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**delezione terminale
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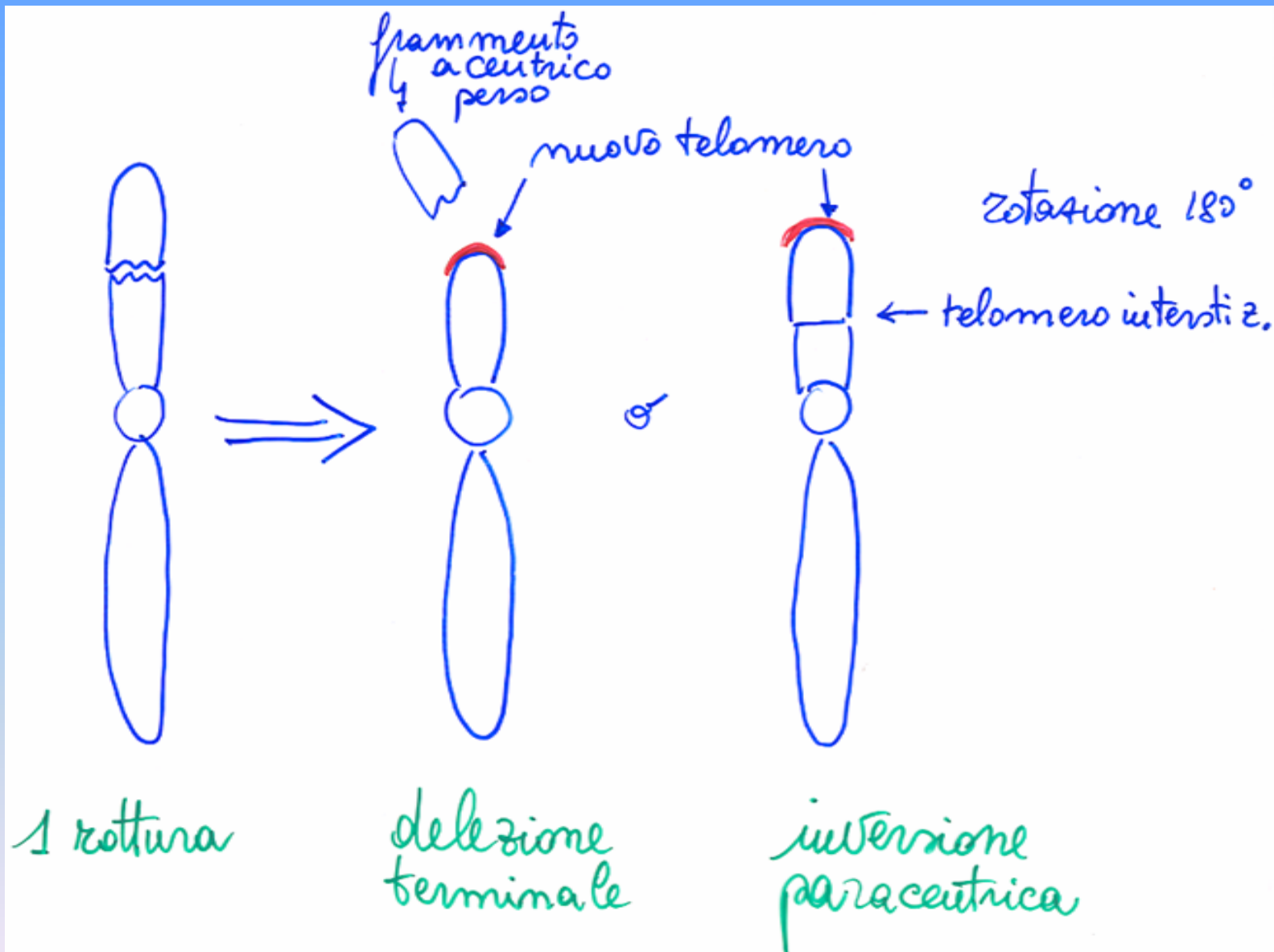
**delezione interstiziale
inversione para- o pericentrica
cromosoma ad anello**

due rotture su cromosomi diversi

**traslocazione reciproca
traslocazione centrica**

**tre rotture di cui 2 almeno
sullo stesso cromosoma**

traslocazione con inserzione



2 rotture nello stesso braccio

attivazione
neocentromero

frammento
acentrico
perso

rotazione 180°



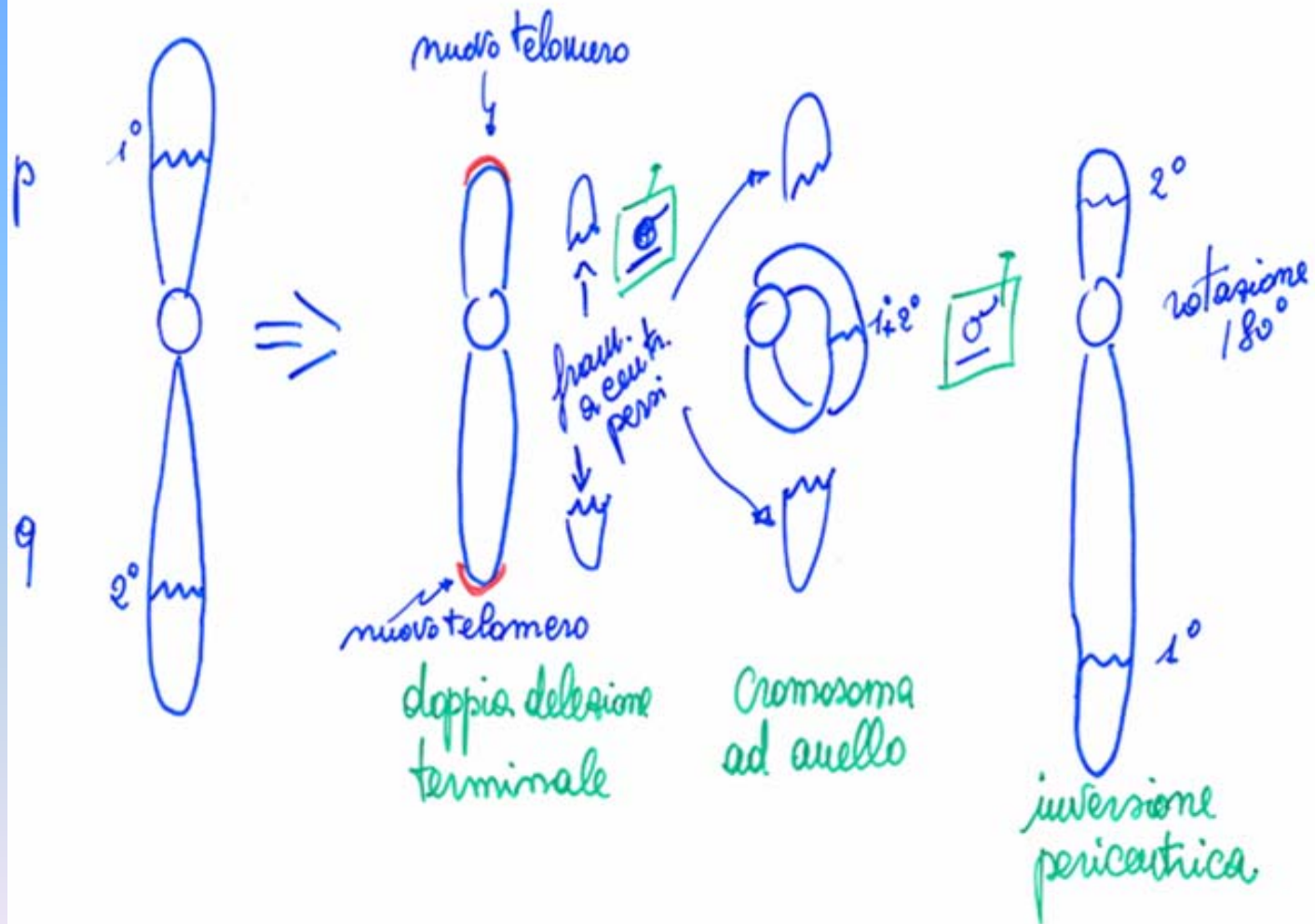
o



delezione
interstiziale

inversione
paracentrica

2 rotture su p e q dello stesso cromosoma



2 rotture sui cromosomi diversi

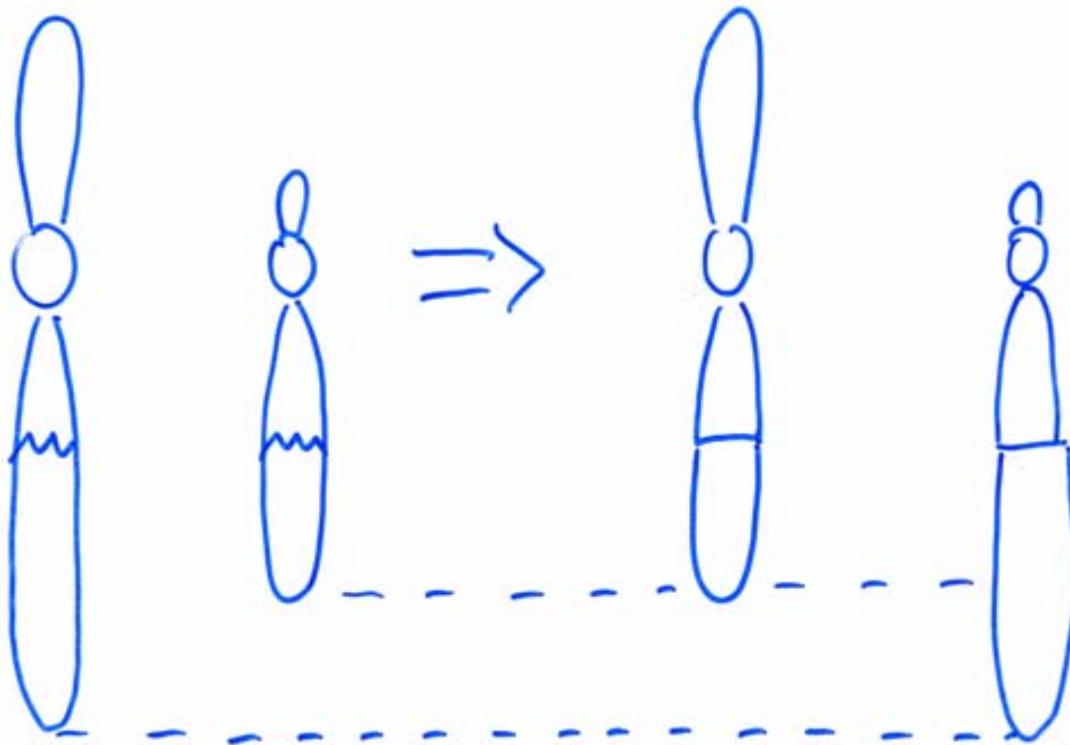
scambi:

$p \leftrightarrow p$

$q \leftrightarrow q$

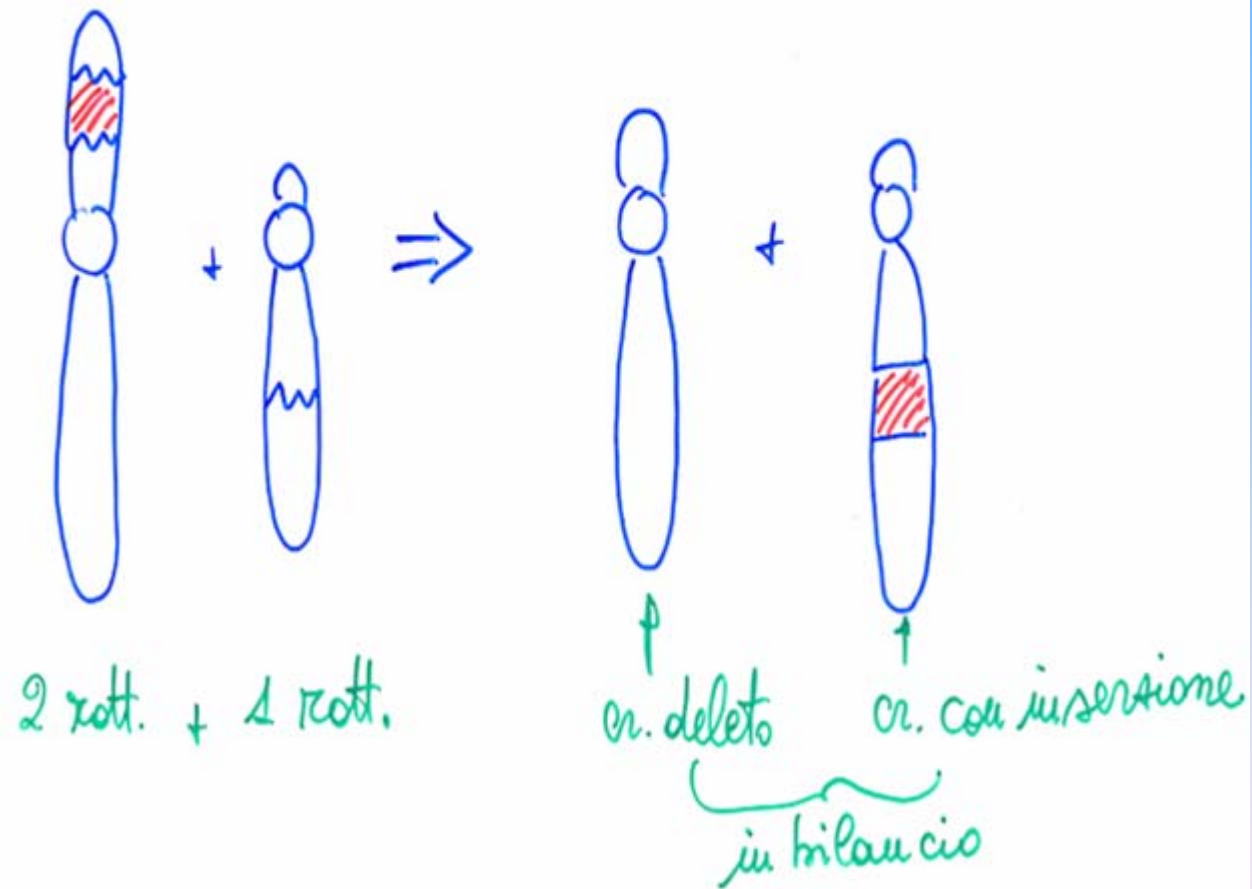
$p \leftrightarrow q$

$cen \leftrightarrow cen$

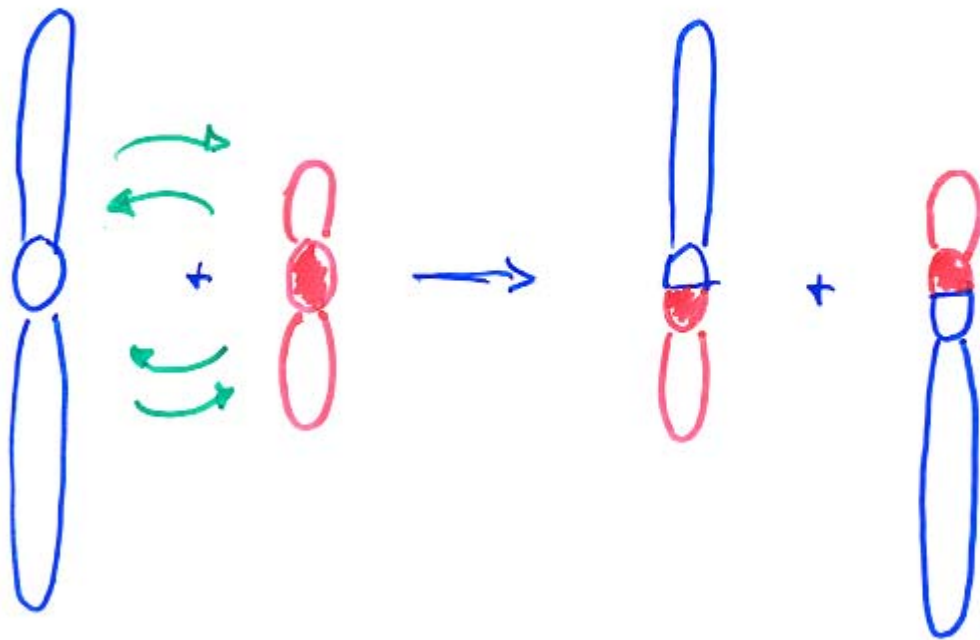


traslocazione reciproca

3 rotture : 2 su un cromosoma + 1 su un altro cr.



2 rotture al centromero $\rightarrow$ fusione centrica



se le anomalie strutturali necessitano di rotture allora diventa di fondamentale importanza in quale tipo di sequenza di DNA avviene l'evento rottura

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sequenze non codificanti non trascritte

sequenze codificanti trascritte

sequenze di regolazione trascritte e no

quali le conseguenze ?

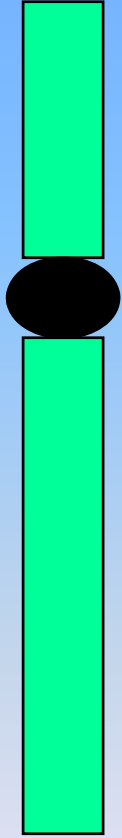
quali le conseguenze ?

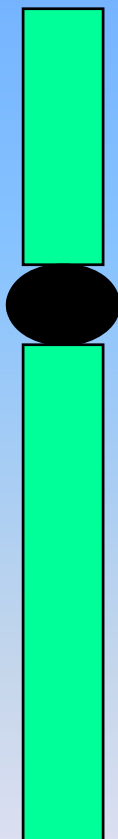
dipenderà dal tipo di sequenza coinvolta

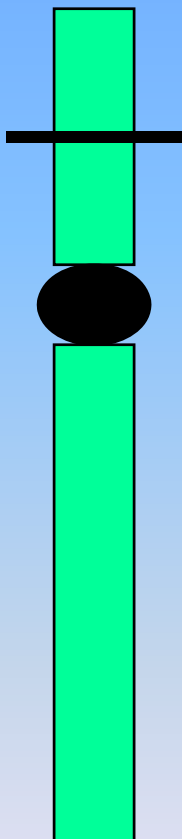
se si considera la delezione cosiddetta terminale...

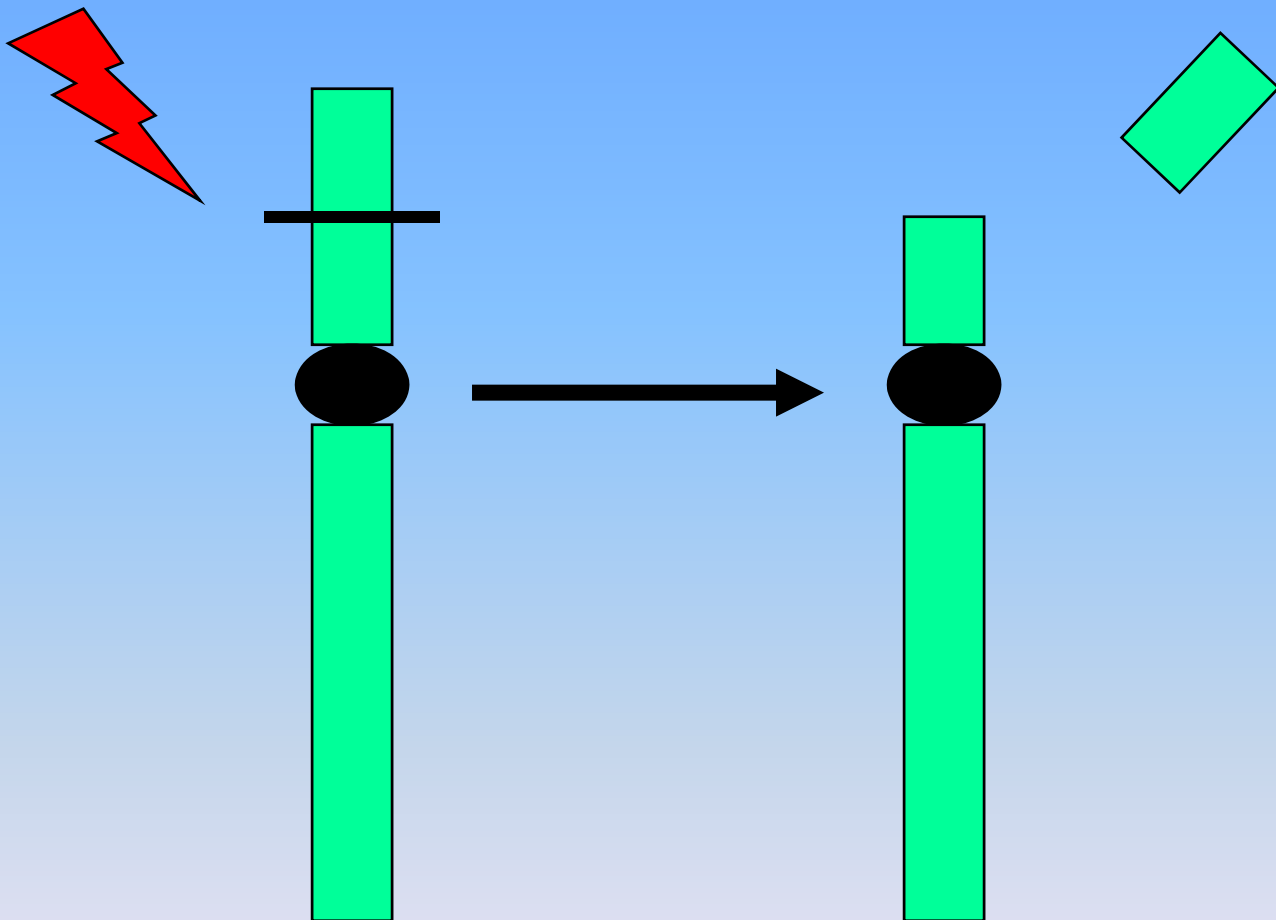
oltre alla sequenza interrotta dalla rottura si deve considerare la perdita del segmento interrotto non contenente il centromero

la perdita di una serie di geni potrà creare aploinsufficienza e potrà mettere in evidenza alleli recessivi sull'omologo non coinvolto

