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ORIGINAL ARTICLE

Karyotype patterns, clinical features, and parental ages of three predominant live born autosomal trisomies of Northeast Malaysia

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Abstract

Chromosomal abnormality is one of the causes of congenital disorders among newborns. Despite aneuploidy being the major cause of first trimester miscarriages, very few aneuploidies such as trisomies of chromosomes 13, 18 and 21 survive to birth. The results of 4,064 patients referred for cytogenetic analysis at Human Genome Centre, Universiti Sains Malaysia, Kelantan, Malaysia between 2008 and 2019 were reviewed. We retrospectively investigated the karyotype patterns, clinical features and parental ages of the three common live-born autosomal trisomies such as trisomy 13, trisomy 18 and trisomy 21. The relative frequency of cases with the total sample received and cultured was calculated in each group and compared with those reported elsewhere. Between 2008 and 2019, a total of 1034 live-born trisomic cases which accounted for 25.4% of the 4064 total referred cases and 73.7% of 1403 suspected trisomy cases, were identified, with age ranging from newborns to 57 years. Down syndrome was the commonest aneuploidy (857 cases; 21.1%) followed by Edwards syndrome (133 cases; 3.3%) and Patau syndrome (44 cases; 1.1%). The number of diagnosed cases for each of the trisomies was fairly stable from year to year. About two-thirds of both maternal and paternal ages were ≥ 35 years. This is the first cytogenetic report on the common live-born autosomal trisomies in the North-Eastern region of Malaysia. The prevalence of trisomies 21 was found to be higher compared to an earlier study in the North-Western region of Malaysia, wherein also, advanced maternal age was a significant risk factor.

Keywords: cytogenetic analysis, Down syndrome, Edwards syndrome, Patau syndrome, live born autosomal trisomies

INTRODUCTION

In humans, chromosomal abnormalities involving the number or structure of chromosomes are responsible for miscarriages, developmental delay, disorders of sexual development, mental retardation, and congenital malformations. Over 60% of first trimester miscarriages have an abnormal karyotype involving autosomal aneuploidies, thereby indicating aneuploidy as the major reason for pregnancy loss.[1] Although high levels of aneuploidy are seen in human spontaneous abortions, very few autosomal aneuploidies in the form of trisomies survive to birth. Autosomal trisomy refers to a condition where there is an extra copy of a particular autosome in the karyotype, resulting in three copies instead of the normal two copies. The most commonly found autosomal trisomies in live births are trisomy 13, trisomy 18 and trisomy 21 which give rise to the syndromes named Patau, Edwards and Down, respectively. Other autosomal trisomies, have been rarely reported in babies born alive but resulted in death soon after birth.[2] Trisomy of chromosome 1 and 11 have never been reported either in mosaic or non-mosaic form in live births.

Cytogenetic analysis is a very important component in making a correct diagnosis and

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for the subsequent management of the newborns with congenital abnormalities. We report here the results of screening for trisomy 13, 18 and 21 in live borns performed over twelve years in the Genetics laboratory of the Human Genome Centre, Universiti Sains Malaysia, Kelantan, Malaysia. It is a referral laboratory for genetic investigations providing service to the North-Eastern region of Malaysia. The region served by the laboratory includes the whole state of Kelantan and a big part of the neighbouring state Terengganu. There are about 20.6 and 23.0 live births per 1000 population per year in Kelantan and Terengganu respectively (Department of Statistics Malaysia, official portal). More than 95 % of the deliveries happen in the hospital and babies are examined by trained neonatologists before discharge. Multiple congenital abnormalities are the most common indications to request for chromosomal studies. Almost all babies, born alive, with the typical features of the common autosomal trisomies and undefined syndromic features get their karyotyping done.

Advanced maternal age is the primary risk factor for trisomy affected pregnancy.[3,4] The risk of an affected pregnancy increases with the mother's age particularly aged 35 onwards**.** Within the region covered by our laboratory, there is no systematic prenatal screening for trisomies in pregnant women in any age group. Our objective was to determine the prevalence, frequency and types of karyotype patterns, clinical features and parental ages in each of these three live born autosomal trisomies, observed from 2008 to 2019 in this part of the country. We also compared our findings with few other previous reports to determine whether any statistical differences in the frequencies exist.

