



SINDROME DI RUBINSTEIN-TAYBI:

MODELLO ASSISTENZIALE
DALL'ETÀ PEDIATRICA
ALL'ETÀ ADULTA

RESPONSABILE SCIENTIFICO
GIOACCHINO SCARANO

14-15
MARZO
2024
CEINGE
NAPOLI

Con il Patrocinio di
CEINGE

La clinica e la diagnosi in età pediatrica

Donatella Milani



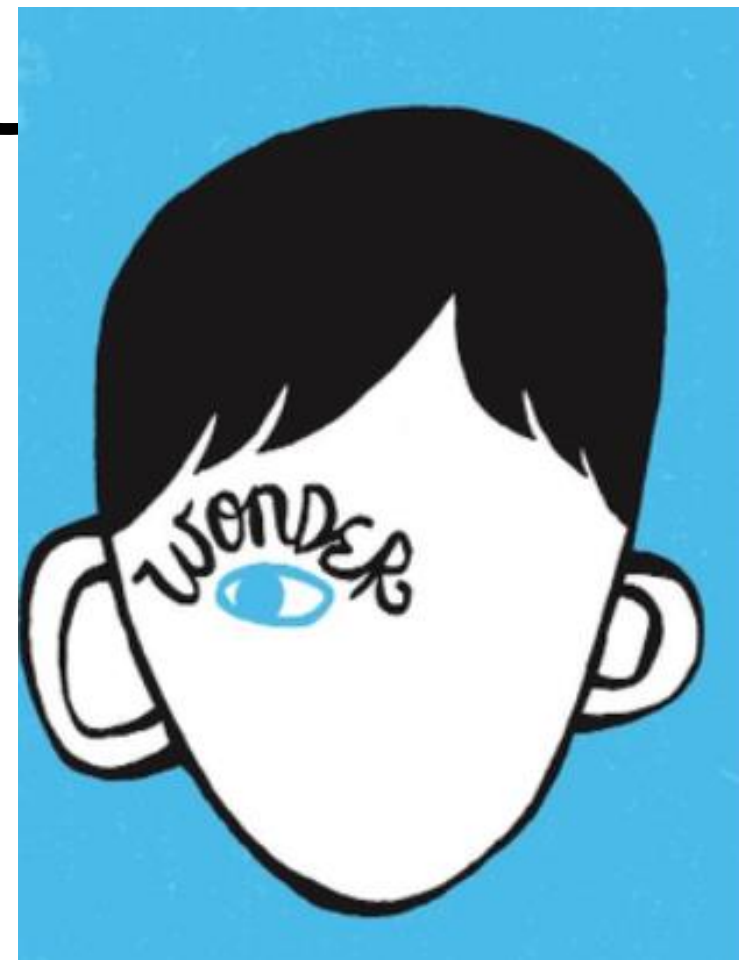
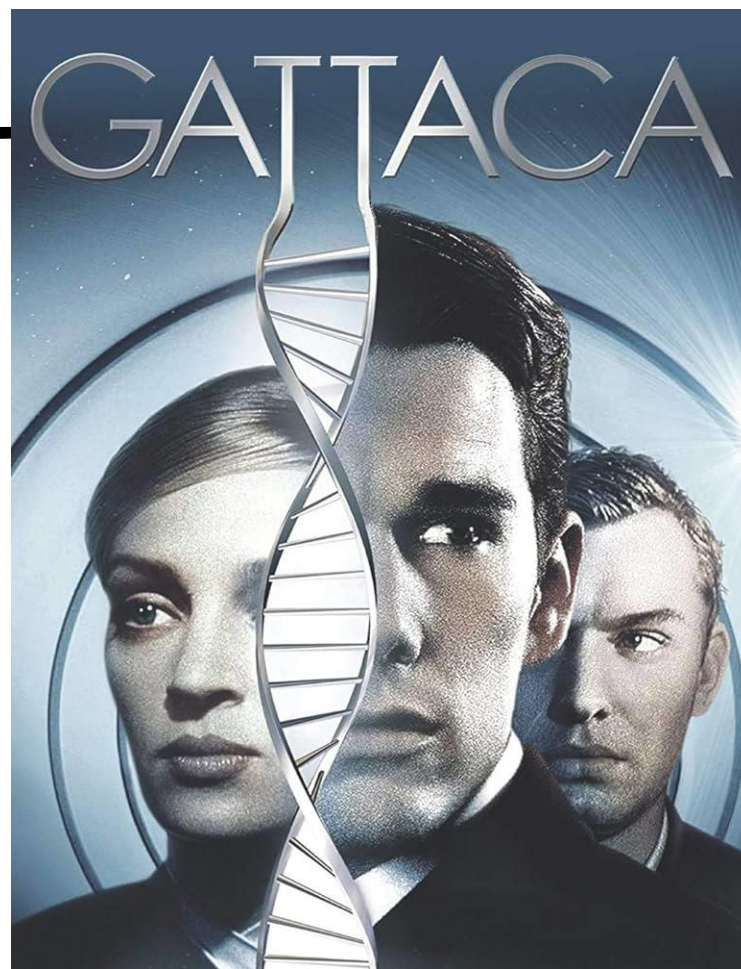
Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario

 Regione Lombardia



European
Reference
Network
for rare or low prevalence
complex diseases
Network
Intellectual Disability
and Congenital
Malformations (ERN ITHACA)



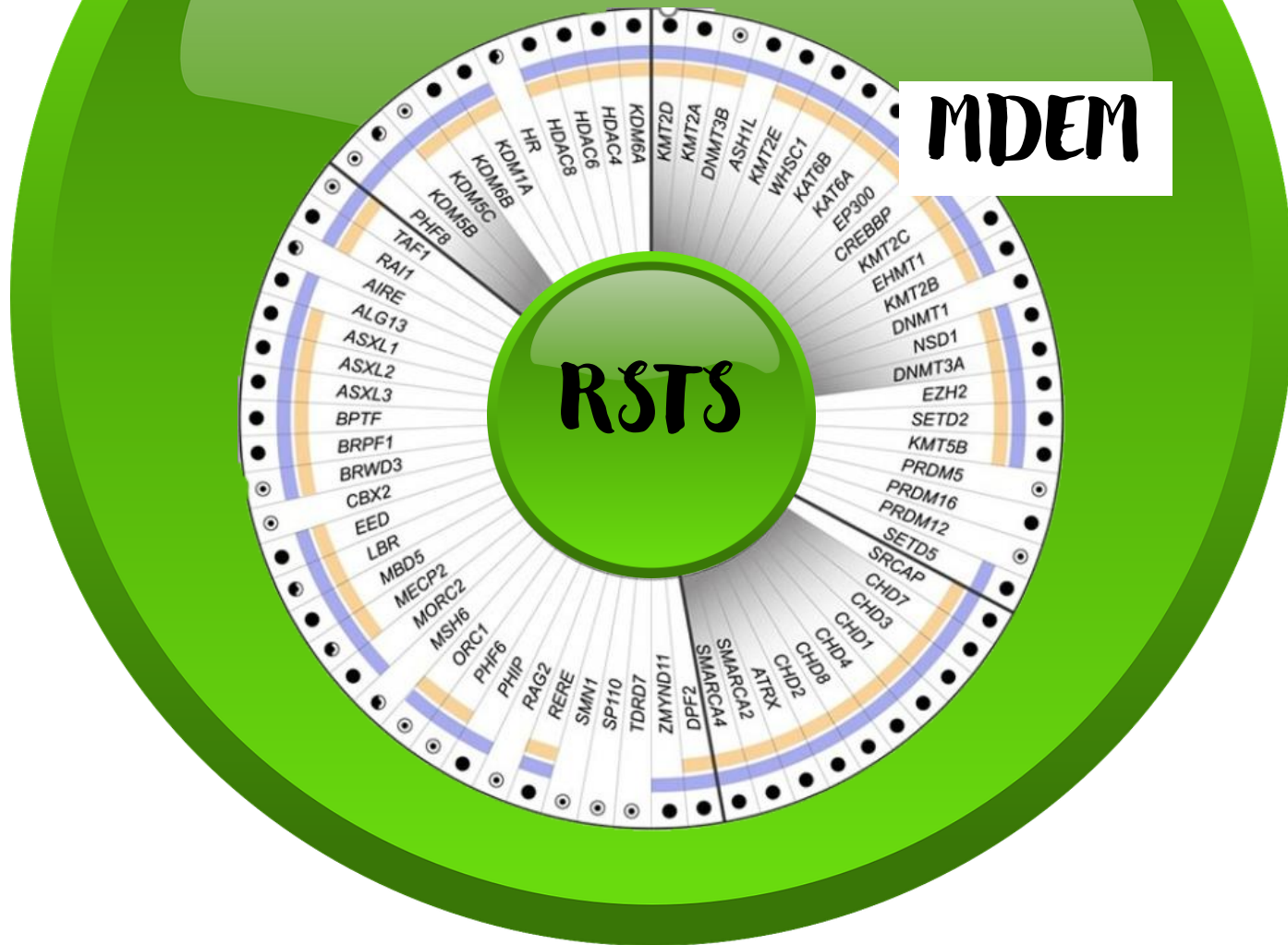
Condizioni comuni

Malattie rare

Sindromi genetiche

Undiagnosed

Sindromi genetiche



Sindrome di Rubinstein-Taybi

1:100.000- 125.000

Ritardo di crescita

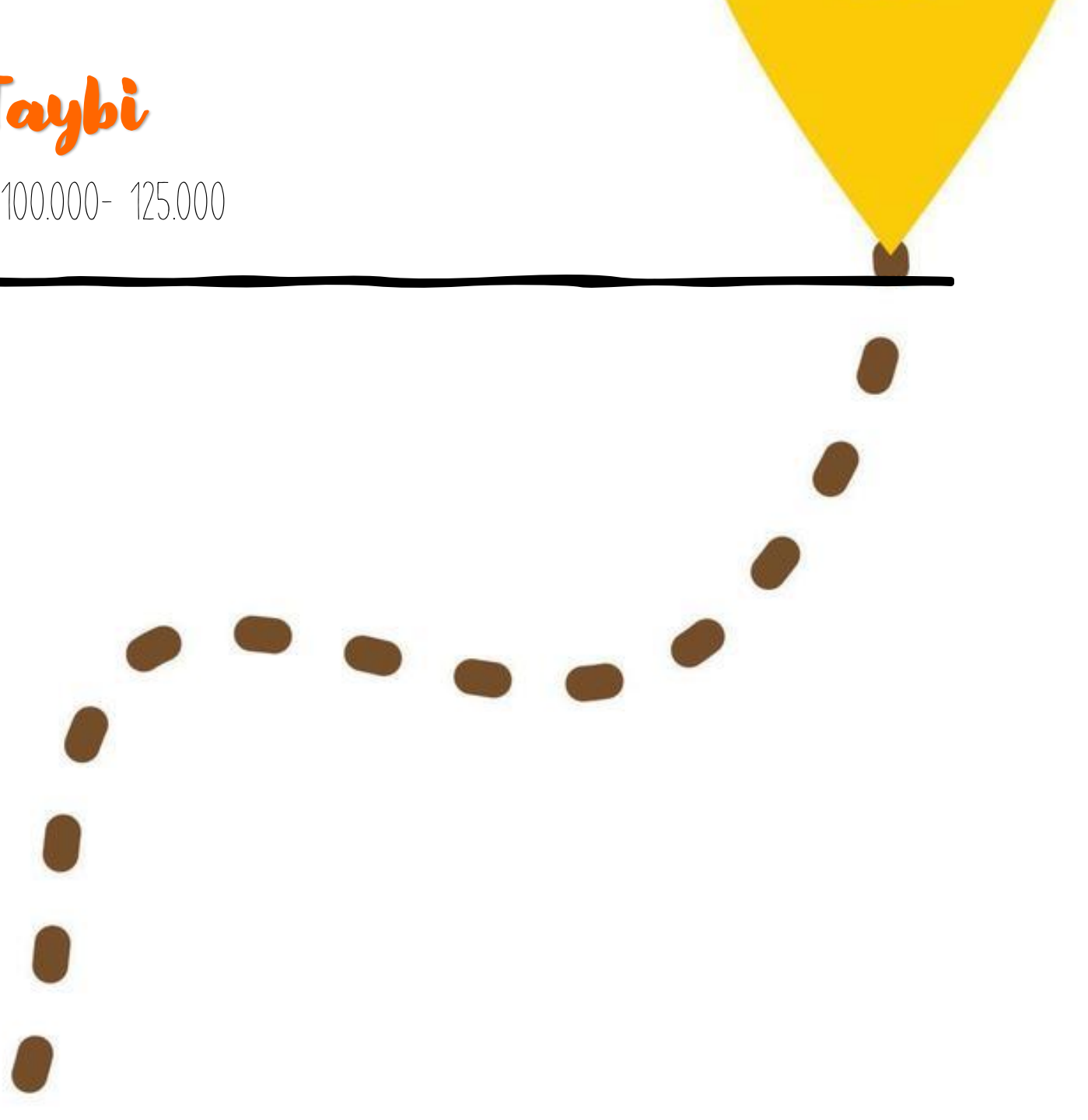
Microcefalia

Tratti del volto tipici (espressione del volto!)