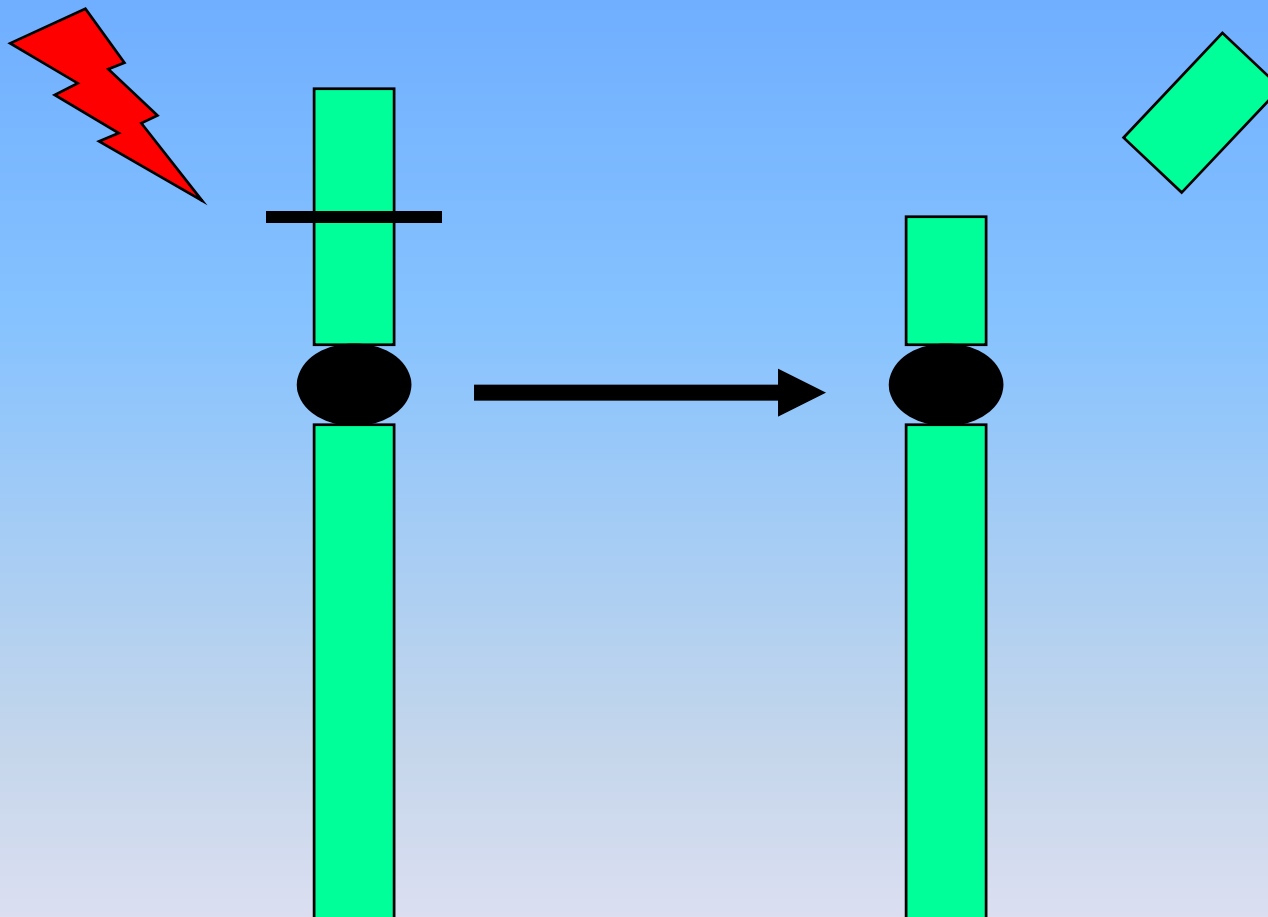






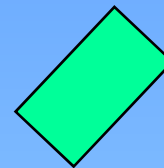
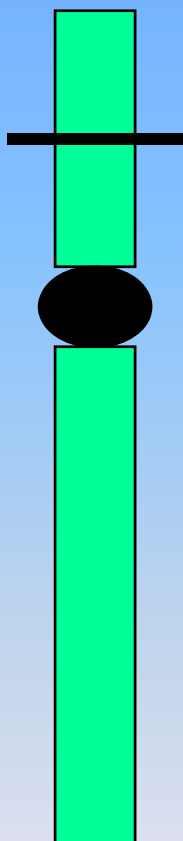


frammento perso



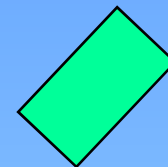
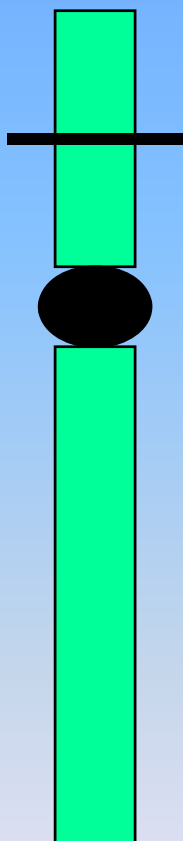
frammento perso

neotelomero

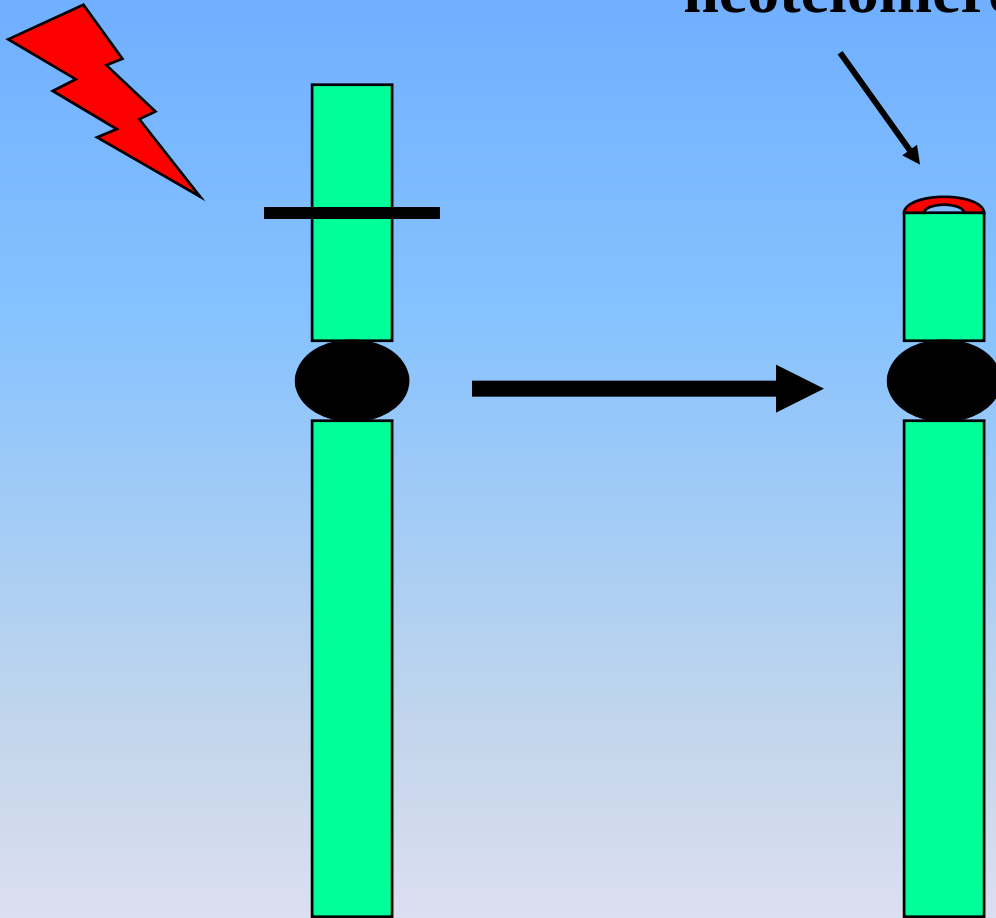


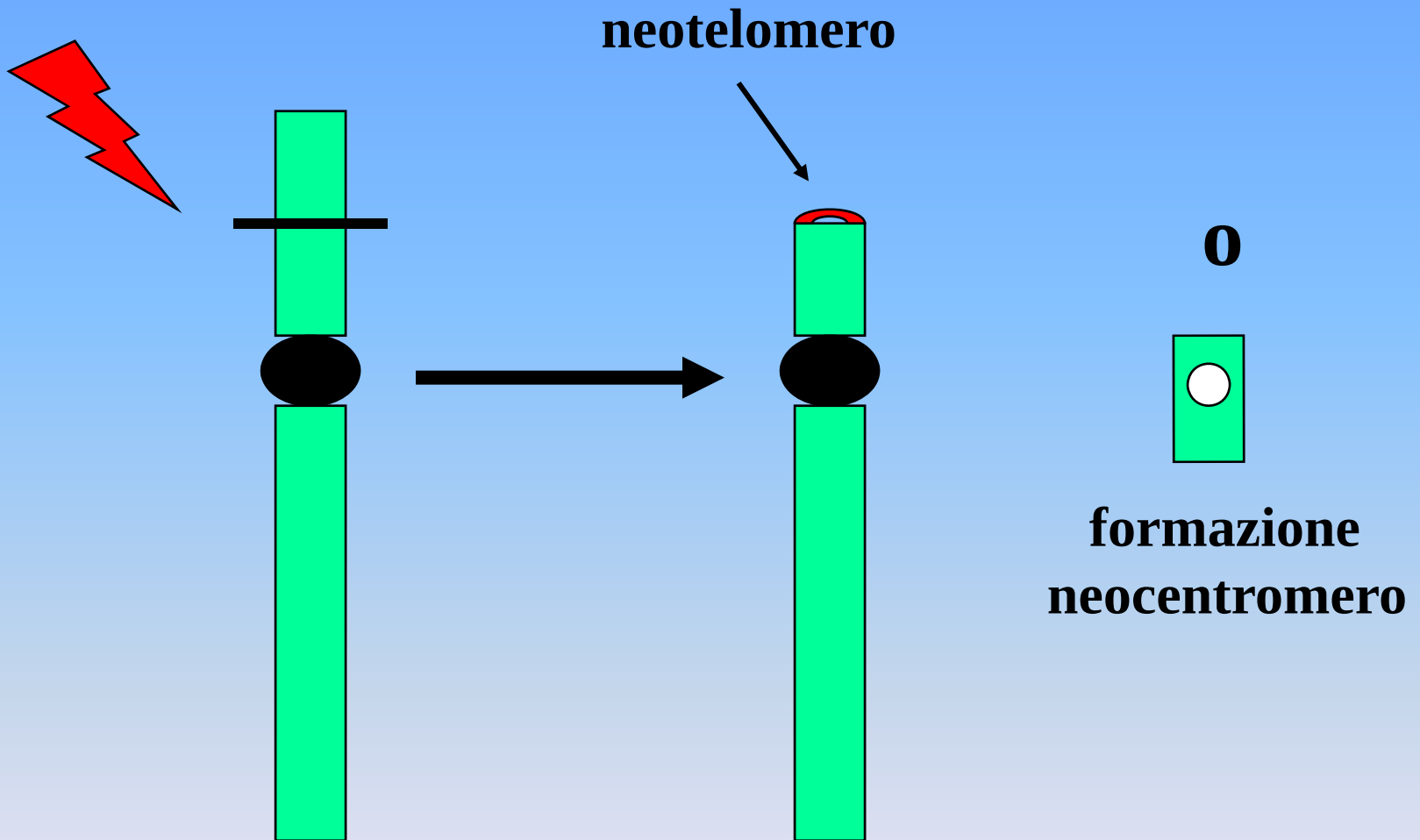
frammento perso

neotelomero

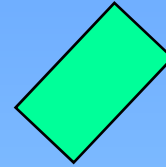


neotelomero

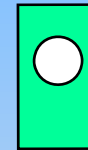




frammento perso

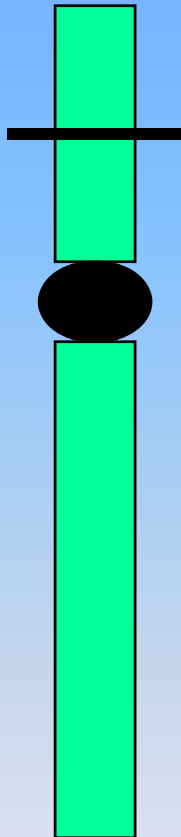


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**formazione
neocentromero**

neotelomero



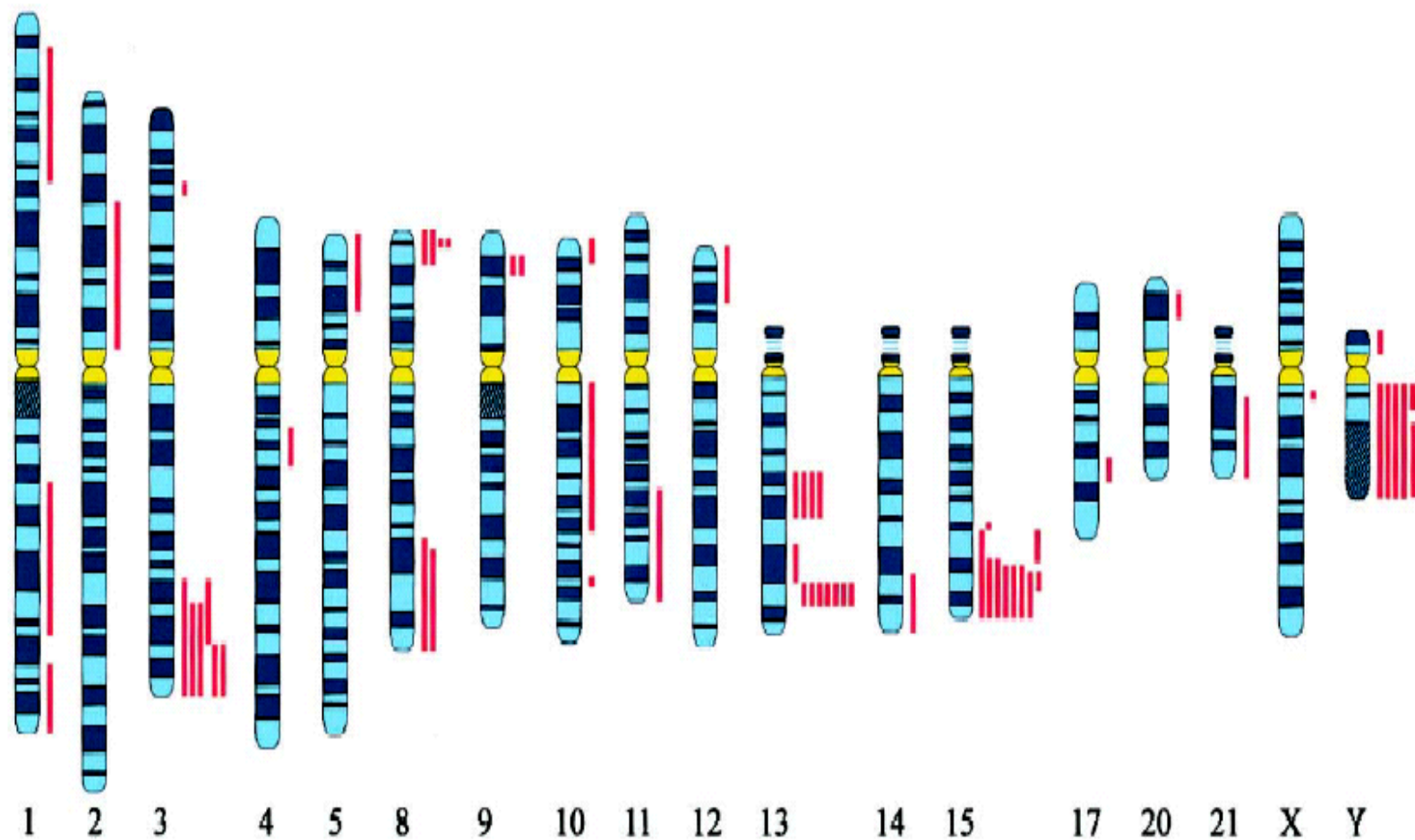


Figure 2 Sites of formation of constitutional neocentromeres within the human genome. A total of 60 cases, originating from 16 different human chromosomes, have been described. The mapped positions of each of the neocentromere cases are indicated by bars to the right of the chromosome ideograms. Longer bars indicate neocentromere sites that have not been precisely localized. Hatch marks on chromosomes 1, 9, and Y represent blocks of constitutive heterochromatin. Adapted from Choo (2001a).

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Sindromi da delezione terminale:

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cromosomiche

s.Wolf-Hirschorn

4p-

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α -talassemia e ritardo mentale 16pter-

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cromosomiche

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4p-

s. del pianto del gatto

5p-

genomiche

α -talassemia e ritardo mentale 16pter-

regioni sub-telomeriche

caratteristiche della sindrome di Wolf-Hirschorn
o monosomia 4p:

ipotrofia grave

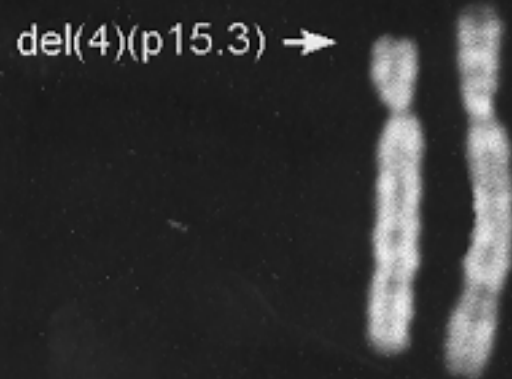
encefalopatia profonda

microcefalia

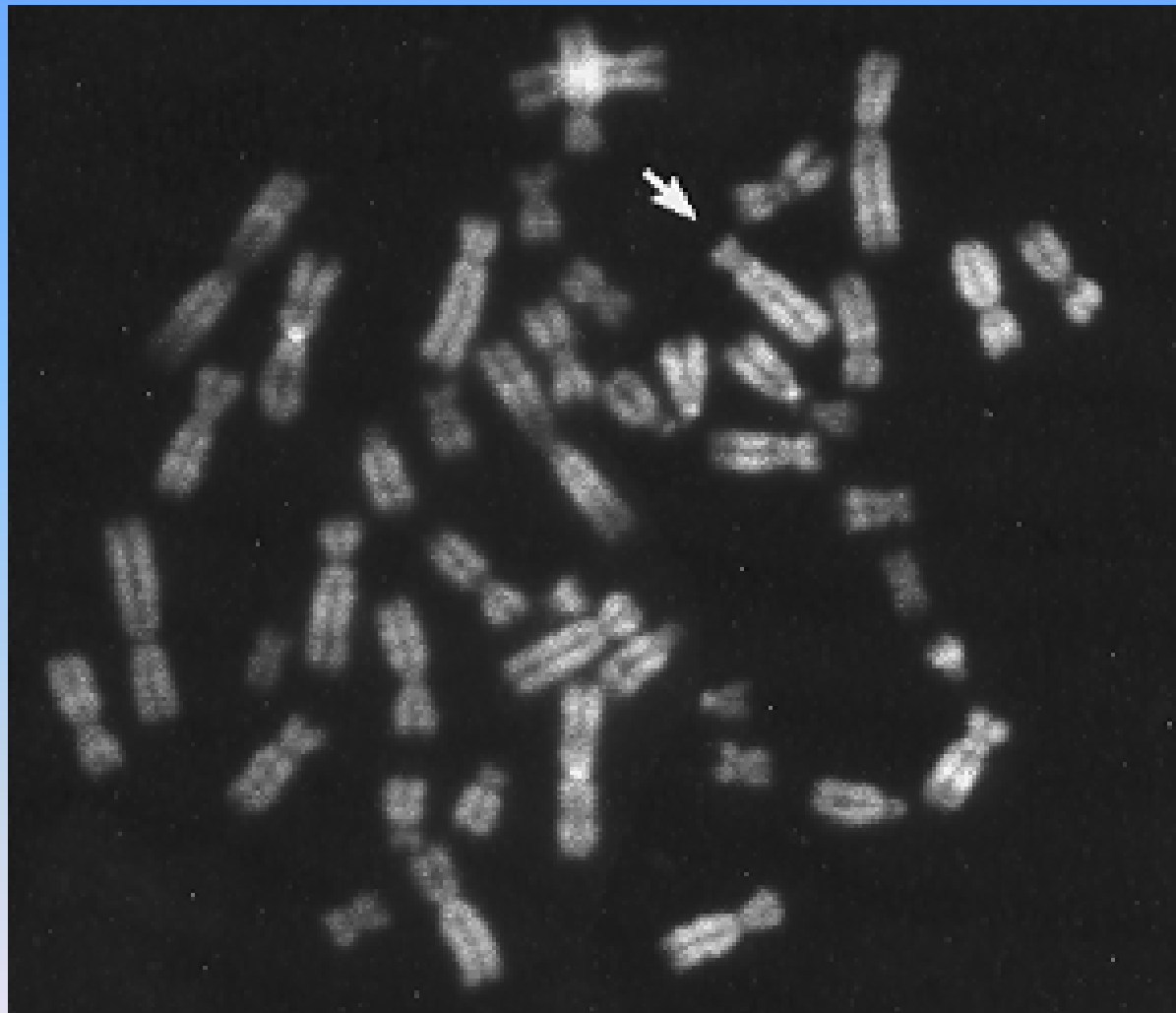
facies a casco del guerriero greco



CROMOSOMI 4



CROMOSOMI 4





11

4.11

Collection Institut de Pro-
thèse (J. Lejeune).

4.12

masque de guerrier grec.

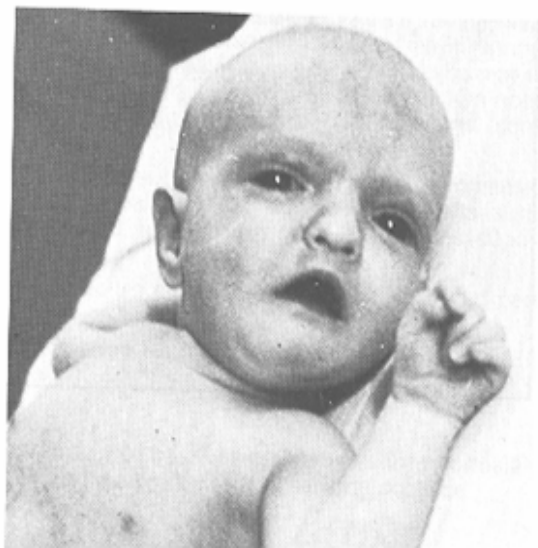
4.13

Collection Institut de Pro-



4.12

4.13



Genotype–Phenotype Correlations and Clinical Diagnostic Criteria in Wolf-Hirschhorn Syndrome

Marcella Zollino,^{1*} Cristina Di Stefano,¹ Giuseppe Zampino,² Pierpaolo Mastroiacovo,² Tracy J. Wright,³ Giovanni Sorge,⁴ Angelo Selicorni,^{5,10} Romano Tenconi,⁶ Alessandro Zappalà,¹ Agatino Battaglia,⁷ Maja Di Rocco,⁸ Giandomenico Palka,⁹ Rosanna Pallotta,⁹ Michael R. Altherr,³ and Giovanni Neri¹

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TABLE I. WHS Patients, Subdivided by Presence (Group A) or Absence (Group B) of Microscopic Deletion*

Patient	Sex	Age at the last observation (yr)	Karyotype
Group A			
1	F	3	46,XX,del(4)(p15.1)
2	F	3	46,XX,del(4)(p15.3)
3	M	3, 6/12	46,XY,del(4)(p15.32)
4	M	2, 4/12	46,XY,del(4)(p15.32)
5	F	5	46,XX,del(4)(p15.32)
6	M	2	46,XY,del(4)(p16.1)
7	M	2, 6/12	46,XY,del(4)(p16.1)
8	M	9	46,XY,del(4)(p16.1)
9	M	1	46,XY,del(4)(p16.1)
10	F	1, 4/12	46,XY,del(4)(p16.1)
11	M	1, 2/12	46,XY,del(4)(p16.1)
Group B			
			Deletion size (Mb)
12	M	11	4.4
13	M	8	3.4
14	M	6	3.2 [+dup(4)(p16.1-p16.3)]
15	F	10	2.8
16	M	15	Undetectable

*F, female; M, male.

