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Original article

Detailed clinical and molecular study of 20 females with Xq deletions with special reference to menstruation and fertility

Catherine L. Mercer [a,*], Katherine Lachlan [a], Alexandra Karcanias [b], Nabeel Affara [b], Shuwen Huang [c], Patricia A. Jacobs [c,d], N. Simon Thomas [c,d]

[a] Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Princess Anne Hospital, Coxford Road, Southampton, UK
[b] Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, UK
[c] Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust, Salisbury District Hospital, Salisbury, UK
[d] Division of Human Genetics, University of Southampton, Southampton SO16 6YD, UK

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ABSTRACT

Integrity of the long arm of the X chromosome is important for maintaining female fertility and several critical regions for normal ovarian function have been proposed. In order to understand further the importance of specific areas of the X chromosome, we describe a series of 20 previously unreported patients missing part of Xq in whom detailed phenotypic information has been gathered as well as precise chromosome mapping using array Comparative Genomic Hybridization.

Features often associated with Turner syndrome were not common in our study and excluding puberty, menarche and menstruation, the phenotypes observed were present in only a minority of women and were not specific to the X chromosome. The most frequently occurring phenotypic features in our patients were abnormalities of menstruation and fertility. Larger terminal deletions were associated with a higher incidence of primary ovarian failure, occurring at a younger age; however patients with similar or even identical deletions had discordant menstrual phenotypes, making accurate genetic counselling difficult.

Nevertheless, large deletions are likely to be associated with complete skewing of X inactivation so that the resulting phenotypes are relatively benign given the amount of genetic material missing, even in cases with unbalanced X;autosome translocations. Some degree of ovarian dysfunction is highly likely, especially for terminal deletions extending proximal to Xq27. In conjunction with patient data from the literature, our study suggests that loss of Xq26–Xq28 has the most significant effect on ovarian function.

1. Introduction

Turner syndrome, in which all or part of a sex chromosome is missing, is well characterised; the clinical features are variably manifested and include short stature and skeletal changes, gonadal dysgenesis and/or ovarian failure, lymphoedema, cardiovascular and renal abnormalities as well as miscellaneous features such as pigmented naevi. While loss of up to 2/3 of the X chromosome short arm is compatible with normal fertility [1], chromosome rearrangements involving Xq are often associated with abnormalities of menstruation and fertility [2].

Cytogenetic studies suggested a large critical region (CR) for normal ovarian function between Xq13 and Xq28 [3]. More detailed characterisation defined two distinct regions involving Xq13–q21 (CR1) and Xq23–q28 (CR2) [2]. For the proximal CR1, deletions are compatible with normal menstruation and fertility and the effect on ovarian function of balanced X;autosome translocations is due to inactivation of autosomal rather than X-linked genes [4]. In contrast terminal and interstitial deletions between Xq23 and Xq28 have been reported in women with premature ovarian failure (POF) [2,5] suggesting that this region may contain specific ovarian genes. However, the precise aetiology has not been established for deletions of CR2 and the few t(X:A) associated with POF that have breakpoints within this interval.

Several studies have recently screened patients ascertained with POF for cryptic deletions and amplifications using array CGH [6–9]. However, all previous studies of large Xq deletions have relied upon conventional cytogenetics for deletion mapping data. The investigation of more deletion cases with greater resolution will be required

* Corresponding author. Human Genetics Division, The Duthie Building (MP808), Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. Tel.: +44 2380 796421; fax: +44 2380 794264.
E-mail address: catherine.mercer@uhs.nhs.uk (C.L. Mercer).

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Table 1
Clinical details for patients 1–10.

No	Karyotype (including array CGH for X chromosome breakpoints, hg18)	Ascertainment	Primary/Secondary amenorrhoea	Age at menopause	Developmental delay	Turner features
1	46,X,del(X) (q13q21.1) .arr cgh (80063711->97424605)x1	Parent of male with Xq deletion	Normal menstruation	Surgical menopause at 44 years	No	Mild pectus excavatum
2	46,X,del(X) (q22.3-q26.1) .arr cgh (RP4-734E5-, RP13-147B3-)x1	Parent of foetus with Turner syndrome	Normal menstruation	No information (but had 2 pregnancies)	No information	No information
3	46,X,del(X)(q25.37) .arr cgh (RP4-753P9-)	Infertility	Secondary	45 years	No	No
4	46,X,del(X)(q24)	POF	Secondary	15 years	No	Streak ovaries, mildly increased carrying angle
5	46,X,del(X)(q22)	Primary amenorrhoea	Primary	Not applicable	No information	No information
6	45,X [29]/46,X,del(X) (q22q27) [51] .arr cgh (97203520->154851631)x1	Short stature	Secondary	18 years	Yes, attended special school	Short stature (145 cm, <0.4th centile), Left Madelung, short neck, high palate, several naevi
7	46,X,del(X)(q21) .arr cgh (89186098->154851631)x1	Primary amenorrhoea	Primary	Not applicable	No	Short neck, narrow palate
8	45,X [6]/46,X,del(X)(q21.2q28) [24] .arr cgh (RP11-135J20-)	Developmental delay	Secondary	14 years	Yes, attended special school	Height 150 cm, (0.4th–2nd), short metacarpals
9	46,X,del(X)(q21.1).arr cgh (RP11-345G21-)	Primary amenorrhoea	Primary	Not applicable	No	Madelung variant, height <0.4th centile
10	46,X,del(X)(q21.1) .arr cgh (RP1-2A2-)	Short stature	Not applicable (<16 years)	Not applicable	Mild – walked at 2 years, immature behaviour	High palate, height on 2nd centile

