CASE REPORT

DOWN SYNDROME AND PATAU SYNDROME IN THE SAME SIBSHIP: RANDOM OR NOT?

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Abstract

Objectives: Chromosomal abnormalities especially aneuploidies are the most common etiology for pregnancy loss. Trisomy 13, trisomy 18 and trisomy 21 are the most common chromosome autosomal aneuploidies with trisomy 21 (Down syndrome) being the most common chromosomal abnormality among liveborn infants. In previous reports, we noted that the recurrence of these aneuploidies in some families may not occur by chance alone. **Methods:** Extraction of relevant data from review of medical case notes of a young couple with two offspring with Down syndrome (DS) and Patau syndrome. **Results:** A family history of DS is a predisposing factor for both DS and other types of aneuploidy**.** Certain instances of non-disjunction error are not random**. Conclusion:** As the maternal age was not advanced in both pregnancies, there is a possibility that the recurrent aneuploidy in this family may not be accounted by chance alone. The risk of having subsequent affected pregnancy cannot be ignored in this family and prenatal diagnosis is strongly recommended in the subsequent pregnancy.

Keywords: Recurrent Aneuploidy, Down Syndrome, Trisomy 21, Patau Syndrome, Trisomy 13
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Introduction

Fifteen percent of clinically recognized pregnancies result in fetal death [1]. Cytogenetic abnormalities are more common in spontaneous abortions (50% of fetal deaths less than 20 weeks) than in stillbirths (6 to 13% of fetal deaths more than 20 weeks) [1]. A 1998 multicentre survey of 103 069 live births in the United States identified major chromosomal abnormalities in 1 in 140 live births [2]. The

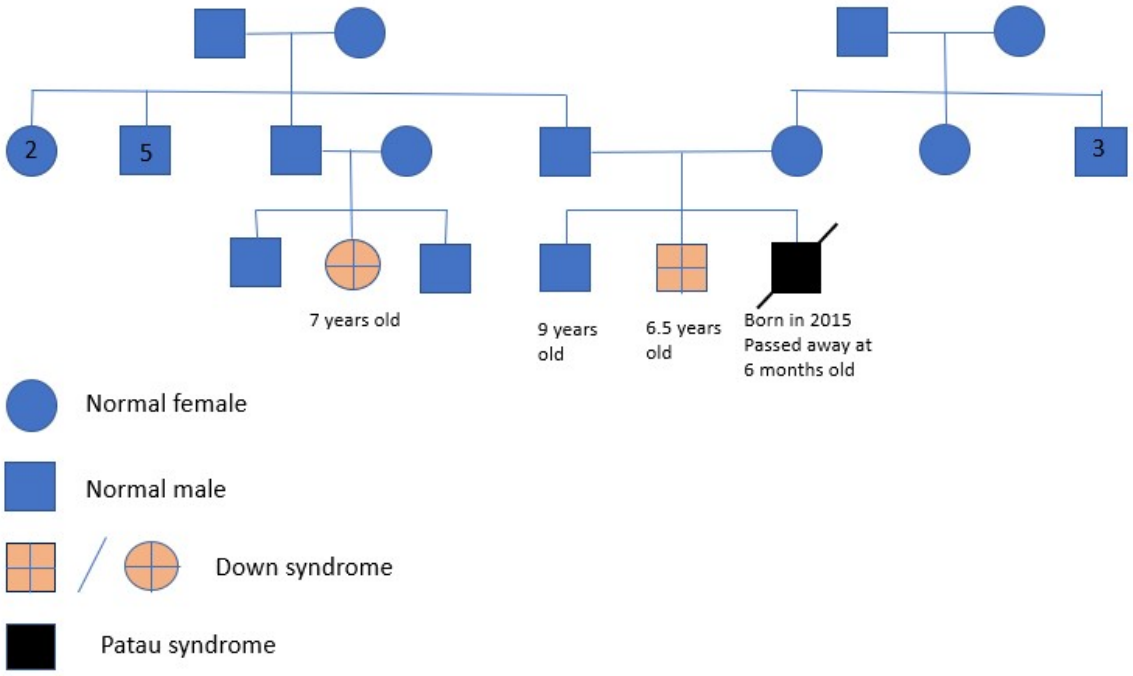
American College of Obstetricians and Gynaecologists also published similar incidence rate in which about 1 in 150 babies is born with a chromosomal abnormality [3-5]. Trisomy 13, trisomy 18 and trisomy 21, the most common chromosome autosomal aneuploidies, accounted for 73.6% of all clinically significant chromosomal abnormalities with a rate of 1.13% [6]. In an earlier report, the incidence of Down syndrome in Malaysia has been reported as 1 in 950 and little variation has been reported among the three largest ethnic groups (Malays 1:981, Chinese 1:940, Indians 1:860) [7,8]. Unfortunately, there are no reports on the recent incidence of Down syndrome in the Malaysian population [8]. This case report describes a family with Down syndrome and Patau syndrome in same sibship. The recurrence of these aneuploidies in this family may not occur by chance alone.

