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Case Report

Familial Transmission of a Robertsonian Translocation rob(21;22): A Case Report

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Abstract

Introduction: Robertsonian Translocations (RT) are the most common balanced rearrangements. However, double Robertsonian translocations, in which two balanced RT occur simultaneously in the same carrier, are extremely rare conditions.

Objective: to study the segregation of an RT rob(21;22) in the offspring of a phenotypically normal couple who were found to carry this RT.

Case report: The first daughter of the couple has Down Syndrome and double RT, her karyotype was 45, XX, rob(21;22)2,+21. The couple's karyotypes reveal RT in both parents involving chromosomes 21 and 22. Prenatal diagnosis in the second pregnancy revealed a double RT: 44, XX, rob(21;22) ×2; the second child was phenotypically normal. The family pedigree also included other cases of Down syndrome.

Conclusion: The consanguinity seems to be a risk factor not only for Mendelian disorders but also for chromosomal rearrangement.

Introduction

Robertsonian Translocations (RT) are translocations involving two acrocentric chromosomes (13,14,15,21, or 22) by centromeric fusion and loss of the two short arms [1]. They are theoretically not accompanied by phenotypic manifestations. The two chromosomes involved can be two homologous or two non-homologous chromosomes, which accounts for approximately 90% of RTs [1]. RT are more common than translocations between other autosomes and occur with an incidence approximately of 1/1000 [2-4].

The RT rob(13;14) is the most common, with an incidence of 1/1500 in live births [5] and 60 to 70% of RT. The RT rob(14;21) is the second most frequent with a proportion of 10% [6,7]. The occurrence of RT in the homozygous condition is an extremely rare event [8-16], which supposes its inheritance from both parents simultaneously; however, consanguinity could increase this probability [17]. Another situation could be the transmission of a RT from one of the two parents and the appearance of a second RT *de novo* which represents an even rarer situation, this situation has not yet been reported for the same translocation, but has been reported for two different RT.

RT does not provide specific phenotypic manifestations; however, it increases the risk of fetal losses, infertility, uniparental disomy, and aneuploidy in offspring through the genesis of unbalanced gametes [18-20].

We report, for the first time, the observation of a couple of relatives and their descendants in whom RT rob(21;22) segregates.

Case presentation

A Tunisian couple (f = 1/16), with no significant pathological history, aged 32 for the husband and 27 for the wife at the time of the first consultation (subject III3 and III4 of Figure 1). The family history is marked by the existence of two cousins of the couple with Down syndrome (subjects III-6 and IV-3 in Figure 1). The couple has a first child with confirmed Down syndrome.

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Informed consent was obtained from the parents before he study of the R-band karyotype on circulating blood lymphocytes that showed the following formula: 45, XX, rob(21;22)(q10;q10)*2,+21 (Figure 2). This result confirms the diagnosis of Down syndrome and permits clarification of its mechanism. This is a trisomy 21 by RT involving a chromosome 21 and a chromosome 22. It is associated with a second RT involving the two other chromosomes, 21 and 22.

The study (after informed consent) of the blood karyotype of the two parents showed that each of them had the same translocation with the following formula: 45, XY, rob(21;22)(q10;q10) in the father and 45,XX,rob(21;22)(q10;q10) in the mother.

During the second pregnancy, the study of the fetal karyotype is proposed from the first trimester. After medical counseling, the couple opted to begin with screening, the nuchal translucency measurement found a value of 1.3 mm for an LCC of 54 mm.

The study of the fetal karyotype is carried out at 16 weeks on amniocytes and finds the following formula: 44, XX, rob(21;22)(q10;q10)*2 (Figure 3).

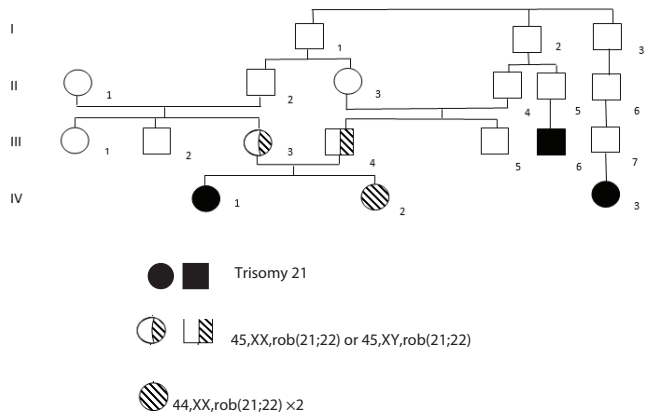

Figure 1: Pedigree of the family.

