La genetica e la delezione del cromosoma 22

M.Cristina Digilio

Genetica Medica - Ospedale Pediatrico Bambino Gesù - Roma

"LA PAROLA del22"

Approccio multispecialistico per la presa in carico di bambini, adolescenti e giovani adulti

Roma, 24 maggio 2013

Bambino Gesù
OSPEDALE PEDIATRICO

La Genetica e la Delezione 22q11.2

- Anomalie facciali
- Cardiopatia congenita
- Anomalie del palato
- Ipocalcemia neonatale
- Deficit immunitario
- Ritardo del linguaggio / Difficoltà di apprendimento

Συν-δρομες

SYN-DROMES

“THINGS THAT RUN TOGETHER”

La Genetica e la Delezione 22q11.2

Confirmation of autosomal dominant transmission of the DiGeorge malformation complex

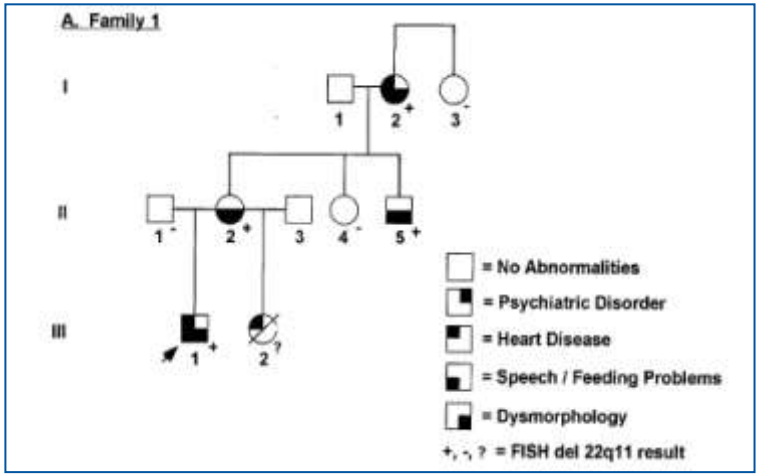
Laura Davis Keppen, MD, James W. Fasules, MD, A. Wesley Burks, MD, Susanne M. Gollin, PhD, Jeffrey R. Sawyer, PhD, and Connie H. Miller, PhD

From the Departments of Pediatrics and Pathology, University of Arkansas for Medical Sciences, Little Rock

TABLE I. Phenotypic Findings in Familial Cases of del22q11*

Family	Patient	Cardiac defect	Cleft palate	VPI	DD/MR	Abnormal face	Thymic abnormalities	Parathyroid abnormalities
1	Mother	–	–	+	+	+	NT	NT
	Daughter	–	–	+	+	+	–	–
	Son	TF	–	NV	+	+	+	+
2	Father	–	–	–	–	+	NT	NT
	Daughter	TF	–	NV	NV	+	NT	NT
	Son	TF	–	NV	–	+	+	+
3	Mother	–	–	+	+	+	NT	NT
	Daughter	TF	–	+	+	+	–	–
4	Mother	–	–	+	+	+	NT	NT
	Daughter	TF-PA	–	NV	+	+	+	+
5	Mother	–	–	+	–	+	NT	NT
	Daughter	TF	+	+	+	+	+	+
6	Mother	–	–	+	–	+	NT	NT
	Son	IAA	–	NV	+	+	–	+
7	Father	–	–	–	–	+	NT	NT
	Son	TF	–	NV	+	+	+	–

*VPI, velopharyngeal insufficiency; DD, developmental disability; MR, mental retardation; –, anomaly absent; +, anomaly present; NT, not tested; TF, Tetralogy of Fallot; NV, not valuable; PA, pulmonary atresia; IAA, interrupted aortic arch.



Letter to the Editor

Familial Deletions of Chromosome 22q11

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Bruno Marino*
Aldo Giannotti
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Human Genetics
Tor Vergata University
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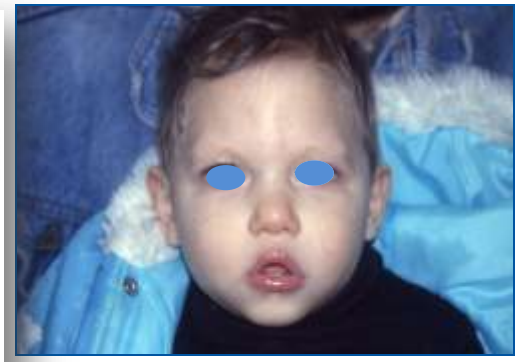
C.S.S. Hospital
San Giovanni Rotondo
Italy

La Genetica e la Delezione 22q11.2

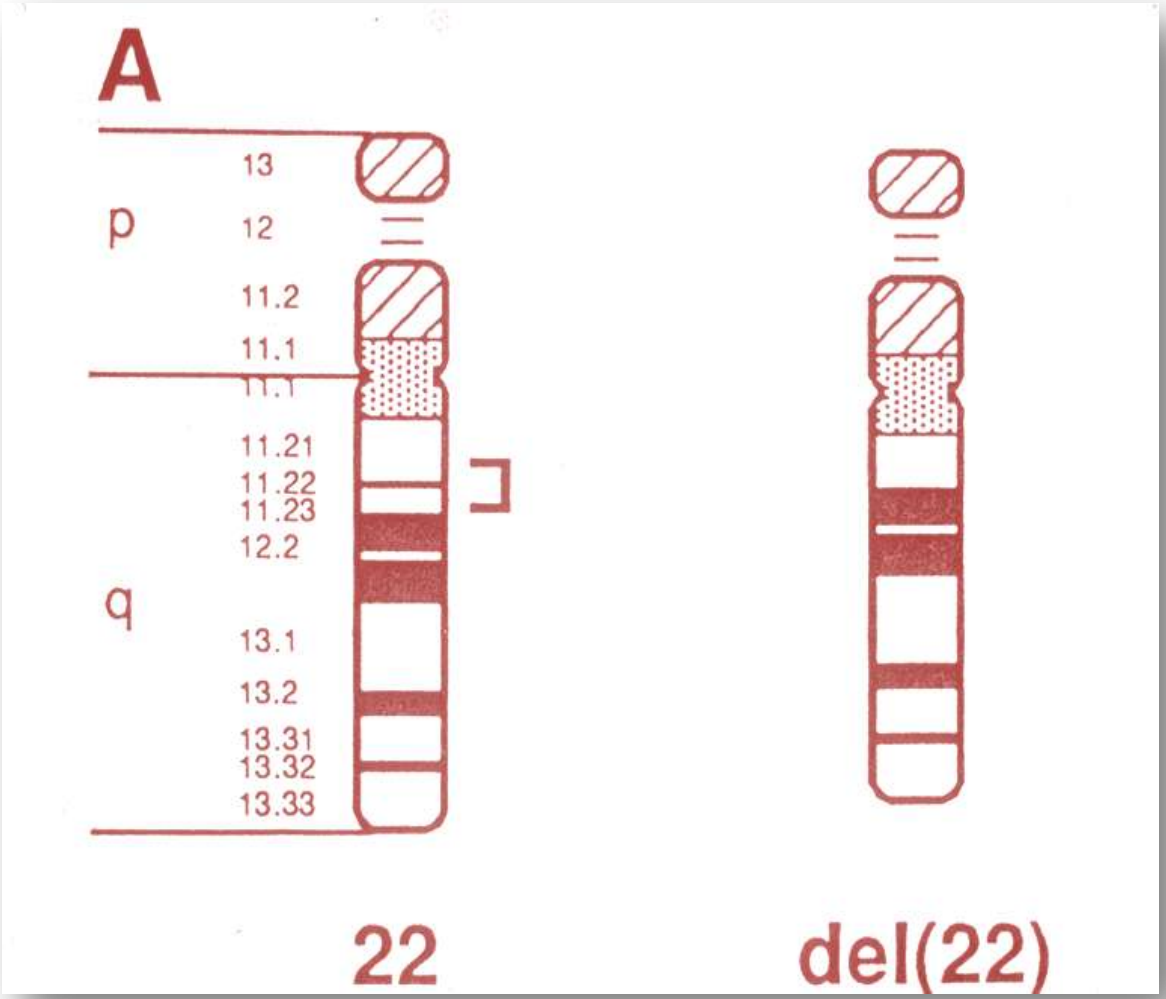
Spectrum of clinical variability in familial deletion 22q11.2: from full manifestation to extremely mild clinical anomalies

Digilio MC, Angioni A, De Santis M, Lombardo A, Giannotti A, Dallapiccola B and Marino B. Spectrum of clinical variability in familial deletion 22q11.2: from full manifestation to extremely mild clinical anomalies.
Clin Genet 2003: 63: 1–6. © Blackwell Munksgaard, 2003

