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## Turner Syndrome and Sex Chromosomal Mosaicism

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### 1. Introduction

Turner syndrome (TS) is defined as the total or partial absence of the second sex chromosome in women (Ford et al., 1959). Its incidence is 1 in every 1,850 newborn girls (7<sup>th</sup> International Conference on Turner Syndrome, 2009) although it is higher at the moment of fertilization, since it is estimated that 3% of all human fertilizations are 45,X (Urbach and Benvenisty, 2009) but only 1% survive beyond 24 weeks gestation (Hook and Warburton, 1983).

The Turner phenotype is quite variable, even among women with the same karyotype, however, there are some cardinal features: low stature (>99%), gonadal dysgenesis (>90%) and anatomic malformations such as *Pterigium colli* or *cubitus valgus* (>80%). In addition, the Turner phenotype can be associated to other less frequent characteristics such as: cardiovascular congenital defects, renal alterations, aorta anomalies, etc, besides a specific neuropsychologic profile which can include selective non-verbal deficiencies: alterations of the sight-space capacity and low capacity of abstraction (Bondy et al., 2007; Ross et al., 2000a; Ross et al., 2000b; Ross et al., 2006; Zinn et al., 2007). Mental deficiency is not a characteristic of TS.

Both the embryonic lethality and the Turner phenotype are considered the result of a haploinsufficiency of genes found on both sex chromosomes (X and Y) and that escape X-inactivation (it is assumed that these genes are expressed in both active and inactive X chromosomes as a means of ensuring the right quantity of genetic product). The sex chromosomal regions causing these two conditions are referred to as pseudoautosomal regions 1 and 2 (PAR1 and PAR2) and are found at the ends of both sex chromosomes.

The high percentage of fetal and embryonic lethality for karyotype 45,X also suggests the need of mosaicism for survival (Held et al., 1992). Natural selection is not as prevalent when mosaicism is operative (Hassold et al., 1988; Hook and Warburton, 1983) although, paradoxically, the resulting phenotype after birth is similar with or without mosaicism.

Some hypotheses argue for the existence of a fetoprotective effect of one or more genes of the sex chromosomes (X or Y). According to this concept, all Turner women are mosaics since the presence of two copies of these gene(s) should be present, either in the fetus or in extra-embryonic tissues (Kalousek et al., 1987). But the detection of mosaicism is not always possible. It is mainly determined by four factors: the type and number of tissues analyzed (Held et al., 1992); the number of cells studied (Hook, 1977); the sensitivity of the techniques applied, and the possible selection which may result in the disappearance of cell lines (Procter et al., 1984). Thus, a small percentage of mosaicism cannot be detected by

conventional cytogenetic techniques unless we sit down case by case in front of the microscope with much patience, analyzing at great number of metaphases. This way, the application of molecular techniques substantially improves the detection of low-frequency cell lines.

Here we present the results of hidden mosaicism on 192 women diagnosed as TS and we focus on the molecular study of the Y chromosome, since numerous studies have shown that 4-20% of Turner women present a Y-chromosome (Kocova et al., 1995), increasing the risk of developing gonadoblastoma (Coto et al., 1995). Although the identity of the gene (or genes) linked to gonadoblastoma has not been established yet, there is evidence indicating that these genes are located near the centromere of the Y chromosome (Salo et al., 1995; Tsuchiya et al., 1995).

## 2. Patients and methods

The selection of the 192 Turner patients was carried out with the aid of the Genetics Division of the "Materno Infantil" Hospital of A Coruña, the Endocrinology Section of the General Hospital of Galicia, the Endocrinology Section of the Hospital of Málaga, and the Turner association from Spain. The age of the analyzed population ranged between 1 month and 43 years and the average age was 13.2 years.

Blood samples were extracted using heparinized test tubes for further cytologic study, and tubes with EDTA anticoagulant for molecular analysis. Standard techniques for the cultivation of lymphocytes from peripheral blood were used (Moorhead et al., 1960), and the preparations were treated with trypsin to obtain G-banding (Seabright, 1971).

### 2.1 Fluorescence *in situ* hybridization

The X chromosome was studied using the probes specified in Table 1: DXZ1, Xq13.2 (XIST), DXZ4, painting for Xp and *SHOX* (short stature homeobox-containing gene) and cosmid LLNOYCO3'M'34F5 kindly provided by Dr. Andrew Zinn.

The DXZ1 probe specifically hybridizes with the centromeric region of the X chromosome. The nature of the material involved in the restructuring was determined by the Xq13.2 inactivation site probe, and the DXZ4 probe specific to the macrosatellite repeat located at Xq23-24. The absence or presence of the Y chromosome was determined with the DYZ1-DYZ3 probe (Oncor), which specifically hybridizes with the centromere and the long arm of the Y chromosome, and the chromosomal material was determined by the painting probe from Vysis.

Independently of the karyotypes, all Turner patients were checked for the presence of the Y chromosome by PCR and FISH. Metaphases from a control male were simultaneously and identically processed, as a positive control. In the case of the DXZ1 probe, the fluorescent signal of the intact X chromosome served as an internal control. The minimum number of analyzed metaphases for each probe was 100, distributed in at least two slides.

The hybridization procedure originally described by Pinkel (Pinkel et al., 1986) was used according to commercial protocols (Oncor and Vysis). The chromosome preparations were counter-stained with propidium iodide (PI) or DAPI, and were observed and photographed by a Zeiss fluorescence photomicroscope.

To achieve simultaneous hybridization of DXZ1 and Xq13.2 probes, the Oncor sequential hybridization protocol was used. For hybridization with the *SHOX* probe, the cosmid was labelled by nick translation using biotin (Roche). The post-hybridization washes spent 15 min at 43°C in 50% formamide/2x SSC and then 15 min at 43°C in 2XSSC.