MATERIALS AND METHODS

We retrospectively reviewed the karyotype analyses reports in the Genetics Laboratory of Human Genome Centre, Universiti Sains Malaysia, Kelantan between 2008 and 2019. All reports were from the culture of peripheral blood samples of cases referred from 12 hospitals. Based on the reason for referral, the study subjects were categorised into three groups: (i) clinically suggestive/ suspected Down syndrome (DS); (ii) clinically suggestive/ suspected Edwards syndrome (ES); and (iii) clinically suggestive/suspected Patau syndrome (PS). Referrals of cases for other suspected chromosomal abnormalities or clinically unidentifiable syndromes were excluded from the study. The medical records of all included cases were reviewed for clinical features, parental ages, test indication and the results of karyotype patterns.

Cytogenetic analyses of the study subjects were performed using standard procedures.[5] In short, peripheral blood samples (0.5 ml – 1.0 ml) collected in heparinised tubes were cultured at 37°C in 5% CO2 incubator for 72 hours to obtain metaphases by stimulation of blood lymphocytes with phytohemagglutinin (PHA). The metaphases were arrested using 0.5µg/ml colcemide and harvested. After hypotonic treatment with 0.075 M KCl, cells were fixed using methanol: acetic acid fixative (3: 1 ratio). Slides were prepared, aged and GTG-banded as per standardized procedure using trypsin and Giemsa's stain.[6] Routinely, a minimum of 30 well-spread metaphases with good quality GTG-bands was captured and the five best metaphases were karyotyped for each case, using the CytoVision software (Leica Microsystems, Germany). The resolution of GTG-bands used was generally around 450-500 bphs. In the doubtful cases of mosaicism, a total number of 60 or up to 100 metaphases were counted.

Whenever chromosomal translocations and unusual karyotypes were detected, the requests for parental blood samples (and siblings, where necessary) were made through the referring hospitals for chromosomal studies to obtain data on the inheritance. Based on the cytogenetic analysis results, the karyotype abnormalities were reported following the recommendations of an International System for Human Cytogenetic/ Cytogenomic Nomenclature (ISCN 2009, 2013, 2016).

The karyotype patterns observed were correlated with the clinical features of these three commonly occurring live born trisomies. Patients who were identified as having chromosomal abnormalities received post-test genetic counselling. Data are presented by using descriptive statistics and no statistical significance tests were performed.

RESULTS

During the 12 years, a total of 4,064 samples with suspected chromosomal abnormalities were referred for cytogenetic analysis. The ages of the referred cases ranged from newborn to 57 years with a mean age of 0.5 ± 2.6 years. The abnormalities consisting of numerical and structural aberrations of chromosomes were

Table 1: Distribution of cases analysed during 2008-2019 in Northeast Malaysia

Chromosomal abnormality	Number of suspected cases	Number of confirmed cases (% of confirmed cases)
Total cases analysed	4064	1034 (25%)
Live born common autosomal trisomies	1403	1034 (73.7%)
Trisomy 21	1030	857 (21.1%)
Trisomy 18	247	133 (3.3%)
Trisomy 13	130	44 (1.1%)

observed in 1034 out of 4064 referred cases. Commonly occurring autosomal trisomies such as trisomy 21, trisomy 18 and trisomy 13 comprised of 25.4 % of the total cases (Table 1).

Among the autosomal trisomies, a total of 1,030 cases were referred for suspected Down syndrome. These cases presented with distinctive phenotypic features including hypotonia (the first abnormality noticed in newborns), dysmorphic facial features such as flat nasal bridge, low set ears, brush field spots around the margin of iris, open mouth with furrowed and protruded tongue, brachycephaly with a flat occiput. Other features noted include short neck with loose skin on the nape, characteristic epicanthic folds and upslanting palpebral fissures, short stature, short and broad hands often with a single transverse palmar crease, incurved fifth finger or clinodactyly, highly characteristic dermatoglyphics and a wide sandal gap between first and second toes. In addition to these characteristic features, congenital heart disease, duodenal atresia and tracheoesophageal fistula were also present in around one-third of the live-born DS patients.

