

Università degli Studi di Messina



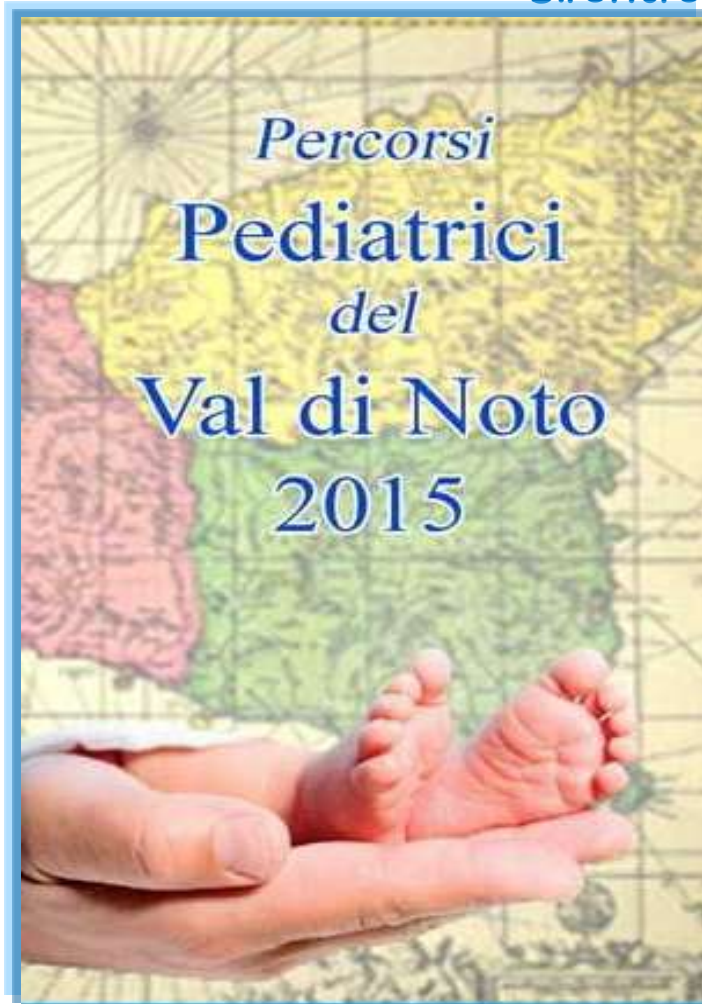
Dipartimento di Scienze Pediatriche, Ginecologiche, Microbiologiche e Biomediche

Scuole di Specializzazione in Pediatria e Genetica Medica

Centro di Riferimento Regionale per la Prevenzione, Diagnosi e Cura delle Malattie Genetiche

U. O. C. di Genetica e Immunologia Pediatrica

Direttore: Prof. Carmelo Salpietro



# EREDITARIETÀ DELLE MALATTIE GENETICHE



# RISCHIO RIPRODUTTIVO 3%

NUMERICHE      STRUTTURALI  
CROMOSOMICHE

GENICHE

MENDELIANE      NON MENDELIANE

AUTOSOMICHE      X-LINKED

DOMINANTI  
RECESSIVE

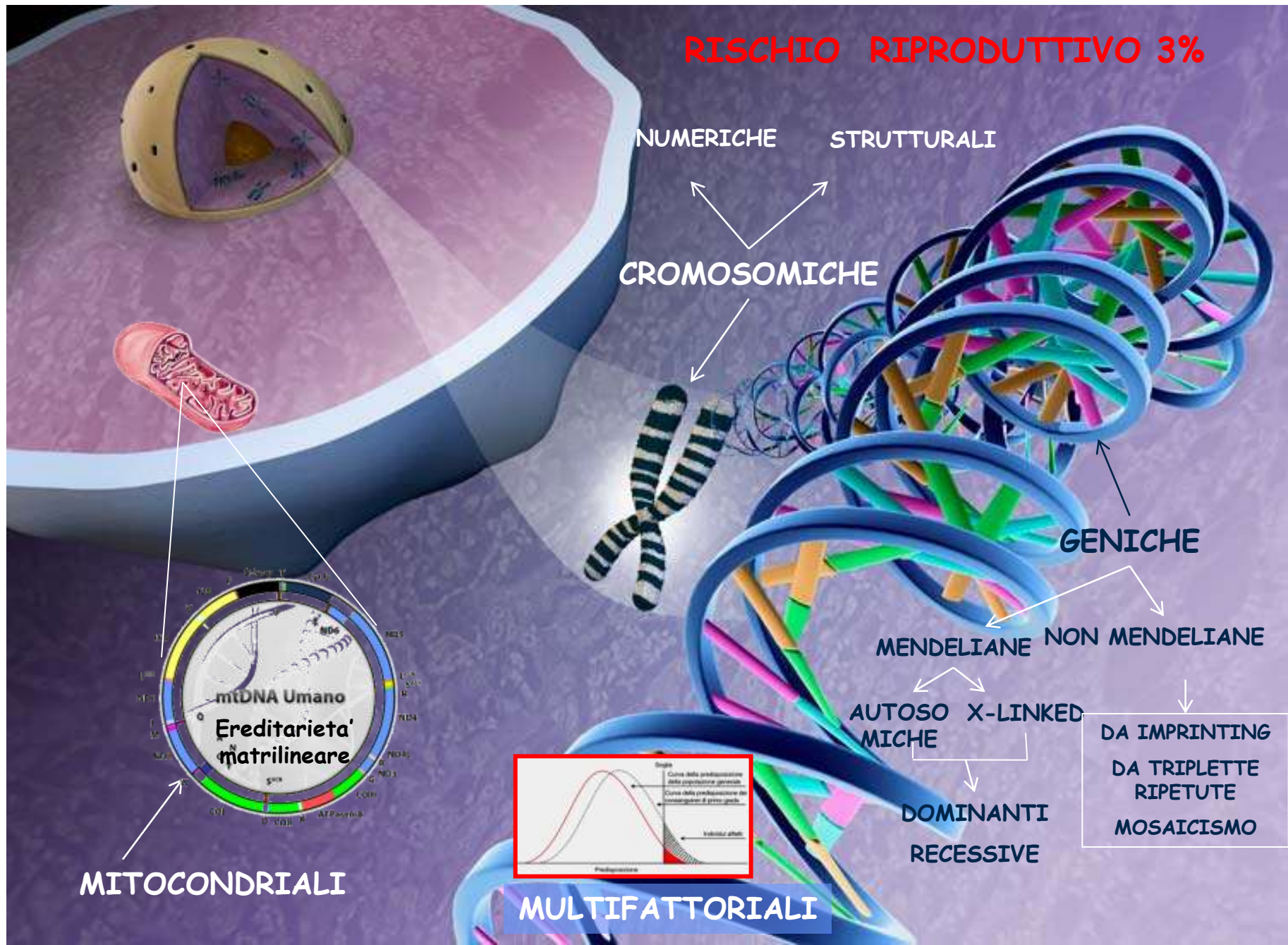
DA IMPRINTING  
DA TRIPLETTE  
RIPETUTE  
MOSAICISMO



MULTIFATTORIALI



MITOCONDRIALI



5.WOLF (4p-)



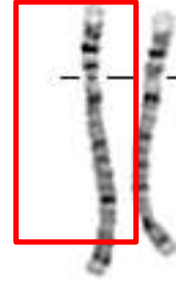
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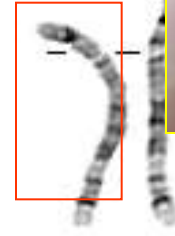
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3



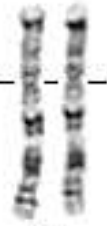
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5



6



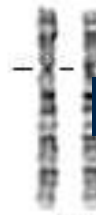
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8



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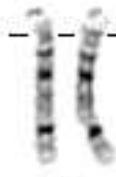


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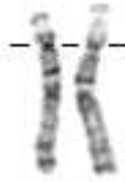
S. KLINEFELTER



13



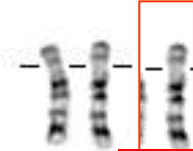
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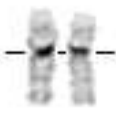
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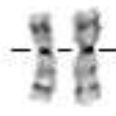
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18



19



20



21



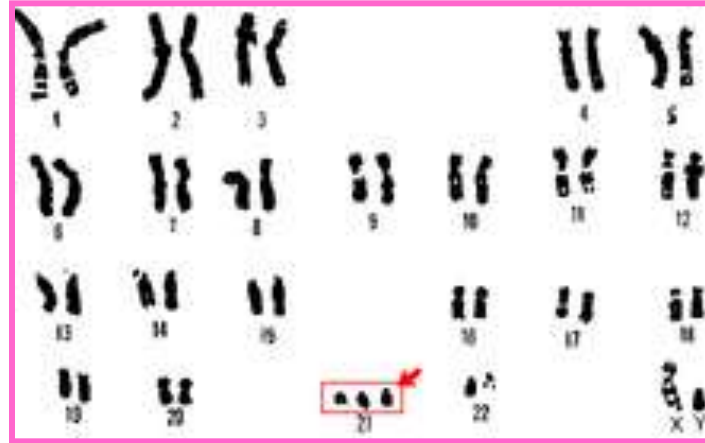
22



X

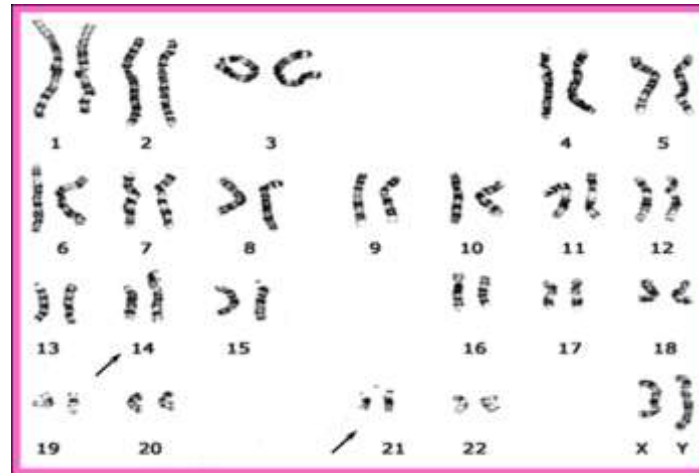


# SINDROME DI DOWN

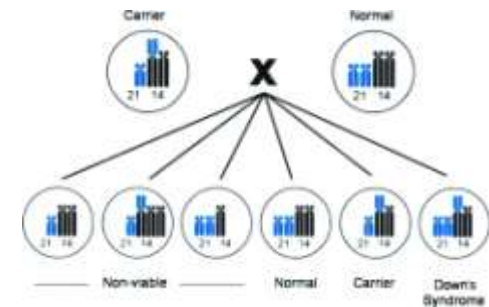


**92%**  
**TRISOMIA LIBERA**

**3%**  
**TRISOMIA A MOISAICO**



**5%**  
**TRISOMIA DA TRASLOCAZIONE**  
**FORMA FAMILIARE**

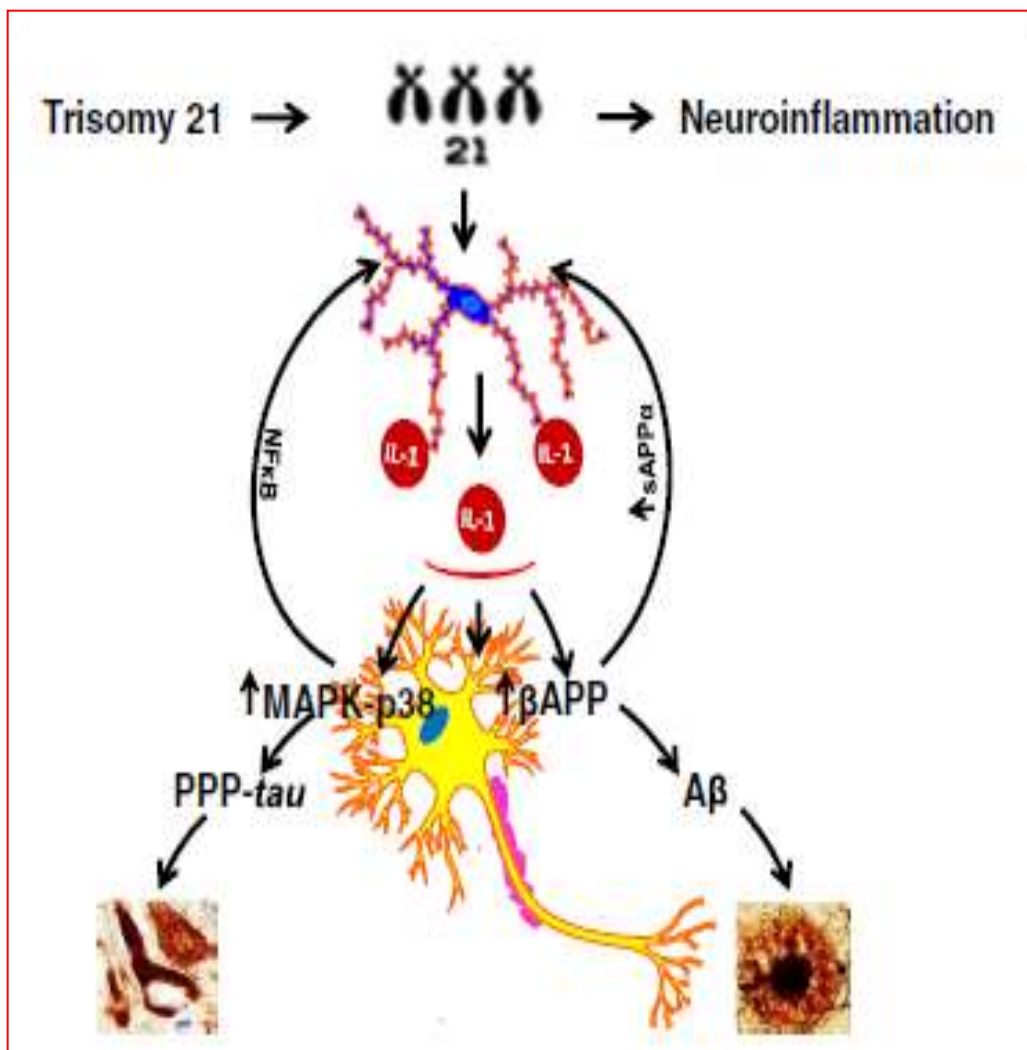


**Table 1 A summary of the inflammation-related genes located on chromosome 21**

Gene	Protein	Function	Reference
<i>βAPP</i>	Amyloid beta precursor protein >5 fold overexpression in DS	Neuronal acute phase protein precursor of fragments Aβ in Alzheimer plaques and sAPP for induction of IL-1β	[16,20,63]
<i>BACE2</i>	β-site APP-cleaving enzymes-2	Cleaves APP for less Aβ and increases IL-1R2, a decoy protein for excess IL-1 capture	[79]
<i>S100B</i>	S100 calcium binding protein astrocyte-derived cytokine	Upregulates IL-1β and βAPP expression, released in response to TNFα	[22,27,82]
<i>CXADR</i>	Coxsackie virus and adenovirus receptor	Activation of JNK and p38-MAPK pathways leading to production of M1 cytokines.	[101]
<i>ADAMTS1</i>	ADAM metalloproteinase with thrombospondin type 1 motif, 1	Secreted protease known to be induced by IL-1β	[102]
<i>ADAMTS5</i>	ADAM metalloproteinase with thrombospondin type 1 motif, 5	Secreted protease known to be induced by IL-1β and TGFβ.	[103]
<i>TIAM1</i>	T-cell lymphoma invasion and metastasis 1	Necessary for cytokine-mediated generation of oxidative species through NADPH oxidase.	[104]
<i>SOD1</i>	Superoxide dismutase 1	Scavenges superoxide radicals producing H <sub>2</sub> O <sub>2</sub> and O <sub>2</sub> .	[105]
<i>IFNAR2</i>	Interferon α, β, and ω receptor 2	Activates JAK/STAT mediated anti-inflammatory pathway	[106,107]
<i>IFNAR1</i>	Interferon α, β, and ω receptor 1	Activates JAK/STAT mediated anti-inflammatory pathway	[106]
<i>IFNGR2</i>	Interferon γ receptor 2	Activates JAK/STAT mediated anti-inflammatory pathway	[107]
<i>RIPK4</i>	Receptor-interacting serine-threonine kinase 4	Necessary for signaling through TNFR1	[108]
<i>CBS</i>	Cystathione-β-synthase	Catalyzes production of hydrogen sulfide (H <sub>2</sub> S) bimodal regulation of inflammation	[109]
<i>PRMT2</i>	Protein arginine methyltransferase 2	Blocks the actions of NFκB in the nucleus	[110]

Aβ β-amyloid, APP precursor protein for β-amyloid, IL interleukin, MAPK mitogen-activated protein kinase, TNF tumor necrosis factor, TGF transforming growth factor, JAK/STAT Janus kinase signal transducer and activator of transcription, TNFR tumor necrosis factor receptor, NFκB Nuclear factor-kappa B.

## S. DI DOWN E MORBO DI ALZHEIMER PRECOCE



➤ Anomalie a livello della corteccia cerebrale, del tronco encefalico e del cervelletto.

➤ Entro i 40 anni di vita tutti i soggetti Down sviluppano cambiamenti patologici simili alla **neurodegenerazione tipica del morbo di Alzheimer**, con placche senili ed ammassi neurofibrillari.

➤ i geni triplicati attivano la microglia con sovraespressione e rilascio di citochine proinfiammatorie, in particolare IL-1 $\beta$ , che, a sua volta, induce ulteriori aumenti di proteina precursore per la  $\beta$ -amiloide (APP), **con deposizione negli strati corticali di placche contenenti la proteina amiloide (APP)**.