Probes	Characteristics of the probes	Provider
<b>X-chromosome</b>		
DXZ1	Specific to the centromeric region of the X chromosome	ONCOR
DXZ4	Specific to the repetitive region on Xq24	ONCOR
ToTelVysion	Specific to the telomeric regions from all chromosomes	Vysis
SHOX	Short stature homeobox. Cosmid LLNOYCO3'M'34F5	Dr. Andrew Zinn
XIST	Specific to the inactivation center at Xq13.2	ONCOR
WCP-X	Whole X chromosome painting probe	Vysis
SCPL116	Partial Xp painting probe	Dr. Rocchi
SCPL102	Partial Xq painting probe	Dr. Rocchi
<b>Y-chromosome</b>		
DYZ1	Specific to the heterochromatic region Yq12	ONCOR
DYZ3	Specific to the centromeric region of the Y chromosome	ONCOR
PCYq	Partial Yq painting probe	Vysis
WCP-Y	Whole Y chromosome painting probe	Vysis

Table 1. FISH Hybridization probes and characteristics

## 2.2 PCR analyses

DNA extraction from peripheral blood was carried out using standard procedures. For PCR analysis, different sets of oligonucleotide primers were used to amplify X and Y-specific sequences:

1. XC1-XC2, located at the centromeric region of the X chromosome, to amplify a 130-bp fragment (Witt and Erickson, 1989; Witt and Erickson, 1991)
2. YC1-YC2, located at the centromeric region of the Y chromosome, to amplify a fragment of 170-bp (Witt and Erickson, 1989; Witt and Erickson, 1991)
3. XES7-XES2, located within the *SRY* open reading frame, to amplify a 609-bp fragment (Berta et al., 1990).
4. DYZ1A-DYZ1B to amplify a 1024-bp fragment from the DYZ1 region contained within the Yq12 (Cooke, 1976; Nakagome et al., 1991)

The PCR amplification was carried out according to standard protocols. The PCR products were detected in 1,5% agarose gels.

## 2.3 Cloning and DNA sequencing of the XES-PCR products

In those patients in which the amplification of the *SRY* gene was positive, we cloned and sequenced the fragment in the following way: the products from three independent PCR reactions were joined to the plasmid pGEM-T (Promega) and subsequently transformed into the *E. coli* JM109 under the conditions recommended by the manufacturer. Six positive clones were sequenced in both directions by using the Thermosequenase fluorescent cycle sequencing kit from Amersham. The sequence reactions were analyzed on a 6.5% polyacrylamide gel in a LICOR-400L automated sequencer.

## 3. Results and discussion

In 1992 Held and others (Held et al., 1992) sent an innovative idea about TS: karyotype 45,X really does not exist, all Turner patients who survive and get to be born are really mosaic.

The karyotype 45,X is really deleterious and the natural selection does not allow it, causing a spontaneous abortion in the first weeks of gestation. The presence of a second cellular line, either 46,XX or 46,XY, in embryonic or extraembryonic tissues, provides a fetoprotective effect which allows the development of a Turner girl.

When only one cellular tissue (blood generally) is analyzed, the resulting karyotype might lead to error, because the second cellular line could be located in any other place, or in extraembryonic cellular tissues, which allow the fetus to develop to maturity. In addition, in order to make a diagnosis, it is necessary to analyze a high quantity of metaphases, specially if the 45,X cells immediately become very apparent through the microscope. Time is very limited and usually not enough time is spent in the detailed observation of over 1000 cells. In our opinion, and according to the words of Santiago Ramon and Cajal "It is not enough to examine, is necessary to contemplate..." (In the fourth edition of his book of Rules and Advice (page 166)

Even so, after applying molecular techniques and studying several cellular lines, some patients are still seemingly 45,X (see Table 2). But we do not discard hypothesis of Held since sensible techniques which discard 100% mosaicism do not exist and it is not possible to analyze all the cellular tissues from one patient because she is alive (obviously).

In the following Table we present the results obtained in our laboratory, after almost twenty years analyzing blood samples of women and children with this syndrome, within the Spanish population. The average number of analyzed metaphases (not including nucleous, which were also analyzed) for each patient was 507,73.

KARYOTYPE	N° Patients	Percentage
<b>No mosaicism</b>		
45,X	20	10,42
45,X, +SRY	1	0,52
46,X,i(Xq)	10	5,21
46,X,del(Xp)	12	6,25
<b>X-Mosaicism</b>	<b>135</b>	<b>70,31</b>
45,X/46,XX	83	43,23
45,X/47,XXX	7	3,65
45,X/46,X,i(Xq)	11	5,73
45,X/46,X,+der(X)	16	8,33
45,X/46,X+r(X)	4	2,08
45,X/46,XX/47,XXX	1	0,52
<b>Others</b>	<b>11</b>	<b>5,73</b>
<b>Complex mosaics (+3 cell lines)</b>	<b>2</b>	<b>1,04</b>
<b>Y-Mosaicism</b>	<b>14</b>	<b>7,29</b>
45,X/46,X,+der(Y)	1	0,52
45,X/46,XY	9	4,69
46,X,der(X)t(X;Y)(qter→p22.3::q11.21→qter)	1	0,52
45,X/46,X,+i(Yq)/46,X,+der(Y)	1	0,52
idic(Y)(qter→p11.32::p11.32→qter)	2	1,04
<b>Total</b>	<b>192</b>	<b>100%</b>

Table 2. Distribution of the karyotypes in a Spanish population of 192 Turner women

### 3.1 Non-mosaic patients: The karyotype 45,X

As we can observe in table 2, of the 192 Turner patients analyzed throughout these years, only 21 (aprox. 11%) showed karyotype 45,X. Or rather we could say that there were 21 patients in whom we were not able to locate a cellular line other than the 45,X, in spite of our efforts. In addition, for those same patients, we analyzed the *AR* gene (androgen receptor gene), in particular a variable region within exon 1, located in Xq11-12 which shows tandem GCA repetitions to let us know if one or two copies of that gene exists (in blood) (Table 3). The results indicated the same outcome. There continues to be 21 patients without an apparent second cellular line (46,XX or 46,XY).