The cytogenetic analysis confirmed a diagnosis of DS in 857 out of 1034 (82.8%) trisomy confirmed cases and 83.2% of the total 1030 suspected DS cases (Table 1). Thus, DS accounted for the highest number of trisomies (82.8%) among the three live born trisomes. The distribution of parental age of all the three autosomal trisomy cases is shown in Table 2. About two-thirds of mothers and fathers had an age of 35 or more at the time of delivery of the reported cases. Among the DS cases, free trisomy (non-disjunction) was present in 813 cases (94.9%), whereas 24 cases (2.8%) were mosaics and 20 cases (2.3%) were translocation DS which involved Robertsonian translocation of the extra chromosome 21 with any one of the acrocentric chromosomes (Table 3). DS affected both males and females almost in an equal ratio (1:1) and no significant difference was noticed. Four cases of trisomy 21 (T21) were associated with additional structural chromosomal aberrations. There were two cases of T21 along with inversion 8. In one of these two cases, inversion 8 was confirmed to be inherited from the father after parental karyotyping showed the presence of similar structural chromosome 8 abnormality in the father's karyotype. In addition to that, one case of T21 with inversion 9 and one case of T21 co-occurring with rob t(13;14) was also recorded. A total of four twin pairs were tested for DS during the reported period. The cytogenetic analysis confirmed two pairs as monozygotic DS twins, whereas the other two pairs are dizygotic twins, each with one affected child.

ES was found to be the second most common

Table 2: Parental age distribution of the three live born autosomal trisomies

	Age group	Trisomy 21		Trisomy18		Trisomy13	
		No	%	No	%	No	%
Maternal	<35	252	31.1	44	33.3	18	40.5
	≥35	573	66.9	82	61.1	25	57.1
	unknown	17	2.0	7	5.6	1	2.4
Paternal	<35	199	23.2	35	26.2	15	33.3
	≥35	608	71	72	54	25	57.7
	unknown	50	5.8	26	19.8	4	8.8

Table 3: Chromosomal abnormalities in children with Down syndrome cases

Karyotypes	No.of cases	%
Non-disjunction	**813**	94.9
47,XX,+21	390	45.5
47,XY,+21	415	48.4
47,XX,inv(8)(p12;q21.3),+21	1	0.1
47,XX,inv(8)(p21;q22),+21	1	0.1
47,XY,inv (9)(p21q21.1),+21	1	0.1
47,XX,15pstk,+21	1	0.1
47,XX,+21,22pss	1	0.1
48,XX,+21,+mar	2	0.2
47,XY,+21/complex abnormalities	1	0.1
Mosaic	**24**	2.8
47,XX,+21/46,XX	15	1.8
47,XY,+21/46,XY	8	0.9
47,XY,+21/48,XXY,+21	1	0.1
Structural rearrangements/ translocation	**20**	2.3
46,XY,rob(14;21)(q10;q10)+21	3	0.4
46,XX,rob(14;21)(q10;q10)+21	3	0.4
46,XX,rob(15;21)(q10;q10)+21	3	0.4
46,XY,rob(15;21)(q10;q10)+21	1	0.1
46,XY,+21,rob(21;21)(q10;q10)	2	0.2
46,XX,+21,rob(21;21)(q10;q10)	7	0.8
46,XY,rob(13;14)(q10;q10),+21	1	0.1
Total	857	100.0

live born autosomal trisomy suspected in 247 cases. A clinical diagnosis of ES was suspected when newborns presented with some combination of the following features: clenched hand with a characteristic grip in which the second finger overlapped the third and the fifth overlapped the fourth, intrauterine growth retardation (IUGR), rocker-bottom feet, micrognathia, prominent occiput, micro-ophthalmia, low set ears, cardiac defects such as ventricular septal defect (VSD), atrial septal defect (ASD) patent ductus arteriosus (PDA), strawberry-shaped calvarium, generalised muscle spasticity, and renal anomalies.

Out of the 247 suspected ES cases, a confirmatory diagnosis of trisomy 18 (T18) was derived in 133 cases which accounted for 3.3% of total cases and 53.8% of T18 suspected cases (Table 1). There were 122 cases (91.7%) of free T18 (non-disjunction), 8 cases (6.0%) mosaics and 3 cases (2.3%) of T18 involving structural aberrations (Table 4). Out of these three cases of T18 with structural aberrations, two were isochromosome for the long arm of one of the chromosome 18, i(18)(q10) and one case was with trisomy of the long arm of chromosome 18 (18q) with an extra-long arm of chromosome 18 attached to the long arm of chromosome 22 which resulted in 46,XY,der(22) t(18;22)(q10;q10) karyotype (Table 4). As shown in Table 2, 54% of father and 61.1% of mother of T18 cases were more than 35 years. There was a female preponderance among T18 cases (female : male ratio of 2:1). During the study period, only one pair of female monozygotic twins was reported as concordant for T18.

