# Pattern of Turner syndrome in Singapore (1999–2004)

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## ABSTRACT

**Introduction: Turner syndrome is the most common sex chromosomal abnormality in female foetuses, and is associated with a high proportion of cardiac anomalies. The aim of this study was to look at the incidence, demographical data and epidemiological pattern of Turner syndrome in Singapore from 1999 to 2004 and to examine the birth defects associated with this condition, specifically with reference to cardiac defects.**

**Methods: Data on Turner syndrome cases born in 1999–2004 were retrieved from the National Birth Defects Registry (NBDR) and analysed. Data on congenital cardiac defect cases notified to the NBDR in the same time period were also retrieved and compared with the Turner syndrome cases.**

**Results: There were a total of 101 cases of Turner syndrome in the six-year period from 1999–2004, yielding an overall incidence of 0.85 per 1,000 female live births, or one in 1,180 female live births. The incidence was lowest among Indians (0.38 per 1,000) compared to Malays (0.72 per 1,000) and Chinese (0.90 per 1,000). 75 cases (74.3 percent) had the 45,X karyotype, while the other 26 cases (25.7 percent) were mosaics. The mean maternal age for 45,X was lower (32.2 years, range 22–42) compared to mosaics (34.5 years, range 27–40). 19.8 percent (20/101) were live births, 38.6 percent (39/101) were terminated pregnancies and 41.6 percent (42/101) were spontaneous miscarriages. 13.9 percent of Turner syndrome babies had cardiac defects compared to 1.2 percent in the general population (p-value is less than 0.0001). Major cardiac defects found among Turner syndrome babies compared to the general population included the coarctation of the aorta (5.9 percent compared to 0.03 percent, p-value is less than 0.0001), atrial septal defects (3.0 percent compared to 0.6 percent, p-value is 0.006), a hypoplastic left heart (2.0 percent compared to 0.05 percent, p-value is less than 0.0001), aortic hypoplasia (3.0 percent compared to 0.01 percent, p-value is less than 0.0001) and dextrocardia (1.0 percent compared to 0.02 percent, p-value is 0.0002).**

**Conclusion: Cardiac defects, particularly left-sided ones, are significantly more common among Turner syndrome foetuses. The true incidence of this syndrome is likely to be higher than that quoted in this study, and can only be solved when a complete screening of an entire population has been performed.**


**Keywords: birth defects, cardiac defects, foetal defects, mosaicism, Turner syndrome**

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## INTRODUCTION

Turner syndrome, first described in 1938,[1] is the most common sex chromosome abnormality in female foetuses and is caused by a complete or partial X monosomy in some or all cells. Morbidity associated with Turner syndrome extends beyond the infant years to include problems with growth, developmental and behavioural issues, as well as multisystem problems with the endocrine, dermatological, gastrointestinal, cardiac, ophthalmological and otological systems.[2] The most frequent karyotype is 45,X, followed by mosaicism; the former is more commonly associated with congenital defects than the latter. Frequent congenital anomalies encountered in Turner syndrome include cystic hygroma, non-immune hydrops, renal and cardiac defects. Cardiovascular anomalies have been found to be very common in patients with Turner syndrome, ranging from coarctation of the aorta to more severe left heart disease like hypoplastic left heart syndrome. The aim of this study was to look at the incidence, demographic data and epidemiological pattern of Turner syndrome in Singapore from 1999 to 2004 and 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 Defect Registry (NBDR) has been previously described.[3] Multiple sources comprising government bodies, public and private

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**Table I. Occurrence of Turner syndrome by race, 1999–2004.**

| Racial group | No. of female births | No. of cases | Rate | |
|---|---|---|---|---|
| | | | Per 1,000 live births | Births per case |
| Chinese | 78,582 | 71 | 0.90 | 1,107 |
| Malay | 22,188 | 16 | 0.72 | 1,387 |
| Indian | 10,482 | 4 | 0.38 | 2,620 |
| Others | 7,906 | 10 | 1.26 | 791 |
| Total | 119,158 | 101 | 0.85 | 1,180 |

medical centres contribute to the collection of birth defect data. These include the Epidemiology & Disease Control Division of the Ministry of Health, 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 at KK Women's and Children's Hospital, all notified cases of Turner syndrome (with karyotyping done) in 1999–2004 were extracted from the registry's database, and the data was then analysed. Data on congenital heart defects notified to the registry from 1999 to 2004 were also extracted and analysed. Care was taken to ensure the confidentiality and anonymity of the extracted and analysed data. Ethics approval was not sought as all data was extracted and analysed anonymously. The population denominators used in computing the rates per 1,000 live births shown in the tables were obtained from the Reports on Registration of Births and Deaths.[4]

## RESULTS

Between 1999 and 2004, a total of 101 cases of Turner syndrome were notified. In the same time period, there were 119,158 female live births, yielding an overall incidence of 0.85 per 1,000 female live births or one in 1,180 female live births. The Chinese population was found to have the highest incidence (0.90 per 1,000 live births or one in 1,111) compared to the Malay (0.72 per 1,000 live births or one in 1,389) and Indian (0.38 per 1,000 live births or one in 2,632) populations (Table I). The mean maternal age was 32.8 (range 22–42) years. The mean maternal age for mosaics was higher, at 34.5 (range 27–40) years, compared to that for 45,X karyotypes, which was 32.2 (range 22–42) years (Table II).