TABLE III. Genotype-Phenotype Correlations in WHS*

Clinical signs	Class 1. large deletions: p15.1-p16.1→pter	Class 2. “large” molecular deletions: 4.4→3.2 Mb	Class 3: “small” molecular or no deletions: 2.8→0 Mb
Characteristic face	+	+	+
MR	+	+	+
Hypotonia	+	+	+
Growth retardation	+	+	+
Seizures	+	+	-
Microcephaly	+	+	-
Midline defects	+	-	-
CHD	+	-	-
Renal abnormalities	+	-	-

*MR, mental retardation; CHD, congenital heart defect; +, present; -, absent.

caratteristiche della sindrome del “pianto del gatto”
(cri du chat) o monosomia 5p:

pianto come miagolio del gatto

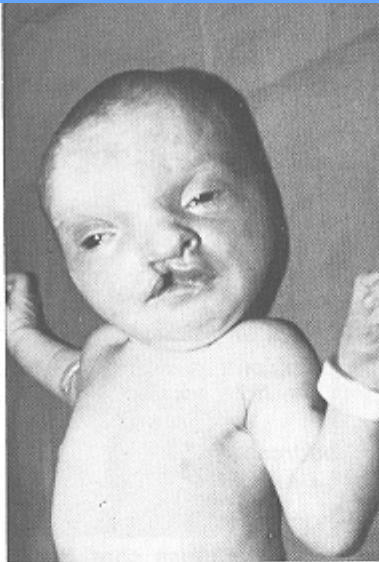
microcefalia

viso lunare

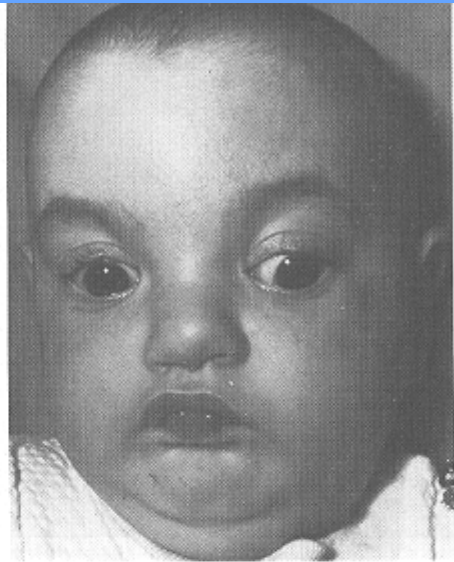
ipertelorismo



4.1

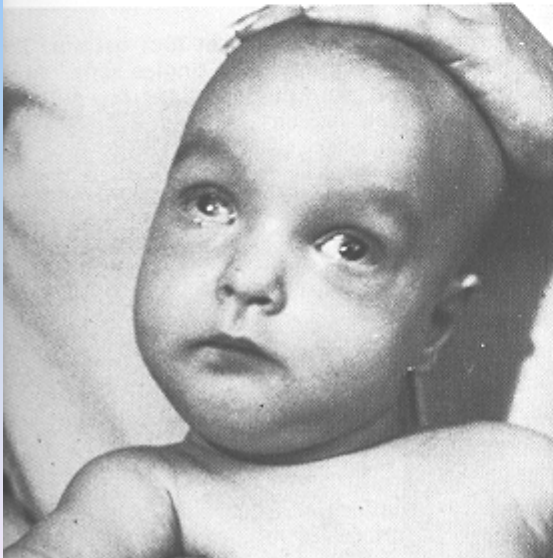


4.2

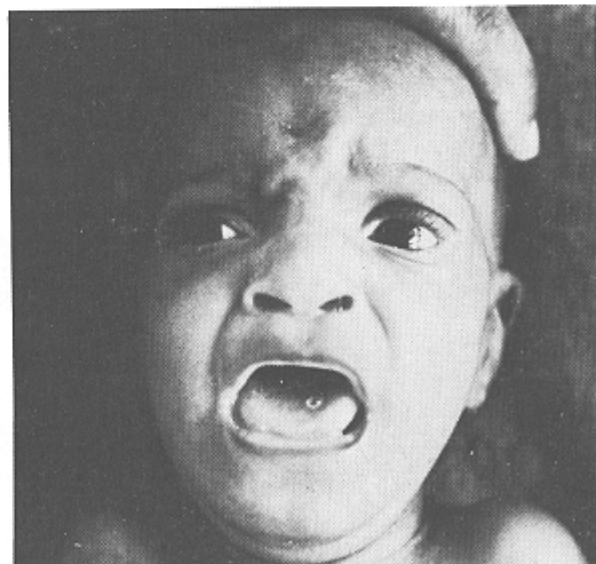


4.3

4.4



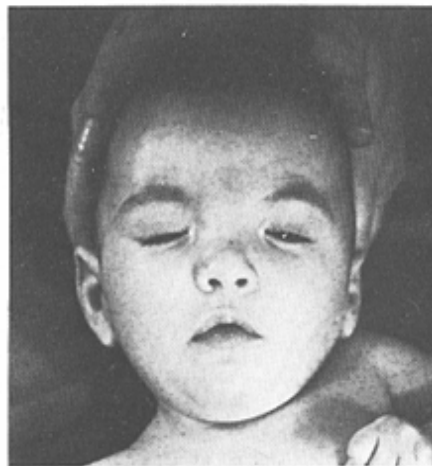
4.5



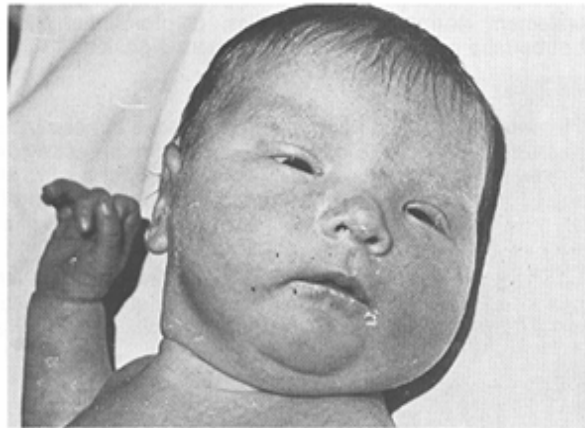


5.1

5.2



5.3



5.4



Fig. 5.1, 5.2, 5.3 et 5.4
Collection personnelle.

Clinical and molecular characterisation of 80 patients with 5p deletion: genotype-phenotype correlation

P Cerruti Mainardi, C Perfumo, A Cali, G Coucourde, G Pastore, S Cavani, F Zara, J Overhauser, M Pierluigi, F Dagna Bricarelli

Abstract

The majority of deletions of the short arm of chromosome 5 are associated with cri du chat syndrome (CdCS) and patients show phenotypic and cytogenetic variability. To perform a genotype-phenotype correlation, 80 patients from the Italian CdCS Register were analysed. Molecular cytogenetic analysis showed that 62 patients (77.50%) had a 5p terminal deletion characterised by breakpoint intervals ranging from p13 (D5S763) to p15.2 (D5S18). Seven patients (8.75%) had a 5p interstitial deletion, four (5%) a de novo translocation, and three (3.75%) a familial translocation. Of the remaining four patients, three (3.75%) had de novo 5p anomalies involving two rearranged cell lines and one (1.25%) had a 5p deletion originating from a paternal inversion. The origin of the deleted chromosome 5 was paternal in 55 out of 61 patients (90.2%). Genotype-phenotype correlation in 62 patients with terminal deletions highlighted a progressive severity of clinical manifestation and psychomotor retardation related to the size of the deletion. The analysis of seven patients with interstitial deletions and one with a small terminal deletion confirmed the existence of two critical regions, one for dysmorphism and mental retardation in p15.2 and the other for the cat cry in p15.3. Results from one patient permitted the cat cry region to be distally narrowed from D5S13 to D5S731. Furthermore, this study lends support to the hypothesis of a separate region in p15.3 for the speech delay.

(J Med Genet 2001;38:151-158)

CdCS has an estimated incidence of between 1:15 000 and 1:50 000 live births.^{7 11} Among the mentally retarded population, the prevalence may be as high as 1:350.⁷ Most CdCS patients have a de novo deletion (about 80%), parental translocations account for slightly more than 10%, and rare cytogenetic aberrations cause less than 10%.⁷ Parent of origin studies show a majority of paternally derived deletions: 20/25¹² and 10/12.¹³

Although CdCS is a well defined clinical entity, subjects with 5p deletion show phenotypic and cytogenetic variability. The existence of a critical region responsible for the CdCS phenotype was suggested from the karyotype analysis of 35 Danish patients with 5p deletion, indicating that a region in 5p15.2-15.3 must be deleted for the typical phenotype of the syndrome to be present.^{7 14} This hypothesis was supported by the identification of subjects with deletions not encompassing 5p15.2 and who either did not display the classical CdCS phenotype¹⁵⁻¹⁸ or were completely normal.¹⁹ Recent molecular cytogenetic analyses^{2 20} have led to the definition of two distinct regions, one for the cat-like cry in 5p15.3 between loci D5S13 and D5S760 and the other for dysmorphism, microcephaly, and mental retardation in 5p15.2 between loci D5S23 and D5S791 (CdCCR). The semaphorin F (*SEMAF*) gene, covering at least 10% of this region, was recently cloned.²¹ Because of its role in guiding axons or migrating neuronal precursors during cortical development in mice, it has been suggested that *SEMAF* may be responsible for some of the features of CdCS.

Church *et al.*^{13 22} in studies involving patients with atypical CdCS features or no symptoms, mapped the cat-like cry to the proximal part of 5p15.3 and to the distal region of 5p15.2. Two

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Genova, Italy

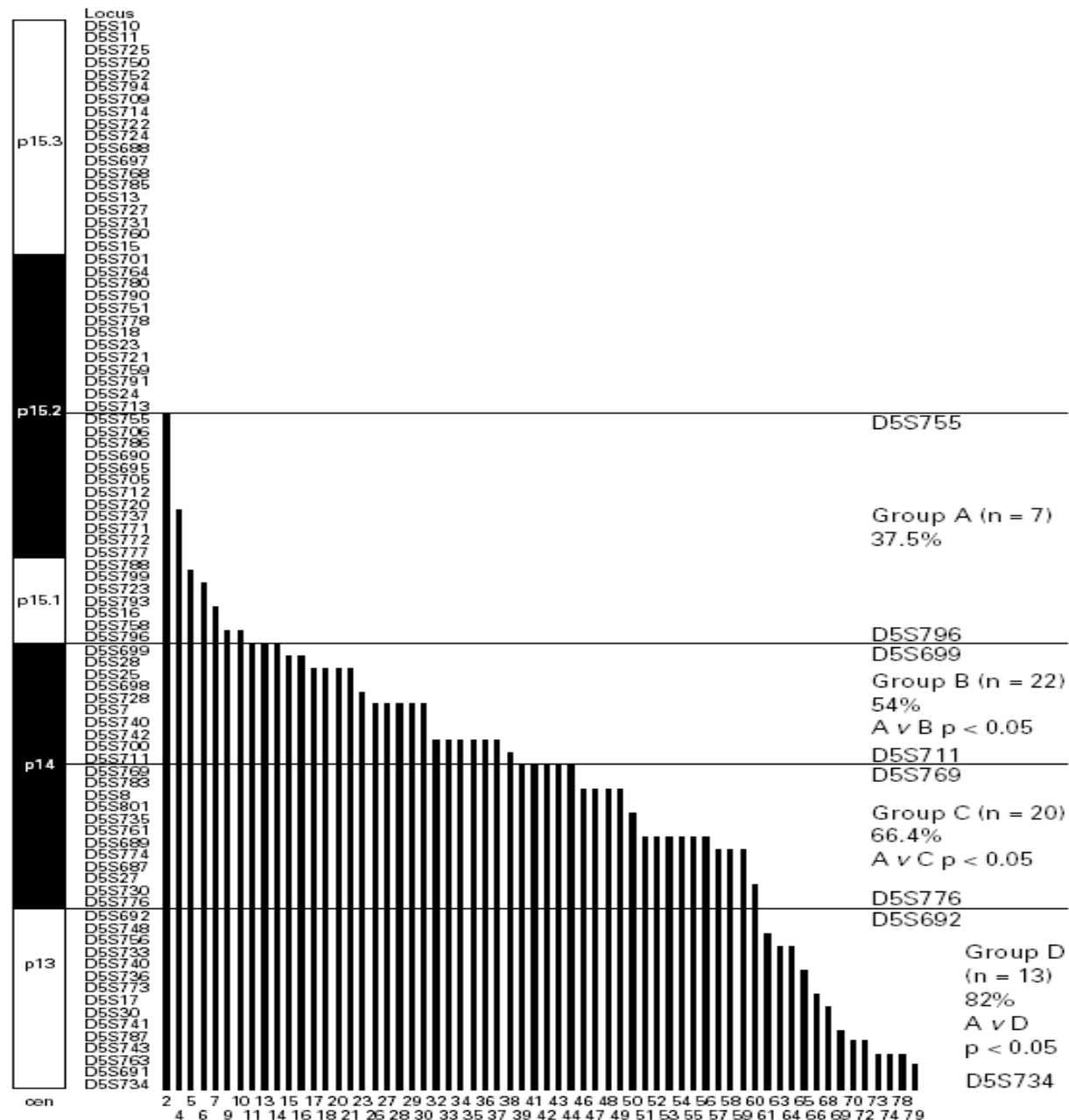


Figure 1 Molecular analysis of 62 patients with 5p terminal deletions. Black bars represent the deleted chromosome 5 of each patient. On the left is a diagram of chromosome 5p and the matching phage probes. Patients were subdivided into four groups according to the deletion size (A, B, C, D). The percentages refer to the frequency of dysmorphism in the patients of different groups (χ^2 for trend $p < 0.05$).

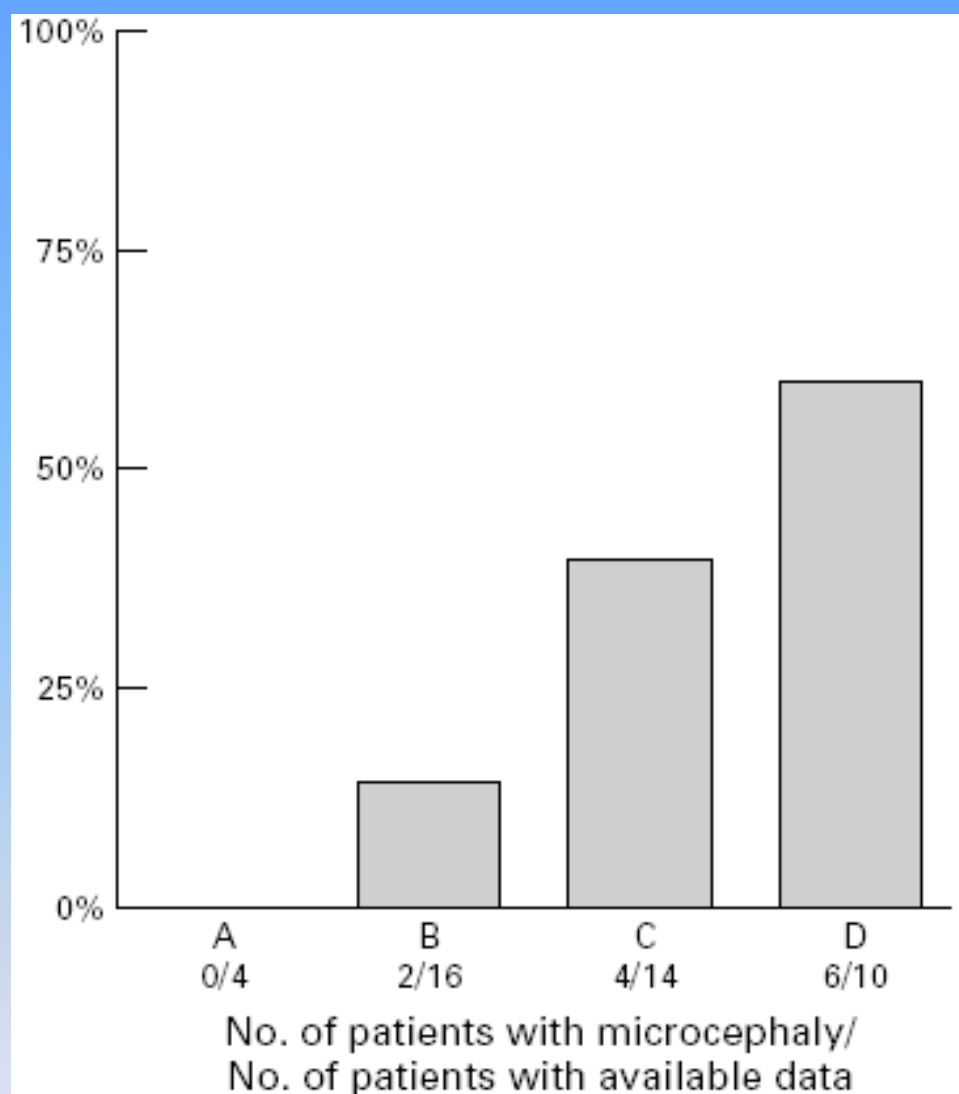


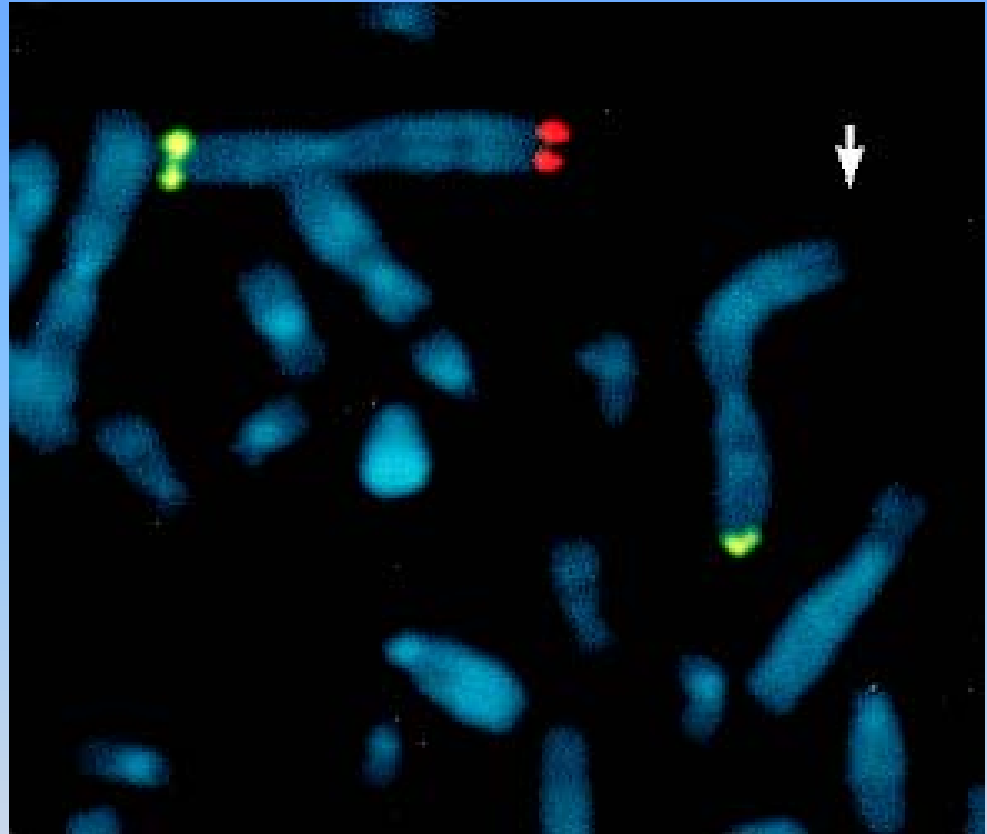
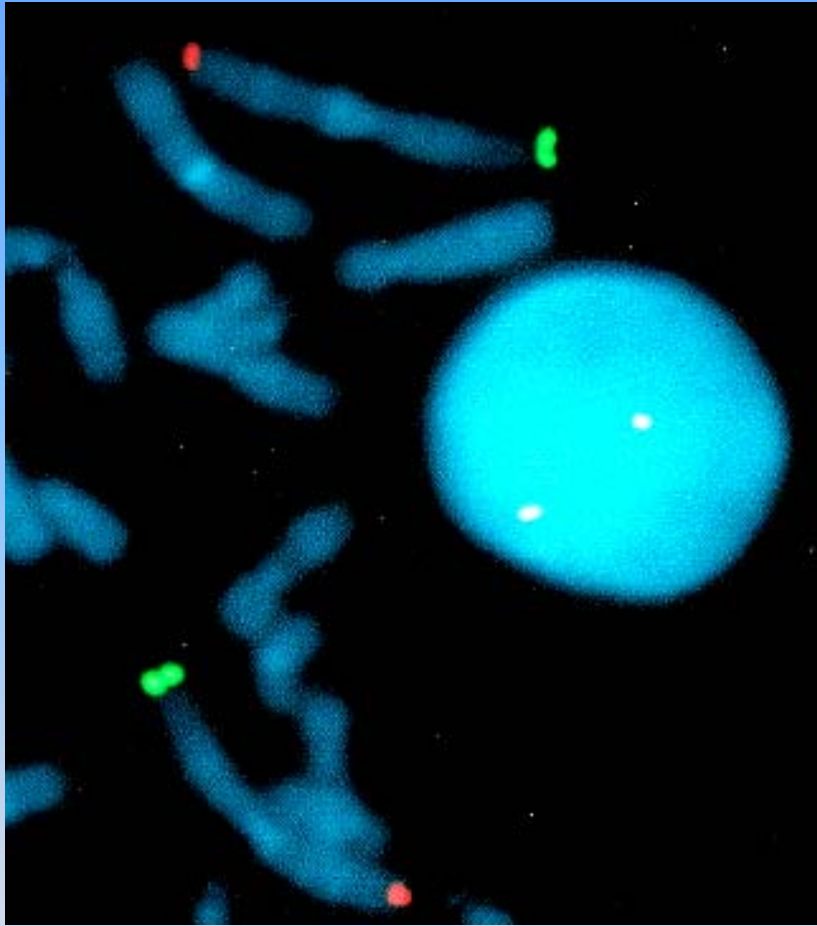
Figure 2 Distribution of microcephaly (head circumference <3rd centile) at birth in 44 patients with 5p terminal deletion (χ^2 for trend $p < 0.05$).

