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First trimester combined screening of fetal chromosomal abnormalities in a low risk population

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Introduction

In the last years different strategies have been developed for prenatal screening of aneuploidies.

The aim of such programmes is to reduce invasive diagnostic procedures which should be reserved to those pregnancies at higher risk of bearing an aneuploid fetus.

The first trimester combined test has been shown to be one of the most efficient approaches.

Objective

To evaluate the effectiveness of the combined test in clinical practice.

Methods

7401 singleton and 142 twins pregnancies between 10+6 and 13+6 gestational ages were enrolled in this study (tab. 1).

Women aged 35 and older represented nearly 22% of the total population (fig. 1).

For each patient detailed informations regarding weight, diabetic deseases and genetic disorders in previous pregnancies were collected. CRL and NT measurements were carried out by single gynaecologists following a standardized method defined by the Fetal Medicine Foundation.

Free beta HCG and PAPP-A values were determined by an immunoassay system (Victor-Wallac and Delfia Express-Perkin Elmer) and a risk figure for Down syndrome and trisomy 18 (Delfia) were derived for each maternal blood sample integrating CRL and NT values.

Invasive diagnostic procedures for the analysis of fetal karyotype were suggested if the combined risk value exceeded the cut-off risk > 1:270.

Follow-up investigations were mainly focused to ascertain the number of aneuploid fetuses detected prenatally or recorded at birth through informations gathered by referring gynaecologists.

Results

315 pregnancies resulted screen positive to the combined test (4,2%).

In the sample of screen positive pregnancies undergoing fetal chromosome analysis by amniocentesis the following chromosomal abnormalities were recorded (tab. 2): Down syndrome (16), Turner syndrome (2), Trisomy 18 (2), Triploidy (1) and structural chromosomal aneusomies (3)(tab. 3).

In two instances newborn babies affected by Down syndrome were recorded in the population of pregnancies with a negative screen result.

A further case of free-trisomy 21 was detected at birth in a pregnant woman with a positive test unwilling to undergo midtrimester amniocentesis.

Conclusions

The results of our study support the feasibility of delivering the first trimester combined screening within a prenatal laboratory setting.

Two critic points of this programme have to be highlighted: 1) the difficulty in pursuing the proper epidemiological surveillance of the pregnant population; 2) the exclusive utilization of the midtrimester amniocentesis to perform fetal karyotype analysis.

Tab. 1 - Pregnancies enrolled in the prospective screening programme grouped by gestional age

between december 2000 - september 2007

Gestional age completed weeks	Pregnancies n°
10 (10+6)	86
11	1263
12 [a]	3524
13 [b] (13+6)	2670