➤ terapia continuativa con antiinfiammatori e antiossidanti utile nel rallentare la comparsa di questa condizione

# SINDROME DEL CRI DU CHAT

## SINDROME 5p-



**Microcefalia**

Difficoltà alla suzione

**Pianto acuto simile a un miagolio** **Facies arrotondata "a luna piena"**

**Ipertelorismo**

**Epicanto**

Rime oculari oblique verso il basso

Sella nasale larga e piatta

Impianto basso delle orecchie

**Micrognazia**

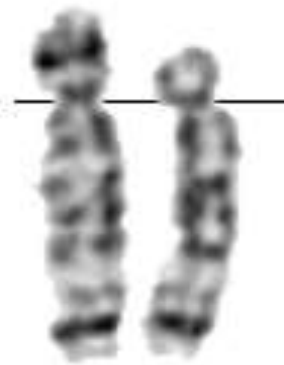
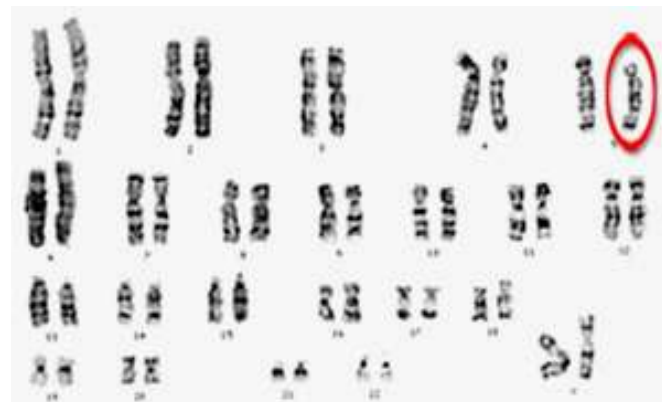
**FISH**



**REGIONE CRITICA**

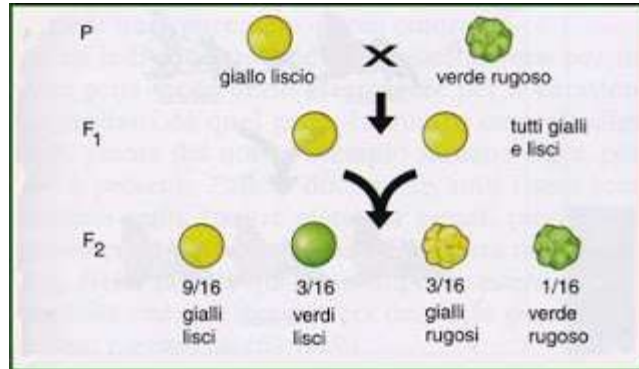
**5p15.3 (pianto)**

**5p15.2 (fenotipo)**



*Deletion of the telomerase reverse transcriptase gene and haploinsufficiency of telomere maintenance in Cri du chat syndrome. Zhang A, Zheng C, Hou M, Lindvall C, Li KJ, Erlandsson F, Björkholm M, Gruber A, Blenow E, Xu D. Am. J. Hum. Genet. 2003 Apr;72(4):940-8. Epub 2003 Mar 10.*

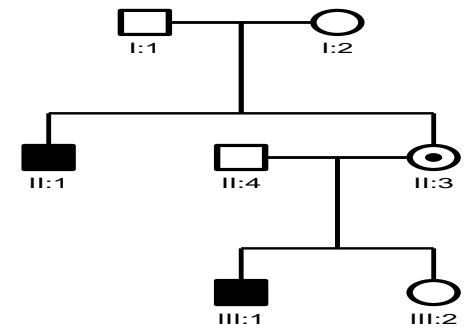
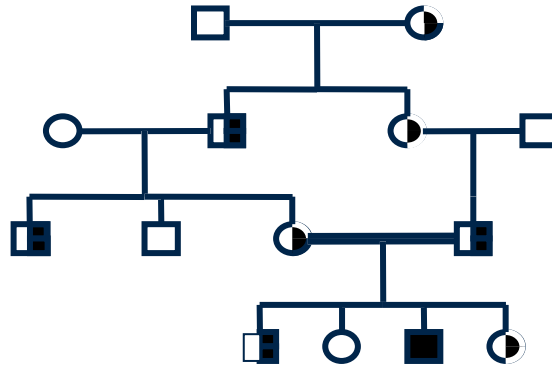
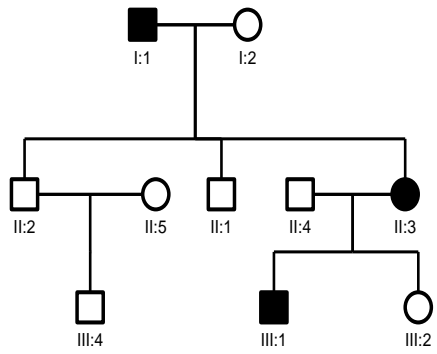




## MALATTIE AUTOSOMICHE DOMINANTI

## MALATTIE AUTOSOMICHE RECESSIVE

## MALATTIE LEGATE AL CROMOSOMA X



## MALATTIE AUTOSOMICHE DOMINANTI

SEGREGAZIONE VERTICALE  
NELLA FAMIGLIA

LE PERSONE **AFFETTE**  
TRASMETTONO LA  
MUTAZIONE  
AL 50% DEI FIGLI

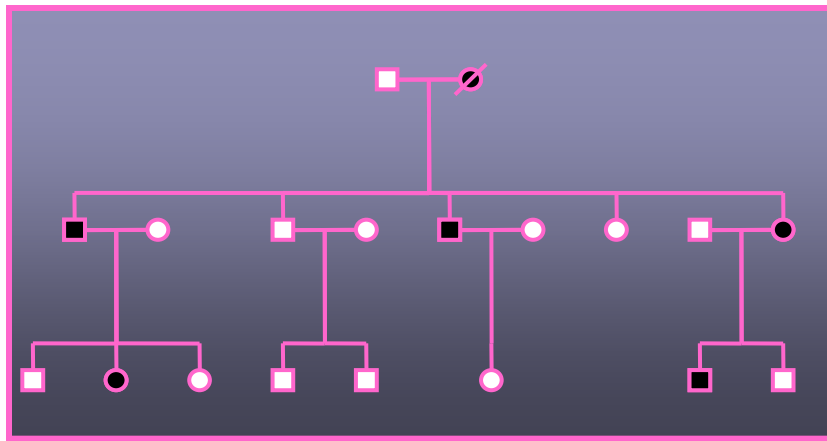
LE PERSONE **NON**  
**AFFETTE** HANNO SOLO  
FIGLI NON AFFETTI

Il genitore affetto di  
solito è eterozigote

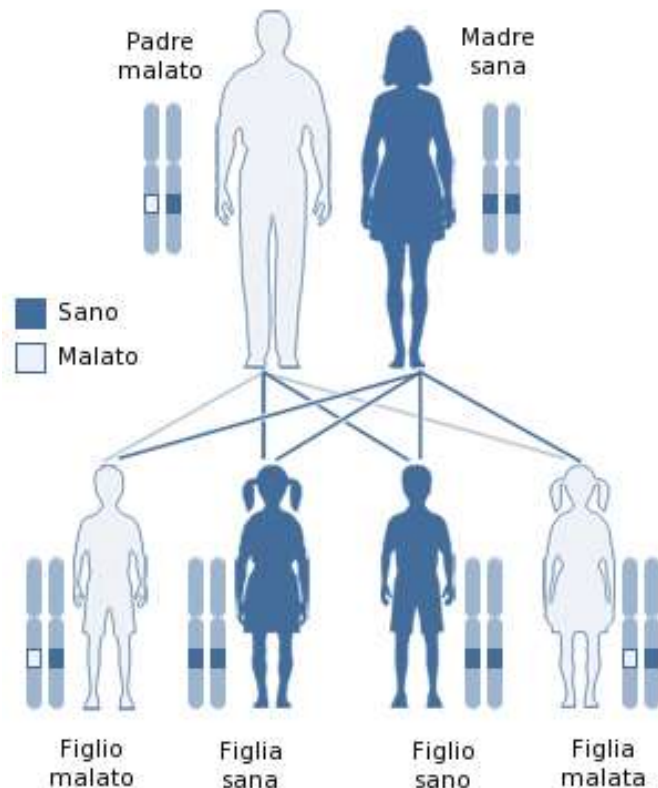


La malattia si trasmette in media al  
50% dei figli

indipendentemente dal loro sesso



Trasmissione autosomica dominante



## ETÀ DI ESORDIO VARIABILE

alcune malattie autosomiche dominanti presentano il fenomeno della anticipazione, che consiste in un **esordio più precoce ed un aggravamento dei sintomi con il passare delle generazioni**



**DISTROFIA MIOTONICA**

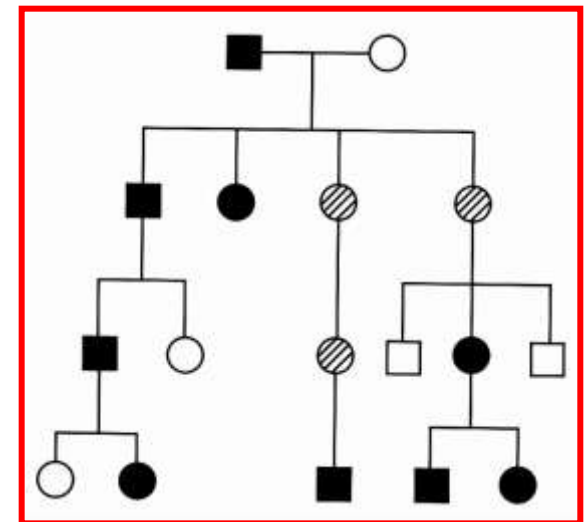
## PENETRANZA

altri geni      ambiente

modulano, fino ad impedire l'espressione di un gene mutato



## DIFETTO DI PENETRANZA



## SALTO DI GENERAZIONE

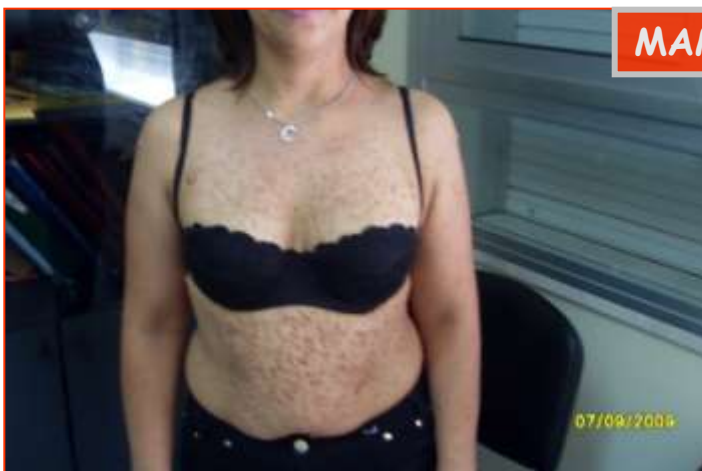
- Soggetto con mutazione affetto
- Soggetto con mutazione non affetto

# ESEMPIO DI MALATTIA AUTOSOMICA DOMINANTE: NEUROFIBROMATOSI TIPO I

GIADA



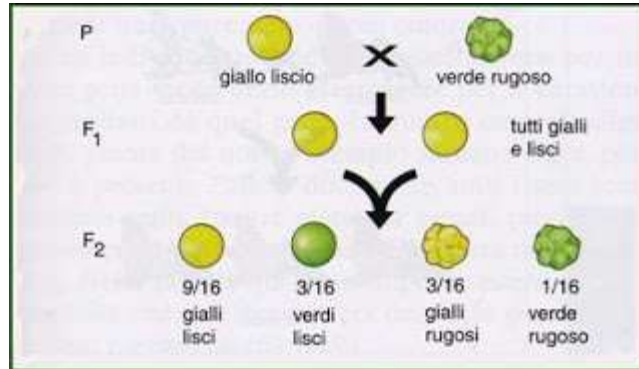
MAMMA



NONNA



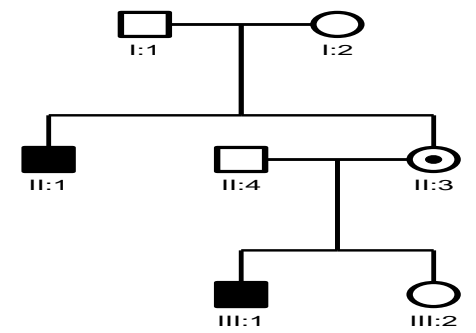
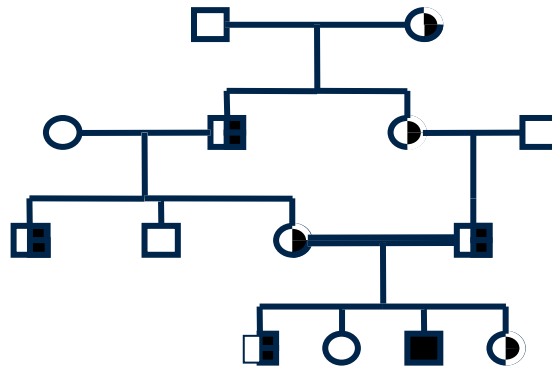
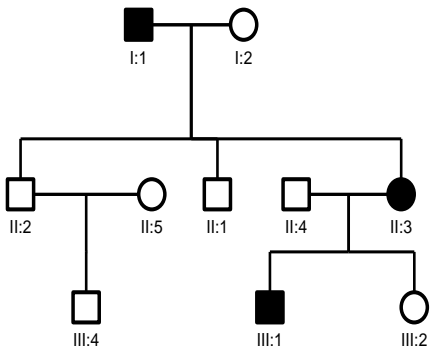
**ESPRESSIVITÀ MOLTO VARIABILE**  
(soprattutto interfamiliare)



## MALATTIE AUTOSOMICHE DOMINANTI

## MALATTIE AUTOSOMICHE RECESSIVE

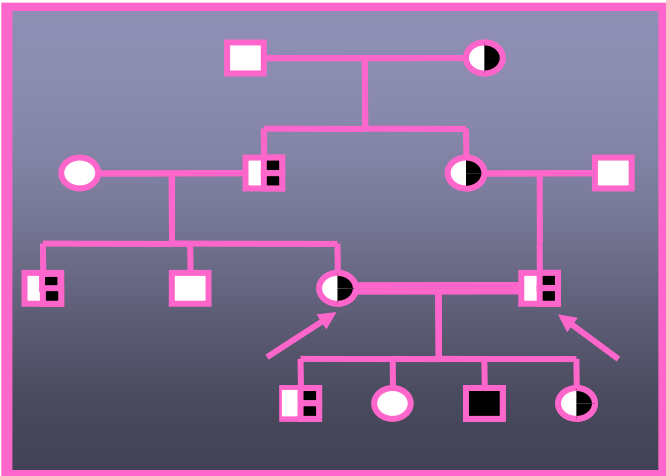
## MALATTIE LEGATE AL CROMOSOMA X



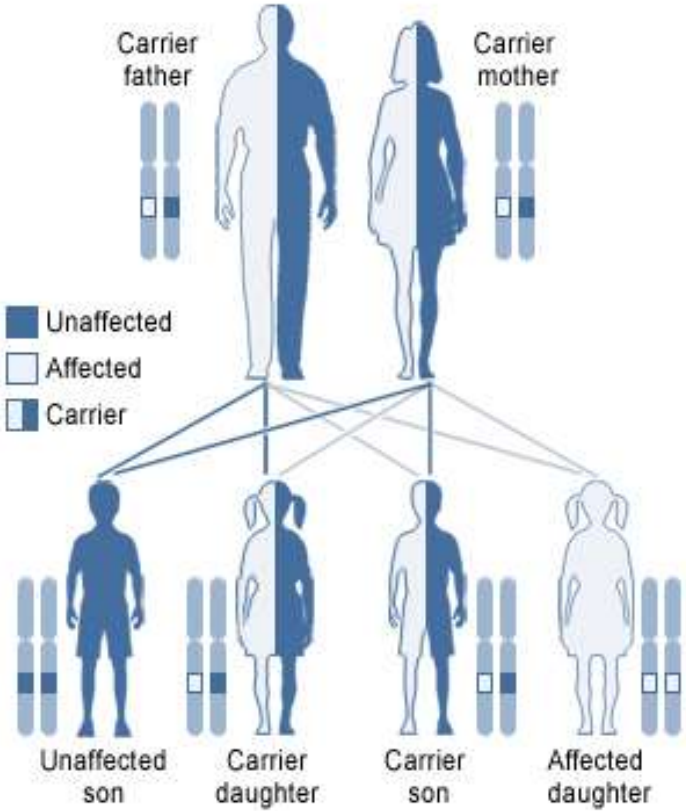
# MALATTIE AUTOSOMICHE RECESSIVE



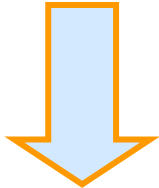
TRASMISSIONE ORIZZONTALE NELLA FAMIGLIA



Autosomal recessive



DA GENITORI NON AFFETTI ETEROZIGOTI



Il carattere si trasmette in duplice dose (omozigosi),  
in media al 25% dei figli indipendentemente dal loro sesso

la malattia si manifesta  
in media in  $\frac{1}{4}$  dei figli

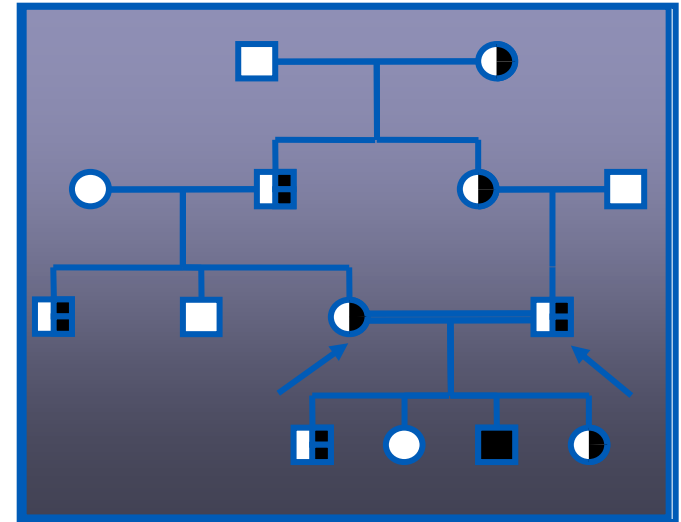
## CONSANGUINEITÀ

Se una malattia autosomica recessiva è rara è tanto più probabile che origini dal **matrimonio tra consanguinei**

**I cugini di primo grado, che hanno i nonni in comune, in assenza di patologie rilevanti in famiglia**



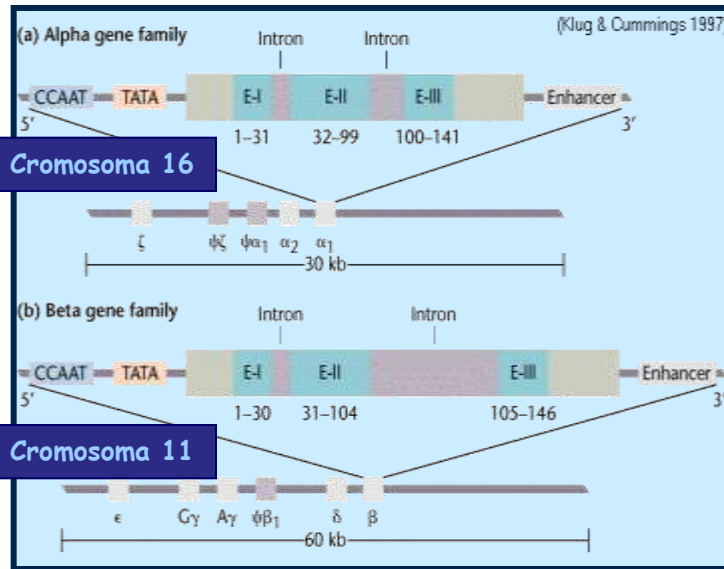
hanno un **rischio riproduttivo doppio (6%)** rispetto a quello della popolazione generale (3%)



