Translocation Down Syndrome among Filipinos and Its Implications on Genetic Counseling

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ABSTRACT

A review of the results at the Medical Genetics Unit, University of the Philippines (UP) College of Medicine (1991-1999) and at the Institute of Human Genetics, National Institutes of Health (IHG-NIH), University of the Philippines Manila (1999-2007) showed that Down Syndrome (DS) or Trisomy 21 accounted for 68.0% of all abnormal results detected. Trisomy 21 is caused by the presence of an extra chromosome 21 and the risk increases with advancing maternal age. There are 3 types of DS—full trisomy 21, mosaic trisomy 21 and translocation DS accounting for 88.3%, 7.2% and 3.3%, respectively. About 25% of translocation DS are familial and 75% are *de novo*. The familial cases are offspring of parents who are carriers of a balanced translocation involving chromosome 21 and another chromosome. This confers an increased risk of recurrence in subsequent pregnancies and the identification of such families is crucial. If the mother is a balanced carrier of a t(13/14/15/22;21), there is about a 12% risk for another DS child to be born in each subsequent pregnancy. If the father is the carrier, the observed risk drops to about 3% for DS. However, for translocation of 2 chromosome 21 [t(21:21)] which accounted for 50.0% of translocations detected, the implications will be different. A parent who is a balanced carrier of a t(21:21) will only have 2 outcomes for the pregnancy, unbalanced translocation DS and a lethal monosomy.

Key Words: Down syndrome, Translocation trisomy 21

Introduction

Down syndrome (DS) is one of the most common genetic birth defects, affecting approximately 1 in 800 babies. It is generally caused by the presence of an extra chromosome 21, and its diagnosis, whether antenatal or postnatal is virtually always confirmed cytogenetically.[1] The risk of DS increases in relation to maternal age.[2, 3]

DS is a genetic disorder that includes a combination of birth defects, some degree of mental retardation, characteristic facial features, heart defects, endocrine problems, problems with hearing and vision, gastrointestinal abnormalities and other health problems such as immunodeficiency. The severity of all of these problems varies greatly among affected individuals.

About 95% of DS cases have an extra chromosome 21 that results from maternal non-disjunction error during meiosis II. The origin of the extra chromosome is maternal in about 80% of the informative cases and paternal in about 20%.[4] In 2% of diagnosed cases, it is the mosaic type of DS which results from a malsegregation of homologous chromosomes or an anaphase lag of one homolog occurring post-zygotically. The remaining 3% of DS cases represent the consequences of a translocation. Almost all translocation types of DS are Robertsonian translocations. About 25% of Robertsonian translocations DS are familial and 75% are *de novo*.[5] It is important to identify patients with the translocation type because parents must be tested for a possible carrier status of the translocation, thus carrying an increased risk of having a second affected child.

The objectives of this paper are to review the types of translocation DS at the Medical Genetics Unit of the UP College of Medicine and at the Cytogenetics Laboratory of the Institute of Human Genetics – National Institutes of Health (IHG-NIH), University of the Philippines Manila; and to discuss the implications of genetic counseling for the different types of translocations.

Methods

Cytogenetic results at the Medical Genetics Unit, UP College of Medicine (1991-1999) and at the IHG-NIH, University of the Philippines Manila (1999-2007) were reviewed. Results of patients with DS were reviewed and classified. Descriptive statistics using percentages of proportion was utilized for the interpretation of the data.

Results

A diagnosis of DS was made in 68.0% of all abnormal cytogenetic results identified by the Cytogenetics Laboratory. Of these, 88.3% were full trisomy of chromosome 21, 7.2% were due to mosaic Trisomy 21 and 3.3% were due to translocation Trisomy 21 (Table 1). Table 2 compares the frequency of cytogenetic types of Trisomy 21 from previously published reports compared to the results of this review of cases. Table 3 shows the various combinations of Robertsonian translocations.