[a] { included 98 twin pregnancies

[b] { included 42 twin pregnancies

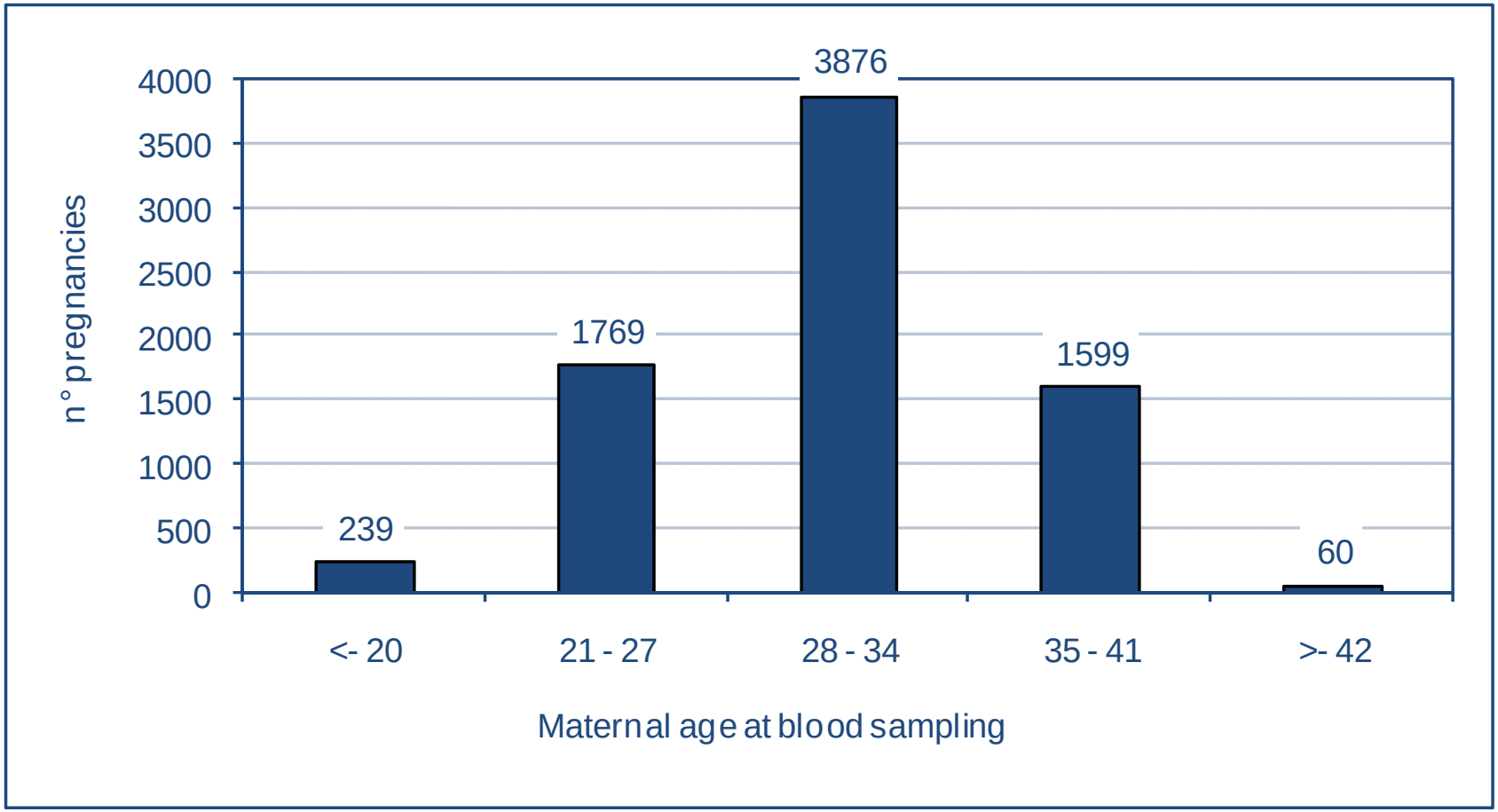
4000
3500
3000
2500
2000
1500
1000
500
0
n° pregnancies
239
1769
3876
1599
60
<- 20
21 - 27
28 - 34
35 - 41
>- 42
Maternal age at blood sampling

Fig. 1

Tab. 2 - Classification by risk group of euploid and aneuploid / aneusomic pregnancies

Karyotype	n	High Risk DS	Low risk [a]
Normal	7543	315	7228
Down syndrome	19	17	2
Trisomy 18	2	2	0
Triploidy	1	1	0
Turner syndrome	2	2	0
Partial aneusomies	3	3	0

[a] number of pregnancies with risk < 1 : 270

Tab. 3 - Partial fetal aneusomies and first trimester NT, PAPP-A, free βHCG

Fetal Karyotype	Pregnancy week / age	PAPPA-A (MoM)	f βHCG (MoM)	NT (MoM)	FDS Risk	T18 Risk
46,XY,del 5p -	12+1 / 39	0,64	3,92	1,17	1 / 60	N.C.
46,XX,del 4(p14-pter)	12+1 / 27	0,34	1,28	1,77	1 / 190	N.C.
46,XX,del 6(q21-q23)	12+3 / 36	0,37	0,96	3,44	1 : 5	1 : 5