In the majority of the T18 doubted cases, the blood samples received for cytogenetic analysis in our lab were from newborns, except for two cases where the cytogenetic analysis was requested at the age of 6 years old. One of them harboured mosaic trisomy 18 and another one was with full trisomy 18 karyotype pattern. After reviewing patient's latest clinical records, we found that the patient with full trisomy 18 was still alive till the time of writing this paper, and currently 16 years old but she was bedbound since birth and had severe developmental delay and epilepsy.

Among the three live born trisomies reported

Table 4: Chromosomal abnormalities in children with Edwards syndrome cases.

Karyotypes	No.of cases	%
Non-disjunction	**126**	**94.7**
47,XX,+18	83	62.4
47,XY,+18	38	28.6
48,XXY,14pss,+18	1	0.8
47,XX,+18/46,XX	4	3.0
Mosaic - 47,XY,+18/46,XY	**4**	**3.0**
Structural rearrangements/translocations	**3**	**2.3**
46,XY,i(18)(q10)	1	0.8
46,XX,i(18)(q10)	1	0.8
46,XY,der(22)t(18;22)(q10;q10)	1	0.8
Total	133	100.0

here, Patau syndrome or trisomy 13 (T13) was the third most common autosomal abnormality encountered in our centre. When a newborn traditionally presented with some combination of the following phenotypic features, a clinical diagnosis of T13 was suspected for which karyotype analysis was indicated to confirm the diagnosis. The features included holoprosencephaly, polydactyly, seizures, deafness, microphthalmia, microcephaly, midline cleft lip, midline cleft palate, abnormal ears, sloping forehead, cutis aplasia (punched out lesions of the scalp), omphalocele, cardiac and renal abnormalities.

Karyotype analysis confirmed 1.1% (44 cases) of all total cases and 4.2%% of live-born trisomies to be Patau syndrome or trisomy 13 (T13). Of these cases, there were 41 (93.2%) free trisomy 13 (non-disjunction) cases, 2 cases (4.5%) of mosaic T13 and 1 case (2.3%) with Robertsonian translocation rob(13;13)(q10;q10) leading to this disorder (Table 5). All the cases were newborns at the time of blood sampling for karyotype analysis. As shown in Table 2, 57% of the parents were more than 35 years. Patau syndrome was also slightly more common in female with a female to male ratio of 1.3 to 1. During the study period, no twins with Patau syndrome were documented in our centre.

DISCUSSION

This is the first report to provide data on the three common live born autosomal trisomies in Northeast region of Malaysia in the last 12 years. We observed that the frequencies of live-born trisomies 21,18 and 13 in this region of Malaysia are high. Few reasons could be attributed to this. Firstly, prohibition on termination of pregnancies because of cultural and social norms differ in Malaysia compared to the western countries. Whereas a higher proportion of trisomy affected pregnancies in Europe ends in termination[7], a pregnancy in Malaysia can only be legally terminated in circumstances where there is a real and substantial risk to the health of the mother. Moreover, termination of pregnancy for foetal anomaly (TOPFA) is not permitted under the

Table 5: Chromosomal abnormalities in children with Patau syndrome cases

Karyotypes	No. of cases	%
Non-disjunction	**41**	**93.2**
47,XX,+13	24	54.5
47,XY,+13	17	38.6
Mosaic - 47,XY,+13/46,XY	**2**	**4.5**
Structural rearrangements/translocation - 46,XX,+13,rob(13;13)(q10;q10)	**1**	**2.3**
Total	44	100.0

Islamic law constitution in Malaysia (Section 312 of the Malaysian Penal Code). Second, in rural areas, the mothers decline to go for follow-ups at health institution to have prenatal diagnosis during pregnancy. Finally, advanced maternal age and the high birth rate of an average of 4 to 5 children in each family (range of existing children 1 to 13 children) in this region of Malaysia could also be other reasons.

