Chiari e Malattie Rare

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Università Cattolica del Sacro Cuore

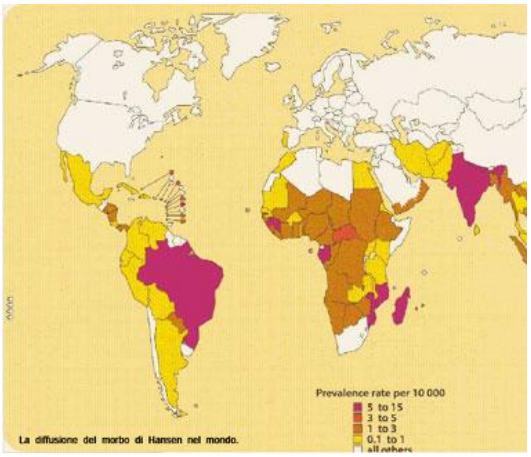
Malattie rare

Definizione

- USA <200.000 pazienti (1 su 1.630)
- Europa < 5/10.000 (<1/2.000)
- Giappone <50.000 pazienti (1 su 2.500)

Prevalenza cumulativa minima: 1,5-6,2%

Ultrarare 1/50.000



1/2.000.000

1/20.700

Perspective

Estimating the number of diseases – the concept of rare, ultra-rare, and hyper-rare

C. I. Edvard Smith,[1,2,3,*] Peter Bergman,[2,4] and Daniel W. Hagey[1]

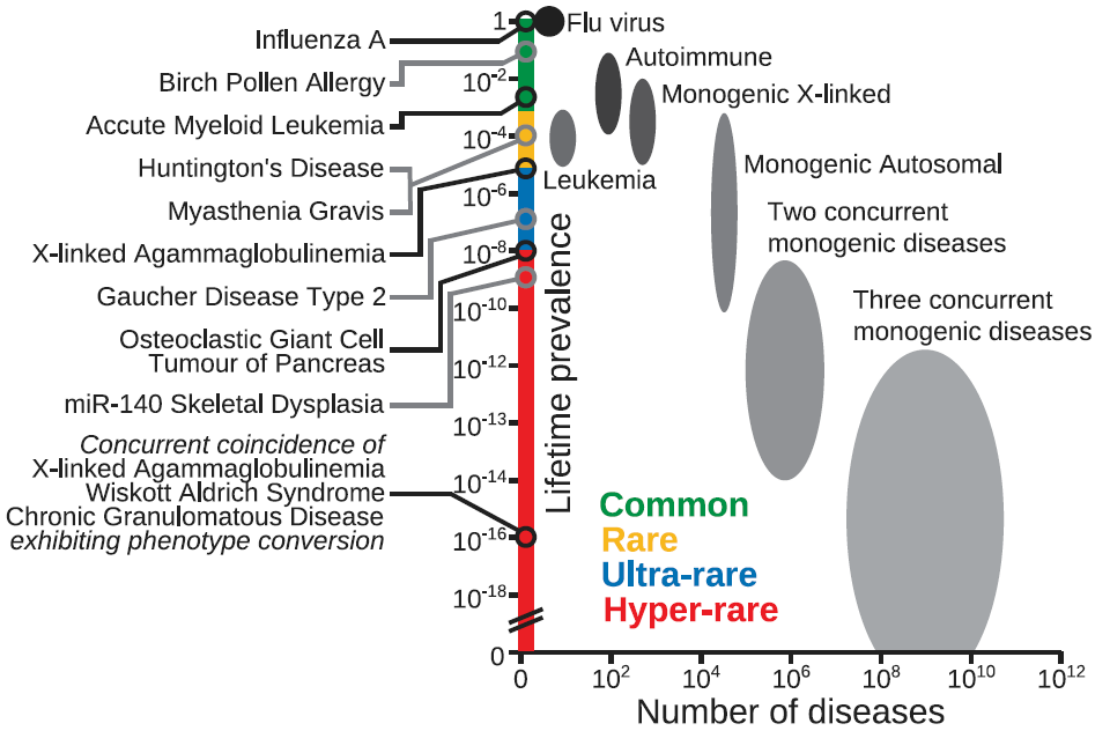
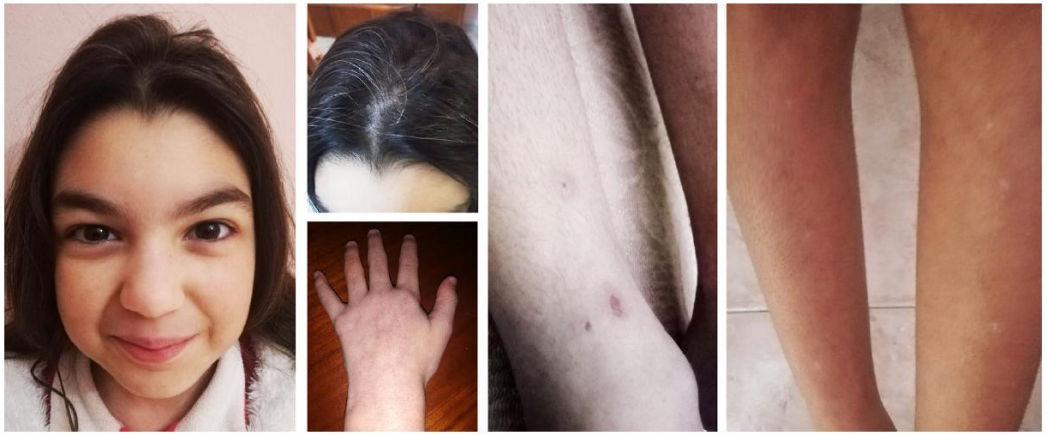


Figure 3. Estimated range in frequency and absolute number of various disease classes

Left, Distinct diseases, including the concurrent coincidence of three primary immunodeficiencies, where the prevalence for chronic granulomatous disease corresponds to mutations in the autosomal *NCF1* gene, encoding a 47 kDa cytosolic subunit of neutrophil NADPH oxidase. Right, the oval-shaped areas correspond to various disease classes. To compensate for that phenotype conversion only appears in certain disease combinations a correction coefficient was introduced, which for three concurrent diseases amounts to $[1/3]^3 = 1/27$.



WRNS signs and symptoms (age of onset in years)[a]	Present case (age of onset in years)
Cardinal features	
Cataracts (bilateral) (in the 30s)	+ (10)
Dermatological features/lesions (in the 20s)	+ (6)
Growth retardation/short stature (adolescence)	+ (since birth)
Premature graying and/or thinning of scalp hair (in the 20s)	+ (5)
Additional features	
Prematurely aged face with beaked nose (in the 30s–40s)	–
Weak/hoarse/high-pitched voice (in the 20s)	+ (12)
Diabetes mellitus (in the 30s)	–
Osteoporosis (in the 30s)	+ (9)
Lipodystrophy (progressive after puberty[b])	–
Soft tissue calcification (over 10–40)	+ (12)
Atherosclerosis (in the 30s–40s)	–
Hypogonadism (in the 30s)	–
Neoplasms (in the 40s[c])	–
Age of diagnosis (late 30s–40s)	+ (11)

NS main signs	Present case
Facial features	
Tall forehead	–
Triangular face	–
Widely spaced and downslanted palpebral fissure	–
Epicantal folds	–
Palpebral ptosis	–
Broad nasal bridge	+
Bulbous nasal tip	–
Deep philtrum	–
Prominent nasolabial fold	+
Broad webbed neck	–
Low-set posteriorly rotated ears	–
Mild intellectual disability	+
Short stature	+
Congenital heart defect	–
Hypertrophic cardiomyopathy	–
Pectus excavatum/carinatum	–
Scoliosis	–
Renal anomalies	–
Lymphedema	–
Bleeding diathesis	–
Ocular anomalies	+

documented as negative. Trio-based exome sequencing was performed (Supplemental Materials and Methods S1), and variant filtering and prioritization allowed to identify a homozygous nonsense variant in *RECQL2* (chr8:30999080T>G, GRCh37.p13; c.3102T>G, NM_000553.6; p.Tyr1034*, NP_000544.2), and a missense change in *PTPN11* (chr12:112910784C>G, GRCh37.p13; c.793C>G, NM_002834.5; p.Arg265Gly, NP_002825.3) as the only clinically and functionally relevant variants (Table S3). The *RECQL2* truncating vari-

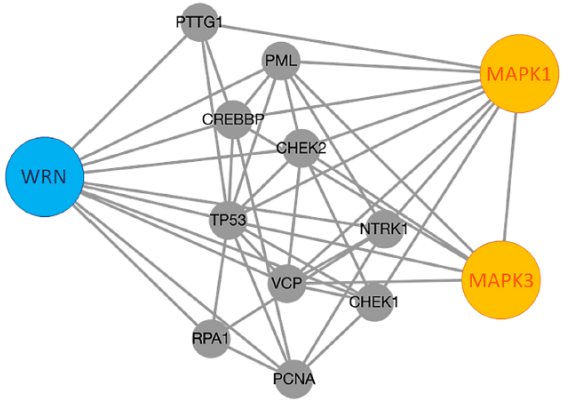
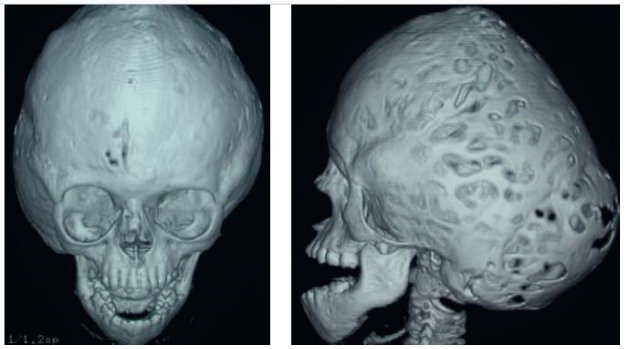


FIGURE 3 Gain-of-function consequences of the Arg265Gly amino acid substitution on SHP2 function. (A) In vitro assessment of the phosphatase activity of recombinant $SHP2^{Arg265Gly}$, basally and following BTAM stimulation. Catalytic activity is compared with that of wild-type (WT) SHP2 and of two Noonan syndrome-causing mutants ($SHP2^{Ala72Ser}$ and $SHP2^{Arg265Gln}$). Phosphatase activity was measured as pmoles of phosphate released using pNPP as a substrate, basally (white bars) and following stimulation with 10 μM BTAM peptide (black bars). Asterisks indicate significant differences compared to basal or stimulated activities of the WT enzyme (*$p < 0.05$; ***$p < 0.001$; Student's *t*-test with Bonferroni correction). (B) Overexpression of $SHP2^{Arg265Gly}$ promotes enhanced EGF-dependent ERK phosphorylation, as assessed by time-course experiments. WT SHP2, or each of the $SHP2^{Arg265Gly}$ and $SHP2^{Ala72Ser}$ mutants, the latter selected as a representative of the GoF mutants associated with Noonan syndrome, are shown for comparison. Representative blots (below) and mean ± SD densitometry values (above) of three independent experiments are shown. HEK293T cells were transiently co-transfected with Flag-tagged Gab1 and V5-tagged SHP2 constructs. Following transfection, cells were serum starved and treated with 30 ng/ml EGF for 5 or 15 min, or left unstimulated. Equal amounts of cell lysates were resolved on 10% polyacrylamide gel. Asterisks indicate statistically significant differences compared with WT SHP2 at the corresponding time upon EGF stimulation (***$p < 0.001$; ****$p < 0.0001$; two-way ANOVA followed by Tukey's multiple comparison test). (C) WRN-MAPK/ERK interaction network. The displayed graph is constructed by random walk analysis starting from seeds (WRN, MAPK1 and MAPK3) to obtain an expanded sub-network in which colored nodes are the input seeds, gray nodes are their 10 top-ranking neighbors, and interactions are depicted as edges [Colour figure can be viewed at wileyonlinelibrary.com]