Gene	Localization	Position	characteristics	Primers	T° annealing
Androgen receptor ( <i>AR</i> )	Xq11-12	exon 1	Tamden repetition GCA	5'-GTTCCATCCAGGACCAGGTA-3' 5'-GTGCGGAAGTGATCCAGA-3' HEX	56° C

Table 3. PCR Primers for Androgen receptor (*AR*)

The choice of this variable region and not another one, was due to its proximity to the center of inactivation of the X chromosome, and therefore, its proximity to the centromere. It is known that a fragment without centromere is generally considered an unstable element since it cannot join the metaphase spindle and therefore, it tends to disappear in successive mitoses. Consequently, we are able to say that a stable chromosome, capable of forming a cellular line, must have a centromere. Otherwise, we know that the loss of the inactivation center (XIC) in a small fragment from the X chromosome produces mental deficiency. Not at all a normal characteristic of this syndrome.

We can emphasize one case in this group which is striking due to its exceptional nature.

#### 3.1.1 The tall and mathematical 45,X non mosaic woman

One of the patients showed a nonmosaic 45,X karyotype in different weaves and by means of cytogenetic and molecular techniques. Her phenotype cannot then be classified as "characteristic" because her height is 170 cm without growth hormone (GH) treatment, and whose only apparent Turner feature is gonadal dysgenesis. The only possible explanation for the absence of a Turner phenotype is the hidden mosaicism combined with an untreated gonadal dysgenesis (Fernandez and Pasaro, 2010). Another characteristic of this patient is that she has completed her studies in mathematics obtaining excellent grades. Taking into account that TS women were defined as *blind to form and space* by Money (Money, 1993), we have to consider this woman is exceptional, since she is a 45,X non-mosaic and breaks away from all the pre-established standards for this syndrome.

The G-banding analysis (blood and skin fibroblast) and the FISH method using all the X probes, showed the same karyotype (45,X) whereas the DYZ1 and DYZ3 probes showed that the Y chromosome was not involved in the karyotype. The parents' karyotype was normal.

The cytogenetic and molecular analysis of the X chromosome always showed that the X present in the karyotype was a normal chromosome without duplication in the PAR1 region.

The absence of the Y chromosome was confirmed by PCR. The study of polymorphism also showed that the X present was inherited from the mother, and that this patient has only one copy of the *SHOX* gene. The analysis of the *AR* showed only one copy of the gene.

The discrepancies between the karyotype and the phenotype found in our patient suggest that previous cases of TS have been undiagnosed or misdiagnosed. Our results support the theory that significant ascertainment bias exists in our understanding of TS, with important implications for prenatal counseling. We think that the real frequency of TS can be greater than 1/1,850 due to females with a normal phenotype.

At first sight we could think that this patient discards the hypothesis of Held, because, in spite of our efforts, we have not been able to find a second cellular line. But we think that it is indeed an optimal test that the TS "always" goes accompanied by one second cellular line which protects it against natural selection and allows it to continue with its fetal development.

We cannot deny the existence of this hypothetical second cellular line which protects the embryo and the fetus, after analyzing a few cells to the microscope. Not even after carrying out a molecular study of the sex chromosomes, since we cannot exclude the different distribution possibilities of the different cellular lines in the many weaves of the organism throughout the embryonic development, which allowed, in this case, the development of a 45,X woman with an absence of a Turner phenotype.

### **3.2 Mosaicism in the Turner syndrome**

The presence of mosaicism (small chromosomal fragments, rings, or isodiscentric chromosomes, derived from X or Y) characterized the second cellular line for the remainder of the analyzed women (70,31%). The ones who had been previously diagnosed as mosaic using G-bands, presented a more complex karyotype after the molecular study due to the presence of new cellular lines. The complex mosaics were always associated to isodicentric chromosomes in both X and Y. The presence of two centromere leads to instability and loss of chromosomes which tend to break and to distribute themselves randomly through the successive mitotic divisions (Fernandez-Garcia et al., 2000; Fernandez et al., 1996).

#### **3.2.1 Implication of the Y chromosome on the chromosomal mosaicism in Turner syndrome**

When the chromosome involved in the second cellular line was Y, we were able to observe isodicentric chromosomes for the short as well as the long arms. These chromosomes had been defined as monocentric fragments of unknown origin using the G-Band technique, and the existence of both centromeres was evident only using FISH. The presence of two centromeric regions unleashes great instability during mitosis, which produces a build-up of chromosomal derivatives which are randomly distributed and which cause a high number of cellular lines due to the formation of different sized rings. An example of this type of mosaicism associated with isodiscentric chromosomes are shown below. They represent the most striking cases within the analyzed group in our laboratory.

##### **3.2.1.1 Molecular analysis of an idic(Y)(qter→p11.32::p11.32→qter) chromosome from a female patient with a complex karyotype**

Here we present a 4-year-old girl with a low to moderate height and a gonadal dysgenesis as the only features associated to TS (Fernandez and Pasaro, 2006). She exhibited a chromosome similar in size to a member of group D, which suggests two Y chromosomes united by the pter ends (Figure 1). The analysis of 506 metaphases by FISH revealed at least

eight cell lines and two different derivatives from the Y chromosome. In 58% of the cells, a double-hybridization signal was observed in the derivative chromosome for probes DYZ1 and DYZ3, corresponding to double heterochromatic and centromeric regions, respectively. The cell line 45,X was found in 19% of the cells, whereas the cell line 46,X,del(Y)(p11.32) was present in 16.5%. Furthermore, five other cell lines were observed in smaller percentages, resulting from the breakage of the idic(Y) (qter→p11.32::p11.32→qter) at p11.32 and a later mitotic random distribution of the two del(Y)(p11.32) and the X chromosome:

- 3% corresponding to a cell line with an X chromosome, a Y chromosome with terminal deletion and an isodicentric Y: 47,X,del(Y)(p11.32), idic(Y) (qter→p11.32::p11.32→qter)
- 1.5% corresponding to a cell line containing two X chromosomes and one isodicentric Y chromosome 47,XX, idic(Y)(qter→p11.32::p11.32→qter).
- 1% of the cells showed a combination of one X chromosome and two isodicentric Y chromosomes 47,X, 2idic(Y)(qter→p11.32::p11.32→qter)
- 0.5% showed one X chromosome and two Y chromosomes with terminal deletion 47,X, 2del(Y)(p11.32)
- 0.5% of the cells showed two X chromosomes and one deleted Y chromosome 47,XX,del(Y)(p11.32).

