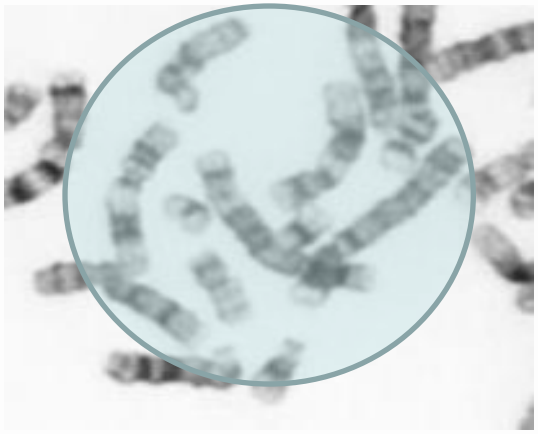
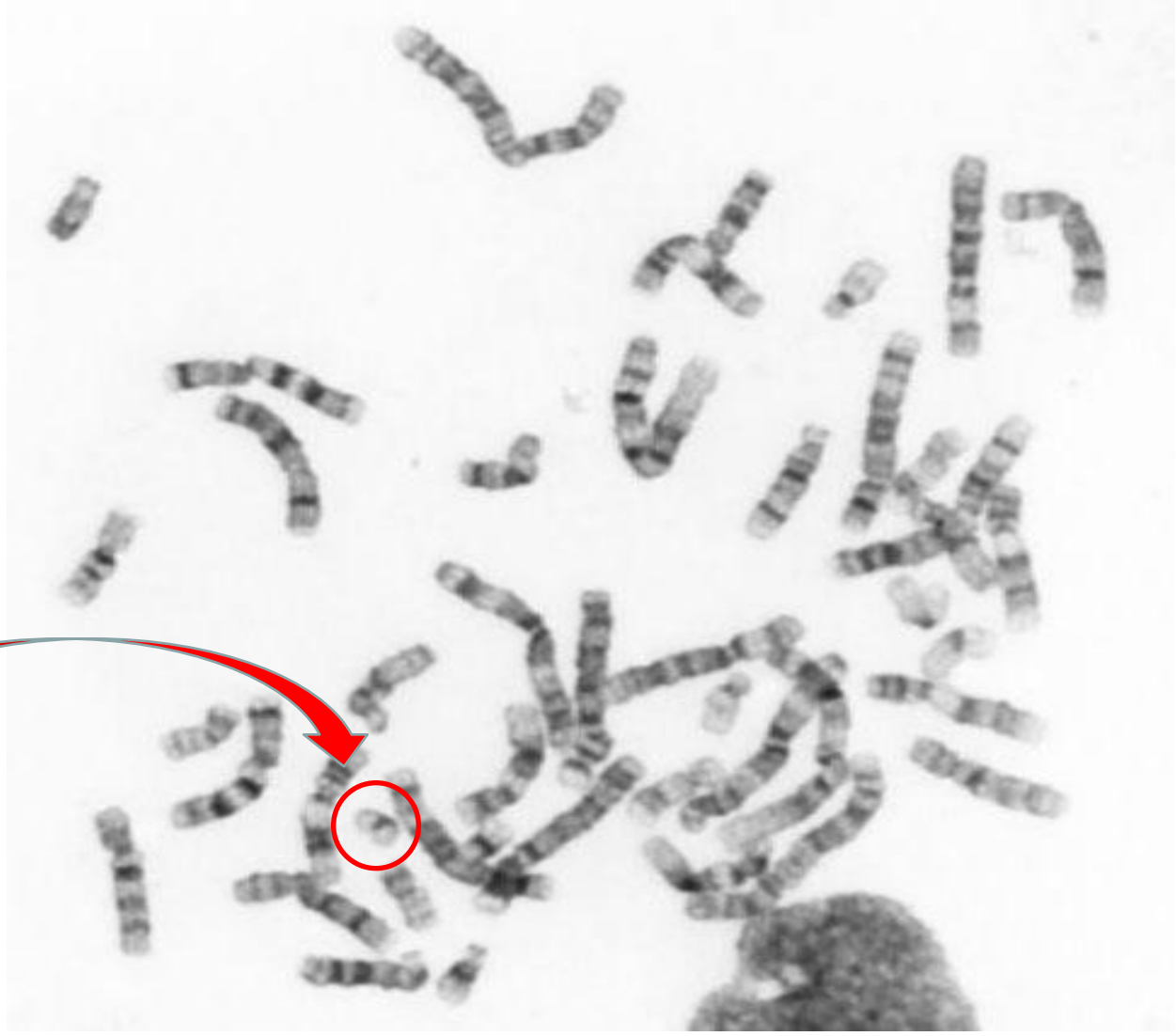
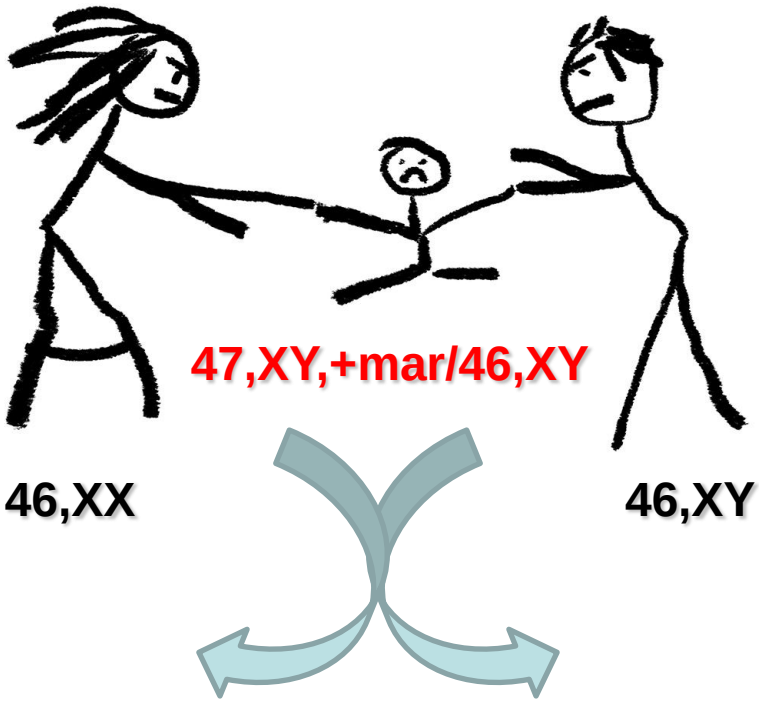
Characterization of a rare analphoid sSMC(7)