Anomalia di Chiari

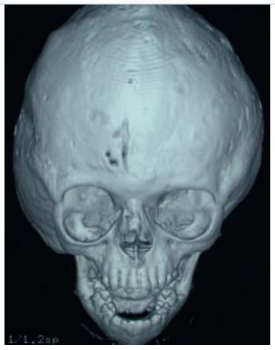
S. con Craniostenosi

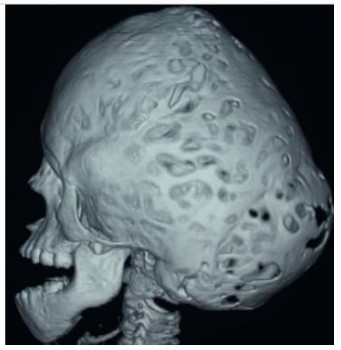


Meccanismi patogenetici:

- **Fossa posteriore piccola**: la fusione prematura delle suture in particolare lambdoidee e della base cranica crea una sproporzione tra la crescita del cervelletto/tronco encefalico e lo spazio disponibile
- **Ipertensione endocranica**: causata dalla fusione multi-suturale e dall'idrocefalo
- **Ipertensione venosa**: stenosi del forame giugulare che compromette il drenaggio venoso
- **Idrocefalo**: contribuisce alla pressione dall'alto che spinge le tonsille verso il basso

Anomalia di Chiari

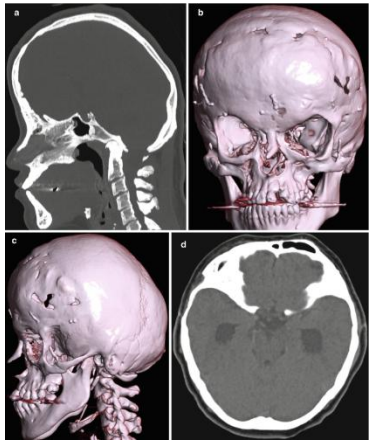


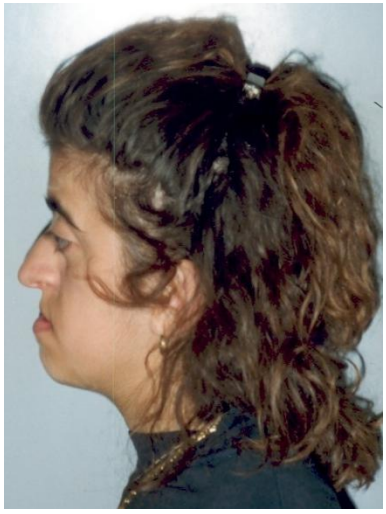


S. con Craniostenosi

Crouzon

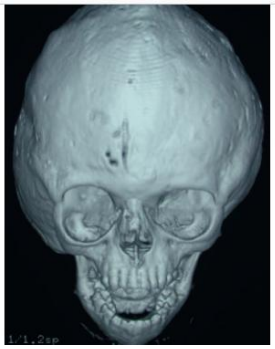
- 73% dei pazienti ha Chiari 1.
- Sinostosi precoce della sutura lambdoidea nei primi 24 mesi di vita, che restringe la fossa posteriore.
- 20% dei pazienti con Crouzon e Chiari I sviluppa siringomielia.
- Mutazioni specifiche di FGFR2 (come Tyr281Cys e Cys342Trp) associate a questa combinazione.

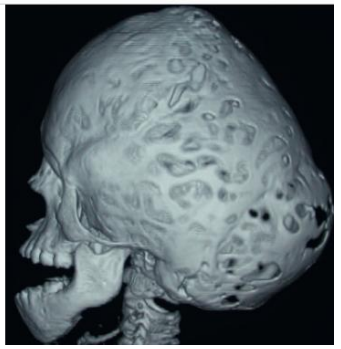




Fujisawa et al. J Neurosurg. 2002. PMID: 12186468.

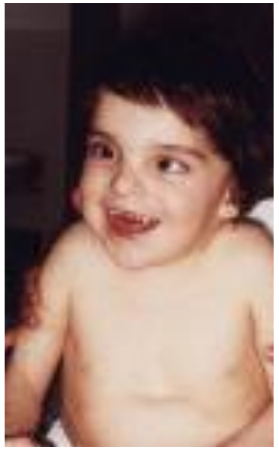
Anomalia di Chiari



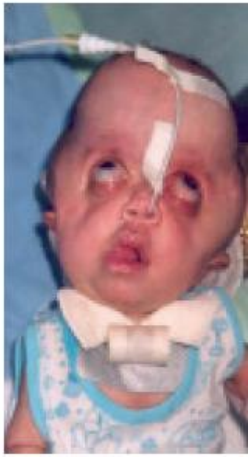


S. con Craniostenosi

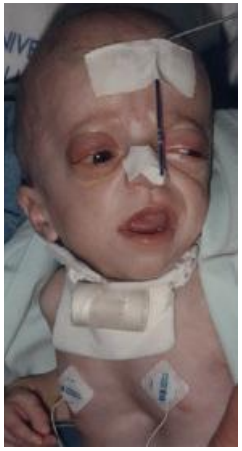
- Crouzon
- Pfeiffer
  - Il 50% dei pazienti con sindrome di Pfeiffer sviluppa malformazione di Chiari tipo 1, con percentuali che raggiungono il 100% nei pazienti con Pfeiffer tipo 2 e tipo 3



Pfeiffer 1

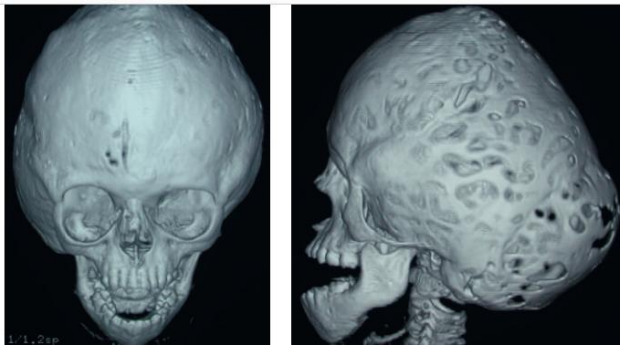


Pfeiffer 2



Pfeiffer 3

Anomalia di Chiari

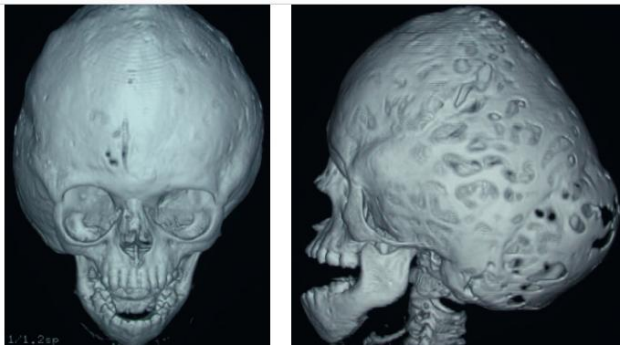


S. con Craniostenosi

- Crouzon
- Pfeiffer
- Saethre Chotzen

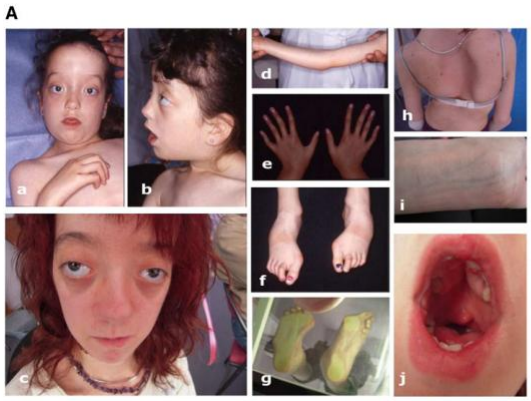
Si ritrova intorno al 10% dei casi perché questa condizione prevede sinostosi coronali

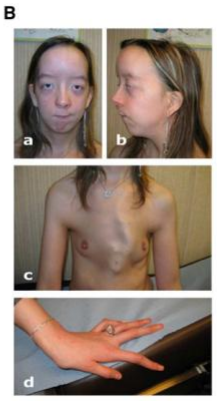
Anomalia di Chiari

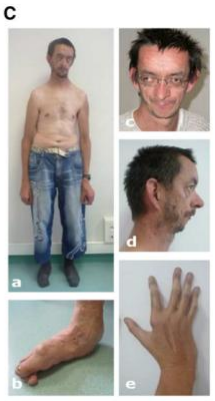


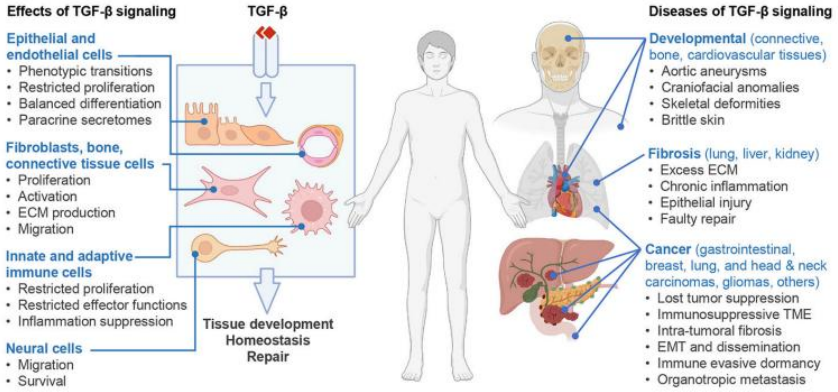
S. con Craniostenosi

- Crouzon
- Pfeiffer
- Saethre Chotzen
- Shprintzen-Goldberg
  - Craniosinostosi, habitus marfanoide, DI e volto distintivo.
  - Causata da mutazioni nel gene SKI e fa parte delle TGF-β-opatie, un gruppo di patologie associate alla via di segnalazione del TGF-β.









Anomalia di Chiari

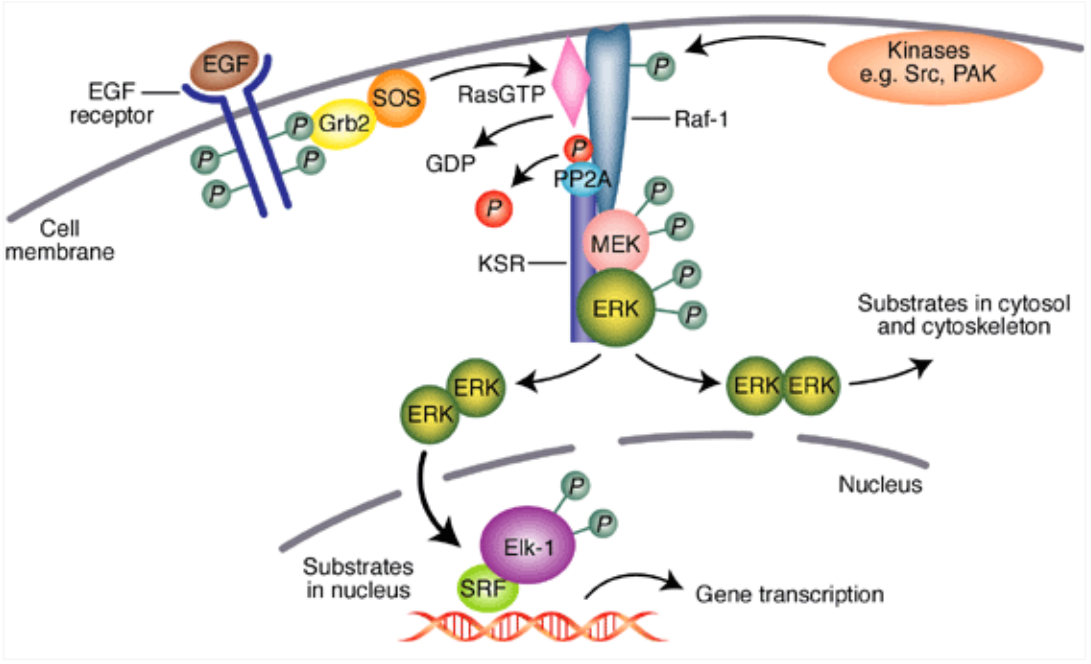
S. con Craniostenosi

RASopatie

RAS proteins are small GTP/GDP-binding GTPases, acting as molecular switches.

