies, palatal abnormalities (including cleft palate), immune deficiencies, hypoparathyroidism (including hypocalcemia), and neuropsychiatric disorders[1-10]. The 22q11.2 deletion syndrome has a variable phenotypic spectrum with more than 180 clinical features reported, involving almost all organ systems and developmental functions[2,5,6]. Clinical presentations of this syndrome vary and accord with type of clinical expertise of each referral center, including cardiovascular malformations (49-83%), dysmorphic facies (46-100%), palatal abnormalities (69-100%), immune deficiencies (67-77%), hypoparathyroidism (17-60%), and neuropsychiatric disorders (75-84%)[1-3,5,7]. FISH (Fluorescence In Situ Hybridization) is commonly used as a diagnostic test of this deletion syndrome[2,5]. The genetic name of 22q11.2 deletion syndrome is now a more preferable use than the former syndromic names like absent thymus[11], Sedlackova[12], DiGeorge[13], cardiofacial[14], conotruncal anomaly face[15], velocardiofacial (Shprintzen)[16], CATCH 22 (Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcemia with chromosome 22 deletion)[17], and autosomal dominant Opitz G/BBB[18] syndromes.

The estimate of a minimum prevalence of 22q11.2 deletion syndrome was one in 4,000 live births[19]. Most of the knowledge on 22q11.2 deletion to date has been derived from hospital-based case

***Correspondence to:***
*Panamonta M, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.*
*Phone: +66-81-7683538; Fax: +66-43-348382*
*E-mail: manat@kku.ac.th*

series[1-10]. However, case series focus on cases from selected hospitals or centers and these might not represent general population regarding the spectrum of clinical presentations or severity of the disease. There are very few data on the estimates of the population-based prevalence of the 22q11.2 deletion syndrome but the precision of those data have been limited by the relatively small sample sizes, the cost and availability of FISH test and the variability of the clinical presentations[1-27]. Although there had been few studies reporting birth prevalence rates of 22q11.2 deletion syndrome[20-25], the worldwide prevalence rates of this deletion syndrome have not been systematically reviewed.

The purpose of the present study was to report a comprehensive systematic literature review of birth prevalence rates of the 22q11.2 deletion syndrome among population-based studies.

## Material and Method

### *Data sources*

FISH test has been routinely used to identify the chromosome 22q11.2 deletion syndrome since 1992[2,5]. A systematic literature search was conducted using electronic databases through the PubMed from 1992 to June 2016 using key words and search terms of 22q11.2 deletion OR 22q11 deletion AND prevalence. The eligible papers in all languages were included and searched. The titles and abstracts of the 322 relevant articles were screened independently by two authors (VP and MP) to identify potentially relevant articles for which full text publications were retrieved. Reference lists of included papers were screened for additional relevant papers that may have been missed in the database search according to the method previously described[28,29].

### *Definitions*

The prevalence rate in this present review was expressed by dividing the number of 22q11.2 deletion syndrome cases (numerator) by the number of live birth infant (denominator) multiplied by 10,000.

All 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 eligible studies included reports on prevalence of 22q11.2 deletion syndrome with a defined population. The authors excluded the followings: studies limited to clinical features and case reports without a mention of the prevalence rate and studies that did not include data for the calculations of the prevalence rates. Two authors (VP and MP) performed the search independently using these inclusion and exclusion criteria. When a study was eligible for inclusion, two authors (VP and MP) independently verified the numerator and denominator and recalculated the estimated birth prevalence to check for accuracy. Disagreements were resolved by discussion.

### *Data extraction*

Data were extracted using a standardized data extraction form, including locations, ethnics, study method, number of 22q11.2 deletion syndrome, and number of live birth infants.

### *Quality assessment*

Each included study was assessed on completeness of data and origins of the data.

### *Statistical analysis*

Birth prevalence rates were presented with number of cases per 10,000 live births and rate of 1 case per number of live births. Total 22q11.2 deletion syndrome birth prevalence rates were presented with average values (95% confidence interval).

## Results

The search combination in the databases identified 322 relevant articles. A thorough evaluation of these articles using the inclusion and exclusion criteria led to the exclusion of 297 articles, leaving 25 papers that met the inclusion criteria. After critical review of the full text, one paper was excluded due to incomplete data, leaving 24 papers containing relevant data. Of these papers, there were two additional papers found after reference checking. Thus, a total of 26 papers were eligible for the inclusion into this systematic review (Fig. 1).