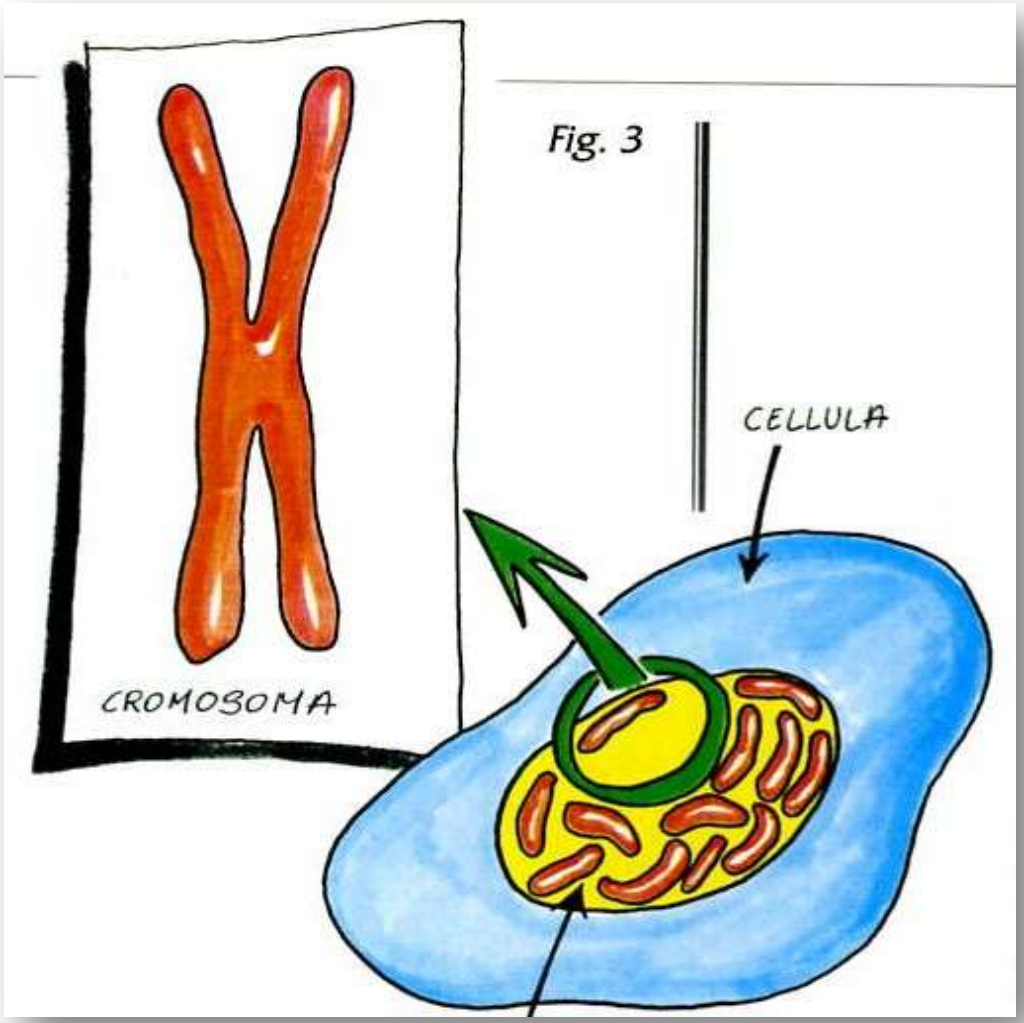
MC Digilio[a], A Angioni[b], M De Santis[c], A Lombardo[b], A Giannotti[a], B Dallapiccola[d,e] and B Marino[f]