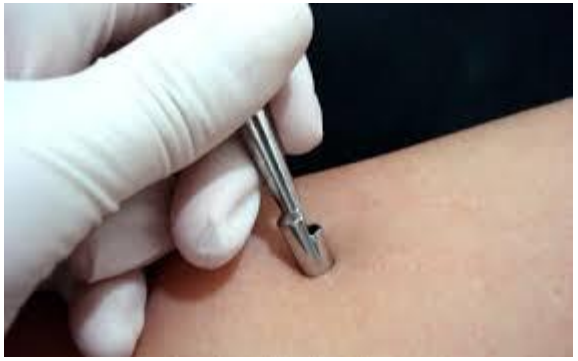
Cristina Ferreira



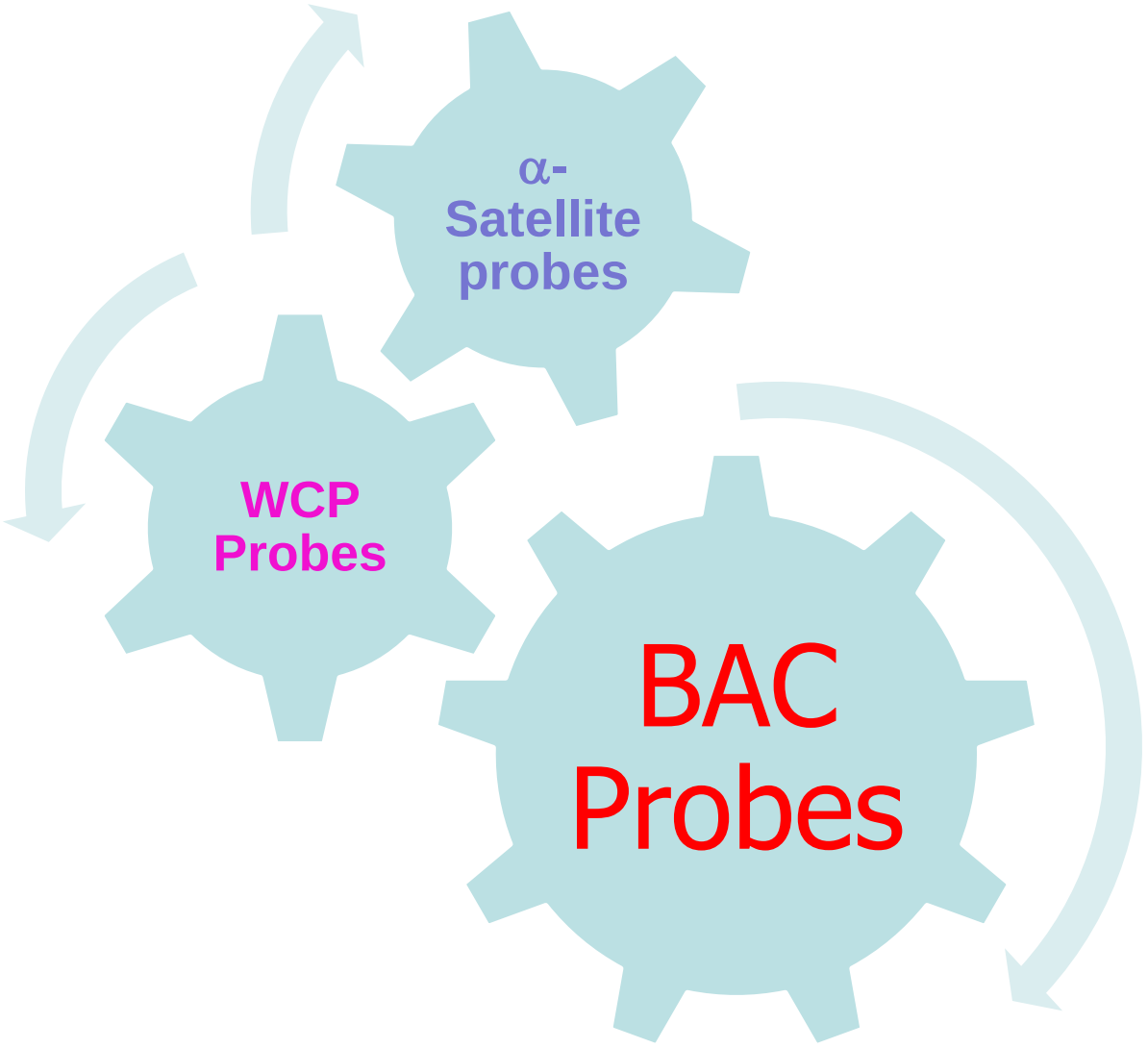
47,XY,+mar[10]/46,XY[40]