The 45,X karyotype was found in 75 cases (74.3%), and the other 26 cases (25.7%) were mosaics. Of the 101 Turner syndrome pregnancies, 38.6% were terminated, 41.6% miscarried and only 19.8% were live births. There was a significantly higher proportion of miscarriages found among the 45,X karyotype (39/75 or 52.0%) compared to mosaics (3/26 or 11.5%) ($p < 0.005$). There were significantly more live births among the mosaics (14/26 or 53.8%) compared to the 45,X karyotype (6/75, or 8.0%) ($p < 0.005$) (Table III).

**Table II. Mean maternal age during the study period, 1999–2004.**

| Characteristic | Mean value (range) |
|---|---|
| Maternal age | 32.8 (22–42) years |
| Maternal age of mosaics | 34.5 (27–40) years |
| Maternal age of 45,X karyotypes | 32.2 (22–42) years |

Congenital cardiac malformations were found in 14 cases (13.9%) of Turner syndrome foetuses compared to a population prevalence of 1.2%. ($p < 0.0001$). Table IV shows the major cardiac defects associated with Turner syndrome compared to the general population. These include coarctation of the aorta (5.9% vs. 0.03%, $p < 0.0001$), atrial septal defects (3.0% vs. 0.6%, $p = 0.006$), hypoplastic left heart (2.0% vs. 0.05%, $p < 0.0001$), aortic hypoplasia (3.0% vs. 0.01%, $p < 0.0001$) and dextrocardia (1.0% vs. 0.02%, $p = 0.0002$). The overall relative risk of cardiovascular defects was 11.9. There was one case of congenital cystic adenomatoid malformation of the lung. Cystic hygroma and hydrops were respectively seen about 500- and 200-fold compared to the normal population.

Table V shows the prevalence of cardiac anomalies among monosomic Turner syndrome and the different structural mosaics, and there was no statistical difference noted between these two groups. There were a total of 2,888 heart defects notified to the NBDR during the time period 1999–2004, yielding an occurrence of 11.7 per 1,000 live births. Turner syndrome was ascertained in 0.48% (or one in 208 cases) of heart defects, one out of every 11 cases of hypoplastic aorta, and one of every 13 cases of aortic coarctation (Fig. 1).

## DISCUSSION

Our study's population incidence of approximately one in 1,176 female live births is much higher than the usual quoted incidence of one in 2,000–2,500, although countries like Japan have reported incidences of up to one in 476 cases.[5] We note that 36 cases (35.6%) of reported Turner syndrome in our series were actually incidental

**Table III. Outcome of Turner syndrome cases, 1999–2004.**

| Karyotype | No. of cases | No. (%) of termination of pregnancies | No. (%) of miscarriages | No. (%) of live births |
|---|---|---|---|---|
| 45,X | 75 | 30 (40.0) | 39 (52.0) | 6 (8.0) |
| 45,X (mosaic) | 26 | 9 (34.6) | 3 (11.5) | 14 (53.8) |
| Total | 101 | 39 (38.6) | 42 (41.6) | 20 (19.8) |

**Table IV. Foetal congenital anomalies in Turner syndrome cases, 1999–2004.**

| Anomaly | No. (%) of TS cases (n = 101) | Population prevalence (%) (n = 247,203) | Relative risk | 95% confidence interval | p-value |
|---|---|---|---|---|---|
| Cardiac defects | 14 (13.9) | 2,888 (1.168) | 11.86 | 7.29–19.31 | < 0.0001 |
| Coarctation of aorta | 6 (5.9) | 79 (0.032) | 185.89 | 82.96–416.51 | < 0.0001 |
| Septal defects | 4 (4.0) | 2,407 (0.974) | 4.07 | 1.56–10.64 | 0.0042 |
| Ventricular septal defect | 1 (1.0) | 870 (0.352) | 2.81 | 0.40–19.80 | 0.2988 |
| Atrial septal defect | 3 (3.0) | 1,537 (0.622) | 4.78 | 1.57–14.58 | 0.006 |
| Hypoplastic left heart | 2 (2.0) | 112 (0.045) | 43.71 | 10.95–174.53 | < 0.0001 |
| Hypoplastic aorta | 3 (3.0) | 33 (0.013) | 222.51 | 69.35–713.84 | < 0.0001 |
| Dextrocardia | 1 (1.0) | 56 (0.023) | 43.71 | 6.11–312.71 | 0.0002 |
| Respiratory abnormalities (CCAM) | 1 (1.0) | 35 (0.014) | 69.9 | 9.67–505.58 | < 0.0001 |
| Cystic hygroma | 23 (22.8) | 105 (0.042) | 536.13 | 356.91–805.35 | < 0.0001 |
| Hydrops foetalis | 17 (16.8) | 175 (0.071) | 237.76 | 150.38–375.93 | < 0.0001 |