Pollici ed alluci ampi ed angolati (99%)

Malformazioni viscerali

Ritardo di sviluppo/ID



Microcefalia

Impianto basso ant e
post dei capelli

Nevo flammeo fronte

Sopracciglia arcuate e
folte

Ciglia lunghe

Downslanting palpebrale

Ipertelorismo

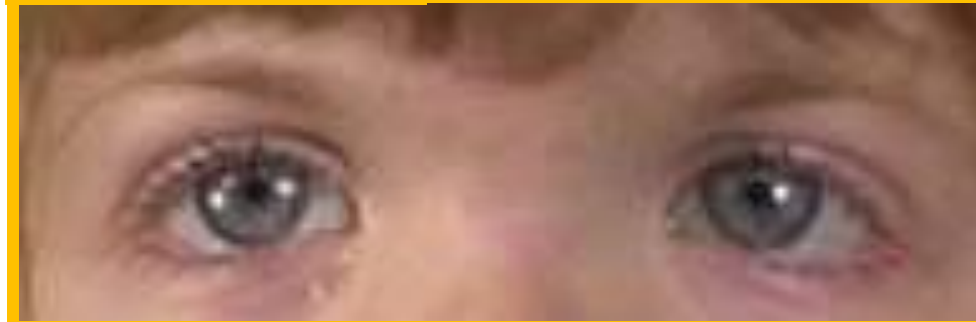
*Naso prominente con
columella sotto le ali
nasali*

Padiglioni auricolari ad
impianto basso e
dismorfici

Palato ogivale

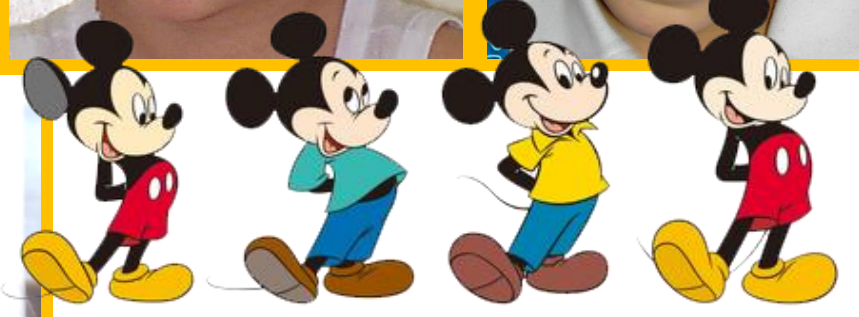
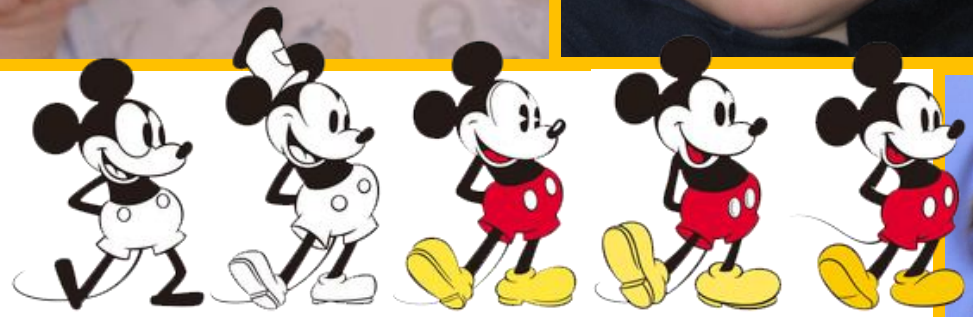
Malocclusione dentaria

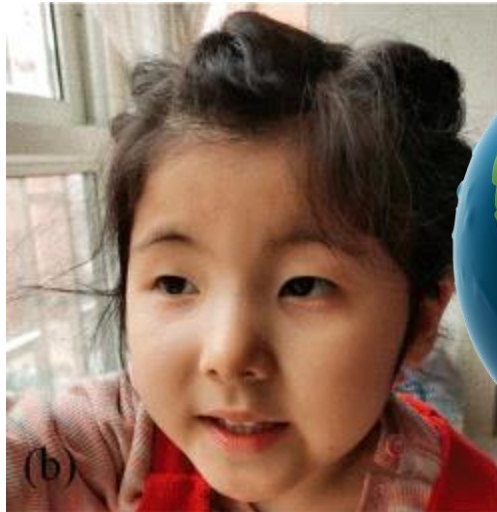
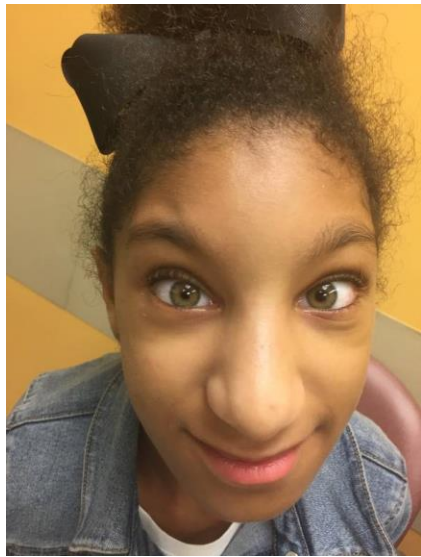
Micrognazia



Grimacing facciale

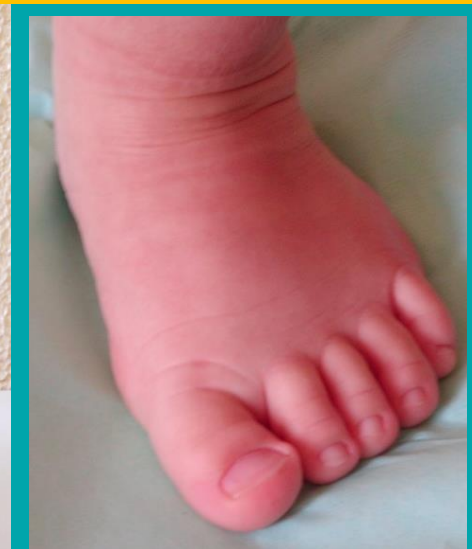








92%



Mani & Piedi



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

Falangette ampie

NASCITA Parametri
normali

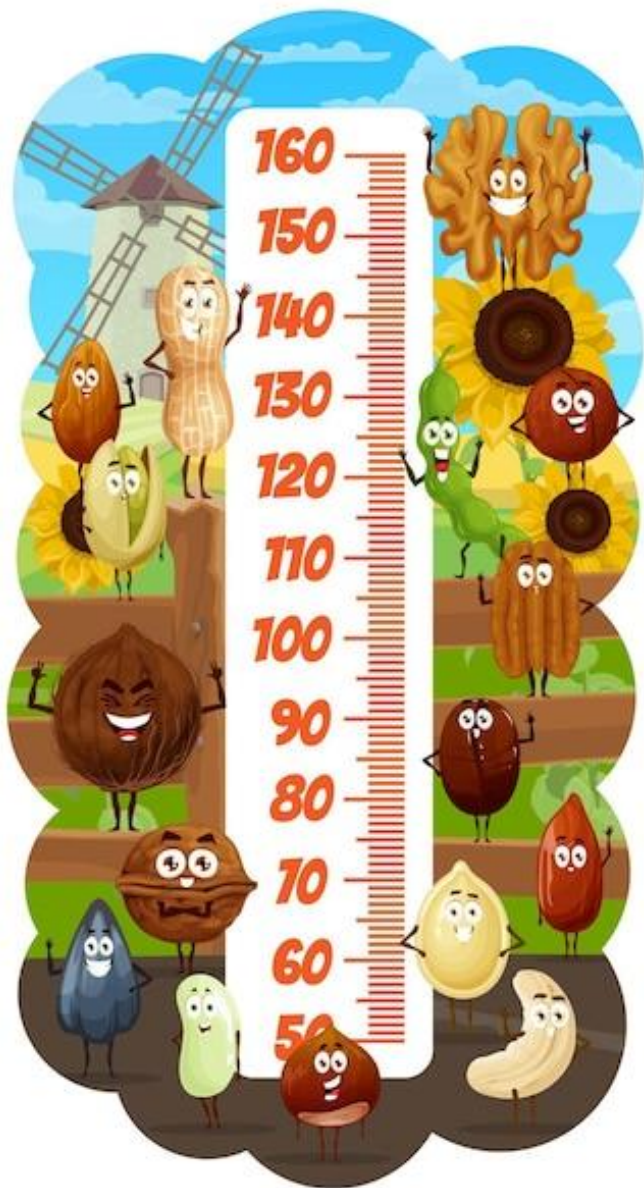
PERIODO PRESCOLARE
>P maschi

PRIMA INFANZIA $P < 3\%$,
L e CC 3%

PRIMA ADOLESCENZA
>P femmine



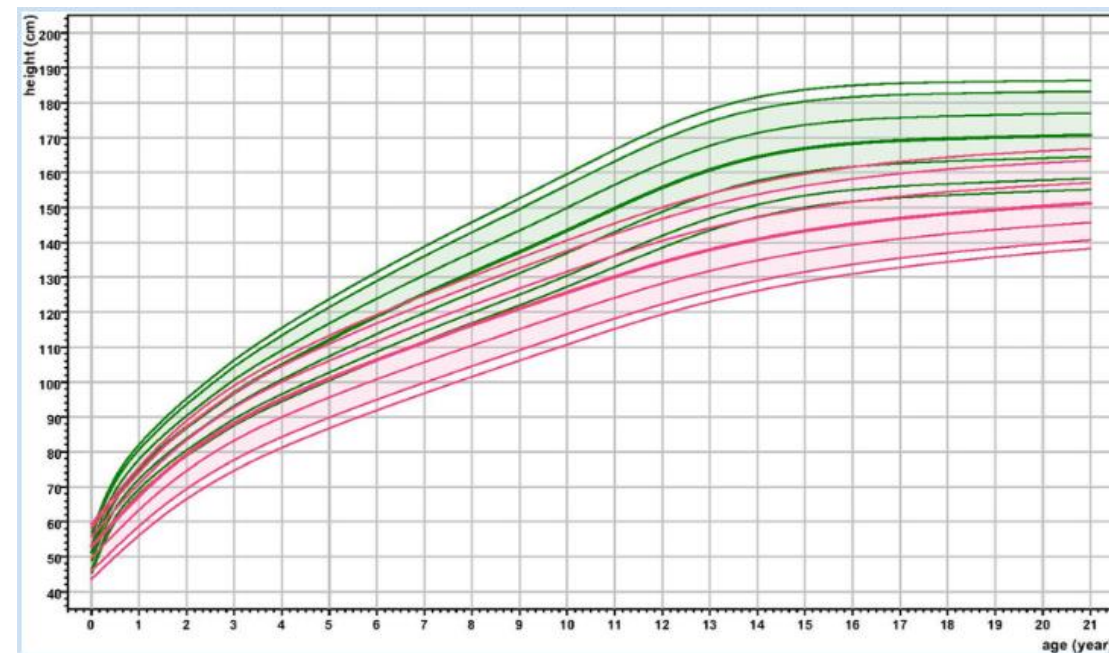
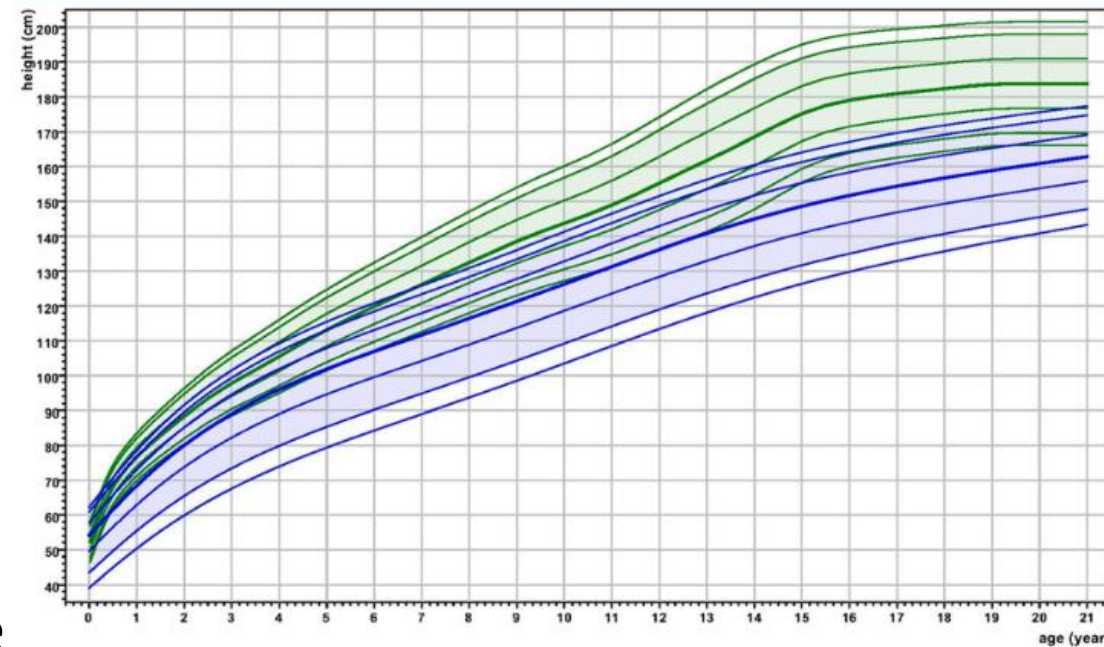
73%