GTP binding, and the consequent RAS/MAPK pathway activation, stimulate a major intracellular network guiding diverse biological functions such as:

- cell proliferation
- migration
- survival
- cell fate determination
- differentiation
- senescence

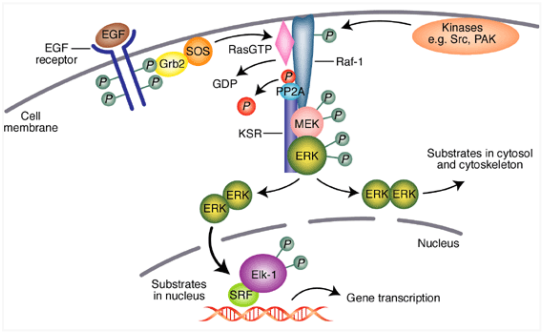


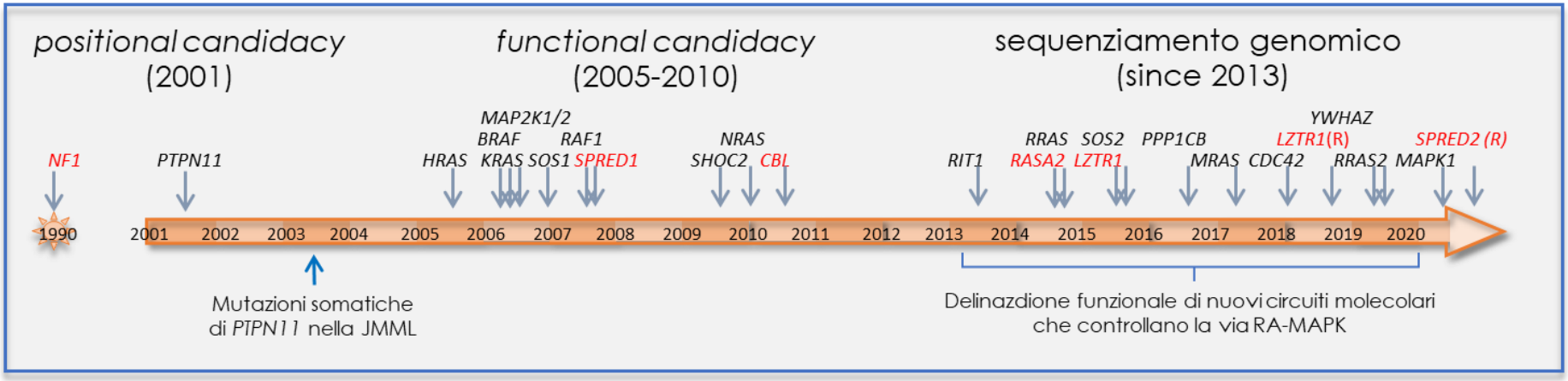
Kamoub et al., 2008; Bader et al., 2000; Malubres et al., 2003

Anomalia di Chiari

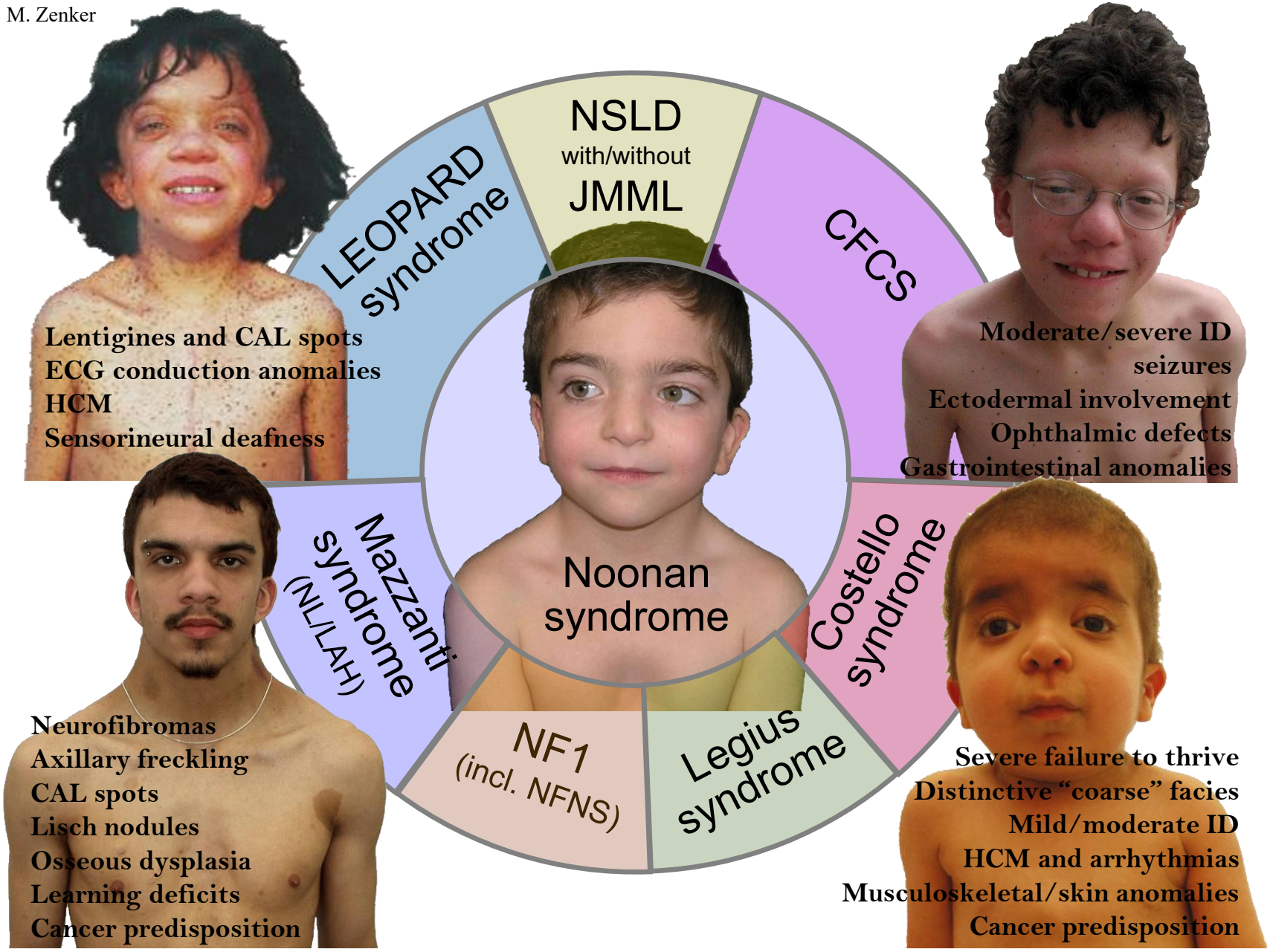
S. con Craniostenosi

RASopatie





M. Zenker

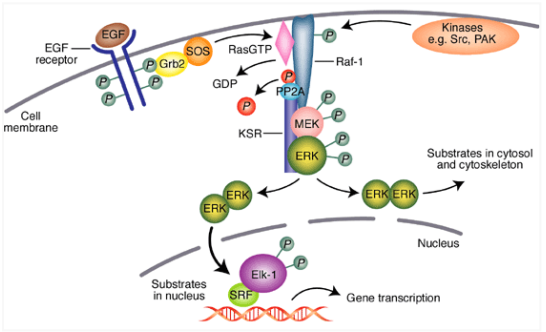

LEOPARD syndrome
NSLD
with/without
JMML
CFCS
Noonan syndrome
Mazzanti syndrome (NL/LAH)
NF1 (incl. NFNS)
Legius syndrome
Costello syndrome
Lentigines and CAL spots
ECG conduction anomalies
HCM
Sensorineural deafness
Moderate/severe ID
seizures
Ectodermal involvement
Ophthalmic defects
Gastrointestinal anomalies
Neurofibromas
Axillary freckling
CAL spots
Lisch nodules
Osseous dysplasia
Learning deficits
Cancer predisposition
Severe failure to thrive
Distinctive "coarse" facies
Mild/moderate ID
HCM and arrhythmias
Musculoskeletal/skin anomalies
Cancer predisposition

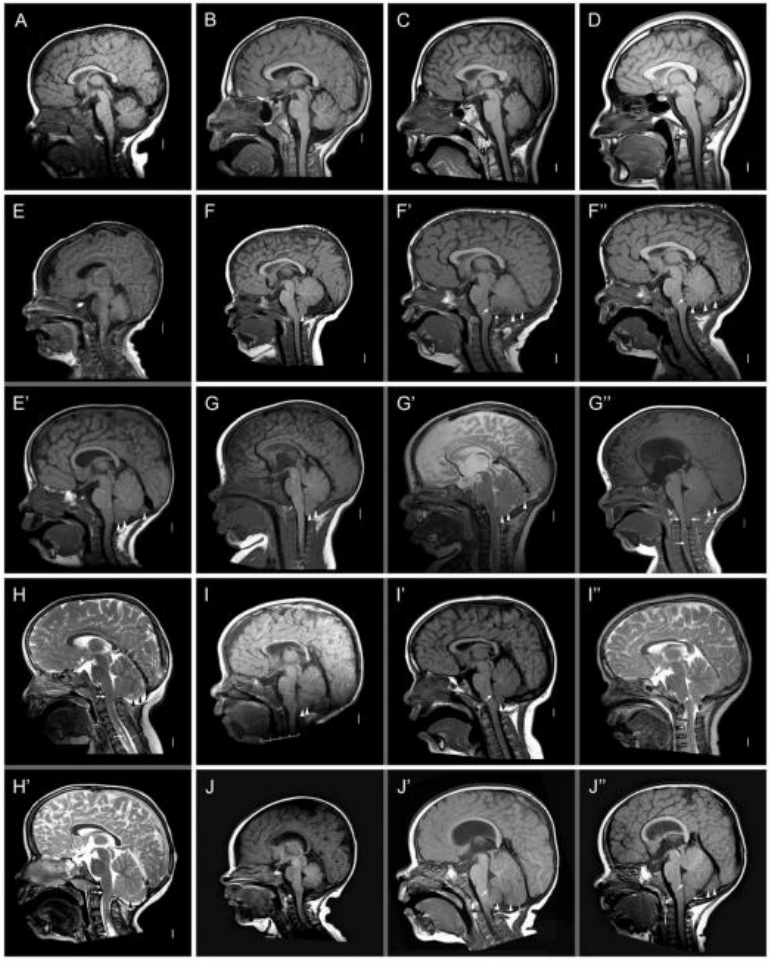
Anomalia di Chiari

S. con Craniostenosi

RASopatie

- **Chiari 1** nel 32% dei casi complessivi, ma fino al **50% nei soggetti di età ≥16 anni**
- **Siringomielia** (25%)
- **Meccanismo patogenetico : Crescita cerebellare postnatale progressiva**.
  Aumento del numero di astrociti e del volume cerebrale, con affollamento progressivo della fossa posteriore.