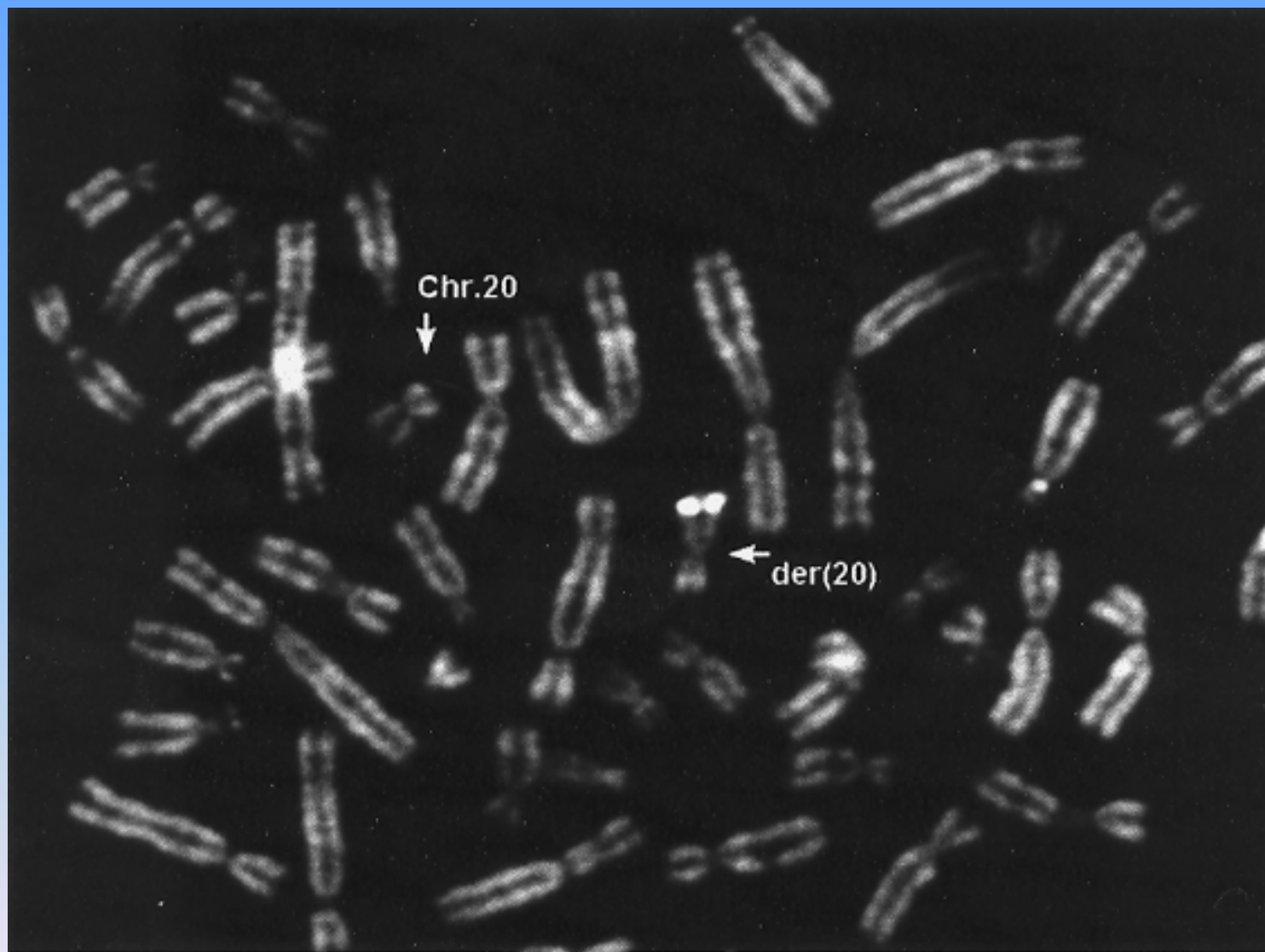
Deletion of the *Telomerase Reverse Transcriptase* Gene and Haploinsufficiency of Telomere Maintenance in Cri du Chat Syndrome

Anju Zhang,^{1,*} Chengyun Zheng,^{2,5,*} Mi Hou,^{2,*} Charlotta Lindvall,^{3,*} Ke-Jun Li,⁴ Fredrik Erlandsson,¹ Magnus Björkholm,² Astrid Gruber,² Elisabeth Blennow,³ and Dawei Xu²

¹Department of Pathology and Oncology, ²Department of Medicine, Division of Hematology, ³Department of Molecular Medicine, and ⁴Department of Biosciences at Novum, Karolinska Institutet and Hospital, Stockholm; and ⁵Shaanxi Provincial Hospital, Xian, China

Cri du chat syndrome (CdCS) results from loss of the distal portion of chromosome 5p, where the *telomerase reverse transcriptase* (*hTERT*) gene is localized (5p15.33). *hTERT* is the rate-limiting component for telomerase activity that is essential for telomere-length maintenance and sustained cell proliferation. Here, we show that a concomitant deletion of the *hTERT* allele occurs in all 10 patients with CdCS whom we examined. Induction of *hTERT* mRNA in proliferating lymphocytes derived from five of seven patients was lower than that in unaffected control individuals ($P < .05$). The patient lymphocytes exhibited shorter telomeres than age-matched unaffected individuals ($P < .0001$). A reduction in replicative life span and a high rate of chromosome fusions were observed in cultured patient fibroblasts. Reconstitution of telomerase activity by ectopic expression of *hTERT* extended the telomere length, increased the population doublings, and prevented the end-to-end fusion of chromosomes. We conclude that *hTERT* is limiting and haploinsufficient for telomere maintenance in humans in vivo. Accordingly, the *hTERT* deletion may be one genetic element contributing to the phenotypic changes in CdCS.

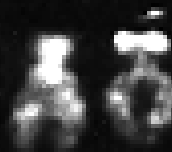
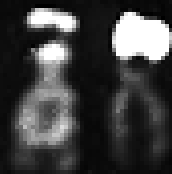




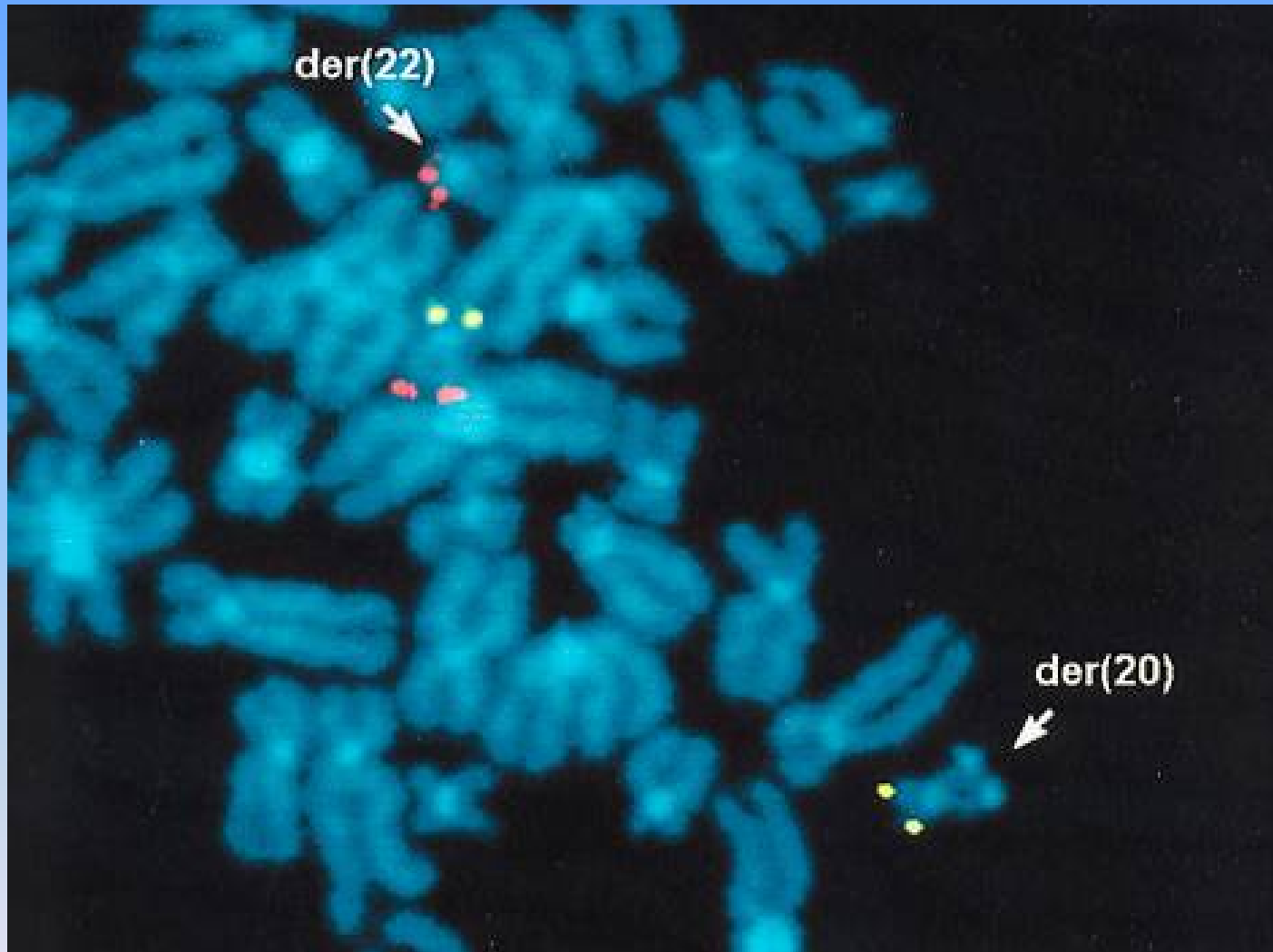
7 V2C4 46.XX.der(20) stampa OFO

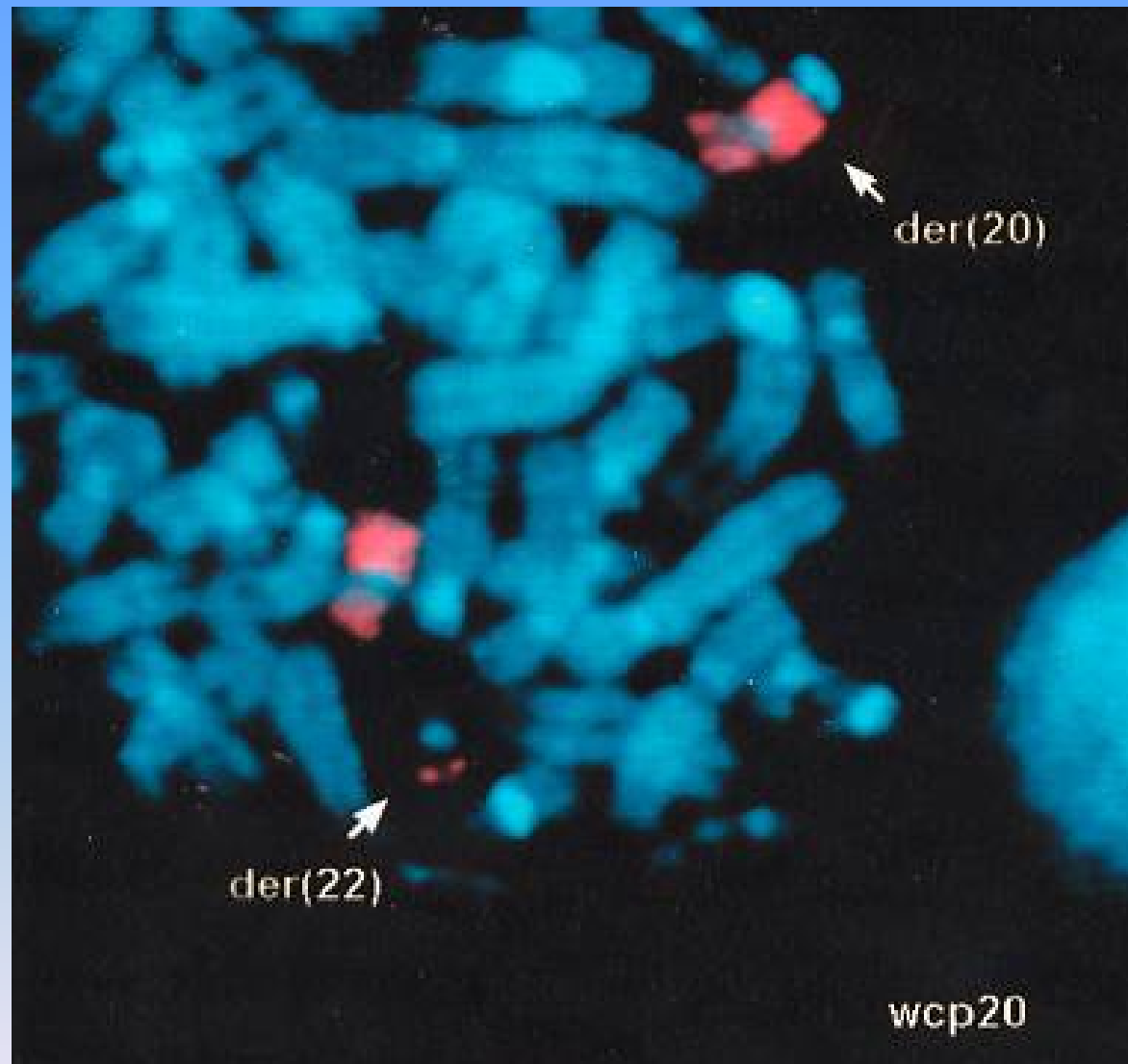
Father

Mother



Fetus





se si rompe un gene espresso

se si rompe un gene espresso

può essere persa la funzione della proteina corrispondente

se si rompe un gene espresso

può essere persa la funzione della proteina corrispondente

può essere prodotta una proteina tronca

se si rompe un gene espresso

può essere persa la funzione della proteina corrispondente

può essere prodotta una proteina tronca

**può formarsi un nuovo gene che produce una proteina nuova
(gene di fusione)**

se si rompe un gene espresso

può essere persa la funzione della proteina corrispondente

può essere prodotta una proteina tronca

**può formarsi un nuovo gene che produce una proteina nuova
(gene di fusione)**

può cambiare la sua regolazione

se si rompe un gene espresso

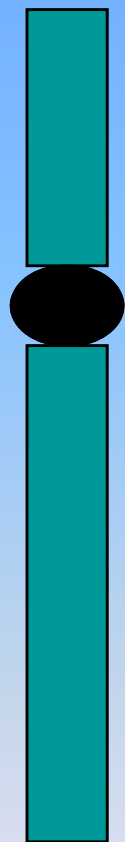
può essere persa la funzione della proteina corrispondente

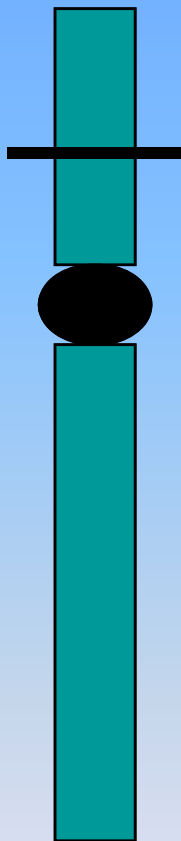
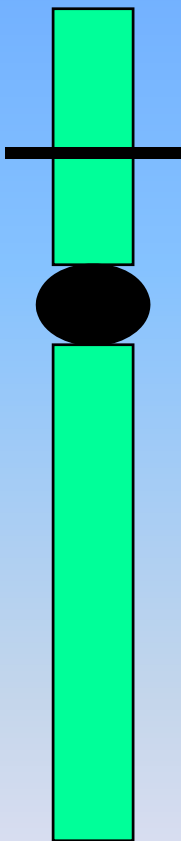
può essere prodotta una proteina tronca

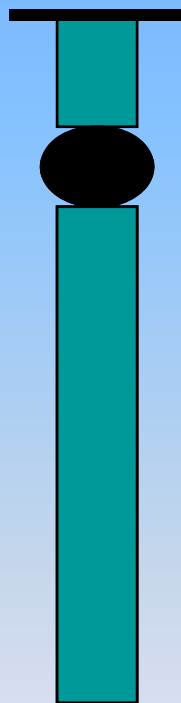
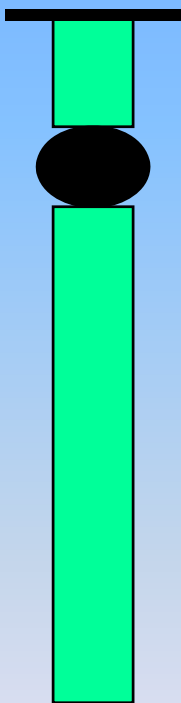
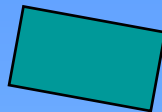
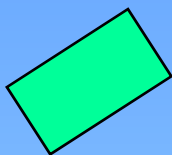
**può formarsi un nuovo gene che produce una proteina nuova
(gene di fusione)**

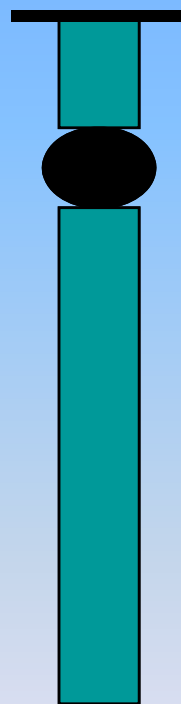
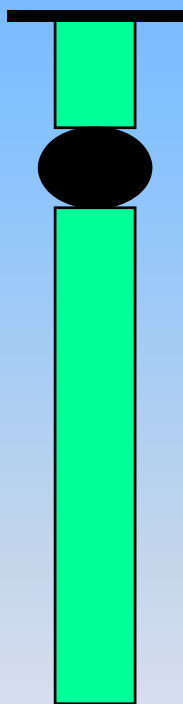
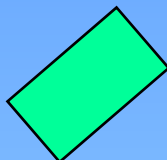
può cambiare la sua regolazione

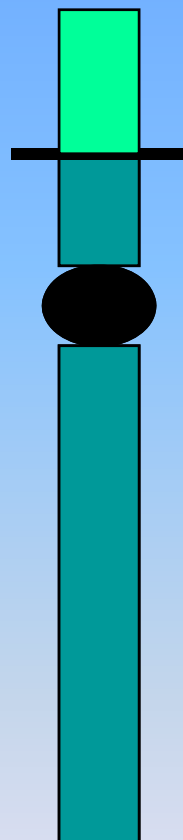
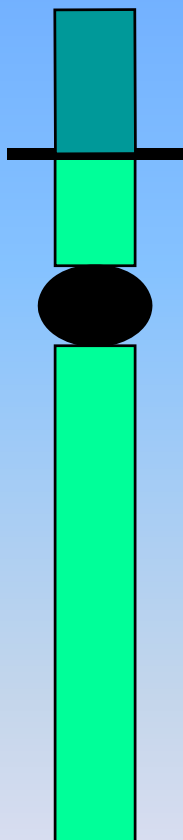
possono cambiare gli eventi post-trascrizionali









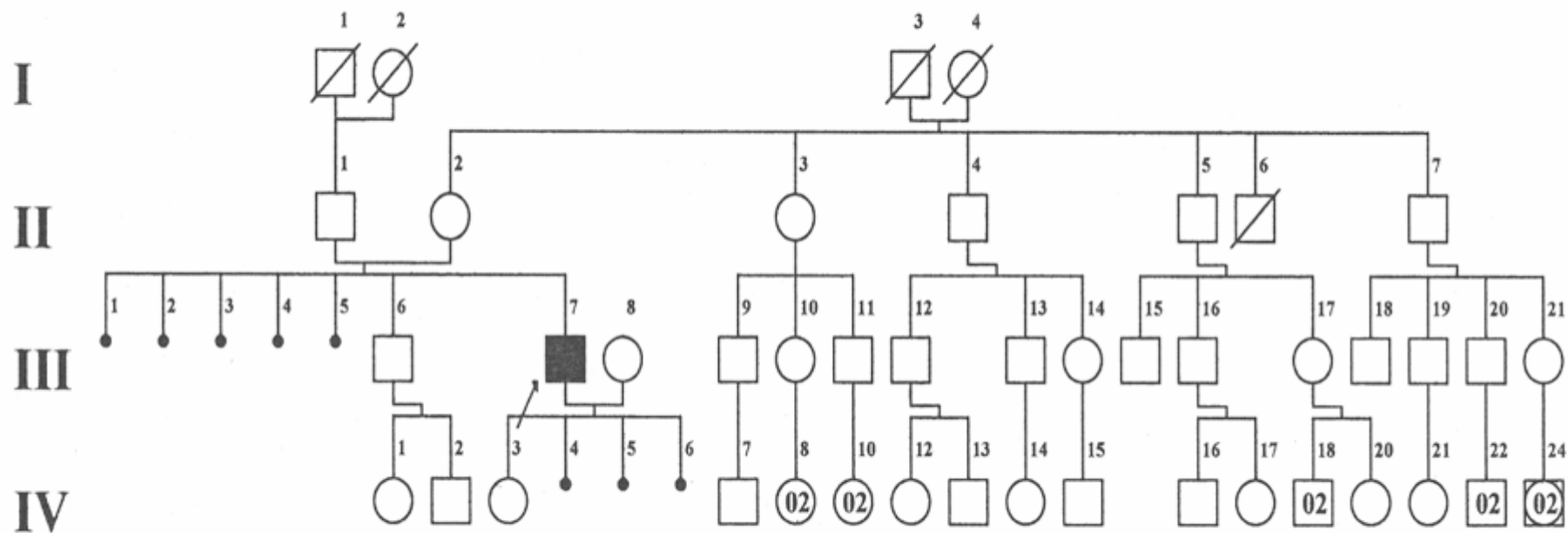


traslocazione reciproca

può anche non succedere nulla a livello fenotipico

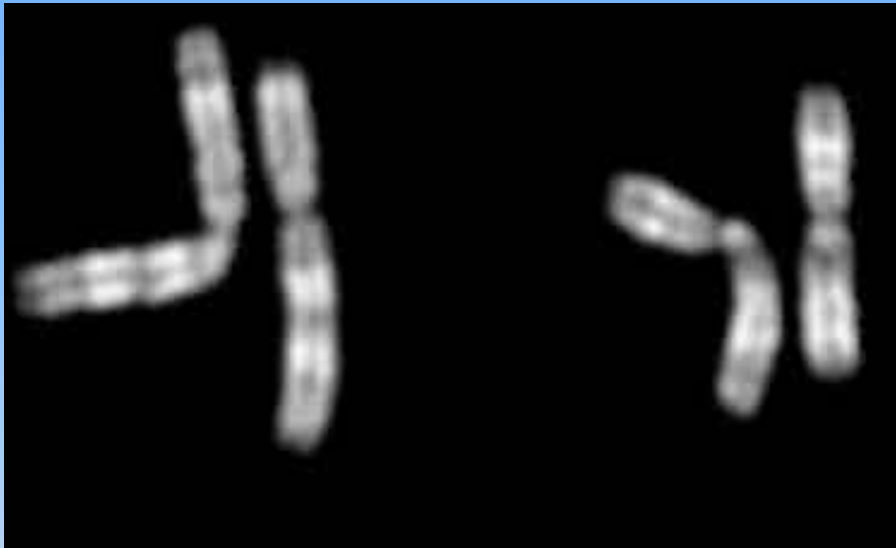
**ma si possono osservare problemi riproduttivi per
il soggetto portatore bilanciato**