The fact that an intact 46,XY line was not found and that all the der(Y) had lost the PAR1 region suggests a meiotic origin for the dicentric Y. Perhaps the isodicentric Y chromosome was present in the sperm before fertilization as a result of an error during gametogenesis.

Errors occurring after the first zygotic division would result in mosaicism including a normal cell line. We think that the dic(Y) was a result of a meiosis I exchange between sister chromatids at a site between *SRY* and the *SHOX*, followed by centromere misdivision in meiosis II (Battin, 2003; Hsu, 1994; Robinson et al., 1999).

The patient showed a total of eight cell lines and at least two morphologically distinct abnormal Y derivatives, all presumably descendants of a progenitor and unstable idic(Y) chromosome. The heterogeneous cell content observed suggests a great mitotic instability of sex chromosome Y and mitotic non-disjunction.

Usually, isodicentric Y chromosomes occur in mosaic form and are generally considered unstable elements since improper alignment of two centromeres on the metaphase spindle may lead to the formation of a bridge during anaphase (Cohen et al., 1973). In the patient studied here, the isodicentric Y chromosome showed two noticeable centromeres. If both centromeres were active, it could be assumed that the Y derivatives observed in the different cell lines would be the result of the breakage of the isodicentric at Yp11:32 due to improper alignment of the two centromeres on the metaphase spindle.

As in all the cases studied in our laboratory and in most of the reports published to date (Robinson et al., 1999), the patient examined here had a 45,X cell line (19%). Such mosaic patients exhibit a phenotype ranging from female to male, depending on the presence or absence of the testis-determining gene *SRY* and, perhaps more importantly, on the degree of mosaicism and the tissue distribution of 45,X cells. It has been proposed that the predominance of XO or XY cells determines gonadal differentiation into a testis or a streak gonad (Bergada et al., 1986).

On the other hand, TS is the result of a haploinsufficiency of a specific gene(s) that must escape from X-inactivation, and also, these individuals must have a functional Y peer. The discovery of the pseudoautosomal region at the termini of Xp and Yp fits well with these two requirements: the meiotic combination maintains nucleotide sequence identity between X- and Y-linked pseudoautosomal genes, and all such genes tested to date escape X

inactivation (Zinn and Ross, 1998). Nevertheless, the only TS features present in this patient were short stature and gonadal dysgenesis. The absence of the PAR1 region in all cells examined in this patient suggests that loci responsible for other Turner features lie outside the pseudoautosomal region (Haddad et al., 2003; Joseph et al., 1996; Spranger et al., 1997). Our data is in agreement with the fact that the only PAR1 gene consistently related to TS is the short stature gene or *SHOX/PHOG*. This gene is a strong candidate for a TS growth gene on the basis of its chromosomal location, its pattern of expression and a mutational analysis (Alves et al., 2003; Rao et al., 1997).

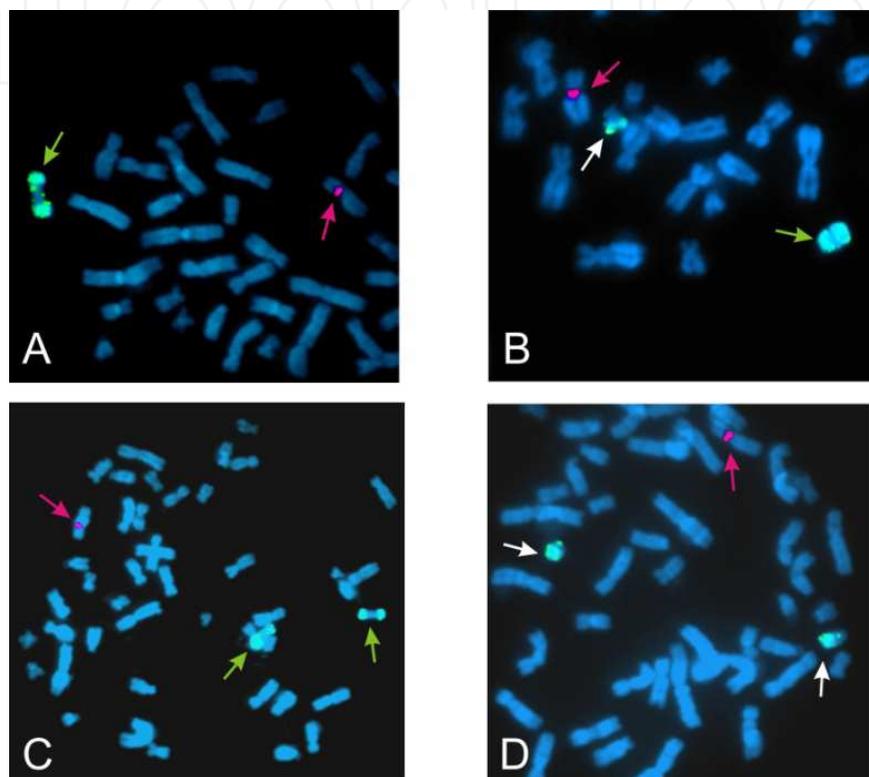


Fig. 1. FISH analysis using DXZ1 (magenta signal) and DYZ1 (green signal). A: 46,X,idic(Y)(qter→p11.32::p11.32→qter) metaphase; the magenta arrow indicates the X chromosome and the green one indicates the idic(Y)(qter→p11.32::p11.32→qter). B: 47,X,del(Y)(p11.32),idic(Y)(qter→p11.32::p11.32→qter) metaphase; the magenta arrow indicates the X chromosome, the white arrow indicates the del(Y)(p11.32) and the green one indicates the idic(Y)(qter→p11.32::p11.32→qter). C: 47,X,2idic(Y)(qter→p11.32::p11.32→qter) metaphase; once again the magenta arrow indicates the X chromosome, and the green arrows indicate the two idic(Y)(qter→p11.32::p11.32→qter). D: 47,X,2del(Y)(p11.32) metaphase; the magenta arrow indicates the X chromosome, and the white arrows indicate the two del(Y)(p11.32)

In conclusion, it appears that the most common abnormal Y chromosome present in TS patients is an isodicentric Y chromosome occurring as part of a mosaic karyotype including a 45,X cell line. It is probable that isodicentric Y chromosomes are usually generated during gametogenesis before spermatid formation, or during the first division after fertilization, and that almost all are present as part of a mosaic karyotype. The TS patients with a Y chromosome studied in our laboratory carried the testis-determining factor gene *SRY*, but the mosaic nature of their karyotypes rendered this insufficient to induce a male phenotype.