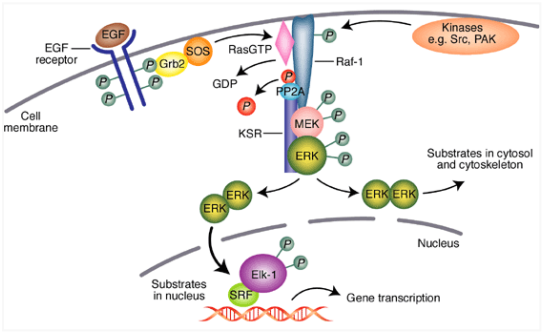


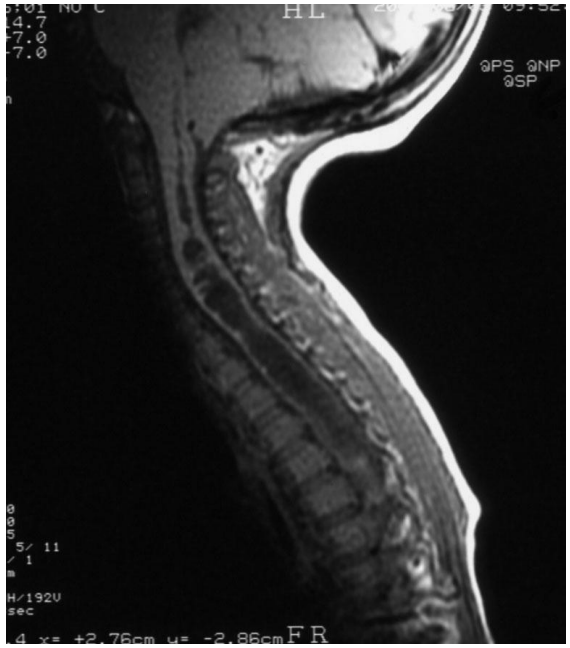


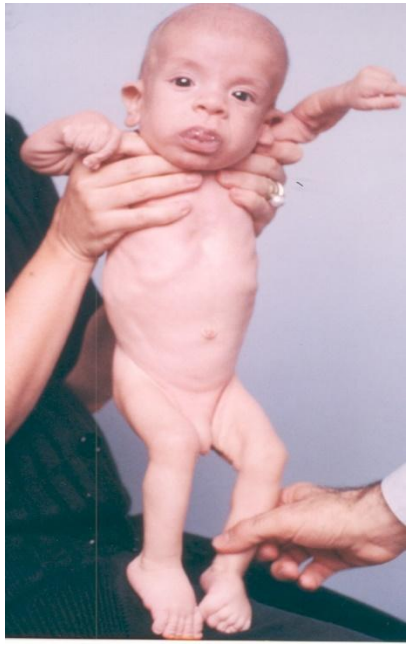
Anomalia di Chiari

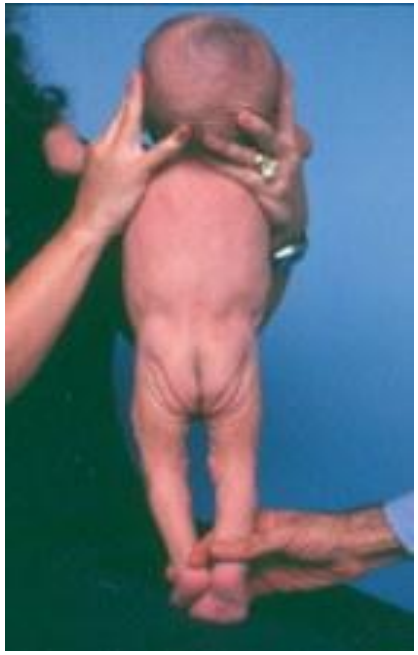
S. con Craniostenosi

RASopatie



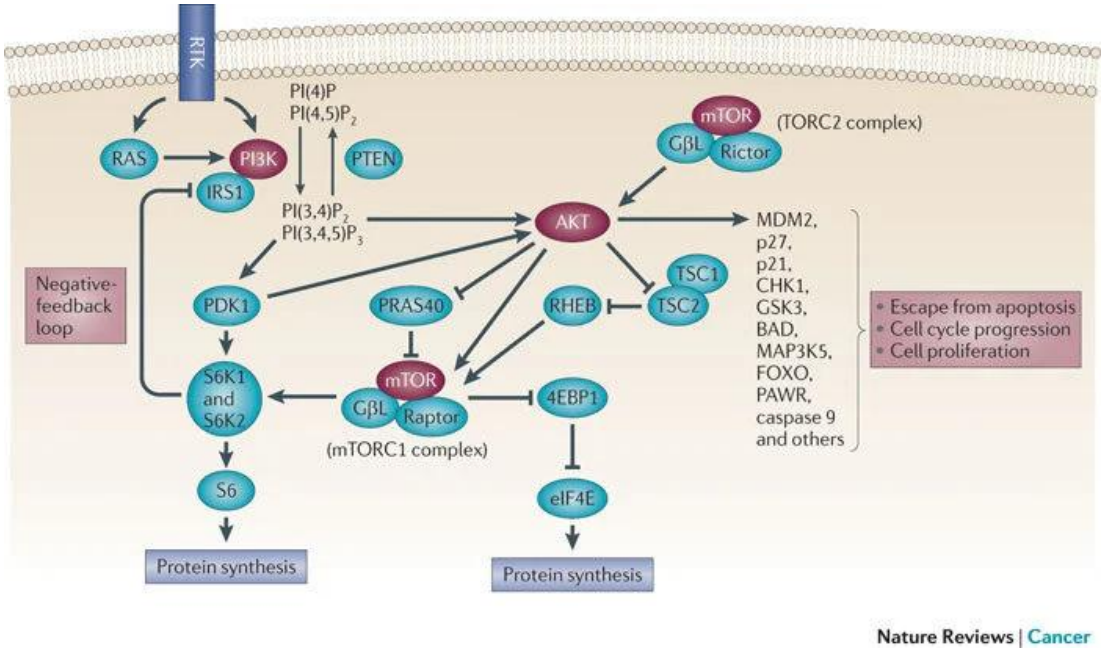






Anomalia di Chiari

- S. con Craniostenosi
- RASopatie
- PTEN-PI3K/AKT



Mutazioni pathway PTEN-PI3K/AKT sono l'8,6% delle Chiari 1 sindromiche

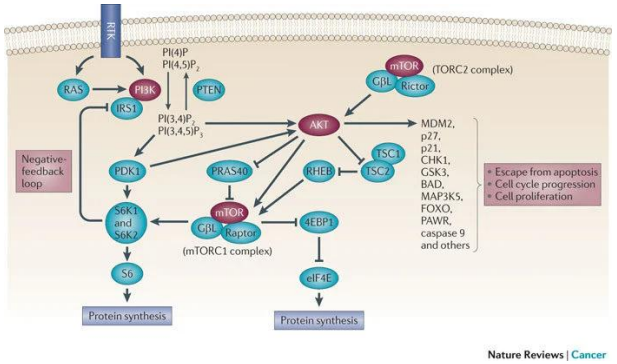
Saletti et al. Childs Nerv Syst. 2019 PMID: 31363831.

Anomalia di Chiari

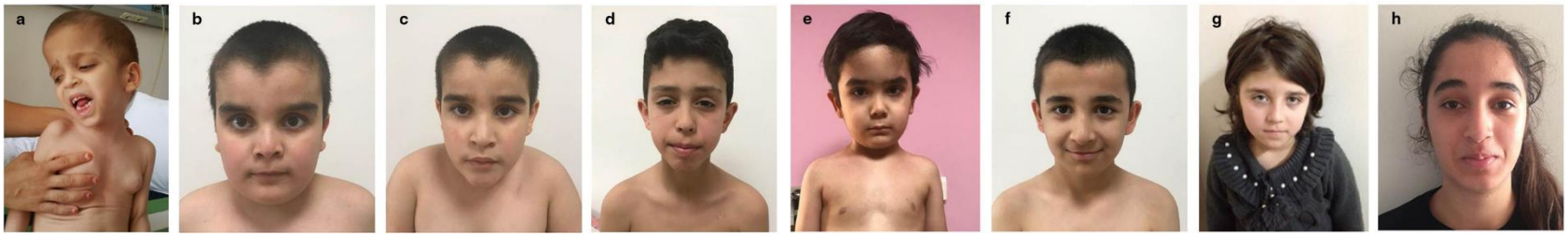
S. con Craniostenosi

RASopatie

PTEN-PI3K/AKT

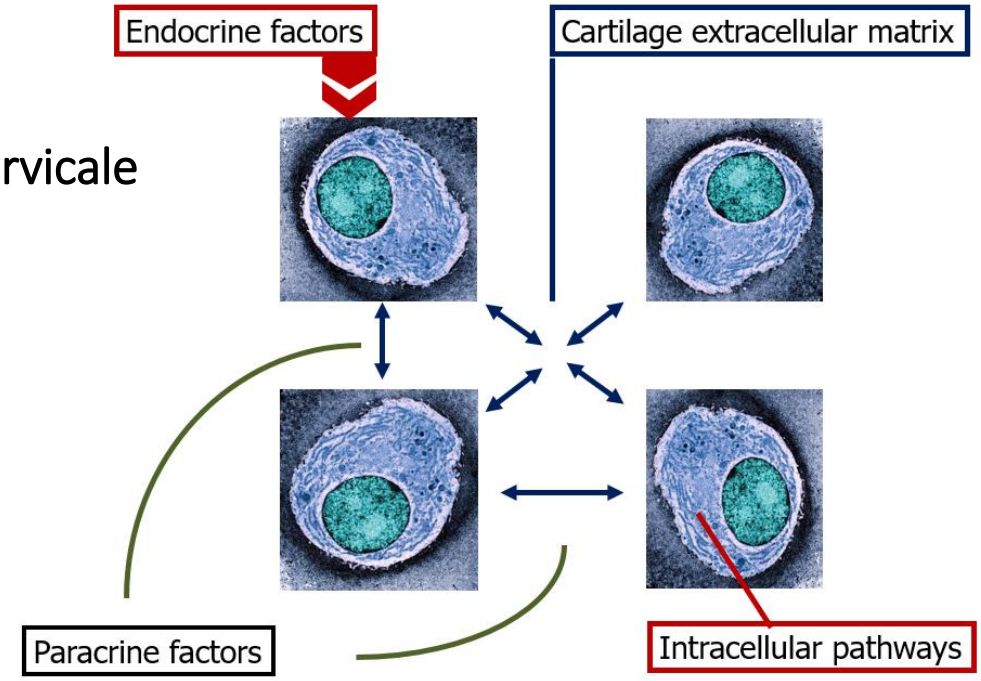


L'overgrowth cerebrale con aumento significativo dei volumi cerebrali globali e regionali, mega-corpo calloso (75% dei casi), e alterazioni della sostanza bianca periventricolare (83%) determina incongruenza tra il volume del contenuto intracranico e la capacità della fossa cranica posteriore, favorendo l'erniazione tonsillare attraverso il forame magno.



