



La Sindrome di Rubinstein-Taybi INQUADRAMENTO DIAGNOSTICO

Donatella Milani



FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Sistema Sanitario  Regione
Lombardia

La storia

- **1957** tre chirurghi ortopedici greci "nuovo caso di malformazione dei pollici assolutamente simmetrica"
- **1963** Rubinstein e Taybi



Incidenza 1:125.000
(1:3-600 pz istituzionalizzati)



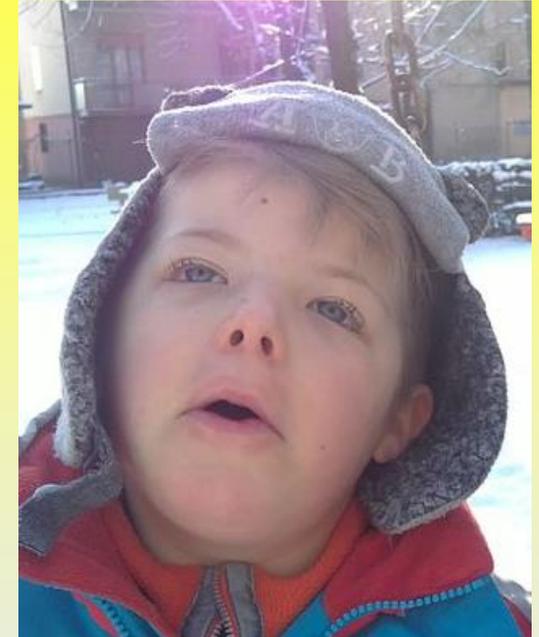
VINI ILVERO
AMAILRARO

Nasce un bambino
speciale...inizio di una
lunga storia di fatica e
di amore



- Alla nascita
- In epoca neonatale
- Nel corso dell'infanzia

Quando è l'inizio del percorso?



Diagnosi a 34 anni!

Qual è l'inizio del percorso?



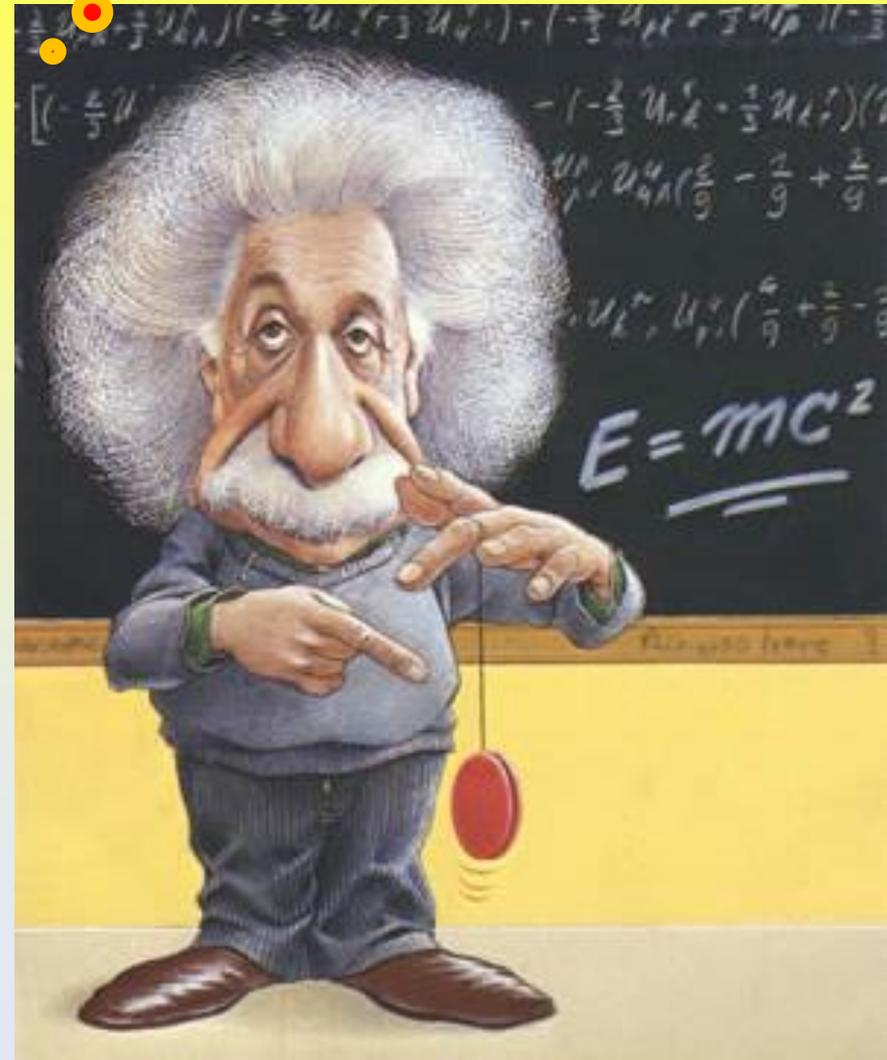
Qual è l'inizio del percorso?

I tratti del volto



Qual è l'inizio del percorso?

Lo sviluppo psicomotorio



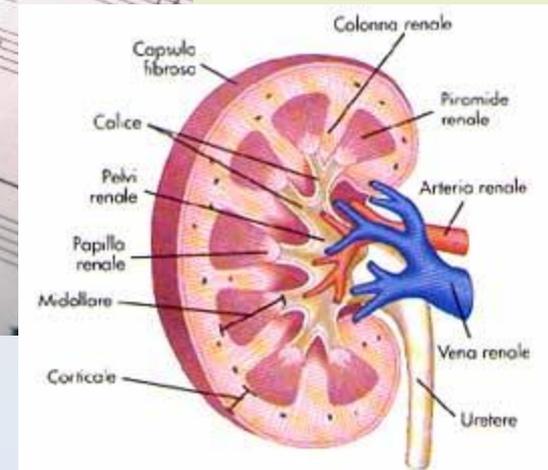
Qual è l'inizio del percorso?

L'accrescimento



Qual è l'inizio del percorso?

