Chromosomal rearrangements in Xq and premature ovarian failure: mapping of 25 new cases and review of the literature

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BACKGROUND: Chromosomal rearrangements in Xq are frequently associated with premature ovarian failure (POF) and have defined a POF ‘critical region’. Search for genes responsible for the disorder has been elusive.

METHODS: We report mapping of novel breakpoints of X;autosome-balanced translocations and interstitial deletions and a review of published X chromosome rearrangements. RESULTS: All the novel POF-associated rearrangements were mapped outside and often very distant from genes. The majority mapped to a gene-poor region in Xq21. In the same region, deletions were reported in women who apparently did not have problems conceiving. Expression analysis of genes flanking breakpoints clustered in a 2-Mb region of Xq21 failed to demonstrate ovary-specific genes.

CONCLUSIONS: Our results excluded most of the possible explanations for the POF phenotype and suggested that POF should be ascribed to a position effect of the breakpoints on flanking genes. We also showed that while the X breakpoint may affect X-linked genes in the distal part of Xq, from Xq23 to Xq28, interruption of the critical region in Xq21 could be explained by a position effect of the Xq critical region on genes flanking the autosomal breakpoints.

Key words: chromosome rearrangements/gene mapping/premature ovarian failure/Xq

Introduction
Premature ovarian failure (POF) (OMIM 311360 and 300511) is a disorder characterized by amenorrhea and elevated serum gonadotropin level before 40 years of age that accounts for about 10% of all female sterility (Luborsky et al., 2003). The disorder may have environmental as well as genetic causes. Autoantibodies, chemotherapy and radiotherapy are the best-known environmental causes. A genetic basis is well established and was definitively demonstrated by the report of numerous familial cases. Identification of genes responsible for autosomal recessive (Aittomaki et al., 1995), X-linked dominant (Di Pasquale et al., 2004) or autosomal dominant syndromic forms (Crisponi et al., 2001; Fogli et al., 2003) of the disease demonstrated a monogenic component, but the genes identified account for a very small percentage of the POF cases. Mutations in genes acting as risk factors for POF have been suggested by pedigree analysis (Vegetti et al., 1998), and one was identified as the premutation allelle of the FMR1 gene at the FRAXA locus in Xq27 (Murray, 2000). The FMR1 pre-mutation was found in about 5% of all POF patients. Taken together, the genes identified show that POF is a very heterogeneous genetic disorder that can be inherited as a Mendelian, but more often as a multifactorial, disorder.

In the search for genes responsible for POF, a role for X chromosome genes was suggested by the frequent observation of X chromosome anomalies in patients. Primary amenorrhea and streak ovaries were associated with X monosomy or Turner syndrome (TS) (Zinn and Ross, 1998). Partial monosomies and X;autosome-balanced translocations were also observed in association with POF, and their description led to the cytogenetic definition of a ‘critical region’ for normal ovarian function on the long arm of the X chromosome, corresponding to the Xq13.3-q27 interval, often divided into two portions, Xq13-Xq21 and Xq23-Xq27 (Therman et al., 1990). Molecular definition of the critical region by fluorescence in situ hybridization (FISH) mapping of X;autosome-balanced translocations confirmed the extent of the critical region and led to the hypothesis that several loci required in double dose for ovarian function were involved in the disorder (Sala et al., 1997). Deletions or balanced translocations could cause gene dosage reduction by disrupting X-linked genes escaping X chromosome inactivation or X-linked genes required in double dose in the oocytes where two active X chromosomes are present throughout the female fertile life. However, a position effect of the rearrangements on flanking genes was also hypothesized, as well as an effect of the rearrangement itself. The presence of unsynapsed regions...
may be recognized by meiotic checkpoints or other checkpoints that may be acting during ovarian follicle maturation (Burgoyne and Baker, 1985; Schlessinger et al., 2002; Turner et al., 2005). Lack of perfect pairing may thus increase apoptosis and reduce the number of ovarian follicles, leading to POF.