Consanguinei (tipo di matrimonio)	Rischio aggiuntivo rispetto al rischio di specie (3%)
V grado (cugini 2°)	1
III grado (cugini 1°)	3
II grado (zio-nipote; fratellastri)	7
I grado (incesto)	30-50

LA CONSANGUINEITÀ È DUNQUE UN POTENZIALE FATTORE DI RISCHIO PER LE MALATTIE AUTOSOMICHE RECESSIVE

# TALASSEMIA



Hb A	$\alpha_2\beta_2$	96%
Hb A <sub>2</sub>	$\alpha_2\delta_2$	3%
Hb F	$\alpha_2\gamma_2$	1%

Beta Thalassaemia	Delta-Beta Thalassaemia	Alpha Thalassaemia
$\alpha_2\beta_2 \downarrow$	$\alpha_2\beta_2 \downarrow$	$\downarrow\alpha_2\beta_2$
$\alpha_2\delta_2$	$\alpha_2\delta_2 \downarrow$	$\downarrow\alpha_2\delta_2$
$\alpha_2\gamma_2$	$\alpha_2\gamma_2$	$\downarrow\alpha_2\gamma_2$

Genotype	Syndrome	Hb A	Hb A <sub>2</sub>	Hb F
$\beta^+ / \beta$	minima	95	3.5-8.0	0-6
	minor	95	3.5-8.0	0-6
$\beta^+ / \beta^+$	intermedia	25-65	1-4	30-70
$\beta^0 / \beta^0$	major	0	1-4	>95
$\beta^0 / \beta^+$	major	<20	1-4	>75

## Mutazioni testate in soggetti con beta-talassaemia in Sicilia

LOCATION	MUTATION	$\beta$ -THAL TYPE
IVS 1-110	G→A	$\beta^+$
CD 39	C→T	$\beta^0$
IVS 2-1	G→A	$\beta^0$
CD 6 A	-A	$\beta^0$
IVS 1-1	G→A	$\beta^0$
IVS 1-6	T→C	$\beta^+$
IVS 2-745	C→G	$\beta^+$
-87	C→G	$\beta^+$

Rigoli L, Meo A, Salpietro DC et al. Molecular analysis of beta-talassaemia patients in high incidence area of southern Italy Clin Lab Haem, 2001



## GENE CFTR: STORIA

cromosoma 7

gene CFTR

descritte più di 1700 mutazioni

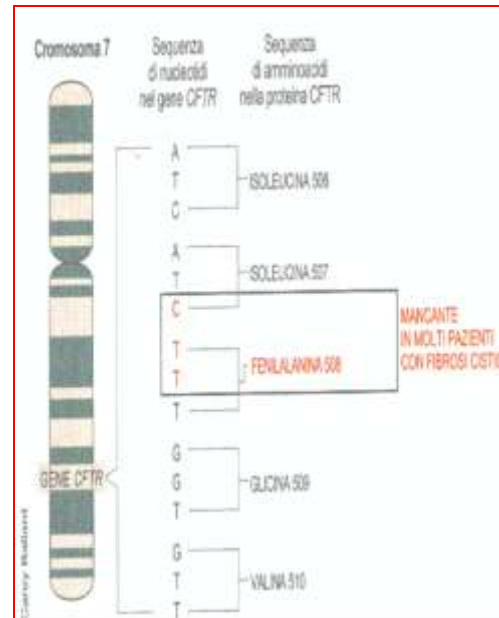
70% dei casi è presenza dell'allele delta F508.

20-30% correla con altre 30 mutazioni più comuni.

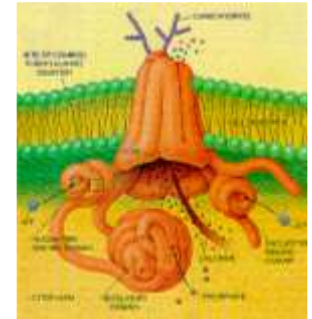
Non esiste una chiara correlazione genotipo-fenotipo.

### Modificazioni del Fenotipo

- eterogeneità allelica
- presenza di mutazioni multiple nello stesso gene
- geni modificatori



# FIBROSI CISTICA



### Infertilità

#### Screening portatori FC anni 2004-2014

Indicazione: -azo-oligo-oligoastenospermia  
-familiarità

Numero totale : 1490 esami eseguiti  
Portatori sani: 16

EMANUELE 2 anni

IRR a carico delle alte e basse vie aeree

due volte positivo allo screening neonatale per fibrosi cistica

TEST DEL SUDORE NEGATIVO

# FIBROSI CISTICA



L997F (ORIGINE MATERNA)

N1303K (ORIGINE PATERNA)

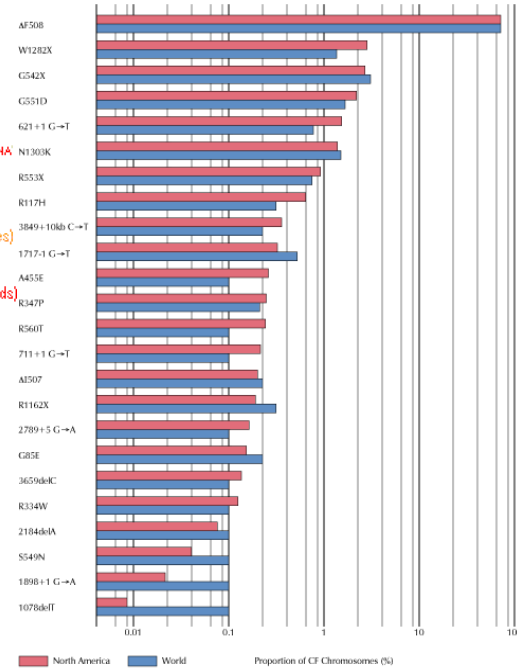
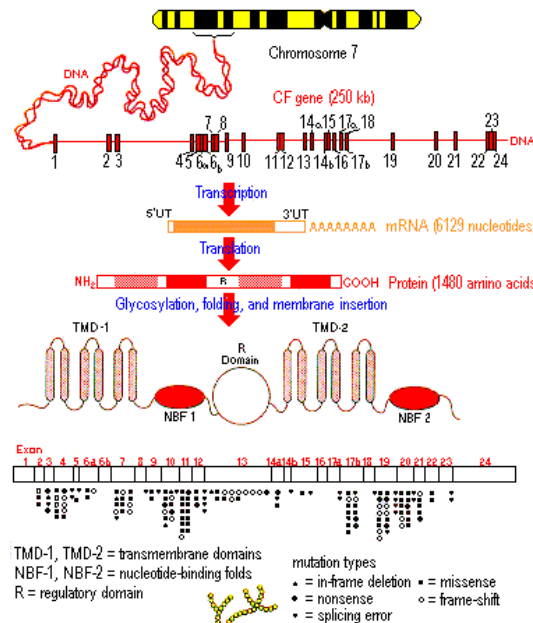
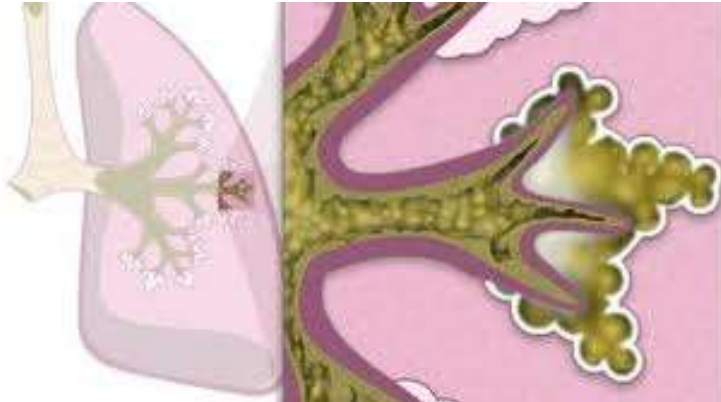


Figure 4. Catalog of relative frequencies of specific *CFTR* mutations displays the prominence of a particular defect, ΔF508, the absence of phenylalanine from the expressed protein's 508 position. Among the 24 mutations each accounting for at least 0.1% of all CF chromosomes, it is a standout: its 66.1% frequency in North American mutations (red) matches its 66% frequency worldwide (blue). Among the rest, only five in North America (and four worldwide) account individually for more than 1% of CF chromosomes, and none accounts for more than 2.5%. The frequencies range downward to 1078delT, identified in a single North American CF chromosome among the 10,438 surveyed. Three types of mutation can make long spans of *CFTR* inexpressible. Those named by a position plus or minus a second number occur in introns rather than exons and interfere with messenger RNA splicing. Those ending in X create a premature stop codon. Those labeled "del" involve loss of a single nucleotide, causing a frameshift in the gene's code. In *CFTR*, these mutation types are remarkably numerous; here, they are 13 of 24.

# SINDROME DI OMENN AUTOSOMICA RECESSIVA

Unigenito, Nato alla 38° settimana di gestazione  
Parto eutocico, PN 3.250 Kg. L 50 cm  
Perinatalità nella norma  
Ittero fisiologico. Allattamento con formula.

1 mese:

ERITRODERMIA E DESQUAMAZIONE CUTANEA DIFFUSA  
DIAGNOSI DI APLV → idrolisato

**EO:** Diarrea importante  
Mughetto al cavo orale  
Xerosi cutanea diffusa in corrispondenza del  
viso, cuoio capelluto, arti inferiori, tronco,  
mani; intensa desquamazione essudativa  
in sede retroauricolare, guance e  
pieghe del collo. distrofia  
Linfoadenomegalia ed epatomegalia

## ESAMI EMATOCHIMICI:

GB: 10420 mmc (E 21%)  
assenza di linfociti B, linfociti T nella norma  
IgA e IgM assenti IgE: 10450 UI/ml

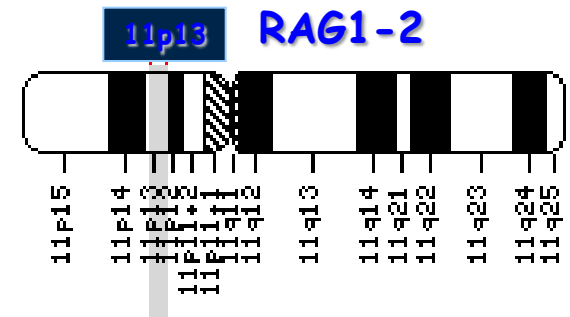


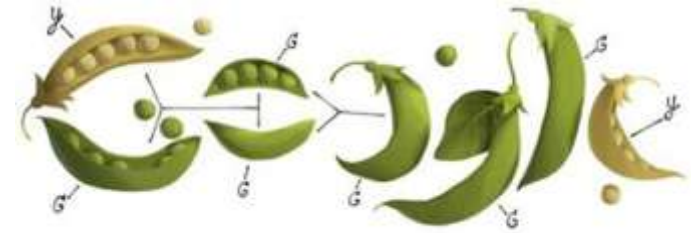
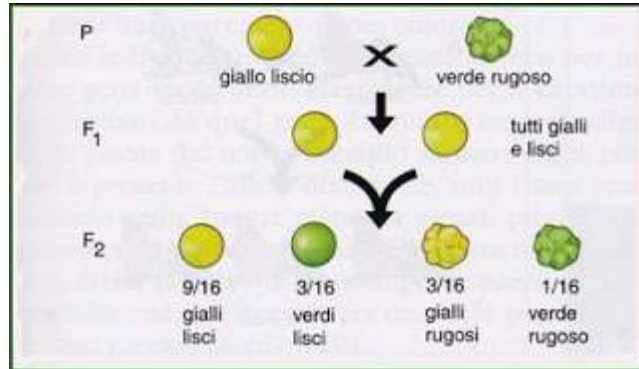
**DAVIDE 3 MESI**



**TMO**

Eterozigote composto  
per la mutazione  
C2387T/C3016G del  
gene RAG1

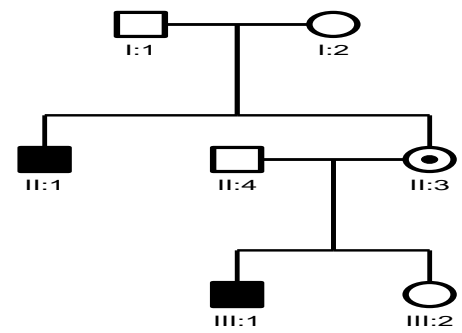
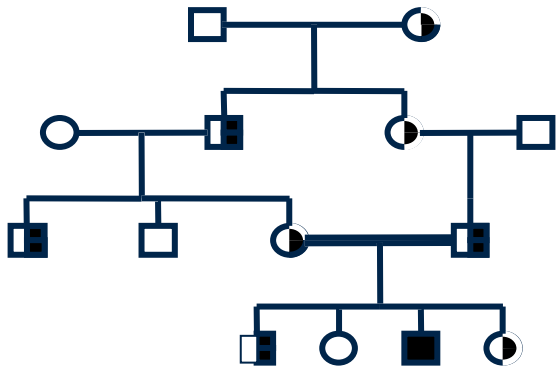
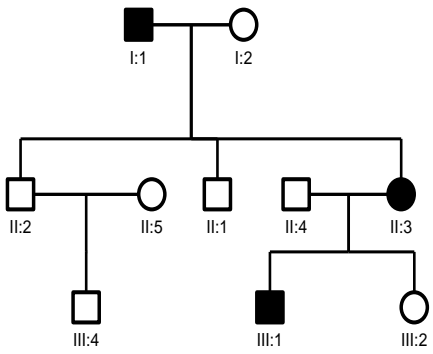




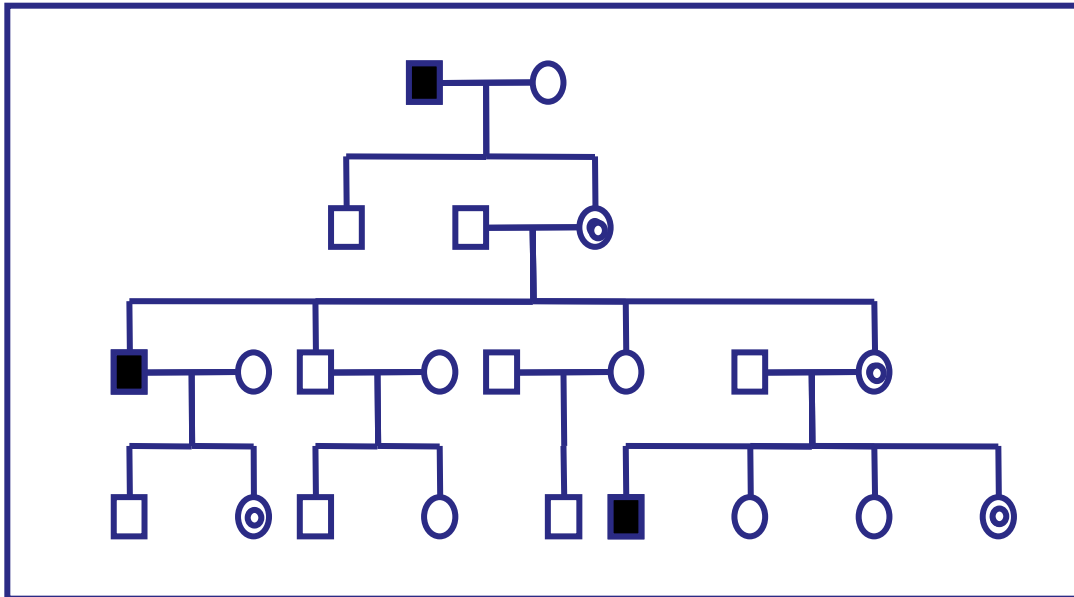
## MALATTIE AUTOSOMICHE DOMINANTI

## MALATTIE AUTOSOMICHE RECESSIVE

## MALATTIE LEGATE AL CROMOSOMA X



# MALATTIE LEGATE AL CROMOSOMA X

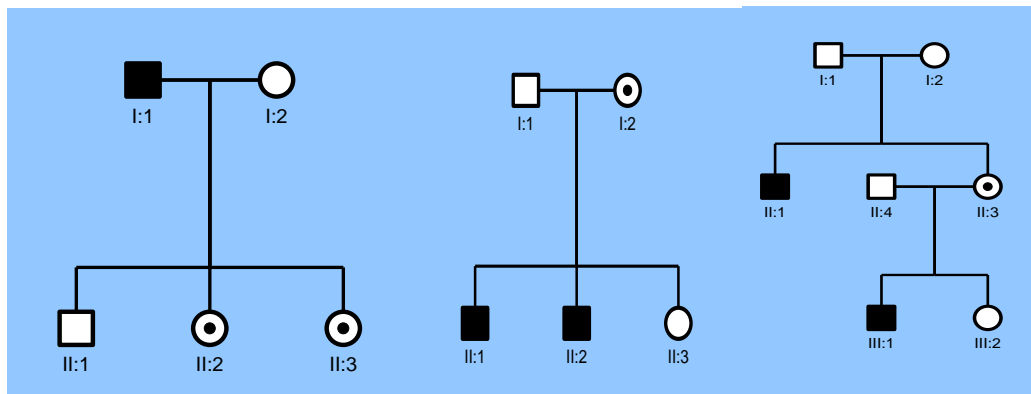


si manifestano essenzialmente nei  
**maschi emizigoti**

Le femmine eterozigoti manifestano  
solo eccezionalmente la mutazione

**50% DEI FIGLI MASCHI È NON AFFETTO**  
**50% È EMIZIGOTE AFFETTO**

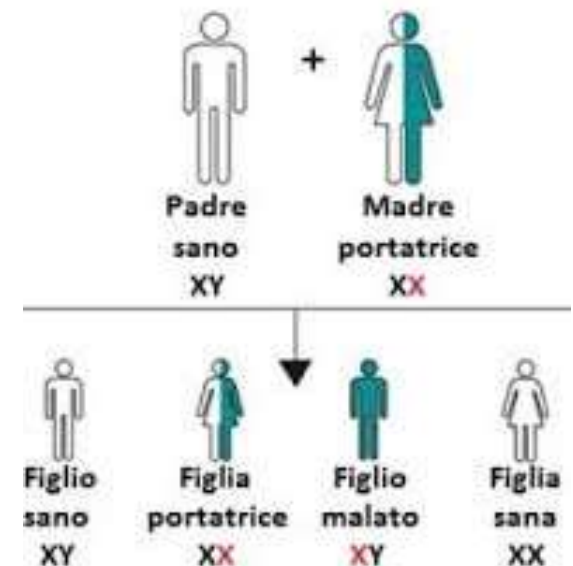
**TUTTE LE FIGLIE SONO NON AFFETTE**  
**LA METÀ SONO ETEROZIGOTI,**  
**COME LA MADRE**