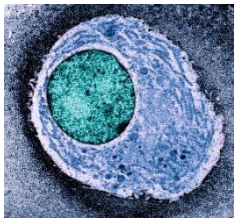
Anomalia di Chiari

- S. con Craniostenosi
- RASopatie
- PTEN-PI3K/AKT
- Displasie scheletriche
  - Anomalie della base cranica
  - Anomale giunzione cranio-cervicale

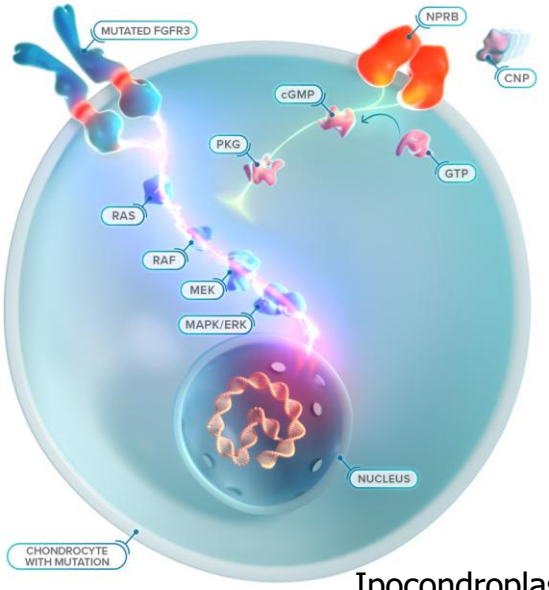


Paracrine factors

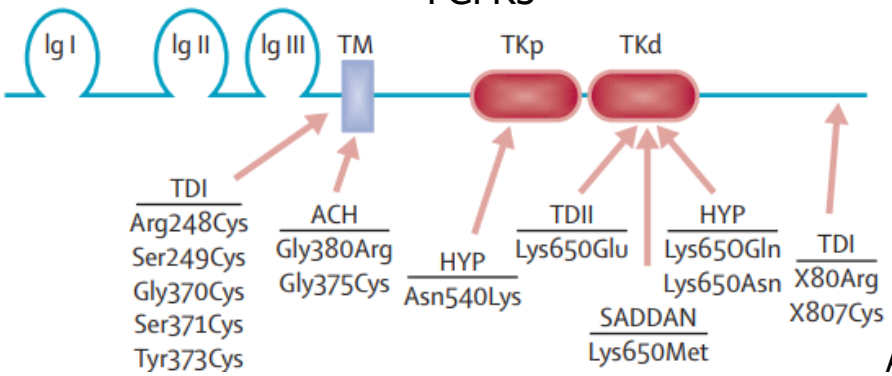
Short Disarmonic Stature



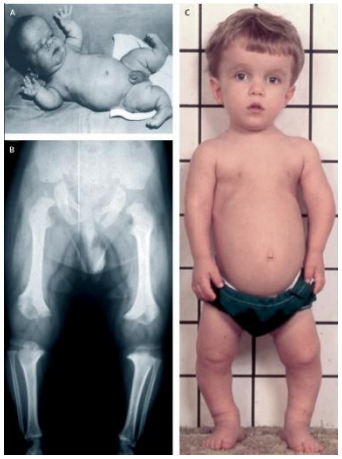
Fibroblast growth factor signalling



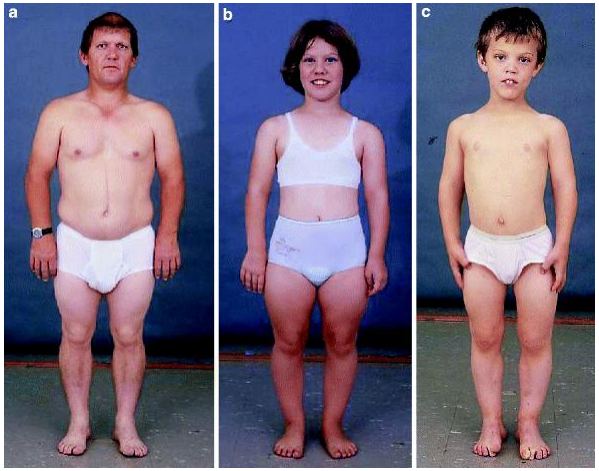
FGFR3



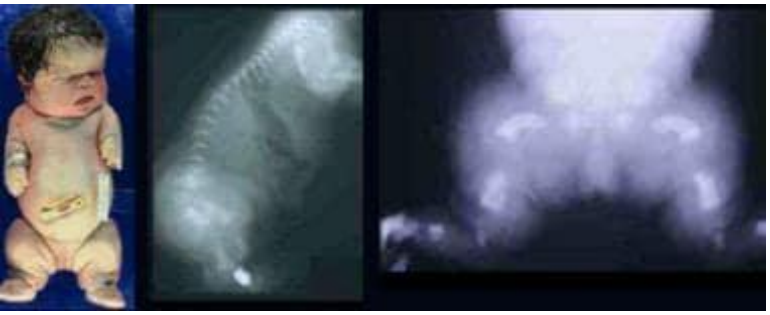
Acondroplasia



Ipocondroplasia

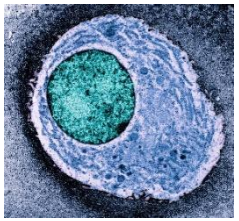


Displasia tanatofora



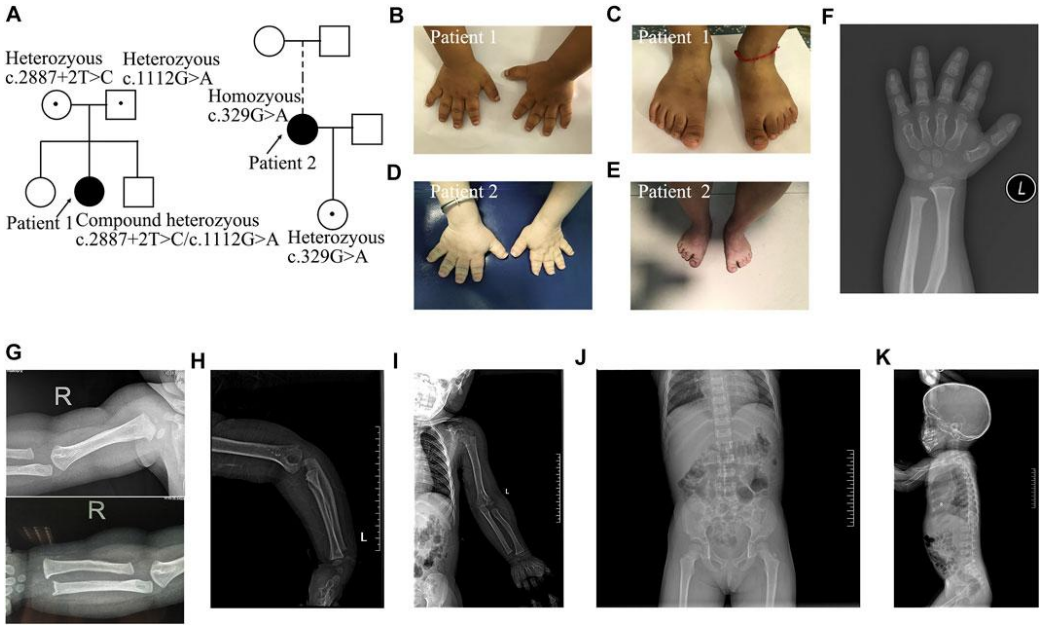
Paracrine factors

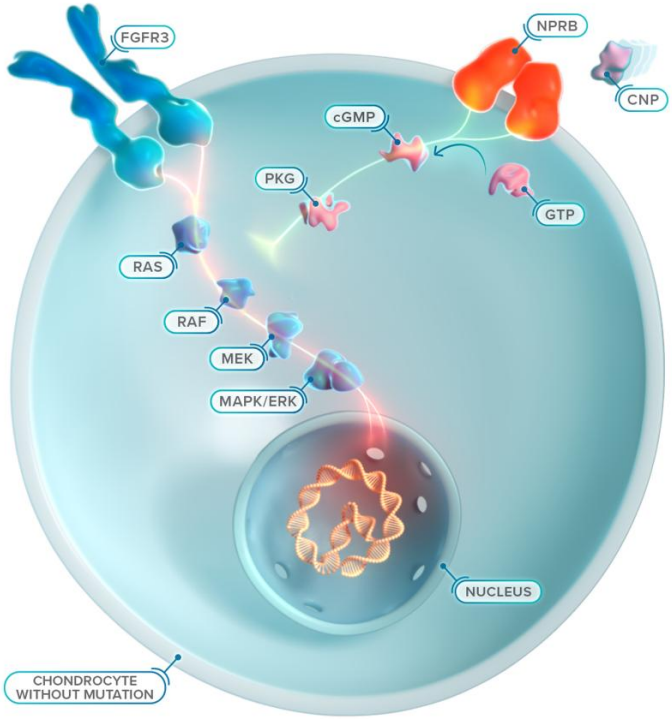
Short Disarmonic Stature



Fiibroblast growth factor signalling

CNP-NPR2 pathway





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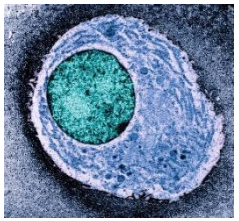
Olney RC et al. Heterozygous mutations in natriuretic peptide receptor-B (NPR2) are associated with short stature. *J Clin Endocrinol Metab*. 2006;91:1229-1232.

Paracrine factors

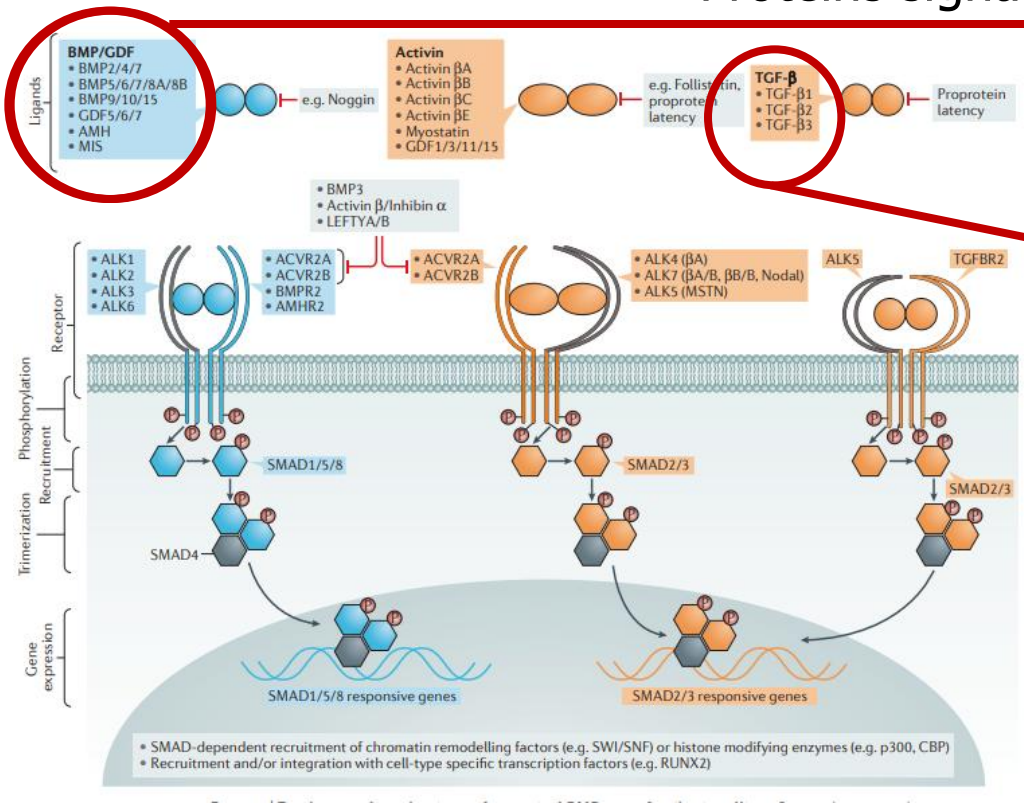
Short Disarmonic Stature

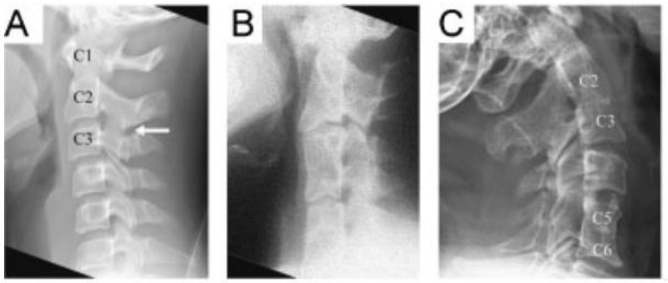


Fiibroblast growth factor signalling

CNP-NPR2 pathway

Bone Morphogenetic Proteins signalling





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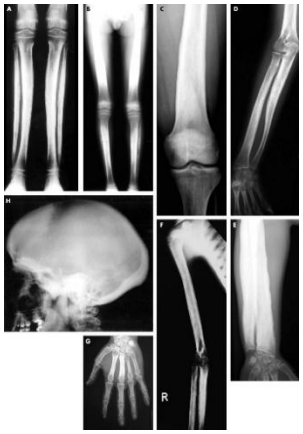
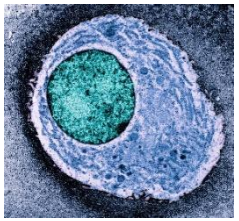