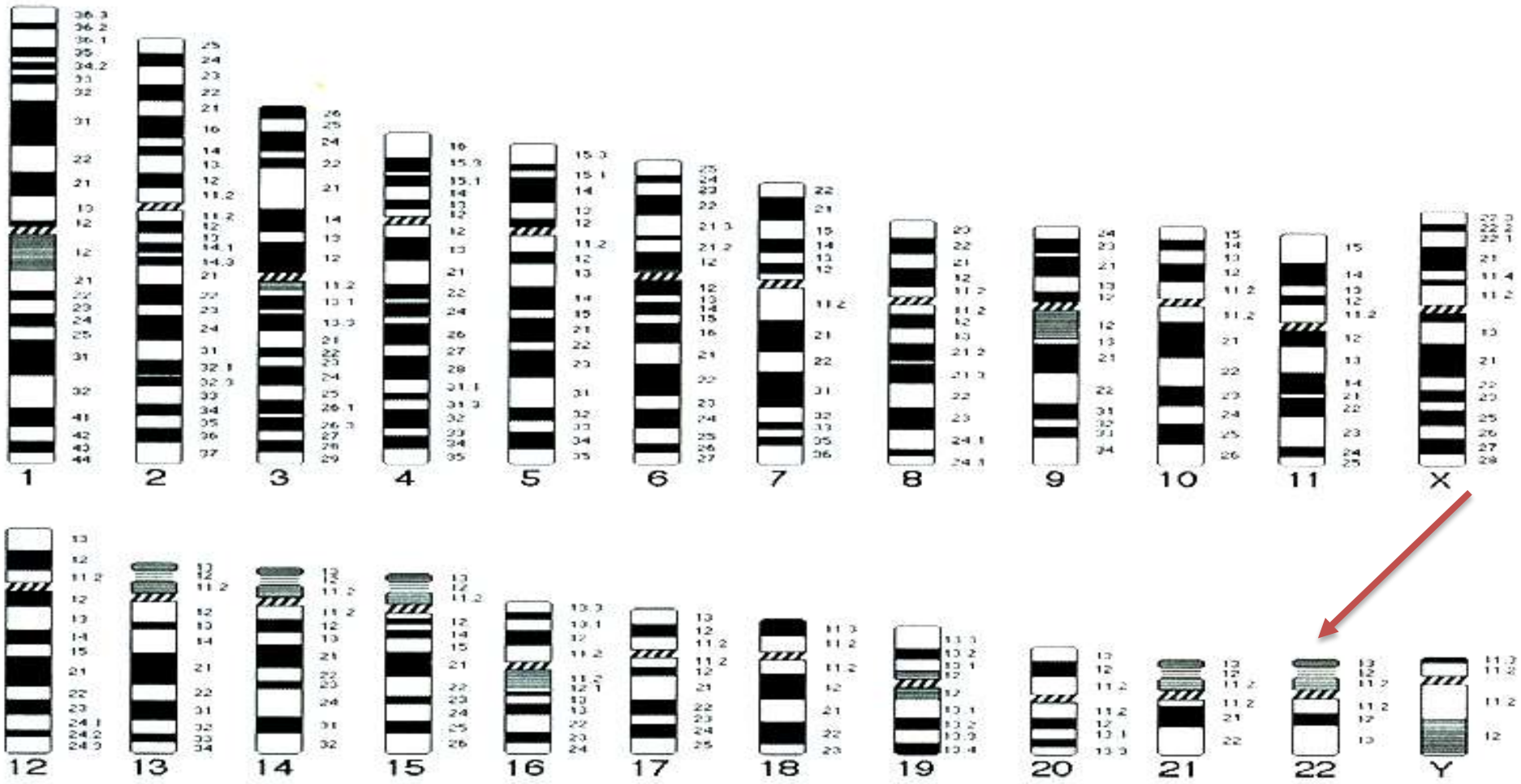
Microdelezione 22



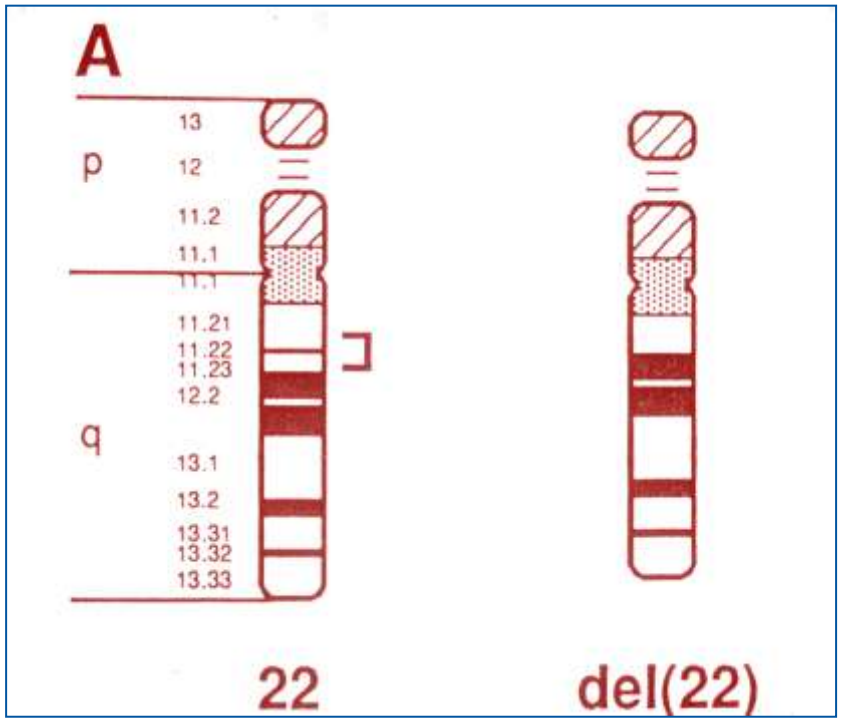
Cromosomi



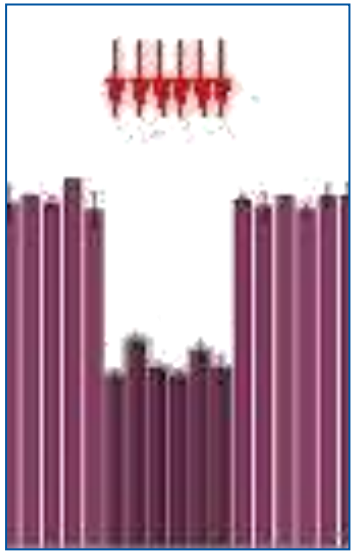
Cromosomi

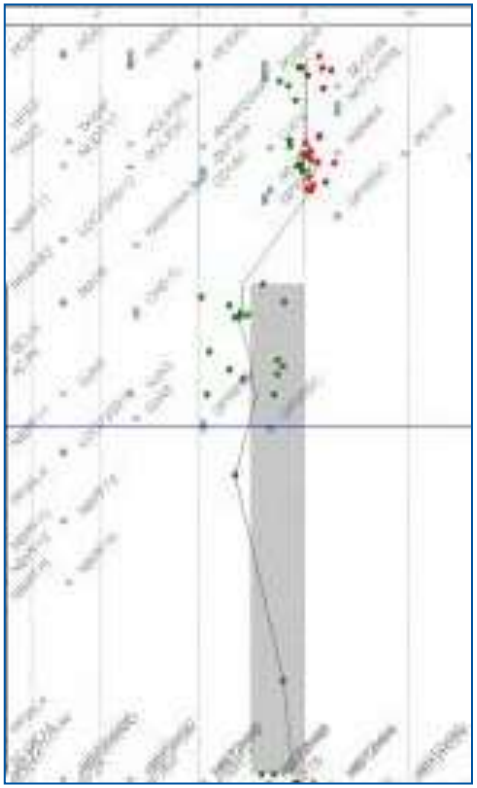


Microdelezione 22

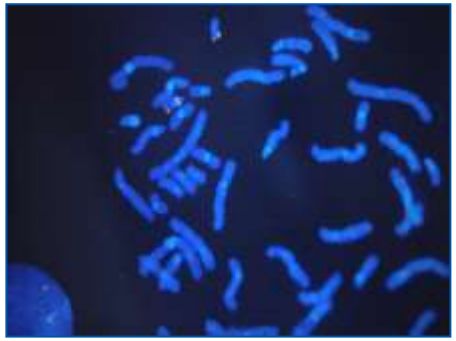