Although consanguinity has been reported to increase the risk for autosomal recessive conditions to offsprings, the effect of consanguinity on trisomies is not known.[8] Moreover, the frequency of consanguineous marriages has an extremely low rate in this part of the country and the study population. So, consanguinity cannot be considered to be a contributory factor in the higher frequency of trisomies in this region. Even in a study from Jeddah where a higher rate of consanguinity of parents was observed, no statistically significant association between consanguinity and the occurrence of trisomies could be observed.[9]

Mot *et al*. (2017) reported 5-year findings from the cytogenetic analysis of referred North-Western region of Malaysia for suspected chromosomal abnormalities.[10] They included all the chromosomal abnormalities and they found that majority of cases were DS (16.5%), followed by ES (3.2%), PS (1.1%) and Turner syndrome (2.0%). However, the current study focused on the frequencies of three most common live born autosomal trisomies out of the total referred cases to our laboratory in the North-Eastern region of Malaysia over the last 12 years. In few other countries also, termination of pregnancy is much less readily accepted by the population where cultural, religious and legal factors contribute to much lower rates of termination of pregnancy and thus contributing to higher rates of live births with trisomies.

Awareness of prenatal diagnosis and genetic counselling have improved with advancing medical research. While in most European countries the average age of pregnant mothers has increased over the last decennia, the incidence of babies born alive with trisomies has been either static or even dropped to extremely low figures (e.g. Iceland and Denmark, where more than 90% of pregnancies with antenatally diagnosed trisomies are terminated). The prenatal detection rate of trisomies and other chromosomal abnormalities has been reported to approach almost 90% in countries where maternal serum biochemical markers combined with foetal ultrasound findings are practised.[11-13] In countries where the prenatal cytogenetic diagnosis is relied upon and where religious factor does not have any influence on elective termination of pregnancies, the incidence of chromosomal aberrations especially trisomies, have significantly reduced.[13]

In the present study, DS with T21 was the commonest autosomal aneuploidy among live borns. This has been probably attributed to the preferential tolerance of trisomy 21 over other trisomies. Chromosome 21 is the shortest human autosome and also with the smallest number of protein-coding sequences. Hence according to O'Connor (2008), an extra copy of chromosome 21 would change the normal function of cells less than an extra copy of any other autosome.[14] DS was the most frequent reason for cytogenetic analysis referral, and the majority of such patients were karyotypically confirmed as having DS. Compared to the findings of Thillainathan et al. (2015)[15] which reported 42.7% of their cases as having DS, our study reported a much lower relative frequency (21.1%) of the total cases. But in Thillainathan *et al*., (2015) study, the frequency was out of a total of 1554 cases, whereas in the present study, the frequency is out of 4064 total cases (Table 6). There are few earlier studies (Balkan *et al*., 2010, Kovaleva and Mutton, 2005)[16,17] which reported a male preponderance in the DS cases. But in the current study, DS affected both male and female in 1:1 ratio. Nearly 92% of the DS cases were infants less than one year old. In agreement with several previous studies,[10,15,16] free trisomy resulting from chromosomal non-disjunction was the main cause in 94.9% of DS children. Translocation DS and mosaic DS were encountered in 2.8% and 2.3% respectively among our DS cases. Several studies reported variable frequencies of translocation and mosaic DS. Some studies reported a higher frequency of translocation DS than mosaic DS whereas others reported vice versa [18]. The frequency of only 2.8% mosaicism in our study was lower when compared to 10.8% in Thillainathan's study. Similar findings were reported in another study conducted in North-Western Malaysia.[10] In their study, the frequency of pure trisomy, mosaicism and translocation was 94.3%, 2.3% and 3.3% respectively (Table 6). The variation observed in frequency could be attributed to the selected study population. An interesting finding of our study was the identification of one rare case of double aneuploidy involing DS/

Table 6: Distribution of autosomal chromosomal abnormalities by karyotype and comparison with other studies

Karyotype	Present study 12 years study [Total:4064]		Mot *et al*, 2017 5years study [Total:1805]		Thillainathan *et al*, 2015 - 6years study [Total:1554]	
	No.	Relative frequency(%)	No.	Relative frequency(%)	No.	Relative frequency(%)
Down syndrome	857	21.1	299	16.5	665	42.7
Non-disjunction	813	94.9	282	94.3	560	84.2
Mosaic	24	2.8	7	2.3	72	10.8
Translocation	20	2.3	10	3.3	33	5.0
Edwards syndrome	133	3.3	57	3.2	18	1.1
Non-disjunction	122	91.7	54	94.7	17	94.4
Mosaic	8	6.0	3	5.3	0	-
Translocation	3	2.3	0	-	1	5.6
Patau syndrome	44	1.1	20	1.1	4	0.2
Non-disjunction	39	92.8	18	90	3	75
Mosaic	2	4.8	0	-	0	-
Translocation	1	2.4	2	10	1	25

Klinefelter syndrome.