Transcriptional characterization of breakpoint regions led to the identification of five genes interrupted by the translocations. The DIAPH2 gene in proximal Xq22 is one of the human homologues of the Drosophila melanogaster dia gene affecting female fruit fly fertility by interfering in cell division of ovarian follicular cells (Castrillon and Wasserman, 1994). We demonstrated that it was interrupted by the X breakpoint in patient BC, carrying a X;12-balanced translocation inherited from the mother who was also affected (Bione et al., 1998). The XPNPEP2 gene in Xq25 (Prueitt et al., 2000), the DACH2 gene (Prueitt et al., 2002) and the POF1B gene in Xq21.1 (Bione et al., 2004) were found interrupted by isolated translocation breakpoints. Finally, the CHM gene in Xq21.1, responsible for X-linked choroideremia in males, was found interrupted in three unrelated patients affected with POF and choroideremia (van Bokhoven et al., 1994; Lorda-Sanchez et al., 2000). Other breakpoints described in POF patients were mapped to genomic regions free of transcribed sequences (Mumm et al., 2001; Prueitt et al., 2002) suggesting that mechanisms other than gene interruption may be responsible for X-linked POF. In agreement with this result was the mutation analysis of the POF1B gene which failed to demonstrate a role for the gene in POF (Bione et al., 2004). Similar analysis of the DACH2 gene suggested that it may be involved in POF but also clearly showed that the mutations found cannot be the only cause of the severe phenotype associated with the balanced translocation interrupting the gene. The involvement of the CHM gene in POF was also quite unlikely, as inherited point mutations or deletions of the gene in male choroideremia patients were never associated with POF in their mothers (van Bokhoven et al., 1994). Here we report the characterization of a large number of X;autosome-balanced translocations and interstitial deletions. Most of the rearrangements were characterized in our laboratory. Mapping data from the literature was also reviewed, and published breakpoints were precisely positioned on the most recent human map and related to those mapped by us. Among the proposed explanations, our analysis favours the hypothesis that interruption of the X chromosome critical region should cause POF by position effect on genes flanking the breakpoints. Because the POF phenotype in Xq21 could be hardly related to a position effect on flanking X-linked genes, not highly expressed in the ovary, we suggest that POF is most likely due to a position effect of the X breakpoints on autosomal genes.

Materials and methods

Cell lines and breakpoint mapping

Characteristics of patients and normal women carrying chromosomal rearrangements are summarized in Table I (and Table I in supplementary information). Lymphoblastoid cell lines were grown in RPMI supplemented with 10% fetal bovine serum. FISH was performed as described (Rossi et al., 1994). Bacterial artificial chromosome (BAC) and P1-derived artificial chromosome (PAC) clones were obtained from the YSC, DIBIT-HSR, Milano. Fine mapping was obtained by digestion of DNA from lymphoblastoid cell lines of patients and male and female controls with restriction enzymes and fractionation by pulsed field gel electrophoresis (PFGE) (Rossetti et al., 2004). Southern blot and hybridization were performed using standard procedures. Exact position of FISH mapping data are in Table I, in supplementary information. Genes were positioned according to the most recent human genome reference sequence (NCBI Build 35).

RNA in situ hybridization

RNA in situ hybridization was performed on CD1 mouse ovary at P20, fixed in 4% paraformaldehyde, equilibrated in increasing concentration of sucrose (6 to 50%) and frozen in isopentan alcohol and liquid nitrogen. 10 μm cryostat sections were hybridized to digoxigenin (DIG)-labelled probes (Roche Diagnostics) prepared from linearized complementary DNA clones, obtained from Image Consortium or by cloning RT-PCR products. Plasmids were digested with the appropriate restriction enzymes, and 1–1.5-kb long sense and antisense probes were prepared. Hybridization was at 56°C overnight in ×5 saline sodium citrate (SSC)/50% formamide humidified chamber. Slides were washed at 56°C, 1 time at ×5 SSC and three times at ×0.2 SSC for 20 min, and developed with anti-DIG alkaline phosphatase and NBT-BCIP (Roche Diagnostics, Basel, Switzerland) from 3 h to overnight.

Results

Map of 23 X chromosome breakpoints

We collected and mapped by FISH 23 novel X;autosome-balanced translocations between Xq and different autosomal regions. Twenty-one were associated with POF, and two were in women with normal fertility (Table I). In all patients, the normal X was inactivated (not shown). All POF patients were characterized by severe infertility. About half had primary amenorrhea, most of the remaining cases had secondary amenorrhea at very young age, following few years of irregular cycles (Table I).

By FISH analysis with overlapping PAC and BAC clones and PFGE, the X chromosome breakpoints were mapped to regions ranging from 15 to 400 kb. None of the newly mapped breakpoints interrupted genes (Table I and Table I in supplementary information).