MLPA



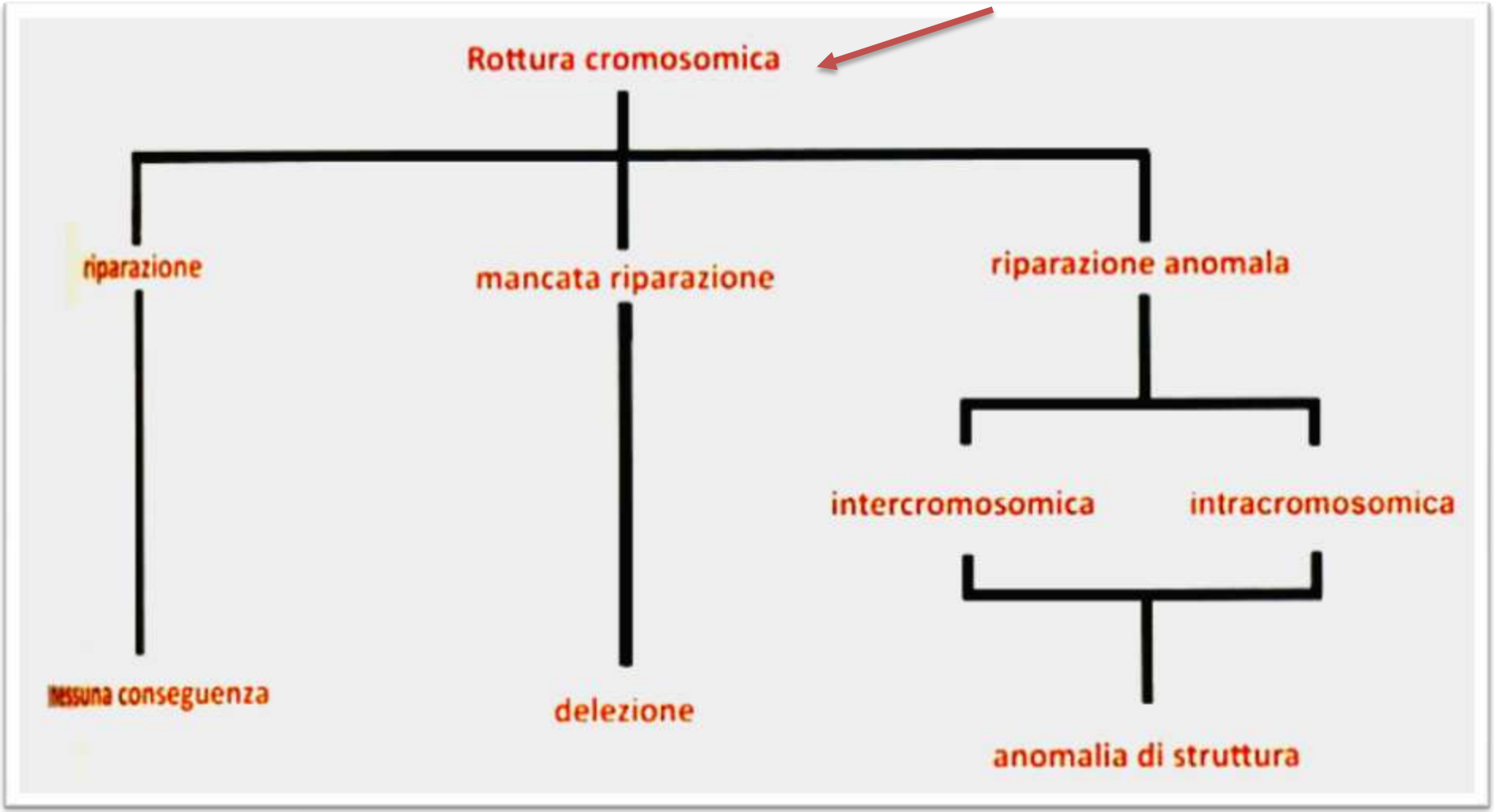


FISH

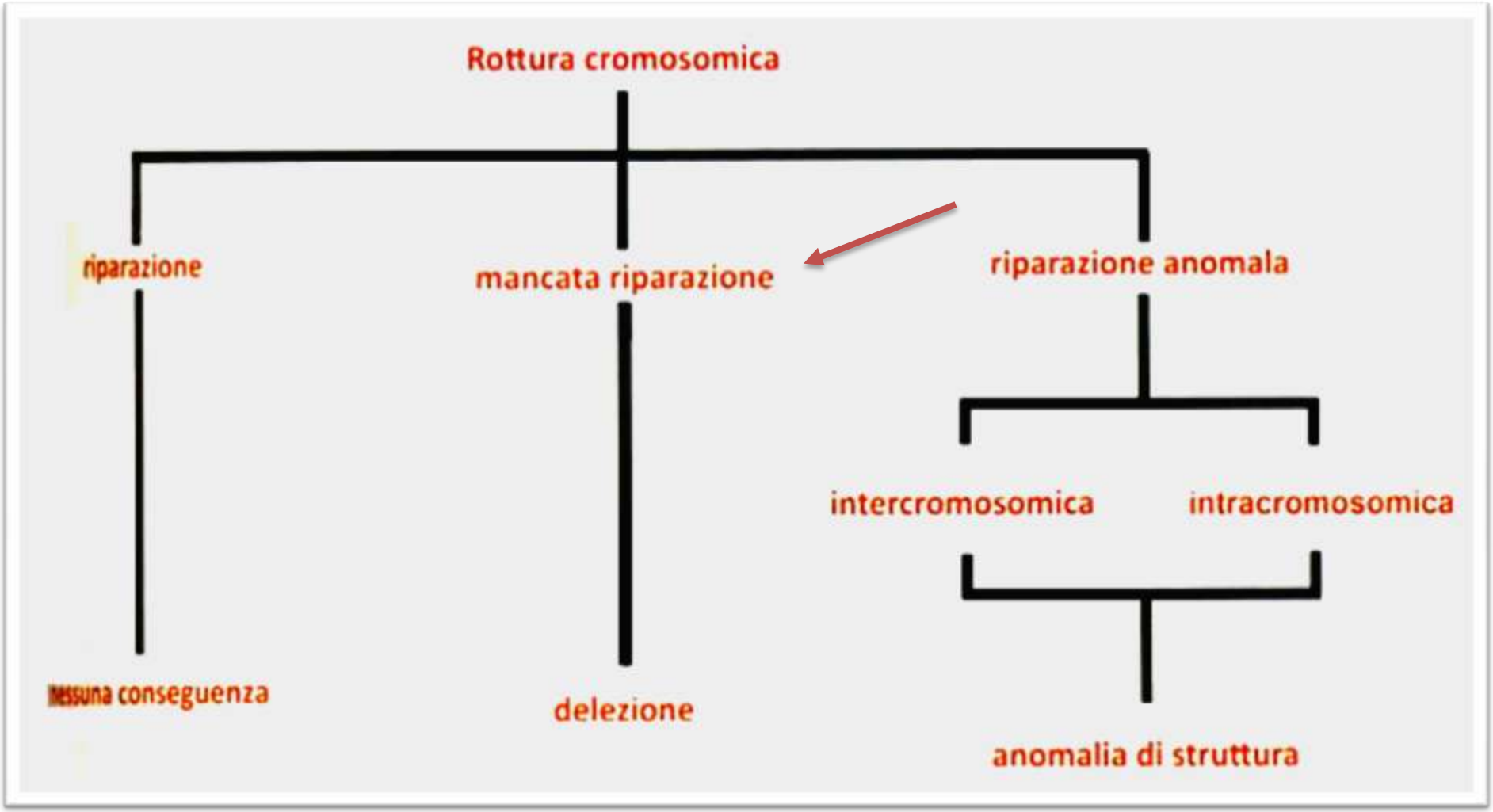


CG H

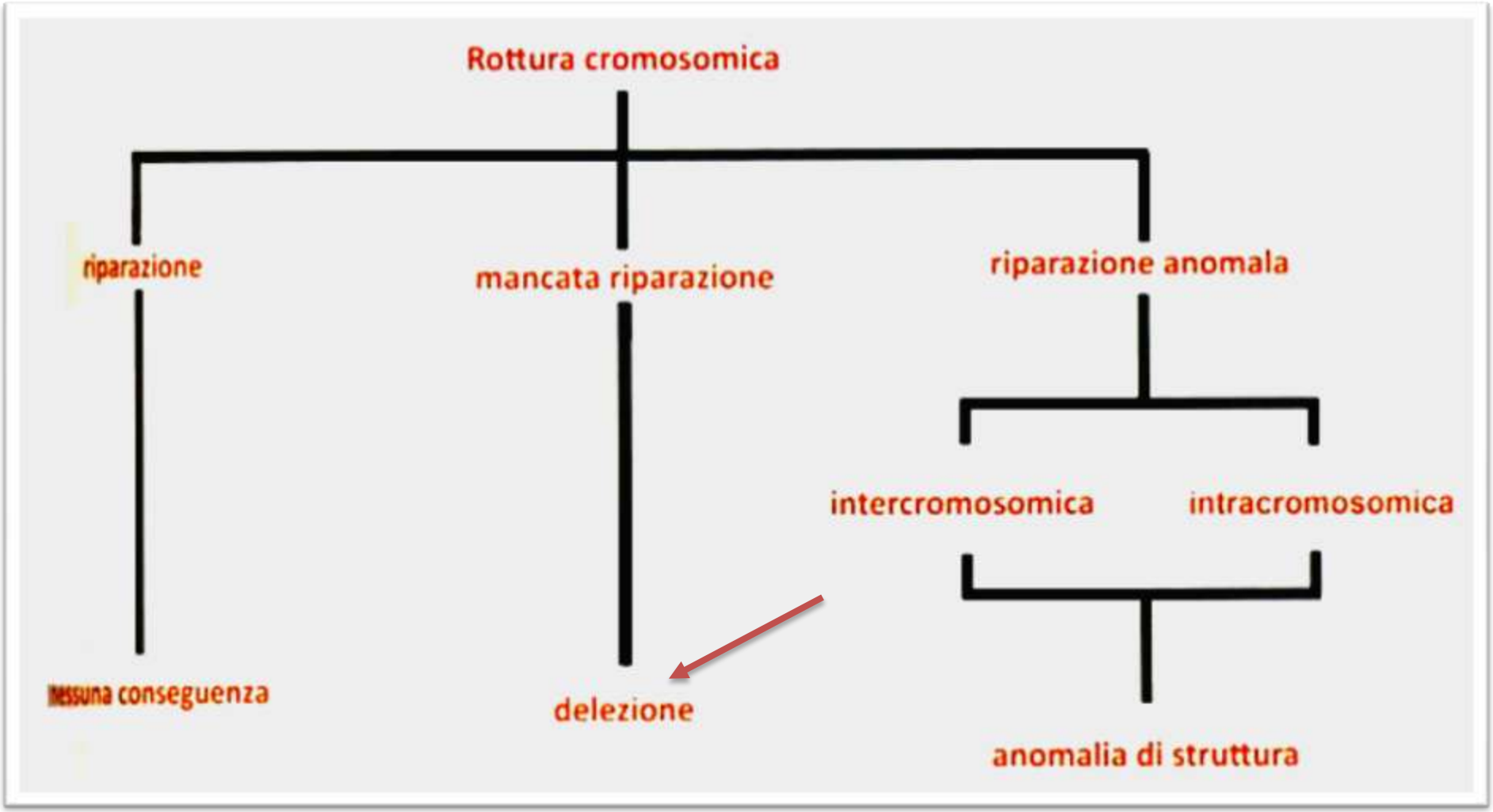
Come si crea una delezione ?



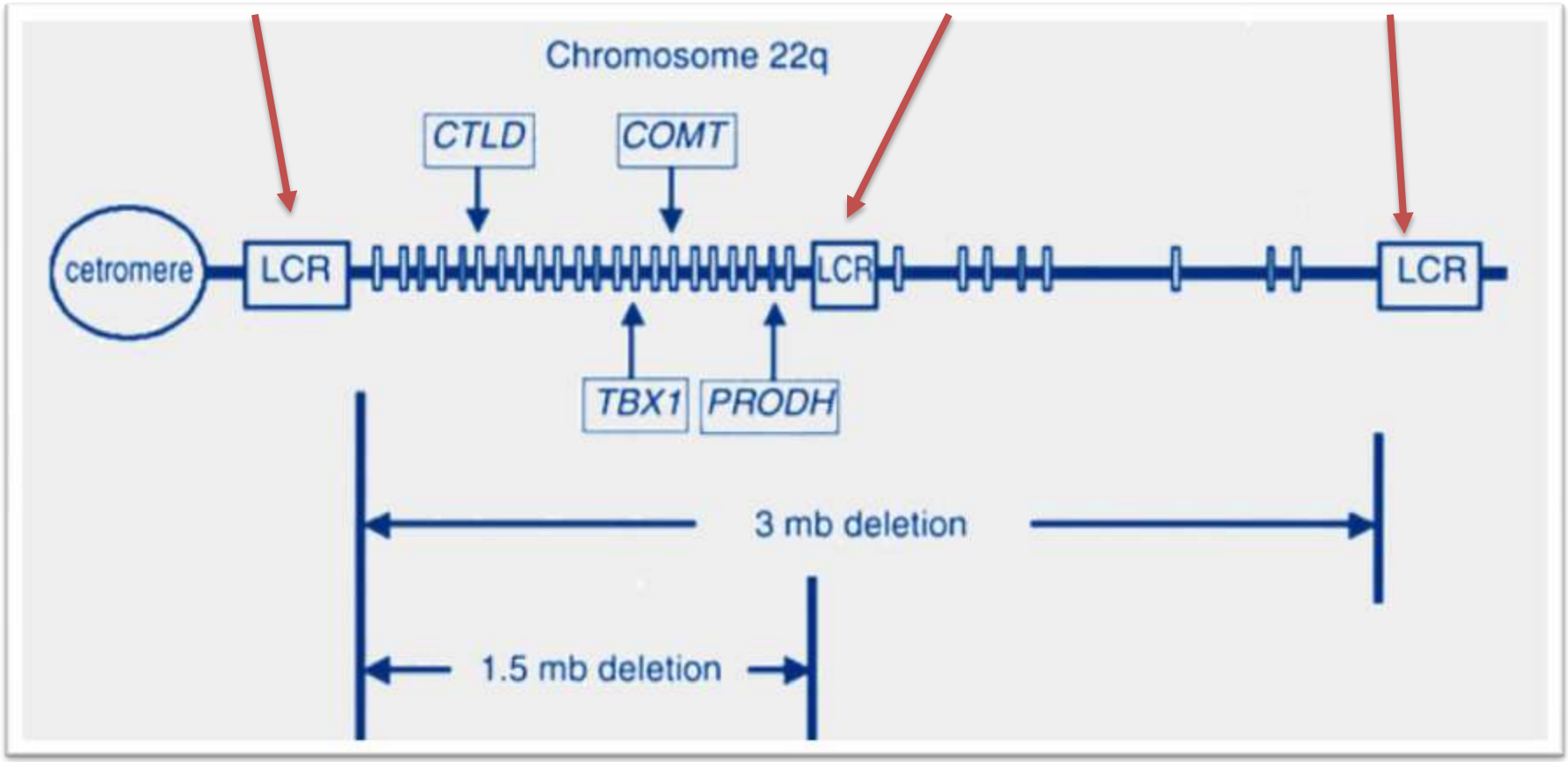
Come si crea una delezione ?