to try to identify causative genes and/or understand the aetiology. We present clinical details from 20 patients with known X chromosome abnormalities and detailed molecular characterization using array CGH.

2. Subjects and methods

2.1. Patients

This study consisted of 20 patients referred for chromosome analysis and found to have a cytogenetically visible Xq deletion. Three of the 20 patients were mosaic for a 45,X cell line. Patients 1–10 had isolated deletions without further complexity (Table 1). Patients 11–20 had derivative X chromosomes with a breakpoint in Xq: for patients 11 and 12 the Xq material was replaced by gain of distal Xp and patients 13–20 had an unbalanced X;automsome translocation (Table 2). The patients were unrelated, except for patients 15 and 16 who are sisters and patients 17 and 18 who are aunt and niece. A detailed history and clinical examination by CLM was possible for 12 of the patients. For the remaining eight patients detailed medical records were available and as much information as possible was drawn from these.

2.2. Cytogenetic analysis

Chromosome analysis was carried out on cultured peripheral blood lymphocytes from each individual in the study using G-banding according to standard laboratory protocols.

2.3. Array CGH

Breakpoint mapping was carried out by array CGH on 18 of the patients either by BAC array or oligo array. The BAC array used an X and Y chromosome tiling path with a resolution of 100–200 kb and

Table 2
Clinical details for patients 11–20.

No	Karyotype (including array CGH for X chromosome breakpoints, hg18)	Ascertainment	Primary/Secondary amenorrhoea	Age at menopause	Developmental delay	Turner features
11	46,X,der(X)t(X; 7)(q27q22) .arr cgh Xq27q28 (148977507->154897403)x1	Developmental delay	Primary	Not applicable	Yes, severe	Severe scoliosis
12	46,X,der(X)t(X; 3)(q27.3; p26.2) .arr cgh Xq27.3q28(145929971->154812674)x1	Premature ovarian failure	Secondary	33 years	No	No
13	46,X,rec(X)dup(Xp)inv(X)(p22.13q28) .arr cgh Xq27Xq28 (144708377->154407311)x1	Amnio for raised risk of Down syndrome	Not applicable (<16 years)	Not applicable	No	No
14	46,X,der(X)(pter->q27.2::p22.31- > pter) .arr cgh Xq27Xq28 (140518817->154582414)x1	POF	Secondary	31 years	No	No information
15	46,X,der(X)t(X; 20)(q26.3; q13) .arr cgh Xq27Xq28 (RP11-35F15-)	Sibling of t(X; 20) carrier	Menstruating at 19 years	Not applicable	No information	No information
16	46,X,der(X)t(X; 20)(q26.3; q13) .arr cgh Xq27Xq28 (RP11-35F15-)	Developmental delay	Menstruating at 16 years	Not applicable	Yes	No information
17	46,X,der(X)t(X; 10)(q26.3; q23.2) .arr cgh Xq26Xq28 (134801361-154886057)x1	Primary amenorrhoea	Primary	Not applicable	No	Short neck
18	46,X,der(X)t(X; 10)(q26.3; q23.2) .arr cgh Xq26Xq28 (134801361-154886057)x1	POF	Secondary	19 years	No	Height 155 cm (9th centile), high palate
19	46,X,der(X)t(X; 11)(q26; p11.2) .arr cgh Xq26Xq28 (134043386->154861379)x1	Developmental delay	Menstruating at 21 years	Not applicable	Yes, but did attend mainstream school	Short neck, low hairline, high palate, scoliosis
20	46,X,der(X)t(X; 14)(q13; q24)[27]/45,X[3] .arr cgh Xq13Xq28 (RP1-2A2-)	Short stature	Not applicable; <16 years	Not applicable	No	Low hairline, ptosis, height <3rd centile