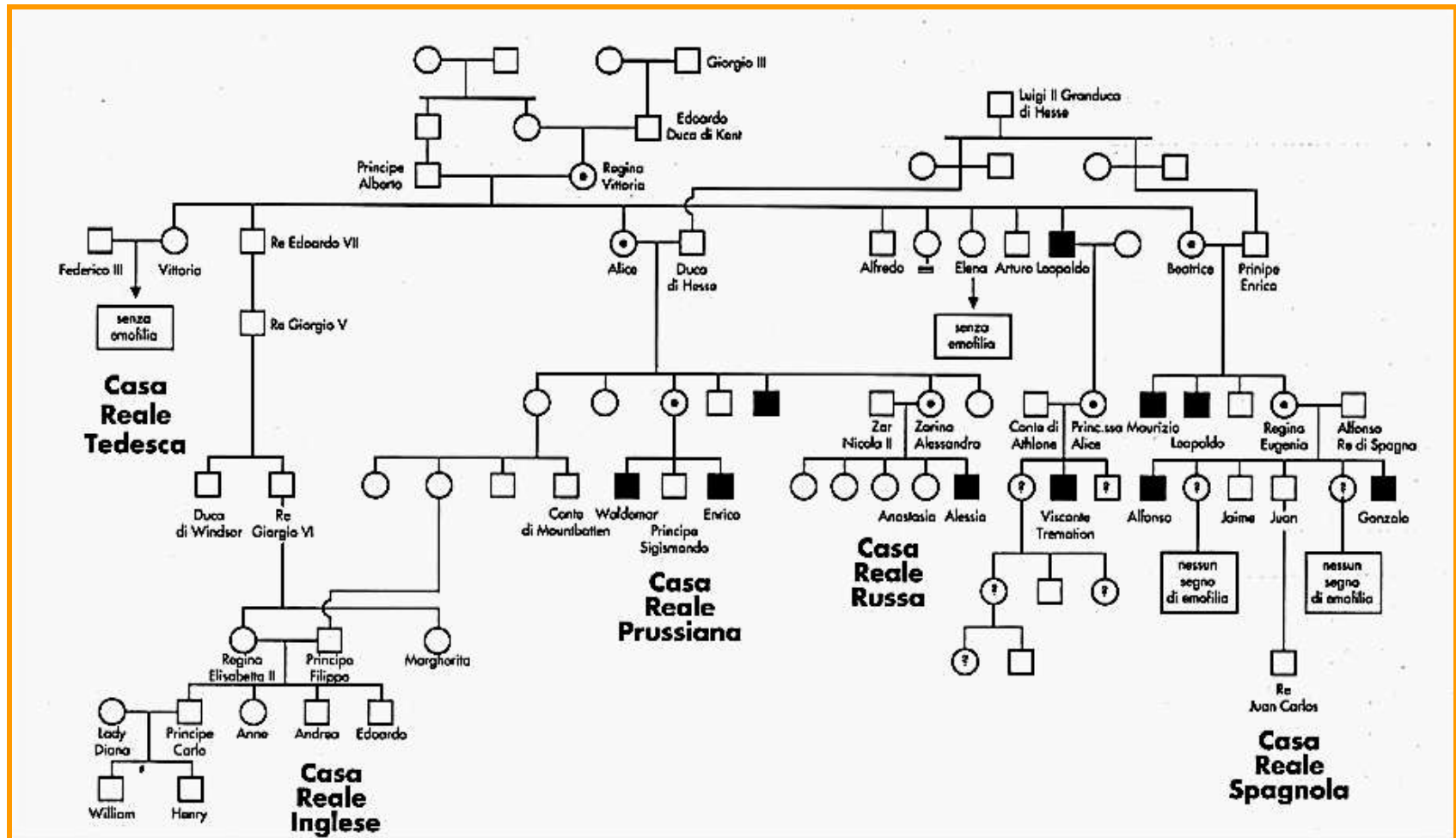
Non si osserva mai la trasmissione della malattia da maschio a maschio

I casi isolati possono originare da nuova mutazione nell'oogenesi

E' importante in queste famiglie definire il genotipo delle femmine



# ALBERO GENEALOGICO DELLA REGINA VITTORIA



Alcuni discendenti maschi delle Case Reali Russa e Spagnola (simboli neri) erano affetti da emofilia

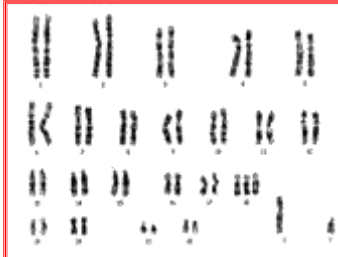
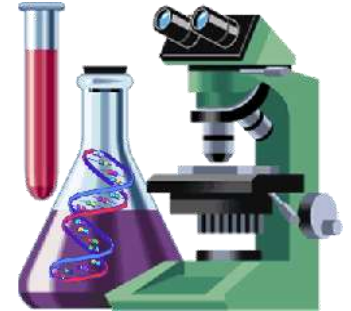
# LE OPPORTUNITA' DIAGNOSTICHE OGGI



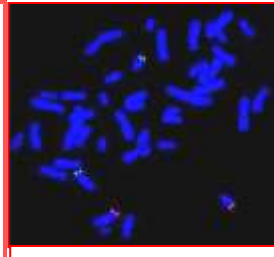
**EVOLUZIONE NELLA  
DIAGNOSTICA FENOTIPICA**

**D  
A  
T  
A  
B  
A  
S  
E**

**ORPHANET  
POSSUM  
OMIM  
LONDON**



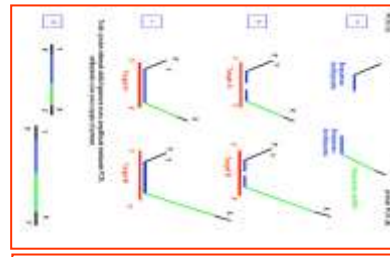
**Cariotipo**



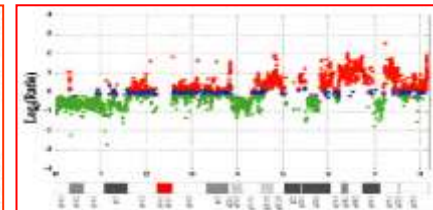
**FISH**



**Analisi di Linkage**



**MLPA**



**Comparative Genomic  
Hybridation**

**ESOMICA**

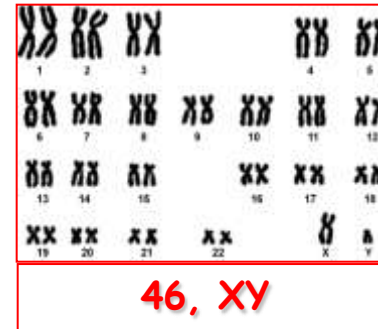
**PROTEOMICA**

**METABOLOMICA**

# ...Il lungo pellegrinaggio sanitario di Alessio....



- Sindrome di Down
- Sindrome ATR-X
- Sindrome velocardiofaciale
- Sindrome Prader-Willi
- Sindrome di Williams
- Sindrome di Chudley-Lowry
- Sindrome dell'X-fragile



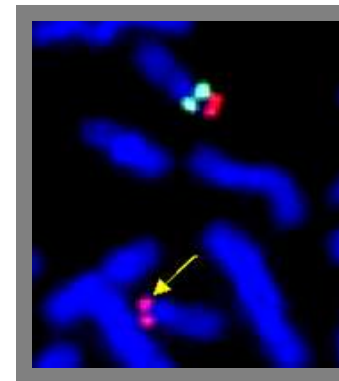
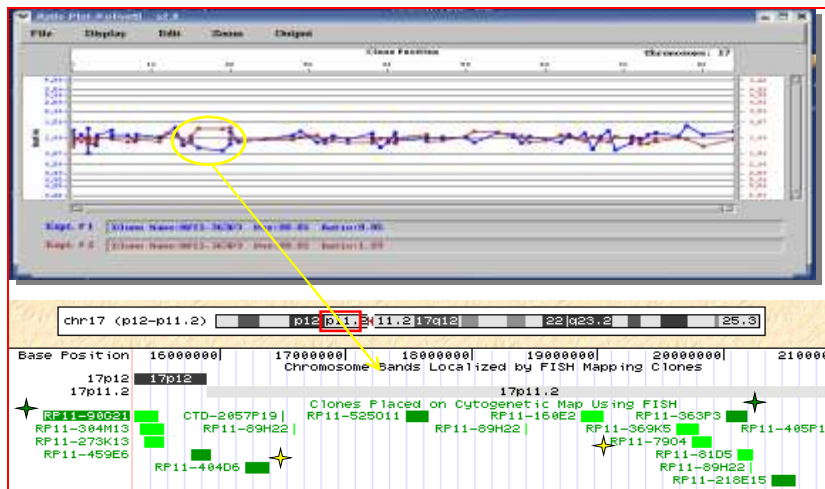
- Ipotonia infantile
- Bassa statura
- Scoliosi
- Criptorchidismo



- Ritardo mentale
- Disturbi del linguaggio
- Iperattività

## SINDROME DI SMITH-MAGENIS

L'analisi array-CGH utilizzando circa 2600 cloni rappresentativi dell'intero genoma ad una risoluzione di circa 1Mb, ha evidenziato la delezione di due cloni che mappano sulla regione 17p11.2



- Brachicefalia
- Profilo piatto
- Prognatismo
- Voce roca
- Brachisindattilia
- FISH CON SONDE SPECIFICHE

**Comparative Genomic Hybridation**  
**Microdelezione interstiziale in 17p11.2**





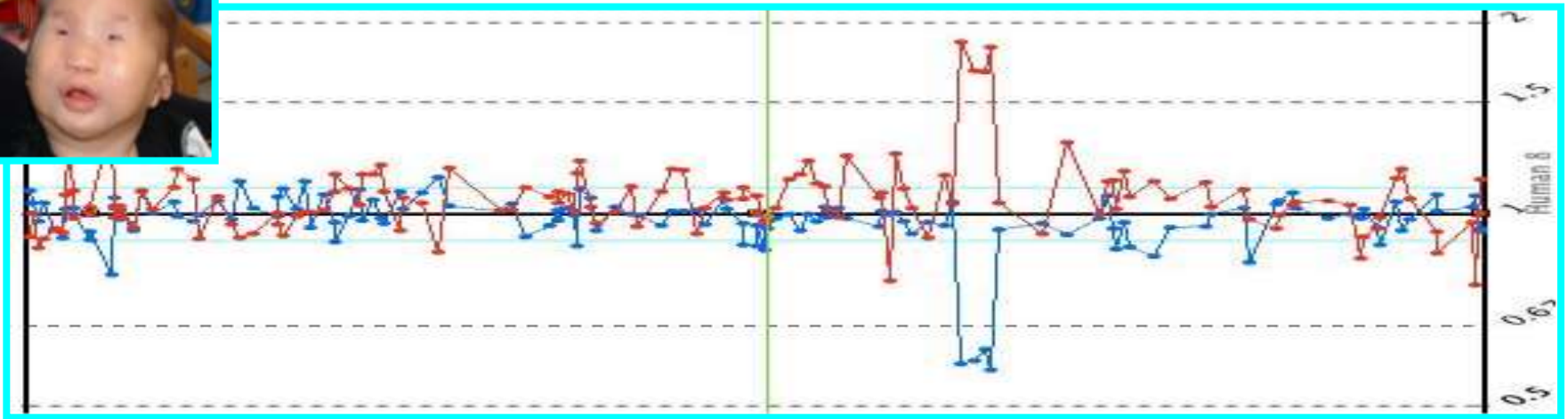
- IPERTELORISMO
- BLEFAROFIMOSI BILATERALE
- CIGLIA SOTTILI SOLO SULLE PALPEBRE SUP
- SOPRACCIGLIA RADE, SOTTILI, ARCUATE
- RADICE NASALE APPIATTITA, NARICI PICCOLE
- FILTRO NASALE LUNGO E LISCIO
- BOCCA PICCOLA, LABBRA SOTTILI,
- LINGUA PROTRUSA
- ORECCHIE DISMORFICHE



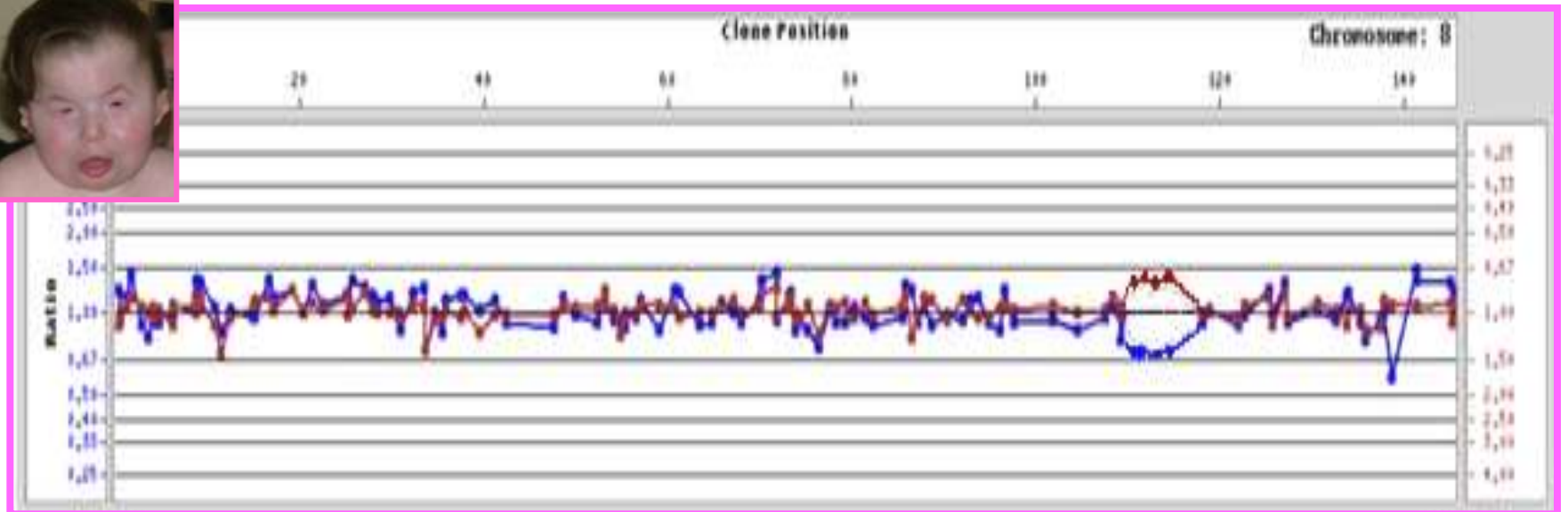
Nablus Mask-Like Facial Syndrome Teebi AS, Am J Med Genet, 2000

Confirmation of NablusMask-like Facial Syndrome CD Salpietro, S Briuglia, MV Merlino, L Rigoli, B Dallapiccola Am J Med Genet, 2003

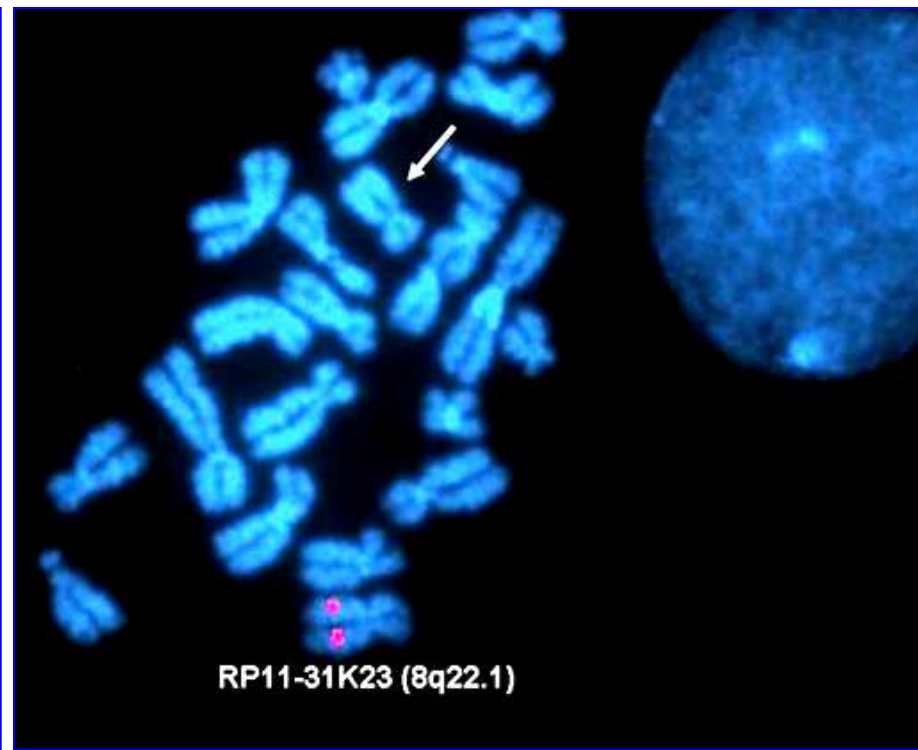
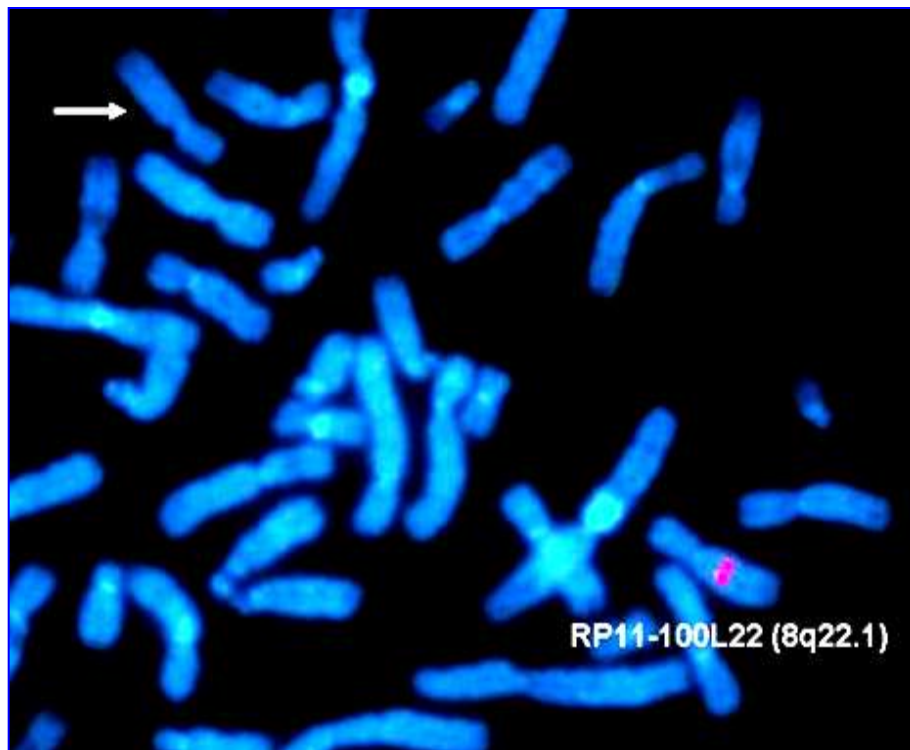
# CGH ARRAY



**del(8)(q22.1q22.1) *de novo***



# FISH



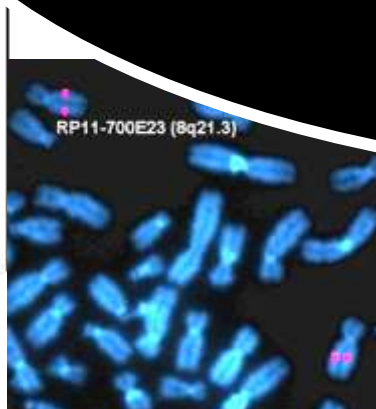
Nablus syndrome maps to 8q21.3-q22.1



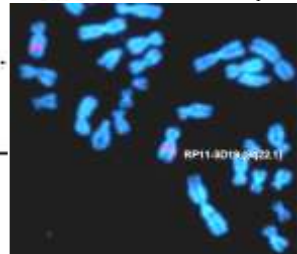
Shieh JT, Aradhya S, Novelli A, Manning MA, Cherry AM, Brumblay J, Salpietro CD, Bernardini L, Dallapiccola B, Hoyne HE. Nablus mask-like facial syndrome is caused by a microdeletion of 8q detected by array-based comparative genomic hybridization. *Am J Med Genet A*. 2006 Jun 15;140(12):1267-73.

