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ORIGINAL ARTICLE

Down syndrome due to rare inherited 15/21 Robertsonian translocation: genetics and reproductive counseling[a]

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KEYWORDS
Down's syndrome;
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Abstract
The carriers of a rearrangement involving with chromosome 21 have a potential risk of genetically unbalanced conceptions, which may result in liveborn children with Down syndrome. Reproductive risks for couples carriers of a balanced Robertsonian translocation depends on the rearranged chromosomes and the sex of the carrier. This article aims to analyze the segregation and reproductive trend of a rare 15/21 translocation in five generations of a family. It was considered the current advances in reproductive technology as a possibility to prevent fetal aneuploidia. Given the genetic risk, the preimplantation diagnosis appears also as an alternative to avoid the option of an unwanted later abortion and to obtain a healthy progeny.

PALABRAS CLAVE
Síndrome de Down;
Aborto;
Reordenamiento cromosómico;
Reproducción;
Fertilidad

Síndrome de Down hereditario poco común debido a la translocación robertsoniana 15/21: asesoramiento genético y reproductivo

Resumen
Los portadores de un reordenamiento que afecta al cromosoma 21 tienen un riesgo potencial de concepciones genéticamente desequilibradas que pueden dar origen a niños con síndrome de Down. Los riesgos reproductivos de las parejas portadoras de una translocación robertsoniana equilibrada dependen de los cromosomas reordenados y del sexo del portador. Este artículo tiene como objetivo analizar la tendencia de segregación y reproductiva de una rara translocación 15/21 en cinco generaciones de una familia. Se consideraron los avances actuales en tecnología reproductiva como una posibilidad para evitar la aneuploidía fetal. Dado el riesgo genético, el diagnóstico de preimplantación aparece también como una alternativa para evitar la posibilidad de un aborto posterior no deseado y para obtener una descendencia saludable.

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Introduction

Balanced Robertsonian translocation (rob) is a frequent structural chromosome abnormality with a prevalence of 1 in 1000 health individuals, often referred for reproductive counseling[1]. The most common form of this translocation involves chromosomes 13 and 14 or 14 and 21[2]. Bandyopadhyay et al.[3] classified the Robertsonian translocations (robs) in two groups, according their frequency of occurrence: common - rob (13q14q) and rob (14q21q) and rare forms as rob (15q21q). The carriers of a balanced rearrangement involving chromosome 21 presents a potential risk of genetically unbalanced conceptions which may result in liveborn children with Down syndrome (DS).

Studies about parental origin, segregation and progeny outcome, for rare ROBs, have not been frequently carried out. Here we presented a family with segregation of a rob (15q21q) in five generations, because of the high occurrence of DS cases, with the purpose of genetic and reproductive counseling. Possibilities of prenatal diagnosis and advances in preimplantation genetic diagnosis were considered in order to predict the likelihood of having a liveborn healthy child.

Patients and Methods

The family was investigated from the propositus with a clinical diagnosis of DS, attended at the Program of Community Genetics (Genetics & Society), Federal University of Bahia. Informations about the family history, pedigree, parental age, birth order, DS outcomes, were recorded. Cytogenetic studies from the propositus and family members were performed on cultured blood lymphocytes using standard method and chromosome identify by GTG banding[4]. At least 15 cells were analyzed for each individual and 5 karyotypes were prepared with photomicrographs take on a Zeiss Axiophot microscope. Informed consent was obtained from patients in the study after the nature of the procedure had been fully explained to them. Participation in the study was voluntary and in concordance to the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

The genealogy is presented at Figure 1. The propositus was a 50 year old woman, with a clinical diagnosis of DS presenting signs as: microcephaly, flat occiput, up-slanting palpebral fissures, bilateral epicanthal folds, flat nasal bridge, small ears, tendency of tongue protrusion, short stature.

A total of 45 individuals descendants of the first known couple are shown in the pedigree, excluding the spouses. Of these, 6 (13%) showed the unbalanced translocation and DS, 3 were diagnosed by clinical examination and 3 others, by cytogenetic analyses; 39 (87%) showed no DS signals. Among relatives cytogenetically investigated or considered obligate carriers by having affected progeny, there were 9 cases of balanced translocations, 6 (67%) female and 3 (33%) male, due to alternate segregation, the meiotic behavior most common in all Robertsonian translocation. Among the other 30 individuals, 3 were confirmed as having normal karyotype and the other were not examined for death (n = 3) or another reasons (n = 24).

Parental age at conception of DS children was below 30 years, in the last three generations, except for child born of second marriage of a man carrier of the balanced translocation (IV-10). The parental origin of the oldest related DS patient could not be determined. In the others cases of 6 translocations DS patients, 4 (67%) were originated from the mother and 1, from the father. The abortion rate was low, even in couples of carriers of balanced translocation.

In the present family, none of the members performed prenatal chromosomal diagnosis, or had access to new reproductive technologies, even though there were young mothers with DS progeny. After the study these individuals learned the advances and the information about the possibility of health outcomes.

