Homozygosity for a Robertsonian Translocation (13q;14q) in an Otherwise Healthy 44, XY Man With a History of Repeated Fetal Losses

Ebtesam M. Abdalla, PhD,1* Soha F. Kholeif, PhD,1 Reem M. Elshaffie, MBBCh1

CLINICAL HISTORY
We report a unique karyotype of 44,XY,der(13;14)(q10;q10)x2 detected in a phenotypically normal man married to a consanguineous healthy woman. The couple had a history of 3 second-trimester intrauterine fetal deaths (IUFDs) that involved multiple congenital anomalies. Together with a few previous observations in living patients who were homozygous for 13;14 and 14;21 translocations, this case supports the idea that subjects with 44 chromosomes can be healthy and lacking in dysmorphic features. Reproductive options for carriers of these translocations are discussed herein.

Keywords: 13;14 Robertsonian translocations, chromosomal structural abnormalities, homozygosity, repeated fetal loss

Abbreviations
IUFDs, intrauterine fetal deaths; PHA, phytohemagglutinin; ICSN, International System for Human Cytogenetic Nomenclature; FISH, fluorescence in situ hybridization; ICE, interchromosomal effect

1Department of Human Genetics, Medical Research Institute, Alexandria University, Egypt

*To whom correspondence should be addressed.
E-mail: drebtesamabdalla@yahoo.com

Despite the relative high incidence of Robertsonian translocations, reports of homozygosity for these chromosomal abnormalities are extremely rare. In a review of the literature, very few cases were found to have 2 translocations involving the same acrocentric chromosomes.7-13 Herein, we report a homozygous (13;14) Robertsonian translocation detected in the male partner of a couple with repeated fetal losses.

Materials and Methods

Case Presentation

The probands are a phenotypically normal consanguineous couple who attended our clinic seeking genetic counseling because of their history of 3 consecutive intrauterine fetal deaths (IUFDs) involving multiple congenital anomalies. The husband was 26 years old and the wife was 23 years old; both were otherwise in good health. They had no living children and no history of previous miscarriages. No history of drug or alcohol abuse or radiation or chemical exposure was reported for either of the probands. We surveyed the probands regarding their reproductive history; no pregnancy losses were reported except for a single first trimester abortion on the husband’s mother (Figure 1).

The couple’s first pregnancy had concluded with premature birth and IUFD during the 6th gestational
month; no medical reports are available for this pregnancy. The parents reported that they had been told by the doctor attending the labor that the baby had multiple congenital anomalies. During the second pregnancy, routine ultrasound imaging performed at the 20th week of gestation detected hydrocephalus. The couple decided to continue the pregnancy; however, IUFD occurred a few weeks later. The parents were advised to undergo amniocentesis and fetal karyotyping in their next pregnancy. They planned for the third pregnancy; regular fetal ultrasound examination was performed on a monthly basis. No fetal anomalies were detected until the date scheduled for the amniocentesis. On that date, the 3D-ultrasound fetal anomaly scan detected brain atrophic changes with dilated ventricles, Dandy-Walker syndrome, large dysplastic kidneys with severe oligohydramnios, cardiomegaly, pericardial effusion, and placentomegaly. A severe deficiency in amniotic fluid precluded the amniocentesis procedure; a few days later, IUFD was discovered.

Cytogenetic Study
Chromosomal analysis was carried out on 72-hour phytohemagglutinin (PHA)–stimulated cultures of peripheral blood lymphocytes according to standard methods.14 For each proband, 30 metaphases were counted, 5 metaphases were analyzed, and 2 were karyotyped. The chromosomal abnormalities were reported according to the International System for Human Cytogenetic Nomenclature (ISCN; 2009).15 Using conventional cytogenetic methods, GTG banding performed on the husband’s cells revealed the presence of a double Robertsonian translocation involving the long arms of chromosome 13 and 14 (ISCN nomenclature, 44,XY,der(13;14)(q10;q10)x2). The translocations were identified in all analyzed metaphases. A metaphase and a partial karyotype for the husband are shown in Figure 2. The wife had a normal female karyotype.

The husband was advised to undergo sperm fluorescence in situ hybridization (FISH) analysis; amniocentesis for prenatal testing was recommended for future pregnancies. All the husband’s family members were offered karyotyping but his parents were unavailable and his siblings declined to be tested.

Discussion
Balanced carriers of Robertsonian translocations are phenotypically normal. Almost all balanced carriers are heterozygous for the translocation and usually experience poor outcomes from pregnancy; they are at increased risk for spontaneous abortions and chromosomally unbalanced offspring.4 Carriers of homozygous Robertsonian translocations, however, have been scarcely reported in the literature.13 The first description of homozygosity for a Robertsonian translocation (13;14) was reported by Martinez-Castro et al in 1984;9 they reported a family in which both parents were heterozygous carriers of the translocation but had 3 healthy homozygous children. Subsequently, a number of other cases of individuals who were homozygous for (13;14) or (14;21) translocations were reported;13 all of those individuals were phenotypically normal.
Robertsonian translocations are the most common type of human structural chromosome anomaly. The 13;14 translocation accounts for approximately 75% of all Robertsonian translocations and is the most common chromosome rearrangement in humans. Although most homozygosity is inherited, reports of homozygosity are relatively rare. In fact, there are fewer reports of 13;14 homozygosity than would be expected from the predicted frequency of this chromosomal aberration within the population. Because most of the homozygous carriers of this translocation are healthy and have a favorable reproductive prognosis, the abnormality may often go undetected.

