# 22q11.2 deletion syndrome in Singapore (2000-2003): a case for active ascertainment

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## ABSTRACT

**Introduction: The 22q11 deletion syndrome (22q11DS) is associated with many congenital structural anomalies, notably cardiac defects (conotruncal anomalies) and velopharyngeal insufficiency, as well as neurodevelopmental and psychiatric findings in later life. Recent studies have tried to ascertain the true population incidence of this condition. However, this is difficult due to possible under-ascertainment from incomplete genetic testing in possible cases. The aim of this study is to investigate the local incidence and association of this deletion syndrome with other congenital structural anomalies, with emphasis on cardiac defects.**

**Methods: Data of 22q11 deletion cases born in 2000-2003 were retrieved from the Singapore National Birth Defects Registry (NBDR) and analysed. Data of congenital cardiac defect cases notified to NBDR in the same period were also retrieved and compared with the deletion cases.**

**Results: There were a total of 17 cases of 22q11DS in the four-year period 2000–2003, giving an overall incidence of 1.02 per 10,000 live-births or one in 9,804 births. 94 percent (16/17 cases) were associated with other structural anomalies, and of these, 68.8 percent (11/16 cases) had single system anomalies. Cardiac anomalies were the most common (100 percent). The deletion contributed to 0.86 percent (one in 116 cases) of all cardiac defects born during the same period. A higher contribution of this deletion was noted for interrupted aortic arch (10 percent), pulmonary atresia (12.7 percent) and truncus arteriosus (11.1 percent).**

**Conclusion: In view of the high proportion of this deletion among certain cardiac defects, genetic testing should be made available to investigate the true burden and contribution of this deletion. As more genetic testing is done for this deletion, we are likely to see an increase in incidence, reflecting the true prevalence of this condition.**


**Keywords: 22q11 deletion syndrome, cardiac defects, congenital anomalies, conotruncal defects**

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## INTRODUCTION

The 22q11 deletion syndrome (22q11DS) encompasses a range of syndromes previously known separately as DiGeorge syndrome, velocardiofacial syndrome and conotruncal anomaly face syndrome. Its range of phenotypic features includes a wide variety of malformations and anomalies occurring in different combinations and severities. Common clinical features include congenital cardiac defects, velopharyngeal insufficiency and other facial features. More recently, as affected children are followed-up into adolescence and adulthood, investigators have found neurological, developmental and psychiatric[1] sequelae associated with this deletion syndrome.

The incidence of 22q11DS among cardiac defects has been estimated at one in 4,000 livebirths,[2] while the incidence among all births has been quoted from one in 9,700 births[3] to one in 5,950 births,[4] although the true incidence is likely to be higher with increasing awareness and genetic testing for this syndrome. Recent population-based studies in Atlanta[4] and western Sweden[5] have quoted incidences from one in 5,950 births to one in 7,092 births, respectively. The assessment of the incidence and prevalence of this condition will aid medical professionals and policy makers in planning for the optimal care of people with this syndrome. The aim of this study is to look at the incidence, demographical data and epidemiological pattern of 22q11 deletion syndrome in Singapore from 2000–2003, and to compare our data with those from other countries, as well as to examine the birth defects associated with this condition, specifically with reference to cardiac defects.

## METHODS

The method of data collection at the National Birth Defects Registry (NBDR) has been previously described.[6] Multiple sources comprising government bodies, public and private medical centres contribute to the collection of birth defect data. These include the Epidemiology & Disease Control Division of the Ministry of Health,

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**Table I. Occurrence of 22q11 deletion, by race, gender and period of birth, 2000–2003.**

| Group | No. of births | No. of cases | Rate | |
|---|---|---|---|---|
| | | | Per 10,000 births | Births per case |
| Total | 166,693 | 17 | 1.02 | 1 in 9,804 |
| By race | | | | |
| Chinese | 110,166 | 10 | 0.91 | 1 in 10,989 |
| Malay | 32,755 | 7 | 2.14 | 1 in 4,673 |
| Indian | 13,780 | 0 | - | - |
| Others | 9,992 | 0 | - | - |
| By gender | | | | |
| Male | 86,248 | 9 | 1.04 | 1 in 9,615 |
| Female | 80,442 | 8 | 0.99 | 1 in 10,101 |
| Over time | | | | |
| 2000–2001 | 88,448 | 5 | 0.57 | 1 in 17,544 |
| 2002–2003 | 78,245 | 12 | 1.53 | 1 in 6,536 |