162.6 cm

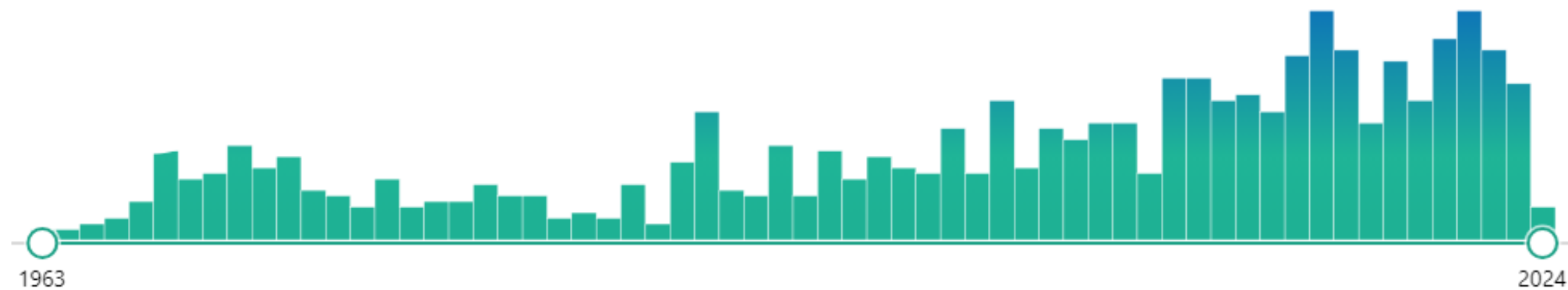
Assenza dello spurt puberale

151 cm



La letteratura

851 articoli



Aspetti oculistici

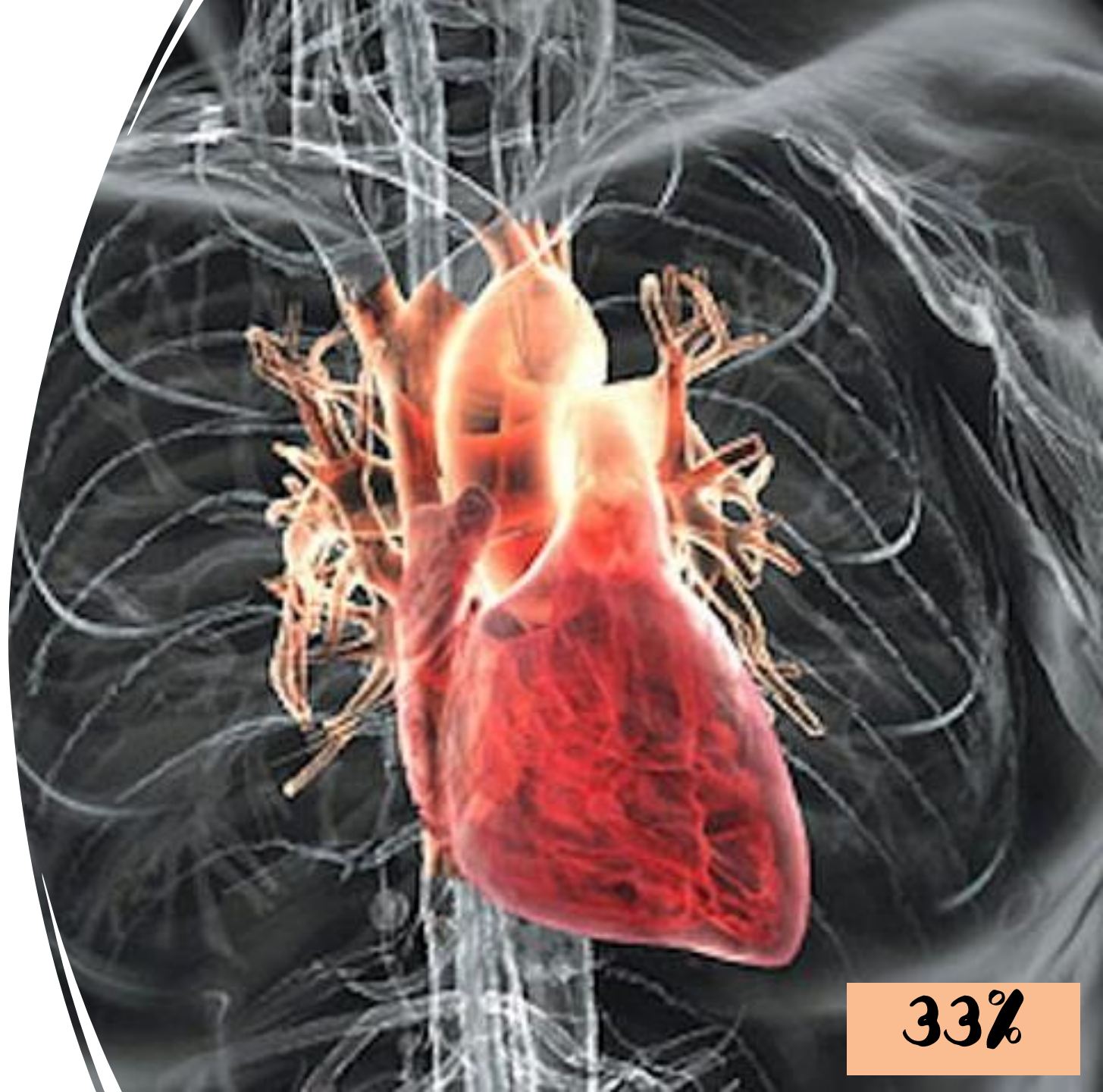
- Strabismo (23%)
- Ptosi (12%)
- Miopia (10%)
- Stenosi dotto nasolacrimale (9%)
- Glaucoma (6%)
- Coloboma (6%)
- Cataratta (5%)

- *Sopracciglia arcuate* (56%)
- *Ciglia lunghe* (52%)
- *Downslanting* (74%)
- *Epicanto* (20%)

80%

Cardiopatie congenite

- Difetti settali, PDA, CoAo/Ao bicuspide, Stenosi polmonare...
- Non associate a maggiore presenza di altre malformazioni
- Necessità di chirurgia nel 15-22%



33%

Vie aeree

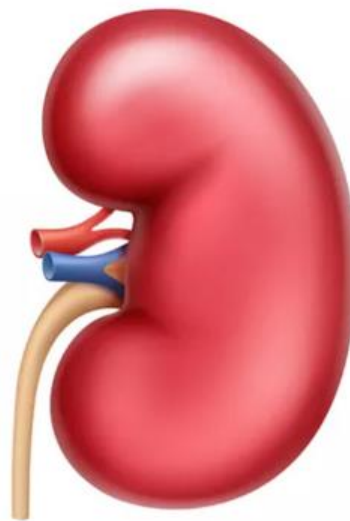
- Nel neonato lieve distress respiratorio
- Rare infezioni delle basse vie (legate a problemi alimentari, microaspirazioni, RGE), talora immunodeficit
- Patologia interstiziale polmonare (rara)
- Malfunzionamento secondario a:
 - Patologia restrittiva legata a scoliosi
 - Ipertensione polmonare da OSAS



Anomalie genitourinarie

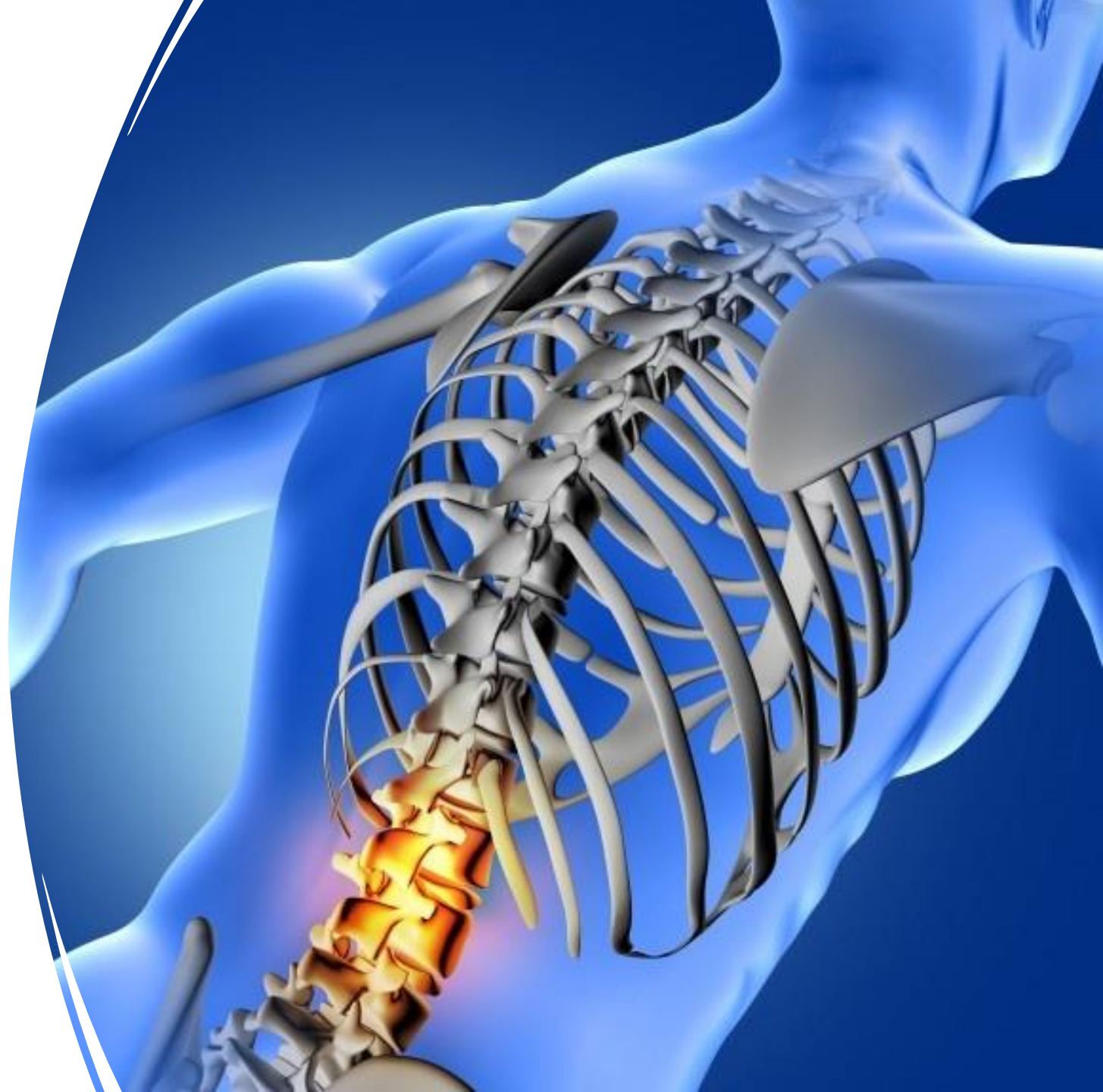
27%

- Utero setto/anomalie Mulleriane
- Disturbi del ciclo mestruale
- Idronefrosi
- RVU
- Nefrolitiasi
- IVU
- Criptorchidismo
- Ipospadia