The breakpoints were distributed in a region of 38 Mb, but the majority (18/23) was clustered in a 16-Mb region of Xq21 (Figure 1). We compiled the position of 13 published X chromosome breakpoints previously mapped by us and by others (Table II in supplementary information): six were in Xq21 and confirmed the clustering of X breakpoints in this chromosomal band. Within Xq21, 10 breakpoints mapped to a region of 2 Mb, between the POF1B and the 3′ flanking region of the DACH2 gene (Figure 2). Two breakpoints were in the POF1B and in the DACH2 genes (Bione et al., 2004), and three in the CHM gene (van Bokhoven et al., 1994; Lorda-Sanchez et al., 2000). The remaining five breakpoints did not interrupt genes and mapped to gene-free regions up to 0.5 Mb away from the closest gene. One of them, 5513, was in a woman with normal fertility (Philippe et al., 1995) and was mapped between two POF-associated breakpoints: LB106, 60 Kb proximal and CC about 150-kb distal.
Table I. Characteristics of patients and normal women carrying chromosomal rearrangements

<table>
<thead>
<tr>
<th>Case</th>
<th>Obtained from</th>
<th>Diagnosis</th>
<th>Karyotype</th>
<th>FISH probes</th>
<th>FISH localization</th>
<th>Breakpoint interval (kb)</th>
<th>Flanking genes (distance from the breakpoint, kb)</th>
</tr>
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<tbody>
<tr>
<td>LB373</td>
<td>J. Gabarron, unpublished</td>
<td>Secondary amenorrhea (20y)</td>
<td>46,X,t(X;5) (q21;q35)</td>
<td>RP5-824G23</td>
<td>X norm, der(X), der(5)</td>
<td>27.1</td>
<td>SH3BGRl (−850)</td>
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<tr>
<td>HJ49497</td>
<td>J.P. Fryns, unpublished</td>
<td>Secondary amenorrhea (17y)</td>
<td>46,X,t(X;3) (q21;p21)</td>
<td>RP4-685D6</td>
<td>X norm, der(X), der(5)</td>
<td>50.5</td>
<td>POU3F4 (+1359)</td>
</tr>
<tr>
<td>AI</td>
<td>P.C. Patsalis, unpublished</td>
<td>Primary amenorrhea (15y)</td>
<td>46,X,t(X;1) (p21.1q31.1)</td>
<td>RP3-349C6</td>
<td>X norm, der(X), der(3)</td>
<td>80.6</td>
<td>SH3BGRl (−2083)</td>
</tr>
<tr>
<td>LB106</td>
<td>G. Croci, unpublished</td>
<td>Secondary amenorrhea (17y)</td>
<td>46,X,t(X;2) (q21;q23)</td>
<td>cosD6.2</td>
<td>X norm, der(X), der(2)</td>
<td>40</td>
<td>POF1B (−85.7)</td>
</tr>
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<td>5513</td>
<td>H. van Bokhoven (Philippe et al., 1995)</td>
<td>Normal</td>
<td>46,X,t(X;22) (q21;p1.3)</td>
<td>RP5-966E1</td>
<td>X norm, der(22)</td>
<td>32.3</td>
<td>CHM (+398.9)</td>
</tr>
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<td>CC165920</td>
<td>J.P. Fryns, unpublished</td>
<td>Primary amenorrhea (15y)</td>
<td>46,X,t(X;4) (q21;q31.3)</td>
<td>RP5-1095M12</td>
<td>X norm, der(X), der(4)</td>
<td>100</td>
<td>CHM (+336.9)</td>
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<tr>
<td>WD</td>
<td>C. Philippe (Philippe et al., 1995)</td>
<td>Normal</td>
<td>46,X,t(X;2) (q21;p25)</td>
<td>RP5-966E1</td>
<td>X norm, der(X)</td>
<td>40</td>
<td>CHM (−108.4)</td>
</tr>
<tr>
<td>LG</td>
<td>C. Philippe (Philippe et al., 1995)</td>
<td>Secondary amenorrhea</td>
<td>46,X,t(X;9) (q21;q33)</td>
<td>RP5–1110P6</td>
<td>X norm, der(X), der(2)</td>
<td>130.6</td>
