

Reporting Sex Chromosome mosaicism in amniotic fluid samples

EQA showed:-

- Incorrect reporting of ISCN
- Incorrect interpretation
- Incorrect clinical advice

Problematic Sex Chromosome results

- MCC
- 45,X/46,XX
- 45,X/46,XY
- 45,X/46,X,der(X) or 46,X,der(Y)
- Other structural rearrangements of X and Y

Maternal Cell Contamination

MCC

- Culture 1: 3/10 female cells, rest 46,XY. Culture 2 & 3, all 46,XY[60].
- 10/50 labs mentioned MCC in report.
- 5/50 labs ISCN error:- 46,XY/46,XX (chimera)
- 2 labs suggested a FBS sample.
- Possible explanations for 46,XX cells?

Original sample/Culture – clumps of tissue?
Splashing when preparing slides
Mixing pipettes
Mixed sample

Internal Audit

Maternal cells
Vanishing twin
Chimera

Maternal Cell Contamination

MCC

- Maternal cells
 - Vanishing twin
 - Chimera
 - When is mixed sex significant?
 - Should not report MCC
- | | |
|------------------------------|------------|
| Frequency of MCC? | infrequent |
| Frequency of vanishing twin? | rare |
| Frequency of chimera? | very rare |

Level 3
mosaicism >10%

European Cytogenetic Guidelines – if relevant
ACC Amniotic Fluid Guidelines – significant risk of incorrect result
– QF-PCR to check origin XX cells

Sex chromosome mosaicism

45,X[34]/46,XY[36]

Three cultures

- FISH:- nuc ish (DXZ1x1)[60]/(DXZ1,DYZ3)x1[26]
- 6/47 labs – mosaic Turner Syndrome!!!!
- 2/47 labs - wrong sex in the ISCN (XX)
- Phenotype variable – 90-95 % clinically normal male
- 10% variable phenotype ranging from normal female to ambiguous genitalia/mixed gonadal dysgenesis to Turner syndrome. Risk gonadal tumour in females.

Original slide – if low numbers, ? broken cells

N.B. Variable phenotype
Majority prenatal normal male
Ultrasound scan and sexing

Normal male born
Mosaicism in blood

Sex chromosome mosaicism

- 45,X/46,XX
- 2/3 labs mosaic Turner Syndrome!!!!
- Phenotype – 90-95 % clinically normal female
- 10% variable phenotype ranging from gonadal dysgenesis to Turner syndrome.
- Mosaicism not always confirmed postnatally
- Longer term studies needed

N.B. Ultrasound scan

Proportion of 45,X cells does not correlate with phenotype

**N.B. even if liveborn Turner phenotype,
the clinical outcome is NOT severe.**

Other mosaic sex chromosome abnormalities

45,X/46,X,der(X)

- Need to determine size of marker- XIST
- XIST present- ring inactivated- amenorrhea, short stature. ? breakpoints.
- XIST absent - disomy X – abnormal phenotype
- Clinical phenotype generally same as postnatal cases

Literature search

Other mosaic sex chromosome abnormalities

45,X/46,X,der(Y)

- Clinical phenotype generally same as postnatal cases
- Variable phenotype - normal male or female or ambiguous genitalia
- Risk of gonadoblastoma in females

Yp loss including SRY – female & Turner Syndrome
Yq loss including AZF - infertility

N.B. Literature search

Other mosaic sex chromosome abnormalities

45,X/46,X,dic(Yp)

45,X/46,X,dic(Yq)

- Clinical phenotype generally same as postnatal cases.
- Variable phenotype - normal male, female, ambiguous genitalia. Gonadal dysgenesis common. Short stature.
- SRY present - some normal male

SRY loss – female; AZF loss –infertility

Ultrasound may be not be helpful

Conclusions

- True mosaicism- level 3?
- Level of mosaicism may be different in different tissues at birth
- XIST/SRY FISH for rings or deletions
- Ultrasound required
- Ascertainment bias in postnatal cases
- Clinical phenotype may not be the same as postnatal cases – variable

N.B. Literature search

Case 1

Sample: Amniocentesis at 22 weeks
Referral: Abnormal ultrasound
Dandy-Walker malformation
Exomphalos
Short femur

FISH: X signal [64]
XY signals [30]
XX signals [6]

Karyotype: 45,X[51]/46,X,idel(Y)[6].ish idic(Y)(p11.2)
(DYZ3++,SRY++)

Pregnancy continued:

Male fetus with Dandy Walker malformation. Confirmed mosaicism

Postnatal blood: 45,X[21]/46,X,idel(Y)(p11.2)[9]

Case 2

Sample: CVS

Referral: Age 44

FISH: X signal [88]
XY signals [11]
XX signals [1]

Karyotype: 45,X[27]/46,XY[3]

XY signals confirmed in CVS culture after mosaicism screen.

Ultrasound scan normal so pregnancy continued:
Clinically normal male. Confirmed mosaic male karyotype.

Postnatal blood: 45,X[8]/46,XY[22]

Case 3

Sample: Amniocentesis at 15 weeks

Referral: Abnormal ultrasound
5mm nuchal fold

FISH: X signal [78]
XY signals [22]

Karyotype: 45,X[50]

XY signals not confirmed in amniotic fluid culture after mosaicism screen. XY signals in uncultured cells mentioned in report

Ultrasound male and no other abnormalities on ultrasound

Pregnancy continued:

Clinically normal male. No XY cells but minute marker found in blood. Mosaic male karyotype confirmed by FISH.

Postnatal blood: 45,X[101]/46,X,+mar[3].ish der(Y)
(DYZ3+,SRY-)

Acknowledgements

Assessors: Lorraine Gaunt
Heleen Schuring
Richard Ellis

UK NEQAS Steering Committee

Quality Manager: Bettina Quellhorst-Pawley

Data:

UKNEQAS - Prenatal EQAs

CEQA - Postnatal EQA

Diagnostic cases – unpublished data