In all our patients, the degree and distribution of the 45,X cell line seem to be decisive factors in phenotype determination.

### **3.2.1.2 A mutation point, R59G, within the HMG-SRY box in a 45,X/46,X,psu dic(Y)(pter→q11::q11→pter) female**

The key step in mammalian sex determination is the development of the undifferentiated embryonic gonads into either testes or ovaries. We have known since 1990 that the *SRY* gene (sex determining region Y), located at the tip of the Y short arm (Yp11.3) and proximal to the pseudoautosomal boundary, is the critical switch leading to testis development (Berta et al., 1990). Mutations in *SRY* result in XY individuals developing as females, and patients with 45,X karyotype who have insertion of *SRY* into an autosome have a male phenotype (Yenamandra et al., 1997).

Mutations in this gene can cause failure of testicular development that may result in complete or partial male to female sex reversal (Cameron and Sinclair, 1997). This means that among all the Y-chromosome-derived sequences, *SRY* is the only one that is both required and sufficient to initiate male sex determination (Gubbay et al., 1990; Koopman et al., 1990; Koopman et al., 1991).

The first evidence for the identification of *SRY* as the testis determining factor (TDF) in humans came from the study of XY females with gonadal dysgenesis harboring de novo mutations or deletions in the *SRY* open reading frame. Since 1990, analysis of a number of the XY females with gonadal dysgenesis has led to the description of 36 mutations (31 nucleotide substitutions, three small deletions, one small insertion and one complex rearrangement) in the *SRY* gene. Most of them were located in a critical portion of *SRY*, namely the HMG-box (high-mobility group). The HMG-box is essential for *SRY* to bind and bend DNA, as well as for transporting the protein into the nucleus (Sinclair, 2001).

On the other hand, the most common abnormal Y chromosome is a dicentric Y chromosome present as part of a mosaic karyotype including a 45,X cell line (Robinson et al., 1999). They are usually generated during gametogenesis before spermatid formation, or during the first division after fertilization, and most are present as part of a mosaic karyotype. There appears to be a region between Yq11 and Yq12 prone to breakage where sister chromatid breakage and inappropriate fusion of broken ends could occur to form isodicentric chromosomes (Kirsch et al., 1996; Robinson et al., 1999; Schwinger et al., 1996). A wide spectrum of phenotypes of patients with a 45,X/46,X,der(Y) karyotype ranges from almost normal males through mixed gonadal dysgenesis to females with TS phenotype. Factors that most influence this variability of sex differentiation are, at least: (1) the presence of certain loci, fundamentally the *SRY* gene, in the developing gonad; (2) the proportion and distribution of 45,X cell line in various tissues, specially in gonads; (3) the moment at which testes degenerate during intrauterine development (Alfaro et al., 1976).

A small marker chromosome was found in 28 of 40 G-banded metaphases from peripheral blood lymphocytes in mosaic karyotype with a 45,X cell line. The G-banding pattern exhibited a marker chromosome similar in size to a member of group F (chromosomes 19 and 20) but did not unequivocally suggest its genetic content (Figure 2) (Fernandez et al., 2002).

When 559 metaphases were analyzed by FISH, the DYZ3 probe revealed, in 60% of the cells, a double hybridization signal in the marker chromosome (Figure 2). However, when the DYZ1 probe was used, no specific hybridization signal was obtained, indicating that the marker had lost the heterochromatic region of the Y chromosome. Application of the WCP-Y probe completely tinted the marker. The study of ovarian tissue using FISH also showed the

same result: double hybridization signal when the DYZ3 probe was used, and absence of specific signal with the DYZ1 probe. Therefore, the results obtained by FISH allowed the marker to be redefined as a pseudodicentric nonfluorescent Y chromosome  $\text{psu dic(Y)(pter}\rightarrow\text{q11::q11}\rightarrow\text{pter)}$  characterized by the presence of two copies of the short arm, two centromeres and two copies of proximal long arm. The heterochromatin region was not present. PCR analysis confirmed the deletion of the Y-heterochromatic region and also the presence of the Y-centromere and the *SRY* gene in blood.

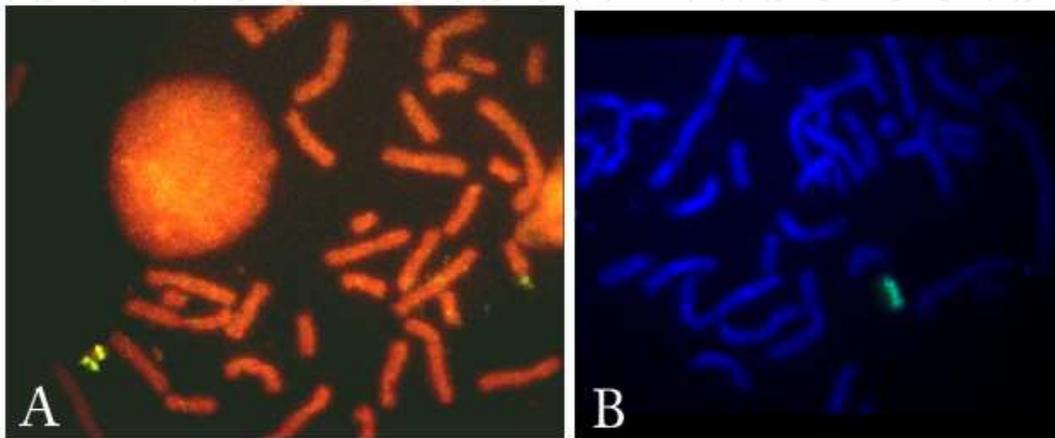


Fig. 2. A. Characterization of the  $\text{psu dic(Y)}$  in blood by FISH and DYZ3 probe. B. Characterization of the  $\text{psu dic(Y)}$  by FISH and whole painting WCP-Y probe