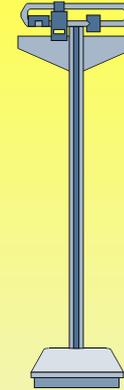
Le malformazioni maggiori



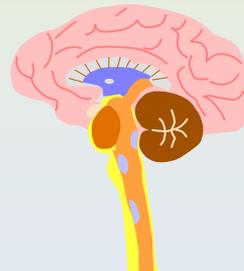
Caratteristiche principali

VOLTO

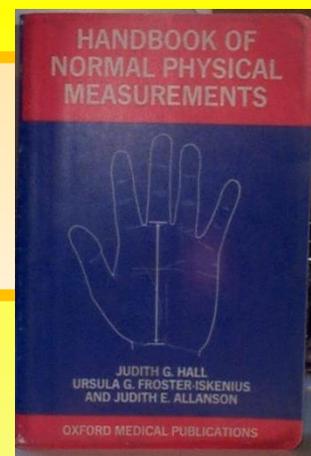
ARTI



- Ritardo di crescita (78%)
- Microcefalia (35-94%)
- Tratti del volto tipici (espressione del volto!)
- Pollici ed alluci ampi ed angolati (99%)
- Malformazioni viscerali
- Ritardo di sviluppo



Accrescimento



■ NASCITA:

- Lunghezza media 49 cm; range 43.9-53.3 cm
- Peso medio 3.1 Kg; range 2.05-4.28 Kg
- CC media 34.2 cm M; 32.2 cm F

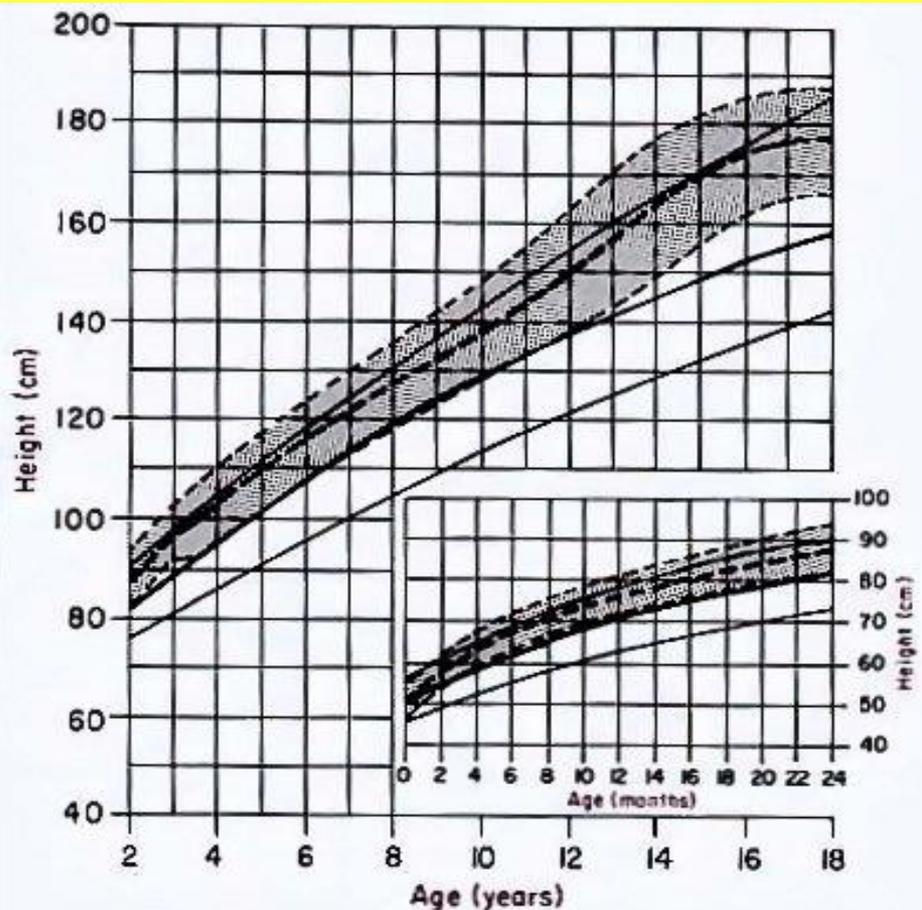
■ PRIMO ANNO: problemi di alimentazione (80%) causati da

- Ipotonia;
- RGE (68%);
- Infezioni respiratorie ricorrenti.

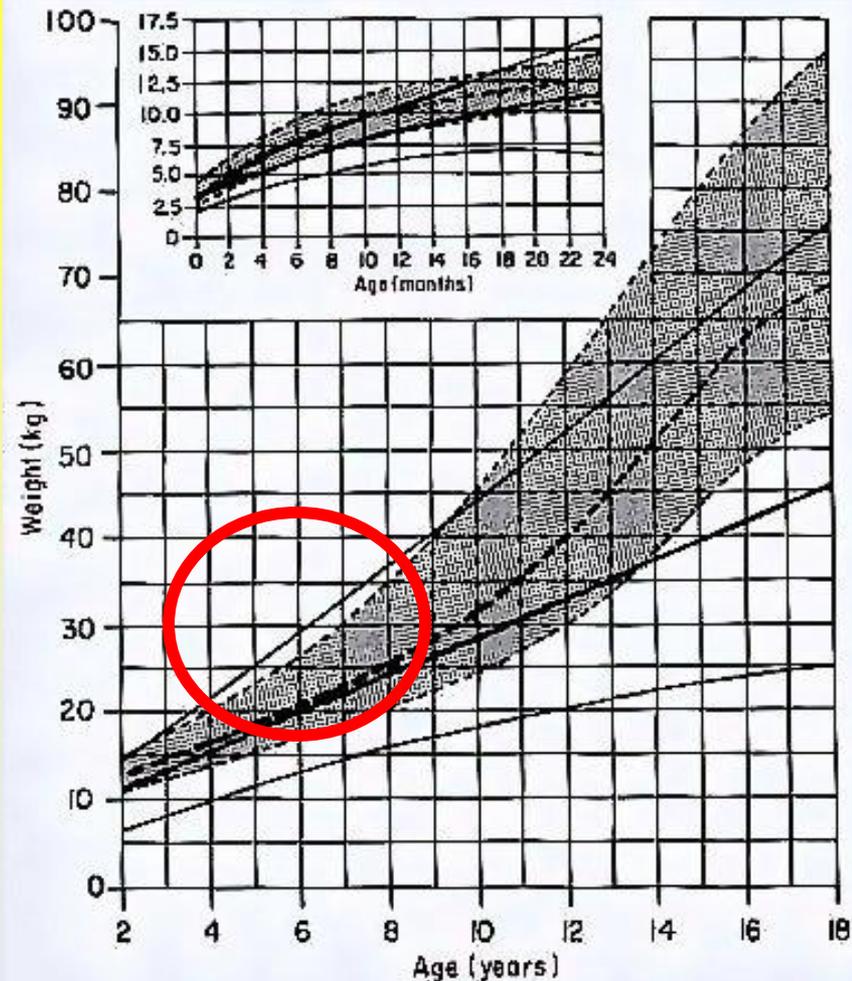
■ PRIMA INFANZIA: L 5%, P <3%, CC 2%.