Aspetti ortopedici

- Lussazione rotula
- M.Perthes
- Lassità articolare
- Scoliosi (20%)
- Anomalie delle vertebre cervicali



Basi biologiche

Altre MDEM

Traiettorie NPI



N E W S



Sonno

Sleep Medicine 112 (2023) 9–11

Infezioni

Anomalie renali

Criptorchidismo

CHD

Fratture, M.Perthes, Lussazioni articolari

Patologie orecchio medio

OSAS

Scoliosi

RGE

Ipoglicemia

Difficoltà di alimentazione

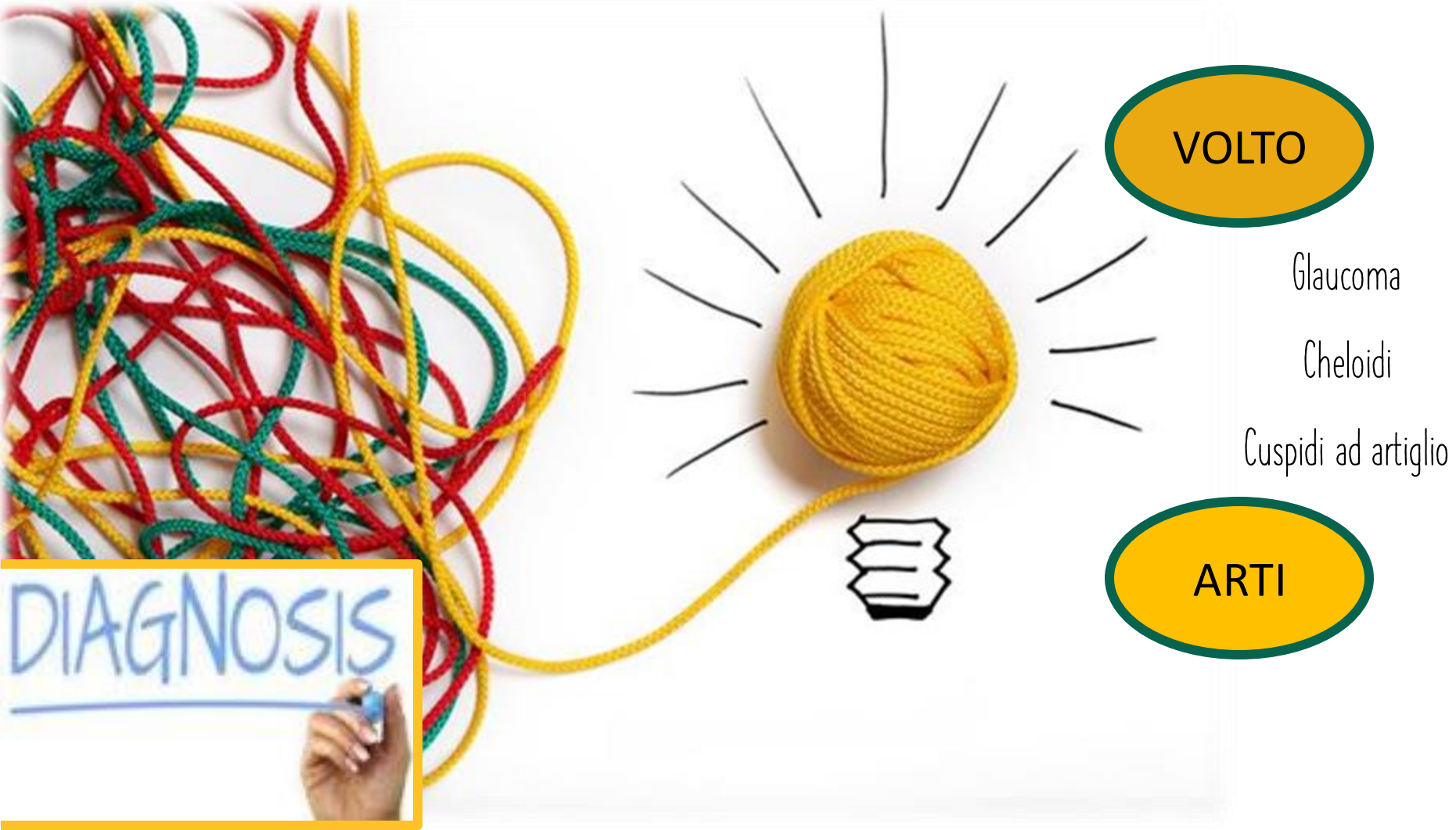
Malrotazione

Unghie/pilomatrixoma

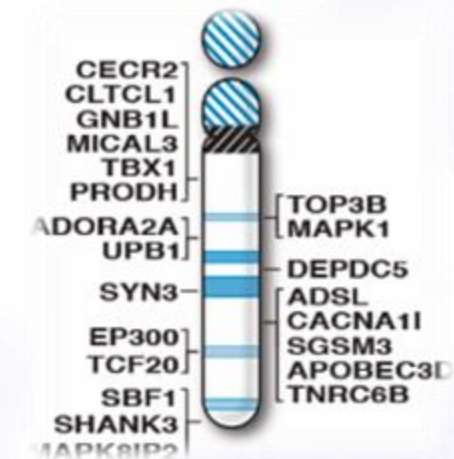
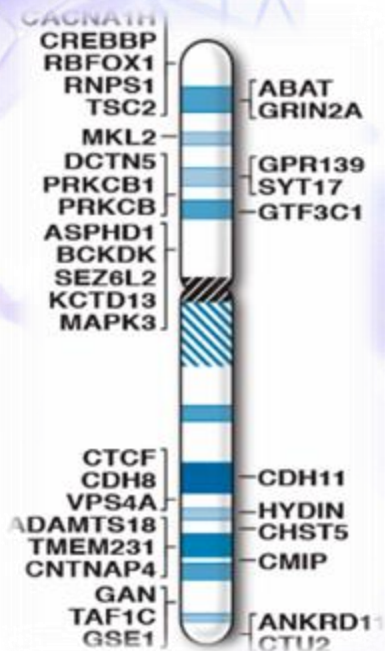


- ✓ Ritardo di crescita postnatale
- ✓ Pollici ed alluci ampi
- ✓ DD/ID moderato-grave

- ✓ Dismorfismi
- ✓ Ipertricosi
- ✓ Malformazioni



CREBBP 50-60%



EP300 5-8%

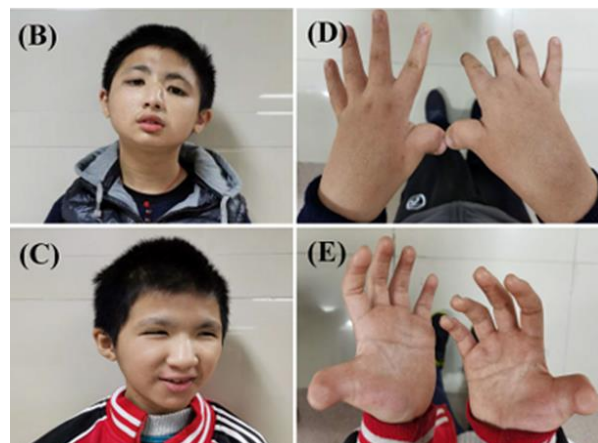
Delezioni complete <10%
Diagnosi clinica 20-30%

Consulenza genetica



- Definizione RR (0.5–1%) e possibilità di diagnosi prenatale
- De novo
- Mosaicismo somatico
- Mosaicismo gonadico

Mosaicismo madre



Fetal phenotype of Rubinstein-Taybi syndrome caused by *CREBBP* mutations

Clinical Genetics. 2019;95:420–426.

Segno più utile a US: **POLLICE AMPIO**.

Segni accessori: IUGR, polidramnios, anomalie encefalo.

Segno nuovo: anomalie colecisti (22%), duplicata o ipertrofica.

Assenza di criteri diagnostici



Prenatale

Fenotipi
sfumati

Fenotipi
overlappanti

Fenotipi
alternativi

Fenotipi
blended

A man with long dark hair and a beard, wearing a dark jacket, is shown from the chest up. He is holding a large, glowing, orange and yellow sphere in his right hand. The sphere has a textured, almost cellular appearance. The background is a blurred interior space with a classical statue visible in the distance.

L'esame genetico

(o dalla genetica alla genomica)



Eterogeneità genetica

Eterogeneità fenotipica

CREBBP/EP300

Mosaicismo

Delezioni/duplicazioni

Macchinario epigenetico

Microdelezioni

FISH studies in 45 patients with Rubinstein-Taybi syndrome: deletions associated with polysplenia, hypoplastic left heart and death in infancy

European Journal of Human Genetics (1999) 7, 748-756

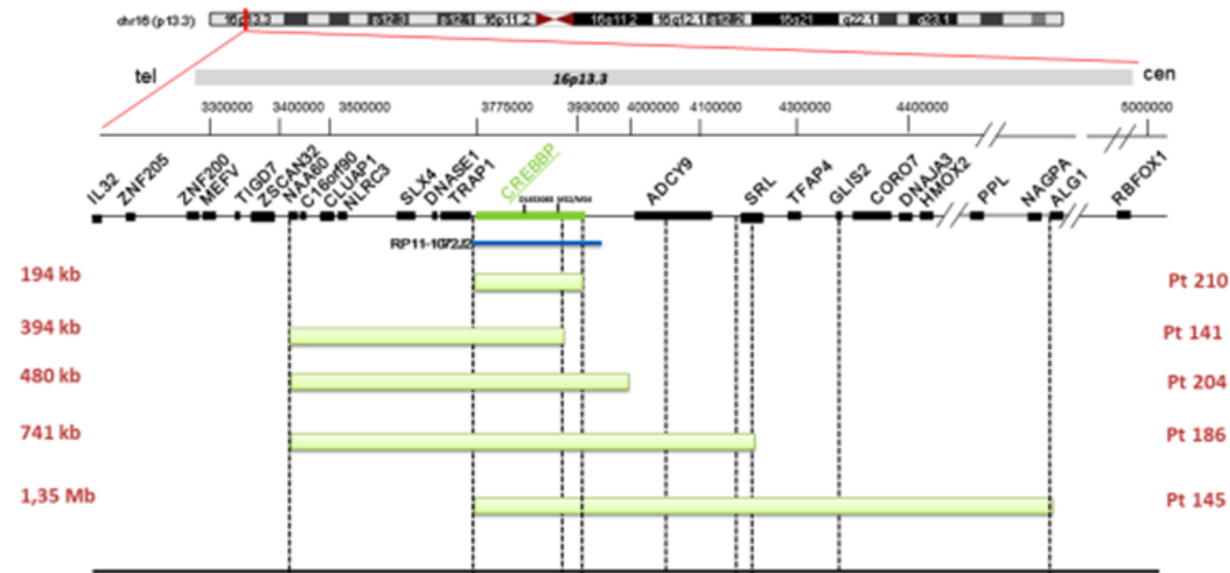
Microcefalia

Role of the ADCY9 gene in cardiac abnormalities of the Rubinstein-Taybi syndrome

Wu et al. Orphanet Journal of Rare Diseases (2020) 15:101

Chromosome 16p13.3 Contiguous Gene Deletion Syndrome including the SLX4, DNASE1, TRAP1, and CREBBP Genes Presenting as a Relatively Mild Rubinstein-Taybi Syndrome Phenotype: A Case Report of a Saudi Boy