CASO N.10



7 nor

11 nor

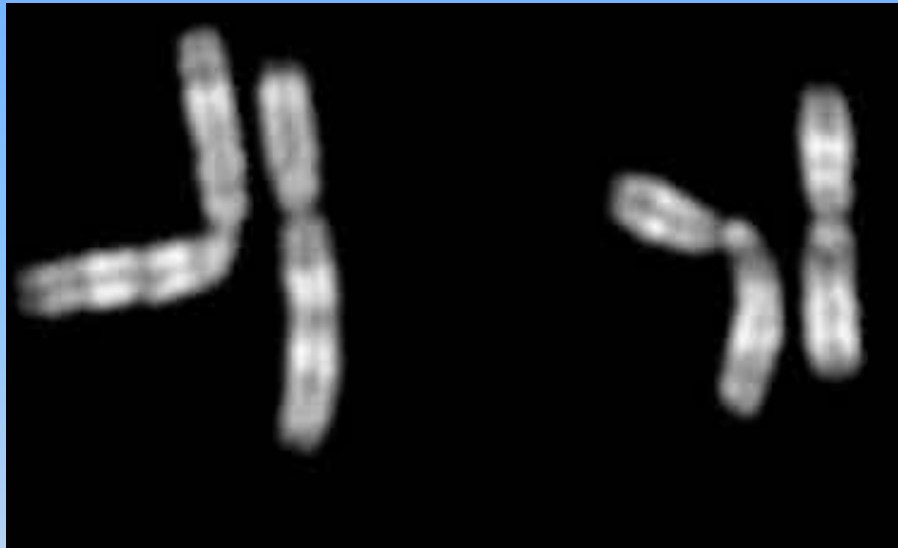


der 7

der 11

7 nor

11 nor



der 7

der 11

7 nor 11 nor



der 7

der 11

Pachytene diagram
t(7;11)(p22;q23)

7

der 11



der 7

11

**Pachytene diagram
t(7;11)(p22;q23)**

7

der 11



der 7

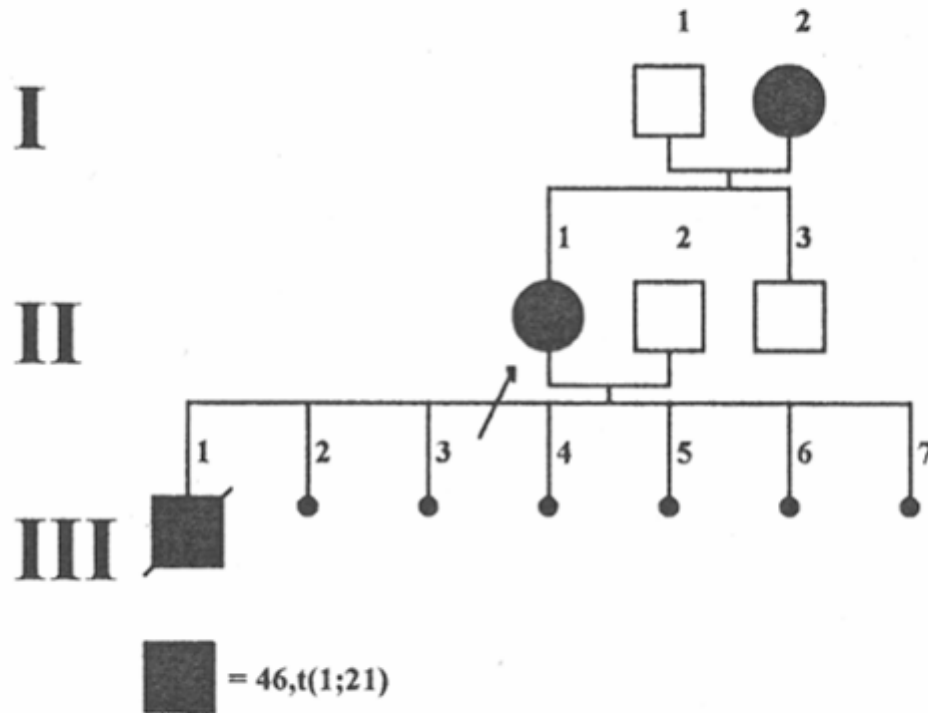
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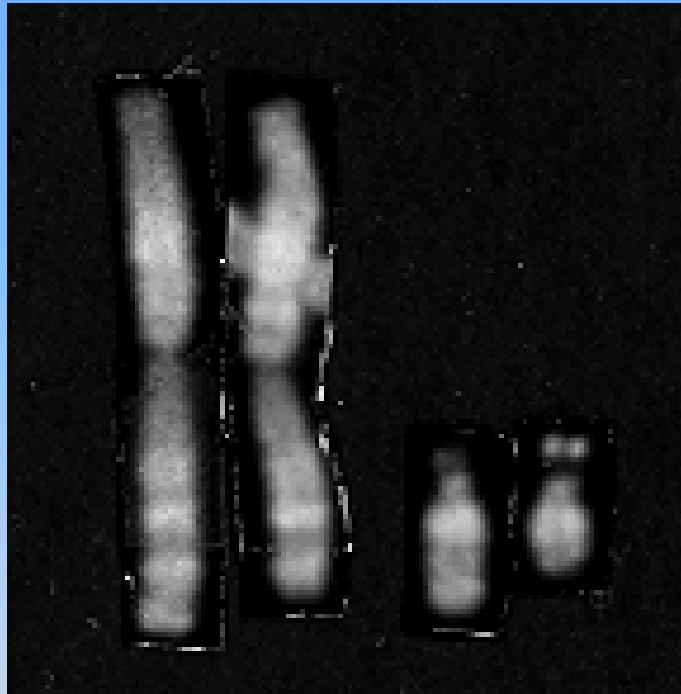
- Short report -

t(7;11)(p22;q23)

- The risk (with a confidence interval of 95 %) of the occurrence of a child who is a carrier of a polymalformation mental retardation syndrome is :
 - **29.28% [24.39-34.69]** if the translocation is of paternal origin.
 - **30.60% [25.95-35.68]** if the translocation is of maternal origin.
- Of the 12 theoretically possible imbalances :
 - 4 are potentially viable and any has been observed at birth.
 - 2 are potentially viable in accordance with the mode **adjacent 1** , the most probable imbalance mode and any has been observed at birth.

CASO N.31





1 nor; der1; der 21; 21 nor

Pachytene diagram
t(1;21)(q42;q22)

1 der 21



der 1 21

Close >>

Pachytene diagram
t(1;21)(q42;q22)

1 der 21



der 1

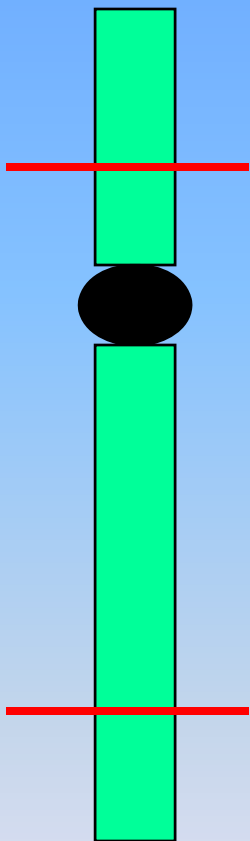
21

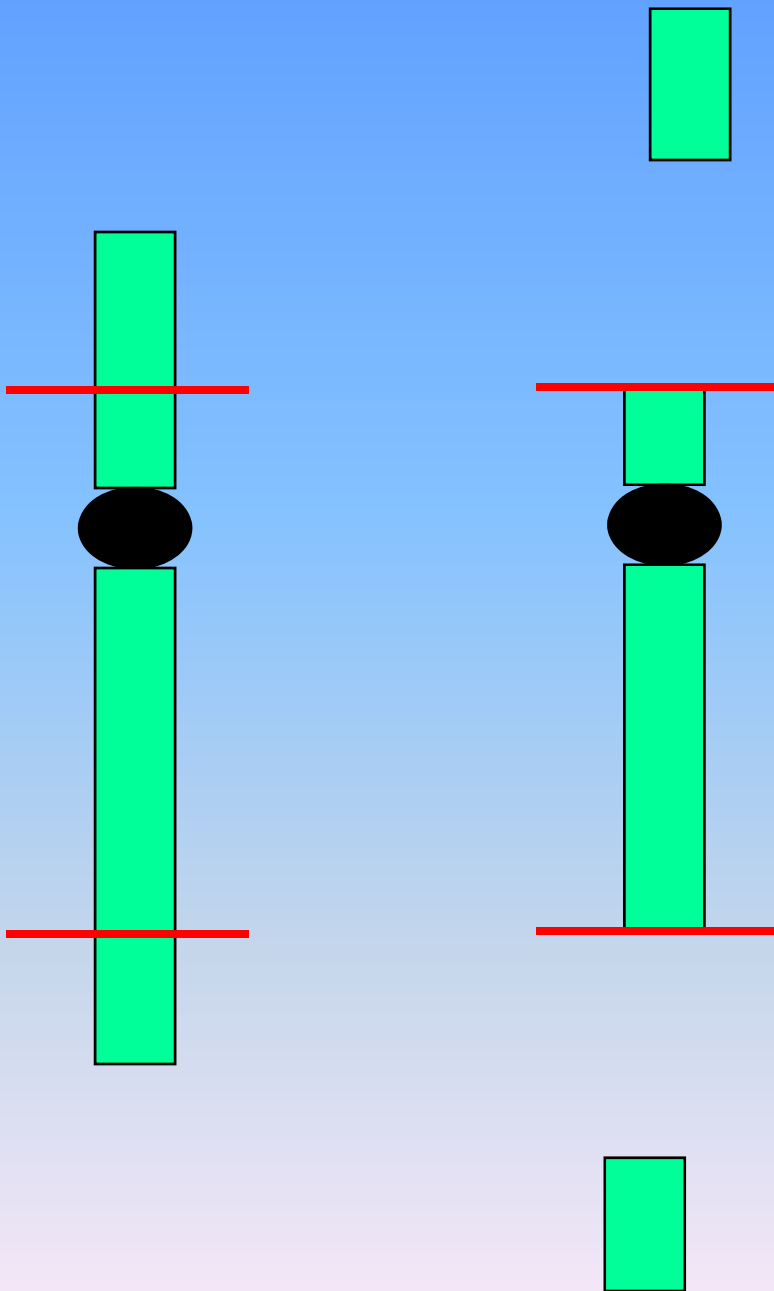
Close >>

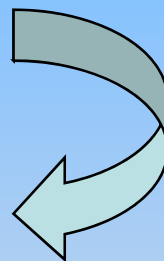
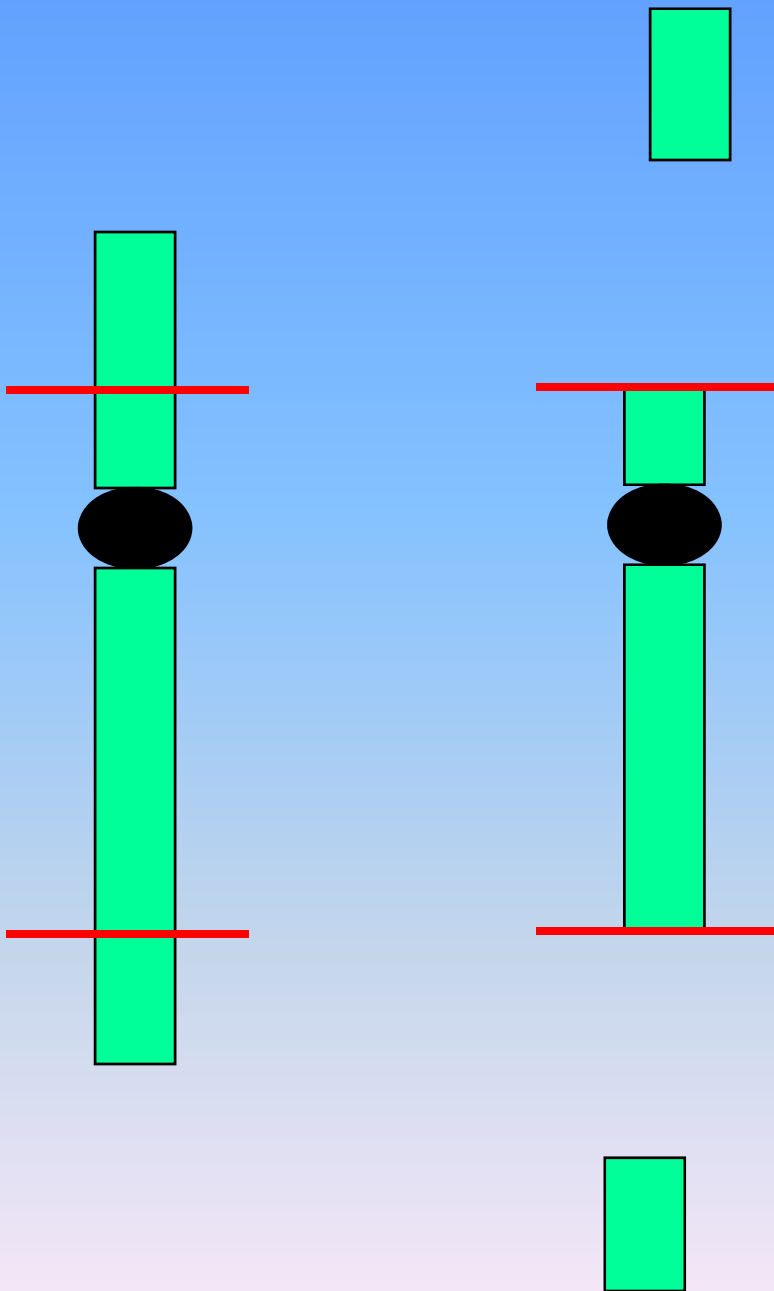
- Short report -

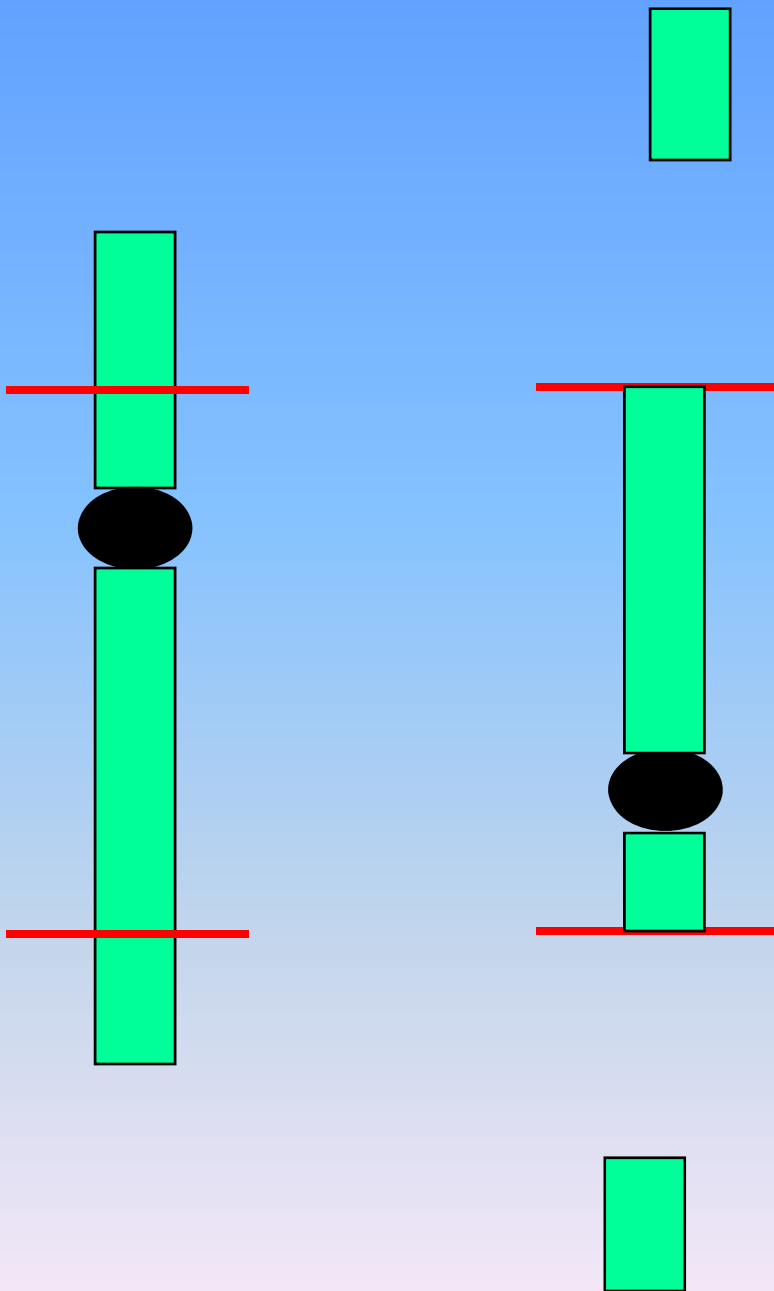
t(1;21)(q42;q22)

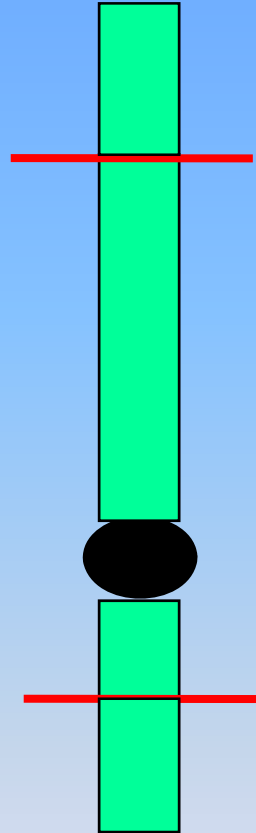
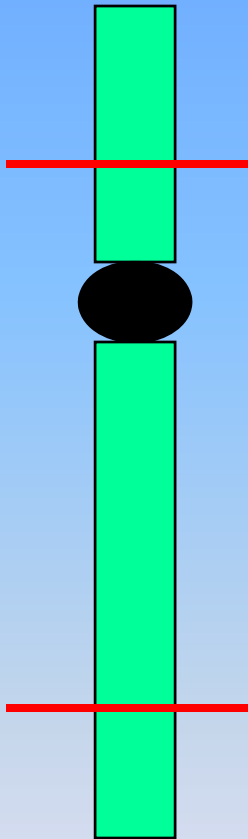
- The risk (with a confidence interval of 95 %) of the occurrence of a child who is a carrier of a polymalformation mental retardation syndrome is :
 - **25.97% [19.99-33.00]** if the translocation is of paternal origin.
 - **43.02% [36.64-49.65]** if the translocation is of maternal origin.
- Of the 12 theoretically possible imbalances :
 - 6 are potentially viable and 1 has already been observed at birth.
 - 2 are potentially viable in accordance with the mode **adjacent 1**, the most probable imbalance mode and 1 has already been observed at birth.