<td>KHLH4 (+492.8)</td>
</tr>
<tr>
<td>LB 368</td>
<td>L. Borgese, unpublished</td>
<td>Secondary amenorrhea (15y)</td>
<td>46,X,t(X;12) (q21;p13)</td>
<td>RP5-849B1</td>
<td>X norm, der(X)</td>
<td>28.7</td>
<td>KHLH4 (−1015.8)</td>
</tr>
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<td>AK163482</td>
<td>J.P. Fryns, unpublished</td>
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<td>46,X,t(X;3) (q21.2;q12)</td>
<td>RP5-1031H7</td>
<td>X norm, der(X), der(12)</td>
<td>75</td>
<td>CPXCR1 (+549.9)</td>
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<tr>
<td>151/98</td>
<td>G. Conway, unpublished</td>
<td>Secondary amenorrhea (16y)</td>
<td>46,X,t(X;3) (q21.2;q12)</td>
<td>RP5-85010</td>
<td>X norm, der(X), der(3)</td>
<td>45.6</td>
<td>CPXCR1 (+424.4)</td>
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<td>GM10386</td>
<td>Coriell rep., unpublished</td>
<td>Primary amenorrhea</td>
<td>46,X,t(X;19) (q21.2;p13.3)</td>
<td>RP5–1166C8</td>
<td>X norm, der(X)</td>
<td>15.3</td>
<td>TGIF2XL (+617.3)</td>
</tr>
<tr>
<td>LR</td>
<td>R. Carrozio, unpublished</td>
<td>Secondary amenorrhea (20y)</td>
<td>46,X,t(X;9) (q21.2;q22)</td>
<td>RP5–972B17</td>
<td>X norm, der(19)</td>
<td>386.3</td>
<td>TGIF2XL (−1574.8)</td>
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<tr>
<td>Cba</td>
<td>M. G., unpublished</td>
<td>Turner-like amenorrhea</td>
<td>46,X,t(X;16) (q21.2;p12)</td>
<td>RP1-212012</td>
<td>X norm, der(X), der(16)</td>
<td>30</td>
<td>TGIF2XL (−1323.9)</td>
</tr>
<tr>
<td>FA</td>
<td>C. Philippe (Philippe et al., 1995)</td>
<td>Secondary amenorrhea</td>
<td>46,X,t(X;15) (q21.3;p12)</td>
<td>RP5-829B3</td>
<td>X norm, der(X), der(16)</td>
<td>103.4</td>
<td>PABPC5 (+187.8)</td>
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<tr>
<td>7B</td>
<td>P.A. Jacobs, unpublished</td>
<td>Primary amenorrhea</td>
<td>46,X,t(X;9) (q21.3;q14)</td>
<td>RP1-1371I0</td>
<td>X norm, der(X), der(9)</td>
<td>100</td>
<td>NAP1L3 (−2360.4)</td>
</tr>
<tr>
<td>DVG</td>
<td>O. Zuffardi, unpublished</td>
<td>Primary amenorrhea</td>
<td>46,X,t(X;3) (q22.3;p12.3)</td>
<td>RP1-155N17</td>
<td>X norm, der(X), der(3)</td>
<td>80.2</td>
<td>DIAHP2 (+988.7)</td>
</tr>
<tr>
<td>SN</td>
<td>C. Philippe (Philippe et al., 1995)</td>
<td>Primary amenorrhea</td>
<td>46,X,t(X;9) (q22.2;q22)</td>
<td>RP1-19N1</td>
<td>X norm, der(X), der(3)</td>
<td>23.4</td>
<td>MUM1L1 (−124.7)</td>
</tr>
<tr>
<td>FR</td>
<td>G. Porta, unpublished</td>
<td>Secondary amenorrhea (13y)</td>
<td>46,X,t(X;12) (q22.p11.2)</td>
<td>RP1-219J10</td>
<td>X norm, der(9)</td>
<td>174</td>
<td>FLJ10178 (+227.7)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RP1-219J10</td>
<td>X norm, der(X), der(12)</td>
<td>174</td>
<td>FLJ10178 (a)</td>
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<td></td>
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<td></td>
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<td>RP1-19N1</td>
<td>X norm, der(X)</td>
<td>80.2</td>
<td>MUM1L1 (−410.3)</td>
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<td></td>
<td></td>
<td></td>
<td>RP1-19N1</td>
<td>X norm, der(X), der(12)</td>
<td>174</td>
<td>FLJ10178 (a)</td>
</tr>
</tbody>
</table>
Deletion map of Xq21