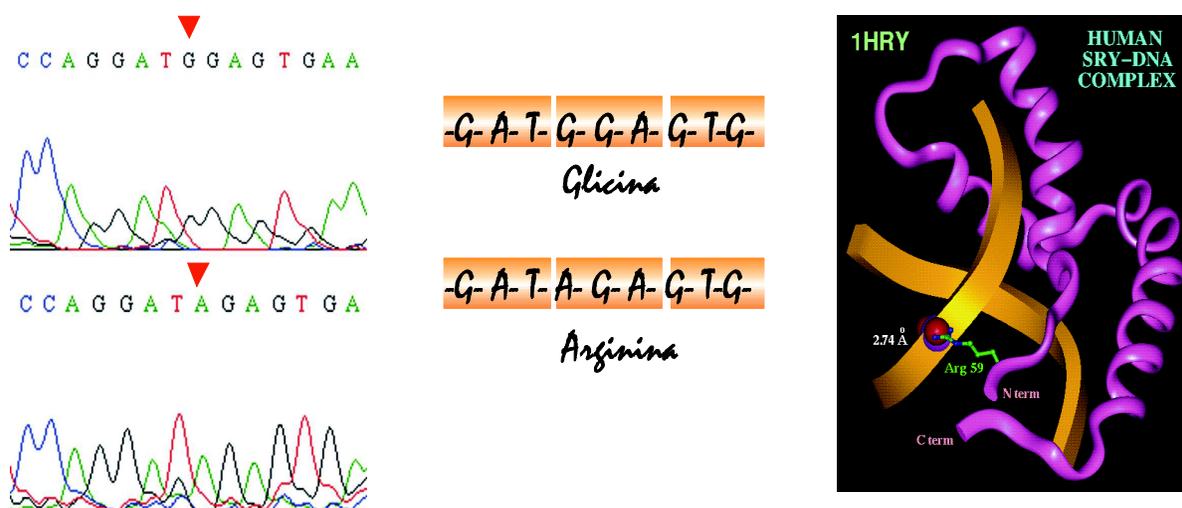


Fig. 3. Sequence of the *SRY* gene, the *top part* showing the A-G mutation produced at codon 59 of the gene and that causes a change from Arg (AGA) to Gly (GGA) within the HMG box. The *bottom* shows the other sequence, also present in the same patient, which is identical to the *SRY* sequence already published. Both copies appear in blood at a frequency of 50%

Due to the possibility of a mutation, a fragment of 609 bp of the *SRY* gene was cloned and sequenced from independent PCR products. Analysis of the sequence revealed, in blood, two copies of the gene. In three of the six clones analyzed, a sequence identical to that of the *SRY* sequence of a male was obtained, whereas the other three clones displayed a non-conservative point mutation, A>G at nucleotide 2,250, codon 59 (Su and Lau, 1993), which

causes a change from arginine (AGA) to glycine (GGA) in the second codon within the DNA-binding HMG box domain (Figure 3). This Arg59 is strictly conserved among the *SRY* genes of all species studied to date, suggesting that it is essential for the function of the protein. Here, we describe a female, with gonadal dysgenesis and mosaic karyotype 45,X/46,X,dic(Y)(pter→q11::q11→pter) in blood and gonads, who displays in her dic(Y) an R59G mutation in one of the two copies of the *SRY* gene. This Arg59 is in electrostatic interaction with a phosphate of the DNA; this type of interaction plays an important role in determining the orientation of the protein in specific binding, usually to DNA bases in the major groove (Werner et al., 1995). The Arg59 is strictly conserved among the *SRY* genes of all species studied to date, suggesting that it is essential for proper protein function. We think that all these data indicate that an R59G mutation would totally, or at least partially, inhibit the capacity of *SRY* to interact with DNA.

On the other hand, dicentric chromosomes are among the most common structural rearrangements of the Y chromosome (Hsu, 1994). Usually these chromosomal alterations occur in mosaic form, and are generally considered unstable elements since improper alignment of two centromeres on the metaphase spindle might lead to the formation of a bridge during anaphase (Cohen et al., 1973). Nonetheless, some dicentrics do persist and replicate normally, since one of the two centromeres becomes inactive and the chromosome may behave as a monocentric marker, as in the present case. Thus, although the dicentric chromosomes showed two noticeable centromeres, one of them is not constricted and it is therefore inactive.

Dicentric Y chromosome formation may occur in different ways: (1) in meiosis, from a break in the long arm of the Y followed by a U type exchange in meiosis I, resulting in a dicentric following meiosis II; (2) a post-zygotic origin of the dicentric Y. The fact that these chromosomal rearrangements usually occur in a 45,X mosaic form would suggest a post-zygotic origin for the dicentric Y. However, a normal 46,XY cell line was absent.

In a review of Y-chromosome aneuploidy by Hsu (Hsu, 1994) no normal cell line (46,XY) was found in 99 of the 102 isodicentric Y chromosomes described. Hsu suggested that the abnormal Y chromosome was either (1) present in the sperm before fertilization and resulted from an error during gametogenesis, or (2) arose from an error in the first zygotic division. Errors occurring after the first zygotic division would result in mosaicism including a normal cell line. The absence of a detectable 46,XY cell line in all 13 isochromosome cases described by Robinson et al. (1999) and in 99 of the 102 described by Hsu et al. (1994) strongly suggests that such errors are more likely to occur during gametogenesis before the spermatid stage, or during the first division after fertilization, rather than during subsequent cell divisions.