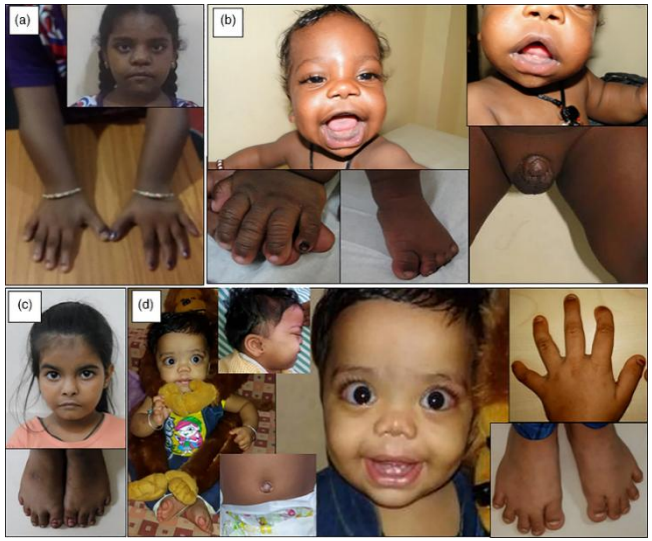
Kinoshita A et al. Domain-specific mutations in TGFB1 result in **Camurati-Engelmann disease**. Nat Genet. 2000;26(1):19-20.

Paracrine factors

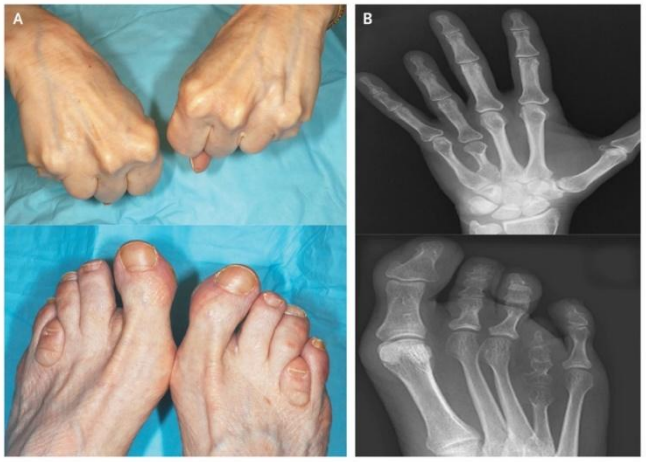


Short disarmonic stature

- Fiibroblast growth factor signalling
- CNP-NPR2 pathway
- Bone Morphogenetic Protein signalling
- WNT signalling
- PTHrP-IHH pathway

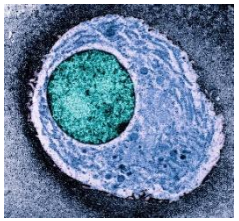


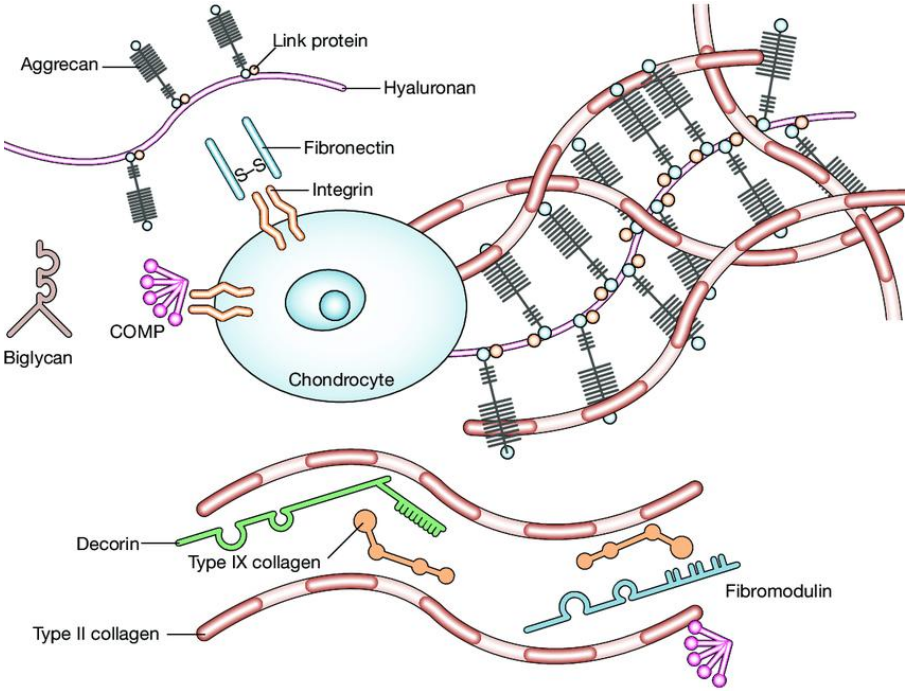
van Bokhoven H et al. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal **recessive Robinow syndrome**. Nat Genet. 2000; 25(4):423-6..



Shore EM et al. Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. *N Engl J Med*. 2002;346(2):99-106. doi:10.1056/NEJMoa011262

Defects in cartilage extracellular matrix





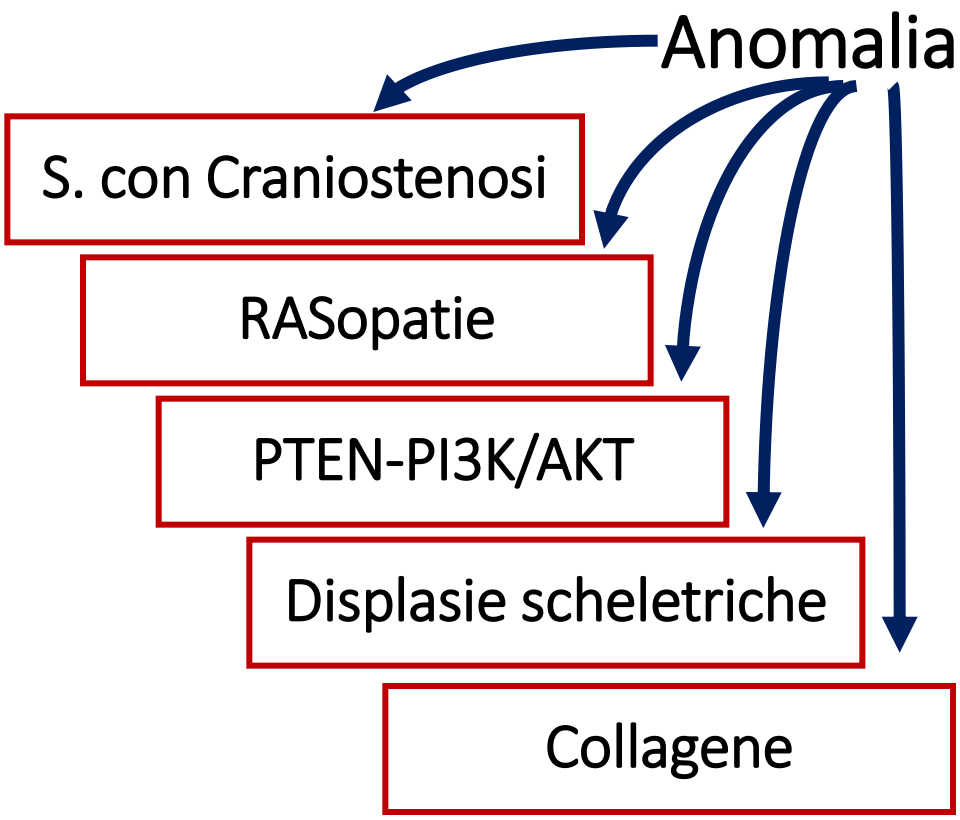
Difetti Collagene II

Most severe (often lethal perinatally)
- Achondrogenesis type II
- Hypochondrogenesis
- Platyspondylic dysplasia, Torrance type

Severe/moderately severe (neonatal presentation)
- Kniest dysplasia
- Spondyloepiphyseal dysplasia congenita (SEDC)
- Spondyloepimetaphyseal dysplasia (SEMD), Strudwick type

Intermediate (neonatal/childhood/adolescent presentation)
- Spondyloperiphyseal dysplasia
- Spondyloepiphyseal dysplasia with metatarsal shortening
- Stickler syndrome type 1

Mild (adolescent/adult presentation). Mild spondyloepiphyseal dysplasia (SED) with premature arthrosis

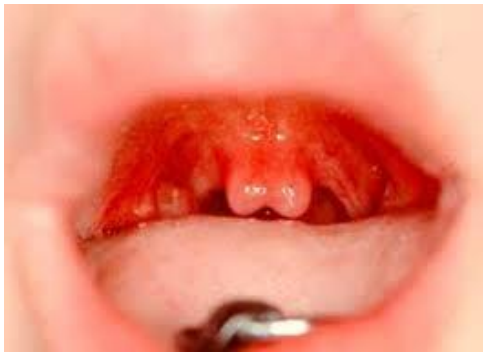


- Il 47% dei pazienti con CM1 presenta varianti in almeno uno dei quattro geni del collagene significativi (COL7A1, COL5A2, COL6A5, COL1A2), e il 26% presenta varianti nel gene COL6A5.
- I geni del collagene contribuiscono significativamente alla eziologia della CM1

I pazienti con disturbi ereditari del tessuto connettivo presentano caratteristiche cliniche distintive rispetto ai pazienti con CM1 isolata.
Prevalenza femminile (rapporto 8:1 rispetto a 3:1)
Maggiore incidenza di sintomi del tronco encefalico inferiore, formazione di panno retroodontoideo e ipoplasia dell'orofaringe.
La presentazione clinica è complicata da instabilità craniocervicale, ipermobilità occipito-atlanto-assiale e "cranial settling" (abbassamento cranico).