N.C.: not calculated

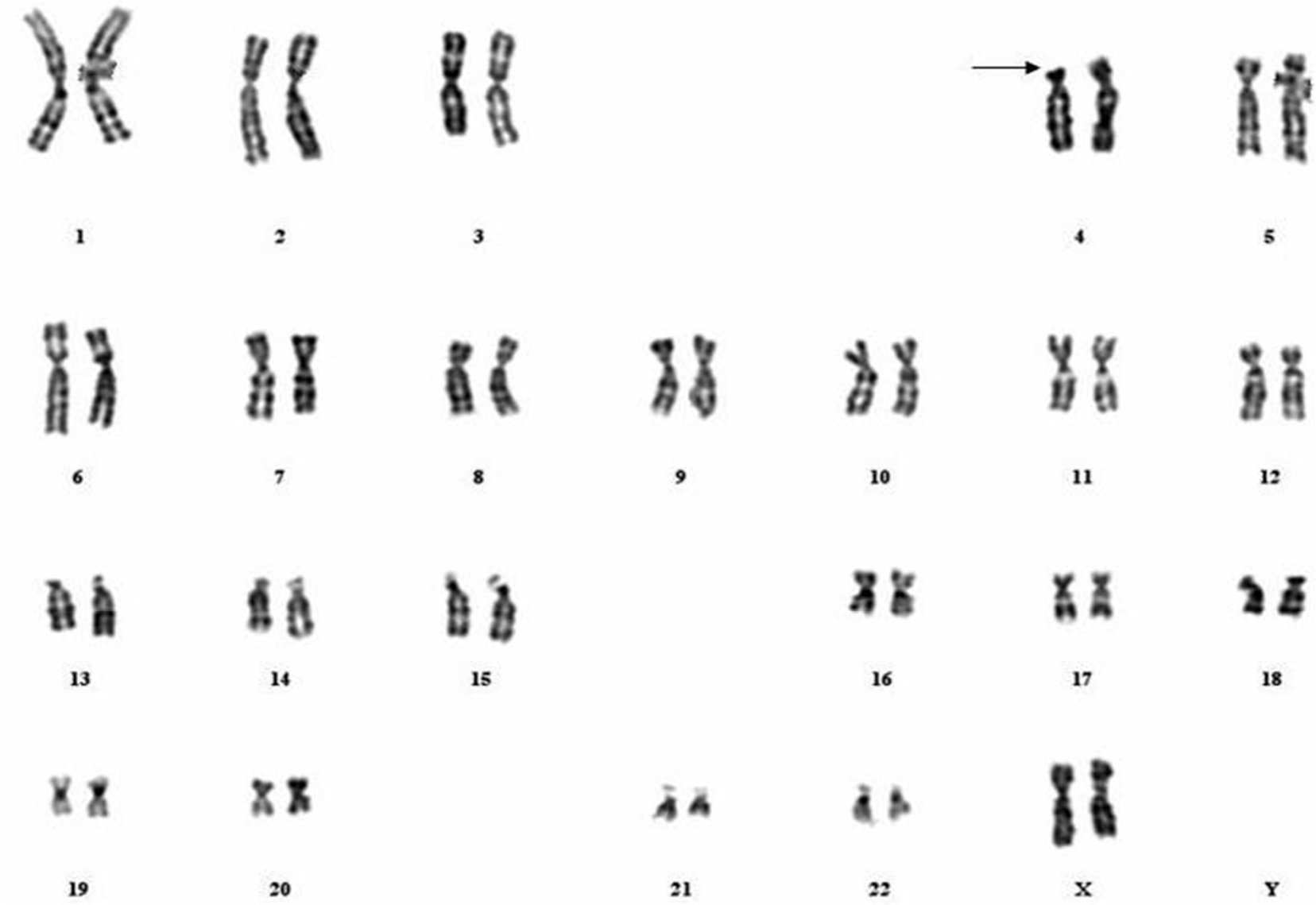

Fig. 2 – 46,XX,del(4)(p14- pter)