Non-disjunction trisomy 21 most commonly occur de-novo due to error in maternal non-disjunction in the first meiotic division, with meiosis I error occurring three times as frequently as meiosis II errors. Advanced maternal age remains the only well-documented risk factor for maternal meiotic nondisjunction.[19] Identification of translocation DS is an indication for a karyotypic screening of both parents as either one of them may be a carrier of a balanced translocation involving chromosome 21. In our study, we detected 4 parental carriers of Robertsonian translocation; 3 involving chromosomes 15 and 21 and one involving chromosomes 14 and 21. The translocations carriers were the mothers of the probands in three cases whereas in the fourth case, father was the carrier. Translocation carriers have a high risk of aneuploid offspring with every pregnancy; the recurrence risk depends on both the sex of the carrier parent and the chromosomes that are fused.[20] Nearly 20% of children from translocation carrier mother and 5-10% from translocation carrier father have the risk to evolve DS.[21] If one of the parents is the carrier of a balanced translocation involving the two chromosome 21s, the recurrence risk for DS is 100%.[22]

Mental retardation is the major cause of concern in DS. Even by end of the first year, delay in development will be obvious. By the time the child is old enough to be tested, IQ will be around 30 – 60. Those DS infants with congenital heart disease (CHD) generally die before one year. Determination of karyotype pattern of DS patients is important not only to indicate the recurrence risk but also in the clinical follow up of certain disorders associated with DS. Babies with DS have 15 fold increased risk of developing malignancies and most commonly leukaemia. Premature dementia associated with neuropathological characteristics of Alzheimer's disease will be higher in DS patients in whom the age of onset will be several decades earlier than the general population. Based on the karyotypic confirmation of DS, patient's family can be counselled about the risk of susceptibility to these disorders so that early medical management can be initiated and thereby the DS patients' life expectancy can be increased.

Trisomy 18 was the second most common live-born trisomy behind DS. T18 has been documented to show a 3: 1 female: male predominance.[23] This is almost in agreement with our study patients where 88 cases were females and 43 were males. In general, around 94 % of T18 cases are free trisomy due to maternal nondisjunction, mosaicism accounts for around less than 5% of cases whereas approximately 2% of cases are due to a translocation.[24] This is in agreement with our results where free trisomy

18 accounted for 91.7%, mosaicism for 6% and structural abnormalities involving chromosome 18 accounted for 2.3% of the total 133 cases. Another interesting observation was one case of double aneuploidy involving ES (trisomy18) and Klinefelter syndrome (reported separately by Amalina Zakaria *et al.* 2020).[25] The proband born to non-consanguinous parents of advanced age survived only for 19 hours after birth. The lymphocyte karyotype was 48,XXY,14pss,+18 in 30 metaphases examined. So far, only 33 cases were reported to have double aneuploidy involving trisomy 18 and sex chromosome trisomy. Out of these, 11 cases were reported double aneuploidy involving ES with Klinefelter syndrome, and with 48,XXY,+18 karyotype pattern similar to the kayotype encountered in our patient. Based on the literature reviewed, median survival time was 24 days and one-year-survival was 7% for these double aneuploidy cases.[26]

The prognosis of T18 cases is lethal and are well known for infant mortality. With severe MR and severe failure to thrive, 50% of T18 patients die by one week of life, 90% of trisomy 18 children die within the first year of life, few pass their first year of life and very few live until their teens and twenties.[23] However, long term survival of few T18 cases have been reported which described 20 year old, [27] 14 year old,[28] 19 year old,[29] 11 year old,[30] and 21 year old,[31] all female patients with T18. Few other cases of affected children with T18 aged >10 years had also been reported.[32-34] During the period 2008-2019, we also encountered two T18 cases, who survived more than 1 year of life. One was a six year old female who had a mosaic T18 karyotype. The second case is a full T18, case who is still alive at 16 year of age, but bed-bound since birth and complicated with developmental delay and epilepsy. Due to the complexity and severity of the clinical presentations at birth, and the high neonatal and infant mortality, the perinatal and neonatal management of babies with T18 is particularly challenging, controversial and unique among multiple congenital anomaly syndromes.[24]