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Table 1. Frequency of cytogenetic types of Trisomy 21

Cytogenetic type	Number (N= 1 858)	Percent (%)
Full	1 640	88.3
Mosaic	134	7.2
Translocation	62	3.3
DS with other chromosome abnormalities	22	1.2

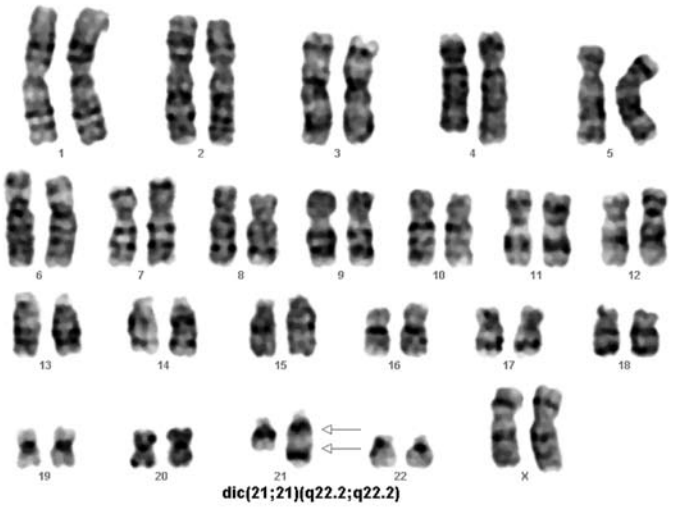
Table 2. Frequency (percent) of cytogenetic types of Trisomy 21 from other literature

Cytogenetic type	Jones[6]	Barch et al.[7]	Mange[8]	This paper
Full	94.0	92.5	94.0	88.3
Mosaic	2.4	4.8	2.0	7.2
Translocation	3.3	2.7	4.0	3.3

Table 3. Frequency of the different types of translocations involving chromosome 21

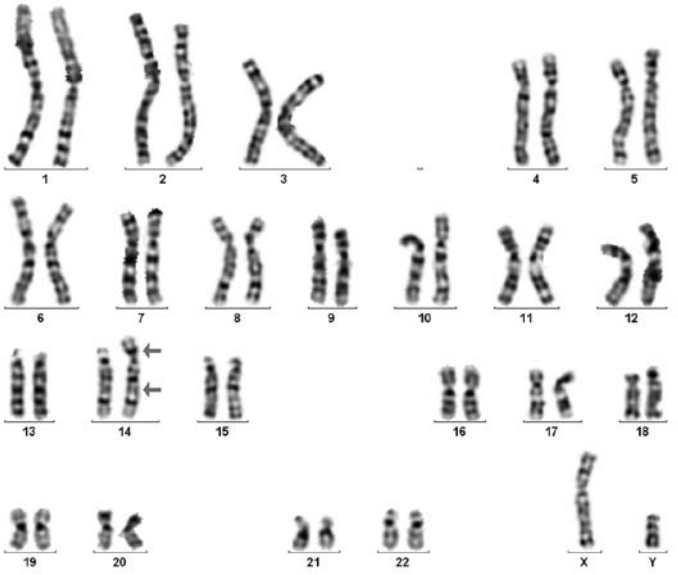
Types of translocation	Number (N= 62)	Percent (%)
t(21;21)[a]	31	50.0
t(14;21)[b]	19	30.6
t(15;21)[c]	6	9.7
t(13;21)[d]	4	6.5
t(21;22)[e]	2	3.2

*Robertsonian translocations occur when fusion of 2 acrocentric chromosomes (chromosome 13,14,15,21 and 22) in the region of the centromere results in one abnormal chromosome. Whereas, non-Robersonian translocation involves chromosomes other than the acrocentric chromosomes
a Figure 1. Translocation between chromosomes 21 and 21 - t(21;21)
b Figure 2. Translocation between chromosomes 14 and 21 - t(14;21)
c Figure 3. Translocation between chromosomes 15 and 21 - t (15;21)
d Figure 4. Translocation between chromosomes 13 and 21 - t (13;21)
e Figure 5. Translocation between chromosomes 22 and 21 - t (21;22)



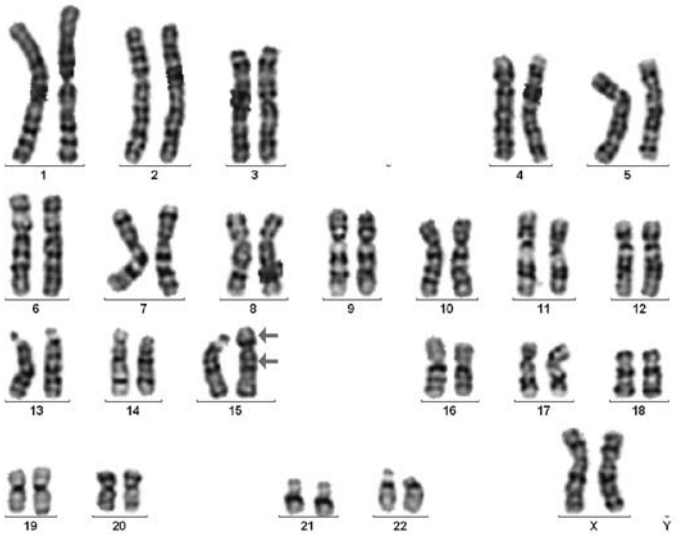
46, XX, dic(21;21) (q22.2;q22.2)