**Table II. Clinical findings among children with 22q11 deletion who have other major diagnostic findings, 2000–2003.**

| Finding | No. (%) |
|---|---|
| Any major diagnostic finding | 16 (100) |
| Single system | 11 (68.8) |
| Multiple system | 5 (31.2) |
| Cardiovascular system | 16 (100) |
| Cleft palate | 2 (12.5) |
| Central nervous system | 1 (6.3) |
| Renal system | 2 (12.5) |
| Hydronephrosis | 1 (6.3) |
| Cystic dysplasia | 1 (6.3) |
| Gastrointestinal system | 2 (12.5) |
| Choanal stenosis | 1 (6.3) |
| Inguinal hernia | 1 (6.3) |

* Percentages rounded to one decimal place

**Table III. Cardiovascular findings among children with 22q11 deletion, 2000–2003.**

| Finding | Total no. (%) | % total* |
|---|---|---|
| Cardiac anomalies | 16 (100.0) | 94.1 |
| Interrupted aortic arch | 1 (6.3) | 5.9 |
| Coarctation of aorta | 1 (6.3) | 5.9 |
| Truncus arteriosus | 1 (6.3) | 5.9 |
| Tetralogy of Fallot | 4 (25.0) | 23.5 |
| Ventricular septal defect | 10 (62.5) | 58.8 |
| Atrial septal defect | 6 (37.5) | 35.3 |
| Pulmonary atresia | 3 (18.8) | 17.6 |
| Pulmonary valve stenosis | 2 (12.5) | 11.8 |

* Percentage among all children with 22q11 deletion (n = 17)

the National Registry of Births and Deaths as well as cytogenetic and histology laboratories, and nursery wards in both public and private hospitals in Singapore.

Using an in-house database software programme NBDR Version 1.0 developed with the Information Service Department of KK Women's and Children's Hospital, all notified cases of 22q11 deletions from 2000 to 2003 were extracted from the registry's database, and the data was then analysed. Care was taken to ensure confidentiality and anonymity of extracted and analysed data. Ethics approval was not sought since all data was extracted and analysed anonymously. The population denominators used in computing the rates per 10,000 live-births shown in the tables were obtained from the Reports on Registration of Births and Deaths.[7]

## RESULTS

Between 2000 and 2003, a total of 17 cases of 22q11 deletion cases were notified. In the same period, there were 166,693 live-births, giving an overall incidence of 1.02 per 10,000 live-births or one in 9,804 births. The race-specific incidence of 22q11DS ranged from ~ 1 in 10,989 among Chinese to ~ 1 in 4,673 among Malays. These differences were not statistically significant. The incidence was similar between female and male patients, ranging from ~ 1 in 9,615 to one in 10,101, respectively. The occurrence rate of the deletion seemed to increase over time. The rate in 2000–2001 was one in 17,544 births, while the rate in 2002–2003 was one in 6,536 births. The difference did not reach statistical significance. ($p = 0.08$) (Table I).

Out of 17 cases of 22q11DS, 16 (94%) had associated major anomalies. Out of these 16 cases, the majority (11/16; 68.8%) were associated with single system anomalies and the rest (5/16; 31.2%) were associated with multiple system anomalies. All 16 cases in our study had associated cardiovascular anomalies. The other structural anomalies by system included central nervous system (1/16), renal (2/16), and gastrointestinal (1/16) systems. There were two cases with cleft palate (Table II). Out of 16 cases of 22q11DS associated with cardiovascular anomalies, four cases (25%) had tetralogy of Fallot, and more than half (10/16; 62.5%) had ventricular septal defect, which was unrelated to Fallot's tetralogy. 37.5% (6/16) had atrial