In 2010, O’Neill16 systematically reviewed all the published cases of homozygosity for constitutional chromosomal rearrangements, with particular attention to origin and phenotype. In the 10 cases of Robertsonian translocation homozygosity reviewed, most individuals were phenotypically normal and had been conceived as a result of inbreeding within a family that carried a familial translocation; their karyotypes were ascertained after identification of an existing familial rearrangement rather than any feature specific to the homozygosity. Also, the individuals in question were fertile, and as expected, their offspring were heterozygous for the translocation.

The likely reason for the husband’s chromosomal aberration is biparental inheritance of a (13;14) translocation. His blood-related parents might be heterozygous for the same translocation, which they could have inherited from a common ancestor. However, apart from a single first-trimester abortion, the reproductive history of those parents was free of adverse events. On reviewing the few reported cases of a sexual union between Robertsonian heterozygotes,8,12,13,17,18 all of them except the family reported by Martinez-Castro et al8 had experienced repeated spontaneous abortions and IUFDs, or had conceived mentally retarded and trisomic children. Another possibility is that only one (13;14) translocation was inherited, whereas the other one arose de novo. A similar case was reported by Rockman-Greenberg et al,7 who described a phenotypically normal fetus homozygous for t(14q21q) translocations, one of which was paternal origin and the other de novo. Although we regard the possibility as remote, the 2 translocations harbored by our

Figure 2
The husband’s metaphase spread (A) and partial karyotype with ideogram (B) illustrating the homozygous (13;14) Robertsonian translocation. Arrows indicate the 2 Robertsonian translocations between chromosomes 13 and 14.
male proband might both have occurred de novo. Cotter et al. described the de novo origin of 2 apparently balanced chromosome rearrangements detected in a 17-week fetus despite the fact that the parental karyotypes were normal. The mystery concerning the origin of the chromosomal rearrangement in our male proband cannot be solved until the karyotypes of family members become known.

Regarding the reproductive prognosis for this couple, 2 important issues are relevant: the chromosomal abnormality and consanguinity. The main risk for carriers of a balanced chromosomal rearrangement, most of which are heterozygous, occurs during the first meiotic division and is due to segregation problems of the rearranged chromosomes leading to the production of a high proportion of unbalanced gametes. However, in the presence of homozygous translocations the chances of successful reproductive outcome are not significantly lowered. Because we could find no studies describing the segregation behavior in homozygosity, we searched for reports on the meiotic segregation analysis of similar rearrangements in other vertebrates. We found an analysis of synaptonemal complexes from a bull that was a homozygous carrier for a 1;29 Robertsonian translocation. The results of this study confirmed that this homozygous translocation did not lead to any meiotic impairment.

For heterozygous carriers of a translocation, experimental data show that the frequency of the abnormality in their embryos far exceeds the expected frequency due only to parental meiotic segregation errors. Much of the abnormality is chaotic (affecting multiple chromosomes) and clearly postzygotic in origin. The frequency of abnormality in the embryos confirms that these couples are affected by the increased risk of parental meiotic segregation errors, compounded by additional factors that result in higher-than-normal rates of postzygotic anomalies. One such factor that has been studied in translocation carriers is the interchromosomal effect (ICE), which is the effect of a structural chromosome abnormality on the segregation behavior of other chromosomes not involved in the translocation. Studies suggest that an ICE may be more pronounced in Robertsonian translocations because a higher rate of aneuploidy was found for the chromosomes not involved in the translocation compared to control individuals or reciprocal translocation carriers. The relevant contribution of aneuploidy exposes the couples to an additional risk of abnormal pregnancy. Although the concept of an ICE has been suggested in the setting of balanced Robertsonian heterozygotes, we believe that homozygous translocations experience the same effect. Thus, if homozygous translocations do not show abnormal segregation behavior, their carriers might experience an ICE; their offspring are still prone to chaotic postzygotic anomalies. For these reasons, meiotic segregation analysis performed on sperm from homozygous Robertsonian translocation carriers can predict gamete behavior and hence can be useful for genetic counseling. Also, cytogenetic analysis of aborted fetal tissue or samples from viable offspring of the couple may be helpful.

Their status as first cousins is another relevant issue when discussing these probands. The condition that affected the couple’s 3 fetuses could have been an autosomal recessive multiple congenital anomaly syndrome; the paternal chromosomal anomaly could have been merely a coincidence. The congenital anomalies that affected the first 2 fetuses were not recorded, whereas those detected in the third fetus point to several genetic syndromes. Therefore, a definitive diagnosis could not be reached. The couple was offered meticulous follow-up in any future pregnancies with all available means of diagnosis.

In conclusion, a (13;14) homozygous Robertsonian translocation was detected in an otherwise healthy man married to a karyotypically normal woman who had experienced 3 second-trimester IUFDs involving multiple congenital anomalies. This case adds to the previous evidence that individuals with 44 chromosomes can be healthy and free of dysmorphic features. LM

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References
Available in the full-length version of this article, which can be accessed at http://labmed.ascpjournals.org/content/44/3.toc.