Mosaic 20%

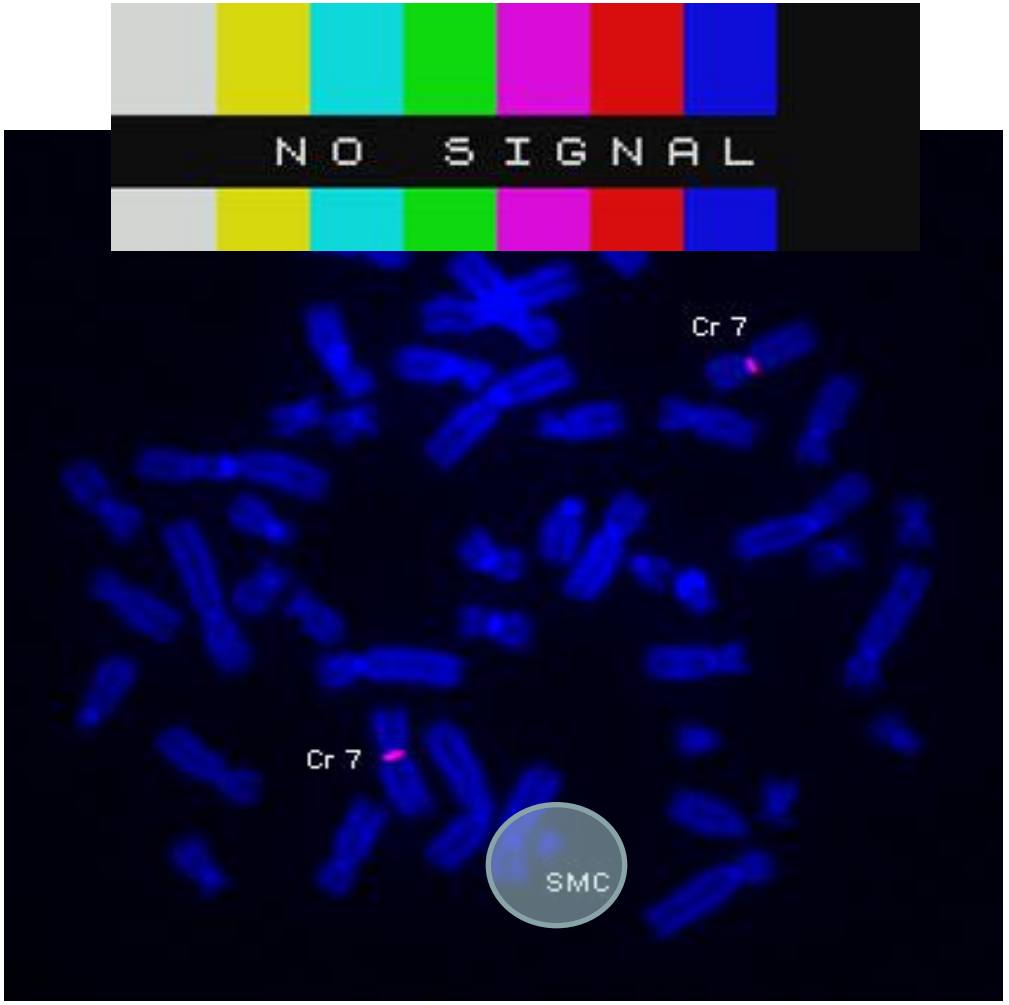


Mosaic 73%

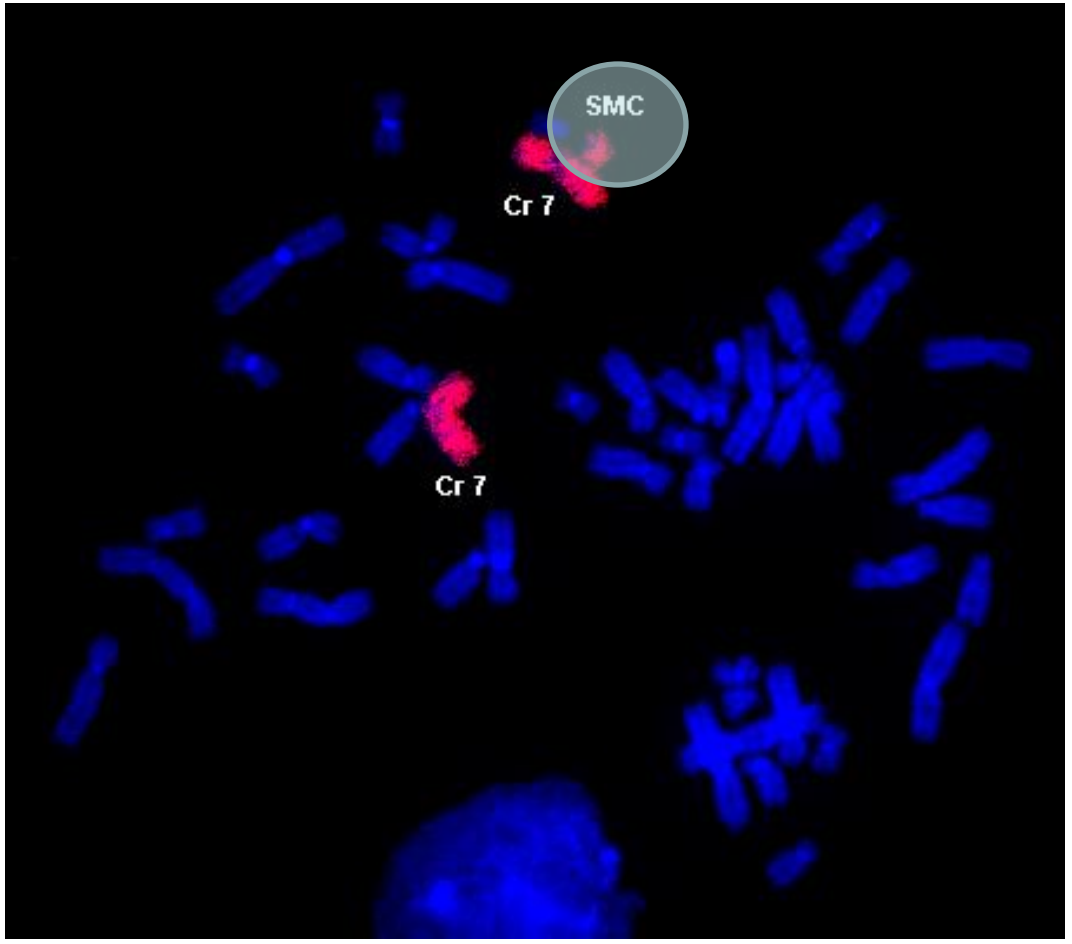

α-
Satellite
probes
WCP
Probes
BAC
Probes

α-Satellite probes

- Chr 15
- Chr 13/21
- Chr 14/22
- Chr X and Y
- …..
- ….
- Chr7
- …..
- …..
- ….