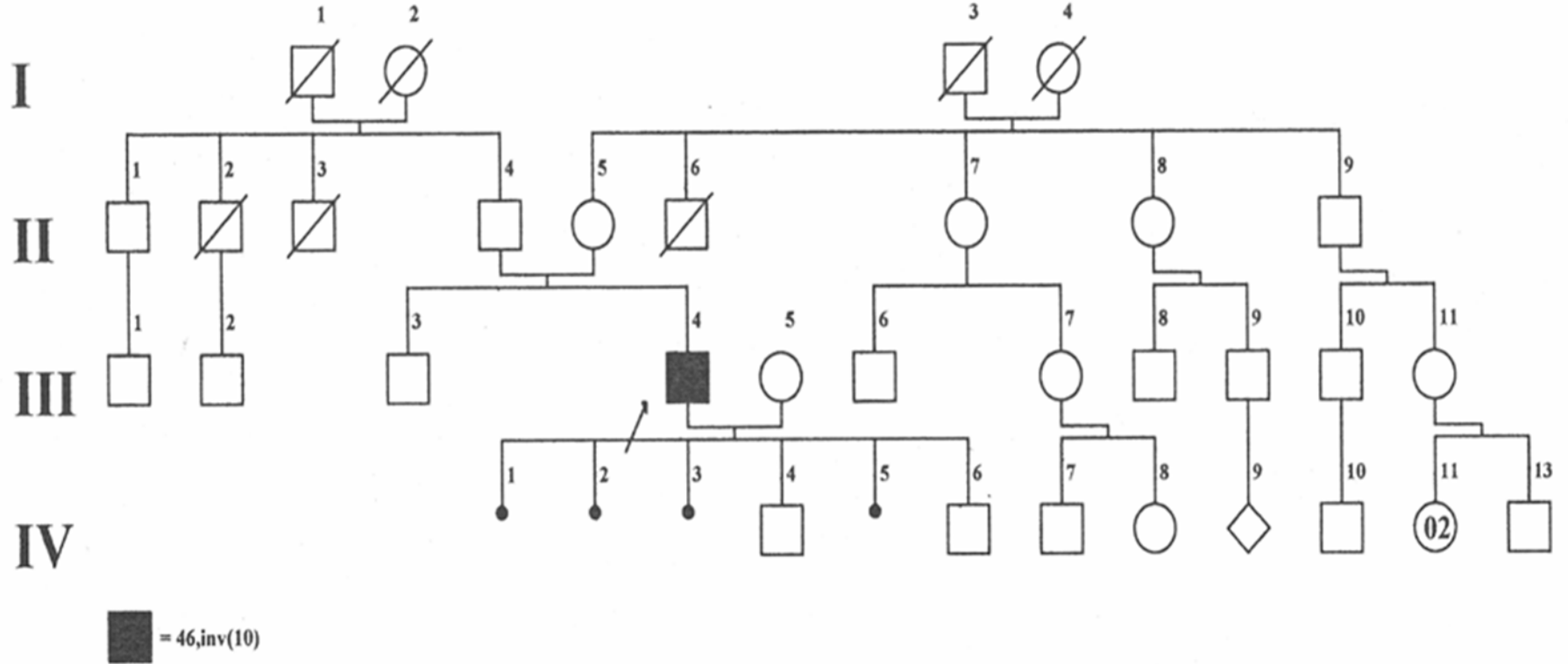


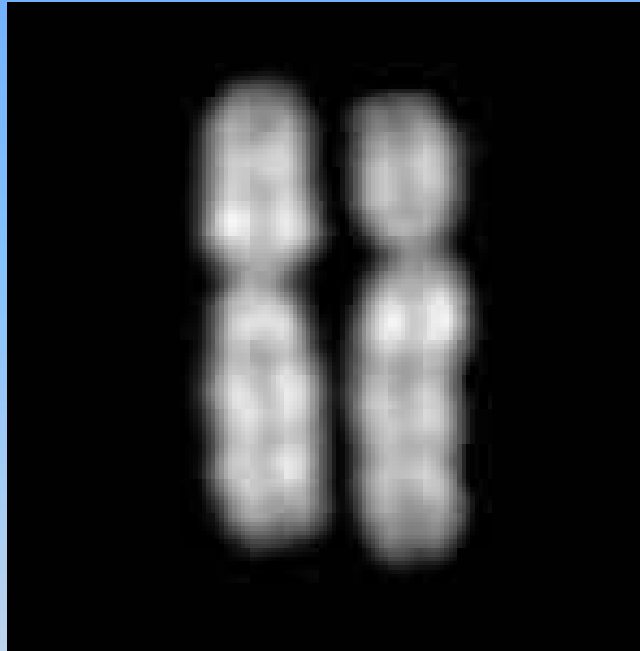




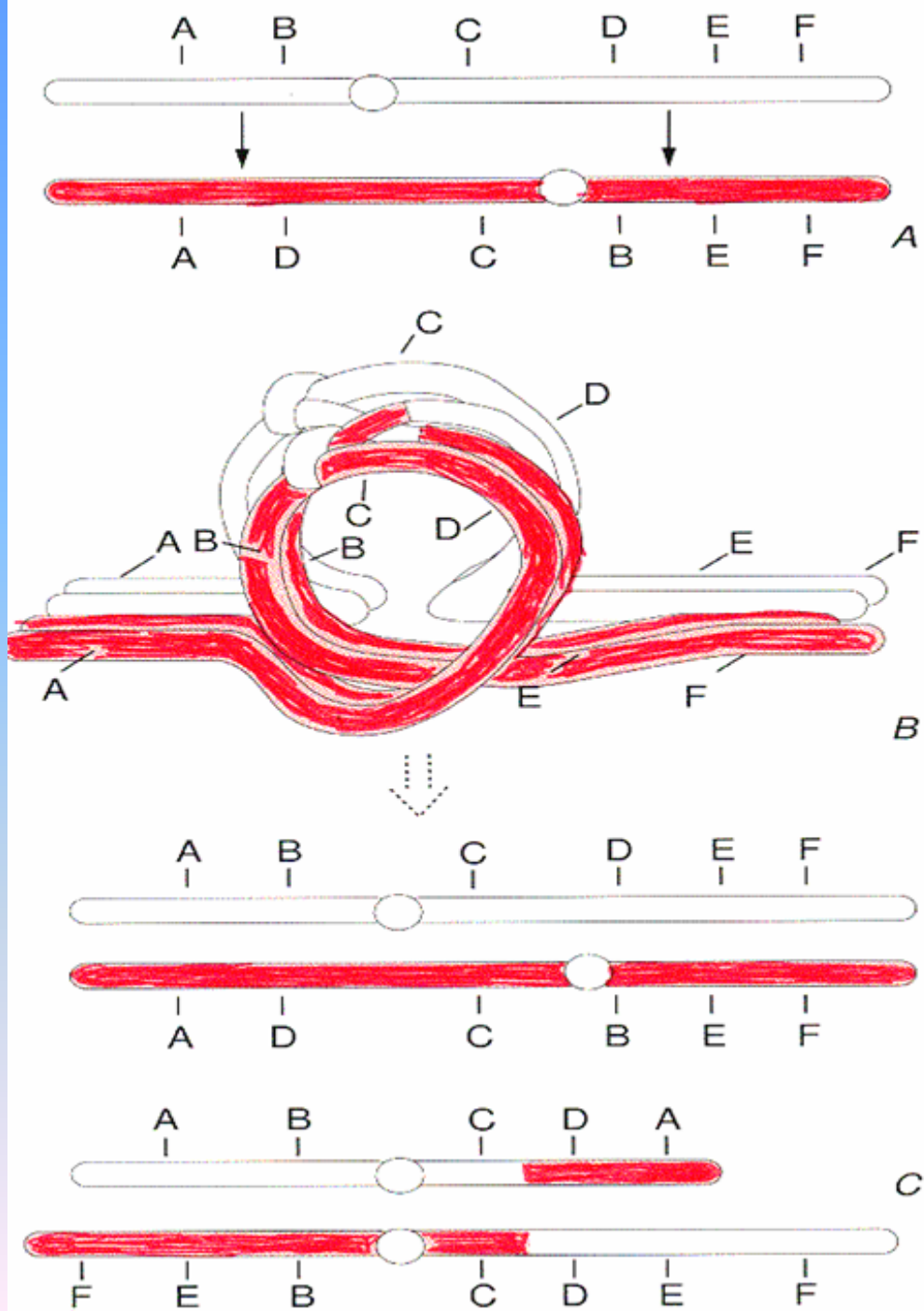
**inversione
pericentrica**

CASO N.9





inv(10) 10 nor



- Short report on pericentric inversion pericentric - inv(10)(p11.2q21)

• The risk of occurrence of a child who is a carrier of a polymalformation mental retardation syndrome associated to this inversion is :

- **1.95%.**

• Of the 2 imbalances theoretically possible :

- only dupq is potentially viable

**le anomalie strutturali dei cromosomi bilanciate
influiscono sulla riproduzione causando**

- sterilità**
- aborto spontaneo ripetuto**
- feto o nato malformato**

**impossibilità o difficoltà quindi di raggiungere
l'obiettivo di “un bambino in braccio”**

se si rompe un gene espresso

può essere persa la funzione della proteina corrispondente

The Elastin Gene Is Disrupted by a Translocation Associated with Supravalvular Aortic Stenosis

Mark E. Curran,* Donald L. Atkinson,*
Amanda K. Ewart,* Colleen A. Morris,†
Mark F. Leppert,*‡ and Mark T. Keating*§1

*Department of Human Genetics

§Cardiology Division

‡Howard Hughes Medical Institute

IEccles Program in Human Molecular Biology
and Genetics

University of Utah

Salt Lake City, Utah 84112

†Department of Pediatrics

University of Nevada School of Medicine

Las Vegas, Nevada 89102

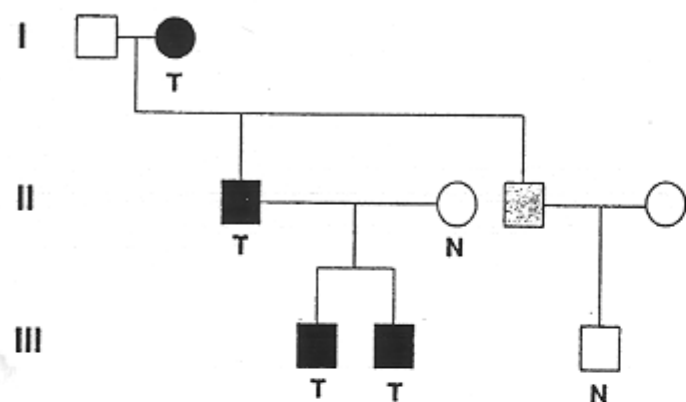
Summary

To identify genes involved in vascular disease, we investigated patients with supravalvular aortic stenosis (SVAS), an inherited vascular disorder that causes hemodynamically significant narrowing of large elastic arteries. Pulsed-field gel and Southern analyses showed that a translocation near the elastin gene cosegregated with SVAS in one family. DNA sequence analyses demonstrated that the translocation disrupted the elastin gene and localized the breakpoint to exon 28. Taken together with our previous study linking SVAS to the elastin gene in two additional families and existing knowledge of vascular biology, these data suggest that mutations in the elastin gene can cause SVAS.

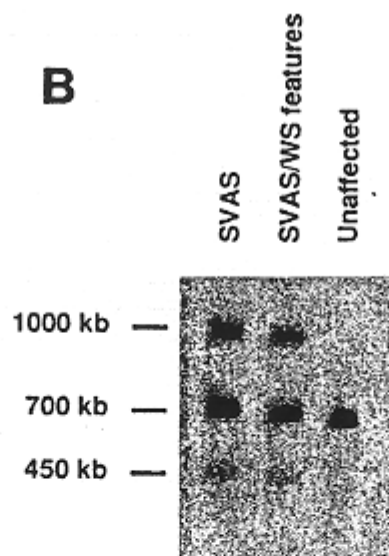
morphic facial features, hoarse voice, diverticulosis of the bladder and colon, and infantile hypercalcemia (Beuren, 1972; Morris et al., 1988). The pathogenic relationship between SVAS and Williams syndrome is uncertain.

The molecular basis of SVAS is unknown. The association between SVAS, Williams syndrome, and infantile hypercalcemia led to suggestions that mutations in genes responsible for calcium metabolism might cause this vascular disease, but to date no causal relationship has been found (Black and Carter, 1963; Jones and Smith, 1975; Ewart et al., 1993). Pathologic studies of patients affected by SVAS have shown hypertrophy and hyperplasia of smooth muscle cells in affected vessels (Perou, 1961; O'Connor et al., 1985). These studies also demonstrated reduced ground substance, increased collagen, and disruption of the normal pattern of smooth muscle cells alternating with elastic fibers in diseased arteries. These studies, coupled with existing knowledge of vascular histology and physiology, have suggested a number of candidate genes for SVAS, including genes encoding growth factors or their receptors, second messengers, contractile proteins, connective tissue proteins, or proto-oncogenes. To test these hypotheses, we recently performed linkage analyses in two unrelated families with autosomal dominant SVAS (Ewart et al., 1993). After excluding several candidate genes, we identified linkage (multipoint lod score of 8.4) between the SVAS phenotype and polymorphic markers on the long arm of chromosome 7. Among the linked markers was a polymorphism within the elastin gene, previously mapped to 7q11 (Fazio et al., 1991; Tromp et al., 1992), which showed no recombination with the SVAS locus.

A K1861

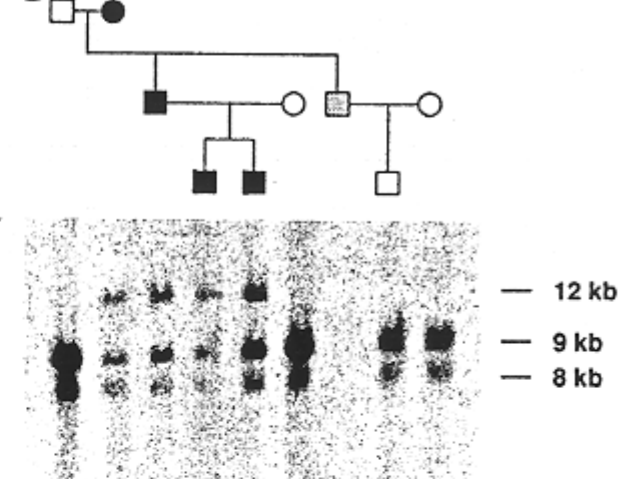


B



Probe: Elastin cDNA

C



Probe: N-2.8

Figure 1. Inheritance of Anomalous Restriction Fragments on Pulsed-Field Gel and Southern Filters Defined by Elastin Probes in DNA Isolated from SVAS K1861

(A) Pedigree structure for SVAS K1861. Individuals with the characteristic features of SVAS are indicated by closed circles (females) or closed squares (males). Open circles or squares indicate unaffected individuals. Individual II-3 was not available for examination and is shown as stippled. Individuals carrying a balanced t(6;7)(p21.1;q11.23) translocation are indicated by a T. Individuals not carrying the translocation are indicated by an N. Individual III-2 has SVAS and some features of the Williams syndrome. The translocation cosegregates with the disease phenotype in this family.

(B) Hybridization of a full-length elastin cDNA probe to NotI digests of DNA from SVAS patients II-1 (affected with SVAS) and III-2 (affected with SVAS and phenotypic features of Williams syndrome) reveals aberrant restriction fragments of 450 and 1000 kb. The 700 kb fragment is seen in both unaffected (individual I-1) and affected members of K1861 and represents the normal allele. The identification of two anomalous fragments and a normal fragment with elastin cDNA probes suggests that the elastin locus is disrupted by the translocation.

(C) Hybridization of a 2.8 kb elastin genomic probe (N-2.8) to BamHI digests of DNA from members of K1861 reveals 12 kb aberrant fragments in SVAS patients. Pedigree information is identical to (A). The probe N-2.8 also hybridizes with two BamHI fragments of 8 kb and 9 kb in both affected and unaffected individuals of K1861. These fragments represent the normal elastin allele. These observations confirm PFGE data and indicate that the SVAS-associated translocation disrupts sequences near the elastin locus.

Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 3226–3230, April 1993
Genetics

A human vascular disorder, supralvalvular aortic stenosis, maps to chromosome 7

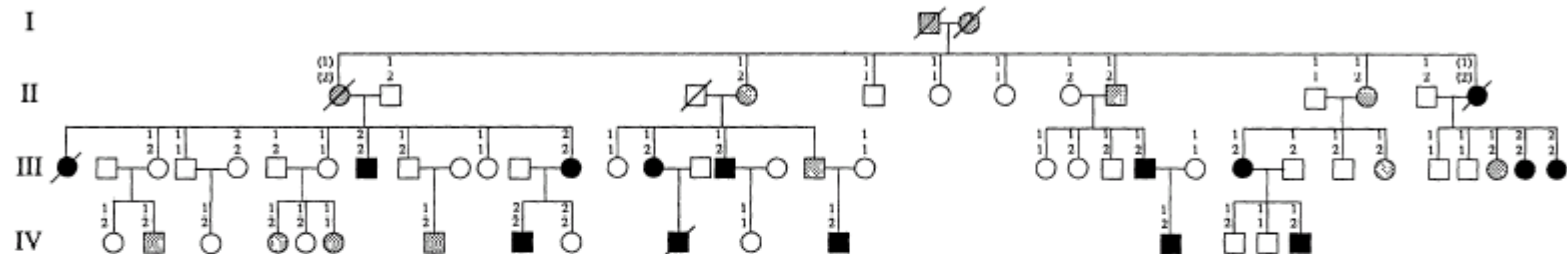
(linkage analysis/elastin/Williams syndrome)

AMANDA K. EWART*, COLLEEN A. MORRIS[†], GREGORY J. ENSING[‡], JAMES LOKER[‡], CYNTHIA MOORE[§],
MARK LEPPERT*[¶], AND MARK KEATING*^{||**}

*Department of Human Genetics, ^{||}Cardiology Division, [§]Howard Hughes Medical Institute, and ^{**}Eccles Program in Human Molecular Biology and Genetics, University of Utah, Salt Lake City, UT 84112; [†]Department of Pediatrics, University of Nevada School of Medicine, Las Vegas, NV 89102; and [‡]Department of Pediatrics, Division of Pediatric Cardiology, and [§]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN 46202

A

K1773



B

K1779

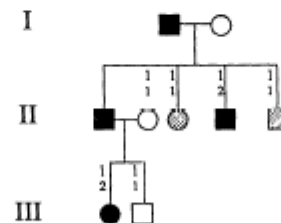


FIG. 1. Pedigree structure and *ELN* genotypes for SVAS families K1773 (A) and K1779 (B). Affected individuals having the characteristic pattern of elevated Doppler velocity and narrowing of the ascending aorta or pulmonary arteries on echocardiogram are represented by ● (females) and ■ (males). Unaffected individuals are represented by □ or ○. Family members who had an equivocal phenotype or for whom no phenotypic data were available are represented by ◻ and ◯. Above each symbol, individual alleles (1 or 2) are listed for the *ELN* polymorphic PCR marker (17). At this marker locus the restriction enzyme *Bst*NI revealed two alleles within the families. The disease gene cosegregated with the 244-bp allele (allele 2) in both families. Alleles shown in parentheses were inferred. The pedigree structures were altered to protect confidentiality.

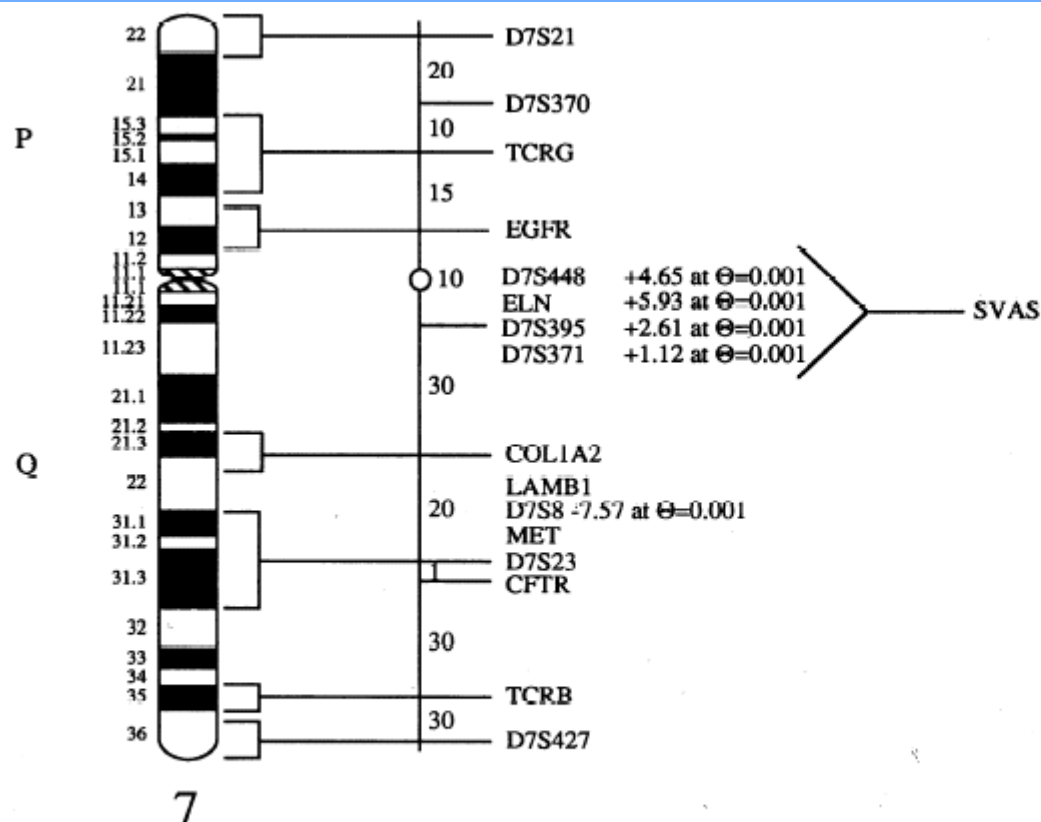


FIG. 2. Approximate map location of the SVAS disease gene. Genes and polymorphic loci mapped to chromosome 7 are shown at right. The approximate genetic distance between these loci in centimorgans is shown on the diagram at center (24). The approximate subsegmental location of these loci is shown on the idiogram at left. In K1773 and K1779, SVAS is linked to *D7S395*, *D7S371*, *D7S448*, and *ELN*, which are mapped approximately to 7q11 between the centromere and *COL1A2* (collagen). SVAS is not linked to *D7S8*, which is located adjacent to *LAMB1* (laminin B1). Pairwise lod scores between a DNA marker and the disease phenotype are indicated.

se si rompe un gene espresso

può essere persa la funzione della proteina corrispondente

**può formarsi un nuovo gene che produce una proteina nuova
(gene di fusione)**

Tabella 18.3: Geni chimerici prodotti mediante riarrangiamenti cromosomici specifici di certi tumori

Tumore	Riarrangiamento	Gene chimerico	Natura del prodotto chimerico
CML	t(9;22)(q34;q11)	<i>BCR-ABL</i>	Tirosino-chinasi
Sarcoma di Ewing	t(11;22)(q24;q12)	<i>EWS-FLI1</i>	Fattore di trascrizione
Sarcoma di Ewing (variante)	t(21;22)(q22;q12)	<i>EWS-ERG</i>	Fattore di trascrizione
Melanoma maligno dei tessuti molli	t(12;22)(q13;q12)	<i>EWS-ATF1</i>	Fattore di trascrizione
Tumore desmoplastico a piccole cellule rotonde	t(11;22)(p13;q12)	<i>EWS-WT1</i>	Fattore di trascrizione
Liposarcoma	t(12;16)(q13;p11)	<i>FUS-CHOP</i>	Fattore di trascrizione
AML	t(16;21)(p11;q22)	<i>FUS-ERG</i>	Fattore di trascrizione
Carcinoma papillare della tiroide	inv(1)(q21;q31)	<i>NTRK1-TPM3</i> (oncogene <i>TRK</i>)	Tirosino-chinasi
ALL a cellule pre-B	t(1;19)(q23;p13.3)	<i>E2A-PBX1</i>	Fattore di trascrizione
ALL	t(X;11)(q13;q23)	<i>MLL-AFX1</i>	Fattore di trascrizione
ALL	t(4;11)(q21;q23)	<i>MLL-AF4</i>	Fattore di trascrizione
ALL	t(9;11)(q21;q23)	<i>MLL-AF9</i>	Fattore di trascrizione
ALL	t(11;19)(q23;p13)	<i>MLL-ENL</i>	Fattore di trascrizione
Leucemia acuta promielocitica	t(15;17)(q22;q12)	<i>PML-RRA</i>	Fattore di trascrizione + recettore dell'acido retinoico
Rabdomiosarcoma alveolare	t(2;13)(q35;q14)	<i>PAX3-FKHR</i>	Fattore di trascrizione

Si noti come lo stesso gene possa essere coinvolto in vari riarrangiamenti differenti. Per ulteriori dettagli si veda Rabbitts (1994). CML, leucemia mieloide cronica; ALL, leucemia linfoblastoide acuta.