In our case, the presence of a dicentric Y and the absence of the 46,XY cell line indicates that the chromosomal rearrangement took place previously or during early embryonic development. Also, the existence of different sequences of the *SRY* gene in the dicentric Y indicates that the formation of the dicentric took place prior to the mutation of the *SRY* gene. The data suggest that the patient suffered a postzygotic mutation early in development. She retained a remnant of functional *SRY* protein in an amount not sufficient to allow normal male differentiation.

The presence of a Y chromosome in gonads is in discordance with the absence of virilization features in the patient. Hence, one of the possible causes of this discordance can be the presence of the mutation R59G in one of two copies of the *SRY* gene. Furthermore, the presence of the 45,X cell line in gonads prevents the development of testicular tissue.

In conclusion, to our knowledge this is the first time that a mutation is described in codon 59 within the HMG-SRY box, and also the first case of a psu dic(Yp) chromosome that displays two different sequences of the SRY gene. We think that presence of the 45,X cell line in gonads prevents the development of testicular tissue. The magnitude in which the 45,X cell line or the SRY mutation affected the existing phenotype cannot be ascertained.

### 3.2.1.3 Xp22.3; Yq12.2 chromosome translocation and its clinical manifestations

Here we report a cytogenetic and molecular investigation in a 8 years old girl referred for chromosomal analysis because mild disproportionate short stature (short neck and pectum excavatum) with an initial diagnosis of TS and karyotype 46,X,+der(X) in 100% of her blood lymphocytes. By means of FISH and PCR analysis the karyotype of the patient was interpreted as 46,X,der(X)t(X;Y)(qter→p22.3::q11.2→qter).

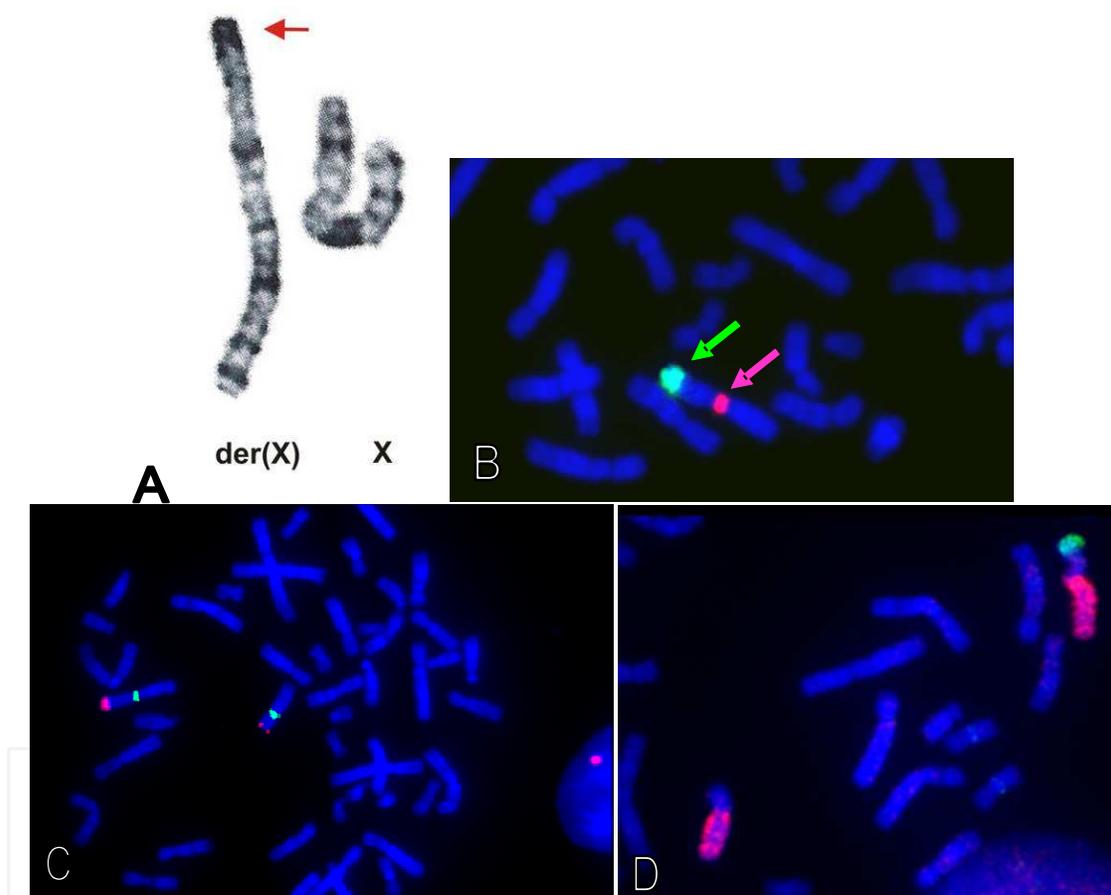


Fig. 4. The der(X;Y) is taught in detail: A. Derivated (X;Y) on the left and X chromosome on the right, with a G-banding pattern. The der(X;Y) appeared to be a metacentric X chromosome with a brightly fluorescing heterocromatin attached to its short arm ( red arrow) . B. Partial FISH with the probes DYZ1 (green) and DXZ1 (red). C. Partial FISH with DXZ1 (green) + DYZ1 (red) + SHOX (red). D. Partial FISH with partial painting Yq (green) and partial painting Xq (red) probes

Xp;Yq rearrangements occur rarely in the human population, and result from aberrant recombination between homologous sequences on Xp and Yq (Yen et al., 1991). The distal Xp chromosomal region can be divided into two parts: a pseudoautosomal region which exhibits complete homology with the distal Yp (PAR1) and regularly exchanges with it

during male meiosis, and a more proximal region which shares 85-95% similarity with sequences in Yq11 and only occasionally exchanges with Xp22 (Ballabio et al., 1989). Males with Xp;Yq translocations are usually nullisomic for a small portion of Xpter and their phenotype depends on the extent of the Xp deletion. When the deletion is large they can present short stature, bony deformities, ichthyosis, attention problems, generalized epilepsy, etc (Meindl et al., 1993). The phenotype of females carrying a normal X and an Xp;Yq translocation with the concomitant deletion of Xp material is usually normal, except for short stature (Van den Berghe et al., 1977).