Patier

Patient 2



SRO ~ 4.2 Mb



LEGENDA:

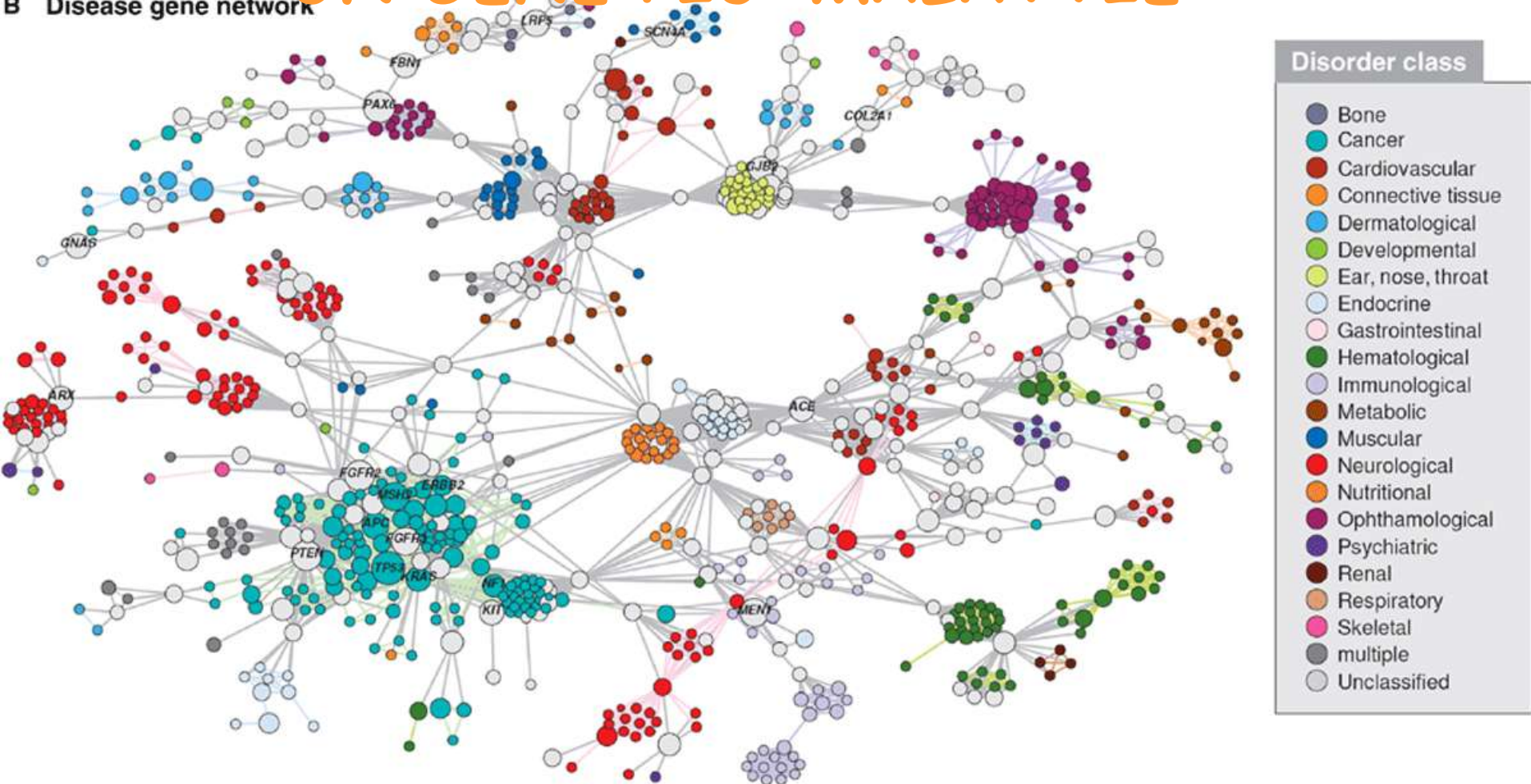
No del  
Del

# UN GENE UNA MALATTIA



# UN GENE PIU' MALATTIE

B Disease gene network



# STESSA MALATTIA= PIU' GENI

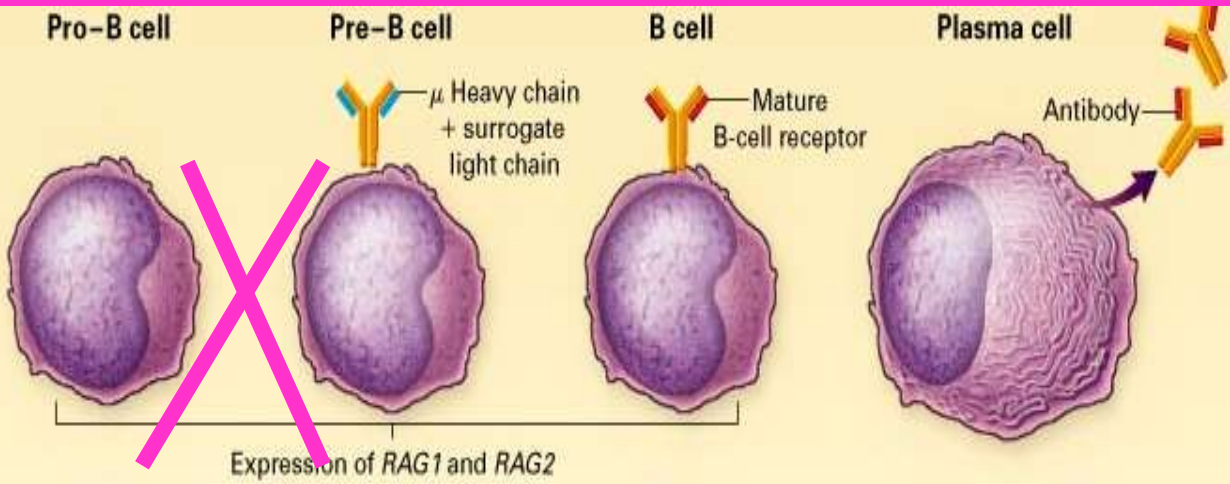
X-Linked

# AGAMMAGLOBULINEMIA CONGENITA (MALATTIA DI BRUTON)



- 1: 100.000 NATI VIVI
- RICORRENTI INFEZIONI GRAVI DA PIOGENI
- Ig BASSE O INDOSABILI CON B-LINFOCITI ASSENTI

## POLIOMIELITE PARALITICA POSTVACCINALE



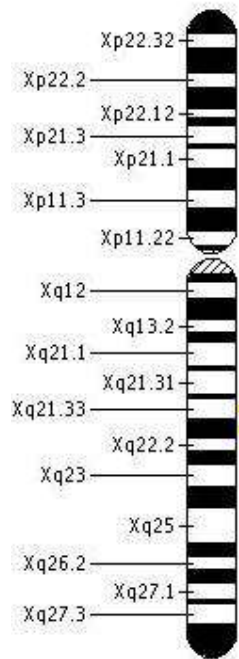
**B cell**

B-cell receptor  $Ig\beta$   $Ig\alpha$

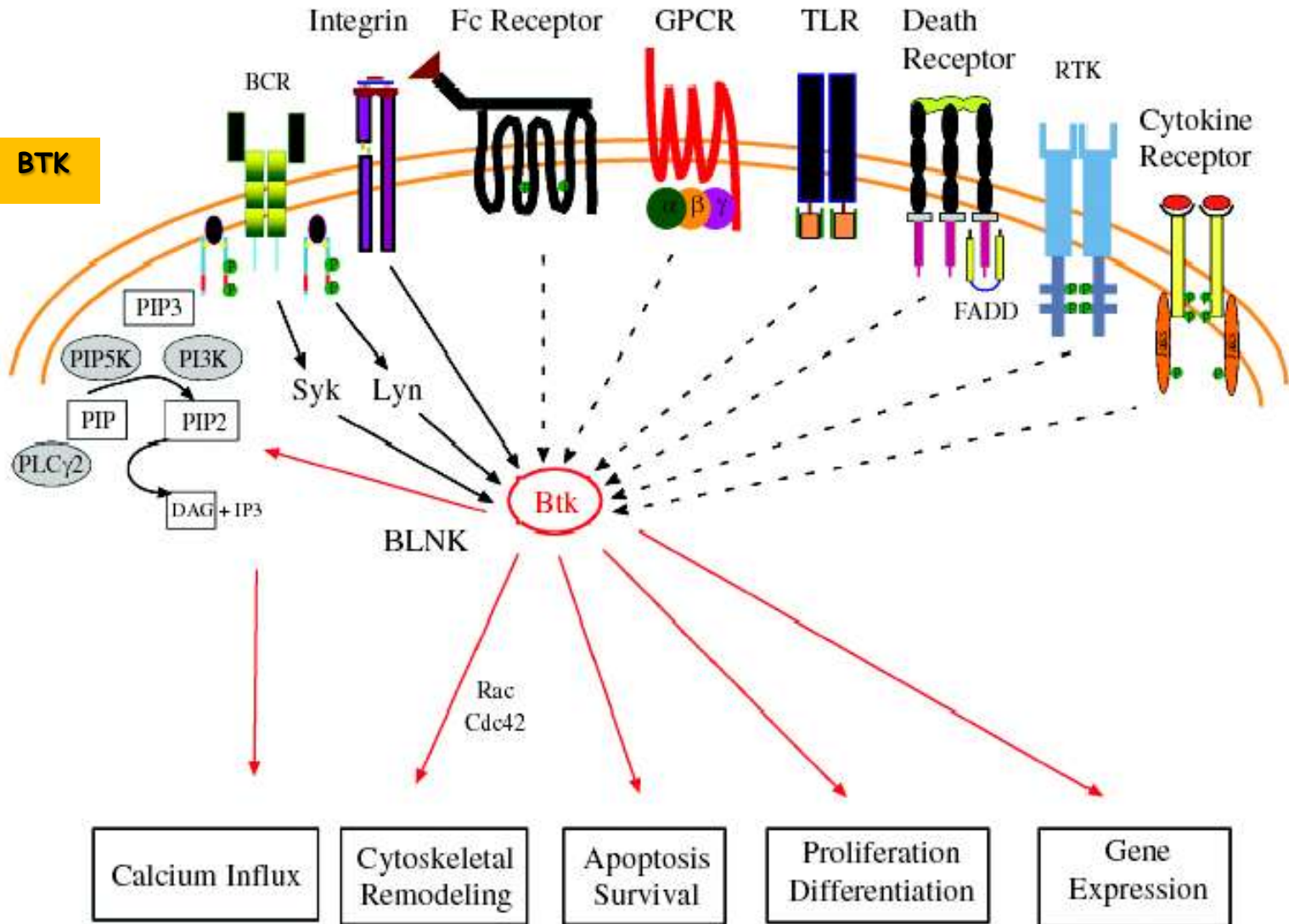
**ARRESTO DELLA  
DIFFERENZIAMENTO  
DEI PRECURSORI DEI B-  
LINFOCITI**



# SEGNALE BTK



**BTK**



# PAZIENTI CON AGAMMAGLOBULINEMIA

Casi familiari

Analisi Btk

+

100%

-

0

Casi sporadici

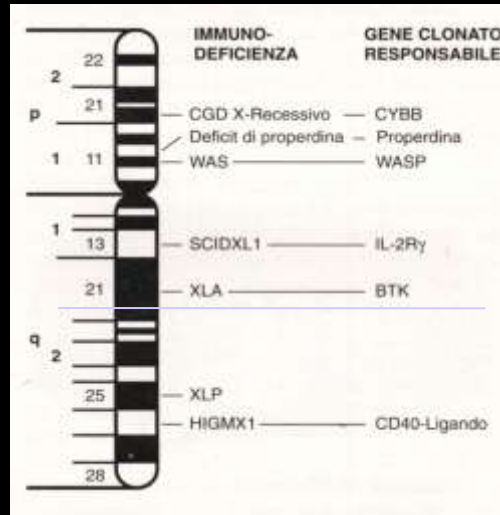
Analisi Btk

+

82%

-

18%



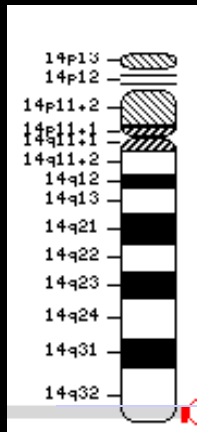
**FORMA LEGATA AL SESSO**

**FORMA NON LEGATA AL SESSO**

**AGAMMAGLOBULINEMIA, NON-BRUTON TYPE**

**AR, locus 14q32.33**

Conley, M. E.; Sweinberg, S. K., 1992; de la Morena et al. (1995); Conley (1999)



Protocollo AIEOP  
Novembre 2000



AGAMMAGLOBULINEMIE	Cr	OMIM
AGAMMAGLOBULINEMIA 5, AUTOSOMAL DOMINANT; AGM5	9q34.11	613506
AGAMMAGLOBULINEMIA, X-LINKED, TYPE 2; AGMX2	Xp22	300310
AGAMMAGLOBULINEMIA 2, AUTOSOMAL RECESSIVE; AGM2	22q11.23	613500
AGAMMAGLOBULINEMIA 4, AUTOSOMAL RECESSIVE; AGM4	10q24.1	613502
AGAMMAGLOBULINEMIA 7, AUTOSOMAL RECESSIVE; AGM7	5q13.1	615214
AGAMMAGLOBULINEMIA 3, AUTOSOMAL RECESSIVE; AGM3	19q13.2	613501
AGAMMAGLOBULINEMIA 6, AUTOSOMAL RECESSIVE; AGM6	17q23.3	612692
AGAMMAGLOBULINEMIA 1, AUTOSOMAL RECESSIVE; AGM1	14q32.33	601495
INHIBITOR OF BRUTON AGAMMAGLOBULINEMIA TYROSINE KINASE; IBTK	6q14.1	606457
BRUTON AGAMMAGLOBULINEMIA TYROSINE KINASE; BTK	Xq22.1	300300

# SINDROME CON IPER IgE o S. DI GIOBBE

HIERIS (*Hyper-IgE Recurrent Infection Syndrome*) HIES (*Hyper-IgE Syndrome*)

## AUTOSOMICA DOMINANTE

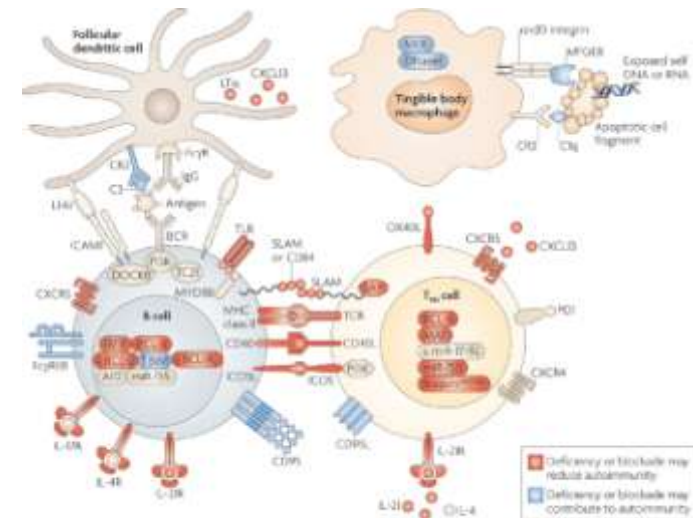
MUTAZIONI GENE STAT3 (17q21) (5 diverse mutazioni)

- FACIES CARATTERISTICA (asimmetrica con fronte prominente, occhi infossati, sella nasale larga e punta del naso carnosa)
- FRATTURE PATOLOGICHE RICORRENTI
- DIFETTI DENTINOGENESI

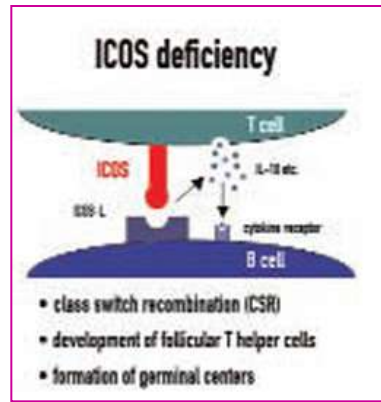
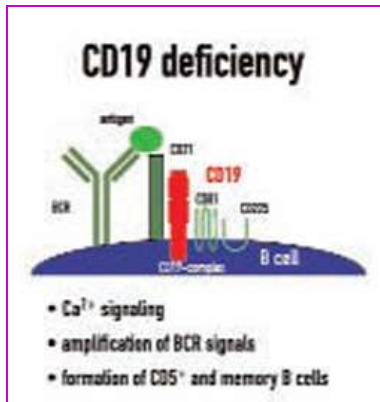
## AUTOSOMICHE RECESSIVE