Two women carrying interstitial Xq deletions (PP and GM0089) were analysed (Table III in supplementary information). In both the deleted, X was inactivated. GM0089 was reported as normal and carried a 6.5–7.5 Mb deletion in Xq21 with the proximal breakpoint between DXS1125 and DXS986 and the distal breakpoint between ZNF6 and CHM. The second case, PP, had amenorrhea at 35 years of age. Her mother carried a cytogenetically identical deletion but was normal: she had two children and entered menopause at 50. The centromeric breakpoint of the deletion mapped between the DXS454 and the PLP gene (Figure 1 and Table III in supplementary information). The deletions overlapped with the region where most of the X chromosome breakpoints in balanced translocations were clustered as well as many interstitial deletions in women who did not apparently have problems conceiving (Figure 1 and Table III in supplementary information). All deletions were quite large and most caused skewing of inactivation. POF-associated interstitial deletions were reported in the literature, and they all mapped distal to Xq21 (Figure 1 and Table III in supplementary information).

From the interstitial deletion map, the POF critical region could thus be distinguished into a region I, corresponding to Xq13-Xq21 where deletions were rarely associated only with a mild form of POF and a region II between Xq23 and Xq28. Deletions in region II were frequently associated with POF (Figure 1).

X-linked genes flanking breakpoints: gene expression in the ovary

Xq21 is a gene-poor region: 23 genes were localized in a 16-Mb region between the genes NSBP1 and NAPIL3, where 18 of 23 X chromosome breakpoints were clustered. Gene expression from the GNF expression database (http://symatlas.gnf.org/SymAtlas/) based on Affymetrix chips, was available for 20 of the 23 genes. Among the genes expressed in the ovary (average difference value >200), none was differentially expressed in the ovary or in the oocytes (ratio of maximum expression to median expression in all tissues >3) (Su et al., 2002) (not shown). RT-PCR from human and mouse tissues (brain, fetal brain, heart, ovary and testis) confirmed the results (not shown).

To gain better insight into ovarian expression of the genes ZNF6, POIF1B, CHM and DACH2, in the 2-Mb region in Xq21.1 where 10 breakpoints were clustered, we performed RNA in situ hybridization on mouse P20 ovaries. This analysis showed that none of the X-linked genes tested was specifically expressed in the oocyte or in the ovarian follicles (not shown).

Discussion

Several hypotheses had been put forward to explain the POF critical region in Xq (Schlessinger et al., 2002; Goswami and Conway, 2005). In this paper, we report FISH mapping of 23 novel X;autosome-balanced translocations and two interstitial deletions and a review of 32 published rearrangements (13 X;autosome-balanced translocations and 19 deletions) in the POF critical region, in Xq. Mapping such a large number of X chromosome rearrangements contributed to definitively excluding some of the proposed hypothesis and allowed us to suggest a novel mechanism for the X-linked POF phenotype.