Periodo prescolare: aumento di peso nei **M.**
 P medio al 25-50%, ratio peso-altezza >95%



Height curve of males with Rubinstein-Taybi syndrome (solid lines) compared with normal males (dashed lines).

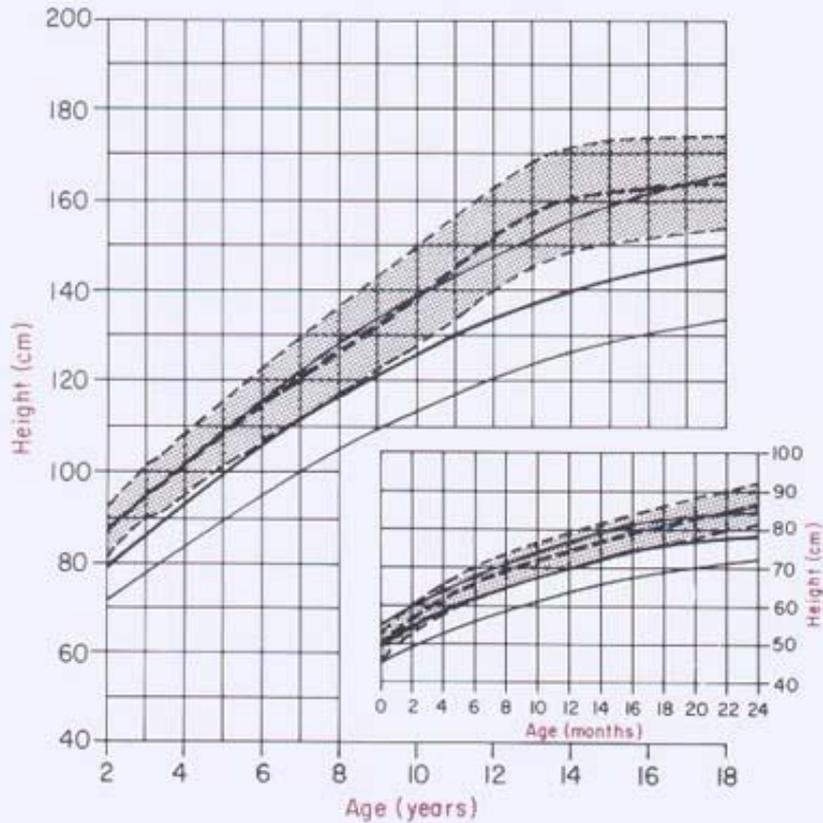


Weight curve of males with Rubinstein-Taybi syndrome (solid lines) compared with normal males (dashed lines).

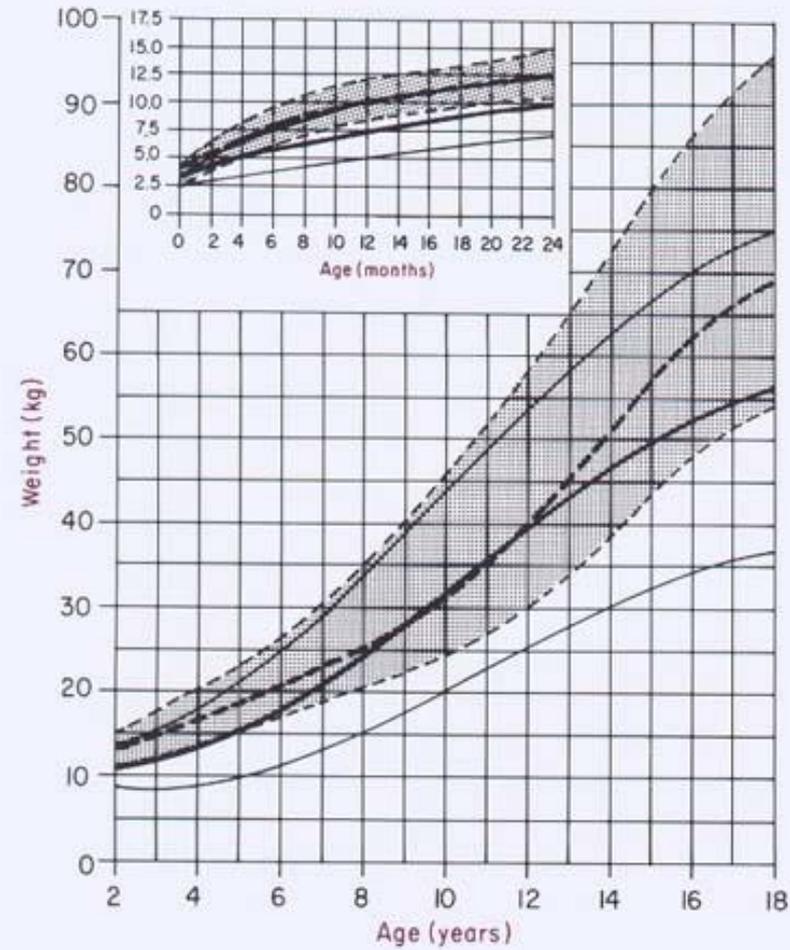


Prima adolescenza: eccesso ponderale F

Problema che permane nel tempo.



Height curve of females with Rubinstein-Taybi syndrome (solid lines) compared with normal females (dashed lines).



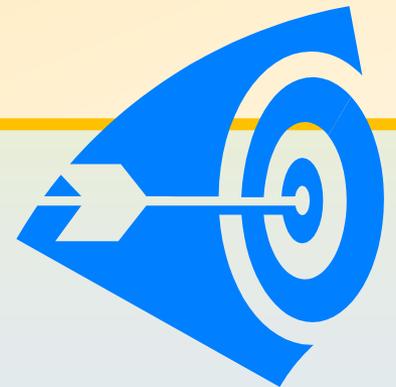
Weight curve of females with Rubinstein-Taybi syndrome (solid lines) compared with normal females (dashed lines).

In entrambi i sessi è assente lo spurt puberale, e ciò contribuisce alla **bassa statura** definitiva (78%);

altezza finale

153.1 cm **M**

146.7 cm **F**



QUINDI

Lo scarso accrescimento iniziale e l'andamento della crescita possono essere utili in senso diagnostico

Ma ci sono criteri più specifici...