MUTAZIONE GENE Tyk2 (19p13.2)

MUTAZIONE GENE DOCK8 (9p24.3)



# IMMUNODEFICIENZA COMUNE VARIABILE



❑ difetto  
intrinseco delle  
cellule B  
(da mutazione di  
CD19; 16p11.2)

❑ difetto  
intrinseco delle  
cellule T  
(da mutazioni di  
ICOS; 2q33)

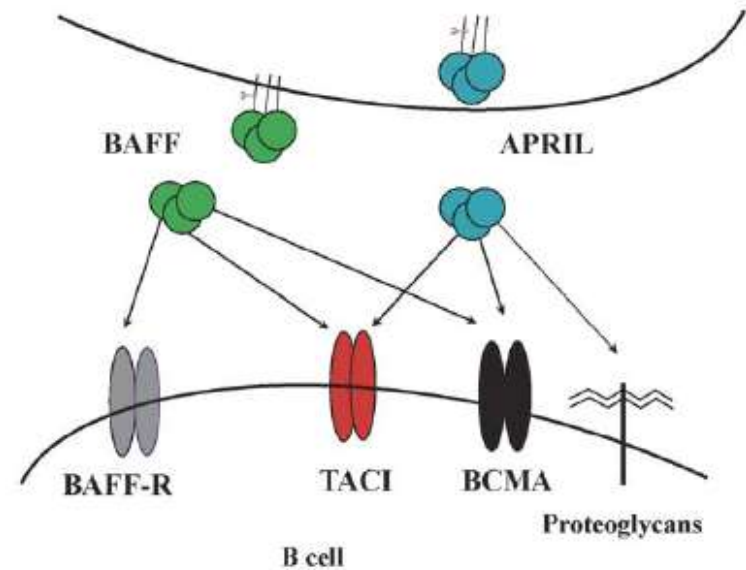
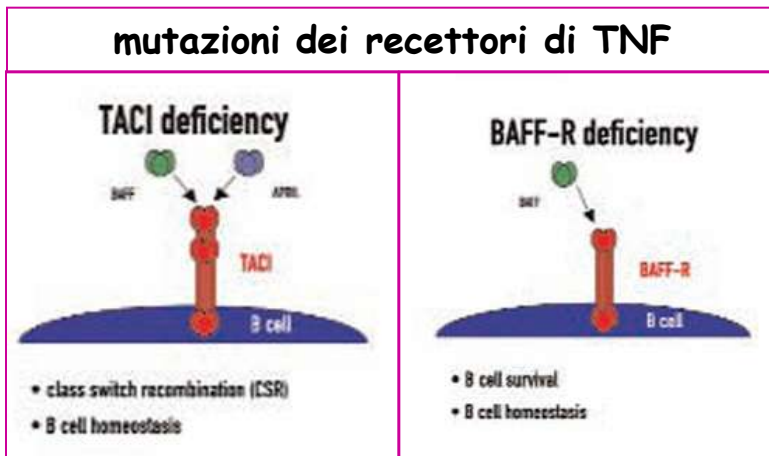


FIG 1. BAFF, APRIL, and their receptors on B cells.

Altri difetti mendeliani noti sono i deficit di MSH5, CD81 e CD20. La maggior parte dei casi è sporadico, ma si ritiene che **circa il 20% possa essere familiare, a trasmissione autosomica dominante (80%) o autosomica recessiva (20%).**



❑ Mut. TNFRSF13B  
(17p11.2)

❑ TNFRSF13C  
(22q13.1-q13.31)

## GIOVANNI 11anni

## SAMUELE 7 anni

dai primi mesi di vita infezioni recidivanti delle alte e basse vie aeree, otiti e IVU con necessita' di ricovero

**Emocromo:** GR 4660000 mmc GB 3500 mmc  
N 20% L 80% PCR 1 mg/DL VES 19

### IMMUNOGLOBULINE

- IgA 29 (v.n. 60-270)
- IgG 423 (v.n. 707-1919)
- IgM 41 (v.n. 61-276)

### DOSAGGIO SOTTOCLASSI IG

- IgG1 400 (v.n. 646-129)
- IgG2 104 (v.n. 337-100)
- IgG3 47 (v.n. 64- 44)
- IgG4 6 (v.n. 71-54)

### SOTTOPOPOLAZIONI LINFOCITARIE

- CD3 71%(55-84)
- CD4 38%(31-60)
- CD4/CD8 1,65
- CD8 23%(13-41)
- CD19 22%(6-25)

- IgG tosoide 0,43 (0,11-0,5) +
- IgG difterico 0,06 (0,01-0,09) +/-
- HbsAg 12,50 (> 11 positivo)

**Emocromo:** GR 4460000 mmc GB 6800 mmc N  
50% L 43% PCR 0,01 mg/DL VES 10

### IMMUNOGLOBULINE

- IgA 30 (v.n. 41-315)
- IgG 416 (v.n. 633-1016)
- IgM 37 (v.n. 56-261)

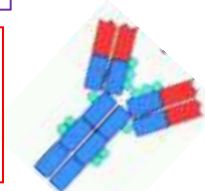
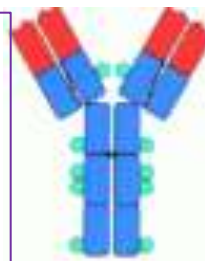
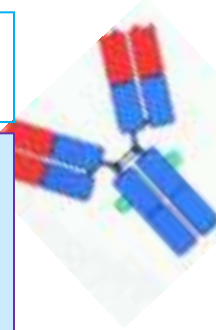
### DOSAGGIO SOTTOCLASSI IG

- IgG1 400 (v.n. 571-116)
- IgG2 73 (v.n. 257-110)
- IgG3 24 (v.n. 61- 34)
- IgG4 6 (v.n. 32-25)

### SOTTOPOPOLAZIONI LINFOCITARIE

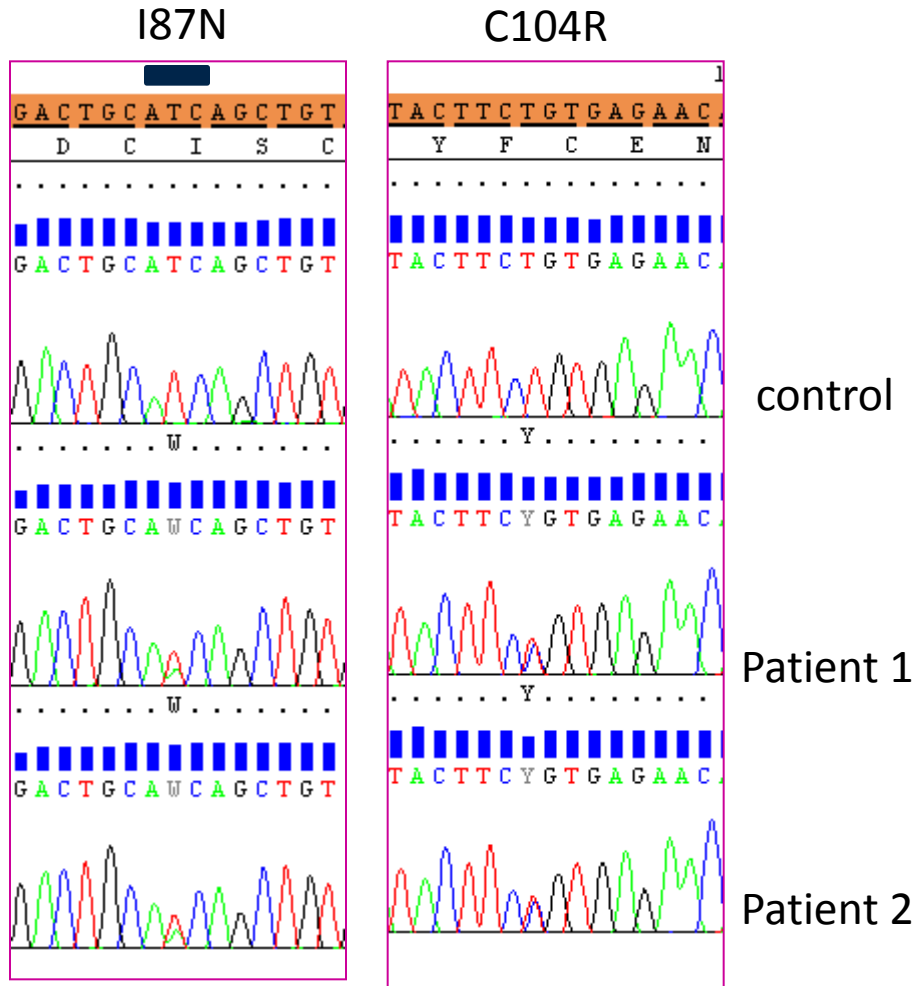
- CD3 64% (55-84)
- CD4 30% (31-60)
- CD4/CD8 1.20
- CD8 25% ( 13-41)
- CD19 22% (6-25)

- IgG tosoide 0,83 (0,11-0,5)
- IgG difterico 0,16 (0,01-0,09)
- HbsAg 6,60 (> 11 positivo)



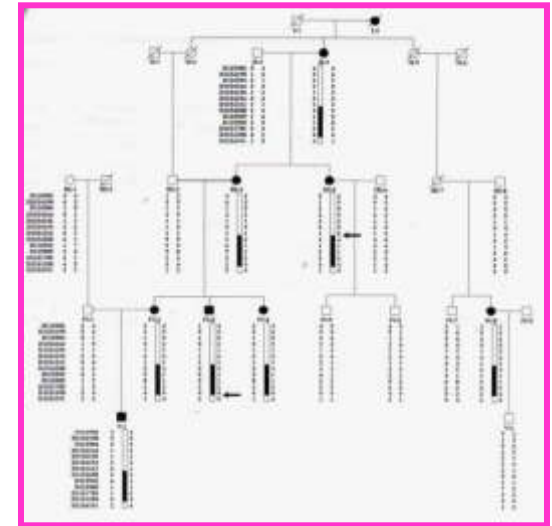
## A novel compound heterozygous TACI mutation in an **autosomal recessive** Common Variable Immunodeficiency (CVID) family

V. Lougaris<sup>1</sup>, R. Gallizzi<sup>2</sup>, M. Vitali<sup>1</sup>, M. Baronio<sup>1</sup>, A. Salpietro<sup>2</sup>, A. Bergbreiter<sup>3</sup>, U. Salzer<sup>3</sup>, R. Badolato<sup>1</sup>, A. Plebani<sup>1</sup>



Common Variable Immunodeficiency (CVID) is a primary immune disorder characterized by low immunoglobulin serum levels and increased susceptibility to infections. Underlying genetic causes are only known in less than 15% of patients and encompass mutations in the genes encoding for ICOS, TACI, BAFF-R, CD19, CD20, CD81 and MSH5. TACI is the most frequently mutated gene among CVID patients. We report on two paediatric Italian male siblings with hypogammaglobulinemia and recurrent respiratory and gastrointestinal infections in association with a novel compound heterozygous TACI mutation. Both patients carry the I87N/C104R mutation that has not been reported yet. This results in aberrant TACI expression and abrogates APRIL binding on EBV B-cells. This study identifies a novel combined mutation in *TNFRSF13B* increasing the spectrum of TACI mutations associated with CVID.

# CANDIDIASI MUCOCUTANEA CRONICA



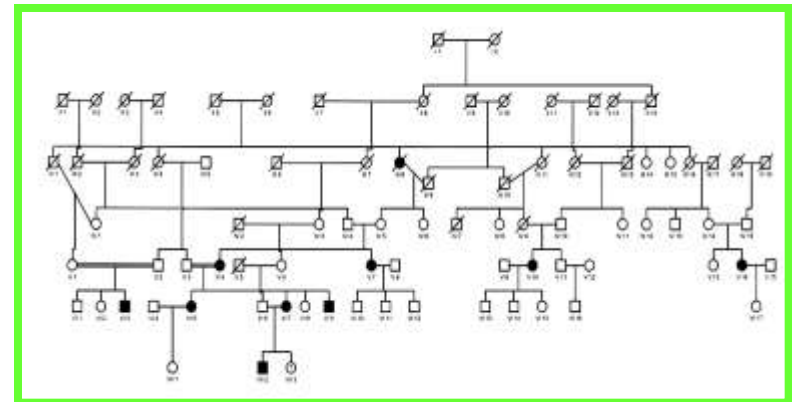
## FAMILIAL CHRONIC NAIL CANDIDIASIS WITH ICAM-1 DEFICIENCY: A NEW FORM OF CHRONIC MUCOCUTANEOUS CANDIDIASIS

Zuccarello D, Salpietro DC, Gangemi S, Toscano V, Merlino MV, Briuglia S, Bisignano G, Mangino M, Mingarelli R, Dallapiccola B J  
Medical Genetics, 39(9): 671-75, 2002

## A GENE FOR FAMILIAL ISOLATED CHRONIC NAIL CANDIDIASIS (CMC) MAPS TO CHROMOSOME 11p13-q12

Mangino M, Salpietro DC, Zuccarello D, Gangemi S, Rigoli L, Merlino MV, Briuglia S, Bisignano G, Mingarelli R, Dallapiccola B.

European Journal of Human Genetics, 21,622-9,2003



# CANDIDIASI MUCOCUTANEA CRONICA

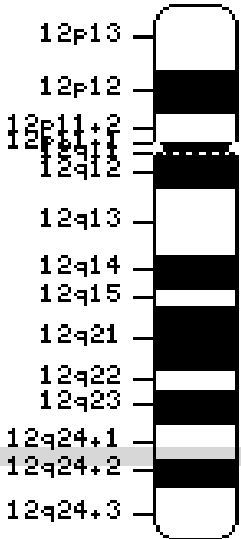
TIPI DI CMC	EREDITARIETÀ /OMIM*	GENE	ETÀ
CANDIDIASI MUCOCUTANEA CRONICA FAMILIARE SENZA ENDOCRINOPATIA.	AUTOSOMICA RECESSIVA (212050*) AUTOSOMICA DOMINANTE (114580*)	SCONOSCIUTO SCONOSCIUTO	INFANZIA
FCMC CON IPOTIROIDISMO	AUTOSOMICA DOMINANTE (606415*)	LOCUS 2P	INFANZIA
POLIENDOCRINOPATIA-CANDIDIASI-DISTROFIA ECTODERMICA AUOTOIMMUNE (APECED1)	AUTOSOMICA RECESSIVA (240300*)	AIRE LOCUS 21	INFANZIA
CANDIDIASI MUCOCUTANEA CRONICA LOCALIZZATA	SCONOSCIUTA	SCONOSCIUTO	INFANZIA
CANDIDIASI MUCOCUTANEA CON SINDROME DA IPER-IGE E SINDROME DI JOBBE	AUTOSOMICA DOMINANTE (147060*) AUTOSOMICA RECESSIVA (243700*)	LOCUS 4Q21 ETEROGENEITÀ	INFANZIA
CANDIDIASI CRONICA CON CHERATITE O DISPLASIA MUCOEPITELIALE	AUTOSOMICO DOMINANTE (158310*)	SCONOSCIUTO	INFANZIA
CANDIDIASI MUCOCUTANEA CRONICA CON ENDOCRINOPATIA AUTOIMMUNE (APECED II)	AUTOSOMICA RECESSIVA O DOMINANTE O MULTIFATTORIALE (269200*)	SCONOSCIUTO	ADULTO
CANDIDIASI ORALE CRONICA	SCONOSCIUTA	SCONOSCIUTO	ADULTO
FCNC CON DEFICIT DI ICAM-1	AUTOSOMICA DOMINANTE (607644*)	LOCUS CR. 11	INFANZIA

# SINDROME DI NOONAN

# SINDROME DI LEOPARD

## GENI-MALATTIA

## CORRELAZIONI CON IL FENOTIPO



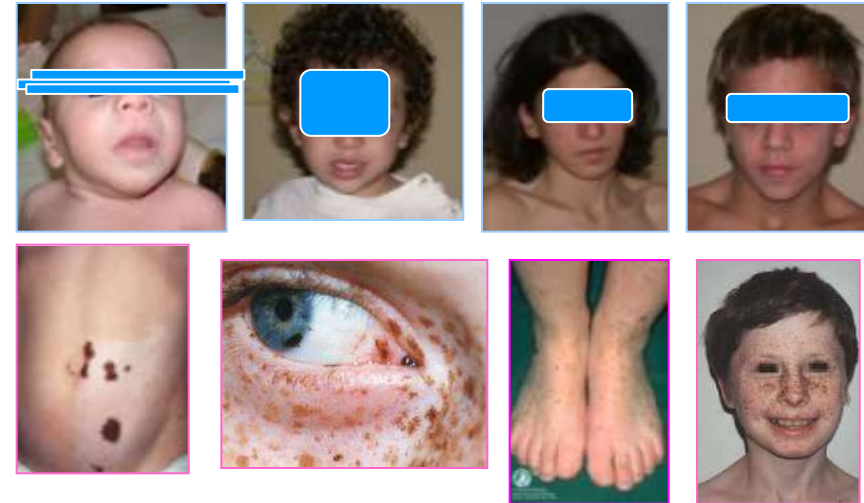
**40% S. NOONAN**

**90% S. LEOPARD**

**S. NOONAN-LIKE**

**Gene PTPN11**

locus 12q22-qter



MUTAZIONI ESONE 3 → DIA

MUTAZIONI ESONE 8 → STENOSI DELLA POLMONARE

## LA VIA DEL SEGNALE DI RAS-ERK

**KRAS**

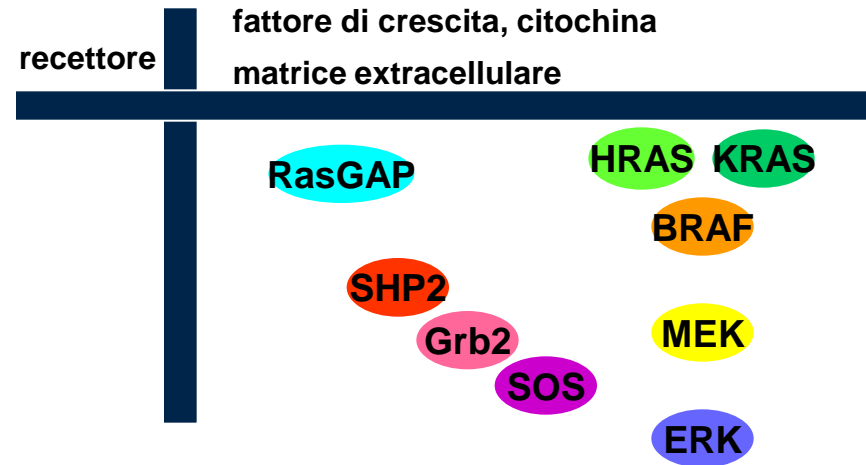
FENOTIPO GRAVE DELLA SINDROME DI NOONAN CON RITARDO MENTALE; CORRELA ANCHE CON UN PICCOLO NUMERO DI LEOPARD