Tan et al found that the prevalence rate of the deletion in Singapore trended to increase over time. The rate in 2000-2001 was one in 17,544 live births, while the rate in 2002-2003 increased to be one in 6,536 live births ($p>0.05$)[20]. The differences did not reach statistical significance[20]. Oskarsdottir et al reported that the prevalence rate of the deletion syndrome in the city of Gothenburg (Sweden) was one in 4,292 live births. This prevalence rate was higher than the rate of the whole Western Gotaland region of one in 7,377 live births[21]. Botto et al reported that the prevalence rate

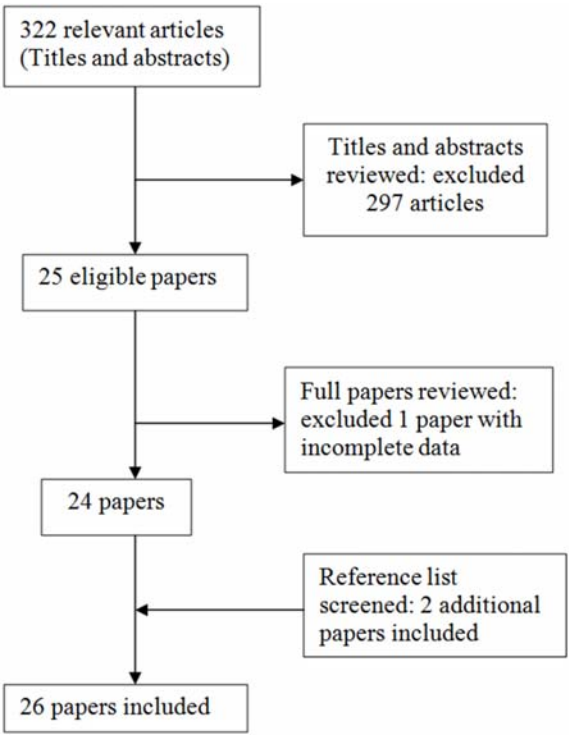


**Fig. 1** Flow diagram of paper search and papers included into this systematic review.

of the deletion in Atlanta was one in 5,950 live births[22]. Five percent of the patients had laboratory-confirmed chromosome 22q11.2 deletion of the parent[22]. Devriendt et al reported that the prevalence rate of the deletion in Belgium was one in 6,395 live births and found that the diagnosis of this deletion syndrome was delayed in patients without an apparent cardiovascular malformation[23]. Goodship et al reported that the prevalence rate of the deletion in United Kingdom was one in 7,681 live births and was about 1/6 of the prevalence rate of trisomy 21[24]. Tezenas Du Montcel et al reported that the prevalence rate of the deletion syndrome in France was one in 9,704 live births and highlight that the prevalence rate, in highest ascertainment year, was 1/4,525 live births in 1993[25]. Of these population-based studies, cardiovascular malformations, found in patients with 22q11.2 deletion, ranged from 58% to 94% (Table 1).

There were three reports of which could be used to calculate minimum prevalence rates of this deletion syndrome[19,22,26]. Estimates of minimum prevalence rates on the basis of the presence of this deletion syndrome in cohorts of patients with cardiovascular malformations or congenital heart diseases ranged from one case per 4,000 to one case per 7,092 live births (Table 2).

There were two papers which provided the prevalence rates of this deletion syndrome among racial groups[20,22]. In Atlanta of Georgia in the United States, patients of Hispanic origin trended to have higher prevalence of the deletion syndrome than in White, Black and Asian groups[22]. About Asian race in Singapore, the prevalence of the deletion among Chinese and Malays was 1 in 10,989 and 1 in 4,673 live births, respectively[20]. However, these variations of prevalence rates among racial group did not reach statistically significant differences due to small numbers of the population in these studies[20,22].

**Discussion**

There have been six population-based studies attempting to assess the prevalence rates of 22q11.2 deletion syndrome in general population. The birth prevalence of chromosome 22q11.2 deletion syndrome in this comprehensive systematic review of the population-based studies indicates that this deletion syndrome is rather common, varying between one case per 4,525 live births to one case per 9,805 live births[20-25]. In addition, estimates of prevalence rates vary from one in 4,000 to one in 7,092 live births according to three reports of the prevalence of 22q11.2 deletion in cohorts of patients with cardiovascular malformation[19,22,26]. Although the prevalence rate of the deletion syndrome of Hispanic population in Atlanta/Georgia in the United States and of Malays population in Singapore trended to be higher than the rate of White, Black, and other Asians, there were no statistically significant differences among the prevalence rates of these racial groups. Larger studies will be needed in the future to assess these differences[20,22].

A FISH test for detection of 22q11.2 gene deletion which is too small to be seen under the microscope, has been commercially available since 1992[2,5]. The FISH test for 22q11.2 deletion has very high sensitivity and specificity for patients with DiGeorge syndrome and velocardiofacial syndrome[1-10]. This special FISH test for 22q11.2 deletions is available in many cytogenetic laboratories[1-10]. However, this special test is performed only when a physician informs the laboratory technicians that a patient is suspected of a 22q11.2 deletion[2,5]. This FISH test is not performed routinely for every patient due to the costliness and inaccessibility of the test[1-10].