Case history

A borderline premature baby was born to a 31-year-old woman who was gravida 2 para 1. He was born vigorous but appeared dysmorphic. He had hypertelorism, depressed nasal bridge, low set ears and single palmar crease. He was clinically diagnosed to have Down syndrome and cytogenetic analysis was sent. He had transient hypothyroidism and required L-thyroxine 25mcg up till 10 months of age. He also had congenital nasolacrimal duct obstruction, borderline hypermetropia and left alternating esotropia. Hearing assessment was normal but he required speech therapy. Otherwise he is well and attends kindergarten.

In the third pregnancy, the maternal age was 35 years old. A baby boy was born and subsequently diagnosed to have Patau syndrome. The labour was uneventful but the baby was born with Apgar score of 6 at 1 minute and 9 at 5 minutes and he required resuscitation. Upon examination, the baby appeared dysmorphic and had cyanosis. He had a broad forehead, depressed nasal bridge, hypertelorism, receding chin, webbed neck, trisomy fingers, micropenis, joint laxity of both ankle, bilateral rocker bottom feet and cutis aplasia congenita. Echocardiography of the heart showed Tetralogy of Fallot with severe pulmonary hypertension. Cranial ultrasound revealed corpus dysgenesis. Cytogenetic analysis was sent. The findings were consistent with a clinical diagnosis of Patau Syndrome. Family counselling was performed and the child was managed conservatively; he died at 6 months of age.

Figure 1. Family tree of the family. One of the paternal brother has a daughter with Down syndrome



Cytogenetics

Chromosomal analysis was performed in the two probands and their parents. Chromosomal preparations obtained from Phytohaemagglutinin (PHA) – stimulated peripheral blood cultures, were subjected to Giemsa-Trypsin-Giemsa (GTG) banding and karyotyping was done according to ISCN 2009 and ISCN 2014. Chromosomal analysis (using ISCN 2009) of first proband revealed 47,XY,+21 [Figure 2]. Chromosomal analysis (using ISCN 2014) of second proband revealed 47,XY,+13 [Figure 3]. Fluorescent in situ hybridization (FISH) analysis was also performed on the second proband and revealed 3 signals for chromosome 13 in 200 interphase nuclei examined. Parental karyotypes according to ISCN 2014 were normal [Figures 4 and 5].

