Cytogenetic profile of Down syndrome in Alexandria, Egypt

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المرتسم الجيني الخلوي لمتلازمة داون في الإسكندرية بمصر

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الخلاصة: في غضون الأعوام 1992–2001، تم إحالة 673 من مرضى متلازمة داون إلى قسم الوراثيات البشرية في الإسكندرية. وقد لوحظ أن حالات تثلث الصبغي 21 تشكل 95.4٪ منها فيما تشكل حالات إزفاء روبرتسون 2.7٪، وحالات الفسيسفائية 0.7٪. وكان هناك شذوذات صبغية متعددة وبنيوية مرافقة لدى 8 حالات من تثلث الصبغي 21، فيما كان الإزفاء موروثاً من الأب لدى 33٪ من الحالات ومن الأم لدى ثلثي الحالات الباقية. وقد تم تشخيص إصابة جنينين اثنين قبل ولادتهما بإصابتهما بمتلازمة داون من اثنتين من الأمهات تحملان التشوه الصبغي بالإزفاء (14؛ 21). وقد كان العمر الوسطي مرتفعاً بين أمهات حالات تثلث الصبغي 21 النظامية (وسطياً 38.2 سنة) ولم يكن مرتفعاً بين أمهات الإزفاء (وسطياً 25.3 سنة). وكان عدد الذكور زائداً في جميع المجموعات عدا مجموعة الفسيسفاء حيث كانت نسبة الذكور إلى الإناث 0.67. إن الاستقصاءات الخلوية البنيوية تساعد في التدبير العلاجي للحالات المرضية وفي توعية الأسر.

ABSTRACT During 1992–2001, 673 Down syndrome patients were referred to the Department of Human Genetics in Alexandria. Regular (free) trisomy 21 constituted 95.4% of cases; Robertsonian translocation 2.7%; and mosaicism 0.7%. In 8 cases, regular trisomy 21 was associated with structural or numerical chromosome anomalies. Translocation was parentally inherited for 33.3% of cases and maternal transmission was twice as common as paternal. Two translocated Down syndrome fetuses were diagnosed prenatally in a t(14;21) carrier mother. Mean maternal age was high in regular trisomy 21 (38.2 years) but not in translocation (25.3 years). There was an excess of males in all groups except the mosaic group where the male:female ratio was 0.67. Cytogenetic investigations assist in patient management and family counselling.

Profil cytogénétique du syndrome de Down à Alexandrie (Egypte)

RESUME De 1992 à 2001, 673 patients atteints du syndrome de Down ont été orientés vers le Service de Génétique humaine à Alexandrie. La trisomie 21 courante (libre) constituait 95,4 % des cas, la translocation robertsonienne 2,7 % et le mosaïcisme 0,7 % des cas. Dans 8 cas, la trisomie 21 courante était associée à des anomalies chromosomiques numériques ou structurelles. La translocation avait été transmise par les parents dans 33,3 % des cas et la transmission maternelle était deux fois plus fréquente que la transmission paternelle. Le diagnostic a été posé avant la naissance pour deux fœtus atteints de trisomie 21 par translocation sur une mère porteuse de la t(14 ;21). L'âge moyen de la mère était élevé pour la trisomie 21 courante (38,2 ans) mais pas pour la translocation (25,3 ans). Il y avait davantage de sujets de sexe masculin dans tous les groupes sauf dans le groupe du mosaïcisme où le rapport de masculinité était de 0,67. Les examens cytogénétiques aident à la prise en charge des patients et au conseil familial.