First, we confirmed that X-linked gene interruption is not a common finding in the group of POF patients. Second, we demonstrated that translocations in non-POF women (GM0089 and 5513) are interspersed with POF-associated breakpoints: the GM0089 breakpoint was mapped within 3 Mb between the LB263/96 and the LB374 in Xq23. The 5513 breakpoint was mapped within 200 kb between LB106 and CC in Xq21. This finding definitively showed that it is not the chromosomal translocation per se that is responsible for the ovarian disorder. Finally, analysis of interstitial deletions in Xq21 confirmed that unsynapsed chromosomal regions do not necessarily have a role in gametogenic failure and POF, as previously suggested (Burgoyne and Baker, 1984; Burgoyne and Baker, 1985; Turner et al., 2005).
Figure 1. The premature ovarian failure (POF) ‘critical region’ and chromosomal rearrangements in Xq. Above a schematic representation of the region, vertical lines indicate the positions of the X;autosome-balanced translocations breakpoints mapped by us and by others (underlined). The normal cases are in italics. Below is a schematic gene map (from http://www.ensembl.org/) demonstrating gene frequency variations along Xq. Interstitial deletions and small terminal deletions involving Xq only, mapped by us (PP and GM10254) or reported in the literature, are shown as horizontal bars; dotted regions indicate map intervals. Above are the normal cases (no POF), and below are the POF-associated cases. POF critical regions I and II are shown as shaded areas.
therefore that interruption of Xq21 may have a position effect
likely explanation of the balanced translocation phenotype is
balanced translocations associated with POF, mapped by us or by
expression and RNA
may have a position effect on such genes.
ian function. Balanced translocations in the critical region II
more X-linked genes required in double dose for normal ovar-
tral deletions were reported in women presenting with POF.
Non-overlapping deletions suggested the presence of two or
women that apparently did not have problems conceiving (see
references in supplementary information). One deletion in PP
and in her mother, reported here for the first time, was associ-
ated with late secondary amenorrhea in the proband only. For
all the other published deletions, a normal reproductive pheno-
type was either reported or deduced by us from family trees.
Their phenotype might have been compatible with secondary
amenorrhea (as in patient PP) or early menopause but was
definitely different from the early onset of POF in the
patients presenting balanced translocations in Xq21, mostly
affected with primary amenorrhea.
The complete overlap in Xq21 of the two groups of rear-
rangements and their different effect on gonadal function were
very peculiar and showed that POF, in this group of patients,
cannot be due to monosomy for genes in Xq21, as in TS or in
partial X monosomies. The deletion map of Xq shows that the
two portions of the POF critical region, previously defined by
chromosome banding, are functionally different regions. We
defined them as POF critical regions I and II. In POF critical
region II, from Xq23 to Xq28, partial monosomies and intersti-
tial deletions were reported in women presenting with POF.
Non-overlapping deletions suggested the presence of two or
more X-linked genes required in double dose for normal ovar-
ian function. Balanced translocations in the critical region II
may have a position effect on such genes.
On the other end, in the critical region I, in Xq21, most dele-
tions were never reported to be associated with POF. The most
likely explanation of the balanced translocation phenotype is
therefore that interruption of Xq21 may have a position effect
on autosomal genes translocated to the X chromosome. Gene
expression and RNA in situ hybridization analysis of the four
genes flanking the 2-Mb region of Xq21.I where 10 break-
points were clustered showed that none of the X-linked genes
were highly expressed in the ovary or had an ovarian follicle or
oocyte-specific expression pattern. This result tentatively
excludes that the X chromosome breakpoints may have a posi-
tion effect on X chromosome genes and supports the prediction
that ovary-specific genes may be found at the autosomal
breakpoints: preliminary results indicate that this is the case
(Rizzolio et al., in preparation).

Position effect on the expression of flanking genes was dem-
strated for several cytogenetic rearrangements. FOXL2
(Crisponi et al., 2001) or SOX9 (Foster et al., 1994; Wiunderle
et al., 1998) are examples of genes flanked by chromosomal
rearrangements affecting their expression (Kleinjan and van
Heyningen, 2005). The very large size of the POF critical
region I (>15 Mb) however indicates that mechanisms different
from those described for other genomic regions may be
involved. The known properties of the Xq21 band, low gene
density (http://www.ensembl.org) and low recombination fre-
quency (Kong et al., 2002) indicate that it may be an hetero-
chromatic region and may play a dominant role on euchromatic
gene-rich regions mislocalized next to it. Indeed, analysis of
the gene density of the autosomal bands involved in the bal-
anced translocations (from 4.17 to 32.35 genes/Mb) demon-
strated gene density higher than that in the Xq21 critical region
(1.4 gene/Mb). Xq21 may thus have an effect similar to posi-
tion effect variegation in Drosophila (Schotta et al., 2003).
Genes that have been mislocalized next to heterochromatin by
chromosomal rearrangements or transposition are transcription-
ally silenced in Drosophila and acquire a heterochromatic-
like appearance in polytene chromosomes and significant
changes in higher order chromatin structure (Wallrath and
Elgin, 1995; Schotta et al., 2002). A similar phenomenon
may occur when genes are translocated to the POF critical region.
Further experiments are required to provide a definitive proof,
delineate the molecular mechanisms of the phenomenon and
help to distinguish between such a very long range chromatin
effect and the more localized position effect due to mislocali-
zation of regulatory regions. Finally, we should also explain
why the position effect seems to act mainly on the ovary,
whereas other disease phenotypes are not commonly found.
This may be due to a very fine control of the genes involved in
oogenesis that may be more easily disrupted than other devel-
opmental processes. Alternatively, an unknown mechanism,
required to maintain two active X chromosomes throughout
the fertile life of female mammals, may play a role in the ovarian
specificity of the position effect of the critical region in Xq.

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