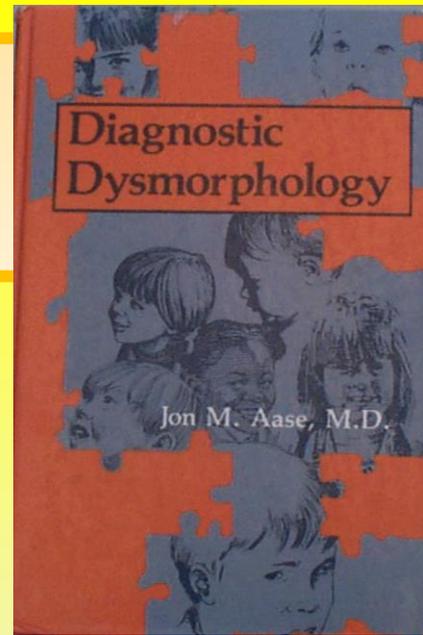
Viso ed espressione





Volto

- Impianto basso anteriore dei capelli
- Nevo flammeo fronte
- Sopracciglia folte ed arcuate
- Ciglia lunghe
- Ptosi, downslanting fessure palpebrali (82%), epicanto
- Radice nasale ampia, naso prominente (92%), setto nasale deviato, columella prominente
- Padiglioni auricolari ad impianto basso
- Palato ogivale
- Bocca piccola
- Micrognazia





Impianto basso ant e post dei capelli



Padiglioni auricolari
-malformati
-impianto basso
- ruotati
posteriormente



Sopracciglia lunghe, arcuate,
pronunciate



Occhi: downslanting, edema
palpebrale, ptosi, ipertelorismo,
epicanto, strabismo



Naso prominente,
ipoplasia ali e filtro,
columella prominente

Bocca piccola, labbra
sottili, palato ogivale

Retro/micrognazia,
malocclusione

Ipoplasia mascellare (più
evidente nei maschi)



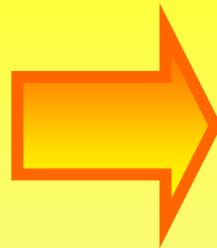
Il sorriso

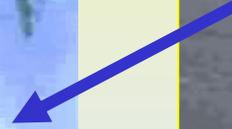
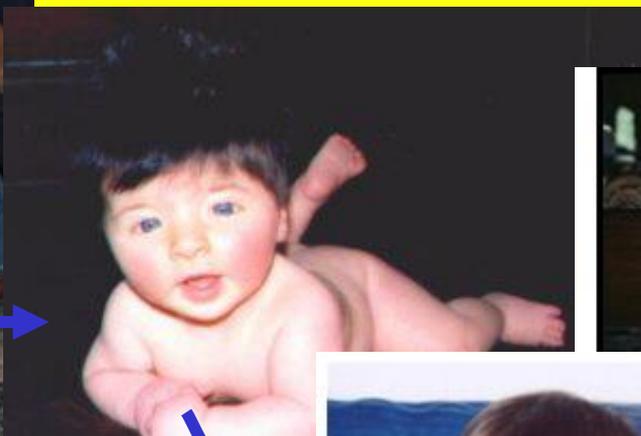


Volto

NEONATI: volto edematoso, capelli molto scuri, upslanting delle rime palpebrali, labbro inferiore carnoso e lieve micrognazia.

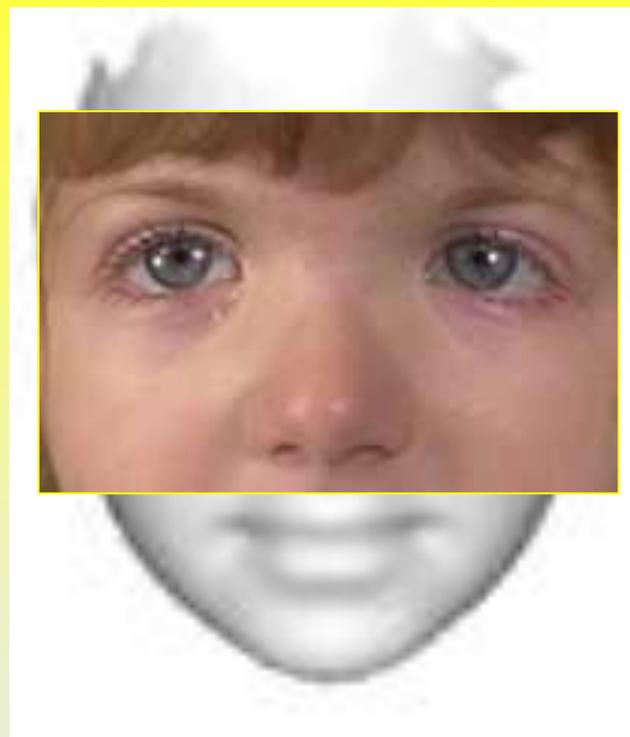
SUCCESSIVAMENTE: il volto si allunga, le fessure palpebrali si inclinano verso il basso a causa della relativa minore crescita della regione malare, il naso diviene prominente e la columella si rende evidente oltre le ali nasali, e il labbro inferiore diventa più carnoso. I padiglioni auricolari sono spesso semplici e poco disegnati e/o piccoli.





Morphometric analysis of face in dysmorphology

COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 85 (2007) 165-172



MORFOMETRIA
GEOMETRICA

Pollici ed alluci

Da un criterio
specifico a un
criterio
specifico...