Among these three live born autosomal trisomies, trisomy 13 (T13) was the third common live-born trisomy disorder. This disorder showed almost equal distribution between affected males and females. Among our total T13 cases, 19 were males and 25 were females. Approximately 75 % of T13 cases are reported to be due to maternal non-disjunction, 20% of cases are due to translocation and 5% of cases are due to mosaicism.[35,36] Out of our 44 T13 cases, 41 were nondisjunction cases, 2 cases were mosaics, and 1 case was a translocation type. Compared to T18 or T21, T13 tends to present with more severe craniofacial midline defects. A defect in the fusion of the midline prechordial mesoderm in the first three weeks of gestation is the main reason for the major midline dysmorphic features of T13.

Although the majority of T13 cases present with the clinical triad of signs namely microphthalmia, polydactyly and cleft palate, some of our patients did not have all these signs together. A variety of phenotypic expression was evident when mosaicism existed for trisomy cell line in some of these patients. This highlights that in order to make a diagnosis, a clinical diagnosis alone is not enough. A T13 was implicated for cases who presented with even partial typical features, including or not the clinical triad. Such condition stresses the importance of cytogenetic analysis as mandatory for an accurate diagnosis and genetic counselling. Due to severe clinical manifestations especially cardiac defects, T13 babies rarely do survive to one year of life. The mean survival time (MST) reported for T13 is seven days.[37] However, like T18, exceptions do exist for T13 also. Few reports of unusual babies with T13 surviving their first year of life have been documented.[38,39] But they were not able to to live independently and needed constant care. During the 12 years study period, we have not come across any T13 patients surviving first year of life.

The mechanism by which gametes that contain trisomy usually arise as a result of errors in meiosis, (non-disjunction). Studies have suggested that most trisomies are of maternal origin. Hassold and Hunt (2001) had proposed three general rules of human non-disjunction by which trisomies originate (i) regardless of a specific chromosome, most trisomies originate during oogenesis (ii) for most chromosomes, maternal meiosis I (M1) errors are more common than maternal meiosis II (MII) errors, (iii) the proportion of cases of maternal origin increases with maternal age.[40] This was quite evident in our study, where nearly 55-70% of the parents were more than 35 years.

It has been reported that for 90% of the trisomy cases, non-disjunction occurs during maternal meiosis I and for about 10% of the cases, nondisjunction occur during paternal meiosis II.[14] In T13 and T21, 90% of nondisjunction events are maternal, usually arising at meiosis I. Whereas

in T18, two-thirds of the 90% of maternal origin cases arise at meiosis II.[41] According to Delhanty (2018), trisomies may arise during any one of the three stages in development; during gamete formation, at fertilisation or during early stages of embryo development.[42] Using polymorphic DNA markers, researchers have already established that most trisomies result from the nondisjunction of chromosomes during parental meiosis.[40] Considering the fact that human oocytes can be arrested in prophase I for several decades, this observation makes sense. Apparently, the risk of trisomy also increases sharply with maternal age, particularly as women near the end of their reproductive phase in life. It is because of this awareness among medical community that prenatal diagnosis of foetal chromosome abnormalities is advised for pregnant women over the age of 35.

However, a major limitation of this study is that these data are from a single clinical service centre. So, it is probable that some samples might have been sent to other laboratories in other parts of the country and hence our data do not represent the exact prevalence. Thus, the comparison with the prevalance of chromosomal abnormalities from other countries is not feasible. There is a need to establish Malaysian chromosomal abnormalities registries as these could help in the planning of specific strategies to reduce the incidence of live-born trisomies by offering genetic counselling to elderly mothers for effective family planning, providing a way to track trends in the occurrence, planning for cytogenetic assessments and follow-up studies in babies who are born with abnormal clinical features. Another limitation is that the association between types of chromosomal abnormalities and maternal/paternal age was analysed based on the available data.

Despite these, the high rate of cytogenetic confirmation of these three clinically suspected live-born autosomal trisomies reflects the clinical skills of neonatal paediatricians in this region as well as the recognizable phenotype of these syndromes. As chromosome abnormalities contribute to the aetiology of significant congenital disorders, cytogenetic analysis is an essential tool in establishing a definitive diagnosis. In cases where the structural abnormality is observed, there is the need to determine whether it is inherited or de novo in origin. Thus cytogenetic analysis has tremendous implications for genetic counselling.

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