Case Reports in Genetics
Volume 2020, Article ID 6143050,



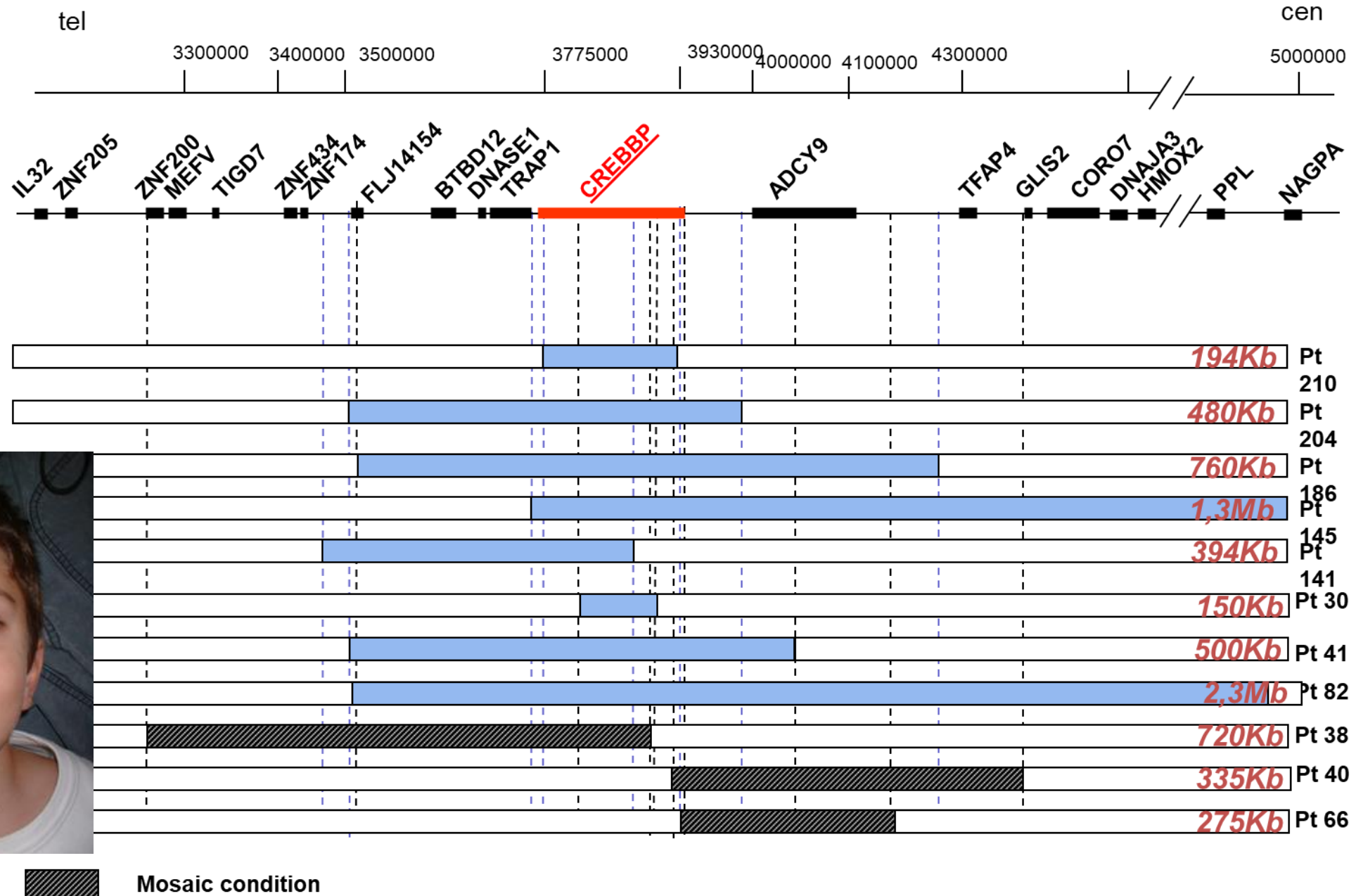
FISH

MLPA

ArrayCGH

Ruolo limitato dei geni limitrofi nel fenotipo specifico

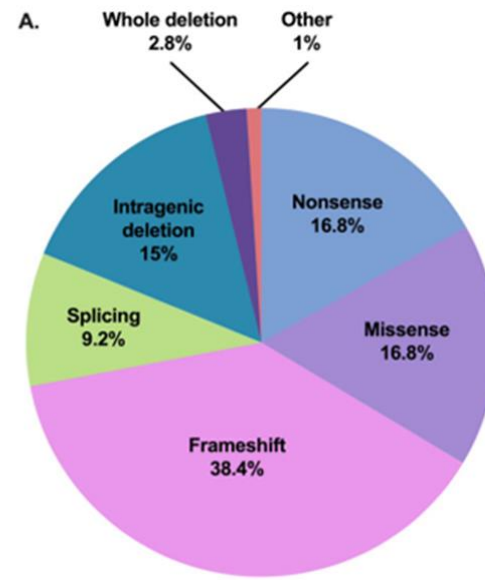
whole CREBBP deletions





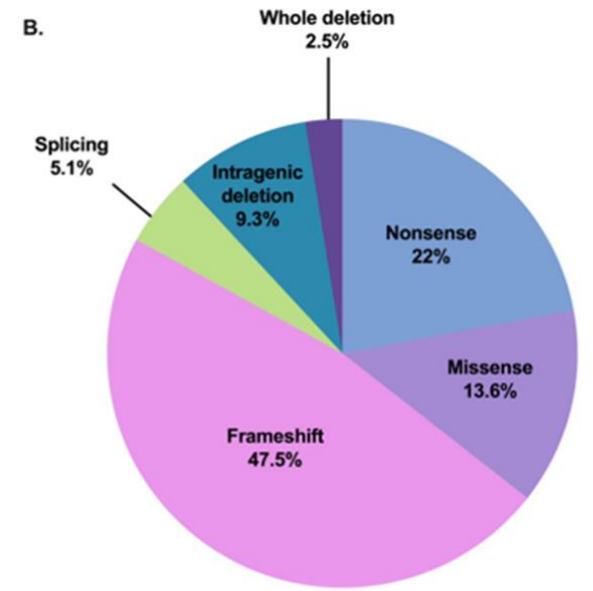
Variabilità

- ✓ Tipo di mutazione
- ✓ Sede di mutazione



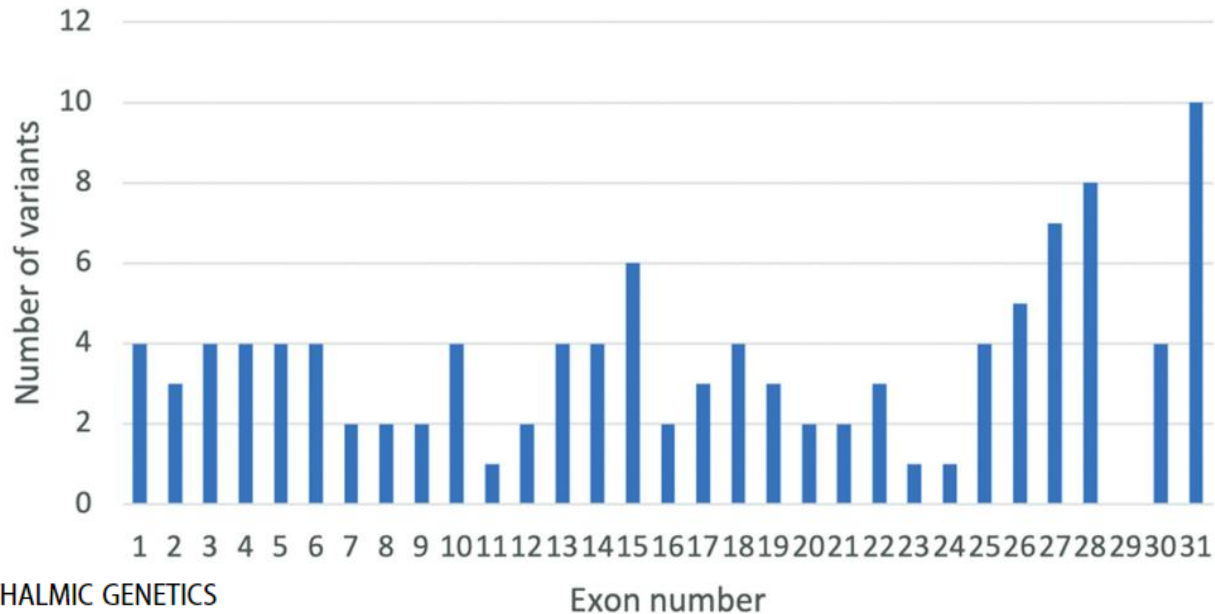
CREBBP

Genes 2021, 12, 968.



EP300

Mutation distribution across *CREBBP* exons



Eterogeneità di locus

Eterogeneità allelica

>500 varianti *CREBBP* (<https://databases.lovd.nl/shared/genes/CREBBP>)

>100 varianti *EP300* (<https://databases.lovd.nl/shared/genes/EP300>)



Fenotipi sfumati



Mosaicism a basso livello...



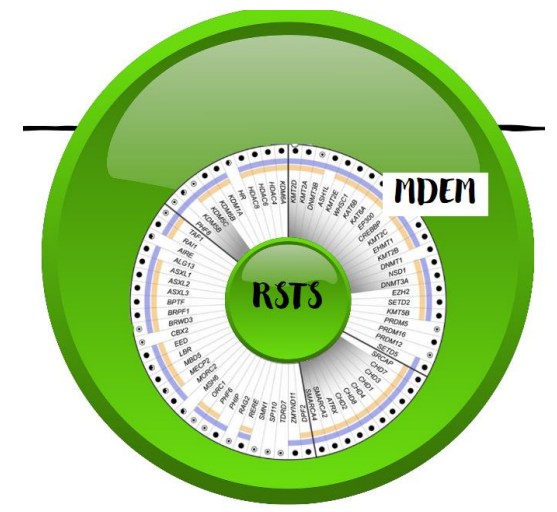
RSTS2 (dal 2005)



- ↓ ID
- ↓ Ritardo di crescita
- ↓ Cheloidi (*Lopez et al., 2018*)
- ↓ Dismorfismi, eccetto columella (*Korzus, 2017*)
- ↓ Anomalie estremità
- ↓ Deviazione radiale del pollice

- ↑ Microcefalia (83-86% vs 54%)
- ↑ Malformazioni strutture facciali
- ↑ Preeclampsia (10-33%) vs 3%
CREBBP (Fergelot et al., 2016)
- ↑ IUGR (50% vs 25%)
- ↑ Fetal pads





Exploring by whole exome sequencing patients with initial diagnosis of Rubinstein-Taybi syndrome: the interconnections of epigenetic machinery disorders

**Fenotipi
overlappanti**

Chromosomal microarray analysis (CMA)