Figure 1. Translocation between chromosomes 21 and 21 - t(21;21). (Source: Cytogenetics Laboratory, Institute of Human Genetics, NIH-UP)



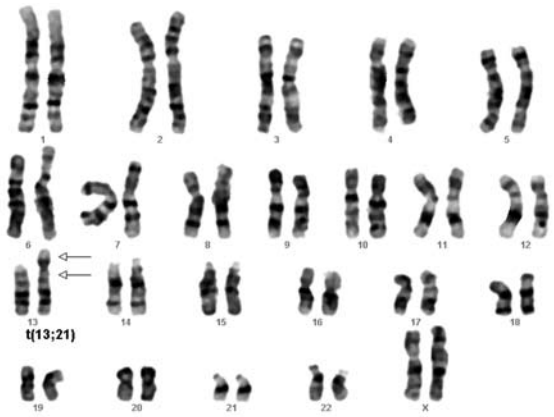
46, XY, t(14;21) (q10;q10)

Figure 2. Translocation between chromosomes 14 and 21 - t(14;21). (Source: Cytogenetics Laboratory, Institute of Human Genetics, NIH-UP)



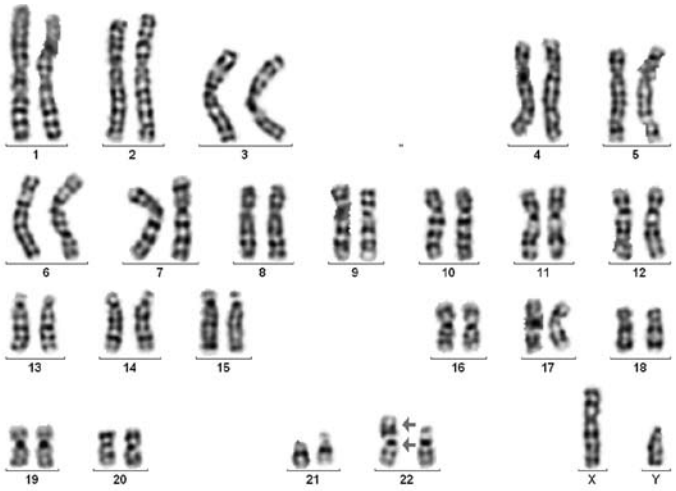
46, XY, t(15;21) (q10;q10)

Figure 3. Translocation between chromosomes 15 and 21 - t(15;21). (Source: Cytogenetics Laboratory, Institute of Human Genetics, NIH-UP)



46, XY, t(13;21) (q10;q10)

Figure 4. Translocation between chromosomes 13 and 21 - t(13;21). (Source: Cytogenetics Laboratory, Institute of Human Genetics, NIH-UP)



46, XX, t(21;22) (q10;q10)

Figure 5. Translocation between chromosomes 21 and 22 - t(21;22). (Source: Cytogenetics Laboratory, Institute of Human Genetics, NIH-UP)

Discussion

The great majority of cases of Down syndrome have 47 chromosomes due to Trisomy 21, but in about 5% of cases, the number is normal (46) and the extra chromosome material is translocated onto another chromosome. This type of rearrangement is known as a translocation.

Generally, translocations are the most common structural abnormalities in the human chromosome complement. It involves the exchange of genetic material between two or more non-homologous chromosomes when they break at the same time. Breakages tend to occur at or near the centromere or the chromosome ends and at the euchromatic-heterochromatic (light and dark bands) junctions. A translocation is said to be balanced when no genetic material is lost in the exchange. Unbalanced translocations, on the other hand, cause serious problems in cell division and may lead to viable dysmorphic infants or spontaneous abortions. Robertsonian translocations occur when fusion of 2 acrocentric chromosomes (chromosome 13, 14, 15, 21 and 22) in the region of the centromere results in one abnormal chromosome.[7] In this paper, the translocation of two 21 chromosomes was the most commonly encountered. This is in contrast with what has been reported that two chromosome 21 are the least commonly involved in translocation DS compared to the other acrocentric chromosomes.[3, 9] This occurrence has to be further investigated locally whether maternal age or low grade mosaicism of 21q21q cell line is present in the parents of the probands with this particular type of translocation DS.