Figure 2: Karyotype of the first child of the couple showing trisomy 21 and double RT 45, XX, rob(21;22)(q10;q10) ×2,+21.

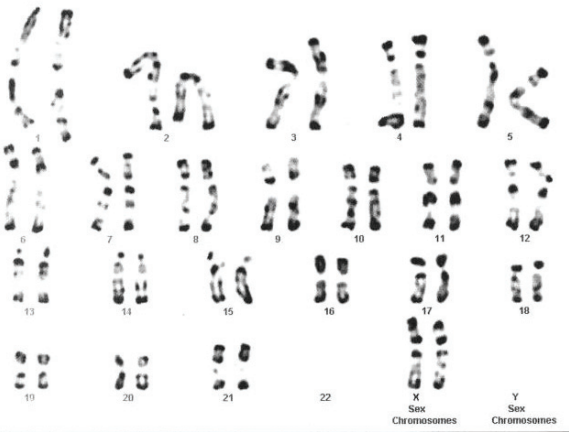

Figure 3: Fetal balanced karyotype: 44, XX, rob(21;22)(q10;q10) ×2.

Discussion

This is the first observation reporting the homozygous transmission of the Robertsonian translocation involving chromosomes 21 and 22. The RT rob(21;22) is one of the rarest TRs involving two non-homologous acrocentric chromosomes with a frequency of 1.9% [6,7].

Carriers of balanced chromosomal rearrangements are couples at high risk of having descendants carrying chromosomal aberrations and a high risk of infertility, particularly through recurrent miscarriages [19,20]. The production of gametes balanced for RT is higher during male meiosis, reaching 82% compared to 60% during female meiosis [21-24]. This difference is explained by the blocking of male meiosis during the checkpoints of metaphase I leading to apoptosis of spermatocytes with chromosomal imbalances; only those with balanced content survive without abnormalities or with balanced abnormalities survive [24,25] while the occurrence of RT is more frequent during oogenesis especially *de novo* and without blocking the gametogenesis thus the proportion of balanced gametes will be lower since there are also unbalanced ones [26].

Homozygous transmission of RT in phenotypically healthy subjects is a rare condition. Around twenty observations have focused on the most frequent Robertsonian translocation rob(13;14) for which cases of homozygosity have been reported, particularly in consanguineous subjects [27,28]. The RT (14;21) in the homozygous state has also been reported in an Indian patient with primary amenorrhea [29]. The couple reported in our observation is also consanguineous. The observations, already reported, show, for the most part, a history of fetal loss [8,28], which is not the case for our couple.

Two prenatal observations with a karyotype with 44 chromosomes have also been reported, it is about a rob (14;21) in the homozygous state and the postnatal follow-up found a normal child [9,10].

Even more exceptional are the 44-chromosome karyotypes with two different Robertsonian translocations. This is a situation reported only once [30]. Theoretically, the phenotype

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should be normal since the two rearrangements are balanced. However, the effect on the possible combinations at the level of gametes at the time of meiosis makes the situation complex [30].

In our observation, the parents are related and carry the same translocation in the heterozygous state. This is probably a translocation inherited from a common ancestor, according to its low incidence and the probability of finding it in the same couple is low [6,7]. Studying the karyotype of other family members was not possible.

The two other related children, cousins of our couple, carrying Down syndrome, would very likely have the same RT at least in the heterozygous state.

We provided adequate genetic counseling for the couple and advised them to carry out a fetal karyotypic study for each pregnancy (preimplantation diagnosis is currently not available in Tunisia).

Most carriers of RT in the homozygous state are healthy and do not present particular phenotypic traits with preserved fertility; their descendants are in all cases carriers of the same RT in the heterozygous state [15].

The detection of RT in the homozygous state makes it possible to find heterozygous descendants who present a high risk of having children with unbalanced chromosomal rearrangements and enables the proposal of prenatal diagnosis for their offspring or better a preimplantation diagnosis which avoid pregnancy termination and its psychological damages [10].

No difference in the production of unbalanced gametes depending on the sex of the carrier parents has been reported [24].

Conclusion

This case adds further evidence that people with 45 chromosomes are mostly healthy and free of dysmorphic features. Identification of a RT makes it possible to find heterozygous parents who are at risk of having children with imbalanced chromosomal rearrangements, and then prevent the birth of abnormal offspring. People with 44 chromosomes are extremely rare conditions that must lead to more familial investigations.

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