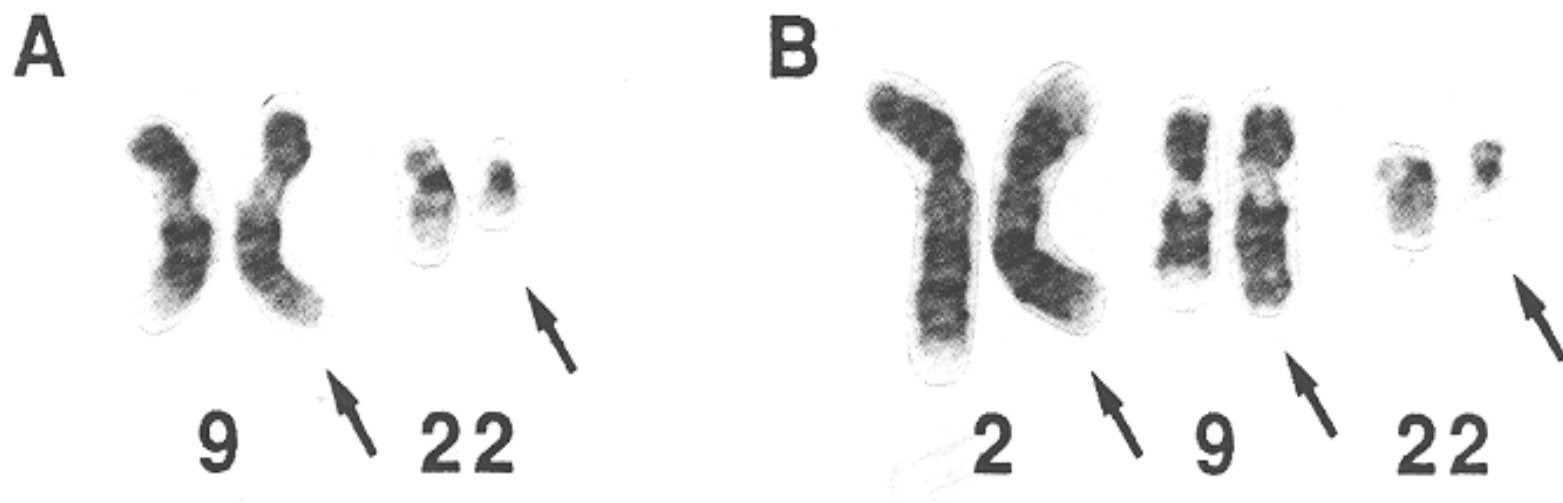
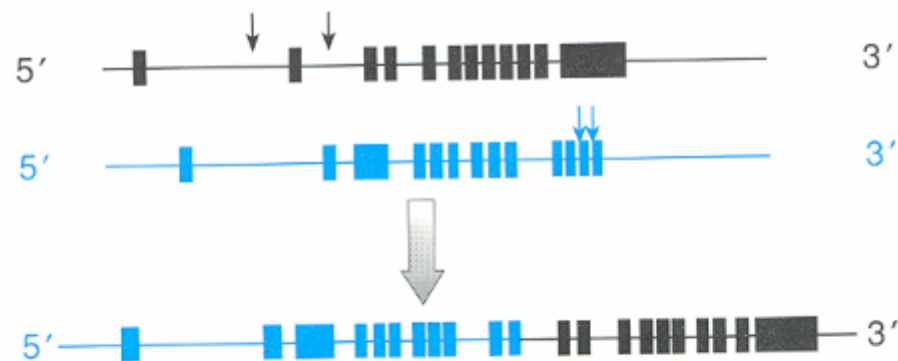
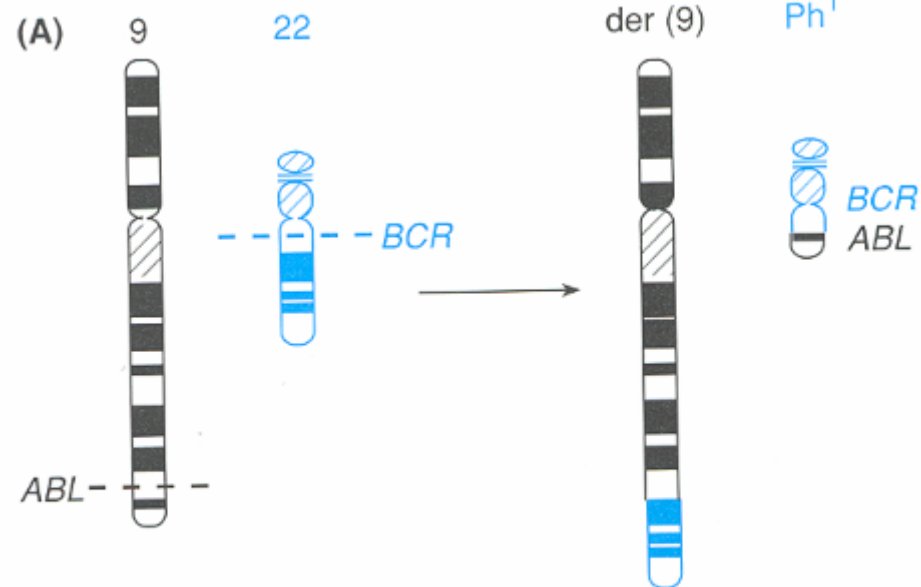


FIG. 2. Partial karyotypes of trypsin-Giemsa-banded metaphase cells obtained from bone marrow aspirates of two CML patients. **(A)** $t(9;22)(q34;q11)$. The der(9) and der(22) chromosomes are identified with arrowheads. **(B)** Variant Ph^1 translocation. Three-way translocation involving chromosomes 2, 9, and 22 $t(2;9;22)(p23;q34;q11)$. Chromosomal material from the short arm of chromosome 2 is translocated to chromosome 9, the long arm of chromosome 9 is translocated to 22q, and material from 22q is present on 2p. The rearranged chromosomes are identified with arrows.



Gene di fusione

mRNA di BCR/ABL lungo 8,5 kb

Proteina di fusione p210
(tirosina-chinasi costitutivamente attiva)

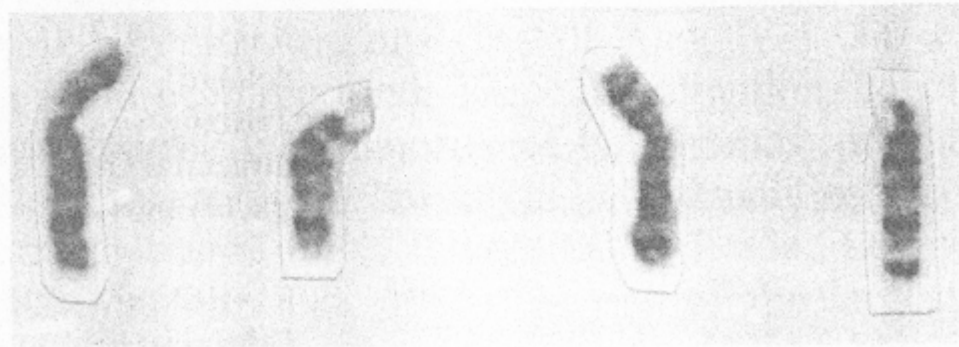
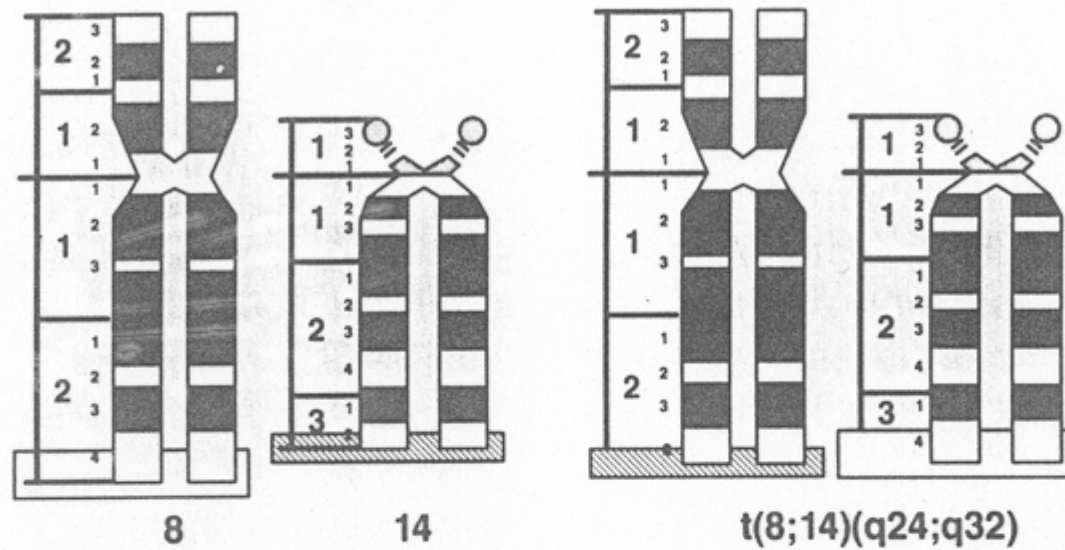


Fig. 1. $t(8;14)(q24;q32)$ is found in three-fourths of all Burkitt's lymphoma patients.

Anomalie di struttura a meccanismo non noto

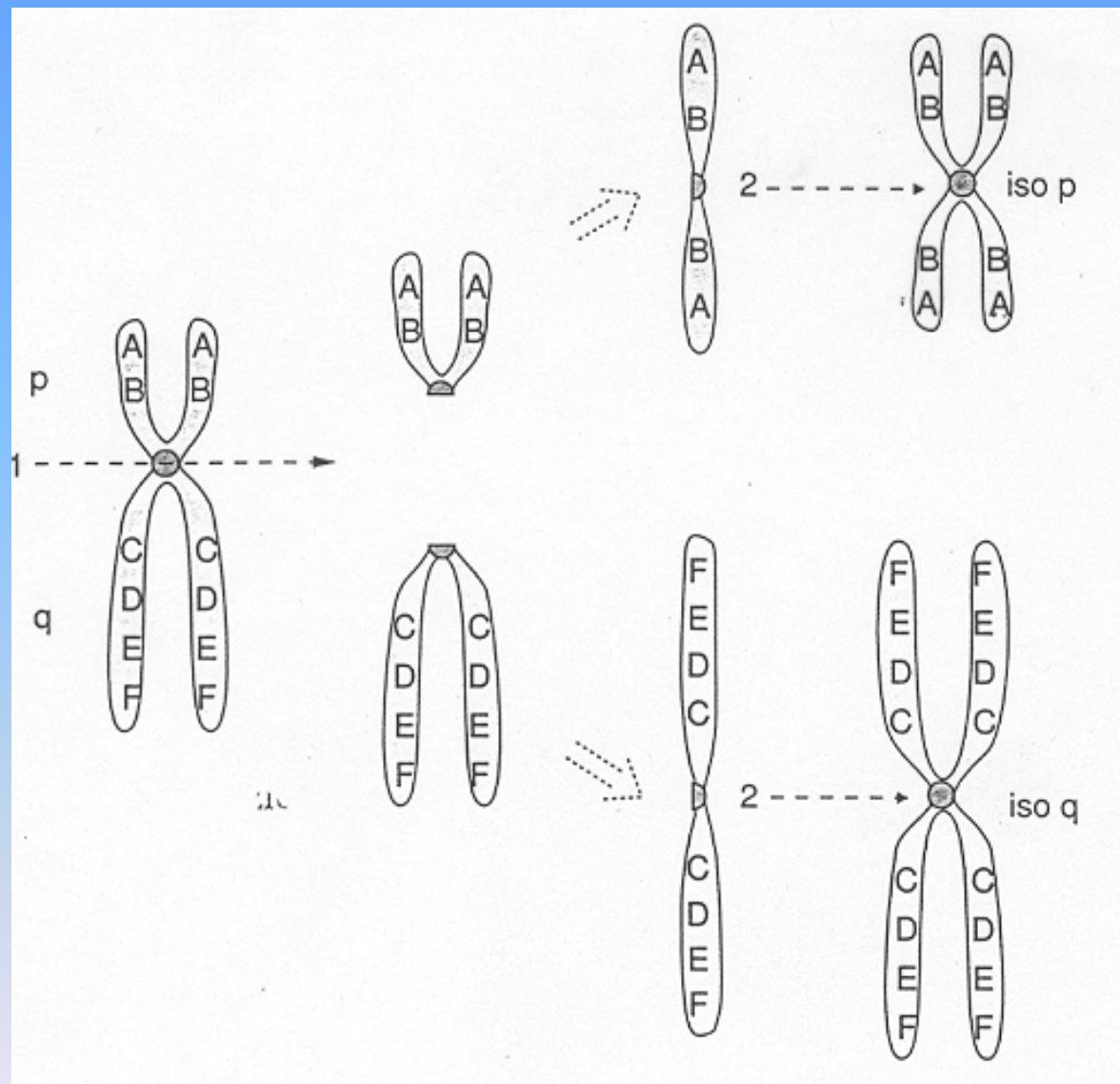
rottura o errore di replicazione ?

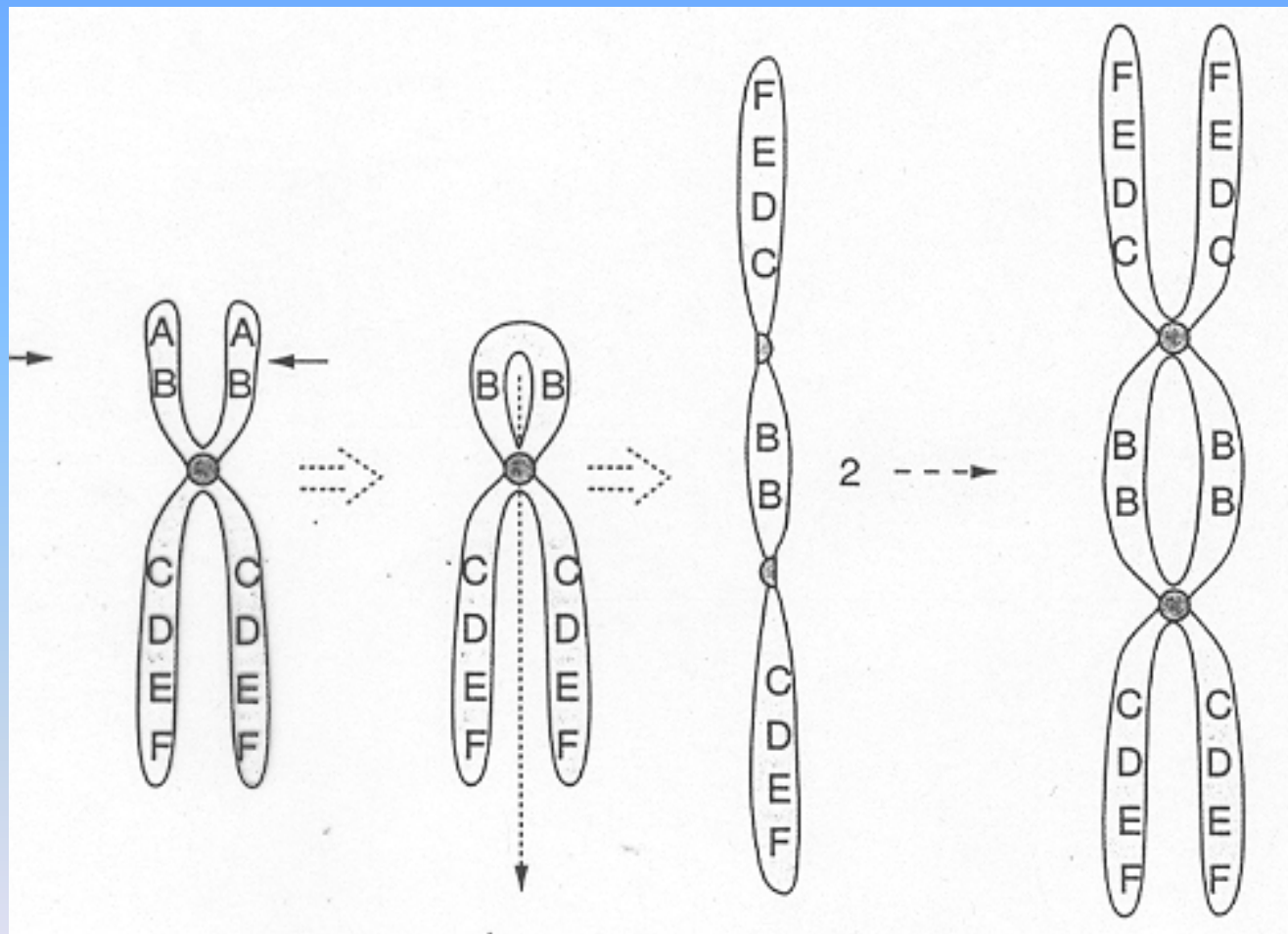
duplicazione (triplicazione)

diretta	dirdup
invertita	invdup

isocromosomi **iso(p)** **iso(q)**
mono- o di-centrici

noti in popolazione umana:	$\text{iso}(18)(p)$	mono
	$\text{iso}(21)(q)$	dic
	$\text{iso}(22)(q)$	dic
	$\text{iso}(X)(q)$	dic





- frequenza tra i nati vivi 1/ 1027 D;D
 1/3879 D;G
- de novo in liquido amniotico 0.011%
- possono essere monocentriche o dicentriche
- tipi: tutte le combinazioni possibili

		D;D	G;G	D;G	
<u>13;13</u>	13;14	13;15	<u>21;21</u>	13;21	13;22
<u>14;14</u>	14;15		<u>22;22</u>	14;21	14;21
<u>15;15</u>			21;22	15;21	15;22

Le traslocazioni robertsoniane sono

- **associate a sterilità maschile**
- **causa di aborto spontaneo e**
sindromi note Down tris 21
Patau tris 13
- **causa di disomia uniparentale (UPD)**
sindromi note PW/AS per il cr.15 e
sindrome da UPD14

Table 6.9. Segregations in Robertsonian translocations

Type of Translocation	Number of Diagnoses	Offspring		
		Normal	Balanced	Unbalanced
13q14q	230	96	134	—
13q15q	15	4	11	—
14q15q	6	4	2	—
13q21q	31	17	12	2
13q22q	3	—	2	1
14q21q	188	68	99	21
14q22q	3	—	3	—
15q21q	14	7	6	1
15q22q	5	2	3	—
21q22q	22	11	8	3
Total	517	209	280	28

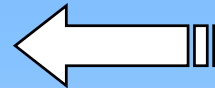
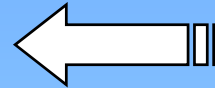
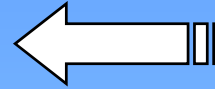
Source: Data from Boue⁷ and Gallano 1984⁶¹

punti di rottura:

p;p

p;q

cen;cen



satellite

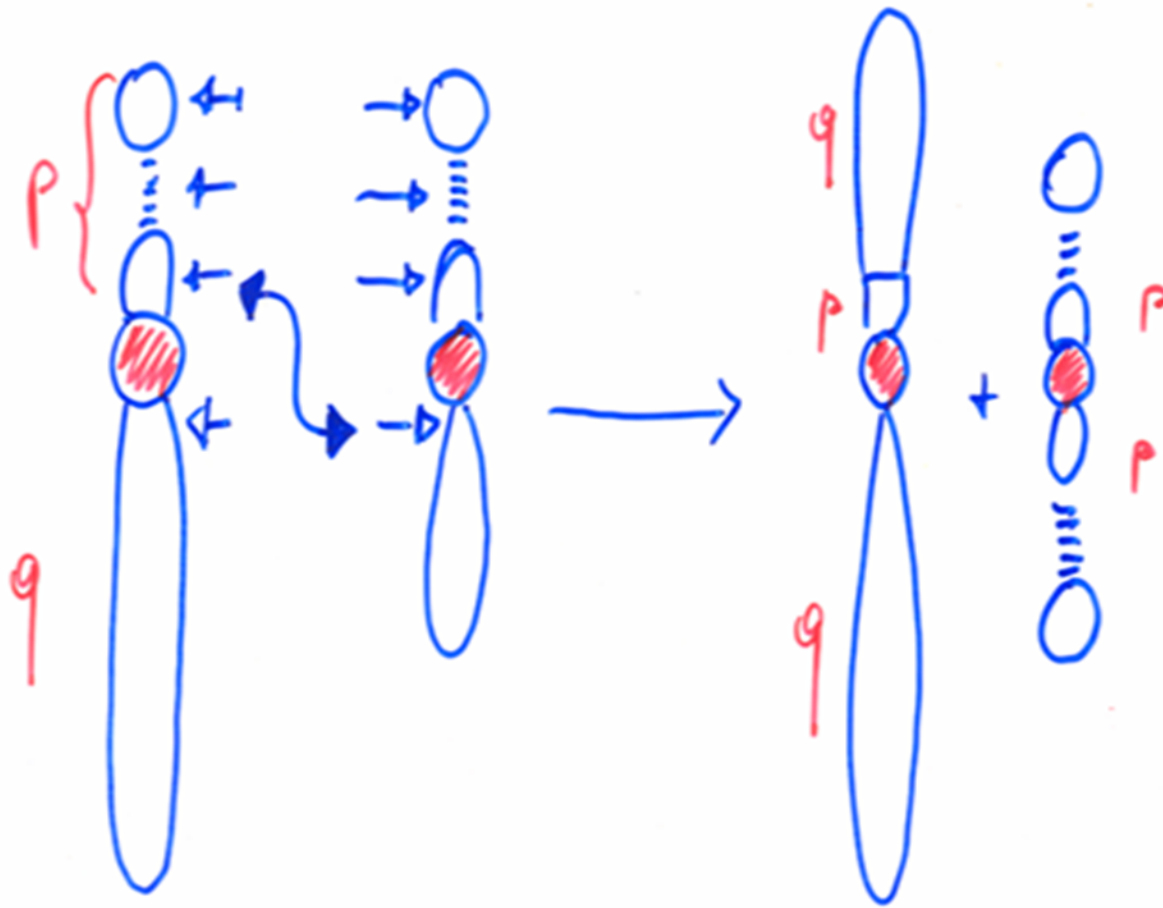
costr. sec.

braccio p

centromero

braccio q

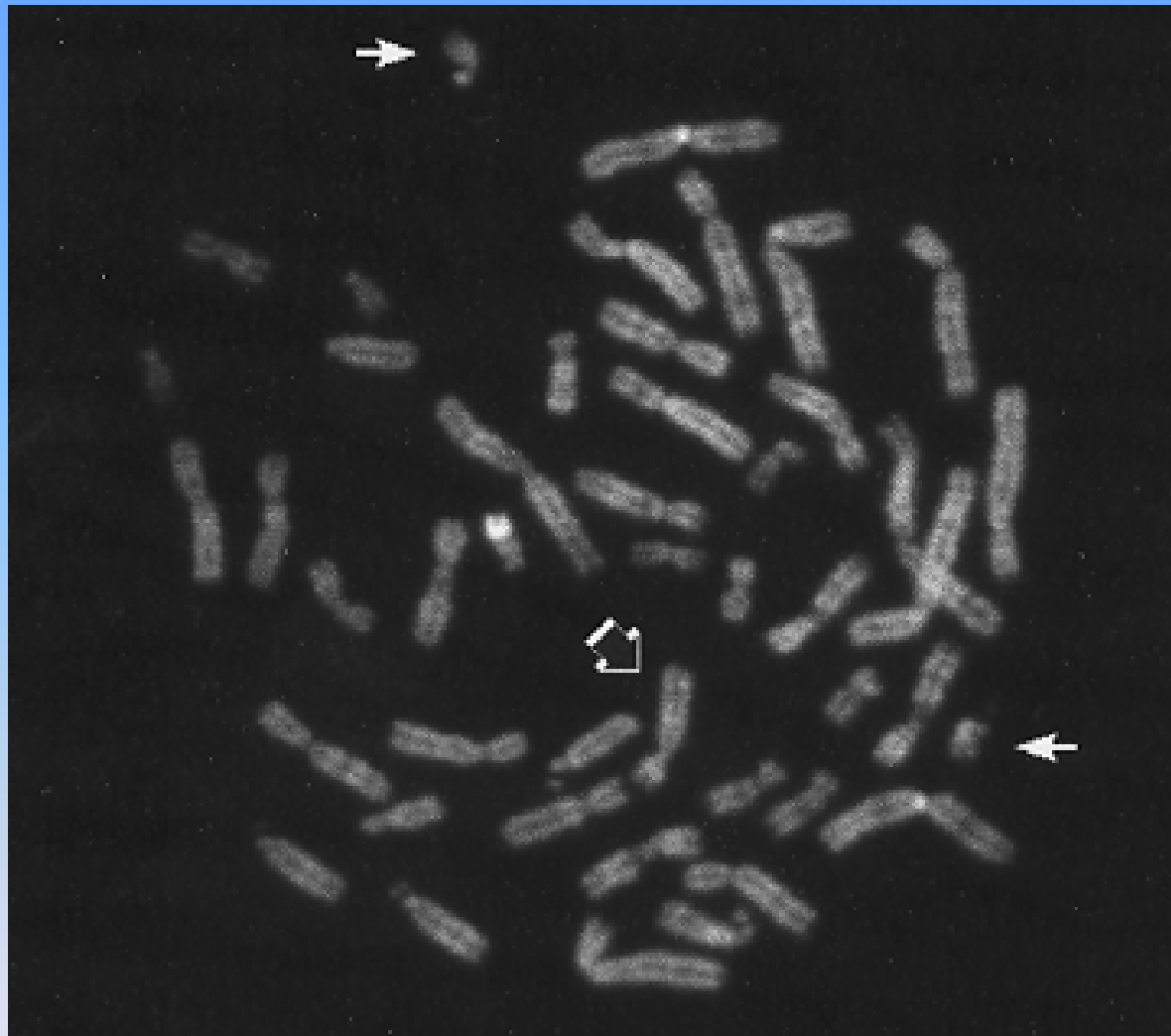
traslocazione robertsoniana (D: 13, 14, 15 e G: 21, 22)

