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Cytogenetic Profile in 1,921 Cases of Trisomy 21 Syndrome

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Background and Aims. Trisomy 21 is the most frequent genetic cause of intellectual disability. It is caused by different cytogenetic aberrations: free trisomy, Robertsonian translocations, mosaicism, duplication of the critical region and other structural rearrangements of chromosome 21. The aim of the study was to identify in Mexican trisomy 21 patients who attended Hospital Infantil de México Federico Gómez from 1992–2011 the type and frequency of the cytogenetic aberration and to evaluate the effect of maternal age.

Methods. A retrospective analysis of epidemiological data and karyotype reports were carried out; type and frequency of the cytogenetic variants were determined.

Results. We identified 2,018 cases referred with a clinical diagnosis of trisomy 21. In 1,921 analyses (95.2%) a cytogenetic variant of trisomy 21 was identified: free trisomy 21 in 1,787 cases (93.02%), four cases (0.21%) had an additional non-contributory aberration; Robertsonian translocations in 92 cases (4.79%); mosaicism in 31 cases (1.61%) and seven cases (0.36%) had other chromosomal abnormalities, five (0.26%) had other contributory structural rearrangements and two corresponded to double aneuploidies (0.10%). Gender distribution was 1,048 (54.56%) males and 873 (45.44%) females. A maternal age effect was observed in patients with free trisomy 21 with mothers >36 years of age.

Conclusion. The present work reports the experience of a Mexican referral center regarding the karyotype diagnosis of patients with trisomy 21 and is one of the most extensive studies published so far. Percentages of the cytogenetic abnormalities present in our population reflect the ones previously reported for these cytogenetic alterations worldwide.

Key Words: Trisomy 21, Down syndrome, Robertsonian translocation, Mosaicism, Chromosome 21.

Introduction

Down syndrome (DS) was described by John Langdon Down in 1866 (1) and, because it is caused by an extra copy of chromosome 21 (2), is also called trisomy 21 syndrome. DS is the most frequent cause of intellectual disability of genetic origin with a general presentation from 1:850–1 in 1,000 newborns (3,4). In Mexico its frequency is 1:650 newborns (5).

The cytogenetic variants that cause DS are free trisomy 21, Robertsonian translocations, mosaicism, duplication of the DS critical region and other structural rearrangements involving chromosome 21 (6–8). In 90–95% of DS patients the presence of the extra chromosome 21 was originated from a meiotic nondisjunction event. In 80% of these cases it occurred during maternal meiosis and was associated with a maternal age effect >35 years (6,9,10).

In 4% of DS cases, chromosome 21 may be translocated to another acrocentric chromosome. These so-called Robertsonian translocations usually involve chromosome 14 or another chromosome 21 even if the latter are mostly isochromosomes 21q or rea(21;21). In 25% of the

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translocation cases, one of the parents is a carrier (7,11). Mosaic cases account for 3−5% of DS and are caused by a nondisjunction postzgotic event (12). Other structural rearrangements are less frequent causes of DS and the diagnosis requires molecular cytogenetic techniques such as FISH (7). SD associated with chromosomal alterations other than trisomy 21 has also been reported (13−15).

DS is one of the main causes for consultation at the Genetic Department of the Hospital Infantil de México Federico Gómez (HIMFG) in Mexico City, Mexico for diagnosis and follow-up of patients. In this study we analyzed the cytogenetic results of the large population of DS patients who have attended our institution during a 20-year period in order to determine the type and frequency of cytogenetic alteration and to evaluate the effect of maternal age.

Patients and Methods

All karyotype GTG banding technique reports from the Cytogenetics Laboratory, Department of Genetics, HIMFG from 1992−2011 associated with a clinical and/or cytogenetic diagnosis of DS were included. Cases identified with a confirmatory trisomy 21 chromosomal aberration were reviewed to register the age of the patients and the age of the parents. The frequency of each type of cytogenetic variant associated with DS was determined. Cases with a cytogenetic diagnosis of trisomy 21 and another chromosomal alteration were also included. When the cytogenetic report corresponded to a clinical diagnosis different from DS, the clinical chart was reviewed. The research board of our institution approved the study.