Come si crea una delezione ?

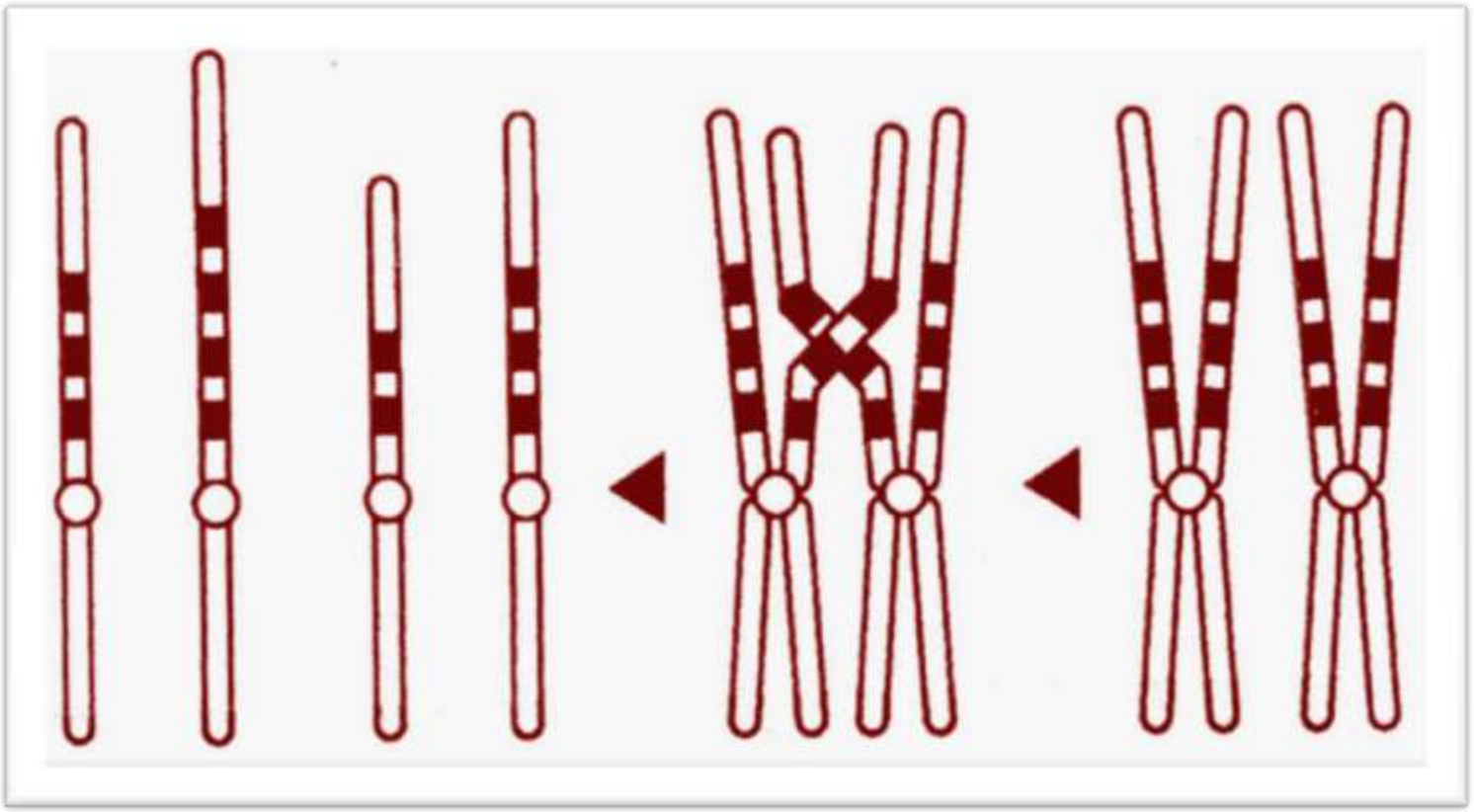


Perché avviene la rottura ?



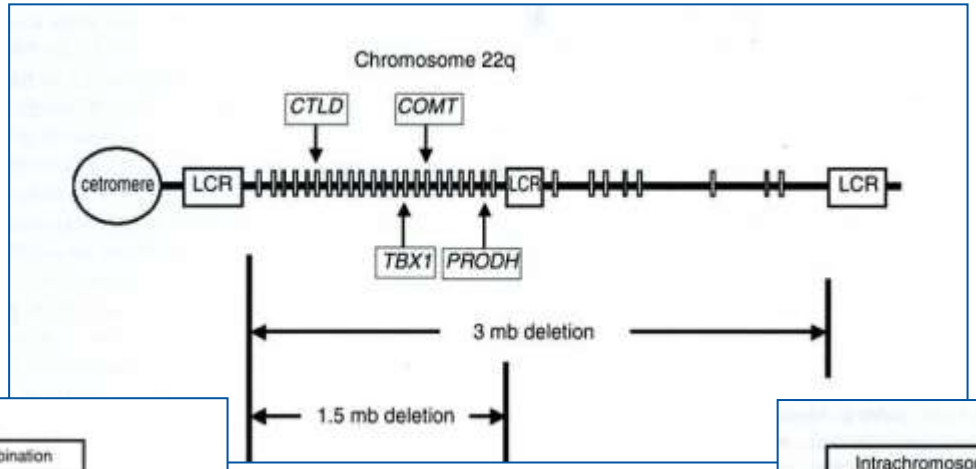
LCR : "low copy repeats" sequences

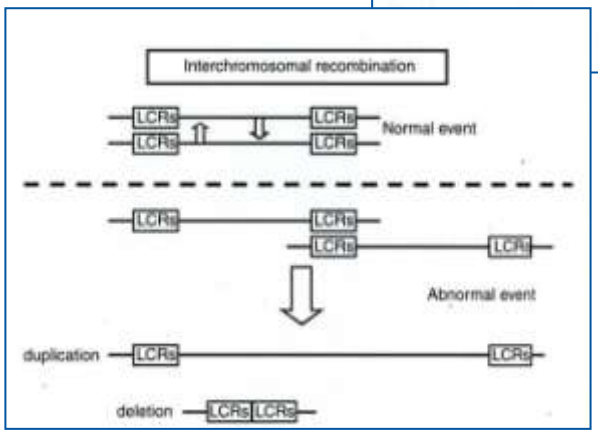
Perché avviene la rottura ?



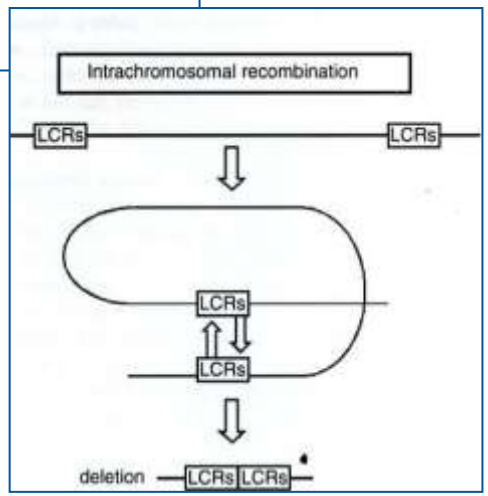
"Crossing over" ineguale – Errore di lettura del DNA

Perché avviene la rottura ?