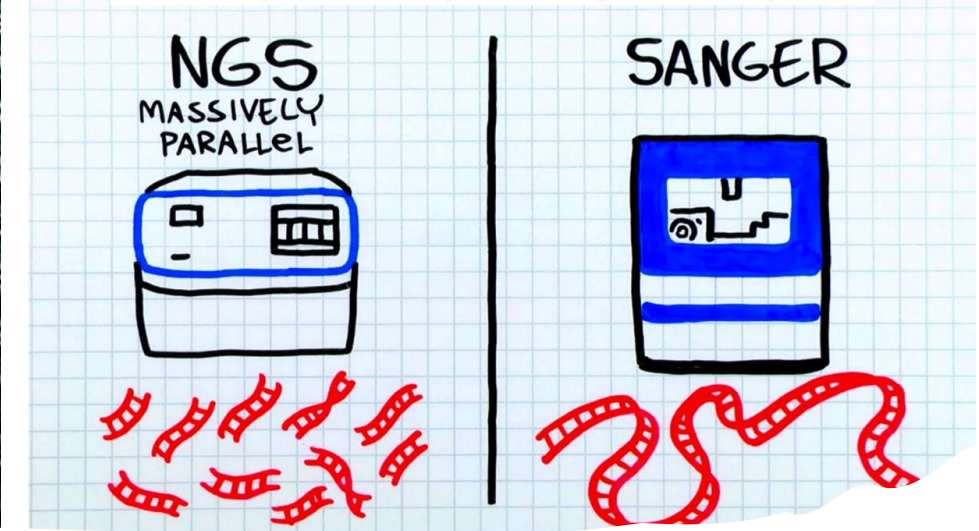
Serial single-gene testing



Multigene panel

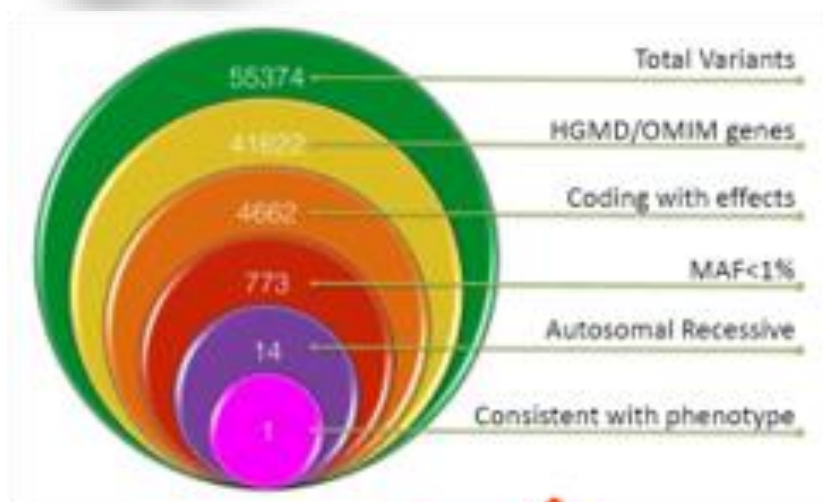
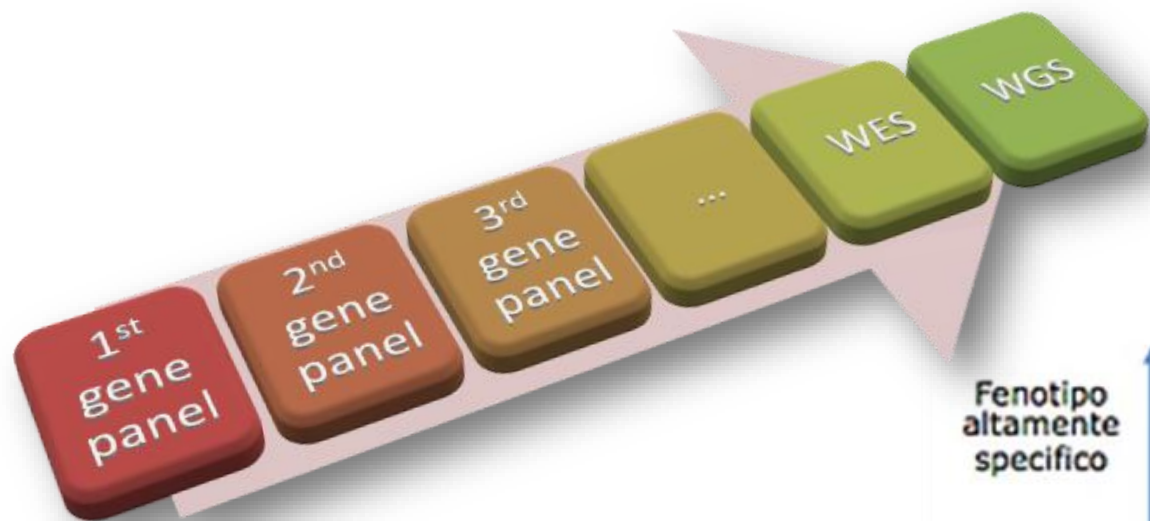
TESSUTO?

Exome sequencing



NGS: Sequenziamento di Nuova Generazione

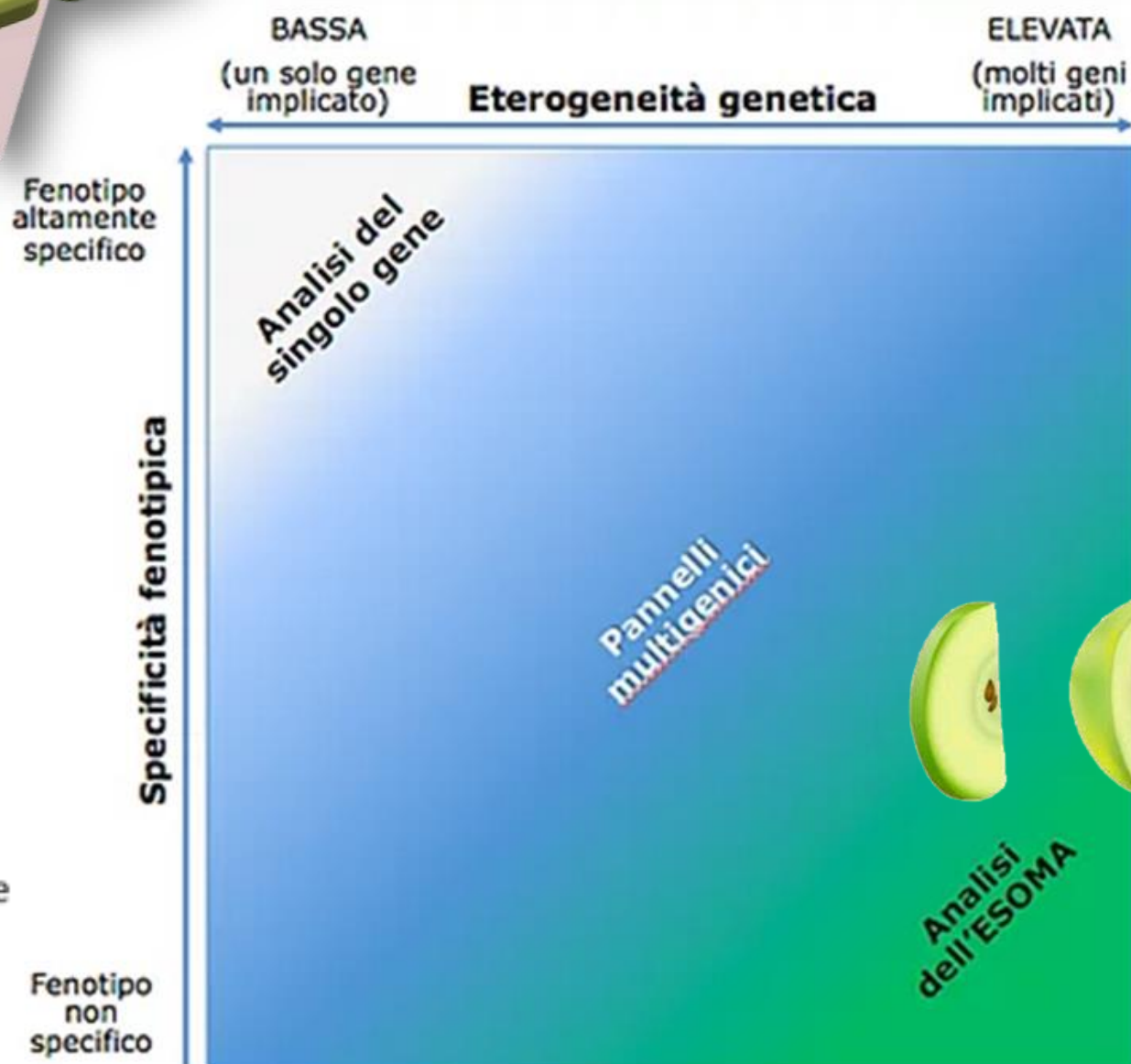
Quantità di informazioni e tempi di risposta



Identificazione

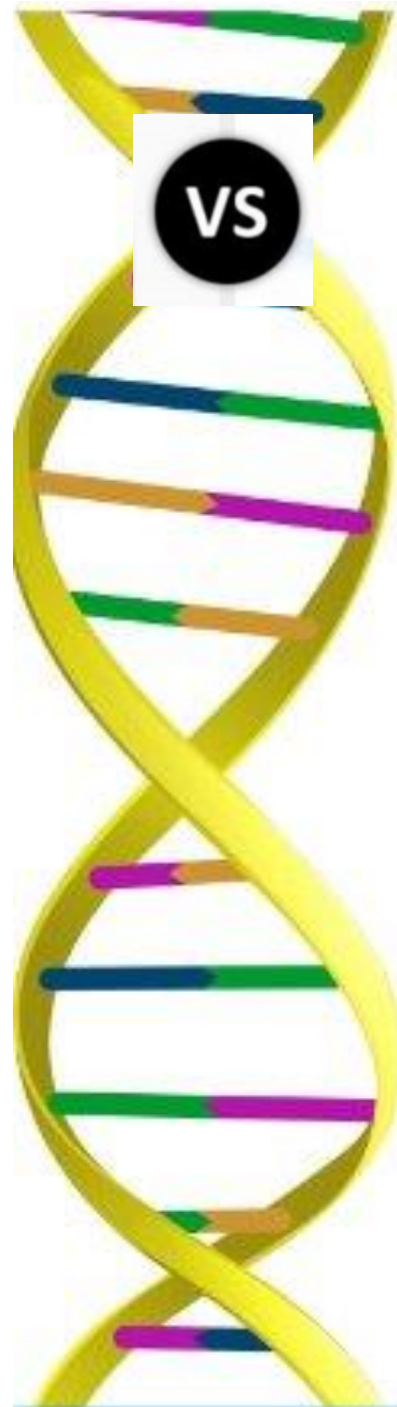


Interpretazione





Gene malattia già noto
Espansione del fenotipo
Associazione tra variante prima non
valorizzata e fenotipo del pz