Results

During the study period a total of 9,862 GTG banding analyses were reported; a clinical diagnosis of DS was the indication for the chromosomal analysis in 2,018 (20.46%) of these cases. In 1,921 of the cases, a confirmatory cytogenetic diagnosis of trisomy 21 was established corresponding to 1,048 (54.56%) reports in males and 873 (45.44%) in female patients.

Age data were established in 1,782 patients. Age range was from 1 day−25 years old. Most patients (1,359 cases/76.26%) were <1 year of age, with the most frequent age group from 1 to 12 months with 857 cases. The second most frequent age group was from 1 to 30 days and included 502 patients. When age data were not available, the cases were not considered in this analysis but were taken into consideration for the type of karyotype variant result analysis. With one exception, all patients were from the Mexican mestizo ethnic group.

A normal chromosome complement was reported in 96 cases (4.75%); one patient (0.05%) had a 48,XXXX karyotype. The remainder of the reports corresponding to 1,921 analyses (95.2%) had one cytogenetic variant causing DS. A free trisomy 21 was identified in 1,787 cases (93.02%); in four patients (0.21%) another non-contributory chromosomal abnormality in addition to the free trisomy 21 was identified. Robertsonian translocation or a rea(21;21) was present in 92 cases (4.79%), mosaicism in 31 cases (1.61%), five (0.26%) patients had other contributory structural rearrangements and in two patients double aneuploidy was detected (0.10%) (Table 1 and Figure 1).

Regarding the 92 cases with a Robertsonian translocation, rob(14;21) was the most frequent type with 59 patients (64.13%) followed by rea(21;21) in 28 cases (30.43%), four (4.34%) cases had a rob(13;21) and only one (1.1%) had a rob(15;21).

Mosaics were the least frequently reported cytogenetic variant in this study with 31 cases identified that corresponded to <2% of the total. All patients had two cellular lines; 30 had a normal one and another line with a free trisomy 21. The one remaining case (0.05%) had a trisomy 21 due to a *de novo* rea(21;21) and a normal cell line (Table 1). The average number of analyzed cells was 52; the trisomic line range was 6−75%. At present, the number of analyzed metaphases in our laboratory is 25/case; however, the number of analyzed metaphases during the period of study varied from eight up to 100.

Table 1. Chromosomal abnormalities in children with Down syndrome

Karyotype	Number of cases	%
Free trisomy 21		
47,XX,+21	812	42.27
47,XY,+21	975	50.75
Other non-contributory aberrations		
47,XY,inv(3)(p12q24),+21	1	0.052
47,XX,inv(9)(p22q13)pat,+21	1	0.052
47,XX,t(1;15)(q32;q22)pat,+2[a]	1	0.052
46,XY,t(13;14),+21	1	0.052
Robertsonian translocations		
rob(13;21),+21	4	0.21
rob(14;21),+21	59	3.07
rob(15;21),+21	1	0.05
rea(21;21),+21	28	1.46
Mosaicism		
mos 47,XX,+21/46,XX	14	0.73
mos 47,XY,+21/46,XY	16	0.84
46,XX,rea(21;21)(q10;q10),+21/46,XX	1	0.05
Other contributory structural rearrangements		
46,XX,der(5)t(5;21)(p11;p11),+21	1	0.052
47,XY,der(9)(pter->q22::?),+21	1	0.052
47,XY,+der(21)t(21;?)(q22;?) pat	1	0.052
46,XX,+21,idic r(21,21) (::q22.3->p11.2?::p11.2?->22.3::)	1	0.052
mos 46,XX,+21,idic(21)(q22.3)/46,XX	1	0.052
Double aneuploidies		
48,XXY,+21	1	0.05
mos 48,XYY,+21/47,XY,+21	1	0.05
Total	1921	

[a]Case reported by García-Delgado et al. (16).