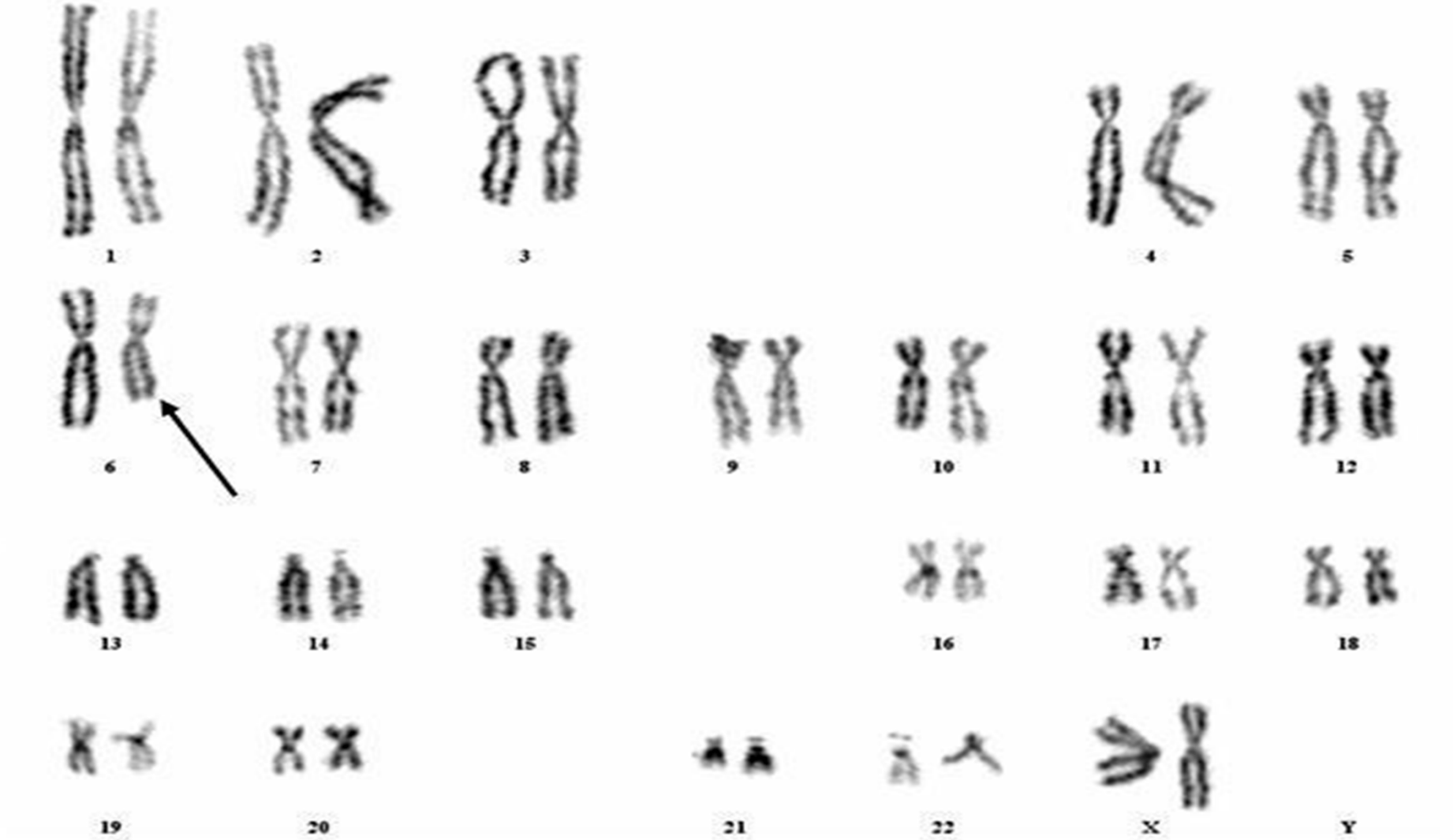

Fig. 3 - 46,XX,del 6(q21-q23)