Pollici ed alluci ampi e deviati

99%

1/3



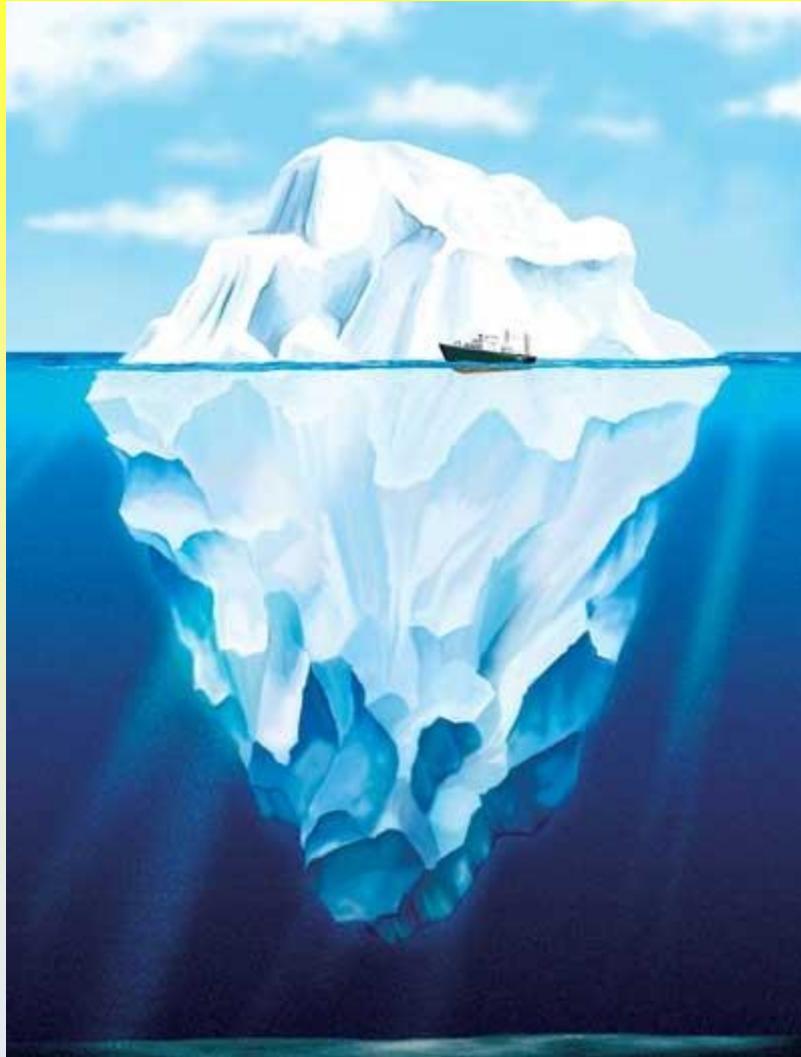


Radiologia

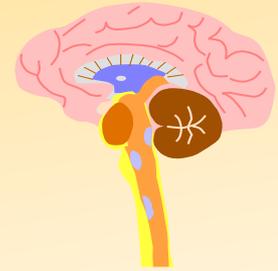
- Allargamento o duplicazione parziale 1° MTC/MTS e falangi prossimali/distali 1° raggio
- Falangi prossimali del pollice a delta
- Falange distale del pollice corta, ampia e angolata (dup/fusione)
- Falangette ampie



Le malformazioni



Neuroimaging



- Microcefalia (35%)
- Ritardo della chiusura della fontanella anteriore (24%)
- Bozze frontali (33%)
- Agenesia del corpo calloso (17%) (Jones 1997)
- Malformazione di Dandy- Walker (Bonioli et al 1989, Mazzone et al 1998, Agarwal 2002)
- Anomalie corticali (Sener 1995)

Rubinstein–Taybi Syndrome Associated With Chiari Type I Malformation Caused by a Large 16p13.3 Microdeletion: A Contiguous Gene Syndrome?



Am J Med Genet Part A 152A:479–483.

Rubinstein–Taybi syndrome in children with tethered spinal cord

J Neurosurg (4 Suppl Pediatrics) 105:261–264, 2006

- ✓ Debolezza agli arti inferiori (78%)
- ✓ Dolore arti inferiori o regione sacrale (42%)
- ✓ Disturbi funz.vescicale o intestinale (35%)
- ✓ Disturbo del cammino
- ✓ Scoliosi
- ✓ Segni cutanei (50%)

In this retrospective review of eight children with RTS and tethered spinal cord, early intervention to release the cord led to dramatic improvement of symptoms in six. All

FREQUENZA
<5%

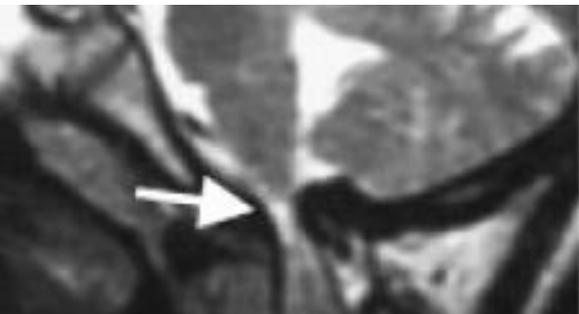
Congenital Anomaly of Cervical Vertebrae Is a Major Complication of Rubinstein–Taybi Syndrome

American Journal of Medical Genetics 135A:130–133 (2005)



Radiologic findings

C1	Dens	Relationship between C1 and C2	Other vertebral fusion	Spinal canal stenosis	Spinal cord
Hypoplasia Occipitalization	—	—	C2–C3	+	Compression High signal on T2WI
— Occipitalization	Hypoplasia	Atlanto-axial dislocation	—	+	Atrophy
—	Hypoplasia Os odontoideum	Fusion of atlas and os odontoideum	—	+	Compression n.e.
—	Os odontoideum	—	Posterior element of C2–C3	n.e.	n.e.



Rubinstein–Taybi syndrome

European Journal of Human Genetics (2006) 14, 981–985

However, although such anomalies are not rare in RSTS, symptoms caused by the vertebral anomalies are extremely infrequent in the opinion of this author. It is suggested to perform radiological studies only if clinical symptoms (gait, reflexes, bladder, and bowel function) are present.



Anomalie scheletriche



- Pollici ed alluci ampi, deviati, con duplicazione falange distale
- Clinodattilia 5° dito
- Polidattilia (postassiale piedi)
- Ritardo età ossea (74%)
- Scoliosi (cifosi, lordosi)
- Aumentato rischio di fratture (Wiley, 2003)
- Lussazione della rotula (2.5%)/testa radiale (2%)/anca (1.4%)

Dolore/variazione
nel cammino

Ridotta abduzione
anca

DIM >8-10 cm

Fratture

M.Perthes

Rotazione esterna
in flessione
dell'anca

Ginocchio valgo

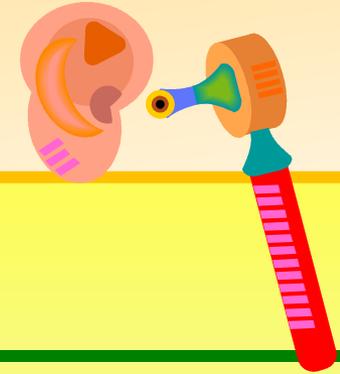
Lussazione
capitello
femorale

**Second report of slipped capital femoral epiphysis
in Rubinstein-Taybi syndrome**

Clinical Dysmorphology 2011, 20:55-57



Udito



- Ipoacusia lieve 24%
- Patologie dell'orecchio medio più frequenti (50%) e con maggior rischio di perforazione

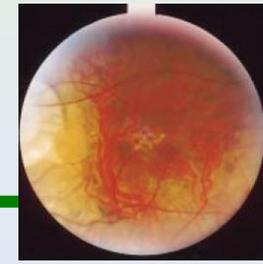
BAER nel periodo neonatale

Occhi

- Ptosi (29-32%)
- Strabismo (60-71%)
- Stenosi dotti nasolacrimali (38-47%)
- Miopia (41-56%)
- Cataratta (6%)
- Glaucoma (7%)
- Coloboma (9-11%)
- Ipoplasi del nervo ottico
- Opacità corneale
- Anomalia di Duane (8%)
- **Disfunzioni retiniche (78%)**



findings in individuals with RTS that mimic glaucoma include corneal lesions, megalocornea, colobomatous or cystic optic nerve, excavation of papilla, and large cup-to-disc ratio [Brei et al., 1995]. Intraocular pressure monitoring should be obtained at the time of concern.