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Table 3 **Frequency of different karyotypes among the studied Down syndrome cases and pooled data from worldwide surveys**

Source	Total	Regular trisomy 21		Translocation		Mosaic		Non-classical	
	No.	No.	%	No.	%	No.	%	No.	%
Current study, Egypt	673	642	95.4	18	2.7	5	0.7	8	1.2
Belgium [*14*]	88	81	92.1	6	6.8	1	1.1	0	0
Sutherland [*16*]	49	47	95.5	1	2.0	1	2.0	0	0
Scotland [*12*]	153	144	94.1	2	1.3	7	4.6	0	0
Jacobs [*15*]	26	22	84.6	4	15.4	0	0	0	0
England [*17*]	65	63	96.9	1	1.5	1	1.5	0	0
England and Wales [*13*]	5737	5411	94.3	220	3.8	66	1.2	40	0.7
Kuwait [*11*]	1024	985	96.2	24	2.3	9	0.9	6	0.6
France [*3*]	391	368	94.1	14	3.6	9	2.3	0	0

than some other studies have shown: 92.1% [*14*], 84.6% [*15*] and 87.9% [*7*].

Previous studies have reported that the frequency of Down syndrome mosaicism varies from 0%–4.6% [*12,15*]. Only 0.7% of Down syndrome cases in the present study had mosaic karyotypes. Despite extensive studies it is not possible to clinically differentiate patients with mosaicism or translocation from those with regular trisomy 21.

The frequency of Robertsonian translocation in patients included in the present study was 2.7%. This figure agrees with Sutherland et al. 2% [*16*], al-Awadi et al. 2.3% [*11*] and Stoll et al. 2.3% [*3*], but is higher than other reports of 1.1% [*14*], 0% [*15*], 1.5% [*17*] and 1.2% [*13*]. In contrast, it is lower than that reported by Speed et al. (4.6%) [*12*] and other previous studies (5.6%, 4.4%, 5.2% and 6.8%) [*2,7,18,19*].

Among all cases studied here, the frequency of translocation (2.7%) and mosaicism (0.7%) was very much lower than the frequency of standard regular trisomy 21 (95.4%). This could be attributed to the high fertility rate and trends towards reproduction even at an advanced maternal age [*20*].

It has been reported that Robertsonian translocation may arise as a sporadic event (*de novo*) or may be transmitted by a carrier parent (familial). One-quarter of Robertsonian translocations in Down syndrome are familial and three-quarters are *de novo* [*21*]. In the present study, 50% (4/8) of cases with t(14;21) were sporadic while the other 50% were inherited from a carrier mother. One of these mothers was subjected to amniocentesis in her two subsequent pregnancies, in which the karyotype was a translocated Down syndrome in both fetuses. In familial Robertsonian transloca-

Table 4 **Non-classical Down syndrome karyotypes in the present study and in other published reports**

Source	Year	Total No.	Non-classical No.	%
Current study, Egypt	1992–2001	673	8	1.2
Farag [*27*]	1977	3295	16	0.5
Kuwait [*11*]	1991	1024	5	0.5
England and Wales [*13*]	1996	5737	40	0.7
Korea [*28*]	1999	4117	0	0

tion Down syndrome one of the parents (almost always the mother) is a translocation heterozygote and has transmitted the translocation in an unbalanced state to the offspring. Males with Robertsonian translocation are occasionally associated with infertility due to oligospermia because the translocation may disrupt spermatogenesis [*22*]. The distinction between *de novo* and familial forms of translocation Down syndrome is crucial. For the *de novo* translocation, a recurrence risk of less than 1% is applicable. In the case of familial Robertsonian translocation Down syndrome, the genetic risk for the female carrier to have a liveborn child with translocation Down syndrome is about 10%, while the likelihood to detect translocation trisomy 21 at amniocentesis is about 15%. For the male carrier, the risk to have a child with translocation Down syndrome is small, i.e. about 1% [*23*].

The homologous translocation (21q21q) is one of the most common chromosomal rearrangements in Down syndrome. Classically this rearrangement has been termed Robertsonian translocation. Molecular studies had proved that most *de novo* rearrangements (21q21q) are isochromosomes derived from a single parental chromosome 21 and only a small proportion are consistent with true Robertsonian translocations [*24*]. In the present study 33.3% (6/18) of translocation cases were t(21;21). Two cases inherited this translocation from the father and 4 cases were *de novo* where one of them had a similarly affected sibling. Molecular studies suggest that many of these *de novo* cases originate at an early postzygotic mitosis, so the recurrence risk is low [*25*]. However, a small number of recurrences in subsequently born siblings are otherwise recorded and parental gonadal mosaicism can be the basis of such recurrence [*26*].