WCP Probes



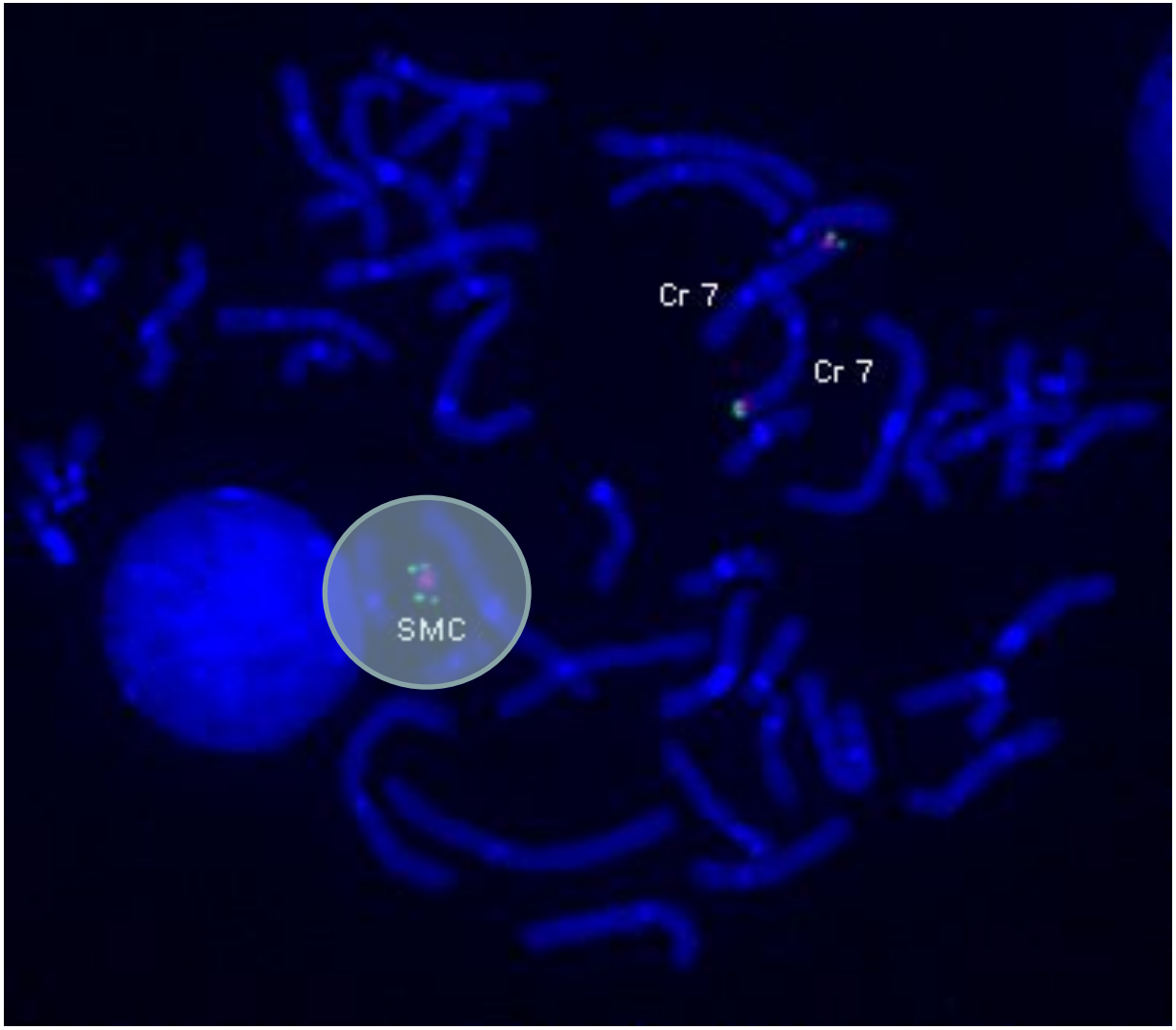
- What looks like this sSMC?