Figure 2. Cytogenetic analysis of the male infant with Down Syndrome

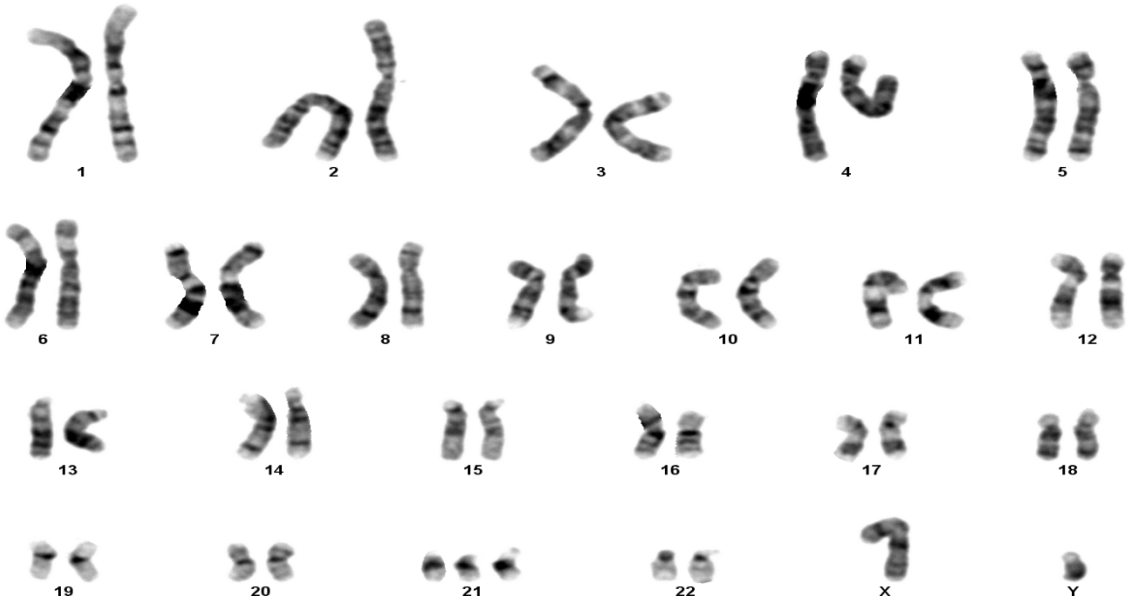


Figure 3. Cytogenetic analysis of the male infant with Patau Syndrome

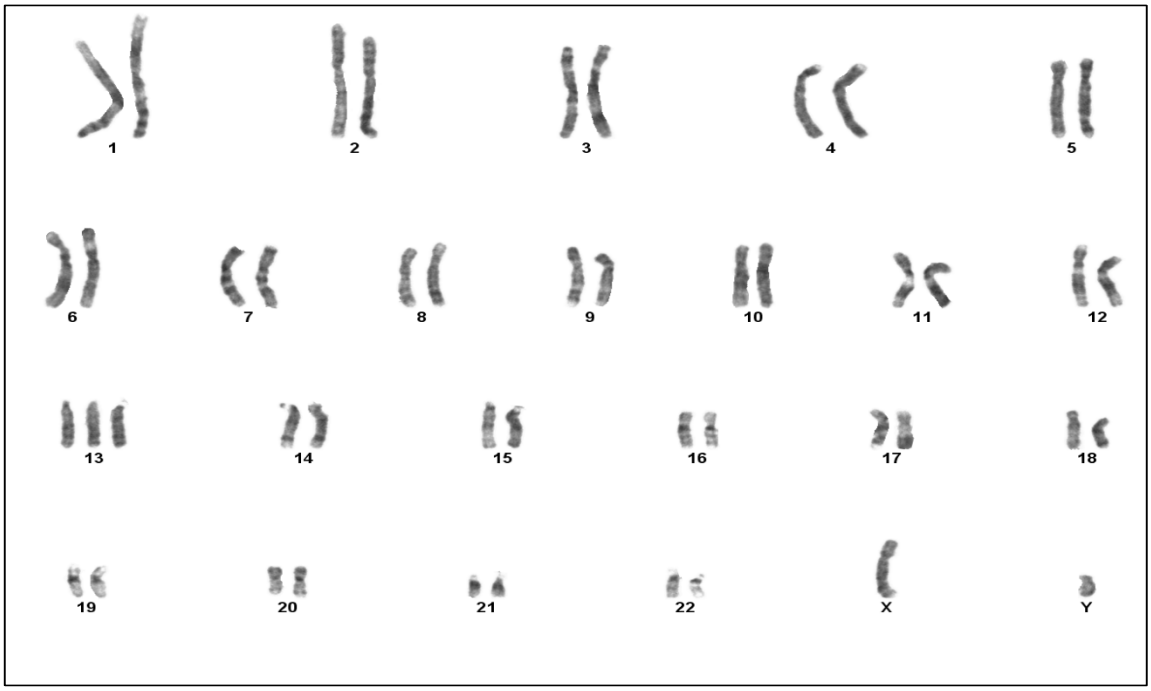


Figure 4. Cytogenetic analysis of the father showing a karyotype of 46,XY

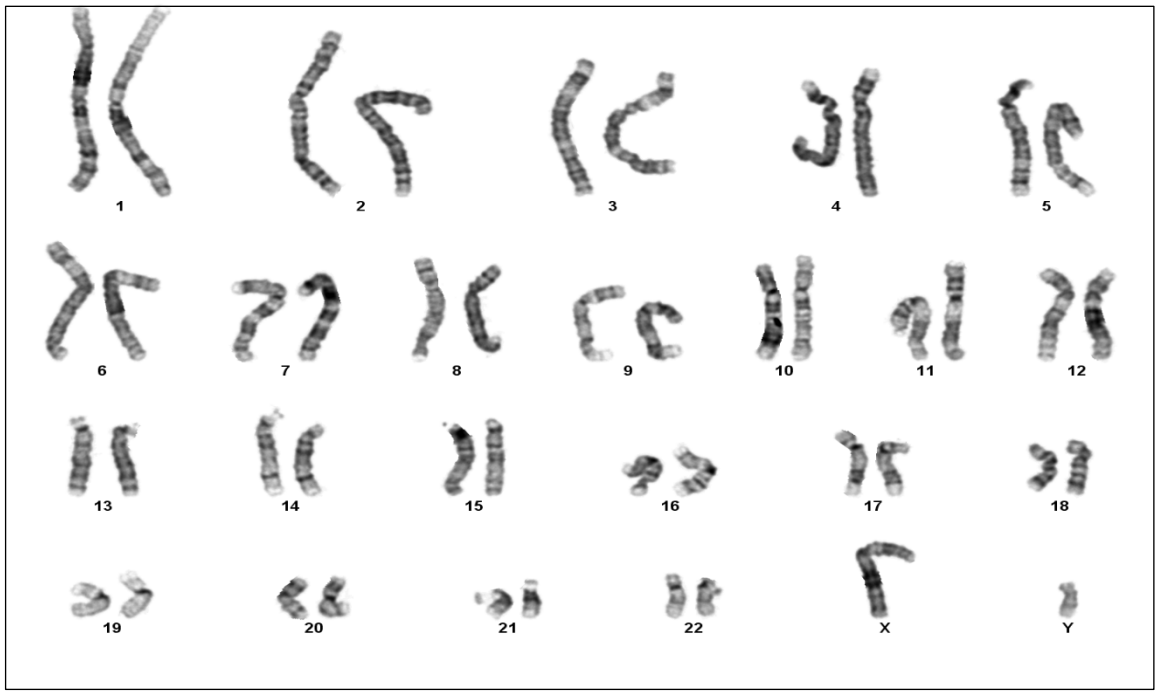
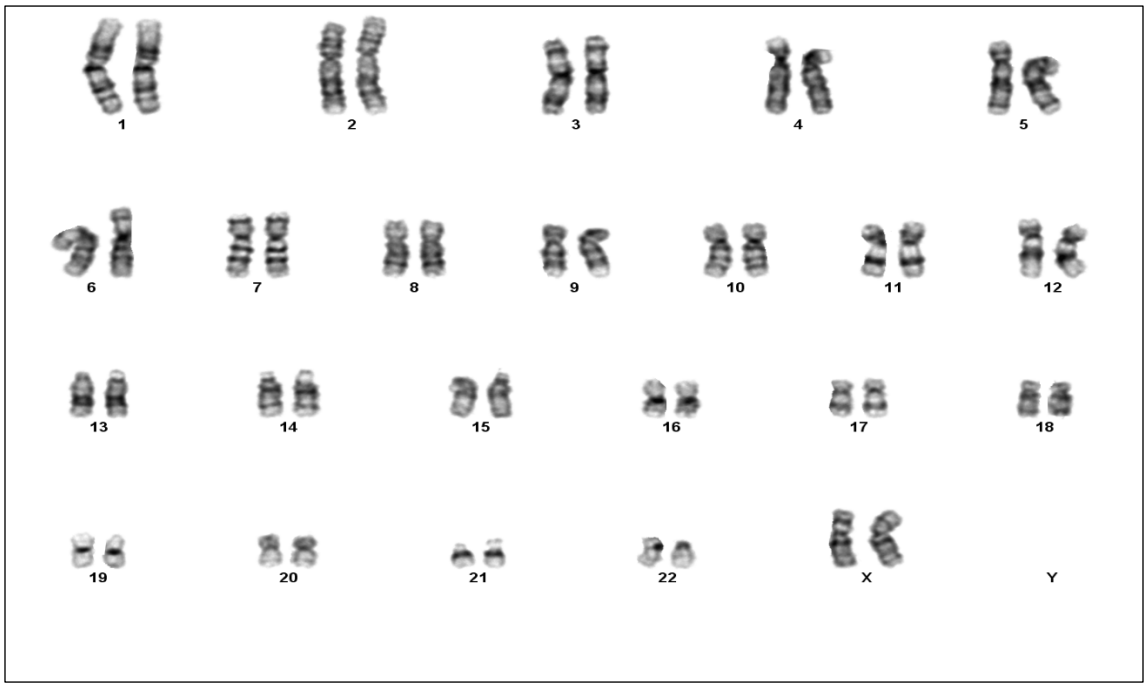


Figure 5. Cytogenetic analysis of the mother showing a karyotype of 46,XX



Discussion

To date, chromosomal abnormalities especially aneuploidies are the most common etiology for pregnancy loss. Trisomy 21 (Down syndrome-DS) remains the most common chromosomal abnormality among liveborn infants [6,9-11]. In our case report, this family had a son with Down syndrome during the second pregnancy. A family history of DS is a predisposing factor for both DS and other types of aneuploidy [12-16]. Some of these recurrences may occur by chance alone but this cannot account for most of them. Familial concentrations of patients with different cytogenetic abnormalities has supported that certain instances of non-disjunction error are not random [17-25]. As seen in our case report, this family also had a son with Patau syndrome. As the maternal age was not advanced in both pregnancies, there is a possibility that the recurrent aneuploidy in this family may not be accounted by chance alone.