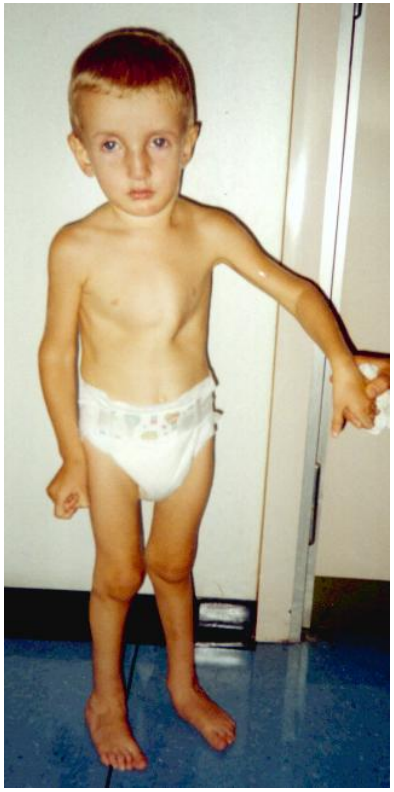
Anomalia di Chiari

- S. con Craniostenosi
- RASopatie
- PTEN-PI3K/AKT
- Displasie scheletriche
- Collagene

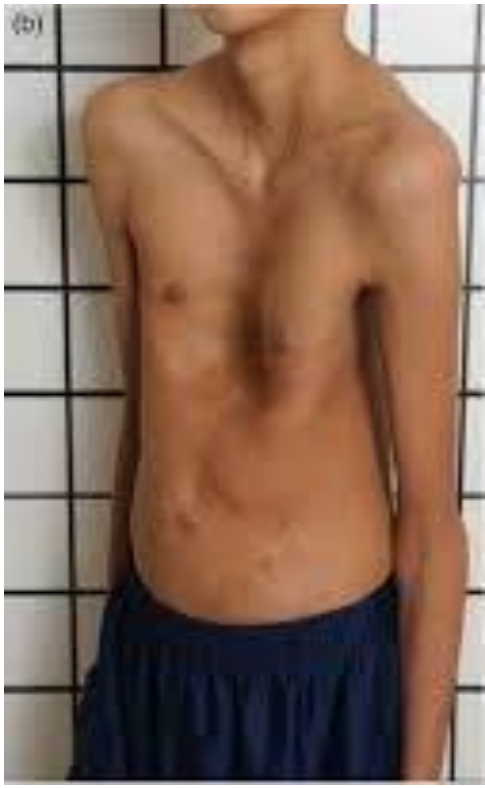


s. Ehlers-Danlos

s. Stickler



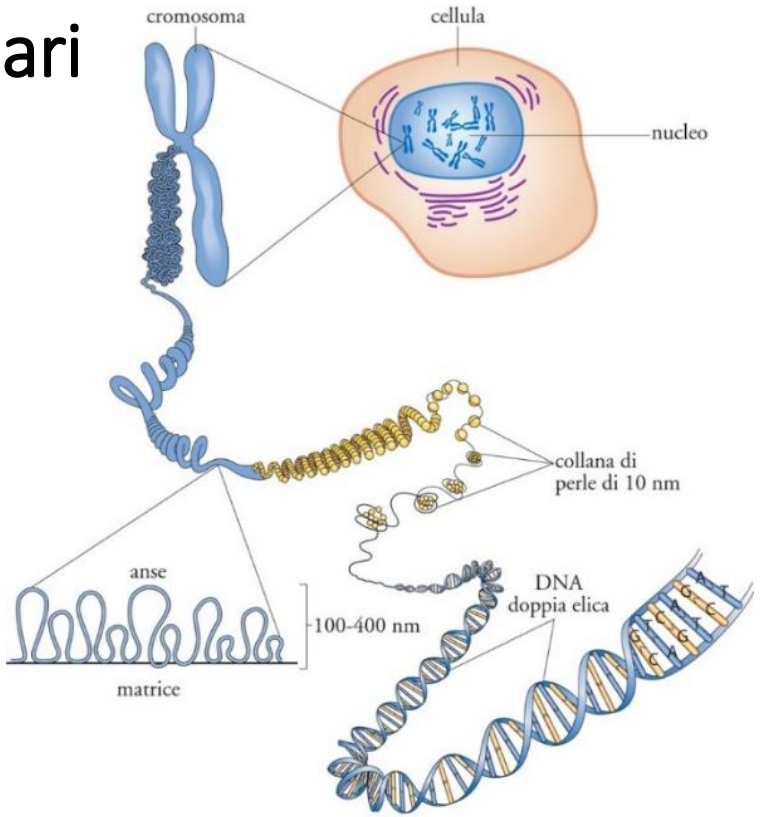
s. Marfan

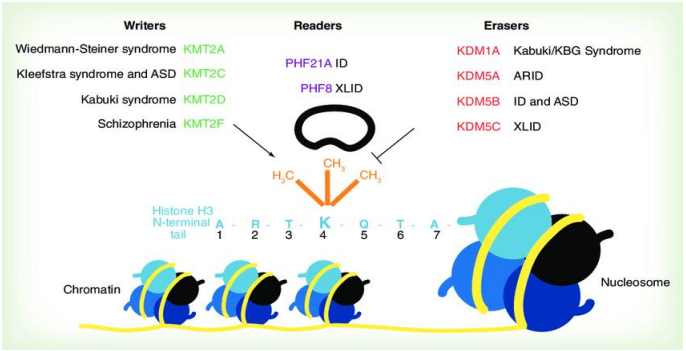


s. Loyes Dietz

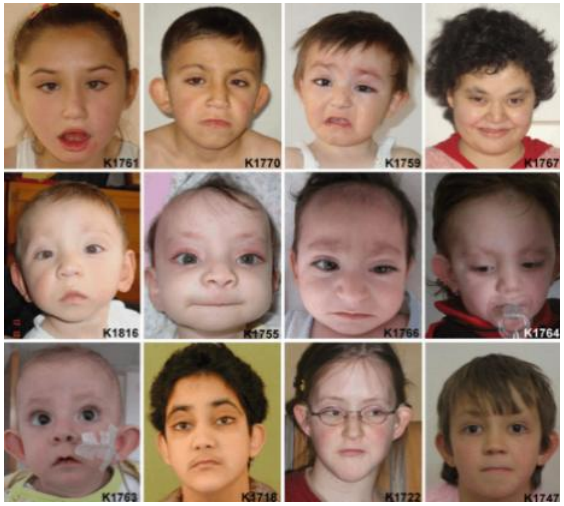
Anomalia di Chiari

- S. con Craniostenosi
- RASopatie
- PTEN-PI3K/AKT
- Displasie scheletriche
- Collagene
- Cromatinopatie





S. KBG



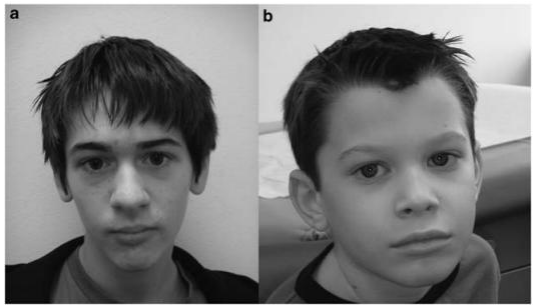
S. Kabuki

Anomalia di Chiari

- S. con Craniostenosi
- RASopatie
- PTEN-PI3K/AKT
- Displasie scheletriche
- Collagene
- Cromatinopatie
- Cromosomopatie

Chromosomal rearrangements	6/35
del16p11.2	2
del2p15	1
dupXp22.31	1
del5q14.3 (MEF2C haploinsufficiency)	1
Potocki-Lupski syndrome	1

Saletti V et al. Chiari I malformation in defined genetic syndromes in children: are there common pathways? Childs Nerv Syst. 2019 PMID: 31363831.



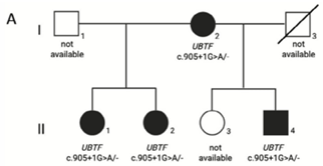
Expanding the clinical spectrum of the 16p11.2 chromosomal rearrangements: three patients with syringomyelia

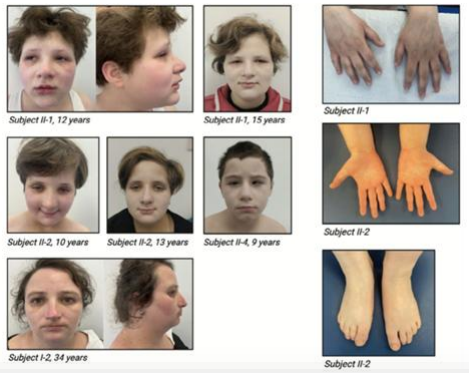
Christian P Schaaf[1], Robin P Goin-Kochel[1], Kerri P Nowell[1], Jill V Hunter[2], Kirk A Aleck[3], Sarah Cox[3], Ankita Patel[1], Carlos A Bacino[1] and Marwan Shinawi*[,4]

Anomalia di Chiari

- S. con Craniostenosi
- RASopatie
- PTEN-PI3K/AKT
- Displasie scheletriche
- Collagene
- Cromatinopatie
- Cromosomopatie
- Miscellanee

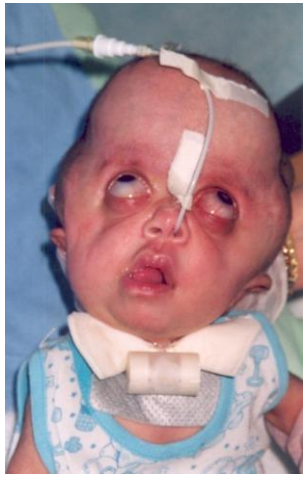
Sedláčková L et al.
UBTF Mutation Causes Complex Phenotype of Neurodegeneration and Severe Epilepsy in Childhood.
Neuropediatrics. 2019
PMID: 30517966.



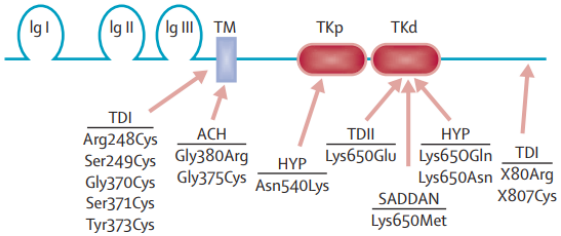


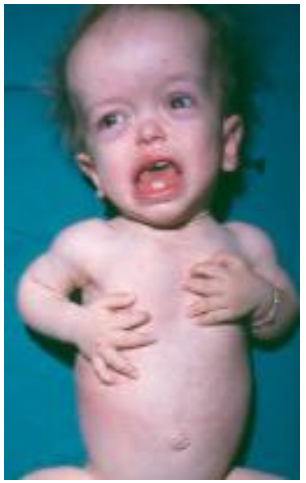
***UBTF* Haploinsufficiency-Related Disorder: Report of a New Case Series and Definition of the Facial Gestalt**

Perché ?