**Table 1.** Summary of six population-based studies with information on population and prevalence

| References | Study place, period (year) | Live births (N) | Types of data collection | 22q11.2 DS case (N) | Number of cases (95% CI) per 10,000 live births | Rate of 1 case per N of live births | N with CVS defects | % of CVS defects with 22q11.2 DS |
|---|---|---|---|---|---|---|---|---|
| Tan et al (2008)[20] | Singapore, 2000-2003 | 166,693 | National birth defect registry, Medical centers, Cytogenetic laboratory | 17 | 1.02 | 9,805 | 16 | 94.1 |
| Oskarsdottir et al (2004)[21] | Sweden, 1991-2000 | 177,047 | Hospital-based | 24[a] | 1.36 (0.91-2.08) | 7,377[b] | 14 | 58.3 |
| Botto et al (2003)[22] | United States, 1994-1999 | 255,849 | Population-based registry with active case ascertainment, regional heart center, centralized laboratory service | 43[c] | 1.68 (1.22-2.26) | 5,950 | 35 | 81.3 |
| Devriendt et al (1998)[23] | Belgium, 1992-1996 | 326,166 | Four genetic centers | 51 | 1.56 (1.33-1.72) | 6,395 | 37 | 72.5 |
| Goodship et al (1998)[24] | United Kingdom, 1994-1995 | 69,129 | Regional genetics and pediatric cardiology centers | 9 | 1.30 (0.45-2.15) | 7,681 | 6 | 66.7 |
| Tezenas Du Montcel et al (1996)[25] | France, 1989-1993 | 116,452 | Birth defect registry with voluntary notification from maternity hospitals | 12[d] | 1.03 (0.53-2.23)[d] | 9,704[d] | 11[e] | 91.7 |

N = number; DS = deletion syndrome; CVS = cardiovascular system; NA = not available; CI = confidence interval

[a] One fetus, with confirmed positive FISH test and the pregnancy terminated before birth, was excluded from this analysis

[b] Prevalence rate of the deletion in the city of Gothengurg (Sweden) was one in 4,292 live births

[c] Two patients had carrier mothers with cleft palate and with laboratory-confirmed 22q11.2 deletion

[d] Prevalence rate in 1993, when FISH test was available, 2.21 cases per 10,000 live births (1 case per 4,525 live births)

[e] Ten patients had congenital heart diseases and one patient had an aberrant subclavian artery

Increasing awareness, availability of genetic screening test, and better clinical skills for this deletion syndrome can result in having higher prevalence rates as shown in studies of Tan et al[20], Oskarsdottir et al[21], and Botto et al[22]. Availability of the FISH test could result in a higher prevalence rate as documented from the study of Tezenas Du Montcel et al[25]. Longer follow-up duration could ascertain more additional patients who had no or mild cardiovascular defects and this finding was confirmed by Oskarsdottir et al[21].

Estimates of prevalence rate, i.e. 1/4,000 live births, on the basis of the presence of this syndrome in cohorts of patients with cardiovascular malformations, is a popular estimation of this deletion syndrome[19]. However, it is probable that at least one third of cases are not diagnosed until later in life[5]. Therefore, the true population prevalence would be higher than the estimation prevalence.

### *Study limitations*

The present study has potential limitations. Some cases with this deletion syndrome may have been missed since genetic testing for the deletion depends on clinical referral and incomplete ascertainment of cases is possible, particularly for those patients whose clinical findings are minimal, late onset or atypical.

## Conclusion

This systematic review of the population-based studies indicates that the deletion syndrome is rather common. The better method to find the accurate prevalence of this syndrome is through population-based screening or survey, but it would be too expensive and have an ethical question in screening a large population. Screening of populations at risk would be more appropriate. Increased awareness and good clinical skills of the syndrome[20-22], diagnostic guidelines[30,31] and a long follow-up time[21] are important to obtain more correct prevalence rates. Data on prevalence rate of this deletion syndrome in population-based settings can help physicians, health care planners, and other health professionals to plan

**Table 2.** Estimations of prevalence rate of chromosome 22q11.2 deletion syndrome from the percentage of the deletion in patients with cardiovascular malformation

| References | Study place, period (year) | Prevalence of CVS malformation cases per 1,000 live births | % of 22q11.2 DS in cohorts of CVS defects | Estimates rate of 1 case of 22q11.2 DS per N of live births |
|---|---|---|---|---|
| Wilson et al (1994)[19] | United Kingdom, 1993 | 5.0[a] | 5.0[b] | 4,000 |
| Botto et al (2003)[22] | United States, 1994-1999 | 9.4 | 1.5[c] | 7,092 |
| Agergaard et al (2012)[26] | Denmark, 2000-2008 | 8.6 | 1.9 | 6,120 |