Counseling Issues

The genetic risk in translocation types of Trisomy 21 depends entirely on whether the translocation is *de novo* or familial. This distinction is made by doing chromosomal studies of the parents. If their chromosomes are normal as in 75% of cases (*de novo*), the risk to further offspring is minimal, probably similar to that following a trisomic

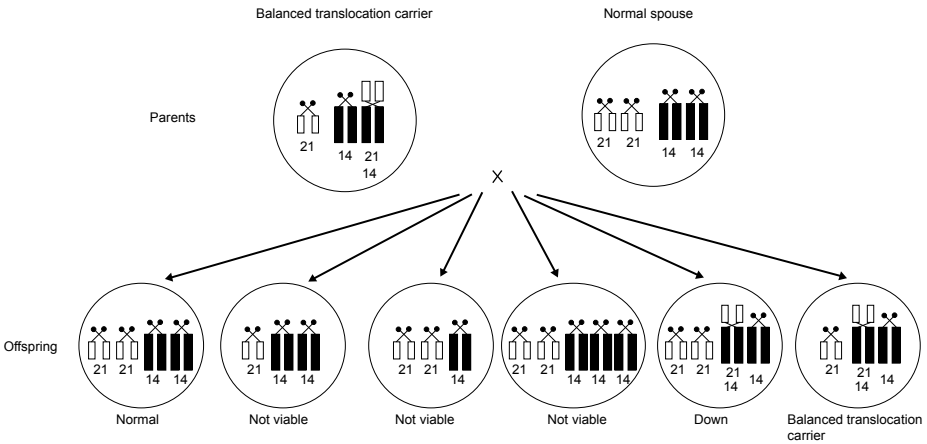


Figure 6. Possibilities for offspring in families with translocation Down syndrome

child at the same maternal age, and under 1% in younger women.[3]

The usual parental abnormality is a balanced translocation, in which the chromosome number is 45, but the total amount of chromosomal material is normal; one chromosome 21 will be absent and an abnormal chromosome will be seen composed of the 21 and the chromosome onto which it has been translocated.

The possibilities for offspring of translocation carrier parents specifically involving chromosome 21 and either chromosomes 13, 14, 15 and 22 are shown in Figure 6. In theory, one might expect all the categories to occur in equal proportions, but since trisomies 13, 14, 15 and 22 or the absence of one chromosome 13, 14, 15, 21 and 22 are lethal and rarely result in an unidentified pregnancy, the risk of a child with translocation DS is considerably less than it should be theoretically, particularly when the father is carrying the balanced translocation.[3] Generally, when the mother is a balanced carrier of a t(13/14/15/22;21), there is about a 12% risk for another DS child to be born in each subsequent pregnancy. When the father is the carrier, the observed risk drops to about 3% for DS. The reason for this difference in risks is not at all clear.[10]

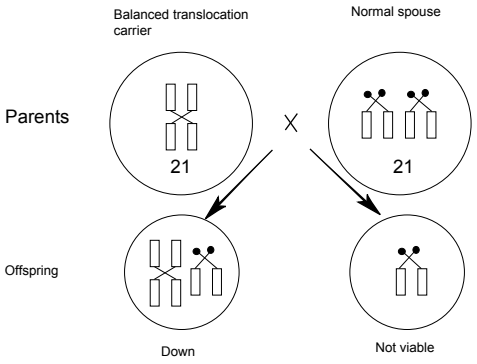


Figure 7. Possibilities for offspring of a balanced 21/21 translocation carrier. All viable offspring of such an individual will have DS.

However, in the case of 21/21 balanced translocation, all pregnancies will be abnormal because the only alternatives are the unbalanced translocation DS and the lethal monosomy (Figure 7).[3]

Thus, once a case of translocation DS has been identified, it is essential to test the parents. If the translocation is *de novo*, a recurrence risk figure of 1% is applicable. If one of them is a translocation carrier, the genetic risk for future offspring depends on the sex of the parent and the type of chromosome 21 translocation they carry. Prenatal diagnosis in any future pregnancy may also be offered to these couples.

Conclusion

The chromosomal studies of the child suspected to have DS remains a critical component of diagnostic examinations. The type of translocation DS, whether it is familial or de novo determines the counseling that will be offered to the family.

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