**Table IV. Comparison of studies.**

| Population area | France | West Sweden | Belgium | United Kingdom | United States | Singapore |
|---|---|---|---|---|---|---|
| Birth years | 1989–1993 | 1991–2000 | 1992–1996 | 1994–1995 | 1994–1999 | 2000–2003 |
| Data sources | Birth defect registry | Hospital -based | Four genetic centres | Regional genetic and paediatric cardiology | Population -based | National birth defects registry |
| No. of cases | 12 | 24 | 51 | 9 | 43 | 17 |
| Rate per 10,000 births | 1.0 | 1.4 | 1.6 | 1.3 | 1.7 | 1.02 |
| Rate (1 in) | 9,704 | 7,092 | 6,395 | 7,681 | 5,950 | 9,804 |
| No. with cardiac anomalies | 11 | 14 | 37 | 6 | 35 | 16 |
| As % of cases with deletion | 92% | 58% | 73% | 67% | 81% | 94% |
| As % of all heart defects | NA | NA | NA | 1.2% | 1.5% | 0.86% |
| Reference | Tézenas du Montcel et al[3] | Oskarsdóttir et al[5] | Devriendt et al[8] | Goodship et al[9] | Botto et al[4] | Tan et al (current study) |

Structure of table adapted from Botto et al's study[4] for ease of comparison

septal defect. Other associated cardiac defects included interrupted aortic arch (IAA) (1/16), coarctation of aorta (1/16), truncus arteriosus (1/16), pulmonary atresia (3/16) and pulmonary valve stenosis (2/16) (Table III).

There were a total of 1,851 heart defects notified to the NBDR during the period 2000-2003, giving an occurrence of 11.1 per 1,000 live-births. The 22q11 deletion was ascertained in 0.86%, or one in 116 cases of heart defects. The contribution of this deletion was found to be highest for truncus arteriosus, IAA and pulmonary atresia. One out of every ten cases of truncus arteriosus, IAA and pulmonary atresia, and one out of every 20 cases of tetralogy of Fallot's in the population, were attributable to this deletion (Fig.1).

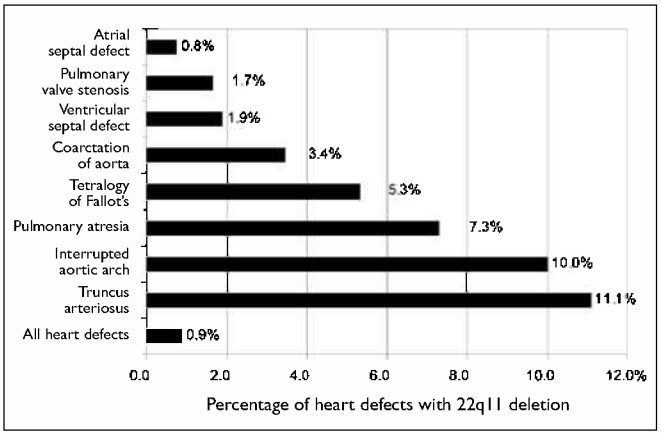


**Fig.1** Bar chart shows contribution of 22q11 deletion to heart defects in the population, 2000–2003.

## DISCUSSION

Our study's population incidence of ~ 1 in 9,804 live births is lower than many other studies.[3-5,8,9] (Table IV). We postulate that our incidence is an under-representation of the true population incidence of this condition. This is suggested by the increase in incidence of this deletion from 2000–2001 to 2002–2003, which, although not statistically significant, could reflect an increasing awareness of this condition and a consequential increase in genetic testing for this deletion among paediatricians. As awareness increases and more parents are willing to undergo genetic testing for their children, this incidence is likely to increase further. The difference in the occurrence of this condition between the races did not reach statistical significance. Although race and ethnicity are not known to be a contributing cause of this condition, further studies should be done to investigate and confirm this. We are also aware that these might not be true incidences within the races, as we have not been able to ascertain the proportion of and likelihood of genetic testing among the different races.

We have shown that a high proportion of 22q11DS (95%) have associated cardiac defects. Goldmuntz et al in 1998 found 50% of patients with IAA, 34.5% of patients with truncus arteriosus, and 15.9% of patients with tetralogy of Fallot, had deletion in chromosome 22q11.[10] Rauch et al found 9/15 cases of IAA with this deletion, with a clustering among children with IAA type B.[11] Kessler-Icekson et al found 48% of patient with tetralogy of Fallot to have this deletion.[12] Our rates are much lower than the quoted studies. This is likely to reflect the much lower threshold of our clinicians to perform the FISH test for this syndrome in cases with these cardiac conditions. This could be attributed to both a lack of awareness of this condition or a reluctance on the parents' part to perform this expensive genetic test.