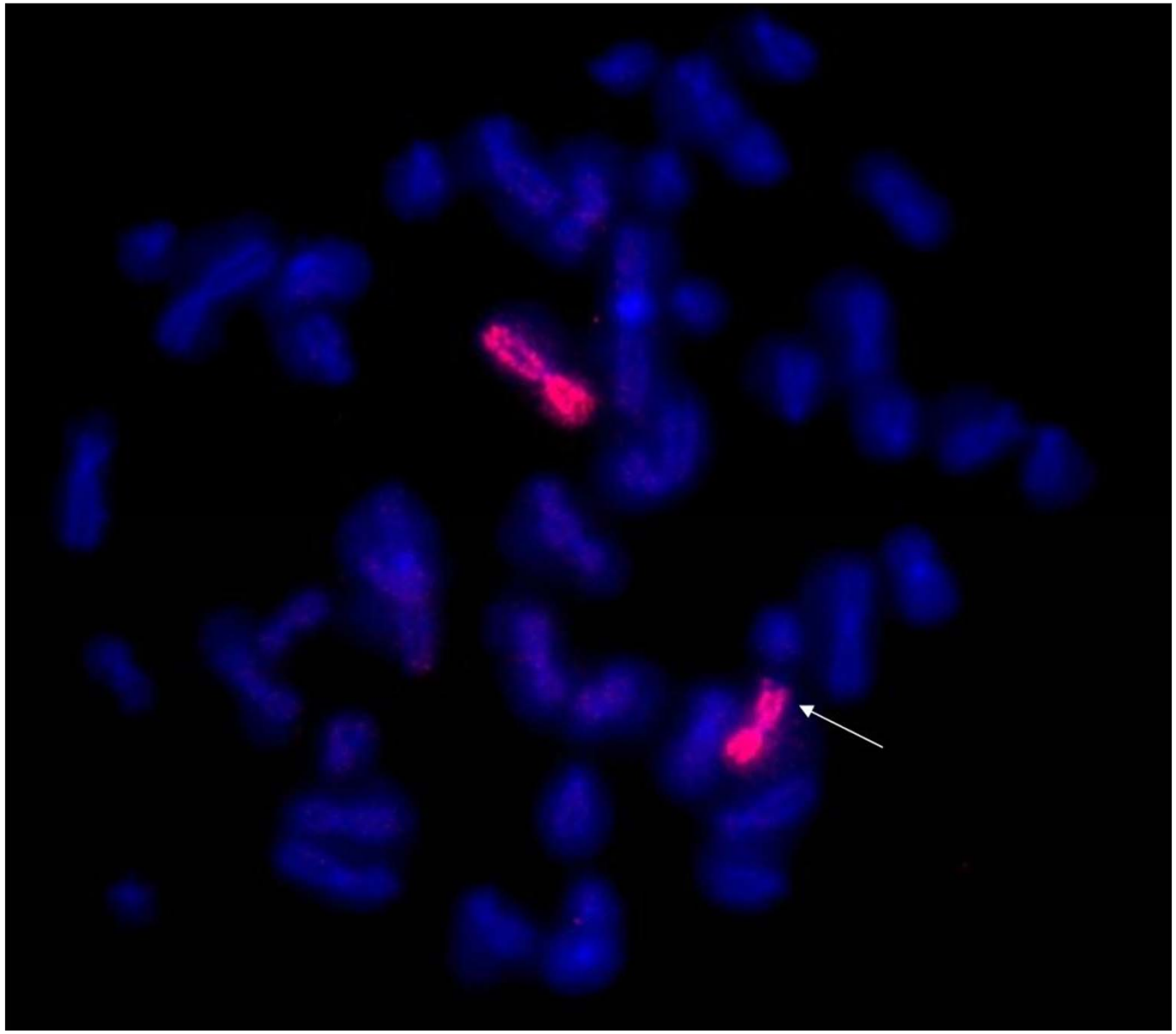

Fig. 4 – FISH analysis - WCP 6 sprectrum orange (Vysis, inc)