BAC Probes

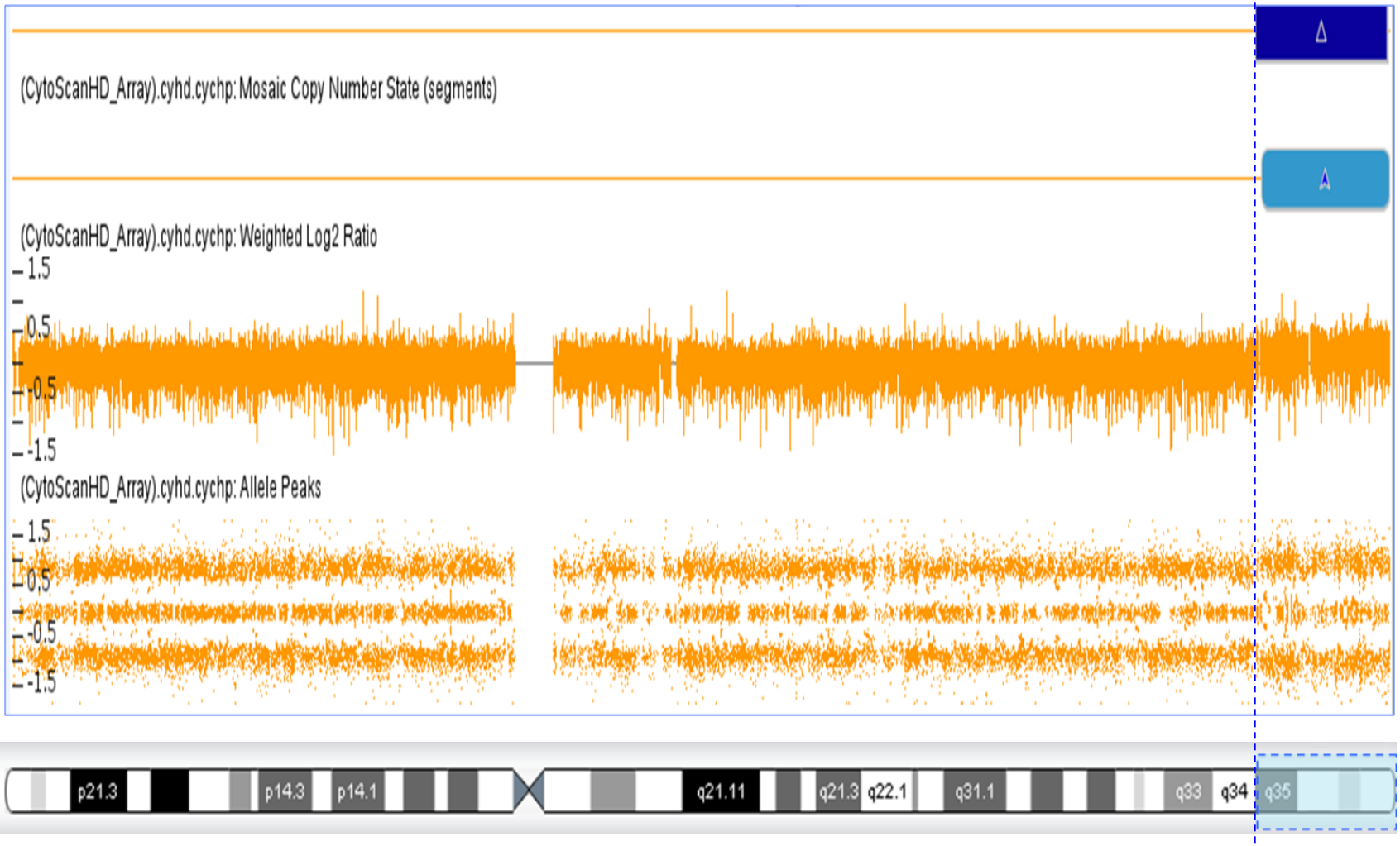
RP11-237G17 (7q34) —

RP11-298A10 (7q35) +

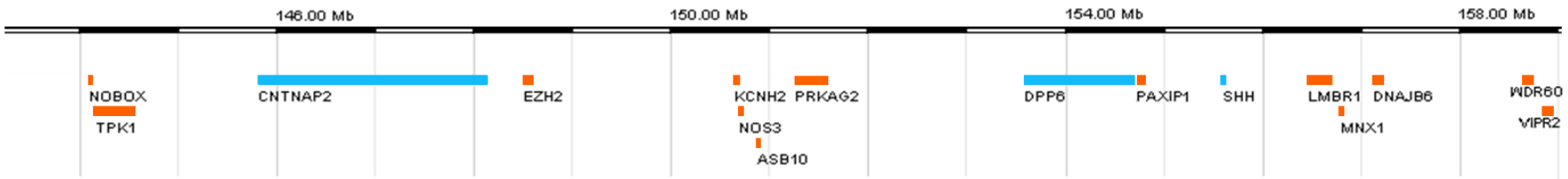
TelVysion (7qter) ++

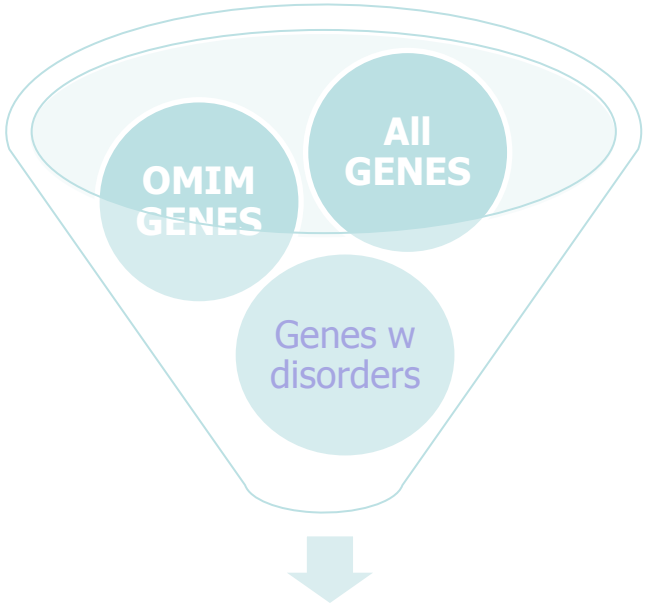


47,XY,+mar[10]/46,XY[40].ish invdup(7)(qter→q35::q35→neo→qter)(wcp7+,D7Z1-,RP11-298A10+,TelVysion 7q++)



47,XY,+mar[10]/46,XY[40].ish invdup(7)(qter→q35::q35→neo→qter)(wcp7+,D7Z1-,RP11-298A10+,TelVysion 7q++).arr[hg19] 7q35q36(143696249-159119707)x2~3





Fenotype/genotype correlations

CHARACTERIZATION OF A RARE ANALPHOID SUPERNUMERARY MARKER CHROMOSOME IN MOSAIC

Bárbara Marques[1], Filomena Brito[1], Cristina Alves[1], Sónia Pedro[1], *Cristina Ferreira*[1], Marta Amorim[2], Hildeberto Correia[1]

[1] Unidade de Citogenética, Departamento de Genética Humana, Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P., Lisboa, Portugal.