N = number; DS = deletion syndrome; CVS = cardiovascular system; NA = not available
[a] 10 patients with 22q11.2 DS found in 202 cases with congenital heart diseases (4.95%)
[b] 1,009 congenital heart disease patients found among 191,700 live births (5.3 cases per 1,000 live births)
[c] 1 patient with 22q11.2 DS found in 68 cases with congenital heart diseases (1.47%)

**Table 3.** The birth prevalence of 22q11.2 deletion syndrome among races

| Ethnics | Study place, period (year) | Live births (N) | 22q11.2 DS case (N) | Case number per 10,000 live births | Rate of 1 case per N of live births | Reference |
|---|---|---|---|---|---|---|
| White | United States, 1994-1999 | 116,459 | 18 | 1.5 | 6,470 | Botto et al (2003)[22] |
| Black | United States, 1994-1999 | 103,247 | 17 | 1.6 | 6,073 | Botto et al (2003)[22] |
| Hispanic | United States, 1994-1999 | 22,584 | 6 | 2.7 | 3,764 | Botto et al (2003)[22] |
| Asian | United States, 1994-1999 | 12,747 | 2 | 1.6 | 6,374 | Botto et al (2003)[22] |
| Chinese | Singapore, 2000-2003 | 110,166 | 10 | 0.9 | 10,989 | Tan et al (2008)[20] |
| Malays | Singapore, 2000-2003 | 32,755 | 7 | 2.1 | 4,673 | Tan et al (2008)[20] |

N = number; DS = deletion syndrome

and manage better care of these patients.

**What is already known on this topic?**

This deletion syndrome is rather common according to population-based studies.

**What this study adds?**

Increased awareness and good clinical skills of the syndrome, diagnostic guidelines and a long follow-up time are important to obtain more correct prevalence rates.

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**Potential conflicts of interest**

None.

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## *ความชุกแต่กำเนิดของกลุ่มอาการ chromosome 22q11.2 deletion: การศึกษาทบทวนอย่างเป็นระบบในกลุ่มประชากรทั่วไป*

*วิภาวี ปะนะมณฑา, กุณฑล วิชาจารย์, อรรมิศา ไชกิจภิญโญ, มนัส ปะนะมณฑา, สุธีรา ประดับวงษ์, บวรศิลป์ เชาวน์ชื่น*

***ภูมิหลัง:*** *ความชุกแต่กำเนิดของกลุ่มอาการ chromosome 22q11.2 deletion ในประชากรทั่วไป ยังไม่มีการศึกษาอย่างเป็นระบบ*
***วัตถุประสงค์:*** *เพื่อศึกษาความชุกแต่กำเนิดอย่างเป็นระบบของกลุ่มอาการนี้ในประชากรทั่วไป*
***วัสดุและวิธีการ:*** *ศึกษาความชุกแต่กำเนิดของกลุ่มอาการนี้จากรายงานในฐานข้อมูล PubMed ตั้งแต่ปี พ.ศ. 2535 ถึง เดือนมิถุนายน พ.ศ. 2559*
***ผลการศึกษา:*** *ผู้ป่วย 156 ราย ในเด็กแรกเกิดมีชีพจำนวน 1,111,336 ราย จาก 6 รายงาน ความชุกแต่กำเนิดของกลุ่มอาการนี้ (ความเชื่อมั่นในระดับร้อยละ 95) แยกตามรายประเทศได้แก่ สหรัฐอเมริกา, เบลเยี่ยม, สวีเดน, สหราชอาณาจักร, ฝรั่งเศส, และสิงคโปร์ 1.68 (1.22-2.26), 1.56 (1.33-1.72), 1.36 (0.91-2.08), 1.30 (0.45-2.15), 1.03 (0.53-2.23), และ 1.02 ต่อทารกแรกเกิดมีชีพ 10,000 ราย ตามลำดับ ประมาณความชุกขั้นต่ำทางอ้อมของกลุ่มอาการนี้ในผู้ป่วยที่มีความผิดปกติของหัวใจและหลอดเลือดพบ 1/4,000 ถึง 1/7,092 ของทารกแรกเกิดมีชีพ*
***สรุป:*** *กลุ่มอาการนี้พบได้ค่อนข้างบ่อยในประชากรทั่วไป ซึ่งบุคลากรทางการแพทย์จะได้ใช้เป็นข้อมูลในการดูแลรักษาผู้ป่วยกลุ่มนี้ให้ดีขึ้น*