**SOS1**

IN 20% CIRCA DI NOONAN CON IMPORTANTE COMPONENTE ECTODERMICA, MENO BASSA STATURA E RITARDO PSICOMOTORIO, CON MACROCEFALIA, E PIÙ FREQUENTE STENOSI POLMONARE

**RAF1**

7 CASI DI NOONAN SU 83 NEGATIVI PER PRECEDENTI GENI SONO RISULTATI POSITIVI PER MUTAZIONI DI RAF1; POSITIVI ANCHE 2 SOGGETTI CON LEOPARD; FORTEMENTE CORRELATO CON CARDIOMIOPATIA IPERTROFICA (76%)





# SINDROME DI JOUBERT

RITARDO MENTALE DI GRADO VARIABILE

APRASSIA OCULOMOTORIA

NISTAGMO

ATASSIA

IPOTONIA

NORMOREFLESSIA OSTEOTENDINEA

CIRCONFERENZA CRANICA NELLA NORMA

POLIURIA E POLIDIPSIA

ALTERAZIONE PARAMETRI DI FUNZIONALITÀ RENALE

AUMENTO ECOGENICITÀ RENALE

RIDOTTA CAPACITÀ DI CONCENTRAZIONE URINARIA

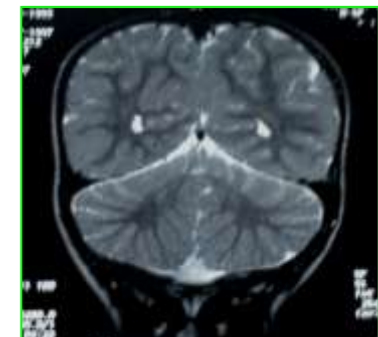
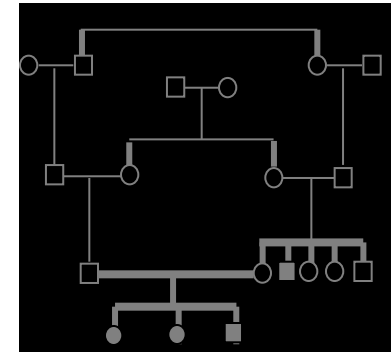
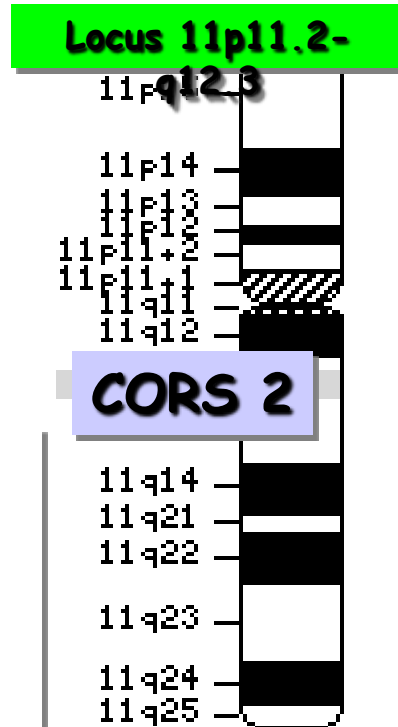
APLASIA DEL VERME CEREBELLARE

IV VENTRICOLO ALLARGATO E DEFORMATO

ISPESSIMENTO DEI PEDUNCOLI CEREBELLARI SUPERIORI

QUARTO VENTRICOLO APERTO AD OMBRELLO

FOSSA INTERPEDUNCOLARE ABNORMEMENTE AMPIA



Description, nomenclature, and mapping of a novel cerebello-renal syndrome with the molar tooth malformation. Valente EM, Salpietro DC, Brancati F, Bertini E, Galluccio T, Tortorella G, Briuglia S, Dallapiccola B. *Am. J. Hum. Genet.* 73: 663-670, 2003

Distinguishing the four genetic causes of Jouberts syndrome-related disorders. Valente EM, Marsh SE, Castori M, Dixon-Salazar T, Bestini E, Al-Gazali L, Messer J, Barbot C, Woods CG, Boltshausen E, Talari AA, Salpietro DC, Kaysereli H, Koenig M, Dalla piccola B, Gleeson JG. *Ann Neurol* 57 (4):513-9, 2005

# 250 FAMIGLIE

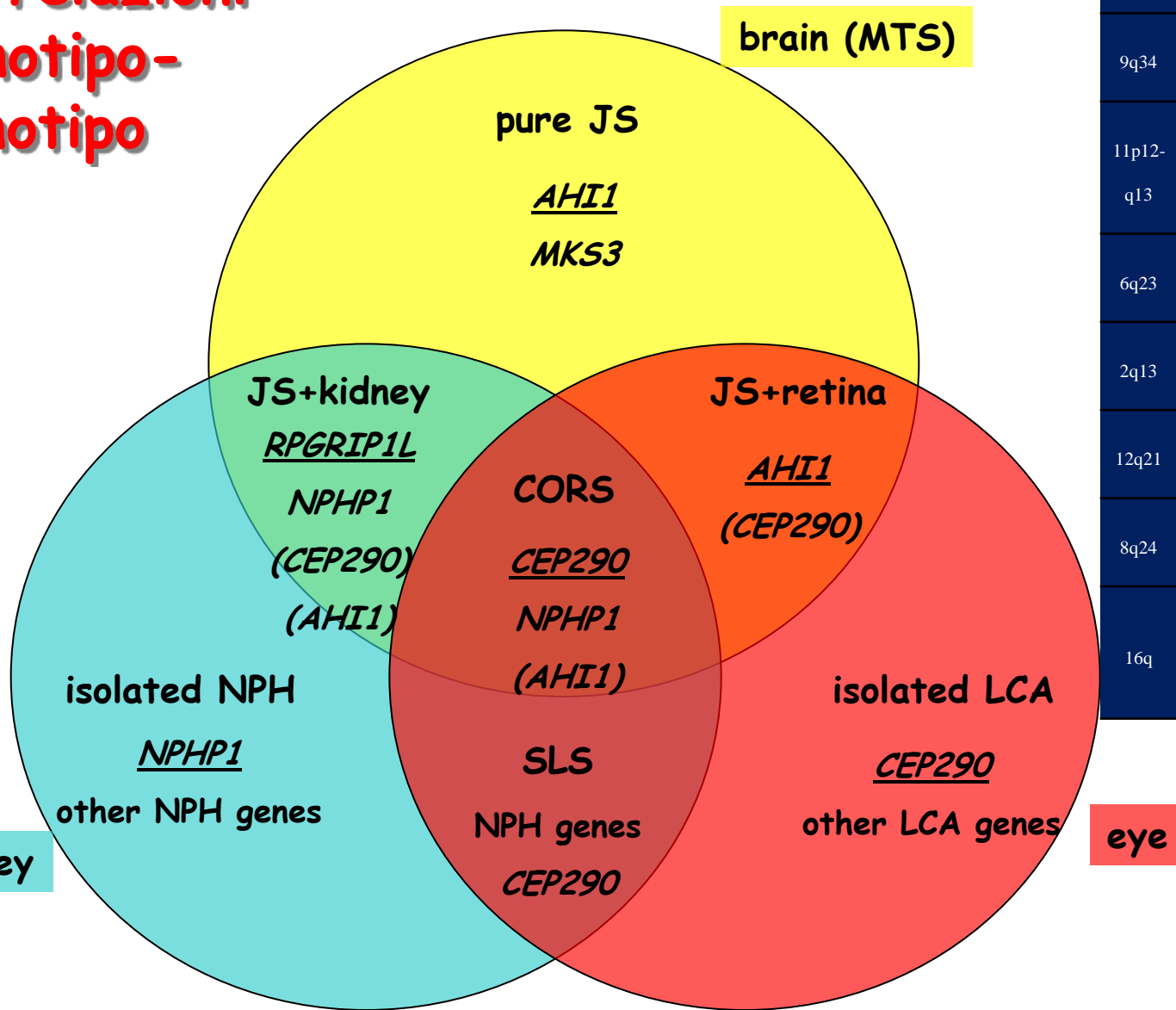
CHICAGO  
SAN DIEGO  
BOSTON  
HOUSTON  
PARIGI  
CAMBRIDGE  
MADRID  
BELFAST  
ZURIGO  
CAIRO



**AHI1 gene mutations cause specific forms of Joubert Syndrome Related Disorders.** Valente EV, Brancati F, Silhavy JL, Castori M, Marsh SE, Barrano G, Bestini E, Boltshauser E, Zaki MS, Abdel-Aleem A, Abdel-Aleem GMH, Bellacchio E, Battini R, Cruse RP, Dobyns WB, Krishnamoorthy KS, Lager-Tourenne C, Magee A, Pascual-Castroviejo I, Salpietro DC, Sarco D, International JSRD Study Group, Dallapiccola B, Gleeson JG. *Ann Neurol.* 2006 Mar;59(3):527-34.

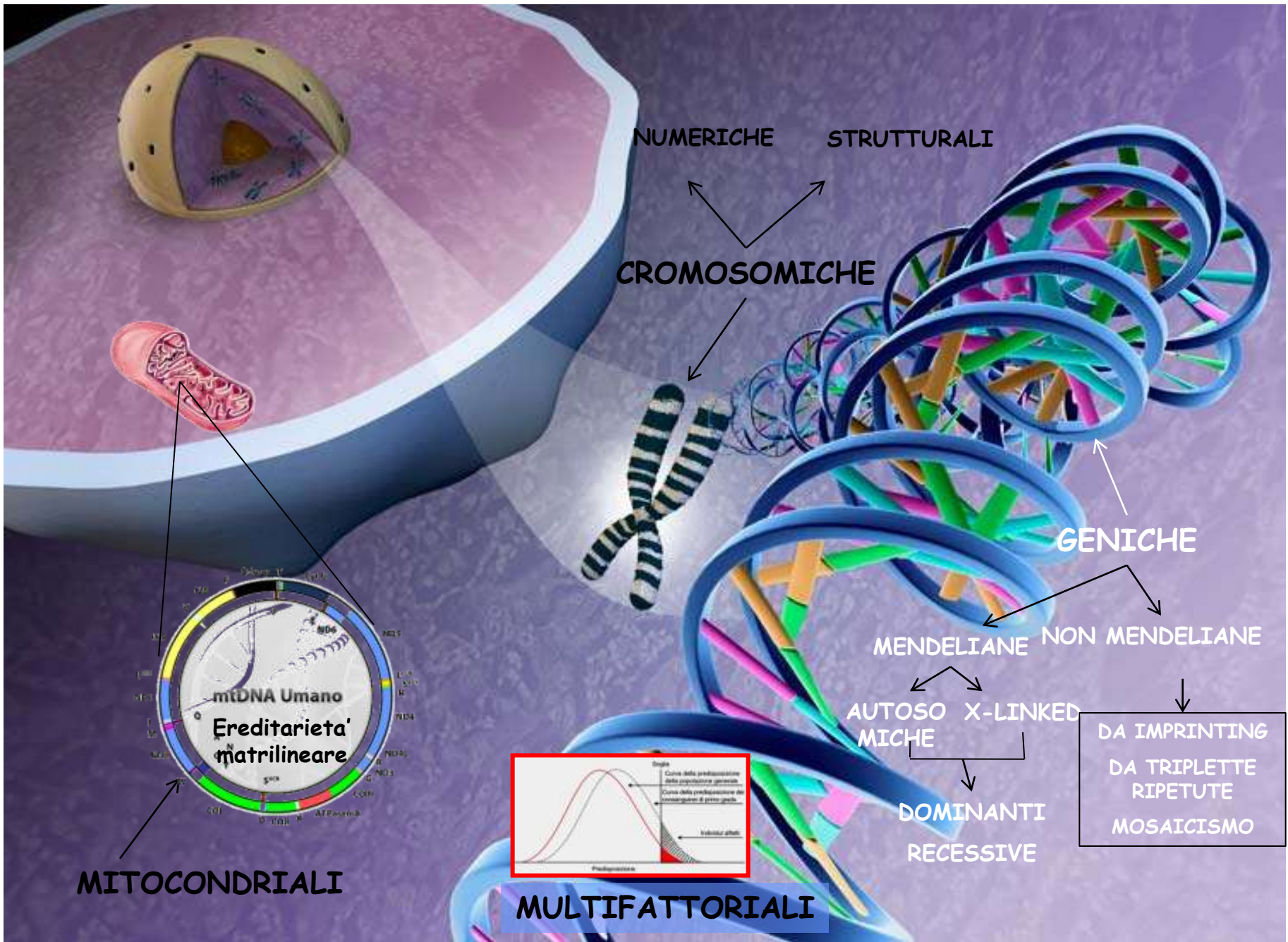
Valente EM, Logan CV, Mougou-Zerelli S, Lee JH, Silhavy JL, Brancati F, Iannicelli M, Travaglini L, Romani S, Illi B, Adams M, Szymanska K, Mazzotta A, Lee JE, Tolentino JC, Swistun D, Salpietro CD, Fede C, Gabriel S, Russ C, Cibulskis K, Sougnez C, Hildebrandt F, Otto EA, Held S, Diplas BH, Davis EE, Mikula M, Strom CM, Ben-Zeev B, Lev D, Sagie TL, Michelson M, Yaron Y, Krause A, Boltshauser E, Elkhartoufi N, Roume J, Shalev S, Munnich A, Saunier S, Inglehearn C, Saad A, Alkindy A, Thomas S, Vekemans M, Dallapiccola B, Katsanis N, Johnson CA, Attié-Bitach T, Gleeson JG. **Mutations in TMEM216 perturb ciliogenesis and cause Joubert, Meckel and related syndromes.** *Nat Genet.* 2010 Jul;42(7):619-25

# Correlazioni genotipo- fenotipo



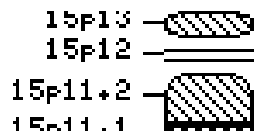
locus	gene/protein	NP H	SLS	JB TS	MK S
9q34	---	---	---	JBT S1	---
11p12- q13	---	---	---	JBT S2	(M KS2 )
6q23	AHI1/Joubertin	---	---	JBT S3	---
2q13	NPHP1/Nephro cystin	NP HP1	SLS N1	JBT S4	---
12q21	CEP290/CEP290 0	NP HP6	SLS N6	JBT S5	MK S4
8q24	TMEM67/Meck elin	---	---	JBT S6	MK S3
16q	RPGRIP1L/RP GRIPL	NP HP8	---	JBT S7	MK S5

CEP290 mutations are frequently identified in the oculo-renal form of Joubert syndrome-related disorders. Brancati F, Barrano G, Silhavy JL, Marsh SE, Travaglini L, Bielas SL, Amorini M, Zablocka D, Kayserili H, Al-Gazali L, Bertini E, Boltshauser E, D'Hooghe M, Fazzi E, Fenerci EY, Hennekam RC, Kiss A, Lees MM, Marco E, Phadke SR, Rigoli L, Romano S, Salpietro CD, Sherr EH, Signorini S, Stromme P, Stuart B, Sztriha L, Viskochil DH, Yuksel A, Dallapiccola B; International JSRD Study Group, Valente EM, Gleeson JG. *Am J Hum Genet.* 2007 Jul;81(1):104-13. Epub 2007



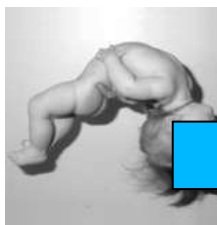
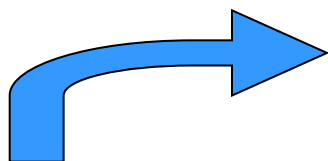
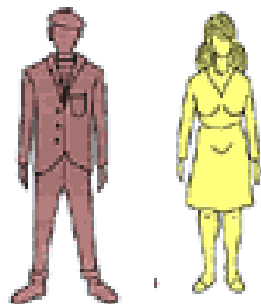
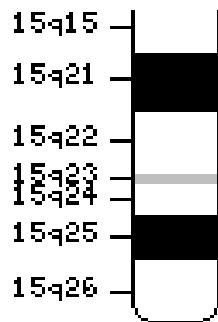
# SINDROME DI PRADER-WILLI

## UN GENE DUE MALATTIE

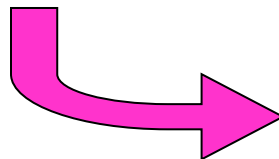


**Locus 15q11-q13**

Gene SNRPN



- ✓ Ipotonia nei primi anni
- ✓ Difficoltà suzione
- ✓ Mani e piedi piccoli
- ✓ Ritardo psicomotorio
- ✓ Da 6-12 mesi appetito vorace e obesità grave
- ✓ Bassa statura



- ❖ ritardo mentale
- ❖ assenza del linguaggio
- ❖ ritardo motorio
- ❖ umore allegro
- ❖ frequenti scoppi di riso (happypuppet)
- ❖ prognatismo, bocca grande, tendenza a protrudere la lingua, microcefalia lieve, spesso capelli e occhi chiari
- ❖ atassia, epilessia

# SINDROME DI ANGELMAN

# SINDROME X-FRAGILE



ANOMALIE COMPORTAMENTALI

DISTURBI LINGUAGGIO

**FACIES CARATTERISTICA (FACCIA LUNGA, ORECCHIE GRANDI, PROGNATISMO)**

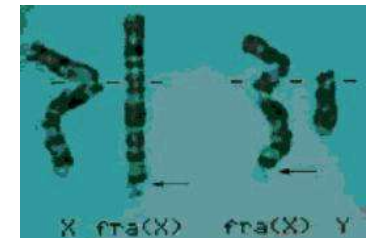
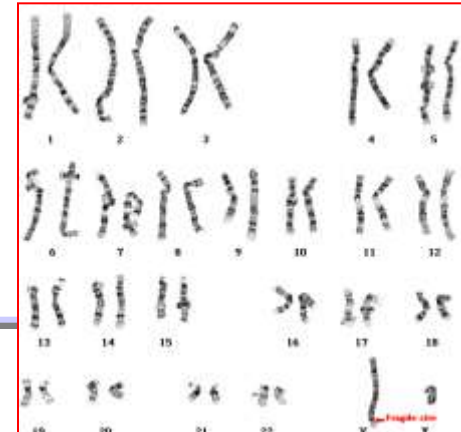
IPERESTENSIBILITÀ