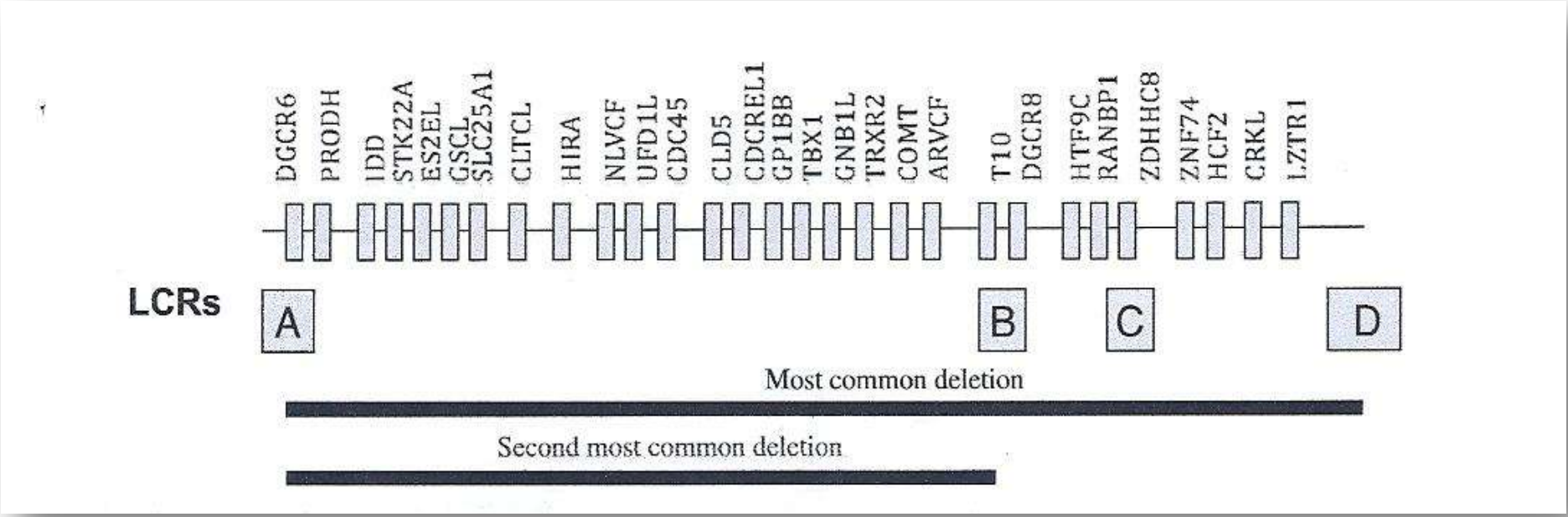


RICOMBINAZIONE INTERCROMOSOMICA

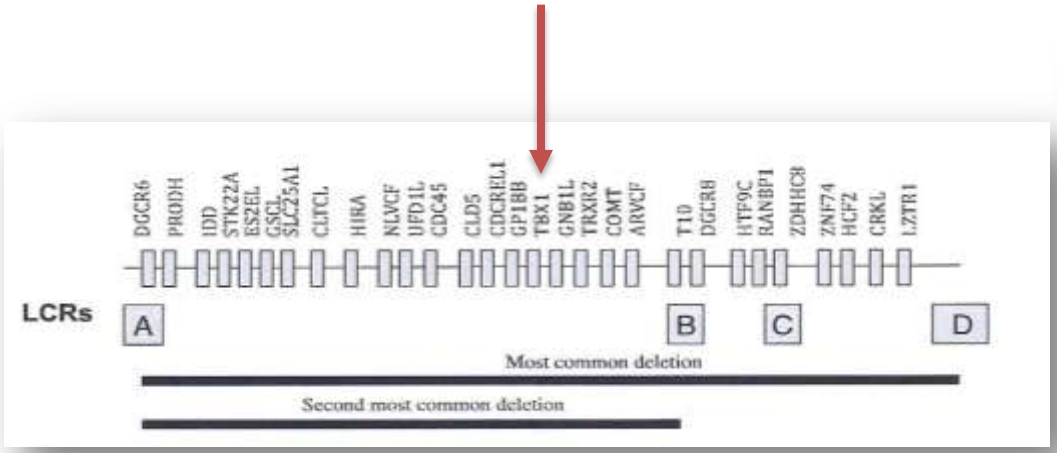


RICOMBINAZIONE INTRACROMOSOMICA

"Regione critica 22q11.2 - Geni"

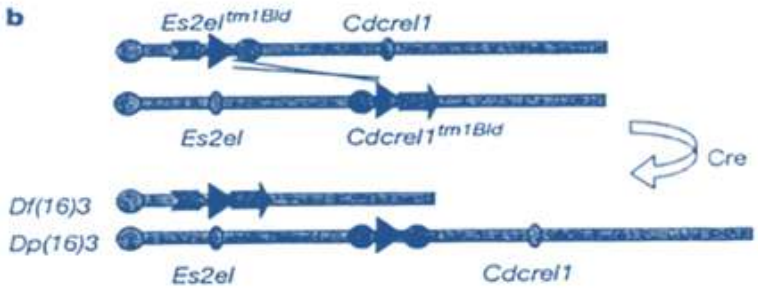


Gene TBX1

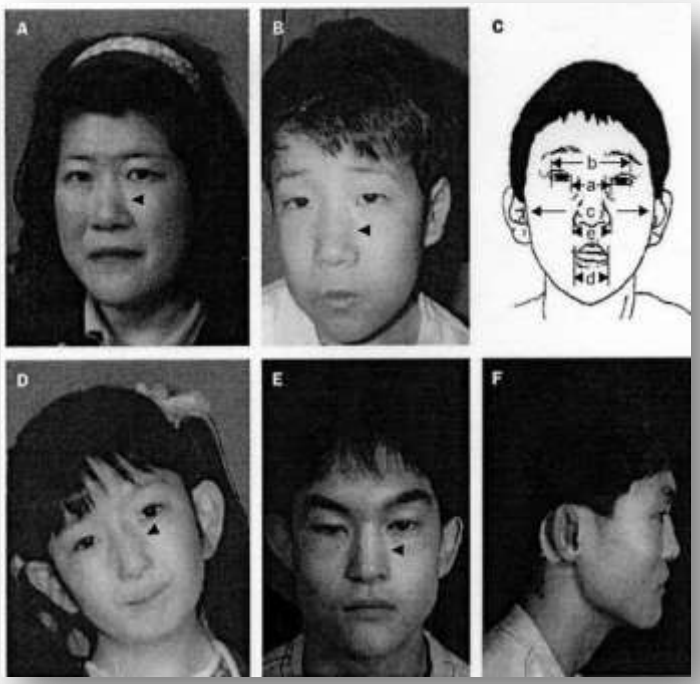


Tbx1 haploinsufficiency in the DiGeorge syndrome region causes aortic arch defects in mice

Elizabeth A. Lindsay*, Francesca Vitelli*, Hong Su†, Masae Morishima*, Tuong Huynh*, Tiziano Pramparo*, Vesna Jurecic‡, George Ogunrinu§, Helen F. Sutherland||, Peter J. Scambler||, Allan Bradley†¶# & Antonio Baldini*†



TBX1 gene mutations



Lancet, 2003

Mechanisms of disease

Role of *TBX1* in human del22q11.2 syndrome

Hisato Yagi, Yoshiyuki Furutani, Hiromichi Hamada, Takashi Sasaki, Shuichi Asakawa, Shinsei Minoshima, Fukiko Ichida, Kunitaka Joo, Misa Kimura, Shin-ichiro Imamura, Naoyuki Kamatani, Kazuo Momma, Atsuyoshi Takao, Makoto Nakazawa, Nobuyoshi Shimizu, Rumiko Matsuoka

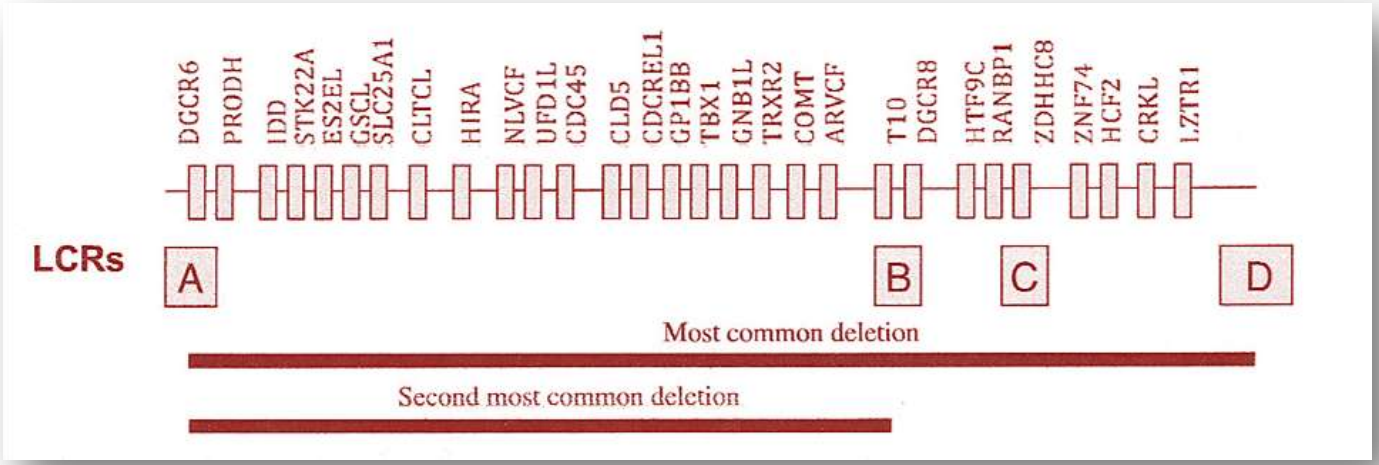
TBX1 e palato

Overt Cleft Palate Phenotype and TBX1 Genotype Correlations in Velo-Cardio-Facial/DiGeorge/22q11.2 Deletion Syndrome Patients

