Identification by molecular diagnosis of mosaic Turner's syndrome in an obligate carrier female for fragile X syndrome

M I Tejada, E Mornet, E Tizzano, M Molina, M Baiget, A Boue

Abstract

A case of mosaic Turner's syndrome with a 45,X/46,XX/47,XXX karyotype, who was also a fragile X obligate carrier as the mother of an affected boy, was identified by molecular diagnosis. Complete haplotyping and direct DNA analysis showed that the X chromosome in all metaphases was the normal X. At the age of 57, she is mentally normal. Her external appearance was typical of Turner's syndrome.

This report shows that molecular studies in conjunction with cytogenetic analysis can help in the clinical diagnosis of a rare case and can show the uniqueness of a case such as the one here described.

Figure 1  Pedigree of the family with the haplotypes of the fra(X) region. Proximal to the centromere: FIX, CxS5.7, 55E, 4D8, and RNI. Distal, UG.2, IA1, and St.14.
intensity of the male type. There were at that
time no further data available regarding this
woman.

Last year we again studied all our fra(X)
pedigrees using the direct probe StB12.3 isolated
and described by Oberlé et al.7 The pattern found
in subject II.1 was that of a normal
male (fig 2).

Having seen these results, we asked the
patient to be examined. She is mentally
normal, aged 57 years, with the typical appearance
of Turner’s syndrome: short stature (1·31 m),
webbed neck, cubitus valgus, pectus excava-
tum, abnormal ear lobes, and very convex
nails. Menarche occurred at 16 years and
menopause at 30. She said that she had suf-
f ered no health problems in the past, apart
from arthritic pains and renal colic suffered
over the past five years. Cytogenetic study
showed 83-8% 45,X/11-7% 46,XX/4-5% 47,XXX
(mosaic Turner’s syndrome).

Having made this diagnosis, we re-ex-
a mined the Southern blots that had been car-
rried out two years ago. With a few of the
markers, bands of very low intensity could be
seen. These bands correspond to the X chro-
mosome of maternal origin (fig 3). We con-
cluded that the X chromosome present in all
cells is the normal X from the father, whereas
the fra(X) chromosome from the mother is
present only in 16·2% of the cells.

Discussion

Mosaicism of the type 45,X/46,XX/47,XXX
arises from non-disjunction in a chromo-
 somally normal female during mitosis after
fertilisation. In general, mosaic Turner’s syn-
drome shows milder signs than other cases of
Turner’s syndrome with 45,X only. When the
proportion of 45,X cells increases, symptoms of
Turner’s syndrome begin to appear. Our
case II.1, having 83·8% of 45,X cells, is
phenotypically typical of Turner’s syndrome
except for fertility. The proportion of 45,X
cells increases in older women6 because, in
general, mitotic non-disjunction, as well as
other chromosome aberrations, increases in
older persons, who show more aberrant cells
than younger ones. We thus felt that our
patient, karyotyped at 57 years, should have
had fewer abnormal cells before. Moreover,
the karyotype was performed on a blood
sample and blood cells are different in origin
from gonadal ones, which are of extra-embry-
onic origin. Hence if there were more normal
cells in gonadal tissue, this could explain this
woman’s 14 year fertility. Nielsen et al.6
reported 23 similar cases of mosaic Turner’s
syndrome in which there were 56 pregnancies.

Fertility might have given problems for this
patient because she was also a carrier for fra(X)
syndrome. Direct molecular diagnosis and
haplotyping showed that the X chromosome
carrying the fra(X) mutation was the one
involved in the Turner mosaicism, or rather
the one lost in many cells. We thus consider
that there was a process of natural selection
working against the abnormal X, and that this selection, being incomplete, failed to preclude fertility and made possible the transmission of the fra(X) to the only son.

Initially the aim of the study was to find out whether our index case (III.2) was a carrier for fra(X) syndrome. The finding we report here emphasizes, however, that although direct DNA analysis of fra(X) syndrome is now frequent in laboratories, cytogenetics still has an important role to play in the identification of certain cases. Our conclusion is that molecular studies in conjunction with cytogenetic analyses can enhance the clinical diagnosis of rare cases and furthermore can facilitate the identification of unique cases like the one reported here.