**MACRORCHIDISMO**

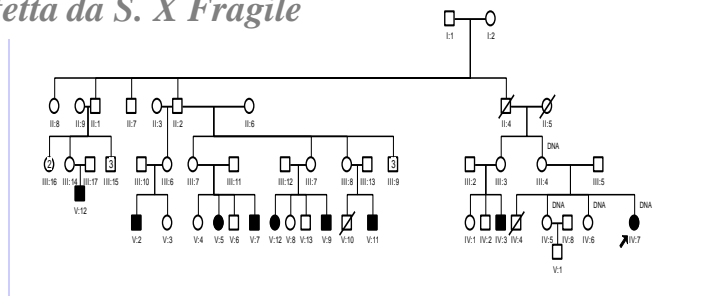
CONVULSIONI

PSICOSI

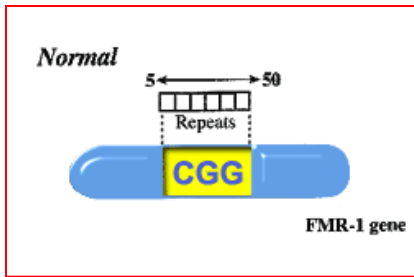
AUTISMO



*Famiglia affetta da S. X Fragile*

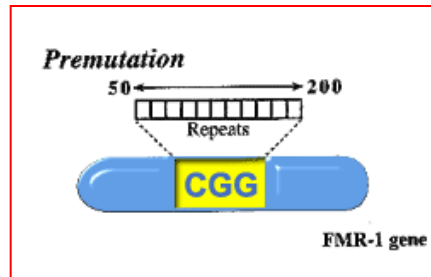


- Locus xq27.3
- gene **FMR-1**
- codifica per una **proteina FMRP**



**6-55**

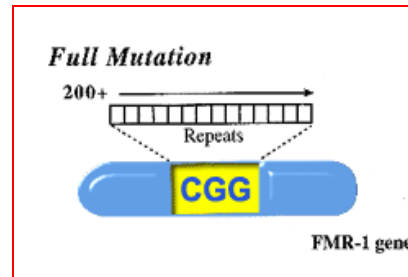
Condizione di normalità



**56-200**

Maschi trasmettitori

Femmine portatrici

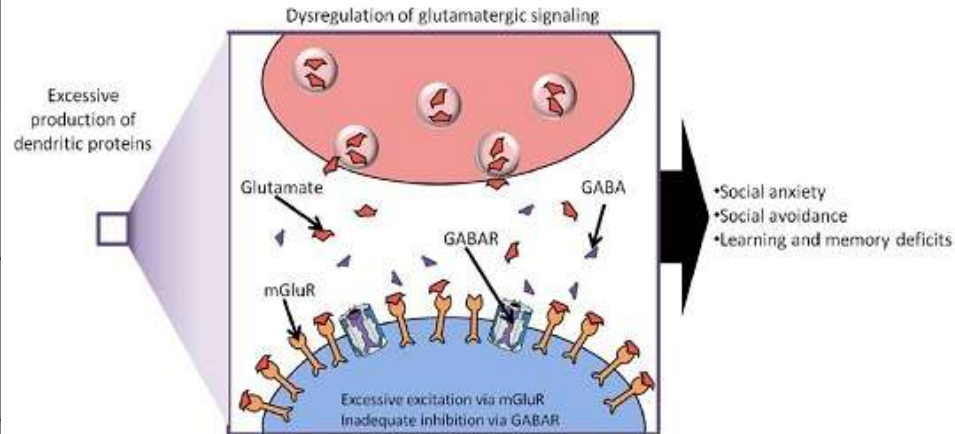
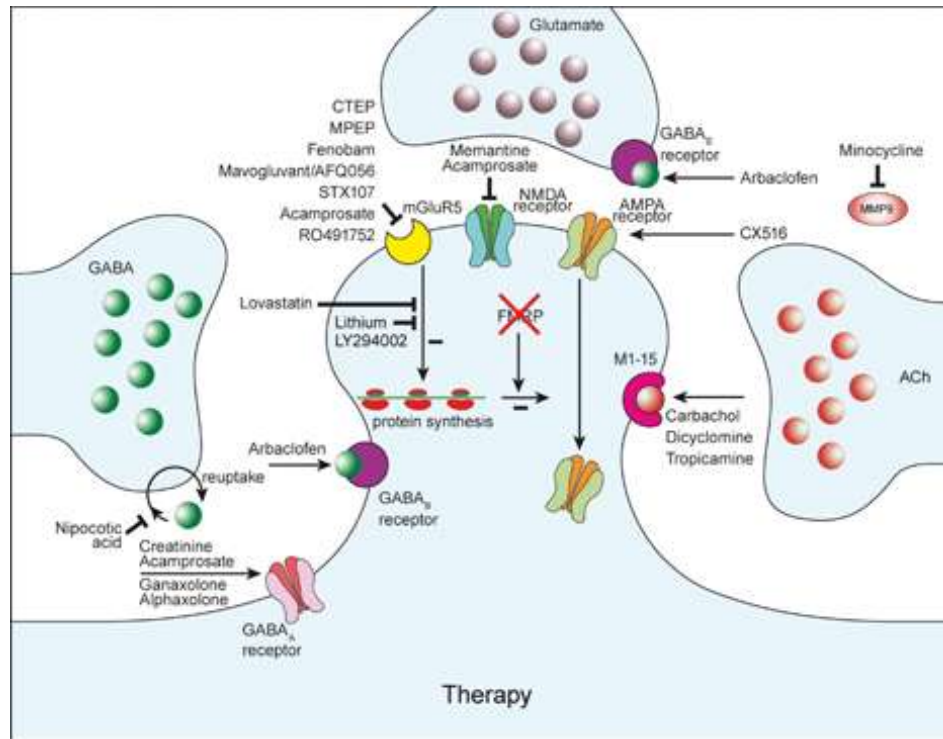


**>200**

Espressione clinica

**IL GENE FMR-1 PUÒ ESPANDERSI (OSSIA PASSARE DALLA PREMUTAZIONE ALLA MUTAZIONE PIENA) NEL PASSAGGIO DA UNA GENERAZIONE ALL'ALTRA**

# Fragile X Syndrome: From Protein Function to Therapy



**ANTAGONISTI DEL RECETTORE DEL GLUTAMMATO**

**AGONISTI DEL GABA<sub>A</sub> E GABA<sub>B</sub>**

**TERAPIE MOLECOLARI ALTERNATIVE**

In addition to the two major theories, others propose that disruptions at several other levels, among which the matrix metalloproteinase-9 (MMP-9) and striatal-enriched protein tyrosine phosphatase (STEP), could also account for the abnormal pheno-

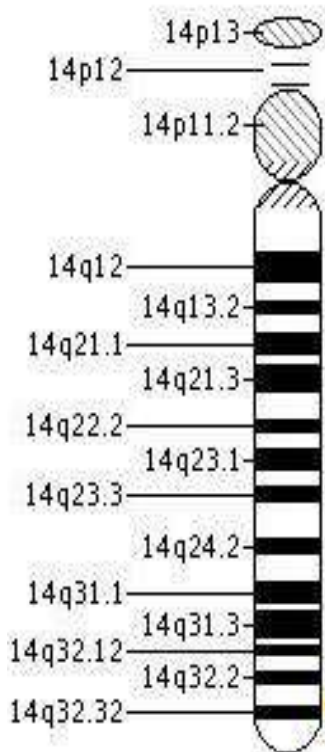
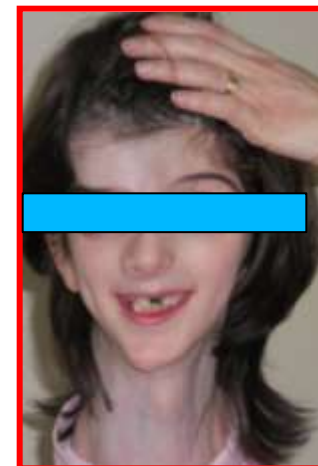
# SINDROME DI PROTEUS

## MALATTIA A MOSAICO

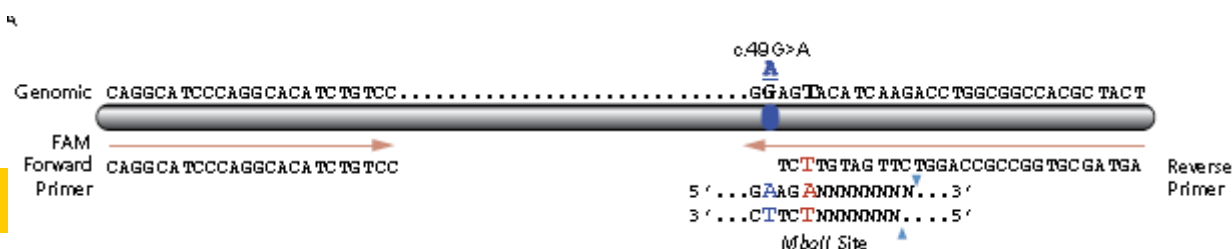
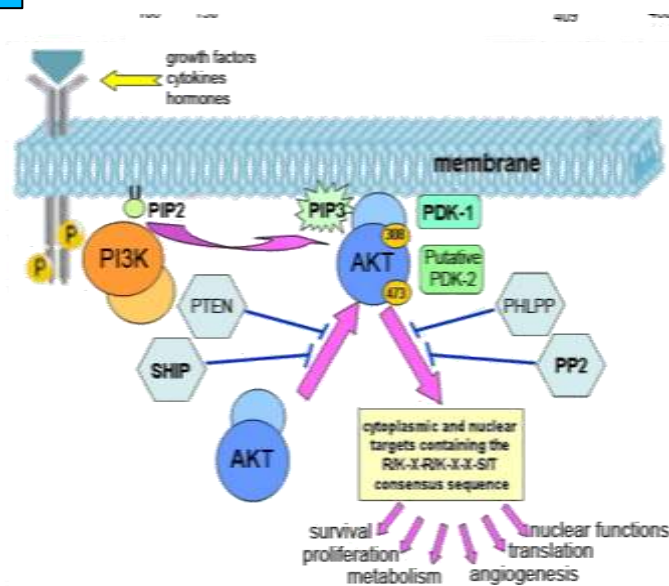
### A Mosaic Activating Mutation in *AKT1* Associated with the Proteus Syndrome

Marjorie J. Lindhurst, Ph.D., Julie C. Sapp, Sc.M., Jamie K. Teer, Ph.D., Jennifer J. Johnston, Ph.D., Erin M. Finn, B.A., Kathryn Peters, M.S., Joyce Turner, M.S., Jennifer L.

*N Engl J Med*. 2011 August 18; 365(7): 611–619. doi:10.1056/NEJMoal104017.



**AKT1 gene**





# BASI GENETICHE DELLE OBESITA' MONOGENICHE

## MUTAZIONI

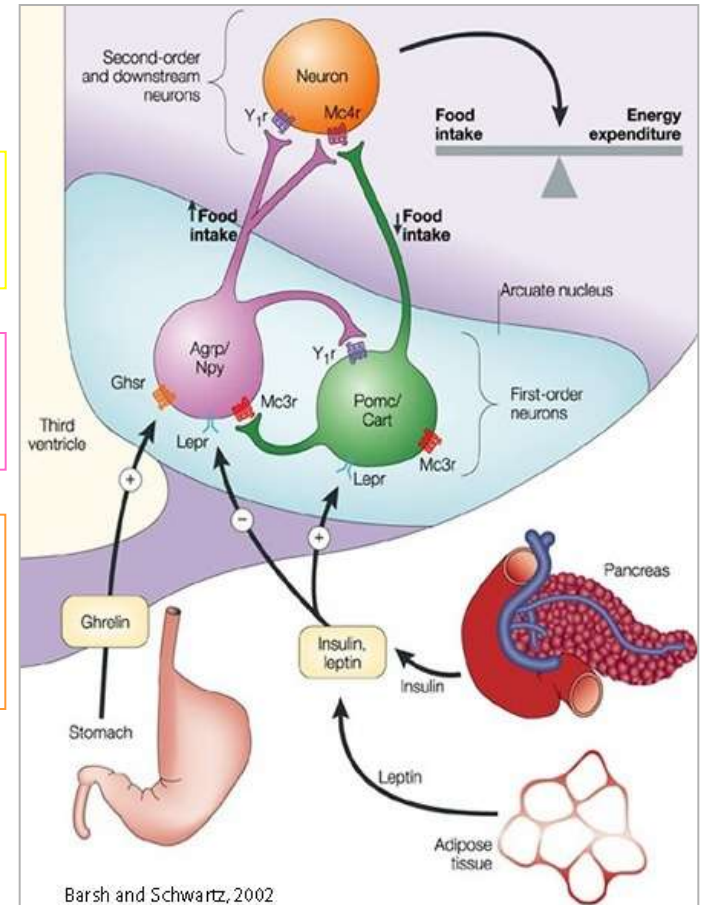
GENE CODIFICANTE LA LEPTINA (*lep*)

GENE CODIFICANTE IL RECIPTORE DELLA LEPTINA (*lepr*)

GENE CODIFICANTE LA PROOPIOMELANOCORTINA (POMC)

GENE CODIFICANTE IL "COCAINE AND AMPHETAMINE REGULATED TRANSCRIPT" (CART)

GENE CODIFICANTE IL "MELANOCORTIN-4-RECEPTOR" (MC4R)



Ricercatori del gruppo di Stephen O'Rahilly dell'Università di Cambridge hanno osservato che nella loro popolazione di obesi, costituita da bambini inglesi, caucasici e non, la prevalenza di mutazione su MC4R è di circa il 5%

# OBESITA' MONOGENICHE: DEFICIT DI LEPTINA



3 ANNI, 42 kg

7 ANNI 32 kg

GRAVE OBESITA' PRECOCE

IPERFAGIA

RIDUZIONE SPESA ENERGETICA  
*Faroqi et al,  
1999*

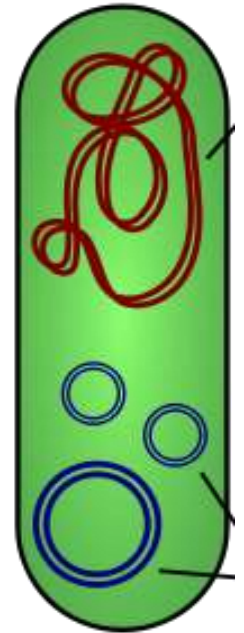
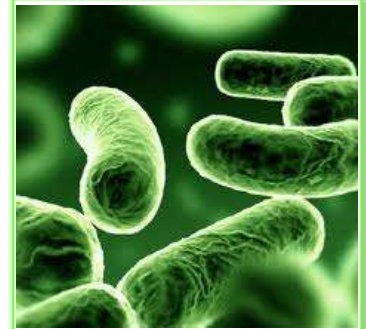
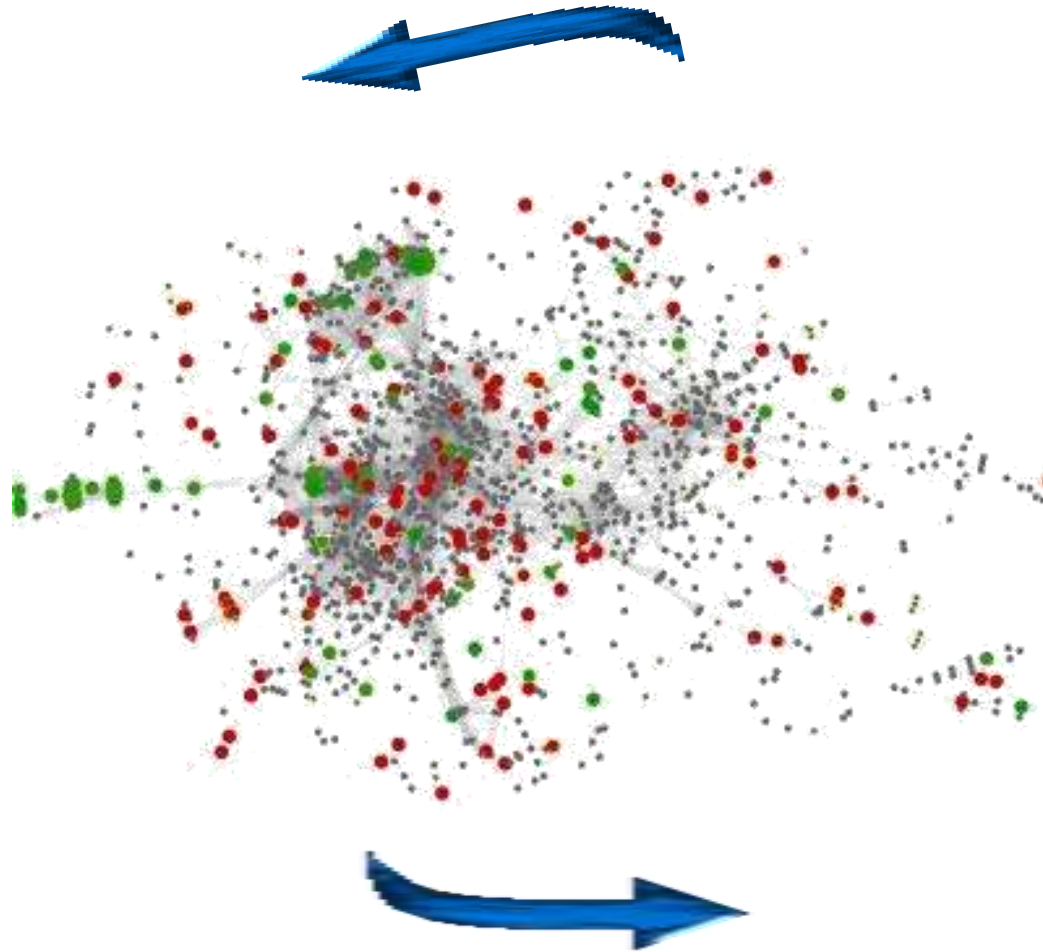
IPOGONADISMO IPOGONADOTROPO  
**DEFICIT RECETTORE  
LEPTINA**

clinicamente simile al deficit di leptina associata a

- comportamento aggressivo
- ritardata velocità di crescita staturale, bassi livelli di IGF1
- ipotiroidismo ipotalamico
- ipogonadismo ipogonadotropo
- età ossea avanzata rispetto

Effects of recombinant human leptin treatment in a child with leptin deficiency

# NETWORK GENOMA UMANO/GENOMA MICROORGANISMI



# Genetic variations in toll-like receptor pathway genes influence asthma and atopy

R. Tesse, R. C. Pandey & M. Kabesch

Center for Pediatrics, Clinic for Pediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany

