Down's Syndrome in Kuwait: Recurrent Familial Trisomy 21 in Sibs

S.A. Al-Awadi K.K. Naguib L. Bastaki S. Gouda
F.M. Mohammed S.J. Abulhasan W.A. Al-Ateeqi
D.S. Krishna Murthy

Kuwait Medical Genetic Centre, Maternity Hospital, Kuwait

Key Words

Down's syndrome · Non-disjunction
mosaicism · Consanguinity · Trisomy 21

Abstract

Objective: To study the families with recurrent trisomy 21 in sibs, and to understand the increased risk of recurrence in some selected families. The importance of parental mosaicism as a cause for non-disjunction or the possibility of genetic predisposition to non-disjunction is addressed. **Methods:** Three young unrelated Kuwaiti families each confirmed to have 3 sibs with regular trisomy 21 were investigated. Detailed chromosome analysis of the peripheral blood culture in Down's syndrome children and their parents was carried out. At least 100 cells in each of the cases were scored to exclude low grade mosaicism. **Results:** Regular trisomy 21 was confirmed in all the sibs in the three families. Mosaicism was not detected in parents. However, gonadal tissue mosaicism could

not be excluded, as it is not practical to study the gonadal biopsy in the parents. **Conclusion:** Though parental mosaicism (gonadal, more often maternal), has been reported in familial recurrent trisomy 21 cases, no mosaicism could be confirmed in our study. Our finding suggests that the possibility of a genetic predisposition to non-disjunction parental mosaicism should be considered in counselling families having sibs with trisomy 21.

Introduction

Trisomy 21 is the most common aneuploidy occurring as a sporadic event with a frequency of 1 in 600–800 live births [1, 2]. Down's syndrome due to primary trisomy 21 in 2 or more sibs of healthy, normal young parents (<30 years) occurs rarely. Although the recurrence of trisomy 21 is 1–2% for young mothers after the first case [3, 4], there

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 1999 S. Karger AG, Basel
1011–7571/99/0082–0156\$17.50/0

Accessible online at:
<http://BioMedNet.com/karger>

Dr. K.K. Naguib
PO Box 2900
Salmiyah 22029 (Kuwait)

Table 1. The characteristic features of the three families with recurrent trisomy 21

	Family I			Family II			Family III		
	1	2	3	1	2	3	1	2	3
Age of child years	13	10	induced abortion	17	14	10	10	9	4/12
Sex	female	female	female	male	male	male	male	male	male
Nationality	Kuwaiti	Kuwaiti	Kuwaiti	non-Kuwaiti	non-Kuwaiti	non-Kuwaiti	Kuwaiti	Kuwaiti	Kuwaiti
Maternal age	25	28	33	33	36	40	22	23	32
Paternal age	30	33	38	33	36	40	29	30	39
Consanguinity	less than second cousin			second cousin			non-consanguinity		
Birth order	3	4	6	4	5	7	2	3	4
Presentation	cephalic	cephalic	–	cephalic	cephalic	cephalic	cephalic	cephalic	cephalic
Gestation	term	term	13 weeks	term	term	term	term	term	term
Mode of delivery	spontaneous	spontaneous	–	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous
Patient karyotyping	47,XX,+21	47,XX,+21, 16qh+	47,XX,+21	47,XY,+21	48,XXY,+21	47,XY,+21	47,XY,+21	47,XY,+21	47,XY,+21
Affected relatives		2			0			0	
Maternal karyotyping		46,XX			46,XX			46,XX	
Paternal karyotyping		46,XY 16qh+			46,XY			46,XY	
Satellite association		high (55%)			not tested			not tested	
Tissue culture		46,XY, 16qh+			46,XY			46,XY	
Associated anomalies		–			–			imperforated anus	

are no figures for the risk of multiple recurrence of trisomy 21 or other aneuploidy in young parents, but there are several reports suggesting that the probability is greater than expected. The aetiology of familial non-disjunction is not well established. There are several possible explanations for familial occurrence of aneuploidy. The first of these is of cryptic parental mosaicism [5–9]. The other possibility is ‘genetic predisposition’, as sug-

gested by Alfi et al. [10] and others [11–13]. Whatever the cause, counselling young parents with 2 or more sibs with trisomy 21 poses difficulties.

We report here recurrent trisomy in three families, each of them having 3 sibs with primary trisomy 21, and a brief review of families with 3 or more cases of trisomy 21 reported in the literature, speculating on its possible aetiology.

Fig. 1. Pedigree of family I with trisomy 21 in sibs and paternal aunt (II-7). Note consanguinity in parents and grandparents.

Materials and Methods

Three unrelated Kuwaiti families each with 3 Down's syndrome sibs were ascertained, clinically and cytogenetically. The clinical history of the three families is presented in table 1 and figures 1 and 2.

Family I

The proband is a female infant, the product of the 4th pregnancy to consanguineous (less than first cousin) phenotypically normal parents. At birth, the parental ages were 23 and 28 years for the mother and father, respectively. Preconceptional and first trimester histories were unremarkable. At birth the baby showed the clinical stigmata of Down's syndrome. Pedigree study revealed that the proband has 2 elder phenotypically normal female sibs, 2 younger phenotypically normal sibs (brother and sister; fig. 1), 1 elder female sib with Down's syndrome and 1 early spontaneous abortion. Four years later the proband's mother conceived and prenatal diagnosis using transabdominal microvillus sampling technique revealed a regular trisomy 21 fetus, subsequently terminated.

Family II

The proband is a non-Kuwaiti male neonate, the product of the 7th pregnancy to his consanguineous (second cousin) phenotypically normal parents. At birth the parental age was 40 years for both parents. Preconceptional, first and second trimester histories were unremarkable. A healthy normal male child was delivered at term by vaginal delivery with an average birth weight. On examination at birth he showed the typical features of Down's syndrome. His 2 elder brothers showed clinical features of Down's syndrome with regular trisomy 21 cytogenetically. Interestingly, although 1 of the children had double aneuploidy 48,XXY,+21, he presented with clinical features of Down's syndrome.

Family III

The proband, a Kuwaiti male neonate, the result of the 3rd pregnancy to his non-consanguineous phenotypically normal parents. At birth parental ages were 23 and 28 years for both his mother and father, respectively. Preconception, first and second trimester histories were unremarkable and the pregnancy ended at

Fig. 2. Pedigree of families II and III showing trisomy 21 in 3 male sibs and parental consanguinity in family II.

term by spontaneous vaginal delivery. Pedigree study revealed that the proband had 2 elder male sibs, 1 of whom was similarly affected, and subsequently the proband's mother delivered a male child who also showed clinical features of Down's syndrome.

Cytogenetic Studies

Cytogenetic analysis in all the sibs and parents of the three families were carried out using peripheral blood lymphocyte culture and Giemsa trypsin banding technique. A minimum of 20 metaphases were scored and 3–5 cells were karyotyped in each case. In order to exclude mosaicism, 50–100 cells were scored. Mosaicism was not detected in the parents of the three families in the peripheral blood cultures. However, the possibility of tissue-specific mosaicism (gonadal) cannot be excluded.

Discussion

The presence of 2 or more sibs affected with a chromosome abnormality may suggest the existence of a familial factor leading to an error in chromosome segregation in families having multiple members with aneuploidy [14–16], i.e., a genetic susceptibility to non-disjunction. Mosaicism in man may be under genetic control as has been shown in maize and drosophila. However, the presence of trisomy 21 in multiple sibs may be either due to mosaicism in one of the parents or an inherited predisposition [17]. The prevalence of

Table 2. Recurrent trisomy 21 in sibs: summary of reported cases

Family No.	Sibs with trisomy 21	Parental age		Mosaicism		Reference
		maternal	paternal	maternal	paternal	
1	3	25, 28, 29	–	+	–	Weinstein and Warkany [26]
2	3 ^a	30–32	29–31	–	–	Dallaire and Fraser [27]
3	3	19–32	–	+	–	Aarskog [28]
4	3	22–24	–	+	–	Nuzzo et al. [29]
5	3		–	+	–	Begleiter et al. [30]
6	3	24, 27, 29	–	+	–	Osuna and Moreno [31]
7	4	17, 19, 21, 25	36, 38, 39	–	–	Frohlich et al. [32]
8	3	25, 28, 29	–	+	–	Harries et al. [5]
9	3		–	+	–	Maximillian et al. [33]
10	3	27, 29, 31	29, 32, 33	+	–	Uchida and Freeman [34]
11	3	25, 26, 34	–	–	–	Cavalli et al. [35]
12	6	23–30	26–33	+	–	Nielsen et al. [36]
13	4	–	–	+	–	Sachs et al. [8]
14	3	24, 29, 35	25, 30, 36	–	–	Pangalos et al. [37]
15	3	<30	–	–	–	Therman and Susman [38]
16	3	22, 23, 27	39, 40, 44	+	–	Tseng et al. [39]
17	3	19, 25, 29	–	–	–	Quaife and Al-Gazali [40]
18	3	18, 19, 26	22, 23, 30	+	–	Krishna Murthy and Farag [41]
19	3	31, 33, 34	36, 38, 39	–	–	Krishna Murthy and Farag [41]
20	3	21–43	32–49	–	–	Petersen [42]
24	7	<35	<35	+	–	Ives et al. [43]
21	3	25, 28, 33	30, 33, 38	–	–	present study
22	3	33, 36, 40	33, 36, 40	–	–	present study
23	3	22, 23, 32	29, 30, 39	–	–	present study

Mosaicism: + = present; – = absent.

^a This family was reinvestigated by Uchida and Freeman [34]. Maternal mosaicism was confirmed in 2% of the cells. Mosaicism: 47,XX,+21 in ovarian tissue (100%).

chromosome 21 mosaicism in a random normal population is not known in most newborn surveys because large numbers of cells are not scored to exclude low grade mosaicism. Very few authors agree with the existence of a single-gene hypothesis [10, 18, 19]. However, other authors reported no evidence to support the suggestion of an inbreeding effect [12, 20–25]. In the literature very few reports describe Down's syndrome in sibs (table 2), but some authors found maternal mosaicism as the underlying cause for recurrent Down's syndrome [29, 31, 44]. On the other hand,

Bartsch et al. [45] described a Spanish family who had 2 sibs with dup (21q) Down's syndrome whose mother has three different chromosome anomalies: a chromosome 22 with an unusual pericentromeric region that contains alphoid DNA from chromosome 21/13 and chromosome 22, an isochromosome 21p, and an isochromosome 21q in a rare second cell line.

In the present study, we report three families with 3 sibs having regular trisomy 21, in addition to nine other families who had 2 sibs with regular trisomy 21 Down's syndrome

who were recorded among the 1,650 families with 1 Down's syndrome registered in Kuwait making a prevalence rate of 7.3/1,000 Down's patients. This recurrent rate of familial Down's syndrome is higher than the expected prevalence in a highly inbred population like Kuwaitis where the incidence of consanguinity is estimated to be 54.3% [46]. However, this rate does fit with the high incidence rate of Down's syndrome registered in Kuwait where the incidence rate was estimated to be 4/1,000 live births [unpublished data]. This finding necessitates the need to correct the figures of estimated recurrence risk after the 1st Down's syndrome patient in the general Kuwaiti population from 2.6/1,000 to 8/1,000 births. This new estimate is based on the new incidence figure of Down's syndrome registered in Kuwait. After the 2nd Down's syndrome child the estimated recurrence risk will be as high as 30%.

Cytogenetically, neither mosaicism nor cytogenetic abnormality were found in any of the parents. Mosaicism cannot be excluded completely, particularly in the gonadal tissues of the parents. Accordingly, if we refer to the assumed genetic factor and consider it as a single recessive gene, one would expect multiplex families to be more prevalent especially in a highly inbred population like the Kuwaiti population. A similar finding was concluded by Basaran et al. [23]. The authors recorded 20 cases of Down's syndrome in sibs out of a population of 1,598 making a prevalence rate of 12.5/1,000 Down's patients. These findings together with our findings do not support the contribution of an autosomal recessive gene to the aetiology of non-disjunction, especially in highly inbred populations. Such a mechanism has not been assumed for other trisomies and it is unlikely that aneuploidy genes would preferentially affect chromosome 21.

Non-disjunction could possibly be attributed to genetic, environmental or a combina-

tion of the two factors. Theoretically genes predisposing to increased non-disjunction can be classified in several different ways: (a) gene(s) resulting in non-disjunction of a specific chromosome (e.g. chromosome 21)-homoaneuploidy, (b) gene(s) that can predispose non-disjunction of different autosome/sex chromosome in the same individual, or in sibs, due to parental and/or postzygotic non-disjunction-heteroaneuploidy (e.g. 48,XX, or XY,+21,+18; 48,XXY,+21 46,X,-X,+21). The occurrence of 'heteroaneuploidy' would not prove the existence of predisposition gene(s). Such outcome may be carried by parental mosaicism which has been demonstrated in some families with >2 trisomy 21 sibs. Familial 'heteroaneuploidy' is very rare. However, the occurrence of aneuploidy for different chromosomes is a better evidence for genetic predisposition although environmental factors could also be invoked as a possible cause. Amniocentesis and live birth data provided little evidence for a strong 'heteroaneuploidy effect' although a weak effect cannot be excluded. Studies in abortions are suggestive of genetic mosaicism of heteroaneuploidy [25].

In conclusion, non-disjunction could be possibly attributed to genetic, environmental or combined factors. Unfortunately, the nature of the mechanism of the genetic factor is yet to be revealed. The single-gene hypothesis is not yet accepted and even if accepted it must be limited to very specific situations. A hidden low grade mosaicism in one of the parents' blood or gonadal mosaicism may be the underlying cause and is not absolutely excluded in this report. Further investigations for all families including cytogenetic, FISH and DNA studies are highly recommended and will be arranged in the near future. The present report strongly supports that a subgroup of Down's syndrome families are at increased risk of recurrence.

References

- 1 McKusick VA: Mendelian Inheritance in Man: A Catalogue of Human Genetics and Genetic Disorders, ed 11. Baltimore, Johns Hopkins University Press, 1994, vol II, MIM-158250; MIM-190685; MIM-257300.
- 2 Hook E, Cross P, Schrenemacheis D: Chromosomal abnormalities at amniocentesis and in liveborn infants. *JAMA* 1983;249:2034–2038.
- 3 Mikkelsen M: Down syndrome. *Hum Genet* 1971;121:1–28.
- 4 Mikkelsen M, Stene J: Previous child with Down syndrome and other chromosome aberration: Group report; in Murken JD, Stengel-Rukowski S, Schwinger E: Prenatal Diagnosis of Genetic Disorders. Stuttgart, Enke, 1989, pp 22–29.
- 5 Harries D, Beyleiter M, Chamberlin J, Hankins L, Mogenis R: Parental trisomy 21 mosaicism. *Am J Hum Genet* 1982;34:125–133.
- 6 Parke J, Gross F, Pixley R, Deal J: Trisomy 21 mosaicism in two successive generations in a family. *J Med Genet* 1980;17:48–49.
- 7 Richards B: Investigation of 142 mosaic mongols and mosaic parents of mongols: Cytogenetic analysis and maternal age at birth. *J Ment Defic Res* 1974;18:199–208.
- 8 Sachs E, Joshoda M, Los F, Pijpien H, Wladimiroff J: Trisomy 21 mosaicism in the gonads with unexpected high recurrence risk. *Am J Med Genet Suppl* 1990;7:186–188.
- 9 Tuck C, Bennet J, Vamla M: Down's syndrome and familial aneuploidy; in Berg JM (ed): Perspectives and Progress in Mentally Retarded, ed 2. Baltimore, University Park Press, 1984, pp 167–180.
- 10 Alfi OS, Chang R, Azen SP: Evidence for genetic control of nondisjunction in man. *Am J Hum Genet* 1980;32:477–483.
- 11 Bell A, Gripps M: Familial aneuploidy: What risk to sib? *Can J Genet Cytol* 1974;16:113–119.
- 12 Kwitrovich P, Cross J, McKusick VA: Mongolism in an inbred population. *Bull John Hopkins Hosp* 1966;119:268–275.
- 13 Devoto M, Prosperi L, Bricarelli D, Coviello D, Croci G, Zelantel L, Ferranti G, Tenconi R, Stomeo C, Romeo G: Frequency of consanguineous marriages among parents and grand parents of Down syndrome patients. *Hum Genet* 1985;70:256–258.
- 14 Ford CE, Jones K, Miller O, Mittwoch U, Penrose L, Ridler M, Sapiro A: The chromosome in a patient showing both mongolism and Klinefelter's syndrome. *Lancet* 1959;i:709.
- 15 Lanman JL, Shlarin B, Cooper H, Hirschhorn K: Klinefelter's syndrome in a ten months old mongolism idiot. *N Engl J Med* 1960;263:887.
- 16 Therman E, Patau K, Smith D, Demers R: D trisomy and XO gonadal dysgenesis in two sisters. *Am J Hum Genet* 1961;13:193–204.
- 17 Hamerton JL, Briggs S, Gianelli F, Carter C: Chromosomal studies in detection of parents with high risk of second child with Down's syndrome. *Lancet* 1961;iii:788.
- 18 Bakker B, Carpenter A, Esposito M, Esposito R, Sandler L: The genetic control of meiosis. *Annu Rev Genet* 1976;10:53–134.
- 19 Puri R, Khanna K, Bhargava I, Balakrishnan S: Role of consanguinity in chromosomal syndromes. *Indian J Med Res* 1977;65:859–864.
- 20 Matsunaga E: Down's syndrome and maternal inbreeding. *Acta Genet Med Gamellol* 1966;15:224–229.
- 21 Juberg R, Davis L: Aetiology of non-disjunction lack of evidence for genetic control; in McKusick VA (ed): Medical Genetics Studies of the Amish. Baltimore, Johns Hopkins University Press, 1978, pp 449–458.
- 22 Naguib KK: Consanguinity and Chromosomal Aberrations; thesis Medical Research Institute, Alexandria University, 1984.
- 23 Basaran N, Cenani A, Sayh BS, Ozkinay C, Artan S, Seven H, Basaran A: Consanguineous marriages among parents of Down patients. *Clin Genet* 1992;42:13–15.
- 24 Naguib K, Al Awadi S, Moussa M, Mohammed F, Attia M: Down syndrome in sibs: A study of recessive hypothesis controlling nondisjunction. *Bull HIP H* 1992;22:125–133.
- 25 Hecht F, Brynat J, Gruber D, Townes P: The nonrandomness of chromosomal abnormalities: Association of trisomy 18 and Down's syndromes. *N Engl J Med* 1964;271:1081–1086.
- 26 Weinstein ED, Warkany: Maternal mosaicism and Down syndrome. *J Pediatr* 1963;63:599–604.
- 27 Dallaire L, Fraser FC: Two unusual cases of familial mongolism. *Can J Cytol* 1965;4:540–547.
- 28 Aarskog AJ: Cited from Hamerton JL (ed): Human Cytogenetics. Academic Press, 1970.
- 29 Nuzzo F, Stefanini M, Simoni G, Larizza L, Mottura A, Reali E, Franceschini P: A family with three sibs carrying trisomy 21. *Ann Génét* 1975;18:111–116.
- 30 Begleiter et al: Cited from Frohlich et al. [32].
- 31 Osuna A, Moreno A: Regular G21 trisomy in 3 sibs from mother with trisomy 21 mosaicism. *J Med Genet* 1977;14:286–287.
- 32 Frohlich GS, Schdnhaut AG, Tortora JM: Trisomy 21 Down syndrome in sibship. *N Y State J Med* 1979;79:929–930.
- 33 Maximillian C, Pop T, Duca D, Simionescu L, Danielescu M, Loan D: Familial Down syndrome. *Endocrinologie* 1981;19:65–68.
- 34 Uchida IA, Freeman VCP: Trisomy 21 Down syndrome paternal mosaicism. *Hum Genet* 1985;70:246–248.
- 35 Cavalli J, Fontoura E Jr, Sbaluiero IJ: Letter to the Editor: Down syndrome owing to simple trisomy 21 in first cousins. *Am J Med Genet* 1985;22:831.
- 36 Nielsen KG, Poulsen H, Mikkelsen M, Stender E: Multiple recurrence of trisomy 21 Down syndrome. *Hum Genet* 1988;78:103–105.
- 37 Pangalos CG, Talbot CC Jr, Lewis JG, Adelsberger PA, Petersen MB, Serre JL, Rethore MO, et al: DNA polymorphism analysis in families with recurrence of free trisomy 21. *Am J Hum Genet* 1992;51:1015–1027.