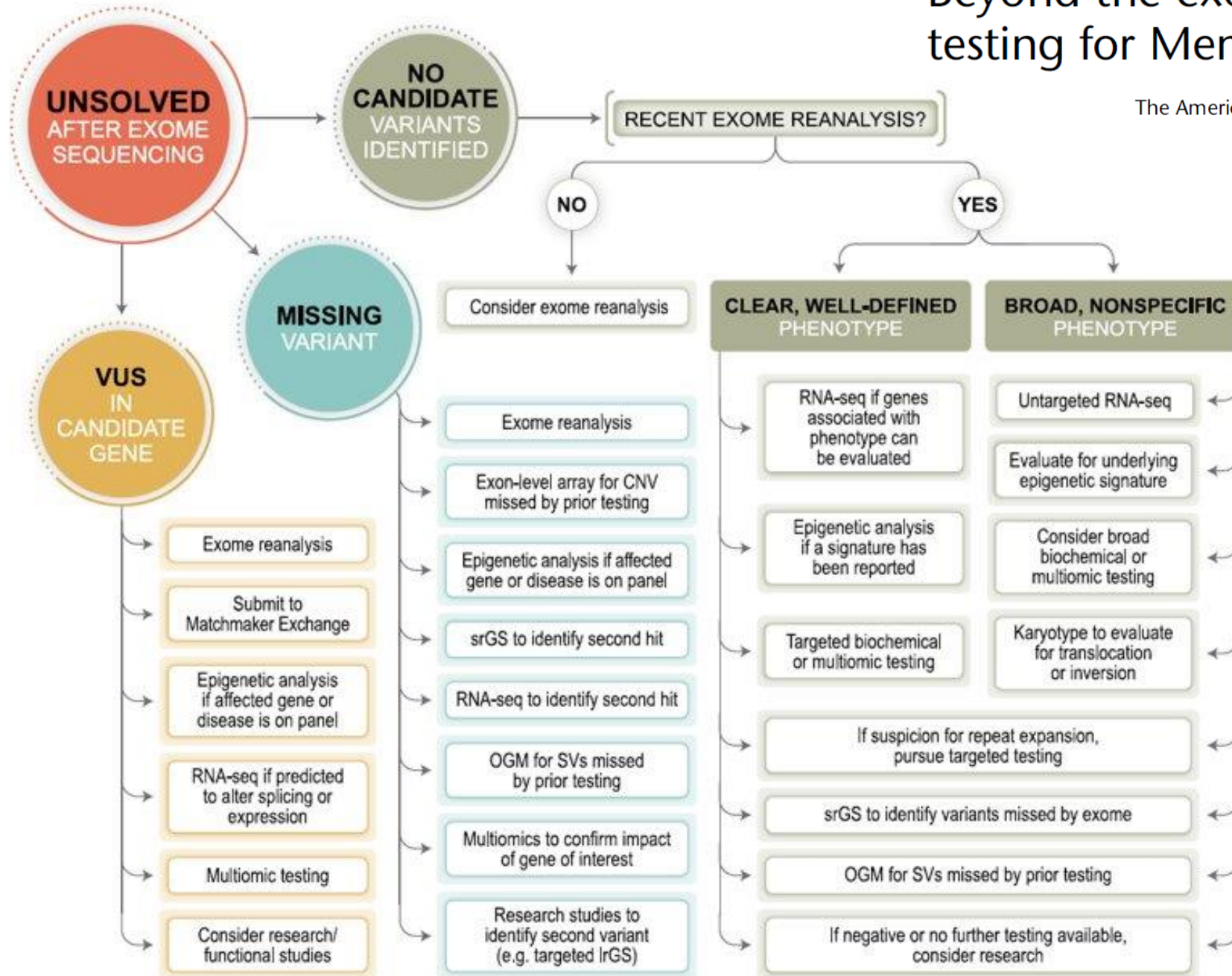


VUS riclassificata

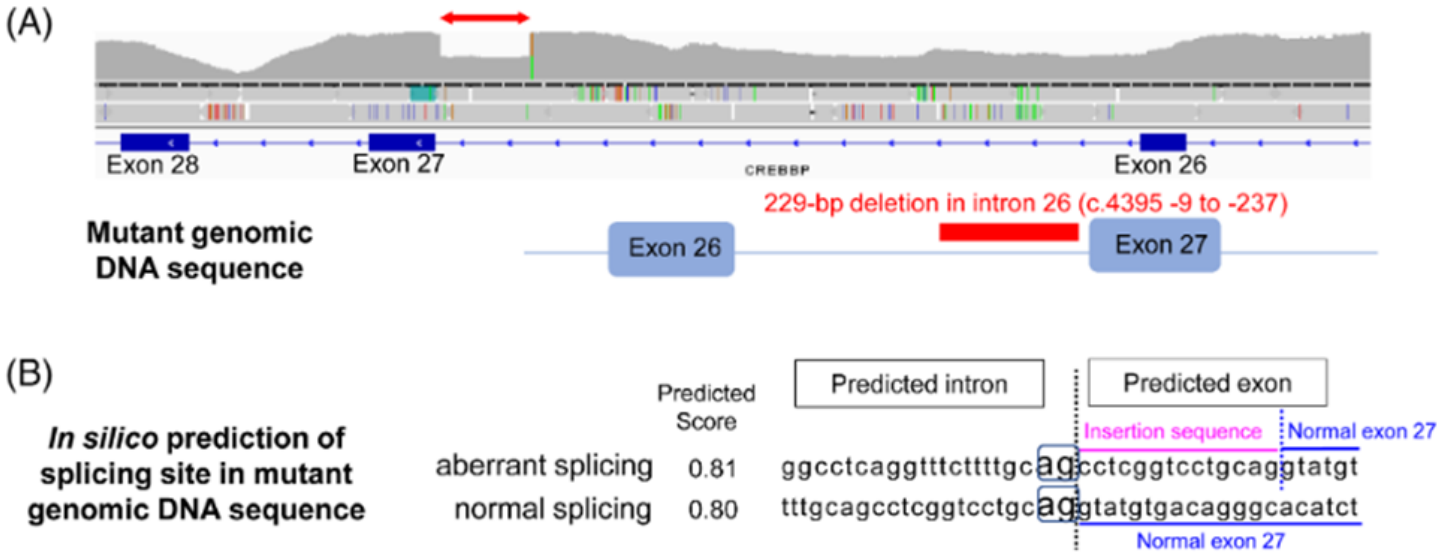
- **Pathogenic variant**
- **Likely pathogenic variant**
- **Variant of uncertain significance (VUS)**
- **Likely benign variant**
- **Benign variant**

Beyond the exome: What's next in diagnostic testing for Mendelian conditions

The American Journal of Human Genetics 110, 1229–1248, August 3, 2023



two patients had causative variants in non-coding regions (10.5%). These results provide insights into the underlying mechanism of RSTS and the feasibility of WGS as a diagnostic approach

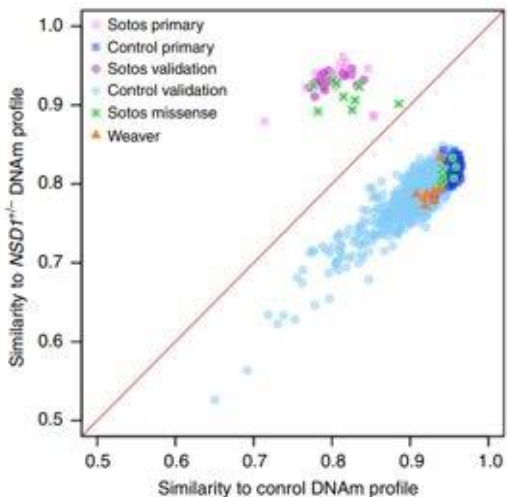




GENOMA

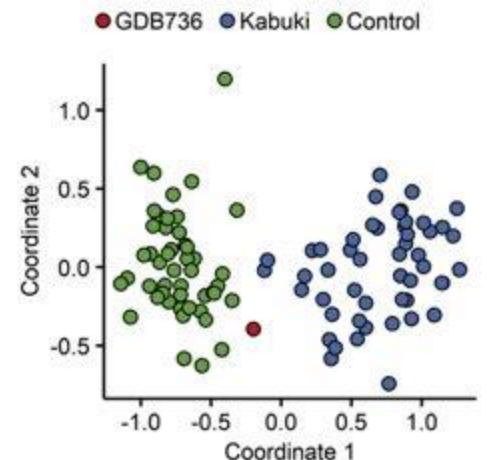


EPIGENOMA

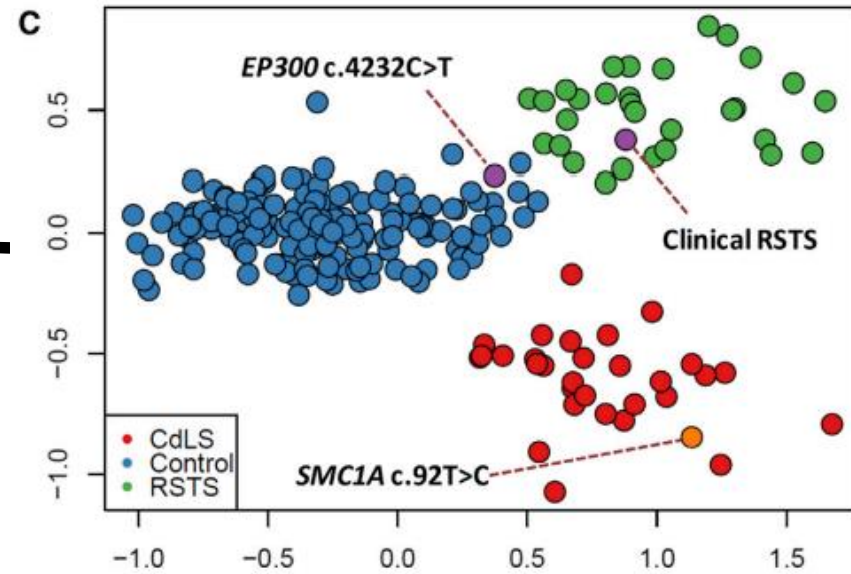
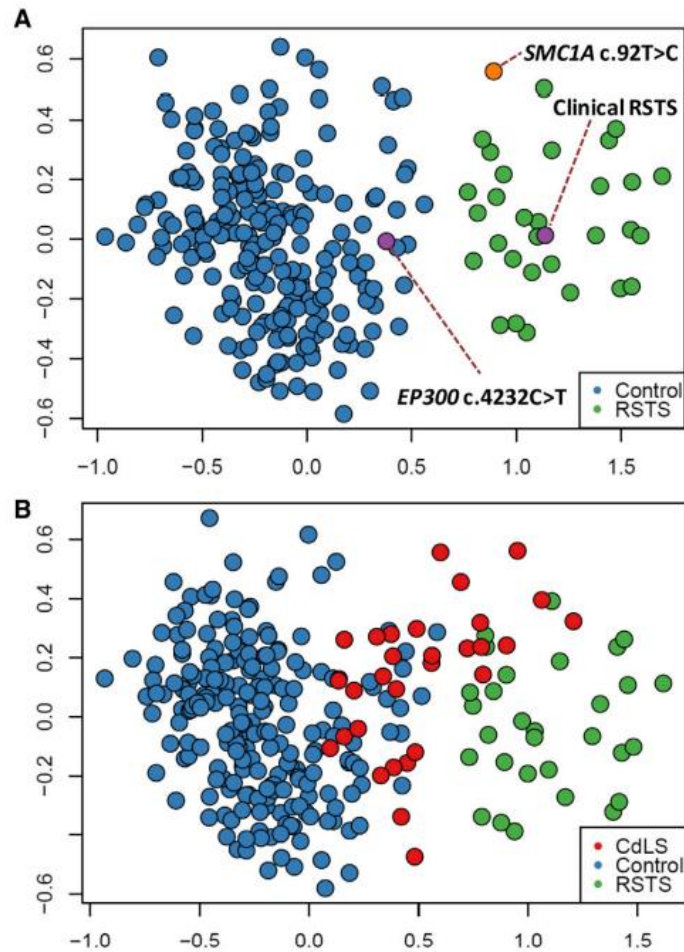


DNA methylation episignature testing improves molecular diagnosis of Mendelian chromatinopathies

Genetics in Medicine (2022) 24, 51–60



Metiloma



The episinature of RSTS partially overlapped with that of CdLS

(C) Incorporation of probes specific to CdLS in the analysis demonstrates that CdLS subjects are indeed distinct from RSTS cases. The uncertain sample from the individual suspected of having CdLS now clearly clusters with the other confirmed CdLS subjects.