Sean B. Herman,1 Tingwei Guo,1 Donna M. McDonald McGinn,2 Anna Blonska,1,3 Alan L. Shanske,4 Anne S. Bassett,5,6 Eva W.C. Chow,5,6Mark Bowser,2 Molly Sheridan,2 Frits Beemer,7 Koen Devriendt,8 Ann Swillen,8 Jeroen Breckpot,8 M. Cristina Digilio,9 Bruno Marino,10 Bruno Dallapiccola,9 Courtney Carpenter,11 Xin Zheng,12 Jacob Johnson,1 Jonathan Chung,1 Anne Marie Higgins,13 Nicole Philip,14 Tony Simon,15 Karlene Coleman,16 Damian Heine-Suner,17 Jordi Rosell,17 Wendy Kates,18 Marcella Devoto,2 Elaine Zackai,2 Tao Wang,19 Robert Shprintzen,13 Beverly S. Emanuel,2 Bernice E. Morrow1

and the International Chromosome 22q11.2 Consortium

Am J Med Genet 2012



Gene COMT

Gene PRODH

Gene GNB1L

Gene TBX1

Gene ZDHHC8

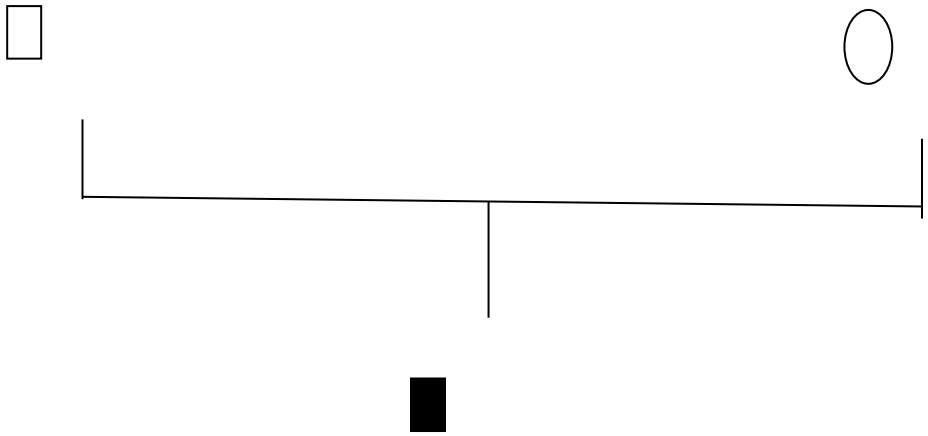
Gene ARVCF

Gene CTLD

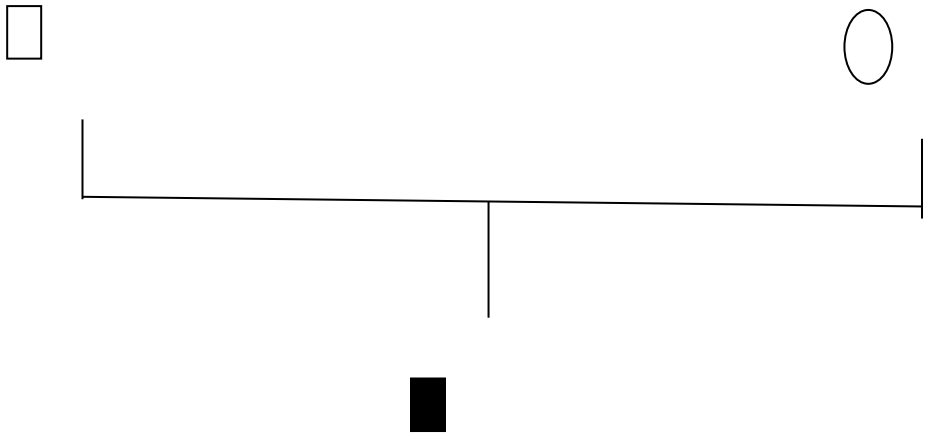
"Profilo neuropsicologico"

Disturbo dell'attenzione
Iperattività
Ansia
Disturbo fobico
Schizofrenia
Disturbo bipolare
Depressione
Ipotonia

Delezione "de novo"

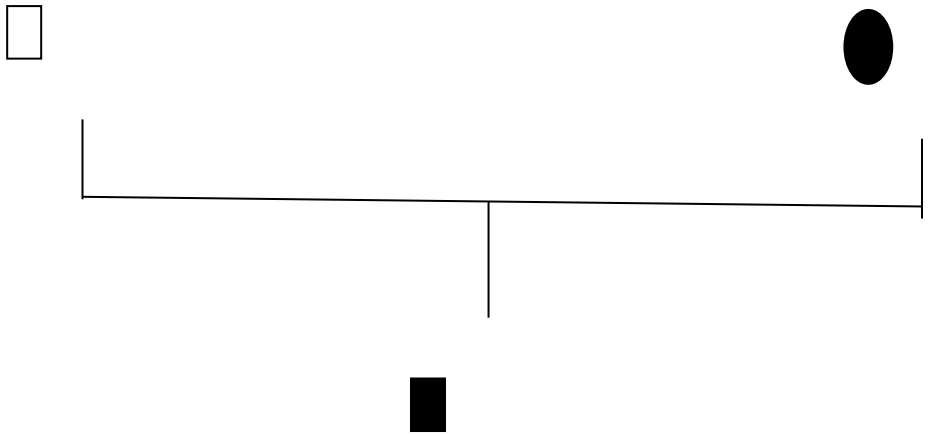


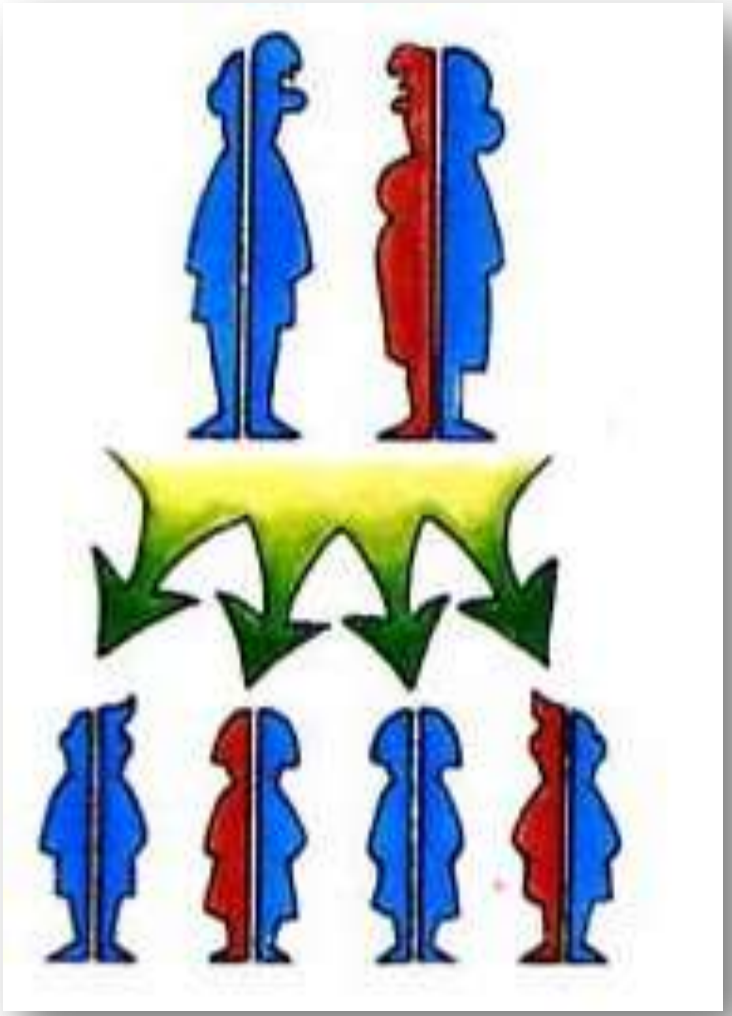
Delezione "de novo"



Delezione "de novo": rischio di ricorrenza per Del22 = 0

Delezione "familiare"