- 38 Therman E, Susman M: Meiotic abnormalities; in Human Chromosome Structure, Behaviour and Effects, ed 3. Berlin, Springer Verlag, 1993, pp 190–202.
- 39 Tseng LH, Chuang SM, Lee TY, Kotm: Recurrent Down syndrome due to maternal ovarian trisomy 21 mosaicism. *Arch Gynecol Obstet* 1994;255:213–216.
- 40 Quaife R, Al-Gazali L: Trisomy 21 in sibs. *Emirate Med J* 1994;12: 150–153.
- 41 Krishna Murthy DS, Farag TI: Recurrent regular trisomy 21 in two Bedouin families: Parental mosaicism versus genetic predisposition. *Ann Génét (Paris)* 1995;38:217–224.
- 42 Petersen MB: Origin and mechanism of chromosome aneuploidy in Down syndrome. *Cytogenet Cell Genet Suppl* 1997;77:1.
- 43 Ives EJ, Alderdice PW, Bridge PJ, Barret IJ, Kolousek DK, Conolly Wilson MJ, Crowley MR: A mosaic trisomy 21 woman with seven trisomy and cytogenetically normal pregnancies. *Am J Hum Genet Suppl* 1997;4:726,A-128.
- 44 Perroni L, Dagna Bricarelli F, Grasso M, Pierluigi M, Baldi M, Pedemonte C, Strigini P: Crossing over and chromosome 21 nondisjunction: A study of 60 families. *Am J Med Genet* 1990(Suppl 7):141–147.
- 45 Bartsch O, König U, Petersen M, Poulsen H, Mikkelsen M, Palau F, Prieto F, Schwinger E: Cytogenetic, FISH and DNA studies in 11 individuals from a family with two siblings with dup(21q) Down syndrome. *Hum Genet* 1993;92:127–132.
- 46 Al-Awadi S, Moussa M, Naguib K, Farag T, Teebi A, El-Khalifa M, El-Dossary L: Consanguinity among the Kuwaiti population. *Clin Genet* 1985;27:483–486.