TS: Turner syndrome; CCAM: congenital cystic adenomatoid malformation

**Table V. Cardiac anomalies in monosomic Turner and structural mosaics.**

| Karyotype | No. (%) of TS (n = 101) | No. (%) of TS + CVS (n = 14) |
|---|---|---|
| Monosomy: 45,X | 75 (74.3) | 10 (71.4) |
| X-mosaic monosomy: 45,X / 46,XX, etc | 16 (15.8) | 3 (21.4) |
| X-structural anomaly | 7 (6.9) | 1 (7.1) |
| Isodicentric chromosome: 46,X, idic (Xp), etc | 6 (5.9) | 1 (7.1) |
| Deletion: 46,X, del (Xp), etc | 1 (1.0) | – |
| Marker chromosome: 45,X + marker | 1 (1.0) | – |
| Exact karyotype unknown | 2 (2.0) | – |

TS: Turner syndrome; CVS: cardiovascular system

findings after karyotyping was performed on products of conception from first trimester miscarriages. It is a known fact that there is a high spontaneous *in utero* loss of Turner syndrome foetuses, with a suggested incidence of up to 80% dying after ten weeks' gestation.[6] It is thus likely that the true incidence of Turner syndrome is much higher than reported simply due to the fact that many more miscarriages are not karyotyped.

Mansfield et al conducted a systematic literature review to estimate termination rates after prenatal diagnosis, and reported an average termination rate of 72% (range 44%–100%) for Turner syndrome. They also noted that there was no significant change in the termination rates over the two decade periods of the 1980s and 1990s.[7] Our study showed that 38% of diagnosed Turner syndrome cases were terminated. However, we note that this percentage would have been higher if we did not take into consideration the cases of spontaneous miscarriages which had been karyotyped. Various studies have shown a majority of Turner foetuses to have complete monosomy 45,X with frequencies ranging from 55% to as high as 80%.[8,9] Our study similarly shows a higher percentage of monosomy (74%).

The association of Turner syndrome with an increased risk of heart defect has been shown in various studies, ranging from 10% to as high as 60%,[9-11] of which the commonest is aortic coarctation.[9,11,12] Our study found a statistically significant number of left-sided heart defects, in particular aortic coarctation and hypoplasia, hypoplastic left heart and dextrocardia, compared to the incidence in the general population. Our cardiac defect incidence rate (13.9%), however, is lower than that of many other studies,

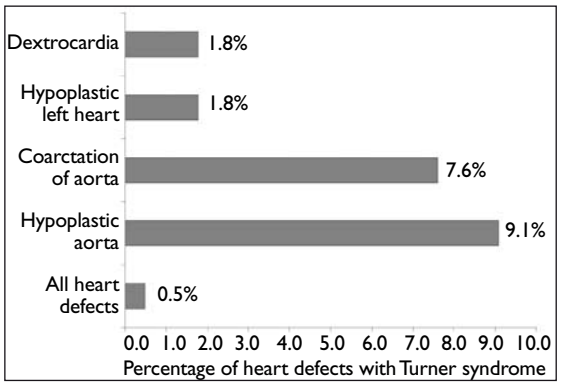


**Fig. 1** Contribution of Turner syndrome to heart defects in the population, 1999–2004.

likely due to the small number of post-mortems performed either postnatally or post-termination to confirm the presence of associated cardiac defects. We were, however, unable to show any significant difference in cardiac defect occurrence between the monosomic and mosaic Turners.

Our data shows a significant number of phenotypically normal Turner as well as mosaics. In a small study that looked at four foetuses diagnosed as 45,X at amniocentesis, Amiel et al found that in three phenotypically normal foetuses (but having 45,X karyotype), an additional normal cell line could be found in the foetal tissues.[13] They suggested that in 45,X cases in which no malformation is detected, the possibility of mosaicism should be raised. Could it then be that a significant number of our monosomic Turner foetuses are, in fact, mosaics? This question can only be answered if karyotyping is done on multiple foetal tissues, and is likely to be of more academic than practical interest, since we know that a prognosis of mosaics who are diagnosed after birth because of phenotypic features suggestive of Turner syndrome have a prognosis similar to that of 45,X children.[14]

Our data, together with others, indicates the importance of a detailed cardiovascular examination in early pregnancy, because anomalies of the aortic arch and left heart may serve as pathological markers for Turner syndrome. Other markers, like cystic hygroma and hydrops, should also alert obstetricians to this possible syndrome. It should be noted that a high proportion (about 30%) of the mosaic Turners in our study also have some form of cardiac defect. The true incidence of Turner syndrome is likely to be higher than that quoted in this study, and can only be solved when a complete screening of an entire population is performed.

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