[2] Serviço de Genética Médica, Hospital D. Estefânia, Centro Hospitalar Lisboa Central, Lisboa, Portugal.

INTRODUCTION

Analphoid small supernumerary marker chromosomes (asSMC) are a rare subclass of C-band-negative sSMC that are devoid of alpha-satellite DNA. These marker chromosomes cannot be identified unambiguously by conventional banding techniques alone , being necessary to apply molecular cytogenetic methods in favour of a detailed characterization [1].

Approximately 135 asSMC have been described until now involving 20 of the 22 autosomes and both sex chromosomes, with about 50% resulting from chromosomes 15, 13 and 8 [2]. Only three cases are sSMC(7) and just two of them have been reported with a sparse details [2].

In terms of clinical findings, there are three major groups to be considered: no clinical consequences (~5%), moderate to severe clinical consequences (~7%) and the largest group with the most severe clinical consequences. If an analphoid sSMC does not cause an imbalance and/or the sSMC causing a large imbalance is present only in mosaic, clinical findings may be absent or mild [2].

We report on a child with several dysmorphic features and severe development delay presenting a *de novo* analphoid sSMC in mosaic, which by molecular cytogenetics and microarray analysis was shown to be originated from the terminal long arm of chromosome 7 and to harbour an invdup rearrangement of 7q35-qter region.

PATIENT CLINICAL INFORMATION

The patient was a newborn male, the first child of an healthy and non consanguineous couple. He was born at 28th week of gestation with normal somatometric parameters (weight 1167g corresponding to a P50). In the neonatal period he had respiratory distress syndrome and feeding difficulties. He was diagnosed with bronchopulmonary dysplasia (pos-prematurity?).

At physical examination he revealed open and wide anterior fontanelle, bi-frontal narrowing, bilateral eyelid edema, low insertion ears, short nose with wide and depressed root, small mouth, full lips, short neck, fingers and toes nail hypoplasia. He had bilateral hip dysplasia, cryptorchidism and bilateral inguinal hernia. He was submitted to a tracheotomy and a gastrostomy.

Currently, he is 10-years-old and has severe development delay without language, bruxism and auto-aggressive behaviour (started at age of 8 years-old). He has an unstable, assisted broad-based walk. He still depends on enteral feeding and has a tracheostomy tube for breathing. The physical exam reveals an accentuation of the dysmorphic features with straight eyebrows with synophrys, short palpebral fissures, opened mouth and protrusion of the tongue. He has supernumerary teeth, divergent strabismus and anterior chamber asymmetric optic malformation.

He has recurrent respiratory infections. Renal and cardiac malformations were excluded by ultrasound.

RESULTS & DISCUSSION

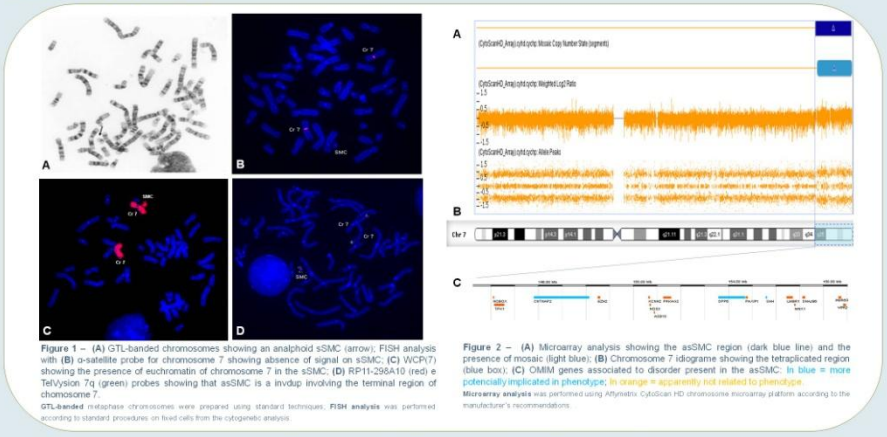


Figure 1 – **(A)** GTL-banded chromosomes showing an analphoid sSMC (arrow); FISH analysis with **(B)** α-satellite probe for chromosome 7 showing absence of signal on sSMC; **(C)** WCP(7) showing the presence of euchromatin of chromosome 7 in the sSMC; **(D)** RP11-298A10 (red) e TelVysion 7q (green) probes showing that asSMC is a invdup involving the terminal region of chromosome 7.

GTL-banded metaphase chromosomes were prepared using standard techniques; **FISH analysis** was performed according to standard procedures on fixed cells from the cytogenetic analysis.