Regular trisomy 21, Robertsonian translocations and mosaicism are the classic anomalies. In the last few years, non-classical types of chromosomal anomalies (whether numerical or structural) have been reported in major Down syndrome studies with frequency ranging from 0%–0.7% [*11,13,27,28*]. Our figure of 1.2% (8/673) is higher than that previously reported in these studies. It is important to consider non-classical cases in genetic counselling and also to try to establish the precise recurrence risks for such distinct groups. The origin of such rare non-classical karyotypes needs to be understood.

Yamada reported an incidence of 1.52% for pericentric inversion of chromosome 9 (per inv 9) in Down syndrome patients [*29*]. In the present work there were 0.4% of cases (3/673) with regular trisomy 21 in association with per inv 9, which was paternally derived in one case. It was reported that per inv 9 might have an interchromosomal effect leading to higher incidence of mitotic disturbances finally resulting in aneuploidy [*30*]. Serra et al. demonstrated a strong association between the presence of

per inv 9 in one parent and the birth of Down syndrome offspring. There was a 3-fold increased risk of Down syndrome child for such families [*31*]. In the present work, 2 Down syndrome patients had a free extra 21 chromosome as well as a Robertsonian translocation (13;14) which was inherited from the mother in one case, and a translocation (7;14) in the other case, but the parents refused karyotyping.

Schinzel et al. have studied families in which a child with trisomy 21 also had a balanced translocation, and while in some cases the translocation could be of paternal origin, the extra chromosome 21 came from the mother. There is no evidence at least for a paternal interchromosomal effect [*32*].

In the present study 2 cases had an extra supernumerary chromosomal marker associated with an extra 21, the nature of which could not be identified. Blennow et al. reported a large study of 50 extra structural chromosomes, 25% of which were harmless and derived from acrocentric chromosomes [*33*].

The sex ratio of Down syndrome patients has long been recognized [*34,35*]. The overall M:F ratio in this study was 1.24, which is similar to that previously reported for Down syndrome [*16*]. However, it varied according to the type of Down syndrome, being 1.23 in regular trisomy, 1.25 in translocations and falling to 0.67 in mosaic cases. Nielsen et al. reported an excess of females (M:F sex ratio 0.82) in translocation and mosaicism, compared with 1.31 in regular trisomy 21 [*36*]. The high sex ratio in regular trisomy is a well-known phenomenon. Peterson et al. [*37*] investigated the possibility that this is accounted for by cases of paternal origin. These researchers used DNA probes to study the errors in 27 cases with confirmed paternal meiotic non-disjunction and found that the M:F sex ratio was 3.5 (21/6) with a mean maternal age of 31.8 years when the error was maternal. The authors suggested this shift of sex ratio was due to paternally derived aneuploids that could be a factor in determining the male preponderance in Down syndrome.

Advanced maternal age is still the only established risk factor known to be involved in the etiology of Down syndrome [*8*]. The present data revealed marked differences between maternal ages in different groups ranging from a mean of 25.3 years in the translocation group up to 38.2 in those with regular trisomy 21. Several investigators have reported a higher maternal age in regular trisomy emphasizing the positive role of advanced maternal age on non-disjunction [*8,17*]. In the present study all cases with translocation had low maternal age. These findings were in the line with the observation of Mutton et al. (28.4 years) [*13*] as well as Pulliam and Huethers (21.6 years) [*38*].

In conclusion, the identification of specific types of chromosomal abnormalities in Down syndrome children is important as it enables clinicians to accurately counsel the parents regarding the recurrence risk and available options.

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