Oro-Dental Features as Useful Diagnostic Tool in Rubinstein–Taybi Syndrome

American Journal of Medical Genetics Part A 143A:570–573 (2007)

Cuspidi ad artiglio fino al 92% (73%)

Ipo-iperodontia 15-30%

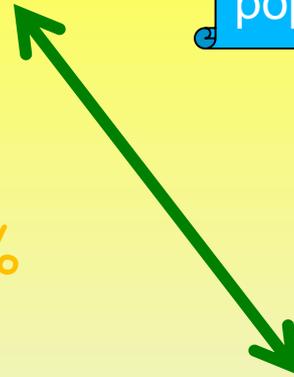
Palato alto e stretto 84-93%

Ipoplasia smalto 23-28%

Problemi nella cura dei denti 43%

Carie 15-36%

2.5%
popolazione

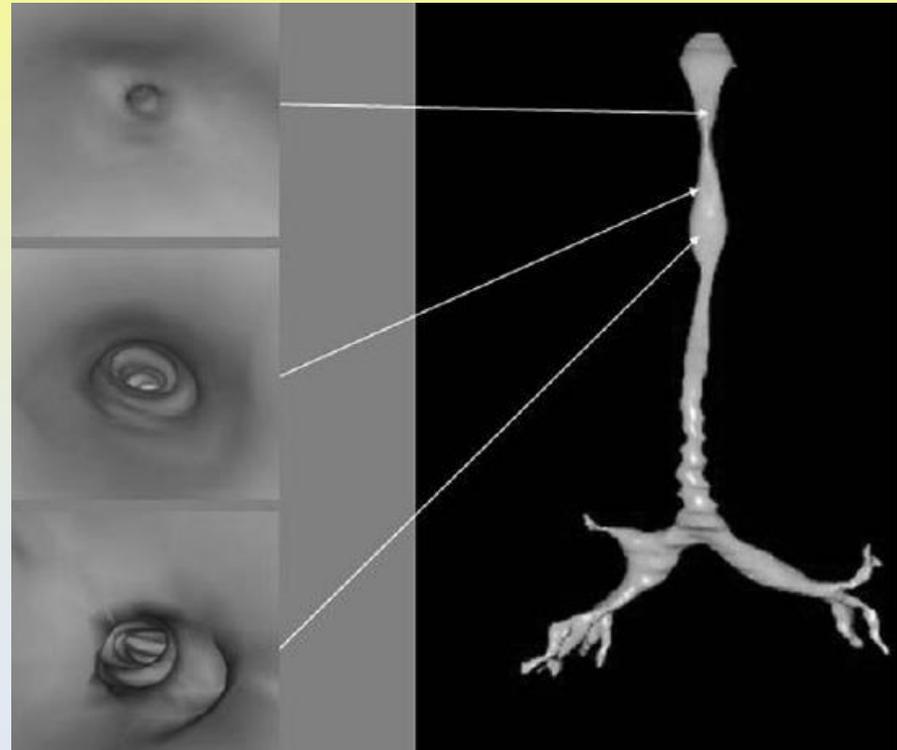


Diagnosi e trattamento delle cuspidi ad artiglio: prevenzione di carie, problemi occlusivi e periodontali



Vie aeree

- Web post-cricoideo
- Stenosi tracheale congenita
- Compressione tracheo-esofagea da ring vascolare
- Infezioni ricorrenti vie respiratorie (75%)
- Apnea ostruttiva nel sonno (palato, micrognazia, ipotonia, obesità, collassabilità pareti laringee)



Deficit immunitari

Assenza di studi sistematici

Studi in presenza di infezioni significative

Rubinstein-Taybi syndrome: An immune deficiency as a cause for recurrent infections

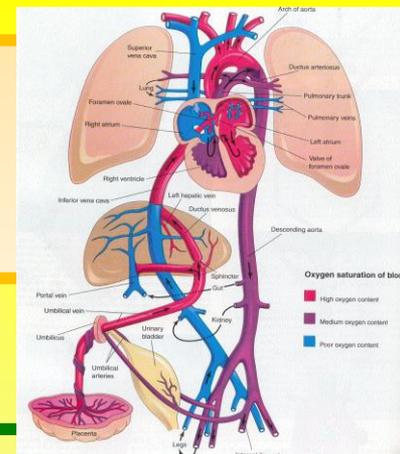
Allergy and Asthma Proceedings 2006, 27(3): 281-284

Deficit risposta anticorpale

Evaluation of the immune humoral response of Brazilian patients with Rubinstein-Taybi syndrome

Braz J Med Biol Res, December 2010, Volume 43(12) 1215-1224

Apparato cardiovascolare



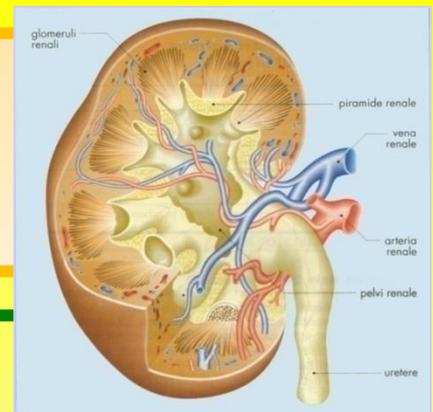
CHD (24-38%): DIA, DIV, PDA, CoAo, stenosi polmonare, valvola aortica bicuspidale, pseudotruncus, stenosi aortica, destrocardia, rings vascolari, difetti di conduzione

Nel 65% dei casi difetto unico

Età media alla diagnosi 15 mesi

I pazienti con malformazione cardiaca congenita hanno maggior incidenza di altre malformazioni rispetto ai bambini non cardiopatici

Apparati GI e GU



- Anomalie renali 52%
 - Idronefrosi
 - Doppio distretto calico-pielico
 - RVU
 - IVU
 - Calcoli
 - S.nefrosica
- Criptorchidismo 78-100%
- Ipospadias 11%
- Ipermenorragia/metrorragia
- Stipsi 40-74%