Figure 2 – **(A)** Microarray analysis showing the asSMC region (dark blue line) and the presence of mosaic (light blue); **(B)** Chromosome 7 idiograme showing the tetraplicated region (blue box); **(C)** OMIM genes associated to disorder present in the asSMC: In blue = more potencially implicated in phenotype; In orange = apparently not related to phenotype.

Microarray analysis was performed using Affymetrix CytoScan HD chromosome microarray platform according to the manufacturer's recommendations.

Cytogenetic analysis revealed a mosaic karyotype with the presence of an sSMC, *de novo*, in 20% of the lymphocytes and 73% of the fibroblast cells (Fig. 1A).

FISH analysis with alpha-satellite probes for all chromosomes indicated that the sSMC was an analphoid marker (Fig.1B), while the presence of euchromatic material was revealed with WCP(7) (Fig. 1C). Hybridization with RP11-298A10 and TelVysion 7q probes, allowed establishing that the asSMC results of an invdup rearrangement of 7q35-qter region (Fig. 1D).

Affimetrix CytoScan HD microarray analysis redefined the asSMC to a region of 15.42 Mb (Fig. 2A e B) enclosing 67 OMIM genes, 16 of which are associated to disease (Fig. 2C).

The karyotype was established as: 47,XY,+mar[10]/46,XY[40].ish invdup(7)(qter-->q35::q35-->neo-->qter)(wcp7+,D7Z1+, RP11-298A10+, TelVysion 7q++); arr[hg19] 7q35q36(143696249-159119707)x2~3

The asSMC consists of an inverted duplication of the distal region of chromosome 7q that results in tetrasomy of 7q35qter region. This region encloses 67 OMIM genes and 16 of them are associated with disease (Fig 2C). From the analysis of genes content in the tetraplicated region we highlight CNTNAP2 (OMIM*604569) that plays an important role in neurodevelopmental disorders [3] and in language development [4,5]; DPP6 (OMIM*126141) that has been related to microcephaly and mental retardation [6] as well as in the pathogenesis of autism spectrum disorder and Gilles de la Tourette syndrome [7] and SHH (OMIM*600725), which belongs to a family of genes that code for a class of proteins that act as signalling molecules during embryo development, namely for the development of the nervous and skeletal systems and the formation of the testis cord [8]. However, in literature there are only delections, mutations or disruptions of these genes which associate the phenotype to haploinsufficiency and not to overexpression.

Several clinical features are frequently described in literature and numerous attempts have been made to correlate syndrome manifestations with specific chromosome segments duplications; however, phenotype-genotype correlation is still controversial perhaps because a pure 7q partial trisomy is a rare occurrence [9]. Lehnen H. *et al* described a girl with a partial tetrasomy 7q, arr 7q35q36(145,281,329-158,811,268)x4 that shares some phenotypic features with our patient but with a more severe clinical consequences including cardiac problems, which is not strange because our patient is a mosaic which expression varies from different tissues.

REMARKS

To our knowledge, this is the first case of an asSMC (7) full characterized and with a complete clinical description, and the fourth case reported so far, which contributes to a better understanding of asSMC(7). This case confirms that supernumerary material at distal 7q can cause a severe phenotype with mental retardation, dysmorphisms wherein the most obvious affected area of development is speech and language, which is common in duplications of 7q.

REFERENCES

[1] Shaffer LG, McGowan-Jordan J, Schmid M (Eds): ISCN 2013: An International System for Human Cytogenetic Nomenclature. Basel: S. Karger; 2013.

[2] Liehr T. (2015) The sSMC homepage: http://ccmd.jena.de/sSMC.html (Accessed 15 Jun 2015).

[3] Poot M., Mol Syndromol. (2015); 6:7-22.

[4] Alarcón M. et al. , Am. J. Hum Genet. (2008); 82, 150-159.

[5] Condro M. C. and White S. A., J. Comp. Neurol. (2014); 522(1): 169-185.

[6] Liao Can et al., Eur. J. Med. Genet (2013); 56:484-489.

[7] Prontera P. et al., Neurogenetics (2014); 15:237-242.

[8] Pereira J. et al., PLoS ONE 9(12):e74132. Doi:10.1371/journal.pone.0074132.

[9] Lehnen H. et al. Cytogenet Genome Res (2009); 125:248-252

[10] Scelsa B. et al. J Child Neurol. (2008); 23:573-579.

Bárbara Marques[1], Filomena Brito[1], Cristina Alves[1], Sónia Pedro[1], *Cristina Ferreira*[1], Marta Amorim[2], Hildeberto Correia[1]

[1] Unidade de Citogenética, Departamento de Genética Humana, Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P., Lisboa, Portugal.

[2] Serviço de Genética Médica, Hospital D. Estefânia, Centro Hospitalar Lisboa Central, Lisboa, Portugal.

Permanent Working Group_Marker Chromosomes_ ECC 2015

Thanks for your attention!!!