The proband is the unique child of non-related healthy young parents. She was born after 39 weeks of gestation with a birth weight of 3,050 gr (36th percentile) and length of 49 cm (3rd percentile). At the age of 7 she initiates the treatment with GH, and after 9 months the growth has been of 10.5 cm/year. Her height is now 119.6 cm and weight 47 kg at the age of 8 years. The bone age correlates well with her chronological age. External genitals were normal. No mental retardation was observed.

Conventional G-banding were performed on cultured blood lymphocytes showing a X/Y translocation in the proband, and a normal karyotype in her parents. All metaphase spreads showed 46 chromosomes with one normal X chromosome and one metacentric derivate 46,X,+der(X) (Figure 4). With DAPI banding, the der(X) appeared to be a metacentric X chromosome with a brightly fluorescing heterocromatin attached to its short arm. The probes DYZ1, DYZ3 and Y painting confirmed that the translocation implicated the Yq arm and that the translocated fragment lacked its centromere. With partial painting probes (Xp, Xq, Yq) there was demonstrated that not other chromosomal material was involved in the translocation. All metaphases from the parents were normal. PCR analysis showed the absence of the genes *SRY* and *SHOX* (hemi- or homozygosity), the absence of the centromeric Y region, and the presence of the heterocromatic Yq12 region. This translocation probably result from a recombination secondary to DNA homologies within misaligned sex chromosomes in the paternal germline with the derivatives segregating at anaphase I.

Amplification of two microsatellite markers located at the *SHOX* locus resulted in only one single fragment size at both markers, suggesting hemi- or homozygosity of the *SHOX* locus. For further analysis, parental DNA was available. By amplification of the parental alleles *SHOX* deletion was confirmed.

Normally, the X and Y chromosomes pair during male meiosis and exchange DNA only within the pseudoautosomal regions at the distal short and long arms of both sex chromosomes (PARs regions). However, it has been suggested that aberrant recombination involving other segments of high homology could be responsible for the production of X/Y translocations.

Sequences in Xp/Yp PAR (PAR1) are identical and, during male meiosis, there is a single and obligatory X-Y crossover within this region (Ellis and Goodfellow, 1989). Recombination assures the homogenization of DNA sequence and like most autosomal genes, those in the PAR1 region are expressed from both X and Y alleles (Disteche, 1995). A formally comparable second pseudoautosomal region, Xq/Yq PAR (PAR2) was discovered during the mapping of the X chromosome (Freije et al., 1992). It contains sequences that had been earlier recovered from both X and Y, and shows recombination over its entire extent. However, it also shows properties distinct from those of PAR1, thus PAR2 exhibits a much lower frequency of pairing and recombination than PAR1 and is not necessary for fertility (Kuhl et al., 2001).

Occasionally the X-Y interchange occurs outside the pseudoautosomal region. It has been found homologous sequences on the long arm of the X chromosome and the short arm or

the proximal long arm of the Y chromosome. In addition, several loci in the Xpter-Xp22 region were found to share 85-95% similarity with sequences in Yq11 or the pericentric region of the Y chromosome.

The majority of these translocations X/Y occur in Xp22 and Yq11 when analyzed cytogenetically. Some of these translocations are sporadic events, like the patient showed here, whereas others are inherited. The analysis of parent's karyotypes were normal, so in our case the translocation was a de novo product.

Most Xp;Yq translocations in males are associated with a large Xp22.3 deletion and the phenotype can be explained by the extension of the deleted region. Main clinical features include short stature, chondrodysplasia punctata, mental retardation, ichthyosis, deficiency, Kallmann syndrome, etc. On the other hand, most females with Xp;Yq translocation have normal intelligence and gonadal function. Short stature is commonly observed and is attributed to the deletion of the *SHOX* gene in the PAR1 region on Xp22.3.

The low stature observed in the subject is due to the deletion of the *SHOX* gene in the PAR1 region in Xp22.3. Treatment with the GH is recommended, in spite of not being able to define it as TS. The rest of the X chromosome is apparently intact, hence the little affectation of the phenotype. Due to the absence of a centromere for Y a gonadectomy is not advisable

#### 4. Conclusions

*First:* The joint application of cytogenetic and molecular techniques has allowed a better definition of chromosomal mosaicism (77.6%). The increase in mosaicism was due mainly to the presence of the 46,XX cell line. This combined use should be routine in the diagnosis of this syndrome.

*Second:* The data suggest that the frequency of occurrence of the Y chromosome in TS is relatively low (7.29%), but its determination is crucial, hence, a molecular study of the Y chromosome in all women with TS is recommended. The analysis must preferably include the study of the centromeric region for the Y chromosome.

*Third:* Most of the fragments of the Y chromosome present in TS tend to be isodicentric chromosomes, combined with the 45,X cell line. It is probable that most of these isodicentric chromosomes were formed during spermatogenesis, or during the first cell division after fertilization.

*Fourth:* The location of the 45,X cell line seems to be fundamental in sex determination, even in the presence of the *SRY* gene.

*Fifth:* The frequency of karyotypes causing Turner syndrome, in our opinion, is much higher than what was originally believed, 1 in every 1,850 newborn girls (7<sup>th</sup> International Conference on Turner Syndrome, 2009) due to the phenotypes which are not altered or are so mild that are hidden among the population.

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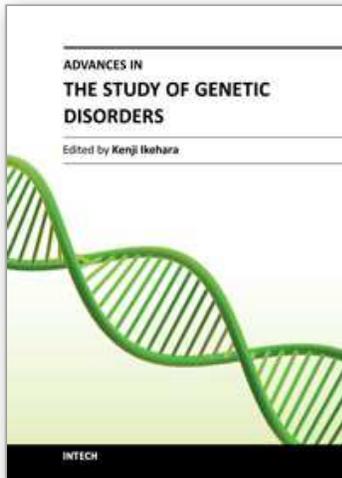
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## **Advances in the Study of Genetic Disorders**

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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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