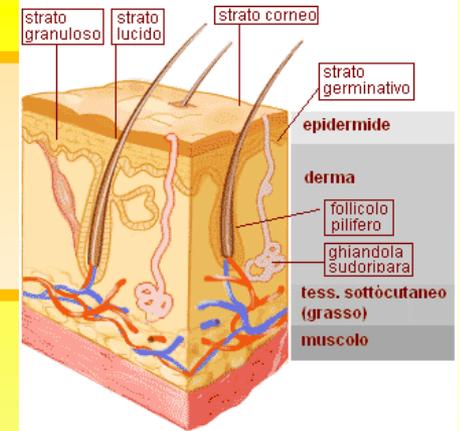
Manifestazioni cutanee

- Emangioma capillare
- Nevus flammeus
- Macchie caffè-latte
- Cheratosi follicolare
- Cheloidi (22%)
- Cicatrizzazione ipertrofica (16%)
- Dermatite seborroica



Altro

- Irsutismo (spalle e dorso) (76%)
- Capezzoli sovranumerari 16%
- Paronichia dita delle mani 9%
- Paronichia dita dei piedi 44%
- Cheratoderma



Problematiche cliniche

<i>Feature</i>	<i>Percentage</i>
Polyhydramnios	30
Neonatal respiratory problems	51
Neonatal feeding problems	80
Tear duct obstruction	39
Strabismus	58
Refractive error	41
Upper airway infections	60
Hearing loss	24
Congenital heart defects ^a	32
Keloid formation	25
Malignancies	5? ^b
Seizures	23
Growth retardation < 3rd centile	75



Miller e Rubinstein, 1995

Diagnosi differenziale



Sindrome di Cornelia de Lange

Sindrome di Saethre-Chotzen

Trisomia 13

Sindrome di Floating-Harbor

Sindrome di Gorlin-Chaudry-Moss



VOLTO



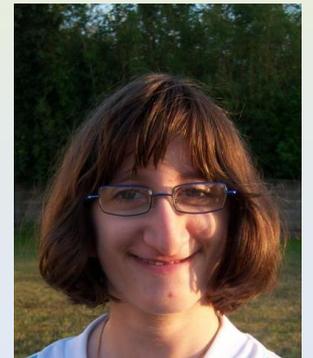
Sindrome di Apert

Sindrome di Pfeiffer

Sindrome di Greig.



MANI/PIEDI





Ogni bambino è un individuo diverso...e non tutto è parte della condizione

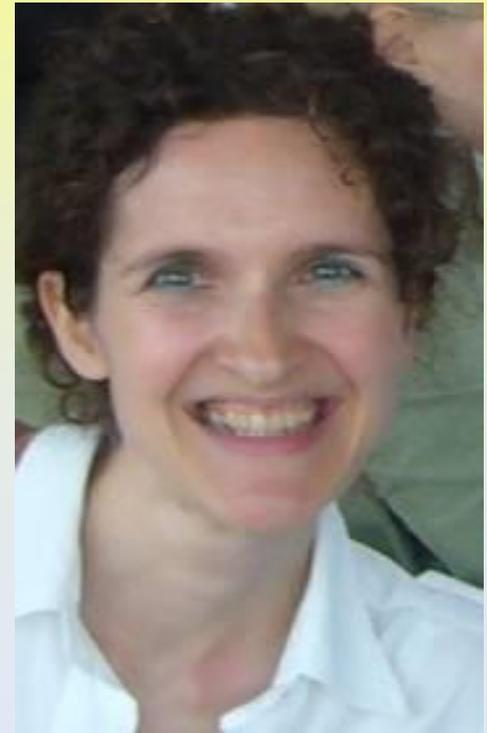
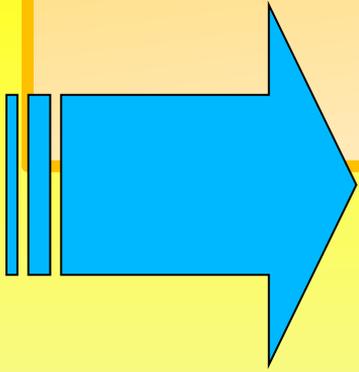


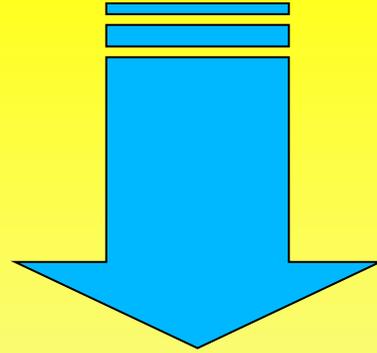
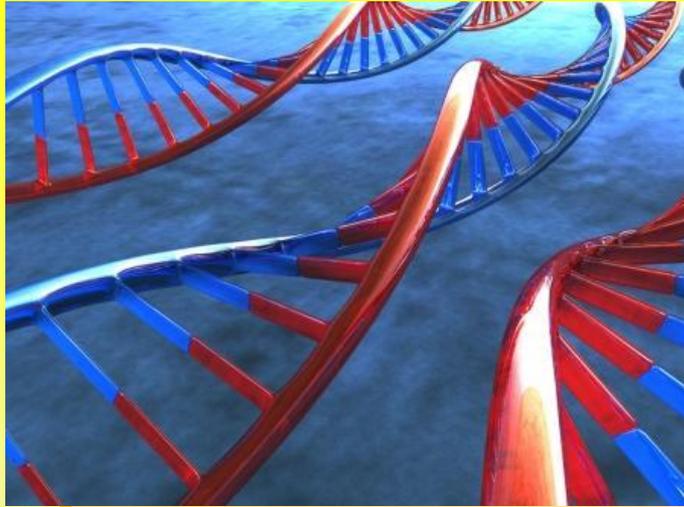
Non tutte le
problematiche e
caratteristiche
associate sono presenti
in tutte le persone con
RSTS





Aspetti genetici





**Dalla
genetica
alla
clinica**



DNA sequencing of *CREBBP* demonstrates mutations in 56% of patients with Rubinstein–Taybi syndrome (RSTS) and in another patient with incomplete RSTS

Hum Genet (2005) 117: 485–493

Alcuni tipi di mutazioni avrebbero un aspetto clinico più sfumato

High frequency of mosaic *CREBBP* deletions in Rubinstein–Taybi syndrome patients and mapping of somatic and germ-line breakpoints

Genomics 90 (2007) 567–573

Forme a mosaico più sfumate

Genotype–Phenotype Correlations in Rubinstein–Taybi Syndrome

American Journal of Medical Genetics Part A 146A:2512–2519 (2008)

In the current study, the degree of postnatal growth retardation was somewhat more severe in those *without a CREBBP* mutation, and could be a segregating feature for the search for additional genes causal to RTS. Seizures were also seen significantly more often in RTS patients with *CREBBP* mutations. No significant differences were found in any of the other features or congenital anomalies associated with RTS and any particular mutation or mutation type. It appears that *CREBBP* mutation may modify the RTS phenotype for certain features such as growth retardation and propensity for seizures; however, most other features remain similar between *CREBBP* and non-*CREBBP* patients.