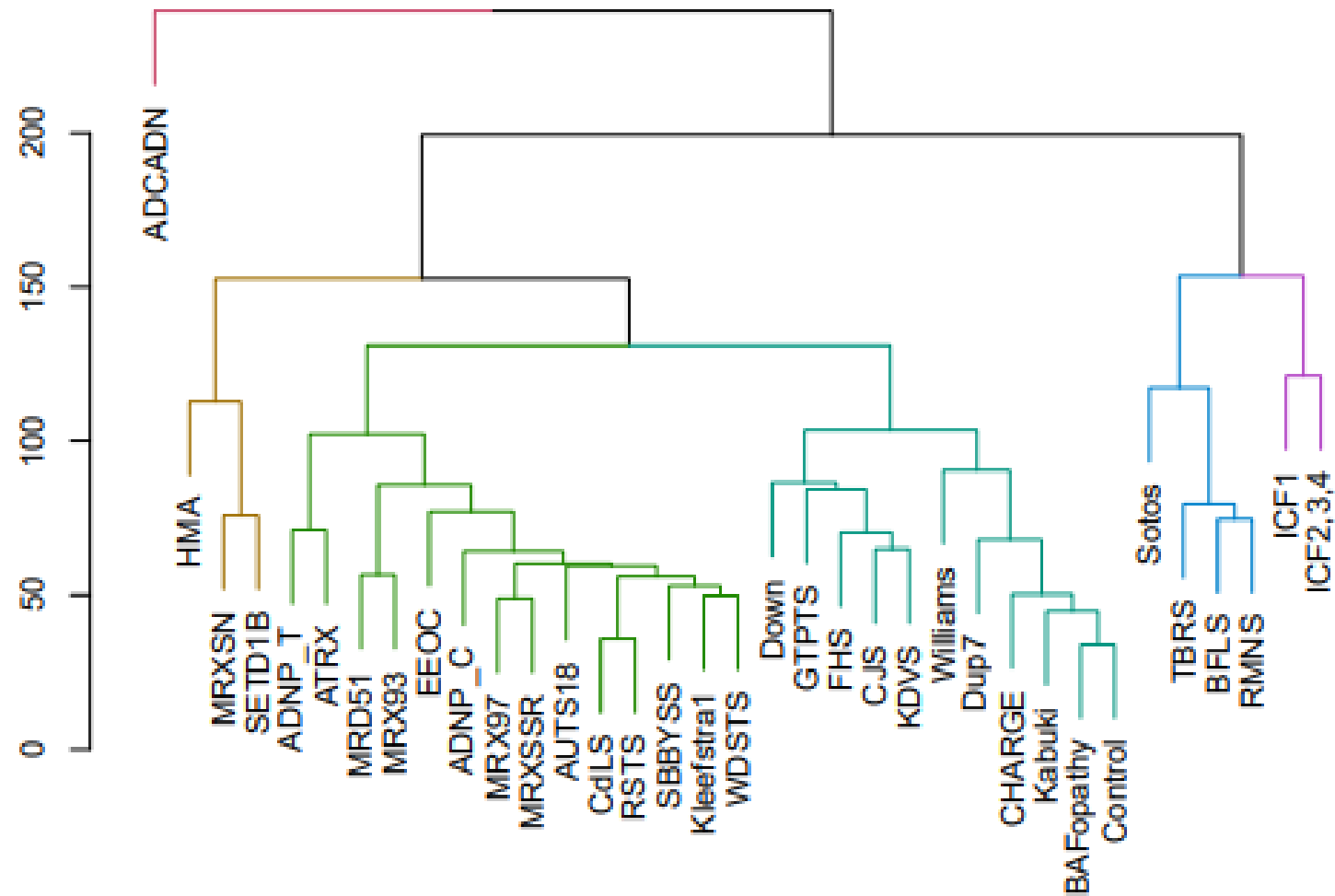


Figure 3. Distance and Hierarchical Orders across 34 Episignatures

Fenotipo

Genotipo

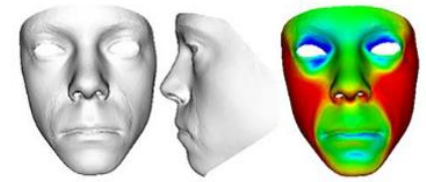
*Genotipo
(esami wide)*

Fenotipo

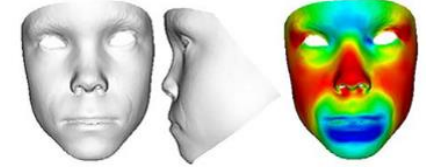


Fenotipi alternativi

Dup 16p13.3



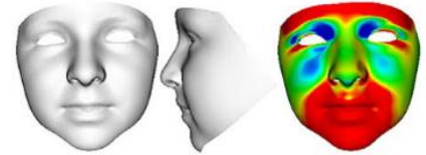
Patient C11



Inverted face
of patient C11



Mean RSTS



Fenotipi alternativi

- ✓ Microduplicazioni
- ✓ S.Menke-Hennekam

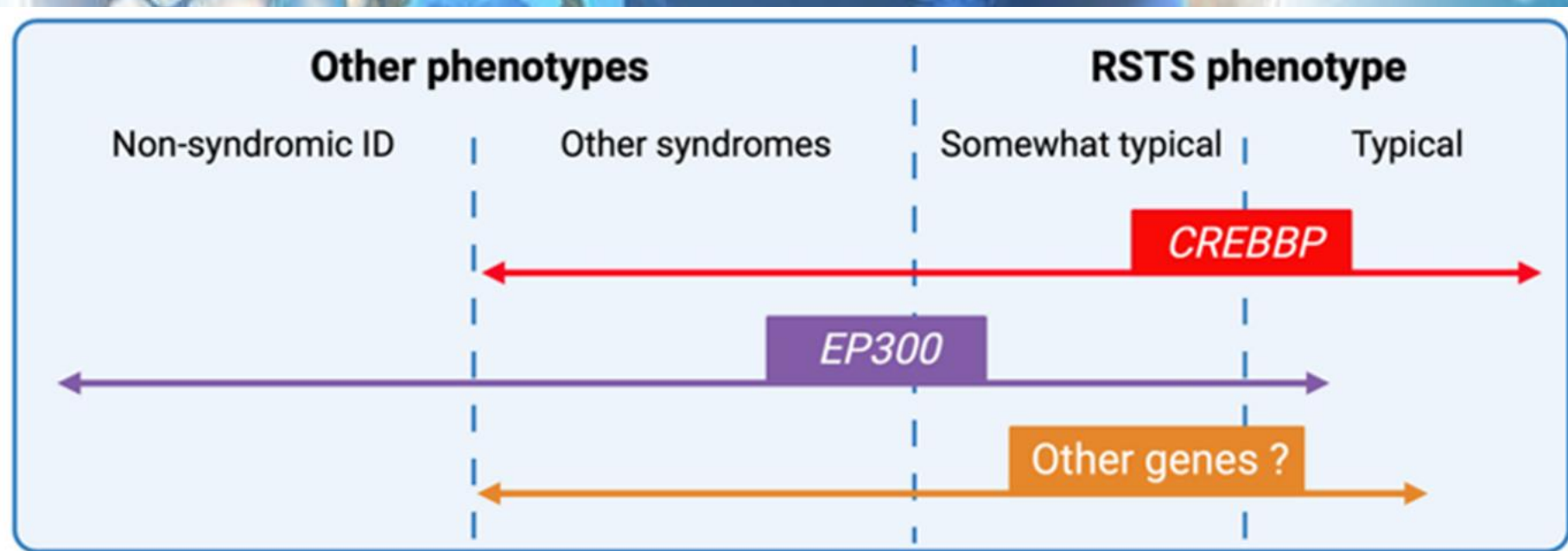
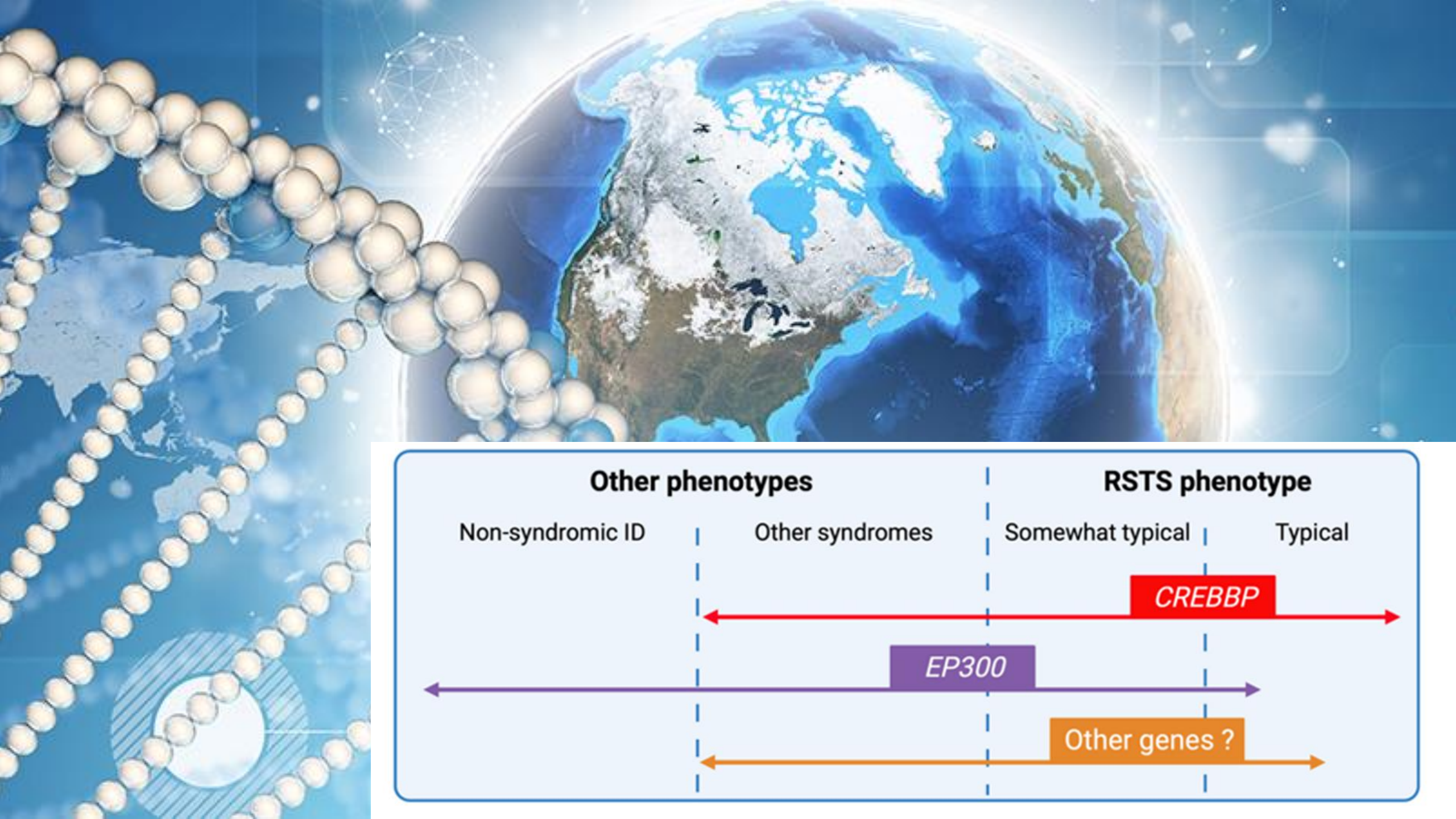


CLINICALLY BLENDED PHENOTYPES

EXPANDED PHENOTYPE



BLENDED PHENOTYPE





Diagnosis and management in Rubinstein-Taybi syndrome: first international consensus statement

Didier Lacombe ,¹ Agnès Bloch-Zupan,² Cecilie Bredrup,³ Edward B Cooper,⁴ Sofia Douzgou Houge,⁵ Sixto García-Miñaur,⁶ Hülya Kayserili ,⁷ Lidia Larizza ,⁸ Vanesa Lopez Gonzalez,⁹ Leonie A Menke,¹⁰ Donatella Milani,¹¹ Francesco Saettini,¹² Cathy A Stevens,¹³ Lloyd Tooke,¹⁴ Jill A Van der Zee,¹⁵ Maria M Van Genderen,¹⁶ Julien Van-Gils,¹ Jane Waite,¹⁷ Jean-Louis Adrien,¹⁸ Oliver Bartsch,¹⁹ Pierre Bitoun,²⁰ Antonia H M Bouts,²¹ Anna M Cueto-González,²² Elena Dominguez-Garrido,²³ Floor A Duijkers,²⁴ Patricia Fergelot,¹ Elisabeth Halstead,²⁵ Sylvia A Huisman,^{10,26} Camilla Meossi,¹¹ Jo Mullins,²⁷ Sarah M Nikkel,²⁸ Chris Oliver,²⁹ Elisabetta Prada,¹¹ Alessandra Rei,³⁰ Ilka Riddle,³¹ Cristina Rodriguez-Fonseca,³² Rebecca Rodríguez Pena,³³ Janet Russell,³⁰ Alicia Saba,³⁴ Fernando Santos-Simarro,³⁵ Brittany N Simpson,³⁶ David F Smith,³⁷ Markus F Stevens,³⁸ Katalin Szakszon ,³⁹ Emmanuelle Taupiac,¹ Nadia Totaro,³⁰ Irene Valenzuela Palafoll ,²² Daniëlle C M Van Der Kaay,⁴⁰ Michiel P Van Wijk,⁴¹ Klea Vyshka,⁴² Susan Wiley,³¹ Raoul C Hennekam¹⁰

Table 2 Clinical diagnostic criteria for Rubinstein-Taybi Syndrome

Cardinal	Supportive
1.Face (at least three of six).	a. Maternal pre-eclampsia.
a. Highly arched eyebrows.	b. Keloids.
b. Downslanted palpebral fissures.	c. Hypertrichosis.
c. Convex nasal ridge.	1 point if c is positive, or
d. Columella below alae nasi.	3 points if a and/or b (with or without c) are positive.
e. Highly arched palate.	
f. Typical smile.	
3 points or	
4 points if d and/or f are positive.	
2.Skeletal.	
a. Angulated thumbs and/or halluces.	
b. Broad thumbs.	
c. Broad halluces.	
3 points if b and/or c is positive, or	
4 points if a (with or without b/c) is positive.	
3. Growth.	
a. Microcephaly.	
b. Postnatal growth retardation.	
2 points if a and/or b are positive.	
4. Development.	
Delayed development/intellectual disability	
2 points.	
Cardinal Score is positive only if two of the four groups score positive and also at least either skeletal or craniofacial scores positive	
Definitive clinical diagnosis of Rubinstein-Taybi syndrome: Score ≥12 and positive cardinal score.	
Likely clinical diagnosis of Rubinstein-Taybi syndrome: Score 8–11 and positive cardinal score. This score warrants molecular analyses of <i>CREBBP</i> and <i>EP300</i> .	
Possible clinical diagnosis of Rubinstein-Taybi syndrome: Score 5–7 and negative cardinal score. This score warrants molecular analyses of <i>CREBBP</i> and <i>EP300</i> .	
Unlikely clinical diagnosis of Rubinstein-Taybi syndrome: Score 0–4 and negative cardinal score. Further studies for other aetiologies indicated.	

Lacombe D, et al. *J Med Genet* 2024;**0**:1–17.