Delezione "familiare": rischio di ricorrenza per Del22 = 50%

"Traslocazione" familiare

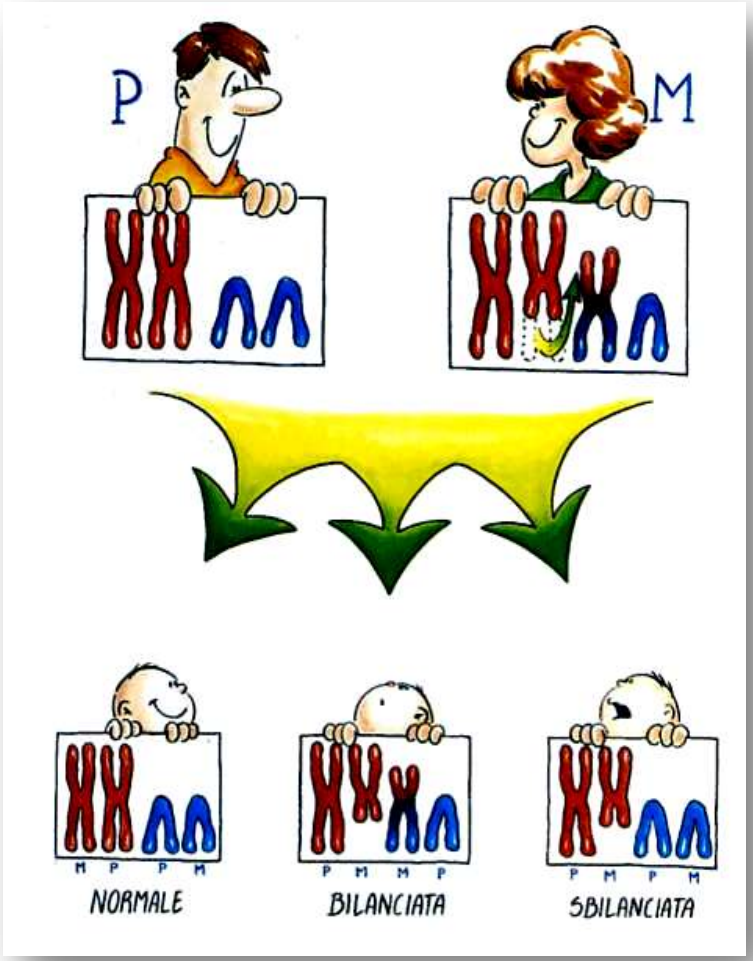


Fig. 3. – Partial G-banded karyotype of patient showing normal 22 (left) derivative X (middle), and normal X (right).

"Inserzione" cromosomica familiare

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics

Genetic Dosage Compensation in a Family with Velo-Cardio-Facial/DiGeorge/22q11.2 Deletion Syndrome

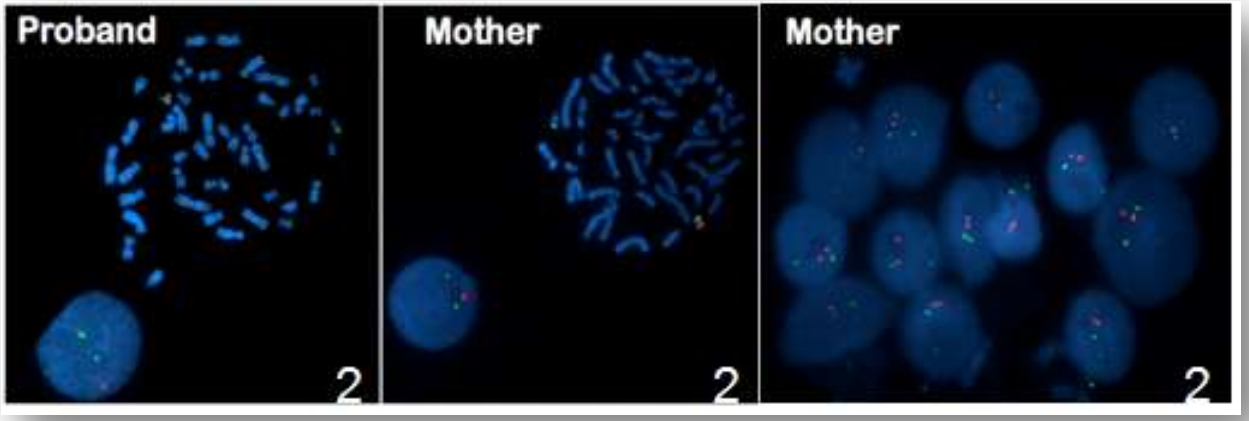
Avishai A. Alkalay,[1] Tingwei Guo,[2] Cristina Montagna,[2] M. Cristina Digilio,[3] Bruno Dallapiccola,[3] Bruno Marino,[4] and Bernice Morrow[2]*

[1]Department of Obstetrics and Gynecology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York

[2]Department of Genetics, Albert Einstein College of Medicine, Bronx, New York

[3]Bambino Gesú Pediatric Hospital, IRCCS, Rome, Italy

[4]University La Sapienza, Pediatric Cardiology, Rome, Italy



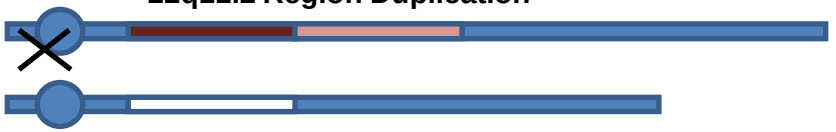
Grandfather ?

Grandmother
(IT31_5388)

Father ?

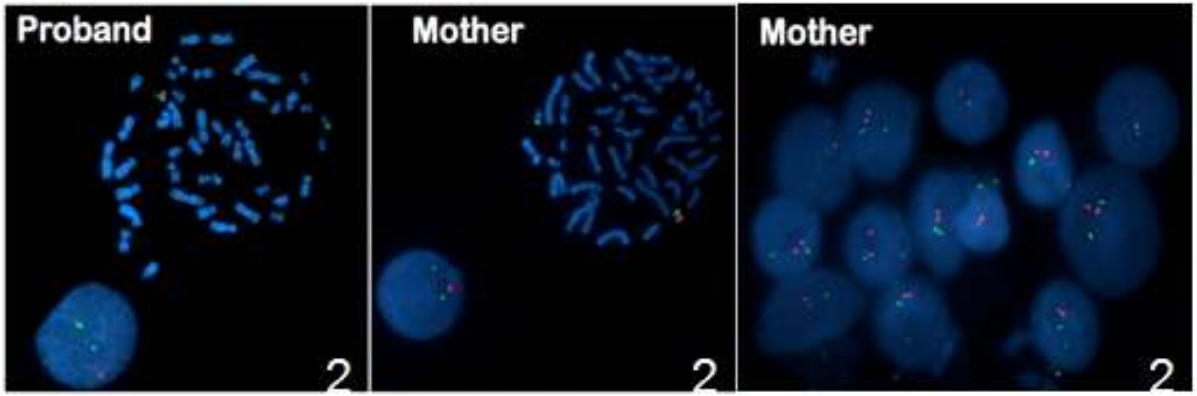
Mother
(IT31.100_7985)

22q11.2 Region Duplication

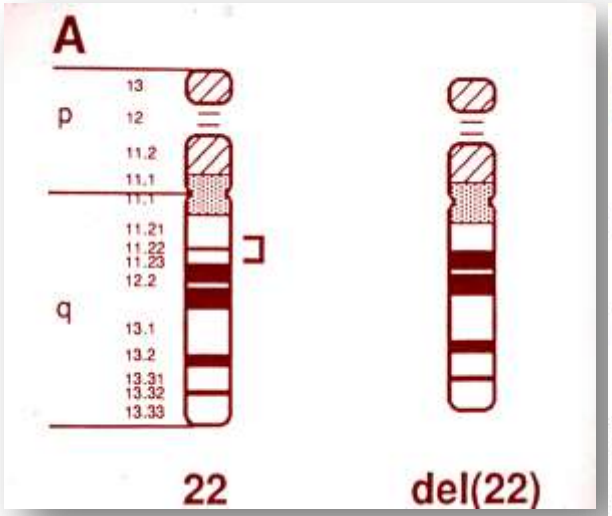


22q11.2 Region Deletion

Son
(IT31.700_7986)



Variabilità del fenotipo e geni modificatori



RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY

Genotype and Cardiovascular Phenotype Correlations with *TBX1* in 1,022 Velo-Cardio-Facial/DiGeorge/22q11.2 Deletion Syndrome Patients

Tingwei Guo,[1] Donna McDonald-McGinn,[2] Anna Blonska,[1,3] Alan Shanske,[4] Anne S. Bassett,[5] Eva Chow,[5] Mark Bowser,[2] Molly Sheridan,[2] Frits Beemer,[6] Koen Devriendt,[7] Ann Swillen,[7] Jeroen Breckpot,[7] Maria C. Digilio,[8] Bruno Marino,[9] Bruno Dallapiccola,[8] Courtney Carpenter,[10] Xin Zheng,[11] Jacob Johnson,[1] Jonathan Chung,[1] Anne Marie Higgins,[12] Nicole Philip,[13] Tony J. Simon,[14] Karlene Coleman,[15] Damian Heine-Suner,[16] Jordi Rosell,[16] Wendy Kates,[17] Marcella Devoto,[2,18,19] Elizabeth Goldmuntz,[18,20] Elaine Zackai,[2,18] Tao Wang,[21] Robert Shprintzen,[12] Beverly Emanuel,[2,18] Bernice Morrow,[1]* and the International Chromosome 22q11.2 Consortium

[1]Department of Genetics, Ob/Gyn and Pediatrics, Albert Einstein College of Medicine, Bronx, New York; [2]Division of Human Genetics, Children's

GRAZIE

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OSPEDALE PEDIATRICO