Delezione CREBBP: RM più importante

Maggior compromissione psichiatrica

Maggior frequenza di crisi epilettiche

Genetic Heterogeneity in Rubinstein-Taybi Syndrome: Mutations in Both the *CBP* and *EP300* Genes Cause Disease

Am. J. Hum. Genet. 76:572–580, 2005

Fenotipo simile per mutazioni *CBP* ed *EP300*

Confirmation of *EP300* gene mutations as a rare cause of Rubinstein–Taybi syndrome

European Journal of Human Genetics (2007) 15, 837–842

Similarly, the very different frequencies of *CREBBP* and *EP300* mutations with the RSTS phenotype and the observed (although not very striking) phenotypical differences with the *EP300* mutations⁴ (also this study) suggest that mutations in *EP300* could be underdiagnosed due to phenotypes different from classical RSTS. A possible explanation could be the different functions of *CREBBP* and *EP300* during embryogenesis.^{7,9,18}

Genetic heterogeneity in Rubinstein–Taybi syndrome: delineation of the phenotype of the first patients carrying mutations in EP300

J. Med. Genet. 2007;44;327-333

	RSTS	Mutazioni EP300
Epicanto	+	-
Padiglioni auricolari	Anomala posizione, forma, dimensione	Rotazione posteriore
CHD	PDA, DIA, DIV	-
Ritardo cognitivo	QI 30-80	Lieve

Fenotipo scheletrico più lieve

Mutations in either gene are associated with the classic facial features, mental retardation and other abnormalities typically associated with RSTS. Interestingly, however, none of the presently known patients with *EP300* mutations showed the classic malformations on both hands and feet, which originally have been considered mandatory for the diagnosis of RSTS.





Two Patients With *EP300* Mutations and Facial Dysmorphism Different From the Classic Rubinstein–Taybi Syndrome

Am J Med Genet Part A 152A:181–184.



Microcephalia

No downslanting fessure palpebrali

Alterazioni più pronunciate della mascella



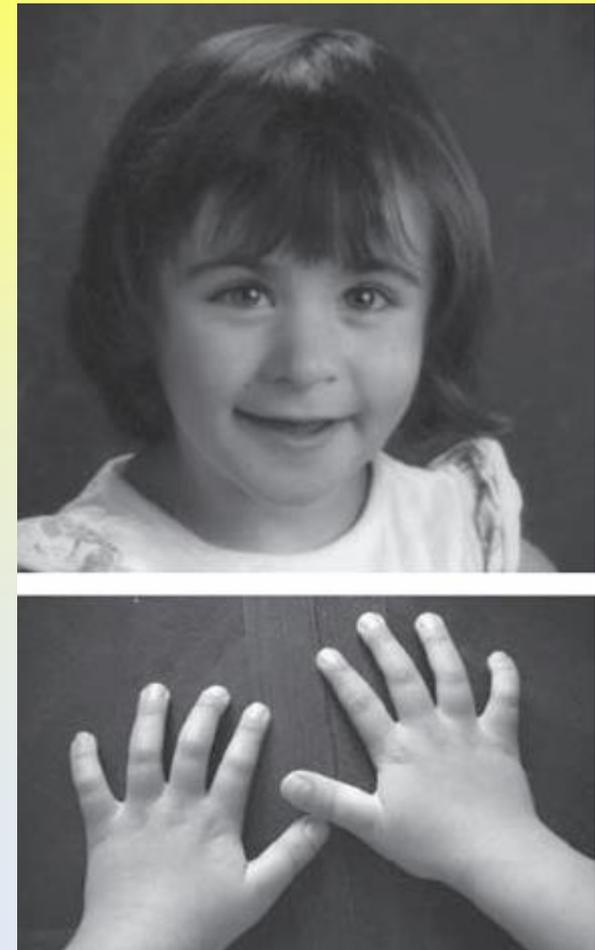
Bartholdi et al. [2007] and Foley et al. [2009] reported on a milder skeletal phenotype of RTS patients with *EP300* mutations; the typical broadening and angulation of the thumb and hallux were absent in some patients. Here we have described individuals with *EP300* mutations and phenotypes that are not only milder but distinct from typical RTS. The findings included severe microcephaly, severe retrognathia, and normal (not downslanting) palpebral fissures. Possibly, the very low frequency of *EP300* mutations in RTS (~3%, compared to 50–70% *CREBBP* mutations), despite the high similarity of the genes and proteins, might be due to an only limited phenotypic overlap of *CREBBP* and *EP300* mutations. Possibly, *EP300* mutations may be more prevalent than we think because the phenotype is different and therefore such patients are not ascertained and not studied. More clinical data are needed to elucidate the phenotype in patients with RTS due to *EP300* mutations.

Exon deletions of the *EP300* and *CREBBP* genes in two children with Rubinstein–Taybi syndrome detected by aCGH

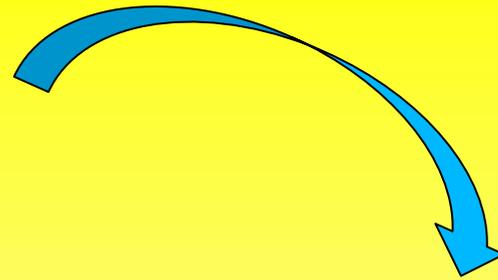
European Journal of Human Genetics (2011) 19, 43–49

Both our case and others in the literature with *EP300* mutations have a modified RSTS phenotype, and, in particular, we confirm the milder skeletal phenotype.

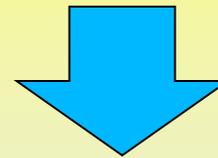
In addition, we propose that preeclampsia during pregnancy may be a new feature for RSTS caused by *EP300* mutations. Together, these cases demonstrate the importance of considering *EP300* RSTS in patients who have facial features of RSTS but lack broad and angulated thumbs and halluces.



Variabilità clinica



Approccio
multidisciplinare



DIAGNOSI
ASSISTENZA



Eterogeneità genetica