Mutazioni dei geni FGFR





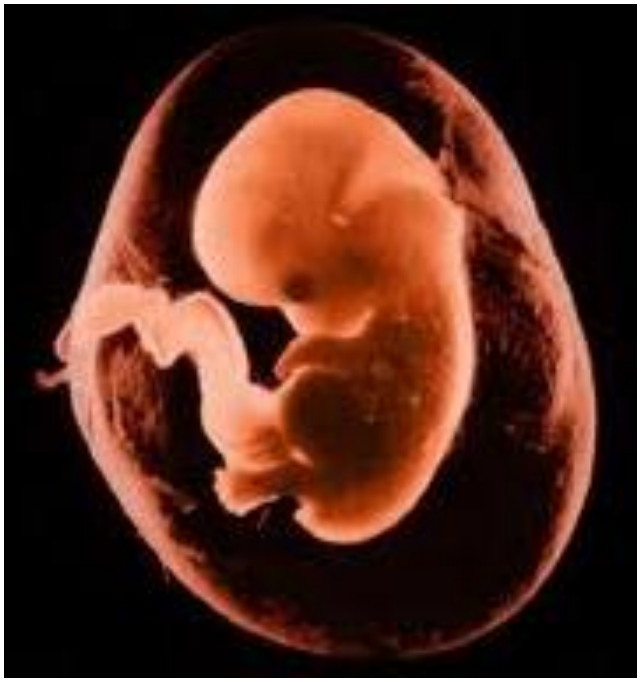
La scienza non conosce la categoria di FINE e di SENSO

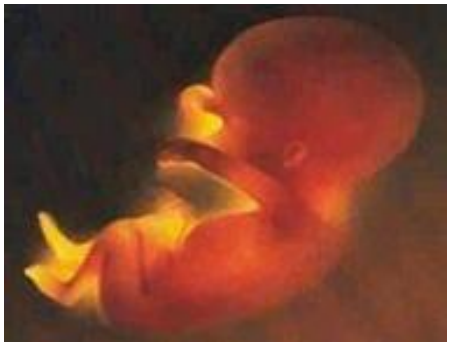
«Noi sentiamo che, persino nell'ipotesi che tutte le possibili domande scientifiche abbiano avuto risposta, i nostri problemi vitali non sono ancora neppure sfiorati»

L. Wittgenstein

Salmo 139 , 13-16

Sei tu che hai creato le mie viscere
mi hai tessuto nel grembo di mia madre,
Ti lodo, perché mi hai fatto come un prodigio, sono stupende le tue opere,
Tu mi conosci fino in fondo.
Non ti erano nascoste le mie ossa
quando venivo formato nel segreto
intessuto nelle profondità della terra.
Ancora embrione mi hanno visto i tuoi occhi e tutto era scritto nel tuo libro



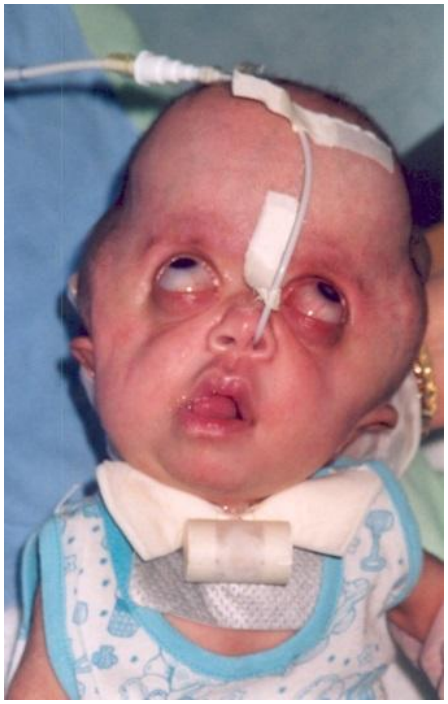


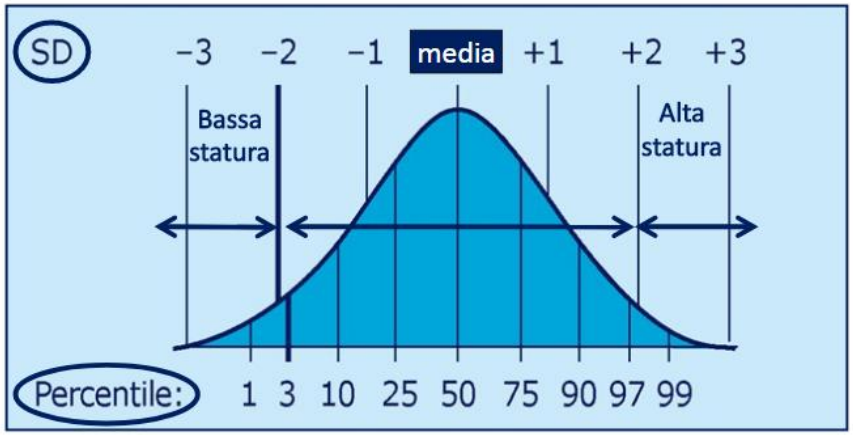
Corano Sura III,6

Allah che vi plasma come vuole negli uteri

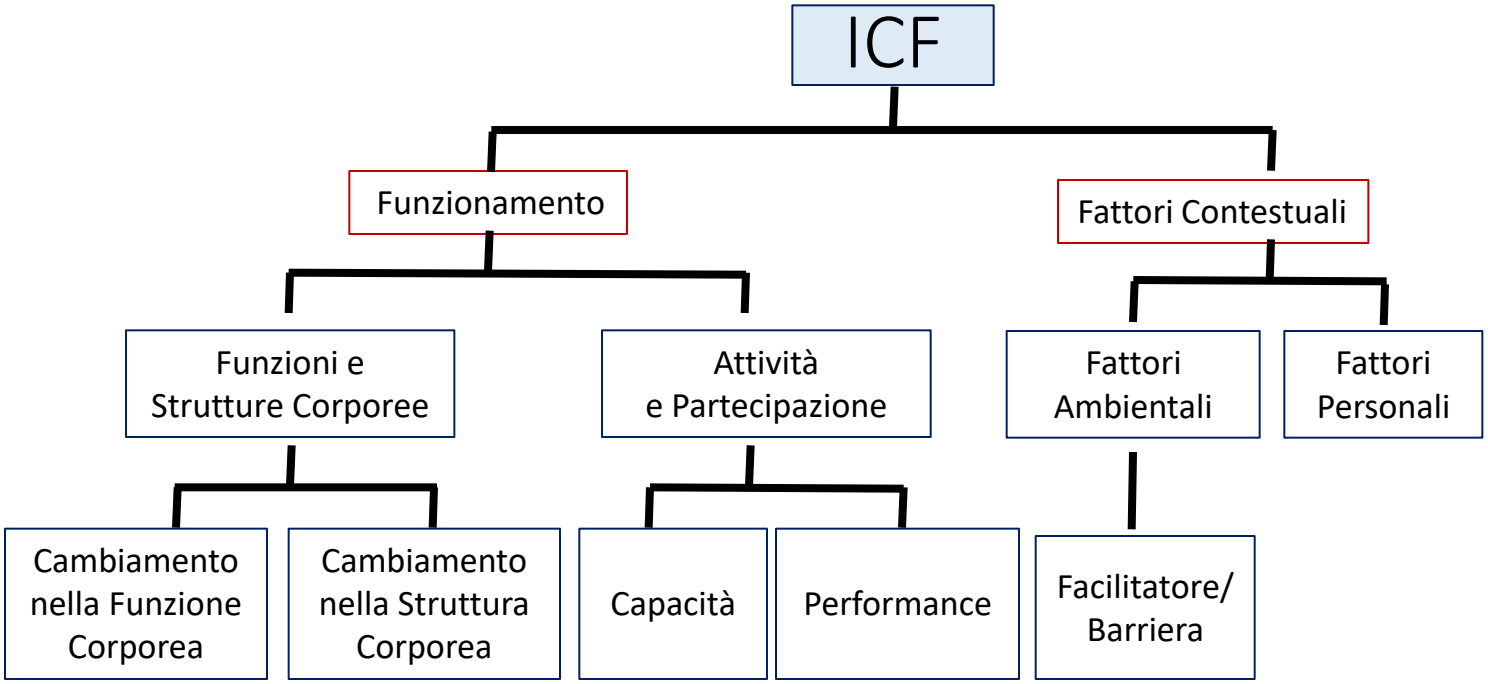
Perché ?

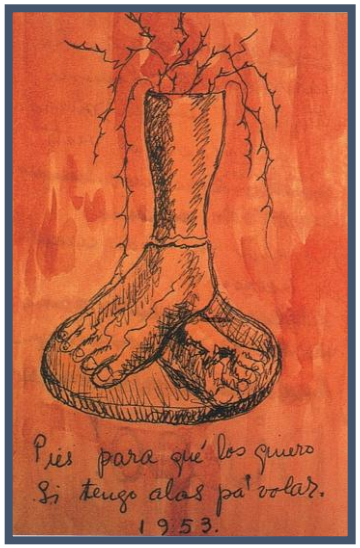
Passando vide un uomo cieco dalla nascita e i suoi discepoli lo interrogarono: «Rabbì, chi ha peccato, lui o i suoi genitori, perché egli nascesse cieco?».





«Non è vero che le eccezioni confermano la regola; non è vero che distruggono ogni regola. E' vero che la regola è data da tutto ciò che avviene: casi normali ed eccezionali».
Vito Mancuso – Etica dei giorni difficili





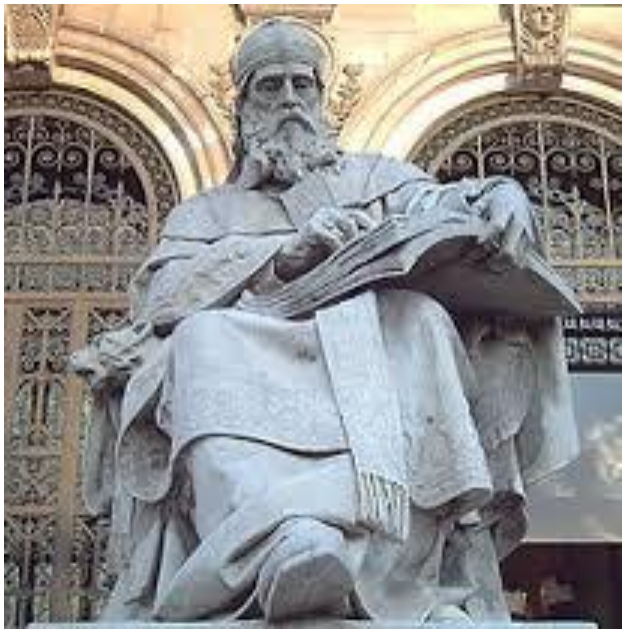
Definizione:

I **fattori ambientali** costituiscono gli atteggiamenti, l'ambiente fisico e sociale in cui le persone vivono e conducono la loro esistenza.

di vita.

Le **limitazioni dell'attività** sono le difficoltà che un individuo può incontrare nello svolgere delle attività.

Le **restrizioni alla partecipazione** sono i problemi che un individuo può sperimentare nel coinvolgimento nelle situazioni di vita.



Isidoro di Siviglia VII sec DC

SPES - PES

- Camminare verso obiettivi definiti
- Camminare insieme verso obiettivi condivisi

Stato motivazionale positivo basato su senso di energia positivo diretto verso il raggiungimento di un obiettivo

EDITORIALS

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

The Power of Hope

James C. Harris, MD
Catherine D. DeAngelis, MD, MPH

THE HOLIDAY SEASON IS TRADITIONALLY A TIME FOR HOPEfulness as the new year begins. With the promise of a new administration in Washington, there is a renewed sense of optimism for health care reform and hope for better health care for all in the United States. In this Editorial, we start today by reflecting on the essence of personal health care that is based on the depth of the relationship between patient and physician so eloquently described

Often a patient comes to a physician with a sense of disquiet and dis-ease, not knowing what to expect but hoping to be restored, while fearing the worst. Anxiety is distracting to a patient and makes it difficult for him or her to listen to what a physician has said or is saying. Worse still is despair, when a patient gives up hope completely and shuts down emotionally. How can a physician reassure a patient who is so distressed and ensure that the patient leaves with the expectation that something can be done and is hopeful about his or her condition? To illustrate the importance of this reassurance, Engel[11] described the course of a patient in an emergency department who had a first myocardial in-

Non si può vivere senza speranza e non si può sperare senza orientare la propria vita secondo un progetto di pienezza. La speranza è propriamente una virtù, ovvero una disposizione dell'animo che serve ad aiutare gli altri a trovare il senso della vita anche nelle situazioni estreme. La speranza può cambiare il corso di una malattia, aiutando il paziente a vincerla, poiché può essere considerata un catalizzatore della guarigione.

UNIVERSITÀ CATTOLICA del Sacro Cuore

La disabilità non è una scelta…

…… La nostra attitudine si