There are several limitations to this study. Firstly, the numbers are small. This could be due to under-reporting of this deletion syndrome to the NBDR by physicians. Another reason could be due to low genetic testing rates among the medical fraternity in Singapore. Since genetic testing depends on clinical referral, incomplete ascertainment is a definite possibility, especially among cases of minimal phenotypic abnormalities, late onset, or uncommon presentations. This suggests that our incidence rates are likely to represent the tip of the iceberg. Secondly, our study did not assess other minor malformations associated with this condition, as the NBDR may not be able to accurately capture the number of 22q11DS cases with anomalies, like facial asymmetry, developmental as well as psychiatric findings, all of which are unlikely to be notified to the registry. These are interesting features which can be investigated in another study specifically designed to capture this data.

In conclusion, while this study has small numbers, it has attempted to elucidate the minimal incidence of 22q11 deletion syndrome in Singapore from 2000–2003. It has also shown the significant contribution of this deletion to congenital heart defects, in particular to certain major malformations like IAA, tetralogy of Fallot and truncus arteriosus. The apparent rise in the number of notified cases from 2000–2001 to 2002–2003 could be due to increased awareness and genetic testing for this condition. In view of the other associated conditions with this deletion syndrome, there is a definite case for promotion of increased awareness of this significant deletion syndrome among medical practitioners, in particular obstetricians and paediatricians, as well as active ascertainment of this condition in cases of congenital cardiac defects. This will enable a more accurate ascertainment of the true incidence of this syndrome in Singapore, and an increased understanding of its association with other birth defects will enable multidisciplinary prenatal and postnatal care involving more than the obstetrician and paediatrician, to include other medical colleagues like the geneticist and cardiologist in the care of babies born with this condition. It is also hoped that this paper will encourage more resources to be allocated to the local study and investigation of this syndrome.

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## REFERENCES

1. Takahashi S, Cui YH, Kojima T, et al. Family-based association study of markers on chromosome 22 in schizophrenia using African-American, European-American, and Chinese families. Am J Med Genet B Neuropsychiatr Genet 2003; 120:11-7.
2. Wilson DI, Cross IE, Wren C, et al. Minimum prevalence of chromosome 22q11 deletions. Am J Hum Genet 1994; 55:A169.
3. Tézenas du Montcel S, Mendizabai H, Aymé S, Lévy A, Philip N. Prevalence of 22q11 microdeletion. J Med Genet 1996; 33:719.
4. Botto LD, May K, Fernhoff PM, et al. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. Pediatrics 2003; 112(1 pt 1):101-7.
5. Oskarsdóttir S, Vujic M, Fasth A. Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. Arch Dis Child 2004; 89:148-151.
6. Lai FM, Woo BH, Tan KH, et al. Birth prevalence of Down Syndrome in Singapore from 1993 to 1998. Singapore Med J 2002; 43:70-6.
7. Registrar-General of Births and Deaths Singapore. Report on Registration of Births and Deaths 2004. Singapore: Registry of Births and Deaths; Immigration and Checkpoints Authority, 2004.
8. Devriendt K, Fryns JP, Mortier G, et al. The annual incidence of DiGeorge/Velocardiofacial Sydrome. J Med Ganet 1998; 35:789-90.
9. Goodship I, Cross I, Liling J, et al. A population study of chromosome 22q11 deletions in infancy. Arch Dis Child 1998; 79:348-51.
10. Goldmuntz E, Clark BJ, Mitchell LE, et al. Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol 1998; 32:492-8.
11. Rauch A, Hofbeck M, Leipold G, et al. Incidence and significance of 22q11.2 hemizygosity in patients with interrupted aortic arch. Am J Med Genet 1998; 78:322-31.
12. Kessler-Icekson G, Birk E, Weintraub AY, et al. Association of tetralogy of Fallot with a distinct region of del22q11.2. Am J Med Genet 2002; 107:294-8.