Table 1 shows the second trimester amniocentesis results in four studies of women who had the procedure because of a previous pregnancy with trisomy 21. Overall, of the 4953 pregnancies, 42 (0.85%) had DS, a highly statistically significant excess of 27 (0.54%) compared with the number expected on the basis of maternal age alone (chi-squared=46; p $\leq$0.0001) [26]. The studies in Table 1 also documented aneuploidies other than DS among these group of women. There were 30 affected pregnancies (0.61%), a statistically significant excess of 12 (0.25%) compared with the number expected from the maternal age alone (chi-squared=8.3; p <0.005). Of the 30 affected pregnancies, three have Patau syndrome. This clearly supports that some of the recurrences of cytogenetic abnormalities are not explained by chance alone.

Table 1. Risk of DS and other aneuploidy in 4 studies of women having amniocentesis because of previous DS pregnancy, Arbuzova S et al, 2001 [26]

Study (reference)	Down syndrome						Other aneuploidy*
	Maternal age					Total	
	<25	25-29	30-34	35-39	40+		
Canada (22)	0/51	0/96	1/64	0/24	1/7	2/242	2
Europe I (8)	2/199	1/452	1/418	3/244	0/75	7/1388	10
Europe II (9)	3/331	7/826	2/734	6/343	1/119	19/2353	13
Japan (10)	0/41	5/301	3/394	5/195	1/39	14/970	5
Total	5/622	13/1675	7/1610	14/806	3/240	42/4953	30
Rate (%)	0.80	0.78	0.43	1.74	1.25	0.85	0.61
Expected (%)**	0.10	0.13	0.20	0.59	2.20	0.31	0.36
Excess (%)	0.70	0.65	0.23	1.15	-0.75	0.54	0.25

*Klinefelter (6), Edwards (4), Turner (4), Patau (3), XYY (3), XXX (2), +fragment, +marker and 5 others of unspecified karyotype.
**Based on prevalence rates for each chromosomal abnormality among livebirths in 5-year maternal age intervals, adjusted for the estimated rate of fetal loss from the time of amniocentesis (1).

Arbuzova S et al., [26] also emphasized that familial aggregation of DS and other aneuploidies is not attributable to chance alone and cannot be satisfactorily explained by parental mosaicism. Evidence from several sources strongly suggests the involvement of mitochondrial DNA (mtDNA) in the aetiology of DS and other aneuploidies [26-31]. Mutations in mtDNA bring about an increase in the generation of free radicals and reduce ATP levels, and thereby may affect the synaptonemal complex, chromosomal segregation and division spindle, alter recombination (the enzymes participating in recombination and DNA repair are ATP dependent [32, 33]) and thus lead to aneuploidy. It is well established that the number of mtDNA mutations increases with age in different cells, particularly in oocytes [28], as does the risk of trisomy 21 [6, 27, 30, 31], trisomy 13 and trisomy 18 [6]. However, in our case report, as maternal age was not advanced, involvement of mtDNA mutation may not be the aetiology of her recurrent aneuploidy.

In this case report, we postulate that the recurrence of trisomy 13 after trisomy 21 in the same siblingship may not be purely by chance. Firstly, maternal age was not advanced in both pregnancies. Secondly, maternal factor as a cause of recurrent aneuploidy is questionable as there is family history of Down syndrome within the paternal family. The risk of having subsequent affected pregnancy cannot be ignored in this family and prenatal diagnosis is strongly recommended in subsequent pregnancy. These instances of multiple aneuploidy within families may have resulted from common factors producing repeated meiotic errors possibly due to mutation of gene involved in meiosis. Hence further study is needed to determine factors which influence non-disjunction.

For this family, we have counselled the couple on the nature, consequences and general management of children with Down syndrome and Patau syndrome. We also informed the couple on the probability and risk of occurrence of each disorder in their future pregnancy. We advised them on proper family planning. The importance of early planning is emphasized if they wish to have more children as the likelihood of recurrent fetal aneuploidy is increased not only due to genetic factors but also non-genetic factors such as advanced maternal age, nutritional status and radiation exposure. Information and importance of fetal aneuploidy testing to screen for common aneuploidies in future pregnancy was offered to this couple. Information about community resources and support groups were provided to the family. All of these were done to facilitate the process of informed choices.

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