Discussion

According to Scriven et al.[5], translocated couples need assisted conception for subfertility. Keymolen et al.[1], considering all pregnancy of ROB carriers with balanced translocation, observed that 52,7% females carriers and 61,8% of males, led to the birth of a healthy child. The frequency

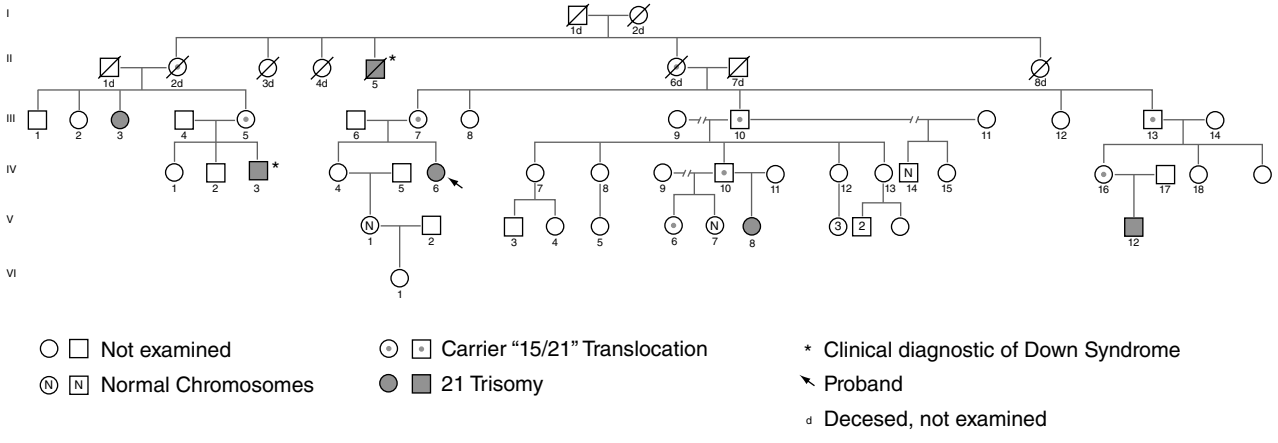

Figure 1 Family pedigree.

of normal and balanced karyotype confirms the previous study of chromosome segregation in sperm[6], showing alternate segregation, which results in gametes with balanced genetic material, as the most frequent mode of segregation in this chromosomal rearrangement. Furthermore occur an excess of balanced karyotypes when comparated to normal karyotypes[1,7].

Jyothy et al.[8] refer that translocated DS children are often born from mothers aged bellow 25 years and argue that this can be explained by the high frequency of primigravidae in these women and the fact that the incidence of miscarriage is low in women conceiving at first pregnancy for unknown reasons. The fact of the presently studied family does not mention abortion, confirms the referred reproductive trend or can reflect an underestimation by the absence of prior genetic register.

Couples with a translocation carrier, often perform the prenatal diagnosis even fearing the possibility of option of pregnancy termination when the child has trisomy by translocation. In these cases, the preimplantation genetic diagnosis (PGD) can be a valuable screen to prevent the occurrence of an unbalanced conception. The alternated embryos (normal/balanced) are the main types of conceptus and with PGD, these embryos can be selected for transfer into the uterus[9]. The donor of gametes in procedures of *in vitro* fertilization (IVF) offers an additional alternative to reduce the risk of fetal aneuploidy.

Conn et al.[10] observed that couples that suffer repeated pregnancy termination are leaning forward genetic diagnosis before implantation to avoid later abortion. PGD for Robertsonian translocations has been undertaken successfully in some centers of advanced research, whether by polar body biopsy[11] or blastomere at day 3, after fertilization[12,13]. These new methods however are still not routine procedures.

Despite these advances, Keymolen et al.[1] observed that the likelihood of a healthy liveborn child of the pregnancy in couples with a Robertsonian translocation carrier is around 50-70%, either by spontaneous conception or assisted reproductive technologies, with or without PGD. Many couples do not use these technologies, either for lack of knowledge, economic reasons, or yet ethical and moral reasons.

Bernicot et al.[14] studying 2 carriers of rare Robertsonian translocation rob (13;21) and rob (15;22) combining analysis of meiotic segregation in sperm and PGD, refered respectively 86,3% and 87,5%, of gametes with normal or balanced chromosome complement. The authors also observed a high rate of mosaic or chaotic embryos but both studied showed cases of normal pregnancy and outcomes, showing the benefices of the PGD advances.

Given the genetic risk for carriers of Robertsonian translocations, there is a real need for new studies about chromosomal segregation especially because these rearrangements are becoming an important indication for pre-implantation genetic diagnosis. We also recommend additional studies to establishing the success of the advances of assisted reproductive between carriers of rare Robertsonian translocations.

Conflict of Interest

The authors declare that they have no conflict of interest.

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