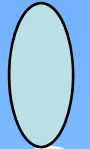


↑
13-14 } le più frequenti
14-21 }

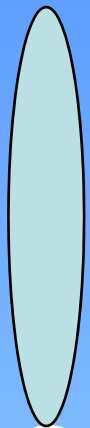
**I PORTATORI BILANCIATI
SONO A 45 CROMOSOMI**

**I PORTATORI SBILANCIATI SONO
A 46 CROMOSOMI**





14



14/21

21q

**cen (14, fusione 14,21, 21 o dicentrico
dipendendo dai punti di rottura**

14q

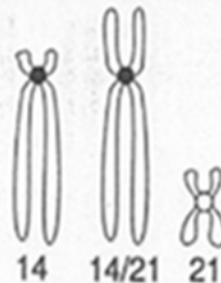


21



21

portatore

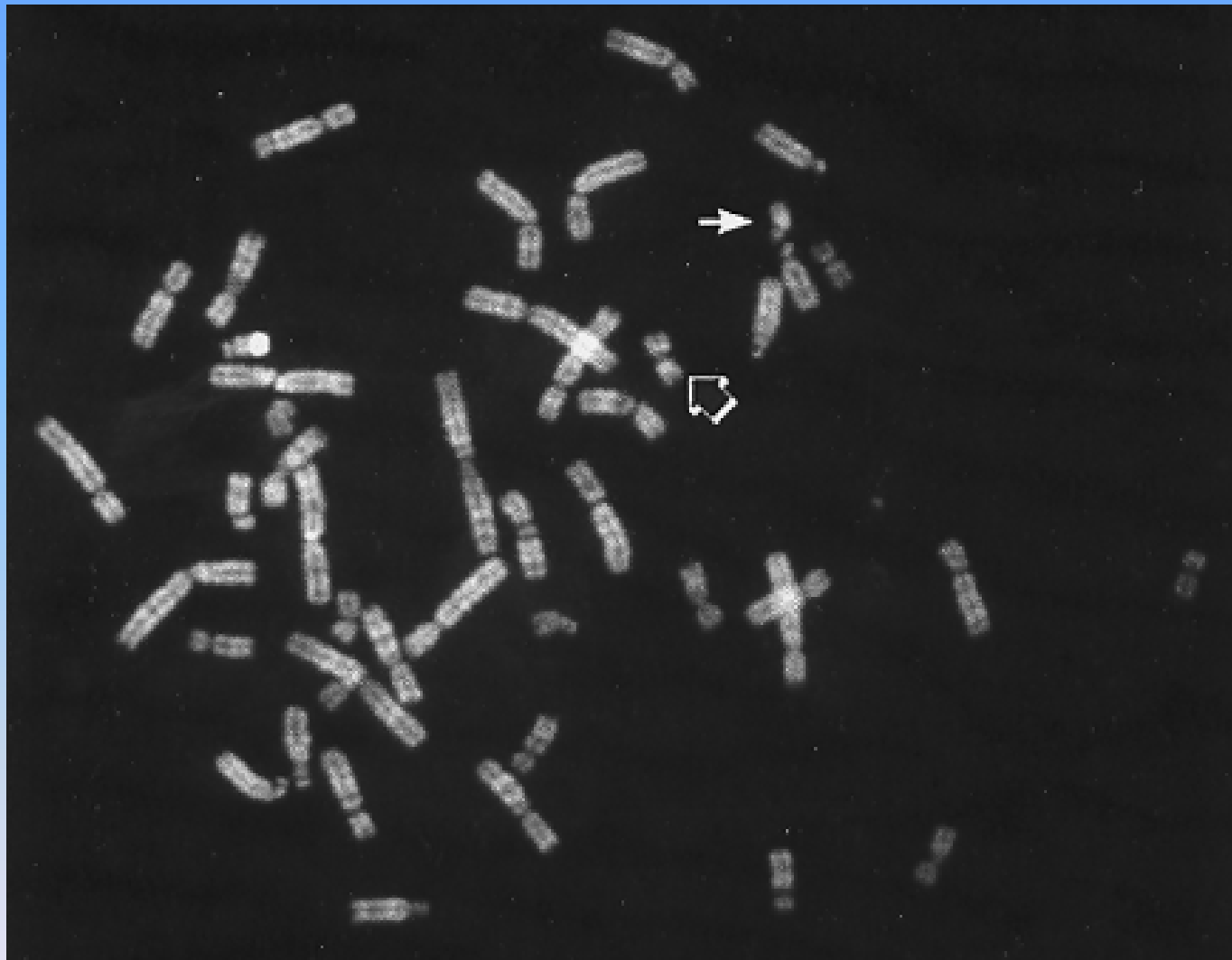


appaiamento
alla meiosi
(schema)



gameti

gameti						gameti normali
segregazione alternata	segregazione adiacente-1	segregazione adiacente-2	segregazione adiacente-1	segregazione adiacente-2	segregazione adiacente-2	
 14 21	 14/21	 14 -21	 14/21 21	 -14 21	 14/21 14	 14 21
 14 14 21 21 NORMALE	 14 14/21 21 PORTATORE	 14 14 21 MONOSOMICO 21	 14 14/21 21 21 TRISOMICO 21	 14 21 21 MONOSOMICO 14	 14/21 14 14 21 TRISOMICO 14	



portatore



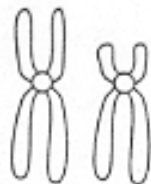
21/21

gameti



21/21

-21



21/21 21

TRISOMICO 21



21

MONOSOMICO 21

gameti normali



21

Olfactory Receptor–Gene Clusters, Genomic-Inversion Polymorphisms, and Common Chromosome Rearrangements

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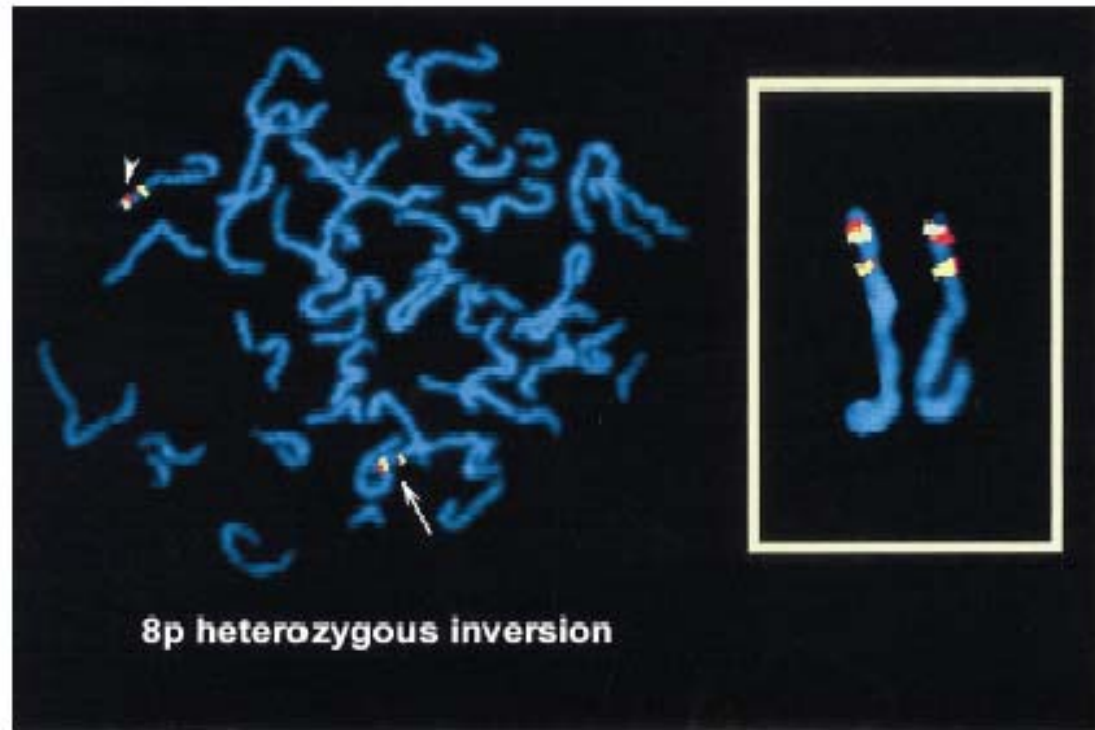


Figure 3 Metaphase from the mother of a subject with inv dup(8p), showing the normal (*arrow*) and the inverted (*arrowhead*) chromosomes 8 (magnified in the box). FISH was done with GS173o4 (*red*, D8S351), GS257o3 (*green*, D8S1130), both inside the inverted region (see fig. 1), and RP11-563o19 (*yellow*, D8S1733), ~24 cM proximal to the inverted region.

Heterozygous Submicroscopic Inversions Involving Olfactory Receptor–Gene Clusters Mediate the Recurrent t(4;8)(p16;p23) Translocation

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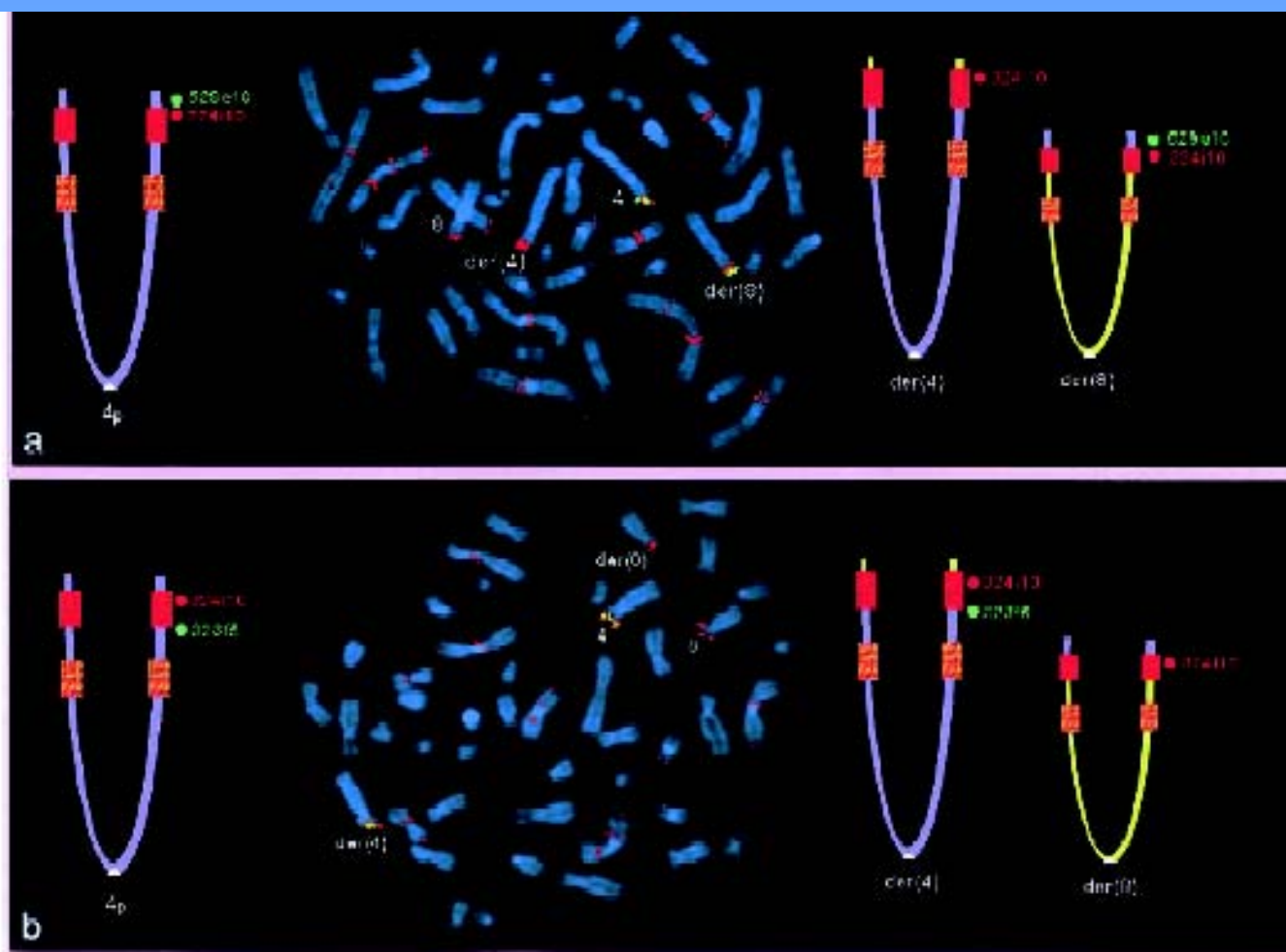


Figure 2 Metaphase FISH on case subject 7 (with the 46,XY,t(4;8)(p16;p23.1) translocation), showing the der(4) breakpoint. In the ideograms, the normal 4p is on the left, and the two derivative chromosomes are on the right; the red and orange squares indicate the REPD and the REPP, respectively. Red signals correspond to the distal 4p-REPD BAC RP11-324i10; these signals are present in several OR-gene cluster regions. *a*, Probe RP11-529e10 (*green signals*), which maps distal to the 4p REPD. This clone is translocated to the der(8). *b*, Probe RP11-323f5 (*green signals*), which is one of the more distal clones in the region included between the two 4p REPs. This clone remains on the der(4). These data demonstrate that the 4p breakpoint in case subject 7 is within the REPD (see also fig. 1).

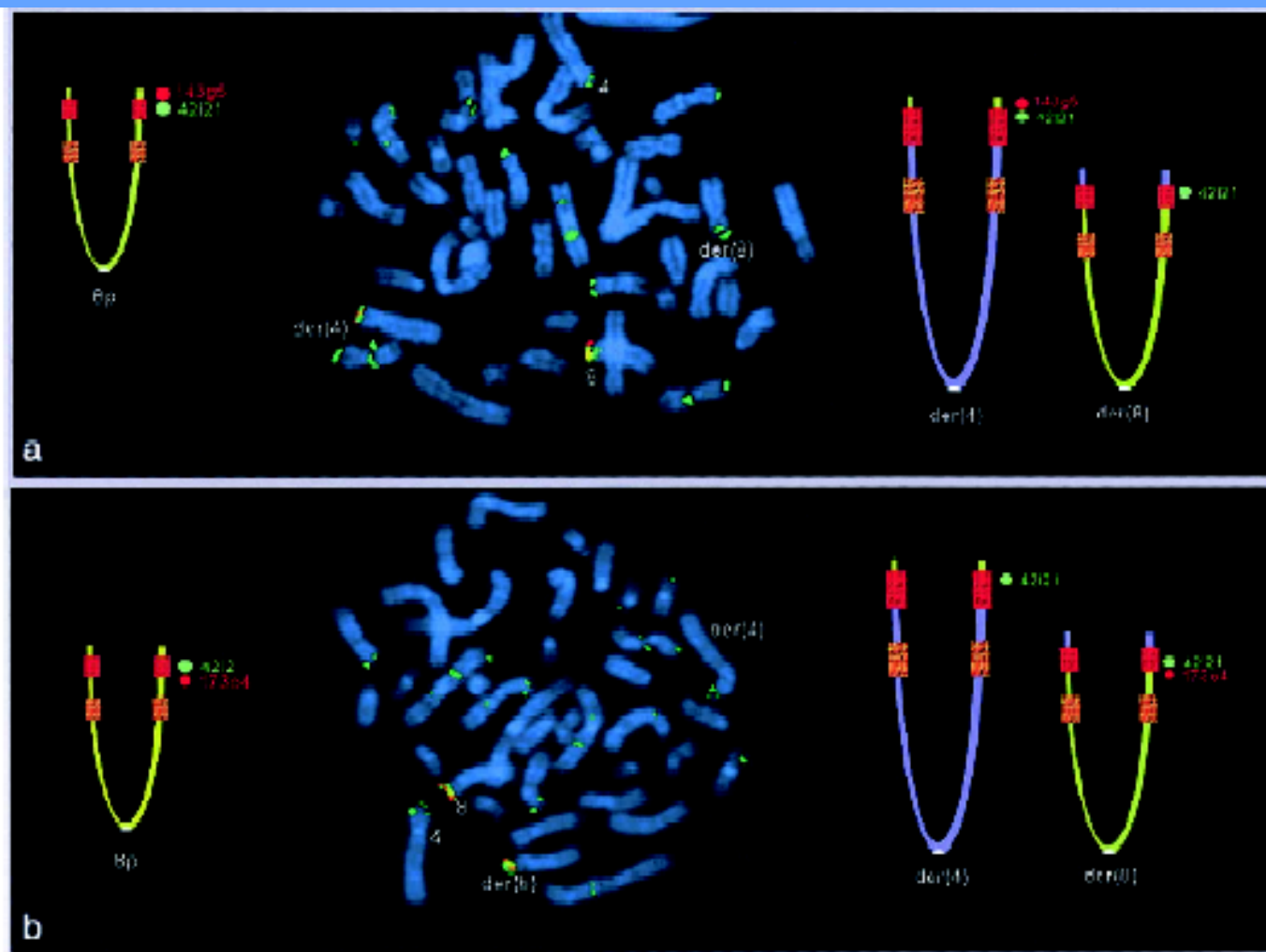


Figure 3 Metaphase FISH in case subject 7 (with the 46,XY,t(4;8)(p16;p23.1) translocation), showing the der(8) breakpoint. In the ideograms, the normal 8p is on the left, and the two derivative chromosomes are on the right; the red and orange squares indicate the REPD and the REPP, respectively. Green signals correspond to GS-42i21, which maps within the 8p REPD; these signals are present in several OR-gene cluster regions. *a*, Probe GS-143g5 (red signals), which is distal but adjacent to the 8p REPD. This clone is transposed to the der(4). *b*, Probe GS-173o4 (red signals), which is the most distal clone within the region included between the two 8p REPs. This clone remains on the der(8). These data demonstrate that the 8p breakpoint is within the REPD (see also fig. 1 in Eichler 2001).

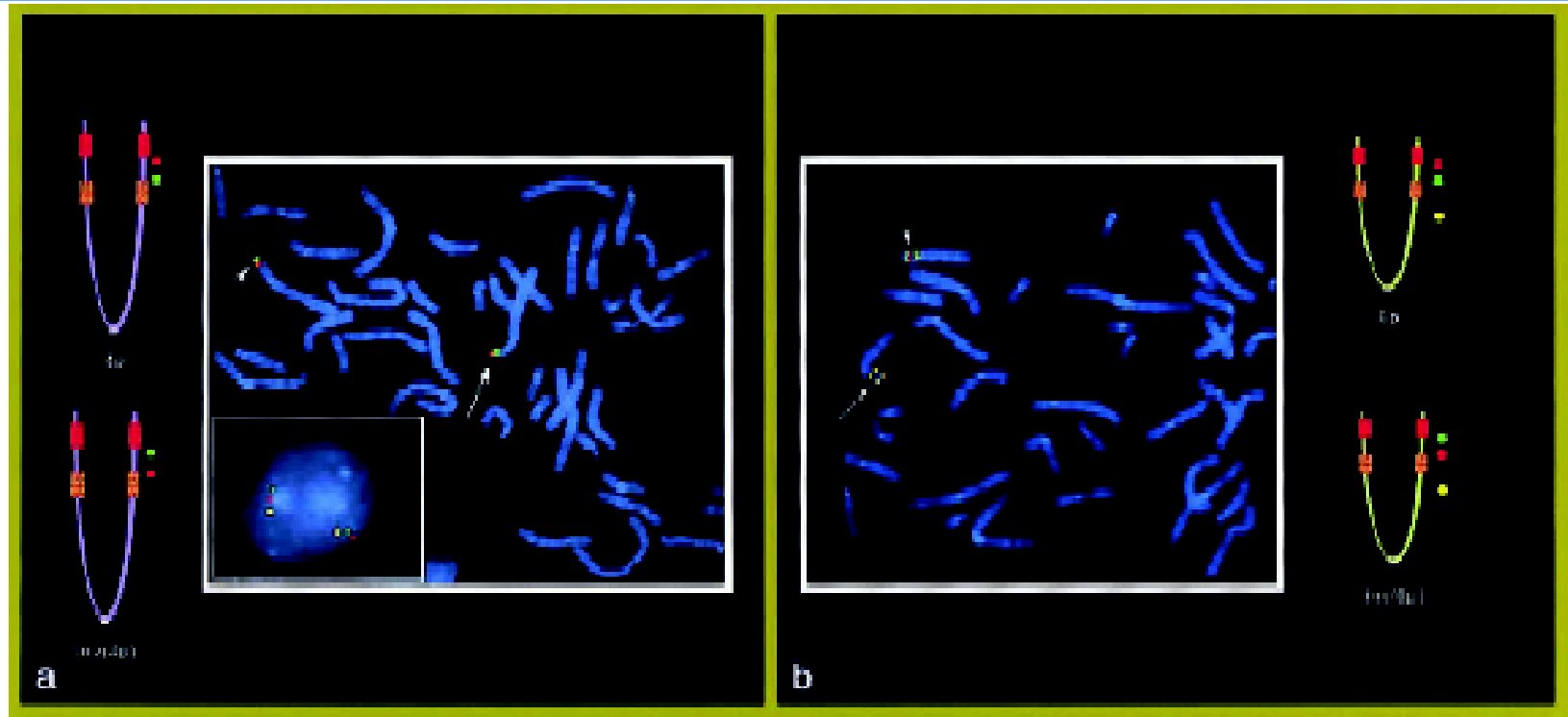


Figure 4 FISH in the mother of case subject 3 (with 46,XX). *a*, Normal and inverted 4p. At left, the ideograms show that clones RP11-323f5 (*red signals*) and RP11-448g15 (*green signals*), included between the two 4p REPs, are inverted in the chromosome 4 (*arrowhead*). In the square, a nucleus shows the same inversion; yellow signals refer to the control probe RP11-520m5, which is distal to the 4p REPD (see fig. 1), and red and green signals refer to RP11-323f5 and RP11-19016, respectively (these two clones are at a distance of ~2 Mb and thus are more appropriate for interphase FISH). *b*, Normal and inverted 8p. At right, the ideograms show that clones GS-173o4 (*red signals*) and GS-257o3 (*green signals*), included between the two 8p REPs, are inverted in one chromosome 8 (*arrowhead*). RP11-563o19 (*yellow signals*), at 8p12, was used as a control probe.